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Preparation And Evaluation of Floating Microsphere

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Abstract

Nitazoxanideis belongs to the class of drugs known as thiazolides which used for the treatment of diarrhea. The present work is formulation of Nitazoxanide floating microspheres by using xanthan gum, eudragit s100and HPMC K4M. All the formulations were subjected for pre formulation evaluation. Results of pre-formulation studies, FTIR, SEM, particle size and size distribution, %yield, drug content, buoyancy time, entrapment efficiency, in vitro dissolution and release kinetics. The FTIR Spectra revealed that, there was no interaction between polymers and Nitazoxanide. On the basis of release data of Nitazoxanide formulation F12 showed a good controlled release profile with maximum entrapment efficiency because of optimum polymer concentration i.e., 1:4 ratio (eudragit s100)withsodiumalginate thanother drug: polymer ratios.The invitro dissolution data for best formulation F12were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F12 shows zero order drug release with Super case II transport mechanism.

Key words: nitazoxanide; eudragit s100; sodiumalginate; FTIR; SEM

Introduction:

Novel Drug Delivery System

The design of oral controlled DDS should be primarily aimed to achieve more predictable and increased bioavailability. Now a days most of the pharmaceutical scientist is involved in developing the ideal DDS. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release systems. Controlled release implies the predictability and reproducibility to control the drug release, drug conc in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.1 However, this approach is be dealed with several physiological difficulties such as in ability to restrain and locate the controlled drug delivery system within the desired region of the GIT due to variable gastric emptying and motility. Furthermore, the relatively brief GET in humans which normally average 2-3 hrs through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a DDS in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.2

The basic goal of novel drug delivery system (Remington, 2001) is to achieve a steady state blood or tissue level that is therapeutically effective and non toxic for an extended period of time.

Conventional drug delivery involves the formulation of the drug into a suitable form, such as compressed tablet for oral administration or a solution for IV administration. These dosage forms have been found to have serious limitations in terms of higher doses required lower effectiveness, toxicity and adverse effects. NDDS are being developed rapidly, so as to overcome the limitations of conventional drug delivery.

The method by which a drug is delivered can have a significant effect on its efficacy (Costas Kaparissides et al., 2006). Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues.

From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology.

To minimize drug degradation and loss, to prevent harmful side-

effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. Among drug carriers one can name soluble polymers, micro Chapter I Introduction Formulation Development and In vivo Evaluation of Niosomesparticles made of insoluble or biodegradable natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, niosomes and micelles. The carriers can be made slowly degradable, stimuli-reactive (e.g., pH- or temperature- sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug- loaded system to the site of interest. Two major mechanisms can be distinguished for addressing the desired sites for drug release: (i) passive and (ii) active targeting. An example of passive targeting is the preferential accumulation of chemotherapeutic agents in solid tumours as a result of the enhanced vascular permeability of tumor tissues compared with healthy tissue. A strategy that could allow active targeting involves the surface functionalization of drug carriers with ligands that are selectively recognized by receptors on the surface of the cells of interest. Since ligand–receptor interactions can be highly selective, this could allow a more precise targeting of the site of interest.

Controlled drug release and subsequent biodegradation are important for developing successful formulations. Potential release mechanisms involve:

(i) desorption of surface-bound /adsorbed drugs;
(ii) diffusion through the carrier matrix;
(iii) diffusion (in the case of nanocapsules) through the carrier wall;
(iv) carrier matrix erosion; and
(v) a combined erosion/diffusion process.

The mode of delivery can be the difference between a drug's success and failure, as the choice of a drug is often influenced by the way the medicine is administered. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time.

Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug- carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature).

For over 20 years, researchers have appreciated the potential benefits of nanotechnology in providing vast improvements in drug delivery and drug targeting. Improving delivery techniques that minimize toxicity and improve Chapter I Introduction Formulation Development and In vivo Evaluation of Niosomes efficacy offers great potential benefits to patients, and opens up new markets for pharmaceutical and drug delivery companies. Other approaches to drug delivery are focused on crossing particular physical barriers, such as the blood brain barrier, in order to better target the drug and improve its effectiveness; or on finding alternative and acceptable routes for the delivery of protein drugs other than via the gastro-intestinal tract, where degradation can occur.

Advantages of Novel Drug Delivery System

1. Reduce the number and frequency of doses required to maintain the desired therapeutic response.
2. Reduction in the total amount of drug administered over the period of drug treatment.
3. Reduced blood level oscillation characteristic of multiple dosing of conventional dosage forms.
4. Reduction in the incidence and severity of both local and systemic side effects related to high peak plasma drug concentration.
5. Protection from first pass metabolism and gastro intestinal tract degradation.
6. Maximizing availability with minimum dose.
7. Safety margin of high potency drugs can be increased.
8. Targeting the drug molecule towards the tissue or organ reduces the toxicity to the normal tissues.

Improved patient compliance.

- Increased efficacy of the drug.
- Site specific delivery.
- Decreased toxicity / side effects.
- Increased convenience.
- Shorter hospitalization.
- Viable treatments for previously incurable diseases.
- Potential for prophylactic application.
- Lower health care costs- both short and long term.
- Better patient compliance.

A novel drug delivery system is a system that offer multiple drug delivery forms.

- Oral drug delivery systems,
- Nasal and pulmonary drug delivery systems,
- Parenteral drug delivery systems,
- Implant drug delivery systems,
- Trans dermal drug delivery systems,
- Topical drug delivery systems,
- Protein and peptide drug delivery systems.

Oral Controlled Release Drug Delivery Systems

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed for controlled release systems, the oral route of administration has by far received the most attention with predict to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than other routes.

The most common and popular route for delivering drug in controlled manner or conventional way is known oral route. Historically, oral route of drug administration is predominant route and convenient route for drug delivery. The reasons for selection of oral route include easy of administration and well known gastrointestinal physiology offering flexibility in drug design as dosage forms in different ways. Oral route of drug administration requires least aseptic constraints and their easy manufacturing.

Solid dosage forms (i.e. tablets and capsules) are the majorly administered through oral route before the advances introduced in drug delivery technology. In the last two decades development in drug 3 delivery technology is rapid and many oral novel drug delivery systems invented.

In spite of tablets, capsules, solutions, emulsions and suspensions, they are more superior to the oral conventional formulations. The aid of drug development is to increase safety and efficacy of therapy when administered to patients. In such a way many pharmaceutical industries challenged, optimization of drug properties and the way in which they are delivered from different dosage forms.

Novel oral drug delivery systems are controlled release dosage forms and targeting dosage forms, due to GIT act as barrier for systemically acting drugs and as target site for local action purpose. Generally controlled drug delivery systems delivered drug in controlled manner for systemic absorption and no specified particular area in GIT. While in targeted preparations show their action in a specified area or tissue of the GIT (e.g.: colon, duodenum etc). Targeting systems are either controlled release or in burst at the specific area of the GIT. A new generation in oral drug delivery technology is osmotic activated systems, have recently entered into the market through regulatory approval. All formulations for systemic delivery through oral route of administration, independent of mode of

delivery (immediate or controlled release) and the design of dosage form (either solid or liquid), must be developed within the characteristics of gastro intestinal physiology. Therefore, fundamental understanding of GI physiology, pharmacokinetics, pharmacodynamics and formulation design, are plays an important role in achieve a systemic approach to 4 the successful development of an oral pharmaceutical drug delivery systems.

The successful developments of an oral drug delivery system need the scientific frame work of understanding basic aspects include[3]

- Biopharmaceutical characteristics of the drug,
- The anatomy and physiology of GIT , and
- Physicochemical properties and model delivery by the dosage form to be designed.

though, it is impractical to alter biopharmaceutical characters of drug to be delivered by chemical modifications, such as synthesis of an analog, medically undesirable to modify the anatomy and physiology of GIT, the design of controlled release oral dosage form with optimization of dosage form characteristics with GIT characteristics could provide some opportunity to rationalize the systemic drug delivery with maximum therapeutic benefits.

The term "controlled release oral dosage form" is not new those people working in various fields of pharmaceutical R&D. Really, approximately 30 years ago, the USFDA published regulatory requirements for controlled release systems. From last decades there has also been an increase in the use of controlled release products.

In the searching of oral controlled release drug administration, potential challenged areas include

- Proper delivery system developed for therapeutically effective rate to desirable site for direction required for optimal treatment.
- Change or alteration of GI transit time leads to drug delivery to a target site or to the vicinity of an absorption site and prolongation in drug delivery.
- Reduction of hepatic first pass metabolism via bypass or minimization of extent.

Advantages

- Reduction in dosing frequency easily acceptance of patient.
- Loss of drug can be reduced by targeting.
- Decreasing GI side effects and toxicological effects.
- Fluctuation in plasma drug level minimized.
- Better patient compliance.
- Convenient to administration compared to other routes of administration.
- Stability of drug can be increased.
- Uniform drug effect achieved.
- Delivery of drug in the vicinity of site of action.
- Maintenance of optimal and effective dosage levels for long action.

Disadvantages

There are some disadvantages also encountered in controlled oral drug delivery systems. They are

- It is an expensive process.
- Poor in vitro-in vivo correlation.
- Dose dumping occurred due to polymer burst action at a particular site.
- It is difficult to terminate the toxicity by withdrawal process.

Need Of Controlled Oral Drug Delivery Systems

Controlled release of active ingredients from oral dosage forms may be required for the following reasons,

- Avoidance of undesirable local side effects.
- Local treatment of diseases of GI tract.
- Protection of active ingredients against the influence of digestive fluids.
- Influencing the pharmacokinetics of active ingredients.

Classification Of Oral Controlled Release Systems

The majority of oral controlled release drug delivery systems depends on, diffusion, dissolution or a combination of diffusion and dissolution mechanisms to produce slow release of drug. Depending upon the manner of drug release these systems are classified as

- Dissolution controlled release systems
- Diffusion controlled release systems
- Dissolution and diffusion controlled release systems
- Ion exchange resins
- pH independent formulations
- Osmotic controlled release systems
- Altered density release systems
- AlProdrugs
- Delayed release systems

Dissolution controlled release systems

A drug with a poor dissolution rate will yield an inherently controlled blood drug level. The preparation of controlled release products of highly water soluble drugs by reducing dissolution rate by

- Preparing an appropriate salt derivatives,
- By coating the drug with a slowly dissolving material or
- By incorporation into a tablet with a slowly dissolving carrier.

Encapsulated dissolution systems prepared by application of coating on particles or granules of drug with varying thickness of slowly soluble polymers or by microencapsulation. 9 Matrix dissolution devices are prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet by congealing or aqueous dispersion methods.

Ion exchange resins

This principle has been used for a long time in analytical and protein chemistry. It is an attractive one of controlled drug delivery because drug release characteristics related to the ionic charges of the resin containing drug and should therefore be less susceptible to environmental conditions like enzyme content and pH at the site of absorption. Drug release can be modified by application of coating on the drug-resin complex.

pH independent formulations

The GI tract presents different features that are not fond in other routes of drug administration. The variable nature of the chemical environment throught the GIT is a constraint on dosage form design. Indeed, drugs administered orally would encounter a spectrum of pH ranging from 1 to 1.6. The pH dependency of drug release from controlled release formulations has been demonstrated by study of papaverine hydrochloride.

Osmotically controlled release systems[4]

In these systems, osmotic pressure provides the driving force that produce constant drug release. This system is prepared by applying a semi permeable membrane around an osmotically active drug core or osmotically inactive drug core in combination with 11 osmotically active salt. A delivery orifice made on the system by a high speed – mechanical drill.

Altered density controlled release systems

The GI transit time varies depends on person. In most human subjects, it is the range of 8 to 62 hrs has been found. The specific density of these subunits is found to be a more significant factor than their diameter in influencing theirGI transit time, s

pecifically; increasing density

from 1to 1.6 increases the average transit time from 7 to 25 hrs.

This approach helped in design of floating drug delivery systems and swelling systems.

Prodrugs

A prodrug is chemically modified one which will liberate the active pharmaceutical ingredient in the body either enzymatic or hydrolytic cleavage. The main objective of a prodrug for oral administration is to increase absorption rate or to reduce local side effects.(i.e. GI irritation by aspirin).

Delayed release systems

The development of these systems involves release of drug only at a specific site in the GIT. The drugs formulated in such a systems include i. Known to cause gastric distress, ii. To sensitive of gastric juice or intestinal enzymes, iii. Absorption occurs at a specific intestinal site or iv. To localization at a specific GIT site. 12 The most common ones are intestinal release systems and colonic release systems.

Anatomy and physiology of stomach

The stomach is the most dilated part of the GIT and is situated between the lower end of the oesophagus and the small intestine .Its opening to the duodenum is controlled by the pyloric sphincter .The stomach can be divided into four anatomical regions, namely the fundus, the body, the antrum and the pylorus.

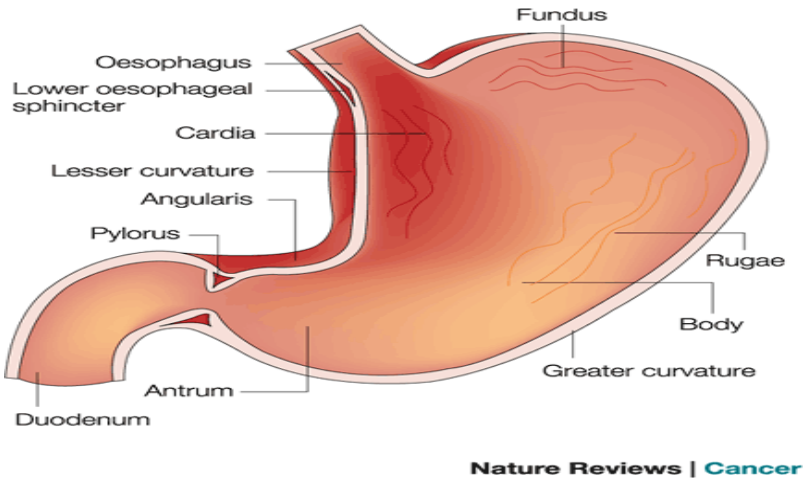

Figure 1: ***Anatomy of stomach***

The two major functions of the stomach are

- To act as a temporary reservoir for ingested food and to deliver it to the duodenum at a controlled rate.
- To reduce the ingested solids to uniform creamy consistency, known as chime, by the action of acid and enzymatic digestion. This enables better contact of the ingested material with the mucous membrane of the intestines and their by facilitates absorption.

Another perhaps less obvious, function of stomach is its role in reducing therisk of noxious agents reaching intestine.

Gastric motility

Gastric emptying occurs during fasting as well as fed states. During the fasting state an inter digestive series of electrical events take place, which cycles through stomach and intestine every 2 to 3 hrs. This is called the inter digestive myloelectric cycle or migrating myoelectric cycle (MMC), which is further divided into 4 phases as described by Wilson and Washington. **5**

Phase I (basal phase) lasts from 40 to 60 min with rare contractions. **Phase II** (preburst phase) lasts for 40 to 60 min with intermittent action and potential contractions. As the phase progresses the intensity and frequency also increases gradually. **Phase III** (burst phase) lasts for 4 to 6 min. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 min and occurs between phases III and I of 2 consecutive cycles.

After the ingestion of a mixed meal, the pattern of contractions, changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm),

which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complication, that of short gastric residence time and unpredictable gastric emptying rate.[6, 7]

Criteria for selection of drug candidate for GRDDS [8]

The GRDDS are suitable for following types of drug therapy

- *Absorption from upper GIT, drugs have a particular site for maximum absorption eg. Ciprofloxacin, whose maximum absorption is in the stomach only. The absorption of Metformin hydrochloride is confirmed to small intestine only and the conventional sustained release dosage forms may have poor bioavailability since absorption appears to diminish when the dosage form pass in to large intestine.*
- *Drugs having low PKa, which remains unionized in stomach for better absorption.*
- *Drugs having reduced solubility at higher pH eg. Captopril and Chlordiazepoxide and the bioavailability of drugs that get degraded in alkaline pH can be increased by formulating gastro-retentive dosage forms eg. Doxifluridine, which degrades in small intestine.*
- *Local action as it is seen in the treatment of H. Pylori by Amoxicillin and Misoprostol for ulcers.*
- *To minimize gastric irritation that may be caused by sudden increase of drug concentration in the stomach eg. NSAIDs.*
- *Improve effectiveness of particular drugs eg. Antibiotics in the colon tend to disturb the micro flora causing overgrowth of micro organisms like Clostridium difficile causing colitis.*
- *Factors affecting gastro retentive system*

The GRT of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, gender, sleep and disease state of the individual (eg. Crohn"s disease and diabetes) and administration of drugs such as prokinetic agents (Mosapiride and Metoclopramide). 9

Density of dosage form

Dosage forms having a density lower than that of gastric fluid experiencefloating behavior and hence gastric retention. A density of <1.0 gm/cm3 is required toexhibit floating property. However, the floating tendency of the dosage form usuallydecreases as a function of time, as the dosage form gets immersed into the fluid, as aresult of the development of hydrodynamic equilibrium.10 The GRDDS are suitable for following types of drug therapy

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Size and shape

Dosage form unit with a diameter of more than 7.5 mm are reported to have an increased GRT competed to with those with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 KSI are reported to have better GIT at 90 to 100 % retention for 24 hrs compared with other shapes.11

Fed or unfed state

Under fasting conditions, the GI motility is characterized by periods of strongmotor activity or the MMC that occurs every 1.5 to 2 hrs. The MMC sweepsundigested material from the stomach and if the timing of administration of theformulation coincides with that of the MMC, the GRT of the unit can be expected tobe very short. However, in the fed state, MMC is delayed and GRT is considerablylonger.12

Nature of the meal

Feeding of indigestible polymers of fatty acid salts can change the motilitypattern of the stomach to a fed state, thus decreasing the GER and prolonging thedrug release.13

Caloric content

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

Frequency of feed

The GRT can increase by over 400 min when successive meals are given compared with a single meal due to the low frequency of MMC.14

Effect of gender, posture and age

Females showed comparatively shorter mean ambulatory GRT than males,and the gastric emptying in women was slower than in men.15The floating and non-floating systems behaved differently. In the uprightposition, the floating systems floated

to the top of the gastric contents and remainedfor a longer time, showing prolonged GRT. But the non-floating units settled to thelower part of the stomach and underwent faster emptying as a result of peristalticcontractions, and the floating units remained away from the pylorus.16 However, insupine position, the floating units are emptied faster than non-floating units of similarsize.17

APPROACHES TO GASTRIC RETENTION

A number of approaches have been used to increase the GRT of a dosage formin stomach by employing a variety of concepts. These include

Floating systems 18

FDDS have a bulk density lower than gastric fluids and thus remain buoyantin the stomach for a prolonged period of time, without affecting the GER. While thesystem is floating on the gastric contents, the drug is released slowly at a desired ratefrom the system. After the release of the drug, the residual system is emptied from thestomach. These results in an increase in the GRT and a better control of fluctuations in the plasma drug concentration. Floating systems can be classified into two distinct categories, effervescent and non-effervescent systems.

Bio/Muco-adhesive systems 19

Bio adhesive or mucoadhesive systems are used to localize a delivery devicewithin the lumen and cavity of the body to enhance the drug absorption process in asite-specific manner. The approaches involve the use of bio adhesive polymers thatcan be adhering to the epithelial surface of the GIT. The proposed mechanism of bioadhesive is the formation of hydrogen and electrostatic bonding at the mucus polymerboundary.

Swelling and expanding systems 20, 21

These are the dosage forms, which after swallowing; swell to an extent thatprevents their exit from the pylorus. As a result, the dosage form is retained in thestomach for a longer. These systems may be named as “plug type system” since theyexhibit the tendency to remain logged at the pyloric sphincter if that exceed adiameter of approximately 12-18 mm in their expanded state. Such polymericmatrices remain in the gastric cavity for several hrs even in the fed state.A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linkingretards the swelling ability and maintains its physical integrity for prolonged period.

High density systems 22

These systems with a density of about 3 g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6- 2.8 g/cm3 acts as a threshold value after which systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is done by heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, and iron powder.

Incorporation of passage delaying food agents 23

Food excipients like fatty acids eg. Salts of myristic acid change and modifythe pattern of the stomach to a fed state, thereby decreasing GER and permittingconsiderable prolongation of release. The delay in the gastric emptying after mealsrich in fats is largely caused by saturated fatty acids with chain length of C10-C14.

Ion exchange resins 24

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place, as a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

Osmotic regulated systems 25

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio erodible capsule. In the stomach the capsule quickly disintegrates to release the Intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components, drug reservoir compartment and osmotically active compartment.

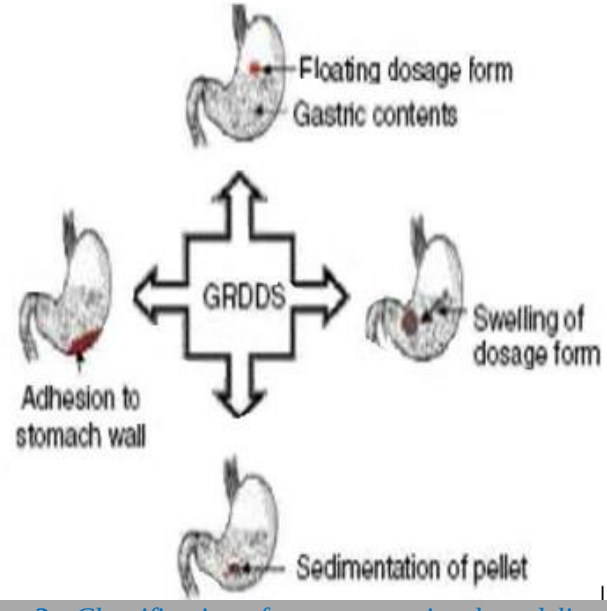

Figure 2 : *Classification of gastro retentive drug delivery*

Floating Drug Delivery Systems (FDDS)

Based on the mechanism of buoyancy, two distinctly

different technologies have been utilized in the development of FDDS, which are effervescent system andnon- effervescent system.

Effervescent system [26, 27, 28]

Effervescent systems include use of gas generating agents, carbonates (Sodium bicarbonate) and other organic acid (Citric acid and Tartaric acid) to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it to float on the gastric fluid. These effervescent systems further classified into two types

- Gas generating systems
- Intra gastric single layer floating tablet or Hydro dynamically balanced system (HBS)

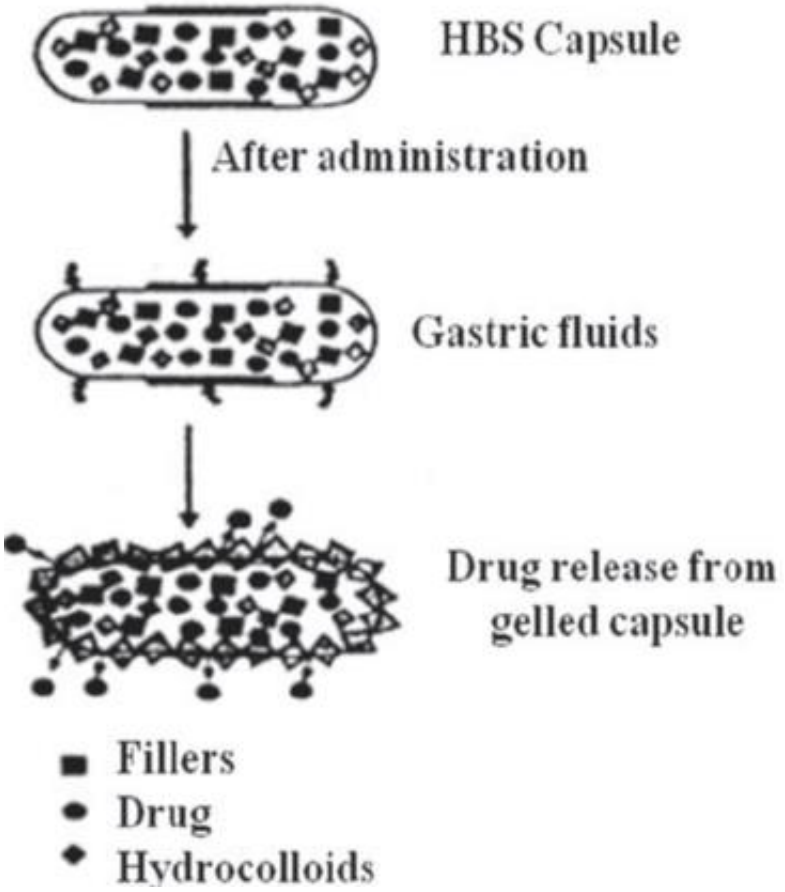

Figure 3 : *Hydro dynamically balanced system*

These are formulated by mixing the CO_2 generating agents and the drug within the matrix tablet (Fig1.3). These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the GER for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

Intra gastric bilayered floating tablets

These are also compressed tablet and contain two layers for:

- Immediate release layer and
- Sustained release layer.

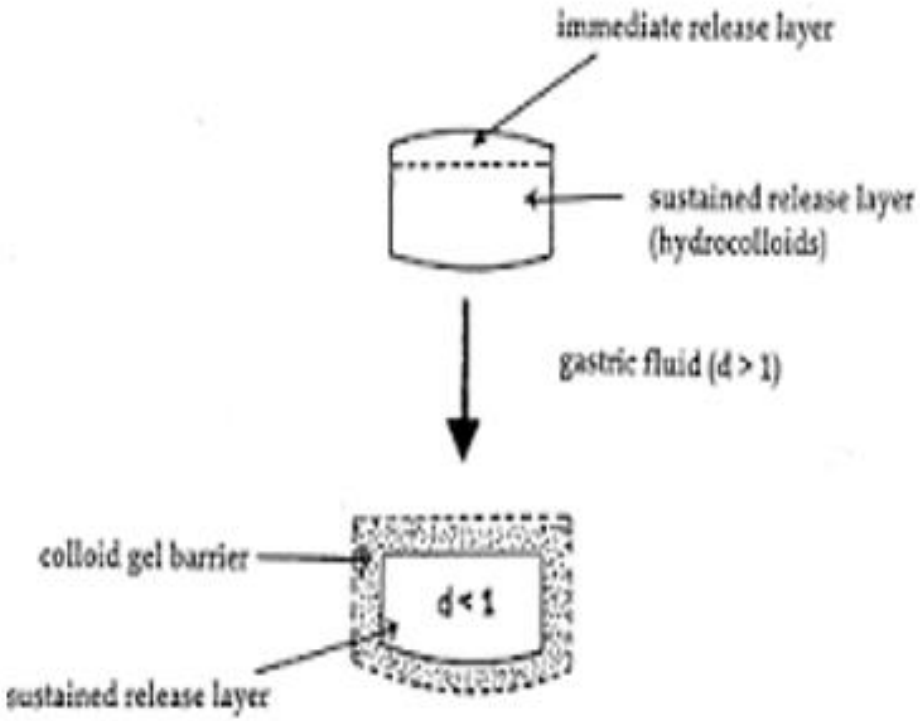

Figure 4 : *Intra gastric bilayer floating tablet*

Multiple unit type floating pills

These systems consist of sustained release pills as seeds surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature it sinks at once and then forms swollen pill like balloon and float as the density decreases.

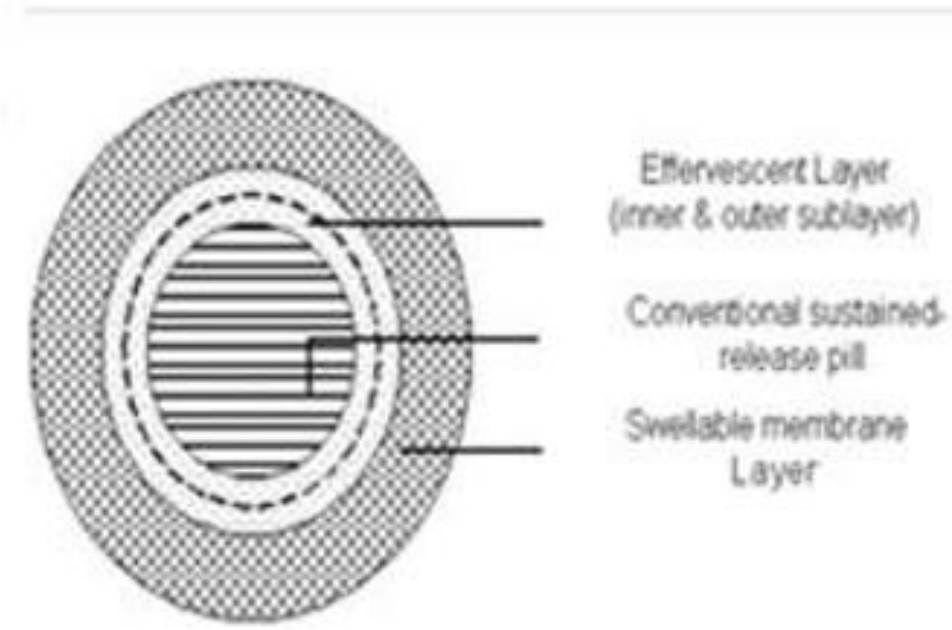

Figure 5 : ***A multi-unit type oral floating dosage system***

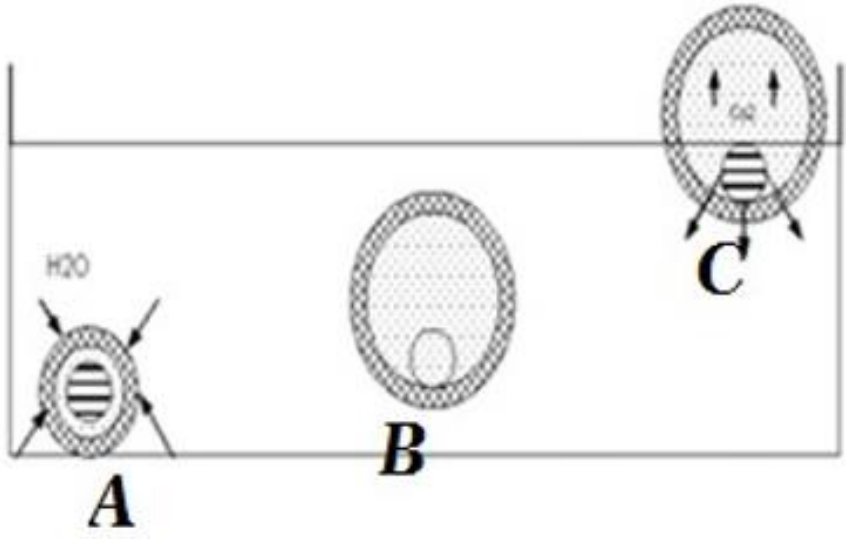

Figure -6 : *Stages of floating mechanism*

A. Penetration of water
B. Generation of CO2 and floating
C. Dissolution of drug

Intra gastric floating gastrointestinal drug delivery system

This system can be made to float in the stomach because of floatation chamber, which may be a vacuum or filled with air or a harmless gas, while drug reservoir is encapsulated inside a microporus compartment.

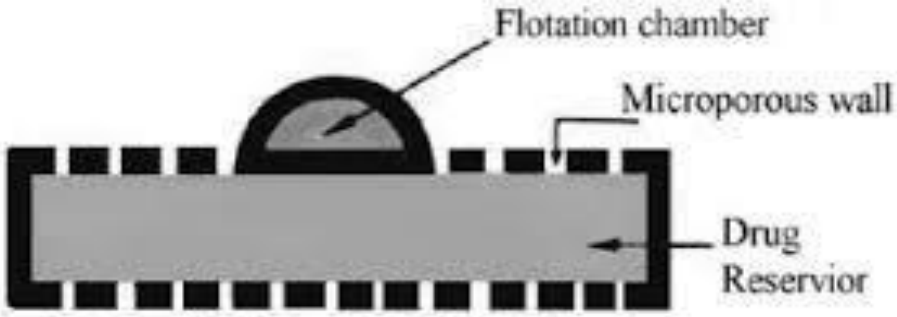

Figure 7 :*Intra gastric floating gastrointestinal drug delivery device Inflatable gastrointestinal delivery systems*

In these systems an inflatable chamber is incorporated, which contains liquid that gasifies at body temperature to cause the chamber to inflate in the stomach. These systems are fabricated by loading the inflatable chamber with a drug reservoir, which can be a drug, impregnated polymeric matrix, then encapsulated in a gelatin capsule. After oral administration the capsule dissolves to release the drug reservoir together with the inflatable chamber. The inflatable chamber automatically inflates and retains the drug reservoir compartment in floating position. The drug continuously released from the reservoir into the gastric fluid.

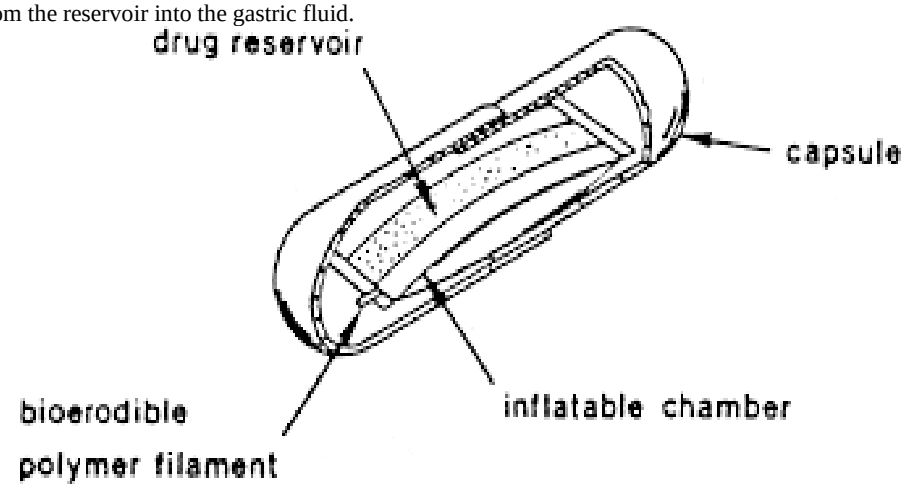

Figure 8 :*Inflatable gastrointestinal delivery system Intragastric osmotically controlled drug delivery system*

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery device consists of two components; drug reservoir compartment and an osmotically active compartment. The drug reservoir compartment is enclosed by a pressure responsive collapsible bag, which is impermeable to vapour and liquid and has a drug delivery orifice. The osmotically active compartment contains an osmotically active salt and is enclosed within a semi permeable housing. In the stomach, the water in the GI fluid is continuously absorbed through the semi permeable membrane into osmotically active compartment to dissolve the osmotically active salt. An osmotic pressure is thus created which acts on the collapsible bag and turns in forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release in solution form through the delivery orifice.

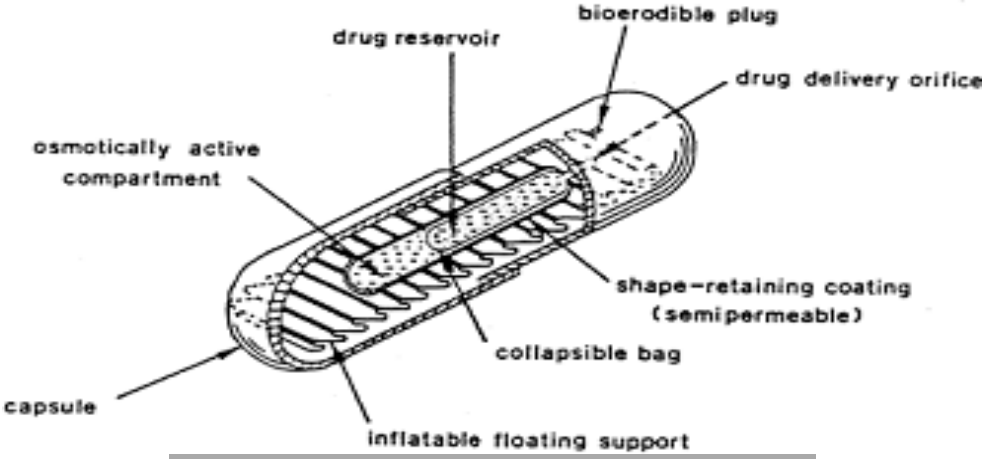

Figure 9 :*Intra gastric osmotically controlled drug delivery system*

Multiple-unit floating (hollow) microspheres by emulsion solvent diffusion technique were prepared with Drug and acrylic polymer. These were dissolved in an ethanol-dichloromethane mixture, and poured into an aqueous solution of PVA with stirring to form emulsion droplets.

The rate of drug release in micro balloons was controlled by changing the polymer to drug ratio. Microbaloons were floatable in vitro for 12 hrs when immersed in aqueous media. Radio graphical studies proved that microbaloons orally administered to humans were dispersed in the upper part of stomach and retained there for 3 hrs against peristaltic movements.

Low density system / floating drug delivery system (FDDS)

Low density system 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.31

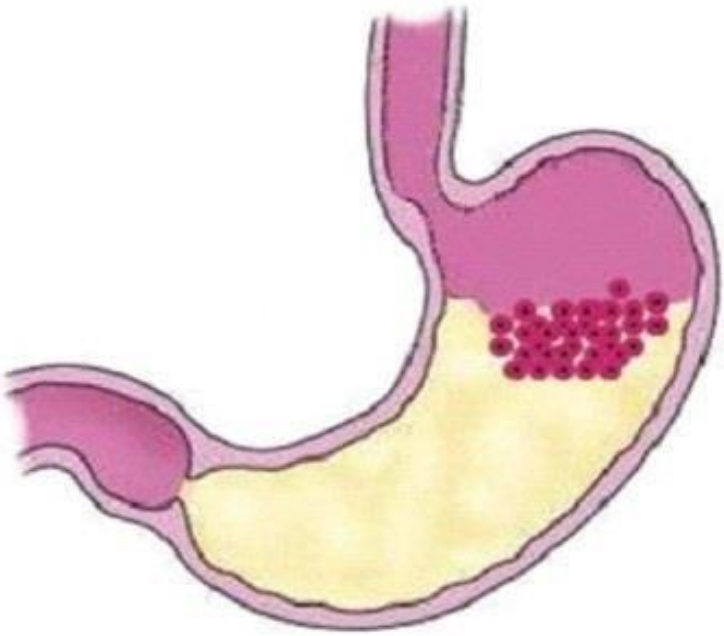

Figure -10 :*Intragastric floating microbaloons drug delivery system*

These are made of the low density materials because of low density core these are called microbaloons. The low density materials used in this method of preparation are Polycarbonate, Eudragit S, cellulose acetate, calcium alginate; agar and low methoxylated pectin are commonly used as polymers.32

Advantages of FDDS 33

The gatroretentive systems are advantageous for drugs absorbed through the stomach eg. Ferrous salts, antacids. Acidic substances like aspirin cause irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
Administration of prolongs release floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents.
It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.

- The gatroretentive systems are advantageous for drugs meant for local action in the stomach eg. Antacids.
- When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Disadvantages of FDDS

- Floating system is not feasible for those drugs that have solubility or stability problem in GIT.
- These systems require a high level of fluid in the stomach for drug delivery tofloat and work efficiently.
- The drugs that are significantly absorbed through out gastrointestinal tract, whichundergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa.

AIM AND OBJECTIVES

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the GRT of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

REVIEW OF LITERATURE

Sachan A.K et al., The work investigated the design and evaluation of microspheres of Nitazoxanide by Ionotropic gelation technique method. 32 Factorial designs were used and concentration of polymer carbopol-934 (X1) and Ethyl cellulose (X2) were selected as the independent variables. The surface morphology study by SEM indicated that microspheres were spherical with smooth surface. There was no interaction between the drug and polymers, as studied by FTIR study. The prepared microspheres were characterized by entrapment efficiency, particle size micromeritic properties. It was observed that on increasing polymer concentration of formulations, % yield, the entrapment efficiency and particle size were increased whereas % drug release decreased. The In Vitro release study was done using U.S.P. dissolution rate basket type apparatus in phosphate buffer pH 7.4 for 10 hr. It shows that on increasing polymer concentration the drug release of all formulations was gradually decreased. In Vitro mucoadhesion study depicts that as the polymer concentration increased, mucoadhesive nature of the formulation was also increased. The microspheres of NTZ (formulation F9) showed best results due to highest drug entrapment efficiency (85.50%), and percentage drug release after 10.0 hr. was 50.25%. The rate of release followed First order kinetics. The microspheres exhibits good mucoadhesive properties in in- vitro wash-off test at pH 7.4 (Intestinal pH) than pH 1.2 (gastric pH),because the drug was completely absorbed in Gastrointestinal tract, Therefore, it can be concluded that Nitazoxanide Loaded algino- carbopol-934 microspheres can be formulated for sustained drug delivery of Nitazoxanide used in Chronic Hipatitis-C. Keywords: Mucoadhesive microspheres, Nitazoxanide, Carbopol-934, Ethyl cellulose, Sodium Alginate, Factorial design.38
Noopur Pandey et al., Gastro retentive dosage forms have potential for use as controlled- release drug delivery systems. Gastro retentive floating drug delivery systems have a bulk density lower than that of gastric fluids and thus increase residence time of drug in stomach and provide controlled delivery of many drugs. The aim of the present study is formulation and characterization of floating microspheres using nateglinide as a model drug for the management of type-2 diabetes mellitus. Floating microspheres were prepared by oil-in-water emulsion solvent evaporation technique using ethyl cellulose and eudragit S-100 as release retarding polymers. The floating microspheres were evaluated for percentage yield (%), particle size, drug content, drug entrapment efficiency, in-vitro floating ability and in-vitro drug release studies. The surface morphology of prepared microspheres was characterized by scanning electron microscopy. The microspheres were found to be spherical in shape and

porous in nature. Compatibility studies were performed by fourier transform infrared (FTIR) technique. The prepared microspheres showed prolonged drug release of 12 h and remain buoyant for more than 12 h. In-vitro release kinetics were studied in different release kinetics models like zero order, first order, higuchi and korsmeyerpeppas model and the best fit model was found to be higuchi plot with release exponent n value less than 0.89. It was concluded that developed floating microspheres of nateglinide offers a suitable and practical approach for prolonged release of drug over an extended period of time and thus oral bioavailability, efficacy and patient compliance is improved. Keywords: Antidiabetic, Ethyl cellulose, Eudragit S-100, Gastro retentive drug delivery, Floating drug delivery system, Emulsion solvent evaporation method.39
Bharti Patel et al., Floating drug delivery system is one of the novel drug delivery system. Floating drug delivery system have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Various approaches have been used to retain the dosage form in stomach as a way of increasing the gastric residence time, including floatation systems, high-density systems, mucoadhesive systems, magnetic systems, unfoldable, extensible, or swellable systems and superporous hydrogel systems. The objective of this study was to prepare and evaluate floating microspheres of losartan potassium for the prolongation of gastric residence time. The microspheres were prepared by solvent diffusion–evaporation method using ethyl cellulose, hydroxypropyl methyl cellulose and sodium alginate as natural polymers. Ethanol/dichloromethane blend was used as solvent in a ratio of 1:2. The floating microspheres were evaluated for flow properties, particle size, zeta potential, drug entrapment, as well as In-vitro release studies and stability studies. The shape and surface morphology of the microspheres were characterized by optical and scanning electron microscopy. The floating microspheres showed particle size, buoyancy, drug entrapment efficiency and yield in the ranges of 331.6 nm, 69±3 to 81±2%, and 60.25±0.25 to 75.65±0.74%and 69.98±0.56

to81.47±0.52%, respectively. Maximum drug release after 12 hr was 99.45 % for formulations F4. Scanning electron micrographs indicate pores both on the surface and interior of the microspheres. Accelerated stability study was also performed for three months indicated that optimized formulation was stable. The developed losartanmicrosphere system is a promising floating drug delivery system for oral sustained administration of losartan.40

Kapil Kumar et al., To prepare and evaluate floating microspheres of curcumin for prolonged gastric residence time and increased drug bioavailability. Floating microsphere were prepared by emulsion solvent diffusion method, using hydroxylpropyl methylcellulose (HPMC), ethyl cellulose (EC), Eudragit S 100 polymer in varying ratios. Ethanol/dichloromethane blend was used as solvent in a ratio of 1:1. The floating microspheres were evaluated for flow properties, particle size, incorporation efficiency, as well as in-vitro floatability and drug release. The shape and surface morphology of the microspheres were characterised by optical and scanning electron microscopy. The floating microspheres showed particle size, buoyancy, drug entrapment efficiency and yield in the ranges of 251 - 387 µm, 74.6 - 90.6 %, and 72.6 - 83.5
%, and 45.5 - 82.0 %, respectively. Maximum drug release after 20 h was 47.1, 55.7, 69.4 and
81.3 % for formulations F1, F2, F3 and F4, respectively. Scanning electron micrographs indicate pores both on the surface and interior of the microspheres. Conclusion: The developed curcumin microsphere system is a promising floating drug delivery system for oral sustained administration of curcumin.Gastro-retentive, Sustained release, Curcumin, Floating microspheres; Ethyl cellulose, Hydroxylpropyl methylcellulose, Eudragit.41

Bharti Patel et al., Floating drug delivery system is one of the novel drug delivery system. Floating drug delivery system have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. Various approaches have been used to retain the dosage form in stomach as a way of increasing the gastric residence time, including floatation systems, high-density systems, mucoadhesive systems, magnetic systems, unfoldable, extensible, or swellable systems and superporous hydrogel systems. The objective of this study was to prepare and evaluate floating microspheres of losartan potassium for the prolongation of gastric residence time. The microspheres were prepared by solvent diffusion–evaporation method using ethyl cellulose, hydroxypropyl methyl cellulose and sodium alginate as natural polymers. Ethanol/dichloromethane blend was used as solvent in a ratio of 1:2. The floating microspheres were evaluated for flow properties, particle size, zeta potential, drug entrapment, as well as In- vitro release studies and stability studies. The shape and surface morphology of the microspheres were characterized by optical and scanning electron microscopy. The floating microspheres showed particle size, buoyancy, drug entrapment efficiency and yield in the ranges of 331.6 nm, 69±3 to 81±2%, and 60.25±0.25 to 75.65±0.74% and 69.98±0.56
to81.47±0.52%, respectively. Maximum drug release after 12 hr was 99.45 % for formulations F4. Scanning electron micrographs indicate pores both on the surface and interior of the microspheres. Accelerated stability study was also performed for three months indicated that

optimized formulation was stable. The developed losartan microsphere system is a promising floating drug delivery system for oral sustained administration of losartan.Losartan Potassium, Floating microspheres, Drug entrapment, In-vitro drug release, Ethyl cellulose, Hydroxyl propyl methylcellulose.42

Ain AK et al., formulated Famotidine floating microspheres by solvent evaporation method using polymer acrycoat S100 and cellulose acetate. The microspheres exhibit prolonged drug release (18 hrs) and remain buoyant for more than 12 hrs.43

Basavaraj B.V et al., studied micro balloons loaded with drug Diclofenac Sodium in their outer polymer shells by novel emulsion solvent diffusion. The ethanol: dichloromethane solution of drug and eudragit-S were poured into an aqueous solution of PVA that was thermally controlled at 40 C. The gas phase generated in the dispersed polymer droplet by the evaporation of solvent formed an internal cavity in the microsphere of the polymer with the drug. The microspheres continuously float for more than 12 hrs in the acidic medium.44

Klausner A et al., were prepared micro baloons by the emulsion-solvent diffusion method using drug Tranilast and acrylic polymer. The drug release profiles from micro baloons exhibited enteric behavior. The release rate was controlled by changing the ratio of polymer to drug in the micro baloons. Most of the micro baloons were floatable in vitro even testing for 12 hrs when immersed in aqueous media, owing to their low particle density (less than unity).45

Sunil KJ et al., studied on porous carrier-based floating Orlistat microspheres for gastric delivery. Calcium silicate is used as porous carrier and eudragit S as polymer. Floating microspheres of Orlistat prepared by the solvent evaporation method, the microspheres found to be regular in shape and highly porous. The microspheres containing 200 mg calcium silicate showed the best floating ability (88% buoyancy) in simulated gastric fluid.46

Chavanpatil M et al., developed Ofloxacin sustained release floating oral delivery system in order to prolong the gastric retention time. Different polymers such as psyllium husk, HPMC K100M, crospovidone were used. It was found that dimensional stability of the formulation increases with the increasing psyllium husk concentration and also in vitro drug release rate increased with increasing amount of crospovidone.47

Srivastava AK et al., prepared floating microspheres of Cimetidine by solvent evaporation method using polymers HPMC and ethyl cellulose. In vitro drug release studies showed that

the prepared microspheres exhibited prolonged drug release (~8hrs) and remained buoyant for more than 10 hrs.48

Nikhil Gupta et al.,studied the tensile properties of glass microbaloons of epoxy resin syntactic foams. Four types of glass microbaloons, having 220, 320, 380 and 460 kg/m3 density, are used with epoxy resin matrix for making the syntactic foam samples. These foams contain 30%, 40%, 50% and 60% microbaloons by volume. The foams containing low strength microbaloons showed lower tensile modulus compared to that of the neat resin but the presence of high strength microbaloons lead to an increase in the tensile modulus of the composites.49

Deepa MK et al., formulated the Cefedoxime Proxetil floating microspheres by non-aqueous solvent evaporation method using polymers such as hydroxyl propyl methyl cellulose (HPMC K 15 M), ethyl cellulose in different ratios of Cefpodoxime Proxetil formulation. The best drug release profiles were seen with formulation at the ratio of drug to polymer was 1:2.50

14.Sahoo SK et al., studied floating microspheres of Ciprofloxacin Hydrochloride. The microspheres were prepared by simple dripping method by using sodium alginate and hydroxy propyl methyl cellulose (HPMC) as a carrier, Sodium bicarbonate was used as the gas forming agent and 1% calcium chloride solution containing 10% acetic acid for carbon dioxide release and gel formation. The enhanced buoyancy and controlled release properties of sodium bicarbonate containing microspheres made them an excellent candidate for floating drug dosage form.51

Madhavi BB et al., developed a new class of antidepressants its higher solubility in water results in burst effect with sudden peak levels of drug in blood. The half lives of Venlafaxine Hydrochloride (VEN). The microbeads were prepared by the ionotropic gelation of sodium alginate in calcium chloride solution. The method had resulted in good encapsulation efficiency and micron sized alginate spheres. The drug release was found to be sustained for 16 hrs and was found to follow the KorsemeyerPeppas kinetics.52

Narendra C et al., developed bilayer floating tablet of Metoprolol Tartarate using different ratio of HPMC K4M and HPMC K10M cp, SCMC and PVP K30. Tablets were studied for in vitro dissolution studies, buoyancy determination, floating time. It showed that increase in conc of both HPMC K4M and HPMC K100M increase floating time and SCMC is required in formulation to maintain the integrity of tablet.53

Jain SK et al., prepared porous carrier based floating granular delivery system of Repaglinide using calcium silicate as porous carrier, HPMC K4M, ethyl cellulose and carbopol 940 as matrix forming polymers and evaluated for its gastro-retentive and controlled release properties, particle morphology, micromeritic properties, in vitro floating behaviour, drug content (%), in vitro drug release, comparison with marketed capsule and in vivo study in albino rat.54

Joseph NJ et al.,developed floating type dosage form (FDF) of Piroxicam in hollow polycarbonate (PC) microspheres capable of floating on simulated gastric and intestinal fluids was prepared by a solvent evaporation technique. Incorporation efficiencies of over 95% were achieved for the encapsulation. In vitro release of Piroxicam from PC microspheres into simulated gastric fluid at 37oC showed no significant burst effect. The amount released increased with time for about 8 hrs after which very little was found to be released up to 24 hrs.55

Guerrero S et al., prepared Ketotifen (KT)-loaded chitosan microspheres (MS) for controlled release delivery systems. Microspheres were prepared by a spray-drying technology followed by treating with glutaraldehyde solutions in methanol as crosslinker. Results showed that very small spherical microspheres with a high load of KT were obtained. KT loading decreased with cross-linking .Interactions between KT and chitosan avoided total KT release from cross- linked MS. After intraperitoneal (i.p.) administration, microsphere aggregations were adhered to muscle subjacent to the tegument and to adipose tissue, and there were no evident sings of rejection; KT was detected in blood stream (0.37–0.25 l g/ml) at 24 hrs, which was longer than the i.p. administration of the drug in solution (39.4 l g/ml at 24 hrs).56

Muzzarellia C et al., prepared chitosan-polyuronan microspheres, in which chitosan were used as cationic polymer and alginic acid, polygalacturonic acid, carboxymethyl cellulose, carboxymethyl guaran, acacia gum, 6-oxychitin, xanthan, hyaluronic acid, pectin, k-carrageenan, and guaran as an ionic polymer. Those made of chitosan– xanthan or chitosan– guaran was unexpectedly found to be soluble in water; similarly, the chitosan–pectin microspheres were almost soluble. The microspheres containing hyaluronic acid or k-carrageenan underwent swelling when contacted with water; the other ones were insoluble. The microspheres were characterized by FTIR, X-ray diffraction spectrometry and scanning electron microscopy. The structural alterations detected were mainly due to interactions between the amino groups and the carboxyl groups.57

Streubel A et al., evaluated single unit FDDS consisting of propylene foam powder (Accurel MP 1002, MP 1000), matrix forming materials, drug and filler. It is observed that all foam powder containing tablets remained floating for at least 8 hrs in 0.1 N HCL at 37oC.58

Li S et al., studied the effect of HPMC (different viscosity grades) and carbopol 934P on the release and floating properties of gastric drug delivery system carried out using factorial design. The study concluded that polymer with lower viscosity was found to be beneficial than the higher viscosity grades of HPMC type in improving the floating properties and incorporation of carbopol however was found to compromised the floating capabilities and release rate of active drug, which might be due to difference in the basic properties of three polymers due to their water uptake potential and functional group substitution.59

Sawicki W et al., prepared Verapamil Hydrochloride (VH) floating pellets using kollicoat SR
30 D as a coating agent and 10% plasticizers like propylene glycol, triethyl citrate and dibuthylsebecate. Two kinds of cellulose, microcrystalline and sodium hydrocarbonate were the main components of pellet core. Tablets were evaluated as regards to effect of upper punch compression force on mechanical strength, friability and floatation starting time. It was proved that increasing compression force contributed to greater hardness, lower friability, lower release and delayed start of floatation time.60

Sriamornsak P et al., prepared Metronidazole emulsion gel beads using calcium pectinate by emulsion-gelation method. It was found that increasing drug to pectin ratio in the beads slowed the drug release from the conventional and EMG beads. The result suggests the release behaviour of EMG beads could be modified by hardening with 2% glutaraldehye or by coating with eudragit RL.61

Rao, MR et al., developed Rosiglitazone maleate microspheres by solvent diffusion– evaporation. A full factorial design was applied to optimize the formulation. The results of 32 full factorial design revealed that the conc of ethyl cellulose 7 cps (X1) and stirring speed (X2) significantly affected drug entrapment efficiency, percentage release after 8 hrs and particle size of microspheres.62

Kamila M et al.,developed multiunit floating drug delivery system of Rosiglitazone maleate (RZM) by encapsulating the drug into eudragit RS100 through non aqueous emulsification/solvent evaporation method. In vitro release was optimized by a {3, 3} simplex lattice mixture design to achieve predetermined target release. The in vivo performance of the optimized formulation was evaluated in streptozotocin-induced diabetic rats. In vivo evaluation

in albino rats suggested that floating microspheres of RZM could be a promising approach for better glycemic control.63

Senthil Kumar SK et al., developed floating microsphere using Rabeprazole Sodium (RS) as a model drug for prolongation of the gastric retention time. The microspheres were prepared by the solvent evaporation method using different polymers like hydroxy propyl methyl cellulose and methyl cellulose. The average diameter and surface morphology of the prepared microsphere were characterized by optical microscope and scanning electron microscopic methods respectively. In vitro drug release studies were performed and the drug release kinetics was evaluated using linear regression method. The effect of various formulation variables on the size and drug release was investigated.64

Barhate SD et al., developed multiparticulate gastro retentive drug delivery system of Ketorlac Trometamol. The gastro retentive drug delivery system can be prepared to improve the absorption and bioavailability of ketorlac Trometamol by retaining the system in to the stomach for prolonged period of time. The floating drug delivery system of Ketorlac Trometamol was prepared by emulsion solvent diffusion method by using ethyl cellulose, HPMC K4M, Eudragit R 100, Eudragit S 100 polymers in varying concentration. The optimized formulation shows good buoyancy and In vitro controlled release of Ketorlac Trometamol.65

METHODS

Preformulation studies:68-69 Solubility studies:
Nitazoxanide :

Solubility of Nitazoxanide wasdetermined in water, 0.1 N HCl, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Nitazoxanide in different beakers containing different solvents. The mixtures were shaken for 48hrs in rotary shaker. The solutions were centrifuged for 10mins at 1000 rpm and supernatant were analyzed at 238 nm by using UV Spectrophotometry.

Determination of UV spectrum of Nitazoxanide:

10mg of Nitazoxanide was dissolved in 2ml of methanol then makeupto10ml with 0.1N HCl so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 0.1N HCl to get the concentration of 100µg/ml concentration. From this stock solution pipette out 1ml of the solution and makeup the volume to 10ml using 0.1N HCl to get the concentration of 10µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of standard calibration curve of Nitazoxanide in 0.1N HCl Preparationof StandardCalibrationCurveofNitazoxanide in pH 1.2 Acidic buffer 10mgofNitazoxanide wasaccurately weighedandtransferredinto10mlvolumetric flask.It was dissolved and diluted to volumewith pH 1.2 Acidic buffer to give stock solution containing1000µg/ml. Thestandardstocksolutionwasthenserially dilutedwithpH 1.2 Acidic buffer toget5to30µg/mlofNitazoxanide .Theabsorbanceof the solutionwere measuredagainstpH
1.2 Acidic buffer asblankat238 nm using UV visible spectrophotometer. The absorbance valueswereplotted againstconcentration (µg/ml) to obtain the standard calibration curve.

Drug-Excipient Compatibility Studies:

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation studies must generate the needed information.
FT-IR Studies:

Physical compatibility studies were assured by FT-IR studies. The IR spectrums of the mixed powders were taken by preparing Potassium bromide pellets under dry condition by using pellet press. Spectra are superimposed. The transmission minimal (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards.

Results

PREFORMULATION STUDIES:

Solvents	Solubility (µg/ml)
6.8pH Buffer	0.468
7.4pH Buffer	0.653
0.1N Hcl	1.201

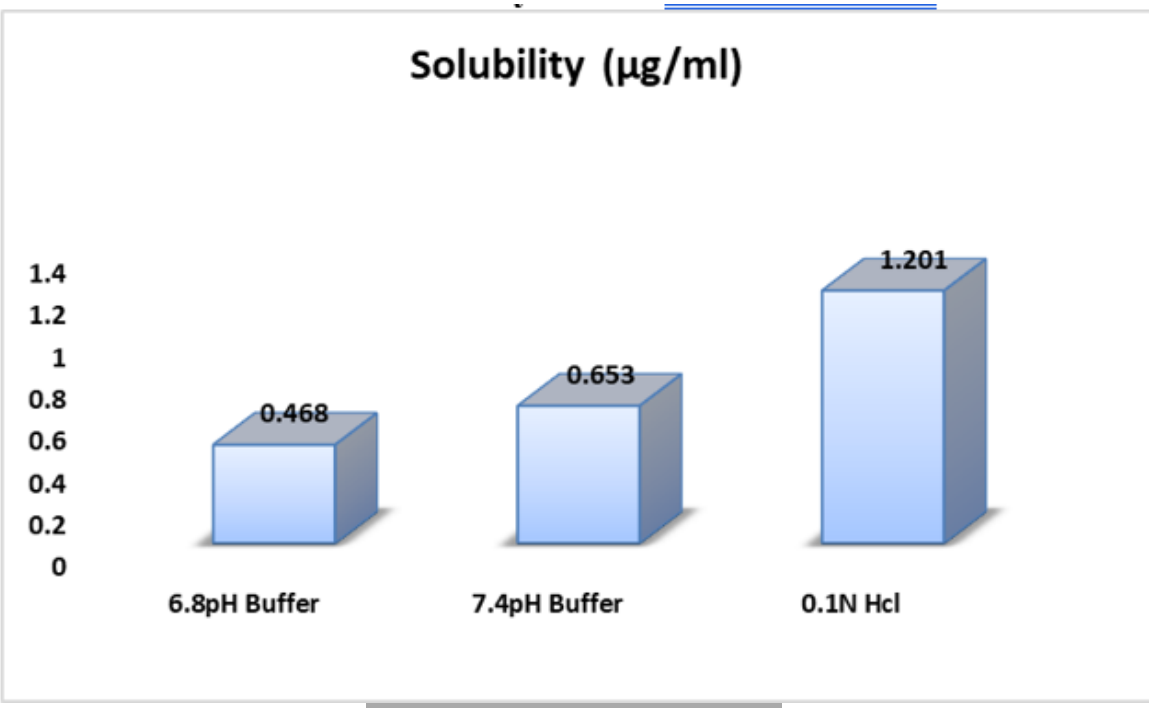

Figure : ***Solubility studies of Nitazoxanide***

Discussion: The IR spectrum of pure drug was found to be similar to the standard spectrum of Nitazoxanide. From the spectra of Nitazoxanide, combination of Nitazoxanide with polymers, it was observed that all characteristic peaks of Nitazoxanide were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and excipients.

CONCLUSION

The concept of formulating floating microspheres containing Nitazoxanide offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. In present work, floating microspheres of Nitazoxanide were prepared successfully by ionotropic gelation method using different polymers. From the above experimental results itcan beconcluded that:

- Preformulation studies like melting point, solubility and UVanalysis complied with standards.
- The FTIR Spectra revealed that, there was no interaction between Nitazoxanide and polymers.
- Surface smoothnessof the Nitazoxanide microspheres was confirmed by SEM.
- As the ratio of polymer was increased, the mean particle size of Nitazoxanide floating microspheres was decreased. Nitazoxanide floating microspheres with normal frequency distribution were obtained.
- From the results of entrapment efficiency it can be inferred that there was a proper distribution of Nitazoxanide in the microspheres and the deviation was within the acceptable limits.
- The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. The in vitro performance of Nitazoxanide Floating microspheres showed prolonged andcontrolled releaseof drug, with Xanthan gum and HPMC K4M then Eudragit s100.
- From the drug release kinetics of the Nitazoxanide floating Microspheres, it was concluded that the formulation F12 follows zero order drug release with super case-II transport mechanism.
- Based upon the preliminary data and in vitro dissolution studies of Nitazoxanidefloating microspheres it was concluded that the formulation of floating microspheres was successfully formulated by using sodium alginate along with Eudragit S100.

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