Chapter 1.1
Introduction to Stomach Specific drug delivery systems
1.1 Stomach Specific drug delivery systems

1.1.1 Introduction

The design of oral control drug delivery systems (DDS) should be primarily aimed to achieve more predictable and increased bioavailability. Approximately 50% of the drug available in the market are oral DDS and these systems have more advantages due to patients acceptance and ease of administration. Nowadays most of the pharmaceutical scientist is involved in developing the ideal DDS. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release systems. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.

Under certain circumstances prolonging the gastric retention of a delivery system is desirable for achieving greater therapeutic benefit of the drug substances. For example, drugs that are absorbed in the proximal part of the gastrointestinal tract and the drugs that are less soluble or are degraded by the alkaline pH may benefit from the prolong gastric retention. In addition, for local and sustained drug delivery to the stomach and the proximal small intestine to treat certain conditions, prolonging gastric retention of the therapeutic moiety may offer numerous advantages including improved bioavailability, therapeutic efficacy and possible reduction of the dose size. It has been suggested that prolong local availability of antibacterial agents may augment their effectiveness in treating H. Pylori related peptic ulcers. Gastroretentive Drug delivery systems (GRDDS), however are not suitable for drugs that may cause gastric lesions, e.g., Non-steroidal anti-inflammatory agents.

1.1.2 Basic physiology of the gastrointestinal tract

The complex anatomy and physiology of the GIT, including variations in acidity, bile salts, enzyme content, and the mucosal absorptive surface, significantly influence the release, dissolution, and absorption of orally administered dosage.
forms. Two distinct patterns of gastrointestinal (GI) motility and secretion exist, corresponding to the fasted and fed states. As a result, the BA of orally administered drugs will vary depending on the state of feeding. The fasted state is associated with various cyclic events, commonly referred to as the migrating motor complex (MMC), which regulates GI motility patterns. The MMC is organized into alternating cycles of activity and quiescence and can be subdivided into basal (Phase I), preburst (Phase II), and burst (Phase III) intervals (Figure 1.1.1). Phase I, the quiescent period, lasts from 30 to 60 min and is characterized by a lack of secretory, electrical, and contractile activity. Phase II exhibits intermittent action for 20–40 min during which contractile motions increase in frequency and size. Bile enters the duodenum during this phase, whereas gastric mucus discharge occurs during the latter part of Phase II and throughout Phase III. Phase III is characterized by intense, large, and regular contractions, termed housekeeper waves, that sweep off undigested food and last 10–20 min. Phase IV is the transition period of 0–5 min between Phases III and I. This series of electrical events originates in the foregut and continues to the terminal ileum in the fasted state, repeating every 2–3 hrs. Feeding sets off a continuous pattern of spike potentials and contractions called postprandial motility.

The particular phase during which a dosage form is administered influences the performance of peroral CRDDS and GRDDS. When CRDDS are administered in the fasted state, the MMC may be in any of its phases, which can significantly influence the total gastric residence time (GRT) and transit time in the GIT. This assumes even more significance for drugs that have an absorption window because it will affect the amount of time the dosage form spends in the region preceding and around the window. The less time spent in that region, the lower the degree of absorption. Therefore, the design of GRDDS should take into consideration the resistance of the dosage form to gastric emptying during Phase III of the MMC in the fasted state and also to continuous gastric emptying through the pyloric sphincter in the fed state. This means that GRDDS must be functional
quickly after administration and able to resist the onslaught of physiological events for the required period of time.

Figure 1.1.1: Motility patterns of the GIT in fasted state

1.1.3 Gastric emptying and problems

It is well recognized that the stomach may be used as a depot for Sustained release dosage forms, both in human and veterinary applications, stomach is anatomically divided into three parts: Fundus, body and pylorus. The proximal stomach made up of the fundus and body region serves as a reservoir for ingested materials, while the distal region (antrum) is the major site for the mixing motion, acting as a pump to accomplish gastric emptying. The process of the gastric emptying occurs both during fasting and fed stages. Scintigraphy study involving measurement of gastric emptying rates in healthy human subject have revealed that an orally administered Controlled release dosage form is mainly subjected to two physiological adversities,

a) The short GRT (Gastric Residence Time)

b) Variable (unpredictable) GET (Gastric Emptying Time)

Yet another major adversity encountered through the oral route is the first pass effect, which leads to reduce systematic availability of a large number of a drug. These problems can be exacerbated by alteration in the gastric emptying that occur due to factors such as age, race, sex and disease states, as they may seriously affect the release of a drug from DDS. It is therefore desirable to have a
Chapter 1.1

Introduction to stomach specific drug delivery system

Controlled release product that exhibits an extended, GI residence and a drug release profile independent of patients' related variables.

1.1.4 Potential drug candidates for stomach specific drug delivery systems

1. Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.
2. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-dopa, paraaminobenzoic acid, furosemide, riboflavin etc.
3. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
4. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
5. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

1.1.5 Drugs those are unsuitable for stomach specific drug delivery systems

1. Drugs that have very limited acid solubility e.g. phenytoin etc.
2. Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3. Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

1.1.6 Approaches to gastric retention/ stomach specific delivery systems

Various approaches have been paused to increase the duration of oral dosage form in the stomach, including floating systems, swelling and expanding system, modified shape system, high density systems and other delayed gastric emptying devices. (Magnetic systems, super porous – biodegradable hydrogel systems).

1.1.6.1 High density (sinking) system or non-floatong drug delivery system

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content (~ 1.004 gm/cm³). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc. The materials increase density by up to 1.5- 2.4 gm/cm³. A density close to 2.5 gm/cm³ seems
necessary for significant prolongation of gastric residence time. But, effectiveness of this system in human beings was not observed and no system has been marketed \(^{16}\).

### 1.1.6.2 Bioadhesive or mucoadhesive drug delivery systems

Bioadhesive drug delivery systems are used as a delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bioadhesive polymers are used and they can adhere to the epithelial surface in the stomach. Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism.

These mechanisms are:

1. The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
2. The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
3. The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
4. The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin network and the bioadhesive material.

Materials commonly used for bioadhesion are polyacrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol (PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

### 1.1.6.3 Expandable, unfoldable and swellable systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus,
their configurations are required to develop an expandable system to prolong gastric retention time (GRT):

1. a small configuration for oral intake,
2. an expanded gastroretentive form, and
3. a final small form enabling evacuation following drug release from the device.

Thus, gastroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery. Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4-label disc or 4-limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach. Swellable systems are also retained in the gastrointestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid (Figure 1.1.2). Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective. Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal adhesion and gastropathy\textsuperscript{17}. 
1.1.6.4 *Super porous hydrogel systems*
These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micrometer, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material.

1.1.6.5 *Magnetic systems*
This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

1.1.6.6 *Ion exchange resins*
Ion exchange resins are loaded with bicarbonate, and a negatively charged drug is bound to the resin. Resultant beads are then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions takes place. As a result of this reaction, carbon dioxide is
Chapter 1.1

_Introduction to stomach specific drug delivery system_

released and trapped in the membrane thereby carrying beads towards the top of the gastric contents and producing a floating layer of resin beads – in contrast to uncoated beads, which sink quickly.

### 1.1.6.7 Raft systems

Raft systems incorporate alginate gel solution (e.g. sodium alginate solution containing carbonates or bicarbonates) that upon reaction with gastric fluid, swell and form a viscous cohesive gel containing entrapped carbon dioxide bubbles, enabling floatation of the drug delivery system. Because raft-forming systems (Figure 1.1.3) produce a layer on the top of the gastric fluids, they are often used for gastroesophageal reflux treatment, as with Liquid Gaviscon (GlaxoSmithKline).

![Schematic representation of the barrier created by a raft-forming system](image)

_Figure 1.1.3: Schematic representation of the barrier created by a raft-forming system_

Other delayed gastric emptying approaches of interest include sham feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby degressing the gastric emptying rate and permitting considerable prolongation of the drug release. But some of this has certain drawbacks, which could limit their uses described in the following Table 1.1.1⁰⁹.
Table 1.1.1: Drawback associated with different types of GRDDS

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drawback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorporation of passage delaying food excipient such as fatty acids</td>
<td>Affect the emptying mechanism of the entire content</td>
</tr>
</tbody>
</table>
| Bio adhesive drug delivery systems                                           | a. Adhesive is non specific  
|                                                                               | b. Efficiency is limited by the possible interaction with food.                                                                         |
| Biodegradable and non biodegradable (swelling) formulation in which the size and shape retain in the dosage form. | Present the hazard of permanent retention and might lead to serious life threatening effects if multiple dosing is predicted. |

1.1.6.8 Floating drug delivery systems

Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for a prolong period. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating system can be effervescent or Non effervescent in nature.

1.1.6.8.1 Effervescent systems

1.1.6.8.1.1 Volatile liquid containing systems

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

1.1.6.8.1.2 Gas-generating systems

These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO₂, which gets
entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chime \(^1\)\(^,\)^\(^1^8\). How the dosage form float is shown in the following figure (Figure 1.1.4) \(^2^1\).

**Figure 1.1.4: The mechanism of floating systems**

### 1.1.6.8.2 Non-effervescent systems

#### 1.1.6.8.2.1 Colloidal gel barrier systems

Hydrodynamically balance system (HBS\(^\text{TM}\)) was first design by Sheth and Tossounian in 1975. Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids, e.g. HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to these dosage forms \(^2^2\).

#### 1.1.6.8.2.2 Microporous compartment system

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the
apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

1.1.6.8.2.3 Alginate beads

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen and freeze dried at -40°C for 24 hrs, leading to the formation of porous system, which can maintain a floating force over 12 hrs.

1.1.6.8.2.4 Hollow microspheres

Hollow microspheres (microballoons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ethanol: dichloromethane solution of the drug and enteric acrylic polymers was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballoons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hrs in-vitro.

1.1.7 Factors affecting gastric retention

1.1.7.1 Density

Density of the dosage form should be less than the gastric contents (1.004gm/mL).

1.1.7.2 Size and shape

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT compared to those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devices with a flexural modulus of 48 and 22.5 kilopond per square inch (KSI) are reported to have better GIT ≅ 90 to 100 % retention at 24 hrs compared with other shapes.
Chapter 1.1

Introduction to stomach specific drug delivery system

1.1.7.3 Fed or unfed state
Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complexes (MMC) that occurs every 1.5 to 2 hrs. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer 18.

1.1.7.4 Nature of the meal
Feeding of indigestible polymers of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release 14.

1.1.7.5 Caloric content
GRT can be increased between 4 to 10 hrs with a meal that is high in proteins and fats.

1.1.7.6 Frequency of feed
The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC 22.

1.1.7.7 Gender
Mean ambulatory GRT in meals (3.4 ± 0.4 hrs) is less compared with their age and race-matched female counterparts (4.6± 1.2 hrs), regardless of the weight, height and body surface.

1.1.7.8 Age
Elderly people, especially those over 70 years have a significantly longer GRT 23.

1.1.7.9 Posture
GRT can vary between supine and upright ambulatory states of the patients 24.

1.1.7.10 Concomitant drug administration
Anticholinergic like atropine and propentheline opiates like codeine and prokinetic agents like metoclopramide and cisapride.
1.1.8 Formulation of stomach specific dosage form

Following types of the ingredients can be incorporated in to HBS dosage form in addition to drugs$^{23,25}$.

- Hydrocolloids
- Inert fatty materials
- Release rate accelerants
- Release rate retardant
- Buoyancy increasing agents
- Miscellaneous

1.1.8.1 Hydrocolloids

Suitable hydrocolloids are synthethics, anionic or non ionic like hydrophilic gumes, modified cellulose derivatives. E.g. accasia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having pH 1.2. Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

1.1.8.2 Inert fatty materials

Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation and hence increases the buoyancy. Example: Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and minaral oils can be used. Such materials may be present from about 5-75 % by weight.

1.1.8.3 Release rate accelerant

The release rate of the medicament from the formulation can be modified by including excipient like lactose and/or mannitol. These may be present from about 5-60% by weight.
Chapter 1.1

Introduction to stomach specific drug delivery system

1.1.8.4 Release rate retardant

Insoluble substances such as dicalcium phosphate, talc, magnesium strearete decreased the solubility and hence retard the release of medicaments. Such, materials may be present about 5-60 % by weight.

1.1.8.5 Buoyancy increasing agents

Materials like ethyl cellulose, which has bulk density less than one, can be used for enhancing the buoyancy of the formulation. It may be added up to 80 % by weight.

1.1.8.6 Miscellaneous

Pharmaceutically acceptable adjuvant like preservatives, stabilizers, and lubricants can be incorporates in the dosage forms as per the requirements. They do not adversely affect the hydrodynamic balance of the systems.

1.1.9 Evaluation of stomach specific systems

Various parameters need to be evaluated for their effects on gastric residence time of different formulations. These parameters can be categorised into the following classes:

- Galenic: diametral size (‘cut-off size’), resultant weight flexibility and density of matrices.
- Control: floating time, dissolution, specific gravity, content uniformity, and hardness and friability (of tablets).
- Geometric: shape.
- Physiological: age, sex, posture, food and bioadhesion.

1.1.9.1 Bio/mucoadhesive systems

1.1.9.1.1 Bioadhesive strength

Bioadhesive strength of a polymer can be determined by measuring the force required to separate a polymer specimen sandwiched between layers of either an artificial (e.g. cellophane) or a biological (e.g. rabbit stomach tissue) membrane. This force can be measured by using a modified precision balance or an automated texture analyzer.
1.1.9.1.2 In-vivo evaluation

The effects of the mode of riboflavin-5-phosphate administration on the resulting mean drug plasma concentrations and cumulative amounts of riboflavin absorbed in dogs were studied. In contrast, with both a non-gastroretentive control formulation (multilayer film without rigid frame; 5.0 × 2.5 mm) and an oral solution, which resulted in shorter time periods with elevated riboflavin concentrations, the gastroretentive device (multilayer film with rigid frame; 5.0 × 2.5 mm) produced elevated plasma drug concentrations for at least 48 hrs. The absolute bioavailabilities were 17.1 ± 3.5%, 3.9 ± 0.4% and 3.9 ± 1% for the gastroretentive dosage form, control formulation and oral solution, respectively.

1.1.9.2 Magnetic systems

1.1.9.2.1 In-vitro dissolution study

In-vitro release experiments were carried out according to the US Pharmacopeia (USP) XXIII Paddle method at 37°C and 100 rpm, using 0.01 N HCl as dissolution medium. The measured values were continuously recorded using an IBM compatible AT (Advanced Technology) computer (Friedrich, Munster, Germany). During the release experiments, the magnetic tablets were located at the wall of the release vessel 5 cm under the surface of the liquid, using an external magnet. The distance between the external magnet and the magnetic depot tablet was 8 cm. The release from the tablet is directly proportional to the distance between the external magnet and tablet.

1.1.9.2.2 In-vivo evaluation

Groning et al developed a method for determining the gastrointestinal transit of magnetic dosage forms of acyclovir under the influence of an extracorporeal magnet, using a pH telemetering capsule (Heidelberg capsule). Small magnets were attached to the capsule and administered to humans. In-vivo human studies showed that, in the presence of an extracorporeal magnet, the plasma concentrations of aciclovir were significantly higher after 7, 8, 10 and 12 hrs. Furthermore, the mean area under the plasma concentration-time curve from zero to 24 hrs (AUC 0–24) was ≈2800 ng • h/mL with the external magnet and ≈1600 ng • h/mL without the external magnet.
1.1.9.3 Swelling and expanding systems

1.1.9.3.1 Water uptake study

The swelling of the polymers can be measured by their ability to absorb water and swell. Water uptake studies of the formulation (tablet or granules) are performed using USP dissolution apparatus II. The medium used is usually distilled water or 0.1 N HCl (900 mL) rotated at 50 rpm, and maintained at 37±0.5°C through-out the study. After a selected time interval, the formulation is withdrawn, blotted to remove excess water, and weighed. Swelling characteristics of the tablets expressed in terms of water uptake (WU) are calculated as (equation 1):

\[
\text{WU} (\%) = \frac{\text{swollen weight} - \text{initial weight}}{\text{initial weight}} \times 100
\]

*In-vitro* dissolution studies in swelling and expanding systems are usually carried out by a modified dissolution method, as in the case of FDDS.

1.1.9.4 Floating drug delivery systems

1.1.9.4.1 In-vitro floating time determination

Floating time is determined by using the USP disintegration apparatus containing 900mL of 0.1 N HCl solution as a testing medium maintained at 37±0.5°C. The time required to float different dosage forms is noted as floating (or buoyancy) lag time, and floating duration of the dosage form is determined by visual observation.

1.1.9.4.2 In-vitro dissolution study

Dissolution tests are performed using USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium; replenished with the same volume of fresh medium at sampling time points. Recent methodology as described in the USP XXIII states “the dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of a wire helix may be attached to the dosage units that would otherwise float”. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of *in-vitro* performance for floating dosage forms.
Pillay and Fassihi investigated the application of a helical wire sinker to the swellable floating system containing theophylline (a sparingly water-soluble drug). They observed that the procedure tends to inhibit the three-dimensional swelling process of the dosage form, and consequently drug release from the formulation was suppressed. Based on their observations, the researchers proposed an alternative method in which the floatable delivery system was fully submerged under a ring/mesh assembly. The results showed a significant increase in drug release (20%). In addition, the proposed method was found to provide reproducible hydrodynamic conditions and consistent release profiles. However, in the case of a swellable floating system, which contained diltiazem (a highly water-soluble drug), the researchers did not find any difference in release between the proposed method and the USP method. These findings led to the conclusion that drug release from swellable floating systems depends on full surface exposure, unhindered swelling, and the drug solubility in water.

1.1.9.4.3 Physiological parameters
Age, sex, posture, food, bioadhesion, health of subject and GIT condition.22,26.

1.1.9.4.4 Galenic parameter
Diametrical size, flexibility and density of matrices.26.

1.1.9.4.5 Geometric parameter
Shape

1.1.9.4.6 Control parameter
Floating time, specific gravity, dissolution, content uniformity, hardness and friability.26.

1.1.9.4.7 Specific gravity
Specific Gravity of the floating system can be determined by the displacement method using benzene as a displacing medium.18.

1.1.9.4.8 Resultant weight
The in-vitro measuring apparatus has been conceived to determine the real floating capabilities of buoyant dosage forms as a function of time. It operates by fource equivalent to the fource F required to keep the object totally submerged in the fluid. This fource determines the resultant weight of the object when
immersed and may be used to quantify its floating or nonfloating capabilities. The magnitude and direction of the force and the resultant weight corresponds to the Victoria sum of buoyancy ($F_{\text{buoy}}$) and gravity ($F_{\text{grav}}$) forces acting on the objects as shown in the equations:

\[
F = F_{\text{buoy}} - F_{\text{grav}}
\]
\[
F = d_f g V - d_s g V = (d_f - d_s) g V
\]
\[
F = (d_f - M/V) g V
\]

In which the $F$ is total vertical force (resultant weight of the object), $g$ is the acceleration due to gravity, $d_f$ is the fluid density, $d_s$ is the object density is the object mass and $V$ is the volume of the object.

1.1.10 Types of floating dosage forms

- New floating bilayer compressed matrices
- New multiple unit oral floating dosage form
- Sustained release intragastric floating granules
- Floatable asymmetric configuration drug delivery system
- Floating non compressed sustained release tablets
- Microballoons

1.1.10.1 New floating bilayer compressed matrices

One of the tablet layers mainly contains the carbon dioxide generating blend and a hydrodynamic polymer. The carbon dioxide being entrapped in the gasified hydrocolloid as liberated by the action of the gastric medium produces the upward motion of the tablet and maintains its buoyancy. The outer layer is hydrophilic matrix and contained the drug which is release in the prolong and controlled way.

**Advantages**

- Double layer matrix tablet shows a more homogenous behavior with regard to erosion and is less sensitive to the GI peristalsism and the formulation of the matrix dosage form with two distinct layers allows the separate regulation of the floating capabilities and the drug release kinetics.
Chapter 1.1

Introduction to stomach specific drug delivery system

• Consequently this type of sustained release matrix could be advantageously used for conveying drugs which are sufficiently stable and soluble in acidic media, better reabsorbed in the proximal or middle portion of the GI tract, requiring a sustained release period to improve the bioavailability of poorly soluble products in non acid media or aiming to produce a local and specific effect in the stomach.

1.1.10.2 New multiple unit oral floating dosage forms

The Gastric Emptying Time in the humans is in fed state from 1-6 hrs has been reported. Accordingly when a sustained release dosage form was administered orally, sufficient bioavailability and prolongation of the effective plasma level occasionally could not be obtained especially for drug having a limited absorption site in the intestinal tract. Recently some studies have been reported prolongation of GET (Gastric Emptying Time) of certain preparations, such as the floating dosage systems and bioadhesive systems.

However, as most of the floating dosage systems were single unit preparations, it was possible that a single unit type might be transited in to the small intestine in a short time, irrespective floating ability. A Multiple type of oral floating dosage systems has been prepared in order to prolong the GET of the preparation.

The system was composed of the sustained release pills containing the drug and the double layer surrounding the pills. Inner layer was an effervescent layer containing both sodium bicarbonate and the outer layer was swellable membrane was divided into two sub layers to avoid direct contact between sodium bicarbonate and tartaric acid in the outer one.

Advantages

• Preparation process of the floating dosage systems is easy and simple. Moreover, conventional sustained release pills, such as matrix type or barrier membrane type, can be used as the central seeds of the system.
• The floating dosage system is compact before immersion in water, the system has higher density compared with other floating systems and is easy to handle.
Chapter 1.1

Introduction to stomach specific drug delivery system

1.1.10.3 Sustained release floating granules

Drug granules, which remain in the stomach, comprise core-pharmaceutically effective ingredients coated with expansive films. Drug used was Dextromethorphan HCl (20%). Granules are developed based on chitosan of different buoyancy, both in acidic and neutral fluids, and gave the sustained release of prednisolone. The release rate of indomethacine from chitosan granules was compared with that of conventional commercial indomethacine capsules. Furthermore, enhancing the mixing ratio of drug and chitosan can control the release rate.

In case of conventional capsule, the plasma concentration reach the maximum level one-hour after administration, while in case of granules with a 1:2 mixing of drug and chitosan, the chitosan produced a sustained plateau level of the drug.

1.1.10.4 New self-correcting floatable asymmetric configuration drug delivery systems

Apart from encountered difficulties in pulsatile delivery system design, the most challenging controlled drug delivery in the last two decades among pharmaceutical scientists has been design of the systems that would provide zero order kinetics for total drug release with no lag time or burst effect over a prolong period.

Features

- The system is design in such a manner that it floats, thus being likely to prolong gastric residence time in-vivo, resulting in longer total transit time within the GIT environment with maximum absorptive capacity and consequently greater bioavailability.
- These particular characteristics would be applicable to drugs, which have pH dependent solubilities, a narrow window of absorption and are absorbed by active transport from either the proximal or distal portion of the small intestine.
- Complete dissolution of the whole system.
- Oral drug release.
- Absences of both burst and lag time.
and the release pattern could be easily tailored by adjusting the amount or composition of each layer, which offers a greater degree of flexibility to formulation scientists.

- The absence of the real burst effect which is usually seen with matrix type delivery system is highly significant.

- Drug release from these systems may not be affected by changes in pH of the GIT and *in-vivo* situation.

- One feature of these swelling hydrophilic matrices is their low density and the ease with which the system can be easily trapped, adding to floating behavior after exposure to dissolution medium delay gastric emptying of stomach.

- Zero order kinetic is achievable.

- Drug is totally released but always in a controlled manner.

1.1.10.5 *Floating noncompressed sustained release tablets* \(^{31}\)

Sustained release noncompressed tablets having a network of multitude air holes and passage there in a density of less than one and capable of floating on gastric juice *in-vivo* comprises a matrix containing

- Gelling agents (0.5-0.4%)
- Inert oil (10-20%)
- Therapeutic agent (50-75%)
- Water up to 100%

Example by an adding an agar solution to a theophyllin oil mixture at 70 °C with vigorous stirring to get O/W emulsion, which was poured into a tablet mould, allowed to cool and gel removed from the mould and air dried. The average diameter of the tablet was 0.70 mm.
1.1.10.6 Microballoons

Multiple units floating system which can be distributed widely through out the GIT providing a possibility of achieving a longer lasting and more reliable release of drugs, has been brought. To achieve this goal a novel method to prepare floating microspheres loaded with drug was developed as a modification of the emulsion solvent diffusion method for the preparation of the polymeric microsponge for a controlled drug delivery system. This microsphere was termed as “microballoons” due to its characteristic internal hollow structure and excellent floatability in-vitro. The method of preparation of the microballoons is described earlier in the article\textsuperscript{12,32}.

Parameters mainly affect the microballoons preparations

1. Temperature
2. Concentration of PVA in aqueous solution
3. Agitation speed
4. Ethanol dichloromethane ratio

Advantages\textsuperscript{33}

- More predictive drug release kinetic
- Less chances of localized mucosal damage
- Larger margin of safety against dosage form failure e.g. air compartment multiple unit system for gastric retention

1.1.11 Advantages of stomach specific drug delivery systems\textsuperscript{23, 34}

1. The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of nongastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption.

2. For drugs with relatively short half life, sustained release may result in a flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
Chapter 1.1

Introduction to stomach specific drug delivery system

3. They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

4. Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.

5. The controlled, slow delivery of drug form gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.

6. Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index.

7. Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.

8. Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.

9. The sustained mode of drug release from Gastroretentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

1.1.12 Limitations/disadvantages

- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently-coat, water.

- Not suitable for drugs that have solubility or stability problem in GIT.
Chapter 1.1

Introduction to stomach specific drug delivery system

- Drugs such as nifedipine which is well absorbed along the entire GIT and which undergoes first pass metabolism, may not be desirable.
- Drugs which are irritant to Gastric mucosa is also not desirable or suitable\(^1\).
- The drug substances that are unstable in the acidic environment of the stomach are not suitable candidates to be incorporated in the systems\(^1\).
- The dosage form should be administered with a full glass of water (200-250 mL)\(^3\).
- These systems do not offer significant advantages over the conventional dosage forms for drugs, which are absorbed throughout the gastrointestinal tract.

1.1.13 Application of floating drug delivery system\(^5\)

- Recent study indicated that the administration of Diltiazem floating tablets twice a day might be more effective compared to normal tablets in controlling the Blood pressure of hypertensive patients.
- Modapar® HBS containing l-dopa and Benserazide, here the drug was absorbed over a period of 6-8 hrs and maintained substantial plasma concentration for Parkinsonian patients. Cytotech\(^\text{®}\) - containing Misoprostol, a synthetic prostaglandin –EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDS).
- As it provides high concentration of drug within gastric mucosa, it is used to eradicate \textit{H.pylori} (a causative organism for chronic gastritis and peptic ulcers).
- 5-fluorouracil has been successfully evaluated in the patients with stomach neoplasm.
- Developing HBS dosage form for tacrin provide better delivery systems and reduced its GI side effects.
- Treatment of gastric and duodenal ulcer.
1.1.14 Future potential

- Floating dosage form offers various future potential as evident from several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.
- Drugs that have poor bioavailability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.
- Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
- The floating concept can also be utilized in the development of various anti-reflux formulations.
- Developing a controlled release system for the drugs, which are potential to treat the Parkinson’s disease.
- To explore the eradication of Helico-bacter pylori by using the narrow spectrum antibodies.

<table>
<thead>
<tr>
<th>Types of dosage forms</th>
<th>Drugs explored in stomach specific dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microspheres</td>
<td>Aspirin, Griseofulvin, P-nitro aniline, Ibuprofen, Terfenadine, Tranilast</td>
</tr>
<tr>
<td>Granules</td>
<td>Diclofenac Sodium, Indomethacin, Prednisolone</td>
</tr>
<tr>
<td>Films</td>
<td>Cinnarizine</td>
</tr>
<tr>
<td>Powders</td>
<td>Several Basic Drugs</td>
</tr>
<tr>
<td>Capsules</td>
<td>Chlordiazepoxide HCl, Diazepam, Furocemide, L-dopa and Benserazide, Misoprostol, Propranolol HCl</td>
</tr>
<tr>
<td>Tablets/Pills</td>
<td>Acetaminophen, Aspirin, Amoxycillin, Ampicillin, Atenolol, Chlorpheniramine maleate, Cinnarizine, 5-Fluorouracil, Isosorbide mononitrate, Diltiazem, Isosorbide dinitrate, Piretenide, Quinidine, Varapamil HCl, Riboflavin, Sotalol, Theophylline</td>
</tr>
</tbody>
</table>
### Table 1.1.3: Commercial stomach specific floating formulations

<table>
<thead>
<tr>
<th>Name</th>
<th>Type and drug</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>MadoparHBS® (PropalHBS)</td>
<td>Floating capsule, Levodopa and benserazide</td>
<td>Floating CR capsules</td>
</tr>
<tr>
<td>Valorelease®</td>
<td>Floating capsule, Diazepam</td>
<td>Floating Capsules</td>
</tr>
<tr>
<td>Topalkan®</td>
<td>Floating Antacid, aluminum and magnesium mixture</td>
<td>Effervescent floating liquid alginate preparation</td>
</tr>
<tr>
<td>Amalgate Float Coat®</td>
<td>Floating antacid Floating gel</td>
<td>Floating dosage form</td>
</tr>
<tr>
<td>Conviron</td>
<td>Ferrous sulphate</td>
<td>Colloidal gel forming FDDS</td>
</tr>
<tr>
<td>Cifran OD®</td>
<td>Ciprofloxacine (1 gm)</td>
<td>Gas generating floating form</td>
</tr>
<tr>
<td>Cytotech®</td>
<td>Misoprostol (100 mcg/200 mcg)</td>
<td>Bilayer floating capsule</td>
</tr>
<tr>
<td>Liquid Gaviscone®</td>
<td>Mixture of alginate</td>
<td>Suppress gastro esophageal reflux and alleviate the heart burn</td>
</tr>
</tbody>
</table>

#### 1.1.15 Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product, which assures its safety and efficacy up to the end of shelf life at defined storage conditions and pack profile. The stability studies of different GRDDS are usually carried out as per the International Conference on Harmonisation guidelines.
Chapter 1.1

Introduction to stomach specific drug delivery system

1.1.16 References


Chapter 1.1  
*Introduction to stomach specific drug delivery system*


Chapter 1.2
Introduction to polymers
1.2 Introduction to polymers

1.2.1 Introduction to chitosan

Chitosan are biodegradable, high molecular weight cationic polysaccharides. Industrially they are produced from chitin, the world’s second most abundant biopolymer, by deactivation process involving alkaline hydrolysis. The term chitosan refers to a family of polymers, individually characterized by their ratio of acetylated to deactivated units and molecular weight, both parameters being equally responsible for the properties of the polymer. Chitosan has been used for a range of applications as diverse as for water purification, as a food ingredient and as a pharmaceutical excipient. Braconnot\(^1\) first described chitin in 1811. A good deal of fundamental research on chitin occurred in the next century and a half but most of the information available today had been obtained since 1950.

Chitin is the major polysaccharide of the shells of crustacean and exoskeletons of insects. It is also found in the cell walls of many fungi, yeast and algae. Chitosan was discovered by Rouget\(^1\) in 1859 and was prepared by Hope Seylar\(^1\). Chitosan is deactivated chitin derivative. It is found naturally in fungal cell walls but can also be produced by alkaline treatment of chitin.

1.2.1.1 Preparation of chitosan\(^2\)

Chitin is treated for 1 or 2 hrs in 47% sodium hydroxide solution in nickel crucible at 60 °C under nitrogen atmosphere. The chitosan obtained by alkali treatment is washed to neutrality, the deactivation being about 80% or less by the first alkali treatment. The chitosan after washing in water is treated again in the alkaline solution twice or more to obtain chitosan which has the deactivation of 90-05 % for even further deactivation, thread like chitosan is again subjected to alkali treatment.

1.2.1.2 Structure and properties of chitosan\(^2\)

Chitosan is \((1-4)-2\text{-amino-2-deoxy-B-D glucan}\). It has similar structural characteristics as that of glucosaminoglycans. It is tough, biodegradable and nontoxic.
Chapter 1.2

Introduction to polymers

\[ R = -\text{NH}_2 \quad \text{Chitosan} \]

Chitin, poly-B-(1-4) linked N-acetyl-D-glucosamine is a highly hydrophobic material that is insoluble in water and most ordinary solvents. This property of chitin restricts its use to applications that do not require solubilization of the polymer. Considering chitosan as a weak base, a certain minimum amount of acid is required to transform the glucosamine units into the positively charged, water-soluble form. At neutral pH most chitosan molecules will lose their charge and precipitate from solution. Chitosan is soluble in dilute organic acids like formic, acetic, propionic, oxalic, malonic, succinic, adipic, lactic, pyruvic, malic, tartaric and citric.

Chitosan is also soluble in dilute nitric and hydrochloric acids, marginally soluble in 0.5% phosphoric acid and insoluble in sulfuric acid at room temperature. Formic acid is the best solvent, overall good solutions being obtained in aqueous systems containing 0.2 to 100% of this acid. Acetic acid has been selected as the standard solvent for solution property measurement. Chitosan readily dissolves in 3:1 glycerol water when the mixture contains 1% acetic acid, resulting in clear colorless and very viscous solution.

Solutions of Chitosan in 10% w/v aqueous oxalic acid show thermo-reversible gel property. A solution containing more than 7% chitosan will gel in less than a day and 3% solution will gel in about 3 weeks. The chitosan films were cross-linked by glutaraldehyde vapors in a closed chamber for 24 hrs at ambient temperature. This process was done to retard the chitosan degradation rate. The decrease in degradation rate of cross-linked chitosan was probably due to the retarded hydrolysis of Schiff’s bases induced by the glutaraldehyde cross-linked of chitosan’s amino groups.
Chapter 1.2

Introduction to polymers

Chitosan, a linear polyelectrolyte at acidic pH, is soluble in variety of acids and interacts with polyanionic counterions. It forms gels with a number of multivalent anions and also with glutaraldehyde. It has a high charge density i.e. one charge per glucosamine unit. Since many minerals carry negative charges, the positive charge of chitosan interacts strongly with negative surfaces. Chitosan is a linear polyamine where amino groups are readily available for chemical reactions and salt formation with acids. The important characteristics of chitosan are its molecular weight, viscosity, deacetylation degree (DA) crystallinity index, number of monomeric units (n), water retention value, $pK_a$ and energy of hydration.

1.2.1.3 Pharmaceutical requirements of chitosan

Particle size $< 30 \ \mu m$, density between 1.35 and 1.40 g/cc, pH 6.5-7.5, insoluble in water, and partially soluble in acids. Chitosan can also be characterized in terms of its quality, intrinsic properties and physical forms. The quality characteristics of chitosan are levels of heavy metals and proteins, pyrogenicity and degree of deacetylation are the intrinsic properties.

1.2.1.4 Biological and chemical properties of chitosan

Biocompatibility (e.g. Nontoxic, biodegradable, natural), bioactivity, wound healing acceleration, reduced blood cholesterol levels, and immune system stimulant effect. Biomedical properties biological activity and biodegradation of chitosan are stated by Knapczyk et al. Muzzarelli gives the chemical behavior of chitosan and modified chitosan. Sanford summarized the chemical and biological properties of chitosan that relate to applications. Tables 1.2.1 and 1.2.2.

<table>
<thead>
<tr>
<th>Table 1.2.1: Chemical properties of chitosan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cationic polyamine</td>
</tr>
<tr>
<td>High charge density at pH $&lt; 6.5$</td>
</tr>
<tr>
<td>Adheres to negatively charged surfaces</td>
</tr>
<tr>
<td>Forms gels with poly anions</td>
</tr>
<tr>
<td>High molecular weight linear polyelectrolyte</td>
</tr>
<tr>
<td>Viscosity, high to low</td>
</tr>
<tr>
<td>Chelates certain transitional metal</td>
</tr>
</tbody>
</table>
Amiable to chemical modification reactive amino / hydroxyl groups

Table 1.2.2: Biological properties of chitosan

<table>
<thead>
<tr>
<th>Property</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocompatibility</td>
<td>Natural Polymer</td>
</tr>
<tr>
<td>Biodegradable</td>
<td>to normal body constituents</td>
</tr>
<tr>
<td>Safe and non-toxic</td>
<td></td>
</tr>
<tr>
<td>Haemostatic</td>
<td></td>
</tr>
<tr>
<td>Bacteriostatic</td>
<td></td>
</tr>
<tr>
<td>Fungistatic</td>
<td></td>
</tr>
<tr>
<td>Spermicidal</td>
<td></td>
</tr>
<tr>
<td>Anticarcinogen</td>
<td></td>
</tr>
<tr>
<td>Anticholesteremic</td>
<td></td>
</tr>
</tbody>
</table>

1.2.1.5 Mucoadhesive properties of chitosan

Lehr et al. first evaluated mucoadhesive properties of chitosan. A number of characteristics are necessary for mucoadhesion (a) strong hydrogen bonding groups (-OH, -COOH), (b) strong anionic charges, (c) high molecular weight, (d) sufficient chain flexibility, and (e) surface energy properties favoring spreading on to mucus. However, chitosan is a poly-cationic polymer and does not have any anionic charge. Instead, a positively charged hydrogel is formed in acidic environment that could develop additional molecular attractive forces by electrostatic interactions with negatively charged mucosal surfaces or the negatively charged sialic acid groups of the mucus network. High molecular weight chitosan gave the best mucoadhesive properties.

1.2.1.6 Toxicological studies of chitosan

In-vivo toxicity tests indicated that chitosan is non-toxic, inert and sterilized films was free of pyrogens. LD 50 and oral toxicity levels of chitosan were estimated in both rats and mice. Lack of cute oral toxicity to chitosan was noticed as evidenced by an oral LD 50, 10g/kg in mice. Acute systemic toxicity tests in mice did not show any significant toxic effects of chitosan.
1.2.1.7 Preparation of chitosan microspheres

Chitosan microspheres can be prepared by the following methods.

1.2.1.7.1 Ionotropic gelation

In this method, chitosan solutions in acetic acid are prepared and extruded dropwise through a needle into different concentrations of aqueous solutions of magnetically stirred tripolyphosphate. The beads are removed from the counter ion solution by filtration, washed with distilled water, dried by an air jet and further air dried at ambient temperature.

1.2.1.7.2 Extrusion- spheronization

In this method, ingredients are mixed with chitosan and the wet mass is passed through an extruder. The cylindrical extrudate obtained is immediately processed in a spheronizer. The beads are collected and dried in a hot air oven at 40 °C for 12 hrs.

1.2.1.7.3 Solvent evaporation technique

Chitosan dissolved in an aqueous acetic acid solution. The solution is added to toluene and sonicated to form a w/o emulsion. Glutaraldehyde solution in toluene is added to the emulsion and stirred at room temperature to give cross-linked microspheres. The suspension is centrifuged. Following evaporation of the solvent, the microspheres are separated, washed with distilled water and dried.

Li et al. 7 modified the solvent evaporation method and named it “Dry-in-Oil” method. Here the system is warmed to 50 °C and the pressure is reduced. When the solvent is evaporated completely, the microspheres are separated, washed with sodium hydroxide solution, distilled water and diethyl ether and dried.

1.2.1.7.4 Multiple emulsion method

Multiphase emulsions are also prepared by the solvent evaporation technique by a three-step emulsification process.

Aqueous drug solution and oil phase containing emulsion stabilizers are combined to give water-in-oil emulsion (step 1).

Later, the w/o emulsion is dispersed in the polymer solution (step 2).

The solvent is evaporated under reduced pressure (step 3).
1.2.1.7.5 Spray drying method

Chitosan microspheres are prepared by using a spray drier apparatus. Microspheres have been prepared from solutions of different concentrations of chitosan in glacial acetic acid/water/acetone.

1.2.1.7.6 Precipitation / coacervation method

Berthold et al.\(^8\) prepared chitosan microspheres by a novel precipitation method using sodium sulphate as precipitant. In this method chitosan is dissolved in acetic acid containing polysorbate 80. A solution of sodium sulphate is added dropwise during stirring and ultrasonication. The formation of microspheres is indicated by turbidity. The formed microspheres are purified by centrifugation and resuspended in dematerialized water. This method avoided the use of organic solvents and glutaraldehyde for preparation of chitosan microparticles with high loading capacity and sustained release effect.

Chitosan microparticles can also be prepared by complex coacervation. Sodium alginate, sodium carboxymethylcellulose, kappa-carregeenan and sodium poly acrylic acid are used in the complex coacervation procedure with chitosan. Here the microparticles are formed by interionic interaction between oppositely charged polymers. Formulation of coacervate capsules of chitosan-alginate and chitosan- kappa-carregeenan is carried out by extruding either an aqueous solution of kappa-carregeenan in a solution of sodium alginate through a hand operated syringe into potassium chloride or calcium chloride solution. The counterion solution consisted of chitin. The obtained capsules were agitated to harden in the counterion solution before washing and drying.

1.2.1.7.7 Coating by chitosan

In this method, previously formed microparticles are coated with chitosan. HAS microspheres are prepared and added to various concentrations of chitosan-acetic acid solutions and mixed; the chitosan treated microspheres are filtered and dried.
1.2.2 Introduction to alginate

Alginate is a naturally occurring biopolymer that is finding increasing applications in the biotechnology industry. Alginate has been used successfully for many years in the food and beverage industry as a thickening agent, a gelling agent and a colloidal stabilizer. Alginate also has several unique properties that have enabled it to be used as a matrix for the entrapment and/or delivery of a variety of proteins and cells. These properties include: (i) a relatively inert aqueous environment within the matrix; (ii) a mild room temperature encapsulation process free of organic solvents; (iii) a high gel porosity which allows for high diffusion rates of macromolecules; (iv) the ability to control this porosity with simple coating procedures and (v) dissolution and biodegradation of the system under normal physiological conditions.

1.2.2.1 Sources of alginate

Commercial alginates are extracted primarily from three species of brown algae (kelp). These include Laminaria hyperborea, Ascophyllum nodosum, and Macrocystis pyrifera. Other sources include Laminaria japonica, Eclonia maxima, Lesonia negrescens and Sargassum species. In all of these algae, alginate is the primary polysaccharide present and it may comprise up to 40% of the dry weight.

1.2.2.2 Extraction and preparation

To commercially prepare alginates, the algae is mechanically harvested and dried before further processing except for M. pyrifera which is processed when wet. Alginate is then extracted from dried and milled algal material after treatment with dilute mineral acid to remove or degrade associated neutral homopolysaccharides such as laminarin and fucoidin. Concurrently, the alkaline earth cations are exchanged for $\text{H}^+$. The alginate is then converted from the insoluble protonated form to the soluble sodium salt by addition of sodium carbonate at a pH below 10. After extraction, the alginate can be further purified and then converted to either a salt or acid.
1.2.2.3 Chemical structure

![Chemical structure diagram]

1.2.2.4 Microbead preparation

There are three widely-known methods used to prepare alginate microbeads that are less than 0.2 mm in diameter; atomization, emulsification and coacervation. The most commonly used technique is an atomization or spraying method using an extrusion device with a small orifice. A general overview of alginate microbead preparation is as follows. Solutions containing the alginate and protein, as described above in the preparation of large beads, are well mixed and loaded into a syringe mounted on a syringe pump. The mixture of alginate and protein solution is then delivered through an atomization device with a defined diameter (~1 mm) orifice at the tip. Much smaller diameter orifices can be used but may run the risk of orifice clogging/plugging by the high viscosity alginate solution. The sizes of these beads can be controlled by either the pressure of the infusing nitrogen gas, the flow-rate of the syringe pump or the distance between the orifice and the surface of the cross-linking solution. Fine droplets of sodium alginate and protein solution will form the microbeads when cross-linked with the divalent solution. Outer coatings of poly-L-lysine and alginate can then be performed. The second method of microbead preparation involves protein encapsulation by an oil-in-water emulsification technique. Complex coacervation of oppositely charged polyelectrolytes has been commonly used as a method for preparing microbeads. Complex coacervation between alginic acid, gelatin\textsuperscript{11}, chitosan\textsuperscript{12}, and albumin\textsuperscript{13} has been reported. In the alginate–chitosan system, the complex is formed by spraying a sodium alginate solution into the chitosan solution. The resultant alginate–chitosan microbeads are mechanically strong and stable over a wide pH range. With the alginate–albumin system,
coacervation is found to be limited compared to other polypeptide–polysaccharide systems due to the high viscosity of the albumin–alginate acid complex and a propensity to precipitate. The optimum conditions for maximum coacervate yield are a pH of 3.9, an ionic strength of 1 mM and a 0.15% w/v total polyion concentration.

1.2.2.5 Physical properties
The functional and physical properties of cation cross-linked alginate beads are dependent on the composition, sequential structure, and molecular size of the polymers. The flexibility of the alginate polymers in solution increases in the order MG>MM>GG (G=α-L-guluronic acid; M= β-D-mannuronic acid). Beads with the lowest shrinkage, highest mechanical strength, highest porosity, and best stability towards monovalent cations are made from alginate with an α-L-guluronic acid content greater than 70% and an average length of the α-L-guluronic acid blocks higher than 15. These polymers are called "high G" alginates and for molecular weights higher than 2.4×10⁵, the gel strength is independent of the molecular weight. For lower molecular weight alginates however, there is a certain critical molecular weight below which the gel forming properties of alginites are reduced. While a gel made from a high α-L-guluronic acid alginate may be rigid and brittle, gels produced from alginites with a low α-L-guluronic acid content are more elastic. Alginate forms stable gels over the temperature range of 0-100°C, although the modulus of rigidity of the gels decreases with an increase in temperature. The gels can be prepared in either hot or cold water.

1.2.2.6 Chemical reactivity
Although the microenvironment in an alginate bead can be relatively inert to protein drugs and cells (alginate beads typically contain up to 95% water) a positively charged protein can potentially compete with calcium ions for available carboxylic acid sites on the alginate. This has been observed with small drugs by several investigators\textsuperscript{14-15} and has been shown to result in protein inactivation in the case of the protein transforming growth factor-beta (TGF- β₁).
1.2.2.7 Porosity and macromolecular diffusion

Proteins encapsulated in alginate matrices are released by two mechanisms: (i) diffusion of the protein through the pores of the polymer network and (ii) degradation of the polymer network. Analysis of calcium alginate gels microbeads by electron microscopy has shown that the pore size ranges from 5 to 200 nm in diameter \(^{16}\). In a different approach the porosity was determined by packing alginate beads in a column and recording the exclusion volumes for macromolecular standards \(^{17}\). A cut off value of 12–16 nm was determined which is smaller than the pore size distribution obtained by electron microscopy. Diffusion of small molecules such as glucose and ethanol is unaffected by the alginate matrix while diffusion of larger proteins from the gels has been shown to be dependent on their molecular weight. The diffusion of several proteins from alginate beads has been reported including immunoglobulin G (IgG) \(^{18-19}\), fibrinogen \(^{18}\) and insulin. Increasing the concentration of alginate in the beads decreases the rate of diffusion of the proteins from the gel.

1.2.2.8 Chemical stability/degradation

Degradation of a Ca\(^{2+}\) cross-linked alginate gel can occur by removal of the Ca\(^{2+}\) ions. This can be accomplished by the use of a chelating agent such as ethylene glycol-bis (β-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), lactate, citrate and phosphate or by a high concentration of ions such as Na\(^{+}\) or Mg\(^{2+}\). As Ca\(^{2+}\) ions are removed, the cross-linking in the gel decreases and the gels are destabilized. This can lead to leakage of entrapped material and solubilization of the high molecular weight alginate polymers. Alginate gels will also degrade and precipitate in a 0.1 M phosphate buffer solution and will completely dissolve in 0.1 M sodium citrate at pH 7.8. If Ca\(^{2+}\) is used in the cross-linking solution and phosphate is used as the dissolution medium, the dissolution medium will turn turbid due to the Ca\(^{2+}\) dissociating from the polymer network and forming calcium phosphate precipitate.
1.2.2.9 Biological properties

1.2.2.9.1 Immunogenicity

There are many factors involved in determining the successful application of polymers as drug delivery carriers in humans, with polymer biocompatibility or/and immunogenicity being two of the more important issues. There are numerous reports addressing the fibrotic reaction of implanted alginates. Alginates can be readily purchased in several different grades namely, ultra pure, food or research grade.

1.2.2.9.2 Bioadhesion

Alginate possesses, among other features, a bioadhesive property which could serve as a potential advantage in mucosal drug delivery. The term bioadhesion can be generally defined as the adhesion or contact between two surfaces, with one being a biological substratum. If one of the surfaces involved is a mucosal layer, the term mucoadhesion is then used. Studies have shown that polymers with charge density can serve as good mucoadhesive agents. Peppas and colleagues believed that mucoadhesion is achieved by chain penetration across a polymer–mucosa interface. It has been reported that polyanion polymers are more effective bioadhesives than polycation polymers or nonionic polymers. Alginate, with its carboxyl end groups, is classified as an anionic mucoadhesive polymer. Alginate mucoadhesion studies, conducted by Chickering et al., were performed with a tensile testing apparatus in which the adhesive forces between different polymers and living intestinal epithelium were evaluated. The intestinal epithelium used in these experiments was from excised rat jejunum. In brief, individual polymer beads were placed on an inverted jejunum. The force required to detach the beads from the jejunum’s surface was recorded and compared with the values obtained from other types of polymer beads. These studies showed that alginate has the highest mucoadhesive strength when compared to polymers such as polystyrene, chitosan, carboxymethylcellulose and poly(lactic acid). Mucoadhesive drug delivery systems work by increasing the drug residence time at the site of activity or resorption. This mucoadhesive feature of alginate may aid in its utility as a potential delivery vehicle for drugs to
mucosal tissues such as the gastrointestinal tract or the nasopharynx. The adherence of these microbeads to the mucosal tissues localizes the drug and delays the protein transit time, therefore potentially improving the overall drug effectiveness and bioavailability.

1.2.2.10 Microsphere and liposome encapsulation

Alginate gels have been used to encapsulate other delivery systems including microspheres and liposomes. Ethylcellulose microspheres were dispersed into an aqueous solution of sodium alginate which was subsequently dropped into a CaCl$_2$ solution $^{29}$. The authors suggested that the beads could potentially be useful as an oral delivery system for micro- or nanoparticles. Liposomes that contained the model proteins BSA or horse-radish peroxidase were incorporated into alginate spheres with a diameter of 500-800 µm $^{30-31}$. Prior to their entrapment, the liposomes were coated with either phospholipase C, D, or A$_2$. The alginate microbeads that contained the liposomes remain stable at 10°C. Upon heating to 37°C, release of the protein is triggered by the enzymatic degradation of the phospholipids by the phospholipases. By selecting the appropriate phospholipase the duration of protein release could be controlled.
1.2.3 Introduction to hydroxypropyl methyl cellulose

1.2.3.1 Nonproprietary names
BP/USP: Hypromellose
PhEur: Hypromellosum

1.2.3.2 Synonyms
Methyl hydroxypropyl cellulose, propylene glycol ether of methyl cellulose, methyl cellulose propylene glycol ether, methocel, HPMC.

1.2.3.3 Chemical names
Cellulose, 2-hydroxy propyl methyl ether.

1.2.3.4 Structural formula

1.2.3.5 Functional category
Suspending and/or viscosity increasing agent, tablet binder, coating agent, Viscosity increasing agent, adhesive anhydrous ointment ingredient, film former, emulsion stabilizer, rate-controlling polymer for sustain release.

1.2.3.6 Method of manufacture
A purified form of cellulose fibers obtained from cotton linters or wood pulp, are treated with caustic (sodium hydroxide) solution. The alkali cellulose thus obtained is in turn treated with methyl chloride and propylene oxide to provide methylhydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules.

1.2.3.7 Description
An odorless, tasteless, white or creamy-white fibrous or granular powder.

1.2.3.8 Applications in pharmaceutical formulation or technology
Hypromellose is widely used in oral and topical pharmaceutical formulations. In oral products, primarily used as a tablet binder, in film-coating and as an extended-release tablet matrix. Concentrations between 2 % and 5 % w/w may
be used as a binder in either wet or dry granulation. Depending upon the viscosity grade, concentrations of 2-20 % w/w are used for film-forming solutions to film-coat tablets. Hypermellose is also used as a suspending and thickening agent in topical formulations, particularly ophthalmic preparations. Concentrations between 0.45-0.1 % w/w may be added as a thinking agent to vehicles for eye drops and artificial tear solutions. It is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. It is used as an adhesive in plastic bandages and wetting agent for hard contact lenses.

**1.2.3.9 Typical properties**

- Acidity/ alkalinity: pH = 5.5-8.0 for a 1 % w/w aqueous solution.
- Autoignition temperature: 360 °C
- Density (bulk): 0.341 g/cm³
- Density (tapped): 0.557 g/cm³
- Density (true): 1.326 g/cm³
- Melting point: browns at 190-200 °C, chars at 225-230 °C, glass transition temperature is 170-180 °C.
- Moisture content: hypromellose absorb moisture from the atmosphere, the water absorbed depending upon the initial moisture content and temperature and relative humidity of the surrounding air.
- Specific gravity: approximately 1.3

**1.2.3.10 Solubility**

Soluble in cold water, forming a viscous colloidal solution; in soluble in alcohol, ether and chloroform, but soluble in mixtures of methyl alcohol and methylene chloride. Certain grades are soluble in aqueous acetone, mixtures of methylene chloride and isopropyl alcohol and other organic solvents.

**1.2.3.11 Stability and storage conditions**

Very stable in dry condition. Solutions are stable at pH 3-11. Aqueous solution is liable to be affected by microorganisms when used as a viscosity-increasing agent in ophthalmic solutions and anti-microbial agent. Hypermellose powder should be store in a well-closed container, cool place and dry place.
1.2.3.12 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.
Chapter 1.2

1.2.4 Introduction to carbopol

1.2.4.1 Nonproprietary name
Carbopol-934P, Carborner, Carbomera.

1.2.4.2 Synonyms
Carboxy polymethylene; carboxyvinyl polymer; acrylic acid polymer, carbopol.

1.2.4.3 Chemical name
Carboxy polymethylene.

1.2.4.4 Structural formula

\[ \text{C}_n\text{C=O} \]

1.2.4.5 Method of manufacture
A synthetic, high molecular weight, cross-linked polymer of acrylic acid co-polymerized with approximately 0.75-2.0 % w/w of polyalkylsucrose. The end product contains 56-68% carboxylic acid groups.

1.2.4.6 Description
A white, fluffy, acidic, hygroscopic powder with a slight characteristic odor.

1.2.4.7 Functional category
Bioadhesive, suspending and/or viscosity-increasing agent, release-modifying agent, tablet binder.

1.2.4.8 Typical properties
Carbopol is soluble in water, alcohol and glycerin. Agents that can neutralize carbopol include sodium hydroxide; potassium hydroxide; sodium bicarbonate; borax; amino acids; polar organic amines.
Specific gravity: 1.41
Density (bulk): 5 g/cm³
Density (tapped): 1.4 g/cm³
Viscosity (0.2%): 20.5-54.5 poise and (0.5%): 305-394 poise.
Acidity/alkalinity: pH = 2.7-3.5 for a 0.5 % w/v aqueous dispersion, pH = 2.5-3.0 for a 1 % w/v aqueous dispersion.
Chapter 1.2

Introduction to polymers

Glass transition temperature: 100-105 °C.
Moisture content: normal water content is up to 2 % w/w. Carbomers are hydroscopic and typical equilibrium moisture content at 25 °C and 50 % relative humidity is 8-10 % w/w.

1.2.4.9 Applications in pharmaceutical formulation or technology

Carbomers are mainly used in liquid or semisolid pharmaceutical formulations as suspending or viscosity-increasing agents. Formulations include creams, gels and ointments for use in ophthalmic, rectal and topical preparations. Carbomer having low residuals only of ethyl acetate, such as carbomer 971P or 974P, may be used in oral preparations, in suspensions, tablets or sustain release tablet formulation. Carbomer resins have also been investigated in the preparation of sustained-release matrix beads as enzyme inhibitors of intestinal proteases in peptide containing dosage forms, as a bioadhesive for a cervical patch and for intranasally administrated microspheres and magnetic granules for site specific drug delivery to the esophagus.

1.2.4.10 Stability and storage conditions

Dry powder forms of carbopol do not support the growth of molds and fungi; however, microorganisms grow well in unpreserved aqueous dispersions. Dispersions maintain their viscosity on storage during prolonged periods at room temperature or elevated temperature when stored away from light or with the addition of an antioxidant. Store in an airtight or well-closed container.

1.2.4.11 Incompatibilities

Carbopol is incompatible with phenol, cationic polymers, strong acids and high concentrations of electrolytes, and is discolored by resorcinol. Exposure to light causes oxidation, which is reflected in a decrease in viscosity.

1.2.4.12 Safety

Acute oral doses of carbopol-934P to rats, mice and guinea pigs produce LD{sub 50} values of 4.3, 4.6 and 2.5 g/kg, respectively. In dogs, no fatalities were noted with doses as high as 8g/kg. No primary irritation or any evidence of sensitivity or allergic reaction in humans following topical application of dispersions containing
carbopol-934P has been observed. Carbopol-934P in contact with the eye is very irritating.
Chapter 1.2

Introduction to polymers

1.2.6 References


Chapter 1.3
Introduction to Drugs
1.3 Introduction to drugs

1.3.1 Introduction to famotidine

1.3.1.1 Therapeutic class
Long-acting histamine H₂-receptor antagonist.

1.3.1.2 Chemical name

1.3.1.3 Empirical formula
CH₅N₇O₂S₃

1.3.1.4 Molecular weight
337.43

1.3.1.5 Structural formula

1.3.1.6 Dose
20 mg twice and 40 mg once a day.

1.3.1.7 Description
Famotidine is a white to pale yellow nonhygroscopic crystalline substance. It is very slightly soluble in water and practically insoluble in ethanol, acetone, ethyl acetate, ethyl ether and acetone. It is freely soluble in glacial acetic acid.

1.3.1.8 Indications

- Duodenal ulcer (40 mg daily by mouth twice daily for 6 to 12 weeks)
- Benign gastric ulcer
- Hypersecretory conditions such as Zollinger-Ellison syndrome (20 mg every 6 hrs)
- Prevention of relapses of duodenal ulceration
- Prevention of relapses of benign gastric ulcer
- Symptomatic relief of gastro-esophageal reflux disease (40 mg twice daily for 6 to 12 weeks)
Chapter 1.3

Introduction to drugs

- Healing of esophageal erosion or ulceration associated with gastro-esophageal reflux disease. Prevention of relapses of symptoms and erosions or ulcerations associated with GERD.

1.3.1.9 Pharmaceutical precautions

Store in a dry place below 30°C.

1.3.1.10 Medicine classification

Prescription Medicine.

1.3.1.11 Stability

Famotidine at a concentration of 2 mg per mL, diluted with glucose 5%, sodium chloride 0.9%, or sterile water was stable in PVP syringes stored at 4°C for 14 days. It is also stable at room temperature for a 5 days as a 0.2 mg per mL. When stored at -20°C in polypropylene syringes it was stable for 3 weeks when diluted with glucose 5%, and for 8 weeks when diluted with sodium chloride 0.9% or sterile water. The stability of famotidine in a range of parenteral nutrition solutions containing amino acids, glucose lipids, electrolytes, vitamins and trace elements has been investigated. In the system tested famotidine was stable for up to 74 hrs at room temperature.

1.3.1.12 Pharmacokinetic parameters of famotidine

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (%)</td>
<td>40-45</td>
</tr>
<tr>
<td>Time to peak plasma concentration (hrs)</td>
<td>1-3</td>
</tr>
<tr>
<td>Peak plasma concentration (µg/mL)</td>
<td>0.076-0.1</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>15-20</td>
</tr>
<tr>
<td>Volume of distribution (L/kg)</td>
<td>1.1-1.4</td>
</tr>
<tr>
<td>Elimination (%)</td>
<td></td>
</tr>
<tr>
<td>-Urine unchanged (Oral, IV)</td>
<td>25-30(Oral), 65-70 (IV)</td>
</tr>
<tr>
<td>-Metabolized</td>
<td>30-35</td>
</tr>
<tr>
<td></td>
<td>25-30</td>
</tr>
</tbody>
</table>
1.3.1.13 Contraindications
Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, famotidine should not be administered to patients with a history of hypersensitivity to other H2-receptor antagonists.\textsuperscript{7,8}

1.3.1.14 Overdosage
There is no experience to date with overdosage. Patients with Zollinger-Ellison Syndrome have tolerated doses up to 800mg/day for more than a year without development of significant side effects. The usual measures to remove unabsorbed material from the gastro-intestinal tract, clinical monitoring, and supportive therapy should be employed.

1.3.1.15 Adverse effects
Famotidine has been demonstrated to be generally well tolerated. Headache, dizziness, constipation and diarrhea have been reported rarely. Other adverse experiences reported even less frequently included dry mouth, nausea and/or vomiting, abdominal discomfort or distension, anorexia, fatigue, rash, pruritus and urticaria, liver enzyme abnormalities, cholestatic jaundice, anaphylaxis, angioedema, arthralgia, muscle cramps, reversible psychic disturbances including depression, anxiety disorders, agitation, confusion and hallucinations. Toxic epidermal necrolysis has been reported very rarely with H2-receptor antagonists. In addition to the above adverse effects, A-V block has been reported very rarely with H2-receptor antagonists administered intravenously.\textsuperscript{9-12}

1.3.1.16 Official preparations
\textit{USP 23}: Famotidine Tablets\textsuperscript{12}
1.3.2 Introduction to glipizide

1.3.2.1 Chemical name

1.3.2.2 Chemical formula
\[ \text{C}_{21}\text{H}_{27}\text{N}_{5}\text{O}_{4}\text{S} \]

1.3.2.3 Molecular weight
445.54

1.3.2.4 Chemical structure
![Chemical structure of glipizide]

1.3.2.5 Category
Antidiabetic

1.3.2.6 Description
A white powder.

1.3.2.7 Solubility
Practically insoluble in water and ethanol; soluble in chloroform, dimethylformamide, and in dilute solution of alkali hydroxides, sparingly soluble in acetone.

1.3.2.8 Pharmacokinetics
Glipizide is completed and rapidly absorbed ensuring prompt and constant activity. Peak plasma concentrations are attained within 1.5 to 2.0 hrs after a single oral dose. The half-life of elimination ranges from 2 to 3 hrs. The drug is excreted in the urine as virtually inactive metabolites. When taken before each meal, glynase controls post-prandial hyperglycaemia without the risk of delayed episodes of hypoglycaemia.[13]

1.3.2.9 Mechanism of action
The primary mode of action of glipizide in experimental animals appears to be the stimulation of insulin secretion from the beta cells of pancreatic islets tissue and is thus dependent on functioning beta cells in the pancreatic islets. In human
glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islet. In man stimulation of insulin secretion by glipizide in response to a meal is undoubtedly of major importance. Fasting insulin levels are not elevated even on long term glipizide administration, but the post-prandial insulin response continues to be enhanced after at least six months of treatment. The insulinotopic response to a meal occurs within 30 min after an oral dose of glipizide in diabetic patients, but elevated insulin levels do not persist beyond the time of the meal challenge. Extrapancreatic effects may play a part in the mechanism of action of oral sulfonylurea hypoglycemic drugs. Beginning 2 to 3 hrs after the administration of glipizide sustained release, plasma concentrations of glipizide gradually rise reaching to a maximum concentration within 3 to 8 hrs after dosing. With subsequent once daily dosing of glipizide sustained release, effective plasma concentrations are maintained throughout 24 hrs period with fewer peaks to trough fluctuations. In view of the time required to reach an optimal concentration in plasma, drug may be more effective when given 30 min before eating. Drug in plasma 98.3 % bound to plasma protein especially with albumin. Drug is metabolized in liver, and the metabolites are excreted in the urine. Less than 5 % drug excreted unchanged in urine. 

1.3.2.10 Indication and dosage
Management of Type 2 diabetes (Non Insuline Dependent Diabetes mellitus) where diet control alone is not effective in controlling the hyperglycemia. Dosage should be adapted to patients individually, on basis of periodic tests of glycosuria and blood sugar. The maximum daily dose should not exceed 10 mg.

1.3.2.11 Contraindications
Like other sulfonylurea, glipizide is contraindicated in: Insulin dependent diabetes mellitus, diabetic-keto-acidosis, diabetic coma, pregnancy, subjects with severely impaired kidney or liver function, adrenal insufficiency and cases of confirmed individual hypersensitivity to the drug. In latent diabetes or prediabetic states, the use of sulfonylurea is not advisable.
1.3.2.12 Interaction
The hypoglycemic actions of sulfonylurea may be potentiated by certain drugs including nonsteroidal anti-inflammatory drugs and other drugs that are highly protein bound salicylates, sulphonamides, and chloramphenicol. When such drugs are administered to a patient receiving Glipizide, the patient should be observed for hypoglycemia.

1.3.2.13 Side effect
Hypoglycemia, gastrointestinal disturbances, allergic reactions including erythema urticaria.

1.3.2.14 Precaution
Patients should be instructed to closely follow their physician’s prescription as regards diet, dosage and schedule for taking the drug, and should be taught to recognize promptly the early symptoms of hypoglycemia, that generally are headache, irritability, sleep disorders, tremor and heavy sweating, so they can contact a doctor in good time.
1.3.2 Introduction to amoxicillin

1.3.2.1 Chemical name
2S,5R,6R)-6-[(2R)-2-amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

1.3.2.2 Chemical formula
C\textsubscript{16}H\textsubscript{19}N\textsubscript{3}O\textsubscript{5}S

1.3.2.3 Molecular weight
365.40

1.3.2.4 Chemical structure

![Chemical structure of amoxicillin]

1.3.2.5 Category
Anti-Bacterial Agents

1.3.2.6 Description
A broad-spectrum semisynthetic antibiotic similar to ampicillin except that its resistance to gastric acid permits higher serum levels with oral administration.

1.3.2.7 Solubility in water
3430 mg/L

1.3.2.8 Indication
For the treatment of infections of the ear, nose, and throat, the genitourinary tract, the skin and skin structure, and the lower respiratory tract due to susceptible (only b-lactamase-negative) strains of *Streptococcus* spp. (a- and b-hemolytic strains only), *S. pneumoniae*, *Staphylococcus* spp., *H. influenzae*, *E. coli*, *P. mirabilis*, or *E. faecalis*. Also for the treatment of acute, uncomplicated gonorrhea (ano-genital and urethral infections) due to *N. gonorrhoeae* (males and females).
1.3.2.9 Pharmacology
Amoxicillin is a moderate-spectrum antibiotic active against a wide range of Gram-positive, and a limited range of Gram-negative organisms. It is usually the drug of choice within the class because it is better absorbed, following oral administration, than other beta-lactam antibiotics. Amoxicillin is susceptible to degradation by β-lactamase-producing bacteria, and so may be given with clavulanic acid to increase its susceptibility. The incidence of β-lactamase-producing resistant organisms, including *E. coli*, appears to be increasing. Amoxicillin is sometimes combined with clavulanic acid, a β-lactamase inhibitor, to increase the spectrum of action against Gram-negative organisms, and to overcome bacterial antibiotic resistance mediated through β-lactamase production.

1.3.2.10 Mechanism of action
Amoxicillin binds to penicillin-binding protein 1A (PBP-1A) located inside the bacterial cell wall. Penicillins acylate the penicillin-sensitive transpeptidase C-terminal domain by opening the lactam ring. This inactivation of the enzyme prevents the formation of a cross-link of two linear peptidoglycan strands, inhibiting the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that amoxicillin interferes with an autolysin inhibitor.

1.3.2.11 Absorption
Rapidly absorbed after oral administration.

1.3.2.12 Toxicity
Serious toxicity is unlikely following large doses of amoxicillin. Acute ingestion of large doses of amoxicillin may cause nausea, vomiting, diarrhea and abdominal pain. Acute oliguric renal failure and hematuria may occur following large doses.

1.3.2.13 Side effect
All medicines may cause side effects, but many people have no, or minor side effects. Check with your doctor if any of these most common side effects persist or become bothersome when using amoxicillin:
Diarrhea; nausea; vomiting.
Seek medical attention right away if any of these severe side effects occur when using amoxicillin:

Severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); bloody stools; confusion; dark urine; fever, chills, or persistent sore throat; red, swollen, blistered, or peeling skin; seizures; severe diarrhea; stomach pain or cramps; unusual bruising or bleeding; vaginal discharge or irritation; yellowing of the skin or eyes.
1.3.14 References

Chapter 1.3