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Formulation of an anti-tuberculosis drug delivery system

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2008-05-14T11:20:06Z
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CHAPTER 2

Theoretical Considerations for the Design of a Dispersible System Incorporating the Enterosoluble and Reconstitutable Multiparticulate Entities

2.1. Introduction

The proposed design of a novel oral anti-TB drug delivery system focuses profoundly on the principles of targeted delivery of INH and the delivery of this modified release system, together with RIF, to the patient.

INH is the most active drug for the treatment of TB caused by susceptible strains, which is administered in combination with RIF during the intensive and continuation phases of anti-TB chemotherapy. The rationale for targeted delivery of this drug to the small intestine was highlighted in Chapter 1 and arises from the urgent need to modify or segregate the delivery of RIF and INH upon co-administration, such that INH is minimally released in the gastric environment, owing to the induction of accelerated hydrolysis of RIF in acidic medium, with the formation of the poorly absorbed insoluble isonicotinyl hydrazone of 3-FRSV in the presence of INH (Singh et al. 2000a; Singh et al. 2000b; Mohan et al., 2003; Sankar et al., 2003; Mariappan et al., 2004).

This chapter aims to address the issues pertinent to the development of an enterosoluble multiparticulate system for the delivery of INH to the small intestine, i.e. the need for site-specific drug delivery in this system; gastrointestinal (GI) physiology relative to enteric-coating functioning and design rationale; the selection of an appropriate enteric polymer for this system;

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and applicable microencapsulation technologies for fabrication of enterosoluble multiparticulate dosage form.

Ultimately, considerations for delivery of the final dosage form as a dry dispersible system, incorporating the enterosoluble- and reconstitutable- multiparticulate entities, were delineated. Specifically, this relies on incorporation of appropriately selected water-dispersible gel-forming suspending agents within the reconstitutable form.

2.2. Site-Specific Drug Delivery of Multiparticulate Dosage Forms

Enteric-release or site-specific intestinal delivery is commonly prescribed and implemented for acid-sensitive bioactives belonging to the following categories: bioactives unstable or degraded at acidic pH (e.g. enzymes, proteins, macrolide antibiotics such as erythromycin) bioactives affecting gastric performance, bioactives causing local irritation of the gastric mucosa (e.g. valproic acid, NSAIDs such as diclofenac and acetylsalicylic acid), bioactives for which intestinal targeting is required for attainment of adequate concentrations in the lower GI tract (e.g. 5-aminosalicylic acid, prodrugs of mesalazine and sulfasalazine), and bioactives which accelerate the degradation of other bioactives in acidic media (e.g. INH and PYZ as described in Chapter 1) (Schreier, 2001); where the term 'bioactive' relates to a biologically active substance that has an effect upon a living organism, tissue, or cell (e.g. antibiotics, enzymes, vitamins, etc.).

A new concept of controlled release is that of site-specific release; this together with a major development in coating technology, was the concept fuelling the enteric-coating of drug-containing beads. An oral controlled-release system is typically made up of polymers and diffusion, bioerosion or degradation, and swelling or generation of osmotic pressure generally

regulates the mechanisms of release. Diffusion occurs when the polymer-drug mixture is exposed to the GI fluid, resulting in release of the drug from the system. Bioerosion or degradation occurs with certain polymer-drug complexes when they pass through the GI tract and swelling or generation of osmotic pressure commences when these complexes are exposed to the GI fluid, resulting in the release or expulsion of the drug. The advantages of oral controlled-release products are well-established: decreased fluctuation in serum concentration resulting in reduced toxicity and sustained efficacy; decreased dosing frequency with a consequent improved patient compliance; reduced patient care time and possibly reduced amount of drug required for incorporation (Ranade and Hollinger, 2003).

The area of oral controlled drug delivery is also witnessing an increase in popularity of multi-particulate (multi-unit) solid dosage forms such as matrix or coated pellets and granules, microparticles (Lippold, 1990), and currently, nanoparticle-based systems. Formulation as an oral multiparticulate drug-delivery system offers many biopharmaceutical advantages when compared with solid single-unit dosage forms (e.g. tablets and capsules) in terms of a more even and predictable distribution and transportation in the GI tract, which is fairly independent of the nutritional state, predictable GI transit time, and less localised GI irritation and disturbances. Due to their rapid dispersion and uniform spreading in the GI tract, they maximise drug absorption and improve drug bioavailability, reduce peak plasma fluctuations, and minimise potential side effects. Thus, intra and inter-subject variability of plasma profiles, which are common with single-unit regimens, are curtailed. They also provide greater product safety due to diminished retention of nondigestible polymeric materials upon chronic dosing. In view of the many benefits offered by multi-unit dosage forms, it is speculated that such systems are particularly useful for site-specific targeting within the GI tract (Follonier and Doelker, 1994; Ghebre-Sellassi, 1994; Pillay and Fassihi, 1999; Schmidt and Bodmeier, 2001; Hosny et al., 2002). Multiparticulates

also reduce variations in gastric emptying rates and overall transit times and are thus less susceptible to dose dumping than the reservoir or matrix type, single-unit dosage forms (Ghebre-Sellassie, 1994). Ultimately, these formulations provide greater flexibility in achieving desired drug release patterns.

On the other hand, multiple-unit preparations exhibit several disadvantages. Their manufacturing is decisively complicated and more expensive, the filling of gelatin capsules is difficult to accomplish especially in the case where different subunits are involved, and the preparation process of minitablets necessitates extra care and fine adjustments of tabletting machines (Efentakis et al., 2000). These shortcomings must be deliberated during the fabrication of an enteric-release system such that processing steps are limited.

2.3. Selection of an Appropriate Enteric Polymer

Enteric coatings are employed to target or delay drug delivery to the small intestine. Enteric-coated dosage forms have been used since 1884 when Unna coated pills with keratin (Brögmann and Beckert, 2001). Over the years, more than 60 materials have been employed for enteric-coating purposes, and are derived from two major types:

1. Reliance on erosion (e.g.carnauba wax, stearic acid, hydrogenated vegetable oil, ceresin, paraffin, spermaceti, gelatin-formaldehyde, keratin, zein, etc.). These slowly erode after ingestion and are only enteric if the dosage form has emptied into the intestine before the coat has eroded. This category is thus not consistently pH-dependent and, for the purposes of this investigation, not recommended.
2. Reliance on pH change, with demonstration of insolubility in gastric acid and rapid dissolution in intestinal fluid.

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Enteric coating polymers exhibiting pH-dependency/sensitivity are typically carboxylated, possessing mixed acid and ester functional groups, which are unionised and therefore insoluble, interacting with and swelling minimally in the low pH encountered in the stomach. The coating thus remains intact. As the pH increases on progression to the intestinal tract, these functional groups ionise causing swelling, and ultimately dissolution of the polymer.

Common enteric polymers commercially available include methacrylic acid and ethyl acrylate copolymers (Eudragit®L 30D), cellulose acetate phthalate (Aquateric®), polyvinyl acetate phthalate (Coateric®), and hydroxypropyl methylcellulose acetate succinate. Such polymers possess the carboxylic acid and certain ester groups on the polymer backbone and therefore demonstrate highly pH-dependent solubility. Depending on the number of carboxylic acid groups present, different polymers exhibit diverse solubilities at varying pHs (Hillery et al., 2001). Appropriate commercially available enteric polymers for inclusion in the system are represented in Table 2.1.

Table 2.1: Commercially available enteric polymers (adapted from Rathbone et al., 2003)

Polymer	**Threshold pH**	**Brand names**
Phthalate-based enteric polymers		
Cellulose acetate phthalate	6.0-6.4	C-A-P, Aquacoat CPD
Hydroxypropyl methylcellulose phthalate 50	4.8	H.P.M.C.P. 50; HP-50
Hydroxypropyl methylcellulose phthalate 55	5.2	H.P.M.C.P. 55; HP-55
Polyvinylacetate phthalate	5.0	Sureteric
Methacrylic acid-based polymers		
Methacrylic acid-methyl methacrylate copolymer (1:1)	6.0	Eudragit L 100/ L 12.5
Methacrylic acid-methyl methacrylate copolymer (2:1)	6.5-7.5	Eudragit S 100/ S 12.5
Methacrylic acid-ethyl acrylate copolymer	5.5	Eudragit L 100-55/ L 30 D-55
Miscellaneous enteric polymers		
Shellac	7.0	-
Hydroxypropyl methylcellulose acetate succinate	7.0	Aqoat AS-HF
Poly (methyl vinyl ether/ maleic acid) monoethyl ester	4.5-5.0	Gantrez ES-225
Poly (methyl vinyl ether/ maleic acid) n-butyl ester	5.4	Gantrez ES-425

A number of phthalate-based enteric polymers have been exploited commercially. Cellulose acetate phthalate (CAP) was synthesized in 1940 by Hiatt and was one of the first polymers used for its enteric properties (Felton and McGinity, 2003). CAP is insoluble in water, alcohol and chlorinated hydrocarbons but soluble in acetone and its mixtures with alcohol, ethyl acetate-isopropyl alcohol mixture and aqueous alkali (pH 6) (Rathbone et al., 2003). The CAP polymer exhibits rapid dissolution at a pH greater than 6 and is relatively permeable to moisture and gastric juices. Due to its high moisture permeability, CAP is susceptible to hydrolytic decomposition. Phthalic and acetic acid molecules commonly hydrolyse during storage and significantly compromise the degree of enteric protection that the film coating provides. The addition of a plasticising agent has been shown to improve the water resistance of CAP films. The pseudolatex version (Aquacoat® CPD) offers the convenience of aqueous-based processing.

Hydroxypropyl methylcellulose (HPMC) was esterified with phthalic anhydride to produce hydroxypropyl methylcellulose phthalate (HPMCP), which rapidly dissolves in the upper intestinal tract (Felton and McGinity, 2003). HPMCP is a more flexible polymer than CAP. HPMCP is insoluble in water but is soluble in alkaline media (pH 4.5) and in an acetone-water mixture. Several other derivatives of HPMC also exhibit pH-dependent solubility. Due to the limited compatibility of HPMCP with several types of plasticisers, hydroxypropyl methylcellulose acetate succinate (HPMCAS) was developed. HPMCAS consists of a cellulose backbone to which are attached methyl, hydroxypropyl succinate and hydroxymethyl acetate groups. The ratio of these side chains affects the extent to which the polymer becomes soluble in the intestine. The presence of ionisable carboxyl groups in the HPMCAS structure causes the polymer to solubilise at a high pH (> 5.5 for the LF grade and > 6.8-7.0 for the HF grade). This polymer exhibits good compatibility with a variety of plasticising agents and is commercially available under the proprietary name Aqoat® in a powdered form for redispersal in water.

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Polyvinyl acetate phthalate (PVAP) has been commonly utilised for coating solid dosage forms. This polymer is structurally similar to CAP containing the dicarboxylic phthalic acid in a partially esterified form. More rapid release of drug components occurs with PVAP because dissolution of this polymer occurs at a pH of approximately 5.0. Due to its lower moisture permeability, PVAP is relatively more stable to hydrolysis than CAP. PVAP is soluble in methanol and its mixtures with methylene chloride, ethanol and ethanol-water; and acetone and its mixtures with alcohols, ethyl acetate-isopropyl alcohol mixture and alkali (pH 5). Sureteric® is an aqueous dispersion of PVAP commercially available from Colorcon.

In the mid 1960s, Lehmann and Dreher developed copolymers of methyl methacrylate and ethyl acrylate as ester components with methacrylic acid for use as enteric polymers. Produced by an emulsion polymerisation process, they are commercially available in several forms with dissolution properties being dependent on the content of carboxyl groups in the polymer. These acrylic derivatives are anionic copolymers and are commercially available from Degussa Röhm, America under the proprietary name Eudragit®. The methacrylic acid copolymers are very frequently utilised for enteric-coating including application in colonic delivery. The enteric grades dissolve at a raised pH owing to ionisation of the carboxyl groups forming salts. Poly (methacrylic acid-co-ethyl acrylate (Eudragit®L 100-55, methacrylic acid copolymer type C) is a copolymer of methacrylic acid and ethyl acrylate and dissolves at a pH above 5.5. Among the anionic copolymers, it is the only polymer available as an aqueous dispersion. Eudragit®L 30 D-55 is an aqueous-based dispersion containing USP/NF methacrylic acid copolymer Type C and exhibits dissolution above pH 5.5. Acryl-Eze®, commercially available through Colorcon, is a relatively new fully formulated acrylic enteric coating system based on spray-dried USP/NF methacrylic acid copolymer Type C, containing plasticisers, pigments, and neutralising agents in a powder form for redispersion in water (Felton and McGinity, 2003). Other commonly

employed methacrylate polymers are Eudragit®L 100 (methacrylic acid copolymer type A, E L 100) and Eudragit S®100 (methacrylic acid copolymer type B, E S 100), which are copolymers of methacrylic acid and methyl methacrylate and are available as fine solids. Their aqueous solubility depends on the ratio of carboxyl to ester groups, being approximately 1:1 in E L 100 and 1:2 in E S 100. This has a direct effect on solubility with regard to pH sensitivity and these copolymers dissolve at pH 6 and 7 respectively. These are recommended for use with dissolution media such as acetone or alcohols.

Shellac is a material of natural origin and is now less popular in commercial pharmaceutical applications for enteric coatings. It is a purified resinous secretion of the insect *Laccifer lacca*. It is soluble in aqueous alkali at pH 7.0 and suited for drug release in the distal small intestine.

The polymethyl vinyl ether/ maleic acid copolymers are supplied as a 50%$^{w}/_{w}$ solution in ethanol. They are insoluble in aqueous acid pH conditions and suitable for use as enteric materials (Rathbone et al., 2003).

The diversity of enteric materials complicates selection, but trends in terms of implementation and availability must be realised. According to Signorino (2004), the current situation in terms of enteric-coating technology is as follows:

- CAP is still used and is applied from organic solvent and as an aqueous latex
- HPMCP is used and is applied from organic solvent or from an ammoniated aqueous solution
- PVAP is still available, but the manufacturer of this resin is now aggressively promoting an acrylic system
- HPMCAS is promoted as a dispersible powder and a hot-melt resin

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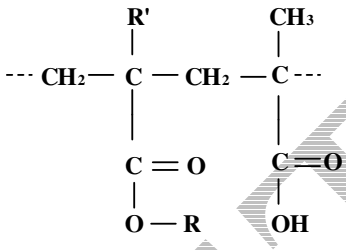
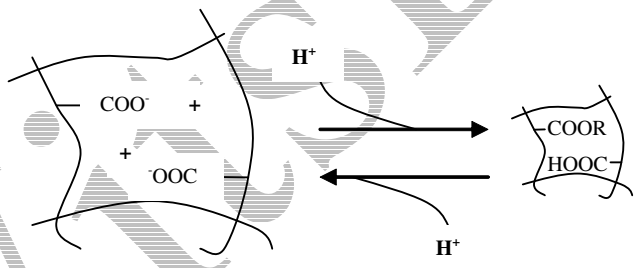
- Shellac is useful as an ammoniated solution but releases at a high pH (usually at pH 7.5)
- Zein is no longer actively used for enteric coatings
- Acrylics are currently the system of choice and competition has made several suppliers available. Chemically similar alternate materials are available, but their equivalence must be verified.

(a)



Methacrylic acid copolymer	R	R'
Type A/B	$-CH_3$	$-CH_3$
Type C	$-CH_2CH_3$	-H

(b)



Swollen state - hydrophilic (small intestine)

Collapsed state - hydrophobic (stomach)

Figure 2.1: Candidate enteric polymer: (a) Chemical structure of the methacrylic acid copolymers and (b) pH-dependent swelling and dissolution behaviour of native copolymers

Preformulation studies identified the methacrylic acid copolymers as being capable of formulating a variety of enteric-release systems when applied in different ways. Due to their versatility, biocompatibility and availability, these coating polymers were elected for further investigation in the formulation of enterosoluble multiparticulates. The pH-dependent, anionic

grades were selected, namely, the methacrylic acid and ethyl acrylate copolymer (methacrylic acid copolymer Type C, Eudragit L 100-55, M_w=250 000D, glass transition temperature, T_g=110°C), and methacrylic acid and methyl methacrylate copolymers (methacrylic acid copolymer Type A: M_w=135 000D, T_g=150°C, and methacrylic acid copolymer Type B, M_w=135 000 D, T_g=160°C), which dissolve at pH 5.5, 6.0 and 7.0 respectively by ionisation of their carboxylic acid groups (Figure 2.1).

2.4. Gastrointestinal Anatomy and Physiology Relative to Enteric-Coating Functioning and Design Rationale

In order to grasp the considerations engaged in during the design of a delivery system for targeting drug release to the small intestine and to evaluate system performance, the relevant anatomy and physiology of the GI tract must be comprehended. The stomach is situated in the left upper part of the abdominal cavity immediately under the diaphragm, with a size varying according to the degree of distention (Washington et al. 2001). Volumes of up to ≈1500mL following a meal and volumes of only 25–50mL when the stomach is in a resting 'collapsed' state following gastric emptying are attained (Bannister, 1995). The stomach is composed of the three parts: the fundus, situated above the opening of the oesophagus into the stomach; the central body; and the antrum or pylorus, situated above the pyloric sphincter connecting the terminal antrum and the duodenum. The fundus and the body store food temporarily, secrete digestive juices and propulse chyme, a milky mixture of food with gastric juices, to the antrum. The antrum grinds and triturates food particles and regulates the secretion of hydrochloric acid and the emptying of food (Hasler, 1995).

The pyloric sphincter has a diameter of 12.8±7mm in humans and acts as a sieve as well as a mechanical stricture to the passage of large particles (Hasler, 1995). The transit time in the

duodenum is comparatively short - less than 1 minute. The small intestine has a large surface area of 463m^2. The transit time in the small intestine of 3±1 hour is relatively constant and is unaffected by food (Davis et al., 1993; Klausner et al., 2003).

Enteric coatings rely on the differences in environment between the stomach and the intestine for their performance. The requirements of the desired enteric-release material thus demands deliberation of the GI physiology and functions. The most important GI physiological conditions affecting the functioning of enteric coatings are:

1. The pH of the stomach and intestinal contents
2. Gastric emptying
3. Enzyme activity in the GI tract

Elaboration of the principals of pH change and gastric emptying are necessitated, dictated by the inherent functionality of the enteric material.

2.4.1 The Significance of pH

This is by far the most important physicochemical and physiological factor parameter predicting the performance of enteric-release dosage forms. The principle of enteric coating is based on the discrepancy in pH in the GI tract. The pH in the stomach varies from 1.0 to 3.5 depending on the presence or absence of food and the reflux of intestinal contents into the stomach. Fasting gastric pH is thus usually steady and approximates 2, but there are short periods of time (7±6 minutes) characterised by higher values. After meal-ingestion is completed, the pH rapidly falls back below 5 and then gradually declines to fasting state values over a period of a few hours (Dressman et al., 1990). The pH of the small intestine usually ranges from 3.8 to 7.0 and duodenal pH averages 6.1. The pH of the large intestine ranges from about 7.5 to 8.0. This range

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results from the progressive dilution of the acid chyme from the stomach by bicarbonate ions in the pancreatic secretion, which is delivered by the bile duct to the duodenum, as well as from intestinal secretions. Based on the pH of the stomach and the small intestine, enteric coatings must be designed to resist dissolution at pH values below 4 to avoid disintegration in the stomach, but begin dissolving at pH 5 and above and be readily soluble at pH 7. The USP 24-recommended general drug release standard for enteric-coated articles thus specifies exposure of the dosage form for 2 hours to 0.1M hydrochloric acid followed by a buffer stage at which the dosage form is subsequently exposed to a solution of pH 6.8±0.05 achieved by drainage of the acid from the dissolution vessel and replacement with a phosphate buffered solution or adjustment of the pH of the acid solution (USP 24, 2000).

2.4.2 Gastric Motility, Emptying and Gastric Residence Time

Anti-TB medication is optimally administered on an empty stomach; however, patients may prefer administration with a meal to minimise GI intolerance. It is thus important to take gastric emptying in the fasting and fed states into account when considering the ultimate delivery system. The motility of the stomach is mostly contractile, which instigates simultaneous grinding of food into smaller particles, mixing with gastric juices, forward and backward movements of gastric contents, and emptying. Gastric emptying occurs during fasting as well as fed states. The pattern of motility differs markedly in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycles every 2 to 3 hours, that is generated in the stomach and progresses aborally to the ileocaecal junction. Its aim is to clear the stomach and the small intestine of indigested debris, swallowed saliva and sloughed epithelial cells (Hasler, 1995; Klausner et al., 2003; Arora et al., 2005). This is called the interdigestive myloelectric motor complex or migrating myloelectric motor complex (IMMC), which is further divided into following 4 phases, as described by Washington et al. (2001):

1. Phase I (basal phase) lasts for 40 to 60 minutes and is generally quiescent with rare low amplitude contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potentials and intermediate amplitude contractions. As the phase progresses, the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular high amplitude contractions for 5 to 15 minutes and is also known as the 'housekeeper wave'. It is initiated in the stomach in most cases (71%), or in the duodenum. Very high amplitude contractions, with a frequency of 4–5 per minute, and maximal pyloric opening, characterise this phase. This enables efficient evacuation of the stomach contents into the small intestine.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of two consecutive cycles and connects the maximal amplitude contractions to the basal phase.

The motor activity in the fed state is induced 5 to10 minutes after ingestion of a meal and persists as long as food remains in the stomach. The larger the amount of food ingested, the longer the period of fed activity, with usual time spans of 2 to 6 hours, averaging 3 to 4 hours. There are phasic contractions, similar to those seen during phase II of the IMMC. The stomach churns food while suspended fine particles, typically less than 1mm is size, are emptied every 20 seconds to the duodenum (Klausner et al., 2003).

Several factors influence the gastric emptying rate in addition to the volume and type of meal; these include the physical state of the gastric contents, various drugs, several disease states, body position, and physical exercise.

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When nondisintegrating dosage forms are administered in the fasting state, they typically are not retained in the stomach for over 2 hours due to the IMMC. On the other hand, in the fed stomach the gastric retention time of nondisintegrating dosage forms depends mostly on the dosage form size as well as the composition and the caloric value of food. Spheres with diameters <2.4 mm pass with the calorie-containing components of a solid meal; very small indigestible spheres can even pass freely into the small intestine at rates faster than solid nutritive food (Hasler, 1995).

In general, the gastric residence time of dosage forms is longer in the fed state in comparison to the fasting state, but this applies in particular to larger dosage forms. According to Khosla and Davis (1990), large dosage forms, such as 13mm diameter nondisintegrating tablets, were reportedly retained in the stomach for 171±29 min, almost an hour more than 7mm tablets, after a light breakfast of 360 kcal. It was suggested that 7mm tablets emptied during the fed state while 13mm tablets were retained until arrival of the subsequent sweeping 'housekeeper wave'. Large dosage forms are retropelled from the pyloric-antrum for further digestion and evacuation at the end of the fed state, or are retained until the arrival of the subsequent 'housekeeper wave'. In such cases, the gastric residence time is a function of the length of the digestive process (Klausner et al., 2003). Gastric emptying of coated tablets has thus been reported to be highly variable, taking from 30 minutes or less to 7 hours or more depending on the presence and type of food in the stomach, in addition to other factors. According to compendia, enteric-coatings should be able to resist gastric acid for at least 1 hour; however, certain tablets may not be able to remain intact if held in the stomach for substantially protracted periods.

Furthermore, because the gastric emptying time varies between individuals and in individuals, this unpredictability is the most serious disadvantage of an oral dosage form, especially when the drug is required to be administered three to four times daily.

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One approach to overcome these inherent disadvantages of an enteric-release dosage form is the use of multiparticulate dosage forms. Theoretically, each particle will act as a delivery system, independent of the other particles. As described, multiparticulate dosage forms suffer less from this disadvantage as the multiple-units offer more predictable gastric emptying, gastric emptying less dependent on the state of nutrition, a high degree of dispersion in the digestive tract and reduced variations in gastric emptying rates and overall transit times (Digenis, 1994).

Extensive investigation by Coupe et al. (1991) on the GI transit times of pharmaceutical dosage forms demonstrated a mean gastric emptying time of 105±45 minutes for multiparticulate dosage forms.

2.4.3 Considerations for Drug Release Testing and Development of an INH Assay Method

The fact that an enteric-release delivery system has adequate protection against gastric acid does not guarantee that it will be an effective dosage form, unless the enteric-coating dissolves or disintegrates on leaving the stomach, when it comes in contact with a new environment (Ranade and Hollinger, 2003). The system must thus demonstrate adequate disintegration with release of the entrapped drug following exposure to the higher pH media. Figure 2.2 depicts the proposed mechanism for targeted delivery of INH from enterosoluble multiparticulates.

Based on the multiparticulate nature of this system, exposure of the enterosoluble units to USP-recommended acidic media for an interval of 2 hours, followed by exposure to the higher pH media (in this study, pH 6.8 or 7.0, dictated in each instance by solubility characteristics of the methacrylic acid copolymer) for determination of adequate drug release, should provide an indication of desirable drug release characteristics. Furthermore, characterisation of the optimum

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system in terms of its erodibility in acidic and phosphate-buffered media will confer an ample picture of the gastroresistance of the system.

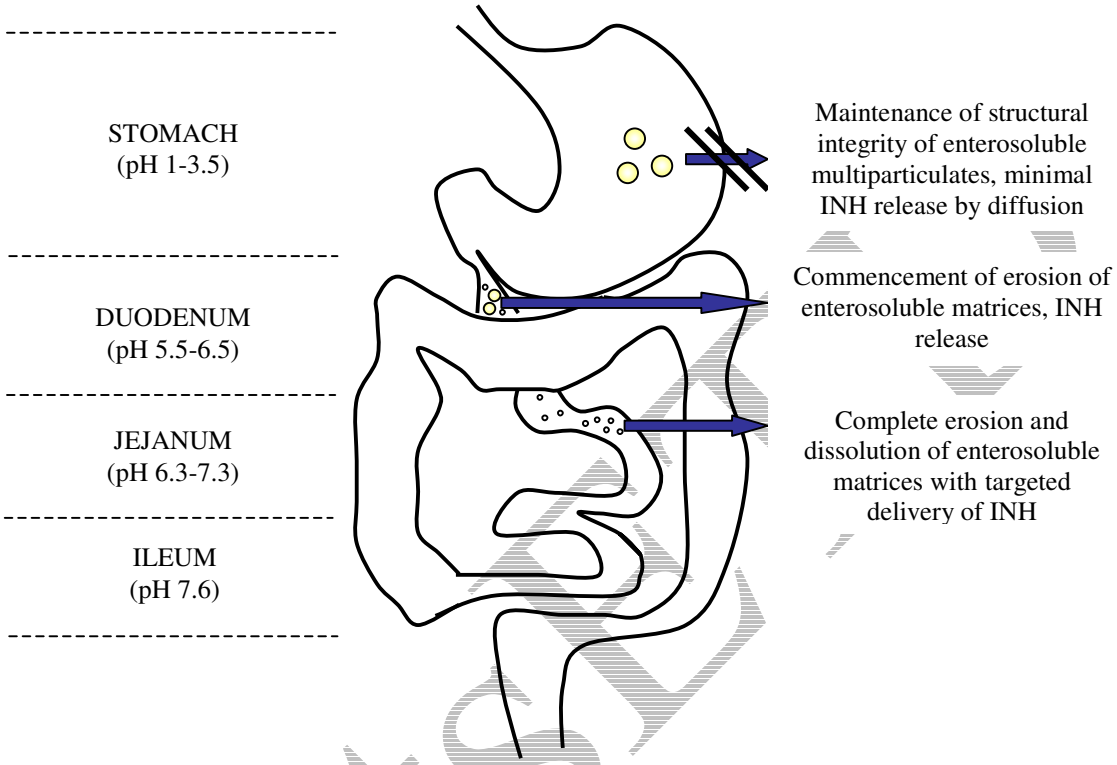

Figure 2.2: Schematic depicting proposed mechanism for targeted delivery of INH from enterosoluble matrices

2.5. Theoretical Design of an Enterosoluble Multiparticulate System Incorporating INH

2.5.1 Microencapsulation Technology

Microencapsulation, a rapidly expanding technology devoted to entrapping a drug entity inside one or more polymeric coatings, can provide a means of controlling the release characteristics of the INH. This process is arbitrarily differentiated from macrocoating in that the former involves the coating of particles with dimensions ranging from several tenths of a micron (µm) to 5000µm in size (Wieland-Berghausen et al., 2002).

Various methods for encapsulating or entrapping the water-soluble drug entity for the formulation of enterosoluble multiparticulates have been investigated during preliminary screening for feasibility and reproducibilty. Encapsulation methods (Table 2.2) that have been adapted to pharmaceutical use include air suspension, coacervation-phase separation (Kondo, 1979; Deasy, 1984), spray-drying (Bodmeier and Chen, 1988) and congealing, pan coating, and aqueous and non-aqueous solvent evaporation techniques (Huang and Ghebre-Sellassie, 1989; Bodmeier et al., 1994; Chang and Bodmeier, 1996). The choice of one particular method is determined to a large extent by the solubility characteristics of the active compound and the carrier material.

Table 2.2: Microencapsulation methods for the formulation of enterosoluble multiparticulates

Encapsulation Process	Applicable Core Material	Approximate Particle Size (μm)
Air suspension	Solids	35-5000
Coacervation-phase separation (salting-out)	Solids and liquids	2-5000
Pan coating	Solids	600-5000
Solvent evaporation (solidified emulsion)	Solids and liquids	5-5000
Spray-drying and congealing	Solids and liquids	600

2.5.2. Fabrication of Enterosoluble Multiparticulates by the Air Suspension Method

A widely used method to produce multi-unit dosage forms has been the production of sachets or capsules that contain enteric-coated granules. The standard technique for manufacturing modified-release multiparticulates consists of coating drug-containing granules or beads with aqueous colloidal latex or pseudolatex polymeric dispersions. In this case, a coating layer is applied to encapsulate the multiparticulate dosage form (Figure 2.3). This process is the paradigm for the design of enteric-coated dosage forms. Flexible polymers are required for this purpose and in terms of investigative work, only the methacrylic acid copolymers seem to have suitable properties to produce these dosage forms, possessing superior mechanical properties and low film

permeabilities (Brögmann and Beckert, 1991).

The use of aqueous-based coating systems in this work was predetermined by the shift in enteric-film coating technology towards such systems for environmental and economic reasons. With aqueous-based systems, the risk of explosions is diminished, costs implicated in solvent disposal are reduced and concerns of potential toxicity due to residual solvents in the films are eliminated (Guo et al., 2002).

For preparation of discrete solid particles coated with aqueous-based coating polymers, a conventional coating pan, fluidised bed, or spray-drying equipment have been used. Aqueous enteric coatings are optimally applied to beads and granules using a fluidised bed coater, a popular technique for coating of fine to intermediate-sized particles (Lehmann, 1989; Lehmann, 1997), and the coating pan being less satisfactory in this regard. Fluidised beds, in general, and the air suspension technique patented by Wurster, in particular, offer an attractive alternative to pan coating of multiparticulates. The coating of particles by the air suspension method has been utilised for several years by the pharmaceutical industry. The advantages of the process include:

- Rapidity of the operation
- Ability to control variables
- Uniformity of the coat produced
- Ability to coat particles of varying shapes and sizes
- No restriction on the kind of coating material or solvents employed
- Rapid evaporation is a characteristic of the fluidised bed system, which aids in avoiding the penetration of solvent into the core.

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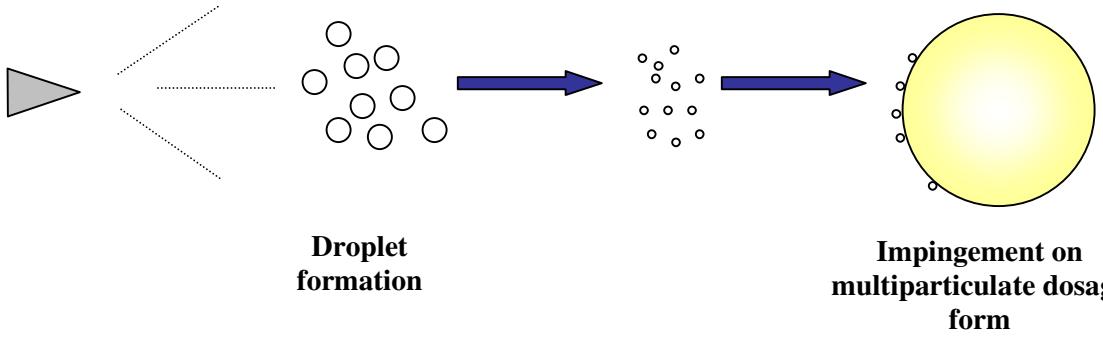

Figure 2.3: Schematic of the film-coating process (Gennaro, 1990)

The fluidised bed process varies with the spraying system (top, bottom, or tangential spray). In the top spray process to be employed in this work, the coating solution or dispersion is sprayed downwards onto particles, fluidised by air from below. During the fluidised bed coating process, consideration must be given to the shape and surface characteristics of the particles being coated as well as the increased physical stress of the procedure. Another important consideration is the amount of enteric coating required for protection. For aqueous film-coating, the drying efficiency of equipment is important to control in order to avoid erosion of the cores, adhesion of particles, penetration of moisture into the core, and decomposition of moisture-sensitive actives.

Proper adjustment of the airflow, the bed temperature, and the fluid application rate are critical to the successful operation of the process. The airflow rate and the temperature influence the drying kinetics. The drying kinetics in turn dictates the fluid application rate to be employed. Drying is a cooling process, thus the temperature at the particle surface is lower than either the inlet or exhaust air temperatures.

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2.5.3. Fabrication of Enterosoluble Multiparticulates by Solvent Evaporation-Emulsification

A convenient way of producing microsized particles is by solution of the bioactive in a dispersed phase also containing the dissolved wall material. To prepare a dispersed phase a suitable solvent must be available. Its nature – aqueous (*w*) or polar organic (*p*) or lipid (*o*) determines whether the emulsion is to be *w/o* or *o/w*, *p/o* or *o/p*. The continuous phase may be an inert mineral oil, vegetable oil or other immiscible solvent in the first case, or water with a viscosity-enhancing agent in the second. Appropriate emulsifiers of suitable hydrophile-lipophile balance are also required for the specific emulsion type. Emulsion may be direct or indirect; the latter involving phase reversal, and when the correct disperse phase is present, the droplet size is reduced to the required range by shear forces and the dispersed droplets finally solidified.

A solvent evaporation *p/o* emulsification method of microencapsulation was ultimately selected for implementation in ensuing investigations owing to its ability to yield uniform gastroresistant particles. The method is more correctly referred to as *p/o* instead of *w/o* since the polymer is dissolved in a polar organic solvent. The water-soluble nature of INH precluded the use of the more common *o/w* solvent evaporation procedure, which would cause partitioning of INH in the external aqueous phase resulting in little or no entrapment. Choice of a solvent system was based on the following criteria - solubility of ingredients, human safety, and compatibility with INH. Preliminary studies have shown that the preparation of microspheres from methacrylic acid copolymer A/B and drug substance was not successful without the use of a surfactant. This was due to the insufficient stability of the emulsion, which leads to the coagulation of the emulsion droplets. In the non-aqueous or *p/o* solvent evaporation method, the drug is dissolved in an organic polymer solution followed by emulsification of this phase into an external oil phase and solvent evaporation to form the microspheres (Huang and Ghebre-Sellassie, 1989; Bodmeier et

al., 1994).

Table 2.3: Parameters and process variables affecting solvent evaporation

Parameter
1. Molecular weight of polymer and concentration
2. Polymer crystallisation
3. Type of drug, method of incorporation, and drug loading
4. Organic solvent employed
5. Vehicle phase employed
6. Type and concentration of surfactant in oil phase
7. Evaporation temperature
8. Processing or stirring rate
9. Processing or stirring time

The uniqueness of this method lies within the smallness of the spheres and their subsequent use and adaptation in a wide variety of dosage forms. The smallness of particles allows for the wide distribution of drug-loaded moieties throughout the GI tract. The resultant microspheres can be used for the preparation of powders or suspensions. During the solvent evaporation process, several factors were considered to have an influence on the microsphere formation (Table 2.3). Factors that notably affected microsphere formation and that were considered in this investigation were the methacrylic acid copolymer type, drug loading (polymer: drug ratio), and stirring speed.

2.5.4. Fabrication of Enterosoluble Multiparticulates Employing the Principles of Phase Separation 'Salting-Out'

Simple coacervation and complex coacervation resulting in deposition of coacervate walls from aqueous solutions of polymer have been defined to signify separation of a colloid-enriched phase from a dilute colloid solution, leaving behind an almost pure water phase. In simple coacervation, the hydrophilic colloid, being uniform in charge is partially desolvated by addition of a competing substance of greater hydrophilicity or concentration, such as a salt or alcohol ('salting out'). Three stages are implicated in this process: in the first stage, the three formulatory components (drug, coating material, and solvent) are mixed. The second stage involves dispersal

of the coating phase in the solvent phase, and culminates in rigidisation of the coating, either thermally, chemically, or by desolvation in the final stage (Gennadios, 2002). Phase separation in lipophilic organic polymers requiring organic solvents for solution has been achieved using the parallel process to coacervation i.e. induction of concentrated-phase separation by temperature reduction or addition of miscible nonsolvents or substances competing for the solvent. Phase separation is a favourable method in investigative microencapsulation studies as apparatus requirements are simple for any operational scale (Donbrow, 1991).

2.6. Delivery of the Enterosoluble Muliparticulates

2.6.1. Rationalising Dispersible Multiparticulates as a Dosage Form

Chapters 3 to 5 focus on the preliminary fabrication, candidate formulation optimisation and characterisation of an enterosoluble multiparticulate system for the delivery of INH to the small intestine. Considering the final dosage form, these multiparticulates could be filled into hard gelatin capsules or compressed into tablets together with RIF. Formulation of these controlled release multiparticulates into these conventional dosage forms may result in several problems being encountered. As has been apparent, risk of tampering in preceding years has somewhat reduced the use of hard gelatin capsules.

For successful compression of multiparticulates, good flow properties are essential and the polymeric coating must be capable of resisting severe mechanical stress during compression. Poor flow properties result in content uniformity problems. Compression under high pressure can cause multiparticulates to rupture with loss of controlled release action. Poor compressibililty of the multiparticulates often requires the addition of large amounts of easily compressible excipients. This dilution effect could thus result in too-low drug content in the final dosage form, which would be undesirable in this system where a large dose of the anti-TB agents need to be

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delivered efficiently to the patient (Bodmeier and Paeratakul, 1994). Fassihi (1988) has studied the consolidation behaviour of polymeric particles. Plastic deformation and particle fusion were reported to be in operation during compression. Thus, the possible fusion that could occur during compression results in a disintegrating matrix with loss of character of the multiparticulated dosage form and a possible reduction in drug release.

An alternative approach for the oral administration of multiparticulates is to suspend them in a liquid vehicle to produce a suspension dosage form or incorporate them into a dry powder system, which is to be reconstituted with water by the patient immediately prior to administration. In addition to overcoming the aforementioned obstacles to the delivery of multiparticulates, they also provide the patient with ease of swallowing and dosing flexibility and are thus preferred among certain patient groups such as infants, children and the elderly (Bodmeier and Paeratakul, 1994).

Problems such sedimentation and caking of the suspended particles, degradation of the RIF or INH, leaching of the INH from the suspended enterosoluble multiparticulates into the carrier vehicle during storage, or alterations in the enteric-release pattern of the enterosoluble entities because of interactions between the vehicle and the enteric-polymeric material, are overcome with reconstitutable multiparticulates that are dispersed in a liquid vehicle just prior to use (Schmidt and Bodmeier, 2001).

2.6.2. Ability of a Suspending Agent to form an Extemporaneous Gel in Tepid Water: Formulation Considerations

It is imperative that the reconstitutable multiparticulates rapidly disperse to form a gelled network that will hinder immediate settling of the enterosoluble multiparticulates in addition to forming an

elegant suspension with favourable textural attributes. A *suspension* is a two-phase system comprising solid particles (the disperse phase) dispersed in a liquid continuous phase (the dispersion medium), representing an ideal dosage form for patients who have difficulty swallowing tablets or capsules. General considerations that are addressed during the development of a conventional drug suspension also apply to the development of a controlled-release suspension including the incorporation of suspending, wetting and sweetening agents (Bodmeier and Paeratakul, 1994).

The primary disadvantage of suspensions is their physical instability due to the tendency to settle over time. Additionally, the texture of suspensions may be unpleasant to patients and should be carefully considered during formulation. The reconstituted suspension system must maintain stability for the period of time lapsing between reconstitution and administration such that the multiparticulates remain suspended, as rapid particle settling may result in the dosage uniformity of the system being compromised. Physical stability in suspensions is controlled by: (1) the addition of flocculating agents to enhance particle dispersibility, and (2) the addition of viscosity enhancers to reduce sedimentation rate in the flocculated suspension. Optimum suspension functionality can be achieved by the inclusion of a gel-forming polymer. An extemporaneous suspension requires the incorporation of readily water-dispersible gel-forming polymeric agents for the formulation of a pharmaceutically acceptable dosage form.

Appropriate polymeric gel-forming suspending agents create a three-dimensional structure of interlacing particles or solvated macromolecules that restrict the movement of the dispersing medium. The definition of a *gel* is still a matter of debate (te Nijenhuis, 1997). Almdal et al. (1992) offered a phenomenological definition of a gel as being a soft solid or liquid-like material of two or more components, one of which is a liquid present in substantial quantity.

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Topologically, a three-dimensional network of chains interconnected by tie points builds up the gel; the space between points being filled by solvent (Hugerth et al., 1999; Hugerth et al., 2003). Gels are formulated employing polymeric gelling agents that undergo a high degree of cross-linking or association when hydrated and dispersed or dissolved in the dispersing medium. This cross-linking or association of the dispersed phase will alter and increase the viscosity of the dispersing medium, through restriction of the movement of the dispersing medium. Gels are classified by the strength of the cross-linkages. Some gels are cross-linked chemically by covalent bonds, whereas others are cross-linked physically by hydrogen or ionic bonds and by the physical entanglement of polymer chains (De Rossi et al., 1991). In general, gels formed by chemical bonding are irreversible gels since re-dissolution is precluded (Kara et al., 2003). A gel may contain small discrete particles (two-phase, thixotropic system), or may not appear to have discrete particles (one-phase system). The inclusion of a wetting agent to minimise clump formation may be necessary as gelling agents have a tendency to clump if added to the dispersing medium in a haphazard manner.

Agents possessing thixotropic properties are desired as such agents result in the formation of structured vehicles, which entrap the suspended particles such that sedimentation is adequately retarded. Upon standing, there is the formation of a structured network and a resultant external phase of high viscosity. The semi-solid structure is capable of undergoing breakdown under high shear stress. Excessive viscosity in the final suspension must be avoided to allow for ease of administration to the patient.

Suspending and gelling agents include hydrocolloids from each of the following categories (Table 2.4), employed in concentrations ranging from 0.5% to 5%$^{w}/_{v}$.

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Table 2.4: Common suspending and gelling agents

Category	Example
Natural hydrocolloids	Acacia, tragacanth, alginic acid, carrageenan, locust bean gum, guar gum, gelatin.
Semisynthetic hydrocolloids	Methylcellulose, sodium carboxymethylcellulose
Synthetic hydrocolloids	Carbopol®
Clays	Bentonite, Veegum®

In addition to possessing thixotropic behaviour and the ability to form a three-dimensional network capable of suspending the multiparticulates, the gel-forming suspending agent must fulfill such criteria as the ability of being easily incorporated into the material to be suspended and ready dispersibility on mixing with an appropriate vehicle, i.e. tepid water, without recourse to special techniques (Farley and Lund, 1976). Various suspending agents for extemporaneous dispensing have been described and proposed for incorporation in pharmaceutical suspensions intended for internal use (Sabra and Deasy, 1983). Trevean (1981) found guar gum, tragacanth and sodium carboxymethylcellulose (carmellose sodium) to be the most suitable suspending agents for extemporaneous use. A disadvantage, however, of commonly used suspending agents such as tragacanth and sodium carboxymethylcellulose, is that they delay rather than prevent sedimentation occurring and redispersion may be very difficult. Permanent suspensions can be achieved using an agent such as Carbopol®, however this is not suitable for extemporaneous use, dictated by the preparatory requirements of a high-speed stirrer and neutralisation with an alkali (Sabra and Deasy, 1983).

A preliminary survey of suspending agents for extemporaneous use conducted by Farley and Lund (1976) showed that the best all round performance was achieved by pregelatinised starches, sodium starch glycolate, calcium and sodium alginates, and aluminium magnesium silicate. Pregelatinised maize starches (Instant Clearjel®) and sodium starch glycolate (Primojel® and Explotab®) have shown good performance as hydrophilic polymer suspending agents for a range

of pharmaceutical suspensions and their *in vivo* degradation products are harmless. These starch derivatives are largely composed of the branched polysaccharides, amylopectin, and the linear polysaccharide, amylose, whose chains have been forced apart either by prior hydrolysis, in the case of Instant Clearjel®, or the introduction of bulky sodium carboxymethyl subsitituents, in the case of Primojel®, to render both components more cold water-soluble. The effect of variation in pH on the apparent viscosity of suspensions prepared from both suspending agents over the range which might be encountered in pharmaceutical suspensions was small and confirmed the general suspension suitability of both these materials, but especially sodium starch glycolate. Sedimentation and ease of dispersal data of sodium starch glycolate indicated that at a $1\%^{w}/_{v}$ concentration it was superior to other modified starches, including Instant Clearjel®, and various other suspending agents, such as alginate or silicate derivatives and tragacanth. The overall results presented thus indicated the aptness of sodium starch glycolate, particularly as a pharmaceutical suspending agent.

2.7. Concluding Remarks

This chapter sought to address the issues pertinent to the development and *in vitro* drug release characterisation of a multiparticulate enterosoluble system for the delivery of INH to the small intestine. The methacrylic acid copolymers were selected to impart enteric-release properties in the multiparticulate system owing to their versatility, biocompatibility and availability. Considerations for the delivery of INH-loaded enterosoluble multiparticulates and the poorly soluble RIF as a dispersible multiparticulate system were described; the properties of an appropriate system being the demonstration of ease of dispersion in tepid water, adequate suspending network formation, and patient acceptance in terms of textural palatability.

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