Synthesis of hydroxyapatite hollow microspheres and their use in gastric retentive drug delivery systems

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**SYNTHESIS OF HYDROXYAPATITE HOLLOW
MICROSPHERES AND THEIR USE IN GASTRIC
RETENTIVE DRUG DELIVERY SYSTEMS**

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Synthesis of Hydroxyapatite Hollow Microspheres and Their Use in Gastric Retentive Drug Delivery Systems

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A thesis submitted to the Nanyang Technological University
in fulfilment of the requirement for the degree of
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Abstract

A totally erodible gastroretentive dosage form made of calcium alginate, sunflower oil and hydroxyapatite (HA) hollow microspheres (HMS) as the radiopacifier was developed. Porous thin-shelled HA HMSs in a ping-pong shape were successfully synthesized in a nozzle-reactor system with a thermosetting polymeric binder. The synthesis mechanism of HA HMSs was investigated in terms of solid content and rheological property of the starting slurry. Multiple-unit alginate floating dosage form was synthesized through an emulsion gelation process with the inclusion of sunflower oil and HA HMS radiopacifier. These beads were able to float continuously on the acidic medium for 24 hours, as well as control release both hydrophobic ibuprofen and hydrophilic niacinamide or metoclopramide HCl in consistency with the extended floatation time. HMS inclusion was found to be able to enhance the niacinamide incorporation and further slow the release rate of ibuprofen. However, radiopacity was achieved at the cost of buoyancy because of disintegration of the HMSs. These beads are considered a promising oral control release dosage form for intragastric drug delivery.

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Yong Dan

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1. Introduction

1.1 Background

Although the administration of pharmaceutical formulations has evolved over the years and a number of ingenious ways, such as nasal, buccal, transdermal, ocular, rectal, intrauterine or intravaginal and parenteral delivery [1] have been put to application, oral delivery remains one of the most acceptable and hassle-free routes.

Drugs by oral intake pass through the gastrointestinal (GI) tract, the essential passage for the human body to assimilate water, nutrients and medicines, and so success in GI delivery of drugs reduces patients' discomfort and simplifies treatment. The necessity for gastric retention lies in the fact that dosage of a few times a day is generally needed because of restricted gastrointestinal transit time [2]. A critical research interest in GI drug delivery is the extension of gastric residence time (GRT). [3] Prolonged gastric residence time (GRT) and controlled release of drugs within the gastrointestinal (GI) tract helps to reduce dosing frequency and total dose, improve patient compliance and convenience, maintain a less fluctuating plasma, as well as reduce GI side effects. [4] Gastric retention of the drug is advantageous specifically when: [5]

- the delivered drug has a narrow absorption window in the small intestine,

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- if the drug is to be delivered in the upper small intestine, for example, in the treatment of peptic ulcer [6]. It enhances the bioavailability of the drug in that the slow release of the drug will be readily absorbed in the GI tract;
- the drug of interest is poorly soluble in alkaline pH;
- the primary absorption site of the drug is in the stomach;
- the release rate of the drug within the GI tract has to be controlled: when the therapeutic window is narrow and/or the drug is cleared quickly in the body;
- for those drugs that degrade in the colon.

As a result of the interest in extended GRT for optimal drug bioavailability and controlled release, the concept of gastric retentive dosage forms (GRDF) surfaced as early as in the late 1960s [7].

Light weight hollow microspheres (HMS) are often preferred to solid materials for certain applications, such as:

- low dielectric constant filler in electrical circuit board laminates [8];
- light weight composites [9];
- syntactic foams [10];
- encapsulation/Microencapsulation for drugs, cosmetics, dyes or inks and protection for biological macromolecules [11, 12, 13, 14];
- substance in catalysis and acoustic insulation. [15]

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The reason is these lighter HMSs, also known as microballoons or microbubbles [15] usually offer better properties such as higher strength-to-weight ratio [16] or lower dielectric constant [17].

Recently hollow microspheres made of biomaterials, especially ceramics and polymers, have found use in drug delivery [18], cell culture or tissue engineering [19, 20, 21, 22]. The introduction of HMSs to gastric retention dates back to 1990 when Kawashima and his co-workers [23] developed polymeric HMSs with Tranilast drug loaded in the shell. Details of the floating HMS drug delivery system will be explained in another section from page 43 onwards.

1.2 Research objective

There is a genuine need for a bioerodible gastro-retentive dosage form that has control over drug release in the stomach. Polymer-mediated floating type of GRDF prolongs gastric retention through escaping the gastric emptying by floatation on the top part of the gastric fluid. This concept appears to be an effective and rational approach to the modulation of the oral drug delivery in the upper GI tract. Nevertheless the floating dosage forms involved in many studies were either “single-unit” (only one floatation chamber available thus unreliable) [24] or were rather complicated for industrial production. For example, the calcium-alginate (Ca-Alg) floating dosage form recently developed by White et al. [25] appears to be an elegant system; however, the formulation was not studied in detail. And to date the controlled drug release

1. Introduction

from GRDFs has not been reported. Increasing gastric retention time without concurrently prolonging drug delivery is practically useless. Although alginate gel is an appropriate material for gastric drug delivery, previous research was unable to achieve a release longer than two hours. Therefore, alternatives have to be developed for drugs with different hydrophilicities to achieve a consistent release profile as well as the extension of GRT.

To facilitate the examination of the intragastric drug carriers for doctors, radiopacity is an important factor. However, the radiopaque labeller in a gastric drug delivery system does not have to be permanent. Secondly heavy ceramics like barium sulfate may compromise the buoyancy performance of the floating dosages. In this case, radiopaque hydroxyapatite (HA) hollow microspheres (HMS) seem a good candidate for acting as radiopacifier since HMSs are light compared with solid materials. The feasibility of using HA HMS as the radiopacifier is worthy of further study.

Therefore this work aims to:

- (a) synthesize hydroxyapatite (HA) hollow microspheres (HMS) as the radiopaque labeller to incorporate into the alginate gel floating dosage system;
- (b) develop a totally erodible drug delivery system based on alginate hydrogel that is capable of constant floatation over the simulated gastric fluid for 24 hours;

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- (c) control the release of both hydrophobic and hydrophilic therapeutic agents from such a hydrogel dosage form during the extended period of GRT;
- (d) understand the release mechanism of the device and model the release profile.

1.3 Outline of this work

The research work addresses the following key points:

- (a) Synthesis of a floatable and erodible GRDF
 - Synthesis of HA HMS as radiopaque fillers
 - Gelation and buoyancy enhancement of Ca-Alg gel beads
- (b) Characterization of such a GRDF and the “in vitro” release profile of the GRDF
 - Physical properties of the GRDF
 - Drug release characteristics of the GRDF
- (c) Release mechanism study and mathematical drug release model application
 - Selection and analysis of critical factors based on experimental results
 - Application of the mathematical model

2. Literature Review

This chapter comprises four major sectors: the HMSs, HA, gastric retentive dosage forms, and mathematical modelling of hydrogel drug delivery systems.

2. 1 Hollow Microspheres (HMS)

2.1.1. Fabrication of Hollow Microspheres

Wilcox et al [15] categorized the conventional synthesis of hollow spherical materials into three major concepts as further elucidated in the following paragraphs.

- Templates or Sacrificial Cores

This approach is to firstly deposit a coating material onto some selected spherical templates or cores, and subsequently to dissolve the cores in a solvent or volatilise them by heating, leaving behind the coating which forms the shell of the desired HMSs (Figure 2-1). [20, 26, 27] A widely reported example was the self-assembly strategy by means of surface charges or chemical properties. [28, 29, 30, 31, 32]

2. Literature Review

Figure 2-1 Mechanism of HMS formation via Sacrificial Cores

- Nozzle-Reactor System

A nozzle-reactor system refers to a certain kind of technical equipment used to create HMSs, for example a spray dryer. [33, 34,35] In a nozzle-reactor system, a large void can be created in a liquid droplet upon heating. (Figure 2-2) [15, 36, 37] Detailed elucidation on spray drying will be discussed under a separate sub-heading.

Figure 2-2 Mechanism of HMS formation involving blowing agent

- Emulsion/Phase Separation Techniques

This synthesis of HMSs relies on surface/interfacial tension forces and immiscibility between the phases to create emulsions of spherical liquid

2. Literature Review

globules. As shown in Figure 2-3, the continuous liquid phase with limited miscibility allows the presence of the emulsion, while it extracts the solvent from the dispersed globules, leading to precipitation of the desired HMS-forming material. Separated from the liquid matrix, the precipitated globules can be processed into rigid hollow or solid spheres of interest thereafter. [18, 22, 38, 39]

Figure 2-3 Mechanism of HMS formation by liquid extraction

2.1.2. Principles governing HMS formation during spray drying

Spray drying consists of four steps, namely, feed atomization (to create a spray), spray-air contact, drying of the spray, and product recovery. [40] It is a transformation of the feed from a fluid state via a suspended spray in hot drying medium then finally to a dry particular form. HMS synthesis in a spray dryer is determined by the drying conditions and the nature of the feed. [41, 42]

In order to understand the HMS formation, a typical drying process with respect to a single droplet in a co-current rotary atomizing spray drying system is explained further. As Kowalski described [43], the drying is made up of three stages. The beginning stage is the preheating period and thereafter a dynamic equilibrium is quickly established. The consecutive stage is the first period of drying, characterized by a constant drying rate and constant droplet surface temperature. Droplet surface saturation is maintained by adequate moisture migration from within. The final stage is the second period of drying. The moisture inside the droplet is being depleted and not able to sustain a constant droplet surface temperature so that drying rate keeps falling and the moisture content is reduced to below the critical moisture content.

Masters' [44] elaboration and Charlesworth and Marshall's illustration [45] about solid formation during the drying of droplets/spray containing dissolved solids are referred to on this occasion. The information may not be exactly applicable but it helps to explain the phenomena. As depicted in Figure 2-4, at the end of the first period of drying (the critical point), the droplet begins to heat up and sub-surface evaporation becomes possible so that the liquid inside the droplet reaches its boiling point and vapour occurs. Meanwhile the surface of the droplet begins to solidify and a crust around each droplet forms. The pressure can be set up within the droplet hence providing the kinetic energy for "bubble blowing". The nature of the crust determines the shape

chang fac2 id of the crust()Tjt

2. Literature Review

droplet to expand. But when the crust is impervious the resultant droplets may rupture or even disintegrate. When it is semi-impervious and elastically flexible, hollow particles can be blown although the chance of collapsed morphology still exists.

Figure 2-4 Diagram of HMS formation during droplet-drying

Masters [44] also established four kinds of tendencies of HMS formation in the book, and Lukasiewicz [46] reorganized the mechanisms as follows:

- A semi-impervious elastic layer to vapour flow forms around the droplet surface. Reduced evaporation results in temperature increase and the interior moisture vaporizes. The droplet expands with the increase in partial vapour pressure as mentioned.
- For soluble salts, liquid flows to droplet surface where evaporation and salt crystallization occur. Drying rate is faster than diffusion of solid back into the droplet interior. On completion of evaporation, air voids are present.

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- For spray of insoluble solids, mass migrates with moisture outwards to the droplet surface under capillary action. This leaves the centre core empty.
- Air entrained or air generated in the feed contributes to air spaces within the droplets.

All in all, the HMS formation in spray drying is a multi-factor issue where both operative parameters and material properties play key roles.

2. 2 Review on Hydroxyapatite (HA)

The main inorganic composition of human hard tissue, appears to resemble predominantly the relatively simple synthetic form, hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$, Mw=1004.8, $\rho=3.16\text{g/cm}^3$ [47, 48, 49]).

Efforts on drug delivery with HA ceramics were seen mostly for antibiotics or anti-inflammatory agents [50 , 51 , 52 , 53 , 54 , 55], anti-cancer chemotherapeutic agents [56, 57, 58], proteins [59, 60, 61, 62], insulin [63], and growth-hormones or growth-factors [64 , 65]. The rationale of the aforementioned works lies in the need for a skeletal drug delivery system (SDDS [66]) because the localized delivery was considered to be able to reduce systemic toxicity and increase the effectiveness of therapy. [67]

2. Literature Review

2.2.1. Physiochemical Stability

Only two forms of calcium phosphates are stable at room temperature and in an aqueous ambient (shown in Figure 2-5 [68]), namely, $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ (dicalcium phosphate, DCP) at $\text{pH} < 4.2$ and $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (hydroxyapatite) at $\text{pH} > 4.2$. In vitro dissolution rate of calcium phosphates is governed by a number of factors: [69, 70, 71]

- composition of the buffered or unbuffered incubating fluid;
- pH of the solution
- degree of saturation of the solution
- solid/solution ratio
- surface per unit weight of the material
- crystallinity and composition of the material

The dissolution of HA in the stomach thus simplifies as a matter of time, depending mainly on the pH value. But pH of gastric fluid varies from 2 to 6.5 at different stages of gastric motility. And this variation will be discussed in detail in the upcoming sections.

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Figure 2-5 Solubility diagrams of various phases in the CaO-P₂O₅-H₂O system as functions of pH

2.2.2. Radiopacity of HA

HA is radiopaque per se since this is the physical basis of modern medical X-ray examination of skeletal tissue. HA is about isodense radiopacity with the bone or dental hard tissue so that it is hard to distinguish the HA implant from the host bone. To date, there is little literature on X-ray opacity of HA. However Shikinami et al [72] studied the radiopacity of a HA reinforced poly-L-lactide composite with a 20-50wt% HA content. Although there was overlapping between bones and composites, the composites were still found to be X-ray detectable and distinguishable in almost all cases. [73] While in a gastric retentive system, the overlapping between bones and HA composites seems not a problem as the stomach organ is X-ray invisible.

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2.3 Gastric Retentive Dosage Forms (GRDF)

2.3.1. Basic Physiology of the Stomach

It is necessary to understand the basic physiology of the stomach and its characteristic motility pattern before designing a proper-functioning GRDF.

2.3.1.1 Anatomy of the stomach

The human digestive system, simply put, is a tortuous pipe about nine meters long (This is the length after death. In a living person, the length is about half of above described (4.5m) because of constant muscle tone). [74] running through the middle of the body from the mouth, throat (pharynx), oesophagus, stomach, small intestine (consisting of the duodenum, jejunum, and ileum), large intestine (including the cecum, appendix, colon and rectum) to the anus (Figure 2-6, [75]). The stomach is essentially a J-shaped organ with a capacity of storage and mixing as shown in Figure 2-7 [76]. It is anatomically divided into four parts: the cardia, the fundus, the body and the antrum (or pylorus). The proximal stomach, made up of the fundus and body region, serves as a reservoir for the ingested materials. They are also responsible for the secretion of digestive juices and propulsion of chyme, a milky mixture of food with gastric juices to the antrum. While the distal region, namely the antrum, acts as a pump for mixing motions and gastric emptying. [77] The pyloric sphincter is a sieve-like stricture with a diameter of 12.8 ± 7 mm in human beings [78, 79]. During digestion, it is closed when the peristaltic wave approaches the distal antrum thus large solid particles are retained in the stomach and only small quantities of food are allowed to pass into the

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duodenum. The volume of the stomach varies from up to 1500ml [80] following a meal to a collapsed state with a resting volume of 15 – 50ml [81] after the food has been emptied.

Figure 2-6 Human digestive system

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(a) Anterior view of regions of the stomach

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Figure 2-7 External and internal anatomy of the stomach

2.3.1.2 pH variation in the stomach

Fasting gastric pH usually is steady around 2, except for some short periods of 7 ± 6 minutes characterized by higher values. In the fed state, food buffers and neutralizes gastric juice, thus raising the pH up to about 6.5. After completion of ingestion, pH falls quickly back below 5 and gradually declines to fasting state values within several hours. [82] The pH values in duodenum

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and other sections of the small intestine are reported to be 6.1 and 6 – 7 respectively [83].

2.3.1.3 Gastrointestinal motility and emptying

The movement of the GI tract is a continuous motility pattern consisting of two modes, the digestive motility pattern and the interdigestive motility pattern corresponding to the fed and the fasting state respectively. The contractile motility duration and characteristics are illustrated in Figure 2-8.

Figure 2-8 Pictorial representation of typical motility patterns in the interdigestive and digestive state [84]

During the fasting state, gastric emptying is characterized by a distinct cycle of electromechanical peristaltic activity known as the interdigestive migrating

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myoelectric complex (IMMC). [85] The IMMC begins in the proximal stomach and migrates aborally through the small bowel. Solids with a size varying from 1 – 2mm [86] to 10mm [87] can be emptied from the stomach in this state. The total IMMC experiences four phases of motoric activities as illustrated in Figure 2-8. Phase I (basal, quiescent) is a period of 30 – 60 minutes with little or no motor activity except for occasional low amplitude contractions. Phase II (preburst) lasts for 20 – 40 minutes with intermediate amplitude of intermittent contractions and bile secretion [88]. Phase III (burst) is also termed as 'housekeeper wave' and has a duration of 10 – 20 minutes. The pylorus remains open and achieves the maximal opening in this phase [89]. Very high amplitude contractions with a frequency of 4 – 5 times per minute [81] sweep the indigestible solids from the stomach down to the duodenum. Phase IV is the transition period between phase III and phase I with a length of less than 5 minutes.

The motor activity in the fed state is induced 5 – 10 minutes after ingestion of a meal until the food has been totally emptied from the stomach. Its contractile motion churns the food, and food particles of less than 1mm [90] are then propelled to the duodenum. Unlike in the fasting state, the pyloric sphincter is closed during the fed state and opens to allow small quantities of food to pass into the small bowel. [85] The residence time of the food in the stomach depends on its nutritive and physical properties. A larger amount of food takes longer to empty from the stomach. Hence the fed activity lasts longer, for usually about 2 – 6 hours, and more typically, 3 – 4 hours [91]. Emptying rate

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is relatively constant at $200 \text{ kcal}\cdot\text{hour}^{-1}$, regardless whether the calories are in the forms of fats, proteins or carbohydrates. [75, 91] Since fats normally have higher calories per unit weight, the weight emptying rate of fats is considerably slower than the others. A large quantity of non-nutrient liquid (more than 150ml) empties in a first-order manner of half emptying time of 8 - 18 minute, by converting the motility into a fed-like state. While the emptying of small volumes of liquid depends on the current phasic activity, most of it is gone before the arrival of phase III. [4] Solids empty much more slowly. Digestible non-fat solids are ground for up to 1 hour and subsequently emptied in zero order kinetics. [91] Indigestible solids of size 2mm or larger stay in the stomach until the arrival of phase III, the housekeeper wave. [4]

As in the cases between food digestion and the phase II of IMMC, the stomach contractions are unable to empty undigested materials (including non-disintegrating dosage forms) through the relaxed pyloric sphincter. A retropulsion reflex is activated to propel the materials from the pylorus and the distal antrum back to the proximal antrum and the stomach body [92,93]. Besides, gastric emptying varies depending on posture [94], gender, age [95], osmolarity, pH of food [96], mental stress and disease state [97].

2.3.2. Requirements for GRDF

Klausner et al summarized that an ideal GRDF would have the following advantageous features: [91]

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- retention according to the clinical demand;
- convenient intake;
- ability to load substantial amount of drug with different physiochemical properties and release in a desirable manner;
- complete degradation or easy removal after completion of its function, preferably within the stomach;
- FDA approved bio-safe ingredients;
- little or no impact on gastric motility including emptying;
- no adverse side effects such as irritation to the gastric mucosa;
- low cost and long shelf-life.

2.3.3. Approaches to Gastric Retention

Therefore the key to gastric retention lies either in delaying the arrival of Phase III housekeeper waves or in escaping the sweeping action of the housekeeper waves.

To date, a number of proposals have been made for the gastric retention of the oral dosage forms. Although there are different nomenclatures for these approaches among reported publications [85, 91, 98], in effect, the mechanisms are similar in most cases. For example, the floating system is known as hydrodynamically balanced system (HBS) or low density GRDF, while the swelling or expanding system is also known as plug type dosage form. In this review, I intend to classify the published approaches based on the following aspects:

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- Floating dosage forms of low density that float above gastric fluid;
- High density GRDFs that sit on the belly of antrum to prevent emptying;
- Swelling or expanding systems that resist the emptying by plugging at the pyloric sphincter;
- Bio- or muco-adhesive GRDFs that stick to the epithelial mucosa in the stomach;
- Drugs or pharmaceutical excipients that slow the motility of gastrointestinal tract.

Some gastric retentive systems are combinations of two or more among the abovementioned different approaches. Among these solutions, the most popular are floating dosage forms and swelling systems, for the reason that there are some practical difficulties in realizing other concepts or the potential side effects are hard to offset. The safer floating dosage form is selected in this study as a potential hazard of clogging exists among swelling systems and floating dosage forms do not adversely affect the gastric motility. The detailed pros and cons of each system are discussed here onwards.

2.3.3.1 High density system and administration of passage-delaying drugs

The effectiveness of high density pellets has not been confirmed because of scarce in vivo data on both animal studies and clinical investigations. [99] Co-administration of gastric-emptying delaying drugs is not favoured either because of questionable benefit-to-risk ratio and potential side effects. [100]

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2.3.3.2 Bioadhesive system

Bioadhesives that bind directly to a biological membrane (cell layers) or to mucus, the heterogeneous secretion layer on epithelial cells, [101] provide another approach for drug immobilization and localization in the GI tract. [102] Bio-adhesion is sometimes quoted as muco-adhesion. The term “muco-adhesion” normally refers to the adhesion to the mucin layer lining. [103]

The idea of adhesion is no less challenging than other means of gastric retention since problems associated with the adhesive systems include three major aspects. Firstly, GI mucosa is not directly accessible so that there is trouble achieving the initial attachment in the absence of mechanical force. Secondly, GI contractile motion is the dislocating force for the bioadhesives and the presence of food makes the attachment difficult. Thirdly, the mucin turnover rate in the stomach is substantial in both fasting and fed state, and so adhesives tend to be detached along with the mucus. [4]

2.3.3.3 Swelling or expanding system

The swelling system experiences three stages in the stomach to achieve its functionality. The first configuration is a small form that is easy to take orally. The swollen or expanded configuration should be achieved in a short period of time once the dosage form is delivered in the stomach. This will prevent emptying like a “plug” to the pylorus before the release of active agents is completed. The final configuration has to be a smaller “collapsed” form for convenient evacuation after the dosage form finishes its function. So far there

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are basically two kinds of design mechanisms. Swelling happens due to osmosis, and expansion occurs due to mechanical shape memory.

Many interesting and smart expansion designs have been reported in this shape memory category. The dosage forms are primarily made up of two parts: the expandable part and the drug reservoir. Normally the expandable part consists of non-disintegrative materials while the drug reservoir is composed of erodible or degradable materials for a desirable release profile.

Figure 2-9 Y-shape unfolding dosage form from Sonobe et al [106]

Griffin and Brewer [104] developed an unfolding sheet-like dosage form which resembles a scroll. The double layer sheet contains a drug layer and a resilient non-erodible layer which springs back to total relaxation after the securing bandages dissolve to achieve an expanded configuration. Recently Klausner and co-workers [105] reported a design similar to that of Griffin and Brewer's. Sonobe et al [106] developed a 'Y-shape' three-arm unfolding

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design (Figure 2-9) which carries the drug in the 'limb', while the Y-shape joint is made of a shape memory material which ensures expansion under prolonged shelf time. There are gas-pressure driven expanding capsules documented too [107]. In this design, the retention bladder is blown against regurgitation thus enabling retention.

Other designs focus on the swelling properties of the materials. Johnson and Rowe [108] suggested a dosage form made of thiolated gelatin, a crosslinking agent and a drug. The gelatin hydrates, swells and crosslinks to form a much larger matrix to prevent emptying through pylorus. Mamajek and Moyer [109] developed an envelope form drug carrier comprising of swellable resin or hydrocolloid as the envelope material. The design of Urquhart and Theeuwes' [110] was similar to Mamajek and Moyer's envelope except the former design was more of a reservoir drug carrier and the latter design was made up of many tiny drug pills contained within a hydrogel, which was considered as a matrix drug carrier. Currently Chen and co-workers [85, 111] have publicised their work on super porous hydrogel (SPH) composites. These hydrogels can swell to a remarkable ratio of over 100 times the original weight of the dried matrix and still retain substantial mechanical properties. Animal trials carried out on beagle dogs showed that retention was achieved for more than 24 hours in the fed stomach while administration to a fasting dog showed rapid evacuation.

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One of the most critical safety demands that swelling and expanding systems should meet is that the presence of dosage form should not interfere with gastric motility or impose any adverse impact on gastrointestinal tissue. Furthermore time for the expansion and the collapse of the dosage form ought to be well controlled and reproducible. A comparatively faster degradation process is normally desired for safety considerations as dosage accumulation is a major clinical concern in reported documents [112,113]. This is because repetitive doses caused by incomplete collapse/degradation can lead to hazardous situations. This is actually thought to be the most important aspect that should be considered during design and development, as the swelling and expanding systems exhibit the tendency to remain lodged at the pyloric sphincter, hence increasing the possibility of repetitive dosage and resultant toxicity.

2.3.3.4 Floating dosage forms

Floating systems that have a bulk density lower than the gastric fluid are among the most researched GRDFs. The drawback of these systems is that they rely on a certain amount of liquid to float on. Yet the advantage is obvious too: there is literally little or no adverse influence on the gastrointestinal motility during the prolonged retention time.

Besides advantages like sustained release during prolonged retention time [114,115], site-specific drug delivery [116,117], and enhanced bioavailability compared with conventional tablets [118,119], floating systems provide

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another perspective for treating gastroesophageal reflux by forming a “floating seal” [120,121] and biliary gastritis [122]. They even help those patients with gagging or choking experience when swallowing medicinal pills. [123]

The last three decades of research on floating dosage forms has generated interesting results. There are two major designs of the floating systems, the non-effervescent system and the effervescent system.

- Non-effervescent system

This category includes the non gas-generating dosage forms that either utilize buoyant materials or have a lower density than that of the gastric fluid.

A typical hydrodynamically balanced system (HBS) is a matrix system made up of a drug and a gel-forming hydrocolloid, which swells in contact with gastric fluid and maintains shape integrity. [124] The air trapped by the swollen polymer confers a bulk density lower than unity within the gelatinous barrier as Figure 2-10 demonstrates. Sheth and Tossounian's [125 , 126 , 127 , 128] formulations of hydrocolloid inclusions such as methylcellulose, HPC, HPMC, hydroxyethylcellulose, and sodium carboxymethylcellulose belong to this category.

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Figure 2-10 Illustration of floating HBS

Bolton and Desai [129] described a design made of agar and light mineral oil to enhance buoyancy. A similar idea of utilizing fat/oil to improve buoyancy was also reported by Ushimaru et al [130].

The buoyancy of the dosage form could be achieved by a specific floatation chamber as shown in Figure 2-11. This kind of device normally comprised of a drug reservoir and a floatation chamber. For example, a granule type of floating carrier for diclofenac sodium documented by Yuasa et al [131] employed a porous calcium silicate coated with hydroxypropylcellulose L grade (HPC-L) and ethylcellulose as the materials for the floatation chamber.

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Figure 2-11 Schematic representation of dosage form with floatation chamber

[132]

In early research, floating dosage forms were mostly single-unit systems, and their performance tended to be unreliable and fortuitous, in other words, the “all-or-nothing” phenomenon. [133] On the contrary, more recent multi-unit systems showed advantages in the following aspects [134]: more predictable drug release kinetics, insignificant impairing of performance due to failure of a few individual units, larger margin of safety against failure, capability of co-administration of units with different release profiles or different substances, less chance of localised mucosal damage, more reproducible emptying time, and reduced intersubject variability.

Known to be insoluble and resistant to acidic media, calcium alginate (Ca-Alg) is the resultant of the complexation of the polyguluronic sequences by calcium ion. [135] Recent development of multi-unit floating systems based on calcium alginate was carried out by three groups of researchers, Whitehead et al. [25], Iannuccelli et al. [134] and Murata et al [136]. Their designs are summarized in Figure 2-12.

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Figure 2-12 Summary of design characteristics of three multi-unit floating systems based on calcium alginate

Whitehead and co-workers developed the Ca-Alg gel beads by dropping a sodium alginate solution into aqueous calcium chloride. Ca^{2+} ions in the latter crosslinks predominantly with one of the monomer blocks, guluronic acid, to form an “egg-box” model of insoluble hydrogel, Ca-Alg. [137] The beads were snap frozen in liquid N_2 and followed by freeze-drying at -40°C for 24 hours. The beads were reported to be approximately 2.5mm in diameter and floated on agitated acidic media (0.1N HCl + 0.05% Tween 80) for over 12 hours.

They went on to examine the in vivo gastric retention properties [138] and the amoxicillin release profile [139]. The floating beads were prepared as described above and radiolabelled with Technetium-99m pertechnetate ($^{99\text{m}}\text{TcO}_4^-$). The non-floating control was oven dried instead of freeze-dried and prepared with radioisotope Indium-111 chloride ($^{111}\text{InCl}_3$) or $^{99\text{m}}\text{TcO}_4^-$.

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Seven healthy individuals participated in the in vivo test and consumed different amounts of food ranging from low calory to high calory-intake based on their own eating habits. The floating beads were reported to adopt a floating position on top of the stomach contents immediately and clump together as a discrete unit. Gastric retention of the floating beads was noted from 5.5 hours to 9 hours. In subjects 4 and 5, retention was continued for 9 hours even with no more food after 6 hours. $^{111}\text{InCl}_3$ labelled non-floating beads scattered strongly so that locating the exact beads became difficult. And as floating and non-floating beads showed distinctive separation, the researchers decided to use the $^{99\text{m}}\text{TcO}_4^-$ label to achieve optimum radiation dose so that the participants would be exposed to fewer hazards. The authors pointed out that their observations supported the proposition that the floating mechanism worked and floating force was sufficient for the beads to move upwards through ingested meal to the surface, and that no other mechanism, such as bioadhesion took place. The floating dosage form was suggested to be suitable for patients with a wide range of eating patterns too as meal size did not dominate its gastroretentive properties.

Amoxycillin release from these alginate beads was conducted spectrophotometrically in 0.1N HCl, pH 1.2 at $37\pm 1^\circ\text{C}$. X-ray analysis revealed that the amoxycillin clustered at the center of the gel beads. This was because of the direct sublimation of ice crystals of the freeze drying process, since drug migration to the periphery normally happened because of liquid solvent removal. In most samples, most of the hydrophilic amoxycillin was

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released in a burst pattern during the first 60 minutes and the phenomenon was explained with Higuchi model. However it is debatable whether the slab geometry is applicable to this system. Higher drug loadings could be achieved too, but at the expense of faster release and lower buoyancy.

Iannuccelli et al [134, 168] developed floating alginate bubbles with an alginate core. However, excellent buoyancy was only achieved in water. In acidic media, the units did not float and even after modification of membrane permeability with PVA addition, buoyancy was still not as good as in water. Beads were radiolabelled with barium sulfate (BaSO_4) for the in vivo X-ray test. In the fed state after a meal, all the floating units showed a floating time of about 5 hours and a GRT prolonged by about 2 hours over the control. However, no drug release characteristics were reported.

Murata et al's [136] design was in fact a modification of Whitehead's. Either vegetable oil for extra buoyancy or chitosan for extra bioadhesion [140] was added into the alginate gel beads. Unlike what Whitehead et al have discovered, the non-oily gel beads failed the buoyancy test and were found to have a lower loading of the drug metronidazole. The drug release profile was somewhat similar to the results Whitehead et al had obtained. 80% of the hydrophilic metronidazole was released during the first 60 minutes. Only chitosan-containing gel beads were administered orally to guinea pigs because oily gel beads were too big (diameter about 4mm) for them to swallow. The floating gel beads were found to be able to maintain a stable

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serum concentration of metronidazole for 4 hours rather than the 2 hours of the conventional dosage. In a later study [141], the metronidazole release in vitro from alginate gel beads containing ethylcellulose lasted for less than 90 minutes.

Next, hollow microspheres (HMS) were studied as a kind of floating dosage form. Through a so-called “emulsion-solvent diffusion” method, Kawashima and co-workers [142,143] prepared microballons loaded with tranilast or ibuprofen, both of which are more hydrophobic than either amoxycillin or metronidazole. These microballoons were made of a kind of enteric pH-dependent polymer, Eudragit S100 (Methacrylic Acid – Methyl Methacrylate copolymer 1:2, Rhom Pharma, Germany). The model drug tranilast and the enteric acrylic polymer were firstly dissolved in an ethanol/dichloromethane mixture solvent, and then added into a stirring 0.75wt% polyvinyl alcohol (PVA) water solution that was thermally maintained at 40°C to form an emulsion. Figure 2-13 explains the formation mechanism of the Eudragit HMSs. As soon as the ethanol/dichloromethane solution was dripped into water, ethanol diffused into water quickly so that the emulsion droplets were covered with a precipitated polymer shell due to the decreasing solvent, while dichloromethane was temporarily entrapped in the polymer shell. Further evaporation of the dichloromethane at 40°C generated an internal cavity in the microspheres. However as the dichloromethane evaporated, the cavity was gradually filled with water due to the reduced pressure inside the droplet. The

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preparation of microballoons was finished by removing the water from the cavity of the microspheres with an oven drying process.

Figure 2-13 Mechanism of emulsion-solvent diffusion technique [143]

More than 80% hollow microspheres with average diameter of 350 μ m floated continuously over the surface of an aqueous acidic medium (0.1N HCl with 0.02%w/v Tween 20) for more than 12 hours. And the larger-sized microballoons were found to have better buoyancy than the smaller fraction of microballoons. In vivo radiographical study proved that the microballoons were dispersed in the upper part of the stomach and remained there for more than three hours against peristaltic action in the fed state while in the fasting state HMSs descended to the lower part of the stomach within 90 minutes. [144] The drug release profile differed as the pH of the media, polymer concentration in the starting solution and sizes of the microspheres varied. The drug released faster either as the pH of the medium increased, or as the drug concentration in the starting solution increased, or as size of the microballoons increased. The release of the drug, either tranilast or ibuprofen, was sustained for more than eight hours in pH6.8 media, while in pH7.2

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media, a major portion of the drugs was released within two to three hours. The initial burst effect was observed as a result of drug deposition on the surface of microspheres. In more acidic media, a significant amount of drug was retained because of solubility limitations, which indicated release would happen when the HMSs passed through the stomach and reached the upper gut. This resembles an enteric release dosage form.

- Effervescent system

Effervescent systems incorporate gas-generating “blowing agents” that react with gastric acid and give off gases such as carbon dioxide to provide an upward force. Some even bloat like a raft with trapped bubbles inside enabling floatation.

Major matrix materials utilized for these effervescent carriers include swellable polymers such as cellulose or polysaccharides. The gas-generating chemicals comprise sodium bicarbonate and citric or tartaric acid [145] or liquids that gasify at body temperature [146,147]. These buoyant carriers are fabricated in such a way that upon contact with the gastric juice, the gas-generating chemicals liberate carbon dioxide and the air bubbles are entrapped in the gelatinous matrices. The decrease in specific gravity results in an upward motion of the dosage forms and maintains their buoyancy. A typical example of this design was reported by Ichikawa and co-workers [148]. Their floating pills were made up of two layers, namely, the drug and effervescent agents at the inner layer, and the surrounding swellable layer. Upon delivery in the

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stomach these pills sank at the beginning, formed a gel balloon soon after swelling, and achieved buoyancy within 10 minutes. 80% of the pills remained buoyant for about 5 hours regardless of the pH and viscosity of the test media. Except for the polyvinyl acetate and shellac utilized by Ichikawa et al., floating pills based on two types of chitosan were developed according to this setup as well. The carbon dioxide generating components could be intimately mixed with the matrix hence a single-layer tablet was produced [149]. Or, it could be separately prepared as mentioned above in which case a double layer tablet was created [150].

Bioadhesion has been incorporated into the effervescent system by Asrani [151] with a bioadhesive hydrogel and this formulation was said to be able to sustain release for up to 24 hours.

In conclusion, non-effervescent multi-unit floating systems, are easy to fabricate, reliable in terms of buoyancy, clinically proven able to prolong GRT and have no potential adverse effect on gastric motility as some of the swelling systems do. However these floating dosage forms made of hydrogel matrix seem not able to maintain a controlled release with one design.

2.3.3.5 Factors concerning performance of the floating system

There are a number of factors attributing to the length of GRT or the gastric emptying rate and here they are discussed within the context of floating dosage forms. These factors comprise physical and chemical properties of the

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dosage forms such as density, size, and materials of the dosage form, biological aspects like gender, posture, age, body mass index, disease status, food digestive states and other issues such as concomitant medicine uses.

- Density

Floating dosage forms are retained in the stomach for prolonged periods of time chiefly by virtue of their buoyancy. According to Archimedes' law, the object acquires buoyancy by having a bulk density lower than that of the medium it floats on. Most of the densities of floating dosage forms reported are less than 1.0g/ml. However, the buoyant capability may be better represented and monitored by resultant-weight measurements and swelling experiments [152] as the magnitude of floating strength may vary as a function of time and usually decreases with time. This is because after immersion of the dosage form into the medium, the floating strength drops as a result of the development of its hydrodynamic equilibrium [153]. Hence density alone might not be the most proper parameter for examining buoyant ability.

Timmermans and Moes [153] mentioned a novel apparatus for the determination of resultant weight (RW). The RW apparatus operates according to Equation 2-1 as indicated below to measure the total vertically-acting force.

$$RW = F_b - G = \rho_m gV - \rho_{df} gV \quad (\text{Equation 2-1})$$

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In the equation, RW is the total vertical force, ρ_m is the density of the medium, ρ_{df} is the density of the object, V is the object volume and g is the gravity acceleration. RW can be represented by the density difference between the medium and the floating dosage form. It is attained by measuring the force required to keep the object submerged in the medium. And this force RW can be plotted as a time-dependant function. The object floats better if the RW is on the higher positive side. The RW measuring apparatus helps in the optimisation of floating dosage forms in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

- Size

Studies have shown that larger tablets were kept until the housekeeper waves occur while smaller-sized tablets were expelled during the digestive phase contractions [154]. In Timmermans and his co-workers' [155] report, γ -scintigraphy showed that floating units with a diameter equal to or less than 7.5mm were found to have longer GRT than non-floating units, because floating units remained buoyant against gastric emptying during digestive phase while non-floating units lying in the antrum region were propelled during the digestive phase by peristalsis. However, among the tablets with a size of 9.9mm, floating and non-floating units had similar GRT.

A study was carried out on non-fasting human volunteers to investigate the effects on GRT of galenic factors such as size and density of matrices [156].

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A remarkable difference in GRTs was found to be present between smaller sized floating and non-floating units. However this difference tapered as the sizes of the units gradually increased, and insignificant difference in GRTs was also observed among the larger sizes as the size factor began to play an important role. It was noteworthy that there was no significant difference of GRTs among the small, medium and large floating dosage forms because buoyancy protected them from random gastric emptying related to antral peristalsis. [157]

- Single- or multiple-unit system

Single-unit system refers to a single-compartment or single- floatation “cabin”. These dosages tend to result in an ‘all-or-nothing’ consequence in case of any manufacturing defect or unforeseen circumstances. Multiple-unit system provides a more predictable and constant profile as failure of several units impairs the overall performance insignificantly. It not only permits a larger margin of safety against dosage form failure but also allows the possibility of co-administration of units with different release profiles or which contain incompatible substances compared with single-unit system.

- Fed or fasting state

A meal can largely alter the GRT by changing the reactive pattern of GI tract. Under a fasting condition, the GI motility is characterised by periods of IMMC waves that sweep undigested materials from the stomach regardless of size. Hence the GRT of the drug in the fasting state is expected to be very short if

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the administration of the dose is in coincidence with one of the IMMCs. In the fed state, the IMMC is delayed by the presence of the meal. Thus the GRT is considerably longer than that of the fasting state.

A consensus seems to be shared by most of the studies [158,159,160,161] related to the effects of food on GRT. Actually, food intake is the major determinant of the delayed gastric emptying, while buoyancy acts as a secondary factor on the emptying process. Studies showed that both floating and non-floating units were quickly (less than 2 hours) emptied from the stomach of fasting subjects, but the floating units were retained much longer (about 4 hours) in the fed stomach compared with non-floating units. [158, 161] Agyilirah et al. [162] experimented on floating balloons both in the fed state and in the fasting state and a similar result was reported. Singh et al. [133] thus concluded that although floating systems possess an inherent ability for gastric retention, they rely more on the presence of a meal to retard their emptying.

- Nature of the meal

In addition to the motility pattern changes following a meal, food containing hard-to-digest polymers or fatty acid salts is able to decrease the gastric emptying rate, hence prolonging gastric retention time further [163,164,165,166,167]. Fats and proteins normally have higher caloric content so it takes longer for digestion and absorption. Thus GRT can be extended by four to ten hours with a meal that is high in proteins and fats. [100]

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- Frequency of feed

GRT can be increased by over 400 minutes when successive meals are given compared with a single light meal because of the decreased frequency of IMMCs [100]. Iannuccelli et al. [168] proved that successive meals helped to prolong the floating time of dosage forms up to 6 hours and the GRT to up to 9 hours.

- Gender and age

According to Mojaverian et al. [169], females generally have a longer mean ambulatory GRT (4.6 ± 1.2 hours) compared with the male counterparts (3.4 ± 0.6 hours) of the same age and race, regardless of the weight, height, body surface area or even hormone level. Also older people, especially those over 70, have a significantly longer GRT (about 5.8 hours).

- Posture

The mean GRT of food in supine state did not differ significantly from those in the upright, ambulatory state (3.4 ± 0.8 hours v.s. 3.5 ± 0.7 hours, $P > 0.05$). [133] GRT of a dosage form, whether floating or non-floating, is influenced by the specific posture of the subject. The study by Van Gansbeke and his co-workers [156] looked into physiological factors such as posture. In upright subjects, all the floating units stayed continuously above the gastric content regardless of their sizes whereas the non-floating units sank rapidly to the antrum. The floating dosages showed a prolonged and more reproducible

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GRT compared with the non-floating units. In the supine subjects, size factor was more influential than buoyancy effect. Floating and non-floating dosages of the same size ranges differed little in GRTs.

Bennett et al. [170] discovered that an alginate raft was emptied faster than food in subjects lying on their left side and slower in subjects lying on their right. The result was explained that as the raft was positioned near to the pylorus ahead of the meal, it was emptied faster than the food when subjects were in a leftward supine posture. And when the subjects were in a rightward supine posture, the raft was “hidden” in the greater curvature of the stomach.

- Other issues

Disease status like diabetes and Crohn's disease etc. do affect the normal gastric emptying. And concomitant administration of anticholinergics such as atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide HCl and cisapride, alters the motility pattern of gastrointestinal tract. [100]

Moreover as aforementioned, adhesion of floating dosage forms to the gastric mucosa may produce a synergic effect on the prolongation of GRT.

2.3.3.6 Design and evaluation of the floating system

The task of designing a floating dosage form includes consideration in the following aspects:

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- Situation for application

Performance of the floating systems is limited under several occasions. Firstly, the biggest disadvantage for the floating systems is that they require sufficient liquid in order to float. And the prolongation of GRT demands a light meal accompanying the administration of the floating system. Or at least, the patient should not take the floating dosage with an empty stomach to ensure the desired sustained drug absorption. Secondly, floating systems are redundant for some drugs that are well absorbed in the entire GI tract or have multiple absorption sites within the GI tract. The system is not feasible for drugs that are poorly soluble or practically insoluble in the gastric juice or drugs that are irritative to the gastric mucosa.

It is a logical strategy to implement polymer-mediated non-effervescent and effervescent floating dosage forms in situations such as: undesirable gastrointestinal (GI) transit time, low bioavailability caused by incomplete drug release from devices or too short a gastric residence time, and when the major absorption site or drug acting site is in the upper part of GI tract. Implementation of floating dosage forms appears to be an effective and rational approach to the modulation of oral drug delivery in upper GI tract. The advantages include improved bioavailability, extended and more reproducible GRT, a sustained release of the drug and less fluctuation of drug concentration in blood, targeted-site delivery etc. However, the pros and cons

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should be weighed carefully to avoid drawbacks and disadvantages in order to maximize the benefit-to-demerit ratio of the floating preparations.

- Evaluation of the system

Singh et al. [98] recommended that the following parameters should be evaluated in order to find out their influences on GRT of buoyant formulations.

- (a) Galenic parameters such as diametral size, flexibility and density of the matrices;
- (b) Control parameters: floating time, dissolution, specific gravity, content uniformity, and hardness and friability (if in tablet form);
- (c) Geometric parameters: shape;
- (d) Physiological parameters: age, sex, posture, food and bioadhesion.

The test for buoyancy and in vitro drug dissolution are normally required to be conducted in simulated gastric juice, e.g., 0.1N HCl solution, thermally maintained at body temperature.

The specific gravity of floating dosage forms can be determined by the displacement method in analytical grade benzene [160]. Reasonably, the initial (dry state) bulk density of the dosage form and changes in the floating strength with time should be measured prior to in vivo comparison between floating and non-floating units. Further, stability and durability of the floating strength should be taken as the key issue during formulation optimization so as to minimize unforeseeable variations in the in vivo stage. Resultant-weight

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(RW) measurement was developed for this sake to determine the buoyant capability [171,172]. In vivo gastric retentivity can be performed using γ -scintigraphy [155] or roentgenography [148, 173, 174].

2. 4 Mathematical modeling of the drug release pattern

2.4.1. Introduction to models

The effort to mathematically interpret the drug release profile aims to define the release mechanism or kinetics with the physical and chemical characteristics of the drug incorporated delivery devices. Mathematical models are claimed to be helpful in predicting release patterns hence avoiding excessive experimentation. In addition, they help in explaining the behavior of the drug transport process by comparison with experimental data, in designing new systems based on general expressions, and in optimizing release kinetics. [175]

Considering the complexity of a plurality of factors affecting drug transportation within the delivery device, there is no one-for-all solution to model all the release processes. And it is equally important to identify the crucial determinants among the pool of factors so as to simplify the mathematical procedures.

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2.4.2. Principles and factors concerning drug transportation

2.4.2.1 Fickian release behavior

The drug release from drug delivery systems is influenced by the nature of the drug and the excipients, how the delivery devices are prepared, and where the release takes place.

Mechanisms of drug release can be generally classified into three types, diffusion-controlled, swelling-controlled and chemically-controlled. [175] Differences between them are mainly in the ways the drug diffuse or dissolve into the surrounding media.

In a typical one dimensional diffusion-controlled release, Fick's laws of diffusion define the mass transport of a drug through a polymer into the media as the following equations.

$$J_1 = -D_{12} \frac{\partial C_1}{\partial x} \quad (\text{Equation 2-2}) [176]$$

$$\frac{\partial C_1}{\partial t} = D_{12} \frac{\partial^2 C_1}{\partial x^2} \quad (\text{Equation 2-3}) [208]$$

Where J_1 is the molar flux of the drug (in mol/cm²·s), D_{12} is the mutual diffusion coefficient of the drug in the polymer (in cm²/s), C_1 is the drug concentration (in mol/cm³), and x is the position in the polymeric device (in cm). Equation 2-2 is the expression of Fick's First Law corresponding to mass flux changes and Equation 2-3 stands for Fick's Second Law which

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determines the variation of the drug concentration within the device with time. These equations are based on the assumption of constant diffusion coefficient and constant boundary condition.

Assuming J_1 and D_{12} are constant, Equation 2-2 can be integrated to give the integrated form of Fick's Law:

$$J_1 = D_{12}K \frac{\Delta C_1}{\delta} \text{ (Equation 2-4) [207]}$$

K is the partition coefficient representing the ratio between the drug concentration at the interface and the drug concentration in the bulk, and δ is the thickness of the device.

The Fick's Law of diffusion can thus be solved mathematically to obtain drug release profiles in polymer devices. Crank [208] provided solutions to the diffusion equation for many initial and boundary conditions in infinite and semi-infinite media and for various geometries. In fact, basic Fickian principles were applied and modified according to the specific situations such as multi-dimensional diffusion and material morphology and geometry to produce numerous publicized mathematical expressions of release profiles. Among all these factors, the modification to diffusion coefficient D_{12} and partition coefficient K seems to be most popular.

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- Diffusion coefficient

Diffusion coefficient, or diffusivity D_{12} , reflects the proportionality between the driving force for diffusion, i.e. the concentration gradient $\frac{\partial C_1}{\partial x}$, and the diffusion mass flux J_1 as Equation 2-2 has shown.

Solute diffusion in polymer is highly dependant on the structure of the pores or on the structure of the polymeric network. Depending on the pore sizes, polymer structure can be differentiated into macroporous, where pore size is much bigger than that of the solute molecule; microporous, where pore size is comparable to that of the solute molecule; and non-porous. Solute diffuses through solvent-filled pores in the macroporous and microporous polymers. As for non-porous polymers, the diffusion is more complicated because both solute molecules and the polymeric network affect the diffusion process. Influential factors include degree of crystallinity, size of crystallites, degree of swelling, molecular weight between crosslinks, and the state of the polymer. [177]

A semi-empirical expression has been given for convenient incorporation of porosity ϵ (void volume fraction) and tortuosity τ into the effective diffusion coefficient D_{eff} as follows [178]:

$$D_{eff} = D \frac{\epsilon K_{ps} K_{rs}}{\tau} \quad (\text{Equation 2-5})$$

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where

D = the diffusion coefficient of the solute through solvent filled pores

K_{ps} = the equilibrium partition coefficient (i.e., the ratio of the concentration inside the pore to the concentration outside the pore at equilibrium), if there is any [179]

K_{rs} = the fractional reduction in diffusion coefficient within the pore which results when the solute and pore sizes are of comparable magnitude [179].

Generally, K_{ps} and K_{rs} are more important in membrane-controlled system than in the matrix controlled system. For the case of a monolithic matrix release system with drug loading much greater than the drug solubility in the polymer, K_{ps} and K_{rs} are considered equal to unity, since pores are much larger than the solute molecules.

Pore size about 50 to 200 Å is considered microporous, [178] where the solute molecule may experience some frictional resistance and steric hindrance. Kuu et al [210] elucidated several corrections based on the ratio of the solute molecule radius to the pore radius, solute molecular weight and polymer concentration in weight percent.

Diffusional problems in non-porous polymer are much more complex as the solute molecules have to diffuse through the polymeric network (meshes) rather than pores. Peppas and co-workers [180,181,182,183,184] have

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published some semi-empirical equations for rubbery polymers with different degrees of crosslinks and crystallinity.

- Partition coefficient

Compared to the non-equilibrium diffusion coefficient, the partition coefficient is a thermodynamic equilibrium parameter defined as:

$$K = \frac{C_b^*}{C_b} \text{ (Equation 2-6) [210]}$$

C_b^* = the solute concentration in the polymer phase adjacent to polymer/bulk interface

C_b = the solute concentration in the bulk

If the partition coefficient is independent of the drug concentrations, Equation 2-9 can be written as,

$$K = \frac{C_s}{C_{bs}} \text{ (Equation 2-7) [210]}$$

C_s = drug solubility in the polymer

C_{bs} = drug solubility in the bulk media

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Diffusion coefficient is the reflection of solute mobility based on the molecular volume of the permeant and polymeric structure, while partition coefficient depends largely on the chemistry of the polymer-permeant pair.

- Other membrane and matrix parameters

Diffusion coefficient and partition coefficient are normally fixed once the drug candidate is chosen. On the other hand, the parameters of the device, such as surface area, geometry, amount of drug loading, recipient environment and temporal idiosyncrasies regulate the release rate as well.

2.4.3. Models for hydrogel drug delivery systems

- Diffusion-controlled models

In this context, the chemically-controlled or degradation-controlled drug release mechanism is excluded. The diffusion-controlled models are normally obtained by solving the transient diffusion equation (Equation 2-3) for a variety of initial and boundary conditions. [175] The classic Higuchi model [185] was introduced under the assumption that solute particle diffuses through a one-dimensional film under pseudo-steady state and negligible boundary effects. The derivation gives the amount of drug released at time t , M_t , is

$$M_t = A\sqrt{DC_s(2C_0 - C_s)t} \text{ (Equation 2-8) [217]}$$

C_0 = the initial drug concentration dispersed in polymer matrix

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C_s = the drug solubility in the polymer, $C_s < C_0$

D = drug diffusion coefficient in the polymer

A = the cross-sectional area for diffusion

The Higuchi equation is valid for pseudo-steady state assumption, which means a linear drug concentration profile when C_0 is much greater than C_s .

Lee [186] presented that the square root of time dependence of the drug mass released could be extended to dissolved drug matrix systems where $\frac{C_0}{C_s}$

can be any other values as well. Lee's parametric form of solution [187] for the release of dispersed drug from spherical matrices under perfect sink condition is given below:

$$\frac{M_t}{M_\infty} = [1 - (1 - \delta)^3] \left(1 - \frac{C_s}{C_0}\right) + 3\delta \left(\frac{C_s}{C_0}\right) \left[\left(a_1 + \frac{a_2}{2} + \frac{a_3}{3}\right) - \left(\frac{a_1}{2} + \frac{a_2}{3} + \frac{a_3}{4}\right)\delta\right] \quad (\text{Equation 2-9})$$

2-9)

$$\frac{Dt}{r^2} = \frac{1}{12} \left[6\left(\frac{C_s}{C_0}\right) - 4 - a_3\right] - \frac{1}{3} \left(\frac{C_s}{C_0} - 1\right) \delta^3 \quad (\text{Equation 2-10})$$

$$\frac{M_t}{M_\infty}$$

fractional release

$$\delta$$

diffusion front position

$$r$$

radius of the spherical matrix

$$D$$

diffusion coefficient of the drug in the polymer matrix

$$a_1$$

= 1

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$$a_2 = -a_3 - 1$$

$$a_3 = 1 - \left(1 - \frac{C_0}{C_s}\right)(1 - \delta) - \left\{ \left[1 - \left(1 - \frac{C_0}{C_s}\right)(1 - \delta)\right]^2 - 1 \right\}^{\frac{1}{2}}$$

- Swelling-controlled models

A typical swelling controlled system is the tablet made of solvent free glassy hydrogel and dispersed drug. Colombo et al [188] presented a good description of the swelling process and experimentally proved the existence of a drug dissolution front that separated dissolved from solid drug, a swelling front that separated the glassy from the rubbery region of the hydrogel, and an erosion front which separated the matrix from the ambient solvent. Lee and Kim [189] observed the front transition as shown in different sample loadings of two model drugs, one of high solubility and the other of low solubility. For the drug of high solubility, only one swelling front was observed and penetration rate of the swelling front increased with increasing drug loading levels. For the drug of low solubility, drug loadings diversified the situations. A similar single swelling front was observed among low loading levels of the poorly soluble drug, but as loading increased, precipitation of the drug occurred and developed into a slow-moving drug dissolution front. The transition of a fast-moving swelling front into a slow-moving drug dissolution front occurred sooner among higher loading levels of poorly soluble drugs. At even higher loadings, the transition became absent and only the drug dissolution front was visible.

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Figure 2-14 Schematic presentation of swelling boundaries and dimensional changes in terms of drug solubilities [221]

Figure 2-15 Dimensional changes in hydrogel beads [189]

2. Literature Review

Colombo and his co-workers also noticed that the size of the swelling drug-loaded beads went through a maximum followed by a gradual approach to equilibrium, whereas the unloaded beads increased monotonically toward the equilibrium value in all sample cases. Swelling has a tendency to increase, whereas the drug release tends to decrease the dimension of the hydrogel beads, resulting in the dimensional changes as plotted in Figure 2-14.

This type of diffusional behavior belongs to a category known as Stefan-Neumann, or moving-boundary problems. [175] Mass transport in these physical situations is generally governed by three types of driving forces: a penetrant concentration gradient, a polymer stress gradient, and osmotic forces. [190] The semi-empirical power law proposed by Ritger and Peppas [191] provides a simple yet comprehensive explanation of exponential time dependence of drug release behavior in terms of both the diffusional and relaxational factors (Equation 2-11).

$$\frac{M_t}{M_\infty} = kt^n \quad (\text{Equation 2-11}) \quad [223]$$

k = a constant incorporating characteristics of the macromolecular network and the drug

n = diffusional exponent

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This equation is valid for the first 60% of the fractional release $\frac{M_t}{M_\infty}$. The diffusional exponent is an indication of the release mechanism of the devices. The geometric dependence, as shown in Table 2-1, should be acknowledged before determining the release by the exponent n to be either Case I (Fickian diffusion), Case II (relaxational release), or anomalous (in between Case I and Case II).

Table 2-1 Geometric dependence of the diffusional exponent [192]

Diffusional exponent n			Drug release mechanism
Slab	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
$0.5 < n < 1$	$0.45 < n < 0.89$	$0.43 < n < 0.85$	Anomalous transport
1	0.89	0.85	Case II transport

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2.5 Summary

The research on GRT to date has thrown up many ingenious approaches to improving gastric retention time. However, to date there is no successful product that can lay claim to prolonged delivery of drug using GRT. The survey shows that one of the main problems has been to demonstrate sufficiently sustained release of both hydrophobic and hydrophilic drugs with one vehicle or design. By far, one of the most promising approaches to improving GRT is to develop floating dosage forms, as these have many benefits in addition to improving GRT. In this light, this work focuses on floating dose forms, and their capability to incorporate and sustain the release of both hydrophilic and hydrophobic drugs.

3. Materials and Experiments

This chapter is composed of two sectors, synthesis of HA HMSs and synthesis Ca-Alg floating dosage form.

3. 1 Synthesis of HA HMS radiopacifier

Spray drying is selected as the synthesis approach because of equipment availability and the processing simplicity. Since bubbling takes place during the transition from a liquid droplet to solid microsphere, the viscoelastic and rheological properties of the starting materials are critical to produce a semi-permeable and expandable shell for bubbling. Hence a viscoelastic polymer, or binder, is needed to provide such an expandable matrix as HA ceramic is known to be less flexible. And viscosity and partial gas pressure released by the blowing agent are considered counteractive in the bubbling process and can be adjusted through controlling the solid content, specifically water/binder ratio, ceramic/binder ratio and blowing agent amount. Based on these hypotheses, the formulation studies are carried out as described below.

3.1.1. Materials

Hydroxyapatite powder (Berkeley Advanced Biomaterials, USA) was used as received. The mean particle size of the powder was $1.28 \pm 0.40 \mu\text{m}$, determined by Particle Size Analyzer (90Plus, Brookhaven Instruments, USA).

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The Transmission Electron Microscope (TEM) (JEM2010, Jeol, Japan) examination (Figure 3-1) indicated that these HA particles were in fact the agglomerates of smaller needle-shaped crystals of about 100nm length. The bulk density of the HA powder was about $3.03 \pm 0.08 \text{ g/cm}^3$, determined by helium Pycnometer (AccuPyc 1330, Micromeritics, USA), slightly lower than the HA theoretical density of 3.16 g/cm^3 .

Figure 3-1 TEM picture of BAB[®] HA crystals

Aerolite CB[®] (Dynochem, UK), the powder form of fast curing resin urea-formaldehyde was used as the binder. Two chemicals, SEA101[®] (Ammonium salt of acid, Dynochem, UK) and Unicell-OH[®] (p.p-Oxybis benzene sulfonylhydrazide OBSH, $\text{C}_{12}\text{H}_{14}\text{N}_4\text{O}_5\text{S}_2$, Dongjin Semichem, Korea) were the

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hardener and blowing agent respectively in the setup. The glass transition temperature (T_g) of the binder UF resin was about 14°C, determined by Differential Scanning Calorimetry (DSC) (Q10, TA Instruments, USA) as indicated in Figure 3-2. The onset decomposition temperature of the blowing agent was about 157°C, measured by Thermogravimetric Analyzer (TGA) (TGA2950, TA Instruments, USA) (shown in Figure 3-3).

Figure 3-2 Glass transition temperature of UF resin, Aerolite CB®

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Figure 3-3 Thermostability of the Unicell-OH[®]

3.1.2. Synthesis procedure

The HMS synthesis procedure illustrated in Figure 3-4 was carried out on a custom-made spray dryer system, which was an open-cycle co-current layout with a rotary atomizer installation. The synthesis of HA HMSs underwent three processes, starting with the slurry formulation and preparation, followed by the spray drying of the feed, and then the collection and post-drying heat treatment. In order to achieve good homogeneity, the formulated amount of HA powder, UF resin powder and deionized (D.I.) water were blended in a sealed jar n ball milled for 50 minutes. Thereafter the blowing agent and hardener were added in and the mixture was ball milled for another 10 minutes until a foamy and milky final slurry was obtained. The slurry was then fed into the atomizer via a peristaltic pump and spray dried at a designated

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temperature, atomizing frequency, and cyclone pressure. The dried microspheres were collected and kept in the desiccator. HA HMSs are obtained after calcination.

Figure 3-4 Flow chart of HA HMS synthesis

3.1.3. Slurry formulation

During spray drying, the slurry will be nebulised into micro droplets. These droplets will go through drying, expansion and solidification thereafter. The viscoelastic properties of these aqueous droplets and the viscosity of the slurry are key determinants for HMS formation. Composition variations control the rheological properties of the slurry hence different slurry formulations are proposed and studied here. The formulation of the slurry composition

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comprising four groups of samples is tabularized in Table 3-1 in terms of three ratios: the water/binder (W/B) weight ratio, ceramic/binder (C/B) weight ratio, and blowing agent/binder (BA/B) weight ratio. The four groups of samples were formulated by varying one ratio among the above three each time.

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Table 3-1 Formulation of slurry composition

Samples		Water/Binder Ratio (wt)	Ceramic/Binder Ratio (wt)	Blowing Agent/Binder Ratio (wt)
Group 1	Vis01	1.5	0.6	0.025
	Vis02	1.5	1	0.025
	Vis03	1.5	1.5	0.025
Group 2	Vis04	1.5	0.6	0.05
	Vis05	1.5	1	0.05
	Vis06	1.5	1.5	0.05
Group 3	Vis07	1.5	0.6	0.075
	Vis08	1.5	1	0.075
	Vis09	1.5	1.5	0.075
Group 4	Vis06	1.5	1.5	0.05
	Vis10	2	1.5	0.05
	Vis11	2.5	1.5	0.05
	Vis12	3	1.5	0.05

3.1.4. Characterization and post heat treatment

Ceramic particles are known to be rigid and of low flexibility; thus when spray dried alone from a form of ceramic suspension to a particulate form, spongy porous or solid microspheres are often the result. This is mainly because of the rigid and vapour-permeable crust formation at the beginning of micro droplet drying process of such ceramic suspension. As blowing is the key to

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the formation of HA HMSs in this case, a unique polymeric binder helps to formulate a expandable “bubble-shell”. To understand the slurry formulation properties, the following rheology and curing tests were conducted.

The rheological behaviour of the four groups of slurries was studied on a parallel plate rheometer (RheoStress 300, ThermoHaake, Germany) under constant stress of 10 Pa from angular velocity ω from 0.628 rad/s to 62.8 rad/s. The spray dried microspheres of these slurries were then examined under SEM (JSM5410LV, Jeol, Japan).

In order to find out the mechanism of HMS formation, curing characteristics of the polymeric binder during spray drying were studied on differential scanning calorimetry (DSC Q10, TA Instruments, USA). Formulations of the DSC samples followed sample vis01 without the blowing agent and water. DSC runs were performed at a heating rate of 45°C/minute from room temperature to 220°C.

The as-sprayed microspheres were first sieved to 32 μm to 150 μm , then sent for calcination at 700°C for 60 minutes at a temperature ramp of 1°C per minute, unless otherwise stated.

Particle sizes, surface morphology and cross-sections of these microspheres were monitored under Scanning Electron Microscope (SEM) (JSM5410LV, Jeol, Japan) and analysed using the affiliated software SemAfore (Jeol,

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Japan). Phase composition of the microspheres before-spraying, as-spraying and post-calcination was studied under the X-ray Diffractometer (XRD) (LabX XRD6000, Shimadzu, Japan). The surface area of these calcined HMSs was obtained by gas adsorption analysis based on Brunauer, Emmett, and Teller theory (BET) (ASAP 2000, Micromeritics, USA). Porosity of calcined HA HMSs was measured by mercury porosimetry (AutoPore II 9220, Micromeritics, USA).

The density determination of calcined HA HMSs was different from the conventional process as the HMS shells were water-permeable. The calcined HMSs were sealed in epoxy resin, and because of viscosity and surface tension the resin could not permeate through the shells and finally solidified. The densities of the composite envelope and epoxy resin were obtained by Archimedean water displacement method. The envelope density of the HMSs was calculated based on the equation below.

$$\rho_H = \frac{\frac{m_r}{\rho_r} + m}{\frac{1}{\rho} - \frac{1}{\rho_r} \times \frac{m_H}{m}} \quad (\text{Equation 3-1})$$

where,

ρ_H = envelope density of HMSs

ρ_r = density of epoxy resin

ρ = density of the composite of HMS and epoxy resin

$m = m_H + m_r$ mass of the composite of HMS and epoxy resin

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m_H = mass of the HMSs

m_r = mass of the epoxy resin

3.2 Synthesis of Ca-Alg mediated floating GRDF

Since single-unit floating systems are not reliable in buoyancy and alginate gelation normally takes place in aqueous environment, an emulsion-gelation approach has been developed to produce a multiple-unit floating system as a large number of tiny oil drops can be encapsulated into a single alginate bead in one process. The buoyancy is thought to be related to non-aqueous content but whether the bulk density is directly related to the buoyancy is not clear and needs to be investigated. Another assumption is the hydrophilic substance will greatly enhance the burst effect during drug release, so that alginate alone is not considered ideal carrier for hydrophilic drugs as the matrix is highly hydrophilic itself. Hence the fast water ingress into the hydrophilic matrix will most likely trigger a burst release of the hydrophilic drug. The application of a hydrophobic barrier to this alginate matrix is considered effective and necessary to achieve a sustained release. Detailed experimental procedures are stated hereafter.

3.2.1. Nomenclature of alginate gel beads

The alginate bead samples were named in accordance with certain notations listed in Table 3-2. The letters of the alphabet symbolized the materials inclusion in the pre-gelation liquid formulation and the numbers represented

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the corresponding concentration or amount of materials. The drug input was the specific amount (indicated in Table 3-2) of ibuprofen, niacinamide or metoclopramide HCl per 10ml initial sodium alginate solution. The number following the prefix “H” indicates the HMS loading per 10ml initial sodium alginate solution. All gelation results were obtained in 0.3wt% CaCl_2 solution (about 0.02Mol/l), unless otherwise described. For example, the code “A3-2I200H200C1” denotes the following information: A3-2 means that the beads were made from pre-gelation liquid containing 3wt% sodium alginate solution and oil of 2ml per 10ml sodium alginate solution; I200 means that there was 200mg ibuprofen per 10ml sodium alginate solution; H200 means that the HMS amount was 200mg per 10ml sodium alginate solution; C1 means that gelation of the beads was obtained in 0.3wt% CaCl_2 solution. When gelation was conducted in 0.3wt% CaCl_2 solution, “C1” was normally omitted. If “E” was absent, it meant that the beads were not coated with Eudragit.

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Table 3-2 Nomenclature of alginate bead samples

Materials Inclusion	Concentration or amount of mixing
A - alginate	1 – 1wt%
	2 – 2wt%
	3 – 3wt%
	4 – 4wt%
	5 – 5wt%
Oil per 10 ml alginate solution	1 – 1ml
	2 – 2ml
	3 – 3ml
I – Ibuprofen per 10ml alginate solution	200 – 200mg
	400 – 400mg
	800 – 800mg
	1600 – 1600mg
N – Niacinamide per 10ml alginate solution	200 - 200mg
	800 – 800mg
	10000 – 10000mg
	20000 – 20000mg
M – Metoclopramide per 10ml alginate solution	200 – 200mg
	10000 – 10000mg
	20000 – 20000mg
H – HA HMS per 10ml of alginate solution	200 – 200mg
	400 – 400mg
	800 – 800mg
	1600 – 1600mg
C – CaCl ₂ concentration for gelation	1 – 0.3wt%
	2 – 2.5wt%
	3 – 5wt%
	4 – 10wt%
E – Eudragit concentration in ethanol	1 – 1/12 g/ml
	2 – 1/6 g/ml

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(w/v)	3 – ¼ g/ml
Example of sample name	<p>A3-2I200H200C1</p> <p>A3-2 – alginate beads made of pre-gelation liquid containing 3wt% initial sodium alginate solution and 2ml oil per 10 ml sodium alginate solution</p> <p>I200 – 200mg ibuprofen per 10ml alginate</p> <p>H200 – 200mg ibuprofen per 10ml alginate</p> <p>C1 (normally omitted) – gelation took place in 0.3wt% CaCl₂</p>

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3.2.2. Materials for floating GRDF

Alginic acid sodium salt (Aldrich, Viscosity 200,000~400,000 cps), Sunflower oil (Naturel), polyvinyl alcohol (PVA, Aldrich, 87~89% hydrolysed, Average Mw 13,000~23,000), ibuprofen (1mg/ml in water, about 25mg/ml in sunflower oil, Tokyo Kasei), niacinamide (50mg/ml in water, Sigma), metoclopramide HCl (about 650mg/ml in water, Sigma) and calcium chloride dihydrate ($\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$, Fisher Scientific) were purchased and used as received. HA HMSs were synthesized in the laboratory based on the synthesis process previously described. The particle sizes of the HA HMSs used were sieved to between 71 μm and 150 μm . Eudragit (S100, Rohm Pharma, Germany) was a gift from Degussa Asia. The simulated gastric fluid (SGF) used for the experiment was made of 0.1Mol/l HCl solution (Merck) and 0.02%(w/v) Tween 20 (Tokyo Kasei). The PBS (phosphate buffer saline, pH4.0, Merck) solution was a standard laboratory agent.

3.2.3. Synthesis of alginate GRDF

All gel beads described in this thesis were prepared following the same gelation and freeze drying procedure. A pre-gelation liquid was prepared by mixing sodium alginate solution, the prescribed amount of sunflower oil, and the drug, either ibuprofen, niacinamide or metoclopramide HCl, with or without HA HMS as the radiopacifier. The amount and coding of various formulations have been tabulated in Table 3-2. 3ml pre-gelation liquid was then added, drop by drop through a syringe, into the 10ml 0.3wt% CaCl_2 solution (unless otherwise described) and kept for 30 minutes. The beads were then

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recovered from the CaCl_2 solution and washed with D.I. water, freeze dried at -20°C over night, and then kept in desiccators.

In order to prolong the niacinamide release, Niacinamide beads with Eudragit S100 coatings were also investigated. Eudragit was a pH dependent polymer of methacrylic acid and methyl methacrylate copolymer (1:2). It is also intensively applied for pharmaceutical coatings and films. Selected niacinamide beads were dip coated in different concentrations of Eudragit ethanol solution and dried in air on a Teflon plate. To avoid leakage, a single bead was coated three times, each time after the previous coating dried in air at room temperature. Concentrations of Eudragit ethanol solutions are given in Table 3-2.

Metoclopramide HCl release from Eudragit coated beads was examined to validate the sustained release efficacy of the Eudragit coating. Three metoclopramide loadings were studied, i.e., 200mg, 10000mg and 20000mg per 10ml sodium alginate solution.

3.2.4. GRDF Morphological studies

The freeze dried beads were visually observed under a stereo zoom optical microscope (MZ6 optical microscope, Leica, Germany) and under a scanning electron microscope (SEM, JSM5410LV, Jeol, Japan). Heywood Diameters [193] of the beads were obtained using the Image Analysis software (AIS4.0, Imaging Research Inc., USA). As most beads were not in perfect spherical

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shapes, there was no uniform diameter. The Heywood Diameter was employed as an approximation so that every bead could be evaluated with a single variable to quantify its size.

Heywood diameter is defined as the diameter of a circle having the same area of the zone in consideration.

Figure 3-5 Schematic illustration of Heywood Diameter

Subsequently, envelope density of the alginate beads was calculated according to the equation below, where envelope density equals to the quotient of bead mass divided by the total bead volume, which was calculated with average Heywood Diameter D_H .

$$\rho = \frac{M}{\Sigma\left(\frac{\pi \times D_H^3}{6}\right)} \text{ (Equation 3-2)}$$

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3.2.5. Density and buoyancy test

Envelope densities of the beads were calculated based on Heywood Diameter results. Flotation of the beads was tested by visual inspection. Twenty middle-sized beads were selected within each sample and the twenty beads were placed into a 10ml capped-bottle filled with 10ml of SGF fluid as Figure 3-6 schematizes. The bottle was put in a water bath thermally controlled at $37\pm1^{\circ}\text{C}$. Beads inside the SGF were kept agitated with a magnetic stirrer for 24 hours and buoyancy was recorded after 24 hours. The sample was considered buoyant only when all the twenty beads were still floating after 24 hours of agitation.

Figure 3-6 Demonstration of buoyancy test

3.2.6. Radiopacity examination

The radiopacity test was carried out on a digital X-ray imaging system (OEC9800, GE, USA) at the National Heart Center, Singapore General

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Hospital. Visibility of four HMS loadings of alginate beads under X-ray, A3-2I800H200, A3-2I800H400, A3-2I800H800 and A3-2I800H1600, were tested under standard angiogram conditions for cardiovascular imaging and observed visually. EDX mapping of the four HMS loadings of beads was also recorded on a SEM system (JSM6360, Jeol, Japan) to give quantitative illustrations of the radiopacity.

3.2.7. Gel water uptake test

In order to find out the swelling ratio of the alginate beads, water uptake test of beads was conducted in SGF medium. Twenty middle-sized beads of each sample were selected and wrapped in a nylon mesh and then soaked in SGF medium at $37\pm1^{\circ}\text{C}$. The weight of the starting beads and nylon mesh were recorded. And at certain time intervals the wrapped beads were recovered from the SGF to record their weights again. Excessive SGF was removed with tissue paper and the weight of swollen beads was recorded. Nylon mesh was considered as non-swelling in this case.

3.2.8. Drug release test

The drug release test was carried out in the SGF. Each sample ($n=20$) was put into 10ml SGF that was thermally controlled at $37\pm1^{\circ}\text{C}$. Experiments were conducted twice to ensure the results were consistent, with the average values recorded. At a prescribed time, all 10ml SGF from the sample bottles containing the dissolved drug were taken out for analysis. And another 10ml SGF was refilled to its original volume. After completion of the release test,

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the residual drug amount was determined by solvent extraction for ibuprofen and niacinamide. The total release amount of Eudragit coated niacinamide and metoclopramide HCl was determined by depletion method instead. For ibuprofen, 20 individual beads were recovered and blended with 10ml ethanol. The milky suspension was centrifuged and the clear solution was oven dried, the residue was dissolved with 50ml of SGF, and the concentration was monitored. As for niacinamide, the beads were blended with 10ml SGF before centrifugation, and the measurement of drug concentration followed right after centrifugation. In this way, the total incorporated amount of drug, M_{∞} was calculated. The drug incorporation efficiency was calculated according to Equation 3-3.

$$\eta = \frac{M_{\infty}}{M_0} \times 100\% \text{ (Equation 3-3)}$$

where,

η = Drug Incorporation Efficiency

M_{∞} = Incorporated Drug Amount

M_0 = Initial Drug Input Amount

The drug concentration was assayed on a UV-visible spectrometer (UV1700, Shimadzu, Japan) at 220nm for ibuprofen, at 261nm for niacinamide and at 309nm for metoclopramide HCl respectively. The additional information on the molecular formulae of these three drugs and their UV absorbance calibration curves are given below respectively. These drugs are UV visible because they

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contain conjugated systems as the chromophore groups such as benzene rings or pyridine rings to absorb the UV light.

(a)

(b)

Figure 3-7 Ibuprofen information: (a) molecular structure; (b)caliberation curve of ibuprofen concentration versus UV absorbance in SGF

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Nicotinic Acid

Nicotinamide

(a)

(b)

Figure 3-8 Niacinamide information: (a) molecular structure; (b) calibration curve of niacinamide concentration versus UV absorbance in SGF

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(a)

(b)

Figure 3-9 Metoclopramide HCl information: (a) molecular structure; (b) calibration curve of metoclopramide HCl concentration versus UV absorbance in SGF

4. Results and Discussion

The results are discussed under several separate subtitles, examination of HA HMS, analysis of alginate GRDF, release profiles and release characteristics, and kinetic analysis for the release profiles.

4. 1 Examination of HA HMS

4.1.1. HMS formation mechanism

The uniqueness of the HA HMS formation lies in the fast curing polymeric binder, Urea-formaldehyde (UF) resin. It ensured the formation of non-porous plastic crust, and the fast curing/hardening of the resin prevented collapse of the HMS structure during cooling so that the formation of blistered or irregular shape microspheres and collapsed HMSs (see Figure 2-4, page 10) were excluded. The curing/crosslinking mechanism is presented in Figure 4-1, where the methylene bridges connect the individual dimethylol urea to form the urea-formaldehyde resin. The curing is largely due to the condensation between function group $-NH-$ and $-CH_2-OH$ forming a $-N-CH_2-$ linkage. And the condensation reaction is accelerated by acid catalysts and elevated temperatures.

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Figure 4-1 UF polymerization and condensation [194]

The simulation of such a curing process on DSC was to find out at what temperature the condensation takes place and how long the curing process lasts. The results are shown in Figure 4-2. A distinct exothermal peak can be seen at about 115°C, corresponding to the condensation reaction. The condensation completed before 180°C where endotherm appeared again indicating release of other condensation by-products. The duration of the crosslinking reaction was seen less than half a minute. However, the experimental simulation was not an exact resemblance to the spray drying process because of the heating rate limitation of the DSC equipment. As the inlet temperature was pre-heated to 180°C and the micro droplets in the spray were much smaller, the rate of condensation could be much expediated so

4. Results and Discussion

that the crosslinking could be accomplished within the limited chamber residence time. Once the curing process was accomplished, the blown micro bubble solidified and the hollow core structure was maintained.

(a) Heat flow versus temperature

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(b) Heat flow versus time

Figure 4-2 Condensation temperature and duration

During bubbling, two forces are playing the relevant roles in the final thickness of the HMS shell. One is the outward gas pressure generated by blowing agent, the other is the resistance related to the slurry viscosity. Supposingly, the more viscous the slurry is, the more difficult it is to blow a bubble hence the shell thickness will increase accordingly. Specifically, if the storage modulus G' of the slurry is very high, the slurry may have large amount of solids so its viscoelastic property seems more Hookean. If the storage modulus G' is very low or almost zero compared with the loss modulus G'' , the slurry may be very “watery” and Newtonian. Both situations may be unfavourable for bubbling. The amount of blowing agent is considered another critical factor in determining the shell thickness and modifying the rheological

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properties of the slurry. A conventional belief is that the more the blow agent is there, the larger cavity there will be in the core domain of the HMS.

Another critical factor in HMS synthesis is the formation of a non-porous plastic crust at the end of the first stage of drying. Thus both the storage modulus G' and loss modulus G'' of the material within the droplet have to be within a proper range so that a bubble can be generated. The rheological properties of the final slurries with different material compositions are presented in the following charts (Figure 4-3 to Figure 4-4, from page 77 to page 80). Viscosities of groups 1, 2 and 3 are compared in Figure 4-3. Basically higher solid content yielded higher viscosity, thus coinciding with the Krieger-Dougherty equation [195] (Equation 4-1). As ϕ_m and $[\eta]$ are experimentally fixed, the closer ϕ approaches ϕ_m , the higher η will be.

$$\eta = \eta_0 \left(1 - \frac{\phi}{\phi_m}\right)^{-[\eta]\phi_m} \quad (\text{Equation 4-1})$$

η	Viscosity of the suspension
η_0	Viscosity of the suspending liquid
ϕ	Volume fraction of the filler
ϕ_m	Maximum possible solids volume fraction
$[\eta]$	Intrinsic viscosity

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Figure 4-3 Viscosity comparison of the Group 1, 2 and 3

The influence of compositional variation on viscoelastic properties of the slurries are demonstrated here onwards. All samples exhibited some shear-thinning property, as the complex dynamic viscosity decreases when shear rate increases except the viscosity of low-solid-content samples (vis01, vis04 and vis07) showed a disrupted curvy trend at high shear rates. This might suggest a partial and temporary inhomogeneity caused by air bubbles between the suspended ceramic particles, polymer particles, and water. It might be an instrumental artefact at high frequencies too.

Another trend observed was a descending viscosity related to the increasing amount of blowing agent at the same water/binder and ceramic/binder ratio. It

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was observed during the viscosity test that concentrated suspensions of higher amount of blowing agent seemed more creamy and foamy. This might suggest that the blowing agent created air bubbles as “lubricant” in concentrated suspensions so that resistance to shear force was lower. But that does not apply to relatively dilute suspensions, namely vis01, vis04 and vis07, mostly resulted from the fact that the increasing amount of blowing agent could not produce an as prominent effect for the dilute suspensions of enough-low viscosities.

Storage modulus G' and loss modulus G'' of selected samples were plotted in Figure 4-4 (a). Vis06 had a comparatively consistent G' and G'' trend throughout the testing shear rate range. And the storage modulus was always larger than the loss modulus. This represented the slurry was more Hookean than Newtonian, which might not be easy for bubble-blowing. As the water/binder ratio increased, vis10 showed a smaller difference between G' and G'' than vis06, and at high shear rates, G' of vis11 and G' of vis12 discontinued. The phenomena of absence of storage modulus G' at high shear rates were also observed among aforementioned samples of low solid content (Figure 4-4 (b)). In conclusion, solid content change could be the reason of the modulus change which in the end resulted in microsphere morphology change.

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(a) G' and G'' of selected samples with different water/binder ratios

4. Results and Discussion (b) G' and G'' of samples with low solid contentFigure 4-4 G' and G'' of selected solid contents

Cross-sections of spray dried samples from vis01 to vis12 are shown in Figure 4-5. From these observations, the relationship between viscosity and the HMS formation is established. Viscosities of samples can be classified into four levels in terms of numeric values. Vis01, vis04 and vis07 had similar and the lowest level of viscosity; vis02, vis05 and vis09 the medium, vis08 in between the lowest and middle, and vis03 and vis06 the highest. Microspheres of vis01, vis04 and vis07 were thin-shelled and spherical with large portions of hollow cavities. Although the slurries of vis01, vis04 and vis07 contained different amounts of blowing agent and essentially the same

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composition of other ingredients, contrary to conventional belief, the amount of blowing agent did not change the micro morphology and the slurry rheological properties seem more important. The relative low G' values among the three low solid-content samples are considered indispensable to successful bubbling. When the blowing agent decomposed, a large quantity of gas was generated in a short time, as if the droplet experienced high shear rate, and G' of these samples was absent and G'' was low so that bubbling took place.

The shell of the microspheres, shown in Figure 4-5, thickened and became uneven as the viscosity increased. The shells became even thicker and more inhomogeneous and some honeycomb-like or sponge-like topographic features were observed when viscosity was brought up another notch as illustrated by vis02, vis05 and vis09. And finally the sign of HMS microstructure disappeared completely in vis03 and vis06 where viscosity had been so high that bubbling at this level of viscosity became unsuccessful, and that only some inner pores were distinguishable. These observations further proved that the blowing agent played a less important role in HMS formation unless the viscosity of the droplet suspension was in the right range.

4. Results and Discussion

Vis01

Vis02

Vis03

Vis04

Vis05

Vis06

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Vis07

Vis08

Vis09

Vis10

Vis11

Vis12

Figure 4-5 Cross-sections of spray dried microspheres from slurries with different viscosities

4. Results and Discussion

Next, appropriate viscosity is considered a necessary but not a sufficient condition to the formation of HMS during spray drying. Vis10, vis11 and vis12 all had a lower viscosity level than vis06 as their water content was higher compared with vis06. However, this only resulted in larger porosity but no micro-bubble morphology was seen. Because the bubble shell have to be semi-permeable during bubbling and hardened after bubbling with sufficient polymeric binder, otherwise the bubble might burst or collapse. Excessive ceramic particles change the permeability of the crust and give rise to a rigid and porous crust formation after the critical point of drying. Vapour or generated gas will hence be released and the desired inflation will not occur. In the case of non-porous plastic crust, the droplet may undergo the bubbling process just as vis01, vis04 and vis07 did, and the possibility of subsequent collapse or blistering is expelled by the thermal setting nature of the UF resin binder.

Thus the determination of optimal water/binder ratio was the key to successful synthesis of HMSs. Based on SEM analysis and envelope densities plotted in Figure 4-6, it could be concluded that water/binder ratio at 1.5 was optimal. Exceeding or below this value, the envelope density of the microspheres increased. A ceramic/binder ratio from 0.6 to 0.8 seemed to be appropriate.

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Figure 4-6 Envelope densities of samples with different water/binder ratios

4.1.2. Physical and compositional properties

The HA HMSs synthesized with vis01 slurry were selected as the typical set of HA HMSs. These HMSs were sieved to be between 32 to 150 μm before calcination. Micrographs of the typical HMSs were shown in Figure 4-7. The typical diameter to shell thickness ratio of these HMSs was about 10, determined via the image analysis software SEMafore (Jeol, Japan). It was seen that before calcination the shells of HMSs were covered with polymer binder UF resin and HA particles. After calcination the UF binder was completely removed and the HMS shells became porous.

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The porosity is dependent on the calcination temperature and duration since the driving force for necking and grain growth between neighbouring particles will be greater at higher temperatures. As shown in Figure 4-7 (c), the picture on the left stands for the surface porosity of microspheres calcined at 700°C for 60minutes; on the right represents the sample calcined at 800°C for 6 hours. The submicron pores in the left picture nearly disappeared in the right one as a result of prolonged calcination. However, higher calcination temperature and longer calcination duration were not desired, as higher shrinkage rate result in spheroidicity loss and higher envelope density. Furthermore, necking happened not only between neighbouring particles in one individual microsphere, but also between the contacting microspheres. The situation could worsen if the polymeric binder was burnt out at a fast heating rate exceeding 5°C per minute. In such a situation, the polymer could not be effectively evaporated or oxidized in time, and the blistering of polymer residue could draw the neighbouring microspheres closer in contact and result in coalescence of microspheres as shown in Figure 4-7 (d), rather than separate microspheres.

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(a) before calcination

(b) after calcination

700°C for 60 min

800°C for 6 hrs

(c) close up examination on surface porosity

(d) coalescence between the contacting microsphere after calcination at high temperature for a long duration

Figure 4-7 Typical HA HMSs before and after calcination

4. Results and Discussion

X-ray diffraction showed no major phase change between the starting HA powder, as-sprayed HMSs, and post-heat treatment HMSs below 800°C (plotted in Figure 4-8). Secondary phase tricalcium phosphate (TCP) was found in the sample calcined at 1000°C.

Thermostability of the HA HMSs was found to be irrelevant to the compositional parameters as the onset decomposition temperatures of samples overlapped well (in Figure 4-9). The average onset decomposition temperature was $275.0 \pm 2.2^\circ\text{C}$. Weight loss of all samples was completed below 600°C. Thus, considering both the phase examination result and the thermostability result, a calcination temperature of between 600°C and 750°C was considered appropriate.

4. Results and Discussion

Figure 4-8 Phase examination of the HA HMSs

Figure 4-9 Thermostability of HA HMSs

4. Results and Discussion

The additional physical data of these HA HMSs are provided in Table 4-1. The envelope density of the typical batch of HMSs was found to be about 1.2g/cm^3 , which was about 40% of the absolute density 3.16g/cm^3 of HA. The close-to-unity density makes the HA HMSs ideal for the application where X-ray opacity and low density are needed, for example, in the case of intragastric floating dosage form. The empty core domain may serve other functionalities such as encapsulation of drugs or other therapeutic agents.

Table 4-1 Physical properties of typical HA HMSs

<i>Physical parameters</i>	<i>Numerical value</i>	<i>Determination means</i>
Envelope density	$1.2 \pm 0.05\text{g/cm}^3$	Archimedean water displacement
Porosity	$67.1 \pm 3.4\%$	Mercury porosimetry
Surface area	$8.701 \pm 0.001\text{m}^2/\text{g}$	BET surface area
Average shell thickness	$7.0 \pm 4.4\mu\text{m}$	SEM image analysis
Particle size distribution	$150\mu\text{m} > 22\% > 105\mu\text{m};$ $105\mu\text{m} > 59\% > 71\mu\text{m};$ $71\mu\text{m} > 19\% > 32\mu\text{m}$	SEM image analysis

4. Results and Discussion

4. 2 Analysis of alginate GRDF

4.2.1. Dimensional results

A2-2

A2-3

A4-2

A4-3

Figure 4-10 Stereographs of selected alginate beads of different oil or alginate concentrations

The alginate beads were not ideally spherical as Figure 4-10 shows. Beads of higher non-aqueous content, either with higher oil or alginate concentration, exhibited a more plumpy appearance. Hence it was necessary to implement a

4. Results and Discussion

single variable, Heywood diameter D_H as an approximation to the sizes of the beads via image analysis. It was presumably considered that the higher the non-aqueous content would produce beads of larger D_H as there would be lesser shrinkage during drying. Five levels of alginate concentrations and four levels of oil concentrations have been prepared in order to investigate the possible influence on D_H .

Figure 4-11 compares the D_H of beads of different alginate and oil concentrations (free of drugs). There was an ascending trend of the D_H with increasing alginate concentration among non-oily beads (the first column) although the increase was not significant. Such a trend of increasing bead size with increasing alginate concentration was disrupted by oil inclusion and there seemed no obvious trend to the D_H with different oil concentrations, of which the reason is still not clear. However, the size of beads with 1ml, 2ml and 3ml of oil inclusion in their respective pre-gelation liquids were at the similar level. And the overall size differences between the samples with different starting alginate and oil concentrations were not significant. This is in agreement with what Kikuchi et al [196] reported.

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Figure 4-11 Heywood Diameters of beads with various alginate and oil concentrations (free of drugs)

The Heywood diameters of drug loaded beads (including HMS-loaded beads) were plotted in Figure 4-12. The HMS-loaded niacinamide beads, in Figure 4-12 (a), were compared with non-HMS beads, the HMS inclusion brought about a slight size expansion, which might suggest better drug incorporation and little impact on buoyancy. In contrast, as shown in Figure 4-12 (b), the inclusion of HMSs did not have the same effect on the sizes of the ibuprofen beads. The overall D_H of niacinamide beads was slightly larger than those of the ibuprofen beads, especially among the HMS loaded beads. HMS incorporation is thought to be a contributing factor to the size difference

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because better niacinamide incorporation was found among the HMS loaded beads. Generally, it is very hard to tell a distinguishable trend in size variations between drug free beads and drug loaded beads. This obscurity may be magnified by drug loading besides oil incorporation. The only trend observed is HMS incorporation resulted in a size expansion in niacinamide beads. But this trend is not consistent in ibuprofen beads. Maybe as a filler, HA enlarges the D_H of beads by increasing the solid content, but the factors like rheological property change of the pre-gelation liquid by oil and drug inclusion as well as experimental errors during handling resulted in such a discrepancy.

Overall, these beads were larger than 2mm in diameter before administration. Considering some swelling after bead immersion into the aqueous medium, these beads will be large enough to be retained during the fed state rather than immediate evacuation.

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(a) Heywood diameters of beads with niacinamide (N200)

(b) Heywood diameters of beads with ibuprofen (I200)

Figure 4-12 D_H Comparison of beads with and without HA HMSs

4. Results and Discussion

4.2.2. Density and Buoyancy

In Figure 4-13, envelope densities of beads (free of drugs) were plotted and compared. Similar to the D_H result of the beads, the trend of increasing envelope density with increasing alginate concentration was only observed in non-oily beads, and the increment was limited compared with the fluctuation of the density values among oily beads. Thus pure alginate beads of higher alginate concentrations were not only larger in size as manifested in Figure 4-11, but also heavier than those of lower alginate concentrations. Generally oily beads were heavier than non-oily beads as the envelope densities of oily beads of the same alginate concentration were higher than those of non-oily beads. The prediction for mass and density based on the composition of pre-gelation liquids for the beads seems barely possible. The large variation in density depending on oil and alginate content is considered a multi-factor experimental error. These factors include: inhomogeneity during pre-gelation liquid mixing, inhomogeneity during gelation, incomplete gelation, incomplete drying or moisture absorption.

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Figure 4-13 Envelope densities of beads of different alginate and oil concentrations (free of drugs)

The envelope densities of the ibuprofen beads were plotted in Figure 4-14 (a). Densities varied to a great extent but all were smaller than unity. Although no indicative density trend in terms of alginate and oil concentration was observed, there was a general phenomenon that HMS-loaded ibuprofen beads were lighter than the non-HMS counterparts. The decrease of envelope density due to HMS inclusion was even more obvious among the niacinamide beads as demonstrated in Figure 4-14 (b) the densities were observed to be distributed at two different levels. This was believed to result from the light nature of the HMSs and the increase in D_H of HMS-loaded niacinamide beads.

4. Results and Discussion

(a) Non-HMS or HMS-loaded ibuprofen beads

(b) Non-HMS and HMS-loaded niacinamide beads

Figure 4-14 Envelope density of drug loaded alginate beads

4. Results and Discussion

As Singh et al [98] mentioned in their review, low density is not considered a sufficient condition for good buoyancy. It was found that the buoyancy after long hours of administration was not related to their envelope densities, whether the beads were drug loaded or free of drug. The alginate imbibed a large quantity of medium thus densities changed when immersed in the SGF.

Contrary to the findings of Whitehead et al (in which case non-oily beads floated well) [137], as listed in

Table 4-2, although non-oily beads were much lighter than oily beads, none of them floated constantly over the SGF during the test. Sedimentation happened either upon contact with the SGF or soon after agitation began, which meant a drastic density change in very short time. This was probably due to fast swelling caused by a large quantity of water infiltrating into the beads so that they became non-floatable.

In contrast, all oily alginate samples (free of drug) kept floating for 24 hours regardless of their envelope density results. These results were similar to the finding obtained by Murata et al that oily beads surpassed non-oily beads in all buoyancy test [136]. So it may be inferred that buoyancy attributed to air bubbles inside the alginate gel matrix were not reliable and persistent in such a water-permeable hydrogel matrix. Further, disintegration of the alginate beads was found at alginate concentration as low as 1wt% although alginate was believed to be acid-resistant. The 1wt% alginate beads disintegrated totally and formed a milky suspension after 8 hours of stirring.

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Table 4-2 Buoyancy of pure alginate beads and oily alginate beads (free of drugs)

Alginate%	0ml oil	1ml oil	2ml oil	3ml oil
1%	NF			
2%	NF	F	F	F
3%	NF	F	F	F
4%	NF	F	F	F
5%	NF	F	F	F

NF – Non floating; F – Floating

4. Results and Discussion

Table 4-3 Buoyancy of drug loaded beads (non-HMS and H200)

Sample	Alginate amount	Oil amount (non-HMS)			Oil amount (H200-loaded)		
		1ml	2ml	3ml	1ml	2ml	3ml
I200- loaded beads	2wt%	NF	F	F	NF	F	F
	3wt%	NF	F	F	NF	F	F
	4wt%	NF	F	F	NF	F	F
N200- loaded beads	2wt%	NF	F	F	NF	F	F
	3wt%	NF	F	F	NF	F	F
	4wt%	NF	F	F	NF	F	F

Table 4-3 lists the results for the buoyancy of the drug loaded beads. The results show that buoyancy dropped among the drug loaded beads with less oil inclusion. This coincided with Whitehead et al's [138] finding that drug loading impaired buoyancy to some extent. This effect applies to beads with higher HMS loading too as results listed in Table 4-4 below.

Table 4-4 Buoyancy of HMS-loaded beads (drug-loaded)

Sample	HMS loading	Buoyancy
A3-2I800	Non-HMS	F
	H200	F
	H400	NF
	H800	NF
	H1600	NF
A3-2N10000	Non-HMS	F
	H200	F
	H400	NF
	H800	NF
	H1600	NF

4. Results and Discussion

Figure 4-15 Buoyancy comparison of non-HMS and low-loading HMS beads
(I200 after 24 hours of agitation)

Low loadings of HMSs did not affect the buoyancy of drug loaded beads as Figure 4-15 shows. But high loadings of HMSs apparently jeopardized the

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floating ability. Presumably, addition of HMS will increase the porosity of the beads. However, if the HMSs break and disintegrate during the mixing process, the porosity increase may not occur. The decline in buoyancy caused by high loading of HMSs was thought to be due to the disintegration of majority of HMSs. This hypothesis is later proved by SEM examination on the bead cross-sections.

The buoyancy of Eudragit coated beads is tabularized in Table 4-5 below. Similar to the drug incorporation, thick coating impaired the buoyancy of the niacinamide or metoclopramide HCl beads. The difference was, unlike the instant precipitation of overloaded drug or HMS incorporated beads, all coated beads were able to float at the beginning; but as the water infiltrated, beads of higher drug loadings or thicker coatings sedimented gradually.

Table 4-5 Buoyancy of Eudragit Coated Beads (Niacinamide and Metoclopramide HCl)

<i>Eudragit Coating Thickness</i>	<i>Niacinamide</i>				<i>Metoclopramide HCl</i>		
	N200	N800	N10000	N20000	M200	M10000	M20000
A3-2C3E1	F	F	NF	NF	F	F	NF
A3-2C3E2	F	F	NF	NF	F	F	NF
A3-2C3E3	NF	NF	NF	NF	NF	NF	NF

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4.2.3. Topological analysis

Figure 4-16 Cross-sections of oily and non-oily gel beads (free of drug and non-HMS)

Figure 4-16 gives the details of the cross-sectioned beads free of drugs or HMSs. Pure alginate beads (A2 and A4) were featured with thin skin and large inner cavity. In contrast, oily beads (A2-2 and A4-2) had an orange peel outlook with much thicker skin. Emulsification of the sunflower oil in the pre-gelation liquid and fast gelation of alginate gel matrices resulted in a large number of tiny oil pockets encapsulated either on the bead surfaces or deep

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within the bead matrices, hence creating a totally different morphology. The oil pockets small as several microns spread evenly over the surface and the inner shell. Leakage of a certain number of these tiny compartments would not necessarily result in a failure of the gel bead; hence the safety margin against premature sedimentation was increased.

The cross-sections of non-HMS ibuprofen beads are displayed in Figure 4-17. The drug loaded beads seemed much more condensed than the beads free of drugs. The empty cavities seen among the beads free of drugs were not found in the drug loaded beads. No drug particle was seen on the bead cross-sections at all starting drug concentrations. Instead, roughness of the bead cross-sections increased on increasing drug concentration and oil pockets seemed increasing too. This was thought that the ibuprofen might dissolve or precipitate in the oil pockets since ibuprofen solubility in oil is higher than in water. Because all four ibuprofen samples were prepared as the initial drug concentration (C_0) exceeding the saturated drug concentration (C_s) in water (this is attested through calculation of initial loadings in drug release test; page 134, Table 4-6), if ibuprofen had not been well dispersed and encapsulated into the oil pockets, there would be drug precipitates seen on SEM. Although C_0 of ibuprofen in oil is much larger than C_s of ibuprofen in oil too, it was observed that fine ibuprofen particles could suspend in oil for more than 10 minutes without precipitation during the solubility test. Hence it was suspected that ibuprofen was largely drawn to emulsified oil droplets in the pre-gelation liquid. The uniform ibuprofen dispersion in oil pockets is thought

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to be able to maintain the release in a controlled-manner, since oil provides more partitioning for the ibuprofen.

A3-2I200C3

A3-2I400C3

A3-2I800C3

A3-2I1600C3

Figure 4-17 Cross-sections of ibuprofen beads (non-HMS)

The cross-sections of niacinamide beads of the four initial concentrations are shown in Figure 4-18. The first two concentrations N200 and N800 were $C_0 < C_s$ (in water), while the other two, N10000 and N20000 were $C_0 \gg C_s$ (in water). There was little drug deposition on the cross-sections of N200 and N800 while on those of N10000 and N20000, the cross-sections were packed

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with solids which might be particles of the oversaturated niacinamide. It was revealed that both ibuprofen and niacinamide beads were either a dissolved-drug or dispersed-drug matrix system as no evidence of inhomogeneous drug distribution was found. The porosity of drug-loaded beads was also different from the beads free of drugs. No large inner cavity or porosity was found among drug-loaded beads.

A3-2N200C3

A3-2N800C3

A3-2N10000C3

A3-2N20000C3

Figure 4-18 Cross-sections of niacinamide beads (non-HMS)

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The cross-sectional images and their corresponding EDX mapping on the Phosphorus element of HMS-loaded beads are presented in Figure 4-19. Basically it was found that the HMS content increase brought about the same effect of niacinamide increase; porosity decreased. HMSs inside the alginate-oil matrices were mostly disintegrated, because there was no HMS micro-structure observed on the cross-sections of the HMS loaded gel beads under SEM examination. This was thought as a result of the disintegration of HMSs during mixing of pre-gelation liquid. The diffraction intensity of the phosphorus element increased with the increase of HMS content. The beads were visually monitored under X-ray angiogram, and it was found that only the H1600 was visible, the other three HMS loadings being totally invisible or too pale (H800) to be recognized easily.

Results shown in Figure 4-20 are the EDX mapping of the same set of HMS-loaded beads after 6 hours of SGF immersion. It was found that after 6 hours of immersion the diffraction intensity of phosphorus element dropped drastically for H200 and H400. This was primarily because at pH 1.2, hydroxyapatite was not stable and transformed into $\text{Ca}(\text{HPO}_4) \cdot 2\text{H}_2\text{O}$ which dissolved in ambient SGF solution, hence resulting in the abatement of the phosphorus element. Whereas for H800 and H1600, the diffraction intensity did not differ too much from the beads before immersion. This was probably because the condensed solid content left little space for medium penetration so that the reduction of phosphorus intensity might take longer time. The

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result suggests that by varying the HMS loading, the radiopacity could be tailored for the desired duration too.

An unexpected finding was that HMS-loaded beads were less sticky than non-HMS loaded beads. Some non-HMS beads exhibited a tendency to adhere to one another and oil leakage was observed when kept on the shelf for a long time (two months), but the HMS-loaded beads seldom had the same problem. Similar as Rouge et al. [197] mentioned, the addition of a filler excipient into the floating capsule could prevent the sticking tendency. Maybe the HA filler is non-swellable so that the moisture absorbed by HMS-loaded beads will be much less than the HMS-free beads hence less adhesion and stickiness will be caused.

A3-2I800H200

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A3-2I800H400

A3-2I800H800

A3-2I800H1600

Figure 4-19 Cross-sections of HMS-loaded beads (A3-2I800) and their EDX mapping of phosphorus element

4. Results and Discussion

A3-2I800H200

A3-2I800H400

A3-2I800H800

4. Results and Discussion

Figure 4-20 Cross-sections of HMS-loaded beads (A3-2I800) and their EDX mapping of phosphorus element after 6 hours of SGF immersion

4.2.4. Bead water uptake

Bead water uptake in this case was presented as normalized weight gaining ratio (defined in Equation 4-2) in the following figures.

$$Y = \frac{M_{wet}}{M_{dry}} \quad (\text{Equation 4-2})$$

Y = Normalised weight gaining ratio

M_{wet} = bead weight after swelling (including water uptake)

M_{dry} = initial dry bead weight

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Figure 4-21 Water uptake of pure alginate beads

Water uptake of pure alginate beads is plotted in Figure 4-21. Pure alginate beads achieved maximum weight gain in about 10 to 20 minutes' time and quickly dropped to a plateau region where the bead weight stabilized. The weight gain is considered primarily a result of alginate swelling. The swelling of calcium alginate (Ca-Alg) happens when water is trapped in the network of the complexation of the polyguluronic sequences by calcium ion (as described on page 28). Understandably, if there are more calcium ion knots, the chain length between every two knots will be shorter, leading to a more limited chain relaxation/swelling. And presumably the higher the CaCl_2 concentration was, the more gelation knots would be in the alginate network, leading to higher gelation densities at the same alginate concentration. The time to reach peak weight gain was considered irrelevant to gelation densities since the time to

4. Results and Discussion

reach peak swelling for each initial concentration was similar, regardless of the gelation densities. Beads of low gelation densities obtained at least about eight times that of the original mass for the equilibrium swelling weight at the plateau region, while the beads of high gelation densities obtained at most four times. The reason is thought to be the smaller mesh size between every two crosslinks, so that shorter chain length between the crosslinks restrained the extent of swelling.

Also, for the beads formed by a higher alginate concentration, the decline towards the plateau region is due to the dissolution of un-reacted sodium alginate (because of low CaCl_2 amount). Conversely, the networks with higher CaCl_2 amounts did not show this decrease in swelling beyond the maximum, as there was clearly less sodium alginate. In general, the beads achieved relatively low degrees of swelling as Figure 4-21 shows, probably because the ionization of $-\text{COOH}$ containing alginate hydrogel was suppressed in acidic pH.

Oil encapsulation inhibited bead water uptake as Figure 4-22 demonstrates. Peak weight gains of beads of the same gelation density escalated in a high-to-low order as the initial oil concentration dropped. And the water uptake of beads with high initial oil concentration and high gelation density was nearly negligible, as the A3-3C4 curve shows in Figure 4-22. The oil weight percentage was in fact quite high for oily beads and oil does not swell so the

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fact limited the water uptake in total. But compared with pure alginate beads, there was no difference in the time to reach the maximum weight gain.

Figure 4-22 Water uptake of oily beads of different gelation densities (free of drugs and non-HMS)

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Figure 4-23 Water uptake of drug and HMS-loaded beads

The water uptake of drug- and HMS-loaded beads is presented in Figure 4-23. Ibuprofen encapsulation seemed to have made the beads more hydrophobic compared with beads that are free of drugs, both the peak weight gain and the equilibrium weight gain decreased but the time to reach the peak swelling weight remained unchanged. The effect was similar to more oil addition. While water uptake of niacinamide beads seemed different, generally the time to reach peak weight gain was delayed to about 30 minutes after immersion. The increased osmotic pressure caused by niacinamide incorporation may be responsible for the higher extent of water uptake than that of those pure alginate beads. And the HMS-loaded beads behaved like their niacinamide non-HMS counterparts, peaked and went into plateau at about the same time, but at a much lower weight gaining ratio. Because HA is non-swelling ceramic mass, the more HMSs were included, the less swellable mass in a single bead would be.

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Figure 4-24 Water uptake of Eudragit coated beads (non-oily and oily)

The water uptake of the Eudragit coated beads is given in Figure 4-24 in order to find out the possible influence on their drug release behaviour. The water uptake of oily beads with thicker coatings was largely inhibited by the coating. Time to reach the peak weight gaining was slightly brought forward, from 10 to 20 minutes after immersion. In general no major difference was found regarding the trend of water uptake between coated beads and uncoated beads.

In conclusion, the low degree of water uptake translates into low degree of alginate swelling which consequently limits the possibility of relaxational control of drug release. Moreover, the macrostructure of the matrix was highly

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porous, so medium would penetrate easily through the interconnected pores, so that the chain relaxation would hardly control the solute release.

4.2.5. Release profiles and release characteristics

4.2.5.1 Drug incorporation efficiency

(a) Ibuprofen incorporation efficiency of non-HMS and HMS-loaded beads

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(b) Niacinamide incorporation efficiency of non-HMS and HMS-loaded beads

Figure 4-25 Comparison of drug incorporation efficiency between non-HMS and HMS loaded beads (H200)

Figure 4-25 (a) compares the ibuprofen incorporation efficiency of between non-HMS beads and HMS loaded beads. The results show that among the non-HMS beads, an increase in oil concentration from 2ml oil per 10ml alginate to 3ml oil per 10ml alginate brings about 10% to 20% increase in ibuprofen incorporation. However, no obvious correlation between alginate concentrations and ibuprofen incorporation was seen among the non-HMS beads. For HMS loaded beads, at a low alginate concentration, a generally higher ibuprofen incorporation is observed. But as alginate concentration increases, the advantage diminishes since all HMS loaded beads exhibit

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declining incorporation efficiency as alginate concentration increases. So HMS inclusion might only help to improve incorporation efficiency at only low alginate concentrations.

Figure 4-25 (b) shows the results for hydrophilic niacinamide beads. The trend of decreasing incorporation efficiency with increasing alginate concentration is still seen among HMS loaded beads. But the incorporation efficiencies of HMS loaded samples were more than double of the non-HMS samples, indicating that HMS inclusion enhanced the drug encapsulation and distribution. The significant elevation of incorporation efficiency by HMS inclusion was thought to be due to capillary forces introduced by pores on the HA surface. Another possible explanation is the better partitioning of niacinamide into HA due to better niacinamide affinity to HA. This affinity may result from surface charge attraction or chemical bonding. Or there is some preferential adsorption or absorption of niacinamide by HA.

4.2.5.2 Ibuprofen release profiles

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Figure 4-26 Ibuprofen release from beads of same drug loading (I200),
different initial alginate and oil concentrations

The release profiles of floatable ibuprofen beads are plotted in Figure 4-26. All the samples released the ibuprofen in a controlled manner and no burst release was seen. Faster release was seen among beads of higher alginate concentration. On the other hand, the higher oil concentration caused a slower release rate among beads with the same alginate concentration. The reason is probably the same for both observations: higher alginate concentration represents relatively less oil. This leads to lesser availability of oil for the ibuprofen to dissolve into and lesser ibuprofen partitioned into oil therefore results in a higher release rate, and vice versa for higher oil concentrations.

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(a) Ibuprofen beads of 2ml initial oil concentration

(b) Ibuprofen beads of 3ml initial oil concentration

Figure 4-27 Release profiles of non-HMS and HMS-loaded (H200) ibuprofen beads

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Figure 4-27 depicts the difference between release profiles of non-HMS and HMS-loaded ibuprofen beads. The release from the HMS-loaded ibuprofen beads seemed Fickian too, but at a slower release rate than the non-HMS counterparts. However, the difference between the A2-3I200H200 and A2-3I200 was not very critical compared to the rest of the samples. Most likely, the HMS inclusion separated the contact between neighboring oil pockets and made the drug less accessible to the release medium.

Figure 4-28 Release from different initial ibuprofen concentrations

Release profiles from beads of different initial ibuprofen concentrations were compared in Figure 4-28. The release profiles seemed dependent on the initial concentration C_0 . Higher drug loadings achieved longer release.

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Figure 4-29 Release from ibuprofen beads of different gelation densities

Ibuprofen release from beads of different gelation densities was also studied. The result is shown in Figure 4-29. Overlapping release profiles are observed. This finding revealed that the ibuprofen release from the alginate matrix were irrelevant to the mesh size of alginate network, probably due to the small molecular size of the drug, ibuprofen ($C_{13}H_{18}O_2$) which is at only a M_w of 206.28. Most reasonable explanation for the above observations is, all ibuprofen might be saturated in oil and the excessive are suspended in the oil domains because the saturation concentration in oil was found to be about 25mg/ml, well above the solubility in water 1mg/ml; release of ibuprofen was driven by partitioning from oil into surrounding water, for example, in the pores. Thus the observed release was due to partitioning effects only, which did not depend on gelation density.

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All in all, it has been observed that ibuprofen release in a Fickian manner without the burst release normally seen on spherical drug carriers. The release lasted for 24 hours, regardless of initial drug loading and gelation density because it was thought to be related to oil partitioning only.

4.2.5.3 Niacinamide release profiles

Niacinamide release from uncoated beads was totally different as Figure 4-30 shows. Most of the niacinamide was released during the first 30 minutes from non-HMS beads, regardless of the alginate concentration and oil concentration. The HMS-loaded beads also exhibited the fast burst pattern of release. Because niacinamide is hydrophilic, it would be likely to be entrapped within the alginate network rather than in the oil pockets. So when water penetrated into the network, the niacinamide ($C_6H_6N_2O$, Mw 122.12) whose molecules were even smaller than ibuprofen diffused out of the matrix rapidly through aqueous channels. This was proved since the swelling peaked at about 30 minutes after immersion, and the niacinamide amount released after 30 minutes was limited.

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Figure 4-30 Niacinamide release from non-HMS beads

Figure 4-31 Niacinamide release comparison of non-HMS and HMS-loaded (H200) samples

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All the above profiles show a considerable amount of “burst” release, due to rapid water ingress and creation of aqueous channels for the niacinamide to permeate out. Clearly, even if gastric retention time were prolonged for these formulations, sustained release is not achieved, hence the value of these formulations for release of hydrophilic drugs is limited; to overcome this, Eudragit® coating of the beads was studied.

Figure 4-32 Niacinamide release from beads with different Eudragit coating thickness

It was found that the Eudragit coated beads were able to extend the release for a longer duration than non-coated niacinamide beads as Figure 4-32 shows. E1 released niacinamide with a pronounced burst effect and after 6 hours, all drug had been released. The release from E2 differed as

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niacinamide was released (after a short initial burst) in a zero-order manner for the first 5 hours, followed by a slower release till drug was exhausted. The 3rd sample, E3, showed virtually no burst and a sustained zero-order profile for the entire duration of release.

A3C3E1

A3C3E3

A3-2C3E1

A3-2C3E3

Figure 4-33 Eudragit coating thickness shown on cross-sections

The rationale is considered as follows: the Eudragit coating makes the bead a reservoir/membrane system. When Eudragit concentration increased, the

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coating thickness increased as shown in Figure 4-33. The thicker the Eudragit coating, the slower the permeation was through the membrane.

Figure 4-34 Niacinamide release from beads of different gelation densities

Eudragit coated beads of different gelation densities were also studied and their release profiles were shown in Figure 4-34. These samples, being gelled in different concentrations of CaCl_2 solution, may have different drug incorporation, different internal porosity, and different gelation densities. Thus drug transport differentiated as a result of the abovementioned factors, but all in all, the gelation density changes did not modify the drug release pattern of Eudragit coated beads as four release profiles were basically similar.

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4.2.5.4 Metoclopramide HCl release profiles

In order to prove the efficacy of Eudragit coating on sustained release, metoclopramide release from Eudragit coated beads were studied and the results are shown in Figure 4-35. The release pattern seems a typical reservoir system, beginning with a zero-order release followed by a plateau region when the drug is about to deplete. After a short delay during the first half hour's immersion, the metoclopramide release sustained for 12 hours.

(a) release for 132 hours

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(b) zoom-in at 12 hours

Figure 4-35 Metroclorpromide release from Eudragit coated beads

Similar to the niacinamide release, the beginning stage of the release profile seemed to be a burst after a short period of delay which was about the time for the beads to hydrate and swell. At higher initial metoclopramide HCl loadings, the initial burst was about 4 hours and after that a zero-order was achieved. This burst was not obvious for low initial metoclopramide HCl loading except the delay during the first half an hour.

4.2.6. Kinetic analysis for the release profiles

4.2.6.1 Kinetics of ibuprofen release

Inspection showed that ibuprofen was saturated in the oil pockets and these oil pockets were trapped in alginate matrix. The ibuprofen transportation from

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the carrier to the ambient medium underwent two steps. Firstly, it diffused out of the oil pockets into the swollen alginate. Secondly, it diffused out of the swollen alginate into the ambient. The second step is considered very fast compared to the first. According to on Kuu et al [178] and Lee [186], no matter $C_0 > C_S$ or $C_0 < C_S$, as long as it was a diffusion controlled case, the Higuchi square root time dependence (Equation 4-3) of fractional drug release is still applicable for the first 60% of M_∞ . After subtracting the initial delay, selected ibuprofen releases (up to 60% of M_∞) were fitted into Equation 4-5 below, an alternation from Koizumi et al's [198] equation (Equation 4-4) specifically derived for non-degrading spherical matrix systems. And the results are shown in Figure 4-36, Figure 4-37 and Table 4-6.

$$M_t \sim Kt^{\frac{1}{2}} \text{ (Equation 4-3) [175]}$$

$$M_t = 4\pi r^2 \left[\sqrt{2(C_0 - C_S)C_S Dt} + \frac{4C_S Dt}{9r} \left(\frac{C_S}{2C_0 - C_S} - 3 \right) \right]$$

$$\text{(Equation 4-4) [198]}$$

$$M_t = At^{\frac{1}{2}} - Bt \text{ (Equation 4-5)}$$

Where

$$A \sim \sqrt{2(C_0 - C_S)C_S} \text{ and } B \sim \left| \frac{C_S^2}{2C_0 - C_S} - 3C_S \right|$$

C_0 is the initial ibuprofen concentration in oil; C_S is the saturation concentration of ibuprofen in oil; D is an overall average diffusion coefficient

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while r is the radius of the spherical matrix system, which can be approximated from the average Heywood diameter of the beads.

The experimental data fit nicely into the first-order release pattern hence it is safe to claim that there is a strong dependence between the accumulative release amount M_t and the square-root-of-time when the zero-order part in Equation 4-5 equates to zero. And the A values obtained were consistent for the four initial ibuprofen loadings as Figure 4-37 shows. Assuming a pseudo-steady diffusion, the slope of Figure 4-37 yields the diffusion coefficient D , which is approximately $7.65 \times 10^{-3} \text{ cm}^2/\text{hr}$ or $2.1 \times 10^{-6} \text{ cm}^2/\text{s}$, which is indicative of diffusion of a drug of M_w about 200 through a non-viscous liquid.

Figure 4-36 First-order fitting of ibuprofen accumulative release

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Sample	C_0 (in oil)	A value	B value	R^2
A3-2I200C3	55.3mg/ml	0.493 ± 0.006	0	0.989
A3-2I400C3	90.6mg/ml	0.665 ± 0.009	0	0.985
A3-2I800C3	114.4mg/ml	0.830 ± 0.008	0	0.988
A3-2I1600C3	233.6mg/ml	1.278 ± 0.015	0	0.981

Figure 4-37 Correlation between A value and $C_0^{1/2}$

Hence the ibuprofen release from the oily beads can be concluded as a diffusion-controlled case. The mechanism may be elaborated as follows: after a short period of alginate swelling, nearly all the oil pockets started to release

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ibuprofen at the same time, rather than the outer periphery being hydrated first and starting the release before the release from the inner core. This is thought to be the reason why no obvious decline of the release driving force was observed. Since every oil pocket can be regarded as an ibuprofen matrix ($C_0 > C_S$), the whole bead can thus be deemed as a matrix system too. Unreleased ibuprofen had to dissolve in oil before it diffused out of the oil pocket. And the ibuprofen diffusion time from oil to alginate dominated the release rate while the diffusion time from alginate to the ambient medium was considered negligible compared with the former.

4.2.6.2 Kinetics of niacinamide and metoclopramide HCl release

Release mechanism of niacinamide and metoclopramide HCl from Eudragit coated beads was considered identical. Because the Eudragit coating is deemed hydrophobic at an acidic pH, the bead is thus seen as a drug reservoir and the partition between the saturated drug concentration in Eudragit and the drug concentration in ambient SGF determines the release rate. In the experimental setup, Sink condition was fulfilled so the drug concentration in ambient SGF was considered as zero.

Time dependence release profile (Equation 4-6) is applied.

$$\frac{M_t}{M_\infty} = kt \quad (\text{Equation 4-6})$$

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Initial burst for the first 5 hours was excluded from the analysis and a fair correlation between niacinamide accumulative release and release time was obtained (Figure 4-38). It is clear that from 6 hours to 12 hours the data points match the linear fitting quite well (Table 4-7). From 12 hours to 18 hours there is a drop in release rate as the slope begins to level off. So is the slope from 18 hours to 24 hours. It can be inferred as the decrease in drug concentration from 12 hours onwards. And the bursts at 12 hours and 18 hours might be due to the coating defects or some other unknown reason.

Figure 4-38 Zero-order fitting of niacinamide accumulative release versus time from Eudragit coated beads

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Table 4-7 Time dependence of niacinamide accumulative release

Sample	k value	R ²
A3-2N10000C3E2	0.038±0.002	0.986
A3-2N10000C3E3	0.015±0.001	0.990

The zero-order fitting of metoclopramide HCl release from Eudragit coated beads is presented in Figure 4-39 and Table 4-8. The analysis excludes the initial delay and the burst during the first 4 hours as well as the plateau region of drug depletion after 12 hours. It is found that all three profiles match the zero-order time dependence reasonably. So the results reconcile with the previous hypothesis that Eudragit coated beads were reservoir drug carriers. Based on the fitting results, it is fair to conclude that from 4 hours to 12 hours, the formulations release 30wt% to 40wt% of total encapsulated metoclopramide HCl in a zero-order, while the first 30wt% to 50wt% were released at a faster rate during the first 4 hours. The time-dependence of fractional release was achieved with the drug partitioning through the acid resistant Eudragit coating.

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Figure 4-39 Zero-order fitting of metoclopramide HCl accumulative release versus time from Eudragit coated beads

Table 4-8 Time dependence of metoclopramide HCl accumulative release (Eudragit coated beads)

Sample	k value	R ²
A3-2M200C3E2	0.016±0.001	0.988
A3-2M10000C3E2	0.482±0.013	0.999
A3-2M20000C3E2	0.687±0.021	0.998

Study on two hydrophilic drugs verifies the efficacy of a Eudragit coated alginate floating dosage forms. The alginate core ensures the buoyancy and

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drug incorporation, while the Eudragit coating serves as the rate-controlling membrane for the hydrophilic drug reservoir.

In summary, the more hydrophobic ibuprofen was released from the oil chambers into the alginate matrix and then into the ambient SGF, in a typical diffusion-controlled first-order pattern. The release lasted for 24 hours and no burst effect was observed. This release pattern is ideal for a once-a-day dosage form although the GRT has to be further prolonged to tally with such an ibuprofen release. Zero-order release of niacinamide and metoclopramide HCl was achieved from 6 to 24 hours and from 4 to 12 hours respectively, through the acid resistant Eudragit coating. Release rate was dependent on Eudragit coating thickness and drug loading. However, only 30%wt to 40%wt of the initial loading was released in a zero-order. Initial delays and prominent burst effect was seen among samples with thinner coatings. The duration and stability of the release of the hydrophilic niacinamide or metoclopramide HCl was not as good as that of ibuprofen. The cause is most probably due to coating defects. Nevertheless, considering the average GRT of about 5 to 8 hours of floating dosage forms, larger amount of hydrophilic drugs can be released during this time span, which may achieve a more effective therapeutic outcome in situ.

5. Conclusions

This work has succeeded in synthesizing a floatable and erodible GRDF, in characterizing such a GRDF and collecting its release profiles, and in release kinetic studies. The major findings are summarized below:

5. 1 HMS Synthesis

HA HMSs were generated in a bubbling and polymer curing procedure, during which a starting slurry of a suitable viscosity, the formation of a plastic semi-permeable membrane by the polymer binder, gas discharge from the blowing agent and in situ crosslinking of the polymer are crucial. These processes during spray drying were found to rely on the following criteria:

- Appropriate water/binder ratio
- Appropriate solid content
- Optimal water/binder ratio was found to be about 1.5 and ceramic/binder ratio about 0.6 to 0.8.

Typical HA HMS physical properties were provided in Table 4-1.

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5.2 Alginate GRDF

Multiple-unit alginate beads were synthesized through an emulsion gelation process. The large number of tiny oil chambers ensured the superior buoyancy over single-unit floating systems. Hence non-oily beads failed the buoyancy test owing to its single-unit nature, while oily beads floated constantly for 24 hours. However, there is no immediate relation between the envelope density and buoyancy as alginates are swellable and water permeable. For example, lighter non-oily beads have poor buoyancy compared with denser oily beads.

A 24-hour sustained ibuprofen release without any burst effect was achieved among the oily beads. The controlled ibuprofen release was believed to be a result of unique drug distribution and oil partitioning. Ibuprofen was found saturated in the oil pockets and these oil pockets were trapped in alginate matrix. Hence it diffused from the oil pockets into the swollen alginate, then from swollen alginate into the ambient medium. And the first-order diffusion from the oil chambers to the alginate matrix was the main control mechanism of ibuprofen release.

Uncoated beads released the niacinamide in a typical Fickian burst because niacinamide is hydrophilic and there was no oil partitioning for niacinamide. Eudragit coated beads were able to maintain a 24-hour release. The release rate was dependent both on initial loadings as well as Eudragit coating thickness but unrelated to alginate gelation density. As the sample with thin

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coatings still produced a pronounced burst effect and less durable release, the sample with thicker coatings showed virtually no burst and a sustained zero-order profile for the entire duration of release. The Eudragit coating makes the membrane system so that the partition from the drug-loaded alginate core through the Eudragit coating to the ambient SGF was the key kinetic to the zero-order release after the initial burst. The hypothesis was reconfirmed as metoclopramide HCl, another more hydrophilic drug, was released from Eudragit coated beads in an essentially identical manner.

The initial objective to radiolabel the alginate beads was achieved by HMS inclusion, and radiopacity might be adjusted by HMS-loading. However radiopacity was attained at the cost of buoyancy because of disintegration of the HMSs during mixing. HMS inclusion helped to reduce the envelope density of the beads and enhance the incorporation efficiency of the hydrophilic drugs. HMS inclusion could further adjust the release rate of hydrophobic drugs, although there was no improvement on drug incorporation. The incorporation efficiency for HMS-loaded niacinamide beads was boosted more than double, but no control over release rate was found. HMS inclusion was also found to be able to stabilize oil leakage and improve non-stickness. A measure to counter HMS disintegration must be implemented otherwise the HMS incorporation is of no enough value. Or these HMS have to be made water impermeable to improve buoyancy as well as of better radio-opacity.

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Further, we recommend these floating dosage forms be taken after a meal, because floating systems require sufficient liquid to float on and better still, a meal to retard their emptying. Eventually the floating system will be emptied from the stomach. However fat (oil) will be emptied at the end of the emptying sequence. Although these alginate-oil matrices were able to float for 24 hours, the floating time in the stomach is expected to be much shorter. It will be helpful to conduct a resultant weight study in vitro and an in-vivo x-ray imaging on an animal model to determine the actual floating duration too.

6. Recommendations for Further Work

6. 1 HMS synthesis

In this study, it was found that HMSs did not help to enhance buoyancy and radiopacity of these HMS-loaded beads were found to be poor mainly because of the disintegration of the HMSs. So the following work is recommended for further study:

- Dense shelled, water-impermeable HMSs might be a good alternative.
- Barium sulfate may replace HA to be the HMS material if permanent radiopacity is needed.

6. 2 Alginate GRDF

The following work is also considered worthy of further investigation:

- GRDF design enhancement to accommodate both high drug loading and good buoyancy
- Resultant weight (RW) study for the in-situ evaluation of the GRDF and to plot buoyancy variation versus time
- Animal study to test the in-vivo floatation of the GRDF and in-vivo drug release characteristics
- Human trials to test the GRT extension and plasma concentration of the drug of interest

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