GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF SALBUTAMOL SULPHATE: FORMULATION AND IT'S IN VITRO EVALUATION

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CERTIFICATE

This is to Certify that this dissertation entitled "**GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF SALBUTAMOL SULPHATE: FORMULATION AND IT'S *IN VITRO* EVALUATION"** by **Mr.V.Narayanan** for the award of "**Master Of Pharmacy"** degree, comprises of the bonafide work done by him in the Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Tiruchirapalli, under my supervision and guidance and to my full satisfaction.

Place: Tiruchirapalli

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I recommend this research work for acceptance as project for the partial fulfillment of the degree of "**Master of Pharmacy"** of the Department of Pharmaceutics, Periyar College of Pharmaceutical Sciences for Girls, Tiruchirapalli, for the year March 2008.

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Date: (**Dr.R.Senthamarai)**

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V.NARAYANAN

1. Introduction

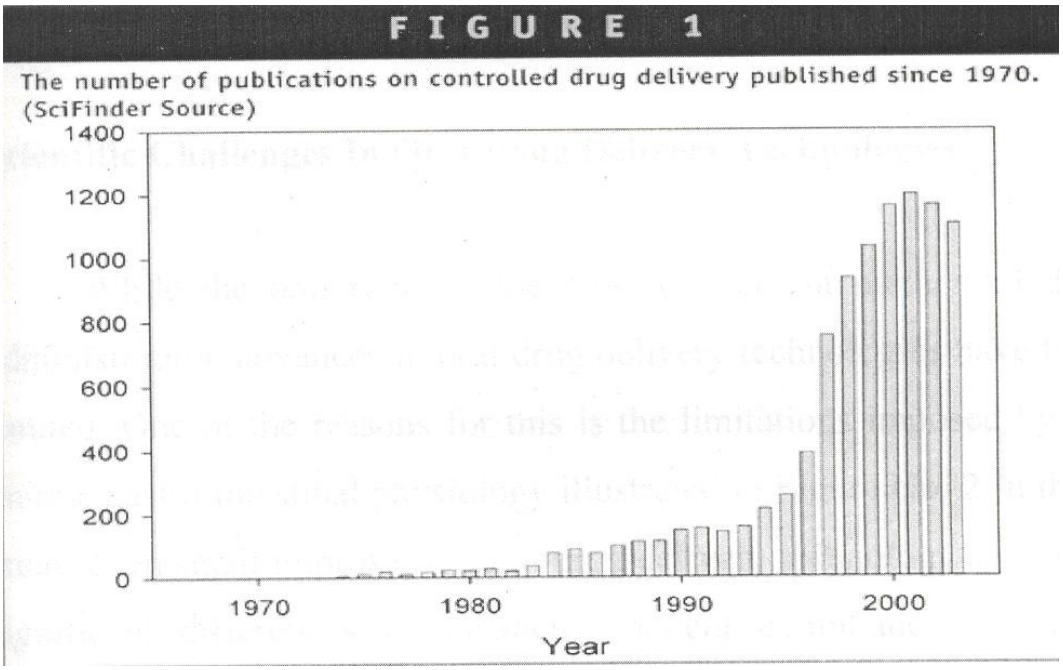
1.1 **Oral Controlled Drug Delivery System**

Pharmaceutical technologists today are able to provide drug delivery system with very precise control over drug release for a prolonged period of time, eliminating need for frequent dosing and minimizing side effect and increasing patient compliance and comfort.

The history of controlled drug delivery technologies spans over five decades since the introduction of the SpansuleR[1] formulation by Smith Kline And French Laboratories in 1952 (www.gsk.com/about/background.htm) for the first controlled-release delivery over the past two decades, have been significant. The ability to control the drug release kinetics is such that drug delivery for days and years can be achieved. Since the first book on controlled drug delivery was published in 1978, drug delivery has advanced significantly.

At the beginning of 2004, a keyword search on controlled drug delivery using the Scifinder scholar database would have resulted in 9,612 references. Figure No.1 shows the number of publications since 1970. As can be seen, research on controlled drug delivery has continued a steady rise until the second half of 1990s. Research in the 1980s was focused mainly on mathematical modeling on various types of controlled drug delivery system, and clear understandings on how to control the release kinetics may have contributed to the explosive growth of the controlled-release technology area throughout the past ten years. It is difficult to read all those past publications even only for abstracts. It is desirable to have a single volume that summarizes work done from past to present using comprehensive and coherent information on controlled-release dosage forms. Such a book does becomes available once every decades or so! Examples are Novel Drug Delivery System, second Edition published in 1992, and Modified Release Drug Delivery Technology published in 2003.

Figure No.1 Number of Publications on Controlled Drug Delivery System



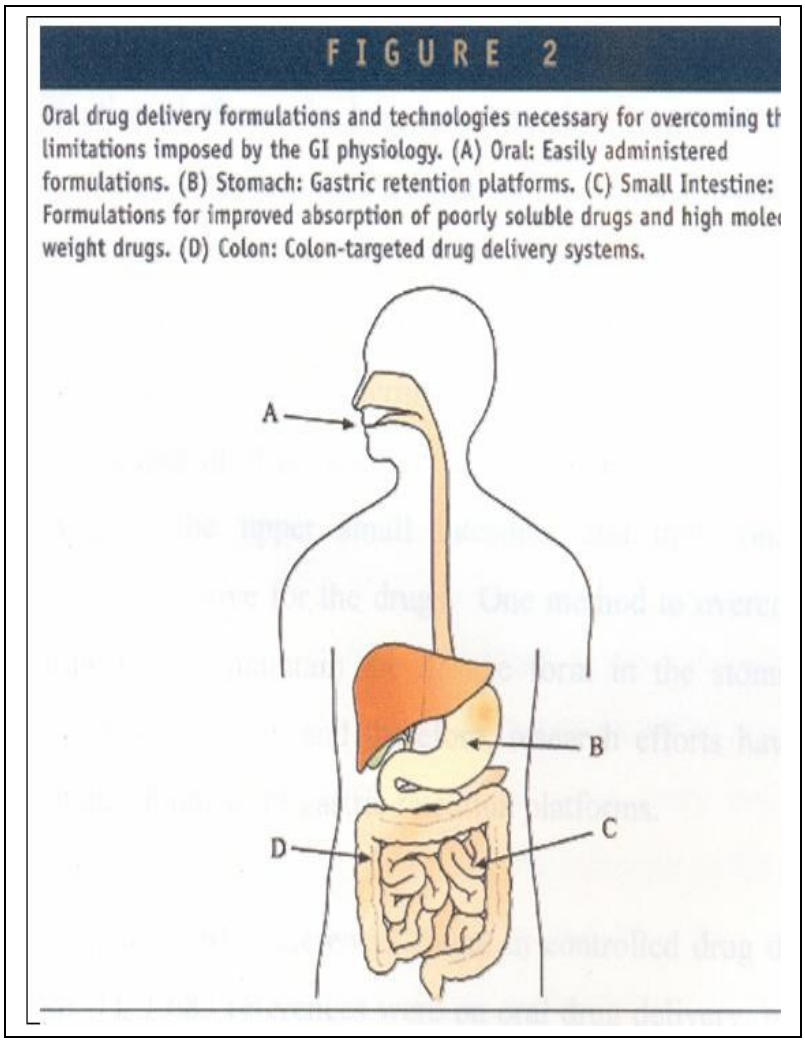
In the recent past, controlled release concept and technology have received increasing attention in the face of growing awareness to toxicity and ineffectiveness of drugs. When drugs are administered in the form of conventional drug delivery system, usually produce wide ranging fluctuations in drug concentration in the blood stream and tissues and consequently leads to undesirable toxicity and inefficiency. This factor, as well as other factors such as repetitive dosing and unpredictable absorption, led to the concept of controlled drug delivery systems or therapeutic system.

As controlled drug delivery advances further, the pharmaceutical industry has realized that the introduction of new delivery technologies would extend the patent protection of their drugs. Such an incentive provides significant motives for investment in this lucrative area. Despite extensive research in drug delivery, the advances in oral application have been relatively slow. Some of the scientific challenges and opinion about the oral controlled drug delivery systems are discussed in the coming paragraphs.

Scientific Challenges in Oral Drug Delivery Technologies

While the oral route is the most convenient method of drug administration, advances in oral drug delivery technologies have been limited. One of the reasons for this is the limitations imposed by the unique gastro intestinal physiology illustrated in Figure No.2 In these areas, even small improvements in drug delivery technology can make significant differences in enhancing patient compliance and drug bioavailability.

Figure No.2 Physiology of Gastrointestinal Tract



Formulation for Ease of Administration (Oral Delivery)

It is estimated that approximately one-third of the population has pill-swallowing difficulties, primarily the geriatric and pediatric populations. The geriatric and pediatric populations are more prone to have swallowing difficulties. It is common to see those afflicted carrying a small device with them, which is used for crushing tablets, enabling easy ingestion. To alleviate the problems associated with swallowing difficulties, a new dosage form, known as fast-dissolving tablets, has been developed. Since 1986 when the Zydis R Lyophilized, fast-dissolving dosage form were first introduced, a number of other fast-dissolving formulation were developed, and the technology is still improving. The fast-dissolving tablets are also called fast-melt or fast disintegrating. And one more dosage form for controlled release of drug is developed called as **Gastro Retentive** Drug Delivery System**.**

Gastric Retention Platform

One of the "holy grails" in oral drug delivery is to develop gastric retention platform for long-term (ranging from 6 to 24 hours) delivery of drugs by oral administration. Currently, there are a number of drugs that can be delivered using once-daily formulations. This is possible only for drugs that are well absorbed throughout the GI tract or typically have long terminal elimination half-lives. There are a large number of drug that are not absorbed to the same extend once they pass the upper small intestine, and thus, once-daily formulations are elusive for the drugs. One method to overcome the fast GI transit is maintain the dosage form in the stomach for extended period of time, and therefore, research efforts have been focused on development of gastric retention platforms.

One of the 9,612 references found in controlled drug delivery (Figure No.1) 1,683 references were on oral drug delivery, but only 20 were on gastric retention on particular topics. Clearly, the progress on developing gastric retention platforms has been show

Table No.1 lists some of the approaches that have been applied to the development of gastric retention platforms.

Only a small number of companies are actively working on their development. This is mainly due to the inherent difficulty associated with achieving gastric retention. The lack of a suitable in vitro model to study gastric retention has compounded the problem. To alleviate this problem, an in vitro model designed to mimic the gastric retention of oral dosage forms is under development.

TableNo.1 Approaches for making Gastric Retention Platforms

S No	Technology	Website
1	Low density micro spheres with bioadhesive coats	www.westpharma.com
2	Moderately swelling matrix system	www.depomedinc.com
3.	Bioadhesives	www.kypharmaceutical.com
4.	Super swelling hydro gel system	www.kospharm.com

One of the major scientific challenges in the development of gastric retention devices is overcoming the housekeeping waves that consist of strong gastric contraction that occur every few hours, particularly in the fasted stated. If the gastric retention technology is based on swelling or expansion of the system, this then must be sufficient to maintain the delivery system in the stomach in the fasted condition. The extensive swelling or expansion; however tends to result in mechanically weak properties, which may not withstand the compression exerted by the housekeeper waves. For this reason, fast swelling hydro gel with mechanically strong and elastic polymers have been developed.

1.2 GASTRO RETENTIVE DRUG DELIVERY SYSTEM

Introduction to Gastric Retention[2]

Over the past three decades the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in term of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft system, expanding systems, swelling systems, bioadhesive system and low-density systems.

Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease. Furthermore, improved bioavailability is expected for drugs that are absorbed readily upon release in the Gastro intestinal tract. These drugs can be delivered ideally by slow release from the stomach.

Many drugs categorized as once-a-delivery have been demonstrated to have sub optimal absorption due to dependence on thee transit time of the dosage form, making traditional extended release development challenging. Therefore, a system designed for longer gastric retention will extend the time within drug absorption can occur in the small intestine. There are certain situations where gastric retention is not desirable.

Aspirin and non-steroidal anti-inflammatory drugs are known to cause gastric lesions, and slow release of such drugs in the stomach is unwanted. Thus, drugs that may irritate the stomach lining or are unstable in its acidic environment should not be formulated in gastro retentive systems. Certain types of drugs can benefit form using gastric retentive s devices.

These include:

- Drugs acting locally in the stomach,
- Drugs that are primarily absorbed in the stomach,
- Drug those are poorly soluble at an alkaline pH,
- Drugs with a narrow window of absorption,
- Drugs that degrade in the colon,

Physiology of the stomach

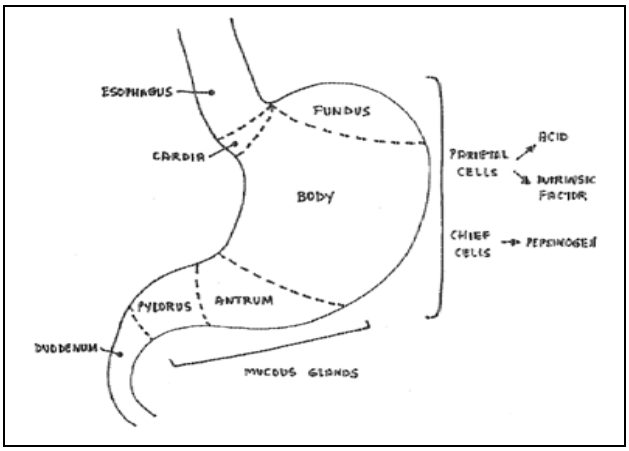
The GI tract is essentially a tube about nine meters long that runs through the middle of the body from the mouth to the anus and includes the throat (Pharynx), oesophagus, and stomach, small intestine (Consisting of the duodenum and ileum) anus large intestine (consisting of the cecum, colon and rectum). The wall of the GI tract has the same general structure throughout most of its length. The Stomach is an organ with a capacity for the mixing and grinding of gastric contents. Under fasting conditions, the stomach is a collapsed bag with a residual volume of approximately 50 ml and contains a small amount of gastric fluid (pH 1-3) and air. The mucus spreads and covers the mucosal surface of the stomach as well as the rest of the GI tract. The GI tract is in a state of continuous motility consisting of two modes: interdigestive motility pattern and digestive motility pattern. The former is dominant in the fasted state with a primary function of cleaning up the residual content of the upper GI tract.

The interdigestive motility pattern is commonly called the 'migrating motor complex' ('MMC') and is organized in cycles of activity and quiescence each cycle lasts 90-120 minutes and consists of four phases. The concentration of the hormone motilin in the blood controls the duration of the phases. In the interdigestive or fasted state, an MMC wave migrates form the stomach down the GI tract every 90-120 minutes. A full cycle consists of four phases, beginning in the lower oesophageal sphincter/gastric pacemaker, propagating over the whole stomach, the duodenum and jejunum, and finishing at the ileum. Phase III is termed the 'housekeeper waves' as the powerful

contractions and indigestible debris. The administration and subsequent ingestion of food rapidly interrupts the MMC cycles, and the digestive phase is allowed to take place. The upper part of the stomach stores the ingested food initially, where it is compressed gradually by the phasic contraction.

The digestive or fed state is observed in response to meal ingestion. It resembles the fasting Phase II and is not cyclical, but continuous, provided that the food remains in the stomach. Large objects are retained by the stomach during the fed pattern but are allowed to pass during Phase III of the interdigestive MMC. It is throughout that the sieving efficacy (i.e. the ability of the stomach to grind the food into smaller size) of the stomach is enhanced by the fed pattern and/or by the presence of food. The fasted-state emptying pattern is independent of the presence of any indigestible solids in the stomach. Patterns of contraction in the stomach occur such that solid food is reduced to particles of less than 1mm diameter that are emptied through the pylorus as suspensions. The duration of the contractions is dependent on the physiochemical characteristics of the ingested meal. Generally, a meal of 450 kcal will interrupt the fasted state motility for about three to four hours. It is reported that the antral contractions reduce the size of food particles to ≤1 mm and prople the food through the pylorus. However, it has been shown that ingestible solids equal's to ≤7 mm can empty from the fed stomach in humans.

Figure No.3 Anatomical Sketch of Stomach



Physiology of Gastric Emptying

Before going into the requirements of gastric retention, we should know the physiology of gastric emptying. There are two distinct modes (i.e. fasted and fed) of gastrointestinal motility that consumes food in humans and animals. In fed state, the stomach handles liquids and solid materials in different ways. Liquid are emptied first within 30 minutes by the slow and sustained contractions of proximal stomach. The gastric emptying time of solids meal depends on the type, nutrition density, quality, and particle size of the meal. It can be extended to over 14 hours, if fed state conditions are maintained. Particles less than 5mm in diameter are known to be emptied by the contraction of the distal stomach following the emptying of liquids. Emptying of the solid digestible food particles larger than 5 mm is delayed until they are reduced in size by the grinding action of the stomach. Indigestible solids larger than 5mm in diameter are retained within the stomach until the digestive process is completed. The gastric emptying time for regular meal is about 2-6 hours.

Table No.2 The Transit Time Of Different Dosage Forms

Dosage Form	Transit Time (h)		
	Gastric	Small intestine	Total
Tablets	2.7±1.5	3.1±0.4	5.8
Pellets	1.2±1.3	3.4±1.0	4.6
Capsules	0.8±1.2	3.2±0.8	4.0
Oral solution	0.3±0.07	4.1±0.5	4.4

The emptying of large indigestible objects from the stomach is dependent on the contraction of the interdigestive migration motor complex (IMMC). The IMMC, which occurs in the fasted state, (i.e. the state in which the liquids and digestible solids foods

been cleared from the stomach completely), is characterized by three phase of myoelectric and motor activity.

Phase- I: Represented by the period of motor inactivity with only rare contraction lasts about 45 - 60 minutes.

Phase-II: Marked with random peristaltic activity with increased frequency and amplitude, lasts for over 30 - 45 minutes periods.

Phase-III: The active front represents the intense burst of action potentials and contractions with continue for 5 - 10 minutes.

This powerful electromechanical activity of phase III sweeps slowly from the stomach to the ileum and is responsible for emptying of indigestible debris left over from a meal. This is called the housekeeper wave of the GIT. The gastric emptying time for the conventional non-disintegrating dosages forms is mainly determined by the pattern occurs every 120 minutes in fast humans. Under the fasted condition, the gastric empty time of insoluble drug formulation is usually 1-2 hours. Consequently, for once a day oral drug delivery to be feasible, the gastric retention device must be constructed to overcome the peristaltic contraction associated with phase III of the IMMC.

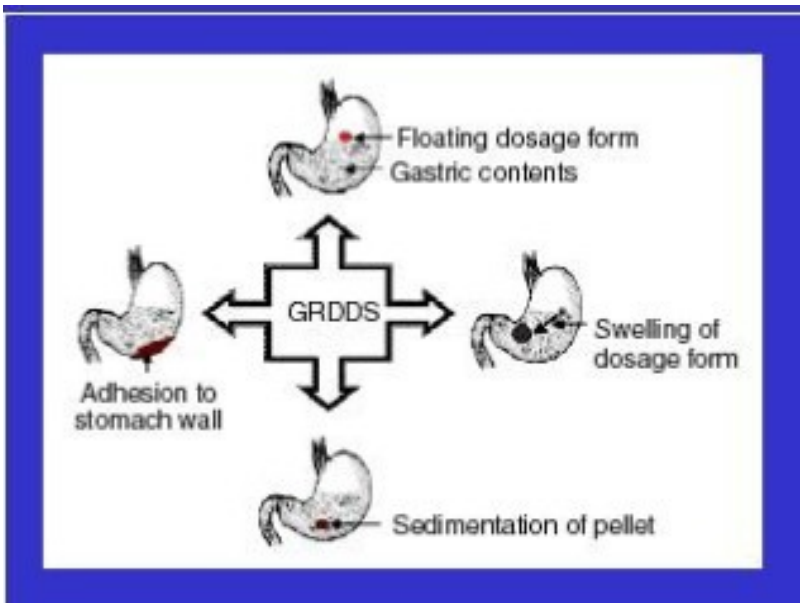
Requirement for Gastric Retention

From the discussion of the physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage from must be able to with stand the forces caused by peristaltic waves in the stomach and the constant contraction and grinding and churning mechanisms to function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the devices should be removed from the stomach with case.

Approaches to Gastric Retention

Various approaches have been followed to encourage gastric retention of an oral dosage form. Floating system has low bulk density so that they can float on the gastric juice in the stomach. The problem arises when the stomach is completely emptied of gastric fluid. In such a situation, there is nothing to float on.

Figure No.4 Various Approaches to Gastric Retention



Floating Systems Can Be Based on The Following:

- **Hydro dynamically balanced system**

  Incorporated buoyant materials enable the device to float.

- **Effervescent system**

  Gas-generating materials such as carbonates are incorporated. These materials react with gastric fluid and produce carbon dioxide, which allows them to float.

- **Low density system**

  Low-density system has a density lower than that of the gastric fluid so they are buoyant.

- **Biodhesive or mucoadhesive system**

  These system permit a given drug delivery system to be incorporated with bio/muco adhesive agents, enabling the device to adhere to the stomach (or other GI) wall, thus resisting gastric emptying. However, the mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

Multifarious Uses of Gastro Retentive Drug Delivery Systems[3]

Gastro retentive drug delivery system extends significantly the period of time over which the drug may be released. Thus, they not only prolong dosing interval, but also increase patient compliance beyond the level of existing controlled release dosage forms. This Gastro retentive dosage forms can be used carriers for drugs with so-called absorption window. These substances, for example antiviral, antifungal and antibiotic agent (sulphonamides, quinolones, penicillin's, cephalosporin's, amino glycosides and tetracycline etc., are taken up only from very specific sites of the GI mucosa. In addition, by continually supplying the drug to its most efficient site of absorption, the dosage forms allow for more effective oral use peptide and protein drugs such as calcitonin, erythropoietin, vasopressin, insulin, low-molecular-weight heparin, protease inhibitors and luteinising releasing hormone analogues.

Mechanistic Aspects of Gastro Retentive Drug Delivery Systems

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. This attempt includes introducing floating dosage forms (Gas-generating systems and Swelling or expanding system), mucoadhesive

systems, high-density system, modified shape systems, gastric-emptying delaying devices. Among these, the floating dosage forms have been used most commonly. However, most of these approaches are influenced by a number of factors that affect their efficacy as gastro retentive system.

Factors affecting gastric retention

1. **Density**

Gastric residence time is a function of dosage form buoyancy that is dependent on the density.

2. **Shape of dosage form**

Tetrahedron and ring shaping devices with flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better Gastric residence time 90 to 100percent retention at 24 hours compared with other shapes.

3. **Single or multiple unit formulation**

Multiple unit formulation show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profile or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms.

4. **Fed or unfed state**

Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migration myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that 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.

5. **Nature of meal**

Feeding of indigestible polymer 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, caloric content Gastric residence time can be increased by four to ten hours with a meal that is high in protein and fat

6. Frequency of feed

The gastric residence time can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.

7. Gender

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.

8. Age

Elderly people, especially those over 70, have a significantly longer GRT

9. Posture

GRT can vary between supine and upright ambulatory state of the patient.

10. Concomitant drug administration

Anti-cholinergics like atropine and propantheline opiates like codeine and prokinetics agents like metoclopramide and cisapride.

11. Biological factors

Diabetes and Crohn's disease, etc.,

1.3 TYPES OF GASTRO RETENTIVE SYSTEMS

Floating Drug Delivery Systems[3]

Floating drug delivery systems (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. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a

better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a 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, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability.

$$\mathbf{RW \text{ or } F = F_{buoyancy} - F_{gravity} = (Df - Ds)\ gV}$$

Where

RW - Total vertical force,

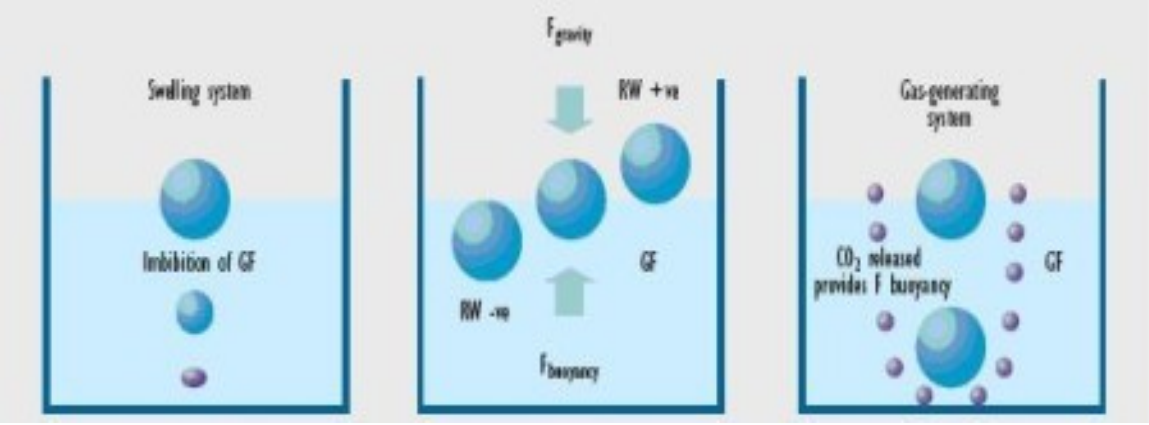
Df - Fluid density,

Ds - Object density,

V - Volume of the fluid,

g - Acceleration due to gravity,

Figure No .5 The Mechanism of Floating System



The FDDS Can Be Divided Into Two Different Categories

Non-effervescent systems- The device can float in the stomach due to swelling of the polymer and get density lower than that of gastric content.

Effervescent systems - The device can float in the stomach due to gas-forming agents.

Non-Effervescent Systems

The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose-type hydrocolloids, polysaccharides, and matrix forming polymers, such as polycarbonate, polyacrylate, polymethaacrylate, and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of the drug with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained release because the drug is slowly released by a controlled diffusion through the gelatinous barrier.

Sheth and Tossounian postulated that when such dosage forms come in contact with an aqueous medium, the hydrocolloid starts to hydrate by first forming a gel at the surface that controls the rate of diffusion of solvent in and drug out of the dosage forms.

Sheth and Tossounian developed SR floating tablets that hydro dynamically balanced in the stomach for an extended period of time until all the drug loading dose. Tablets were composed of an active ingredient and one or more hydrocolloids, such as methylcellulose, hydroxy ethyl cellulose, and sodium car boxy methylcellulose, which **up**

on contact with the gastric fluid provided water impermeable colloid gels barriers on the surface of the tablets.

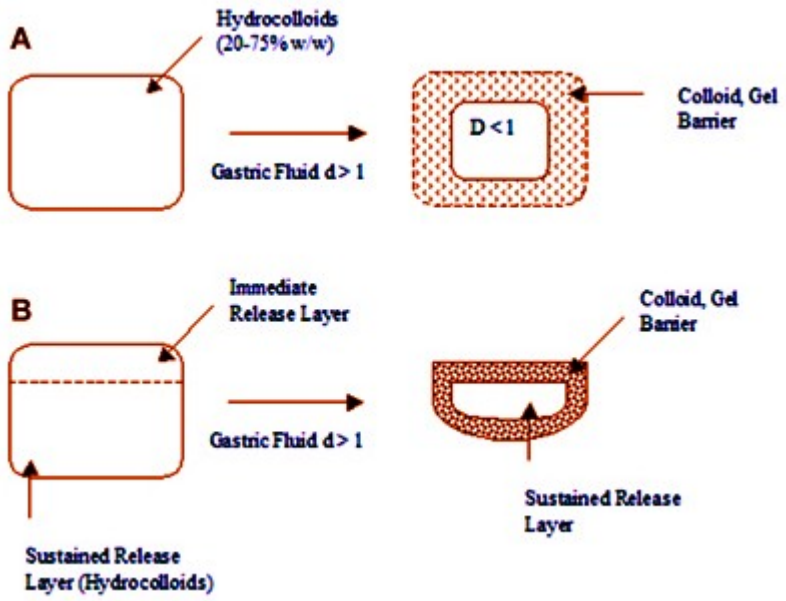
Harrigan described an intragastric floating drug delivery device, which was composed of a drug reservoir encapsulated in a micro porous compartment having pores along its top and bottom surfaces. The peripheral wall of the drug reservoir compartment was completely sealed to prevent any physical contact of the undissolved drug with the stomach wall. The floating chamber caused the system to float in the gastric fluid.

Kamel et.al., developed floating microspheres of ketoprofen using different ratios of Eudragit S 100 and Eudragit RL 100 by emulsion solvent diffusion technique.

Lee et.al,. Studied effected of non-volatile oil as a core material for floating microspheres Eudragit S 100 prepared by emulsion solvent evaporation method. They reported that microsphers prepared without non-volatile oil releases the drug faster compared with formulation with non-volatile oil.

Joseph et al developed a floating-type oral dosage of piroxicom based on hollow polycarbonate microspheres and performed *in vitro* and *in vivo* evaluation in rabbits. I et al studied the effect of hydroxymethylcellulose and carbopol on the release and floating properties of gastric floating drug delivery systems using factorial design. Strubel et al developed floating micro spheres based on low-density polypropylene foam powder.

Figure No.6 The Mechanism of Non-effervescent Floating System



Effervescent System

These buoyant systems utilize matrices prepared with swellable polymer like methocel, polysaccharides like chitosan, effervescent components like sodium bicarbonate, citric acid and tartaric acid for chamber containing a liquid that gasifies at body temperature. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethyl cellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbondioxied is released, causing the beads to float in the stomach (Figure No.5).Other approaches the material that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginates and sodium bicarbonate, a multiple unit floating pills that generate carbondioxide when ingested, floating mini capsule with a core of sodium bicarbonate, microcrystalline cellulose and polyvinyl pyrrolidone coated with hydroxyl propyl methyl cellulose and floating systems based on ion exchange resin technology etc.,

Recent developments include use of super porous hydro gels that expand dramatically (hundreds of times their dehydrated form within a matter of seconds) when immersed in water. Oral drug delivery formulations made from the gels would swell rapidly in the stomach to the intestines and be absorbed more efficiently by the body.

Table No .3 Drug Reported to Be Used in the Formulations of Floating Dosage Forms[4]

S. No	Dosage Form	Model Drugs
1.	Floating micro spheres	Ketoprofen, Piroxicam, Verapamil HCl, Cholestyramine, Tranilast, Ibuprofen, Aspirin, Griesofulvin, and p-Nitroaniline, Terfenadine, Theophylline, Ketoprofen, Cinnaxicam, and Tenaxicam, Riboflavin, ,Salicylic acid, Ethoxybenzamide,, Acetohydroxamic acid.
2.	Floating granules	Diclofenac sodium, Indomethacin and Prednisolone
3.	Floating capsules	Misoprostol, Chlordiazepoxide Hcl, Propranolol Hcl, Diazepam, Furosemide, Misoprostol, L-Dopa and Benserazide, Ursodeoxycholic acid
4.	Floating tablets	Theophylline, Chlopheneramine maleate, Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxycillin trihydrate, Riboflavin-5-phosphate Isosorbide di nitrate, Atenolol, Diltiazem, Fluorouracil, Isosorbide mononitrate, Para-benzoic acid, Piretamide,Theophylline and Verapamil Hcl
5.	Floating Pellets	Verapamil and Nor-verapamil
6.	Floating Powders	Several basic drugs

Excipients used most commonly in these systems include HPMC, Polyacrylate polymer, polyvinyl acetate, Carbopol, Agar Sodium alginate Calcium chloride, Polyethylene oxide and Polycarbonates.

Table No.4 Marketed Products of GRDDS [4]

S.No	**Brand Name**	**Delivery System**	**Drug(with dose)**	**Company Country**
1.	Madopar	Floating CR Capsules	Benserazide(25mg), L-Dopa(100mg)	Roche Products,USA
2.	Valrelease	Floating Capsules	Diezepam(15 mg)	Hoffmann-LaRoche,USA
3.	Liuqid Gaviscon	Effervescent floating liquid alginate preparation	Al hydroxide(95mg) Mg carbonate (358mg)	Glaxo SmithKline, India
4.	Topalkan	Floating liquid alginate preparation	Al-Mg antacid	Pierre Fabre Drug, France.
5	Almagate Float Coat	Floating dosage form	Al-Mg antacid	-
6.	Conviron	Colloidal gel forming FDDS	Ferrous sulphate	Ranbaxy, India
7.	Cifran OD	Gas-generating floating form	Ciprofloxacin(1gm)	Ranbaxy, India
8.	Cytotec	Bilayer floating capsule	Misprostol(100mcg/ 200mcg)	Pharmacia, USA

Bio Adhesive Systems

Bioadhesive drug delivery systems (BDDS) are used to localize a delivery device within the lumen to enhance the drug absorption in site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach. A microbalance-based system is reported for measuring the forces of interaction between the GI mucosa and the individual polymers, and the Cahn Dynamic contact Angle Analyzer has been used to study the adherence. Gastric mucoadhesion does not tend to be strong enough to impart the dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastro retentive force. Some of the most promising excipents that have been used commonly in these systems include polycarbophil, carbopol, lectin, chitosan, CMC and gliadin, etc., Some investigators have tried out a synergistic approach between floating and bioadhesion systems. Other approaches reported include used of a novel adhesive material derived from the fimbriae (Especially Type1) of bacteria or synthetic analogues combined with a drug to provide for attachment to the gut, thereby prolonging the transit time, a composition comprising a n active ingredient and a material that acts as a visogenic agent (for example curdlan and/or a low substituted hydroxypropylcellulose) etc.,

High-Density Systems

Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3 g/cm^3) trapped in rugae also ten to withstand the peristaltic movements of the stomach wall. With pellets the GI transit time can be extended from an average of 5.8 - 25 hours, depending more on density than on diameter of the pellets, although many conflicting reports stating otherwise also abound in literature. Commonly

used excipents are barium sulphate, Zinc oxide, titanium dioxide and iron powder etc. These materials increase density by up to 1.5 - 2.4 g/cm^3. However, no successful high-density system has made it to the market.

Large Single- Unit Dosage Form with Special Shapes

These dosage forms are larger than the pyloric opening and so are retained in the stomach. Certain elastomers or plastics made from polyethylene or nylon could increase the gastric retention time. Tetrahedrons (each leg 2 cm in length) and ring (3.6 cm in diameter) provided gastric retention than 24 hours. These dosage forms, however, were neither digestible nor easy to load and release drugs. There are some drawbacks associated with this approach permanent retention of rigid large-sized single-unit forms can cause bowel obstruction, intestinal adhesion and gastroplasty

Magnetic Dosage Forms

This type of dosage forms is formulated by mixing with ferrite powder with other excipients. After administration, these tablets were retained in the stomach by an externally applied strong magnetic field. The strong magnetic field, however, is not readily available in practical use.

Balloon Devices

These devices comprises of collapsed envelope containing a liquid, such as n-pentane converting to a gas at body temperature. The device can expand to a size larger than the pyloric canal for retention in the stomach. Instead of low - boiling point organic solvents, osmotic agents can be used to inflate the envelope. This approach, while effective, is not easy to implement.

Highly Swelling Hydrogel Dosages Forms

Hydro gels can be retained in the stomach by swelling to size larger of the pyloric canal. Although a hydro gel can swell to hundreds of times its dried size, it swelling is very slow. Its takes several hours before it reaches a size large enough to be retained in the stomach. Because the cyclic IMMC movement occurs every 2 hours, the hydro gel is most likely to be expelled from the stomach before it swells to required size. Thus hydro gels should posses a fast swelling property to be useful as a gastric retention device.

Co-Administration of Gastric-Emptying Delaying Drugs

This concept of simultaneous administration of a drug to delay gastric emptying together with a therapeutic drug has not received the favour of clinicians and regulatory agencies because of the questionable benefit-to-risk ratio associated with these devices.

Advantages of Prolonged Gastric Retention on Dosage Forms

1. Prolonging the gastric retention of dosage forms provide therapeutic benefits such as local treatment and enhanced bioavailability.
2. Reduce drug wastages.
3. One group of drugs that would benefit form retentive formulations is those are absorbed in a relatively narrow region in the proximal part of the gastrointestinal tract.
4. Drugs that are less soluble in the higher pH environment of the small intestine than in the stomach may also benefit from gastric retention.
5. Another application of gastric retentive devices is for local delivery to the stomach and proximal, small intestine.

Advantages of Floating Dosage Forms

1. Floating dosage forms offers various future potential as evident form several recent publications. The reduced fluctuations in the plasma level of drug results from delayed gastric emptying.
2. Drugs that have poor bioavailability because of their limited absorption to the upper gastro intestinal tract absorption and improving their absolute bioavailability.
3. Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.
4. The floating concept can also be utilized in development of various anti-reflux formulations.
5. Developing the control release system for drugs, which are potential to treat Parkinson's diseases.
6. To explore the eradication of Helicobacter pylori by using the narrow spectrum antibiotic

Limitations of Floating Drug Delivery System

1. The major disadvantage of floating systems is requirement of a sufficiently high level of fluid in the stomach for the drug. However this limitation can be overcome by coating the dosage form with the help of bioadhesive polymers that easily adhere to the mucosal lining of the stomach.
2. The dosage form should be administered with a minimum of glass full of water (200 - 250 ml)
3. Floating system is not feasible for those drugs that have solubility or stability problems in gastric fluids.
4. Some drugs present in the floating system causes irritation to gastric mucosa.

Table No.5 Patents of Some Floating Delivery Systems [4]

S. No	US Patent Number	Patent Title
1.	6,207,197	Gastroretentive controlled-released microspheres for improved drug delivery
2.	5,972,389	Gastricretentive, oral drug dosage form for the controlled release of sparingly soluble drugs and insoluble matter
3.	5,443,843	Gastric retention system for controlled drug release
4.	5,232,704	Sustained-release,bilayer buoyant dosage form
5.	5,169,638	Buoyant controlled release powder formulation
6.	4,814,179	Floating sustained –release therapeutic compositions
7.	4,767,627	Drug delivery device that can be retained in the stomach for a controlled period of time
8.	4,167,558	Novel sustained – release formulation
9.	4,140,755	Sustained – release tablet formulation
10.	4,126,672	Sustained – release pharmaceutical capsules

1.4 Tablets [5]

Among all the oral administered forms of dug the tablet are most conventional both from the point of view of the patient as well as the manufacturer. The tablets are the unit dosage forms these are mainly spherical in shape but the shape can be round, oval, oblong etc., these are manufactured by the compression and compaction of the granules and other additives. Tablets have the following advantages along with all advantages of solid dosage form.

Advantages of Tablets:

1. Ease of handling: The tablet unique the liquid they do not require more space for storage.
2. Transportation: The drug when present in the Tablet can be easily transported from one place to another.
3. Less prone to Microbial Infections: These drugs have a definite dose and the accuracy is maintained. This dose accuracy is not maintained in liquid dosage form.
4. Tamper proof: Tablet can not be easily tampered or they are less prone to adulteration as compared to their liquid dosage forms.
5. Ease of Manufacturing: Manufacturing of Tablet is not as complicated and costly as the
6. Liquid dosage form.
7. Their cost is lowest of all the oral dosage forms.
8. They are the lightest ad most compact of all the dosage forms.
9. They are in general the easiest and cheapest to package and ship of all other dosage forms.
10. Product identification is simplest and cheapest when employing an embossed or monogrammed punch.
11. They provide the case of swallowing with least tending to hang up especially above the stomach.

12. They lend themselves o certain special release profile such as enteric coated or delayed release products.
13. They are later suited to large scale productions the other unit oral forms.
14. Greatest dose precision and the least content variability.

Disadvantages

1. Some drugs resist compression into dense compact owing to their amorphous nature or flocculent, low density character.
2. Drugs with poor wetting, and slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still associate adequate or full dug bioavailability.
3. Bitter tasting drug with an objectionable odor or that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment.
4. They do no give maximum bioavailability in the same duration in which the liquids achieve maximum plasma levels.

Properties of Tablets

1. Tablets should be an elegant product having own identity which being free of defect. Such as chips, cracks, discoloration, contaminant etc.,
2. Should have the strength to withstand the rigors of mechanical shocks encountered in its production, packaging, shipping etc.,
3. Should have the chemical and physical stability to maintain its physical attribute over times.
4. It should be able to release the medicinal agent in predictable and reproducible manner.
5. Must have a suitable chemical stability over time so as not to allow alteration of the medicinal agents.

Types and Class of Tablets

The tablets an be classified by their

1. Route of administration or functions.
2. By the type of drug delivery system they represent within that route.
3. By the form and method of manufacture.

Tablets ingested orally:

- Compressed Tablets or Standard Compressed Tablets
- Multiple Compressed Tablets
- Sugar Coated Tablets
- Film Coated Tablets
- Gelatin Coated Tablets
- Enteric Coated Tablets
- Buccal or Sublingual Tablets
- Lozenges or Troches
- Chewable Tablets
- Effervescent Tablets
- Molded Tablets
- Tablet Triturates
- Hypodermic Tablets
- Immediate Release Tablets
- Vaginal Tablets
- Modified Release Tablets

Floating Tablets

Floating systems: These systems are retained in the stomach and are useful for drugs that are poorly soluble or unstable in intestinal fluids. The underlying principle is very simple. One attempts to make the dosage form less dense than the gastric fluids so that it can float on them. The density of the system can be reduced by incorporating a number of low density fillers into the systems such as hydroxyl cellulose, lactates or microcrystalline cellulose. However, this system is not ideal because its performance is highly dependent on the presence of food and fluid in the stomach. It is not reliable and is highly variable. The basic idea behind the development of such a system was to maintain a constant level of drug in the blood plasma inspire of the fact that the drug dose not underage disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a predetermined rate to release the drug from the dosage form and maintain constant drug levels in the blood. The concept of floating tablets is mainly based on the matrix type drug delivery system such that the drug remains embedded in the matrix which after coming in contact with the gastric fluid swells up and the slow erosion of the drug without disintegration of the tablet takes place. Sometimes for generating a floating system we even need to add some effervescent or gas generating agent which will also ultimately reduce the density of the system and serve the goal of achieving a floating system for onward drug delivery.

These systems have particular advantage that they can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the G.I. tract. There systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.

Several approaches are currently used to prolong the gastric retention time. These include floating drug delivery systems also known as hydro dynamically balanced systems, polymeric bio-adhesives systems, modified shape systems, high density systems and other delayed gastric emptying devices, The principle of buoyant preparation offers a

simple and practical approach to achieve increased gastric gastric residence time for the dosage form and sustained drug release.

Formulation of Floating Tablets

Non-effervescent System

Commonly used excipients, here are gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming polymers such as polycarbonate, polyacrylate, polymethacrylate and polystyrene. One of the approaches to the formulation of such floating dosage forms involves intimate mixing of drug with a gel forming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier.

The air entrapped by the swollen polymer confers buoyancy to these dosage forms. The gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier.

Effervescent System

This Buoyant Delivery System is prepared with swellable polymers such as methocel or polysaccharide e.g.chitiosan and effervescent component e.g. sodium carbonate e.g. sodium bicarbonate, citric or tartaric acid or matrices containing chamber of liquid that gasify at body temperature. The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the gelyfied hydrocolloid. This produces upward motion of the dosage form and maintains its buoyancy. The carbon dioxides generating components may be intimately mixed within the tablet matrix to produce a single-layered tablet or a bi-layered tablet may be compressed which contains the gas generating mechanism in one

hydrocolloid containing layer and the drug in the other layer formulate for the sustained release effect. The floating dosage forms are kept in the stomach for extended periods of time the therapeutics agents not immediately released after ingestion. Controlled release of such therapeutic agents from the dosage forms prevents enzyme saturation thereby improving the biovailability of such therapeutics agents. So it improves the biovailability of by administering such therapeutic agent in a floating dosage form.

Excipients for Floating Tablets

1. Hydrophilic Polymers: Hydroxy propyl methyl cellulose (Metolose)
2. Gel forming hydrocolloids Matrix Formers: Polyacrylate, Polymethacrylate, Polycarbonate, Polystyrene
3. Swellable polymers used in Effervescent Systems: Chitosan and Sodium bicarbonate and Citric acid or Tartaric acid
4. Matrix forming polymers: HPMC, Polysaccharides, Carageenan gum, Gum Arabic
5. Fillers: Lactose, Microcrystalline cellulose
6. Lubricants: Magnesium stearate, Purified talc
7. Buoyancy agents: Hydrocolloids, Sodium bicarbonate and Citric acid or Tartaric acid
8. Porosity Agents: Lactose

1.5 Asthma Management [6]

Asthma remains one of the most common diseases, affecting an estimated four to five percent of the population. It perhaps the only common treatable condition that is increasing in terms of prevalence, severity and mortality. Intensive research over the fast decades has significantly enhanced our understanding of the pathophysiology of asthma. This has also expanded the scope for new therapies; consequently the management of asthma has undergone a remarkable transformation resulting in more effective use of existing therapies.

The introduction of inhaled beta 2 adrenergic agonist, which remains the most useful bronchodilators, has been an important landmark in asthma therapy. However the development of inhaled anti-inflammatory therapy (corticosteroids) has an even greater impact. The drugs act on the all-important inflammatory component the root cause of asthma.

Figure No.7 (a) Asthma prevalence world wide

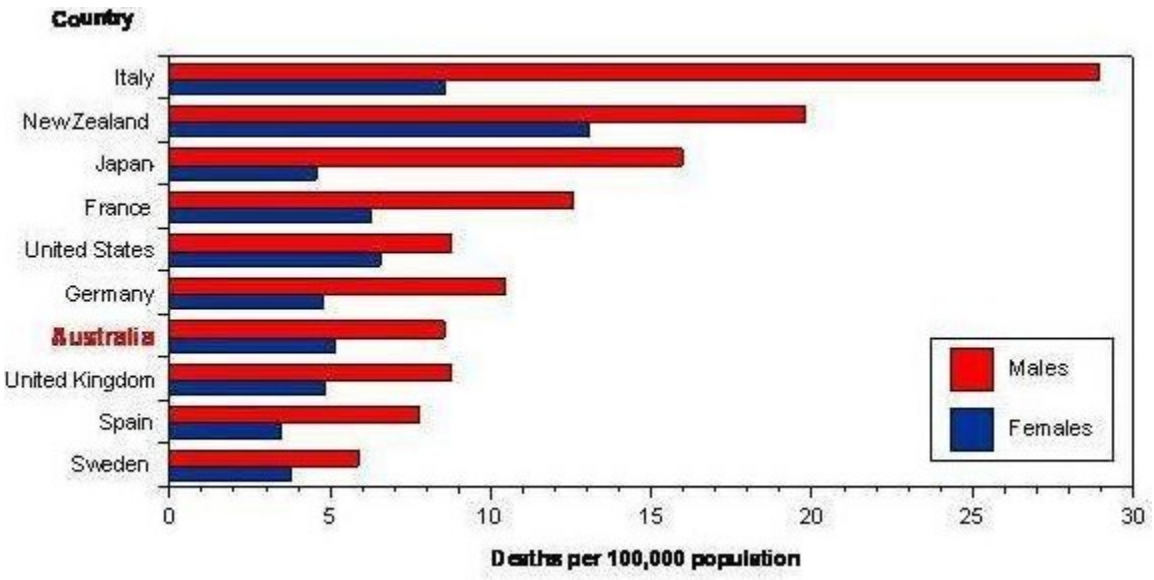
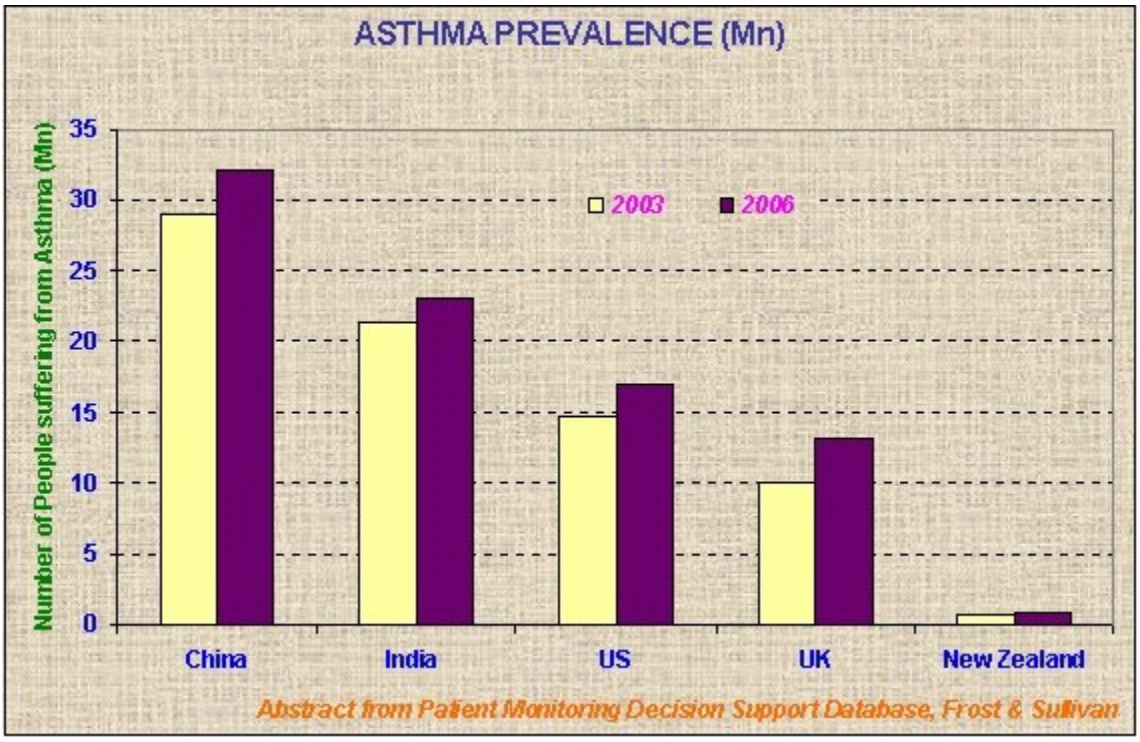


Figure No.7 (b) Asthma prevalence world wide

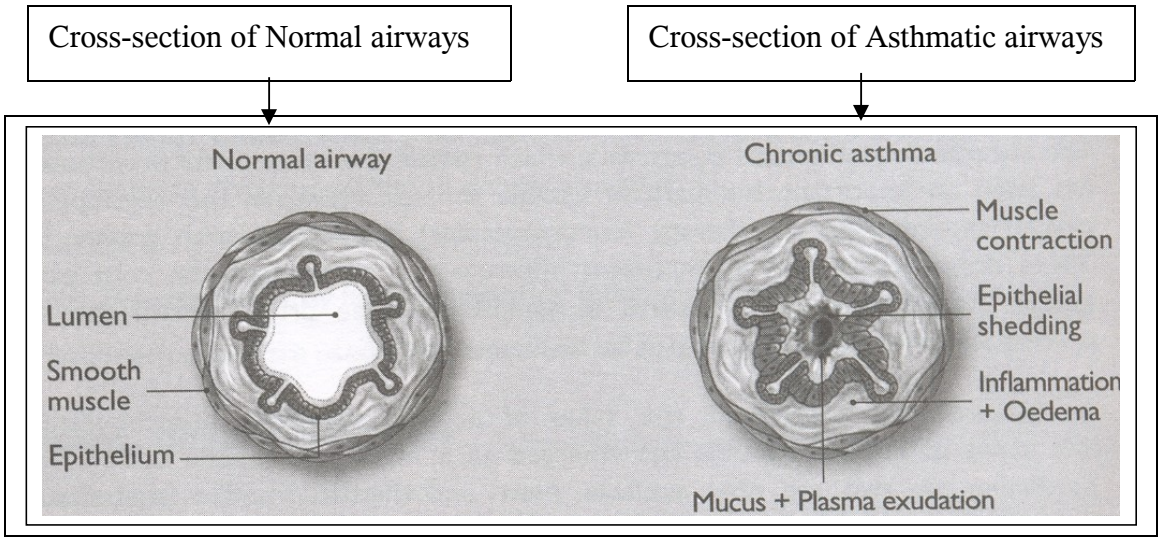


Asthma

Definition

Asthma is a reversible obstructive airway disease (ROAD) characterized by bronchial hyperactivity (BHR).

Mechanism of Bronchial Obstruction in Asthma



Asthma is related to atopy. Atopy is a familial tendency to develop hypersensitivity after exposure to allergens. It is an autosmal dominant trait. Atopic individual frequently suffer from allergic Rhinitis, bronchial asthma, atopic dermatitis, eczema or urticaria. These disorders, mediated by immunoglobulin E (Ig E). Atopic do not develop the disease. What causes atopic individual to develop is not exactly known.

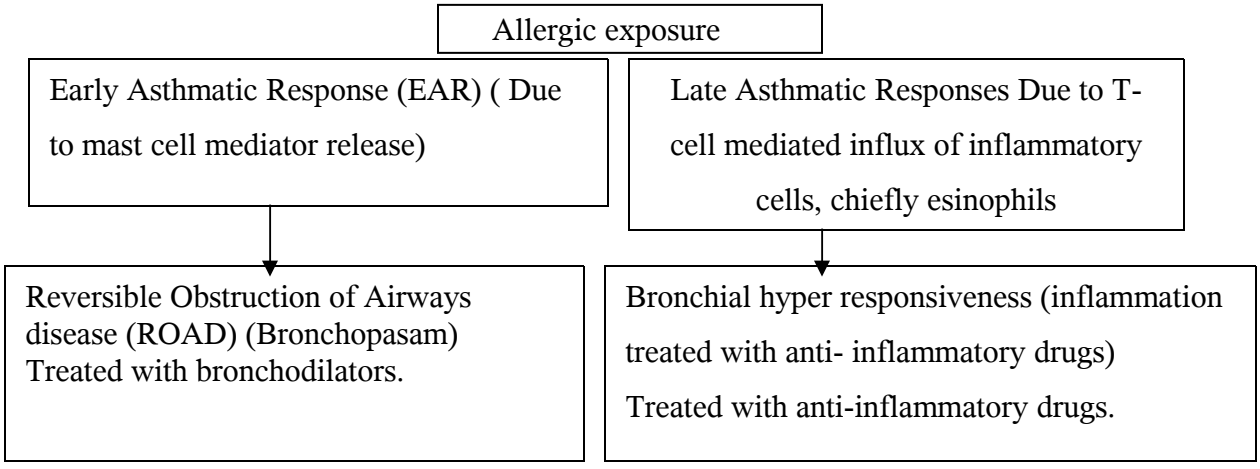
Development of Asthma

Atopic individual are to sensitized after an exposure to allergens and develops Ig E antibodies, subsequently exposure to an allergens causes a dual response, which is protracted and more severe.

Components of Asthma

1. ROAD (Bronchopasam), which can be reversed with bronchodilators.
2. BHR due to inflammation (which predisposes patients to recurrent bronchospasm with minor triggers like exercise, smoke, dust exposure etc.,). This is treated best with anti-inflammatory drugs such as corticosteroids.

Mechanism of Asthma Development



Triggers

1. Allergic

a) Allergen

Inhaled eg. Dust, pollen, house dust mice (carpets, drapes and soft toys). Animal dender (pets) fungi, molds and spores, cockroaches.

b) Additives in foods

Tartrazine yellow dye as a colouring agent.

Met bisulphate preservative used in beers, wines and preserved foods.

c) Occupational allergens e.g. Grain dust, wood dust.

II. Non Allergic

a) Infection, mainly viral.

b) Exercise.

c) Emotions e.g. Extreme joy, sorrow

d) Change in environmental temperature, humidity, gra

Other causative agents

1. Gastro-oesophageal reflux disease (GERD).
2. Rhinits, Sinusitis, post-nasal drip.
3. Aspirin/NSAID sensitivity.
4. Beta-blockers
5. Discontinuation or irregular use of preventive therapy.

Management of Asthma

1. Allergen avoidance
2. Pharmacotherapy
3. Immunotherapy

Allergen Avoidance

Prevention consists of avoidance of allergens and provoking factors. A detailed and appropriated history should help in identifying the Dust free atmosphere in the house or work place. Keeping minimum furniture, avoiding carpets using wet mopping or vaccum can do this. Cleaning and making use of mattresses or pillows.

Immunotherapy

Immunotherapy by use of allergen injection was introduced in the early 20 th century. In North America, it was the treatment of choice for allergic Rhinitis and Asthma. In United Kingdom, however it was never widely use, perhaps due to availability of selective beta -agonist and inhaled steroids 15 year before they would be prescribed in US. Recent recommendations do not advise allergen-injection immunotherapy for asthma due to the uncertain efficacy multiplicity to the allergens and potential for serious side effect.

Pharmacotherapy

The pharmacotherapy of asthma consists of two basic classes of medication, quick-relief and long-term preventive medication.

1. **Quick- relief medications**

   Otherwise called Relievers, bronchodilators that gives immediate relief of symptoms, but their affect does not last for none than 4 to 6 hours eg. Salbutamol

2. **Preventer (Long term preventive medication)**

   Will not give immediate relief, but when given over prolonged periods of time will control the asthma better and prevent further attack. The anti-inflammatory glucocorticosteroids are most important in this class of medication.

Asthma management today focuses on the judicious and adequate usage of preventive medication so that minimal or nil usage of quick-relief medication is required.

TableNo.6 Class of Drugs Used For Management of Asthma

S.No	Relievers	Preventers
1.	**Short acting beta 2 agonist** E.g. Salbutamol, Terbutaline, Levo-Salbutamol	**Corticosteroids** E.g. **Oral** Prednisolone, Betamethasone, **Inhaled** Fluticasone, Budesonide, Beclomethasone
2.	**Anti-cholinergic** Iprtropium bromide,	Long acting beta 2 agonist **Inhaled** Salbutamol, Formeterol **Oral** Sustained release dosage form Salbutamol, Terbutaline,Bambuterol
3.	**Short acting Theophylline**	**Combination therapy** Fluticasone and Salmeterol Budesonide and Formeterol
4.	Adrenaline injection	**Leukoterine modifier** Montilukast Zafirlukast
5.	-	**Mast cell stabilizer** Sodium chromo glycolate

V. F. Patel et. al., [7] (2007) Statistical evaluation of influence of viscosity of polymer and type of filler on Dipyridamole release from floating matrix tablets. The study investigates the influence of viscosity of HPMC and types of filler on dipyridamole release from floating matrix tablets.

Dave B.S, Amin AF et. al.,[8] (2007) Gastro retentive drug delivery system of ranitidine hydrochloride formulation and invitro evaluation, the floating tablet were formulated by using guar-gum, xanthangum, HPMC, by gas forming agent and also studied the effect of stearic acid and citric acid on the drug release profile and floating profile was investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature, the result showed that low amount of citric acid and high amount of stearic acid favor sustained release of ranitidine hydrochloride from the gastro-retentive formulation.

V.F Patel et.al.,[9] (2005) Studies on formulation and evaluation of ranitidine floating tablets. Present investigation highlights the formulation and optimizations of floating tablets of ranitidine hydrochloride, formulation were optimized for type of filler, polymer was used. Study revealed the type of filler had significant effect on the release of drug from the hydrophilic matrix tablets and floating properties.

J.Goole et.al., [10] (2007) Development and evaluation of new multiple-unit Levo-dopa sustained-release floating dosage forms by melt granulation. The investigation shows mini tablet composition and mini tablet diameter had the grate influence on the drug release. This was sustained for more than 8 hours.

Xu Xiaogiang et.al., [11] (2006) Floating matrix dosage form for Phenorporlamine Hcl based on Gas-forming agent. The study has investigated the release of a highly aqueous soluble drug, Phonorporlamine form a gastric retention based on floating matrix tablets.

Garg S. Sharma.S et.al., [12] (2003) Gastro retentive drug delivery systems, the size and shape of the dosage unit also affect the gastric emptying. The tetrahedron and ring shape device have better gastric residence time as compared with the other shape.

Nur Ao, Zhang J.S et.al., [13] (2000) Captopril floating and or bio adhesive tablet, design an release kinetics. Developed floating tablets of captopril using HPMC (4000, 5000 cps) and carbopol 934 invitro buoyancy studies revealed that tablet of 2 kg/cm^2 hardness after immersion into the floating media floated immediately and the tablets with hardness 4 kg/cm^2 sank for 3 to 4 minutes and then came to the surface. Tablet in both cases remained floating for 24 hours. The tablet with 8-kg/cm^2 hardness shows no floating capability. It was concluded that the buoyancy of the tablet is governed by both the swelling of the hydrocolloids particles on the tablet surface when it contact the gastric fluids and presence of internal voids in the center of the tablet. a prolonged release from these floating tablet was observed as compared with the conventional tablets and 24 hours controlled release from the dosage from of captopil was achieved.

EI-Glibaly I et al., [14] (2002) Prepared and evaluated floating chitosan microcapsules for oral use by comparing with non-floating chitosan microcapsules. Floating microcapsules containing melationi were prepared by the ionic interaction of chitosan and a negatively charged surfactant, sodium diethyl sulfosuccinate and evaluated for its drug release and floating tendency by comparing with non floating microcapsules.

Rouge N et al.,[15] (1998) Studied the pharmacokinetic parameters of floating multiple- unit capsule, a high-density multiple-unit capsule and immediate –release tablet containing 25 m atenolol. Atenolol was chosen as a model drug because of its poor absorption in the lower gastrointestinal tract. The bioavailability of the two-gasroretentive preparations with sustained release characteristics was significantly decreased when compared to the immediate-release tablet. This study concluded that it was not possible to increase the bioavailability of a poorly absorbed drug such as atenolol using gastro retentive formulations.

Manuel Efentakis et al., [16] (2000) Developed and Evaluated Oral Multiple-unit and Single-unit Hydrophilic Controlled-release Systems using furosemide as model drug. This study compared the release behavior of single-unit release systems of furosemide by using two hydrophilic swellable polymers sodium alginate (high viscosity) and carbopol 974 p. Swelling and erosion experiments showed a high degree of swelling and limited erosion or the carbopol preparation, Whereas less swelling but greater erosion was observed for the sodium alginate preparations. It is concluded that all three carbopol dosage forms (single and multiple-unit) displayed similar release behavior while sodium alginate dosage forms displayed a different and more distinctive behavior. This shows polymer characteristics influence the drug release.

A.Streubel et al., [17] (2003) Developed a new preparation method for low density foam-based, floating micro particles and to demonstrate the systems' performance invitro. The prepared floating micro particle consisting of polypropylene foam powder, model drug chlorpheniramine maelate, diltiazem Hcl, theopylline or verapamil Hcl and polymer (Eudragit RS or polymethyl methacrylate (PMMA) by soaking the micro porous foam carrier with a organic solution of drug and polymer and subsequent drying. And they studied the effects of various formulation and processing parameters on the resulting in vitro floating behavior, internal and external particle morphology, drug loading, invitro drug release and physical state of the incorporated dug. They concluded that all the formulation shows good floating behavior as well as shows a broad variety of drug release pattern.

Umamaheswari RB et al., [18] (2003) studied a new approach in gastro retentive drug delivery system using cholestyramine. They prepared cellulose acetate butyrate coated cholestyramine microcapsules endowed with floating ability due to the carbon dioxide generation when exposed to the gastric fluid. These microcapsules also have a mucoadhesive property. And loaded particle in ion exchange resin. The studied the effect of cellulose acetate butyrate: drug resin ration (2:1, 4:1, 6:1 w/w) on the particle size, floating time and drug release. And it was concluded that the buoyancy time of the

cellulose acetate butyrate-coated particles and it shows good mucoadhesive property. They suggest that cellulose acetate butyrate micro particles could be a floating as well as a mucoadhesive drug delivery systems.

Inouye K et al., [19] (1988) Prepared and studied buoyant sustained release tablets based on chitosan. Two kinds of chitosan with different degrees of deaetylation Chitosan H and L) were used, and two types of preparations (type A and B) were examined using prednisolone as model drug. Type A is direct compressible tablets using sodium bicarbonate and citric acid and Type B is direct compressible layer of chitosan H enclosing sodium bicarbonate. The study concluded that Type B preparation gives quick buoyancy and a good sustained release of drug when compared to the Type A preparation.

Sato Y et al., [20] (2003) Performed in vivo evaluation of riboflavin-containing micro balloons for floating controlled drug delivery system in healthy human volunteers. Microballons were prepared by emulsion solvent diffusion method utilizing enteric acrylic polymer dissolved in a mixture of dichloromethane and ethanol. Riboflavin powder, riboflavin-containing microballons, and riboflavin-containing non-floating micro spheres wee administered orally to each of three healthy volunteers. Riboflavin pahrmacokinetics was investigated via analysis of urinary excretion of riboflavin. It was concluded that riboflavin containing microballons shows good floating property and a efficient sustained release compared to the other preparations.

John T. Fell et.al., [21] (2000) Prepared and evaluated amoxycillin release from a floating dosage form based on alginates. The study has investigated the release of soluble drug, amoxyicillin tri hydrate from a gastric retentive system based on alginates.

Shoufeng Li et al., [22] (2001) Studied the statistical optimization of gastric floating system for Oral Controlled Delivery of calcium properties, Optimization of the formulation was calcium, a very important building mineral for our bones, is absorbed

primarily in the duodenum as a result of the presence of active absorption sites (calcium binding protein) in the upper GI tract. The development of an optimized gastric floating drug delivery system us described by statistical experimental design and data analysis using response surface methodology. A central, composite Box-Wilson design for the controlled release of calcium was use with formulation variables Hydroxyl propyl methyl cellulose loading, Citric acid loading, and Magnesium stearate loading. Dissolution studies and floating kinetics wee performed on these formulation and data are fitted to power law. It was concluded that all three-formulation variable were found to be significant for the release properties ($p<0.05$), while only HPMC loading was found to be significant for floating properties.

Sunil K.Jain et al., [23] (2005) Prepared calcium silicate based microspheres of repaglinide as gastro retentive floating drug delivery and carried out invitro evaluation, The calcium silicate microsphere are prepared by emulsion solvent diffusion technique consisting of calcium silicste as porous carrier, repaglinide , an oral hypoglycemic agent and Eudragit S as polymer. Various parameters where evaluated and physical stare of the incorporated drug was studied. Encapsulation efficiencies close to 100% was achieved by varying either the ratio amount of ingredients volume of the organic phase or the relative amount of polymer. In all cases, good invitro floating behavior was observed. The release rate increased with increasing drug loading and with decreasing polymer amounts. The type of polymer significantly affected the drug release rate, which increased in the following rank order: PMMA<EC<Eudragit RS.

Choi B.Y. et al., [24] (2002) Prepared alginate beads as floating drug delivery system and studied the effect of CO_2 gas forming agents. Floating beads were prepared from a sodium alginate solution containing $CaCO_3$ or $NaHCO_3$ as gas forming agents. The effects of gas forming agents on bead size and floating properties were investigated. The study concluded that $CaCO_3$ in superior to $NaHCO_3$ as a gas forming agent in alginate bead preparations. The enhanced buoyancy and sustained release properties of $CaCO_3$ - containing beads make them an excellent candidate for floating drug dosage systems (FDDS).

EI-Kamel A.H.et al,. [25] (2001) Prepared and evaluated ketoprofen floating oral delivery system. Floating micro particles were prepared by emulsion-solvent diffusion technique. Four different ratios of Eudragit S100 (ES) with Eudragit RL (ERL) were used to form the floating micro particles. All floating micro particle formulations showed good flow properties and packability. It is concluded that release rate were generally low in 0.1 N HCL especially in presence of high content of ES while in phosphate buffer pH 6.8, high amount of ES tended to give a higher release rate. The formulation containing ES:ERL exhibiting high percentage of floating particles in all examined media.

Y.Murata et al., [26] (2000) Prepared floating alginate beads using metronidazole as model drugs. Two types of alginate beads containing vegetable oil and chitosan were prepared and drug is loaded. The preparation are compared and evaluated. The concentration of drug at the gastric mucosa after administration of chitosan beads was higher than that in the solution, though the drug serum concentration was the same regardless of which type of gel was administered. It is concluded that the release properties of alginate gels are applicable not only for sustained release of drugs but also for targeting the gastric mucosa.

A.K. Hilton et al., [27] (1992) Studied in- vitro and in-vivo evaluation of an oral sustained-release dosage form of Amoxicillin Trihydrate. Various hydrophilic polymers were investigated for the preparation of amoxicillin trihydrate sustained-release tablets. The study concluded that further formulation to enhance gastric retention time (GRT), by incorporation of gas-generating system, yielded either bilayer tablets that prematurely failed or large single –layer which remained buoyant for 6 hours and had satisfactory invitro sustained release of the drug.

S.Sangekar et al., [28](1987) Evaluated the effect of food and specific gravity of tablets on gastric retention time. In this study the effect of food and specific gravity on the gastric retention time of floating (spec. grav. 0.96) and non-floating (spec. grav. 1.59) tablet formulation was investigated using gamma scitigrapy in humans. The results obtained indicate that the presence of food in the stomach appears to significantly prolong gastric retention of both the floating and non-floating tablets while specific gravity does not seem t play and important role in the residency time of the tablets in the stomach.

Pronsak Sriamornsak et al., [29] (2004) Studied the morphology and buoyancy of oil-entrapped calcium pectinate gel beads. Anew emulsion-gelation method to prepare oil-entrapped calcium pectinate gel beads capable of floating in the gastric condition was designed and tested. The type and percentage of oil-entrapped CaPG beads were promising as a carrier for intragastric floating drug delivery.

Talukder R et al., [30] (2000) Studied on various attempts to develop gastro retentive delivery systems through floating, swelling, mucoadhesive, and high-density systems to increase gastric retention time of the dosage forms was studied and the differences in gastric physiology, gastric pH and gastric motility in both intra as well as inter subject variability, significant impacts on gastric retention time and drug delivery behavior was found to be investigated.

Streubel A et al., [31] (2000) Prepared and evaluated of floating microparticles based on low-density foam powder was studied. The study developed a novel multiparticulate gastro retentive drug delivery system and to demonstrate its performance in vitro. Floating microparticles consisting of polypropylene foam powder, verapamil Hcl as model drug, Eudragit RS, ethyl cellulose or polymethamethacrylate as polymers were prepared with an O/W solvent evaporation method. The various formulations and processing parameters on the internal and external particle morphology, drug loading, in vitro floating, in vitro drug release kinetics, particle size distribution and physical state if the incorporated drug was studied.

Arora J et al., [32] (2004) Studied the development and evaluation of floating drug delivery system for cefecoxcib using hydrocolloids to increase the gastric residence time of the celecoxcib in gastro intestinal tract and Eudragit RS 100, REO WSR 60 K were found to have good buoyancy , and it is suitable for floating drug delivery.

Archana et al., [33] (2004) Studied celecoxib multi-unit controlled release gastro retentive drug delivery systems. It was prepared by microencapsulation of drug and swellable polymer along with gas generating agent for prolonged residence in the stomach and controlled release of the drug.

Muthusamy K et al., [34] (2005) Prepared and evaluated for lansaprozole floating micro pellets by emulsion solvent diffusion technique. Floating micro pellets of 1:1,1:2 and 1:3 drug to carrier ratios were prepared using hydroxypropylmethylcellulose, methylcellulose, and chitosan as a carrier. Stability studies, scanning electron microscopy and particle size analysis, particle size distribution, and were studied.

Basak S.C. et al., [35] (2004) Studied the development and in vitro evaluation of an oral floating matrix tablet formulation of ciprofloxacin. In vitro drug release study of tablets indicated that gas powered floating matrix tablet could be promising delivery sys tem for ciprofloxacin with sustained release action and improved drug availability.

Julijana kristl et al., [36] (2000) Studied the optimization of floating matrix tablets and evaluation of their gastric residence time. Crushing force, floating properties, *in vitro* drug release properties was examined.

Masaki Ichikawa et al., [37] (199) Studied a new multiple unit oral floating dosage system. Multiple unit oral floating dosage system. Multiple unit type of oral floating dosage system has been prepared in oral to prolong the gastric emptying time of the preparation. The floating ability and the sustained release character of the system have been evaluated by invitro dissolution method.

Kawashima Y. et al., [38] (1992) Studied a hallow miocrospheres floating controlled drug delivery system loaded with drug in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The drug release behavior of the microballons was characterized as an enteric property and the drug release rate were drastically reduced depending on the polymer concentration

Fassiahi et al,. [39] (1996) The multi layered tablets was prepared and developed. An asymmetric three-layered table was found in that one of the outer layer consisted of a gas generating system with the produced carbon dioxide trapped in a hydrated gel matrix. The outer layer was similar but lacked the gas-generating element. The function of these layers was to provide the necessary buoyancy and to controlled the passage of fluids in to the central drug containing layer

. Strebel et al., [40] (1997) Studied the multiple unit gastro retentive drug delivery system by a new preparation method for low-density micro particles were prepared and the invitro performance demonstrated.

Ingani et al., [41] (1997) Studied the floating drug release properties of a conventional capsule was prepared and compared with a tablet containing a gas generating bilayer formulation.

Nadio passerine et al.,[42] (2002) Studied the preparation and the characterization of carbamaxepine-gellucire 50/10 micro particulates by spray congealing method using ultra sounds were prepared. The SEM analysis showed that it was possible to obtain spherically shaped and non-aggregated micro particles. The particle size was in the range 150-20 µm and the microsphees had good encapsulation efficiency.

Sato Y et al.,[43] (2003) Studied the floating hallow microsphere was prepared by emulsion solvent diffusion method and the in vitro evaluation and drug releasing behaviors were studied.

U.S. patent[44] No. 5,232,704 described bilayer, sustained release dosage form. One layer and other was a buoyant or floating layer. Each layer contained hydrocolloid gelling agent such as gums, polysaccharides, and hydroxypropyl methylcellulose. Patent claimed buoyancy of system in gastric fluid for a period up to 13hrs.

U.S. patent No.4, 418,179 described non-compressed sustained release floating therapeutic composition containing agar and light mineral oil. The light mineral oil used helps in preventing entrapped air from escaping when system is placed in gastric fluid and thus system attend buoyancy.

U.S. patent No. WO 01/10405 described hydro dynamically balanced multiparticulate oral drug delivery system comprising of a drug; gas generating components, sugar, release controlling agent and a spheronizing agent. As system is multiparticulate, incorporation of high dosage of drugs is a serious limitation.

U.S. patent No.5, 783,212 described a controlled release tablet having at least 3 layers, two extreme barrier layers containing swellable polymer(s), gas generating component and middle layer contained drug and release retarding polymer.

U.S. patent No.WO 00/15198 (PCT) and WO 01/64183 described a very complicated floating drug delivery system comprising of a drug, a gas generating component, a swelling agent, a viscolyzing agent and a gel forming polymer. This system used higher percentage of superdisintegrant class of polymers as swelling agent combination with viscolyzing agent /gel forming polymer entrapping gas, generated due to gas generated component. According to claims, system retained in upper part of gastrointestinal tract releasing drug in controlled rate. The system is complicated due to presence of so many controlling and floating ingredients. It is not cost effective in terms of manufacturing as well as packing is concerned, as it will require special packing to protect from moisture.

List of Drug Formulated as Single and Multiple unit of FDDS[45]

S.No	Approaches	Model drugs	References
1.	Floating Tablets	Chlorpheniramine maleate	**Hirtz J et.al.,** J.Clin.pharmacol 1985(19), 77-87.
2.	Floating Tablets	Theophylline	**Yan L et.al.,** J.pharm.Sci 1996(85)170-173.
3.	Floating Tablets	Frusemide	**Yang L et.al.,** J.Control release 1999(57)215-222
4.	Floating Tablets	Ciprofloxacin	**Talwa N et. al.,** US patent 6261601, July,17,2000
5.	Floating Tablets	Pentoxyfillin	**Baumgartner et.al.,** Int.J. pharm. 2000 (195)125-135.
6.	Floating Tablets	Captopril	**Nur Ao et.al.,** Drug Dev. Ind pharm 2000 (26)2965-969.
7.	Floating Tablets	nimodipine	**Wu W et.al.,** Yao Xue,Xue Bao 1997 (32) 786-790.
8.	Floating Tablets	Amoxycillin trihydrate	**Hilton Ak et.al.,** Int.J.Pharm Sci 1992 (81)135-140.
9.	Floating Tablets	Verapamil	**Chen GL et.al.,** Drug Dev.Ind Pharm 1998 (24)1067-1072.
10.	Floating Tablets	Isosobide di nitrate	**Ichikawa M et al.,** J.Pharm Sci 1991 (80) 1153-1150.
11.	Floating Tablets	Sotalol	**Cheuh HR et.al.,** Drug Dev.Ind Pharm 1995 (21)1725-1747.

12.	Floating Tablets	Atenolol	**Rouge N et.al.,** PharmActa Helv. 1998 (73) 81-87.
13.	Floating Tablets	Cinnarazine	**Machid Y et.al.,** Drug Des Deliv 1989 (9) 155-161.
14.	Floating Tablets	Diltiazem	**Gu TH et.al.,** (in Chinese) Chung Kao Yao Li Hsuesh Pao 1992 (13) 527-531
15.	Floating Tablets	Florouracil	**Watanbe K et.al.,** Arch Pract Pharm Yakuzaigaku 1993 (53) 1-7.
16.	Floating Tablets	Piretamide	**Rouge N et. al.** Pharm Dev Technol 1998 (3) 73-84.
17.	Floating Tablets	Prednisolone	**Inouye K et. al.,** Drug Des Deliv 1988 (2) 165-175.
18.	Floating Tablets	Ribofluvin- 5' phosphate	**Ingani et.al.,** Int.J.Pharm 1987 (35) 157-164.
19.	Floating capsules	Nicardipine	**Moursy NM et.al.,** Pharmazie 2003 (58) 38-43.
20.	Floating capsules	L-dopa and Benserazie	**Erni W et.al.,** Eur Neurol 1987 (27) 215-275.
21.	Floating capsules	Hlordiazepoxide Hcl	**Sheth PR et.al.,** Drug De Ind Pharm 1984 (10) 313-319.
22.	Floating capsules	Furosemide	**Menon A et.al.,** J.Pharm Sci, 1994 (83) 239-245.
23.	Floating capsules	Diazepam	**Gustafson J.H et. al.,** J.Pharmacokinet.Biopharm 1981 (9) 679-691.
24.	Floating capsules	Propranolol	**Khattar D et. al.,** 1990 (45) 356-358.

25.	Floating microspheres	Verapamil	**Soppimath KS et.al.,** Drug Metab Rev 2001 (33) 149-160.
26.	Floating microspheres	Aspirin, Griseofluvin and p-nitro aniline	**Thanoo BC et.al.,** J. Pharm.Pharmacol 1993 (45) 21-24.
27.	Floating microspheres	Ketoprofen	**El-Kamel AH et.al.,** Int. J.Pharm 2001 (220) 13-21.
28.	Floating microspheres	Tranilast	**Kawashima Y et.al.,** J. Control release 1991 (16) 276-290.
29.	Floating microspheres	Ibuprofen	**Kwawashima Y et.al.,** J.Pharma.Sci 1992 (81) 135-140.
30.	Floating Micro balloons	Terfenadine	**Yayanthi G et.al.,** Pharmazie 1995 (50) 769 –770.
31.	Floating Granules	Indomethacin	**Hilton AK et.al.,** Int.J.Pharm 1992 (86) 79-88.
32.	Floating Granules	Diclofenac sodium	**Macolm SL et.al**., Eur Neurol 1987 (27) 28S-35S.
33.	Floating Granules	Predinisolone	**Inouye K et.al.,** Drug Des Deliv 1989 (4) 55-67.
34.	Floating Films	Drug delivery device	***Harrigen BM*** US patent 4 055 178 october 25 977.
35.	Floating Powder	Several basic drugs	**Dennis A Timminis P et.al.,** . US patent 5 169 638 December 8, 1992.

3. Aim and Objectives

Salbutamol sulphate is a short acting bronchodilators (β_2 adrenergic agonist), which have short biological half -life about 2.7 - 5 hours. It is available as conventional oral tablets, solution, inhalation (inhaler, nebulised solution). The recommended dose of salbutamol in conventional dose 2 or 4 mg three or four times per day.

The aim of this project work is to develop the Salbutamol sulphate as Gastro Retentive Drug delivery System by Floating Matrix Tablets with extended drug release, for administration as once daily dose. Floating matrix tablets were formulated by different methods.

1. Non-effervescent method- by using Hydrocolloids
2. Effervescent method - by using Gas-forming agents

Thus, it is an object of the present invention to provide a Salbutamol as floating matrix tablets, which have gastro-retentive controlled oral drug delivery system. The objects include.

To formulate a floating matrix tablet by using different matrix forming materials

1. **Hydrophilic Floating Matrix Tablets**

Matrix forming material - Hydrocolloids like Methylcellulose, HPMC (K 100 M, K4M) etc.,
Approach - Non-effervescent method.

2. **Insoluble Floating Matrix Tablets**

Matrix forming material - Ethyl cellulose, and Eudragit RSPO
Approach - Effervescent method.

3. Combined Floating Matrix Tablets

Matrix forming material - HPMC (K 100 M) hydrophilic polymer
Ethyl cellulose, Eudragit RSPO as hydrophobic polymer

Approach - Non-effervescent method.

Floating matrix tablets formulation

Wet granulation method non-aqueous solvents were used as granulating agents.

To control the release of the salbutamol sulphate from the Floating Matrix Tablets throughout 24 hours for administration as once daily dose. To achieve sustained release of the drug from the dosage form by retaining the dosage form in the stomach for prolonged period (GRDDS) and controlled their drug release from the matrix tablet.

The Scheme of Proposed Work is as Follows:

Floating matrix tablets were formulated by using different matrix forming material and grouped as follows

1. Hydrophilic Floating Matrix Tablets
2. Insoluble Floating Matrix Tablets
3. Combined Floating Matrix Tablets

Hydrophilic Floating Matrix Tablets

Formulation of Floating Matrix Tablets by Non- effervescent method.

Optimization of formula for formulation. The formula was optimized by varying the following variables.

- Hardness
- Polymer , Polymer concentration 25, 50, 75 % w/w
- Shape
- Effect of stearic acid on the drug release

Insoluble Floating Matrix Tablets

Optimization of Gas forming agent, and Polymer concentration**.**

Formulation of Insoluble Floating Matrix Tablets.

Combined Floating Matrix tablets

Optimization of formula for formulation Floating Matrix Tablets

Formulation of Combined Floating Matrix Tablets.

Preformlation Studies

1. Identification of drug by spectrophotometric method (UV, IR)
2. Bulk density
3. Carr's index
4. Angle of Repose

Evaluation

1. Physical Evaluation

   Weight variation

   Hardness test

   Friability test

2. Chemical Evaluation

   Drug content analysis

3. *In vitro* Drug Release

   Drug dissolution profile in Simulated Artificial Gastric Fluid and Water

4. Floating properties

   Floating lag time

   Duration of floating time

5. Stability studies

   As per ICH guidelines

5.1 DRUG PROFILE[46]

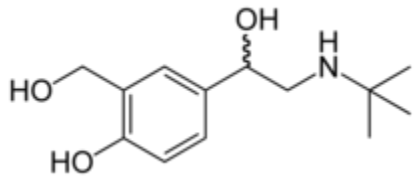
Drug Name - Salbutamol sulphate

Classification - β_2 adrenergic agonist

Proper Name - The World Health Organization recommended name for Albuterol base is salbutamol.

Synonym - Albuterol sulphate

Chemical structure



H_2SO_4

Chemical Name - α1-[(tert-butylamino) methyl]-4-hydroxy-m-xylene-α,α'-diol sulfate

Molecular weight - 576.71

Molecular formula - $(C_{13}H_{21}NO_3)_2 \ H_2SO_4$

Description

Colour - White to almost white powder

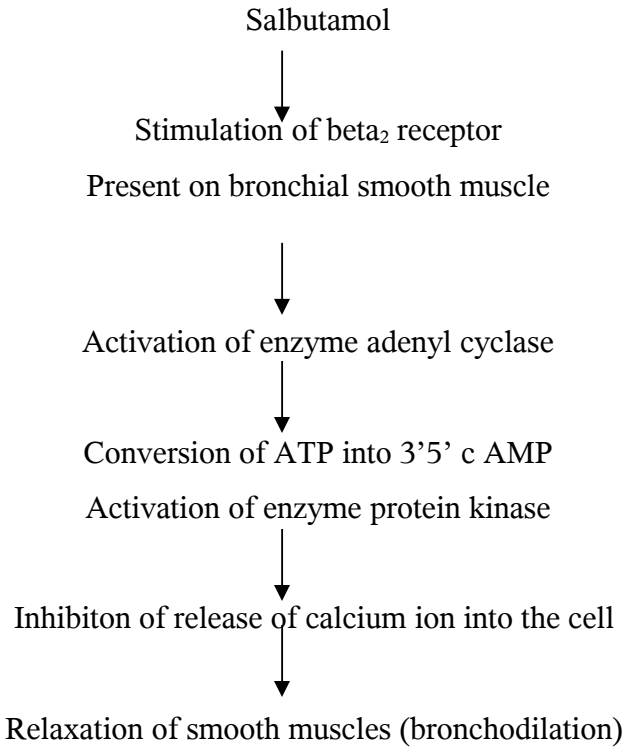
Odour - Odourless

Solubility - Soluble in four parts of water
Slightly soluble in 96% ethanol

Melting point - 155ºC

Optical rotation - Racemic mixture

Mechanism of action[47]



Albuterol is a moderately selective β_2 -adrenergic agonist that stimulates receptors of the smooth muscle in the lungs, uterus, and vasculature supplying skeletal muscle. Albuterol is racemic beta-agonist, comprised of an equal mixture of R- and S-isomers. The R-isomer, known as levalbuterol, is primarily responsible for bronchodilation. Although not confirmed during clinical trials, the S-isomer of albuterol has bronchoconstrictive properties inanimalmodels.Intracellularly; the actions of albuterol are mediated by cyclic AMP, the production of which is augmented by β_2-stimulation. Albuterol is believed to work by activating adenylate cyclase, the enzyme responsible for generating cyclic AMP, an intracellular mediator. Increased cyclic AMP leads to activation of proteinkinase A, which inhibits phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. The net result of β_2-receptor agonist in the lungs is relaxation of bronchial and tracheal smooth muscles, which in turn relieves bronchospasm, reduces airway resistance, facilitates mucous drainage, and increases vital capacity.

Albuterol can also inhibit the degranulation and subsequent release of inflammatory autocoids from mast cells. Stimulation of β_2-receptors on peripheral vascular smooth muscle can cause vasodilation and a modest decrease in diastolic blood pressure. Albuterol is an effective adjunctive treatment for hyperkalemia; β_2-adrenergic stimulation results in intracellular accumulation of serum potassium due to stimulation of the Na/K ATPase pump, leading to moderate degrees of hypokalemia.

Pharmacokinetics[47]

Albuterol can be administered as oral tablets or oral solution, but is more commonly administered by oral inhalation. Following oral inhalation, albuterol is absorbed over several hours from the respiratory tract. It is postulated from studies with other inhaled bronchodilators that most of an albuterol inhaled dose (approximately 90%) is actually swallowed and absorbed through the GI tract. Onset of bronchodilation occurs within 5—15 minutes after oral inhalation, peaks in 0.5—2 hours, and lasts 2—6 hours. Administration via nebulization does not appear to significantly alter the pharmacokinetics of albuterol. When administered orally, albuterol is well absorbed through the GI tract. Onset of action begins within 30 minutes, peak levels are reached in 2—3 hours, and duration of action is 4—6 hours for the conventional-release tablets and 8—12 hours for the sustained release product.

Albuterol crosses the blood-brain barrier and may cross the placenta. The liver metabolizes albuterol extensively to inactive compounds. Excretion of albuterol occurs through the urine and feces. After oral inhalation, 80—100% of a dose is excreted via the kidneys within 72 hours; up to 10% may be eliminated in feces. After oral administration, 75% of a dose is excreted in urine within 72 hours as metabolites; 4% may be found in feces. The elimination half-life of albuterol ranges from 2.7-5 hours, with orally administered albuterol having a shorter half-life than the inhaled product.

Clinical Pharmacology

Absorption-Well absorbed from the GI tract

Metabolism-Considerable pre-systemic metabolism, the major metabolite is a sulphate conjugates

Elimination-Oral administration of salbutamol sulphate excretes via kidney 58% to 78%Of radiolabel appearing in the urine within 24 hours

Pharmacokinetic parameters

Oral absorption	- 50%
Protein binding	– 10%
Presystemic metabolism	- Considerable
Plasma half life	- 2.7 to 5 hours
Volume of distribution	- 3.4 ± 0.6l kg-
Maximum plasma concentrations	- 18 ng/mL

Clinical Trials

In controlled clinical trials in patients with asthma, the onset of improvement in pulmonary function, as measured by maximum midexpiratory flow rate (MMEF), was within 30 minutes after a dose of Albuterol tablets, with peak improvement occurring between 2 and 3 hours. In controlled clinical trials in which measurements were conducted for 6 hours, clinically significant improvement (defined as maintaining a 15% or more increase in forced expiratory volume in 1 second [FEV1] and a 20% or more increase in MMEF over baseline values) was observed in 60% of patients at 4 hours and in 40% at 6 hours. In other single-dose, controlled clinical trials, clinically significant improvement was observed in at least 40% of the patients at 8 hours. No decrease in the effectiveness of Albuterol tablets was reported in patients who received long-term treatment with the drug in uncontrolled studies for periods up to 6 months.

Indications and Usage for Albuterol

Albuterol tablets are indicated for the relief of bronchospasm in adults and children 6 years of age and older with reversible obstructive airway disease.

Contraindications

Albuterol tablets are contraindicated in patients with a history of hypersensitivity to Albuterol, or any of its components.

Warnings

Paradoxical Bronchospasm

Albuterol tablets can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, Albuterol tablets should be discontinued immediately and alternative therapy instituted.

Cardiovascular Effects

Albuterol tablets, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of Albuterol tablets at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, Albuterol tablets, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of Albuterol, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema. Albuterol, like other beta-adrenergic agonists, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes. Rarely, erythema multiforme

and Stevens-Johnson syndrome have been associated with the administration of oral Albuterol sulfate in children.

Precautions

General

Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

Large doses of intravenous Albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. As with other beta-agonists, Albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Information for Patients

The action of Albuterol tablets may last up to 8 hours or longer. Albuterol tablets should not be taken more frequently than recommended. Do not increase the dose or frequency of Albuterol tablets without consulting your physician. If you find that treatment with Albuterol tablets becomes less effective for symptomatic relief, your symptoms get worse, and/or you need to take the product more frequently than usual, you should seek medical attention immediately. While you are taking Albuterol tablets, other asthma medications and inhaled drugs should be taken only as directed by your physician. Common adverse effects include palpitations, chest pain, rapid heart rate, and tremor or nervousness. If you are pregnant or nursing, contact your physician about use

of Albuterol tablets. Effective and safe use of Albuterol tablets includes an understanding of the way that it should be administered.

Drug Interactions

The concomitant use of Albuterol tablets and other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects. This recommendation does not preclude the judicious use of an aerosol bronchodilator of the adrenergic stimulant type in patients receiving Albuterol tablets. Such concomitant use, however, should be individualized and not given on a routine basis. If regular coadministration is required, then alternative therapy should be considered.

Monamine Oxidase Inhibitors or Tricyclic Antidepressants

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of Albuterol on the vascular system may be potentate.

Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as Albuterol tablets, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics.

Digoxin

Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of Albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving Albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and Albuterol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2- year study in Sprague-Dawley rats, Albuterol sulfate caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium at dietary doses of 2, 10, and 50 mg/kg (approximately 1/2, 3, and 15 times, respectively, the maximum recommended daily oral dose for adults on a mg/m2 basis, or, 2/5, 2 and 10 times, respectively, the maximum recommended daily oral dose for children on a mg/m2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist.In an 18-month study in CD-1 mice Albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg, (approximately 65 times the maximum recommended daily oral dose for adults on a mg/m2 basis, or, approximately 50 times the maximum recommended daily oral dose for children on a mg/m2 basis). In a 22-month study in the Golden hamster, Albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg, (approximately 8 times the maximum recommended daily oral dose for adults on

an mg/m^2 basis, or, approximately 7 times the maximum recommended daily oral dose for children on a mg/m2 basis).

Albuterol sulfate was not mutagenic in the Ames test with or without metabolic activation using tester strains S. typhimurium TA1537, TA1538, and TA98 or E. Coli WP2, WP2uvrA, and WP67. No forward mutation was seen in yeast strain S. cerevisiae S9 nor any mitotic gene conversion in yeast strainS. cerevisiae JD1 with or without metabolic activation. Fluctuation assays in S. typhimurium TA98 and E. Coli WP2, both with metabolic activation, were negative. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay at intraperitoneal doses of up to 200 mg/kg.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses up to 50 mg/kg (approximately 15 times the maximum recommended daily oral dose for adults on a mg/m2 basis).

Pregnancy

Teratogenic Effects. Pregnancy Category C

Albuterol has been shown to be teratogenic in mice. A study in CD-1 mice at subcutaneous (sc) doses of 0.025, 0.25, and 2.5 mg/kg (approximately 3/1000, 3/100, and 3/10 times, respectively, the maximum recommended daily oral dose for adults on a mg/m2 basis), showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. The drug did not induce cleft palate formation at the lowest dose, 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated with 2.5 mg/kg of isoproterenol (positive control) subcutaneously (approximately 3/10 times the maximum recommended daily oral dose for adults on a mg/m2 basis).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses when Albuterol was administered orally at a 50 mg/kg dose (approximately 25 times the maximum recommended daily oral dose for adults on a mg/m2 basis).There are no adequate and well-controlled studies in pregnant women. Albuterol should be used

during pregnancy only if the potential benefit justifies the potential risk to the fetus. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been rarely reported in the offspring of patients being treated with Albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between Albuterol use and congenital anomalies has not been established.

Tocolysis

Albuterol has not been approved for the management of preterm labor. The benefit/risk ratio when Albuterol is administered for tocolysis has not been established. Serious adverse reactions, including maternal pulmonary edema, have been reported during or following treatment of premature labor with beta2-agonists, including Albuterol.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for Albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children below 6 years of age have not been established.

Adverse Reactions

In clinical trials, the most frequent adverse reactions to Albuterol tablets were:

Percent Incidence of Adverse Reactions

Reaction	**Percent Incidence**
Central nervous system	
Nervousness	20%
Tremor	20%
Headache	7%
Sleeplessness	2%
Weakness	2%
Dizziness	2%
Drowsiness	<1%
Restlessness	<1%
Irritability	<1%
Cardiovascular	
Tachycardia	5%
Palpitations	5%
Chest discomfort	<1%
Flushing	<1%
Musculoskeletal	
Muscle cramps	3%
Gastrointestinal	
Nausea	2%
Genitourinary	
Difficulty in micturition	<1%

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of Albuterol.In addition, Albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypertension, angina, vomiting, vertigo, central nervous system stimulation, unusual taste, and drying or irritation of the oropharynx.The reactions are generally transient in nature, and it is usually not necessary to discontinue treatment with Albuterol tablets. In selected cases, however, dosage may be reduced temporarily; after the reaction has subsided, dosage should be increased in small increments to the optimal dosage.

Over dosage

The expected symptoms with over dosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under Adverse Reactions, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and sleeplessness. Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of Albuterol tablets. Treatment consists of discontinuation of Albuterol tablets together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for over dosage of Albuterol tablets. The oral median lethal dose of Albuterol sulfate in mice is greater than 2000 mg/kg (approximately 250 times the maximum recommended daily oral dose for adults on a mg/m^2 basis, or, approximately 200 times the maximum recommended daily oral dose for children on a mg/m^2 basis). In mature rats, the subcutaneous (sc) median lethal dose of Albuterol sulfate is approximately 450 mg/kg (approximately 110 times the maximum recommended daily oral dose for adults on a mg/m^2 basis, or, approximately 90 times the maximum recommended daily oral dose for children on a mg/m^2 basis). In small young rats, the subcutaneous median lethal dose is approximately 2000 mg/kg (approximately 500 times the maximum recommended daily oral dose for adults on a mg/m^2 basis, or, approximately 400 times the maximum recommended daily oral dose for children on a mg/m^2 basis).

Usual Dosage

Adults and Children Over 12 Years of Age

The usual starting dosage for adults and children 12 years and older are 2 or 4 mg three or four times a day.

Children 6 to 12 Years of Age

The usual starting dosage for children 6 to 12 years of age is 2 mg three or four times a day.

Dosage Adjustment Adults and Children over 12 Years of Age

For adults and children 12 years and older, a dosage above 4 mg four times a day should be used only when the patient fails to respond. If a favorable response does not occur with the 4 mg initial dosage, it should be cautiously increased stepwise up to a maximum of 8 mg four times a day as tolerated.

Indications

1. Brondrodilator for in asthma,
2. Chronic bronchitis,
3. Emphysema.

Table No.7 Salbutamol Sulphate Commercially Available Product [48]

S.No	Brand name	Dosage form	Strength available	Company
1	Asthalin	Tablet	2 mg 4mg	Cipla
	Asthalin	Syrup	2 mg/ 5ml	Cipla
	Asthalin	Res-soln	2.5 mg/2.5ml	Cipla
	Asthalin	AC-inhaler	100 mcg/ 1 puff	Cipla
	Asthalin	MDI	100 mcg/ 1 puff	Cipla
	Asthalin	Roto caps	30 caps	Cipla
2	Asthalin –SA	Tablet	8 mg	Cipla
3	Salbair	MDI	100 mcg/ 1 puff	Lupin
4	Salbetol	Tablet	2 mg 4mg	FDC
5	Salbid	Tablet	2mg 4mg	Micro labs
6	Servent	Inhaler	50 mcg/1 puff	GSK
7	Ventirex	Syrup	2 mg/5ml	Unimack
8	Ventrolin	CR Capsule	8mg	GSK
	Ventrolin	Syrup	2 mg/5ml	GSK
	Ventrolin	MDI	100 mcg/1 puff	GSK

5.2 Excipients Profiles

1. Povidone [49]

Non-proprietary Name Povidone

Functional Category Tablet binder
Suspending agent

Synonyms Polyvidone, Polyvinylpyrolidine,
PVP, Kollidon, Plasdone.

Chemical Name 2-pyrrolidinone, 1, ethyl homopolymer-
1- vinyl-2- pyrrollidionone polymer

Typical properties

Density	1.17 to 1.18 gm/cm^3
Solubility	Readily soluble in water up to 60 %, freely soluble in many organic solvents

Table No.8 Application of Povidone in Pharmaceutical Formulation

S.No	Use	Concentration
1.	Carrier for drug	10 - 25 %
2.	Dispersing agent	Up to 5 %
3.	Suspending agent	Up to 5 %
4.	Tablet binder, diluents, coating agent	0.5 - 5 %

2. Methylcellulose[50]

Non-Proprietary Name	Methyl cellulose
Functional category	Coating agent
	Emulsifying agent
	Suspending agent
	Tablet binder
	Viscosity increasing agent
Synonyms	Metocel
	E 461
	Metholose
Chemical Name	Cellulose methyl ester

Typical Properties

Density 0.276 gm/cm^3

Solubility Practically insoluble in acetone methanol chloroform, ethanol, Soluble in glacial acetic acid. In cold water methylcellulose swells and disperses slowly to form clear to opalescent viscous, colloidal dispersion.

Table No.9 Application of Methyl cellulose in Pharmaceutical Formulations

S.No.	Use	Concentration
1.	Bulk laxative	5.0 to 30 %
2.	Emulsifying agent	1.0 to 3.0 %
3	Sustained release tablet matrix	5.0 to 75 %
4.	Tablet binder	1.0 to 5.0 %
5.	Tablet coating	0.5 to 5.0 %
6	Tablet disintegrant	2.0 to 10 %

3. Hydroxyl propyl methyl cellulose[51]

Non-proprietary Name	Hypromellose
	Hydroxyl propyl methylcellulose
Functional category	Suspending agent
	Coating agents
	Tablet binder
	Film former
Synonyms	Methyl hydroxyl propyl cellulose
	Propylene glycol, ether cellulose
	Hydroxyl propyl methyl cellulose
Chemical Name	Cellulose 2- hydroxyl propyl methyl ether
	cellulose, hydroxyl propyl methyl ether.

Typical properties

Density	0.341 gm/cm^3
Solubility	Soluble in cold water forming viscous colloidal solution. Insoluble in alcohol, ether and chloroform.
Grade	HPMC K 100 M
	HPMC K 4 M
	HPMC K 15M
	HPMC k100 LVP
Viscosity	HPMC K 100 M - 8000 to 120 000 m pas
	HPMC K 4 M - 3000 to 5600 m pas

Application of HPMC in Pharmaceutical Formulation

Film former in tablets film coating. Lower viscosity grades are used in aqueous film coating. Higher viscosity grades may be used to retard the release of drugs from a matrix a levels of 10 - 80 %w/w in tablet and capsule. Depending up on the viscosity grade, concentration of 2 - 20% w/w are used for film forming solution to film coat tablet. Lower viscosity grade are used in aqueous film coating solution, while higher viscosity grades are used with organic solvent.

4. Ethyl cellulose [52]

Non-Proprietary Name	Ethyl cellulose
Synonyms	Ethocel
	Surelease
	Agualon
Chemical Name	Cellulose ethyl ether
Functional category	Coating agents
	Tablet binder

Tablet filler

Typical properties

Density 0.400 gm/cm³

Solubility Ethyl cellulose in glycerin propylene glycol and water. Freely soluble in chloroform, methyl acetate and tetra hydro furan

Table No.10 Application of Ethyl cellulose in Pharmaceutical Formulation

S. No	Use	Concentration
1.	Micro encapsulation	10.0 to 20 %
2.	Sustained release tablet coating	03.0 to 20 %
3.	Tablet coating	01.0 to 3.0 %

5. Polymethacrylates[53]

Non-proprietary Name Methylic acid copolymer

Synonyms Eurasia
Kollicoat MAE 30 D
Kollicoat MAE 30 DP

Functional Category Film former
Tablet binder
Tablet diluents

Polymethacrylic are synthetic cationic and anionic polymer of methyl amino ethyl methacrylic acid and methacrylic acid esters in various ratios. Several type of commercially available and may be obtained as dry powder aqueous dispersion or organic solution Eudragit S 100, is a white free flowing powder with at least 95 % dry polymer. Eudragit RPS, are fine white powder with a slight amine like odour.

Typical properties

Density

Eudragit RSPO 0.816 to 0. 836 gm/cm³

Solubility

Eudragit RSPO is soluble in acetone and alcohol.

Eudragit S 100 is soluble in intestinal fluid pH 7.0.

Eudragit RSPO aqueous dispersion of polymethacrylates which has low permeability with sustained release effect.

Application of Polymethacrylate in Pharmaceutical Formulations

Polymethacrylate are primarily used in oral capsule and tablets formulation as enteric coating agents. Eudragit RSPO is used to form water insoluble film coat for sustained release formulation. Eudragit RL 100, Eudragit RSPO, Eudragit RS 100 were found to have buoyancy hence suitable for floating drug delivery. Polymethacrylate are used as binder in both aqueous and organic wet granulation. Larger quantities (5 - 20 %) of the drug polymer are used to control the active substance from the tablet matrix.

6. Stearic acid[54]

Non-proprietary Names	Stearic acid
Synonyms	Emersol
	Hystrene
	Kortacid
	Pristerene
Chemical Name	Octa decanoic acid
Functional category	Emulsifying agent
	Tablet capsule lubricant

Typical properties

Density	0.537 gm/cm^3
Solubility	Freely soluble in benzene, carbon tetra chloride, chloroform, ether,. Soluble inn ethanol, hexane, and polyethylene glycol. Insoluble in water.

Table No.11 Application of Stearic acid in Pharmaceutical Formulations

S. No	Use	Concentration
1	Ointments and creams	1 - 20 %
2.	Tablet lubricant	1 - 3 .0 %

7. Magnesium sterate[55]

Non-proprietary Name Magnesium state

Functional category Tablet and capsule lubricant

Glidant, Anti adherent

Typical properties

Density 1.03 to 1.08 gm/cm^3

Solubility Insoluble in water, alcohol and ether and slightly soluble in hot alcohol and benzene

Application of Magnesium Sterate in Pharmaceutical Formulations

Tablet anti-adherent in the concentration of 0.25 to 20 percent

6.1 List of Instruments

Table No.12 List of Instruments Used

S. No	Instrument Name	Company
1.	Digital weighing balance	Sartorius
2.	Tray drier	Mixofill
3.	Rotary tablet punching machine	Rimeck minipress
4.	pH Meter	Thermovorision
5.	Tap density tester	Electrolab
6.	Mechanical sieve shaker	Retsch
7.	Friability tester	Roche
8.	Hardness tester	Pfizer
9.	UV-Visible spectrophotometer	Shimandzu
10.	Dissolution tester USP	Electrolab
11	Environment Chamber	Heco

6.2 List of Excipients and Chemicals

Table No.13 List of Excipients and Chemical Used

S. No	Excipients	Company
1	Methyl cellulose	Nice chemical Pvt. Ltd.,
2.	HPMC (K 100 M, K 4 M)	Kemphasol
3.	Ethyl Cellulose	Loba chemice
4.	Eudragit RSPO	Rohmgmbh,Germany
5.	Stearic acid	Lancaster synthesis
6	Sodium bicarbonate	Hi-pure fine chem. Industries
7	Citric acid	Reachem laboratory chemicals Pvt. Ltd.,
8.	Microcrystalline cellulose	Hi-pure Fine Chemical industries
9	Magnesium striate	Reachem laboratory chemicals
10.	Talc	Nice chemical Pvt. Ltd.,
11.	Isopropyl alcohol	Micro fine chemicals

List of Reagents

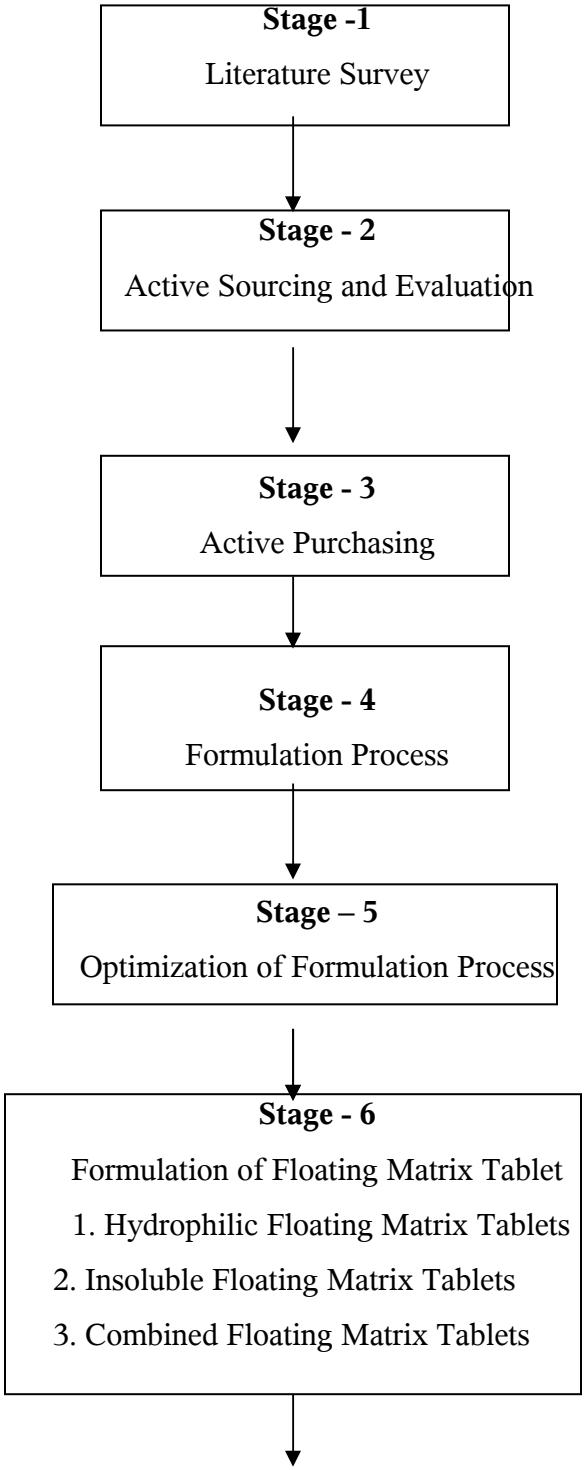
0.1 N Hydrochloric acid [57]

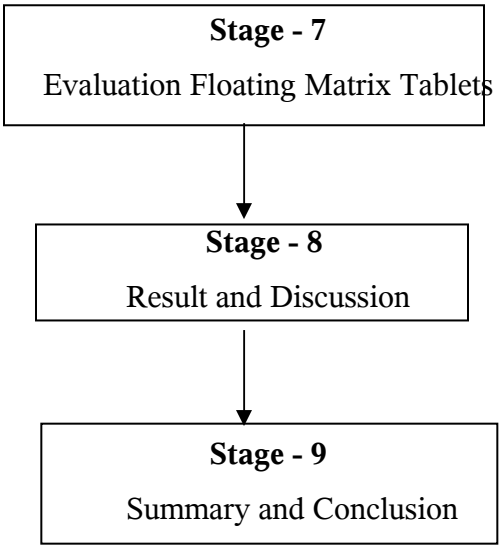
8.5 ml of Concentrated Hydrochloric acid is dissolved in 1000 ml of distilled water.

Stimulated Gastric Fluid pH 1.2 (without pepsin) [58]

0.2 gm of sodium chloride, 0.07 ml of concentrated hydrochloric acid were mixed, to this mixture 100 ml of distilled water was added and final solution was adjusted to pH 1.2 with diluted sodium hydroxide solution.

6.4 Formulation Development and Evaluation of Floating Matrix Tablet Containing Salbutamol Sulphate




Stage - 7
Evaluation Floating Matrix Tablets
Stage - 8
Result and Discussion
Stage - 9
Summary and Conclusion

6.5 Standard Curve for Salbutamol sulphate[59]

Standard Curve for Salbutamol sulphate in Simulated Gastric fluid pH 1.2

Requirement

Salbutamol sulphate

Stimulated gastric fluid with pH 1.2

Procedure

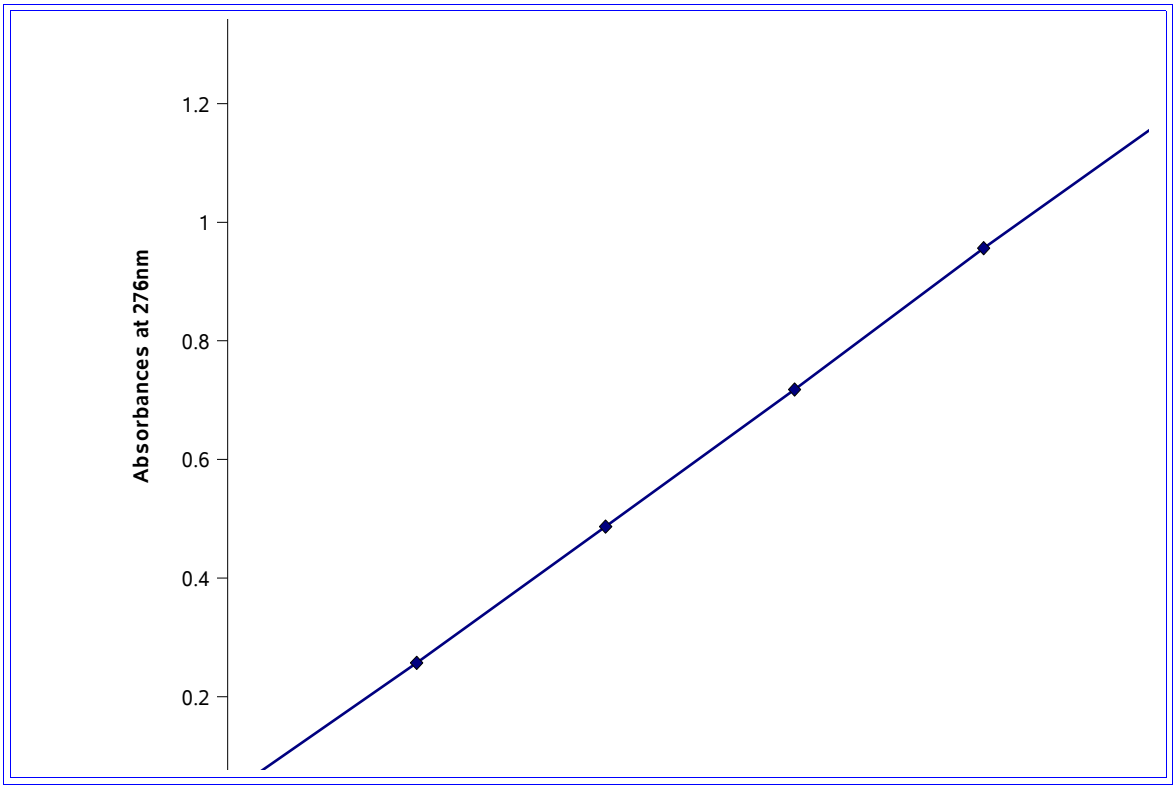
Weigh accurately 100mg of Salbutamol suphate is dissolved in 100ml of simulated gastric fluid from this solution 0.5, 1, 1.5, 2, 2.5,3 ml of drug solution was made up to 10ml with simulated gastric fluid. The absorbance was measured at 276 nm using stimulated gastric fluid as blank. The above procedure was repeated for three times and average absorbance was calculated. The standard curve was made by plotting concentration Vs absorbance.

Table No.14 Standard Curve of Salbutamol sulphate in Simulate Gastric Fluid pH 1.2

S.No.	Concentration in mcg/ml	Absorbance at 276 nm
1	50	0.270
2	100	0.487
3	150	0.697
4	200	0.956
5	250	1.183
6	300	1.397

*Average value of three observations

Figure No.8 Standard Curve of Salbutamol Sulphate in Simulated Gastric Fluid pH 1.2



Standard Curve for Salbutamol sulphate in Distilled Water

Requirement

Salbutamol sulphate

Distilled Water

Procedure

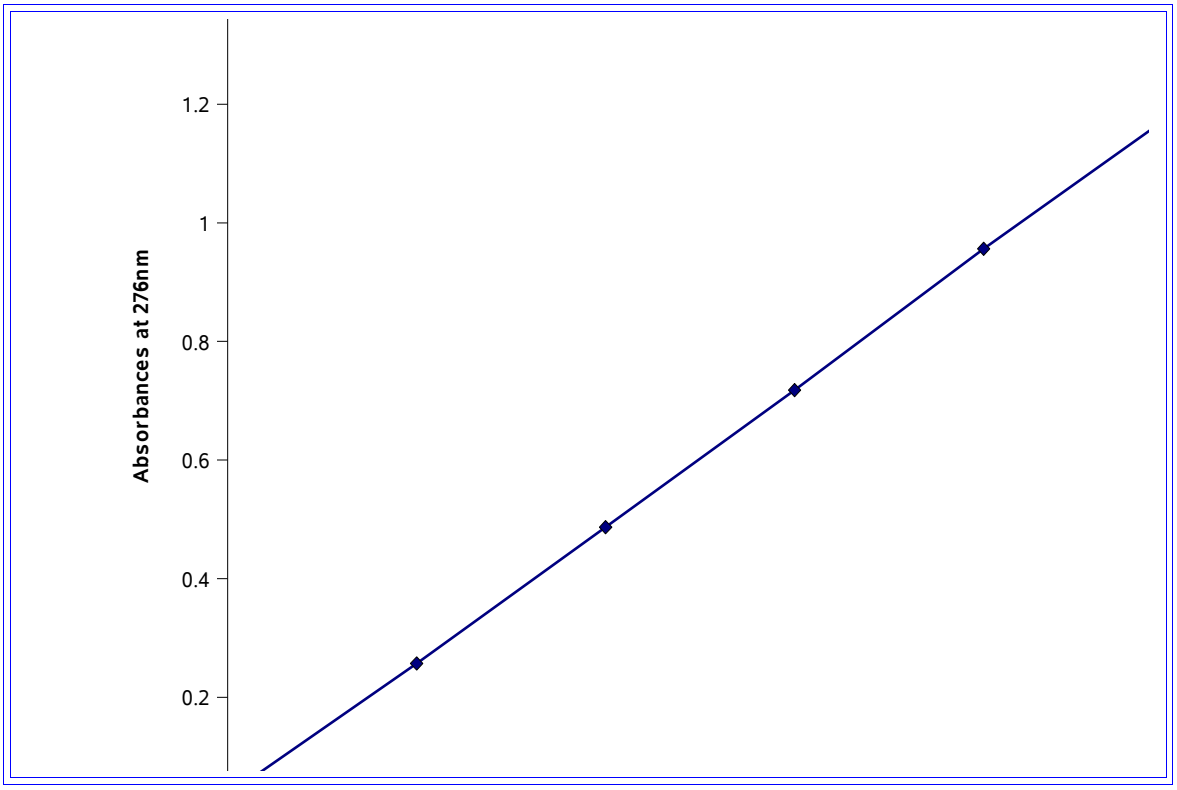
Weigh accurately 100mg of Salbutamol suphate is dissolved in 100ml of distilled water from this solution 0.5, 1, 1.5, 2, 2.5,3 ml of drug solution was made up to 10ml with distilled water. The absorbance was measured at 276 nm using distilled water as blank. The above procedure was repeated for three times and average absorbance was calculated. The standard curve was made by plotting concentration Vs absorbance

Table No.15 Standard Curve of Salbutamol sulphate in Distilled water

S.No.	Concentration in mcg/ml	Absorbance at 276 nm
1	50	0.336
2	100	0.580
3	150	0.889
4	200	1.145
5	250	1.427
6	300	1.740

*Average value of three observations

Figure No.8 Standard Curve of Salbutamol Sulphate in Simulated Gastric Fluid pH 1.2



6.6 Formulation Development of Floating Matrix Tablets

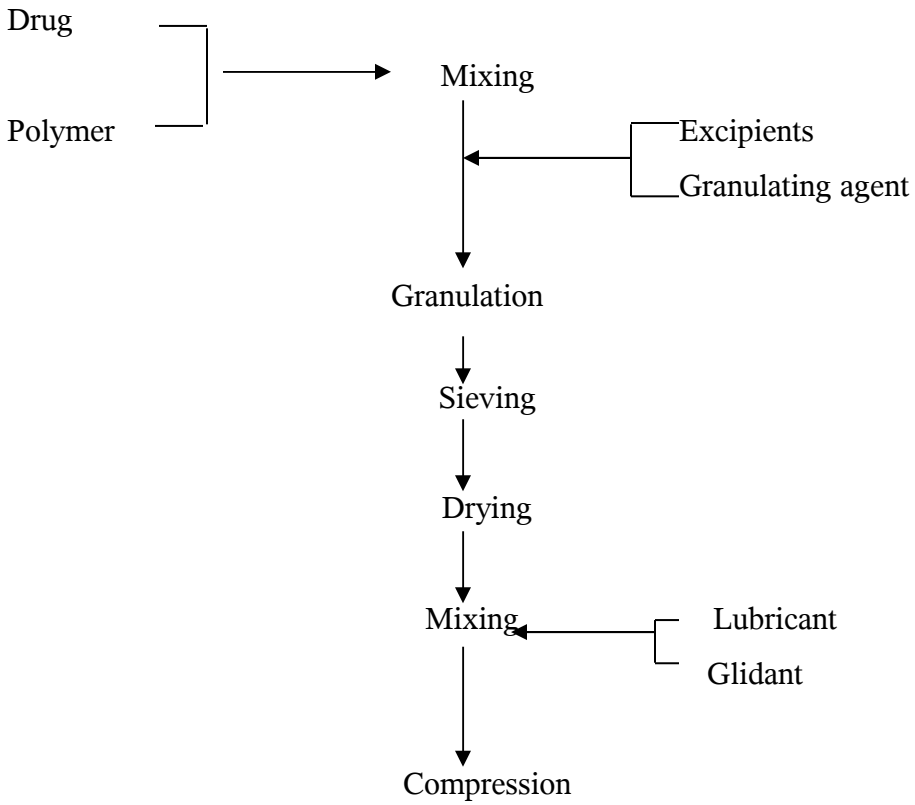
Floating Matrix Tablets

A modified release drug delivery system with prolonged gastric residence time in the stomach is of particular interest for dug

- The drug with an absorption window in the stomach or in the upper art of the small intestine
- The drug which are locally active in the stomach,
- The drug which are unstable in the intestinal or colonic environment,
- The drug with low solubility at high pH value,
- The drug that undergo first pass metabolism.

Process Flow Chart

Wet granulation method



Approaches

Floating matrix tablets were formulated by two different methods by using various matrix forming materials.

Hydrophilic Floating Matrix Tablets

Matrix former - Methylcellulose, Hydroxyl propyl methylcellulose (K100 M, K 4 M)

Approach - Non-effervescent method

Buoyancy agent - Methylcellulose, Hydroxyl propyl methylcellulose (K 100 M, K 4 M)

Insoluble Floating Matrix Tablets

Matrix former - Ethyl cellulose, Eudragit RSPO

Approach - Effervescent method

Buoyancy agent - Citric acid, Sodium bicarbonate

Combined Floating Matrix Tablets

Matrix former - Hydrophilic polymer (HPMC K100M)
Hydrophobic polymer (Ethyl cellulose, Eudragit RSPO)

Approach - Non-effervescent method

Buoyancy agent -Hydrophilic polymer.

1. Hydrophilic Floating Matrix Tablets

Matrix former - Methylcellulose, Hydroxyl propyl methylcellulose (K100 M, K 4 M)

Formulation Process

The hydrophilic floating matrix tablets were formulated by incorporating the active dug with hydrocolloids like methylcellulose, hydroxypropyl methylcellulose, microcrystlline cellulose and other excipients were added and compressed in to tablet.

2. Insoluble Floating Matrix Tablets

Matrix former - Ethyl cellulose, Eudragit RSPO

Formulation Process

The insoluble floating tablets were formulated by using the gas-forming agent. The concentration of the gas-forming agents were optimized for its floating behavior in stomach. The optimized concentration of the citric acid and sodium bicarbonate are incorporated with hydrophobic polymer, microcrystalline cellulose other excipents were added and compressed in to tablet.

3. Combined Floating Matrix Tablets

Matrix former - Hydrophilic polymer (HPMC K100M)

Hydrophobic polymer (Ethyl cellulose, Eudragit RSPO)

Formulation Process

The combined floating matrix tablets were formulated by incorporating the active dug with hydrophilic polymer like Hydroxypropylmethylcellulose (HPMC K100M) and hydrophobic polymer like ethyl cellulose and eudragit RSPO, microcrystalline cellulose and other excipients were added and compressed in to tablets.

6.7 Formula for Formulation of Hydrophilic Floating Matrix Tablets

Trial –I

Table No.16 Formulation No.1

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Methyl cellulose (25 %)	37.50
3.	Microcrystalline cellulose	85.50
4.	PVP-K30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium stearate	02.25
7.	Talc	01.50

Table No.17 Formulation No.2

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Methyl cellulose (50 %)	75.00
3.	Microcrystalline cellulose	48.50
4.	PVP-K30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium striate	02.25
7.	Talc	01.50

Table No.18 Formulation No.3

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Methyl cellulose (75 %)	112.50
3.	Microcrystalline cellulose	10.50
4.	PVP-K30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium Sterate	02.25
7.	Talc	01.50

Formulation Process

The amount of hydrocolloids were optimized by varying the concentration of the polymer

F1 - 25 percent w/w

F2 - 50 percent w/w

` F3 - 75 percent w/w

Weighed quantity of salbutamol sulphate, methylcellulose and microcrystalline cellulose were thoroughly mixed and passed through the sieve no. 60, granulation with a solution of calculated quantity of PVP-K30 in sufficient quantity of isopropyl alcohol. The wet mass passed through sieve no.10 and dried at 45°C-55 °C for 2 hours. The dried granules were sized by sieve no.22 and mixed with magnesium streate and talc. The granules are compressed in to tablets on a 10 station rotary Rimeck minipress tablet-punching machine with 7 mm punch size. The tablets were punched in to two different hardness and shape, 5 kg/cm^2, 10 kg/cm^{2}and round, oval shape respectively.

Observation

Harness about 5 kg/cm^2 - Floating lag time is in seconds

Hardness about 10 kg/cm^2 - Floating lag time is in minutes

Round shape - Swelling is good as compared with oval shape, better floating behaviors.

Trial –II

Table No.19 Formulation No-4

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	HPMC K 4M (25 %)	37.50
3.	Microcrystalline cellulose	85.50
4.	PVP-K 30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium striate	02.25
7.	Talc	01.50

Table No.20 Formulation No.5

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	HPMC K 4 M (50 %)	75.00
3.	Microcrystalline cellulose	48.50
4.	PVP-K 30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium striate	02.25
7.	Talc	01.50

Table No.21 Formulation No.6

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	HPMC K 4 M (75 %)	112.50
3.	Microcrystalline cellulose	10.50
4.	PVP-K 30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium striate	02.25
7.	Talc	01.50

Table No.22 Formulation No.7

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	HPMC K 100 M (25 %)	37.50
3.	Microcrystalline cellulose	85.50
4.	PVP-K 30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium striate	02.25
7.	Talc	01.50

Table No.23 Formulation No.8

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	HPMC K100 M (50 %)	75.00
3.	Microcrystalline cellulose	48.50
4.	PVP-K 30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium striate	02.25
7.	Talc	01.50

Table No.24 Formulation No.9

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	HPMC K 100 M (75 %)	112.50
3.	Microcrystalline cellulose	10.50
4.	PVP-K 30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium striate	02.25
7.	Talc	01.50

Formulation Process

The amount of HPMC (K100M, K4M) was optimized by varying the concentration 25, 50, 75 % w/w of its total weight of the tablet. Weighed quantity of salbutamol sulphate, methylcellulose and microcrystalline cellulose were thoroughly mixed and passed through the sieve no.60, granulation with a solution of calculated quantity of PVP-K 30 in sufficient quantity of isopropyl alcohol. The wet mass passed through sieve no.10 and dried at 45-55 ^{o}C for 2 hours. The dried granules were sized by sieve no.22 and mixed with magnesium sterate and talc. The granules are compressed in to tablets on a 10 station rotary Rimeck minipress tablet-punching machine with 7 mm punch size.

Observation

In vitro drug release of the floating matrix tablets were showed their maximum amount of drug released before 12 hours

Formula for Formulation of Hydrophilic Floating Matrix Tablets with Stearic acid

Trial –III

Table No.25 Formulation No.10

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Stearic acid (25 %)	37.50
3.	Microcrystalline cellulose	85.50
4.	PVP K 30 (4.8 %)	07.20
5.	Isopropyl alcohol	q.s
6.	Magnesium stearate	02.25
7.	Talc	01.50

Table No.26 Formulation No.11

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Stearic acid 25%	37.50
3.	HPMC K 100M 50%	75.00
4.	Microcrystalline cellulose	10.00
5.	PVP-K 30 (4.8 %)	07.20
6.	Isopropyl alcohol	q.s
7.	Magnesium state	02.25
8.	Talc	01.50

Table No.27 Formulation No.12

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Stearic 50%	75.00
3.	HPMC K 100M 25%	37.50
4.	Microcrystalline cellulose	10.00
5.	PVP-K 30 (4.8 %)	07.20
6.	Isopropyl alcohol	q.s
7.	Magnesium state	02.25
8.	Talc	01.50

Formulation Process

Weighed quantity of salbutamol sulphate, stearic acid, HPMC K100M and microcrystalline cellulose were thoroughly mixed and passed through the sieve no. 60, granulation with a solution of calculated quantity of PVP-K30 in sufficient quantity of isopropyl alcohol. The wet mass passed through sieve no.10 and dried at 45-55°C for 2 hours. The dried granules were sized by sieve no.22 and mixed with magnesium streate and talc. The granules are compressed in to tablets on a 10 station rotary Rimeck minipress tablet-punching machine with 7 mm punch size.

Observation

In addition of stearic acid in hydrophilic floating matrix tablets was shows sustained the drug release from the matrix tablet and maintain the floating behavoiurs of the tablets up to 24 hours by retarding the penetration of water in to the floating matrix tablets.

6.8 Formula for Formulation of Insoluble Floating Matrix Tablets

Trial –IV

Table No.28 Formulation No.13

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Ethyl cellulose (25 %)	37.50
3.	Microcrystalline cellulose	73.50
4.	Citric acid	02.00
5.	Sodium bicarbonate	10.50
6.	PVP K 30 (4.8 %)	07.20
7.	Isopropyl alcohol	q.s
8.	Magnesium stearate	02.25
9.	Talc	01.50

Table No.29 Formulation No.14

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Eudragit RSPO (25 %)	37.50
3.	Microcrystalline cellulose	73.50
4.	Citric acid	02.00
5.	Sodium bicarbonate	10.50
6.	PVP K 30 (4.8 %)	07.20
7.	Isopropyl alcohol	q.s
8.	Magnesium stearate	02.25
9.	Talc	01.50

Formulation Process

Weighed quantity of salbutamol sulphate, HPMC K100M, citric acid, sodium bicarbonate and microcrystalline cellulose were thoroughly mixed and passed through the sieve no.60, granulation with a solution of calculated quantity of PVP-K30 in sufficient quantity of isopropyl alcohol. The wet mass passed through sieve no.10 and dried at 45-55°C for 2 hours. The dried granules were sized by sieve no.22 and mixed with magnesium streate and talc. The granules are compressed in to tablets on a 10 station rotary Rimeck minipress tablet-punching machine with 7 mm punch size.

Observation

The insoluble floating matrix tablets were showed their floating behavoiurs in simulated gastric fluid up to 12 as in the form of disintegrated particle instead of tablet. The *in vitro* drug release of the floating matrix tablets were showed their maximum amount of drug released before 12 hours

6.9 Formula for Formulation of Combined Floating Matrix Tablets

Trial –V

Table No.30 Formulation No.15

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Ethyl cellulose (25 %)	37.50
3.	HPMC K 100M (50%)	75.00
4.	Microcrystalline cellulose	10.50
5.	PVP K 30 (4.8 %)	07.20
6.	Isopropyl alcohol	q.s
7.	Magnesium stearate	02.25
8.	Talc	01.50

Table No.31 Formulation No.16

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Ethyl cellulose (50 %)	75.00
3.	HPMC K 100M (25 %)	37.50
4.	Microcrystalline cellulose	10.50
5.	PVP K 30 (4.8 %)	07.20
6.	Isopropyl alcohol	q.s
7.	Magnesium stearate	02.25
8.	Talc	01.50

Table No.32 Formulation No.17

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Eudragit RSPO (25 %)	37.50
3.	HPMC K 100M (50%)	75.00
4.	Microcrystalline cellulose	10.50
5.	PVP K 30 (4.8 %)	07.20
6.	Isopropyl alcohol	q.s
7.	Magnesium stearate	02.25
8.	Talc	01.50

Table No.33 Formulation No.18

S. No	Ingredients	Quantity for one tablet in mg
1	Salbutamol sulphate	16.00
2	Eudragit RSPO(50 %)	75.00
3.	HPMC K 100M (25 %)	37.50
4.	Microcrystalline cellulose	10.50
5.	PVP K 30 (4.8 %)	07.20
6.	Isopropyl alcohol	q.s
7.	Magnesium stearate	02.25
8.	Talc	01.50

Formulation Process

Weighed quantity of salbutamol sulphate, HPMC K100M, ethyl cellulose, eudragit RSPO and microcrystalline cellulose were thoroughly mixed and passed through the sieve no.60, granulation with a solution of calculated quantity of PVP-K30 in sufficient quantity of isopropyl alcohol. The wet mass passed through sieve no.10 and dried at 45 - 55°C for 2 hours. The dried granules were sized by sieve no.22 and mixed with magnesium streate and talc. The granules are compressed in to tablets on a 10 station rotary Rimeck minipress tablet-punching machine with 7 mm punch size.

Observation

In vitro drug release of the floating matrix tablets were showed their maximum amount of drug released before 12 hours

6.10 Evaluation of Floating Matrix Tablets

API Consideration

Angle of Repose[60]

It is defined as the maximum angle that can be obtained between the free standing of the powder heap and horizontal plane, which is given by the equation

$$\Theta = \tan^{-1} H/R$$

Where,

Θ - Angle of repose

H-Height of the pile

R- Radius of the base of the conical pile

Procedure

Weighed quantity of the granules was passed through a funnel kept at a height of 1 cm from the base. The powder is passed till it forms a heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated.

$$\Theta = \tan^{-1} H/R$$

Limit

S.No	Angle of repose	Type of flow
1	Less than 25	Excellent
2	25 to 30	Good
3	30 to 40	Passable
4	Above 40	Very poor

Bulk density

It refers to a measurement to desirable packing of particles bulk density is used to determine the amount of the drug that occupies the volumes in mg/ml

$$Pi = m/vi$$

Where,

m - The mass of blend

Vi- Untapped volume

Procedure

Weighed quantity of powder was transferred in to a 100 ml measuring cylinder without tapping during the transfer. The volume occupied by the powder was measured by

$$Pi = m/vi$$

Compressibility index

Weighed quantity of the powder was transferred to 100ml of graduated measuring cylinder and subjected for tapping in a tap density tester (electro lab). The differences between two taps should be less than 2 percent

The compressibility index

$$CI = Vi\text{-}Vt / Vi \times 100$$

Where,

Vi- untapped volume

Vt- tapped volume

Limit

S.No	Carr's index	Type of flow
1	5 to 15	Excellent
2	12 to 16	Good
3	18 to 23	Fair to Passable
4	23 to 25	Poor
5	33 to 38	Very poor
6	Above 40	Extremely poor

Hardness[61]

Although there is no official test for tablet hardness this property must be controlled during production to ensure that the product is firm enough to withstand handling without breaking, chipping etc., the hardness of a tablet is indicative of its tensile strength and is measured in term of pressure required to crush it when placed on its edge. Hardness of about 5 kg/cm^2 is considered to be minimum for uncoated tablets for mechanical stability. The hardness had influence on disintegration and dissolution times. Hardness is the factor that affects the bioavailability.

Friability[62]

Friability generally refers to loss in weight of tablets in the container due to chipping, abrasion, and erosion. The standard device available is "Friabilators" (Consist of circular plastic chamber, a divided into two compartments. The chamber rotates at a speed of 25 r.p.m and drops the tablets by distance of 15 cm). The weight loss should not be more than one percent.

Formula

Percentage Friability = (initial weight-final weight/initial weight) X 100

Procedure

10 tablets are weighed and transferred in to Friabilator. Then after 100 revolutions per minute the tablets were unloaded and weight of the tablets was noted. The difference should not exceed one percent.

Floating Behaviors of Floating Matrix Tablets

Floating properties of tablets were evaluated in a dissolution vessel (USP dissolution tester) filled with 900 ml of Simulated Gastric Fluid pH 1.2 and paddle rotation speeds of 100 rpm were tested. Temperature was maintained at 37±0.5°C. Floating tablets placed in the media and the floating time was measured by visual observation.

***In vitro* Drug release Profiles**

The drug release rate from the floating matrix tablets was carried out by the USP 24 dissolution test apparatus II (paddle method, Electrolab) was used for this test, 900ml of simulated gastric fluid (pH1.2) and distilled water was introduced in to the vessel of the apparatus. The medium was warmed to 37°C ± 0.5°C. The paddle was rotated at the speed of 100 rpm. Tablet was placed in the jar were used for experiment, sample were taken at regular time intervals of 0.25,0.50,0.75,1,2,3,4,5,6,7,8,9,10,11,12 up to 24 hours, 5 ml of samples from the medium was withdrawn and the same volume of fresh dissolution medium was replaced to maintained the sink condition. The absorbance of the sample solution was measured at 276 nm. This test was carried out until there was no further release.

6.11 ACCELERATED STABILITY STUDIES

Stability [63]

Stability is officially defined as the time lapse during which the drug product retains the same properties and characteristics that is possessed at the time of manufacture. This process begins at early devolvement phases.

Instability in modern formulation is often detectable only after considerable storage period under normal condition. To assess the stability of a formulated product its usual to expose it to high stress conditions to enhance its detoriation and therefore the time required for testing is reduce common high stress like temperature and humidity. This will eliminate unsatisfactory formulation.

Strategy of Stability Testing

1. The study of drug decomposition kinetics
2. The development of stability dosage form.
3. Establishment of expiration date for commercially available drug product is some of the needs of stability testing.
4. Data form stability studies should be provided on atleast three primary batches of the drug product.
5. The batches should be manufactured to a minimum of pilot scale.
6. Important point of view of the safety of the patient, patient relieves a uniform dose of drug throughout the shelf life of the product.

Table No.34 The Stability Storage Condition

S.No	Study	Storage condition	Minimum period
1.	Long-term study	25° C ± 2° C 60 % ± 5% RH	12 month
2.	Intermediate study	30 ° C ± 2° C 60 % ±5 % RH	6 month
3.	Accelerated study	40° C ± 2 ° C 75% ±5 % RH	6 month

ICH (International Conference on Harmonization) Guidelines

Specification

1. 5% potency loss from initial assay of batch
2. Any specification degradation that exceed specification
3. Product failing out of pH limit
4. Dissolution out of specification for 12 minutes
5. Failure to meet specification for appearances and physical properties

Any one condition is observed then the stability of the batch is failed.

Procedure

Selected batches were placed in a high density polyethylene container, blister pack, stripe pack etc. they are kept in stability chamber maintained at 40°C and 75 % RH. The stability studies were carried out for a period of one month. The tablets were tested and checked for the above mention specification.

7. Results and Discussion

Preformulation Studies

Drug Identification

Method - Spectrophotometer method (UV)

Table No.35 UV- Absorbance of Salbutamol sulphate in 0.1 N HCL

S. No	Concentration in mcg/ml	Absorbance at 276nm
1	50 mcg/ml	0.379
2.	300 mcg/ml	1.673

Table No.36 UV-Absorbance of Salbutamol Sulphate in water

S. No	Concentration in mcg/ml	Absorbance at 276 nm
1	50 mcg/ml	0.290
2.	300 mcg/ml	1.621

Table No.37 UV-Absorbance of Salbutamol sulphate in Different Solvent

S. No	Medium	Wave length
1.	0.1 N HCL	225 nm-$E_{1\%}$ 1cm value 310 276 nm-$E_{1\%}$ 1cm value 60
2.	pH -2	276nm
3.	pH -12	296 nm
4.	90 % neutral ethanol	276nm, 298nm

Discussion

- The UV- absorbances of the Salbutamol sulphate were performed at different concentration in different medium and their wavelength were found and compared with monograph.

Figure No.10 UV-Absorbance of Salbutamol Sulphate

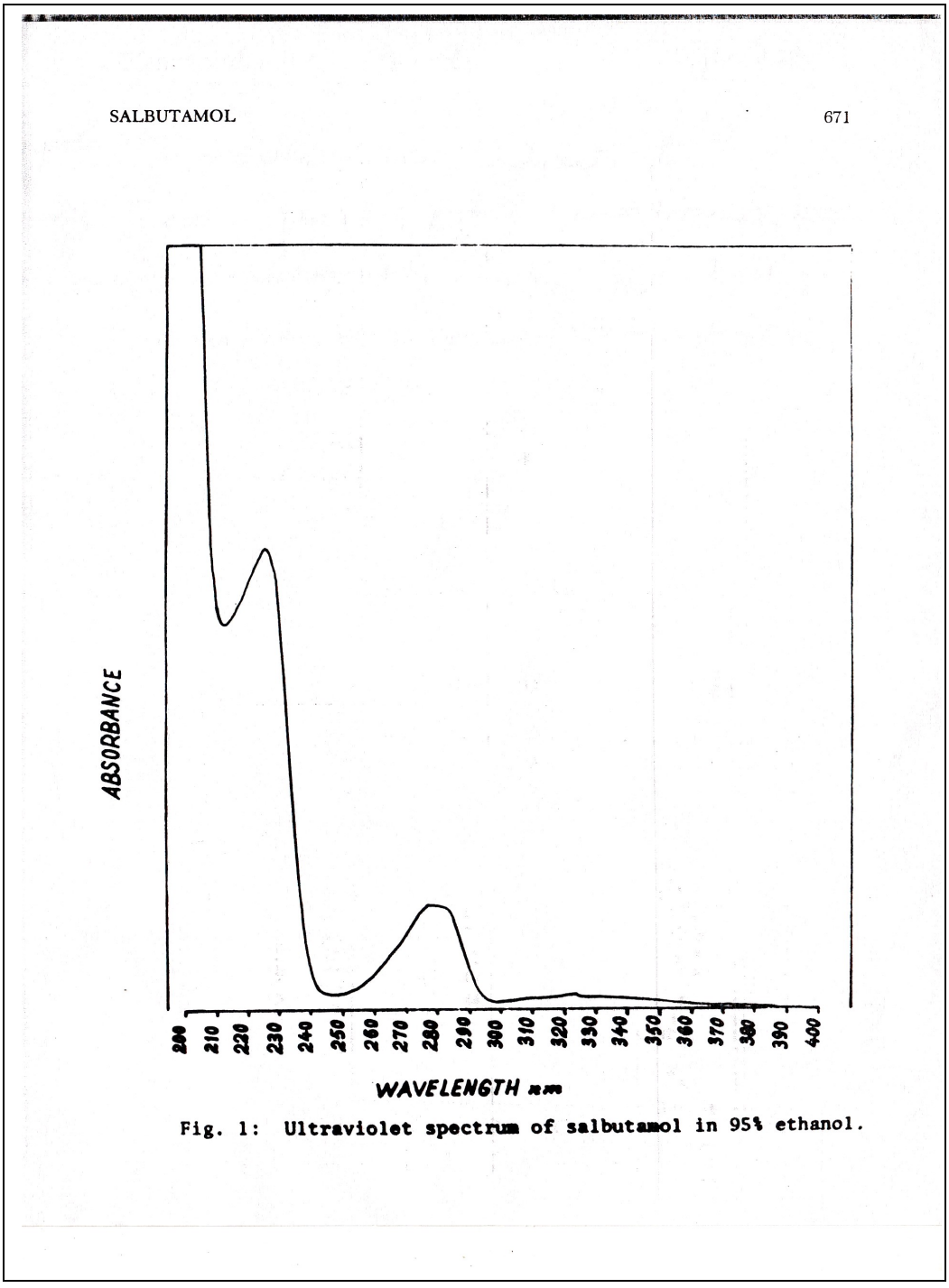
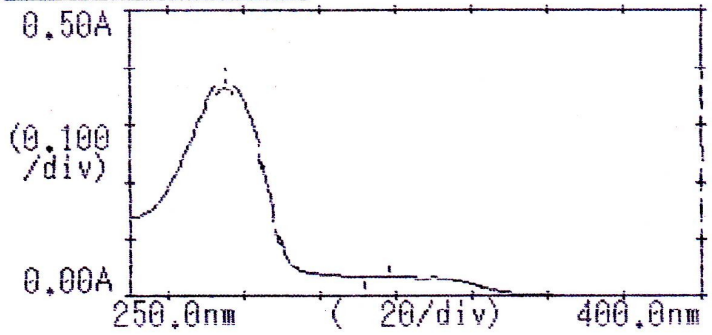


Figure No.11 UV-Absorbance of Salbutamol Sulphate in 0.1 N HCL (Concentration 50 mcg/ml)

Peak
318.5 0.034
275.5 0.379

Valley
312.0 0.033

12/Oct/07 00:26:38
Data Processing



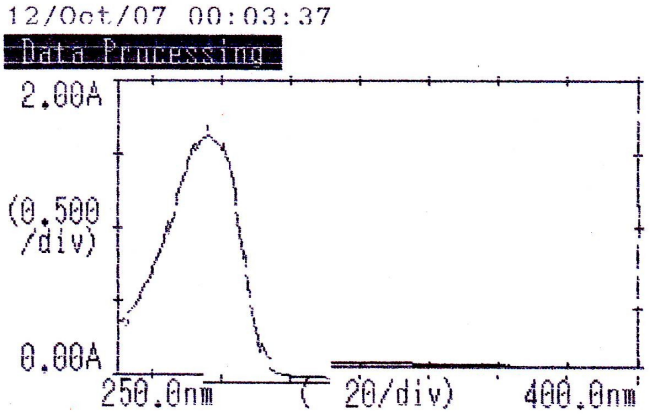
12/Oct/07 00:27:41
Point pick

Abscis.	Ordinat.		Abscis.	Ordinat.
1	300.0	0.039	11	280.0	0.348
2	298.0	0.040	12	278.0	0.367
3	296.0	0.043	13	276.0	0.378
4	294.0	0.050	14	274.0	0.377
5	292.0	0.064	15	272.0	0.360
6	290.0	0.093	16	270.0	0.332
7	288.0	0.141	17	268.0	0.291
8	286.0	0.205	18	266.0	0.269
9	284.0	0.269	19	264.0	0.237
10	282.0	0.317	20	262.0	0.208

Figure No.12 UV-Absorbance of Salbutamol Sulphate in 0.1 N HCL
(Concentration 300 mcg/ml)

Peak
276.0 1.673

Valley



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Point pick

	Abscis.	Ordinat.		Abscis.	Ordinat.
1	300.0	0.052	11	280.0	1.599
2	298.0	0.060	12	278.0	1.651
3	296.0	0.077	13	276.0	1.673
4	294.0	0.116	14	274.0	1.640
5	292.0	0.198	15	272.0	1.545
6	290.0	0.357	16	270.0	1.403
7	288.0	0.617	17	268.0	1.253
8	286.0	0.948	18	266.0	1.103
9	284.0	1.249	19	264.0	0.954
10	282.0	1.471	20	262.0	0.814

Figure No.13 UV-Absorbance of Salbutamol Sulphate in Water (Concentration 50 mcg/ml)

Peak
276.0 0.290

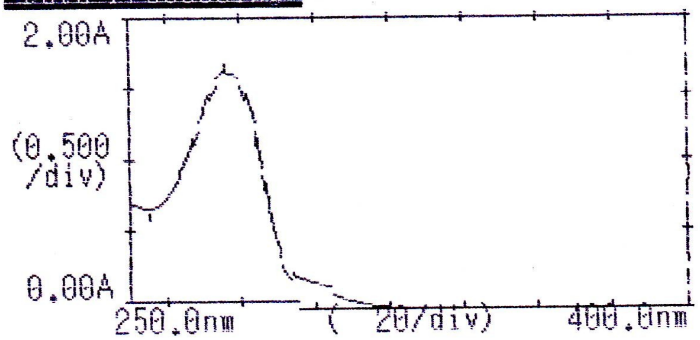
Valley

Peak
276.0 1.621

Valley
255.5 0.664

12/Oct/07 00:23:06

Data Processing



12/Oct/07 00:23:43

Point pick

	Abscis.	Ordinat.		Abscis.	Ordinat.
1	300.0	0.137	11	280.0	1.571
2	298.0	0.151	12	278.0	1.608
3	296.0	0.170	13	276.0	1.621
4	294.0	0.205	14	274.0	1.587
5	292.0	0.278	15	272.0	1.480
6	290.0	0.423	16	270.0	1.335
7	288.0	0.664	17	268.0	1.188
8	286.0	0.971	18	266.0	1.046
9	284.0	1.255	19	264.0	0.912
10	282.0	1.485	20	262.0	0.803

Infra-Red Spectrum

Table No.38 IR Spectrum of Salbutamol Sulphate

S.No	Wave number in cm^{-1}	Functional Group
1	3416	OH and NH Stretching
2	2810	-CH Aliphatic
3	2375	-CH for – CH_2 - Chain
4	1610-1592	Aromatic ring C= C Stretching
5	1370,1270,1190	Phenolic C-O Stretching
6	1150 and lower	Aromatic CH Bending
7	1385	S=O Asymmetric

Discussion

- The structure of Salbutamol sulphate was confirmed by IR spectrum and the spectrum was compared with standard graph in monograph.

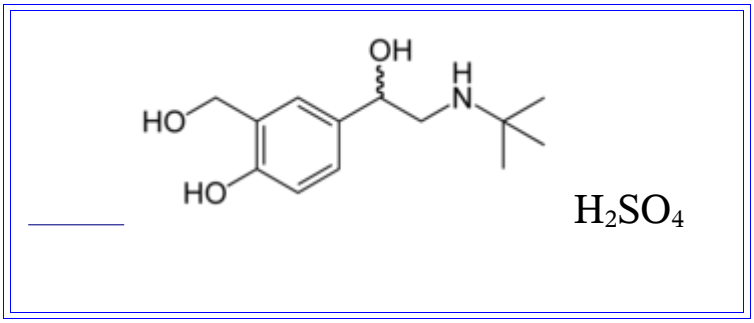


Figure No.15 FT-IR Spectrum of Salbutamol Sulphate (KBr pellet method)

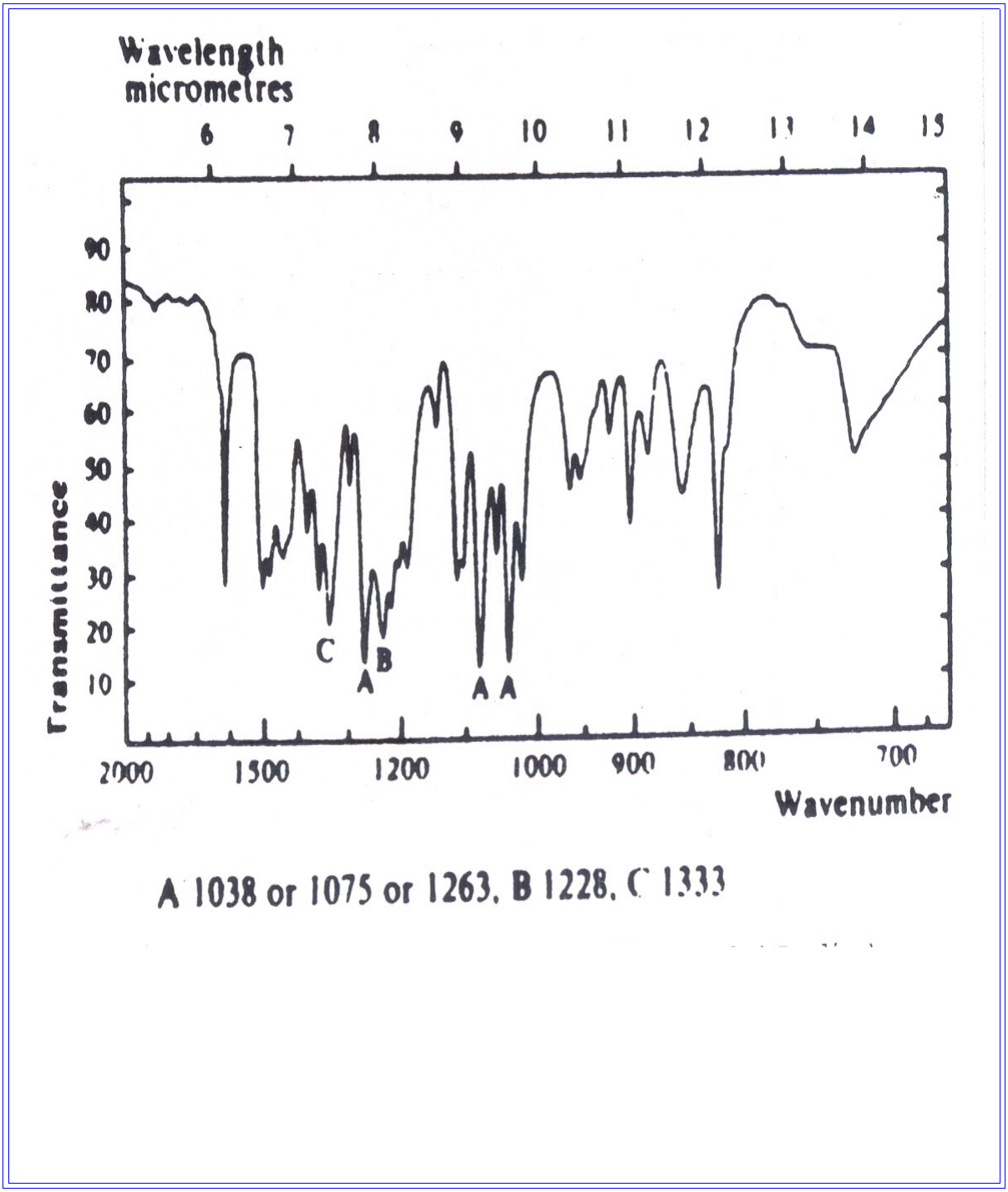
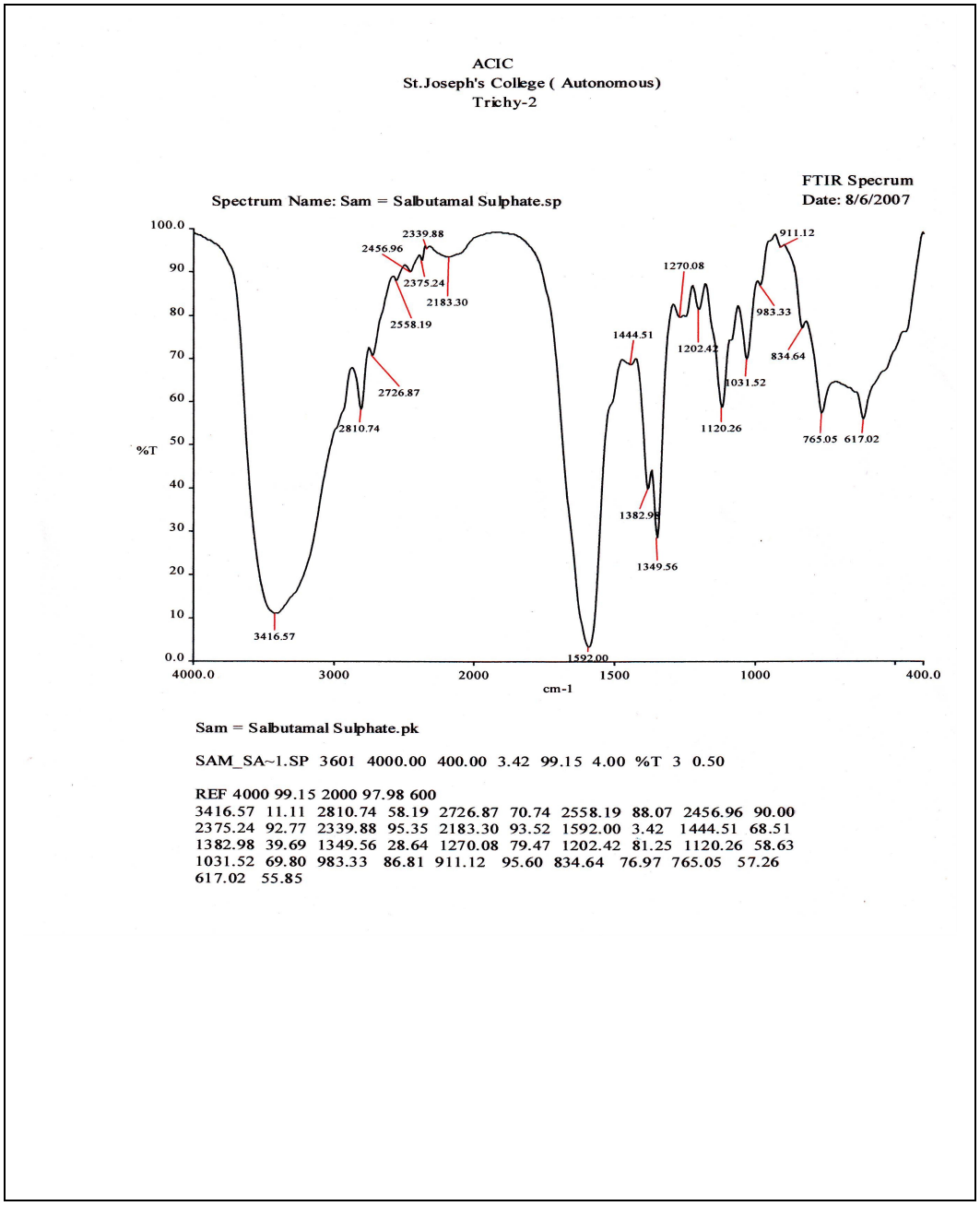


Figure No.16 FT-IR Spectrum of Salbutamol Sulphate (KBr pellet method)



API CONSIDERATION

Flow Property Characterization of Salbutamol Sulphate Floating Matrix Tablets

The various flow property characterizations of Salbutamol sulphate floating matrix tablets were evaluated and the results were listed in the table no.39, 40, and 41.

Table No. 39 Flow property and Physical Parameters of Salbutamol sulphate Hydrophilic-Floating Matrix Tablets

Formulation code	*Bulk density gm/cm^3	*Angle of repose	Carr's index %	Type of flow
F1	0.332	22° 37'	14.2	Excellent
F2	0.357	27° 38'	14.7	Excellent
F3	0.395	22° 22'	12.9	Excellent
F4	0.370	24° 50'	14.5	Excellent
F5	0.350	23° 48'	11.5	Excellent
F6	0.384	23° 13'	16.12	Excellent
F7	0.352	21° 34'	11.76	Excellent
F8	0.333	20° 36'	14.70	Excellent
F9	0.319	25° 27'	16.12	Excellent
F10	0.337	22° 57'	15.15	Excellent
F11	0.348	20° 36'	15.60	Excellent
F12	0.333	22° 37'	14.70	Excellent

* Average value of three observations.

Discussion

The values of angle of repose and Carr's index were less than 25° and 15 % respectively, hence the flow properties of the all formulations complied within the limits.

Table No.40 Flow Property and Physical Parameters of Insoluble Floating Matrix Tablets

Formulation code	*Bulk density gm/cm^3	*Angle of repose	Carr's index %	Type of flow
F13	0.353	22° 37'	14.50	Excellent
F14	0.334	21° 38'	14.00	Excellent

***** Average value of three observations.

Discussion

The values of angle of repose and Carr's index were less than 25° and 15 % respectively; hence the flow properties of the all formulations complied within the limits.

Table No.41 Flow Property and Physical Parameters of Combined Floating Matrix Tablets

Formulation code	*Bulk density gm/cm^3	*Angle of repose	Carr's index %	Type of flow
F15	0.357	22° 22'	13.00	Excellent
F16	0.395	24° 56'	12.00	Excellent
F17	0.370	23° 52'	12.50	Excellent
F18	0.384	20° 36'	13.50	Excellent

***** Average value of three observations.

Discussion

The values of angle of repose and Carr's index were less than 25° and 15 % respectively, hence the flow properties of the all formulations complied within the limits.

Evaluation of Floating Matrix Tablets

Tablet No.42 Physical Parameters of Hydrophilic Floating Matrix Tablets

S.No	Formulation code	Weight variation	*Hardness kg/cm^2	Friability in %
1	F1	Complies with IP	5.0 ±0.31	0.39
2	F2	Complies with IP	5.2 ±0.30	0.25
3	F3	Complies with IP	5.2 ±0.46	0.33
4	F4	Complies with IP	4.8 ±0.65	0.43
5	F5	Complies with IP	4.8 ±0.46	0.25
6	F6	Complies with IP	5.0 ±0.44	0.29
7	F7	Complies with IP	4.9 ±0.41	0.21
8	F8	Complies with IP	5.3 ±0.62	0.25
9	F9	Complies with IP	4.9 ±0.58	0.31
10	F10	Complies with IP	4.9 ±0.20	0.33
11	F11	Complies with IP	5.0 ± 0.74	0.19
12	F12	Complies with IP	5.1 ± 0.25	0.13

* Average value of six observations.

Discussion

The weight variation and friability of the prepared tablet formulations complied within the limits.

Tablet No.43 Physical Parameters Insoluble Floating Matrix Tablets

S.No	Formulation code	Weight variation	*Hardness kg/cm^2	Friability in %
1	F13	Complies with IP	5.2 ±0.30	0.39
2	F14	Complies with IP	4.8 ±0.65	0.45

* Average value of six observations.

Discussion

The weight variation and friability of the prepared tablet formulations complied within the limits.

Tablet No.44 Physical Parameters Combined Floating Matrix Tablets

S.No	Formulation code	Weight variation	*Hardness kg/cm^2	Friability in percentage
1	F15	Complies with IP	4.8 ±0.45	0.45
2	F16	Complies with IP	5.0 ±0.44	0.35
3	F17	Complies with IP	4.9 ±0.41	0.33
4	F18	Complies with IP	5.3 ±0.62	0.30

* Average value of six observations.

Discussion

- The weight variation and friability of the prepared tablet formulations complied within the limits.

Floating Properties of Floating Matrix Tablets

Table No.45 Floating Behaviours of Hydrophilic Floating Matrix Tablets (Simulated Gastric Fluid pH 1.2)

Formulation code	Hardness kg/cm^2	*Lag time in seconds	Hardness kg/cm^2	*Lag time in minutes	Duration of floating in hours
F1	5 kg/cm^2	5.0±0.12	10 kg/cm^2	25±1.6	20
F2	5 kg/cm^2	4.5±0.50	10 kg/cm^2	20±1.5	24
F3	5 kg/cm^2	5.0±0.60	10 kg/cm^2	15 ±1.5	24

* Average value of three observations.

Discussion

- The tablets which have hardness of about 5kg/cm^2 showed lesser lag time lower (in seconds) than the tablet which have hardness of about 10 kg/cm^2 (lag time in minutes), due to reduction of porosity of the material at highest hardness (evidence of the floating behaviours given in the table no.45 and figure no.17,18 and19.
- Based on these observations the other formulations were formulated with hardness of about 5 kg/cm^2 .

Figure No.17 Effect of Hardness and Effect of Stearic acid on floating behaviors of Hydrophilic Floating Matrix tablet and in Simulated Gastric Fluid pH 1.2 at 0 h

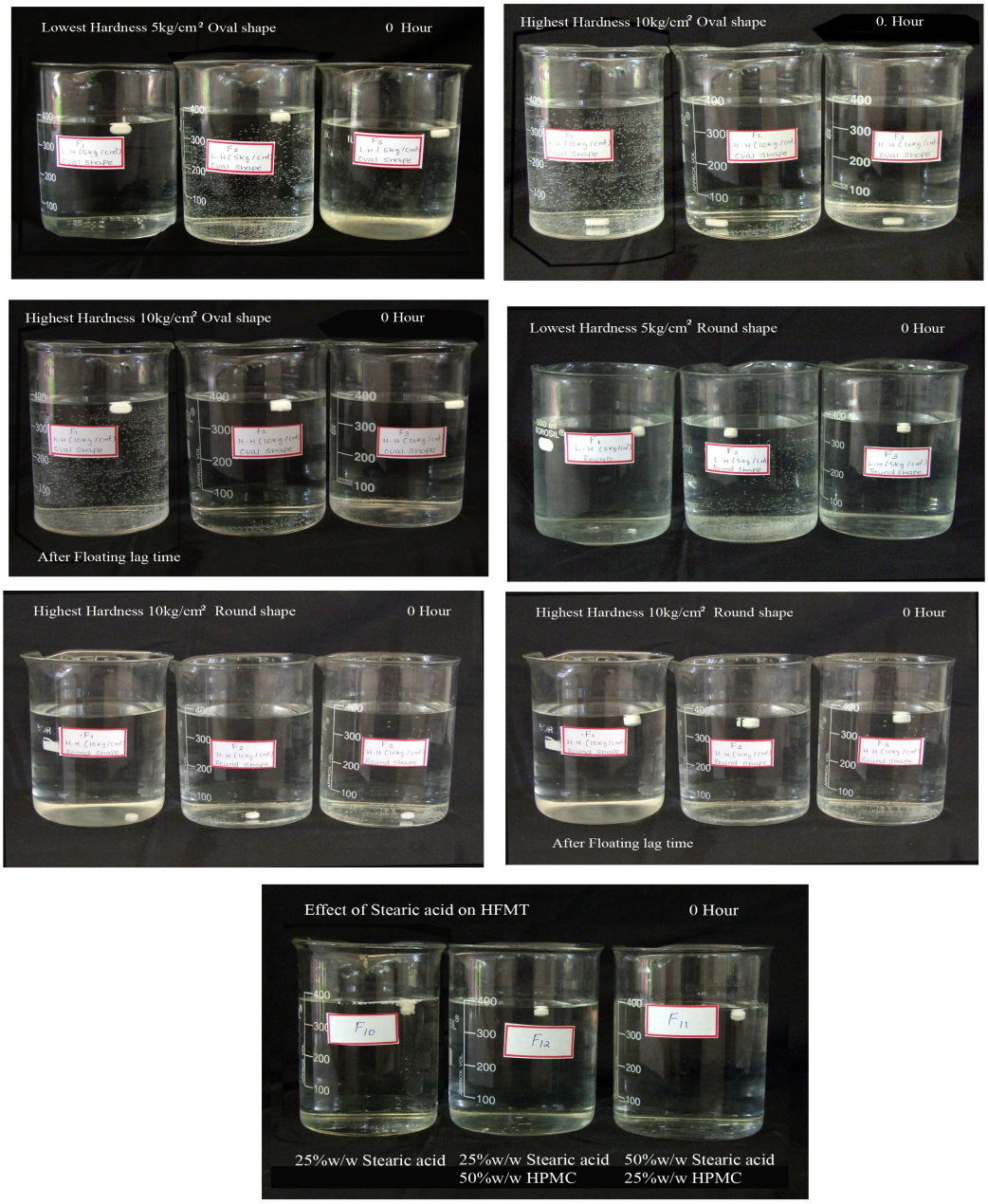
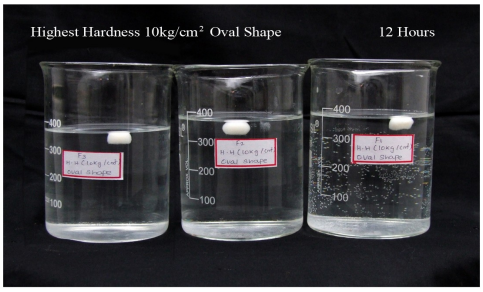
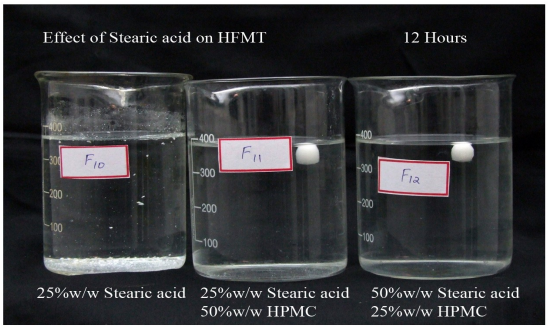
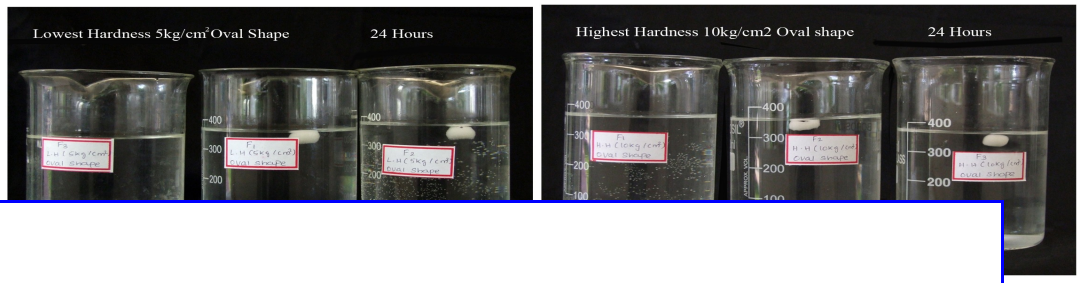


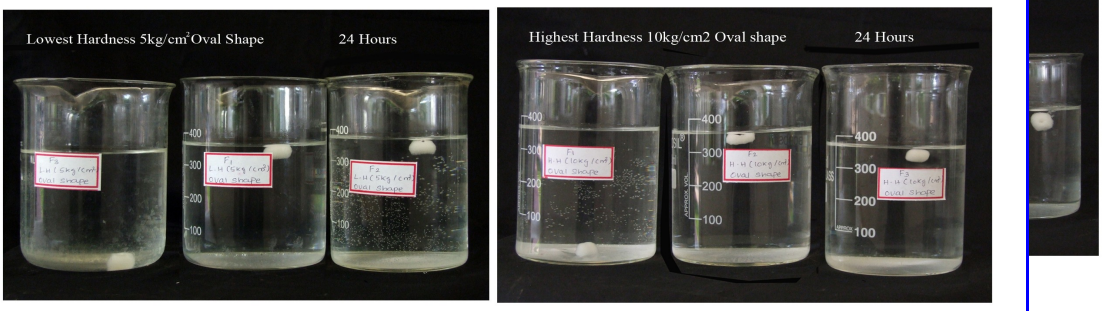
Figure No.18 Effect of Hardness and Effect of Stearic acid on floating behaviors of Hydrophilic Floating Matrix tablet and in Simulated Gastric Fluid pH 1.2 at 12thhr





F
H


Lowest Hardness 5kg/cm²Oval Shape
24 Hours
Highest Hardness 10kg/cm2 Oval shape
24 Hours


Lowest Hardness 5kg/cm²Oval Shape
24 Hours
Highest Hardness 10kg/cm2 Oval shape
24 Hours


Lowest Hardness 5kg/cm² Round shape
24 Hours
Highest Hardness 10kg/cm² Round shape
24 Hours

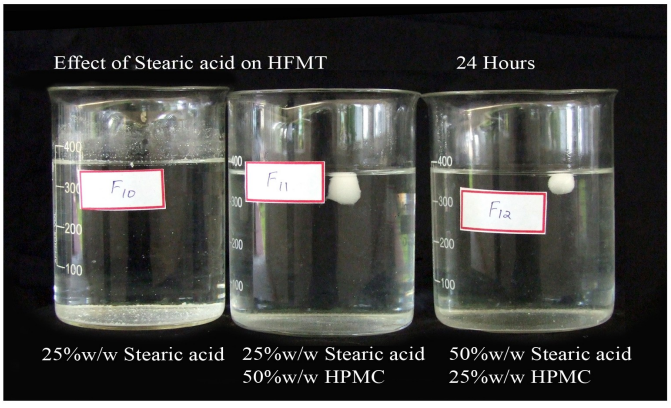

Effect of Stearic acid on HFMT
24 Hours
F10
F11
F12
25%w/w Stearic acid
25%w/w Stearic acid
50%w/w HPMC
50%w/w Stearic acid
25%w/w HPMC

Table No.46 Floating Behaviours of Hydrophilic Floating Matrix Tablets (Simulated Gastric Fluid pH 1.2)

FC	*Lag time in seconds	*Duration of floating time in hours																							
		1	2	3	4	5	6	7	9	8	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
F1	5.0 ±0.10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-
F2	4.5±0.50	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F3	5.0±0.60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F4	4.6±0.40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-
F5	5.0 ±0.50	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F6	5.0±0.40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F7	5.0±0.20	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-
F8	5.0±0.10	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F9	5.0±0.20	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F10	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F11	5.0±0.20	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F12	5.0±0.40	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

***** Average value of three observations

(+) Indicate absence of floating

(-) Indicate presence of floating

Discussion

- The formulations F1, F2, F3 were formulated by using methylcellulose in that F2, F3 showed the better floating in simulated gastric fluid pH 1.2 up to 24 hours.

- The formulations F4, F5, F6 were formulated by using HPMC K 100M in that F5, F6 showed the better floating in simulated gastric fluid pH 1.2 up to 24 hours.
- The formulations F7, F8, F9 were formulated by using HPMC K 4M in that F8, F9 showed the better floating in simulated gastric fluid pH 1.2 up to 24 hours.
- The formulations F10 was formulated by using stearic acid it showed no floating property in the simulated gastric fluid pH 1.2
- The formulations F11, F12 were formulated by using HPMC K 100M and stearic acid in that F11, F12 showed the better floating in simulated gastric fluid pH 1.2 up to 24 hours.

Table No.47 Floating Behaviours of Insoluble Floating Matrix Tablets (Simulated Gastric Fluid)

FC	***Lag time in seconds**	***Duration of Floating Time hours**																							
		1	2	3	4	5	6	7	9	8	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
F13	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-
F14	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-

***** Average value of three observations.

(-) Indicate absence of floating.
(+) Indicate presence of floating.

Discussion

- The Insoluble floating matrix tablets showed Floating behaviour in simulated gastric fluid pH 1.2 up to 12 hours in the form of disintegrated particles instead of intact tablet.

Table No.48 Floating Behaviours of Combined Floating Matrix Tablets (Simulated Gastric Fluid pH 1.2)

FC	*Lag time in seconds	*Duration of Floating Time in hours																							
		1	2	3	4	5	6	7	9	8	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
F15	4.5 ±0.60	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F16	5.0±0.82	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F17	4.8±0.14	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
F18	5.0±0.56	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

***** Average value of three observations.

(-) Indicate absence of floating

(+) Indicate presence of floating

Discussion

- The floating behaviours of Combined Floating Matrix Tablets showed better floating in simulated gastric fluid pH 1.2 for up to 24 hours.

***In vitro* Drug Release Profile**

Dissolution profile for Hydrophilic Floating Matrix Tablets (Simulated Gastric Fluid pH 1.2)

Table No.49 Drug release Characteristics of Hydrophilic Floating Matrix Tablets (Simulated Gastric Fluid pH 1.2)

Time in hours	Methylcellulose			HPMC K100M			HPMC K 4M			Effect of Stearic acid		
	Drug release in %			Drug release in %			Drug release in %			Drug release in %		
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.25	-	-	-	-	-	-	12.50	-	-	-	-	-
0.50	02.99	02.00	01.75	03.37	01.25	-	18.75	05.00	01.23	10.41	1.25	-
0.75	11.70	10.75	10.00	12.50	05.00	05.00	28.75	22.50	06.18	18.75	4.50	-
1	17.90	17.00	16.75	25.00	21.25	12.50	53.75	36.25	12.50	27.08	7.35	2.55
2	29.18	25.40	19.25	33.75	28.75	18.75	63.75	43.75	30.00	40.75	10.00	5.05
3	36.60	36.60	30.45	47.50	40.00	23.75	80.50	62.50	40.00	57.50	15.85	8.75
4	51.60	45.39	50.15	71.25	50.00	32.50	99.00	78.75	48.75	76.04	20.00	12.55
5	95.60	64.60	63.60	87.50	61.25	38.75	-	81.25	62.50	81.66	23.75	16.25
6	-	79.00	79.00	98.50	76.25	46.25	-	98.20	76.25	98.08	27.50	18.75
7	-	97.50	85.35	-	83.75	53.75	-	-	83.75	-	33.75	25.25
8	-	-	92.25	-	97.25	58.70	-	-	96.68	-	37.50	28.75
9	-	-	99.02	-	-	64.50	-	-	-	-	41.25	37.55
10	-	-	-	-	-	75.00	-	-	-	-	46.75	41.25
11	-	-	-	-	-	91.25	-	-	-	-	50.00	43.75
12	-	-	-	-	-	96.42	-	-	-	-	53.75	50.00
14	-	-	-	-	-	-	-	-	-	-	58.90	56.45
16	-	-	-	-	-	-	-	-	-	-	63.75	60.75
18	-	-	-	-	-	-	-	-	-	-	73.75	66.25
20	-	-	-	-	-	-	-	-	-	-	81.50	75.25
22	-	-	-	-	-	-	-	-	-	-	88.75	86.00
24	-	-	-	-	-	-	-	-	-	-	98.75	95.50

Discussion

- The *in vitro* drug release of Hydrophilic Floating Matrix tablet without stearic acid showed their maximum amount of drug release in simulated gastric fluid pH 1.2 before 12 hours.

- The *in vitro* drug release of Hydrophilic Floating Matrix tablet with stearic acid showed controlled drug release from the floating matrix tablet up to 24

Figure No.20 *In vitro* Drug Release Profile of Hydrophilic Floating Matrix Tablets (Methylcellulose as polymer) in Simulated Gastric Fluid pH 1.2

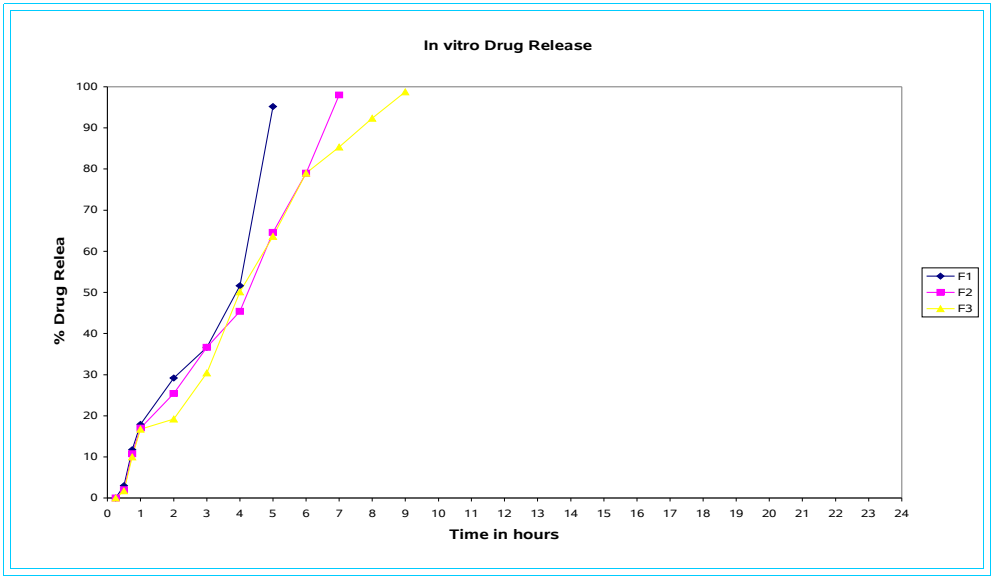


Figure No.21 *In vitro* Drug Release Profile of Hydrophilic Floating Matrix Tablets (HPMC K 100M as polymer) in Simulated Gastric Fluid pH 1.2

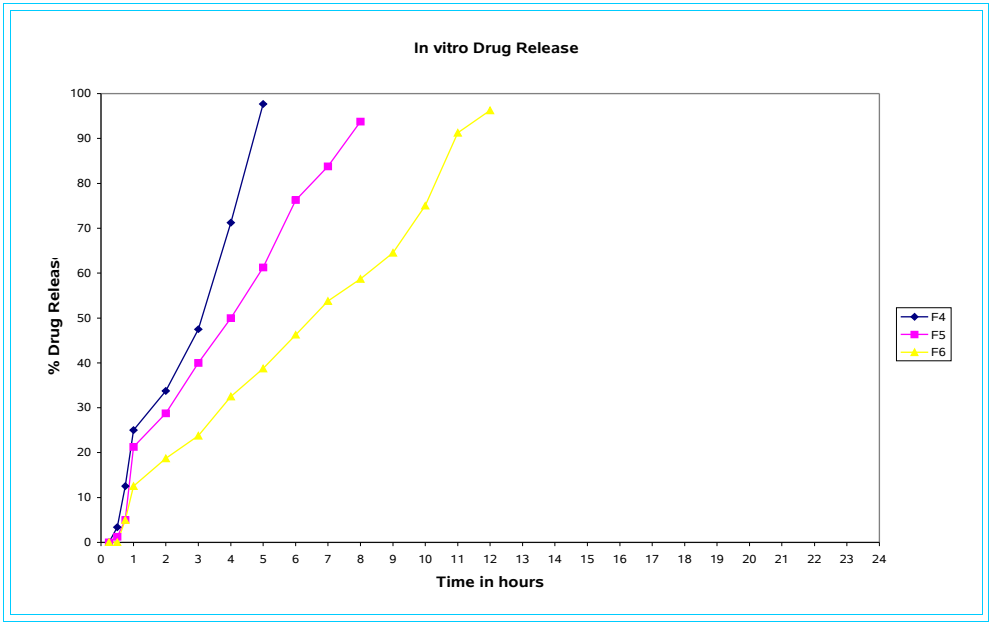


Figure No.22 *In vitro* Drug Release Profile of Hydrophilic Floating Matrix Tablets (HPMC K4 M as polymer) in Simulated Gastric Fluid pH 1.2

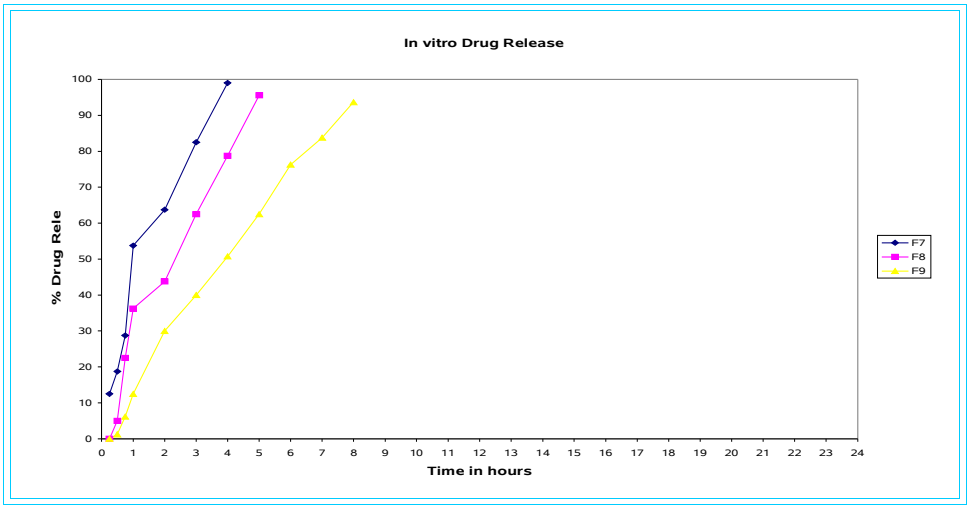
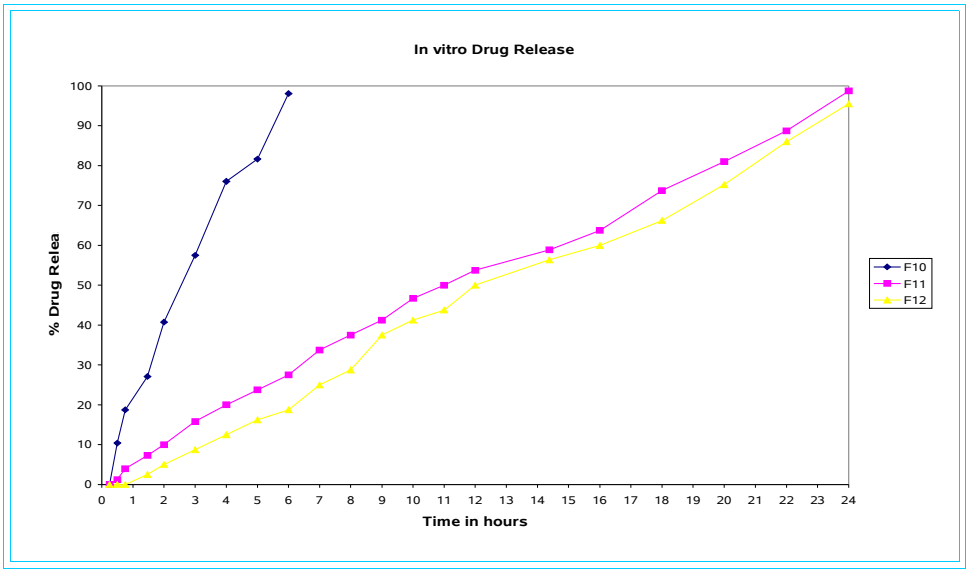


Figure No.23 Effect of Stearic acid in *In vitro* Drug Release Profile of Hydrophilic Floating Matrix Tablets in Simulated Gastric Fluid pH 1.2



hours and maintained their floating in the simulated gastric fluid pH 1.2 up to the required period of time (24 hrs).

Table No.50 Drug release Characteristics of Insoluble Floating Matrix Tablets (Simulated Gastric Fluid pH 1.2)

Time in hours	Ethyl cellulose	Eudragit RSPO
	Drug release in %	Drug release in %
	F13	F14
0.25	-	-
0.50	01.25	03.75
0.75	16.25	17.50
1	37.50	31.50
2	53.75	67.50
3	62.50	77.50
4	68.75	88.50
5	78.75	96.25
6	86.28	-
7	81.25	-
8	94.50	-
9	-	-
10	-	-
11	-	-
12	-	-

Discussion

- The *in vitro* drug release of Insoluble Floating Matrix Tablets showed their maximum amount of drug release in simulated gastric fluid pH 1.2 before 12 hours.

Figure No.24 *In vitro* Drug Release Profile of Insoluble Floating Matrix Tablets in Simulated Gastric Fluid pH 1.2

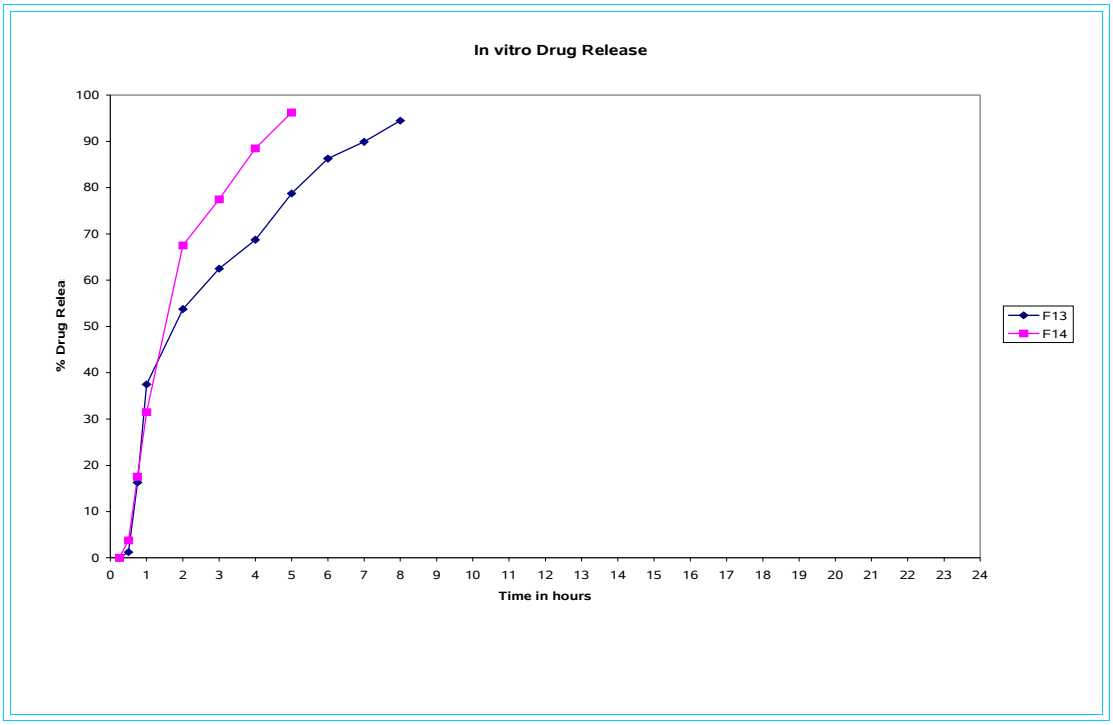


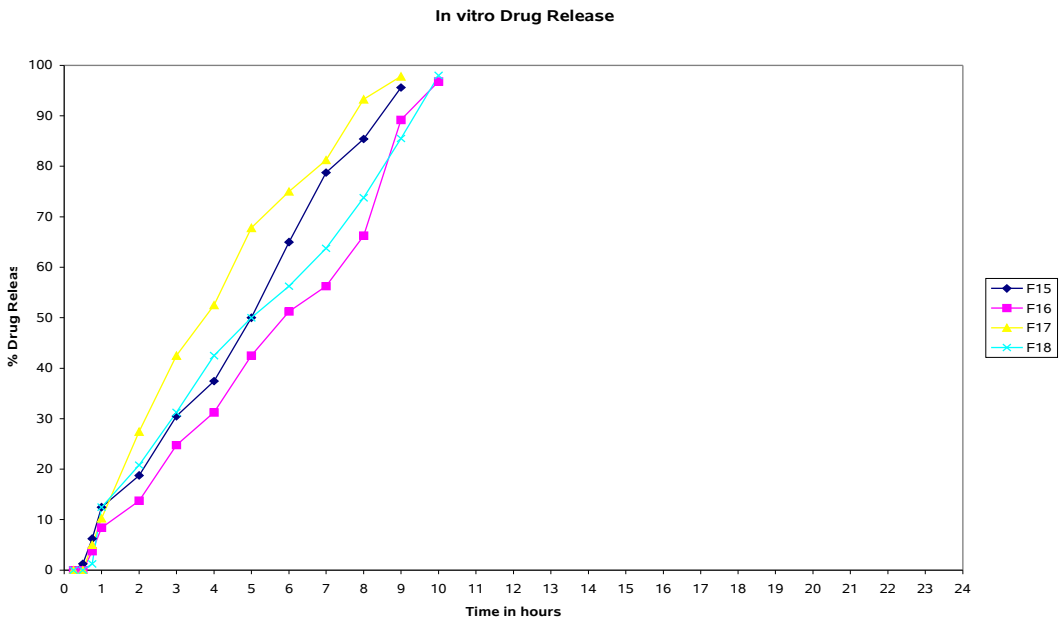
Table No.51 Drug release Characteristics of Combined Floating Matrix Tablets (Simulated Gastric Fluid pH 1.2)

Time in hours	Ethylcllulose and HPMC K 100M		Eudragit RSPO and HPMC K 100 M	
	Drug release in %		Drug release in %	
	F15	F16	F17	F18
0.25	-	-	-	-
0.50	01.25	-	-	-
0.75	06.25	03.75	05.00	01.25
1	12.50	08.40	10.25	12.50
2	18.75	13.75	27.45	20.81
3	30.50	24.75	42.50	31.25
4	37.46	31.25	52.50	42.50
5	50.00	42.50	67.80	50.00
6	65.00	51.25	75.00	56.25
7	68.75	56.20	81.25	63.75
8	81.25	66.40	93.75	73.75
9	95.60	89.20	96.62	88.50
10	-	96.80	-	98.00
11	-	-	-	-
12	-	-	-	-

Discussion

- The *in vitro* drug release of Combined Floating Matrix Tablets showed their maximum amount of drug release in simulated gastric fluid pH 1.2 before 12 hours.

Figure No.25 *In vitro* Drug Release Profile of Combined Floating Matrix Tablets in Simulated Gastric Fluid pH 1.2



***In vitro* Drug Release Profile**

Dissolution profile for Hydrophilic Floating Matrix Tablets in distilled water

Table No.52 Drug release Characteristics of Hydrophilic Floating Matrix Tablets (Distilled Water)

Time in hours	Methylcellulose			HPMC K100M			HPMC K 4M			Effect of Stearic acid		
	Drug release in %			Drug release in %			Drug release in %			Drug release in %		
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.25	-	-	-	-	-	-	-	-	-	-	-	-
0.50	10.41	09.33	10.00	05.00	02.50	-	21.25	06.25	03.71	12.50	-	-
0.75	18.75	15.62	18.73	17.50	06.25	06.25	37.50	25.00	08.00	31.25	01.25	-
1	27.08	27.08	27.08	28.75	21.25	11.25	53.70	37.50	15.00	50.00	05.00	02.55
2	48.75	29.16	33.30	31.25	31.25	26.25	67.50	46.25	32.50	1.25	10.00	05.05
3	57.50	37.50	43.76	46.25	51.25	31.25	97..50	63.75	42.50	80.25	17.50	08.75
4	76.04	55.19	48.75	75.00	65.00	37.50	-	81.25	51.24	86.25	20.00	12.50
5	91.66	72.91	57.00	98.75	78.75	42.50	-	93.75	65.00	98.75	23.75	16.25
6	95.08	77.08	69.37	-	88.75	48.75	-	99.35	80.00	-	27.50	18.75
7	-	85.42	77.50		93.75	55.00	-	-	88.75		33.75	25.00
8	-	96.25	81.25	-	98.75	61.25	-		96.25	-	37.50	28.75
9	-	-	95.65		-	68.75		-	-		41.25	37.50
10	-	-	-	-	-	75.00	-		-	-	43.76	41.25
11	-	-	-	-	-	93.75	-	-	-	-	50.00	43.75
12	-	-	-	-	-	98.70			-		53.75	50.00
14						-	-	-	-	-	56.25	56.25
16	-	-	-	-	-						63.7	60.00

											5	
18						-	-	-	-	-	73.75	66.25
20	-	-	-	-	-						81.00	72.50
22						-	-	-	-	-	88.75	80.00
24	-	-	-	-	-	-	-	-	-	-	98.75	92.50

Discussion

- The *in vitro* drug release of Hydrophilic Floating Matrix tablet without stearic acid showed their maximum amount of drug release in distilled water before 12 hours.
- The *in vitro* drug release of Hydrophilic Floating Matrix tablet with stearic acid showed controlled drug release from the floating matrix tablet up to 24

Figure No.26 *In vitro* Drug Release Profile of Hydrophilic Floating Matrix Tablets (Methylcellulose as polymer) in Distilled Water

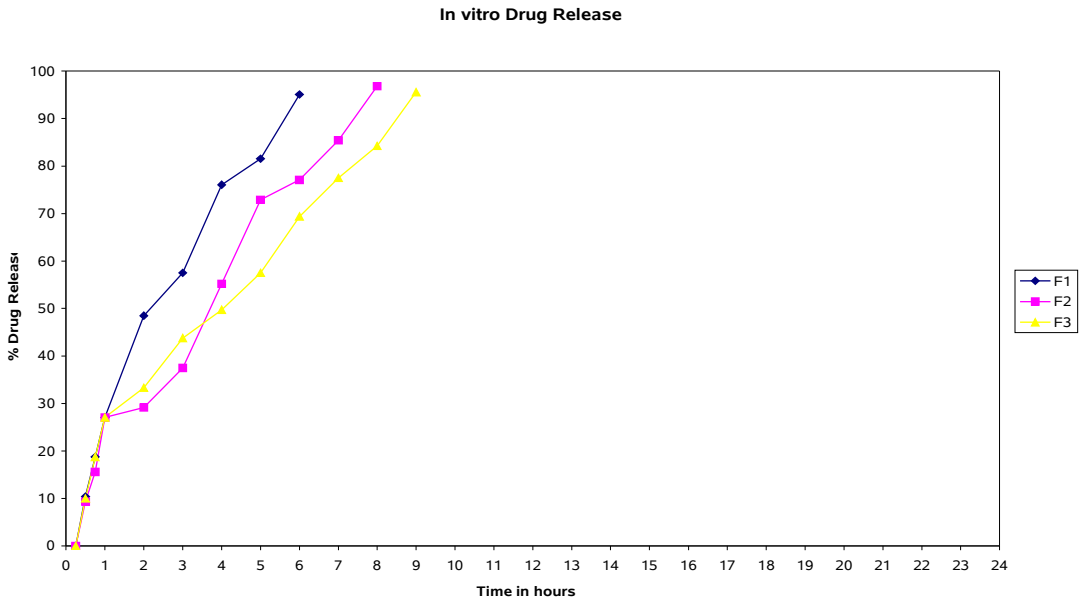


Figure No.27 *In vitro* Drug Release Profile of Hydrophilic Floating Matrix Tablets (HPMC K 100M as polymer) in Distilled Water

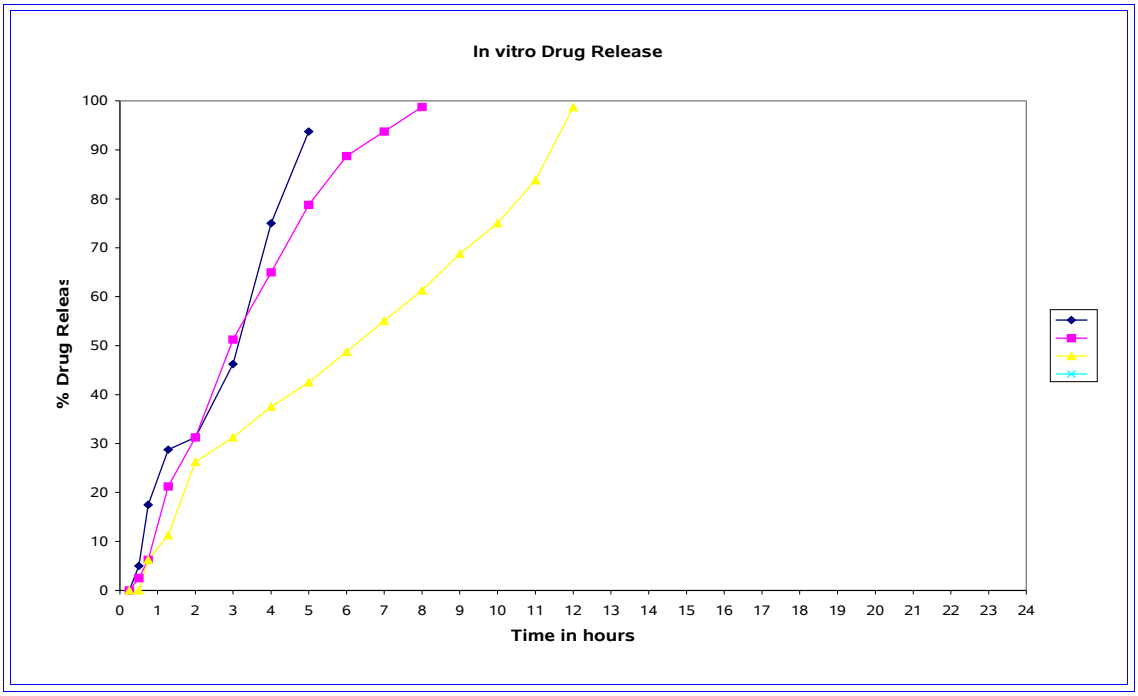


Figure No.28 *In vitro* Drug Release Profile of Hydrophilic Floating Matrix Tablets (HPMC K4 M as polymer) in Distilled Water

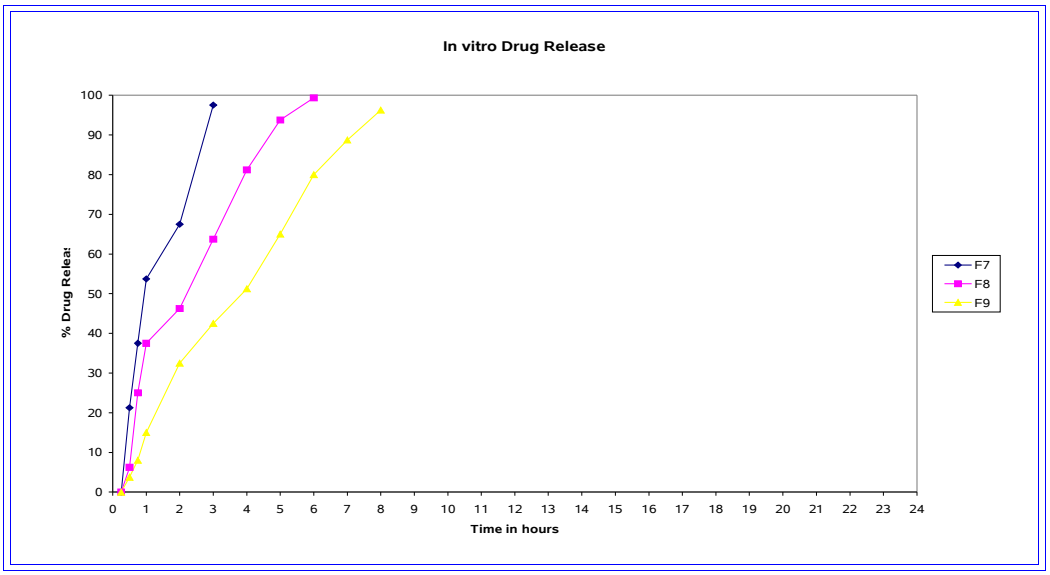
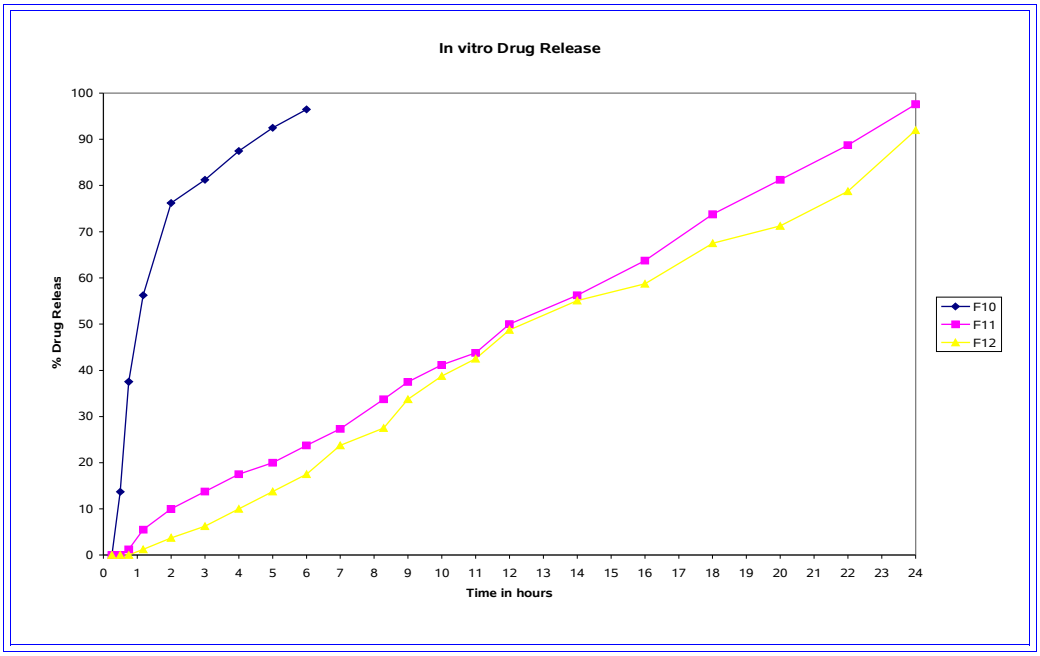


Figure No.29 Effect of Stearic acid in *In vitro* Drug Release Profile of Hydrophilic Floating Matrix Tablets in Distilled Water



o hours and maintained their floating in the distilled water up to the required period of time (24 hrs).

Table No.53 Drug release Characteristics of Insoluble Floating Matrix Tablets (Distilled Water)

Time in hours	Ethyl cellulose	Eudragit RSPO
	Drug release in %	Drug release in %
	F13	F14
0.25	-	-
0.50	03.75	05.00
0.75	17.52	21.25
1	42.50	37.50
2	53.75	67.50
3	64.68	75.00
4	75.00	83.75
5	81.25	96.25
6	92.50	-
7	97.80	-
8	-	-
9	-	-

10	-	
11	-	-
12	-	-

Discussion

- The *in vitro* drug release of Insoluble Floating Matrix Tablets showed their maximum amount of drug release in distilled water before 12 hours.

Figure No.30 *In vitro* Drug Release Profile of Insoluble Floating Matrix Tablets in Distilled Water

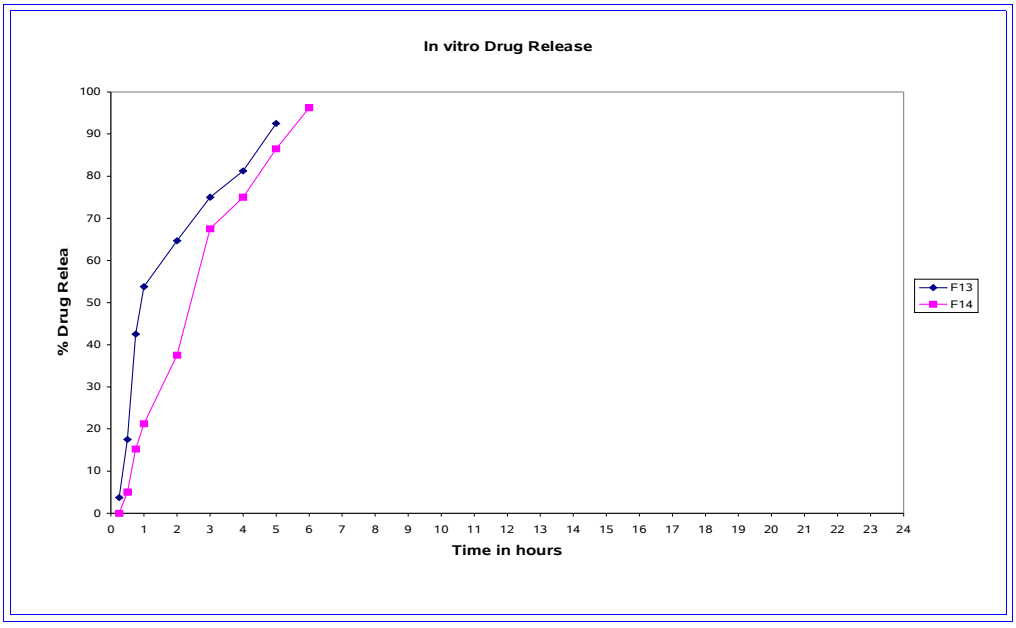


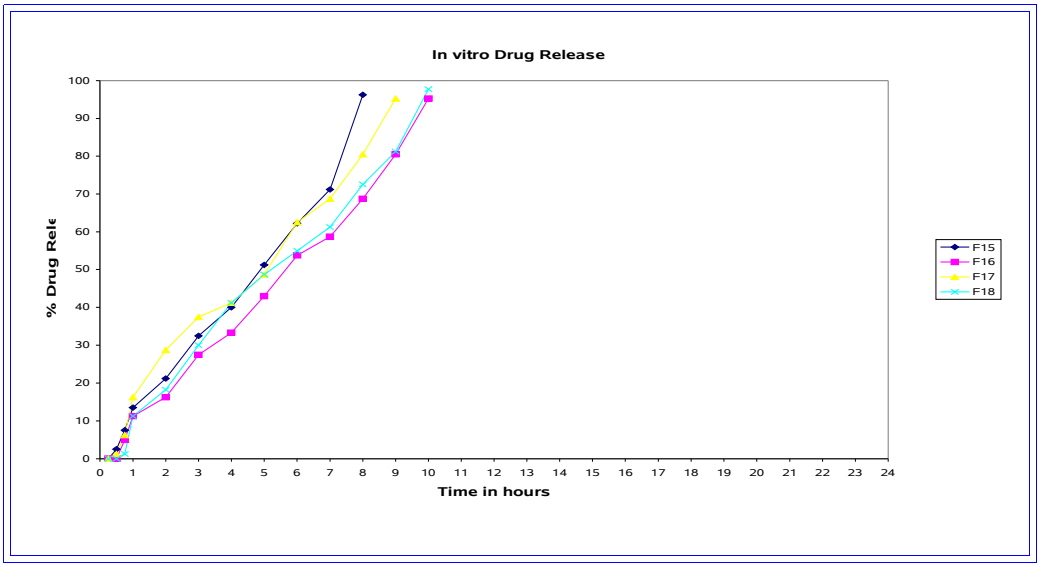
Table No.54 Drug release Characteristics of Combined Floating Matrix Tablets (Distilled Water)

Time in hours	*Ethylcllulose and* HPMC K 100M		*Eudragit RSPO and* HPMC K 100 M	
	Drug release in %		Drug release in %	
	F15	F16	F17	F18
0.25	-	-	-	-
0.50	02.50	-	01.25	-
0.75	07.50	05.00	06.25	01.25
1	13.50	11.25	16.25	11.25
2	21.20	16.25	28.75	18.25
3	32.50	27.50	37.50	30.00
4	40.00	33.35	41.25	41.25
5	51.25	43.00	48.75	48.75
6	62.50	53.75	62.50	55.00
7	71.20	58.75	68.75	61.25
8	96.75	68.75	80.50	72.50
9	-	77.50	97.75	81.25
10	-	95.81	-	96.75
11	-	-	-	-
12	-	-	-	-

Discussion

- The *in vitro* drug release of Combined Floating Matrix Tablets showed their maximum amount of drug release in distilled water before 12 hours.

Figure No.31 *In vitro* Drug Release Profile of Combined Floating Matrix Tablets in Distilled Water



Accelerated Stability Studies

TableNo.55 Stability Studies Reports as per ICH guidelines

Time period in weeks	Parameters				
			Floating behaviours		Drug
	Weight in mg	Hardness kg/cm^2	Lag time (sec)	Duration (hrs)	Content %
0 day	150	5	5	24	98.90
1st week	150	5	5	24	98.78
2nd week	150	5	5	24	98.70
3rd week	151	4.8	5	24	98.66
4th week	151	4.8	5	24	97.89

Discussion

The stability studies of the floating matrix tablets were studied as per ICH guidelines for the period of one month and the percentage drug content of the formulation complied within the limit as per ICH guidelines (ICH limit 5%).

8. Summary and Conclusion

- Several controlled oral drug delivery systems with prolonged gastric residence time have been reported such as Floating system, Swelling system, Mucoadhesive system, High density system and other gastric emptying systems have been commonly used. Floating system has a lower density than the gastric fluid and thus remains buoyancy in the stomach, which retain in the stomach for a prolonged period of time.

- The objective of this thesis work was planned to formulate the floating matrix tablet of Salbutamol sulphate by using different matrix forming material (like hydrophilic, hydrophobic and combined matrix forming material) with an extended drug release for administration as once daily dose.

- Hence this research work entitled "Gastro retentive Drug Delivery System of Salbutamol sulphate: Formulation and its *in vitro* Evaluation" was under taken with the above object to achieve.

- The floating matrix tablet were formulated by using different matrix forming materials and grouped as following:
    1. Hydrophilic Floating Matrix Tablets
    2. Insoluble Floating Matrix Tablets
    3. Combined Floating Matrix Tablets

- The hydrophilic floating matrix tablets were formulated by non-effervescent method by using different hydrocolloids like methyl cellulose, HPMC K100M, HPMC K4M and their floating properties and *in vitro* drug release were evaluated. In addition to the polymer stearic acid was included in the hydrophilic floating matrix tablet and the effects of stearic acid in the *in vitro* drug release were evaluated.

- The insoluble floating matrix tablets were formulated by effervescent method by using different matrix forming material like ethyl cellulose, Eudragit RSPO and their floating properties and *in vitro* drug release were evaluated.

- The combined floating matrix tablets were formulated by non-effervescent method by using hydrophilic (HPMC K100M) and hydrophobic polymer (Ethyl cellulose, Eudragit RSPO) and their floating properties and *in vitro* drug release were evaluated.

- The floating matrix tablets were formulated by optimized formula during the trial on the basis of floating behaviors and *in vitro* drug release for 24 hours.

- The floating matrix tablets were characterized by evaluation of bulk density, flow property, drug content, estimation of hardness and friability .The floating matrix tablets were evaluated for their floating behaviors and *in vitro* drug release in a medium, which mimic the gastric environment like simulated gastric fluid pH 1.2 and water. Different trials were taken to optimize the floating and *in vitro* drug release for prolonged period of time (i.e. upto 24 hours).

- Among the three different floating matrix tablet formulation, the hydrophilic floating matrix tablet formulated with stearic acid showed satisfactory results for the parameters like *in vitro* drug release and floating characteristics. The objective of our project was satisfied.

- The effect of hardness and shape of floating matrix tablets on floating behaviors were studied by formulating floating matrix tablets with different hardness and shape, and their floating behaviors were evaluated. The floating matrix tablet which have hardness of about 5 kg/cm^2 and round shaped tablets shows better

floating than highest hardness of about 10 kg/cm^2 and oval shape as respectively, due to the decrease in porous nature of material were compressed at highest hardness 10kg/cm^2.

- The stability studies of the selected formulation were studied as per ICH specification their drug content, and physical parameters like hardness and floating behaviour were evaluated.

- All the process parameters and results of formulations were found to be satisfactory in the Hydrophilic Floating Matrix tablets with stearic acid for Salbutamol sulphate as Gastro retentive drug delivery system.

- From this study it was concluded that "Gastro retentive Drug Delivery Systems as Floating Matrix Tablets" designed as three different matrix tablet such as Hydrophilic Floating Matrix tablets, Insoluble Floating Matrix Tablets and Combined Floating Matrix Tablets among them the Hydrophilic Floating Matrix Tablets with stearic acid of hardness about 5kg/cm^2 and round shaped tablets could be suitable for floating and controlled the drug release form the dosage form for administration as once daily dose.

Future plan

- Further, the *in vivo* absorption studies by using suitable animal model will confirm their absorption of drug and floating behaviours of the dosage form.

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