ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

FORMULATION AND EVALUATION OF ATENOLOL FLOATING TABLETS

Agaiah Goud Bairi *,Sravanthi. P

Department of Pharmaceutics, SRR College of pharmaceutical sciences, Elkathurthi, Hanamkoda, Telangana, India.

*Corresponding author E-mail: principal.srrcop@gmail.com

ARTICLE INFO

Key words:
Atenolol, HPMC K100M, HPMC K15M, HPMC K 4M

Access this article online Website: **https://www.jgtps.com**
Quick Response Code:

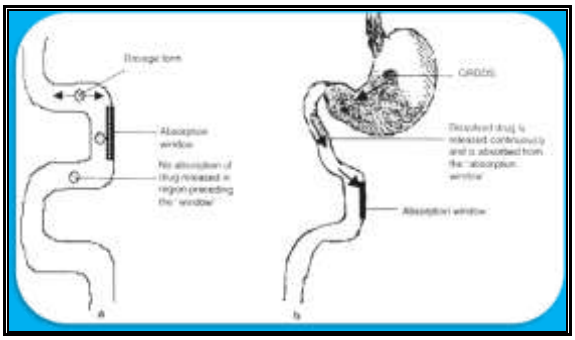
ABSTRACT

Gastroretentive floating drug delivery systems (GFDDS) of atenolol, an anti hypertensive drug, with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed and optimized. Hydroxy propyl methyl cellulose of different viscosity grades (K4M, K15M and K100M) and natural polymers like xanthan gum and guar gum were used as the polymers and sodium bicarbonate as gas generating agent to reduce floating lag time. The tablets were prepared by direct compression method. Estimation of atenolol in the prepared tablet formulations was carried out by extracting the drug with methanol and measuring the absorbance at 224 nm. The prepared formulations were further evaluated for hardness, friability, weight variation, drug content uniformity, swelling index, *in vitro* drug release pattern, short-term stability and drug excipient interactions. Majority of the designed. Formulations displayed nearly first order release kinetics, releasing more than 80%drug in 12 hours and remained buoyant more than 24 hours. The optimized formulation containing atenolol 50 mg, HPMC K100M 150 mg and sodium bicarbonate 20 mg has displayed almost first order release kinetics with a floating lagtime of only 200 sec. This formulation released more than 90% drug in 12 hours. This study proves that GFDDS of atenolol can be designed using HPMC K100M as matrix polymer, which provides nearly first order release kinetics and thus possible enhancement of oral bioavailability of the drug.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the Drug slowly into the gastrointestinal tract and maintain an effective drug concentration in the systemic circulation

For a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract.



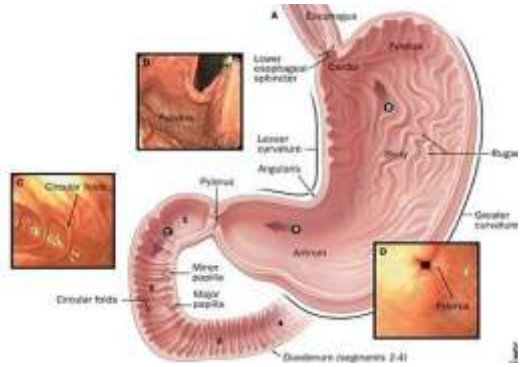


Fig 1.1: Drug absorption in (a) conventional dosage forms, (b) Gastroretentive drug delivery systems (GRDDS).

1.1 ANATOMY AND PHYSIOLOGY OF THE STOMACH

The stomach is located below the diaphragm. Anatomically it can be divided into four regions, namely, fundus, body, antrum and pylorus. The main function of the stomach is to store food temporarily, grind it, and then release it slowly in to the duodenum. In stomach we have four types of cells present which mainly involve in secretions.

- Chief / zymogenic cells which produce pepsinogen,
- Parietal/ oxyntic cells which produce HCL,
- Mucous neck cells/ goblet cells which produce alkaline mucous,
- Entero endocrine cells which produce hormone called as gastrin.

The stomach is an important site of enzyme production. Due to its small surface area, very little absorption takes place from the stomach. It provides a barrier to the delivery of drugs to the small intestine.

The main function of fundus and body is storage, where as that of antrum is mixing and grinding. The fundus adjusts to the increased volume during eating by relaxation of fundal muscle fibers. The fundus also exerts a steady pressure on the gastric contents, pressing them towards the distal stomach. The antrum does this grinding.

Gastric Emptying Rate:

Gastric pH affects the absorption of drugs from controlled release dosage forms. There is a large volume difference in gastric secretion in normal and achlorohydric individuals. The pH of the stomach in fasted condition is about 1.2-2.0 and 3-6.5 in the fed condition. Generally, basic drugs will have a better chance of dissolving in the fed condition than in the fasted condition. Food buffers neutralize gastric acid, thus increasing the pH up to about 6.5. After complete ingestion of a meal, the pH rapidly falls back to below 5.0 and then gradually declines to the fasting state values over a period of few hours.

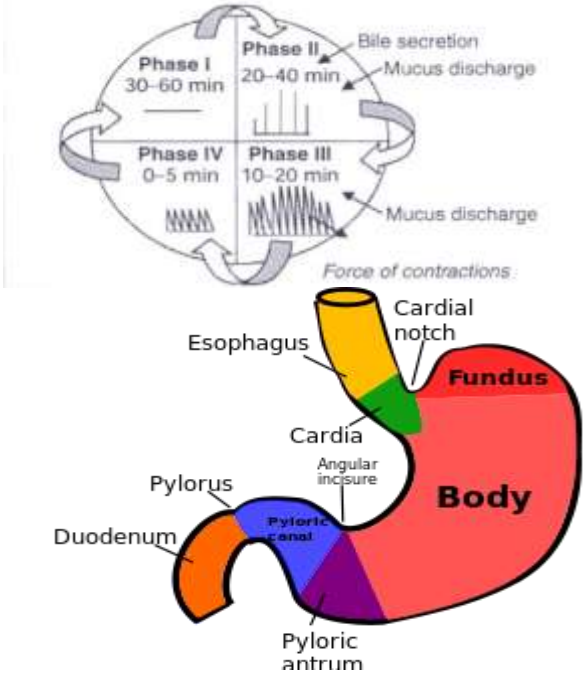


Fig 1.2: Schematic illustration of the stomach anatomical structure.

1.1.1 GASTROINTESTINAL MOTILITY AND TRANSIT TIME

Based on fasted and fed states of the stomach, two distinct patterns of gastrointestinal motility and secretions have been identified. In the fasting state, the stomach usually contains saliva, mucus, and cellular debris. The fasted state is associated with some cyclic contractile events commonly known as migrating myoelectric complex (MMC). Liquid components easily pass through the partially constricted sphincter. On the contrary, the large undigested materials are retained by an ‘‘antral-sieveing’’ process and are retro pulsed into the main body of stomach and remain in the fed state. In the fed state, gastric contractions move the contents towards the antrum and the pyloric sphincter. Usually a series of interdigestive events take place in the stomach. However, feeding disrupts this cycle causing a period of irregular contractile pattern[6]. Apparently there

are four consecutive phases of activity in the migrating myoelectric complex (MMC).

Phase I (basal phase): It is a quiescent period lasting from 45 to 60 minutes with no contractions.

Phase II (preburst phase): It consists of intermittent contractions that gradually increase in intensity as the phase progresses, and it lasts about 35 to 40 minutes. Gastric discharge of fluid and very small particles begins later in this phase.

Phase III (burst phase): This is a short period of intense distal and proximal gastric contractions (4–5 contractions per minute) lasting about 5 to 15 minutes; these contractions, also known as ‘‘house-keeper wave,’’ sweep gastric contents down the small intestine.

Phase IV: This is a short transitory period of about 0 to 5 minutes, and the contractions dissipate between the last part of phase III and quiescence of phase I.

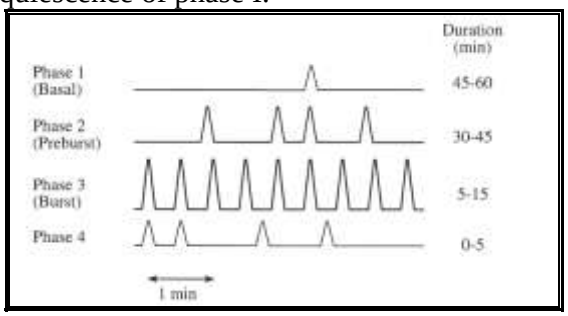


Fig No.1.3: The four phases and their durations of interdigestive migrating myoelectric complex (IMMC).

1.2 PROGRESS IN CONTROLLED GASTRORETENTIVE DELIVERY SYSTEMS

Oral controlled release dosage forms (CRDFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility.

The gastric emptying time in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a drug delivery system in a specific region of the GItract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.

Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs. These efforts resulted in GRDFs that were designed, in large part, based on the following approaches.

- Low density form of the DF that causes buoyancy in gastric fluid.
- High density DF that is retained in the bottom of the stomach.
- Bioadhesion to stomach mucosa.

1.2.1 SUITABLE DRUG CANDIDATES FOR GASTRORETENTION

Appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT; Drugs those are locally active in the stomach e.g. misoprostol, antacids etc. Drugs that disturb normal colonic microbes e.g. antibiotics against H.pylori.

1.2.2 FACTORSCONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The stomach anatomy and physiology contain parameters to be considered in the development of gastro retentive dosage forms. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include: density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture and gender.

Table No.1: Salient Features of Upper Gastrointestinal Tract.

Section	Length (m)	Transit time (h)	pH	Microbial count	Absorbing surface area(m^2)	Absorption pathway
Stomach	0.2	Variable	1- 4	<103	0.1	P, C, A
Small Intestine	6-10	3 ± 1	5-7.5	103– 1010	120-200	P, C, A, F, I, E, CM

P – Passive diffusion, C – Aqueous channel transport, A – Active transport, F – Facilitated transport, I – Ion-pair transport, E – Entero-or pinocytosis, CM – Carrier mediated transport.

Table No.2: Transit Time in Each Segment of the GI Tract.

1.1 Segment	2 Type of food	
	2.1 Liquid	2.2 Solid
Stomach	10-30 min	1-3 hr
Duodenum	Less than 60 sec	Less than 60 sec
Jejenum and ileum	3hr ± 1.5 hr	4hr ± 1.5hr

Density of dosage forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach. A density of < 1.0 gm/ ml is required to exhibit floating property.

Shape and size of the dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage form.

Single or multiple unit formulation: Most Gastroretentive drug delivery systems are single-unit dosage forms, which have in common the risk of losing their effect too early due to their all-or-nothing emptying from the stomach. To overcome this restriction, multiple-unit floating have been proposed.

Fed or unfed state: The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time.

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

Frequency of feed: The GRT can increase by over 400 minutes, when successive meals are given compared with a single meal due to the low frequency of MMC

Caloric content: Increase in acidity and caloric value slows down gastric emptying time (GET), which can improve the gastric retention of dosage forms GRT can be increased by 4 to 10 hours with a meal that is high in Proteins and fats.

Posture: Floating and non-floating systems behave differently. In the upright position, the floating systems floated to the top of the gastric contents and remain for a longer time, showing prolonged GRT. In supine position, the floating units are emptied faster than non-floating units of similar size. GRT can vary between supine and upright ambulatory states of the patient.

Gender: Females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface.

Age: Elderly people, especially those over 70, have a significantly longer GRT**.**

1.2.3 DISADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

These drug delivery systems suffer from mainly two adversities:

- The short gastric retention time (GRT).
- Unpredictable short gastric emptying time (GET).

APPROACHES TO PROLONG GASTRIC RESIDENCE TIME (GRT)

1.3 APPROACHES TO GASTRORETENTION:

Several techniques are reported in the literature to increase the gastric retention of drugs.

1.3.1 High-density systems: These systems, which have a density of ~3g/cm3, are retained in the rugae of stomach and capable of withstanding its peristaltic movements. The only major drawback with these systems is that it is technically difficult to manufacture them with a large amount of drug (>50%) and achieve required density of 2.4-2.8g/cm3. Diluents such as barium sulphate (density= 4.9), zinc oxide, titanium oxide, and iron powder must be used to manufacture such high-density formulation.

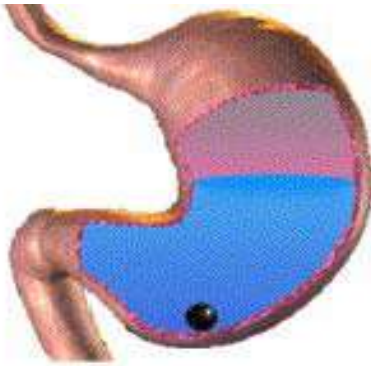


Figure 1.4 High density systems

1.3.2 Swelling and expanding systems:

These systems are also called as "Plug type system", since they exhibit tendency to remain logged in the pyloric sphincters. These polymeric matrices remain in the gastric cavity for several hours even in fed state. By selection of polymer with the proper molecular weight and swelling properties controlled and sustained drug release can be achieved. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical-chemical cross links in the hydrophilic polymer network.

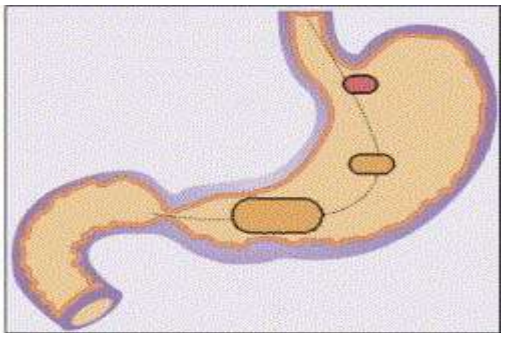


Figure 1.5 Swellable tablet in stomach

These cross link prevents the dissolution of polymer and thus maintain the physical integrity of the dosage form. A high degree of cross linking retards the swelling ability of the system and maintains its physical integrity for prolonged period. On the other hand, a low degree of cross linking results in extensive swelling followed by the rapid dissolution of polymer.

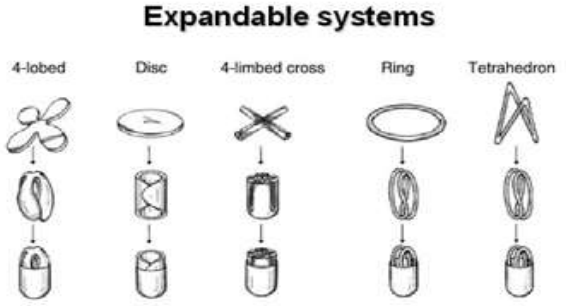


Figure 1.6 Different geometric forms of unfoldable systems

1.3.3 Incorporating delaying excipients:

Another delayed gastric emptying approach of interest include feeding of digestible polymers or fatty acid salts that charges the motility pattern, of the stomach to a fed stage thereby decreasing the gastric emptying rate and permitting considerable prolongation of the drug release. Prolongation of GRT of drug delivery system consists of incorporating delaying excipients like trietanolaminemyristate in a delivery system.

1.3.4 MUCOADHESIVE OR BIOADHESIVE SYSTEMS

An approach to increase gastric residence time of the dosage forms is to bind them to gastric mucosa or epithelial cell surfaces. The mucoadhesive systems

are intended to extend the GRT by adhering them to the gastric mucous membrane. Bioadhesion on soft tissues of certain natural or synthetic polymers has been exploited to control as well as to prolong the gastric retention of the delivery systems. The adhesion of the polymers with the mucous membrane may be mediated by hydration, bonding, or receptor mediated. In hydration mediated adhesion, the hydrophilic polymers become sticky and mucoadhesive upon hydration. Bonding mediated adhesion may involve mechanical or chemical bonding. Chemical bonds may involve covalent or ionic bonds or Vander Waals forces between the polymer molecules and the mucous membrane. Receptor mediated adhesion takes place between polymers and specific receptors expressed on gastric cells. The polymers could be anionic or cationic.

1.3.8 SUPERPOROUS HYDROGELS

These Swellable systems differ sufficiently from the conventional types to warrant separate classification Superporous hydrogels, average pore size >100µm, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores[30]. They swell to a large size and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material.

1.3.9 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, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

1.4 FLOATING SYSTEMS

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are

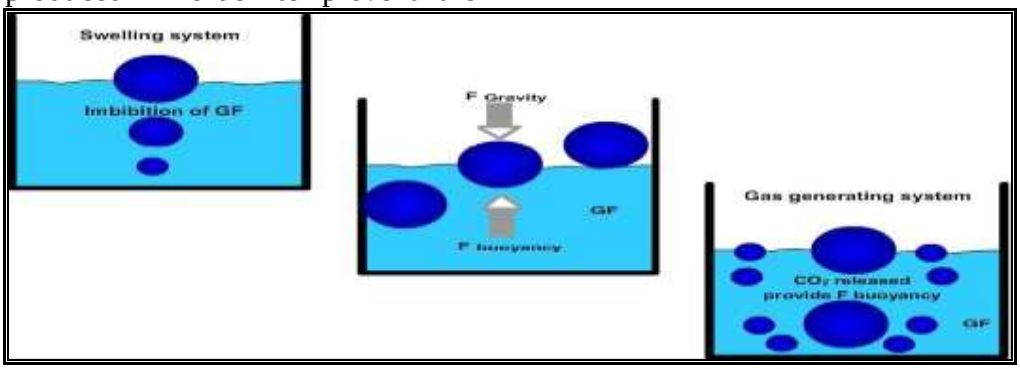
- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents.
- It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder). Stomach Specific FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. The floating sustained release dosage forms present most of the characteristics of hydrophilic matrices and are known as 'hydro dynamically balanced systems' ('HBS') since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of conventional hydrophilic matrices. These forms are expected to remain buoyant on the gastric contents with out affecting the intrinsic rate of emptying because their bulk density is lower than that of the gastric contents.

Mechanism of floating systems

When the system is floating on the gastric contents; the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. Minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, the apparatus operates by

measuring continuously the force equivalent to F that is required to maintain the submerged object. The object floats better if F is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations. F = F buoyancy - F gravity = (Df - Ds) gv--- (1) Where, F= total vertical force, Df = fluid density, Ds = object density, v = volume and g = acceleration due to gravity.



4. DRUG AND EXCIPIENT PROFILE.

4.1 DRUG PROFILE:

Drug name : Atenolol

Solubility: Water solubility 26.5 mg/ mL at 37°C .

It is freely soluble in 1N HCl (300 mg/mL at 25°C).

Physical state: White powder.

Melting point: 152-155°C.

Molecular formula : $C_{14}H_{22}N_2O_3$

Molecular weight : 266.336 g/mol

Dissociation Constant: pKa9.6 (24°).

Bioavailability: 40 to 50%

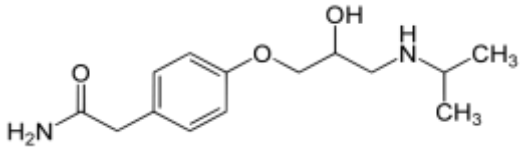
Half-life: Plasma half-life, 6 to 7 h.

Protein binding: In plasma, about 6 to 16%

Dose: 25mg 50mg, 100 mg.

Category: Selective β1 blocker.

Structure



4.1.1 Pharmacology:

Pharmacokinetic Properties:

Absorption of an oral dose is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract, the remainder being excreted unchanged in the feces. Peak blood levels are reached between 2 to 4 hours after ingestion. Unlike propranolol or metoprolol, but like nadolol, Atenolol undergoes little or no metabolism by the liver, and the absorbed portion is eliminated primarily by renal excretion. Over 85% of an intravenous dose is excreted in urine within 24 hours compared with approximately 50% for an oral dose. Atenolol also differs from propranolol in that only a small amount (6%-16%) is bound to proteins in the plasma. This kinetic profile results in relatively consistent plasma drug levels with about a fourfold interpatient variation.

The elimination half-life of oral Atenolol is approximately 6 to 7 hours, and there is no alteration of the kinetic profile of the drug by chronic administration. Following intravenous administration, peak plasma levels are reached within 5 minutes. Decline from peak levels are rapid (5- to 10-fold) during the first 7 hours; thereafter, plasma levels decay with a half-life similar to that of orally administered drug. Following oral doses of 50 mg or 100 mg, both beta-blocking and antihypertensive effects persist for at least 24 hours. When renal function is impaired, elimination of Atenolol is closely related to the glomerular filtration rate; significant accumulation occurs when the creatinine clearance falls below 35 mL/min/1.73m^2.[41]

Precaution and Contraindications

- Bradycardia (pulse less than 50 bpm)
- Cardiogenic Shock
- Asthma (may cause broncho-constriction), although unlikely as atenolol is cardioselective

- Symptomatic hypotension (blood pressure of less than 90/60 mm Hg with dizziness, vertigo etc.)
- Angina of the Prinzmetal type (vasospastic angina)
- Metabolic Acidosis (a severe condition with a more acidic blood than normal)
- Severe disorders in peripheral arterial circulation
- AV-Blockage of second and third degree (a particular form of arrhythmia)
- Acutely decompensated congestive heart failure (symptoms may be fluid retention with peripheral edema and/or abdominal fluid retention (ascites), and/or lung edema)
- Sick Sinus Syndrome (a particular form of arrhythmia)
- Hypersensitivity and/or allergy to atenolol
- Pheochromocytoma (a rare type of tumor of the adrenal glands)

Adverse Effects

Hematologic: Agranulocytosis.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional libility with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with atenolol. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to atenolol therapy with subsequent resolution

Storage: Store at controlled room temperature, 20-25°C (68-77°F).

Materials and Method: Atenolol ,Hydroxy propyl methyl cellulose, Microcrystalline cellulose, magnesium stearate, talc, xanthan gum, guar gum, sodium bicarbonate all chemicals and glass wares were pharmacopeial grade.

5.2 EXPERIMENTAL DESIGN

5.2.1 PREFORMULATION STUDIES:

DRUG-EXCIPIENT COMPATABILITY STUDIES:

Fourier Transform-Infrared spectroscopic studies: A Fourier Transform – Infra Red spectrophotometer was used to study the non-thermal analysis of drug-excipient (binary mixture of drug:excipient 1:1 ratio) compatibility. The spectrum of each sample was recorded over 450-4000cm^{-1}. Pure drug of atenolol, atenolol with physical mixture (excipients) compatability studies were performed.

5.2.2 Analytical method used in the determination of atenolol

PREPARATION OF BUFFER SOLUTION: Before preparation of floating Tablets, standard curve of atenolol in 0.1HCl was constructed.

Preparation of 0.1N HCl

8.65 ml of Conc. HCl was placed in a 1000 ml volumetric flask and the volume was made up with water and pH was adjusted to 1.2.

Preparation of Standard Solution Atenolol

Accurately weighed 100mg of Atenolol was placed in a 100mL volumetric flask and 50mL of 0.1 N HCl was added to dissolve the drug. The volume was made up to 100mL with HCl to give 1000 µg/mL of solution(stock solution -I). A 10mL aliquot from stock solution -I was taken and diluted

to 100mL with in a volumetric flask to get 100µg/mL (stock solution -II).

Determination of absorption maxima (λ_{max}) for Atenolol- A 1mL aliquot of standard stock solution-II was diluted to 10mL to give 10 µg/mL standard solutions of Atenolol in 0.1 N HCl. This solution was scanned on a UV-Visible spectrophotometer against respective media blank. An absorption maxima (λ_{max}) of 224nm was obtained for all solutions and was selected to prepare standard curve.

Preparation of standard curves for atenolol: Aliquots of 0.5, 1, 1.5, 2, 2.5, and 3mL of Atenolol standard solution of 100mcg/ml (stock solution-II) was taken and diluted to 10ml to obtain concentrations from 5 to 30µg/mL with 0.1 N HCl. The absorbances of solutions was determined at 224nm against respective media solutions as blank and a standard curve was plotted.

5.3 METHOD: Atenolol Floating tablets prepared by using direct compression method.

Direct Compression Method: The drug and all other excipients were sifted through #40 sieves and mixed thoroughly. The above blend was pre lubricated with HPMC, MCC and lubricated with magnesium stearate. The above lubricated blend was compressed using standard flat faced punch on a sixteen station rotary tablet punching machine.

5.4 EVALUATION OF TABLETS

5.4.1 Angle of Repose :

The friction forces in a loose powder can be measured by the angle of repose (ɵ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$$\tan(\theta) = h / r$$

$$\theta = \tan^{-1}(h / r)$$

Where, ɵ is the angle of repose.
h is the height in cm
r is the radius in cm.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel.

5.4.2 Bulk Density (Db): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M / Vb$$

Where, M is the mass of powder
Vb is the bulk volume of the powder.

5.4.3 Tapped Density (Dt):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$$Dt = M / Vt$$

Where, M is the mass of powder
Vt is the tapped volume of the powder.

5.4.4 Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is given by

$$I = Dt – Db / Dt \times 100$$

Where, Dt is the tapped density of the powder and Db is the bulk density of the powder.

5.4.5 Hausner's ratio:

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = Dt / Db$$

Where, Dt is the tapped density
Db is the bulk density.

Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

5.4.6 Weight variation:

20 tablets were selected randomly from the batch and weighed individually to

check for weight variation. Weight Variation Specification as per IP Average Weight of Tablet % Deviation 80 mg or less ±10. More than 80 mg but less than 250 mg ±7.5. 250 mg or more ±5

5.4.7 Hardness (or) tablet crushing strength (fc): Hardness or tablet crushing strength (fc) (the force required to break a tablet in a diametric compression test) was measured using Monsanto tablet hardness tester . It is expressed in kg/cm^2.

5.4.7 Thickness: The thickness of the tablets was measured using vernier caliper. It is expressed in mm.

5.4.8 Friability (F): Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = W_{initial} - W_{final} / W_{initial} \times 100$$

5.4.9 Floating Test:

The time between introduction of dosage form and its buoyancy on simulated gastric fluid and the time during which the dosage form remain buoyant was measured. The time taken for dosage form to emerge on surface of medium called floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of floating time (TFT).

5.4.10 Swelling Index:

The individual tablets were weighed accurately and kept in 50 ml of water. Tablets were taken out carefully after 60 minutes, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling (swelling index) was calculated by using the formula:

$$\text{Swelling index} = W_{wet} - W_{dry} / W_{dry} \times 100$$

5.4.11 *in vitro* DissolutionStudy:

The test for buoyancy and *in vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 HCl as a testing medium maintained at 37°C. The time required to float the HBS dosage form is noted as floating (or floatation) time. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn periodically from the dissolution medium, replenished with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non reactive material such as not more than a few turns of 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.

5.4.12 Kinetic Analysis of Dissolution Data:

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics.

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative % drug released versus log time.
5. Hixson-Crowell model - cubic root of unreleased fraction of drug versus time.

Zero order kinetics: Zero order release would be predicted by the following equation:- $\mathbf{A_t = A_0 - K_0 t}$ Where, A_t = Drug release at time 't'. A_0 = Initial drug concentration, K_0 = Zero – order rate constant (hr^{-1}). When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K_0.

First Order Kinetics: First – order release would be predicted by the following equation:-

$$\mathbf{Log\ C = log\ C_0 – K_t / 2.303}$$

Where, C = Amount of drug remained at time't'. C_0 = Initial amount of drug.
K = First – order rate constant (hr^{-1}).
When the data plotted as log cumulative percent drug remaining versus time yields a straight line, it indicates that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

Higuchi's model: Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$\mathbf{Q = [D\varepsilon / \tau\ (2\ A - \varepsilon Cs)\ Cst]^{1/2}}$$

Where, Q = Amount of drug released at time't'. D = Diffusion coefficient of the drug in the matrix. A = Total amount of drug in unit volume of matrix. Cs = the solubility of the drug in the matrix.

τ = Porosity of the matrix. = Tortuosity.

t = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs', and 'A', are constant. Then equation becomes: $\mathbf{Q = Kt^{1/2}}$ When the data plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, it indicates that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the floating tablets of Atenolol, the release data were also fitted to the well – known exponential equation (Korsmeyer equation / Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$\mathbf{M_t / M_a = Kt^n}$$

Where, M_t / M_a = the fraction of drug released at time't'. K=Constant incorporating the structural and geometrical characteristics of the drug / polymer system. n= Diffusion exponent related to the mechanism of the release. Above equation can be simplified by applying log on both sides,

And we get:

$$\mathbf{Log\ M_t / M_a = LogK + n\ Logt}$$

When the data plotted as log of drug released versus log time, yields a straight line the slope of the line is equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release 'n' = 0.5 while for anomalous (non – Fickian) transport 'n' ranges between 0.5 and 1.0.

Table .6: Formulation chart

s.no	Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
1	Atenolol	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
2	HPMC K4M	25	50	75												
3	HPMC K15M				25	50	75									
4	HPMC K100M							25	50	75						
5	Xanthan gum										25	50	75			
6	Guar gum													25	50	75
7	Sodium bicarbonate	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
8	Mg.stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
9	Talk	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
10	MCC	150	125	100	150	125	100	150	125	100	150	125	100	150	125	100

Table no.7: Mechanism of Drug Release as per Korsmeyer Equation / Peppa's Model

S.No	n value	Drug Release
1.	n <0.5	Fickian release
2.	0.5<n<1	Non-Fickian release
3.	n>1	Case II transport

Stability studies:

Short-term stability studies were performed at a temperature of 45°±1°C over a period of three weeks (21 days) on the promising HBS tablet formulation F9. Sufficient number of tablets (15) were packed in amber colored screw capped bottles and kept in hot air-oven maintained at 45°±1°C. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and *in vitro* floating studies were performed to determine the drug release profiles, *in vitro* floating lag time and floating time.

DISCUSSION

The present investigation was under taken to formulate and evaluate floating tablets of Atenolol that retain in stomach for longer period

FLOATING TABLETS:

Using various polymers like HPMC K100M, HPMC K15M, HPMC K4M, Xanthan gum and guar gum tablets were prepared along with other additives. Direct compression method was used for the preparation of tablets. A total number of 15 formulations were prepared and evaluated.

To retain tablet in stomach for long periods, the excipients selected must be water soluble by nature. This excipient was used as a bulking agent to achieve the desired tablet weight. To impart buoyancy nature sodium bi carbonate was included as an effervescence agent. Aerosil was employed as a lubricant and magnasium stearate used as glidant.

Pre compressional studies:

The results obtained by evaluating the powder blends of drug and excipients are shown in table 6.3 and 6.4. Bulk density and tapped density were found in the range 0.48-0.58 g/cc and 0.58-0.65 g/cc respectively. The value of hausner's ratio was in between 1.15-1.29 (< 1.3) indicating that all batches of powder blends were having good compressibility. Values of angle of repose (θ) was found in the range of 24.05-29.02 showing that blend of powder mass was Good flowing and can be used for direct compression (Table 6.2 and 6.3).

Weight variation and Thickness:

The average weight in all the 15 formulations was found to be 247±0.99 mg to 250±0.23 mg. In all 15 formulations no tablets were outside the limit i.e, ±10%of tablet weight in weight variation test. The thickness varied between 1.95 ± 0.7 to 2.02 ± 0.01mm. In all formulations tablet thickness was within ± 5% of standard value. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 3 to 4.5 kg/cm^2 for all the formulations. Assay was performed and percent drug content of all the tablets were found to be between 94.41 % and 98.56% of atenolol, which was within the acceptable limits (Table 6.4 and 6.5).

The swelling index of the tablets increases with an increase in the polymer content and the content of gas generating agent (NaHCO3), as can be seen from the data given in tables-9 & 10.

***In vitro* dissolution:**

In vitro dissolution studies were performed for optimized floating tablets of atenolol mixture in solvent 0.1N HCl using USP dissolution apparatus type 2. The optimized formulations are HPMC K100M containing tablets (F7-F9). Formulations F7, F8, and F9 which contained increasing concentrations of HPMC K100M have recorded drug release 85.32±0.17, 90.38±0.56 and 96.25±0.28 respectively in 12hrs and buoyancy of tablets were maintained up to 24 hrs.

Drug Release Kinetics:

In vitro drug release data of all the HBS formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer – Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in

tables-28 and 29 and plots shown in figures-6 to 25. From the above data, it can be seen that all the formulations have displayed first order release kinetics ('r' values in the range of 0.7015 to 0.9738). From Higuchi and Peppas data, it is evident that the drug is released by fickian diffusion mechanism (n=0.25 to 0.4992) except formulation F4 (n=0.51). From the kinetic data of factorial formulations (table-29), it is evident that all the 15 formulations have shown drug release by first order kinetics. Formulation F9 releases drug by first order kinetics with maximum r^2 value (r=0.9738). The values of 'r' for Higuchi's equation of formulations range from 0.84 to 0.98 and those of 'n' values of Peppas equation range from 0.25 to 0.4992. This data reveals that drug release follows Fickian diffusion mechanism.

Stability Studies:

Short-term stability study was performed on the promising formulation F9 by storing the samples at 45±1ºC for 3 weeks (21 days). The samples were tested for any changes in physical appearance and drug content at weekly intervals. *Invitro* floating ability and *in vitro* drug release studies were performed at the end of 3 weeks storage.

These results indicate that there were no significant changes in drug content and dissolution profile of the formulation F9 during storage at 45ºC for 3 weeks.

SUMMARY AND CONCLUSION

Atenolol is a beta-adrenoreceptor antagonist (beta-blocker) used in the treatment of hypertension and angina pectoris. It is incompletely absorbed from the gastrointestinal tract and has an oral bioavailability of only 50%, while remaining drug is excreted unchanged in faeces. This is because of poor absorption in lower gastrointestinal tract. It undergoes little or no hepatic first pass metabolism and its elimination half-life is 6 to 7 hrs. Therefore, it is selected as a suitable drug for the design of a gastro-retentive floating drug delivery system (GFDDS) with a view to improve its oral bioavailability. In the present study, an attempt was made to design and optimize GFDDS of atenolol using hydroxyl propyl methylcellulose of different viscosity grades (K4M,K15MandK100M 5) and natural polymers (Xanthan gum and Guar gum) as the polymers and sodium bicarbonate as a gas generating agent, to reduce floating lag time. The tablets were prepared by direct compression method. By using this polymers 15 formulations were prepared and these 15 formulations were evaluated for hardness, friability, weight variation, drug content uniformity, swelling index, *in vitro* drug release pattern, short-term stability and drug-excipient interaction.

Estimation of atenolol in the prepared GFDDS was carried out by extracting drug with 0.1 N HCl and measuring the absorbance at 224 nm. *In vitro* drug release studies were performed in USP XXIII tablet dissolution test apparatus employing paddle stirrer at 50 rpm using 900 ml of 0.1N HCl maintained at 37±0.5ºC as the dissolution medium. Majority of the designed GFDDS of atenolol displayed nearly first order release kinetics, releasing more than 80% drug in 12 hrs and remained buoyant for more than 24 hours. The optimized formulation (F9) containing atenolol 50mg, HPMC (K100M) 75mg and $NaHCO_3$ 20 mg has displayed first order release kinetics with a floating lag time of only 200sec, and released more than 90% drug in 12 hrs. This study proves GFDDS of atenolol can be designed using HPMC K100M as matrix polymer, which provides nearly first order release kinetics and thus possible enhancement of oral bioavailability of the drug.

CONCLUSION

Success of the i*n vitro* drug release studies recommends the product for further *in vivo* studies, which may improve patient compliance. From the results, formulation F9 containing atenolol 50 mg, HPMC (K100M) 75mg and $NaHCO_3$ 20 mg evolved as the optimized formulation and it releases more than 90% drug in 12hrs. Short-term stability studies of optimized formulation F9 indicate, that there are no significant changes in drug content and dissolution parameter values after 3 weeks storage at 45±1ºC.

IR spectroscopic studies indicated that there are no drug-excipient interaction in the

optimized formulation. The optimized formulation F9 can be considered.

REFERENCES

1. Anderson NR et al., 1982. Quantitative evaluation of pharmaceuticaleffervescent systems I: design of testing apparatus. J.Pharm. Sci. 71(1): 3–6.
2. Anderson NR et al.,1982. Quantitative evaluation of pharmaceuticaleffervescent systems II: stability monitoring by reactivity and porosity measurements. J. Pharm.Sci.71(1): 7–13.
3. Barra J, Somma R.,1996. Influence of the physicochemical variability ofmagnesium stearate on its lubricant properties: possible solutions.Drug Dev.Ind. Pharm. 22(11): 1105–1120.
4. BillanyMR, Richards JH. ,1982.Batch variation of magnesiumstearate and itseffect on the dissolution rate of salicylic acid from solid dosage forms. Drug Dev. Ind Pharm.8: 497–511.
5. BosCEet al.,1991. Lubricant sensitivity in relation to bulk density forgranulations based on starch or cellulose.Int. J. Pharm.67: 39–49.
6. Bracconi P et al.,2003. Structural properties of magnesium stearatepseudopolymorphs: effect of temperature. Int. J. Pharm. 262(1–2):109–124.
7. BrittainHG.,1997. Rawmaterials. Drug Dev. Ind Pharm.15(13): 2083–2103.
8. Dansereau R., Peck GE., 1987. The effect of the variability in the physical and chemical properties of magnesium stearate on the properties of compressed tablets.Drug Dev Ind Pharm.13: 975–999.
9. Desai DS., 1993. Physical interactions of magnesium stearate with starch-derived disintegrants and their effects on capsule and tablet dissolution. Int. J. Pharm.91(2–3): 217–226.
10. Ebba F., 2001. Stress relaxation studies of granules as a function ofdifferentlubricants.Eur. J. Pharm. Biopharm.52(2): 211–220.
11. Frattini C, Simioni L.,1984 Should magnesium stearate be assessed in theformulation of solid dosage forms by weight or by surface area? DrugDevInd Pharm.10: 1117–1130.
12. He Xet al.,2007. Mechanistic study of the effect of roller compaction and lubricant on tablet mechanical strength. J. Pharm. Sci. 96(5):1342–1355.
13. Javaid KA, Cadwallader DE.,1972. Dissolution of aspirin from tablets containing various buffering agents.J Pharm.Sci.61(9): 1370–1373.
14. KoivistoMetal. ,2004.Effect of temperature and humidity on vegetable grade magnesiumstearate. Powder Technol.147(1–3): 79–85.
15. LeinonenUIet al.,1992 Physical and lubrication properties of magnesiumstearate. J Pharm.Sci.81(12): 1194–1198.
16. Likitlersuang Set al.,2007.The effect of binary mixture composition andmagnesium stearate concentration on the hiestand tableting indices and other related mechanical properties. Pharm. Dev. Tech.12 (5):533–541.
17. Marwaha SB, Rubinstein MH.,1988. Structure-lubricity evaluation of magnesiumstearate. Int. J. Pharm. 43(3): 249–255.
18. Mason WD, Winer N.,1981. Kinetics of aspirin, salicylic acid and salicyluricacid following oral administration of aspirin as a tablet and two buffered solutions. J. Pharm. Sci.70(3): 262–265.
19. Muller BW.,1981 Polymorphism of magnesium stearate and the influence ofthe crystal structure on the lubricating behavior of excipients. Acta. Pharm. Sue.18: 74–75.
20. Okoye P, Wu S.H.,2007.Lubrication of direct-compressible blends withmagnesium stearate monohydrate and dihydrate.Pharm.Techno.31(9): 116–129.
21. Olsson Het al.,1998.Evaluation of the effects of polyethylene glycols

ofdiffering molecular weights on the mechanical strength of sodium.chloride and sodiumbicarbonatetablets. Int. J Pharm.171(1): 31– Thermochim Acta1992; 196: 63–84.
22. Phadke DS, Collier JL.,1994. Effect of degassing temperature on the specificsurface area and other physical properties of magnesium stearate. Drug. Dev. Ind. Pharm. 20(5): 853–858.
23. Phadke DS, Eichorst JL.,1991. Evaluation of particle size distribution andspecific surface area of magnesium stearate. Drug. Dev. Ind Pharm. 17: 901–906.
24. Raghunadha Gupta C, Purushothaman M, Dwarakanadha Reddy P and Vijaya Ratna J. Gastroretentive Delivery Systems: A Short Review, *Journal of Pharmacy and Chemistry*, Vol.4, Issue.1, January - March 2010.
25. Rainsford K.D., 1978. Gastricmucosal ulceration induced in pigs by tablets butnot suspensions or solutions of aspirin. J Pharm. Pharmacol.30:129–131.
26. RaoKP., 2005. Impact of solid-state properties on lubrication efficacy of magnesiumstearate. Pharm. Dev. Technol.10(3): 423–437.
27. Sharpe SA.,1997. Physical characterization of the polymorphic variationsofmagensium stearate and magnesium palmitate hydrate species. Struct. Chem.8(1): 73–84.
28. Steffens KJ, Koglin J.,1993.The magnesium stearate problem.Manuf.Chem.64(12): 16–19.
29. Swaminathan V, Kildisig DO.,2001. An examination of the moisture sorptioncharacteristics of commercial magnesium stearate. AAPS Pharm.Sci. Tech.2(4): 28.
30. Usui F., Carstensen JT., 1985. Interactions in the solid state I: interactions ofsodium bicarbonate and tartaric acid under compressed conditions. J. Pharm. Sci. 74(12): 1293–1297.
31. Wurster DE.,2005. The influence of magnesium stearate on the hiestandtableting indices and other related mechanical properties of maltodex-trins.Pharm.Dev.Tech.10(4): 461–466.
32. Yanze FM., 2000. A process to produce effervescent tablets: fluidised beddryer melt granulation. Drug. Dev. Ind Pharm. 26(11): 1167–1176.

Text Books and Pharmacopoeia

33. Beckett AH, Stenlake JB, Practical Pharmaceutical Chemistry. 4th ed. Delhi: CBS Publisher and Distributors, 1997.
34. Higuchi T AndBrochman E, Hanseen H, Pharmaceutical Analysis, Delhi: CBS Publisher and Distributors, 2005.
35. Mendham J, Denney RC, Barnes JD, Kthomas MJ, Vogel's text Book of Quantitative Chemical Analysis, 6thed. Pearson education Pvt Ltd, 2002.
36. P D Sethi, High Performance Liquid Chromatography, Delhi: CBS Publisher and Distributors.
37. P D Sethi, Quantitative Analysis of Drugs in Pharmaceutical Formulation, 3rded. Delhi: CBS Publisher and Distributors.
38. The Indian Pharmacopoeia, Government of India, Ministry of Health and Family Welfare, Published by the India