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The interactive potential of polyethylene oxide as a tool to adjust drug delivery

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THE INTERACTIVE POTENTIAL OF POLYETHYLENE OXIDE

AS A TOOL TO ADJUST DRUG DELIVERY

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A Research Report submitted to the Faculty of Health Sciences,

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

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

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October 2010

DECLARATION

I, Fatima Ismail, 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.

…….

Signed this ..... day of..... 2010

ABSTRACT

PEO (Polyethylene Oxide) is one of the most important biodegradable polymers used in pharmaceutical formulations, mainly because of its non-toxicity, high water-solubility and swellability, insensitivity to the pH of the biological medium and flexibility during dosage form production (Kim, 1995; Picker-Freyer, 2006; Kiss et al., 2008).

The lack of studies attempting to achieve controlled drug delivery of hydrophilic drugs has provided us with motivation to use a drug of this nature but we have combined it with a PEO-electrolyte combination in order to control drug delivery. This study was aimed at modifying the physicochemical and physicomechanical properties of PEO in order to influence the hydrodynamic diffusion of its three-dimensional network. Hence, through such alteration, it was envisaged that if drug is loaded into its PEO matrix, its solubility and dissolution can be regulated in order to achieve zero-order influx of dissolution medium. The interaction between PEO and electrolytes may allow for precipitation of ions on the polymer backbone. This would lead to the attraction of water molecules to the ions. As a result, this would cause dehydration of the polymer matrix, hence minimising its mobility and relaxation.

In this study, 36 PEO-electrolyte combinations were prepared by combining a high molecular weight PEO with different statistically planned combinations of electrolytes. The 36 formulations were microscopically analyzed and subjected to textural analysis. The salted-out PEO-electrolyte combinations were then further selected and analyzed. Assessment of the molecular structural transition and thermal compatibility analysis indicated minimal interaction between the electrolytes and PEO indicating that the polymer-electrolyte combination was stable enough to be employed as a medium for controlled drug release. The polymer-electrolyte combination was combined with a model drug, diphenhydramine HCl to form a tablet matrix and then subjected to dissolution. *In vitro* drug release varied depending on the different electrolytes and their combinations. The type of polymer, molecular weight of the polymer, concentration of the polymer, different electrolyte combinations and solubility of the drug played a significant role in controlling drug release.

After optimization of the fracture force, resilience and work performed values, results have established that equal concentrations of Na_2CO_3 and K_2HPO_4 are desirable for achieving controlled release of drug from the salted-out PEO combination in a zero-order manner. Furthermore, Na_2CO_3 and K_2HPO_4 had a significant influence on controlling the release of drug from the salted-out PEO combination due to crosslinking between PEO and the electrolytes ultimately leading to zero-order release kinetics. The salting-out of PEO notably modified the physicochemical and micromechanical properties of basic PEO, which demonstrably enhanced the ability of the sample to achieve controlled drug release. The formulation strategy employed in this study where in our sample drug, diphenhydramine HCl was combined with a PEO-electrolyte combination has shown promising results in regulating drug release.

ACKNOWLEDGEMENTS

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 perseverance, patience, kindness and support throughout this study.

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

To my husband Yusuf for his endless support, encouragement, assistance and advice.

To Maria for your time, assistance and patience both to me and to my precious babies.

To my mum, my sister-in-laws and to my brothers, Yusuf and Suleiman for their encouragement, support and financial assistance.

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List of Abbreviations

CP	Carbopol
CVP	Carboxyvinyl Polymer
DoE	Design of Experiments
DSC	Differential Scanning Calorimetry
DTZ	Diltiazem
FTIR	Fourier Transform Infrared
GIT	Gastrointestinal Tract
NP	Nifedipine
NR	Natural Rubber
OCAS	Oral Controlled Absorption System
OIT	Oxidative Induction Time
PBS	Phosphate Buffer Saline
PCL	Polycaprolactone
PEG	Polyethylene Glycol
PEO	Polyethylene Oxide
PLA	Poly(lactide)
PVA	Polyvinyl Alcohol
SIF	Simulated Intestinal Fluid
USP	United States Pharmacopoeia

SECTION 1

LITERATURE REVIEW AND MOTIVATION FOR STUDY

1.1 Introduction

Polymers have found applications in diverse biomedical fields such as tissue engineering, implantation of medical devices, artificial organs, prostheses, ophthalmology, dentistry and bone repair (Jagur-Grodzinski, 1999; Dasgupta et al., 2002; Aray et al., 2003; Dasbach et al., 2003; Alarcon et al., 2005). Polymer based delivery systems enable controlled slow release of drugs into the body. They also make possible the targeting of drugs to sites of inflammation or tumours (Jagur-Grodzinski, 1999).

Biodegradable polymers have become increasingly popular as carriers in the design of drug delivery systems (Park et al., 2005). Polymeric materials suitable for biomedical applications must be 'biocompatible' and 'biodegradable' and harmful degradation products should not be generated as a result of their biodegradation. Functional groups located on the polymer as well as its molecular structure are usually responsible for the biocompatibility and/or biodegradability of polymers and may impart either therapeutic or/and toxic characteristics. For examples, carboxylic groups induce therapeutic activity of many drugs (Jagur-Grodzinski, 1999). As these polymers degrade in the body to smaller molecular weight compounds that are either metabolized or excreted, they obviate the need for removal of the polymeric carrier after the drug load is bioeroded (Diamente et al., 2006; Duncan et al., 2006). In this

regard, biocompatibility and lack of immunogenicity makes polyethylene oxide (PEO) an important polymer for biomedical and drug delivery applications (Harris, 1992; Harris and Zalipsky, 2000; Thompson et al., 2008). PEO is a free flowing, thermoplastic polymer synthesized by the heterogeneous catalytic polymerization of ethylene oxide monomer and is commercially available in a wide range of molecular weights (100,000–8,000,000g/mol) (Crowley et al., 2002).

PEO is usually selected as the hydrophilic block with a role to provide a hydrated steric barrier in order to minimize the adsorption of circulating blood components (Park et al., 2005). When bound to an immunogenic substrate having a desirable function in the body, PEO tends to reduce or eliminate immune responses so that the organism can tolerate the substance (Dhawan et al., 2005). In addition, the PEO has been shown to prevent opsonization and facilitate the recognition of drug delivery carriers by the reticuloendothelial system (RES). Thus, these properties of PEO allow drugs to be administered over prolonged periods of time (Dunn et al., 1988; Park et al., 2002; Soo et al., 2002; Li et al., 2004; Park et al., 2005).

PEO is an inherently dissipative polymer and a non-ionic surfactant of great scientific and technological interest for a wide variety of applications, many of which depend on the properties of the polymer in aqueous solution (Rosner, 2001). Inherently dissipative polymers are co-polymers with a high degree of resistivity (Rosner, 2001; Aray et al., 2003). PEO is one of the most important polymers used in pharmaceutical formulations, mainly because of its non-toxicity, high water-solubility and swellability, insensitivity to the pH of the biological medium and flexibility during

dosage form production (Kim, 1995; Picker-Freyer, 2006; Kiss et al., 2008). PEO is completely soluble in cold and warm water in all ratios due to hydration of the ether oxygen moiety on the polymer backbone (Hong et al., 2008). The inclusion of the oxygen atom within the polyethylene structure enhances its polar character, and facilitates the attraction of water and other ions (Rosner, 2001).

PEO can be chemically modified and reacted with, or adsorbed onto, other molecules and surfaces. Sophisticated applications for PEO have increased the demand for PEO oligomers with tailored functionalities and hetero-bifunctional PEO is often needed. When bound to a water insoluble compound, the resulting PEO conjugate generally displays increased water solubility or dispersibility (Li et al., 1996; Harris et al., 2003; Zubarez et al., 2006). Since the repeating ether units of PEO are essentially non-reactive, these oligomers must be reacted with, or adsorbed onto, other compounds through terminal or pendant functional groups. Examples include PEO with thiol or carboxylic acid end groups that have been adsorbed onto metal or metal oxide surfaces (Otsuka et al., 2001; Zhang et al., 2002; Harris et al., 2003; Uchida et al., 2005; Zhang and Zhang, 2005; Zhang et al., 2007; Thompson et al., 2008).

1.2 The Role of Polyethylene Oxide in Controlled-Release Drug Delivery Systems

Controlled release of therapeutic agents remains a huge challenge in drug delivery (Lyons et al., 2008). Repeated administration of a drug in order to maintain drug concentration within a therapeutic window may cause serious side effects, which in

many cases necessitates the patient to stop taking the medication (Geever et al., 2006). With conventional dosage forms, high peak blood concentrations may be reached soon after administration with possible side-effects related to the transiently high concentrations (Lyons et al., 2008).

The well-known properties of PEO and its regulatory acceptability have helped extend its application to various controlled-release drug delivery systems (Dhawan et al., 2005; Hong et al., 2008). PEO gels and other aggregates of PEO are also superior candidates for controlled drug delivery purposes (Aray et al., 2003).

1.2.1 Release mechanisms from PEO-based monolithic drug delivery systems

The release rate of a dissolved or dispersed drug from a polymeric matrix introduced in a specific environment strongly depends on the nature of the diffusion and sorption processes involving the polymer/environment system and the polymer/drug system. The various mechanisms that control drug release with respect to PEO are briefly discussed hereunder.

i. Diffusion-controlled PEO matrices

   The dissolved drug will diffuse from a matrix which does not actively interact with the external environment according to an ordinary diffusion law.

ii. Swelling-controlled PEO matrices

   Completely different drug release behavior is observed for hydrophilic polymers such as PEO when water sorption is followed by significant polymer

swelling. Zero-order release kinetics may be achieved which swells at a constant rate and with a constant penetration surface area, but only if the counter diffusion of the solute molecules is rapid compared to the swelling rate.

iii. Intermediate cases

There are intermediate cases in which both the swelling and the diffusive control of PEO are important during drug release.

iv. Polymer swelling and dissolution-controlled PEO matrices

Incorporation of hydrophilic polymers such as PEO into monolithic matrices leads to modification of drug release due to swelling and erosion of the polymers (Kim, 1998). PEO swells and forms a compact gel layer on the surface of the tablet which is responsible for the controlled drug release. Only once the gel layer is formed, can controlled release be expected. Prior to this point, formulations have almost immediate release dissolution profiles (Petrović et al., 2009). Either swelling or dissolution can be the predominant factor for a specific type of polymer, but in most cases drug release kinetics is a result of a combination of these two mechanisms (Lee and Lewis, 1981; Tahara et al., 1995; Effentakis and Buckton, 2002; Wu et al., 2005). The controlling mechanism of drug release from PEO tablets is dependent upon the drug solubility, drug loading, the addition of a water-soluble excipient, and the molecular weight of PEOs (Petrović et al., 2009).

Among different technologies used in controlled drug delivery, hydrophilic matrix systems are the most popular because of the simplicity of formulation, ease of

manufacturing, low cost, FDA acceptance, and applicability to drugs with a wide range of solubility (Durig and Fassihi, 2002; Sako et al., 2002; Williams et al., 2002; Jamzad and Fassihi, 2006). Various factors can influence the drug release kinetics from hydrophilic matrices (Pillay and Fassihi, 1999; Jamzad et al., 2005). The main determining factors of a hydrophilic polymer-based matrix are the swellability and erodibility of the polymer matrix, as well as the diffusivity of drug molecules. Besides the concentration gradient between the dosage form and the release medium, this latter property depends highly on the size, molecular mass and solubility of the drug molecule, and the extent and nature of the drug–polymer interaction. On the other hand, swellability and the erodibility of the matrix also depend on the molecular mass and hydration tendency of the polymer, as well as the interaction between polymer molecules. In the case of amorphous or partly amorphous polymers, this latter property can strongly be influenced by a phenomenon known as physical ageing. As such polymers are not in equilibrium below their glass transition temperature, they usually undergo spontaneous, although slow transformations towards low-energy equilibrium (Kiss et al., 2008). A study conducted by Kiss and co-workers (2006), revealed that physical ageing of two types of PEO could be tracked by the combination of differential scanning calorimetry, positron annihilation lifetime spectroscopy and scanning electron microscopy. Structural changes, i.e. an increase in the degree of crystallinity and volume relaxation could be observed even after a short storage time (4 weeks), which highlighted the importance of the effects of physical ageing on the properties of dosage forms comprising PEO (Kiss et al., 2006; 2008). The effect of physical ageing on the drug release behavior of several polymers and lipids was studied and can be found in the literature but not for PEO

(Lovrecich et al., 1996; Vincente et al., 2000; Nafee et al., 2003; Zelkó and Süvegh, 2005, Kiss et al., 2008).

1.2.2 *In Vitro* versus *in vivo* drug release from PEO matrices

PEO matrices can release drugs *in vitro* stably over a long period. However, it has also been shown that a matrix tablet consisting of drug and PEO failed to release the drug sufficiently *in vivo*, even though it successfully achieved extended release *in vitro* (Sako et al., 1996). This was due to a difference in hydration conditions which affected the formation of a hydrogel. Abundant water is available for the formation of a PEO hydrogel in the *in vitro* dissolution test, but the water content in the gastrointestinal tract (GIT) varies by site, i.e., there is ample water in the upper GIT (stomach and small intestine), but little water is available in the lower GIT including the colon. The discontinuous *in vivo* drug release from PEO matrices was caused by insufficient PEO hydration due to its slower rate of swelling. It was found that only 22% of the polymer in various formulations became hydrated within 2 hours. It has been reported that PEO matrices absorb water gradually to reach maximum swelling at approximately 8 hours, which is much longer than the time that the preparations were retained in the upper GIT, where digestive juices are abundant (Davis et al., 1986; Wilding et al., 1995; Maggi et al., 2000; Kojima et al., 2008).

A study by Kojima and co-workers (2008), demonstrated that a combination of polyethylene glycol (PEG) and PEO was useful as an oral controlled absorption system (OCAS). The aim was to develop a PEO-based matrix system that enabled the sustained release of a large quantity of a highly water-soluble drug over 24 hours.

The release property of PEO/PEG matrix tablets containing different percentages (10–75% by mass) of different drugs was evaluated and compared. PEO/PEG matrix tablets have the key features of rapid water uptake and the resulting complete gelation of its polymeric excipients within a few hours. In addition, the feasibility of using a counter polymer, which has the opposite charge to the drug, was evaluated as a tool for the decrease in diffusion of a large quantity of highly water-soluble drug. Diltiazem (DTZ), which is a basic compound, was used as a model drug with high solubility, and crosslinked carboxyvinyl polymer (CVP) was used as a model counter polymer. This study described by Kojima and co-workers (2008), correlates with this investigation in that both are aimed at extending drug release of a highly water soluble compound, but in this study, two polymers were combined rather than ions which is the focus of this investigation. The results demonstrated that drugs with higher water solubilities were released faster from the PEO/PEG matrices. The drug-release rate also increased as the amount of drug content increased. The utilization of a polymer bearing a charge opposite that of the drug effectively restricted the diffusion of DTZ. As a result, the drug was released mainly by matrix erosion, which led to an extended release of 24 hours or longer, even with a high drug content (e.g., 50% by weight). These results suggest that incorporating counter polymer(s) into PEO/PEG matrices may be an effective way to achieve sustained release of large amounts of highly water-soluble drugs with less pH dependency (Sako, 1998; Kojima et al., 2008).

1.3 The Influence of Formulation Variables on the Drug Release Behavior from PEO Matrices

Drug release characteristics of PEO have been studied and discussed in the literature (Kim, 1995; Maggi et al., 2002; Wu et al., 2005; Borgquist et al., 2006). Numerous studies have been performed with high and low molecular weight PEO, the combination of PEO with hydrophilic/hydrophobic drugs and with binary blends of two polymers. These studies are outlined hereunder.

1.3.1 Investigations utilizing varying molecular weight polyethylene oxide

PEO of different molecular weights can be used to control the release of drug due to their matrix forming properties and partly amorphous structure. PEO undergoes structural changes caused by elevated temperature and relative humidity of the storage medium resulting in increased drug release (Kiss et al., 2008). This physical process can be highly influenced by the structure of different drug molecules, such as polymer-binding ability and hydration tendency. Modification of the release kinetics is possible via selecting the appropriate grade of PEO (Maggi et al., 2002). Drug release from PEO matrices may follow zero-order kinetics, and is mainly governed by polymer swelling, erosion and diffusion of drug molecules. It has been reported that both swelling and dissolution are faster in the case lower molecular weight PEO that results in higher drug release rates. Conversely, the extent of swelling is higher for higher molecular weight PEO and this is the dominant factor in controlling drug release (Kiss et al., 2008).

A study by Apicella and co-workers (1993), reviewed the drug release from monolithic water-swellable and soluble polymer tablets. The drug release behavior of l-hydroxyethyl-theophylline (etofylline) from compression-moulded tablets of

hydrophilic pure semi-crystalline PEOs of M_w=600,000g/mol and 4,000,000g/mol and of two blends of the two molecular weights of PEO were described. The drug release from the high molecular weight PEO was principally related to the material swelling rather than polymer dissolution, leading to a progressive decrease of the drug's diffusive conductance in the growing swollen layer, and hence to a non-constant release induced by the prevailing diffusive control. Conversely, drug release from the low molecular weight PEO was strictly related to the polymer dissolution mechanism. This led to the achievement of stationary conditions wherein the rate of swelling equalled the rate of dissolution, and hence ensured a constant release rate. Intermediate behaviors were detected in the case of the two blends. The results indicated that it was possible to obtain different release behaviors by changing the molecular weight of the soluble polymeric matrix-forming monolithic drug delivery devices (Apicella et al., 1993).

The thermal stability of PEO in sustained release tablets prepared by hot-melt extrusion was investigated by Crowley and co-workers (2002). The chemical stability of PEO was found to be dependent on both the storage and processing temperature as well as the molecular weight of the polymer. Storage of the polymer above its melting point significantly increased polymer degradation, and the degradation process was accelerated as the molecular weight was reduced (Crowley et al., 2002). The results of this study provided sufficient motivation for me to utilise a high molecular weight PEO and to undertake investigations at room temperature so as to avoid potential degradation of PEO.

A study by Kiss and co-workers (2008), on two basic drugs, theophylline and metronidazole embedded into PEO matrices was characterized by molecular modelling and their effect on the change of drug release stability was revealed. The findings suggested that both the hydration properties of the active ingredients as well as the molecular masses of PEO influenced the effect of physical ageing of PEO on the drug release properties of the matrix. It was found that the formation of the theophylline–water complex led to higher energy gains than in the case of metronidazole-water complexes. Thus, theophylline was released easier from the PEO matrix, because its interaction with water molecules during storage possibly led to the weakening of the theophylline–PEO interaction. This phenomenon was less remarkable in the case of metronidazole, where drug–water interaction was weaker. The two different molecular mass forms of PEO behaved differently from this aspect, as PEO N-12K matrices presented equally increased drug releases of both kinds of molecules. On the other hand, PEO 303 formed a much thicker matrix, leaving less opportunity for the water molecules to get imbibed and interact with the drug molecules (Kiss et al., 2008). From this study, it was gauged that PEO 303 may be a better polymer to utilise for controlled release due its matrix forming properties.

In this study conducted by Hong and co-workers (2008), an attempt was made to modify the release profile of nifedipine (NP) from the hydrophilic matrix PEO, containing solid dispersed NP, by restricting the drug releasing surface area. The restriction was created by applying polymeric barrier layers to both sides of the tablet using a viscous hydrophilic polymer, carbopol (CP) (Hong et al., 2008). The DSC thermogram and X-ray diffraction results indicated that the formation of crystalline

domain of NP and PEO was not detected. Swelling and morphological changes of the CP layer on both sides of the tablet minimized the erosional release for rapidly swelling PEO 200K, and thus changed the NP release to a diffusion-controlled process. For PEO 900K, the initial release rate was slower than that of PEO 200K, possibly due to the slower swelling and erosional release from the side of the tablet. For the PEO 7000K tablet capped with CP, much slower release was observed. Decreased surface area in contact with the medium by CP capping and the slower diffusion of NP molecules through the PEO and CP hydrogel seemed to work together. The physical mixture of PEO and CP delayed the release of NP remarkably. The increase in pH, ionic strength and buffer concentration of the dissolution medium decreased the release rate (Hong et al., 2008). This study once again indicates that higher molecular weight PEOs results in slower release rates that lower molecular weight PEOs. Addition of a polymeric barrier proved to be useful for prolonging drug release.

Mini-matrices with release-sustaining properties were developed by hot-melt extrusion using metoprolol tartrate as model drug and ethylcellulose as sustained-release agent. PEG or PEO was added to the formulation to increase drug release. Changing the hydrophilic polymer concentration and M_w modified the *in vitro* drug release: increasing concentrations yielded faster drug release (irrespective of M_w), whereas the influence of molecular weight depended on concentration. The sustained-release effect of the experimental formulations was limited, and relative bioavailabilities of 66.2% and 148.2% were obtained for 5% and 20% PEO 1,000,000g/mol mini-matrices, respectively (Verhoeven et al., 2009).

The constant release of prostaglandin E, from crosslinked crystalline-rubbery hydrogel matrices based on PEO which were undergoing solvent sorption and from crystallites melting in aqueous environments was reported. In the case of uncrosslinked PEO matrices, the solubility of PEO can alter the characteristics of the penetrated layer, leading to different behaviors in systems presenting different dissolution features. To control the release of the active agent, there should be a balance between diffusion of the active agent and solubilization of the PEO matrix. The diffusivity of the drug through the matrix, the swelling of PEO, and its solubilization rate can be biased by changing the molecular weight of PEO or blending PEO fractions with different molecular weights (Maggi et al., 2002).

Numerous other studies have also been performed with polyethylene oxide of high and low molecular weights (Apicella et al., 1993; Kim, 1995; Maggi et al., 2002; Wu et al., 2005; Petrović et al., 2009).

1.3.2 Polyethylene oxide and hydrophobic/hydrophilic drugs

Hydrophilic drugs are mainly released by diffusion of dissolved drug molecules across the PEO gel layer, while hydrophobic drugs are more likely released through erosion of the PEO gel (Aldermann, 1984; Maggi et al., 2002). Hydrophilic drugs diffuse through the gel-layer rapidly after water has penetrated a PEO matrix; therefore it is difficult to extend the drug release from these preparations. Due to this, it is necessary to control the drug release; especially when there is a high dose of the hydrophilic drug included, leading to the larger size of the matrix tablet (Kojima et al.,

2008). The contribution of these two phenomena to the overall drug release process is influenced not only by drug solubility, but also by the physical and mechanical properties of the PEO gel layer that forms around the tablet. We have attempted to modify the PEO-matrix by combining it with ions in an attempt to overcome this difficulty associated with controlled release of hydrophilic drugs.

In a study conducted by Agrawal and co-workers (2006), zero-order sustained release behavior for periods of up to 20 days for two hydrophobic drugs, sulindac and tetracaine, from solutions of poly(lactide)-poly(ethylene oxide)-poly(lactide) (PLA–PEO–PLA) triblock copolymer were observed. The drug release from drug/phosphate buffer solution (PBS) with no polymer was very quick, and the entire amount of drug was released in 4–6 hours. In the case of both sulindac and tetracaine, the drug/polymer/PBS systems did not demonstrate a burst type release profile, and release was much slower than in the drug/PBS system with no polymer. Difference in release rates for drugs with different chemical structures could suggest that the strong interaction of the drugs with the polymer may be a major reason for slow release of drugs from the polymer solution (Agrawal et al., 2006).

In another study conducted by Dasbach and co-workers (2003), a composite disk compressed drug delivery system that provided upcurving and constant drug delivery was developed. The objective of that study was to modify the release of a hydrophilic drug utilizing PEO in a compression-coated controlled release tablet. Three different core tablets, compression coated with 200mg, 300mg, and 400mg Polyox^{TM} (Dow Chemical Company, Michigan, USA) were used. The first tablet contained 100%

tramadol HCl. The second tablet contained 90% tramadol HCl and 10% Ethocel™ (Dow Chemical Company, Michigan, USA) and the third tablet contained 90% diphenhydramine HCl and 10% Ethocel™ (Dasbach et al, 2003). For both actives, the presence of the compression coating provided an initial lag and extended the drug release. As the Polyox™ coating was doubled in mass on the core tablets containing Ethocel™, the release of the diphenhydramine HCl was found to decrease from 66% to 25% after 6 hours (Dasbach et al, 2003). The tablet matrices containing only tramadol HCl in the core were found to have the largest weight gain over a 24 hour period compared to tablets that contained the drug and Ethocel™. The presence of Ethocel™ in the core did not typically impact the swelling characteristics of the tablets (Dasbach et al., 2003).

1.3.3 Binary blends of two polymers to modify drug release

This example outlines the use of PEO and polycaprolactone (PCL) blends in the production of monolithic matrices for oral drug delivery as well as the role of interfacial adhesion between PCL/PEO and drug (Park et al., 2005; Lyons et al., 2008). Several batches of matrix material were prepared with carvedilol. Dissolution testing indicated that the incorporation of the hydrophobic PCL polymer into a PEO matrix resulted in a retarded drug release profile with the degree of retardation being proportional to the amount of PCL in the matrix. The matrices prepared in this work demonstrate that the rate of drug release in a PEO/PCL monolithic matrix can easily be tailored by simply altering the composition of the binary blend. Matrices with higher loading of carvedilol were seen to release the active agent at a slightly quicker rate than those with lower loadings. This is thought to be due to less rate controlling

polymer (Lyons et al., 2008). The interfacial adhesion between water and PCL/PEO was increased with increasing the PEO content due to the greater hydrophilicity of PEO. The drug release rate of the microcapsules was significantly increased as the PEO content increased, which could be attributed to an increase in the hydrophilic groups or the degree of adhesion at the interfaces. This indicates that the release rate of drug can be controlled with varying the PEO content (Park et al., 2005).

1.4 The Interaction of Polyethylene Oxide with Various Ions

Table 1.1 provides a detailed illustration of the interaction of PEO with various ions. A typical example of the interaction between ions and PEO is in the area of bone repair. Bonding of foreign materials with bones may take place when a layer of apatite [$Ca_5(PO_4)_3(OH)$], similar to bone in crystallinity and composition, is spontaneously deposited on their surface in contact with blood plasma. Biocompatible materials, which will provide a matrix for the *in vivo* formation of hydroxyapatite deposits, may be suitable for bone repair. After solvent extraction of its cytotoxic components and pre-treatment with γ-glycidyl-oxypropyl trimethoxypropane, it is reacted with the amino-end-capped PEO. When the treated material is immersed in a calcification solution, a continuous layer of calcium hydrogen phosphate ($CaHPO_4$) is formed *in vitro*. This complexation of calcium ions by PEO chains may be expected to provide strong bonds between the inorganic crystals and the polymeric network (Jagur-Grodzinski, 1999).

This literature review has outlined the various avenues where PEO has been utilized in controlling drug delivery. Numerous studies have been conducted using high and

low molecular weight PEOs to improve drug delivery. Hydrophilic and hydrophobic drugs have also been incorporated with PEO to improve their solubility and hence drug delivery. PEO matrix tablets that have achieved the sustained release of diclofenac Na (solubility: 25mg/ml in water) for over 12 hours were formulated (Kim, 1998). However, in another study, PEO tablets containing 49% (by weight) of the highly water-soluble drug, i.e., diltiazem hydrochloride (solubility: >100mg/mL in water) extended drug release for only 8 hours (Maggi et al., 2002). To date, no publications have reported on the quantitative assessment from the contribution of drug diffusion and polymeric erosion to the release process of PEO-based matrices. In addition, there have been no reports of any PEO-based matrix tablets that have achieved the sustained release of a large amount of highly water-soluble drug for 24 hours. So far, acetaminophen is the only drug to be incorporated into a PEO/PEG matrix (Sako et al., 1996). No attempts have been made using any other drugs with different solubilities (Kojima et al., 2008). In addition, as can be seen in Table 1.1, very few studies have been carried out with PEO and electrolytes, although the studies carried out have proven to be successful, thus encouraging further research in this arena. The lack of studies attempting to achieve controlled drug delivery of hydrophilic drugs has provided us with motivation to use a drug of this nature but we have combined it with a PEO-electrolyte combination in order to control drug delivery.

The fact that polymers can be manipulated by interactions with ions means that their physicochemical and mechanical properties can be modified. If these properties are altered, it may be possible to change the processes of drug diffusion, dissolution and hence delivery.

Table 1.1 Interactions of PEO with various ions

Ion character	Specific ions	Reference
Monovalent Cations	Na^+, K^+	(Beaudoin et al., 2002)
Divalent Cations	Ca^{2+}, Mg^{2+}	(Beaudoin et al., 2002)
Counterions of dodecyl sulphates	Li^+ (LDS), Na^+, (NaDS), TMA^+, (TMADS)	(Froehner et al.,1998)
Polymer/surfactant interactions	PEO/NaDS + H_2O solution PEO/NaDS + H_2O + ethanol (Short) PEO/NaDS + ethanol (Short chain) PEO/NaDS + n-octanol (Long chain alcohol)	(Smitter et al., 2001)
Polymer with natural rubber	$(PEO_{1000} – (BSLi)_2)$ + NR (natural rubber) at 40%wt $(PEO_{1000} – (BSLi)_2)$ + NR (natural rubber) at 10%wt $(PEO_{1000}$ – ImB) + NR (natural rubber) at 40%wt $(PEO_{1000}$ – ImB) + NR (natural rubber) at 10%wt	(Yoshizawa et al., 2000)
Ionic salts	Ca^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}, Pb^{2+}	(Huq et al., 1988)
Active chitosan salt blends with water solution of PEO and PVA	Active chitosan salt blends with water solution of PEO and Polyvinyl Alcohol (PVA)	(Mucha, 1998)
(PEO) – NaI complexes with different Na:O ratios	(PEO) – NaI complexes with different Na:O ratios	(Mohamed et al., 1997)
Sodium Nitrate	$NaNO_3$	(Sreekanth et al., 1999)
Cation	K_2TiF_6	(Huguenin et al., 2001)

Key:

LDS:	Lithium Dodecyl Sulfate
NaDS:	Sodium Dodecyl Sulfate
TMADS:	Tetramethylammonium Dodecyl Sulfate
LiBS:	Lithium benzene sulfonate
ImB:	Imidazolium Bromide
NaI:	Sodium Iodide
$NaNO_3$:	Sodium Nitrate
K_2TiF_6:	Potassium Hexafluortitanate complex

1.5 Aim and Objectives of this Study

The aim of this study was to modify the physicochemical and physicomechanical properties of PEO in order to influence the hydrodynamic diffusion of its three-dimensional network. Hence, through such alteration, it was envisaged that if drug is loaded into its PEO matrix, its solubility and dissolution can be regulated in order to achieve zero-order influx of dissolution medium. The interaction between PEO and electrolytes may allow for precipitation of ions on the polymer backbone. This would lead to the attraction of water molecules to the ions. As a result, this would cause dehydration of the polymer matrix, hence minimising its mobility and relaxation. To accomplish this aim, the following objectives are outlined:

i. To undertake preliminary investigations that would allow for understanding of the interactions between PEO and various anionic and cationic entities.
ii. To statistically evaluate the significance of the interactions between the independent variables such as polymer concentration, polymer blends and molecular weights on the dependent variables using an Analysis of Variance (by stepwise forward and backward regression) based on Design of Experiments.
iii. To assess the surface morphology of the modified PEO.
iv. To investigate any changes in the micromechanical properties of the modified PEO such as the materials resilience, fracture force and work performed.
v. To compare the molecular structural transitions of altered with unaltered PEO.
vi. To assess the thermal compatibility of the altered PEO against unaltered PEO.
vii. To compare the drug dissolution characteristics from native and modified PEO delivery systems using a model highly water soluble drug.

1.6 Overview of this Research Report

Section 1 provides a concise literature survey of PEO drug delivery systems in addition to an overview of the rationale and the motivation for this study. It describes the need for specialized drug delivery systems utilizing polymers, in particular PEO. The properties of PEO are described that make it ideal for manipulation and use in diverse biomedical applications and its ability to control the release of drugs into the body. Various PEO-based drug delivery systems and their advantages and uses are discussed. The limitations of *in vitro* and *in vivo* studies are also outlined via reference to previous studies performed with PEO. Numerous studies that report the use of high and low molecular weight PEO plus combination with hydrophilic and hydrophobic drugs are also reviewed and critiqued. This section concludes with describing the modification of PEO by ionic interaction and with the aims and objectives of the current study.

In Section 2, the synthesis of the PEO-electrolyte combinations and the outcomes of the study are explicated. The formulation strategy used in synthesizing the PEO-electrolyte combinations and the variables employed to optimize the tablet formulation process using a Box-Behnken statistical experimental design are described. The PEO-electrolyte combinations were assessed for surface morphology, textural profiling, molecular structural transitions, thermal compatibility and *in vitro* drug release from the modified PEO-based tablet matrices. The methods for these various assessments are also described.

In Section 3, the results of this investigation are illustrated and discussed. These include morphology, textural profiling, molecular structural transitions, thermal compatibility analysis, *in vitro* drug release and optimum drug release profile.

Section 4 provides a conclusion to the key findings of this study and describes the recommendations for further enhancement of the PEO-electrolyte combinations in order to further control drug release for future potential as a novel drug delivery system.

SECTION 2

DEVELOPMENT OF THE POLYETHYLENE OXIDE-ELECTROLYTE COMBINATIONS AND SUBSEQUENT TABLET MATRICES

2.1 Introduction

This section aims to describe the development of the salted-out polyethylene oxide (PEO)-electrolyte combinations. The challenge associated with developing the PEO-electrolyte combinations was in selecting the correct PEO grade and electrolytes. Among desirable features, the PEO grade selected should possess inherent physicochemical characteristics that facilitated the attainment of a high gel-state upon swelling, ability to maintain a constant gel layer integrity over a prolonged period of time and hence reduce the erosion rate, and complete dissolution of PEO upon exhaustion of drug release from a tablet matrix (Pillay, Fassihi, 1999). PEO has been used for controlled-release matrix systems of hydrophobic as well as hydrophilic drugs. PEO is a tough, crystalline polymer at room temperature, and the glass transition temperature decreases from 245-253.8°C with increasing molecular mass. It is non-toxic, non-irritant, and does not generate residue, sediment, or vaporous elements. These properties indicate that PEO grades are sufficiently stable to work with. Since PEO is non-ionic, no interaction between the drug and PEO is expected (Dharwan et al., 2005).

The release rate of drug from biodegradable polymers can be controlled by a number of factors, such as the biodegradation kinetics of the polymer, physicochemical

properties of the polymer and drug, thermodynamic compatibility between the polymer and drug, and the shape of the device. The drug-release mechanism is controlled by several variables in a dynamic process (Dharwan et al., 2005).

Studies by Pillay and Fassihi (1999) have indicated that where previous drug delivery systems relied exclusively on the physical characteristics of the excipients/polymers to provide controlled release, reactions between pharmaceutically acceptable electrolytes or acids and drug can form a 'metamorphic scaffold' for the purpose of providing integrity to a single, hydrophilic polymer system (Pillay and Fassihi, 1999). The metamorphic scaffold controls the rate of intragel swelling and the diffusion of drug. Simple in design, this system has been shown to produce pH-independent, near zero-order dissolution profiles of up to 24 hours (Pillay and Fassihi, 1999). In this study, a Box-Behnken statistical, experimental design was employed to derive the 36 experimental formulation combinations from selected independent and dependant formulation variables.

2.2 Materials and Methods

2.2.1 Materials

Polyethylene oxide (Polyox® WSR303 NF, Mw=7x10^6g/mol) was purchased from Union Carbide Corp. (Danbury, CT, USA). The following electrolytes were combined with PEO: zinc carbonate ($ZnCO_3$), ammonium sulphate [$(NH_4)_2SO_4$], sodium phosphate (Na_3PO_4), sodium carbonate (Na_2CO_3) and di-potassium hydrogen orthophosphate (K_2HPO_4). The model drug used was diphenhydramine HCl (solubility is greater than or equal to 100mg/mL at 21.5˚C).

2.2.2 Methods

2.2.2.1 Preliminary investigations

Various compounds were selected to interact with PEO. These compounds were as follows: $ZnCO_3$, $(NH_4)_2SO_4$, Na_3PO_4, Na_2CO_3 and K_2HPO_4. The ether oxygen of PEO reacts with the positive ions of the selected compounds, e.g.: Na^+, K^+, Zn^{2+} and $(NH_4)^{2+}$. Though direct evidence is not yet available, it is believed acid-base coordination between the cations and the oxygen of the ether of PEO comprises the major interaction. The interactions between PEO and each of the compounds are outlined hereunder:

$PEO + ZnCO_3 \longrightarrow PEO: ZnCO_3$

$PEO + (NH_4)_2SO_4 \longrightarrow PEO: (NH_4)_2SO_4$

$PEO + Na_3PO_4 \longrightarrow PEO: Na_3PO_4$

$PEO + Na_2CO_3 \longrightarrow PEO: Na_2CO_3$

$PEO + K_2HPO_4 \longrightarrow PEO: K_2HPO_4$

2.2.2.2 Building the experimental design

Design of Experiments (DoE) is an efficient statistical tool for planning formulations so that data obtained can be analyzed to yield valid and objective conclusions. The primary objective of this study was to modify the physicochemical and physicomechanical properties of PEO so that we could induce zero-order influx of water and efflux of drug.

A Box-Behnken statistical design composed of 5 factors, 36 random experimental

runs and 5 centre-points was built using Minitab® software release version 14 (Minitab® Inc., PA, USA). A series of 36 different formulations were carefully chosen from a fractional factorial design to formulate and analyze. The combinations were selected so as to give the maximum effective interpretation of results without using an excessive number of experiments which would have been 180 in total. Five different process variables namely $ZnCO_3$, $(NH_4)_2SO_4$, Na_3PO_4, Na_2CO_3 and K_2HPO_4 were optimized using this design and were varied in a series of 36 different formulations. The effect of the variations within each formulation on fracture force, resilience and work performed was observed.

2.3 Formulation of the Polyethylene Oxide-Electrolyte Combinations

For each of the 36 solutions, 2g of PEO was dissolved in 100mL distilled water. Various combinations of $ZnCO_3$, $(NH_4)_2SO_4$, Na_3PO_4, Na_2CO_3 and K_2HPO_4 as listed in Table 2.1 were weighed out, each combination being a total of 2g. The concentration of the PEO to electrolyte was maintained at a constant 1:1 ratio by utilizing 2g of PEO and 2g of electrolyte. The 2g of electrolyte was then weighed, crushed using a mortar and pestle and then added to the PEO solution. Table 2.1 indicates the quantities of electrolyte and PEO for each sample. Each solution was then stirred using a magnetic stirrer for 30 minutes on a medium frequency. After the stirring process, the 36 solutions were covered with Parafilm® M (Pechiney Plastic Packaging Company, Chicago, USA) and cured in a dark area for 24 hours. Thereafter, the PEO-electrolyte combinations were filtered and washed (3x100mL) with de-ionized water and placed on petri dishes to dry. Each PEO-electrolyte sample was then dried under the extractor at 30°C for 1 week. The samples were

then removed and microscopically analyzed and subjected to textural analysis. Table 2.1 depicts the independent formulation variables tested in the 36 experiments. The Box-Behnken statistical design described in Section 2.2.2.1 was employed to optimize and evaluate the main effects and interaction effects of the sample drug (diphenhydramine HCl) in combination with the PEO-electrolytes on drug delivery. The concentrations of the independent variables which were used to prepare the design generated experimental formulations are illustrated in Table 2.1. The dependent variables included fracture force, resilience, work performed and cumulative percentage drug release.

2.4 Assessment of the Surface Morphology of the Polyethylene Oxide-Electrolyte Combinations

The external morphology of the 36 polymer-electrolyte combinations was visually characterized according to texture and color. Each sample was visually analyzed and photographed using Analysis® software on a digital microscope (Olympus, USA).

Table 2.1: Box-Behnken design for synthesis of the PEO-electrolyte combinations

No:	$ZnCO_3$	$(NH_4)_2SO_4$	Na_3PO_4	Na_2CO_3	$ZnCO_3$	PEO(g)	Electrolyte(g)
1	0	16.667	0	16.667	16.667	2	0.667
2	0	0	25	0	25	2	1.000
3	0	12.5	12.5	12.5	12.5	2	0.500
4	5	5	5	30	5	2	0.2/1.2
5	16.667	0	16.667	0	16.667	2	0.667
6	16.667	16.667	0	0	16.667	2	0.667
7	16.667	0	16.667	16.667	0	2	0.667
8	10	10	10	10	10	2	0.400
9	12.5	0	12.5	12.5	12.5	2	0.500
10	0	25	0	25	0	2	1.000
11	25	0	0	0	25	2	1.000
12	25	0	25	0	0	2	1.000
13	0	16.667	16.667	0	16.667	2	0.667
14	0	16.667	16.667	16.667	0	2	0.667
15	0	25	25	0	0	2	1.000
16	16.667	0	0	16.667	16.667	2	0.667
17	12.5	12.5	0	12.5	12.5	2	0.500
18	12.5	12.5	12.5	0	12.5	2	0.500
19	16.667	16.667	16.667	0	0	2	0.667
20	25	0	0	25	0	2	1.000
21	0	0	0	50	0	2	2.000
22	16.667	16.667	0	16.667	0	2	0.667
23	30	5	5	5	5	2	0.2/1.2
24	0	0	16.667	16.667	16.667	2	0.667
25	5	5	5	5	30	2	0.2/1.2
26	0	50	0	0	0	2	2.000
27	0	0	0	25	25	2	1.000
28	0	0	0	0	50	2	2.000
29	5	5	30	5	5	2	0.2/1.2
30	5	30	5	5	5	2	0.2/1.2
31	0	0	25	25	0	2	1.000
32	0	0	50	0	0	2	2.000
33	0	25	0	0	25	2	1.000
34	25	25	0	0	0	2	1.000
35	12.5	12.5	12.5	12.5	0	2	0.500
36	50	0	0	0	0	2	2.000

2.5 Textural Profile Analysis

A calibrated Texture Analyzer (TA.XT*plus*, Stable Microsystems, Godalming, Surrey, United Kingdom) fitted with a steel probe (2mm diameter) was employed in the determination of the textural characteristics of the 36 polymer-electrolyte combinations. The parameter settings employed in this analysis are outlined in Table 2.2. Combinations were analyzed for resilience (N/s), energy absorbed (J) and fracture force (N/mm).

2.5.1 Determination of resilience, energy absorbed and fracture force of the polyethylene oxide-electrolyte combinations

Resilience refers to deformation upon application of a force. Figure 2.1a depicts an example of a force-time profile for the determination of the resilience (N/s). It was calculated as the ratio of the areas under the compression and decompression curve. The energy absorbed (J) was determined by calculating the area under the curve (AUC_{FD}) of a force–distance profile as depicted in Figure 2.1b. The fracture force was calculated as the point at which the material starts to yield, indicated by an indentation in the force-distance profile as depicted in Figure 2.1c

Table 2.2: Textural parameter settings employed in the determination of resilience, energy absorbed and fracture force

Parameters	Settings
Pre-test speed	1mm/sec
Test Speed	0.5mm/sec
Post-Test Speed	1mm/sec
Compression Force	40N
Load Cell	50kg
Trigger Type	Auto
Trigger Force	0.5 N
Return Distance	20mm

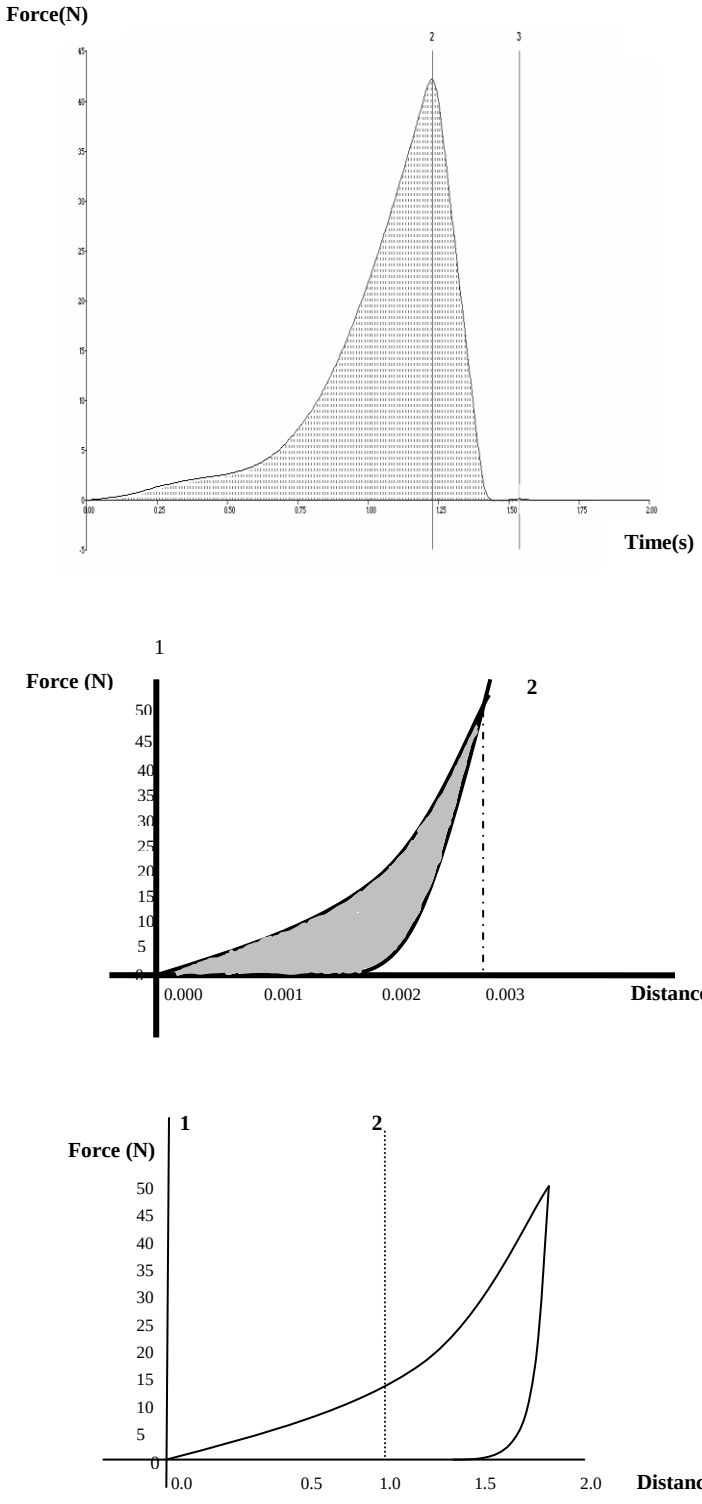

Figure 2.1: Typical profiles for the determination of a) resilience, b) energy absorbed and c) fracture force of the PEO-electrolyte combination (50% Na_3PO_4, 50% K_2HPO_4).

2.6 Assessment of the Molecular Structural Transition of the Salted-Out Polyethylene Oxide -Electrolyte Combinations

A Fourier Transform Infrared (FTIR) spectrometer (PerkinElmer Spectrum One with Spectrum V5.00 software, PerkinElmer Instruments, CT, USA) was used to detect the vibrational characteristics of chemical functional groups in each of the salted-out PEO-electrolyte combinations 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. A typical plot for each of the salted-out PEO-electrolyte combinations was obtained and compared to the plot of native PEO. A profile showing the transmittance of the individual polymer, PEO was produced as well as profiles of the salted-out PEO-electrolyte combinations in order to determine any potential interactions. A sample of the blended preparation was used in the platinum crucible to generate the resulting percentage transmittance profile (Stancanelli et al., 2008; da Silver-Junior et al., 2009).

2.7 Thermal Compatibility Analysis of the Salted-Out Polyethylene Oxide - Electrolyte Combinations

The differential scanning calorimeter (DSC) can be used for determining different thermal properties of a polymeric material such as the glass transition temperature T_g, melting temperature T_m, enthalpy of melting and crystallization and the oxidative induction time (OIT). The sample and the reference are heated in the same chamber (the oven) according to a program which provides the information about the temperature (combination of isothermal and dynamic segments) and the reaction gas (nitrogen for inert and oxygen for oxidative atmosphere). Two separate heat sensors continuously read the temperature of the sample and the reference crucible. In absence of a thermal event the temperatures of the sample and the reference should be the same according to the temperature program.

In case of a thermal event, e.g. melting, the temperature of the sample deviates from that given in the temperature program (the temperature of the reference). Heat (electric effect) is supplied to or withdrawn from the sample in order to correct for this deviation. The deviation in the thermogram from the base-line supplies information about the thermal behaviour of the material in the temperature program range. 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. 10mg to 20mg samples were transferred to aluminium pans and sealed immediately. The heating rate was 5°C per minute and the temperature range captured was 20-300°C.

The polymer, PEO was individually analyzed in order to obtain a base thermogram. Thermograms of all the salted-out PEO-electrolyte combinations were then obtained and compared to the base thermogram in order to note whether any physical interactions had occurred. Potential crosslinking between the PEO and the electrolytes were also noted in order to detect if the crosslinking had any physicochemical interaction when the electrolytes and PEO were physically combined.

2.8 UV Spectrophotometry Analysis of Diphenhydramine HCl Content

2.8.1 Preparation of calibration curves and assay procedure

Stock solutions were prepared by separately dissolving variable accurately weighed quantities of diphenhydramine HCl in 100mL simulated intestinal fluid (SIF) buffer (pH 6.8; 37°C).The following concentrations were prepared: 0.005mg/mL, 0.004mg/mL, 0.003mg/mL and 0.002mg/mL. The UV absorbance of each standard solution was determined at the maximum wavelength of absorption (λ_{max}) of 254nm for diphenhydramine HCl. SIF was used as the reference. No other components absorbed in this range. A calibration curve (R^2=0.99) was constructed as depicted in Figure 2.2. Simulated intestinal fluid was prepared according to the USP method. The pH of the test solution used was 6.8.

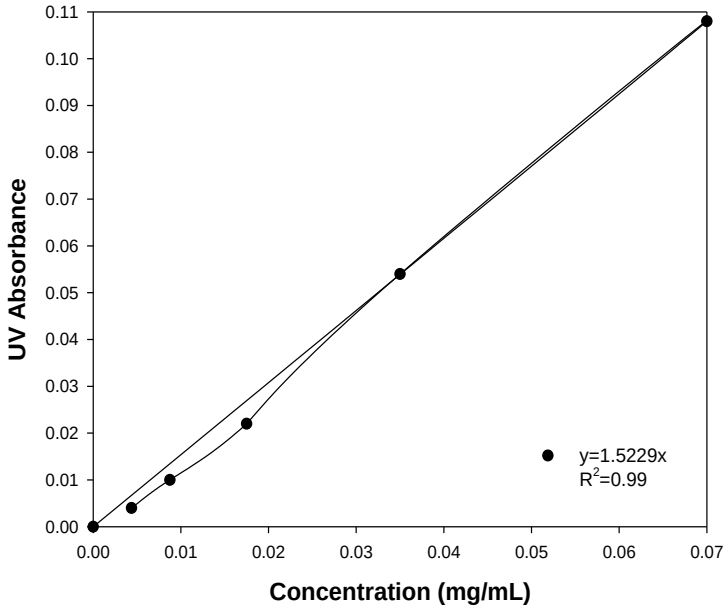

Figure 2.2: Calibration curve of diphenhydramine HCl in simulated intestinal fluid (pH 6.8; 37°C).

2.9 *In Vitro* Drug Release Studies

2.9.1 Dissolution of the salted-out polyethylene oxide-electrolyte combinations

In vitro drug release studies were performed on the eight salted-out PEO-electrolyte combinations. Each salted-out PEO-electrolyte combination was combined with the drug, diphenhydramine HCl to form a 500mg tablet (diameter=13mm, thickness=5mm, friability<1%; N=5) on a Carver Press set at 3 tons. Each tablet was placed in a calibrated six-station dissolution testing apparatus (Caleva Dissolution Apparatus, model 7ST) using a USP25 rotating paddle method at 50rpm with 900mL of simulated intestinal fluid (pH 6.8; 37°C). These studies were performed at specific time intervals over a period of 10 hours. 5ml of sample was withdrawn and replaced with 5ml of buffer solution. Combinations were analyzed by ultraviolet spectroscopy (Specord 40, Analytik Jena, AG) at 254nm.

SECTION 3

RESULTS AND DISCUSSION

3.1 Morphology and Yield of the Polyethylene Oxide-Electrolyte Combinations

The electrolytes appeared to be dispersed evenly within each of the PEO formulations. The combinations visually appeared white in color and were predominantly linear in shape. There appeared to be some variations in the dimensions and the darkness of the PEO-electrolyte combinations between the different formulations. This may be due to the different electrolytes and varying the concentrations of electrolytes used in each formulation. The texture of the PEO-electrolyte combinations appeared porous since each formulation was exposed to a 24 hour period of drying. The 36 formulations were then subjected to textural analysis, after which only the salted-out PEO samples were subjected to further testing. These tests included FTIR analysis, DSC analysis and dissolution studies. It was visually observed that none of the eight salted-out formulations disintegrated in simulated intestinal media, pH 6.8 demonstrating that the concentration ratio and type of polymers used in the dosage form played a vital role in retaining the dosage form intact. The morphology of the PEO-electrolyte combinations is depicted in Figure 3.1 (1-36) and the descriptions are tabulated in Table 3.1

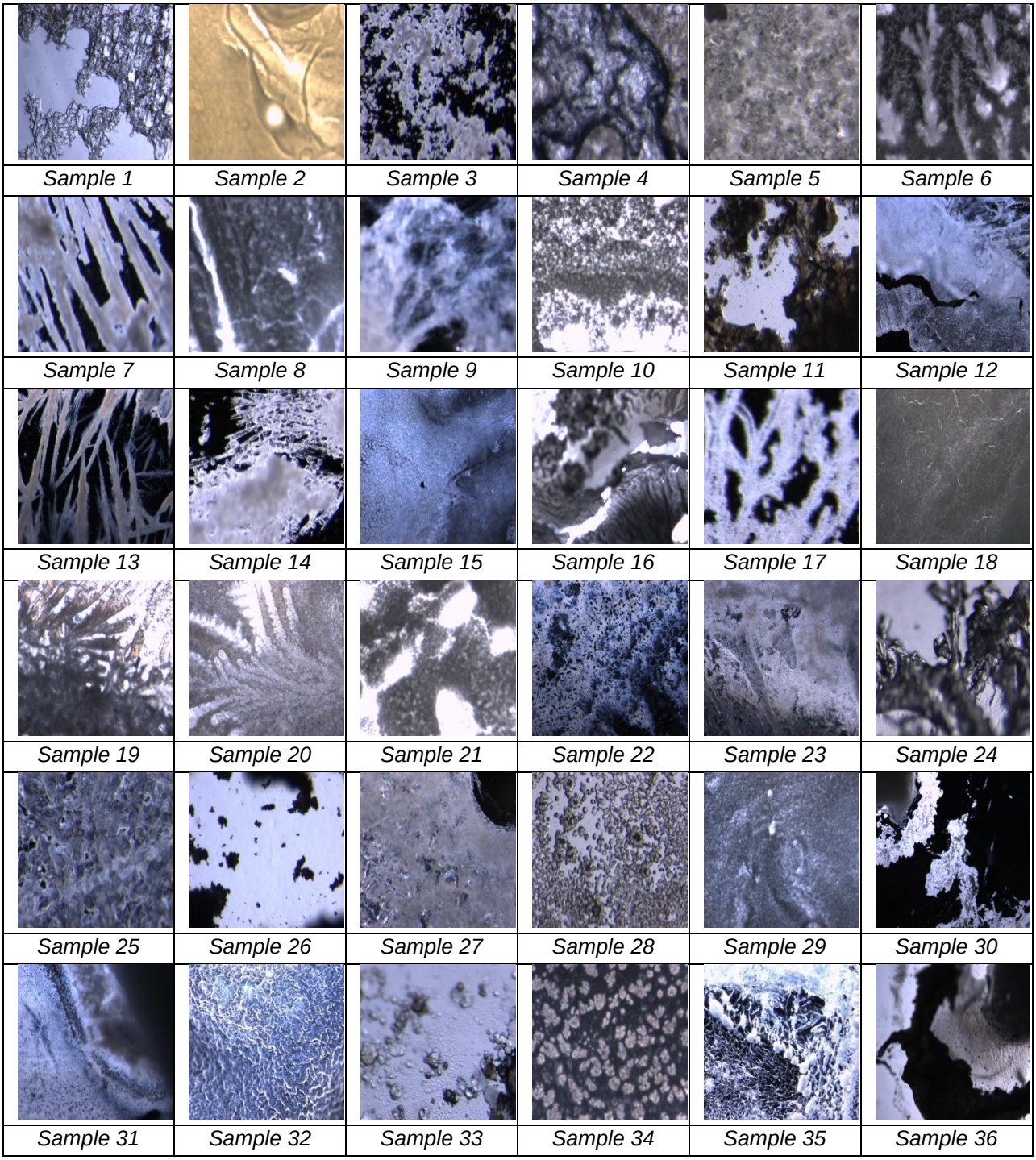

Figure 3.1: Morphology of the PEO-electrolyte combinations (1-36).

Table 3.1: Description of the PEO-electrolyte combinations (1-36)

Sample Number	Texture	Salted-out (SO) or Non Salted-Out (NSO)
1	Sticky and Clumpy	NSO
2	Fine Powder	NSO
3	Fine Powder	NSO
4	Lumpy – formed a sticky lump	NSO
5	Powder	NSO
6	Powder	NSO
7	Paper like – cannot be powdered	SO
8	Powder	NSO
9	Gel-like – cannot be powdered	SO
10	Powder	NSO
11	Cannot be Powdered	SO
12	Powder	NSO
13	Powder	NSO
14	Powder	NSO
15	Powder	NSO
16	Cannot be Powdered	SO
17	Cannot be Powdered	SO
18	Powder	NSO
19	Powder	NSO
20	Powder	NSO
21	Powder	NSO
22	Cannot be Powdered	SO
23	Powder	NSO
24	Powder	NSO
25	Powder	NSO
26	Powder	NSO
27	Partially Powdered	NSO
28	Powder	NSO
29	Powder	NSO
30	Cannot be Powdered	SO
31	Partially Powdered	NSO
32	Partially Powdered	NSO
33	Partially Powdered	NSO
34	Powder	NSO
35	Powder	NSO
36	Cannot be Powdered	SO

Table 3.2: Textural profiling results of the salted-out and non salted-out PEO combinations

	$ZnCO_3$	$(NH_4)_2SO_4$	Na_3PO_4	Na_2CO_3	K_2HPO_4	resilience N/s	fracture force N/mm	work performed J
1	0	16.667	0	16.667	16.667	4.722	18.511	0.025
2	0	0	25	0	25	0.746	38.461	0.203
3	0	12.5	12.5	12.5	12.5	2.573	102.4	2.385
4	5	5	5	30	5	1.106	78.452	2.568
5	16.667	0	16.667	0	16.667	2.606	112.554	3.249
6	16.667	16.667	0	0	16.667	1.104	39.845	0.847
7	16.667	0	16.667	16.667	0	4.125	42.049	4.104
8	10	10	10	10	10	0.621	48.264	0.319
9	12.5	0	12.5	12.5	12.5	0.572	28.857	0.098
10	0	25	0	25	0	4.235	56.02	2.194
11	25	0	0	0	25	1.973	69.155	3.469
12	25	0	25	0	0	1.217	52.156	0.977
13	0	16.667	16.667	0	16.667	2.156	79.971	2.057
14	0	16.667	16.667	16.667	0	3.536	32.334	1.194
15	0	25	25	0	0	4.013	135.09	3.261
16	16.667	0	0	16.667	16.667	0.527	39.218	0.131
17	12.5	12.5	0	12.5	12.5	2.771	115.316	2.791
18	12.5	12.5	12.5	0	12.5	3.542	85.348	2.22
19	16.667	16.667	16.667	0	0	1.438	39.204	0.762
20	25	0	0	25	0	2.293	113.512	0.254
21	0	0	0	50	0	1.3	70.208	0.218
22	16.667	16.667	0	16.667	0	1.845	78.462	0.728
23	30	5	5	5	5	3.355	96.708	1.302
24	0	0	16.667	16.667	16.667	0.408	24.343	0.064
25	5	5	5	5	30	0.758	26.786	0.337
26	0	50	0	0	0	0.676	44.811	0.074
27	0	0	0	25	25	2.897	57.053	0.711
28	0	0	0	0	50	4.235	145.665	3.508
29	5	5	30	5	5	0.303	56.547	0.56
30	5	30	5	5	5	3.245	100.917	0.213
31	0	0	25	25	0	0.689	39.36	0.019
32	0	0	50	0	0	0.462	53.875	0.134
33	0	25	0	0	25	0.954	65.36	0.253
34	25	25	0	0	0	1.953	74.249	1.21
35	12.5	12.5	12.5	12.5	0	2.456	121.23	0.286
36	50	0	0	0	0	0.521	37.286	0.294

3.2 Response Surface Plots Depicting the Effect of Electrolyte Type on the Dependant Formulation Variables

The non-linear surface response plots of the salted-out electrolyte combinations depicting the effect of the electrolyte type on the dependant formulation variables have been outlined and discussed. The salted-out electrolyte combinations listed below have displayed a linear effect and are hence not discussed.

- combination salted-out with Na_2CO_3 and K_2HPO_4
- combination salted-out with $(NH_4)_2SO_4$ and K_2HPO_4
- combination salted-out with $(NH_4)_2SO_4$ and Na_2CO_3
- combination salted-out with $(NH_4)_2SO_4$ and Na_3PO_4
- combination salted-out with $ZnCO_3$ and K_2HPO_4
- combination salted-out with $ZnCO_3$ and Na_2CO_3
- combination salted-out with $ZnCO_3$ and Na_3PO_4

3.2.1 Effect on resilience of the salted-out polyethylene oxide-electrolyte combinations

The combination salted-out with a blend of $ZnCO_3$ and $(NH_4)_2SO_4$ resulted in a rapid decrease in resilience (Figure 3.2.1a) due to the influence of $(NH_4)_2SO_4$ whilst the formulation salted-out with a combination of Na_3PO_4 and K_2HPO_4 resulted in an initial decrease followed by an increase in resilience (Figure 3.2.1b) due to the influence of K_2HPO_4. Interestingly though, only one of the salted-out combinations resulted in an increase in resilience. This was due to the presence of Na_2CO_3 in the formulation salted-out with a blend of Na_3PO_4 and Na_2CO_3 (Figure 3.2.1c). We can hence deduce that only Na_2CO_3 results in an increase in resilience from all the combinations.

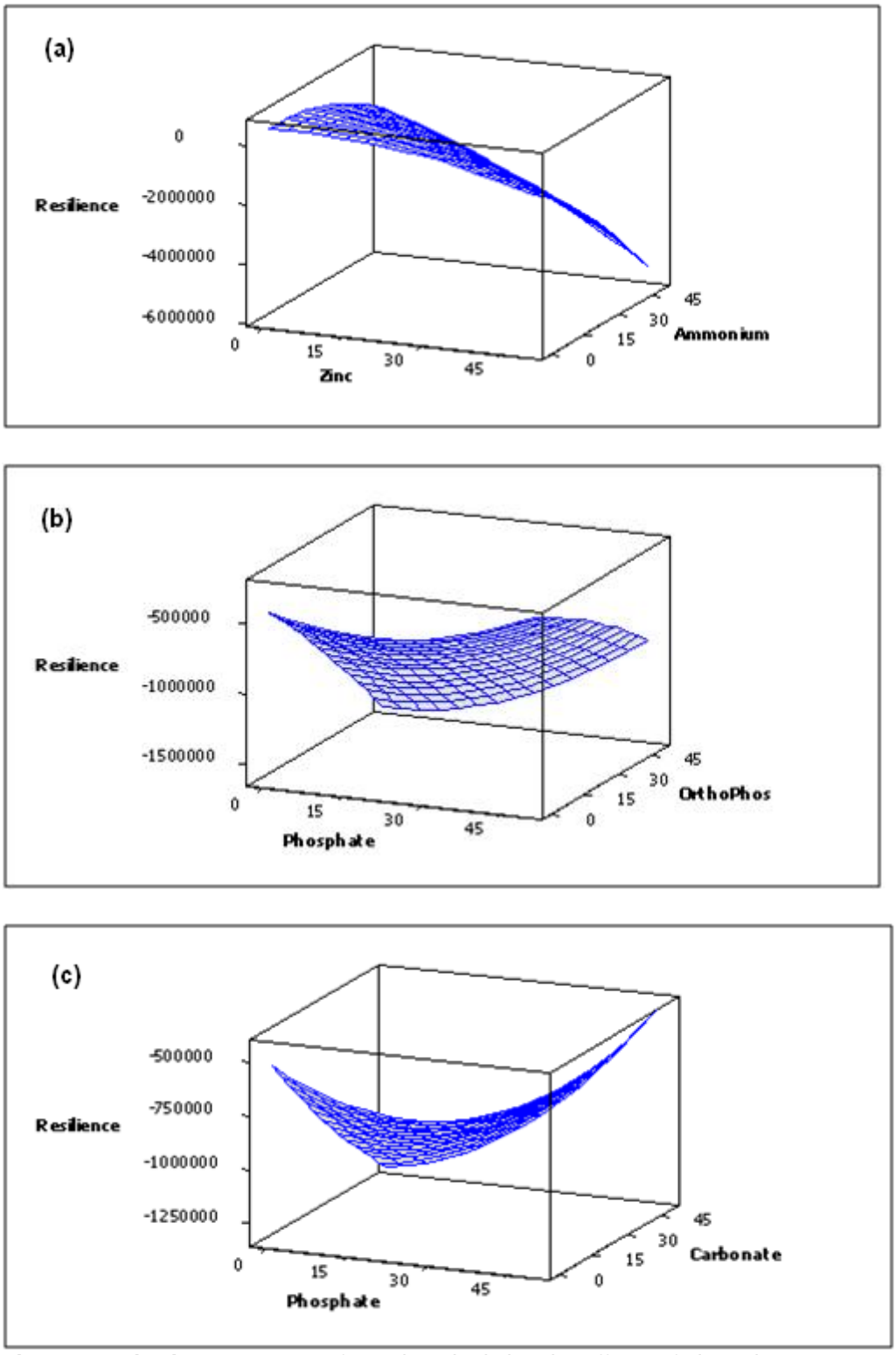

Figure 3.2.1(a-c): Response surface plots depicting the effects of electrolyte types on the resilience of the salted-out non-linear PEO combinations.

3.2.2 Effect on fracture force of the salted-out polyethylene oxide-electrolyte combinations

The presence of $ZnCO_3$ did not have much of an impact on the fracture force but the inclusion of $(NH_4)_2SO_4$ significantly decreased the fracture force in Figure 3.2.2a. In Figures 3.2.2b and c, an increase in Na_3PO_4 levels resulted in a rapid decrease in fracture force whilst an increase in the K_2HPO_4 and Na_2CO_3 (Figures 3.2.2b and c) levels result in an increase in fracture force. We can hence deduce that an increase in Na_3PO_4 concentration decreases fracture force and is not influenced by the presence of other electrolytes.

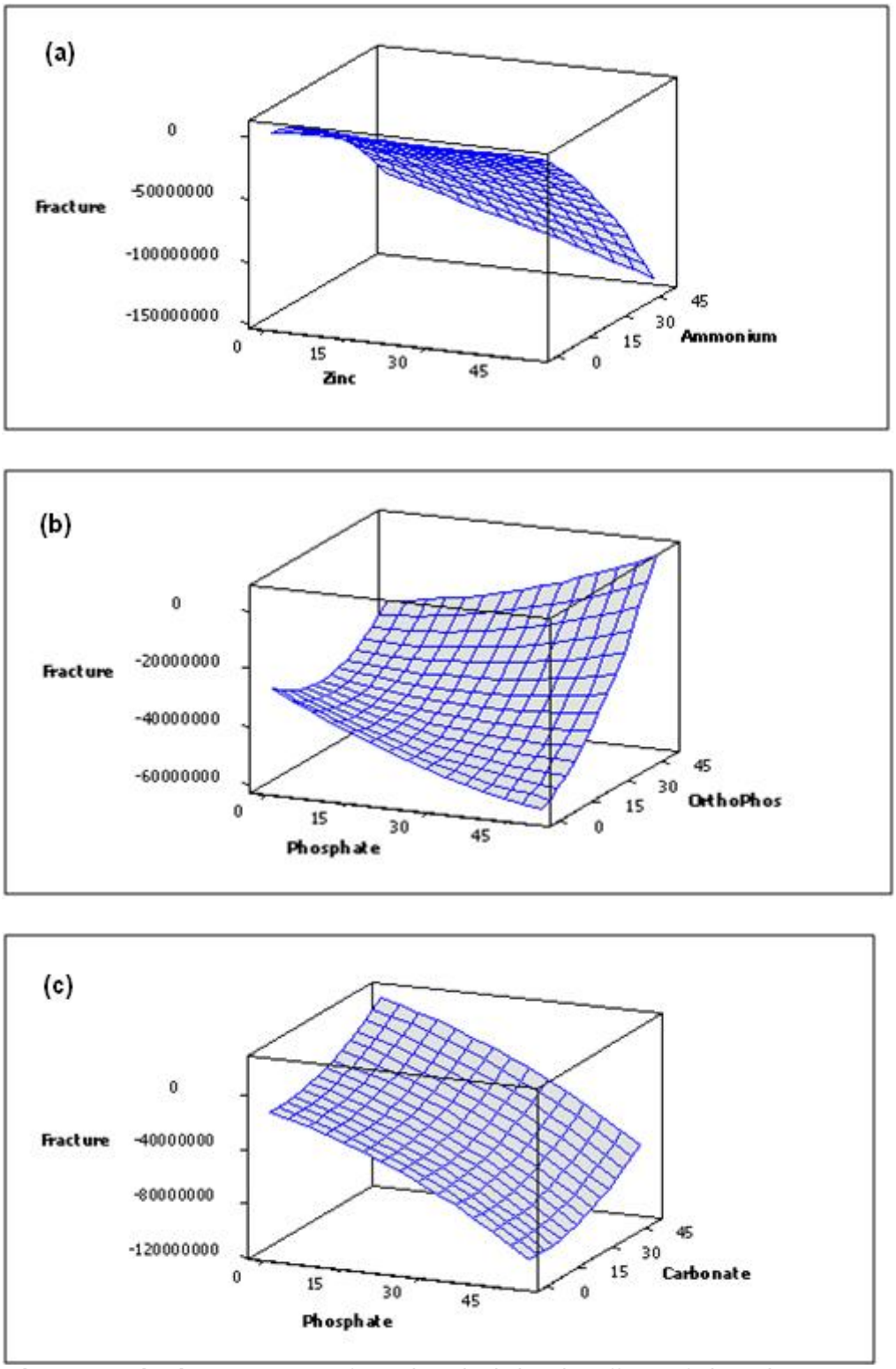

Figure 3.2.2(a-c): Response surface plots depicting the effects of electrolyte types on the fracture force of the salted-out non-linear PEO combinations.

3.2.3 Effect on work performed of the salted-out polyethylene oxide-electrolyte combinations

Higher concentrations of $ZnCO_3$ resulted in an increase in work performed whilst higher concentrations of $(NH_4)_2SO_4$ resulted in a decrease in work performed (Figure 3.2.3a). However, this combination showed a less dramatic increase in work performed compared to the combinations without the presence of $(NH_4)_2SO_4$. Combinations salted-out with a blend of Na_3PO_4 and K_2HPO_4 (Figure 3.2.3b) or Na_3PO_4 and Na_2CO_3 (Figure 3.2.3c) all resulted in an increase in work performed with increasing electrolyte concentration. We can thus deduce that the presence of $(NH_4)_2SO_4$ decreased the work performed indicating that it is a weaker electrolyte and allows for very little crosslinking with PEO whilst all the other electrolytes result in an increase in work performed.

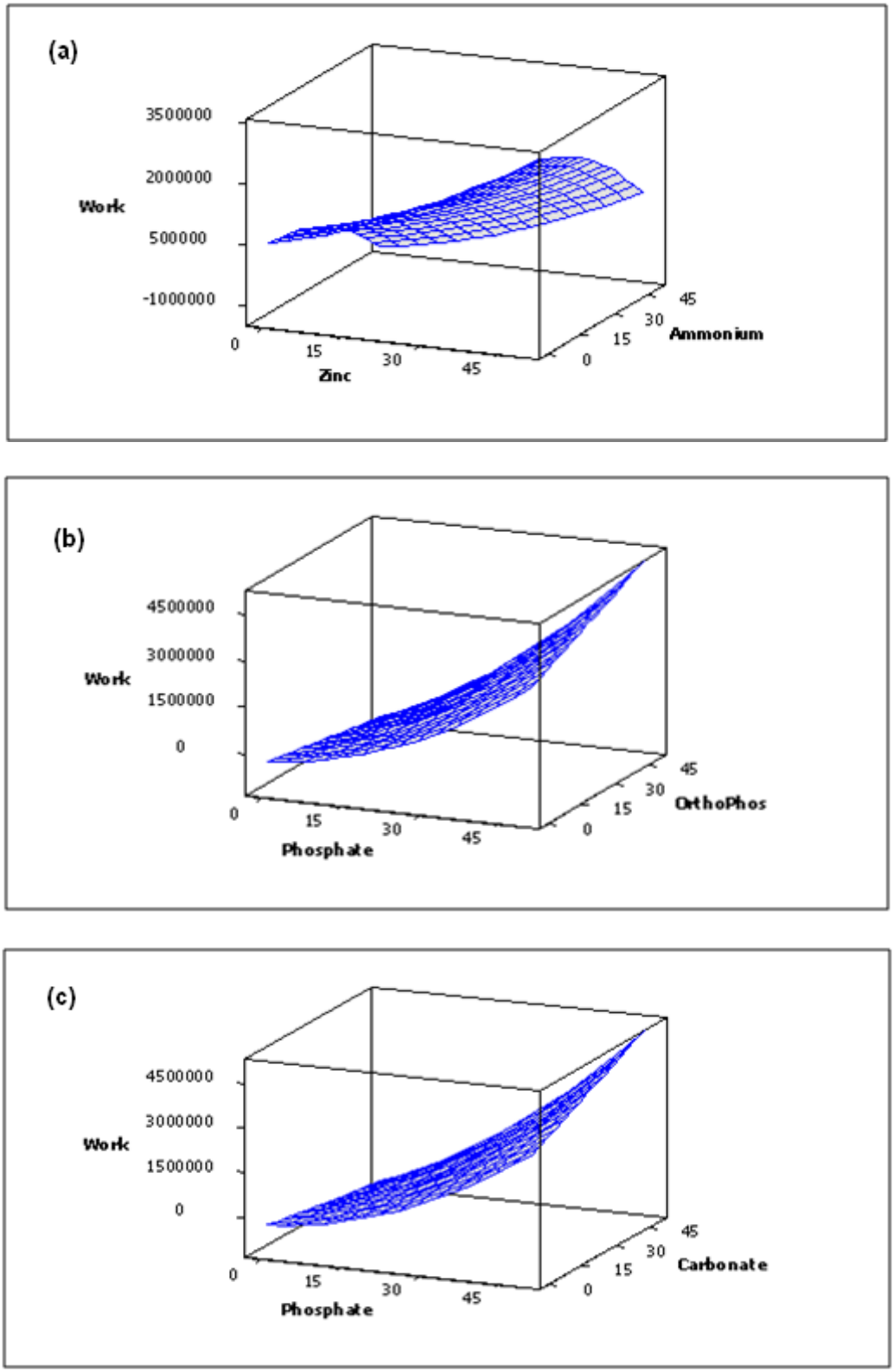

Figure 3.2.3(a-c): Response surface plots depicting the effects of electrolyte types on the work performed of the salted-out non-linear PEO combinations.

3.3 Assessment of the molecular structural transition of the salted-out polyethylene oxide-electrolyte combinations

A FTIR spectrometer was used to detect the vibration characteristics of the chemical functional groups in the salted-out PEO-electrolyte combinations in response to infrared light interactions. A typical plot showing the transmittance of the polymer, PEO alone was first obtained. Thereafter, profiles of all the salted-out PEO-electrolyte combinations were obtained and compared to the profile of the original PEO sample.

Table 3.3 lists the transmittance peaks in the fingerprint region of 650-3500cm^{-1} for PEO and the PEO-electrolyte combinations. Peaks that were not present in the native PEO sample were identified. All the PEO-electrolyte combinations produced new peaks in the region of 650-750cm^{-1} whilst only Figure 3.3.9 produced a new peak at 776.32cm^{-1}. Figure 3.3.7 produced a new peak at 876.07cm^{-1} whilst Figures 3.3.4, 3.3.6 and 3.3.9 produced new peaks in the region of 1000–1050cm^{-1}. Figure 3.3.3 and Figure 3.3.8 produced an extra peak in the region of 1400–1450cm^{-1} and Figure 3.3.5. and 3.3.6 produced extra peaks in the region of 1500–1650cm^{-1}. Figures 3.3.2, 3.3.3, 3.3.5 and 3.3.8 produced extra peaks in the region of 1650–1700cm^{-1} and Figures 3.3.2, 3.3.6, 3.3.7, 3.3.8 and 3.3.9 produced an extra peak in the region of 2050–2300cm^{-1}. All the combinations produced extra peaks in the region of 3000–3500cm^{-1}. From the data it was not possible to ascertain whether these peaks are due to an interaction between the electrolytes and PEO or are part of the fingerprint of PEO present in the combinations. Further studies into possible physical interactions were undertaken via differential scanning calorimetry reported later in this section.

Table 3.3: Wavenumbers for each of the salted-out polyethylene oxide-electrolyte combinations

Wavenumbers	Figure 2.8.1 Native PEO	Figure 2.8.2	Figure 2.8.3	Figure 2.8.4	Figure 2.8.5	Figure 2.8.6	Figure 2.8.7	Figure 2.8.8	Figure 2.8.9
650-700		**685.96**	**685.99**		**682.41**				
700-750		**708.41, 738.81**		**707.68, 740.58**	**708.28, 741.98**	**708.32, 739.13**	**707.64, 738.38**	**707.09**	**706.92**
750-800									**776.32**
800-850	840.81	833.88	840.92	840.96	841.79	840.8	833.29	841.64	831.29
850-900							**876.07**		
900-950	946.32								
950-1000	960.75	960.9	960.42	960.36		960.51	960.48	961.45, 981.70	961.56
1000-1050				**1019.94**		**1018.95**			**1045.07**
1050-1100	1059.31	1059.43, **1099.86**	1094.8						1060.56
1100-1150	1144.61	1145.7	1145.42	1144.62	1100.05, 1145.31	1144.76			1102.63, 1145.91
1200-1250	1241.35	1241.6	1241.57	1241.59	1241.82	1241.58	1241.58	1241.7	
1250-1300	1279.13	1279.9	1279.15	1279.69	1280.6	1279.51	1279.83	1280.06	1280.73
1300-1350	1341.69	1341.6	1341.55	1341.67	1342.24	1341.65	1341.61	1342.04	
1350-1400	1359.91		1359.82	1359.9	1359.77, 1389.53	1359.88	1359.6	1360.18	1380.72
1400-1450			**1413.15**					**1428.8**	
1450-1500	1466.79	1499.8	1466.49	1466.87, 1499.44	1467.62	1466.91	1467.01, 1499.59		
1500-1550					**1501.02**	**1501.36**			
1600-1650						**1648.02**			
1650-1700		**1679.1**	**1684.2**		**1676.92**			**1667.15**	
1850-1900	1980.83	1979.4	1979.34	1979.44		1979.89			
2050-2100		**2050.9**					**2090.5**	**2050.56**	**2085.78**
2150-2200						**2164.79**	**2163.06**		
2250-2300		**2283**							
2850-2900	2878.29	2884.3	2879.14	2882.32	2884.11	2882.24	2879.01	2883.14	2883.9
3000-3100								**3045.29**	
3100-3200								**3195.46**	
3200-3300		**3290.9**			**3289.72**		**3292.82**		**3294.08**
3300-3400				**3308.62**		**3306.83**			
3400-3500			**3460.21**						

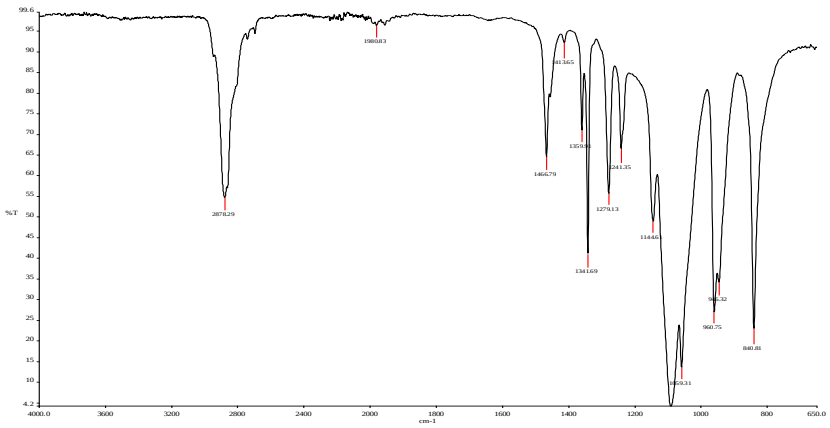

Figure 3.3.1: A typical FTIR plot of native PEO 303.

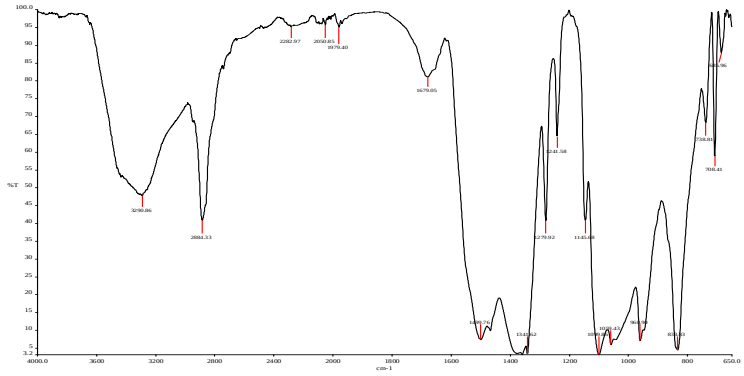

Figure 3.3.2: A typical FTIR plot of the salted-out sample 7 showing the combination of PEO 303, $ZnCO_3$, Na_3PO_4 and Na_2CO_3.

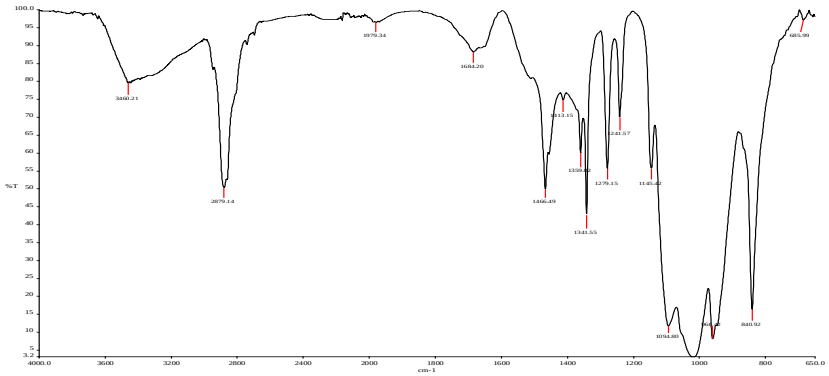

Figure 3.3.3: A typical FTIR plot of the salted-out sample 9 showing the combination of PEO 303, $ZnCO_3$, Na_3PO_4 and K_2HPO_4.

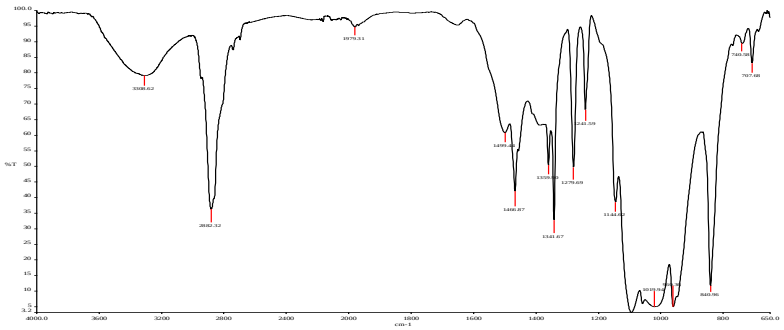

Figure 3.3.4: A typical FTIR plot of the salted-out sample 11 showing the combination of PEO 303, $ZnCO_3$ and K_2HPO_4.

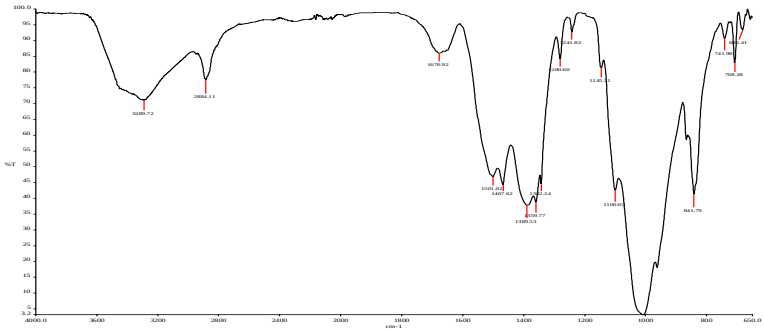

Figure 3.3.5: A typical FTIR plot of the salted-out sample 16 showing the combination of PEO 303, $ZnCO_3$, Na_2CO_3 and K_2HPO_4.

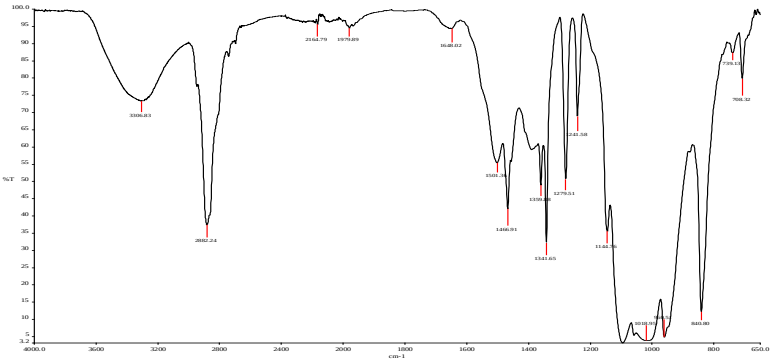

Figure 3.3.6: A typical FTIR plot of the salted-out sample 17 showing the combination of PEO 303, $ZnCO_3$, $(NH_4)_2SO_4$, Na_2CO_3 and K_2HPO_4.

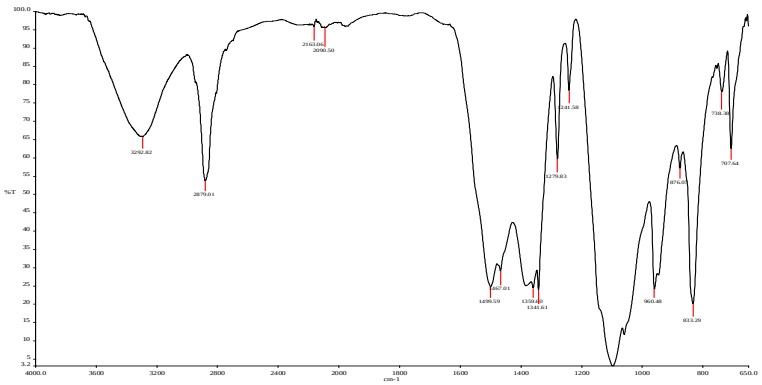

Figure 3.3.7: A typical FTIR plot of the salted-out sample 22 showing the combination of PEO 303, $ZnCO_3$, $(NH_4)_2SO_4$ and Na_2CO_3.

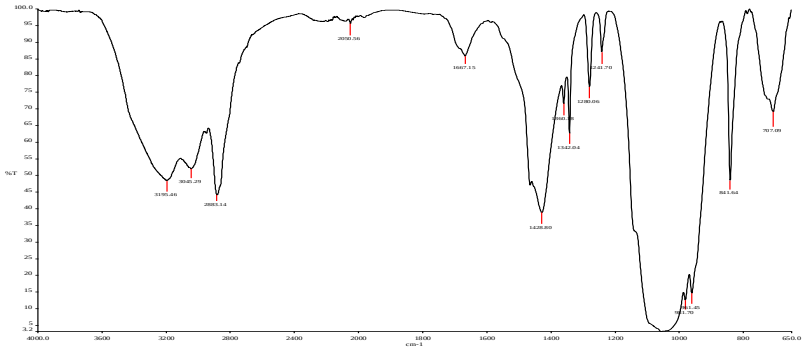

Figure 3.3.8: A typical FTIR plot of the salted-out sample 30 showing the combination of PEO 303, $ZnCO_3$, $(NH_4)_2SO_4$, Na_3PO_4, Na_2CO_3 and K_2HPO_4.

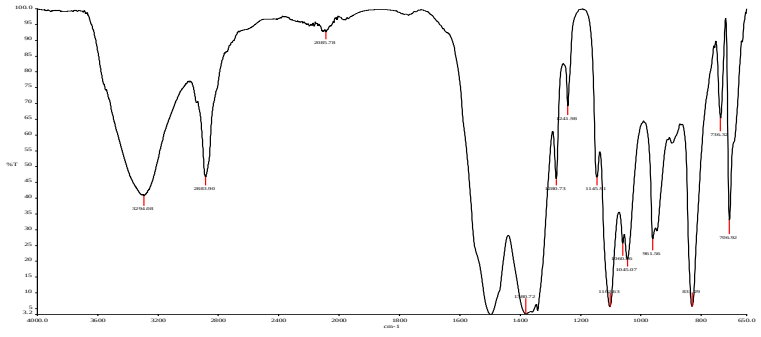

Figure 3.3.9: A typical FTIR plot of the salted-out sample 36 showing the combination of PEO 303 and $ZnCO_3$.

3.4 Thermal compatibility analysis of the salted-out polyethylene oxide-electrolyte combinations

PEO is a thermoplastic semi-crystalline polymer with a flexible chemical structure. It has a melting point ranging from 60°C-75°C and a glass transition temperature of -67°C. DSC testing was carried out on all the salted-out combinations and each thermogram was analyzed in terms of glass transition and melting point. For each thermogram carried out on all the salted-out combinations, the integral onset and end set temperatures were determined for each significant thermal event. The mean values are shown in Table 3.4

Table 3.4: Mean integral, onset and endset temperature values for each of the salted-out combinations.

Sample Number	***Mean sample mass***	***Mean integral (mJ±SD) (N=2)***	***Mean onset temperature (°C±SD) (N=2)***	***Mean endset temperature (°C±SD) (N=2)***
7	13.3	751.07	40.32	65.52
36	16	27.12	42.40	69.83
9	11.4	178.83	39.70	69.10
11	12.8	400.12	43.08	69.26
17	15.5	-31.79	30.04	48.78
30	16.2	134.22	42.76	60.97
22	15.2	6428.95	164.32	214.64
16	12.2	8761.71	125.31	194.40

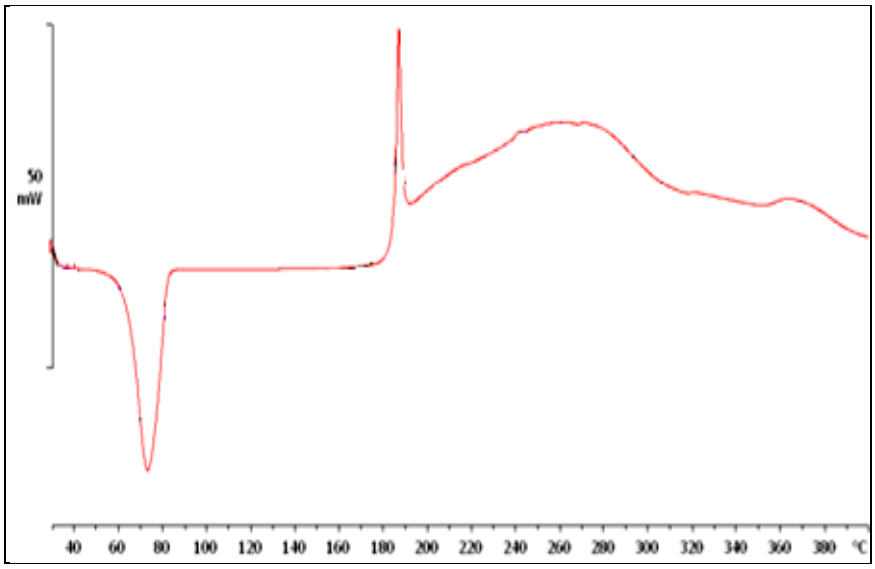

Figure 3.4.1: Thermogram of native PEO 303.

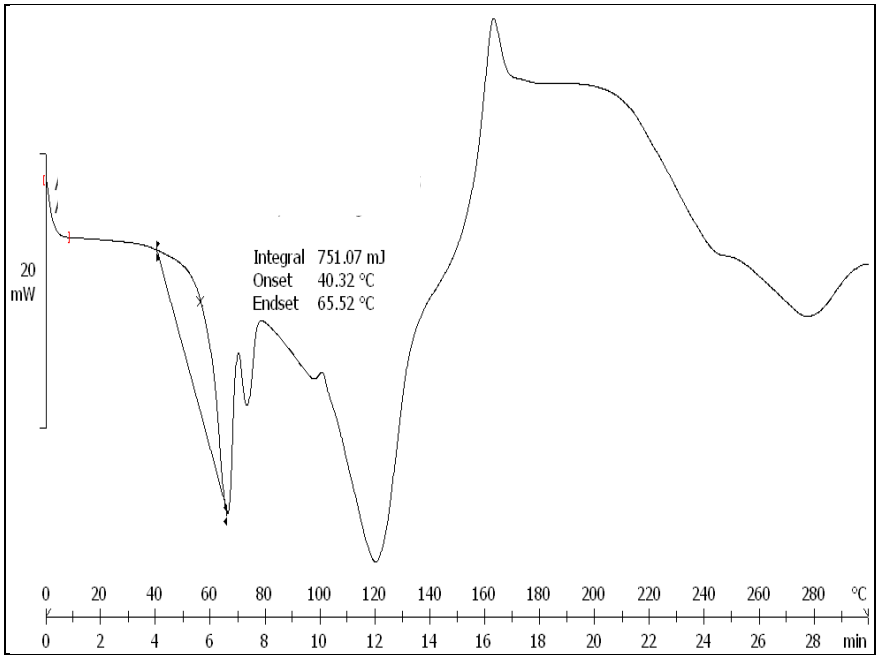

Figure 3.4.2: Thermogram of the salted-out sample 7 showing the combination of PEO 303, $ZnCO_3$, Na_3PO_4 and Na_2CO_3.

Figure 3.4.2 depicts the thermogram of the salted-out PEO sample utilizing the electrolytes $ZnCO_3$, Na_3PO_4 and Na_2CO_3. The first transition occurred at 65.52°C which correlates to the melting point of PEO. There is an additional melting point peak at 120°C which could represent

the melting point peak of one of the electrolytes. The crystallization peak is present at around 160°C for PEO. This indicates minimal interaction between PEO and the electrolytes.

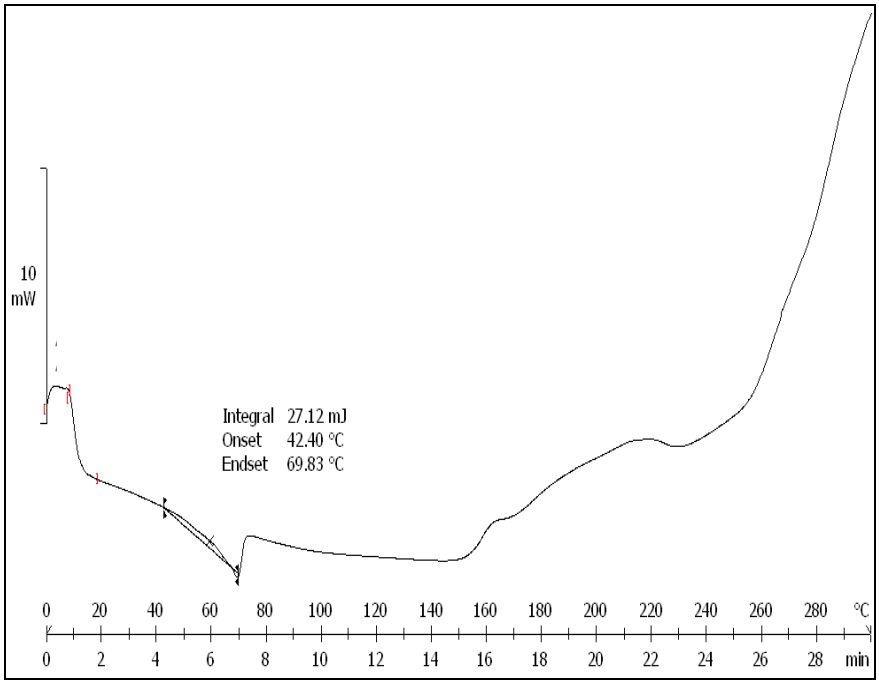

Figure 3.4.3: Thermogram of the salted-out sample 9 showing the combination of PEO 303, $ZnCO_3$, Na_3PO_4 and K_2HPO_4.

Figure 3.4.3 depicts the thermogram of the salted-out PEO sample utilizing the electrolytes $ZnCO_3$, Na_3PO_4 and K_2HPO_4. The first transition occurred at 69.83°C which correlates to the melting point of PEO. The crystallization peak which normally occurs at around 190°C for PEO is absent. This may indicate some form of an interaction between PEO and the electrolytes.

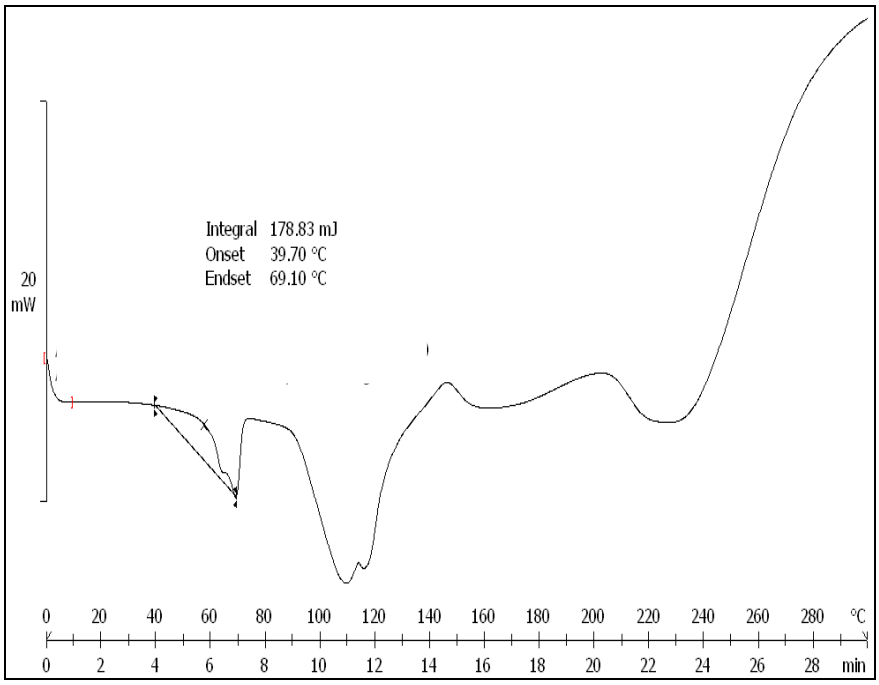

Figure 3.4.4: Thermogram of the salted-out sample 11 showing the combination of PEO 303, $ZnCO_3$ and K_2HPO_4.

Figure 3.4.4 depicts the thermogram of the salted-out PEO sample utilizing the electrolytes, $ZnCO_3$ and K_2HPO_4. The first transition occurred at 69.10°C which correlates to the melting point of PEO. There is an additional melting point peak at approximately 110-120°C representative of the peak of an additional electrolyte and the crystalline peak which normally occurs at approximately 190°C in PEO is absent. The additional peak may account for the peak of either $ZnCO_3$ or K_2HPO_4, and the absence of the crystalline peak could indicate an interaction between the electrolytes and PEO.

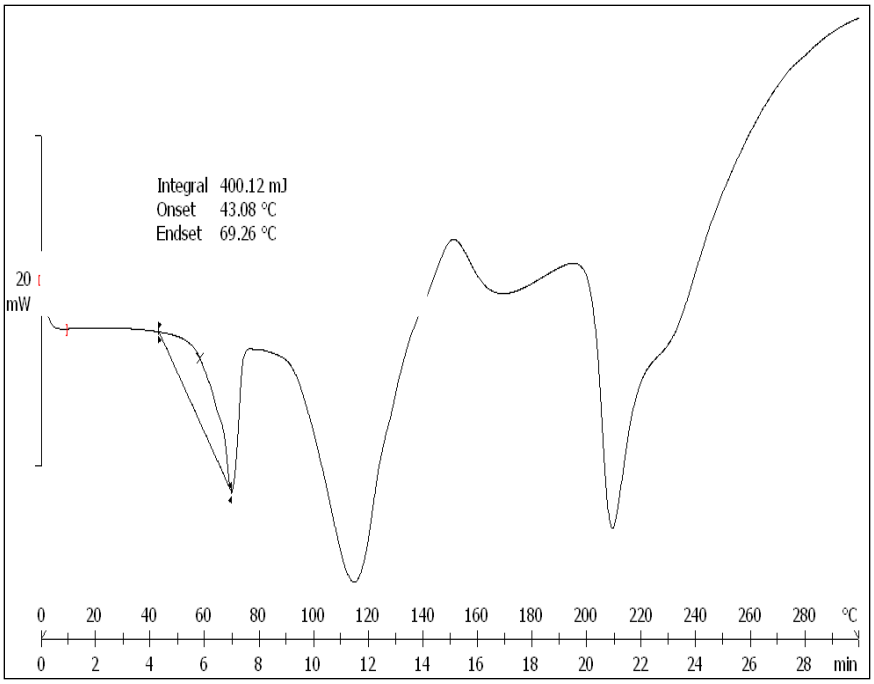

Figure 3.4.5: Thermogram of the salted-out sample 16 showing the combination of PEO 303, $ZnCO_3$, Na_2CO_3 and K_2HPO_4.

Figure 3.4.5 depicts the thermogram of the salted-out PEO sample utilizing the electrolytes $ZnCO_3$, Na_2CO_3 and K_2HPO_4. This thermogram is very similar to Figure 3. The first transition occurred at 69.26°C which correlates to the melting point of PEO. There are 2 additional melting point peaks at approximately 110-120°C and 210°C and the crystalline peak which normally occurs at approximately 190°C in PEO is absent. The additional peaks may account for the peaks of either electrolytes $ZnCO_3$, Na_2CO_3 and K_2HPO_4 and the absence of the crystalline peak could indicate an interaction between the electrolytes and PEO.

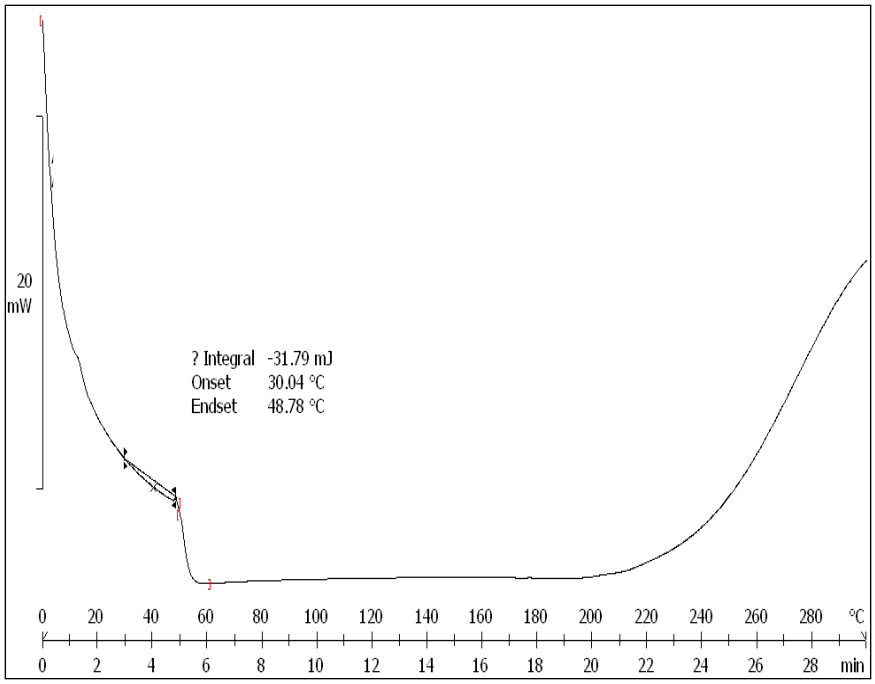

Figure 3.4.6: Thermogram of the salted-out sample 17 showing the combination of PEO 303, $ZnCO_3$, $(NH_4)_2SO_4$, Na_2CO_3 and K_2HPO_4.

Figure 3.4.6 depicts the thermogram of the salted-out PEO sample utilizing the electrolytes $ZnCO_3$, $(NH_4)_2SO_4$, Na_2CO_3 and K_2HPO_4. The first transition occurred at 48.78°C. There were no other peaks present, hence indicating a definite interaction between PEO and the electrolytes. This decrease in melting point may suggest that PEO may have transformed its structure from its original extended crystallite to a more folded chain crystallite and that no crosslinking has occurred.

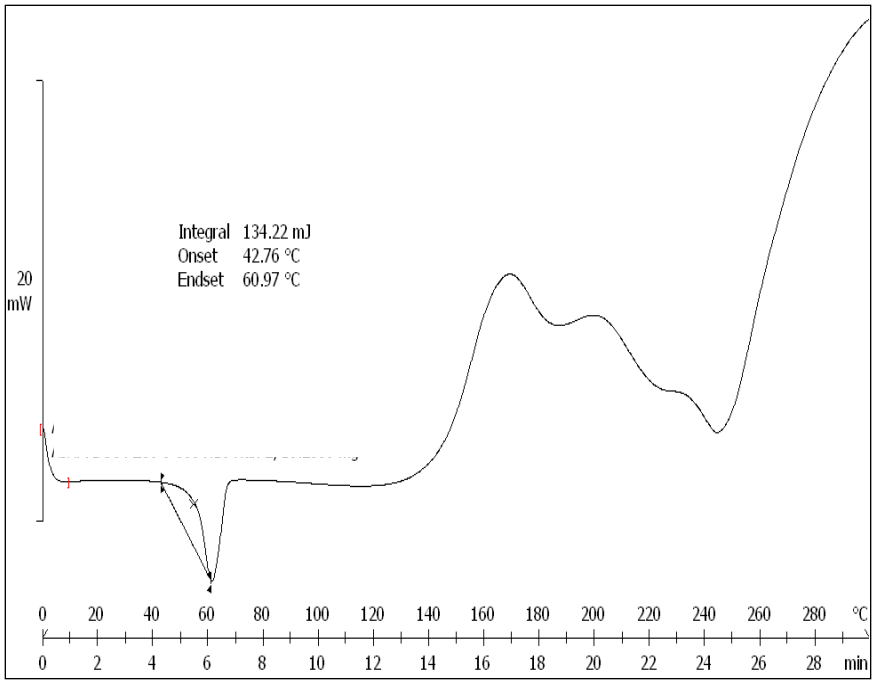

Figure 3.4.7: Thermogram of the salted-out sample 22 showing the combination of PEO 303, $ZnCO_3$, $(NH_4)_2SO_4$ and Na_2CO_3.

Figure 3.4.7 depicts the thermogram of the salted-out PEO sample utilizing the electrolytes $ZnCO_3$, $(NH_4)_2SO_4$ and Na_2CO_3. The first transition occurred at 60.97°C which correlates to the melting point of PEO. The crystallization peak is present at around 170°C which correlates to the crystallization peak for PEO. This indicates minimal interaction between PEO and the electrolytes.

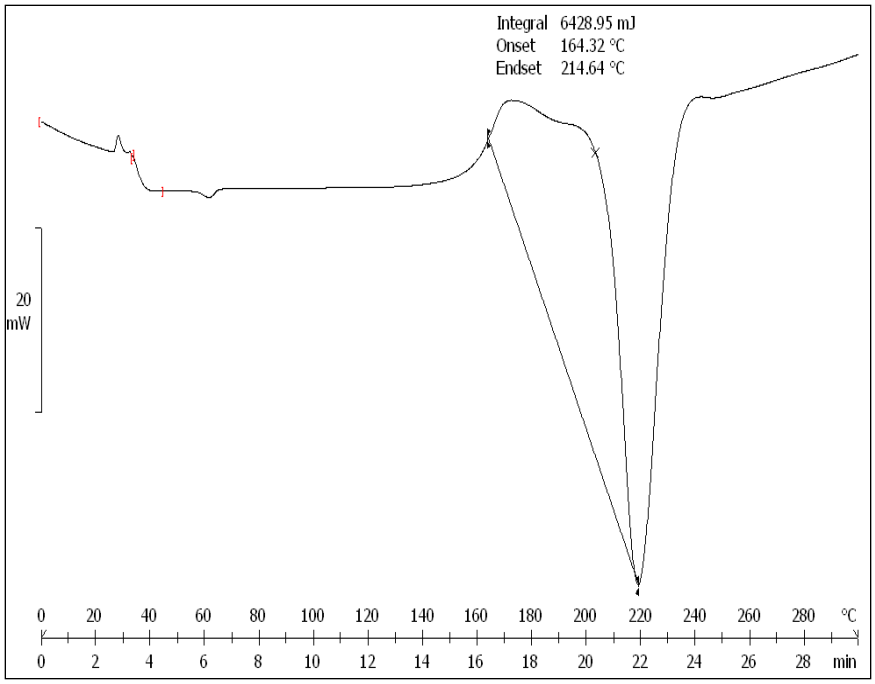

Figure 3.4.8: Thermogram of the salted out sample 30 showing the combination of PEO 303, $ZnCO_3$, $(NH_4)_2SO_4$, Na_3PO_4, Na_2CO_3 and K_2HPO_4.

Figure 3.4.8 depicts the thermogram of the salted-out PEO sample utilizing the electrolytes $ZnCO_3$, $(NH_4)_2SO_4$, Na_3PO_4, Na_2CO_3 and K_2HPO_4. The first transition occurred at 214.64°C. This is an extremely high melting point and indicates that crosslinking has occurred. There are no other peaks present.

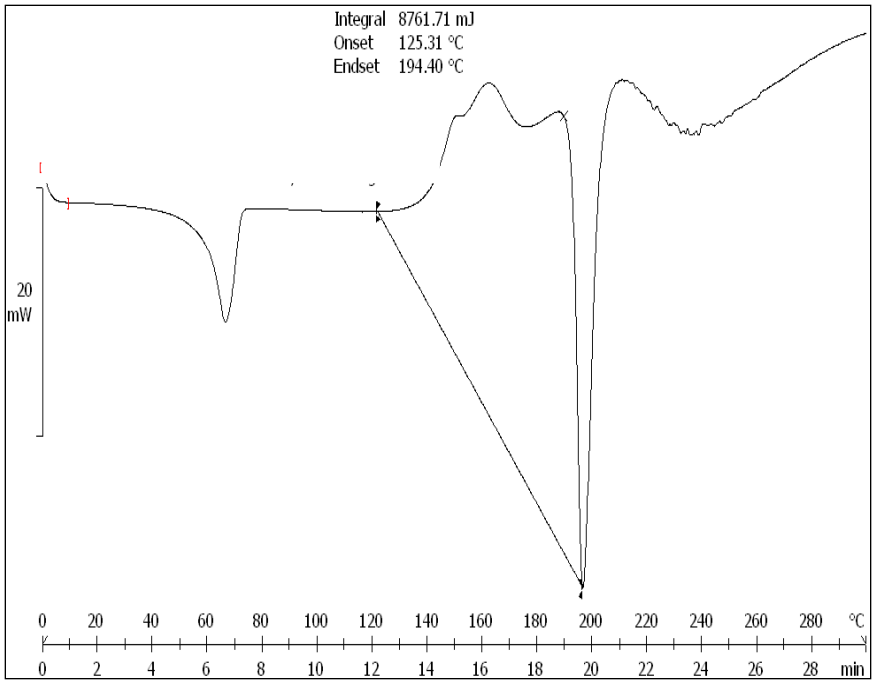

Figure 3.4.9: Thermogram of the salted out sample 36 showing the combination of PEO 303 and $ZnCO_3$.

Figure 3.4.9 depicts the thermogram of the salted-out PEO sample utilizing the electrolyte $ZnCO_3$. The first transition occurred at 194.40°C, This thermogram is very similar to that of Figure seven with a very high melting point. This may also suggest that crosslinking has occurred. From the discussion above we can gauge that the most favorable PEO-electrolyte combination would be that of PEO with $ZnCO_3$, $(NH_4)_2SO_4$, Na_3PO_4, Na_2CO_3 and K_2HPO_4 as it is one of the combinations in which crosslinking may have occurred. This formulation is much more stable at higher temperatures and thus useful for an extended shelf-life.

3.5 *In Vitro* Drug Release Studies

Each salted-out PEO-electrolyte combination was combined with the drug, diphenhydramine HCl to form a tablet. Each tablet was then subjected to dissolution testing over a 10 hour period utilizing a prepared buffer solution at a pH of 6.8. The compositions of each formulation are listed in Table 3.5 hereunder. The dissolution profiles for all eight tablets are depicted in Figure 3.5 (F1 – F8).

Table 3.5: Salted-out formulations and their electrolyte compositions

Formulation	Composition
1	33.3% $ZnCO_3$, 33.3% Na_2CO_3 and 33.3% Na_3PO_4
2	25% $ZnCO_3$, 25% Na_2CO_3, 25% Na_3PO_4 and 25% K_2HPO_4
3	50% $ZnCO_3$ and 50% K_2HPO_4
4	33.3% $ZnCO_3$, 33.3% Na_2CO_3 and 33.3% K_2HPO_4
5	25% $ZnCO_3$, 25% $(NH_4)_2SO_4$, 25% Na_2CO_3 and 25% K_2HPO_4
6	33.3% $ZnCO_3$, 33.3% $(NH_4)_2SO_4$ and 33.3% Na_2CO_3
7	10% $ZnCO_3$, 60% $(NH_4)_2SO_4$, 10% Na_2CO_3, 10% Na_3PO_4 and 10% K_2HPO_4
8	100% $ZnCO_3$

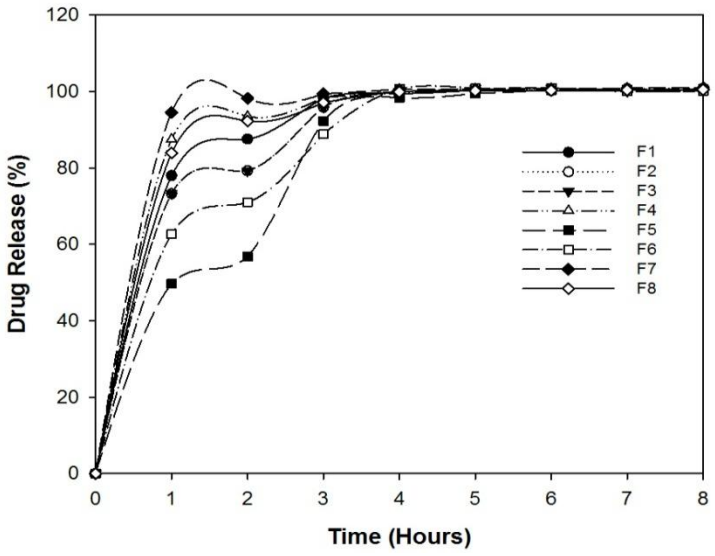

Figure 3.5: Dissolution profiles for the eight salted-out PEO-electrolyte tablets (F1 - F8) (standard deviation<0.5% in all cases, N=3).

Formulation 1 showed a linear release pattern during the entire 8 hour period. It was marked by an initial 40% release of drug during the first hour followed by an a slower diffusional drug release phase during the next 2 hours and then a slightly higher but steady release rate of Diphenhydramine HCl over the last 4 hours. Formulations 2, 3 and 4 were marked by an initial 75–85% release of drug during the first hour followed by a steady release rate of drug over the next 5 hours. Formulation 5 and 6 showed a very similar release pattern. Both formulations showed release rates that were biphasic, marked by an initial 50-60% release of drug followed by a slower diffusional drug release phase. Formulation 7 and 8 did not show the most favorable drug pattern as almost all the drug was released during the first 2 hours. Combinations of the aforementioned formulations comprised of different concentrations of electrolytes combined with an equivalent concentration of PEO. From our discussion above, we can conclude that formulation one was the most favorable formulation as it showed one of the best drug release patterns. There was initial slight increase of drug during the first hour in order to build up levels of drug in the plasma or appropriate tissue followed by a sustained drug release pattern over the next few hours. This may have been due to the precipitation of the electrolyte on the PEO backbone leading to the attraction of water molecules. As a result this may have caused dehydration of the PEO matrix, hence minimizing its mobility and relaxation and thus regulating drug release.

3.6 Optimum Drug Release Profile

Minitab® V14 was used to optimize the following parameters: resilience, fracture force and work performed. These parameters were selected to provide for the qualitative and quantitative kinetic modeling of drug release from the salted-out PEO combinations. The major influence is attributable to the type of electrolyte employed in the formulation. Optimal responses generated by the inherent optimization function of Minitab® are depicted by the plots in Figure 3.6. According to the predictions of the statistical design, the optimal sample that would provide a linear drug release profile would comprise concentrations of 50% Na_2CO_3 and 50% K_2HPO_4 respectively. $ZnCO_3$, $(NH_4)_2SO_4$, and Na_3PO_4 had to be excluded from the formulation in order to achieve a zero order kinetics and slow release of drug over an 8 hour period from the salted-out PEO combinations.

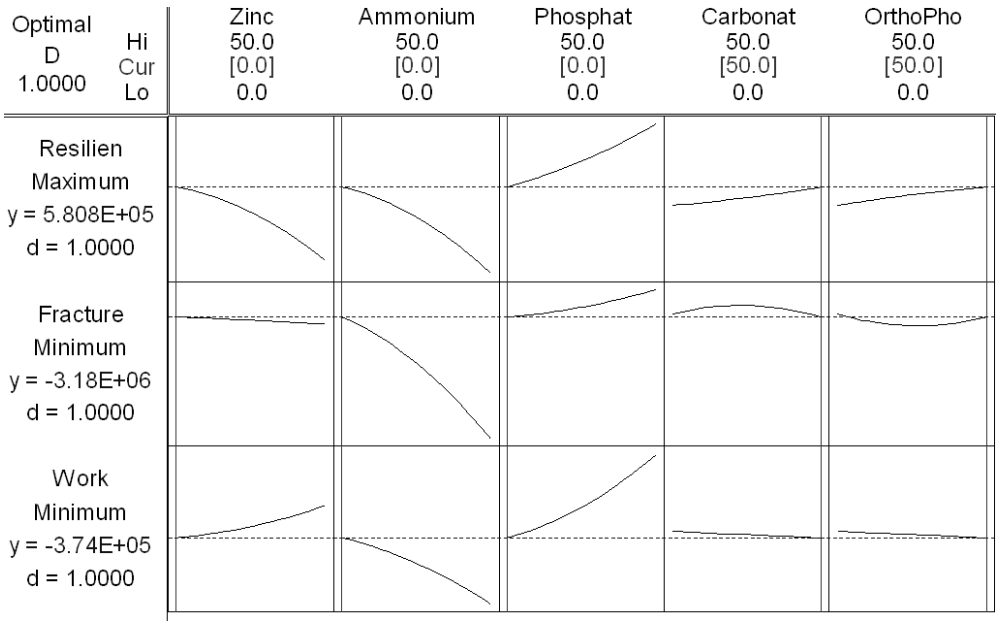

Figure 3.6: Desirability plots depicting the requisite variables for producing a salted-out PEO sample with the desired targeted responses.

The optimized formulation demonstrated ideal zero-order kinetics of drug release over a period of 12 hours (Figure 3.8). The actual release profile of diphenhydramine HCl from native PEO in is demonstrated in Figure 3.7.

The salting-out of PEO notably modified the physicochemical and molecular structural properties of basic PEO, which demonstrably enhanced the ability of the sample to achieve controlled drug release. The synchronized optimization of the resilience, fracture force and work performed for the salted-out PEO sample has facilitated the achievement of zero-order kinetics. Results have established that equal concentrations of Na_2CO_3 and K_2HPO_4 are desirable for achieving controlled release of drug from the salted-out PEO sample in a zero-order manner. Furthermore, Na_2CO_3 and K_2HPO_4 has a significant influence on controlling the release of drug from the salted-out PEO sample due to strong ionic interactions and bond formation between the PEO-chains and the presence of electrolytes ultimately leading to zero-order release kinetics.

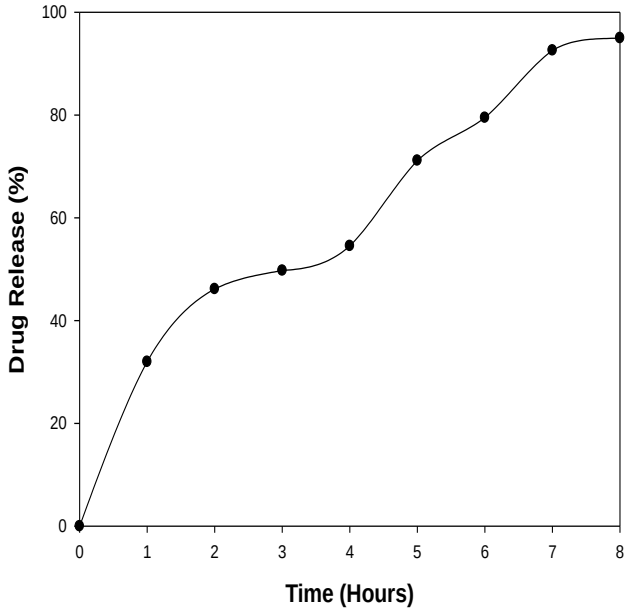

Figure 3.7: Profile of native PEO with Diphenhydramine HCL in PBS (pH 6.8, 37°C).

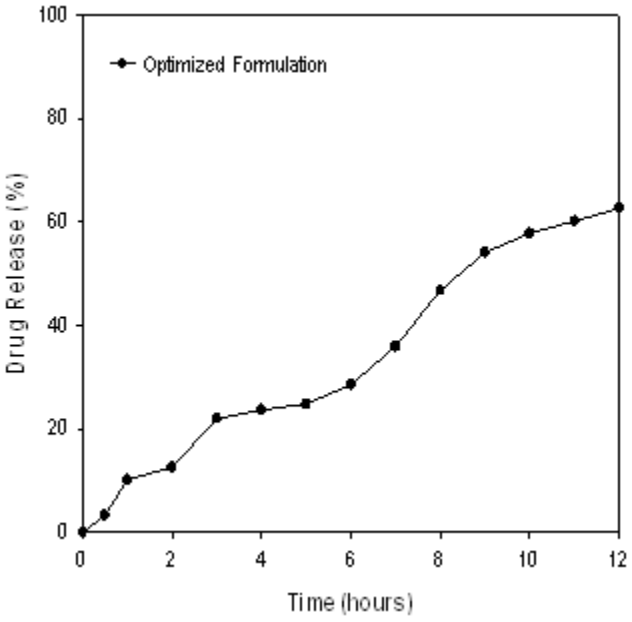

Figure 3.8: Profile of Diphenhydramine HCL displaying zero-order release from an optimized salted-out PEO-electrolyte sample in PBS (pH 6.8, 37°C).

SECTION 4

CONCLUSIONS AND RECOMMENDATIONS

4.1 Conclusions

This study explored the formulation of PEO-electrolyte combinations which were successfully prepared by combining a high molecular weight PEO with different statistically planned combinations of electrolytes. The statistical Box-Behnken design was employed to derive the 36 experimental formulation combinations of the independent formulation variables. The 36 formulations were microscopically analyzed and subjected to textural analysis. The salted-out PEO-electrolyte combinations were then further selected and analyzed. Assessment of the molecular structural transition and thermal compatibility analysis indicated minimal interaction between the electrolytes and PEO indicating that the polymer-electrolyte combination was stable enough to be employed as a medium for controlled drug release. *In vitro* drug release varied depending on the different electrolytes and their combinations. The type of polymer, molecular weight of the polymer, concentration of the polymer, different electrolyte combinations and solubility of the drug played a significant role in controlling drug release. After optimization of the fracture force, resilience and work performed values, results have established that equal concentrations of Na_2CO_3 and K_2HPO_4 are desirable for achieving controlled release of drug from the salted-out PEO combination in a zero-order manner. Furthermore, Na_2CO_3 and K_2HPO_4 had a significant influence on controlling the release of drug from the salted-out PEO combination due to crosslinking between PEO and the electrolytes ultimately leading

to zero-order release kinetics. The salting-out of PEO notably modified the physicochemical and micromechanical properties of basic PEO, which demonstrably enhanced the ability of the sample to achieve controlled drug release. The formulation strategy employed in this study where in our sample drug, diphenhydramine HCl was combined with a PEO-electrolyte combination has shown promising results in regulating drug release.

4.2 Recommendations

Further in depth characterization of the physicochemical and mechanical properties e.g., porosity and rheology of the optimized system may be conducted. *In-vivo* studies comparing the release of diphenhydramine HCl from the optimized formulation and the currently marketed diphenhydramine HCl formulations may also be conducted to determine differences in the bioavailability and the release patterns of the drug. The effects of increasing the electrolyte to polymer ratio and decreasing the electrolyte to polymer ratio should be investigated to determine the effect on the release.

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