DEVELOPMENT OF A NOVEL RATE-MODULATED FIXED DOSE ANALGESIC COMBINATION FOR THE TREATMENT OF MILD TO MODERATE PAIN

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A Research Report submitted to the Faculty of Health Sciences,

University of the Witwatersrand, in the partial fulfilment of the requirements

for the degree of Master of Science in Medicine (Pharmaceutical Affairs)

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2009

DECLARATION

I, Kim Melissa Hobbs, declare that this research report is my own work. It has been submitted for the degree of Master of Science in Medicine in the field of Pharmaceutical Affairs in the Faculty of Health Sciences of the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Signed this 24th day of December 2009

ABSTRACT

Pain is the net effect of multidimensional mechanisms that engage most parts of the central nervous system (CNS) and the treatment of pain is one of the key challenges in clinical medicine (Le Bars et al., 2001; Miranda et al., 2008). Polypharmacy is seen as a barrier to analgesic treatment compliance, signifying the necessity for the development of fixed dose combinations (FDCs), which allow the number of tablets administered to be reduced, with no associated loss in efficacy or increase in the prevalence of side effects (Torres Morera, 2004). FDCs of analgesic drugs with differing mechanisms of nociceptive modulation offer benefits including synergistic analgesic effects, where the individual agents act in a greater than additive manner, and a reduced occurrence of side-effects (Raffa, 2001; Camu, 2002).

This study aimed at producing a novel, rate-modulated, fixed-dose analgesic formulation for the treatment of mild to moderate pain. The fixed-dose combination (FDC) rationale of paracetamol (PC), tramadol hydrochloride (TM) and diclofenac potassium (DC) takes advantage of previously reported analgesic synergy of PC and TM as well as extending the analgesic paradigm with the addition of the anti-inflammatory component, DC.

The study involved the development of a triple-layered tablet delivery system with the desired release characteristics of approximately 60% of the PC and TM being made available within 2 hours to provide an initial pain relief effect and then sustained zero-order release of DC over a period of 24 hours to combat the on-going effects of any underlying inflammatory conditions. The triple-layered tablet delivery system would thus provide both rapid onset of pain relief as well as potentially address an underlying inflammatory cause.

The design of a novel triple-layered tablet allowed for the desired release characteristics to be attained. During initial development work on the polymeric matrix it was discovered that only when combined with the optimized ratio of the release retarding polymer polyethylene oxide

(PEO) in combination with electrolytic-crosslinking activity, provided by the biopolymer sodium alginate and zinc gluconate, could the 24 hour zero-order release of DC be attained. It was also necessary for this polymeric matrix to be bordered on both sides by the cellulosic polymers containing PC and TM. Thus the application of multi-layered tableting technology in the form of a triple-layered tablet were capable of attaining the rate-modulated release objectives set out in the study. The induced barriers provided by the three layers also served to physically separate TM and DC, reducing the likelihood of the bioavailability-diminishing interaction noted in United States Patent 6,558,701 and detected in the DSC analysis performed as part of this study.

The designed system provided significant flexibility in modulation of release kinetics for drugs of varying solubility. The suitability of the designed triple-layered tablet delivery system was confirmed by a Design of Experiments (DoE) statistical evaluation, which revealed that Formulation F4 related closest to the desired more immediate release for PC and TM and the zero-order kinetics for DC. The results were confirmed by comparing Formulation F4 to typical release kinetic mechanisms described by Noyes-Whitney, Higuchi, Power Law, Pappas-Sahlin and Hopfenberg. Using f_1 and f_2 fit factors Formulation F4 compared favourably to each of the criteria defined for these kinetic models.

The Ultra Performance Liquid Chromatographic (UPLC) assay method developed displayed superior resolution of the active pharmaceutical ingredient (API) combinations and the linearity plots produced indicated that the method was sufficiently sensitive to detect the concentrations of each API over the concentration ranges studied. The method was successfully validated and hence appropriate to simultaneously detect the three APIs as well as 4-aminophenol, the degradation product related to PC.

Textural profile analysis in the form of swelling as well as matrix hardness analysis revealed that an increase in the penetration distance was associated with an increase in hydration time of the tablet and also an increase in gel layer thickness. The swelling complexities observed in the

delivery system in terms of both the PEO, crosslinking sodium alginate and both cellulose polymers as well as the actuality of the three layers of the tablet swelling simultaneously suggests further intricacies involved in the release kinetics of the three drugs from this tablet configuration.

Modified release dosage forms, such as the one developed in this study, have gained widespread importance in recent years and offer many advantages including flexible release kinetics and improved therapy and patient compliance.

Key Words: analgesic, pain, paracetamol, tramadol, diclofenac, polymer, PEO, layered tablet, zero-order release, first-order release.

RESEARCH OUTPUTS AND PATENT

Research Outputs

A poster entitled “Rate-modulating Release Effects of Cellulose and Ethylene Oxide-based Polymers on the Kinetics of Combined APIs from Multi-Configured Tablet Formulations” was presented at the Academy of Pharmaceutical Sciences Conference, Cape Town, South Africa 4-7th September 2007.

A podium presentation entitled “Polymeric Configurations for the Alteration of Kinetic Release Mechanisms” was presented at the 2nd Annual Symposium on Biomaterials Research and Development at the University of the Witwatersrand, Johannesburg, South Africa, 26th November 2007.

Patent

A South African Provisional Patent Application entitled “Rate Modulated Delivery of Drugs from a Composite Delivery System” filed by Adcock Ingram Healthcare (Pty) Limited, by inventors Kim Melissa Hobbs, Viness Pillay, Yahya Essop Choonara and Bradley Ryan Parsons, March 2008, pending.

ACKNOWLEDGMENTS

I express my sincere thanks, gratitude and appreciation to the following persons who assisted with this study.

To Professor Viness Pillay for his never-ending guidance, patience and passion for research that assisted me so greatly throughout this study.

To Mr. Yahya E. Choonara for his valuable time, advice, support and willingness to assist.

To Mr. Bradley R. Parsons for the opportunity to pursue this project and continued support.

To my sponsor company Adcock Ingram, for the financial assistance and opportunity to complete the study.

To my colleagues Mr. Ashley Q. Michaels and Mrs. Coleen Philip for their assistance in the analytical aspects and validation of the methods used in this study.

To my husband Gareth, and my family for their support and interest in my work and their unending belief in me.

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LIST OF ABBREVIATIONS

5-HT	5-Hydroxytryptamine
API	Active pharmaceutical ingredient
BP	British Pharmacopoeia
CNS	Central nervous system
COX	Cyclo-oxygenase
DC	Diclofenac potassium
DoE	Design of experiments
DSC	Differential Scanning Calorimetry
EC	Ethylcellulose
EVD	Extreme Vertices Design
FDA	Food and Drug Administration
FDC	Fixed dose combination
FTIR	Fourier Transform Infrared
GIT	Gastrointestinal tract
HEC	Hydroxyethylcellulose
HPC	Hydroxypropylcellulose
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
ICH	International Conference on Harmonization
IVIVC	*In vitro in vivo* correlation
NSAID	Non-steroidal anti-inflammatory drug
PBS	Phosphate Buffer Saline
PC	Paracetamol
PDA	Photodiode array
PEO	Polyethylene oxide
RSD	Relative standard deviation
RSM	Response surface methodology
SA	Sodium alginate
TM	Tramadol hydrochloride
UPLC	Ultra performance liquid chromatography
USP	United States Pharmacopeia

CHAPTER ONE

LITERATURE REVIEW, RATIONALE, MOTIVATION AND OVERVIEW OF THE STUDY

1.1 Introduction

Pain is the net effect of multidimensional mechanisms that engage most parts of the central nervous system (CNS) and the treatment of pain is one of the key challenges in clinical medicine (Le Bars et al., 2001; Miranda et al., 2008). The response and sensation of pain involves many physiological receptors and biochemical processes. As many pharmacological modalities target only one exclusive site in order to attempt to diminish pain, they do not provide adequate pain relief (Polomano et al., 2008).

Nociceptive pain is a term used to describe pain that has an identified and acknowledged source, such as from injury or arthritis (Galluzzi, 2005). Neuropathic pain is defined by the International Association for the Study of Pain (Seattle, Washington, USA) as “pain that is initiated or caused by a primary lesion or dysfunction in the nervous system, and may be central or peripheral.” Pain signals due to harmful stimuli such as inflammation are converted into electrical impulses in the tissue nociceptors within dorsal root ganglions. Nociceptive and neuropathic pain signals both utilize the same pain pathways. The intensity and location of the pain are conveyed to the sensory cortex from the somatosensory thalamus of the brain (Galluzzi, 2005).

In the event of unrelenting pain the interneurons in the dorsal horn of the neuron release endogenous opioids in order to minimize the perceived sensation of pain. Exogenously administered opioids mimic the enkephalin and dynorphin effects of the μ-opioid receptors in the brain and spinal cord (Galluzzi, 2005). Opioids act peripherally during inflammation, inhibit nociceptive signal transmission and at the supraspinal level (Camu, 2002). They are powerful analgesic drugs used as additional therapy to paracetamol or non-steroidal anti-inflammatory

drugs (NSAIDs) (Rubin, 2005). Due to the multiple neural pathways, transmitters and receptors involved in pain perception, optimum pain management requires a multimodal route using several analgesics (Cesare and McNaughton, 1977; Levine et al., 1993; Rang and Urban, 1995; Dickenson and Besson, 1997; Carlton and Coggeshall, 1998; Besson, 1999; Serpell, 2007).

Tramadol [30% aqueous solubility at 25℃ (Alfonso et al. 2003); pKa 9.41; elimination half-life ($t_{1/2}$) 6 hours (Sweetman, 2005)] is a weak μ- and κ-opioid receptor agonist and acts on the monoamine receptors of the autonomous nervous system preventing noradrenaline reuptake and displacing stored 5-hydroxytryptamine (5-HT) (Lee et al., 1993; Camu, 2002; Galluzzi, 2005). The dual mode activity of tramadol is compliant with the fundamental principle of current pain management strategies (Serpell, 2007; Polomano et al., 2008). The synergy of the opioid and monoaminergic actions results in analgesia for the treatment of moderate to severe pain (Sweetman, 2005). It is clinically associated with fewer side-effects (Jung et al., 2004) and a lower addictive potential (Rubin, 2005), due to the binary mechanism of action of tramadol (Cicero et al., 1999; Raffa, 2001) compared to conventional opioids. This makes tramadol effective for various types of post-operative pain as well (Jung et al., 2004). In order to reduce the incidence of side-effects associated with opioid analgesics, they are often combined with non-opioid mediators to reduce the quantity of opioid necessary to produce equivalent analgesia (Jung et al., 2004). Thus, tramadol is frequently prescribed in low-dose combinations with paracetamol or NSAIDs (Camu, 2002). The simultaneous administration of a NSAID with tramadol may produce synergistic antinociception (Tallarida and Raffa, 1996, Schnitzer et al., 1999; Doroschak et al., 1999; Medve et al., 2001; Raffa, 2001).

Paracetamol [1.4% aqueous solubility at 20°C; pKa 9.5; elimination half-life ($t_{1/2}$) 1-3 hours (Sweetman, 2005)], a para-aminophenol derivative, has central antinociceptive activity involving serotonin and serotinergic descending inhibitory pathways (Camu, 2002; Sweetman, 2005). Paracetamol is used for its analgesic and anti-pyretic properties in mild to moderate pain and fever, and in the management of severe pain as an adjunct to opioids (Sweetman, 2005). The

pharmaceutical ingredient is known for its excellent antipyretic effectiveness and safety profile (Jung et al., 2004). Paracetamol demonstrates an upper limit of efficacy above which no increase in dose improves the therapeutic effect, but it is not associated with dependence nor tolerance. In rheumatic conditions the weak anti-inflammatory activity of paracetamol limits its contribution to pain management, usually requiring the anti-inflammatory effects of the NSAIDs (Sweetman, 2005). Co-prescribing a NSAID with paracetamol has been shown to improve post-operative pain treatment (Camu, 2002). As paracetamol has neither the renal nor cardiovascular side-effects typical of anti-inflammatory drugs, it is used in both NSAID- and opioid-sparing roles (Guindon et al., 2007). The low cost and risk profile of paracetamol therapy suggests a highly beneficial benefit/risk ratio justifying its commonplace occurrence in pain management (Guindon et al., 2007).

NSAIDs, (such as diclofenac, a phenylacetic acid derivative) are anti-pyretics and analgesics that have central and peripheral effects (Camu, 2002; Sweetman, 2005). NSAIDs inhibit cyclo-oxygenase (COX) enzymes and synthesize prostaglandin E_2 in traumatized and inflamed tissue, thus increasing the nociceptors threshold of activation. Extensive protein binding and acidic nature results in their anti-inflammatory effects. Plasma protein capillary leakage and the acidic pH in the inflamed tissue extracellular space, allows NSAIDs to concentrate in the injured tissue thereby allowing them to render their analgesic effects (Camu, 2002). As surgical trauma initiates peripheral inflammatory reactions and hence pain, NSAIDs are a valuable post-operative option (Jung et al., 2004). Diclofenac [solubility of 0.00178% at neutral- to 0.0001 in acidic-physiological pH and aqueous solubility of 0.1113% (Spernath et al., 2007); pKa 4.0 (Reza et al., 2004); terminal plasma half-life 1-2 hours (Sweetman, 2005)] is an analgesic, antipyretic and anti-inflammatory agent that is widely used for the long-term symptomatic treatment of rheumatoid arthritis and osteoarthritis and for the short-term treatment of acute musculoskeletal injuries, post-operative pain and dysmenorrhoea (Hardman, 1996).

The administration of NSAIDs with opioids has been shown to reduce post-operative opioid consumption, improve post-operative gastrointestinal functioning and reduce the incidence of bladder contractions. During severe visceral pain, analgesia is less acquiescent to NSAIDs, however, co-administration with opioids may produce superior therapeutic results (Camu, 2002).

This Chapter focuses on the concept of pain management and the rationale for the choice of Active Pharmaceutical Ingredients (APIs) for this fixed dose combination delivery system.

1.2 Rationale for Selecting the Specific Active Pharmaceutical Ingredient Combination

In pain management, it is necessary to develop innovative methods of facilitating medications that promote compliance and simplify prescribing without escalating side-effects (Raffa, 2001; Torres Morera, 2004). Polypharmacy is seen as a barrier to treatment compliance, signifying the necessity for the development of fixed dose combinations (FDCs), which allow the number of tablets administered to be reduced, with no associated loss in efficacy or increase in the prevalence of side effects. The anticipated benefits of analgesic combinations include an extended duration of action, improved efficacy, reduced opioid consumption and diminished side-effects (Torres Morera, 2004).

FDCs of analgesic drugs with differing mechanisms of nociceptive modulation offer benefits including synergistic analgesic effects, where the individual agents act in a greater than additive manner, and a reduced occurrence of side-effects (Raffa, 2001; Camu, 2002). The combinations are most effectual when the single agents act via exclusive analgesic mechanisms and act synergistically by inhibiting several pain pathways. This multimodal exposure offers more effective relief for a more extensive spectrum of pain (Raffa, 2001). The concept of multimodal analgesia involves the use of various classes of analgesics and differing sites of analgesic administration to provide enhanced dynamic reprieve with diminished analgesic-related side-effects (Joshi, 2005; Guindon et al., 2007). Opioids are considered as the first-line medication for relieving severe

nociceptive pain but are inadequate in controlling dynamic pain being associated with significant side-effects. Alternative pain relief using non-opioid analgesics historically relied on paracetamol supplemented with NSAIDs (Camu, 2002).

Analgesic superiority of the FDC of paracetamol and tramadol over either individual component, without an increase in side-effects has been shown (Torres Morera, 2004). The fixed combination allowed for a reduction in the dose of tramadol, and thereby a reduction in its associated side-effects, with an equivalent level of analgesia (Torres Morera, 2004). Data demonstrates that rather than being additive in therapeutic effect, such combinations are, in fact, synergistic (Jung et al., 2004).

In a recent study, a codeine/paracetamol/ibuprofen combination was compared against tramadol/paracetamol for the total pain relief that occurred and the sum of the pain intensity differences. During the 5- and 6-hour assessments, the triple combination that included a different opioid and NSAID, showed significant superiority. The vast improvement in the duration of action observed after 4-6 hours was thought to be due to the anti-inflammatory component (Jung et al., 2004).

A pharmacokinetic explanation for this observation was shown in another study that diclofenac transiently reduced the glomerular excretion of the active codeine metabolites, by decreasing prostacyclin production and reducing renal blood flow. This addition of diclofenac to paracetamol and codeine, significantly prolonged the time until analgesic rescue medication was required (Breivik et al., 1999). No renal pathology is anticipated for the combined used of tramadol and diclofenac as the parenteral combination was tolerated similarly as well as diclofenac or tramadol alone and with no significant increases in side-effects compared with placebo dosing, when used for pain in a recent study (Wilder-Smith et al., 2003).

In a study by Miranda and co-workers (2008), treatment of pain syndromes by multimodal methods seen with the synergy of triple combinations, suggested potential clinical importance. The study involved the co-administration of morphine, ketoprofen and paracetamol and demonstrated that opioid receptor activation as well as two major inhibitory pain pathways in the central nervous system, were involved in the associated antinociceptive synergy induced.

United States Patent 5,516,803 describes a composition of tramadol and a NSAID. In a study using tramadol and ibuprofen on the acetylcholine-induced abdominal constriction in mice, the combination resulted in unexpected analgesic activity enhancement. It was postulated from the results that other NSAIDs, when combined with tramadol, would show similar synergistic activity (Raffa, 1996).

As referenced in United States Patent 6,558,701, describing a multilayer tablet for the administration of a fixed combination of tramadol and diclofenac, the World Health Organisation recommends combining opioid analgesics with NSAIDs for the treatment of moderate to severe pain (Bartholomaeus et al., 2003). The invention of a parenteral suspension of a salt of tramadol and diclofenac, shown in beagle dogs to retard the metabolism of tramadol and thereby prolong analgesia, is described in United States Patent 6,875,447 (Bartholomaeus et al., 2005).

The fixed combination of tramadol and paracetamol in Tramacet™ (Janssen-Cilag Ltd., Berchem, Belgium) has proved to be a therapeutic advantage and the efficacy of both these active pharmaceutical ingredients benefit from the addition of a NSAID according to the above-cited research. United States Patent 5,516,803 describes the superadditive advantage gained by combining tramadol and a NSAID and United States Patents 6,558,701 and 6,875,447 describe advantages in FDCs of tramadol and diclofenac, in particular.

Thus also considering the safety and efficacy profile of the NSAIDs, where diclofenac is clinically associated with the second lowest relative risk (Breivik et al., 1999), and its potency substantially

greater than several other agents (Hardman, 1996), a FDC of tramadol, paracetamol and diclofenac, is proposed in this study, in the form of a triple-layered tablet configuration.

1.3 Aim and Objectives of this Study

The aim of this study was to develop an oral rate-modulated, site-specific drug delivery system comprising a FDC of tramadol, paracetamol and diclofenac.

In order to achieve this aim the following objectives were outlined:

1.3.1. To test the physicochemical feasibility of polymeric materials such as ethylcellulose (EC), hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), polyethylene oxide (PEO), polyamide (PA) or polyvinyl alcohol (PVA) as potential polymers for the FDC formulation.

1.3.2. To undertake a drug-drug, drug-excipient and excipient-excipient compatibility study of all three APIs and the polymer/s within the formulation to assess any unfavourable interactions between the materials.

1.3.3. To develop a stability-indicating High Performance Liquid Chromatography (HPLC) assay method for the simultaneous determination of tramadol, paracetamol and diclofenac content in the FDC tablet and to then transfer the HPLC method to a comparative Ultra-Performance Liquid Chromatography (UPLC) method.

1.3.4. To formulate a FDC comprising a triple-layer tablet of tramadol, paracetamol and diclofenac with the polymer/s identified in 1.3.1 above using an experimental design strategy such as Response Surface Methodology (RSM).

1.3.5. To assess the *in vitro* drug release kinetics using simulated gastric and intestinal media as outlined in United States Pharmacopeia (USP) 32 in both the rotating paddle method (Apparatus II) and the Bio-Dis method (Apparatus III). A comparative dissolution study will be undertaken on specific and relevant registered products containing tramadol, paracetamol and/or diclofenac.

1.3.6. To undertake a textural profiling analysis of the FDC delivery system to assess the various stress-strain parameters such as matrix resilience, tolerance and deformation energy.

1.3.7. To undertake in-process validation testing on the completed FDC formulation through determination of tablet hardness, thickness, diameter, friability, uniformity of mass and disintegration time.

1.4 Overview of this Research Report

Chapter One describes the rationale behind the triple combination of paracetamol, tramadol hydrochloride and diclofenac potassium.

Chapter Two covers the physicochemical characterization of the formulation components. This includes a rheological analysis, assessment of the molecular structural transitions and thermal compatibility analysis.

Chapter Three details the HPLC and UPLC assay method development for the determination of the three APIs and their associated degradation products. This Chapter also details the validation of these methods, in ensuring the data derived is reliable and accurate.

Chapter Four explores the initial formulation development of the delivery system and details the influence of cellulosic polymers, polymeric concentration, layered tableting and electrolytic-crosslinkers.

Chapter Five investigates the optimization of the FDC tablet with the use of the Design of Experiments (DoE) Extreme Vertices Design (EVD). The optimized formula undergoes further examination by *in vitro* comparison to two marketed pharmaceutical products.

Chapter Six analyzes the physicomechanical characteristics of the final product via textural profiling of the delivery system by performing swelling and matrix hardness studies.

Chapter Seven completes the in-process validation testing of the delivery system providing an indication of the performance of the FDC tablet under pharmaceutical manufacturing.

The report concludes with recommendations for potential industrial applications and future investigation into the construction of the delivery system in alleviating debilitating therapeutic conditions such as pain.

1.5 Concluding Remarks

As the fixed combination of tramadol and paracetamol in the marketed product Tramacet™ (Janssen-Cilag Ltd., Berchem, Belgium) had proved to have a therapeutic advantage and the fact that the efficacy of both paracetamol and tramadol is proposed to benefit from the addition of a NSAID according to the above-cited research, a combination of these two APIs with a NSAID was chosen to be explored in this research. Several patents described the potential synergistic use of tramadol and diclofenac, in particular, and based on its relative clinical safety and efficacy profile, diclofenac was the NSAID of choice for this study.

CHAPTER TWO

PHYSICOCHEMICAL CHARACTERIZATION OF THE FORMULATION COMPONENTS

2.1 Introduction

Polymeric platforms may be considered as colloidal systems as they become more fluid the faster they are stirred. This shear thinning behavior is referred to as pseudoplasticity as the viscosity is not constant but decreases with increasing shear. In polymer solutions the entanglement of macromolecules and immobilization of solvent by the entangled macromolecules provide the structure. The threadlike molecules of methylcellulose for instance, are buffeted constantly by the surrounding water molecules in thermal agitation. This causes continuous motion of chain segments by translation and by rotation around bonds between the carbon and oxygen atoms that make up the polymer backbone. As these thermal fluctuations are random, the polymer chains form loose coils that are permeated by water. These coiled macromolecules become tangled and additional water is entrapped inside the open coils (Schramm, 2004).

Upon the application of shear, a unidirectional laminar motion is imposed on the random thermal motion of the water molecules and chained segments. The polymer chains tend to disentangle themselves and align in the direction of flow. As the polymers become elongated they provide less resistance to flow than the original spherical shapes or coils. The amount of water trapped in the coils is decreased as the chains progressively disentangle. These effects on the size and shape of the polymer reduce the viscosity of the solution.

Aqueous polymeric solutions tend to have high viscosities due to the entanglement of the long threadlike chains. The polymer chains are surrounded by a hydration layer, due to water molecules being attracted to the polar groups of the macromolecules by secondary valence bonds. This hydration sheath prevents the chains from forming attachments with other chains in

the molecule by valence bonding as it limits direct contact of the molecules. It allows the chains to slip easily past one another when shear is applied and thereby promotes disentanglement. If the solvent action is decreased, by decreasing the temperature for example, the hydration layer around the dissolved macromolecules becomes thinner and direct contact may occur. These weak secondary crosslinks of the polymer chain offer some resistance to the slippage of the chains past one another when shear is applied. If sufficient links are formed to create a three-dimensional network, the polymer solution may set to form a gel (Schramm, 2004).

Fourier transform infrared (FTIR) spectroscopy was undertaken to assess any possible structural variations in the polymeric backbone, as a result of interactions between the drug combinations or between the drugs and polymers in the formulation. FTIR detects bond vibration characteristics of chemical functional groups in a sample. When infrared light interacts with a sample, chemical bonds stretch, contract and bend. As a result a chemical functional group tends to absorb infrared radiation in a specific wavenumber range regardless of the structure or the rest of the molecule. The correlation of the band wavenumber position with the chemical structure is used to identify a functional group in a sample.

The development of a successful, stable formulation depends on the selection of excipients that are included to facilitate drug administration, provide the desired drug release and bioavailability of the formulation. By screening mixtures of each drug with each excipient, interactions may be observed by comparing the resulting thermogram with that of the individual substance (Agatonovic-Kustrin et al., 2008; Harding et al., 2008).

Differential scanning calorimetry (DSC) was undertaken as part of both physicochemical and compatibility analyses to analyze changes, such as the glass transition temperature (T_g) of the polymer, melting point (T_m) and any interaction between the polymers, excipients and/or drugs during formulation. DSC can be used to determine the energy phenomena produced during heating or cooling and to determine the changes in enthalpy, specific heat and the temperatures

that these occur for a substance or mixture of substances. The difference in heat flow (ΔH) evolved or absorbed by a substance is measured in comparison to a reference cell, usually high purity indium, as a function of temperature.

This Chapter focuses on the physicomechanical aspects of the delivery system including rheological analysis, molecular structural transition and thermal compatibility analysis.

2.2 Materials and Methods

2.2.1 Materials

Polyethylene oxide (PEO) (Polyox® WSR303 NF with a molecular mass of 7 x 10^6 g/mol) was purchased from Union Carbide Corp. (Danbury, CT, USA). The cellulosic polymers, hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC) were purchased from Hercules GmbH, Aqualon Division (Dusseldorf, Germany). Zinc gluconate was purchased from Jiangxi Chinabase, (Changdong, China) and sodium alginate from FMC Biopolymer, (Drammen, Norway). Paracetamol (PC) was purchased from Fine Chemicals Corporation, (Cape Town, South Africa), tramadol hydrochloride (TM) from Zydus Cadila Healthcare Limited, (Ahmedabad, India) and diclofenac potassium (DC) from Kairav Chemicals Limited, (Ahmedabad, India). Only commonly-used, pharmaceutical-grade excipients that are routinely employed in the pharmaceutical industry were considered for use in this study. Such excipients included for example zinc gluconate and pregelatinised starch.

2.2.2 Rheological analysis of polymeric solutions

A HAAKE Modular Advanced Rheometer System (MARS) was used to determine the rheological properties of 5mL of the polymeric solutions, prepared in phosphate buffer (PB) pH 6.8, described in Table 2.1. A C35 sensor with a 1° titanium cone as used for standard linear rheological determinations with a zero point measurement positioned, was used. Rheological profiles were produced with shear rate vs. shear force and viscosity. Data evaluation employed the use of

Haake RheoWin® Data Manager version 3.6 software. Data acquisition was performed over 150 data points ranging from 0-500s^{-1} in a time of 180 seconds. The temperature was maintained at 25℃ throughout the test.

Table 2.1: Solution compositions employed for the rheological analysis.

Polymers/Excipients	Concentration
HEC	4%w/v
HPC	2%w/v
PEO	30%w/v
Sodium alginate	1%w/v
Zinc gluconate	0.5%w/v
Sodium alginate: zinc gluconate	2:1 (66.7:33.3%w/w)
PEO: zinc gluconate	60:1 (98.4:1.6%w/w)
PEO: alginate: zinc gluconate	30:2:1 (90.9 :6.1: 3.0%w/w)

2.2.3 Assessment of the molecular structural transition

A FTIR spectrophotometer (PerkinElmer Spectrum One with Spectrum V5.00 software, PerkinElmer Instruments, CT, USA) was used to detect the vibration characteristics of chemical functional groups in a sample in response to infrared light interactions. The infrared signal after interaction with the sample is uniquely characteristic for a sample. Interferograms are translated via the mathematical technique of Fourier Transformation before being presented as an infrared spectrum, which plots transmittance versus wavenumber. These measurements were performed in triplicate. A typical plot for each individual drug was obtained and compared to the plots of its respective analytical standard.

A profile showing the transmittance of a mixture of all three active pharmaceutical ingredients (APIs) was also produced as well as profiles of the APIs and their potential respective polymers. As TM and PC were to be the hypothetical immediate or first-order release APIs in the delivery system they were tested for chemical interference with the cellulose polymers, HEC and HPC. DC was combined with suggested release-modulating PEO, in order to determine any potential interactions.

In order to produce these profiles an approximately 1:1:1 or 1:1 ratio was prepared by combining the above-mentioned combinations with a mortar and pestle. A sample of the blended preparation was used in the platinum crucible to generate the resulting percentage transmittance profile as described by Stancanelli et al. (2008) and da Silver-Junior et al. (2009).

2.2.4 Thermal compatibility analysis

Thermograms were captured using a Mettler-Toledo TC15, TA Controller System (Switzerland) with a DSC instrument (Mettler DSC 20, Mettler-Toledo AG, Switzerland). An indium calibration was performed for the analyses. Samples of 10mg to 20mg were transferred to punctured aluminium pans and sealed immediately. The heating rate was 10°C per minute and the temperature range captured was 30-300℃ for the stu dies including PC and TM and from 30-400℃ for those involving DC.

Each API, polymer and excipient was analyzed individually to obtain a base thermogram. Physical mixtures of API, polymer and/or excipient were combined in a 1:1 ratio using a mortar and pestle (Agatonovic-Kustrin et al., 2008; Harding et al., 2008). The APIs PC and TM were combined with the polymers HEC and HPC which were hypothesized for use in the more immediate release elements of the delivery system while DC was combined with PEO.

Potential crosslinking between sodium alginate and the electrolyte zinc gluconate were also studied individually and in combination in order to detect if the crosslinking had any physicochemical interaction when the two raw materials were physically combined. Sodium alginate was also studied in combination with PEO to predict any unfavourable physical interactions.

As an interaction between PEO and pregelatinised starch had been reported by L'Hote-Gaston and Willick (2008), as potentially slowing the release of APIs from matrices containing these two

materials due to slower penetration of the matrix core, this potential physicochemical interaction was also investigated. The reported untoward interaction of DC and TM mentioned in United States Patent 6,558,701, as the formation of a sparingly soluble compound that reduces the bioavailability of the two compounds, prompted that this combination be studied in order to eliminate this negative event from being present in the developed delivery system.

2.3 Results and Discussion

2.3.1 Rheologic analysis of polymeric solutions

The mean shear rate (s^{-1}), shear force (t) and viscosity (η) for each single or binary polymeric solution are tabulated in Table 2.2. It can be seen that the shear force and viscosity of HEC (Figure 2.1a) were greater than those of HPC (Figure 2.1b) even though the concentration of the HEC was twice that of HPC. At a concentration of 4%w/v and a viscosity of 647cP it would appear likely that HEC may more stringently restrict drug release than HPC in PBS (pH 6.8, 25℃).

When examining the results for the combined solutions it is evident that both the shear force and viscosity of the zinc gluconate/sodium alginate composition were greater than the sum of the two individual components which may be indicative of the crosslinking effects of the zinc ions within the alginate structure producing a more rigid structure and therefore increased viscosity.

The greatest increase in both viscosity and shear rate was seen in the PEO/zinc gluconate/sodium alginate solutions (Figure 2.1c).The viscosity increased to larger than a factor of five over the sum of the individual viscosities and the shear force by a factor of 3. This indicated that the three polymers used in combination may greatly enhance the retardant release abilities of the FDC tablet, due to the inherent high viscosity seen with PEO as well as the crosslinking effects of sodium alginate and zinc gluconate.

Table 2.2: Mean shear rate, shear force and viscosity produced by the various polymeric solutions (N=2)

Aqueous Polymer/Excipients	***Shear rate (s^{-1}±SD)***	***Shear force (Pa±SD))***	***Viscosity (cP±SD))***
HEC	74.265±0.06	32.435±0.62	647.000±16.55
HPC	74.445±0.56	0.368±0.08	5.156±0.84
PEO	74.600±0.00	6.714±0.00	128.600±0.00
Sodium alginate	73.795±0.02	1.112±0.03	14.890±0.31
Zinc gluconate	73.960±0.06	0.081±0.00	2.187±0.18
Sodium alginate: zinc gluconate	74.655±0.74	1.280±0.01	17.975±0.94
PEO: zinc gluconate	73.790±0.01	9.653±0.09	417.950±20.44
PEO: sodium alginate: zinc gluconate	73.870±0.00	27.420±0.00	786.900±0.00

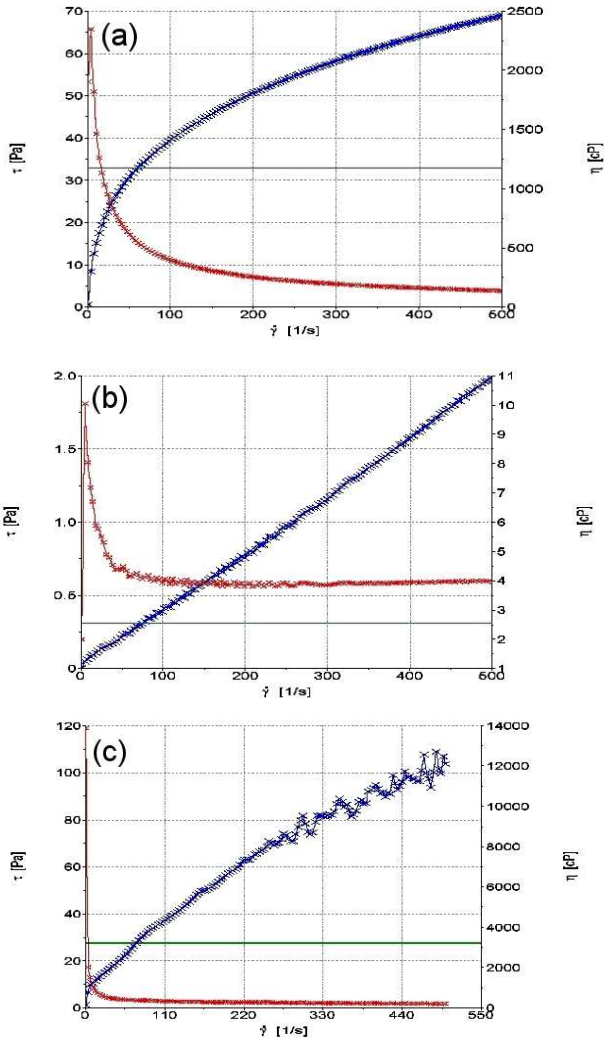


Figure 2.1: A typical shear force, shear rate and viscosity plot of (a) HEC, (b) HPC and (c) combination of PEO, sodium alginate and zinc gluconate.

2.3.2 Assessment of the molecular structural transition

Typical FTIR plots for TM, PC and DC were generated and used as a comparison for the combined samples. In Figure 2.2 is a plot of the percentage transmittance of a combination of PC, TM and DC.

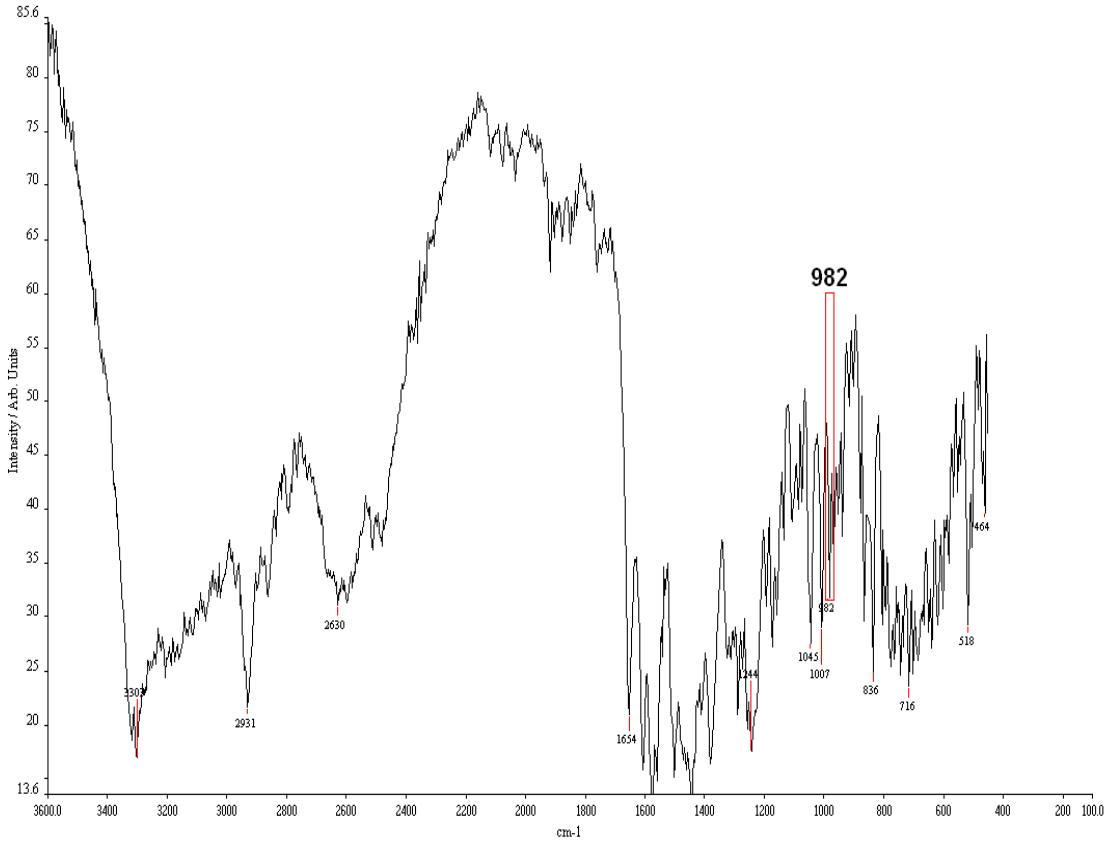


Figure 2.2: A typical FTIR plot of the combination of PC, TM and DC.

The profile in Figure 2.3 is of a combination of DC and the polymer PEO.

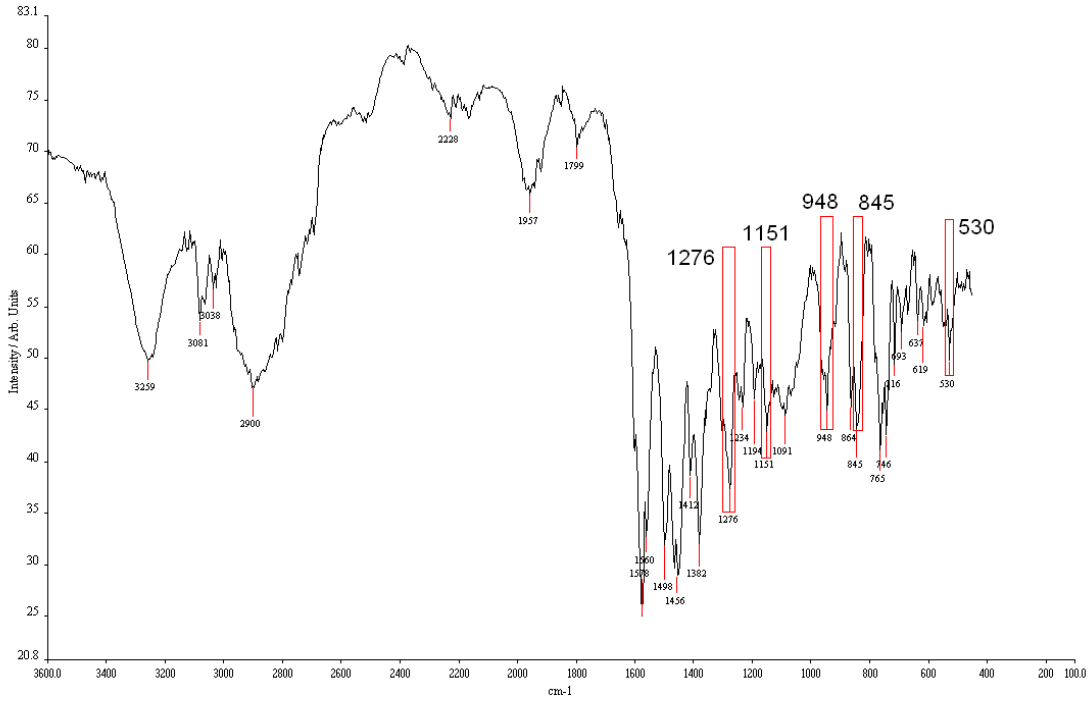


Figure 2.3: A typical FTIR plot of the combination of DC and PEO.

Table 2.3 lists the transmittance peaks in the fingerprint region of 400-1500cm^{-1} for PC, TM and DC. Peaks that were not present in the individual API samples were identified. The principle peaks for DC are observed approximately at wavenumbers 1572, 756, 1504, 775, 1286 and 1308cm^{-1}. Those for TM are observed at 1284, 1601, 1042, 1238, 1575 and 702cm^{-1} and those for PC at 1506, 1657, 1565, 1263, 1227 and 1612cm^{-1}.

The physical mixture of the three APIs produced a new peak at 982cm^{-1} and none of the principle peaks for DC were observed, suggesting a possible interaction. This is in line with literature in United States Patent 6,558,701 on the physical interaction of TM and DC. For the combination of PC, TM and HEC a new peak at 1373cm^{-1} was observed. For the combination of PC, TM and HPC new peaks at 625cm^{-1} and 937cm^{-1} were observed. The DC and PEO sample showed the most likelihood of an interaction between the two compounds as previously unobserved peaks were then seen at 530cm^{-1}, 845cm^{-1}, 948cm^{-1}, 1151cm^{-1} and 1276cm^{-1} and none of the principle peaks for DC were present.

From the data it was not possible to ascertain whether these peaks are due to an interaction between the APIs or polymers or are part of the fingerprint of the polymers present in the combined samples. Further studies into possible physical interactions were undertaken employing differential scanning calorimetry reported later in this chapter.

Table 2.3: Wavenumbers for each sample

Wavenumber	***Tramadol (TM)***	***Paracetamol (PC)***	***Diclofenac (DC)***	***3 APIs***	***TM/PC/ HPC***	***TM/PC/ HEC***	***DC/PEO***
400-450							
450-500		461			466		
500-550		504, 517		520	504, 518	519	530
550-600							
600-650	649				625		
650-700		688					
700-750	703*		716	703*	702*	703*	716
750-800	777		765				765
800-850		807, 835		837	808, 836	808, 837	845
850-900	867	857	864				
900-950					937		
950-1000		964		982	969		948
1000-1050	1007	1014		1006,	1008	1007	
1050-1100	1046*		1089	1045*		1045*	
1100-1150		1108		1111	1109		
1150-1200	1165	1172	1195	1174	1175	1174	1151
1200-1250	1242*	1239*		1243*	1244*	1243*	
1250-1300	1288*				1327	1289*	1276
1300-1350	1317	1328	1305*	1380		1327	
1350-1400		1370	1378				1382
1400-1450		1434		1450	1443	1442	1451
1450-1500	1463	1501*	1488			1506*	1498

* Principle peaks.

2.3.3 Thermal compatibility analysis on the API's, polymers and excipients

For each thermogram as well as that of the combined samples the integral onset and end set temperatures were determined for each significant thermal event. The mean values are shown in Table 2.4.

Figure 2.4 depicts the thermograms of the drugs TM in red, DC in blue and the combined sample of DC and TM in black, with all other thermograms being unremarkable. As indicative in the DC thermogram the analysis shows the typical exotherm at 280℃ followed by an endotherm. The TM thermogram shows an endotherm at 180℃, in line wit h its melting range of 179-180℃.

Table 2.4: Mean integral, onset and endset temperature values for the individual and combined samples

Sample	Mean sample mass (mg)	Mean integral (mJ±SD) (N=2)	Mean onset temperature (℃±SD) (N=2)	Mean endset temperature (℃±SD) (N=2)
PC	10.50	1144.58±217.97	162.05±0.21	170.49±1.76
TM	10.50	997.92±106.42	169.80±0.25	182.98±0.08
DC	12.05	-1990.82±591.67	268.42±0.98	297.08±0.77
		1.64±9.60	300.18±1.34	302.16±1.61
HEC	12.45	-196.11±10.13	180.43±0.01	200.26±0.62
HPC	11.90	-1.25±2.31	195.60±2.28	209.37±0.34
PEO	12.10	787.56±47.19	51.26±0.59	72.32±0.26
		-919.86±66.21	173.30±0.61	188.30±0.08
Sodium alginate	12.50	-625.08±862.61	233.64±15.97	260.00±0.79
Zinc gluconate	12.20	931.73±110.39	104.77±0.32	135.17±3.08
		335.79±54.40	169.46±0.64	194.63±1.49
		-111.88±63.83	194.42±2.40	201.28±0.09
Pregelatinised starch	12.75	-31.06±40.29	86.41±4.00	112.05±1.89
		-0.21±2.23	272.67±1.91	277.82±1.93
PC & HEC	11.50	530.09±18.79	115.87±0.19	170.03±0.18
		-26.08±12.30	230.63±1.46	261.61±2.45
PC & HPC	11.30	3.20±38.40	156.74±1.69	159.41±0.54
		6.53±5.46	159.44±0.50	170.61±0.26
TM & HEC	12.00	44.05±94.24	155.93±0.72	158.70±0.06
		4.99±2.86	168.17±13.34	181.85±0.94
TM & HPC	11.40	-55.34±44.53	155.76±2.27	158.00±1.16
		212.97±17.33	166.10±0.36	184.38±4.31
Alginate & Zinc gluconate	14.10	-135.93±7.64	126.59±0.19	140.36±2.36
		191.64±9.45	172.62±0.26	192.56±0.37
		-167.85±30.87	229.08±1.17	260.10±0.05
		178.89±34.52	53.52±0.87	69.09±0.67
Alginate & PEO	13.45	-291.21±104.75	176.29±1.21	184.48±0.50
		12.09±74.03	206.67±17.85	225.98±0.98
		-7.49±3.92	252.46±0.48	257.31±1.07
		188.28±35.26	55.83±0.00	70.13±0.27
PEO & pregelatinised starch	12.40	-564.19±358.18	171.70±1.13	184.36±1.87
		619.30±124.74	50.65±1.47	71.95±0.57
		-643.50±203.19	248.25±1.15	290.23±0.83
DC & PEO	13.65	-192.11±68.79	359.11±1.40	365.65±1.22
		200.52±24.51	97.26±0.33	133.19±0.42
		3.39±5.31	139.67±0.53	143.17±0.43
TM & DC	13.90	21.56±3.64	174.61±0.62	215.95±1.52
		-3.00±52.58	268.66±13.69	292.01±5.22
		9.02±8.23	353.71±0.88	369.97±0.08

As reported in United States Patent 6,558,701 the potential detriment to bioavailability is as a result of the physical interaction between TM and DC is evident in the combined thermogram depicted below in black where neither the melting point of TM at 180℃ nor the crystallization of DC at 280℃ are present. The combined thermogram undergoes a baseline change or glass transition temperature at 130-140℃ and 210℃, suggesting the resultant compound is susceptible to higher temperatures and hence more stable. This suggests that should the two

APIs be physically combined in the developed delivery system there would be a significant interaction that may reduce the clinical effects of either or both APIs. Thus in order formulate a system in which both APIs are claimed to be together, there may be the need for a physical barrier as suggested in United States Patent 6,558,701.

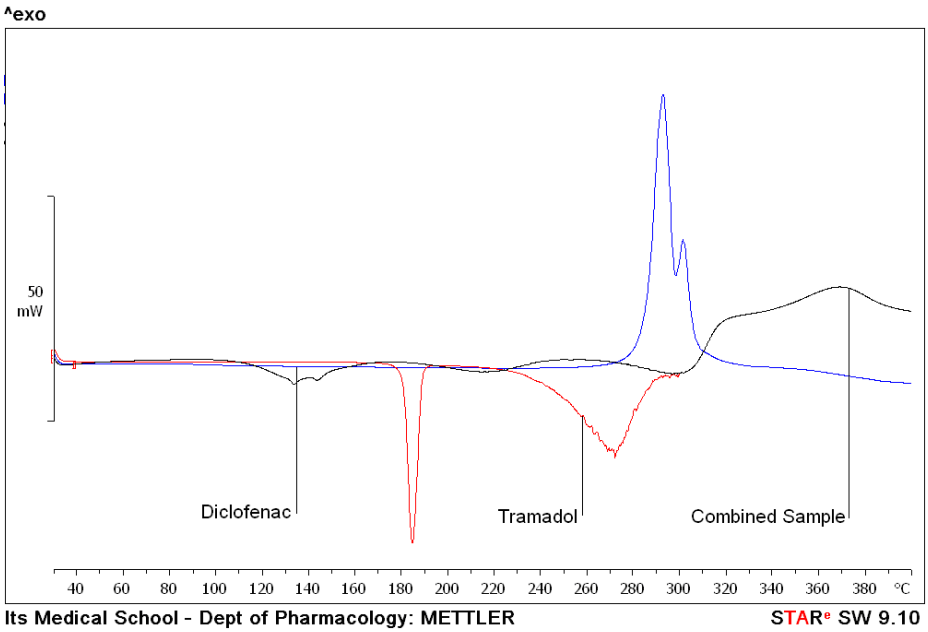


Figure 2.4: Thermograms of DC (blue), TM (red) and the combined sample of the two (black).

2.4 Concluding Remarks

The physicochemical analyses of both the API and polymeric raw materials undertaken in these preformulation studies yielded information critical to further formulation work. The shear force and viscosity results of the zinc gluconate/sodium alginate composition being greater than the sum of the two individual materials suggested a crosslinking effect of the zinc ions within the alginate structure which may be exploited to produce a more rigid structure with increased viscosity. This increased *in vitro* viscosity could prove important to develop the desired release rate for the APIs. Likewise the increased viscosity and shear rate seen in the PEO/zinc gluconate/sodium alginate solutions, could prove useful in enhancing the retardant release abilities of the FDC tablet due to the inherent high viscosity seen with PEO as well as the crosslinking effects of sodium alginate and zinc gluconate.

FTIR analyses produced new peaks in the combined samples of API with polymer alluding to possible physical interaction especially between the API DC and PEO. From the data generated it was not possible to ascertain whether these peaks are due to an interaction between the APIs or polymers or are part of the fingerprint of the polymers present in the combined samples. Further studies into possible physical interactions were undertaken in differential scanning calorimetry.

The DSC studies taken to confirm any physical interaction observed during FTIR analyses showed the likelihood of the detrimental interaction between the APIs and polymers studied were low, even for previously reported interactions. One remarkable physical interaction between DC and TM, that had been reported, was confirmed as being evident with the data generated. This interaction illustrated the importance of creating a barrier within the FDC tablet to physically separate these two APIs in order to preserve or enhance bioavailability.

CHAPTER THREE

LIQUID CHROMATOGRAPHIC METHOD DEVELOPMENT FOR THE ASSAY OF ACTIVE PHARMACEUTICAL INGREDIENTS

3.1 Introduction

The purpose of validating an analytical method is to demonstrate that the analytical procedure meets the requirements for the intended analytical application. The analytical method in this study is intended to determine the purity of the active pharmaceutical ingredients (APIs) and any associated degradation products in the finished product during routine stability studies as well as dissolution testing.

The following analytical characteristics should be employed during a method validation: linearity and range, accuracy, system suitability, specificity, precision, intermediate precision, limit of detection and quantitation, stability of solutions and robustness, according to ICH Q2 (R1) and compendial references (ICH guideline Q2 (R1) – Validation of Analytical Procedures: Text and Methodology, version 4, 2005 and United States Pharmacopoeia (USP) 32<1225> Validation of Compendial Procedures). The linearity and range refer to the ability of a method to elicit results that are directly or by a well-defined mathematical transformation proportional to the analyte concentration within a given range. Accuracy is a measure of the exactness of an analytical method. It is measured as the percentage of analyte recovered by the assay of known added quantities of analyte and degradation product.

System suitability ensures system performance before or during the analysis. It is used to verify that the reproducibility of the system is more than adequate for the analysis to be performed. The parameters are established as a direct result of precision and/or intermediate precision studies. Specificity is the ability of the method to measure the analyte of interest in the presence of other components that could be expected to be present in the sample matrix. This is the measurement

of the degree of influence from the presence of other active ingredients, excipients, impurities or degradation products.

Method precision refers to the measurement of agreement among individual test results when an analytical method is used repeatedly for multiple analysis of a homogenous sample. Intermediate precision is then the degree of reproducibility of the test results obtained by the analysis of the same homogeneous sample as for precision performed by a different analyst, on a different day and using a different lot of column or serial number.

Limit of detection is the lowest concentration of analyte in a sample that can be detected by the method, but not quantitated. The limit of quantitation is the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy under the stated optimal conditions of the method. Stability of solutions for the sample and standards refers to the period of time the sample or standards may be stored in solution phase whilst still remaining suitable for chromatographic determination. Robustness of the method is the capacity of a method to remain unaffected by small but deliberate variations in method parameters.

This Chapter focuses on the development and validation of a suitable chromatographic method for the simultaneous quantitation of the three APIs in the delivery system.

3.2 Materials and Methods

3.2.1 Materials

The analytical reagents used in the validation of the assay method included pharmaceutical grade purified water, acetonitrile (HPLC grade) (Honeywell Burdick and Jackson, Muskegon, MI, USA), orthophosphoric acid 85% (HPLC grade) (Fluka, St. Louis, Missouri, USA), tramadol hydrochloride (TM) secondary standard (Zydus Cadila Healthcare Limited, Ahmedabad, India), paracetamol (PC) primary standard (Sigma-Aldrich, St. Louis, Missouri, USA), diclofenac potassium (DC) secondary standard (Kairav Chemicals Limited, Ahmedabad, India) and 4-aminophenol primary standard (Sigma-Aldrich, St. Louis, Missouri, USA).

3.2.2 High and ultra performance liquid chromatographic methods

Quantitative analyses of TM, PC and DC were performed on a High Performance Liquid Chromatograph (HPLC) (Alliance Waters 2695 Separation Module, Massachusetts, USA) equipped with a photodiode array detector (PDA) (Waters PDA 2996, Massachusetts, USA) at suitable wavelength maxima. The system was fitted with a Waters Atlantis T3 analytical column (4.6 x 75mm).

The suitability of a HPLC method was confirmed by performing linearity plots for the combined APIs. A range of API stock solutions were made (25%, 50%, 75%, 100% and 125%) for PC (81.25; 162.5; 243.75; 325 and 406.25mg/100mL), TM (9.34; 18.75; 28.09; 37.5 and 46.84mg/100mL) and DC (6.25; 12.5; 18.75; 25 and 31.25mg/100mL. Samples were processed by gradient elution techniques using a Waters® 2695 Alliance Separations Module and Waters 2996 PDA. The HPLC chromatographic conditions are mentioned in Table 3.1.

Table 3.1: Chromatographic conditions for combined API HPLC analysis

Component	**Condition**
Column	Atlantis T3 4.6mm x 75mm
Mobile phases	(A) 0.1 % trifluoroacetic acid pH 2.30 with 6M ammonia (pH 2.29) (B) Acetonitrile
Wavelength	275nm
Flow rate	1.0 mL/min
Column temperature	15 to 25℃
Injection volume	10µL
Run time	14 minutes

Due to the availability of newer technology in the form of Ultra Performance Liquid Chromatography (UPLC), the HPLC method was transferred to this specific technology and the validation of the assay method proceeded with this instrument. This instrument allowed for the run-time of the sample to be reduced from 14 minutes using HPLC to 3 minutes due to higher operating pressures.

The mobile phase was prepared by diluting phosphoric acid in water and was degassed through a 0.22µm filter prior to use. The standards were prepared by weighing the APIs into volumetric flasks and diluting to volume with methanol. The samples were prepared by weighing 20 tablets and crushing them in a mortar and pestle. Formulation F4 (refer to Chapter 5), being the optimized formulation, was used in the validation of the method, as this would be the formulation relevant to this method in any future development work. One tablet (mass=1031.68mg) was then weighed and made up to volume with methanol in a volumetric flask. The solution was placed in an ultrasonic bath for 10 minutes. The standard and sample solutions were filtered through a non-sterile 33mm Millex-HV hydrophilic Durapore® (PVDF) 0.45µm syringe filter unit (Millipore, Bilerica, MA, USA) prior to injection onto the column.

The UPLC conditions are described in Table 3.2. An Acquity® TUV/PDA detector, Acquity sample manager, Acquity binary solvent manager and Empower™ 2 Build 2154 software were used. The gradient used by the binary solvent manager is shown in Table 3.3.

Table 3.2: Chromatographic conditions for combined API UPLC analysis

Component	***Condition***
RSD	Not more than 2.0% of six injections on standard solution
Tailing factor	Not more than 2.0
Column efficiency	Not less than 1500 theoretical plates (USP tangent method) for paracetamol peak
Resolution	Not less than 2.0 between 4-aminophenol and paracetamol
Column	Acquity UPLC™ BEH C18, 2.1 x 50mm from Waters Part No.: 186002350 Particle size: 1.7µm Particle shape: hybrid Pore size: 130Å Carbon load: 18% End-capped: proprietary pH range: 1.0 to 12.0
Mobile phase	On-line mixing Line A1: 0.10% phosphoric acid Line B1: acetonitrile
Injection volume	1µL
Loop size	5µL
Retention times	4-aminophenol: 0.3 minutes PC: 0.6 minutes TM: 1.3 minutes DC: 2.2 minutes
Run time	3.0 minutes
Flow rate	0.5mL/min
Column Temperature	40℃
Wavelength	275nm

Table 3.3: Binary solvent manager gradient employed

Time (minutes)	*Flow (mL/min)*	*A (%)*	*B (%)*	*Curve**
Initial	0.50	92	8	-
0.80	0.50	92	8	6
1.00	0.50	50	50	6
2.20	0.50	50	50	6
2.30	0.50	92	8	6
3.00	0.50	92	8	6

*Curve 6 describes a linear rate at which the solvent changes to the new proportions or flow rates.

For the establishment of linearity, solution concentrations of 50-150% for PC, TM and DC and concentrations of 10% to 150% for 4-aminophenol were prepared. Linearity should be demonstrated across the entire range for eight concentrations and each concentration was injected twice into the system. Acceptance criteria of correlation coefficients (R^2) of ≤0.99 and y-intercepts ≥2% were set for PC, TM and DC. For 4-aminophenol, a R^2≤0.99 and a y-intercept ≥5% were set as acceptance criteria.

The accuracy of the method was measured by analyzing a placebo spiked with known quantities of PC (325mg), TM (37.5mg) and DC (25mg) as well as the degradation product of PC, 4-aminophenol. Data from a minimum of 9 determinations over 3 concentration levels ranging over the specified concentrations of 50%w/v, 100%w/v and 150%w/v were required for this analysis. Acceptance criteria of average recoveries of 98% to 102% were set for PC, TM and DC, and 95% to 105% for 4-aminophenol.

System suitability was established by determining column plate count, tailing factor and the percentage relative standard deviation (RSD) from replicate injections (N=6) of the standard as outlined by the analytical procedure. In order to determine the specificity of the method a placebo mixture and standard solution were analyzed and no interference >1.0% in the placebo was accepted.

Precision analysis was performed by assaying samples from a homogeneous powdered batch of tablets. A minimum of 6 individual samples were prepared and analyzed. Intermediate precision was determined by assessing the performance of six samples from the powdered batch of tablets prepared by a different analyst on a different day using a different instrument and column. An RSD of not more than 2% was set as an acceptance criteria.

The limits of detection and quantitation were determined using statistical analysis by Microsoft Excel 2007 on the values derived from the regression analysis of the linearity plots for 4-aminophenol. The equations used are given below in equation 3.1 and 3.2.

Limit of detection = $3.30\delta/S$ *Equation 3.1*

Limit of quantitation = $10.0\delta/S$ *Equation 3.2*

Where δ is the standard deviation of the response and S is the slope of the calibration curve.

The stability of standard and sample solutions was determined by storing the solutions in capped volumetric flasks at laboratory temperature (≈21℃) for periods corresponding to 0, 8 and 24 hours. The area responses were then compared to that occurring initially.

Method robustness was determined by varying the wavelength from 273nm to 275nm, the flow rate from 0.49mL/min to 0.51mL/min and the temperature from 38℃ to 42℃. Any affect on the results was recorded.

3.3 Results and Discussion

3.3.1 HPLC assay method

The HPLC assay method developed displayed superior resolution of the API combinations and the linearity plots produced indicating that the method was sufficiently sensitive to detect the concentrations of each API over the concentration ranges studied (R^2=0.99 for PC, TM and DC).

Initially PC and TM displayed desirable resolution but it appeared that DC was retained for a longer period on the column, due to its basic properties, when a run time of 10 minutes was used. To overcome this, the gradient run time was increased to 14 minutes and the concentration of the organic modifier was increased.

As evident in Figure 3.1, the developed HPLC assay method displayed desirable resolution between each API peak.

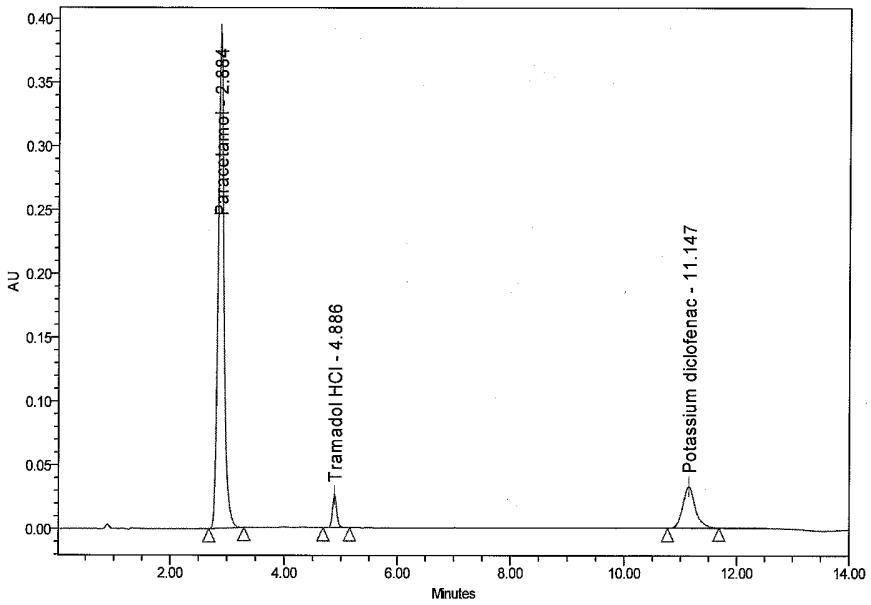


Figure 3.1: A typical chromatographic profile of combined API HPLC analysis.

The calibration curves or linearity plots produced indicated that the method was sufficiently sensitive to detect concentrations of each of the three APIs over the concentration ranges

studied. All three APIs provided linear responses over the tested range. The coefficient of determination (R^2) or the proportion of variability in the data set was R^2=0.99 for PC, TM and DC. As each value was close to 1, it provided assurance that the degree of the goodness-of-fit of the linear model was satisfactory**.**

3.3.2 UPLC assay method and method validation

The validation of the assay method was performed employing UPLC after satisfactory transfer of the method from HPLC to UPLC, via in-house method transfer algorithm protocol. Typical chromatograms for the sample and standards are shown below in Figure 3.2 and Figure 3.3.

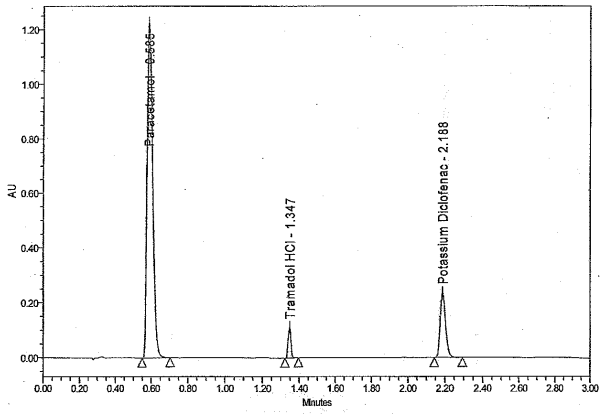


Figure 3.2: Typical sample UPLC chromatogram of the three APIs.

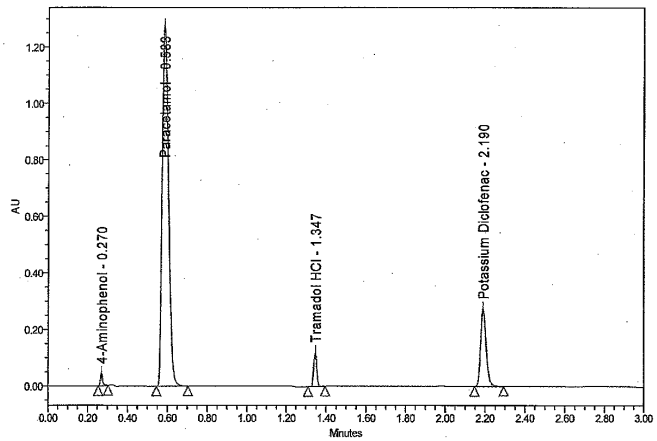


Figure 3.3: Typical standard UPLC chromatogram of the three APIs.

For the linearity analysis the slope of the regression line was derived from the mathematical transformation of the response data using Microsoft Excel Regression Analysis. The acceptance criteria for correlation and deviation were met. No apparent non-linearity was observed. The results in Table 3.4 showed that excellent correlation existed between peak area and the concentration for PC, TM, DC and 4-aminophenol within the concentration range as illustrated in the typical linearity plots for the APIs in Figure 3.4.

Table 3.4: Linearity results for the APIs and degradation product over the concentration range studied

Active ingredient	***Parameter***	***Result***
PC	Correlation coefficient (R)	0.99
	Y-intercept*	1.41%
	Slope	1.0
TM	Correlation coefficient (R)	0.99
	Y-intercept*	0.11%
	Slope	1.0
DC	Correlation coefficient (R)	0.99
	Y-intercept*	0.11%
	Slope	1.0
4-aminophenol	Correlation coefficient (R)	0.99
	Y-intercept*	1.05%
	Slope	1.0

*Percentage response of y-intercept at 100%

The range for the APIs for a concentration of 10-150% was as follows: 0.163 to 2.44 mg/mL for PC, 0.0188 to 1.281 mg/mL for TM and 0.0125 to 0.188 mg/mL for DC. The linearity, accuracy and precision obtained within the specified range were found to be acceptable.

The limits of detection and quantitation were derived from Equations 3.1 and 3.2 extracted from the International Conference on Harmonization (ICH) (Rockville, MD, USA) guidelines, based on the linearity results of 4-aminophenol. The limit of detection was calculated as being 96 and the limit of quantitation as being 249, with these values expressed in area. These results obtained are located in the area of 4-aminophenol content. Any peak that would be obtained in an area <250 should therefore be regarded as baseline noise or interference.

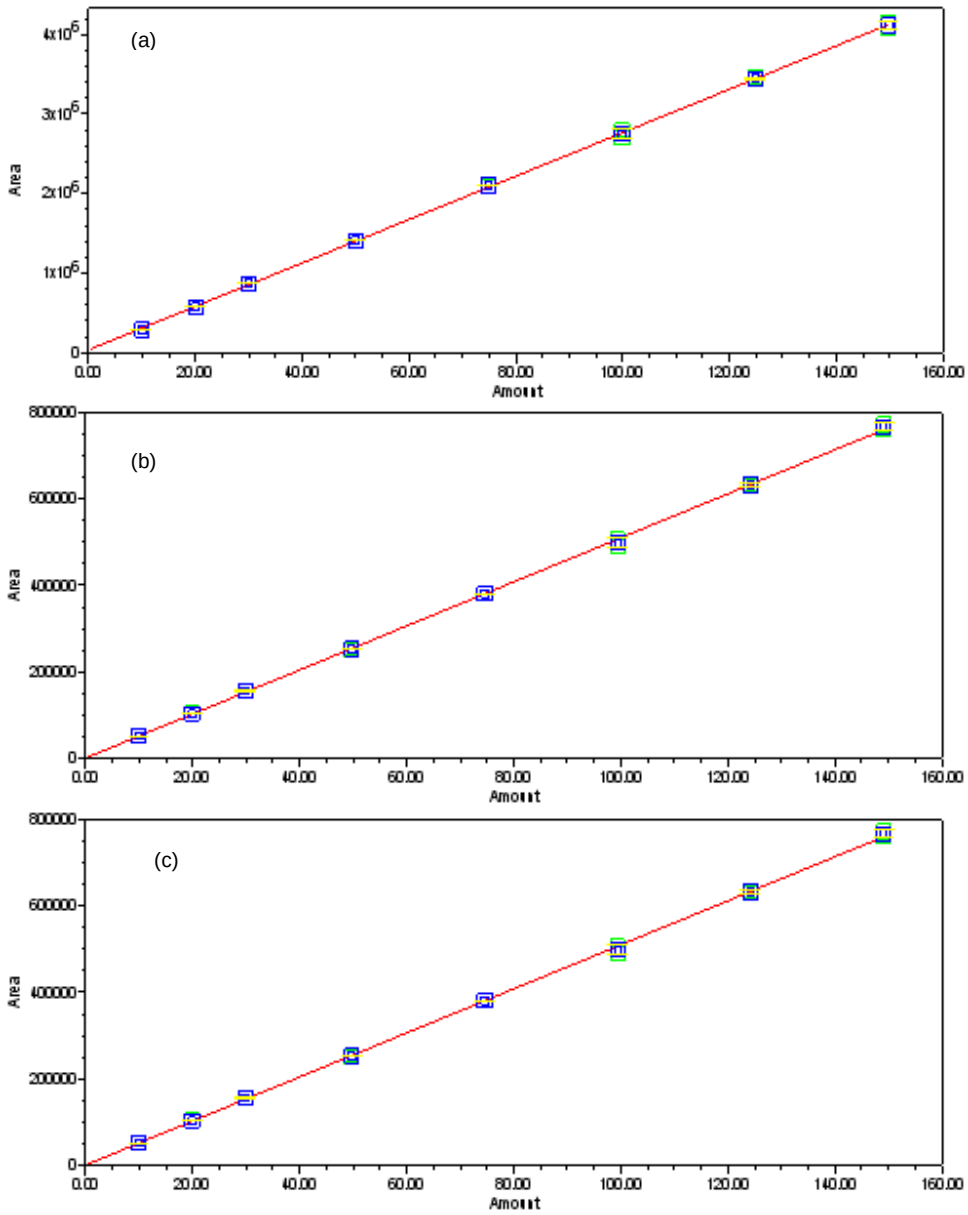


Figure 3.4: Linearity profile for (a) PC, (b) TM and (c) DC.

The accuracy was evaluated by applying known concentrations of actives and degradation product to the mixture of excipients corresponding to 50, 100 and 150%w/v of the label claim. Three tests were prepared at each concentration and each test and standard solution injected once. The relative recovery, mean recovery and RSD values for each analyte are shown in Table 3.5.

Table 3.5: Method validation accuracy results for the FDC tablet

Analyte	Concentration Level (%)	Relative Recovery (%)	Mean Recovery (%)	RSD (%)
PC		103,40		
	50	101.51	100.54	3.433
		96.71		
		99.92		
	100	99.73	99.53	0.511
		98.96		
		99.29		
	150	98.36	98.85	0.468
		98.89		
		103.50		
TM	50	100.93	100.12	3.403
		96.35		
		100.06		
	100	99.38	99.65	0.361
		99.73		
		100.09		
	150	99.18	99.67	0.460
		99.73		
		103.42		
DC	50	101.66	100.67	3.320
		96.95		
		100.26		
	100	100.12	100.05	0.249
		99.78		
		100.33		
	150	99.45	100.05	0.524
		100.38		
		102.81		
4-aminophenol	50	101.32	99.92	3.784
		95.65		
		100.27		
	100	100.25	99.97	0.512
		99.38		
		100.97		
	150	100.30	100.62	0.335
		100.59		

The recovery of APIs ranged from 96.38% to 103.42% and that of 4-aminophenol from 95.65% to 102.81%. The mean percent recoveries fell within 98% to 102% which met the acceptance criteria. Upon statistical evaluation of the linearity between the estimated and actual concentrations, the slopes for the actives were found to be within the range 0.980 and 1.020 and that of the degradation product between 0.950 and 1.050 (where a wider stability limit was used). The 95% confidence intervals all included 1.0, indicating appropriate accuracy of the developed method.

System suitability was demonstrated throughout the method validation studies. Results obtained from precision and intermediate precision analysis are shown in Table 3.6.

Table 3.6: Method validation system suitability results for the APIs and degradation product between Analyst 1 and 2

Active ingredient	Parameter	Analyst 1	Analyst 2
PC	Percent RSD	0.398	0.843
	Tailing factor	1.54	1.41
	Resolution between paracetamol and 4-aminophenol.	7.91	7.83
TM	Percent RSD	0.397	0.909
	Tailing factor	0.98	1.13
DC	Percent RSD	0.412	1.053
	Tailing factor	1.24	1.01
4-aminophenol	Percent RSD	0.428	0.846

These results are within the acceptance criteria of RSD <2%, a tailing factor of <2 and a resolution between PC and 4-aminophenol of >2.

No significant peaks of >1% were observed during the specificity analysis. This indicated that there is no interference of the peaks by the excipients. The peaks of interest in the standard and sample solutions were found to be pure using PDA analysis. The method precision analysis by a different analyst on a different day using a UPLC column of the same make but different lot number resulted in the data tabulated in Table 3.7.

Table 3.7: Recoveries from two analysts during the precision study

Sample	Paracetamol		Tramadol		Diclofenac	potassium
	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2
1	92.65	96.88	93.50	97.58	90.87	92.64
2	97.07	96.16	98.46	96.41	93.06	94.43
3	93.70	97.34	96.80	97.72	92.84	95.52
4	94.08	97.47	94.34	97.85	92.80	94.21
5	96.54	95.64	92.68	96.14	94.49	91.11
6	93.80	96.26	97.41	96.76	89.58	92.85
Mean	94.64	96.62	95.53	97.08	92.28	93.46
RSD (%)	1.852	0.749	2.449	0.754	1.898	1.679
Variance (%)	1.98		1.55		1.18	

The acceptance criteria of the mean percent recoveries not differing by >2% was met, concluding that the method was acceptable with regard to precision. Small but deliberate changes were made to the method in order to assess its robustness. The results from these variations are depicted in Table 3.8.

Table 3.8: Recoveries during robustness analysis

Variable	Parameter	PC Recovery (%)	Variation (%)	TM Recovery (%)	Variation (%)	DC Recovery (%)	Variation (%)
Original method	273 nm	94.64		94.15		92.28	
Wavelength	275 nm	94.61	-0.03	94.16	0.01	92.27	-0.01
		93.66	-0.98	93.32	-0.83	91.49	-0.79
Flow rate	0.49mL/min	94.69	0.05	94.24	0.09	92.37	0.09
	0.51mL/min	95.19	0.55	94.81	0.66	92.98	0.70
Temperature	38℃	93.98	-0.66	93.51	-0.64	91.64	-0.64
	42℃	93.99	-0.65	93.59	-0.56	91.73	-0.55

The acceptance criteria that the variation in results between the original method and the changes made during the robustness study should not differ by >2% were met. The overall results indicated good robustness of the method.

The stability of solutions was evaluated by injecting the sample and standard solutions from the intermediate precision assay both 8 and 24 hours later. The mean of six standard and six sample injections was compared. The acceptance criteria that the difference be >2% was met for the 8 hour samples but not for the 24 hour samples, allowing the conclusion that the solutions are stable for 8 hours to be drawn. The results for the 8 hour study are shown below in Table 3.9.

Table 3.9: Stability of solution peak area results after 8 hours

Time	PC Standard Area	Sample Area	TM Standard Area	Sample Area	DC Standard Area	Sample Area
Initial	2820892	2681877	130288	122734	520529	479475
8 hours	2846971	2717452	131497	124380	524642	485959
Difference	0.92%	1.33%	0.93%	1.34%	0.79%	1.35%

3.4 Concluding Remarks

The results from the validation study showed that the UPLC method for determining PC, TM, DC and 4-aminophenol in the FDC formulation provided linear results in the respective range of analyte and impurities in the test solution, specific, accurate and precise results in the range of 50-150% of the labelled quantity of PC, TM and DC as well as acceptable precision and intermediate precision. The UPLC method showed increased resolution and marked reduction in analysis time. This, combined with reduced solvent usage, makes the method suitable for routine quality control processing. The validated, developed method is thus simple, precise, stability-indicating and selective for the simultaneous determination of the three APIs as well as the degradation product, 4-aminophenol. It can then be concluded that the method is suitable for its intended purpose.

CHAPTER FOUR

IN VITRO DRUG RELEASE STUDIES ON PRELIMINARY FORMULATIONS OF THE FIXED DOSE COMBINATION DELIVERY SYSTEM

4.1 Introduction

Drug absorption from oral dosage forms depends on the adequate release of the Active Pharmaceutical Ingredient (API) from the product. Physicochemical factors such as dissolution or solubility of the API under physiological conditions and its permeability through the membranes of the gastrointestinal tract play pivotal roles in this respect. As these factors play a critical role in determining the intrinsic availability of the actives, *in vitro* dissolution can in certain instances anticipate or predict the *in vivo* characteristics of the product (Karasulu et al., 2003; MCC Dissolution Guideline, 2007; Delalonde et al., 2008; Jantratid et al., 2009; Tedeschi et al., 2009).

During development of a pharmaceutical product dissolution testing is used to identify formulation factors that are influencing or may have a crucial effect on the bioavailability of the APIs. If the active substance is highly soluble, it is reasonable to expect that it will not cause any bioavailability problems if, in addition, the dosage system is rapidly dissolved in the physiological pH expected after product administration. If a product is expected to have a low solubility and a high permeability, the rate-limiting step for absorption may be dosage form dissolution. This could also be the case when one or more of the excipients are controlling the release and subsequent dissolution of the active substances.

Dissolution testing is performed for a number of reasons including product development; bioequivalence testing; as a support for quality control specifications and to demonstrate batch consistency and identify potential problems of bioavailability. Where an *in vitro-in vivo* correlation (IVIVC) can be established the dissolution test could also be used as a means of indicating the *in vivo* performance of a product (FDA Guidance for Industry, 1997; MCC Dissolution Guideline,

2007; Jantratid et al., 2009). This Chapter focuses on the initial *in vitro* investigation into the dissolution of each API in the delivery system.

4.2 Materials and Methods

4.2.1 Materials

The materials used in this Chapter are the same as those used in Chapter 2. Additional materials used in this Chapter include sodium alginate was obtained from FMC Biopolymer, (Drammen, Norway) as well as Sago which was obtained from Koo (Johannesburg, South Africa).

4.2.2 Fixed dose combination (FDC) tablet manufacture and dissolution testing

The triple-layered FDC tablets were produced using both typical granulation and direct compression techniques on a Manesty Single Punch Type F3 compression machine (England) fitted with 22mm x 9mm caplet-shaped punches. A pre-weighed quantity of Layer 1 (paracetamol (PC), tramadol hydrochloride (TM), hydroxyethylcellulose (HEC) and excipients) was placed in the die cavity and compressed lightly for uniform spreading. The upper punch was lifted and powders of the middle Layer 3 (diclofenac potassium (DC), polyethylene oxide (PEO) and various polymers and excipients) was placed and then similarly lightly compresses on top of Layer 1. Finally Layer 2 (PC, TM, hydroxypropylcellulose (HPC) and traditional tablet excipients) was pre-weighed and placed on top of Layer 3 and compressed though a full rotation of the single-punch compression machine to obtain the triple-layered tablets. Tablet hardness was maintained between 50-70N. Where deviations from this procedure occurred in variations of the preliminary studies described in Chapter 4, they are described in the relevant investigational series.

Dissolution studies were conducted using a United States Pharmacopeia (USP) rotating paddle method (Hanson Virtual Instruments SR8 Plus Dissolution Test Stations) at 50 rpm in phosphate buffer pH 6.8 (900mL, 37±0.5℃) for each formulatio n employing an autosampler (Hanson Research Auto Plus Maximiser and AutoPlus™ MultiFill™), as this medium was the most

discriminatory. Samples of 1.6mL were withdrawn over a period of 8 to 24 hours and analyzed via High Performance Liquid Chromatography (HPLC). Release profiles in simulated gastric fluid pH 1.2 without pepsin over a period of four hours were determined to identify any site-specific release induced by the polymers. The dissolution studies were performed under the conditions described in Table 4.1.

Table 4.1: USP rotating paddle dissolution study conditions

Component	Attribute
Apparatus	USP Paddle Assembly
Dissolution Media	a) 900mL of phosphate buffer pH 6.8 b) 900mL of simulated gastric fluid pH 1.2 without pepsin (Preheated and maintained at 37± 0.5℃)
Paddle Speed	50rpm
Sampling (Automated)	Autoplus Maximizer
Filter (Standard solution)	Non-sterile 33mm Millex-HV Hydrophillic Durapore® (PVDF) 0.45µm syringe filter unit (Millipore)
Filter (Test solution)	Hanson Research Online sample filters 10µm P/N 27-101-083 (Autoplus Maximizer)

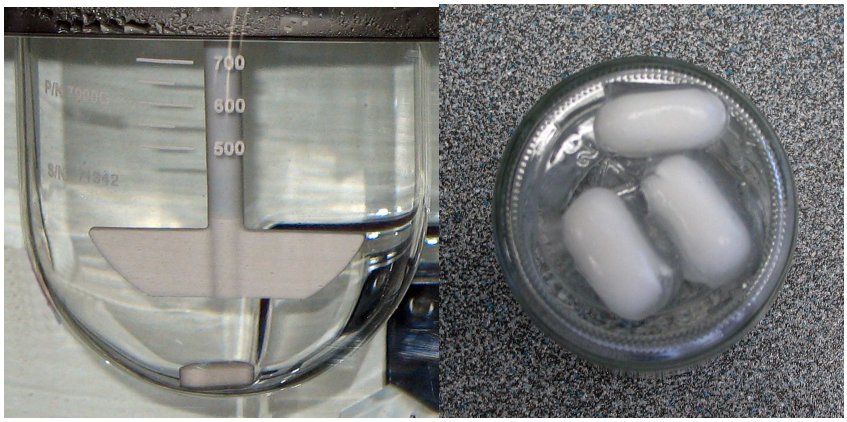
4.3 Results and Discussion

4.3.1 Influence of cellulose polymers

Initial dissolution characteristics of the combination of the three APIs and individual polymers were determined by producing small batches of tablets each with a different polymer. The ratio of polymer to APIs was kept at 2:1 with 0.5%w/w magnesium stearate added to ensure sufficient lubrication during compression. The ingredients were blended in a polyethylene bag-lined V-blender for three minutes prior to compression. The various formulations produced are presented in Table 4.2. Figure 4.1 demonstrated that the HPC- and HPMC-based polymer formulations underwent dissolution and the outer polymeric layers of the tablet after immersion in phosphate buffer pH 6.8 at 37℃ demonstrated significant swel ling. The dissolution profiles obtained for each API are displayed in Figure 4.2.

Table 4.2: Formulations studied using APIs in a 1:2 ratio with various cellulose polymers

Quantity per tablet (mg)	Formulation A	Formulation B	Formulation C	Formulation D
TM	37.5	37.5	37.5	37.5
PC	325	325	325	325
DC	25	25	25	25
Polymer	769.18 HPC	769.18 HPMC (E5-LV premium)	769.18 HPMC E5	769.18 HPMC E4M
Magnesium stearate	5.813	5.813	5.813	5.813
Tablet mass	1162.5	1162.5	1162.5	1162.5



(a) (b)

Figure 4.1: A cellulose polymer based dosage form (a) undergoing dissolution at pH 6.8 and (b) the swollen outer polymeric layers of the dosage form when submersed in phosphate buffer.

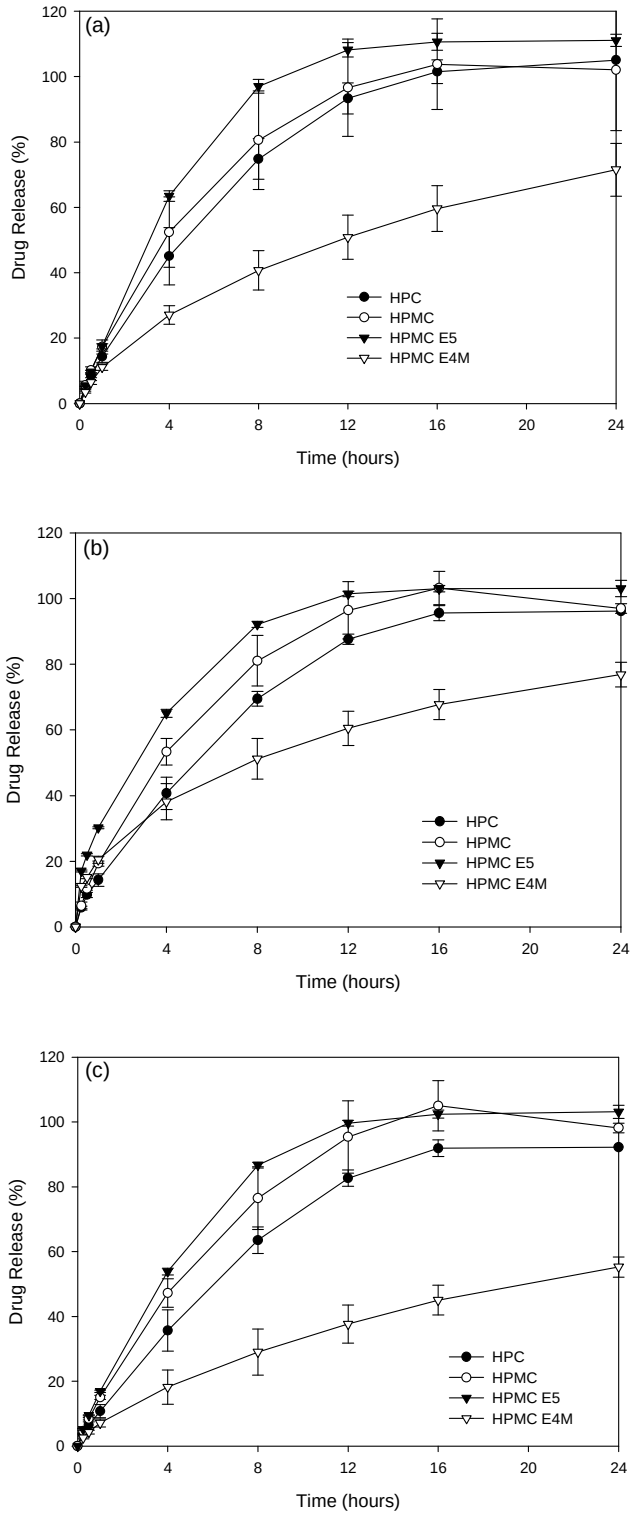


Figure 4.2: A typical dissolution profile obtained with various cellulose polymers at pH 6.8 for (a) paracetamol, (b) tramadol hydrochloride and (c) diclofenac potassium. (N=3; in all cases SD<18.63).

The differing cellulosic polymers studied indicated that for each of the three APIs under investigation both varying the cellulose polymer and the grade of such polymer affected the release profiles. Initial mechanisms for release from cellulosic polymers suggested swelling to be a significant factor.

4.3.2 Influence of layered tableting

A cellulose and PEO-based formulation was subjected to monolithic and layered tableting technology, with the three APIs demonstrating markedly different behaviour dependent solely upon their location within the delivery system. DC demonstrated both first-order and zero-order kinetics, when compressed as a monolithic matrix or layered dosage form respectively (Table 4.3). Figure 4.3 illustrates the combined effect on the three APIs when compressed as monolithic or layered tablets.

Each API displayed remarkably different release characteristics when compressed as monolithic versus layered tablets. Within both layered tablets the position of DC within the tablet changed its release profile from seemingly first-order to zero-order when compressed as an outer or inner layer respectively.

Table 4.3: Formulations investigated during layered tableting

Material	Quantity (mg)
Granulation 1	
PC	162.5
TM	18.75
HEC	181.25
Sodium starch glycolate	4.3
Powdered cellulose	19.21
Pregelatinised starch	4.53
Maize starch	0.645
Magnesium stearate	1.075
Granulation 2	
PC	162.5
TM	18.75
HPC	362.5
Sodium starch glycolate	4.3
Powdered cellulose	19.21
Pregelatinised starch	4.53
Maize starch	0.645
Magnesium stearate	1.075
Blend 3	
DC	25.0
PEO	50.0

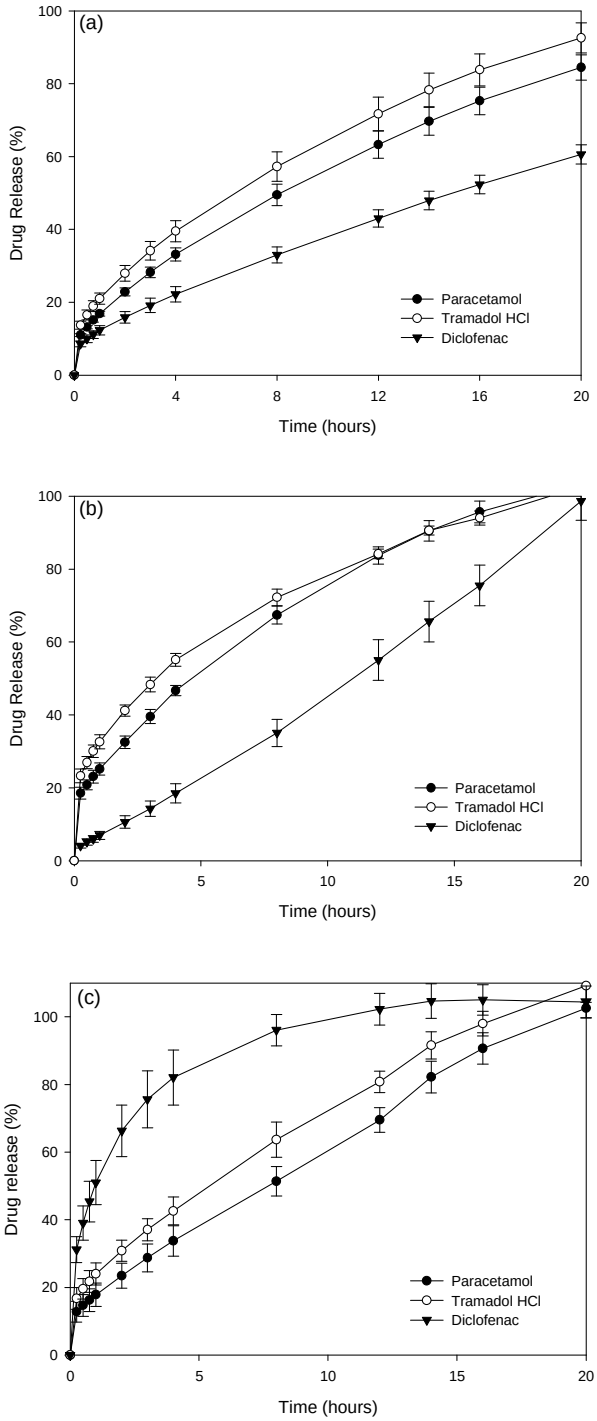


Figure 4.3: (a) Typical dissolution profiles of the three APIs obtained with a monolithic matrix tablet at pH 6.8; (b) with a triple layered tablet with diclofenac potassium in the inner layer at pH 6.8; (c) with a triple layered tablet with diclofenac potassium in the outer layer at pH 6.8. (N=3; in all cases SD<8.41).

4.3.3 Influence of crosslinking

Various pectin, alginate and Eudragit® polymers that displayed desired *in vitro* crosslinking activity with electrolytes (Table 4.4), were incorporated into the triple-layered tablet dosage form, to determine the effects of these polymers on the release characteristics of the combined APIs. PC and TM still showed first-order release while DC retained its zero-order release curve as evidenced in the release profiles in Figure 4.4.

Table 4.4: Formulations investigated for the influence of crosslinking

Material	1	2	3	4	5	6	7	8
Granulation 1								
PC	162.5	162.5	162.5	162.5	162.5	162.5	162.5	162.5
TM	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
HEC	181.75	181.75	181.75	181.75	181.75	181.75	181.75	181.75
Sodium starch glycolate	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
Powdered cellulose	19.21	19.21	19.21	19.21	19.21	19.21	19.21	19.21
Pregelatinised starch	4.53	4.53	4.53	4.53	4.53	4.53	4.53	4.53
Maize starch	0.645	0.645	0.645	0.645	0.645	0.645	0.645	0.645
Magnesium stearate	1.075	1.075	1.075	1.075	1.075	1.075	1.075	1.075
Alginate	45.31		45.31					
Zinc gluconate	22.66		22.66	22.66		22.66	22.66	22.66
Pectin CF005				45.31		45.31		
Eudragit							45.31	
Pectin IV								45.31
Granulation 2								
PC	162.5	162.5	162.5	162.5	162.5	162.5	162.5	162.5
TM	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
HPC	362.5	362.5	362.5	362.5	362.5	362.5	362.5	362.5
Sodium starch glycolate	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
Powdered cellulose	19.21	19.21	19.21	19.21	19.21	19.21	19.21	19.21
Pregelatinised starch	4.53	4.53	4.53	4.53	4.53	4.53	4.53	4.53
Maize starch	0.645	0.645	0.645	0.645	0.645	0.645	0.645	0.645
Magnesium stearate	1.075	1.075	1.075	1.075	1.075	1.075	1.075	1.075
Alginate		90.65	90.65					
Zinc gluconate		45.31	45.31		45.31	45.31		
Pectin CF020					90.65	90.65		
Blend 3								
DC	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
PEO	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0

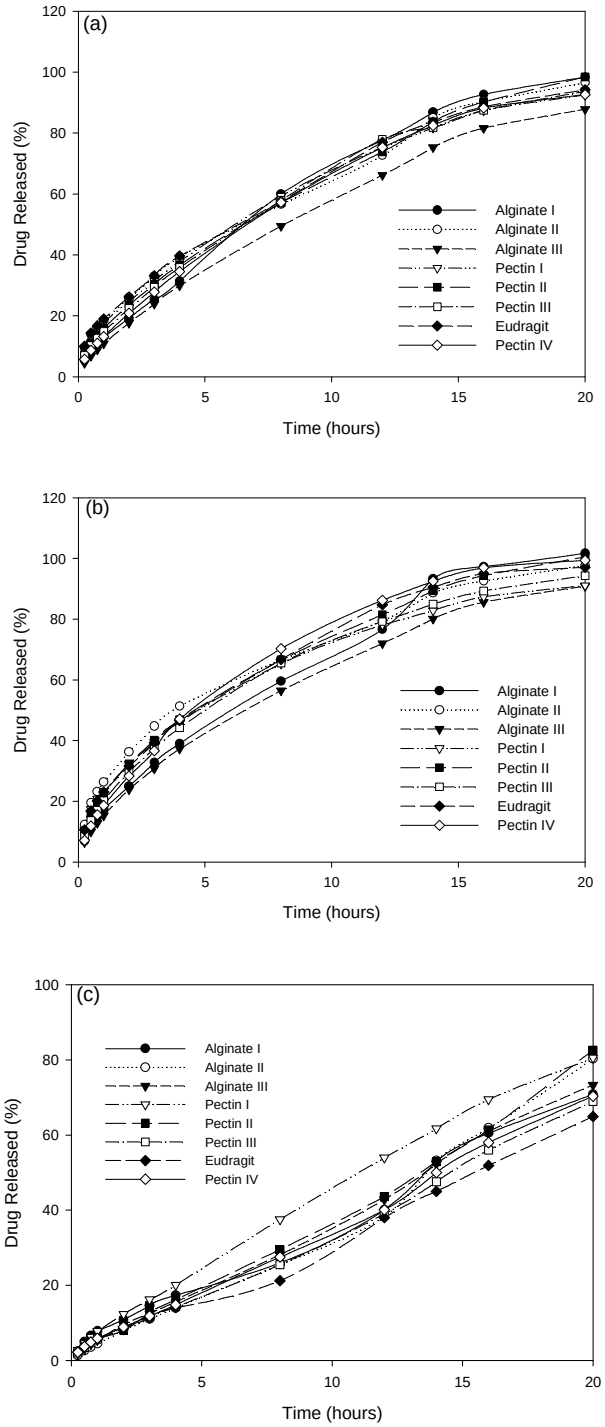


Figure 4.4: Typical dissolution profiles obtained with Various Crosslinking Polymers at pH 6.8 for (a) paracetamol, (b) tramadol hydrochloride and (c) diclofenac potassium. (N=3; in all cases SD<5.72).

Differing grades of differing polymers having previously displayed *in vitro* crosslinking had slightly different effects on each of the three APIs. Overall the desired first-order (Figure 4.4a,b) release of PC and TM and the zero-order (Figure 4.4c) release of DC were maintained, specifically with the use of alginate that had also been demonstrated to display crosslinking at a relatively low concentration.

4.3.4 Influence of cellulose polymer concentration

The concentration of HEC and HPC in PC/TM Layers 1 and 2 were halved to 90.6mg and 181.25mg respectively in the first formulation in this series (Figure 4.5a). The crosslinking polymer sodium alginate (12.5mg) and the electrolyte, zinc gluconate (6.25mg) were incorporated into the DC and PEO layer in the second set of experiments (Figure 4.5b). The alginate and zinc gluconate addition was then included in a formulation where the HEC and HPC had been further reduced to 45.31mg and 90.6mg respectively (Figure 4.5c).To this formulation 128.16mg finely-ground sago was included in PC/TM layer 1 (Figure 4.5d) and then both 128.16mg sago in layer 1 and 150.8mg sago in PC/TM layer 2 (Figure 4.5e). Figure 4.5f represents the formulation shown in Figure 4.5a run in the dissolution medium of simulated gastric fluid pH 1.2 without pepsin, to demonstrate potential site-specific release of DC. The formulations investigated are presented in Table 4.5.

The addition of the crosslinking components of alginate and zinc gluconate to the DC layer contributed to a more pronounced zero-order release curve, by retarding the release of this API. Reducing cellulosic polymers in the outer layers of the FDC resulted in less drug being released from these layers of the period studied. The inclusion of the finely-ground cellulose polymer sago in one of the outer layers of the tablet resulted in minimal changes to the release profiles produced, however sago inclusion in both outer layers resulted in a pronouncedly more rapid release of both TM and PC. The display of the FDC in an acidic medium was shown not to change the pH-based influenced release of DC.

Table 4.5: Formulations investigated for the influence of cellulose polymer concentration

Material	1	2	3	4	5
Granulation 1					
PC	162.5	162.5	162.5	162.5	162.5
TM	18.75	18.75	18.75	18.75	18.75
HEC	90.6	90.6	45.31	45.31	45.31
Sodium starch glycolate	4.3	4.3	4.3	4.3	4.3
Powdered cellulose	19.21	19.21	19.21	19.21	19.21
Pregelatinised starch	4.53	4.53	4.53	4.53	4.53
Maize starch	0.645	0.645	0.645	0.645	0.645
Magnesium stearate	1.075	1.075	1.075	1.075	1.075
Sago				128.16	128.16
Granulation 2					
PC	162.5	162.5	162.5	162.5	162.5
TM	18.75	18.75	18.75	18.75	18.75
HPC	181.25	181.25	90.6	90.6	90.6
Sodium starch glycolate	4.3	4.3	4.3	4.3	4.3
Powdered cellulose	19.21	19.21	19.21	19.21	19.21
Pregelatinised starch	4.53	4.53	4.53	4.53	4.53
Maize starch	0.645	0.645	0.645	0.645	0.645
Magnesium stearate	1.075	1.075	1.075	1.075	1.075
Sago					150.80
Blend 3					
DC	25.0	25.0	25.0	25.0	25.0
PEO	50.0	50.0	50.0	50.0	50.0
Alginate		12.5	12.5	12.5	12.5
Zinc gluconate		6.25	6.25	6.25	6.25
Magnesium stearate		2.81	2.81	2.81	2.81

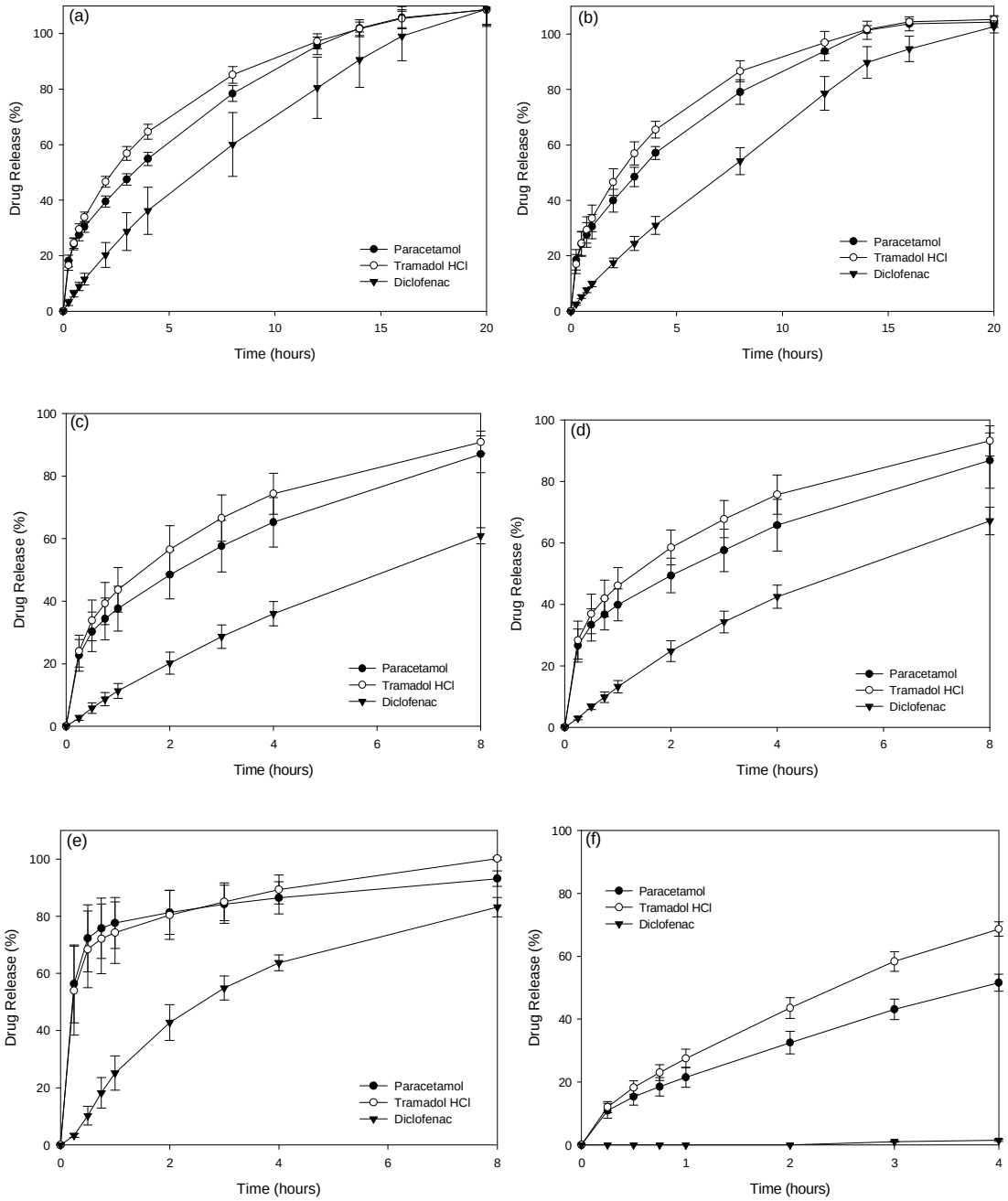


Figure 4.5: Typical dissolution profiles of the three APIs at pH 6.8 reflecting (a) polymers HEC (90.6mg) and HPC (181.25mg) reduced 50 %; (b) alginate (12.5mg) and zinc gluconate (6.25mg) in the PEO (50 mg) layer 3; (c) polymers HEC (45.31mg) and HPC (90.6mg) reduced a further 50 % in layers 1 and 2; (d) polymers HEC (45.31mg) and HPC (90.6mg) in layers 1 and 2 respectively as well as the inclusion of sago (128.16mg) in layer 1; (e) polymers HEC (45.31mg) and HPC (90.6mg) in layers 1 and 2 respectively as well as the inclusion of sago (128.16mg in layer 1and 150.8mg in layer 2); (f) combined APIs in simulated gastric fluid pH 1.2 without pepsin. (N=3; in all cases SD<11.51).

4.3.5 Influence of crosslinking agent concentration

The first experiment in this series involved reducing HEC in layer 1 to 22.6 mg and HPC in layer 2 to 45.31 mg (Figure 4.6a). These quantities were then included in a second formulation where the PEO in layer 3 was increased to 75 mg and the alginate to 18.75mg (Figure 4.6b).The third formulation included HEC (45.31mg) and sago (64.08mg) in layer 1, HPC (90.6mg) and sago (75.4mg) in layer 2 and the PEO in layer 3 was kept at 50 mg (Figure 4.6c).The final experiment in this series used the layer 1 and 2 components as described in formulation 3 and for layer 3 PEO was increased to 75mg, with alginate at 18.75mg and zinc gluconate at 6.25mg (Figure 4.6d).The effect on the dissolution profiles is evident in the figures below.

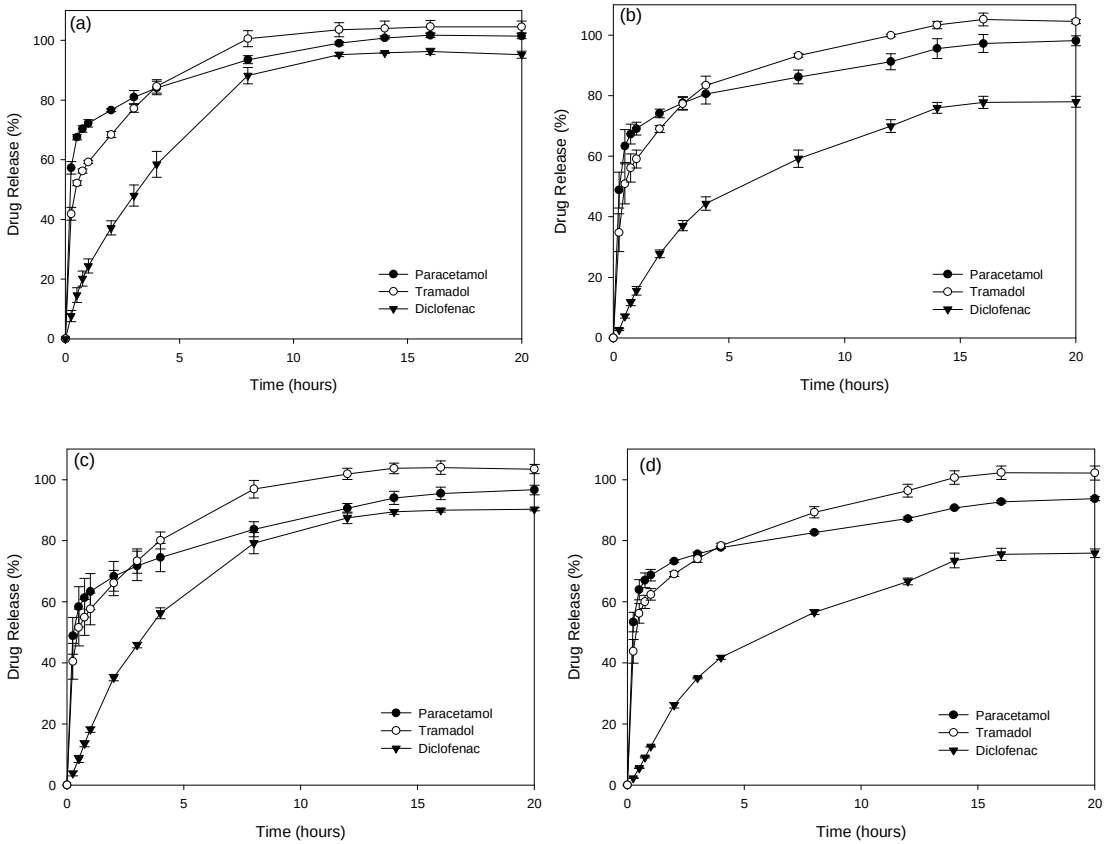


Figure 4.6: Typical dissolution profiles of the three APIs at pH 6.8 reflecting: (a) polymers HEC (22.6mg) and HPC (45.31mg) reduced 50 % and PEO (50mg) in layer 3; (b) polymers HEC (22.6mg) and HPC (45.31mg) and PEO increased to 75 mg (alginate increased to 18.75mg); (c)

polymers HEC and HPC at 45.31mg and 90.6mg respectively and the inclusion of sago in layers 1 and 2 (64.08 and 75.4mg respectively) and PEO remaining at 50 mg; (d) polymers HEC and HPC at 45.31 and 90.6mg respectively and the inclusion of sago in layers 1 and 2 (64.08 and 75.4mg respectively) and PEO increased to 75mg (alginate increased to 18.75mg). (N=3; in all cases SD<6.61).

These studies showed that as the concentration of PEO and the cross-linking agent alginate were increased, the extent of the DC zero-order release improved evidenced by the linearity of the profile produced.

4.3.6 Influence of combined polymer concentration

This formulation reduced the HEC in layer 1 to 27.10mg and the HPC in layer 2 to 54.36mg while the PEO in layer 3 was increased to 100mg. The alginate in layer 3 remained at 12.5mg and the effect on the dissolution profile of each active is evident in Figure 4.7 below.

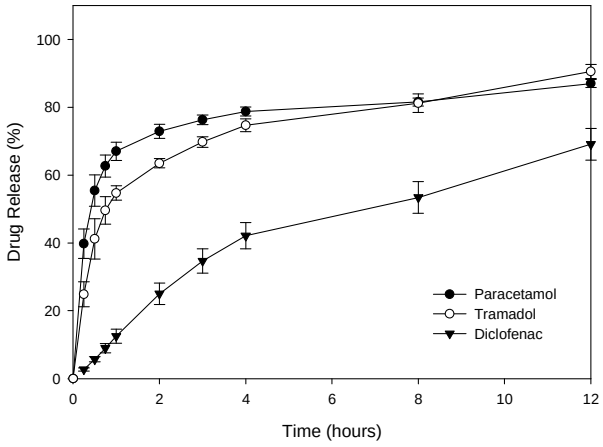


Figure 4.7: Typical dissolution profiles of the three APIs reflecting polymers HEC and HPC at 27.10 and 54.36 mg respectively and PEO at 100 mg at pH 6.8. (N=3; in all cases SD<5.67).

The release rate of PC and TM increased as the outer cellulosic layer concentrations were reduced. A higher PEO concentration in the inner DC layer resulted in overall lower levels of all three APIs being released over the study period.

4.3.7 Influence of tableting process technique

The polymer concentration in layer 1 and 2 was increased by a factor of two (HEC = 54.38mg and HPC = 108.72mg) to slow the release rate slightly and make it more site specific and the PEO was increased to 200 mg/tablet to improve zero-order release. Dissolutions were performed over a period of 12 hours. The first experiment increased PEO to 200 mg per tablet, with layer 3 being blended and undergoing direct compression and layers 1 and 2 being granulated (Figure 4.8a). The second formulation was as the first but all layers were blended and underwent direct compression (Figure 4.8b). In the third and fourth experiments, the quantities in layers 1 and 2 remained as above but the PEO in layer 3 was kept at 100mg per tablet. The DC, alginate and zinc gluconate for these two experiments were granulated with 96% alcohol prior to the PEO being included. The third experiment displayed the effect of all three layers being granulated (Figure 4.8c) and the fourth experiment demonstrated the effect of granulating the third layer and blending with direct compression layers 1 and 2 (Figure 4.8d). For all the remaining experiments as well as through to the Design of Experiments (DoE) stage of formulation layer three (DC and PEO layer) was blended prior to undergoing direct compression whilst layer 1 and 2 (both containing PC and TM) were granulated with alcohol due to the high polymer content making water based granulating fluids difficult. The formulations explored in this section are presented in Table 4.6.

Table 4.6: Formulations (mg) investigated for tableting process technique

Material	**1**	**2**	**3**	**4**
	Granulation	***Blend***	***Granulation***	***Blend***
PC	162.5	162.5	162.5	162.5
TM	18.75	18.75	18.75	18.75
HEC	54.38	54.38	54.38	54.38
Sodium starch glycolate	4.3	4.3	4.3	4.3
Powdered cellulose	19.21	19.21	19.21	19.21
Pregelatinised starch	4.53	4.53	4.53	4.53
Maize starch	0.645	0.645	0.645	0.645
Magnesium stearate	1.075	1.075	1.075	1.075
	Granulation	***Blend***	***Granulation***	***Blend***
PC	162.5	162.5	162.5	162.5
TM	18.75	18.75	18.75	18.75
HPC	108.72	108.72	108.72	108.72
Sodium starch glycolate	4.3	4.3	4.3	4.3
Powdered cellulose	19.21	19.21	19.21	19.21
Pregelatinised starch	4.53	4.53	4.53	4.53
Maize starch	0.645	0.645	0.645	0.645
Magnesium stearate	1.075	1.075	1.075	1.075
	Blend	***Blend***	***Granulation***	***Granulation***
DC	25.0	25.0	25.0	25.0
PEO	200.0	200.0	100.0*	100.0*
Alginate	12.5	12.5	12.5	12.5
Zinc Gluconate	6.25	6.25	6.25	6.25
Magnesium stearate	2.81	2.81	2.81	2.81

*Included after granulation.

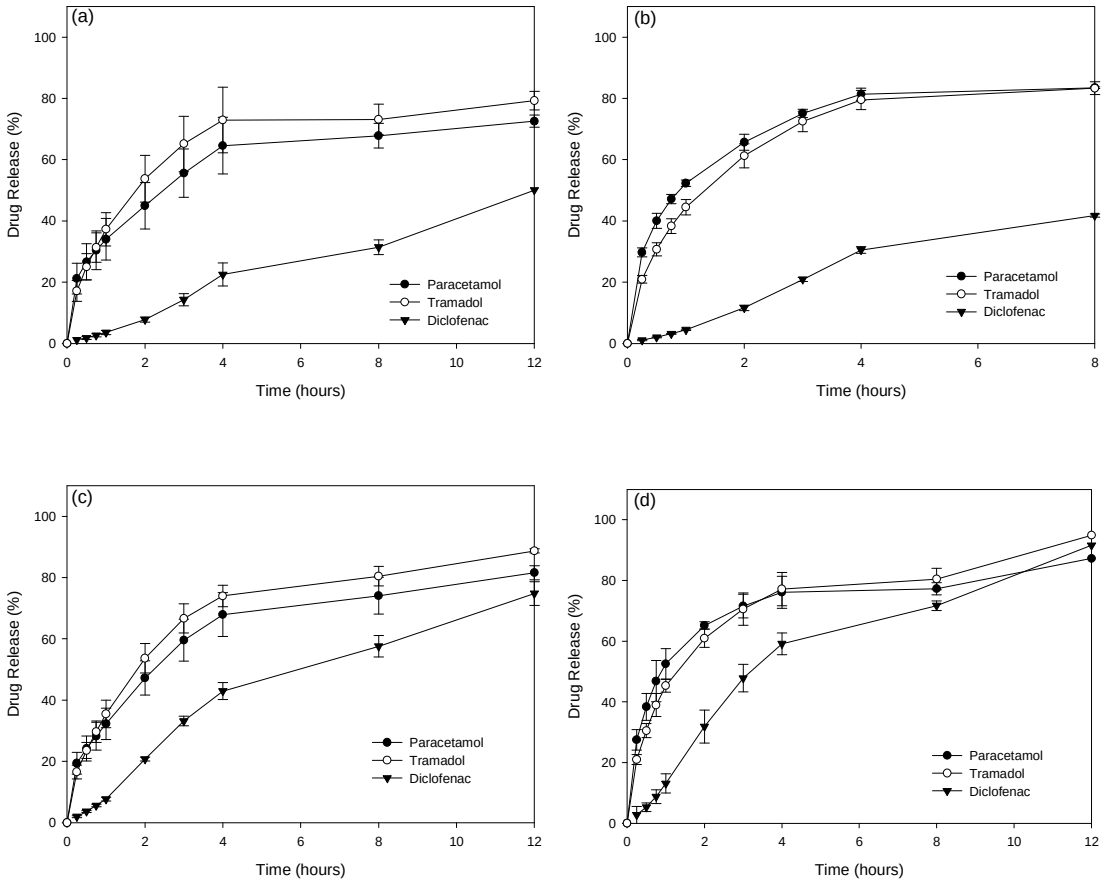


Figure 4.8: Typical dissolution profiles of the three APIs at pH 6.8 reflecting: (a) polymers HEC and HPC increased (54.38 mg and 108.72mg respectively) (granulated) and PEO increased to 200mg (blended); (b) polymers HEC and HPC increased (54.38mg and 108.72mg respectively) (blended) and PEO increased to 200 mg (blended); (c) polymers HEC and HPC increased (54.38mg and 108.72mg respectively) (granulated) and PEO remained at 100mg (granulated); (d) polymers HEC and HPC increased (54.38mg and 108.72mg respectively) (blended) and PEO remained at 100mg (granulated). (N=3; in all cases SD<10.72).

These experiments alluded to the effect of PEO on the zero-order release of DC as well as to the influence of wet granulation versus direct compression tableting techniques. The granulated procedure demonstrated to exhibit PC and TM more controlled, slightly slower release of the two APIs whilst the purely blended DC layer displayed more suitable tendency towards zero-order release than those that were granulated. The manufacturability of PEO as a blended process was also dramatically improved in terms of the ease of material handling.

4.3.8 Influence of PEO on zero-order release

The quantity of PEO in the DC layer was increased to 300mg (Figure 4.9a), 400mg (Figure 4.9b) and 500mg (Figure 4.9c) to see the effect on the zero-order DC profile. The 200mg PEO experiment was repeated with the lower molecular weight material (WSR301, 4 x 10^6) and the dissolution profile is depicted in Figure 4.9d. The 200mg and 400mg experiment were run over both 8 hours and 24 hours to visualize the release effect over a 24-hour period (Figure 4.9e and Figure 4.9f respectively).

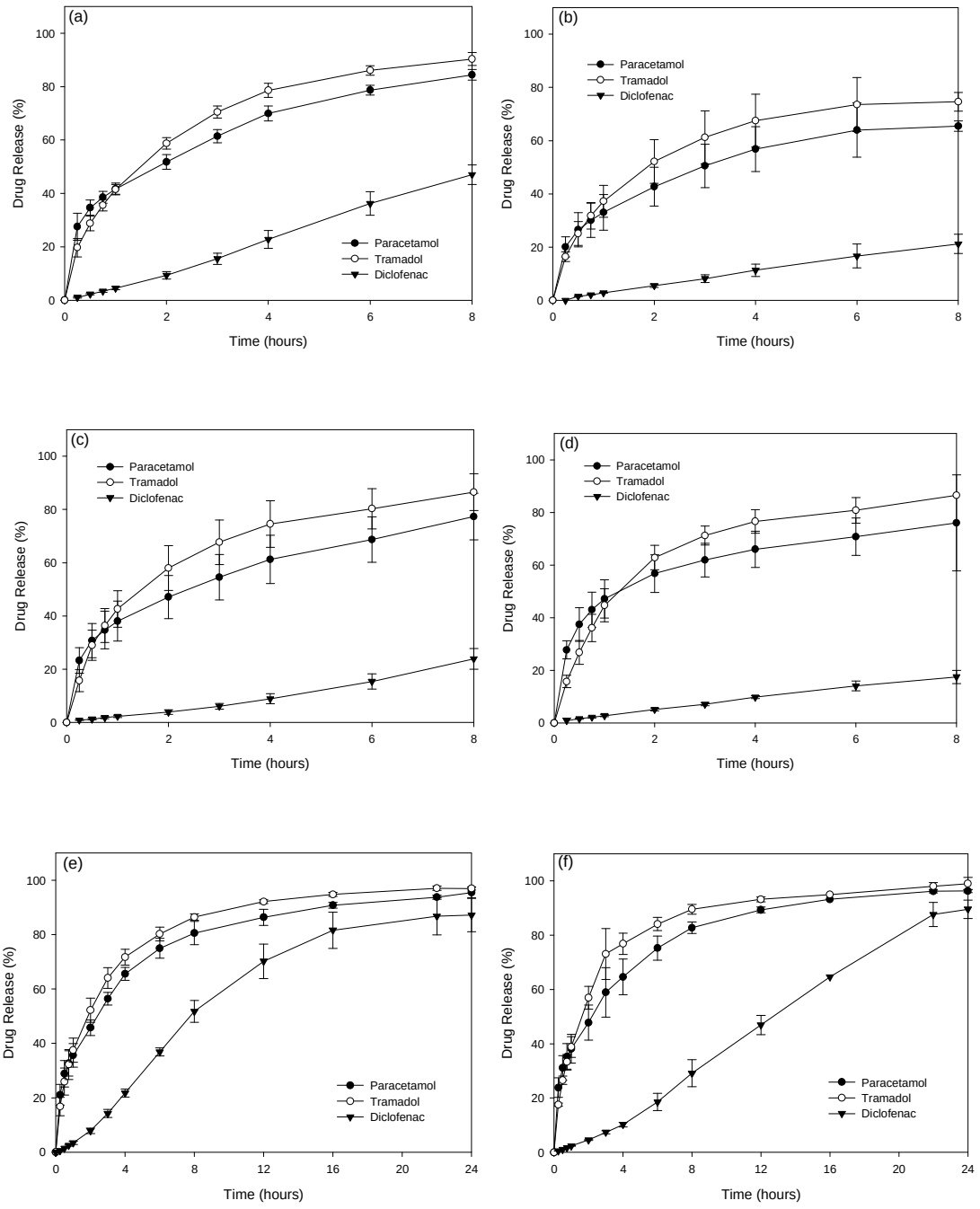


Figure 4.9: Typical dissolution profiles of the three APIs reflecting: (a) 300mg; (b) 400mg; (c) 500mg PEO at pH 6.8 over 8 hours; (d) 200mg LMW PEO at pH 6.8 over 8 hours; (e) 200mg LMW PEO at pH 6.8 over 24 hour and (f) 400mg PEO at pH 6.8 over 24 hours. (N=3; in all cases SD<18.27).

The effect of PEO concentration was evident on the rate and extent of DC release which reduced with PEO increase. The effect of molecular weight was also observed, and whilst looked similar over a short time period did not result in as effective a zero-order release, over the full 24 hour study period. This study also demonstrated that 200mg PEO produced a more desirable DC profile than the higher concentrations studied above in terms of linear release.

4.3.9 Influence of different electrolytic crosslinkers

An additional number of experimental formulations were run based on the previous formulation containing 400mg PEO. In Formulation A the HEC in layer 1 was reduced to 5.12% and PEO included at 15.37% in order to keep the proportion of polymer in layer 1 constant. Layer 2, the other outer layer, was adjusted to include 8.5% HPC and 25.5% PEO, also maintaining the polymer proportion constant. The DC layer remained unchanged in this experimental series. Formulation B displayed the dissolution profile when alginate (12.5mg) and zinc gluconate (6.25mg), as well as the PEO (same concentrations of Formulation A), were included in layers 1 and 2 and in Formulation C calcium chloride instead of zinc gluconate was used as the electrolytic crosslinker. Formulation D was the same as that for C but with the calcium chloride concentration halved. It was also necessary to determine the effect of having 100% of the PC in the one outer layer and 100% of the TM in the second outer layer. Formulation E explored this with the original concentrations of HEC and HPC used in combination with PC and TM respectively and Formulation F was used to display the effect of including PEO in these outer layers. Formulation G and H were performed to display the effect of the addition of alginate and zinc gluconate and alginate and calcium chloride respectively to these layers. The dissolution profiles are displayed below in Figure 4.10 and Figure 4.11 and the formulations investigated in Table 4.7.

Table 4.7: Formulations (mg) investigated for different electrolytic crosslinkers

Materials	A	B	C	D	E	F	G	H
Granulation 1								
PC	162.5	162.5	162.5	162.5	325	325	325	325
TM	18.75	18.75	18.75	18.75				
HEC	13.6	13.6	13.6	13.6	54.38	54.38	54.38	54.38
Sodium starch glycolate	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
Powdered cellulose	19.21	19.21	19.21	19.21	19.21	19.21	19.21	19.21
Pregelatinised starch	4.53	4.53	4.53	4.53	4.53	4.53	4.53	4.53
Maize starch	0.645	0.645	0.645	0.645	0.645	0.645	0.645	0.645
Magnesium stearate	1.075	1.075	1.075	1.075	1.075	1.075	1.075	1.075
PEO	40.78	40.78	40.78	40.78		40.78	40.78	40.78
Alginate		12.5	12.5	12.5			12.5	12.5
Zinc gluconate		6.25					6.25	
Calcium chloride			6.25	3.15				6.25
Granulation 2								
PC	162.5	162.5	162.5	162.5				
TM	18.75	18.75	18.75	18.75	37.5	37.5	37.5	37.5
HPC	27.18	27.18	27.18	27.18	108.72	108.72	108.72	108.72
Sodium starch glycolate	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
Powdered cellulose	19.21	19.21	19.21	19.21	19.21	19.21	19.21	19.21
Pregelatinised starch	4.53	4.53	4.53	4.53	4.53	4.53	4.53	4.53
Maize starch	0.645	0.645	0.645	0.645	0.645	0.645	0.645	0.645
Magnesium stearate	1.075	1.075	1.075	1.075	1.075	1.075	1.075	1.075
PEO	81.54	81.54	81.54	81.54		81.54	81.54	81.54
Alginate		12.5	12.5	12.5			12.5	12.5
Zinc gluconate		6.25					6.25	
Calcium chloride			6.25	3.15				6.25
Blend 3								
DC	25.0	25.0	25.0	25.0	25.0	25.0	25.0	25.0
PEO	400.0	400.0	400.0	400.0	400.0	400.0	400.0	400.0
Alginate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Zinc gluconate	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Magnesium strearate	2.81	2.81	2.81	2.81	2.81	2.81	2.81	2.81

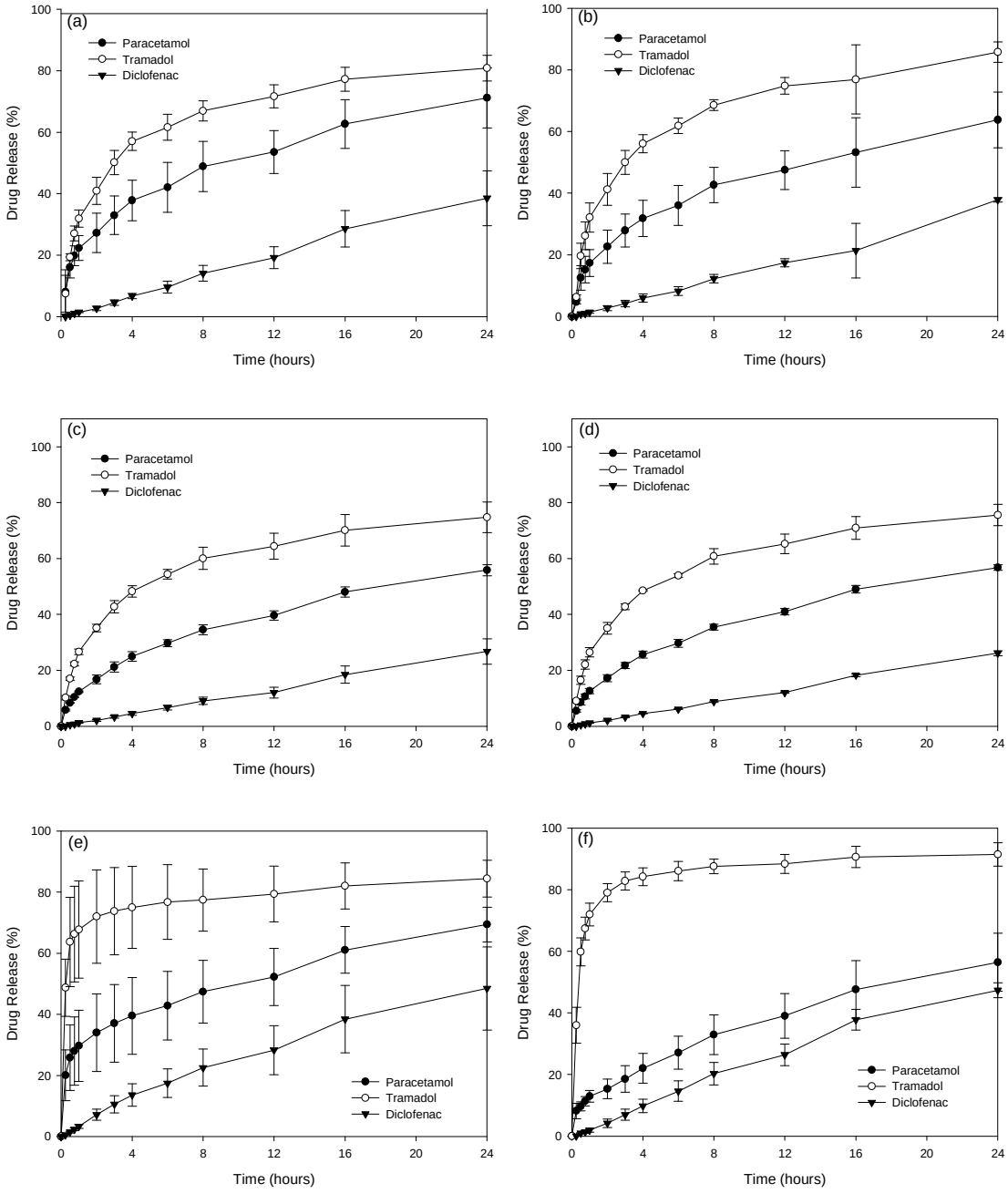


Figure 4.10: Typical dissolution profiles of the three APIs at pH 6.8 over 24 hours reflecting: (a) PEO in the outer layers; (b) PEO and alginate/zinc gluconate in the outer layers; (c) PEO and alginate/calcium chloride in the outer layers; (d) PEO and alginate/calcium chloride (50%) in the outer layers; (e) three APIs each in a separate layer; (f) three APIs each in a separate layer with PEO. (N=3; in all cases SD<11.24).

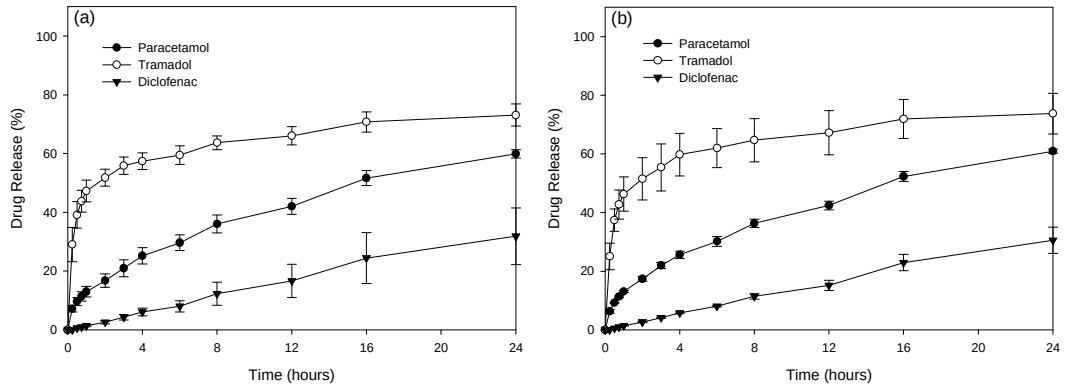


Figure 4.11: Typical dissolution profiles of the three APIs at pH 6.8 over 24 hours reflecting: (a) three APIs each in a separate layer with PEO and alginate/zinc gluconate and (b) three APIs each in a separate layer with PEO and alginate/calcium chloride. (N=3; in all cases SD<11.24).

The effect of PEO in the outer layers of the FDC resulted in reduced levels of the two APIs being released over the study period. The further addition of the crosslinking agents to these outer layers further reduced the amount and rate of API release, as had been previously seen with DC. Placing PC and TM in separate outer layers changed the release profiles of these two APIs remarkably from the similar profiles seen when they were combined. The exchange of calcium chloride for zinc gluconate as the electrolytic-crosslinker had the undesired effect of reducing the quantity of API release further but had no change in result upon concentration adjustment.

4.4 Concluding Remarks

The influence of various cellulose-based polymers on the typical release response of combinations of PC, DC and TM resulted in each API displaying varying drug release responses implying the rate-modulating activity of the polymers. The release profiles of each API obtained were similar despite differing solubilities, indicating that the polymers were influential in controlling drug release.

A cellulose and PEO-based formulation was subjected to monolithic and layered tableting technology, with the three APIs demonstrating markedly different behaviour dependent solely upon configuration within the dosage unit. DC demonstrated both first-order and zero-order

kinetics, when compressed as a monolithic matrix or layered delivery system respectively. The results showed that the physical location of the polymers in either the inner or outer layers of the triple-layered tablets has a pronounced effect on drug release.

Various pectin, alginate and Eudragit® polymers that displayed desired *in vitro* crosslinking activity when electrolytes were incorporated into the delivery system, to determine the effects of these polymers on the release characteristics of the combined APIs. PC and TM showed first-order release while DC retained its zero-order release curve.

In order to establish the potential site-specific release potential or ability of the dosage form to target the API to a specific tissue of the gastro-intestinal tract (GIT), formulations consisting of cellulose, PEO and alginate polymers were subjected to dissolution studies in simulated gastric fluid pH 1.2 without pepsin. Typical results from these studies confirmed that DC was not released in this medium, thus its desired, site-specific release, had been obtained.

Based on the results obtained in the investigational series of experiments performed in this chapter, a formulation showing the desired attributes was chosen on which DoE and formulation optimization was based and discussed in Chapter 5.

CHAPTER FIVE

OPTIMIZATION OF THE FORMULATION COMPONENTS FOR THE FIXED DOSE COMBINATION DELIVERY SYSTEM

5.1 Introduction

Controlled release delivery systems with varied formulation technologies have gained increasing importance in recent years and provide many advantages including adjustable release kinetics, and improved therapy and patient compliance (Velasco et al., 1999; Sako et al., 2002; Durig and Fassihi, 2002; Jamzad et al., 2005). In its most rudimentary form, monolithic dosage forms can be manufactured by incorporating the drug and appropriate excipients in hydrophilic gel-forming matrices (Velasco et al., 1999; Sako et al., 2002; Durig and Fassihi, 2002; Jamzad et al., 2005). Such delivery systems are widely used to control drug release due to their low cost, broad regulatory acceptance, ease of manufacturing and their applicability in controlling the release of drugs with a wide range of physicochemical properties (Williams et al., 2002). Cellulose derivatives and polyethylene oxide (PEO) polymers are extensively used hydrophilic materials in controlled release systems due to their beneficial functionality (Shah et al., 1993; Khurahashi et al., 1996; Yang et al., 1996; Reynolds et al., 1998).

Statistical experimentation is crucial in the investigation of the factors that influence product quality. Adjustments to these parameters in a formulation allow for a product's manufacturability, reliability, quality and performance to be enhanced. Well-designed experiments allow for significantly more information to be obtained in a shorter period of time, using the Design of Experiments (DoE) technology.

Initial dissolution characteristics of the combined Active Pharmaceutical Ingredients (APIs) paracetamol (PC), tramadol hydrochloride (TM) and diclofenac potassium (DC); individual and combined cellulose and ethylene oxide-based polymers were determined by producing investigational batches of tablets. These were produced on a Manesty Single Punch Type F3

machine by direct compression and wet granulation techniques into monolithic matrix and multi-layered systems, as shown in Figure 5.1. *In situ* crosslinking of various alginate, pectin and Eudragit® polymers with electrolytes such as zinc gluconate was also investigated for its influence on the release characteristics from the solid dosage system. The results of these investigational formulation studies were described in Chapter 4.

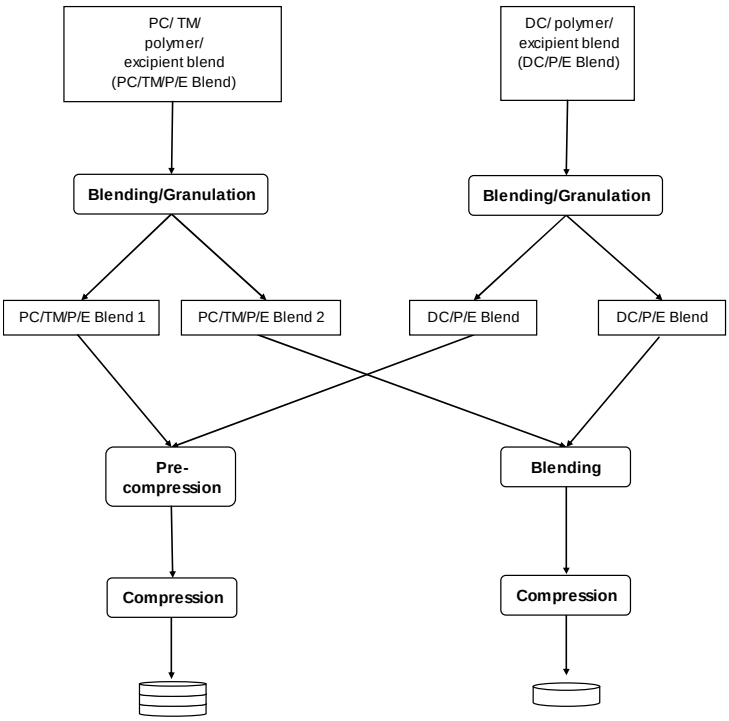


Figure 5.1: A schematic illustrating monolithic matrix and layered tablet configuration methodology. Further details may be found in Chapter 5, Section 5.2.2.

Many pharmaceutical industry experiments involve mixture components, where the experimental factors are the components of a mixture and the response variable is a function of the relative proportion of each component. The relative proportion of each component included is thought to influence the overall product characteristics. These components may include the APIs or the excipients which may influence product characteristics and manufacturability. Finding the optimal combination of components to produce a desirable product is made more efficient by the effective use of DoE and statistical analysis of the resulting data (Anderson-Cook et al., 2004). A well-chosen design will allow formulators to study multiple responses, individually or simultaneously

optimizing some combination of the responses with a desirability or objective function (Anderson-Cook et al., 2004, Wu et al., 2009).

The Extreme Vertices Design (EVD) was developed as a procedure for conducting experiments with mixtures when several factors have constraints in the form of upper and/or lower bounds placed on them. The constraints reduce the size of the factor space which would result had the factor levels been restricted to 0 to 100 percent only (McLean and Anderson, 1966). Physical, theoretical and economic considerations often impose additional constraints in the form of lower and upper bounds on the levels of components (Piepel, 1983).

The constraints placed on individual factors describe an irregular hyperpolyhedron. The EVD for mixture problems is uniquely determined once the investigator decides on the constraints for the chosen factors to be used in the experiment. The design allows the investigation of the extreme points of the factor space as well as internal points (McLean and Anderson, 1966).

Standard response surface designs such as factorial designs or central composite designs may not be sensibly used for mixture experiments as these standard designs assume that individual factors can be adjusted independently of the level of other factors. In mixture experiments changing the proportion of one factor influences the proportion of others since the proportions are constrained to sum to the total mixture quantity (Anderson-Cook et al., 2004).

The inclusion of too many mixture components and processing factors make the design space too large to investigate with typical resource constraints. Thus preceding the implementation of these designs, some degree of screening or preliminary trials should be conducted to find constraints for the components (Wu et al., 2009).

Numerous methodologies, devices and innovations have been utilized and investigated in order to achieve zero-order kinetics over a prolonged period of time. The basic mechanism of drug

liberation from such systems is governed by swelling/erosion, dissolution/diffusion, osmosis, ion-exchange, polymer coating/membrane barrier, specific geometries and surface modifications (Kydonieus, 1992). In terms of formulation, monolithic matrix systems are most widely used for their ease of administration and low cost of manufacturing. Simple matrix systems, however, are incapable of attaining zero-order release due to the inherent limitations that the area of diffusing surfaces decrease and diffusion path length increases as time progresses (Higuchi, 1963). For this invention, from the preliminary studies seen in Chapter 4, PEO was used, in combination with other polymers, to achieve zero-order release of DC over a period of 24 hours. This swellable/erodible polymer is a linear water-soluble resin available over a wide range of molecular weights. It has been shown that drug release from a system using this polymer exhibited zero-order release kinetics and was independent of variation in dissolution media pH or compression force (Yang and Fassihi, 1996).

In vitro dissolution has been acknowledged as a significant constituent in drug development. Under certain conditions it can be used as a surrogate for the assessment of bioequivalence (Costa and Sousa Lobo, 2001). The dissolution test has proved to be an essential *in vitro* test to characterise the performance of an oral drug delivery system (Shishoo et al., 2002). The significance of a dissolution test is such that for a drug to be absorbed from the gastrointestinal tract (GIT) and be available to the systemic circulation, it must first be solubilized (Hoener et al., 2005). Therefore the dissolution test is not used only for quality control of a finished product to assess batch-to-batch consistency, but it is also essential in the development of a formulation for screening and proper assessment of different formulations, as seen in Chapter 4. Precise and reproducible dissolution data derived from physicochemically and hydrodynamically defined environments are required in order to evaluate various *in vitro* dissolution data and be able to use results as a proxy for possible *in vivo* bioavailability, bioequivalence testing and *in vitro-in vivo* correlations (IVIVC) (Pillay and Fassihi, 1999).

Manipulating the dissolution of drugs in solid dose pharmaceutical platforms is a critical factor in therapeutics. Trial data on dissolution tends to consolidate all the successive or simultaneous observations involved in the process, without discriminating between them. The apparent kinetics for the dissolution of a tablet *in vitro* is the result of various linked phenomena of phase change, diffusion, liquid penetration and interstitial fluid drainage. The porous networks of a tablet are initially saturated with air. On contact with the medium in the dissolution batch, the particles in contact with the medium are immediately wetted and change phase and then through the outer boundary layer exposed to the hydrodynamics of the dissolution vessel. The fluid gradually penetrates the porous areas of the tablet and the dissolved molecules undergo further displacement within the porous tablet. This liquid saturation depends on the drainage capacity of the entrapped interstitial air. At a molecular level the phase change rate can be considered very rapid compared to diffusion in the interstitial liquid phase (Bird et al., 1960).

Experimental kinetics are then analyzed using one of many mathematical functions described in the literature (Delalonde, 2008). The kind of API, its polymorphic form, crystallinity, particle size, solubility and quantity in the dosage form can influence the release kinetic (Salomon and Doelker, 1980). The best understood model is that of Higuchi based on the concept of diffusion leading to the linearization of dissolution as a function of the square root of time (Srimornsak et al., 1997). By logically utilizing these models a comparison may be made of the various kinetics (Bouelle et al., 1999).

Dissolution is a dynamic process which is strongly dependant on both the composition of the medium and the hydrodynamics. Since the luminal environment in the proximal GIT varies considerably with site and meal ingestion, it is worth considering the use of several sets of dissolution conditions to arrive at a complete picture of how a dosage form will release its API/s under various dosing conditions (Nicolaides et al., 1999).

The release of a drug from a modified release dosage form and its absorption are predictably influenced by physiological factors in the GIT. Prolonged release dosage forms are more susceptible to these factors than immediate release dosage forms. The physiological characteristics of the GIT (volume, composition, pH, surface tension and viscosity of the luminal content as well as its mobility) vary greatly from site to site. Therefore, physiological conditions of the GIT can affect the release of drugs from prolonged dosage forms far more than conventional ones. Gastric pH varies from acidic to basic and these variations can affect drug release. Thus the transit of the dosage form through the GIT should be fully considered when designing advantageous dosage forms (Ribeiro et al., 2005).

The USP apparatus III (reciprocating cylinder) thus far provides sound hydrodynamic conditions for the evaluation of modified release dosage forms. In contrast to the medium movement in USP apparatus I, the dosage form moves freely through the dissolution medium. USP apparatus III is considered as the first-line apparatus in product development of controlled release products due to its usefulness and convenience in exposing products to mechanical as well as a variety of physicochemical conditions which eventually influence the release of a drug in the gastrointestinal tract (Borst et al., 1997; Joshi et al., 2008). The use of a physiological-based pH-gradient in the type III dissolution apparatus not only facilitates simulation of the upper gastrointestinal transit within one experiment but may also lead to pertinent *in vitro* results as carryover effects can be detected (Klein et al., 2002).

Bioavailability refers to the rate and extent to which the API, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action. Comparative dissolution studies are performed to compare the pharmaceutical availability based on *in vitro* dissolution between the invention and registered products containing the same APIs. Intrinsic dissolution of the APIs is an important consideration when formulating solid oral dosage forms and the dissolution behaviour provides important information to ensure product quality.

This Chapter focuses on the optimization of the dissolution profiles of the delivery system by means of DoE as well as a comparison against marketed pharmaceutical products.

5.2 Materials and Methods

5.2.1 Materials

The materials used in Chapter Five are identical to those used in Chapter Four. Only commonly used, pharmaceutical-grade excipients that are routinely employed by the pharmaceutical industry were considered for use in this study.

5.2.2 Design of experiments

The tablets were produced using both typical granulation and direct compression techniques on a Manesty Single Punch Type F3 compression machine (England) fitted with 22mm x 9mm caplet-shaped punches. For each of the ten DoE formulations, layers 1 and 2 were produced by wet granulation using 96% alcohol, and layer 3 was dry blended only. Each layer composition was passed though a 14 mesh sieve prior to compression. The compression force of the single-punch compression machine was kept constant throughout the run for each formulation and relevant in-process tests as described in Chapter 7 were performed for each of the runs. A pre-weighed quantity of the layer 1 (PC, TM, HEC and excipients) was taken and placed in the die cavity and preliminarily compressed for uniform spreading. The upper punch was lifted and powders of the middle layer 3 (DC, PEO, sodium alginate, zinc gluconate and excipients) was placed and then similarly underwent intermediate compression on top of layer 1. Finally layer 2 (PC, TM and HPC and excipients) pre-weighed and placed on top of layer 3 and underwent final compression though a full rotation of the single-punch compression machine to obtain the triple-layered tablets, illustrated in Figure 5.2.

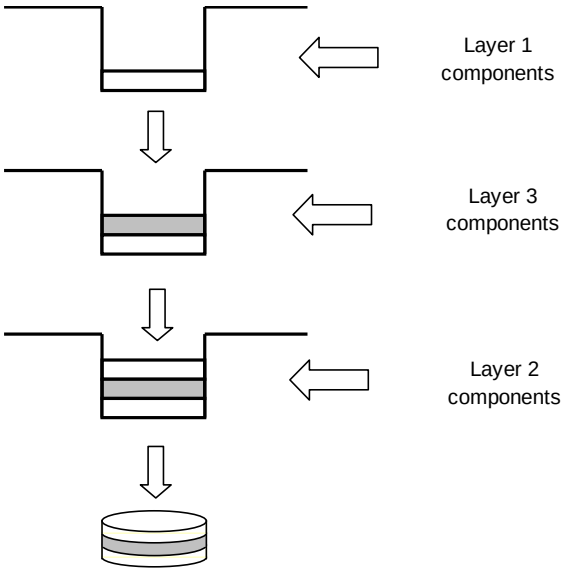


Figure 5.2: Schematic illustrating the compression sequence of the delivery system

An EVD experimental formulation template was generated employing Minitab® V15 (Minitab® Inc., PA, USA) statistical software to produce various tablet formulations and is shown below as the extreme vertices mixture (Table 5.1). Each formulation had an equivalent mass of 1031.68 mg. The preliminary studies discussed in Chapter 4 provided a setting of the levels or constraints for each formulation variable. The design template prompted ten formulations to be generated comprising different levels of variables within each layer, designated layer 1 (L1), layer 2 (L2) and layer 3 (L3). The description of the different levels for each are indicated below in Table 5.1, the extreme vertices mixture for each run are described in Table 5.2, as are the resultant ten formulations that were generated based on this design in Table 5.3. A Manesty Type F3 single-punch tablet press employing caplet tooling (22x9mm) was used to prepare the ten DoE candidate formulations, as described in Chapter 4, in accordance with the EVD template. Dissolution studies were performed in phosphate buffer (pH6.8; 37ºC; 50rpm) and samples were analyzed by HPLC over 24 hours.

Table 5.1: Tablet composition for each layer at extremes of 0 and 1 according to Extreme Vertices Design

Component (mg)	0	1
Layer 1		
HEC	*22.66*	*54.38*
Sodium starch glycollate	4.30	4.30
Powdered cellulose	19.21	19.21
Pre-gelatinised starch	4.53	4.53
Magnesium stearate	1.08	1.08
Maize starch	32.36	32.36
PC	*162.50*	*0.64*
TM	18.75	18.75
Subtotal	**265.39**	**265.39**
Layer 2		
HPC	22.49	108.72
Sodium starch glycollate	0.89	4.30
Powdered cellulose	3.97	19.21
Pre-gelatinised starch	0.94	4.53
Magnesium stearate	0.22	1.08
Maize starch	109.97	0.64
PC	162.50	162.50
TM	18.75	18.75
Subtotal	**319.73**	**319.73**
Layer 3		
Sodium alginate	12.50	12.50
Zinc gluconate	6.25	6.25
Magnesium stearate	2.81	2.81
DC	25.00	25.00
PEO	200.00	400.00
Maize starch	200.00	0.00
Subtotal	**446.56**	**446.56**
Total	**1031.68**	**1031.68**

Table 5.2: Extreme Vertices Design mixture for each run

Run Order	L1	L2	L3
1	0	0	1
2	1	0	0
3	0.5	0.5	0
4	0.5	0	0.5
5	0.2	0.7	0.2
6	0.2	0.2	0.7
7	0	1	0
8	0	0.5	0.5
9	0.7	0.2	0.2
10	0.3	0.3	0.3

5.2.3 USP apparatus III dissolution of the design of experiment formulations

Dissolution tests were performed using USP apparatus 3 (Bio-Dis III extended release rate tester, Varian VK 750D, USA.), at various pH values to simulate the conditions of fasted human GIT. According to published guidelines (FIP guidelines for dissolution testing of solid oral Products, 1995), the pH of test medium used to study the dissolution of extended release oral dosage forms

should be set within pH 1 to 6.8. To simulate the passage through stomach and the small intestine, all dosage forms were tested with a pH-gradient method based on mean physiological pH values in each gastro-intestinal segment.

The pH of the dissolution media and corresponding dissolution durations were set as follow: pH 1.2 (simulated gastric fluid without enzymes) for 1h, pH 4.5 (phosphate buffer) for 0.5h, pH 6.0 (phosphate buffer) for 2.5h and pH 6.8 (simulated intestinal fluid without enzymes) for 8h (according to Ribeiro et al., 2004) and a further 12h sample at pH 6.8 (simulated intestinal fluid without enzymes) was included. The pH values and residence times in each row were selected on the basis of previous findings of the pH values found in different parts of the GIT in fasted state (Khosla et al., 1989; Charman et al., 1997). The vessels were fitted with 220ml of media and the delivery system placed in the dipping tubes which contained a polypropylene bottom screen of 420Å mesh size.

Table 5.3: Composition (mg) for each of the ten formulations produced in the Design of Experiments

Formulation	***F 1 (0,0,1)***	***F 2 (1,0,0)***	***F 3 (0.5,0.5,0)***	***F 4 (0.5;0;0.5)***	***F5 (0.2;0.7;0.2)***	***F6 (0.2;0.2;0.7)***	***F7 (0,1,0)***	***F8 (0;0.5;0.5)***	***F9 (0.7;0.2;0.2)***	***F10 (0.3;0.3;0.3)***
Layer 1	0	1	0.5	0.5	0.2	0.2	0	0	0.7	0.3
Layer 2	0	0	0.5	0	0.7	0.2	1	0.5	0.2	0.3
Layer 3	1	0	0	0.5	0.2	0.7	0	0.5	0.2	0.3
					Layer 1					
HEC	22.66	54.38	38.52	38.52	29.004	29.004	22.66	22.66	44.864	32.176
Sodium starch glycolate	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
Powdered Cellulose	19.21	19.21	19.21	19.21	19.21	19.21	19.21	19.21	19.21	19.21
Pre-gelatinised Starch	4.53	4.53	4.53	4.53	4.53	4.53	4.53	4.53	4.53	4.53
Magnesium Stearate	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.08
PC	162.5	162.5	162.5	162.5	162.5	162.5	162.5	162.5	162.5	162.5
TM	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
Maize starch	32.36	0.64	16.5	16.5	26.016	26.016	32.36	32.36	10.156	22.844
Subtotal	**265.39**	**265.39**	**265.39**	**265.39**	**265.39**	**265.39**	**265.39**	**265.39**	**265.39**	**265.39**
					Layer 2					
HPC	22.49	22.49	65.605	22.49	82.851	39.736	108.72	65.605	39.736	48.359
Sodium starch glycolate	0.89	0.89	2.595	0.89	3.277	1.572	4.3	2.595	1.572	1.913
Powdered Cellulose	3.97	3.97	11.59	3.97	14.638	7.018	19.21	11.59	7.018	8.542
Pre-gelatinised Starch	0.94	0.94	2.735	0.94	3.453	1.658	4.53	2.735	1.658	2.017
Magnesium Stearate	0.22	0.22	0.65	0.22	0.822	0.392	1.08	0.65	0.392	0.478
PC	162.5	162.5	162.5	162.5	162.5	162.5	162.5	162.5	162.5	162.5
TM	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
Maize starch	109.97	109.97	55.305	109.97	33.439	88.104	0.64	55.305	88.104	77.171
Subtotal	**319.73**	**319.73**	**319.73**	**319.73**	**319.73**	**319.73**	**319.73**	**319.73**	**319.73**	**319.73**
					Layer 3					
Sodium alginate	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Zinc gluconate	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Magnesium Stearate	2.81	2.81	2.81	2.81	2.81	2.81	2.81	2.81	2.81	2.81
DC	25	25	25	25	25	25	25	25	25	25
PEO	400	200	200	300	240	340	200	300	240	260
Maize starch	0	200	200	100	160	60	200	100	160	140
Subtotal	**446.56**	**446.56**	**446.56**	**446.56**	**446.56**	**446.56**	**446.56**	**446.56**	**446.56**	**446.56**
Total	1031.68	1031.68	1031.68	1031.68	1031.68	1031.68	1031.68	1031.68	1031.68	1031.68

The mesh size of the top screens was also fixed at 420Å. A standard dip per minute (dpm) of 10 was used in all experiments and dipping tubes were drained for 1 minute before moving to the next station containing a different media pH. The cumulative percent of drug released was calculated. All experiments were performed in triplicate and results for each time point of the dissolution curves were recorded as mean values.

5.2.4 Dissolution of the optimized formulation in three media

Dissolution studies on optimized EVD Formulation were conducted using a USP rotating paddle method (Hanson Virtual Instruments SR8 Plus Dissolution Test Stations) at 50rpm in phosphate buffer pH 6.8 (900mL, 37±0.5℃), employing an autos ampler (Hanson Research Auto Plus Maximizer and AutoPlus™ MultiFill™). Samples of 1.6mL were withdrawn over a period of 24 hours and analyzed via UPLC. Release profiles in simulated gastric fluid pH 1.2 without pepsin as well as acetate buffer pH 4.5, over a period 4 hours were determined to identify any site-specific release induced by the polymers. The dissolution studies were performed under the conditions described in Table 5.4.

Table 5.4: Dissolution study conditions for the optimized formulation

Component	Attribute
Apparatus	USP Paddle Assembly
Dissolution Media	a) 900mL of phosphate buffer pH 6.8. b) 900mL of acetate buffer pH 4.5. c) 900mL of simulated gastric fluid pH 1.2 without pepsin.
Speed	(Preheated and maintained at 37 ± 0.5℃)
Sampling (Automated)	50rpm
Filter (Standard solution)	Autoplus Maximizer Non-sterile 33 mm Millex-HV Hydrophillic Durapore®
Filter (Test solution)	(PVDF) 0.45 µm syringe filter unit (Millipore) Hanson Research Online sample filters 10 µm (Autoplus Maximizer)

5.2.5 Comparative *in vitro* dissolution studies

5.2.5.1 Tramacet™ Tablets

In order to compare the *in vitro* dissolution of the invention to that of a product registered on the South African market, Tramacet™ (Janssen-Cilag, Berchem, Belgium), a product containing 37.5mg tramadol hydrochloride and 325mg paracetamol was chosen for the first part of this study. Janssen-Cilag, is the Holder of the Certificate of Registration in South Africa. Batch number 6JS2T00 was used in these studies.

The *in vitro* dissolution studies, using six units of this product were performed using the dissolution parameters set out in Table 5.5 and the mean percentage drug release for paracetamol and tramadol hydrochloride are listed in Table 5.12.

Table 5.5: Dissolution study conditions for Tramacet™ analysis

Component	Attribute
Apparatus	USP Paddle Assembly
Dissolution Media	a) 900mL of simulated gastric fluid pH 1.2 without pepsin b) 900mL of acetate buffer pH 4.5 c) 900mL of phosphate buffer pH 6.8 (Preheated and maintained at 37± 0.5℃)
Speed	50rpm
Sampling (Automated)	Dissoette II or Autoplus Maximizer
Filter (Standard solution)	Non-sterile 33 mm Millex-HV Hydrophillic Durapore® (PVDF) 0.45 µm syringe filter unit (Millipore)
Filter (Test solution)	Hanson Research Online sample filters 10µm (Autoplus Maximizer) Hanson Research Online sample filters 10µm (Dissoette II)
Withdrawal times (minutes)	5, 10, 15, 30 and 45 minutes

5.2.5.2 Voltaren® SR Tablets

In order to compare the *in vitro* dissolution of the invention to that of a product registered on the South African market, Voltaren® SR Tablets (Novartis (Pty) Ltd., Basel, Switzerland), a product containing 100 mg diclofenac sodium was chosen for the first part of this study. Novartis South

Africa (Pty) Ltd. is the Holder of the Certificate of Registration in South Africa. Batch number S0193 was used in these studies.

The *in vitro* dissolution study, using six units of this product was performed using the dissolution parameters set out in Table 5.6 and the mean percentage drug release for DC is listed in Table 5.14. Only phosphate buffer pH 6.8 was considered due to the low solubility of DC in acidic media and reflected in the release of the two lower pH media experienced in previous studies.

Table 5.6: Dissolution study conditions for Voltaren® SR Tablet analysis

Component	**Attribute**
Apparatus	USP Paddle Assembly
Dissolution Media	900mL of phosphate buffer pH 6.8 (Preheated and maintained at 37± 0.5℃)
Speed	50rpm
Sampling (Automated)	Dissoette II or Autoplus Maximizer
Filter (Standard solution)	Non-sterile 33mm Millex-HV Hydrophillic Durapore® (PVDF) 0.45µm syringe filter unit (Millipore)
Filter (Test solution)	Hanson Research Online sample filters 10µm (Autoplus Maximizer) Hanson Research Online sample filters 10µm (Dissoette II)
Withdrawal times (hours)	0.25; 0.5; 0.75; 1; 2; 3; 4; 6; 8; 12; 16; 24

5.3 Results and Discussion

5.3.1 Design of experiments dissolution results

Each of the ten formulations was manufactured and dissolution studies were performed in phosphate buffer solution (pH6.8; 37ºC; 50rpm) and samples analyzed by UPLC over 24 hours. Each of the resultant dissolution profiles are illustrated in Figure 5.3 and Figure 5.4.

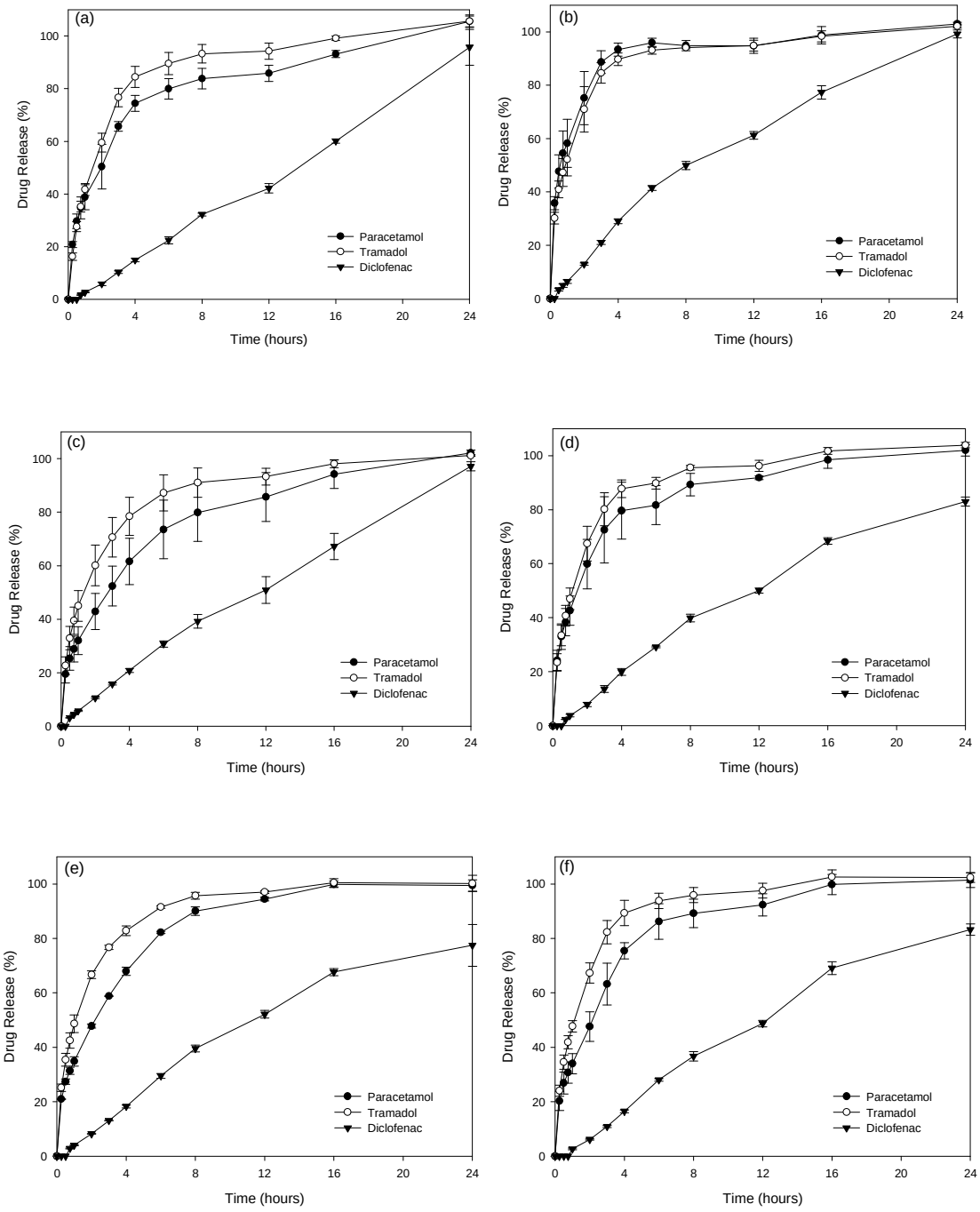


Figure 5.3: Typical dissolution profile of the three APIs at pH 6.8 over 24 hours in DoE formulation (a) F1; (b) F2; (c) F3; (d) F4; (e) F5; (f) F6. (N=3; in all cases SD<12.28).

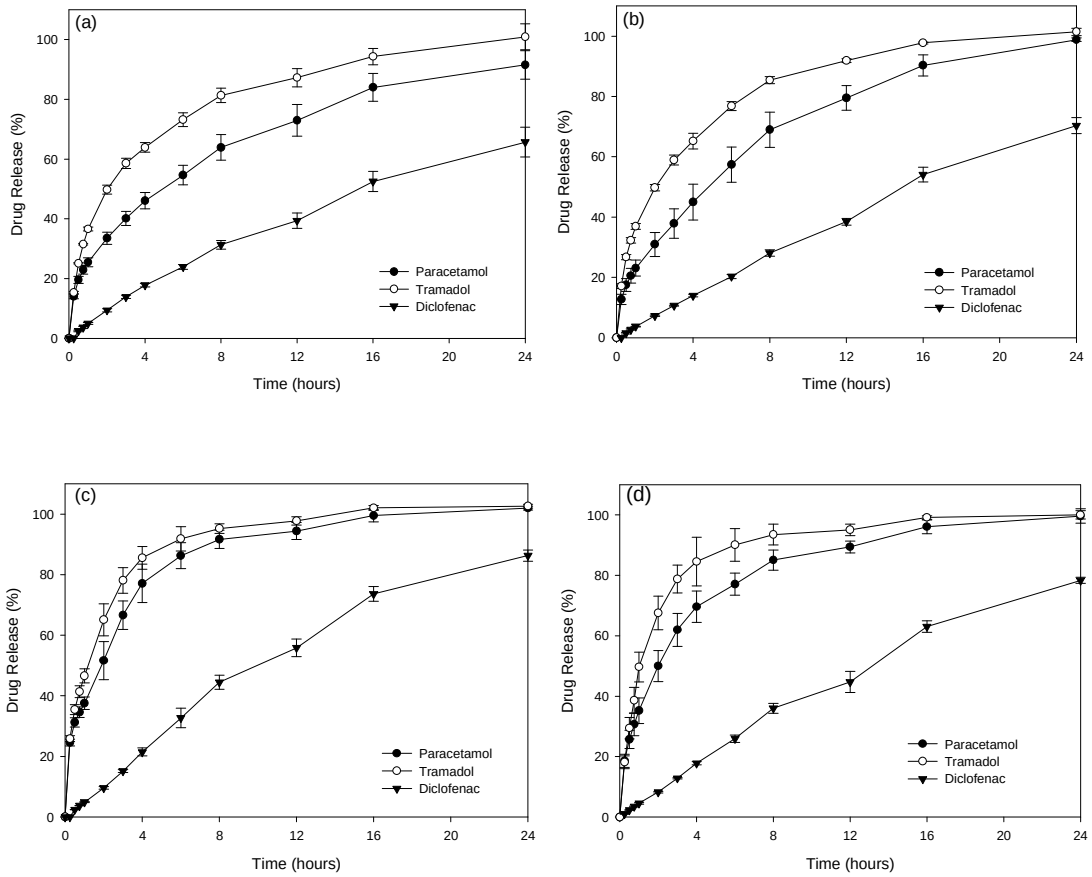


Figure 5.4: Typical dissolution profile of the three APIs at pH 6.8 over 24 hours in DoE formulations (a) F7; (b) F8; (c) F9 and (d) F10. (N=3; in all cases SD<12.28).

In order to establish which variable was the most significant in producing the desired drug release profiles f_1 difference and f_2 similarity factors were determined for each active component in each of the DoE formulations against the corresponding desired release profile for the drug. The similarity factor denoted as f_2 (Moore and Flanner, 1996) directly compares the similarity between percentage drug dissolved per unit time for a test and reference product, in the cases below, the desired release profiles. The similarity factor is a logarithmic transformation of the sum-squared error of differences between test T_j and reference product R_j over all time points as shown in Equation 5.1 below.

$$f_2 = 50 \log \{[1 + (1/n) \sum |R_j - T_j|^2]^{-0.5}\} \times 100$$ *Equation 5.1*

In general, f_2 value between 50 and 100 suggests that the dissolution profiles are similar. The f_2 value of 100 suggests that the investigational and reference release profiles are indistinguishable and as the value becomes lower, the dissimilarity between release profiles increases (Pillay and Fassihi, 1999). In addition Moore and Flanner (1996) describe an f_1 fit factor or difference factor as follows (Equation 5.2):

$$f_1 = \{[\sum |R_j - T_j|] / \sum R_t\} \times 100$$ *Equation 5.2*

where f_1 denotes the relative error between two dissolution profiles. It approximates the percent error between two curves. The error percent is zero when the test and reference profiles are identical and increases proportionally with the dissimilarity between the two profiles.

Generally, f_1 values ≤15 and f_2 values ≥50 indicates that an average difference of no more than 10% at the sample time points ensures equivalence of the curve and thus performance for the test and reference products (Moore and Flanner, 1996). Both f_1 and f_2 equations are very popular methods used to compare dissolution profile data and are recommended for use in a number of FDA guidance documents (FDA Guidance for Industry, 1997; O'Hara et al., 1998).

The similarity factor is useful in providing an overall basis for dissolution profile comparisons (Polli et al., 1997; Pillay and Fassihi, 1998; Pillay and Fassihi, 1999). The fit factors allow for evaluation where the curves may cross without a cancelling effect which may be unavoidable with other methods (Pillay and Fassihi, 1999).

The desired profiles created were calculated according to the Noyes-Whitney, Higuchi, Power Law, Peppas-Sahlin and Hopfenberg equations for PC and TM. The desired zero-order release

profile for DC was kept constant throughout these evaluations. Each model is discussed individually.

Theories applied to dissolution have in general remained unchanged, although their application and understanding is essential for sound design and development for alternative dissolution methodologies as well as deriving complementary statistical and mathematical techniques for unbiased dissolution profile comparison as encouraged by the USP 32 (General Notices). Various model-dependant and independent techniques, such as those to be discussed below, have been used to characterize dissolution profiles for the purpose of comparison. Although not without limitation, the f_1 and f_2 fit factors appear to be statistically most viable, with their unique ability for complete profile characterization, allowing this model-independent approach to statistically surpass other techniques (Pillay and Fassihi, 1999).

5.3.1.1 Zero-order release kinetics

Drug dissolution from pharmaceutical dosage forms that do not readily disintegrate and release the drug gradually, assuming the surface area does not change and no sink conditions are involved, can be represented by the following equation:

$$W_0 - W_t = Kt \qquad \textit{Equation 5.3}$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage at time t and K is a proportionality constant. This equation can be simplified to:

$$F_t = K_0 t \qquad \textit{Equation 5.4}$$

Where K_0 is the zero-order release constant and F_t is the fraction of drug dissolved in time t. A graphical representation of the drug released versus time would therefore be linear if the previously established conditions were fulfilled. Pharmaceutical dosage platforms following this release kinetic imply that the same quantity of drug is released per unit time and are usually ideal extended release delivery systems (Costa and Sousa Lobo, 2001).

The results of the fit factors for DC have been tabulated for completeness with each of the kinetic models employed for PC and TM below. The formulation that showed the greatest similarity to the desired zero-order release profile was that of Formulation F4 with an f_2 value of 88.14, plotted against the desired zero-order release below in Figure 5.5.

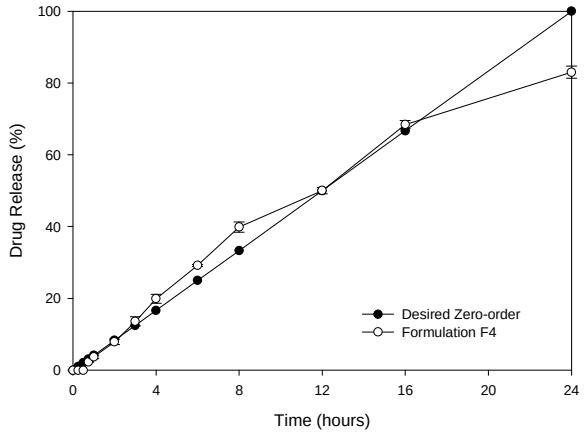


Figure 5.5: Typical dissolution profile of diclofenac potassium in DoE formulation F4 at pH 6.8 over 24 hours compared to the desirable zero order criteria (R^2=0.97).

5.3.1.2 Noyes-Whitney kinetic equation

The Noyes Whitney model (Noyes and Whitney, 1897), which assumes the constant proportionality of dissolution rate to the concentration difference C_s-C_t of the drug in the dissolution medium at time t, is shown below in Equation 5.5.

$$dC/dt = K(C_s - C) \qquad \textit{Equation 5.5}$$

where C is the concentration of the solute in time t, C_s is the solubility in the equilibrium and K is a first-order proportionality constant (Costa and Sousa Lobo, 2001). The Noyes-Whitney model, given by a linear differential equation for the dissolved fraction and therefore called the first-order model. This model, due to its simplicity is most suitable for generalization taking into account fluctuating conditions during the dissolution process (Lansky et al., 2004). This equation was used to calculate a set of desirable drug release percentages over a period of 24 hours with PC and TM showing first-order release (K=0.531 for 100% release after 24 hours), and DC exhibiting zero-order release as defined in this study proposal. A typical zero-order release equation was used to determine the desirable zero-order percentages against which DC was compared for this and the subsequent equations for first-order release below. The DC data will be repeated for each subsequent equation for completeness. The f_1 difference and f_2 similarity factors for each of the DoE formulations were then calculated against the abovementioned desirables in order to assess which formulation compared closest to the desired release state for each active ingredient. The f_1 and f_2 values are shown below in Table 5.7. In order for a formulation to be considered successful it must show an f_1 difference factor of less than 15, with f_1=0 being considered identical and an f_2 between 50 and 100 with f_2=100 considered identical to the desired release percentages.

Table 5.7: f_1 and f_2 values for PC and TM in the DoE formulations compared to Noyes-Whitney Equation. (Appropriate f_2 values have been highlighted in bold)

API		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
PC	f_1	8.90	-13.56	14.81	3.42	10.07	8.36	35.22	27.07	5.72	12.07
	f_2	33.40	26.29	19.82	**57.92**	31.33	34.74	5.56	6.73	46.87	27.41
TM	f_1	1.68	-7.40	1.92	-3.65	-2.98	-5.03	14.51	10.79	-3.70	-0.84
	f_2	**69.02**	37.74	**64.79**	**53.09**	**56.22**	45.73	23.15	27.68	**52.80**	**81.60**
DC	f_1	10.79	-29.11	-5.61	1.41	3.17	6.43	20.16	17.64	-7.89	7.68
	f_2	49.82	30.82	**58.86**	**88.14**	**75.62**	**60.85**	38.78	34.20	**55.05**	**57.40**

From the data above it is evident that Formulation F4 with f_2 values of 57.92 for PC and 53.09 for TM is the most similar to the desired release criteria according to the Noyes-Whitney equation. The release profiles of Formulation F4 have been plotted against the desired Noyes-Whitney release criteria for comparison in Figure 5.6.

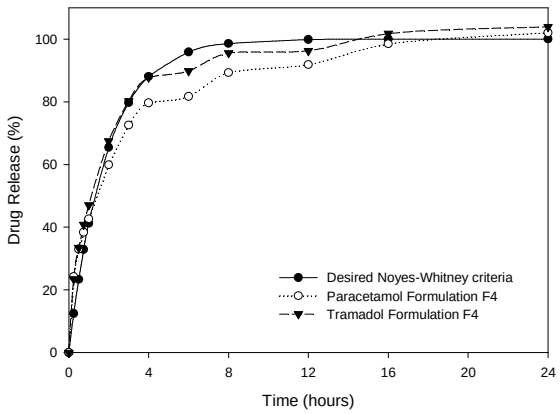


Figure 5.6: Typical dissolution profile of paracetamol and tramadol hydrochloride in DoE Formulation F4 at pH 6.8 over 24 hours compared to the desirable Noyes-Whitney equation criteria.

5.3.1.3 Higuchi kinetic equation

Higuchi (1961, 1963) developed numerous hypothetical models to investigate the release of high and low aqueous soluble drugs incorporated in semi-solid or solid matrices. The Higuchi equation is shown below in Equation 5.9.

$$f_t = K_H t^{1/2} \qquad \textit{Equation 5.9}$$

where K_H is the Higuchi dissolution constant, which has been treated in a different manner by different authors (Desai et al., 1966; Schwartz et al., 1968). Higuchi depicts API release as a diffusion mechanism based on Fick's law, square root time-dependant. This relationship can be used to describe several types of modified release systems (Costa and Sousa Lobo, 2001). A limitation of this representation is the lack of reflection on swelling kinetics of the matrix as the Higuchi model assumes a non-swelling, non-dissolving matrix (Higuchi, 1963).

This equation was used to calculate a set of desirable drug release percentages over a period of 24 hours, with PC and TM showing first-order release as defined in this study proposal. In order to generate the desirable values k=46.2 for t‹3h and k=4.37 for 3h‹t‹24h were used, indicating

that approximately 80% of PC and DC were to be released at approximately 3 hours. The f_1 difference and f_2 similarity factors for each of the DoE formulations were then calculated against the abovementioned desirables, using SigmaPlot V11 (Systat Software Inc., Chicago, IL, USA) statistical software, in order to assess which formulation compared closest to the desired release state for each API. The f_1 and f_2 values are shown below in Table 5.8. In order for a formulation to be considered successful it must show an f_1 difference factor of less than 15, with f_1=0 being considered identical and an f_2 between 50 and 100 with f_2=100 considered identical to the desired release percentages.

Table 5.8: f_1 and f_2 values for paracetamol and tramadol hydrochloride in the DoE formulations compared to the Higuchi Equation. (Appropriate f_2 values have been highlighted in bold)

API		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
PC	f_1	8.96	-13.48	14.87	3.50	10.15	8.43	35.30	27.13	5.81	12.15
	f_2	33.23	26.41	19.72	**57.40**	31.18	34.56	5.52	6.68	46.55	27.28
TM	f_1	1.75	-7.33	1.98	-3.58	-2.91	-4.96	14.59	10.86	-3.63	-0.78
	f_2	**68.18**	37.95	**64.08**	**53.52**	**56.72**	46.03	23.04	27.55	**53.22**	**83.07**
DC	f_1	10.79	-29.11	-5.61	1.41	3.17	6.43	20.16	17.64	-7.89	7.68
	f_2	49.82	30.82	**58.86**	**88.14**	**75.62**	**60.85**	38.78	34.20	**55.05**	**57.40**

From the data above it is evident that Formulation F4 with f_2 values of 57.40 for PC and 53.52 for TM is the most similar to the desired release criteria according to the Higuchi equation. The release profiles of Formulation F4 have been plotted against the desired Higuchi release criteria for comparison in Figure 5.7.

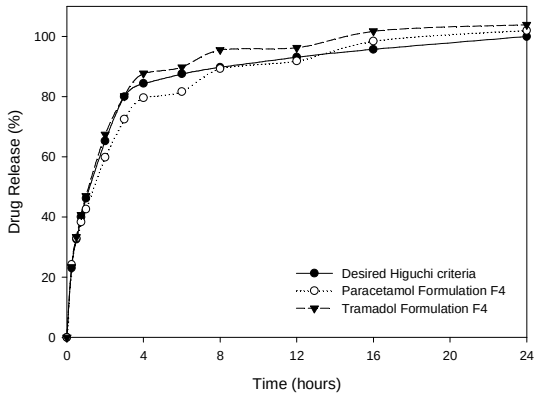


Figure 5.7: Typical dissolution profile of paracetamol and tramadol hydrochloride in DoE Formulation F4 at pH 6.8 over 24 hours compared to the desirable Higuchi equation criteria.

5.3.1.4 Power law kinetic equation

The Power Law equation is shown below in Equation 5.8, describes drug release from simple swellable systems.

$$M_t/M_\infty = k_1 t^n \qquad \textit{Equation 5.8}$$

Where Mt and M_∞ are the amounts of drug dissolved at time t and the overall amount released, respectively, k_1 is a release constant and n is a release exponent indicative of the release mechanism. For the case of cylindrical tablets $n \leq 0.5$ corresponds to Fickian or case I diffusional release; $0.5 \leq n \leq 1$ to an anomalous transport and n=1 to zero-order or case II release kinetics (Ritger and Peppas, 1987). This equation was used to calculate a set of desirable drug release percentages over a period of 24 hours, with PC and TM showing first-order release as defined in this study proposal. In order to generate the desirable values k_1=0.5467 and n=0.19 were used. This n value corresponds to Fickian diffusion for PC and TM. The f_1 difference and f_2 similarity factors for each of the DoE formulations were then calculated against the abovementioned desirables, using SigmaPlot V11 (Systat Software Inc., Chicago, IL, USA) statistical software, in order to assess which formulation compared closest to the desired release state for each API. The f_1 and f_2 values are shown below in Table 5.9. In order for a formulation to be considered successful it must show an f_1 difference factor of less than 15, with f_1=0 being considered identical and an f_2 between 50 and 100 with f_2=100 considered identical to the desired release percentages.

Table 5.9: f_1 and f_2 values for paracetamol and tramadol hydrochloride in the DoE formulations compared to the Power Law Equation. (Appropriate f_2 values have been highlighted in bold)

API		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
PC	f_1	8.71	-13.78	14.63	3.18	9.87	8.18	35.00	26.89	5.48	11.87
	f_2	33.89	25.94	20.08	**59.47**	31.78	35.27	5.70	6.87	47.79	27.78
TM	f_1	1.48	-7.61	1.73	-3.85	-3.17	-5.24	14.31	10.61	-3.90	-1.04
	f_2	**71.62**	37.15	**66.93**	**51.91**	**54.87**	44.88	23.46	28.06	**51.64**	**77.80**
DC	f_1	10.79	-29.11	-5.61	1.41	3.17	6.43	20.16	17.64	-7.89	7.68
	f_2	49.82	30.82	**58.86**	**88.14**	**75.62**	**60.85**	38.78	34.20	**55.05**	**57.40**

From the data above it is evident that Formulation F4 with f_2 values of 59.47 for PC and 51.91 for TM is the most similar to the desired release criteria according to the Power Law equation. The release profiles of Formulation F4 have been plotted against the desired Power Law release criteria for comparison in Figure 5.8.

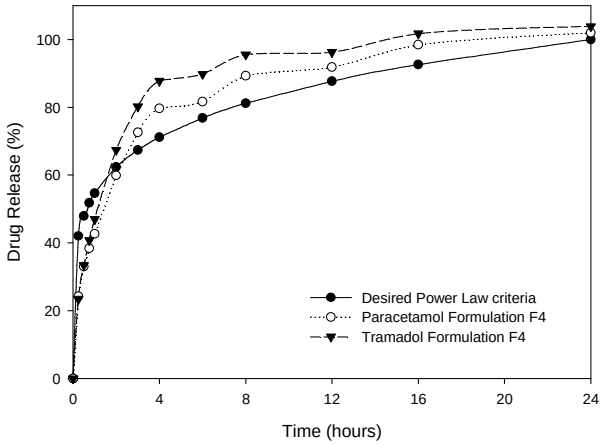


Figure 5.8: Typical dissolution profile of paracetamol and tramadol hydrochloride in DoE Formulation F4 at pH 6.8 over 24 hours compared to the desirable Power Law equation criteria.

5.3.1.5 Peppas-Sahlin kinetic equation

The Peppas and Sahlin equation (1989) is shown below in Equation 5.7, which, irrespective of the shape of the dosage form, reports on the evaluation of the contribution provided by Fickian diffusion through the hydrated outer layers of the matrix and matrix relaxation or erosion.

$$M_t/M_\infty = k_1t^n + k_2t^{2n} \qquad \textit{Equation 5.7}$$

Where k_1 is the Fickian kinetic constant and k_2 is the relaxation or dissolution rate constant (i.e. anomalous transport). This Equation was used to calculate a set of desirable drug release percentages over a period of 24 hours, with PC and TM showing first-order release as defined in this study proposal. In order to generate the desirable values a k_1=0.45 and k_2=0.106 were used. The f_1 difference and f_2 similarity factors for each of the DoE formulations were then calculated

against the abovementioned desirables in order to assess which formulation compared closest to the desired release state for each API. The f_1 and f_2 values are shown below in Table 5.10. In order for a formulation to be considered successful it must show an f_1 difference factor of less than 15, with f_1=0 being considered identical and an f_2 between 50 and 100 with f_2=100 considered identical to the desired release percentages.

Table 5.10: f_1 and f_2 values for paracetamol and tramadol hydrochloride in the DoE formulations compared to the Peppas-Sahlin Equation. (Appropriate f_2 values have been highlighted in bold)

API		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
PC	f_1	9.41	-12.93	15.32	4.10	10.66	8.88	35.85	27.57	6.41	12.66
	f_2	32.05	27.31	19.09	**54.02**	30.10	33.31	5.18	6.33	44.43	26.38
TM	f_1	2.23	-6.82	2.45	-3.06	-2.43	-4.43	15.09	11.33	-3.11	-0.29
	f_2	**62.94**	39.51	**59.64**	**56.81**	**60.57**	48.32	22.30	26.64	**56.46**	**95.34**
DC	f_1	10.79	-29.11	-5.61	1.41	3.17	6.43	20.16	17.64	-7.89	7.68
	f_2	49.82	30.82	**58.86**	**88.14**	**75.62**	**60.85**	38.78	34.20	**55.05**	**57.40**

From the data above it is evident that Formulation F4 with f_2 values of 54.02 for PC and 56.81 for TM is the most similar to the desired release criteria according to the Peppas-Sahlin equation. The release profiles of Formulation F4 have been plotted against the desired Peppas-Sahlin release criteria for comparison in Figure 5.9.

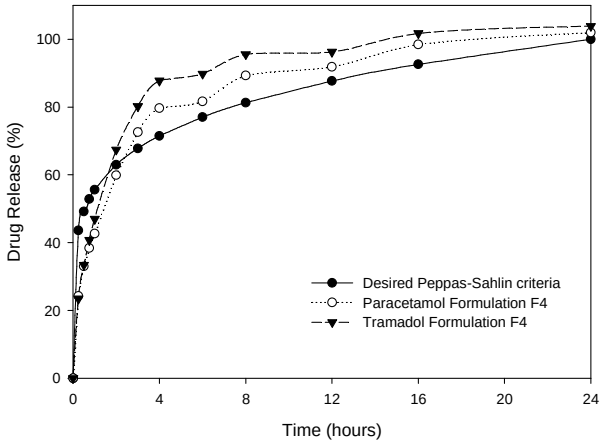


Figure 5.9: Typical dissolution profile of paracetamol and tramadol hydrochloride in DoE Formulation F4 at pH 6.8 over 24 hours compared to the desirable Peppas-Sahlin equation criteria.

5.3.1.6 Hopfenberg kinetic equation

The Hopfenberg model (Hopfenberg, 1976) is shown below in Equation 5.6 and represents API release from systems with surface erosion and varying geometries.

$$M_t/M_\infty = 1-(1-k_1t)^n \qquad \textit{Equation 5.6}$$

Where k_1 is equal to k_0/C_0r_0, k_0 is the erosion rate constant, C_0 is the uniform initial concentration of drug in the matrix, r_0 is the initial radius for a sphere (n=3) or cylinder (n=2) or half the thickness of a slab (n=1). The model assumes that time-dependant diffusional resistances internal or external to the eroding matrix do not influence the release kinetics (Katzhendler et al., 1997). This equation was used to calculate a set of desirable drug release percentages over a period of 24 hours, with PC and TM showing first-order release as defined in this study proposal. In order to generate the desirable values n=3 for a sphere and k_1=0.04 were used. The f_1 difference and f_2 similarity factors for each of the DoE formulations were then calculated against the abovementioned desirables in order to assess which formulation compared closest to the desired release state for each API. The f_1 and f_2 values are shown below in Table 5.11. In order for a formulation to be considered successful it must show an f_1 difference factor of less than 15, with f_1=0 being considered identical and an f_2 between 50 and 100 with f_2=100 considered identical to the desired release percentages.

Table 5.11: f_1 and f_2 values for paracetamol and tramadol hydrochloride in the DoE formulations compared to the Hopfenberg Equation. (Appropriate f_2 values have been highlighted in bold)

API		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
PC	f_1	-41.14	-52.47	-16.74	-39.11	-26.42	-41.97	-3.69	-4.49	-36.18	-24.42
	f_2	9.67	-3.09	17.15	5.22	10.14	9.24	**54.37**	45.67	6.54	12.12
TM	f_1	-52.33	-43.46	-31.13	-39.85	-37.21	-62.72	-21.54	-22.25	-39.9	-35.02
	f_2	4.45	-0.66	4.70	1.31	1.59	0.52	14.55	11.98	1.29	2.87
DC	f_1	10.79	-29.11	-5.61	1.41	3.17	6.43	20.16	17.64	-7.89	7.68
	f_2	49.82	30.82	**58.86**	**88.14**	**75.62**	**60.85**	38.78	34.20	**55.05**	**57.40**

From the data above it is evident that no one formulation is similar to the desired release criteria according to the Hopfenberg equation for PC and TM. This model does not adequately describe the release mechanics observed in the fixed dose combination (FDC), indicating that polymer erosion was not the principle mechanism of API release.

5.3.2 USP apparatus III dissolution of the design of experiments formulations

The cumulative dissolution profiles for each of the ten DoE formulations according to USP Apparatus III are shown in Figure 5.10 and Figure 5.11.

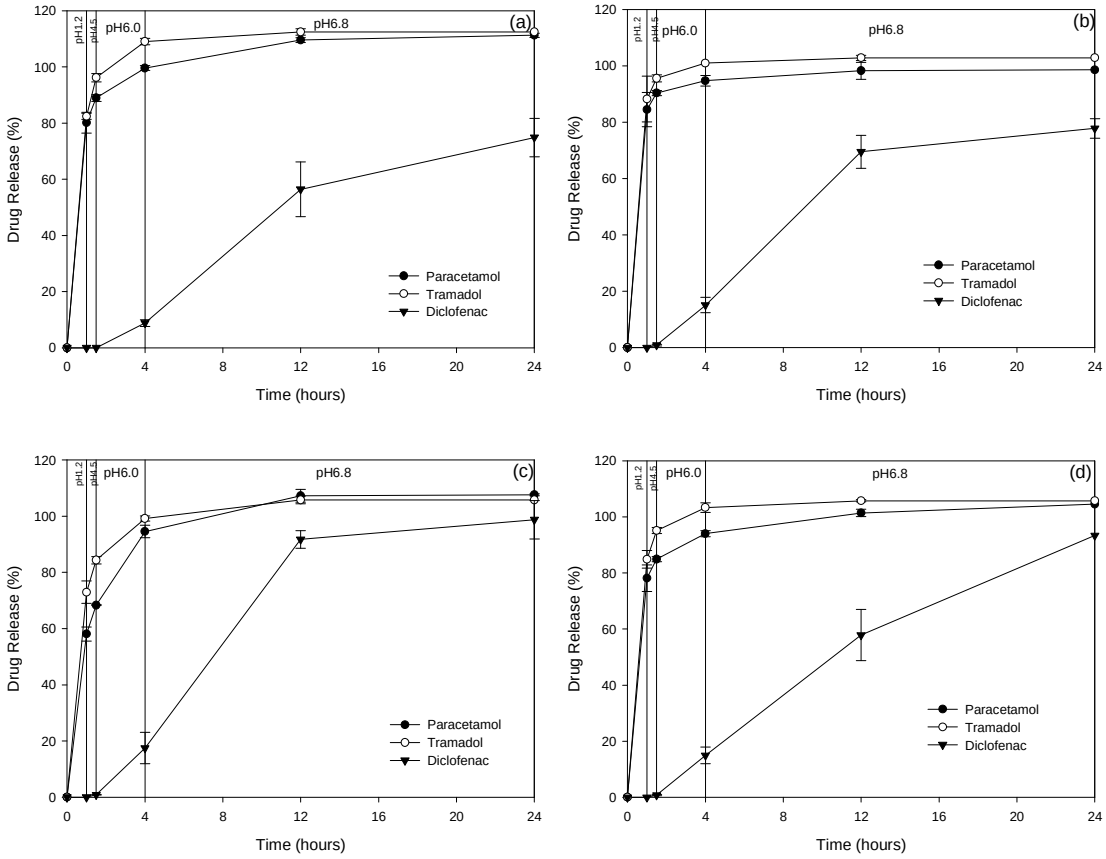


Figure 5.10: Typical cumulative USP Apparatus III dissolution profile of the three APIs over 24 hours in DoE Formulation: (a) F1; (b) F2; (c) F3; (d) F4. (N=3; in all cases SD<9.76).

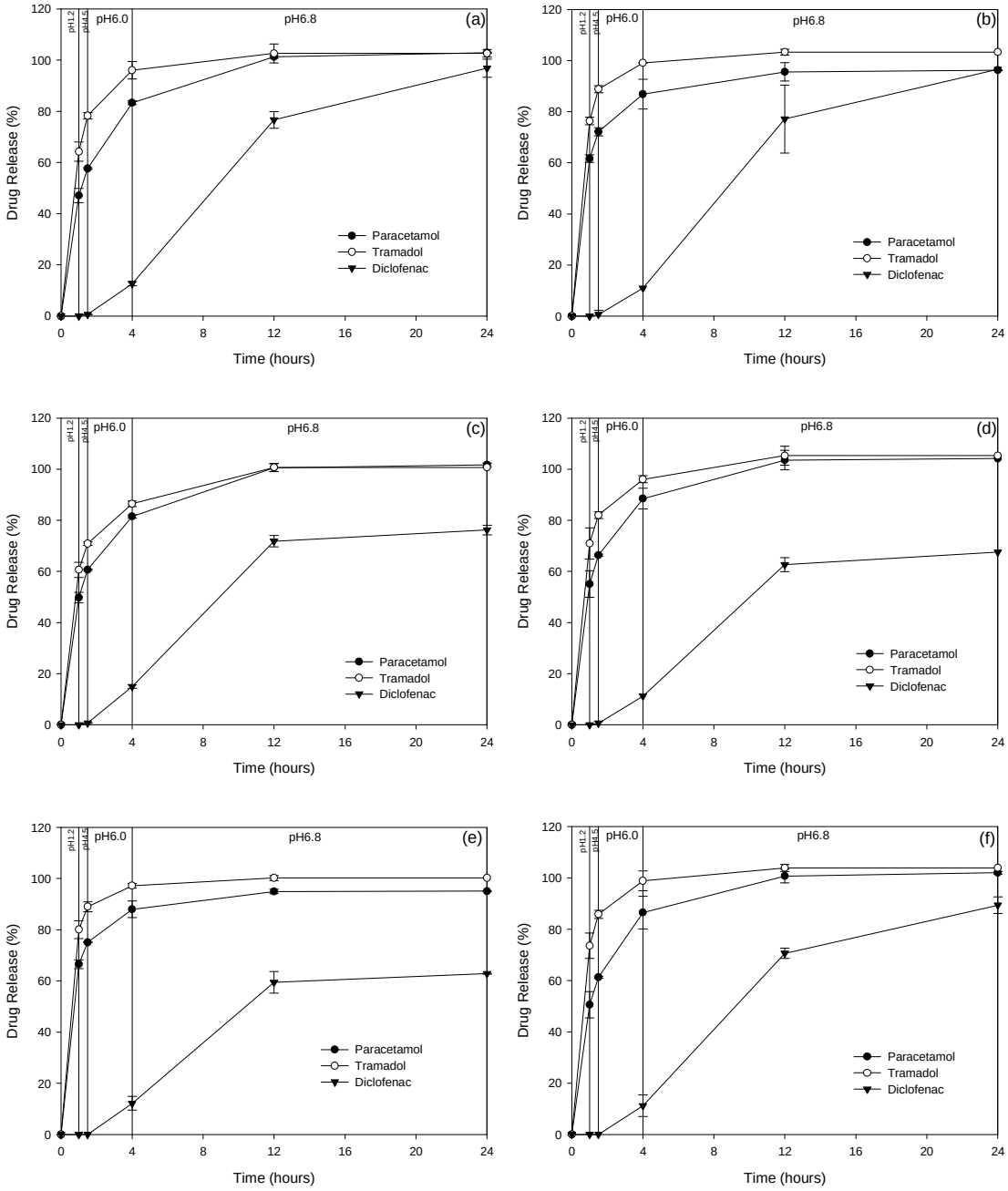


Figure 5.11: Typical cumulative USP Apparatus III dissolution profile of the three APIs over 24 hours in DoE Formulation: (a) F5; (b) F6; (c) F7; (d) F8; (e) F9 and (f) F10. (N=3; in all cases SD<9.76).

As is evident from the profiles above, the first-order-like release of PC and TM is retained in most of the formulations whilst only Formulation F4 retains its zero-order like release of DC. Together

with the confirmed comparability to the desired release profiles for each of the three APIs, Formulation F4 confirms its optimal status according to the proposed formulation. Further to this, dissolution profiles in simulated gastric medium pH 1.2 and acetate buffer pH 4.5 were generated in order to create the dissolution profiles for this formulation over the entire simulated GIT conditions. The dissolution profiles are discussed in Section 5.3.3.

5.3.3 Formulation F4 dissolution in the three media

The release profiles of Formulation F4 are shown below in Figure 5.12, for simulated gastric fluid pH 1.2, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The profiles in Figure 5.12 show that very little DC is released in these two media, suggesting the release of DC is site-specific due to the pH-solubility profile of the DC, with the API being released in a zero-order profile at pH 6.8 relating to the distal intestine of the GIT. Thus the site-specific release of the non-steroidal anti-inflammatory drug may assist in reducing its gastrointestinal side effects as much of the drug will not be available in the sensitive gastric areas. In light of this coating of DC dosage forms (e.g. film coated tablets) is highly questionable. PC and TM retain their first-order release kinetics over the earlier pH release zones as well as pH 6.8. As they are also released simultaneously the synergistic clinical effect of these two drugs in combination seen with Tramacet™ should be evident. The rapid release of the two principle analgesic drugs PC and TM propose an initial pain relief effect with the anti-inflammatory component in DC being released constantly at a zero-order rate as a second wave of relief, has been successfully achieved *in vitro* with the designed delivery system in the form of Formulation F4.

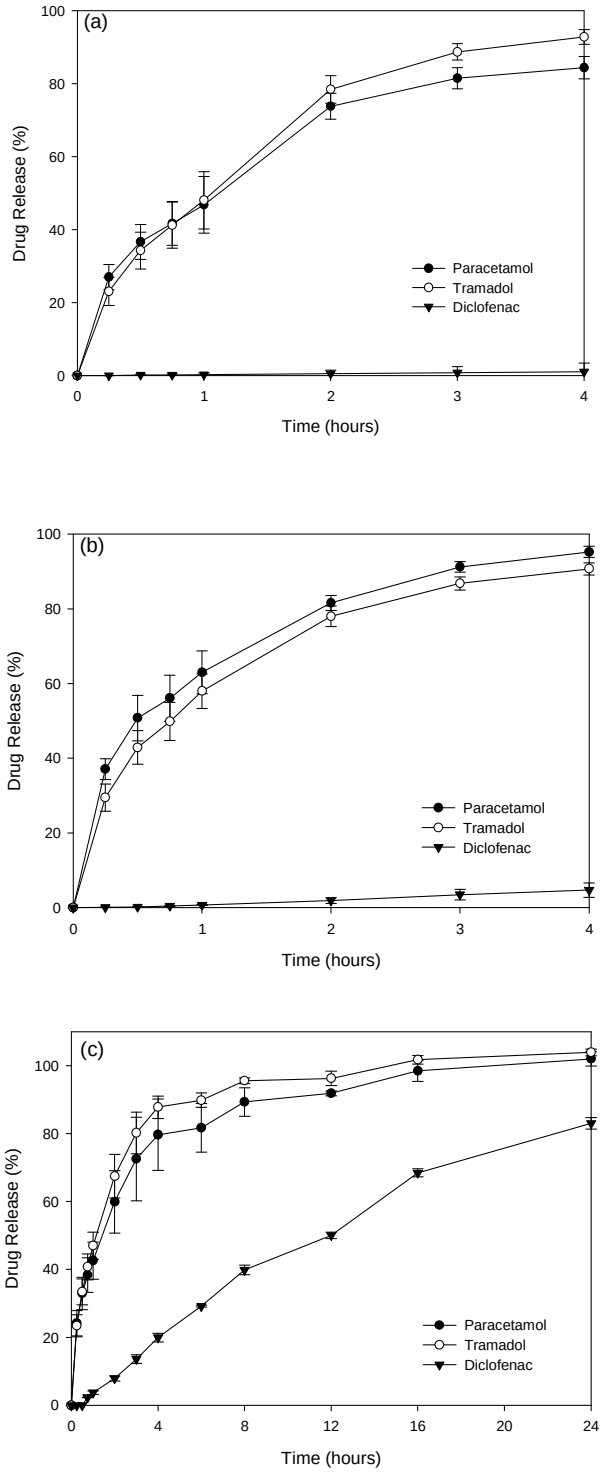


Figure 5.12: Typical dissolution profile of the three APIs in DoE Formulation F4 at: (a) pH 1.2 over 4 hours; (b) pH 4.5 over 4 hours and (c) pH 6.8 over 24 hours. (N=3; in all cases SD<7.86).

5.3.4 Comparative *in vitro* dissolution studies

5.3.4.1 Tramacet™ Tablets

The mean percent API release for Tramacet ™ Tablets in simulated gastric fluid pH 1.2 without pepsin, acetate buffer pH 4.5 and phosphate buffer pH 6.8 is tabulated in Table 5.12.

Table 5.12: Mean API release percentage for Tramacet™ tablets

Withdrawal time (minutes)	PC Release (%)*	TM Release (%)*
Simulated gastric fluid pH 1.2 without pepsin		
5	13.40	12.56
10	46.69	42.05
15	73.25	68.58
30	98.36	97.37
45	101.06	100.52
Acetate buffer pH 4.5		
5	13.57	13.14
10	47.97	43.28
15	74.10	69.37
30	98.24	95.93
45	101.24	99.30
Phosphate buffer pH 6.8		
5	14.13	13.42
10	49.69	45.98
15	76.70	73.49
30	97.47	96.54
45	100.48	99.83

*N=3; in all cases SD<3.78.

The dissolution profiles of PC and TM from Tramacet™ Tablets, in the three prescribed media, are displayed in Figure 5.13.

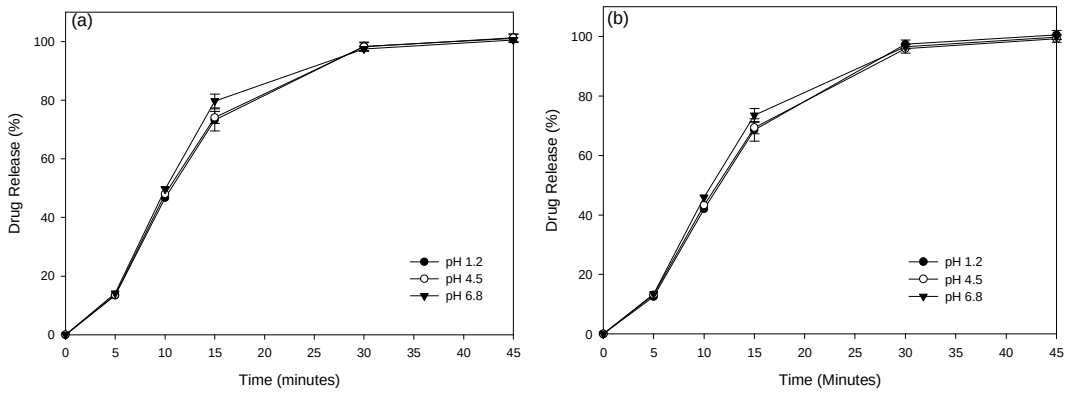


Figure 5.13: Typical dissolution profile of (a) paracetamol and (b) tramadol hydrochloride (b) in Tramacet™ Tablets in each prescribed medium over 45 minutes. (N=6; in all cases SD<3.78).

Figure 5.14 indicates the comparison between Tramacet™ Tablets and the invention in each of the three media over a period of only 45 minutes. Table 5.13 shows the f_1 and f_2 fit factors between PC and TM in the two dosage forms to give an indication of the similarity and difference between the invention and the marketed product in terms of these two APIs. None of the fit factors meet the criteria necessary to indicate comparative dissolution profiles for PC or TM, concluding that the release profiles of the immediate release Tramacet™ Tablet dosage form are not comparable to that of PC and TM in the prolonged-release invention, which was an expected finding due to its polymeric nature and excipients used to influence the drugs' release and the initial intention of this particular delivery system. Although not directly comparable to this marketed product over a short period of 45 minutes the invented dosage form does display simultaneous PC and TM release, with approximately 50% of both APIs being released within the first hour *in vitro*.

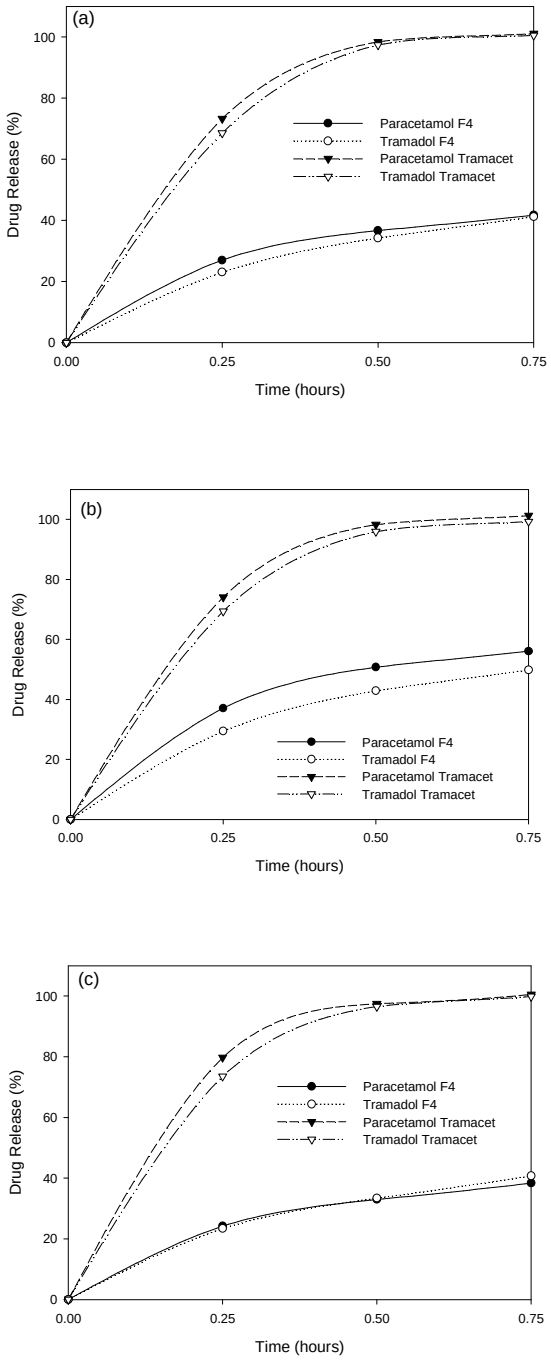


Figure 5.14: Typical dissolution profile of paracetamol and tramadol hydrochloride in the invention and Tramacet™ Tablets over 45 minutes in (a) simulated gastric fluid pH 1.2 without pepsin; (b) acetate buffer pH 4.5 and (c) phosphate buffer pH 6.8. (N=3, in all cases SD<3.45).

Table 5.13: Fit factors f_1 and f_2 comparing Formulation 4 to Tramacet™ tablets over 45 minutes

Withdrawal time (minutes)	f_1	f_2
Simulated gastric fluid pH 1.2 without pepsin		
PC	61.36	15.84
TM	63.02	15.86
Acetate buffer pH 4.5		
PC	47.41	21.37
TM	57.84	19.33
Phosphate buffer pH 6.8		
PC	65.23	14.36
TM	63.83	15.21

5.3.4.2 Voltaren SR® Tablets

The mean percent API release for Voltaren® SR Tablets in simulated gastric fluid pH 1.2 without pepsin, acetate buffer pH 4.5 and phosphate buffer pH 6.8 are tabulated in Table 5.14.

Table 5.14: Mean API release percentage for Voltaren® SR tablets

Withdrawal time (hours)	DC Release (%)*
Phosphate buffer pH 6.8	
0.25	7.86
0.5	13.12
0.75	16.69
1	19.51
2	29.44
3	34.92
4	40.82
6	54.20
8	66.45
12	79.25
16	87.22
24	98.12

*N=3; in all cases SD<2.75.

The dissolution profile of DC from Voltaren® SR Tablets, in phosphate buffer pH 6.8, is displayed in Figure 5.15.

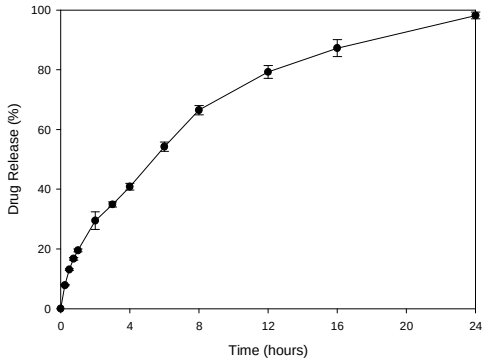


Figure 5.15: Typical dissolution profile of diclofenac in Voltaren® SR Tablets phosphate buffer pH 6.8 over 24 hours. (N=6; in all cases SD<2.75).

The profile below in Figure 5.16 indicates the comparison between Voltaren® SR Tablets and the invention in phosphate buffer pH 6.8 over a period of 24 hours. Table 5.15 shows the f_1 and f_2 fit factors between DC in the two dosage forms to give an indication of the similarity and difference between the invention and the marketed product in terms of this API. None of the fit factors meet the criteria necessary to indicate comparative dissolution profiles for DC, concluding that the release profiles are not comparable. This may be due to the curved-nature of the drug release profile for Voltaren® SR tablets versus the more linear zero-order release of DC in the invention, as intended. If the data obtained from the Voltaren® SR Tablet *in vitro* dissolution is compared against the desired zero-order release data an f_2 value of only 9.44 is obtained revealing that the drug release for Voltaren® SR Tablets is in fact not zero-order and therefore would be unlikely to compare to the zero-order (f_2=88.14) designed DC release of the invention.

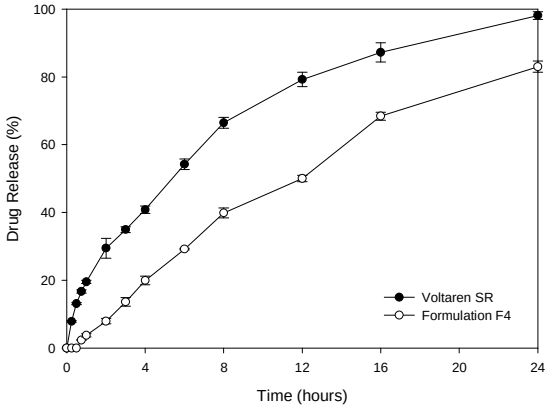


Figure 5.16: Typical dissolution profile of diclofenac in the invention and Voltaren® SR Tablets in phosphate buffer pH 6.8 over 24 hours. (N=3; in all cases SD<2.75).

Table 5.15: Fit factors f_1 and f_2 comparing Formulation 4 to Voltaren® SR tablets over 24 hours

Withdrawal time (minutes)	**f_1**	**f_2**
Phosphate buffer pH 6.8		
DC	*41.92*	*8.97*

5.4 Concluding Remarks

The API transport within pharmaceutical systems and its release sometimes involves multiple steps provoked by different physical or chemical phenomena, making it difficult or almost impossible to get a perfect mathematical model to describe it in the correct way. Based on the successful comparison of Formulation F4 with each of the appropriate kinetic models used to create desirable first-order release for PC and TM as well as the successful comparison of DC with the desirable zero-order release profile, Formulation F4 of the DoE EVD was considered the optimum formulation based on these criteria and underwent further characterization in the subsequent chapters.

CHAPTER SIX

TEXTURAL PROFILING OF THE OPTIMIZED FIXED DOSE COMBINATION DELIVERY SYSTEM

6.1 Introduction

Swellable systems, prepared by incorporating drugs in hydrophilic polymeric matrices have received considerable attention for the preparation of sustained release formulations (Sung et al., 1996; Sujja-arevath et al., 1998; Tajorubi et al., 2009). When a hydrophilic matrix is exposed to biological fluid or dissolution medium it starts to hydrate and swell from the outer boundaries towards the core. A gel layer is formed around the matrix, which significantly influences the dissolution and diffusion of the drug through the polymer. Lee and Peppas (1987) defined the boundary between the matrix surface and the dissolution medium as the erosion front and the boundary between the glassy polymer and its rubbery gel state as the swelling front. A third front within the gel layer (Figure 6.1) was identified as the diffusion front, in between the areas in which the drug has dissolved and not dissolved (Lee and Kim, 1991).

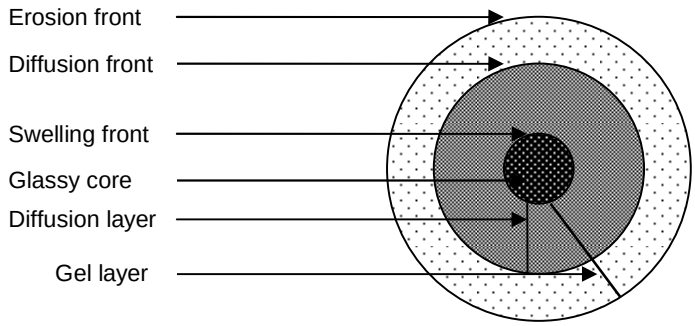


Figure 6.1: Schematic representation of erosion, diffusion and swelling fronts and the gel and diffusion layer of a tablet (adapted from Vlachou et al., 2004).

Hydrophilic swellable polymers in their native state usually demonstrate rapid gelation, first-order dissolution and unsynchronised erosion/relaxation in relation to the timescale required for modulated active pharmaceutical ingredient (API) delivery (Pillay and Fassihi, 1999). These

properties may be adjusted and controlled through the process of crosslinking, which essentially changes the extent of polymer entanglement and hence rate of disentanglement. Crosslinks tend to create three-dimensional voids or pockets within the polymeric matrix and therefore restrains the diffusion of imbibed water, and controls matrix relaxation and erosion (Pillay and Danckwerts, 2002). The rate and method of API release from swellable matrices is dependant on dissolution, diffusion, movement of any undissolved particles in the gel layer and solubility of the drugs used (Vlachou et al., 2004).

The resilient nature of the hydrated delivery device shall also be determined. The fixed-dose combination (FDC) tablets shall be hydrated in 250mL phosphate buffer pH 6.8 and maintained at 37°C. At appropriate time intervals a tablet will be removed and subjected to resilience measurements.

This Chapter focuses on the physicomechanical analysis of the finished delivery system with respect to textural profiling.

6.2 Materials and Methods

6.2.1 Materials

For the swelling study the two most diverse formulations, based on their PEO content, from the Extreme Vertices Design (EVD) were chosen as well as the optimal formulation from the studies described in Chapter 5. This correlated to Formulations F1, F2 and F4. Eudragit® RS, Degussa Rohm GmbH & Co. KG, Darmstadt, Germany, was used for coating the tablets.

6.2.2 Swelling analysis

In order to assess the swelling characteristics of each individual layer of the multi-layered tablet as well as the combined swelling effects of each of the three layers, the tablet layers were coated, using a customized inert fibrous coating probe, with an organic water insoluble coating mixture. Zuleger and co-workers (2002) describe the coating as a mixture of 60 g Eudragit® RS with 50mL

acetone and 50mL isopropanol. Figure 6.2 depicts the coating configurations for each of the layers. With coating layer A corresponding to tablet layer 1 (paracetamol (PC), tramadol hydrochloride (TM), hydroxyethylcellulose (HEC) etc.), coating layer B to tablet layer 3 (diclofenac (DC), polyethylene oxide (PEO) etc.) and coating layer C to tablet layer 2 (PC, TM, hydroxypropylcellulose (HPC) etc.).

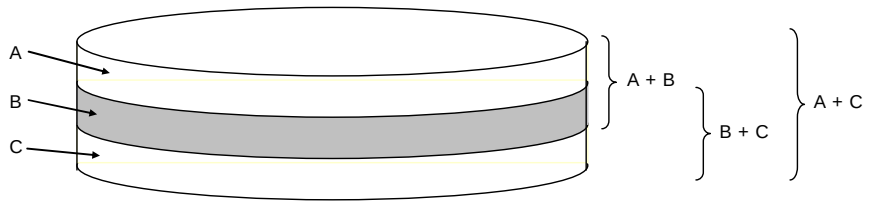


Figure 6.2: Schematic of the triple-layered tablet showing the different coating configurations used for texture analysis.

Three tablets for each of the above coating variations were made. The tablets were fixated using dual-adhesive tape, to a watch glass with their coated side (two to three tablets per dish) and placed at the bottom of the vessels in the dissolution bath (Erweka DT 700). Swelling was performed in 900mL phosphate buffer (pH6.8; 37ºC; 50rpm) over a period of four hours as visually this was when the maximum amount of swelling appeared to occur. The tablets were removed at predetermined time points of 15 minutes; 30 minutes; 1; 2 and 4 hours and were subjected to textural analysis.

Expansion of the tablets and development of a gel layer thickness during the swelling process were investigated using the Texture Analyzer (TA.XT2, Stable Micro Systems, Goldalming, UK). At a test speed of 0.2mm.s^{-1} (pre-test speed 1.0mm.s^{-1} and post-test speed 5.00mm.s^{-1}) the penetration of a flat-tipped cylindrical steel probe (diameter 2mm, height 3cm) under increasing load (max. 1N) was measured and data acquisition and analysis was performed using Texture Exponent software (Version 3.2).

As reported by Yang et al. (1998) the Texture Analyzer was used to examine the gel structure and to determine gel layer thickness and axial expansion of the tablet during swelling. The force necessary for the penetration of a cylindrical probe was measured precisely. At the point of contact of the probe with the swollen tablet, data acquisition is initiated, reaching a threshold load necessary for penetration into the gel layer. During the initial stages of the test only low forces are necessary to penetrate the swollen gel layer. A further sharp increase in the load required for penetration indicates the boundary of the gel layer and unswollen dry tablet core. After the maximum force has been reached, the probe reverses and is withdrawn from the swollen tablet. In contrast to alternative penetration methodology the Texture Analyzer provides information on the gel structure as complete force-distance profiles are created (Zuleger et al., 2002). Textural analysis was performed in triplicate at access points of the layers that were not coated (either A, B or C or A&B, B&C or A&C according to Figure 6.2) and therefore able to swell unimpeded.

6.2.3 Matrix hardness analysis

A calibrated Texture Analyzer (TA.XT2, Stable Micro Systems, England) was fitted with a 2mm diameter ball-tipped plate which was employed for matrix hardness studies. Data was captured at a rate of 200 points per second via Texture Exponent Software (Version 3.2). The parameters and settings employed for the analysis are outlined in Table 6.1. Matrix hardness was measured only on unhydrated tablets of Formulation F1, F2 and F4, in triplicate. For comparability each tablet was measured on its side conforming to the innermost, layer three. Matrix hardness is indicated by the steepness of the upward gradient to the fracture phase. In general a steeper gradient indicates a harder matrix.

Table 6.1: Textural settings for determining matrix hardness

Parameters	Settings
Pre-test speed	1mm/sec
Test speed	0.5mm/sec
Post-test speed	1mm/sec
Compression force	40N
Trigger type	Auto
Trigger force	0.5N
Load cell	50kg
Parameter measured	Distance

6.3 Results and Discussion

6.3.1 Swelling analysis

From visual observation it was evident that as soon as the tablets were exposed to the dissolution medium, the liquid penetrated into their polymeric mass and the hydrated polymers swell to form a gelatinous layer around the tablet. The mean values of the distance the probe travelled are recorded for the triplicate readings performed for each coating variation on each layer, tabulated below in Table 6.2 to Table 6.5 and for Formulations F1, F2 and F4 in the unhydrated and hydrated states.

Table 6.2: Mean distance measured on unhydrated tablets (N=3; in all cases SD<0.01)

Tablet Layer	Distance (mm)		
	F1	F2	F4
L1	0.006	0.020	0.011
L2	0.021	0.010	0.010
L3	0.006	0.013	0.007

Table 6.3: Distance measured (mm) during textural analysis of hydrated F1 tablets (N=3; in all cases SD<6.64)

Coating Variation	Tablet Layer	Distance (mm)				
		15 Minutes	30 Minutes	1 hour	2 hours	4 hours
A	**L2**	0.989	0.962	0.863	1.088	2.100
	L3	1.128	2.791	1.994	3.648	10.879
B	**L1**	1.803	1.551	1.888	2.564	7.708
	L2	1.487	1.575	1.468	1.669	6.996
C	**L1**	0.768	1.533	1.442	3.391	5.156
	L3	1.498	5.391	5.938	5.011	5.799
A+B	**L2**	1.084	1.653	1.893	1.333	2.257
B+C	**L1**	1.482	1.053	1.317	2.628	2.816
A+C	**L3**	1.408	1.598	3.158	2.885	5.168

Table 6.4: Distance measured (mm) during textural analysis of hydrated F2 tablets (N=3; in all cases SD<9.98)

Coating Variation	Tablet Layer	Distance (mm)				
		15 Minutes	30 Minutes	1 hour	2 hours	4 hours
A	**L2**	1.202	1.440	1.254	1.253	3.077
	L3	1.326	1.281	3.577	6.222	4.805
B	**L1**	1.630	1.657	1.605	5.998	5.054
	L2	0.937	2.091	2.323	5.566	4.917
C	**L1**	0.708	1.672	1.217	4.048	1.537
	L3	1.157	1.873	4.853	3.684	5.410
A+B	**L2**	0.906	1.508	1.054	1.539	7.226
B+C	**L1**	0.774	1.393	1.253	2.157	8.091
A+C	**L3**	1.043	1.047	1.911	2.592	5.087

Table 6.5: Distance measured (mm) during textural analysis of hydrated F4 tablets (N=3; in all cases SD<1.931)

Coating Variation	Tablet Layer	Distance (mm)				
		15 Minutes	30 Minutes	1 hour	2 hours	4 hours
A	**L2**	1.145	1.035	1.123	4.991	1.601
	L3	1.038	1.972	2.296	4.118	10.668
B	**L1**	1.535	2.482	2.168	2.803	5.502
	L2	1.114	1.101	1.352	4.277	2.541
C	**L1**	1.626	2.206	1.690	3.725	4.576
	L3	0.967	1.808	2.606	3.733	5.218
A+B	**L2**	1.236	1.276	1.504	4.885	2.763
B+C	**L1**	1.214	2.320	2.065	4.470	4.073
A+C	**L3**	0.927	1.938	2.192	4.398	4.217

Figure 6.3 to Figure 6.5 show the distance the probe could travel before a force of 1N was reached, an indication of the degree of swelling in each layer, for the different coating variations for F1. Typical force-distance profiles are shown in Figure 6.6 over a time-period of 15 minutes to four hours. As can been seen in these figures the distance the probe was able to travel before a force of 1N was reached increased on average as the time for hydration was increased. A strong increase in the penetration distance with swelling time indicates a distinct increase in the gel layer thickness during swelling.

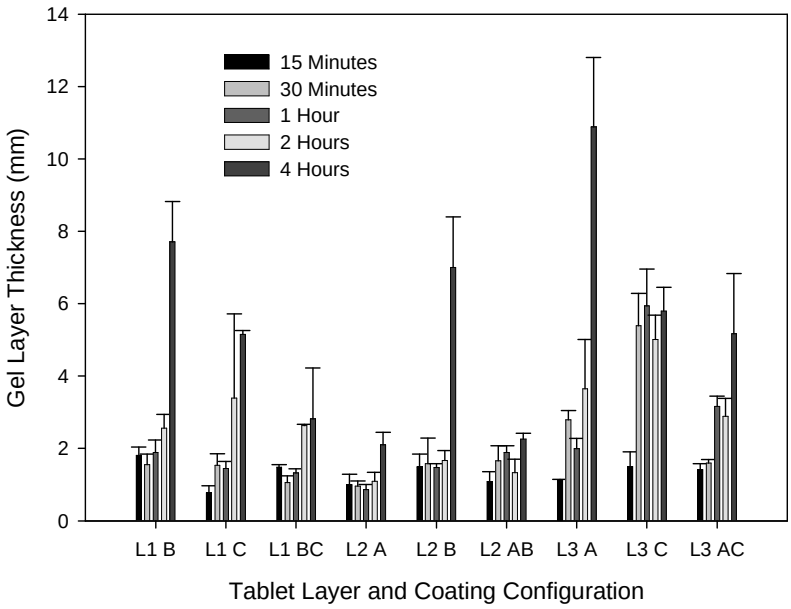


Figure 6.3: Graphical representation of the distance the texture analysis probe was able to penetrate the tablet shown in terms of coating layer variation and hydration time for Formulation F1.

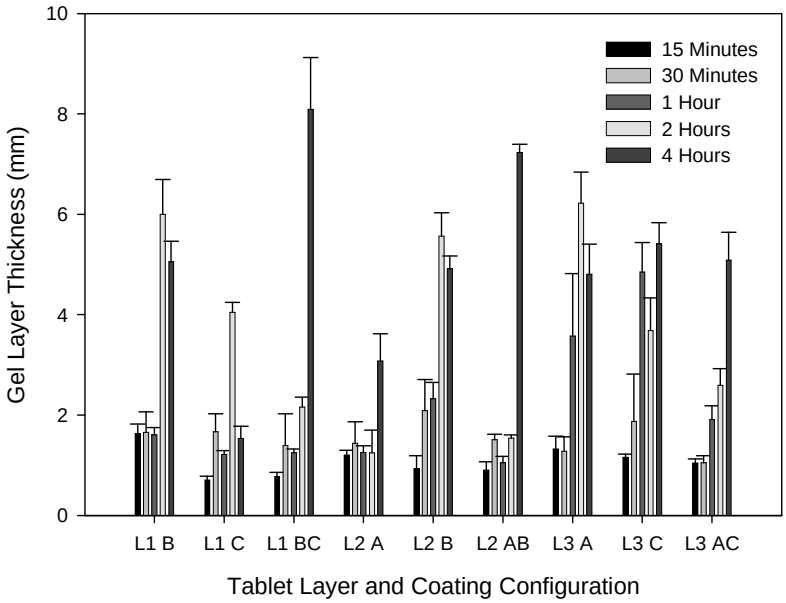


Figure 6.4: Graphical representation of the distance the texture analysis probe was able to penetrate the tablet shown in terms of coating layer variation and hydration time for Formulation F2.

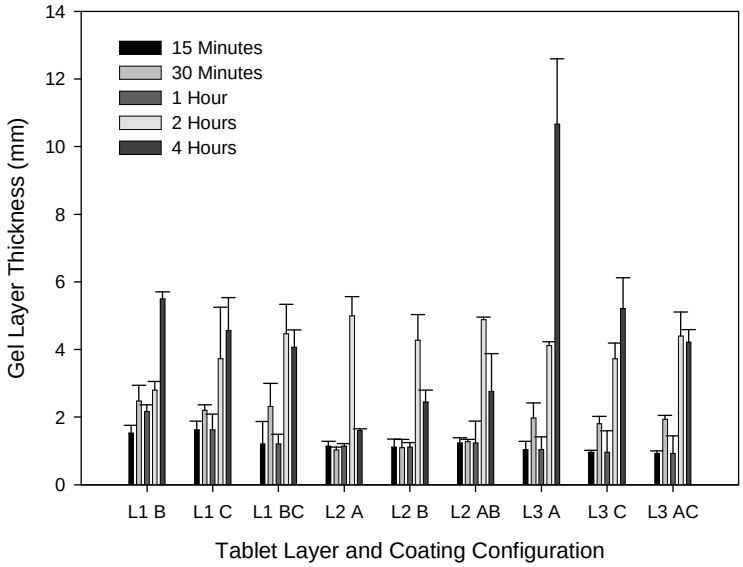


Figure 6.5: Graphical representation of the distance the texture analysis probe was able to penetrate the tablet shown in terms of coating layer variation and hydration time for Formulation F4.

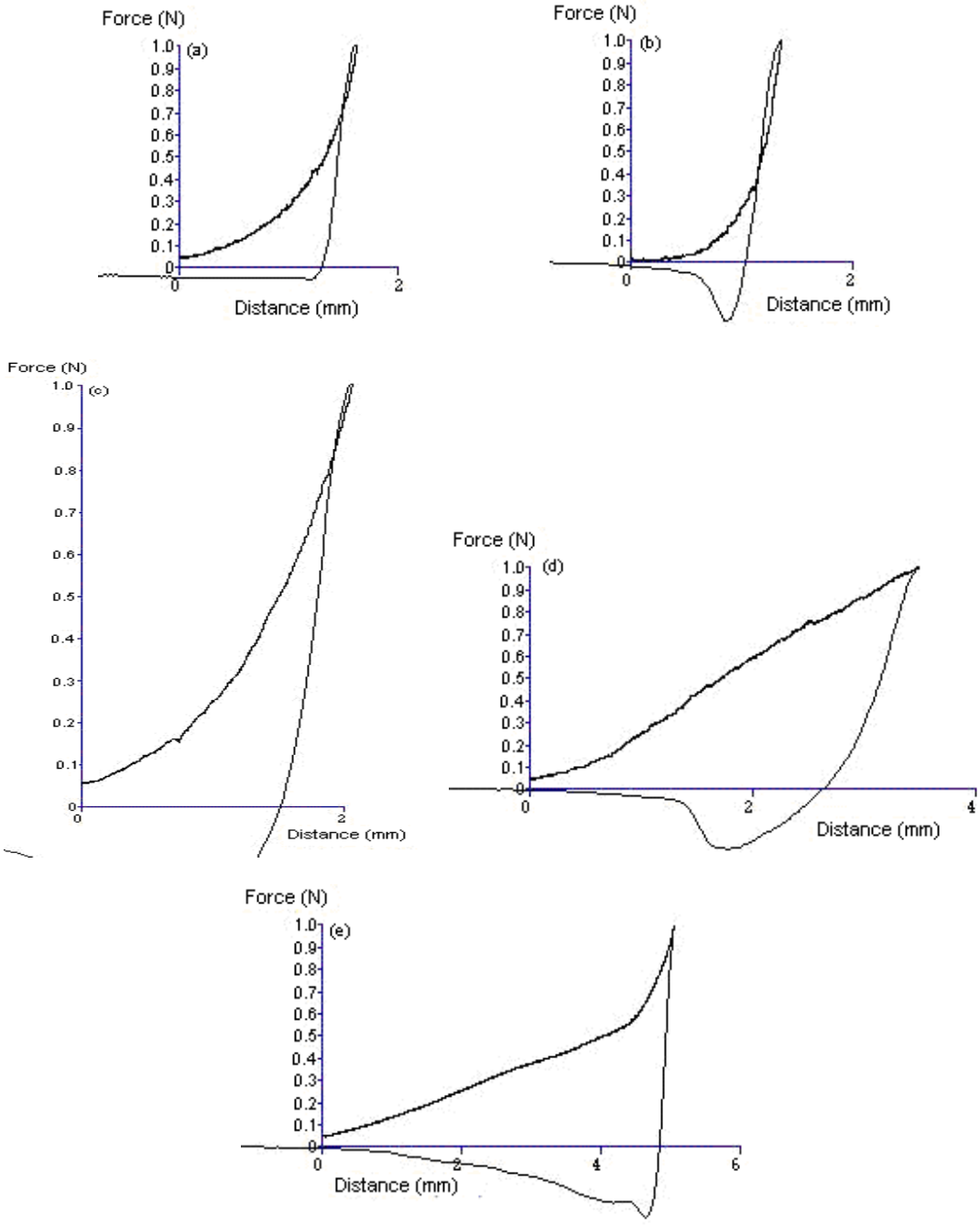


Figure 6.6: Typical force-distance profiles of the triple-layered tablet (Formulation F4) after hydration for (a) 15 minutes; (b) 30 minutes; (c) 1 hour; (d) 2 hours and (e) 4 hours.

The force-distance profiles shown in Figure 6.7 exhibits the distance the probe was able to penetrate in Formulation F4 after 4 hours of hydration for each of the three layers in the triple-layered tablet. From this figure it is evident that layer three, consisting of DC and PEO allowed

the probe to penetrate the furthest, indicating the greater swelling potential of this middle layer of the dosage form.

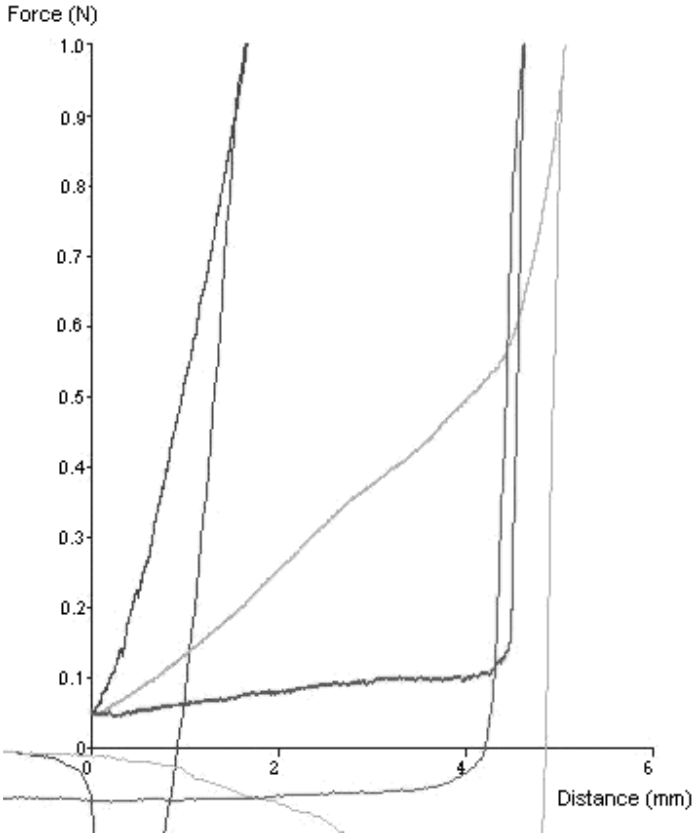


Figure 6.7: Typical force-distance profile of each of the layers in the triple-layered tablet (Formulation F4) after hydration for four hours.

From the data tabulated and illustrated above it can be concluded that layer three, containing the polymer PEO, allowed the probe to penetrate the furthest, owing to its greater swelling potential over the cellulose-based polymers in layers one and two. In Formulation F1 layer three reached a maximum of 10.879mm and 10.668mm in Formulation F4 after four hours of hydration, whilst only 4.805mm in Formulation F2. This could be due to the larger quantity of PEO in Formulations F1 (400mg) and F4 (300mg) while F2 contains only 200mg. If this is viewed in context with the API release percentages of these three formulations, although the swelling method and thus release method remain more complex than such a comparison may allow, the proportion of DC release from Formulation F2 is double that of F1 and F4 after only 45 minutes. This proportion remains at

twice the amount of DC having been released after fours hours when compared to F1 and 1.5 times that of F4. Thus it seems there is a correlation between the quantity of polymer present in the formulation, the extent the dosage form can swell and, the quantity and rate of release of the API.

Information on the gel texture is also provided by the penetration profiles. In the force-distance profile of F4 after a swelling time of 4 hours, it is evident that a force of approximately 0.5N was required to penetrate 4.5mm. For a further penetration of 0.5mm an increase in load of 0.5N was required due to the less hydrated, denser structure if the gel in the inner area of the tablet layer. Subsequently a sharp increase in load was detected, similar to that seen with the unhydrated tablet indicating that the probe had likely reached the dry section of the tablet.

Due to the stronger hydration and corresponding lower polymer concentration the outer areas are characterized by lower gel strength and less resistance to penetration while the inner, less hydrated areas, show greater gel strength in their structure and therefore required higher loads for penetration. The prolonged swelling time produced increase in the penetration distance but also altered the forces required for penetration depth.

6.3.2 Matrix hardness analysis

The mean data produced from the matrix hardness study is tabulated in Table 6.6 in terms of force (N), distance (mm) the probe was able to travel in the compression force was obtained and the time (seconds) taken to reach this force. Figure 6.8 depicts the matrix hardness force-distance diagram of formulation F4.

Table 6.6: Matrix hardness study results (N=3; in all cases SD<0.0997)

Formulation	Force (N)	Distance (mm)	Time (sec)
F1	40	0.9963	2.0283
F2	40	1.0320	2.0987
F4	40	0.9643	1.9667

The difference between the matrix hardness on the unhydrated tablets was minimal with Formulation F2 allowing the probe to penetrate the furthest (1.0320mm) and Formulation F4 allowing the probe to penetrate the least (0.9643mm). These findings correlate to those of the time taken to reach the set force of 40N with Formulation F2 once again taking the longest time at 2.0987sec to reach this force. As there is little difference in the matrix hardness between these formulations in the unhydrated state it may be deduced that the complexity of the swelling and hence release from the dosage form, is present when it undergoes hydration.

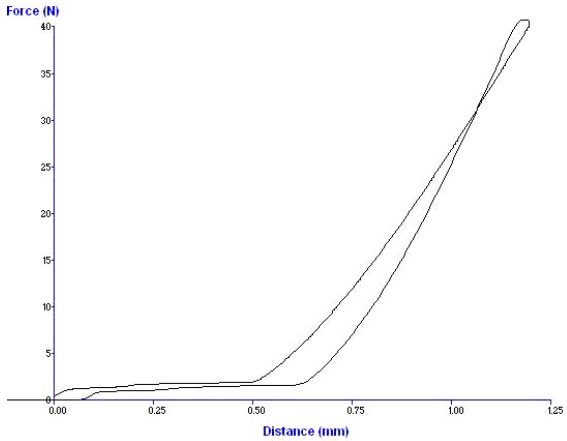


Figure 6.8: Typical force-distance profile of Formulation F4 depicting matrix hardness of the unhydrated tablet.

6.4 Concluding Remarks

Final product physicomechanical analyses undertaken on both the optimal formulation (Formulation F4) evident from previous studies described in Chapter 5, as well as the two theoretically most diverse formulations from the Extreme Vertices Design of Experiments (DoE) (Formulations F1 and F2), showed that layer three, consisting of DC and PEO allowed the probe to penetrate the furthest, indicating the greater swelling potential of this polymeric layer of the FDC tablet.

It appeared that the as the quantity of PEO present in the formulation increased, the distance the probe was able to penetrate also increased. Taking into account the drug release percentages of

these three formulations, although the swelling method and thus release method remain more complex than such a comparison may allow, the proportion of DC release from Formulation F2 is double that of F1 and F4 after only 45 minutes.

As there was little difference in the matrix hardness between these formulations in the unhydrated state it may be deduced that the vast complexity and degree of swelling and hence release from the FDC dosage form, is ignited only when the tablet undergoes hydration.

CHAPTER SEVEN

IN-PROCESS VALIDATION TESTING OF THE OPTIMIZED FIXED DOSE COMBINATION DELIVERY SYSTEM

7.1 Introduction

In order to assess the in-process manufacturability of the invention each of the formulations in the Design of Experiments (DoE) phase underwent the following tests in order to validate the reproducibility of the process. This Chapter focuses on the in-process validation of the delivery system during manufacture.

7.2 Materials and Methods

7.2.1 Materials

The materials used in Chapter Seven are identical to those used in Chapter Four. Only commonly used, pharmaceutical-grade excipients that are routinely employed by the pharmaceutical industry were considered for use in this study.

7.2.2 Length, width and thickness

The thickness and length of each of the 10 formulations was assessed using a calibrated set of vernier callipers (Tesa, Switzerland). The mean value of 10 determinations was recorded.

7.2.3 Hardness

A tablet was placed lengthwise between the metal jaws on the Hardness Tester (Pharma Test Hardness Tester PTB 301, Pharma Test, Hainburg, Austria]. The point at which the tablet fractures is recorded as the hardness of the tablet in Newtons. The mean of ten single tablet determinations is recorded as the hardness of the tablets.

7.2.4 Friability

As the average tablet mass is more than 650 mg, the weight of ten tablets shall be used. The tablets were placed into the Friabilator drum (Pharma Test Friabilator PTF, Pharma Test, Hainburg, Austria) and run for four minutes equivalent to 100 revolutions. On completion of the test, the tablets were removed from the Friabilator, dusted to remove any loose particles and reweighed. The percentage difference between the initial and final weights were recorded as the percentage friability. A robust formulation should not have more than 1%w/w mass loss during friability testing and not more than two tablets should show evidence of capping.

7.2.5 Uniformity of mass

Twenty tablets are individually weighed at random during the compression phase of manufacture on an analytical balance. The average mass is determined. Not more than two tablets may deviate from the average by more than the percentage shown in Table 7.1 below and none may deviate by more than twice that percentage, as detailed in the British Pharmacopoeia (BP) 2009.

Table 7.1: Percentage deviation allowed relative to the average tablet mass

Average tablet mass	***Percentage deviation (%)***
80 mg or less	10
Between 80 mg and 250 mg	7.5
More than 250 mg	5

7.2.6 Disintegration time

One tablet was placed in each of the six cylindrical tubes of the disintegration apparatus (Pharma Test Disintegration Tester PTZ1, Pharma Test, Hainburg, Austria). The aqueous medium in which the tablets disintegrate was kept at 37±2°C for the duration of the test. The disintegration time was recorded as the time at which the last tablet disintegrated. A standard acceptable disintegration time for immediate release tablets should be not more than 15 minutes.

7.3 Results and Discussion

7.3.1 Length, width and thickness

The tablet tooling used to compress the formulations for each of the ten DoE formulations was a caplet-shaped 9mm x 22mm set. Hence the expected length of the tablets is 22mm and the width is 9mm. The thickness of the tablets is determined from the compression force applied during the compression run. The hardness setting was kept unaltered throughout these initial manufacturing. The mean length, width and thickness for each formulation are displayed in Table 7.2.

Table 7.2: Mean in-process length, width and thickness results of the DoE formulations (N=10; in all cases SD<0.0059)

Formulation	*Length (mm)*	*Width (mm)*	*Thickness (mm)*
F1	21.98	9.08	5.77
F2	22.03	9.11	5.72
F3	22.04	9.11	5.64
F4	22.05	9.08	5.78
F5	22.08	9.10	5.67
F6	22.04	9.09	5.77
F7	22.03	9.10	5.79
F8	21.98	9.09	5.72
F9	21.99	9.09	5.79
F10	21.99	9.08	5.70

Each of these results were within a limit of ±3% indicating the uniformity of the length, width and thickness of the tablets among the differing formulations. These limits translated to 21.34 to 22.66 mm for length, 8.73 to 9.27 mm width and 5.58 to 5.92 mm for thickness.

7.3.2 Crushing strength

The mean crushing strength or hardness reading for each formulation is displayed in Table 7.3.

Table 7.3: Mean hardness results of the DoE formulations (N=10; in all cases SD<0.17)

Formulation	*Hardness (N)*
F1	55
F2	53
F3	61
F4	57
F5	55
F6	54
F7	54
F8	60
F9	58
F10	60

Each of these results was within the limit of 50 to 70N indicating the uniformity of the hardness of the tablets among the differing formulations.

7.3.3 Friability

The mean percentage mass loss for each formulation is displayed in Table 7.4, as well as the capping status of each formulation.

Table 7.4: Mean friability results of the DoE formulations (N=10; in all cases SD<0.98)

Formulation	*Mean percentage mass loss (%)*	*Number of tablets capped*
F1	0.02	0
F2	0.30	0
F3	0.04	0
F4	0.08	0
F5	0.12	0
F6	0.24	0
F7	0.15	0
F8	0.15	0
F9	0.47	0
F10	0.33	0

Each of these results was within the limit of less than 1%m/m loss indicating suitable friability of the formulations. It can therefore be deduced that these formulations show sufficient strength to undergo coating, should it be necessary as well as to endure movement within a container-closure system during transport or patient use. The lack of capping of the tablets shows that the layer boundaries are suitably integrated to refrain from separating under simulated in-use conditions.

7.3.4 Uniformity of mass

The theoretical mass of all the tablets in the ten formulations is 1031.68mg. The uniformity of mass limits for a tablet of this size is then:

2/20 tablets may lie outside the range of 980.10mg and 1083.26mg and

0/20 tablets may lie outside the range of 928.51mg and 1134.85mg.

The mean mass of twenty tablets of each of the ten formulations is listed in Table 7.5.

Table 7.5: Mean uniformity of mass results of the DoE formulations (N=20)

Formulation	*Mean mass (mg)±SD*
F1	1.0360 ± 0.0017
F2	1.0166 ± 0.0059
F3	1.0219 ± 0.0039
F4	1.0322 ± 0.0044
F5	1.0221 ± 0.0030
F6	1.0323 ± 0.0010
F7	1.0246 ± 0.0005
F8	1.0304 ± 0.0013
F9	1.0283 ± 0.0030
F10	1.0271 ± 0.0030

From the data above it can be seen that the average masses of each of the ten formulations fell well within both pharmacopoeial limits (BP 2009 and USP 32), indicating the suitable uniformity of mass of these formulations.

7.3.5 Disintegration time

Six tablets of each formulation were subjected to a standard disintegration test. As the polymeric nature of these tablets is such that a large degree of swelling takes place and that this swelling takes place over a period of time, as well as the complexity due to the triple-layered nature of the tablet, the point of complete disintegration could not be documented as the swollen matrix is present to a greater or lesser degree at the end of a 24 hour dissolution run. The point at which disintegration was considered to have been competed was therefore taken as the time at which no white powder or unswollen material was present. The data represented below in Table 7.6 is the time at which this condition was met for each of the six tablets undergoing the test.

Table 7.6: Disintegration results of the DoE formulations

Formulation	*Disintegration time (hours:minutes)*
F1	4h:38min
F2	5h:43min
F3	5h:21min
F4	4h:57min
F5	6h:02min
F6	5h:37min
F7	5h:12min
F8	4h:46min
F9	4h:19min
F10	4h:11min

7.4 Concluding Remarks

Each of the requirements of the abovementioned in-process tests, in accordance with the BP 2009, was met by each of the ten formulations. This validates the manufacturability and reproducibility of each of the formulations, suggesting that, minimal complications during eventual scale-up should be experienced as the manufacturing process and in deed, formulations themselves are sufficiently sound.

CHAPTER EIGHT

CONCLUSIONS AND RECOMMENDATIONS

8.1 Conclusions

This study aimed at producing a novel, rate-modulated, fixed-dose analgesic formulation for the treatment of mild to moderate pain. The fixed-dose combination (FDC) rationale of paracetamol (PC), tramadol hydrochloride (TM) and diclofenac potassium (DC) takes advantage of previously reported analgesic synergy of PC and TM as well as extending the analgesic paradigm with the addition of the anti-inflammatory component, DC.

The study involved the development of a triple-layered tablet delivery system with the desired release characteristics of approximately 60% of the PC and TM being made available within 2 hours to provide an initial pain relief effect and then sustained zero-order release of DC over a period of 24 hours to combat the on-going effects of any underlying inflammatory conditions. The triple-layered tablet delivery system should thus provide both rapid onset of pain relief as well as potentially address an underlying inflammatory cause.

The design of a novel triple-layered tablet allowed for the desired release characteristics to be attained. During initial development work on the polymeric matrix it was discovered that only when combined with the optimized ratio of the release retarding polymer polyethylene oxide (PEO) in combination with electrolytic-crosslinking activity, provided by the biopolymer sodium alginate and zinc gluconate, could the 24 hour zero-order release of DC be attained. It was also necessary for this polymeric matrix to be bordered on both sides by the cellulosic polymers containing PC and TM. Thus the application of multi-layered tableting technology in the form of a triple-layered tablet would be capable of attaining the rate-modulated release objectives set out in the study. The induced barriers provided by the three layers also served to physically separate TM and DC, reducing the likelihood of the bioavailability-diminishing interaction noted in United States Patent 6,558,701 and detected in the DSC analysis performed as part of this study.

The designed system provides significant flexibility in modulation of release kinetics for drugs of varying solubility. The suitability of the designed triple-layered tablet delivery system was confirmed by a Design of Experiments (DoE) statistical evaluation, which revealed that Formulation F4 related closest to the desired more immediate release for PC and TM and the zero-order kinetics for DC. The results were confirmed by comparing Formulation F4 to typical release kinetic mechanisms described by Noyes-Whitney, Higuchi, Power Law, Pappas-Sahlin and Hopfenberg. Using f_1 and f_2 fit factors Formulation F4 compared favourably to each of the criteria defined for these kinetic models.

The Ultra Performance Liquid Chromatographic (UPLC) assay method developed displayed superior resolution of the active pharmaceutical ingredient (API) combinations and the linearity plots produced indicated that the method was sufficiently sensitive to detect the concentrations of each API over the concentration ranges studied. The method was successfully validated and hence appropriate to simultaneously detect the three APIs as well as 4-aminophenol, the degradation product related to PC.

Textural profile analysis in the form of swelling as well as matrix hardness analysis revealed that an increase in the penetration distance was associated with an increase in hydration time of the tablet and also an increase in gel layer thickness. The swelling complexities observed in the delivery system in terms of both the PEO, crosslinking sodium alginate and both cellulose polymers as well as the actuality of the three layers of the tablet swelling simultaneously suggests further intricacies involved in the release kinetics of the three drugs from this tablet configuration.

8.2 Recommendations

Further work to validate the scale-up production process of the layered tablet on a multi-layered industrial tablet press is recommended. Difficulties are not anticipated due to successful in-process validation of the tableting process performed under the small-scale manual process used in this study. Clinical investigations resulting in confirmatory evidence of the theoretical synergistic and clinically relevant analgesic therapeutic effects of the combination of paracetamol, tramadol hydrochloride and diclofenac potassium would also be required in the process of making this novel dosage form accessible to the many potential beneficiaries. *In vivo* animal studies in this field would allow for hypothesis as to varying analgesic API combinations that would benefit from formulation in this polymeric triple-layered tablet delivery system, as well as API combinations outside the pain portfolio.

Modified release dosage forms, such as the one developed in this study, have gained widespread importance in recent years and offer many advantages including flexible release kinetics and improved therapy and patient compliance.

Several advances are anticipated in the clinical study of pain, which will provide advanced novel therapies for patients. Remedial paradigms are transforming from single-API trials to multiple-API therapies and research in multiple-API therapies are required to better alleviate pain in patients. Increased knowledge in the complexity of pain pathways is responsible for this necessity for new strategies involving FDC medication (Guindon et al., 2007).

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APPENDICES

APPENDIX 1

LETTER OF WAIVER FOR ANIMAL ETHICS APPLICATION

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

7 York Road, Parktown, 2193 South Africa • Telegrams 'Witsmed' • Telephone (011) 647-1111 • Fax: (011) 643-4318

Ref: W-CJ-070312-1
12/03/2007

TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: **Kim Hobbs (9802481M)**

Project title: **Formulation and evaluation of a novel rate-modulated, fixed-dose analgesic combination for the treatment of mild to moderate pain.**

Reason: This is a laboratory-based study. There are no human participants.

UNIVERSITY OF THE WITWATERSRAND
PROF PE CLEATON-JONES
HREC (MEDICAL)
2007 -03- 12
JOHANNESBURG

Professor Peter Cleaton-Jones
Chair: Human Research Ethics Committee (Medical)

APPENDIX 2

ABSTRACTS FROM CONFERENCES

Rate-Modulating Effects of Cellulose and Ethylene Oxide-Based Polymers on the Release Kinetics of Combined APIs from Multi-Configured Tablet Formulations

Kim M. Hobbs[1], Viness Pillay[2*], Yahya E. Choonara [2] and Bradley R. Parsons[1]
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Purpose:
The aim of this study was to investigate the possible rate-modulating effects of different cellulose and ethylene oxide-based polymers on the release kinetics of an analgesic combination, as well as to develop an analytical method capable of simultaneously quantifying the concentrations of combined active pharmaceutical ingredients (APIs) such as tramadol hydrochloride and paracetamol.

Methods:
The suitability of a high performance liquid chromatographic (HPLC) method was confirmed by performing linearity plots for the combined APIs. Samples were processed by gradient elution techniques using a Waters 2695 Alliance Separations Module and Waters 2996 Photo Diode Array detector. Initial dissolution characteristics of the combined APIs and individual polymers were determined by producing experimental batches of tablets on a Manesty Single Punch Type F3 machine by direct compression into monolithic matrix and multi-layered systems. Dissolution studies were conducted using a USP rotating paddle method (Hanson Virtual Instruments SR8 Plus Dissolution Test Stations) at 50 rpm in phosphate buffer pH 6.8 (900mL, 37℃±0.5℃) for each formulation employing an autosampler (Hanson Research Auto Plus Maximizer and AutoPlus^{TM} MultiFill^{TM}). Samples of 1.6mL were withdrawn over a period of 20 hours and analysed via HPLC.

Results:
The assay method developed displayed superior resolution of the API combinations and the linearity plots produced indicated that the method was sufficiently sensitive to detect the concentrations of each API over the concentration ranges studied (R^2=0.99 for paracetamol and R^2=0.99 for tramadol hydrochloride). The dissolution profiles obtained with cellulose and ethylene oxide-based polymers displayed flexible yet rate-modulating drug release kinetics for each API. Typical first-order release kinetics was obtained from the monolithic configurations over a period of 20 hours. In addition, the application of multi-layered tableting technology allowed for the attainment of both prolonged first-order ($n \geq 0.5$) and desirable zero-order ($n > 0.9$) release kinetics.

Polymeric Configurations for the Alteration of Kinetic Release Mechanisms

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Purpose

Three common mechanisms by which drugs are released from polymeric systems include dissolution, diffusion and erosion. Water-soluble drugs tend to diffuse across the polymeric gel layer while poorly water-soluble drugs are released due to erosion of the gel layer. The aim of this study was to investigate the potential release altering mechanistics of different cellulose and ethylene oxide-based polymers, as well as in situ cross-linking alginate and pectin biopolymers, on the dissolution profile of an analgesic combination.

Methods

Direct compression and wet granulation techniques were used to produce experimental batches of tablets in monolithic matrix and multi-layered systems, on a Manesty Single Punch Type F3 machine. In situ cross-linking of various alginate, pectin and eudragit polymers with salts such as zinc gluconate was also investigated for an influence on the release characteristics of the solid dosage system.

Dissolution studies were conducted using a USP rotating paddle method (Hanson Virtual Instruments SR8 Plus Dissolution Test Stations) at 50 rpm in phosphate buffer pH 6.8 (900mL, 37℃±0.5℃) employing an autosampler (Hanson Resear ch Auto Plus Maximizer and AutoPlus™ MultiFill™), for each formulation. Samples of 1.6mL were withdrawn over a period of 12 to 20 hours and analysed via HPLC. In order to establish site-specific release potential of the polymeric dosage form, formulations consisting of cellulose, polyethylene oxide and alginate polymers were subjected to dissolution studies in simulated gastric fluid pH 1.2 without pepsin.

Results

The application of multi-layered tableting technology allowed for the attainment of both prolonged first-order ($n \geq 0.5$) and desirable zero-order ($n > 0.9$) release kinetics. Typical first-order release kinetics was obtained from the monolithic configurations over a period of 20 hours. Site-specific delivery via the utilization of hydrophilic ethylene-oxide based polymers was obtained. The resulting dissolution profiles displayed varied drug release kinetics for each API, dependant on the polymeric configuration and concentration employed.

APPENDIX 3

PATENT

SA Provisional Patent Application 2008/07122

PROVISIONAL SPECIFICATION

Applicant: Adcock Ingram Healthcare (Pty) Limited
Cnr Adcock Ingram and Sabax Roads,
Aeroton,
Johannesburg

Inventors: Kim Melissa Hobbs
Viness Pillay
Yahya Essop Choonara
Bradley Ryan Parsons

Title: Rate Modulated Delivery of Drugs from a Composite Delivery System.

RATE MODULATED DELIVERY OF DRUGS FROM A COMPOSITE DELIVERY SYSTEM

FIELD OF THE INVENTION

This invention relates to a multi-configured pharmaceutical dosage form and, more particularly, to a multi-layered tablet pharmaceutical dosage form or various multi-unit formulations suitable for the rate-modulated delivery of single or multiple pharmaceutical compositions.

BACKGROUND TO THE INVENTION

With pain management, it is necessary to develop methods of facilitating treatments that promote compliance with prescriptions and simplify prescribing without increasing adverse effects. Poly-pharmacy is seen as a barrier to prescription compliance and highlights a need for the development of fixed dose combinations which allow the number of tablets taken daily to be reduced, but with no loss in efficacy or an increase in the incidence of side effects. The expected benefits of analgesic combinations include reduced onset of action, increased duration of action, improved efficacy, reduced opioid intake and reduced adverse reactions.

The combining of analgesic drugs with differing mechanisms of nociceptive pain modulation offers benefits including synergistic analgesic effects where the individual agents or components of a therapeutic composition act in a greater than additive manner, and a reduced incidence of side effects. The combinations are most effective when the individual agents act *via* unique analgesic mechanisms and act synergistically by inhibiting multiple pain pathways. This multimodal coverage offers more effective relief for a broader spectrum of pain. Opioids are considered first line medication for relieving severe nociceptive pain but are inadequate in controlling dynamic pain as well being associated with significant side effects. Alternative pain relief using non-opioid analgesics historically relied on paracetamol supplemented with non-steroidal anti-inflammatory drugs (NSAIDs).