Place: Madurai

Date:

CERTIFICATE

This is to certify that the Dissertation entitled **"NOVEL APPROACHES ON THE DESIGN AND EVLUATION OF FLOATING DRUG DELIVERY SYSTEMS OF GLIPIZIDE"** submitted by **D. RAMYA DEVI**, in partial fulfillment of the requirement for the award of degree of **Master of Pharmacy** in **Pharmaceutics** is a bonafide work carried out by her, under my guidance and supervision during the academic year 2007-2008 in the Department of Pharmaceutics, Madurai Medical College, Madurai - 625 020, affiliated to the **The Tamil Nadu Dr. M.G.R. Medical University, Chennai.**

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motivated me in the successful completion of each and every stage of my project work.

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CHAPTER – I

INTRODUCTION

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, aerosols, injectables etc. But historically, oral drug administration has been the predominant route of administration for drug delivery. [1, 85]

Conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescription and over the counter drug market. But, conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment only when taken several times a day. This results in a significant fluctuation in drug levels.

There are several terms used interchangeably viz. controlled release, programmed release, sustained release, prolonged release, timed release, slow release, extended release and other such dosage forms. However, controlled release differs from sustained release systems which simply

least aseptic constraints and flexibility in the design of the dosage form.

The fate of drug after oral administration is shown in Fig 2: [4]

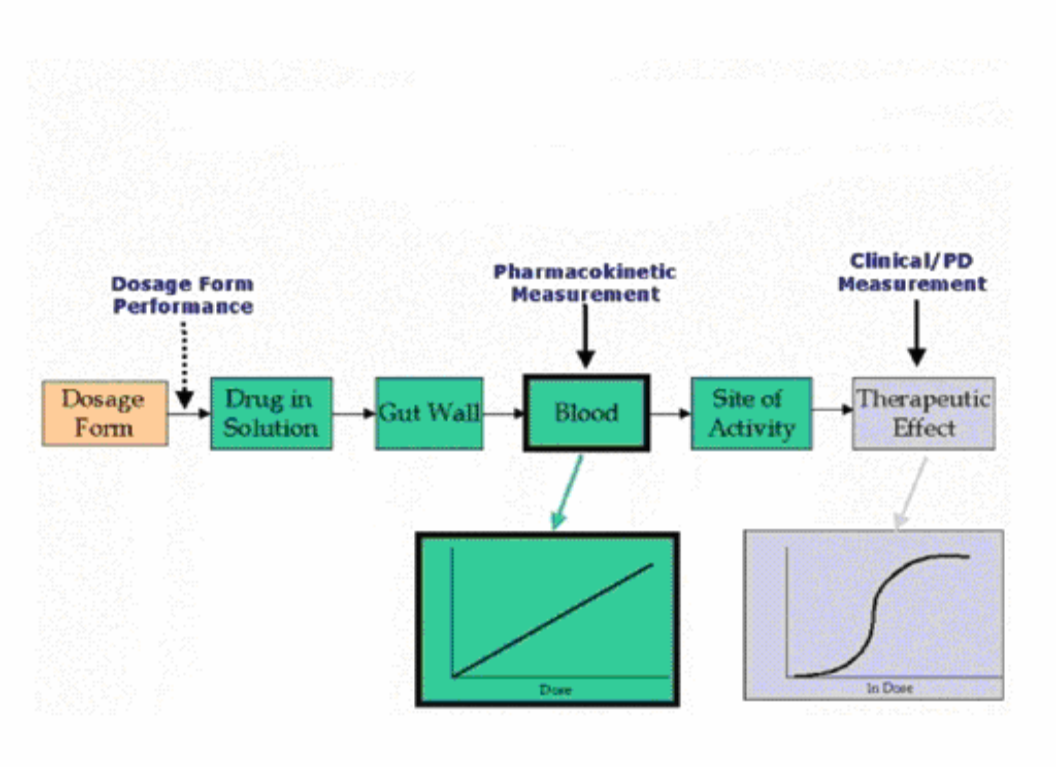


Fig 2: Model of Oral Dosage Form Performance

The objective of any drug delivery system is to release promptly a therapeutic amount of drug at the site of administration, and then to maintain the desired therapeutic drug concentration at the site of action that elicits the desired pharmacological action, also it minimizes the incidence and the severity of unwanted adverse effects. An appropriately designed for extended / sustained release dosage form can be a major advancement in this direction.

Therapeutic advantages of Extended Release dosage forms include,

- reduction in the frequency of drug administration
- improved patient compliance
- maintenance of drug level in blood without oscillations
- reduction in total amount of drug administered
- maximum availability with minimum dose
- improved treatment of many chronic illness
- reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients.

During past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached. [1]

4. Ion-exchange resin-drug complexes
5. Slow dissolving salts and complexes
6. pH dependent formulations
7. Osmotic pressure controlled systems
8. Hydrodynamic pressure controlled systems

B. Delayed Transit and Continuous Release Systems: These systems are designed to prolong their residence in the GIT along with their release. Often, the dosage form is fabricated to detain the stomach and hence the drug present therein should be stable to gastric pH. Systems included in this category are:

1. Altered density systems
2. Muco-adhesive systems
3. Size-based systems

C. Delayed Release Systems: The design of such systems involve release of drug only at a specific site in the GIT. The drugs contained such a system are those that are destroyed in the stomach or by intestinal enzymes, or known to cause gastric distress, or absorbed from a specific intestinal site, or meant to exert local effect

absorption. Bioadhesive, super porous hydrogel, floating and expanding systems shows the most promising potential for achieving the goal of gastric retention. [7] From the formulation and technological point of view, the floating drug delivery system is considerably easy and logical approach. [8]

Gastric retentive dosage forms have been investigated to provide controlled release therapy for drugs with reduced absorption in the lower gastro intestinal (GI) tract or for local treatment of diseases of the stomach or upper GI tract. Gastric retentive dosage forms rely on either natural GI physiology, such as floating or large tablets that depend on delayed emptying from the fed stomach, or those dosage forms that are designed to fight the physiology and avoid emptying in the fasted state through dosage forms of larger sizes with or without flotation or bioadhesion. [9]

Oral administration of a medication by means of controlled drug delivery systems should ideally enable to obtain the required plasma concentration and to maintain the steady state level for a prolonged period of time.

they can float on the gastric juice in the stomach and release the drug in sustained manner.

• the use of passage-delaying excipients (for example triethanolamine myristate)

• the utilization of specially designed dosage forms such as 'heavy pellets' and large single-unit delivery systems

• bioadhesive or mucoadhesive systems containing bio/mucoadhesive agents, enabling the device to adhere to the stomach (or other GI) walls, thus resisting gastric emptying

• epichlorohydrin cross-linked pectins used as colon specific drug delivery carriers to prolong the residence time.

• omeprazole magnesium as multiple-unit pellet systems (MUPS).

Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is

CHAPTER – II

FLOATING DRUG DELIVERY SYSTEMS – A REVIEW

Floating drug delivery systems are the dosage forms that remain buoyant upon the gastric contents for a prolonged period of time and to consequently enhance the bioavailability of all drugs which are well-absorbed from the proximal gastrointestinal tract. The lasting intra gastric buoyancy of a controlled release dosage form also provides a suitable manner to constantly deliver a drug locally into the stomach and hence achieve a sustained site-specific therapeutic action. [12]

A floating drug delivery system with prolonged residence time in the stomach is of particular interest for drugs that: [13]

i) are locally active in the stomach
ii) have an absorption window in the stomach or in the upper part of the small intestine
iii) are unstable in the intestinal or colonic environment
iv) exhibit low solubility at high pH values.
v) have better dissolution in weak bases [14]
vi) are degraded in the colon [15]

produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations.

$$RW \text{ or } F = F_{buoyancy} - F_{gravity}$$

$$= (Df - Ds)\, gV,$$

where RW = total vertical force, Df = fluid density, Ds = object density, V = volume and g = acceleration due to gravity.

In case of gas generating systems, carbon dioxide is released, causing the beads to float in the stomach (Fig. 4c). And in case of non-effervescent systems, the air trapped by the swollen polymer confers buoyancy to these dosage forms (Fig. 4a).

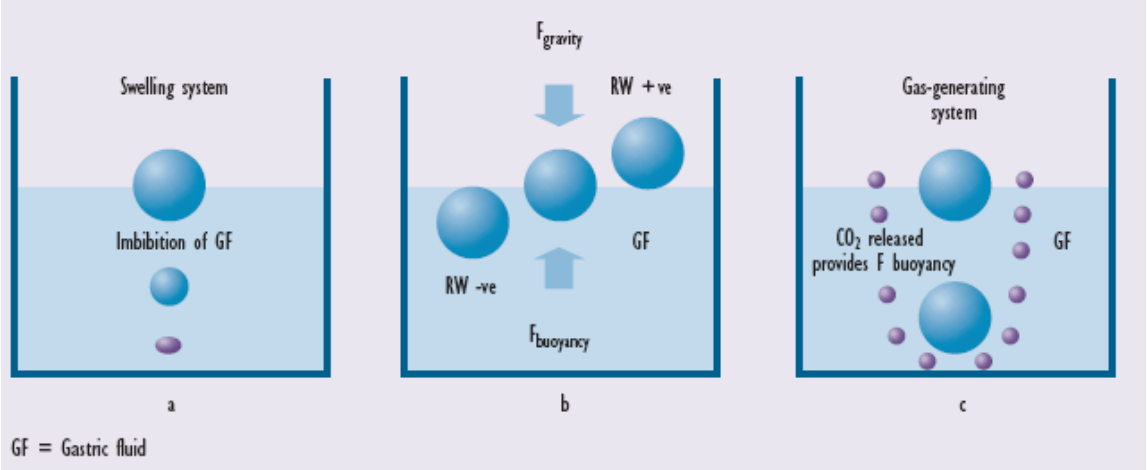


Fig 4: Mechanism of Floating systems

The anatomy of the GI tract is shown in the Fig. 5.

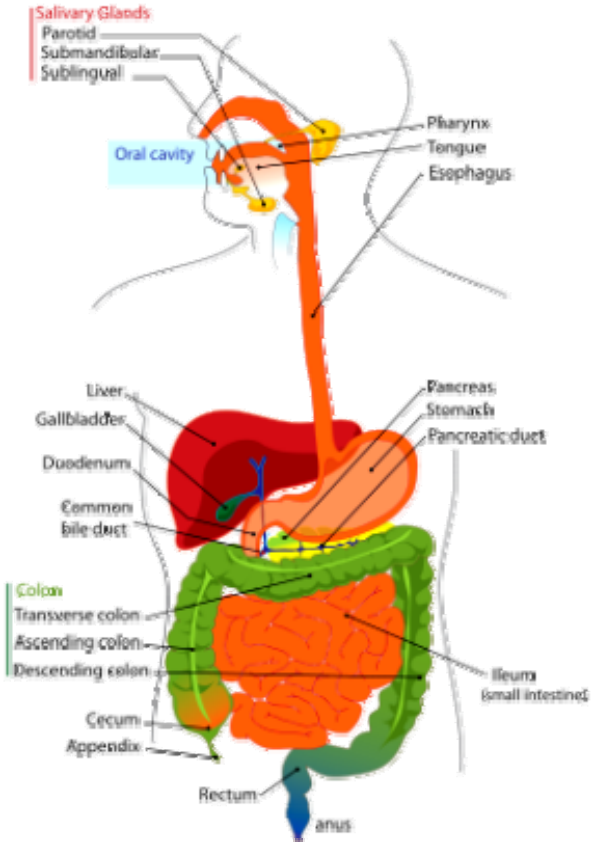


Fig 5: Anatomy of Gastro Intestinal Tract

Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases:

Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically two complications,

- short gastric residence time
- unpredictable gastric emptying rate

REQUIREMENTS OF A DOSAGE FORM FOR GASTRIC RETENTION: [15]

The physiological factors of the stomach show that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions 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 device should be removed from the stomach with ease.

The floating dosage form needs to be in the upper part of the small intestine. The position of floating and non floating dosage forms in the stomach region is shown in the Fig 6.

Studies have revealed that gastric emptying of a dosage form in the fed state can also be influenced by its size. Small-size tablets leave the stomach during the digestive phase while the large-size tablets are emptied during the housekeeping waves.

The effect of size of floating and nonfloating dosage forms on gastric emptying was studied and concluded that the floating units remained buoyant on gastric fluids. These are less likely to be expelled from the stomach compared with the nonfloating units, which lie in the antrum region and are propelled by the peristaltic waves.

• **Shape of dosage form** – Tetrahedron and ringshaped devices with a flexural modulus of 48 and 22.5 kilopounds per square inch (KSI) are reported to have better GRT ≈ 90% to 100% retention at 24 hours compared with other shapes. The diameter of the dosage unit is also equally important as a formulation parameter.

• **Single or multiple unit formulation** – Several formulation parameters can affect the gastric residence time. More reliable gastric emptying patterns are observed for multiparticulate formulations as compared with single unit formulations, which suffer from "all or none concept." As the

partially opened pylorus. Indigestible solids larger than the pyloric opening are propelled back and several phases of myoelectric activity take place when the pyloric opening increases in size during the housekeeping wave and allows the sweeping of the indigestible solids. Studies have shown that the gastric residence time (GRT) can be significantly increased under the fed conditions since the MMC is delayed.

• **pH (Hydrogen Ion Concentration)** – [18] The mean pH (+ S.D.) along the G.I. Tract in normal subjects are given by:

Region	**Mean pH**
Stomach	1.8 + 0.6
Proximal Small Intestine	6.6 + 0.5
Mid Small Intestine	7.4 + 0.4
Distal Small Intestine	7.5 + 0.5
Right Colon	6.3 + 0.6
Mid Colon	6.6 + 0.8
Left Colon	7.1 + 0.7

The pH of the stomach in fasting state is ~1.5 to 2.0 and in fed state is 2.0 to 6.0. A large volume of water administered with an oral dosage form raises the pH of stomach contents to 6.0 to 9.0. Stomach doesn't get time to produce sufficient acid when the liquid empties the stomach.

was fed with a succession of meals given at normal time intervals. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form which is buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach.

• **Nature of meal** – It does not make any difference whether the meal has high protein, fat, or carbohydrate content as long as the caloric content is the same. But, feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.

• **Volume of the meal** – The resting volume of the stomach is 25 to 50 mL. Volume of liquids administered affects the gastric emptying time. When volume is large, the emptying is faster. Fluids taken at body temperature leave the stomach faster than colder or warmer fluids.

• **Caloric content** – An increase in acidity and caloric value slows down gastric emptying time. But GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.

CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEMS: [17]

Floating drug delivery systems are classified depending on the use of 2 formulation variables:

- Effervescent systems
- Non-effervescent systems

Effervescent Floating Dosage Forms

These are matrix types of systems prepared with the help of swellable polymers such as methyl cellulose and chitosan and various effervescent compounds, eg, sodium bicarbonate, tartaric acid, and citric acid or chambers containing a liquid that gasifies at body temperature. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76:1. They are formulated in such a way that when in contact with the acidic gastric contents, carbon dioxide is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. The common approach for preparing these systems involves resin beads loaded with bicarbonate and coated with ethylcellulose. The coating, which is insoluble but permeable, allows permeation of water. Thus, carbon dioxide is released, causing the beads to float in the stomach.

One of the formulation methods of such dosage forms involves the mixing of drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier. It also maintains a relative integrity of shape. The air trapped 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.

Other formulation methods reported are hydrodynamically balanced systems which contain a mixture of drug and hydrocolloids, sustained release capsules containing cellulose derivatives like starch and a higher fatty alcohol or fatty acid glyceride, bilayer compressed capsules, multilayered flexible sheet-like medicament devices, hollow microspheres of acrylic resins, polystyrene floatable shells, single and multiple unit devices with floatation chambers and microporous compartments and buoyant controlled release powder formulations, etc.

Recent developments include use of superporous hydrogels that expand dramatically (hundreds of times their dehydrated form within a

coated shells popcorn, poprice, and polystyrol have been exploited as drug carriers. Sugar polymeric materials such as methacrylic polymer and cellulose acetate phthalate have been used to undercoat these shells. These are further coated with a drug-polymer mixture. The polymer of choice can be either ethylcellulose or hydroxypropyl cellulose depending on the type of release desired. Finally, the product floats on the gastric fluid while releasing the drug gradually over a prolonged duration.

2. ***High-density approach:***

Here, the density of the pellets must exceed that of normal stomach and should be at least 1.40. In preparing such formulations, drug can be coated on a heavy core or mixed with heavy inert materials such as barium sulfate, titanium dioxide, iron powder and oxide. These materials increase density by up to 1.5–2.4g/cm. The weighed pellet can then be covered with a diffusion-controlled membrane.

The use of dosage forms of high density that might remain in the stomach longer when positioned in the lower part of the antrum has been proposed as a means to increase the GI transit duration. The effectiveness of this approach has not been confirmed. *In vivo* data is scarce for both

stratified medicated polymer sheets or swelling balloon hydrogels are examples of such delivery systems. Erodible gastric retention devices fabricated from various polymeric blends were examined for assessment of their gastric retention potential. 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. [16]

4. Fluid- filled floating chamber:

This type of dosage forms includes incorporation of a gas-filled floatation chamber into a microporous component that houses a drug reservoir. Apertures or openings are present along the top and bottom walls through which the gastrointestinal tract fluid enters to dissolve the drug. The other two walls in contact with the fluid are sealed so that the undissolved drug remains therein. The fluid present could be air, under partial vacuum or any other suitable gas, liquid, or solid having an appropriate specific gravity and an inert behavior. The device is of swallowable size, remains afloat within the stomach for a prolonged time, and after the complete release the shell disintegrates, passes off to the intestine, and is eliminated.

dependent solubility, a narrow window of absorption, and are absorbed by active transport from either the proximal or distal portion of the small intestine. But the single-unit forms have problems such as sticking together or being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation.

Multiple-Unit Dosage Forms

The purpose of designing multiple-unit dosage form is to develop a reliable formulation that has all the advantages of a single-unit form and also is devoid of any of the above mentioned disadvantages of single-unit formulations. In pursuit of this endeavor many multiple-unit floatable dosage forms have been designed.

Microspheres have high loading capacity and many polymers have been used such as albumin, gelatin, starch, polymethacrylate, polyacrylamine, and polyalkylcyanoacrylate. Microspheres have a characteristic internal hollow structure and show an excellent in vitro floatability.

Spherical polymeric microsponges, also referred to as "microballoons," have been prepared.

MULTIFARIOUS ADVANTAGES OF FDDS: [16]

FDDS extend significantly the period of time over which the drugs may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms. This application is especially effective in delivery of sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To address this, oral administration of sparingly soluble drugs is carried out frequently, several times per day. As a mechanism to override this problem, erodible, gastroretentive dosage forms have been developed that provide continuous, controlled administration of these drugs at the absorption site. In addition, these dosage forms are useful for delivering drugs incorporated into vesicles such as liposomes, nanoparticles, proteinoid microspheres and pharmacosomes, etc. Compared with other applications, the frequency of dosing may be the same, but the gastro retentive dosage forms will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability.

drug absorption throughout the alimentary canal.

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. Furthermore, other drugs, such as isosorbide dinitrate, that are absorbed equally well throughout the GI tract will not benefit from incorporation into a gastric retention system. [15]

The use of large single-unit dosage forms sometimes poses a problem of permanent retention of rigid large-sized single-unit forms especially in patients with bowel obstruction, intestinal adhesion, gastropathy, or a narrow pyloric opening (mean resting pyloric diameter 12.8 ± 7.0 mm). Floating dosage form should not be given to a patient just before going to bed as the gastric emptying of such a dosage form occurs randomly when the subject is in supine posture.

One drawback of hydrodynamically balanced systems is that this system, being a matrix formulation, consists of a blend of drug and low-

CHAPTER – III

LITERATURE REVIEW

Brijesh Dave et.al., reported a gastro retentive drug delivery of Ranitidine Hydrochloride tablets using guar gum, xanthum gum & hydroxyl propyl methyl cellulose and evaluated its gel forming properties and in-vitro drug release profile. (24)

Dasharath Patel et.al., designed a gastro retentive drug delivery system of Carbamazepine by simple lattice design optimization method, using bees wax, hydroxyl propyl methyl cellulose, ethyl cellulose and sodium bicarbonate. (25)

Narendra et.al., optimized a bi-layer floating tablet of metoprolol tartrate for gastric retention. The regression analysis, numerical optimization and release kinetics were studied for all the formulations. (26)

Viral Patel & Natavarlal Patel developed an intra gastric floating drug delivery system of Cefuroxime Axetil using different grades of HPMC (polymer blend) and employed the 3^2 full factorial design to evaluate the contribution of sodium lauryl sulphate on drug release from the HPMC matrices. (27)

dissolution rate, in-vivo plasma drug concentration by HPLC and the plots of in-vitro in-vivo correlation. [32]

Paradkar et.al., attempted to formulate floating bilayer tablet of Cefuroxime Axetil. The bimodal tablets was formulated by direct compression i.e. type A with immediate release layer and floating matrix layer and type B with immediate release layer and floating press coated layer. Tablets were evaluated for buoyancy lag time, total floating time, in-vitro release, gastro retentive properties by gamma scintigraphy. [33]

Nagar Senker et.al., designed gastro retentive system for Cinnarizine to achieve prolonged therapeutic effect with improved patient compliance. Sodium glycine carbonate (SGC) was used as basic effervescent ingredient & citro glycine as acidic effervescent ingredient. Tablets with SGC reduced in size after 12 hours, due to erosion or disintegration, but it is not seen with tablets containing sodium bicarbonate. [34]

Kamble et.al., developed a hydro dynamically balanced haematinic formulation of Ferrous Sulphate & evaluated for its performance of buoyancy, matrix intregrity, total floating duration and g–scintigraphy. [35]

showing the drug release to be non-fickian diffusion mechanism. [38]

Khattar et.al., formulated hydro dynamically balanced systems as SR dosage form for Propranolol HCl and evaluated its in-vitro release profile. Data to support the mechanism of drug release from the hydro dynamically balanced system capsule was presented & the floating behaviour of the capsule has also been seen in vivo with the help of endoscopy. [39]

Arora et.al., studied the development & evaluation of FDDS for Celecoxib, as a single unit capsules, formulated with different low density floating polymers such as PEO, HPMC, sodium alginate and Eudragits. The in vitro release studies were carried out for 8 hours and based on the buoyancy behaviour and in-vitro release studies, the formulation containing PEO WSR 60 K and Eudragit RL 100 was found to be the optimized formulation. [40]

Ziyaur Rahman et.al., worked for the design and evaluation of bi layer floating tablets of Captopril using HPMC K15 M, PVPK 30 and Carbopol 934p. The floating behaviour and in-vitro dissolution studies were carried out in USP 23 apparatus 2 in simulated gastric fluid pH 1.2.

examined with Mercury Porosimetry and Scanning Electron Microscopy. The results of these studies indicate that $CaCO_3$ is superior to $NaHCO_3$ as a gas forming agent in alginate bead preparations. [43]

John Collett et.al., prepared floating beads of Amoxycillin, using sodium alginate solution containing the drug either in dissolved or suspended form. Drug release studies showed that beads prepared with the drug in solution provided some sustained release characteristics and that these could be improved by addition of amylose. [44]

Forni et.al., studied the effect of matrix composition and process conditions on Casein-gelatin beads floating properties. The beads were prepared by emulsification extraction method and evaluated for its porosity, loading capacity, drug release rate etc. and finally concluded that casein as a material suitable for formation of an air reservoir floating systems. [45]

Freddy et.al., explained the sustained release of hydrophobic and hydrophilic drugs from floating dosage form. Multi-unit floating gel bead was synthesized using calcium alginate and sun flower oil. Three kinds of drugs with different hydrophilicities such as Ibuprofen, Niacinamide and

method showed good in-vitro in-vivo correlation. [49]

Pramod et.al., evaluated the comparative assessment of different dissolution apparatus for floating drug delivery systems, taking Cefuroxime Axetil as model drug. USP type 2 apparatus, mesh designed apparatus, wire helix apparatus and the modified beaker apparatus were compared in construction and release profile features. Statistical analysis of the data was performed by similarity factor assessment. The modified beaker apparatus was more rationally accepted as a substitute for in-vivo dissolution since it more closely simulates the in-vivo conditions. [50]

Asha Patel et.al., studied the in-vitro evaluation & optimization of controlled release floating drug delivery system of Metformin HCl. The floating microspheres were prepared by non-aqueous emulsification solvent evaporation technique and its in-vitro performance was evaluated. This formulation can be used in clinic for prolonged drug release in stomach for > 8 hours, thereby improving the bioavailability and patient compliance. [51]

Gibaly explained the development and in-vitro evaluation of novel floating chitosan micro capsules for oral use, containing Melatonin. The

buoyancy in the stomach. [54]

Gupta et.al., formulated the floating microspheres of Rosiglitazone maleate and evaluated its in-vitro drug release rate. The shape and surface morphology of microspheres were studies by Optical Microscopy and Scanning Electron Microscopy, respectively. The floating microspheres of Rosiglitazone maleate prepared with suitable ratio of Eudragit S–100 to RS–PO provides a convenient dosage form for good floating ability, high encapsulation efficiency and sustained drug release over several hours. [55]

Sokar et.al., prepared floating micro particles of Ketoprofen by emulsion solvent diffusion technique, using four different ratios of Eudragit S-100 (ES) and Eudragit RL (ERL). Scanning Electron Microscopy, particle size analysis, differential scanning calorimetry, floating ability and the release rates was evaluated. The formulation containing ES:ERL 1:1 exhibited high percentage of floating particles. [56]

Govinda Rajan et.al., formulated floating hollow microspheres of Lansoprazole by solvent diffusion method using PVA 1 % as cross linking agent and different ratios of HPMC, methyl cellulose and Chitosan as carriers. The prepared microspheres were subjected for in-vitro

tablets of 5-Flroro Uracil. The release of 5 – FU from the tablets is sustained by occurrence of plasma induced cross link reaction on the outer layer of tablet and the release rate can be well controlled by plasma operational conditions. (60)

Timmermans et.al., proposed a bilayer floating capsule of Misoprostol, as a stomach directed drug delivery system. The parameters influencing the drug release profile are described. Gamma scintigraphic studies were performed to visualize cohesion of two layers in-vivo and to determine gastric residence time as a function of meal regimen. (61)

Mahadik et.al., prepared floating granules of Residronate sodium – Gelucire 43/01 by Melt Granulation method and evaluated in-vivo, in-vitro floating ability, drug content and drug release. Ageing effect on the granules was studied using Hot stage Polarizing Microscopy (HSPM), Differential Scanning Calorimetry, Scanning Electron Microscopy and in-vitro drug release. This study shows phase transformation of gelucire, which is responsible for increase in drug release. (62)

Ambika et.al., formulated the floating drug delivery system using ion exchange resin, taking Chlorpheniramine Maleate as a model cationic

CHAPTER – IV

AIM OF THE WORK

Diabetes mellitus is a progressive and complex disorder that is difficult to treat effectively in the long term. There is an extensive range of oral anti-diabetic drugs, indicated for the treatment of type II (non-insulin dependent) diabetes mellitus which may be used as mono therapy or in combination with others. [88]

Glipizide is a second generation sulphonyl urea used as an oral anti diabetic medication in the treatment of type 2 diabetes. It controls blood sugar level by stimulating the pancreas to secrete more insulin.

Even though Glipizide is readily absorbed after oral administration, it is metabolized by hydroxylation to form a number of inactive metabolites and the plasma half life is only 2 to 4 hours. Its short biological half life necessitates that it be administered in 2 or 3 doses of 2.5 – 10 mg / day. Thus the development of sustained release dosage form would be clearly advantageous. [65, 66, 67]

According to bio-pharmaceutic classification system (BCS), Glipizide is a class II drug (Less solubility and more permeability). [73] Glipizide is

PLAN OF THE WORK

The plan of the present study was to carry out the following:

Part – I

- Calibration curve for Glipizide

Part – II

1. Formulation of Glipizide Floating Matrix tablets as non-effervescent and effervescent types by wet granulation method.
2. Selection of best ratio of the different polymers and gas forming agents from the formulations.
3. Evaluation of the following physico-chemical parameters.
    a) Hardness and Friability
    b) Weight Variation and Drug content estimation
    c) Thickness and Diameter
    d) Buoyancy determination
        - Buoyancy Lag Time
        - Duration of Buoyancy
    e) In-vitro Drug Release
    f) Kinetics of drug release

e) Drug content analysis

f) In-vitro Drug Release

g) Kinetics of drug release

h) Differential Scanning Calorimetry

i) Stability Studies

4. In vivo X-Ray Studies
5. To find out the significant ratio of Polymer : Gas forming agent for floating beads with sustained release and good buoyancy properties.
6. Comparison of release characteristics of selected formulation with the Marketed Product.

Acetone	-	Omega Laboratory Chemicals
Hydrochloric acid	-	Nice Chemicals
Potassium Chloride	-	Merck

All other chemicals were of Analytical Grade.

INSTRUMENTS:

Electronic Weighing Balance	- A & D Company HR 200, Japan
Single Punch Tablet Compression Machine	- Cadmach
UV Visible Spectrophotometer	- Shimadzhu
Digital Tablet Dissolution Test Apparatus	- Disso 2000, Lab India
Friability Test Apparatus	- Indian Equipment Corporation
Incubator	- Tempo Industrial Corporation
Hot air oven	- Sico
Tablets hardness tester (Monsanto)	- Secor India
Vernier Caliper	- Linker
X-ray machine	- Stallion 20, Elpro International Ltd.
Differential Scanning Calorimeter	- DSC 60 Shimadzu
Scanning Electron Microscope	- JEOL JSM-6360

Molecular mass:

445.536 g/mol

Description:

It is a white or almost white crystalline powder. The structure on the R2 group is a much larger cyclo or aromatic group compared to the 1st generation sulfonylureas. This leads to a once a day dosing that is much less than the first generation, about 100 fold.

CHEMICAL PROPERTIES:

Solubility:

It is practically insoluble in water, soluble in methylene chloride, chloroform, dimethyl formamide, sparingly soluble in acetone, practically insoluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

Partition coefficient: [66]

Log P (octanol/water) 1.9

Dissociation Constant: [68]

pKa 5.9

Loss on drying:

Not more than 0.5%, determined on 1g by drying in an oven at 100 – 105^{0}C.

Metabolism:

Glipizide is metabolized in the liver by hydroxylation to form a number of inactive metabolites, principally the 4-trans-hydroxy cyclo hexyl and 3-cis-hydroxy cyclo hexyl derivatives.

Dosages may need to be lowered in patients with liver or kidney dysfunction.

Excretion:

About 65 to 85 % of a dose is excreted in urine in 24 hr. with about 3 to 10 % as unchanged drug, up to 80 % as hydroxylated metabolites, mainly the 4-trans-hydroxy cyclo hexyl derivative and about 1 to 2 % as an N-acetamido metabolite, about 11 % of a dose is eliminated in the faeces.

Plasma Half Life: [68]

2 to 4 hours

Bioavailability:

100 % - Immediate release formulation

90 % - Extended release formulation

Volume of distribution:

About 0.2 L / kg

days. Doses > 15 mg be given in 2 divided doses before meals. Max dose: 40 mg daily.

Dosage of Glipizide must be based on blood and urine Glucose determination and must be carefully individualized to obtain optimum therapeutic effect.

Drug Interactions:

All sulfonylureas can cause low blood sugar (hypoglycemia). Therefore, glipizide must be used cautiously in patients who have other potential reasons for having low blood sugars such as patients with kidney or liver problems, poor food intake, using alcohol or participating in heavy exercise, as well as in patients taking other glucose-lowering drugs.

Drug interactions causing hypoglycemia can occur with nonsteroidal anti- inflammatory drugs (for example, ibuprofen), sulfa drugs, coumadin, miconazole, fluconazole, and beta-blocking drugs. High glucose reactions (hyperglycemia) can occur with thiazide diuretics, corticosteroids, thyroid medicines, estrogens, niacin, dilantin, and calcium channel blocking drugs.

Protein bound drugs: Glipizide is highly protein bound, it is

Generic Available: Immediate-release tablets, Sustained-release tablets

Preparations:

Immediate release tablets – 2.5 mg, 5 mg, 10 mg.

Sustained release tablets – 5 mg, 10 mg.

Brand names: [67]

GLUCOTROL, GLYNASE, GLIPY, GLUCOLIP, GLEZ, GLIDE, GLYTOP,

TRANASE, DIACON, DIAGLIP, DIBIZIDE, GLIBETIC, GLYLIN.

Storage:

Glipizide should be stored at room temperature in a tight container.

Some Viscosity grades of Methocel commercially available and their

Typical Viscosity values for 2 % (w/v) aqueous solutions at 20'C:

Methocel K100M Premium	-	100 000
Methocel K15M Premium	-	15 000
Methocel K4M Premium	-	4000
Methocel K30 Premium	-	30
Methocel K15 Premium	-	15
Methocel E5 Premium LV	-	5
Methocel E3 Premium LV	-	3

CARBOXY METHYL CELLULOSE SODIUM:

Synonym: Cellulose gum, Sodium cellulose glycolate

Empirical formula: Sodium salt of poly carboxy methyl ether of cellulose (USP 28)

Molecular weight: 90 000 – 700 000

Description: White to almost white, odorless, granular powder.

Solubility: Practically insoluble in acetone, ethanol (95 %), ether and toluene. Easily dispersed in water at all temperatures forming clear,

Functional Category: Bulk laxative (5.0 – 30.0 %), Emulsifying agent (1.0– 5.0 %), Tablet binder (1.0 – 5.0 %), Tablet Coating (0.5 -5.0 %), Tablet and capsule disintegrant (2.0 – 10.0 %).

SODIUM ALGINATE:

Synonym: Algin, alginic acid, Sodium polumannuronate.

Description: An ororless and tasteless, white to pale yellowish-brown colored powder.

Empirical formula: Mixture of poly uronic acids composed of residues of D-mannuronic acid and L-guluronic acid.

Solubility: Practically insoluble in ethanol (95 %), ether, chloroform; slowly soluble in water, forming a viscous colloidal solution.

Functional Category: Stabilizing agent (1-3 %), Suspending agent (1-5 %), Tablet and capsule disintegrant (2.5- 10 %), Tablet binder (1-3 %), Viscosity increasing agent.

Functional Category: Alkalising agent.

POTASSIUM BICARBONATE:

Synonym: Carbonic acid mono potassium salt, potassium acid carbonate, potassium hydrogen carbonate

Description: Colourless, transparent crystals or as a white granular or crystalline powder, odourless with a saline or weakly alkaline taste.

Empirical formula: $KHCO_3$

Molecular weight: 100.11

Solubility: Soluble in water, practically insoluble in ethanol (95 %)

Functional Category: Alkalizing agent, therapeutic agent.

POTASSIUM CARBONATE:

Description: Colourless, odorless white granular powder.

Empirical formula: K_2CO_3

Molecular weight : 99.11

Solubility: Soluble in water, practically insoluble in ethanol (95 %)

Functional Category: Alkalizing agent.

Functional Category: Adsorbent, antacid, tablet and capsule diluent.

LACTOSE:

Synonym: Lactopress Anhydrous, Lactosum, Milk sugar.

Description: White to off-white crystalline particles or powder.

Empirical formula: $C_{12}H_{22}O_{11}$

Molecular weight: 342.30

Solubility: Soluble in water, sparingly soluble in ethanol (95 %) and ether.

Functional Category: Binding agent, directly compressible tableting excipient, lyopholization aid, tablet and capsule filler.

CITRIC ACID:

Synonym: 2-hydroxypropane 1,2,3-tricarboxylic acid monohydrate

Description: Colourless or translucent crystals, or as white crystalline, efflorescence powder, odorless and has a strong acidic taste.

Empirical formula: $C_6H_8O_7.H_2O$

Molecular weight: 210.14

TALC:

Synonym: Purified French chalk, Purtalc, Soapstone

Empirical formula: $Mg(SiO_5)_4 (OH)_4$

Description: Very fine, white to grayish-white, odorless, impalpable unctuous, crystalline powder.

Solubility: Practically insoluble in dilute acids and alkalis, organic solvents and water.

Functional Category: Anti-caking agent, glidant, tablet and capsule diluent (5-30 %), tablet and capsule lubricant (1-10 %)

MAGENSIUM STEARATE:

Synonym: Magnesium octadeconoate, Octadecanoic acid

Empirical formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.34

Description: Very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

CHAPTER – VIII

EXPERIMENTAL DETAILS

PREPARATION OF DISSOLUTION MEDIUM: [76]

Hydrochloric Acid Buffer pH 1.2:

50 ml of 0.2 M Potassium chloride was placed in a 200 ml volumetric flask. 85 ml of 0.2 M Hydrochloric acid was added and made up to the volume with distilled water.

0.2 M Potassium Chloride:

14.911 g of Potassium chloride was dissolved with distilled water and the volume was made up to 1000 ml.

0.2 M Hydrochloric acid:

7.292 g of Hydrochloric acid was diluted to 1000 ml with the distilled water.

PREPARATION OF CALIBRATION CURVE FOR GLIPIZIDE:

100 mg of Glipizide was accurately weighed and transferred to a 100 ml volumetric flask. It was dissolved in methanol and made up to the

bulk volume. Apparent bulk density was determined by pouring the weighed granules into a graduated cylinder via funnel and measuring the volume. Density was calculated using the formula,

$$\text{Bulk Density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of the powder}} = \frac{W}{V_0}$$

Tapped Density: (g/ml)

Tapped density is the ratio between a given mass of powder and the constant or final volume of powder after tapping. It was determined by tapping a graduated cylinder containing a known mass of granules for a fix number of taps until the powder volume has reached minimum. The tapped density was computed using the formula,

$$\text{Tapped Density} = \frac{\text{Mass of the powder}}{\text{Minimum (tapped) volume of the powder}} = \frac{W}{V_f}$$

Assessment of flow properties:

Compressibility Index: (I)

Compressibility is an important measure that can be obtained from the bulk and tapped densities. The flowability of the granules was

Values of θ:

- rarely less than 20^0
- Values of 20^0 - 40^0 indicate reasonable flow potential
- Values above 50^0 indicate that powder flows with great difficulty

Percentage Yield:

The granules obtained during the formulation process was accurately weighed and the percentage yield was calculated from the expected theoretical yield, using the formula

$$\% \text{ Yield of granules} = \frac{\text{Practical Yield of granules}}{\text{Expected theoretical yield}} \times 100$$

Drug Content Analysis for granules: [69]

To a quantity of the powder containing 15 mg equivalent of Glipizide, 30 ml of methanol was added and heated gently on a water bath whilst shaking, cooled and sufficient methanol was added to produce 50 ml volume. It was filtered and 5 ml of the filtrate was diluted to 50 ml with methanol. The absorbance of the resulting solution was measured at the maximum of 274 nm, using methanol in the reference cell. The drug

Table 2: Composition of Non Effervescent Floating Matrix Tablet of Glipizide

Ingredients	Quantity (mg) for 1 tablet					
	Trial I	**Trial II**	**Trial III**	**Trial IV**	**Trial V**	**Trial VI**
Glipizide	10	10	10	10	10	10
HPMC K100 M / HPMC K4 M / HPMC K30 / HPMC K15 / Sodium CMC / Methyl Cellulose	20	30	40	50	60	70
PVPK 30	5	5	5	5	5	5
Lactose	63	53	43	33	23	13
Talc	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1
Iso propyl alcohol	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

- The drug, polymer and lactose were passed through 40 # mesh separately and blended thoroughly.
- The granulating fluid was prepared by dissolving PVPK 30 in iso propyl alcohol.
- The blend was granulated with PVPK 30 solution to form a coherent mass.

adjusted so that the average hardness of the tablets was around 4 – 5 kg / cm^2.

Effervescent Floating Matrix Tablets: [24, 25, 27]

The effervescent matrix floating tablets were formulated with lesser amount of polymer concentration and at specific ratio of the polymer : gas forming agents, as given in Table 3.

Table 3: Composition of Effervescent Floating Matrix Tablet of Glipizide

S. No.	Ingredients	Quantity for 1 tablet (mg)
1.	Glipizide	10 mg
2.	HPMC K100 M / HPMC K4 M / HPMC K30 / HPMC K15 / Sodium CMC / Methyl Cellulose	10 – 20 mg
3.	Sodium Bicarbonate	20 – 50 mg
4.	Citric Acid	Q.S. for effervescent and pH maintenance
5.	PVPK 30	5 mg
6.	Lactose	Q.S. for diluent
7.	Magnesium Stearate	1 mg
8.	Talc	1 mg
9.	Iso propyl alcohol	Q.S. for granulation

packaging and shipping operations. So determination of hardness of the tablets is made to assure the need for pressure adjustments on the tableting machine.

Hardness of the tablets were determined using Monsanto Hardness tester. The tablet was placed horizontally in contact with the lower plunger of the Monsanto hardness tester and zero reading was taken. The tablet was then compressed by forcing the upper plunger until the tablet breaks. This force was noted.

Friability:

Fraibility is a tablet property that evaluates the ability of the tablet to withstand abrasion in packaging, handling and shipping. Twenty tablets were weighed and placed in the Roche Friabilator where they are exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions the tablets were dusted and weighed and the loss in weight indicates the ability of the tablets to withstand this type of wear.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Average weight of the tablet	Percentage Deviation
80 mg or less	10
More than 80 mg but less than 250 mg	7.5
250 mg or more	5

FORMULATION OF FLOATING BEADS: [43, 44]

Floating beads were prepared by dropwise addition of Sodium Alginate solution containing drug and different gas forming agents, into Calcium chloride solution (0.5 – 2.0 % w/v) in glacial acetic acid (10 %).

Table 4: Composition of Floating Beads

S. No.	Ingredients	For 100 ml
1.	Sodium Alginate	0.5 – 4 % w/v
2.	Gas forming Agents	1:0 to 1:2 with alginate
3.	Glipizide	200 mg

The final formula for the preparation of beads was decided after evaluating the quality of beads obtained in each trial formulations. For the preparation of beads, the concentration of Sodium Alginate, gas forming

beads, large beads were prepared by replacing 21 G syringe needle with 1 ml pipette, and the hardness of the large beads was tested by Pfizer tester or Monsanto tester.

Morphological Analysis:

The surface and cross sectional morphologies of the beads were examined using Scanning Electron Microscope.

The samples were placed on a metal grids using double side backed adhesive tape. The mounted samples were sputter coated for 5 – 10 min with gold-paladium using fine coat ion sputter in an argon atmosphere and examined under Scanning Electron Microscope.

EVALUATION OF DRUG CONTENT FOR TABLETS / BEADS: [69]

To a quantity of the powdered formulation containing 15 mg equivalent of Glipizide, 30 ml of methanol was added and heated gently on a water bath whilst shaking, cooled and sufficient methanol was added to produce 50 ml volume. It was filtered and 5 ml of the filtrate was diluted to 50 ml with methanol. The absorbance of the resulting solution was measured at the maximum of 274 nm, using methanol in the reference

USP Method: [70]

Medium	-	900 ml of Hydrochloric acid buffer pH 1.2
Rotation	-	50 rpm
Temperature	-	37 ± 1^0C

10 ml of samples were withdrawn at every 30 minutes time intervals for upto 8 hours. The sample volume of fresh dissolution medium was replaced after every withdrawal. The withdrawn samples were analysed by UV-visible spectrophotometer at 275 nm.

Fig 8: USP Dissolution Test Apparatus – 8 basket model

KINETICS OF DRUG RELEASE: [92-98]

The mechanism of drug release from the floating matrix tablets can be described by studying the release profile data, fitted to various kinetic models.

The release rate of drug from the matrix system depends upon several factors such as the type of matrix, characteristics of polymers and incorporated drug substances, additives, and other technological variables. The cumulative percentage release of Glipizide from floating tablets (n=3) in the dissolution medium was investigated and curve fitting & statistical significance were tested.

The data obtained from the cumulative percentage release of Glipizide from the floating tablets at periodic intervals was fitted to zero order, first order, Higuchi, Hixon crowell, Korsemeyer & Peppas model kinetics, to find out whether the drug release from the formulations is providing a constant drug release.

Curve Fitting: [96]

Fitting of release profiles to linear equations was assessed by comparing the coefficients of determinations (R2). The correlation

Release Data Modelling: (93, 95, 98)

Drug release from swellable water-soluble polymer systems is typically described in terms of two simultaneously operating mechanisms. They are fickian diffusion through the hydrated outer layers of the matrix and matrix relaxation / erosion.

The data were evaluated according to the following equations:

Zero Order - $Q_t = Q_0 + K_0.t$

First Order - $In\ Q_t = In\ Q_0 + K_0.t$

Hixson-Crowell - $Q_0^{1/3} - Q_t^{1/3} + K.t$

Higuchi - $Q = KH.\ t^{1/2}$

Korsmeyer - Peppas - $M_t / M_0 = a.tn$

Characterization of Release Profiles:

Some methods to compare drug release profiles were recently proposed and classified into several types:

- Statistical methods based in the analysis of variance or in t-student tests
    - Single time point dissolution
    - Multiple time point dissolution
- Model independent methods
- Model dependent methods

Healthy rabbits weighing about 2 kg were selected and after over night fasting (water was available ad libitum) a tablet / beads containing $BaSO_4$ (20 %) instead of Glipizide was administered orally. This amount of $BaSO_4$ was determined experminetally to allow x-ray visibility but not to shun floatation of the tablet. 60 ml of 5 % Dextrose was administered to the animal through the stomach intubation tube (No: 12 French Catheter) periodically.

Gastric radiography was done at 2, 4, 8, 12 and 24 hours using x-ray machine (Stallion 20, Elpro International Ltd.) at 20 mA selected, 60 Kv for 0.25 secs exposure.

DIFFERENTIAL SCANNING CALORIMETRY: [89]

The presence of any interaction between the pure drug and excipients was investigated by Differential Scanning Calorimetry.

The DSC thermograms of the pure drug and the selected formulations (tablets / beads) were recorded.

The powdered formulations were accurately weighed into aluminium pans and then hermetically sealed with aluminium lids. The

CHAPTER - IX

RESULTS AND DISCUSSION

CALIBRATION OF GLIPIZIDE: [77]

Solutions of different concentrations of Glipizide were measured in UV spectrophotometer at the λmax of 275 nm. A linear relation in the concentration of 1 to 10 μg/ml was observed. The correlation coefficient value was found to be r = 0.999908543. The results are given in Table 5 and the standard calibration graph of Glipizide is shown in Fig: 10.

FORMULATION OF NON-EFFERVESCENT AND EFFERVESCENT FLOATING TABLETS: [20, 24, 25, 27]

From the trial studies, the formulations showing good floating behaviour were found out and the optimized formula for non-effervescent and effervescent floating tablets is given in the Table 6 and 7.

The non-effervescent tablets show good floating property at the concentration of 20-75 % of the polymer. [20] HPMC grades and Sodium CMC showed better buoyancy at 60 % concentration while Methyl

EVALUATION OF TABLETS: [24, 25, 27, 69, 76, 78]

The compressed matrix tablets were evaluated for various physico chemical parameters such as Appearance, Hardness, Friability, Thickness, Weight variation, Drug content analysis, Buoyancy determination.

Appearance:

The formulated tablets were white colour, flat, round shaped without any scoring on any sides. All tablets were elegant in appearance.

Hardness, Thickness, Friability:

Hardness of all the formulation was found to be in the range of 4 – 4.5 Kg/ cm^2. A thickness of 3.4 mm and 2.5 mm was observed for the non-effervescent and effervescent tablets respectively.

Weight Variation and Percentage Drug Content:

The average weight ranges 100 mg approximately and the individual weight variation lies within the limit of $\pm$ 7.5 % as per I.P. The percentage drug content of all the formulations lies within the prescribed limits of 90 – 110 % as per B.P. and U.S.P.

Buoyancy Determination:

The time taken for the tablet to come to the surface of the liquid and

results that the tablet float is significantly reduced.

So, a decrease in hardness of the tablets reduces the floating lag time. This effect was observed in both non-effervescent and effervescent tablets. The results are shown in the Table 12.

FORMULATION OF FLOATING BEADS:

From the trial studies, it has been found that the Sodium Alginate solution of 3 % w/v and 1 % w/v Calcium Chloride in 10 % acetic acid was able to form uniform rigid beads. The needle size of 21 G produced big size, rigid, uniform and porous beads. Hence this composition was used for further production of beads with different gas forming agents.

The results are shown in Table 13, 14 and 15.

Effect of Gas forming agents oh physical nature of beads:

Different gas forming agents such as Calcium Carbonate (FB-1), Magnesium Carbonate (FB-2), Sodium Bicarbonate (FB-3), Sodium Carbonate (FB-4), Potassium Bicarbonate (FB-5) and Potassium Carbonate (FB-6) were used in the ratio of 1:1 with sodium alginate. The formula is shown in the Table 16 (a).

1:0.25 (Alginate:$CaCO_3$) produced smaller beads than the others, where the beads of 1:2 (Alginate:$CaCO_3$) showed bigger beads having diameter of 2.5 mm. The same was observed both in wet diameter and dry diameter. It was found that the increase in concentration of $CaCO_3$ ratio had some impact in increasing the diameter of beads. It may be due to high interaction of $CaCO_3$ with acetic acid during the bead formation.

EVALUATION OF PHYSICAL PROPERTIES OF FLOATING BEADS:

The formulated floating beads were subjected to physical evaluation such as size analysis of wet and dry beads, mechanical strength, percentage drug content and floating duration time.

Since the same needle size (21 G) is used for all the formulations, the beads produced has more or less same wet diameter. But they showed different diameter after drying.

Except $NaHCO_3$, all the other gas forming agents were able to produce spherical beads. But $NaHCO_3$ beads burst immediately after formation before the walls are significantly hardened.

NET-4 showed 59.61 % and 92.29 % release after 8 hours it may be easily disintegrated due to low viscosity grade of the polymer. [29]

Formulation containing HPMC K100M (NET-1) showed more retardant effect than the formulation containing HPMC K4M (NET-2) at the same concentration. This may be due to the high viscosity nature of the polymer HPMC K100M.

Hence drug release is retarded in the following order.

HPMC K100M > HPMC K4M > HPMC K30 > HPMC K15

In the floating tablets containing Methyl cellulose as polymer, NET-6, 7, 8 the increase in concentration of the polymer retards the drug release significantly. The drug release is retarded in the following order:

NET-8 (70 %) > NET-7 (60 %) > NET-6 (50 %)

The formulation containing Sodium CMC also retards the drug release due to its low solubility at pH 1.2 – 3. [26]

The same results were obtained in the dissolution studies by Modified Beaker also. The results are shown in Table 18 and 19 and Fig. 15 and 16.

bicarbonates.

Based on the morphology and release of drug, $CaCO_3$ was chosen for further formulations.

Formulations of FB-I to FB-VI showed the drug release of 3.57 %, 4.95 %, 8.81 %, 9.26 %, 10.03 % and 31.9 % respectively. The formulation FB-I containing 1:0.25 ratio (Alginate:$CaCO_3$) showed more retardant release than the others and the formulation FB-VI containing 1:2 ratio (Alginate:$CaCO_3$) showed more release of drug. The comparative release profile showed that as the concentration of gas forming agents increased, the release rate increased significantly. This may be due to increase in size, floating property and the porous nature of the beads.

The Modified Beaker method also showed similar results.

The results are shown in Table 22, 23, 24 and 25 and Fig. 19, 20, 21 and 22.

KINETICS OF DRUG RELEASE: [92-98]

Non Effervescent Floating Tablets:

Among the non-effervescent floating tablets NET-1 to NET-8,

formulation shows Korsmeyer Peppas kinetics mechanism (R2 = 0.9925).

The results are shown in Table 28 and 29 and Fig. 24.

Floating Beads:

All the bead formulations show anamolous non fickian release mechanism by USP dissolution method and Super case II transport mechanism by modified beaker method. Based on the similarity factor f2, the FB-VI formulation is considered to show better release, nearly similar to marketed sample. (f2 = 79, 85)

It is observed that this formulation follow first order kinetics with Korsmeyer peppas mechanism.

The results are shown in Table 30, 31, 32 and 33 and Fig 25.

The difference in the values of R2, f2 and also K, determined by USP dissolution apparatus and modified beaker apparatus are due to difference in the mechanism of the drug release in these two methods. Even the swelling and release property of the dosage form remains the same in both method, a perfect type of sink condition is maintained in the beaker method which correlates to the in-vivo conditions. So, variations occur in the practical study.

The thermograms of pure drug and the formulations are shown in the Fig: 28, 29 and 30.

STABILITY STUDIES:

The formulation showing better dissolution profile and other parameters was taken for the stability studies.

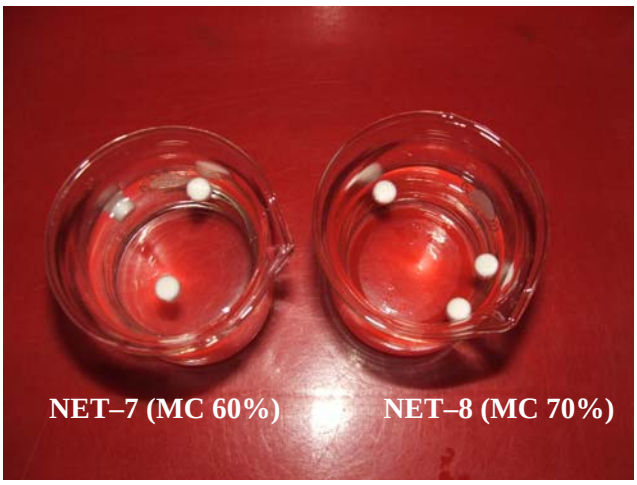
Stability studies were carried out at 45^0C and RH of 75 % for 3 months (as per ICH guidelines) to assess their short term stability. After storage, the formulations were subjected to physical evaluation and assay at 15 days periodic time intervals. There appeared no change in either physical appearance or in drug content.

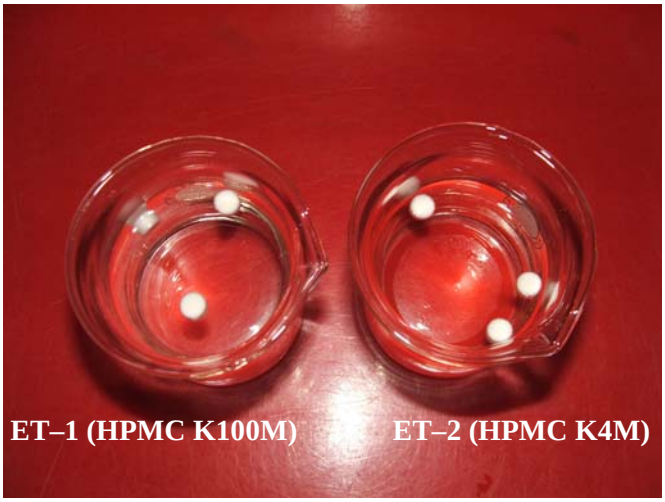
The insignificant change in the physical appearance and the drug content in the formulations show that the formulations remain stable during the process of storage.

The results are presented in Table 34, 35 and 36.

- The pre-formulation parameters of all the preparations were within the required limit that was suitable for formulation of the tablets.
- All the tablets showed elegant appearance & uniform hardness of 4 – 4.5 kg/cm^{2}and acceptable friability limits.
- The weight variation and drug content of all the formulations were within the given standard limits. The buoyancy lag time and duration of buoyancy were found to be satisfied.
- The in-vitro dissolution studies of all the formulations showed sustained release of the drug. Based on the similarity factor, the formulations NET-7 (Methyl Cellulose 60 %) and ET-3 was found to have similar release profile as the marketed formulation. The release of drug from the tablet is of zero order kinetics showing Korsemeyer release mechanism.
- The floating beads were prepared to study the effect of different gas forming agents (FB-1 to FB-6) and also to find the effect of concentration of gas forming agents (FB-I to FB-VI).
- The comparison results of bead size, bead formation, mechanical strength, floating time of all the formulation showed that $CaCO_3$ was

The results of the present study clearly indicate the feasibility to develop Glipizide in the form of Floating Drug Delivery System with prolongation of gastric retention time and sustained drug release. The future studies may be extended to reveal the pharmacokinetic parameters and clinical trial investigations, which may prove that the formulation can be administered safely for the treatment of Type II Diabetes with improved therapeutic efficacy.


NET–7 (MC 60%)
NET–8 (MC 70%)


ET–1 (HPMC K100M)
ET–2 (HPMC K4M)

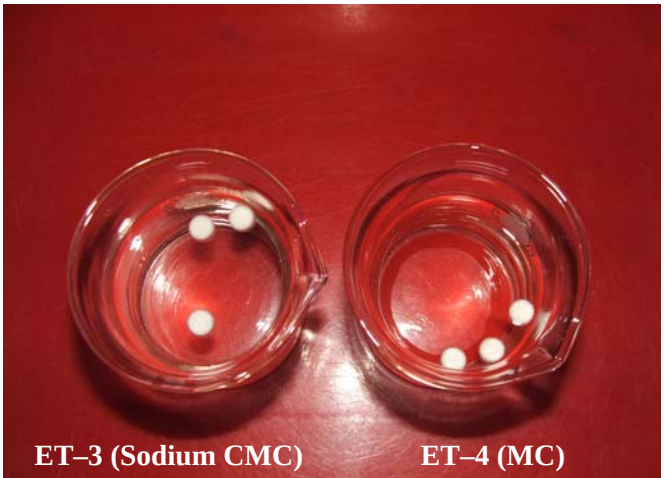

ET–3 (Sodium CMC)
ET–4 (MC)

Table 5: Calibration of Glipizide

Medium : Hydrochloric acid Buffer pH 1.2
λ max : 275 nm

S.No.	CONCENTRATION (μg/ml)	ABSORBANCE *	STANDARD DEVIATION * (± S.D)
1.	1	0.0251	0.0001
2.	2	0.0503	0.0008
3.	3	0.0755	0.0004
4.	4	0.1016	0.0023
5.	5	0.1239	0.0003
6.	6	0.1477	0.0022
7.	7	0.1748	0.0008
8.	8	0.1988	0.0010
9.	9	0.2249	0.0005
10.	10	0.2477	0.0025

* Average of three trials

Table 7: Formulation of Effervescent Floating Tablets

Ingredients	Quantity per tablet (mg)			
	ET-1 HPMC K100M 1:2 ratio	**ET-2 HPMC K4M 1:2 ratio**	**ET-2 Sodium CMC 1:2 ratio**	**ET-2 Methyl Cellulose 1:2 ratio**
Glipizide	10	10	10	10
Hydro colloid Polymer	20	20	20	20
Sodium Bicarbonate	30	30	30	30
Citric Acid	1	1	1	1
PVPK 30	5	5	5	5
Lactose	32	32	32	32
Talc	1	1	1	1
Magnesium Stearate	1	1	1	1
Iso propyl alcohol	Q.S.	Q.S.	Q.S.	Q.S.

4.	4.5	1 minute 22 seconds

* Average of three readings

Table 13: Effect of concentration of Sodium Alginate on Bead formation

S. No.	% Concentration of Sodium Alginate	Bead characters
1.	0.5	Does not form beads
2.	1.0	Beads with tails are formed
3.	2.0	Beads are formed but less rigid
4.	3.0	Rigid beads are formed
5.	4.0	Beads with tails are formed

Table 14: Effect of concentration of Calcium Chloride with 3 % Alginate solution

S. No.	% Concentration of Calcium chloride in	Bead characters

	porous beads are formed	porous beads are formed	beads are formed	porous beads are formed
26 G	Uniform porous beads are formed	Uniform porous beads are formed	Uniform porous beads are formed	Uniform porous beads are formed

Table 16: Formulation of Floating Beads

a) Composition of Beads with different gas forming agents

Ingredients	**Alginate : Gas forming agent 1:1**					
	FB-1 $CaCO_3$	**FB-2 $MgCO_3$**	**FB-3 $NaHCO_3$**	**FB-4 Na_2CO_3**	**FB-5 $KHCO_3$**	**FB-6 K_2CO_3**
Sodium Alginate	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g
Gas forming agent	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g
Glipizide	0.100 g	0.100 g	0.100 g	0.100 g	0.100 g	0.100 g

3.	Drug Content Analysis %	100.51	100.65	99.28	98.89	101.05	101.11
4.	Floating Efficiency *	> 24 hrs	> 24 hrs	> 24 hrs	> 24 hrs	> 24 hrs	> 24 hrs
5.	Formation of Beads	Beads are formed within 20 sec.	Beads are formed within 60 sec.	Beads are formed within 5 sec., but burst immediately	Beads are formed within 10 sec.	Beads are formed within 10 sec.	Beads are formed within 10 sec.
6.	Appearance of Beads	Rigid, spherical and uniform beads are formed	Spherical uniform beads are formed, but less rigid.	Not spherical, not uniform and not rigid. Beads stick to one another.	Spherical and oval shaped beads are formed, less rigid and less uniform in size	Spherical and uniform beads are formed, but less rigid. Some beads collapse and stick to one another.	Spherical and uniform beads are formed, but less rigid.

* Average of three trials

b) Floating Beads with different ratios of $CaCO_3$

S.No.	Parameters	Floating Beads of different ratios of $CaCO_3$ with Sodium alginate					
		FB-I 1:0.25	**FB-II 1:0.50**	**FB-III 1:0.75**	**FB-IV 1:1**	**FB-V 1:1.50**	**FB-VI 1:2.0**
1.	Size Analysis (mm) *						
	Wet diameter	2.8	3.0	3.1	3.3	3.4	3.5
	Dry diameter	1.1	1.5	1.6	2.1	2.3	2.5
2.	Mechanical Strength * (kg/cm^3)	1.0	1.0	1.0	1.0	1.0	1.0

	(hrs)	HPMC K100M	HPMC K4M	HPMC K30	HPMC K15
1.	0.30	4.26 ± 0.1529	6.36 ± 0.1849	9.54 ± 0.4409	13.74 ± 0.5316
2.	1.00	4.97 ± 0.1122	7.12 ± 0.2362	12.32 ± 0.2976	17.07 ± 0.5184
3.	1.30	5.83 ± 0.1158	8.85 ± 0.1855	15.48 ± 0.6861	19.12 ± 0.8384
4.	2.00	6.91 ± 0.2163	10.00 ± 0.1517	17.39 ± 0.2275	23.83 ± 0.3894
5.	2.30	8.34 ± 0.0734	13.31 ± 0.3403	20.25 ± 0.3921	28.14 ± 0.4832
6.	3.00	9.09 ± 0.1122	14.69 ± 0.3393	25.24 ± 0.9455	31.17 ± 0.6141
7.	3.30	10.15 ± 0.1975	15.86 ± 0.2763	29.95 ± 0.2273	35.01 ± 0.4974
8.	4.00	12.51 ± 0.0776	18.16 ± 0.4606	36.12 ± 0.3269	38.96 ± 0.1699
9.	4.30	13.09 ± 0.2286	19.50 ± 0.0093	37.97 ± 0.0817	47.08 ± 0.4788
10.	5.00	14.13 ± 0.1551	23.03 ± 0.2786	39.31 ± 0.1111	58.26 ± 0.7774
11.	5.30	15.38 ± 0.1604	25.46 ± 0.1643	40.89 ± 0.2957	66.53 ± 0.1400
12.	6.00	17.50 ± 0.1515	27.08 ± 0.1510	42.58 ± 0.4553	74.70 ± 0.3655
13.	6.30	18.64 ± 0.2120	28.17 ± 0.1643	45.98 ± 0.5149	80.07 ± 0.2562
14.	7.00	19.85 ± 0.1430	29.60 ± 0.1995	48.11 ± 0.1730	84.60 ± 0.3930
15.	7.30	21.53 ± 0.1596	31.17 ± 0.1704	53.61 ± 1.3192	91.18 ± 0.7484
16.	8.00	22.83 ± 0.1936	32.30 ± 0.2449	59.61 ± 0.2411	92.27 ± 0.6697

* Average of three trials

Cont….

Cont….

S.No.	Time (hrs)	Cumulative Percentage of Drug Release *			
		NET-5	NET-6	NET-7	NET-8
		Sodium CMC	MC 50 %	MC 60 %	MC 70 %

S.No.	Time (hrs)	NET-1	NET-2	NET-3	NET-4
		HPMC K100M	HPMC K4M	HPMC K30	HPMC K15
1.	0.30	0.99 ± 0.1125	1.66 ± 0.5289	2.19 ± 0.1265	5.98 ± 0.2457
2.	1.00	1.55 ± 0.1245	3.08 ± 0.4215	4.09 ± 0.1532	9.81 ± 0.7845
3.	1.30	2.18 ± 0.8423	4.62 ± 0.2145	6.73 ± 0.5213	14.57 ± 0.9587
4.	2.00	3.49 ± 0.2586	6.37 ± 0.8978	9.11 ± 0.8457	19.90 ± 0.4125
5.	2.30	4.47 ± 0.1258	8.12 ± 0.6589	11.84 ± 0.9586	26.24 ± 0.4682
6.	3.00	5.42 ± 0.9654	10.45 ± 0.7459	15.00 ± 0.1255	32.94 ± 0.3152
7.	3.30	6.59 ± 0.2458	12.32 ± 0.2897	18.31 ± 0.2456	40.46 ± 0.2458
8.	4.00	7.75 ± 0.3568	14.33 ± 0.1368	21.77 ± 0.2789	49.04 ± 0.2458
9.	4.30	8.61 ± 0.2478	16.34 ± 0.3265	25.81 ± 0.4578	58.00 ± 0.2457
10.	5.00	9.32 ± 0.2525	19.06 ± 0.4128	30.17 ± 0.2356	64.78 ± 0.4458
11.	5.30	10.17 ± 0.1245	21.27 ± 0.5489	34.29 ± 0.8452	71.12 ± 0.6658
12.	6.00	10.62 ± 0.1489	23.37 ± 0.7458	38.58 ± 0.5672	77.69 ± 0.4785
13.	6.30	11.8 ± 0.9875	25.83 ± 0.6523	42.34 ± 0.7458	85.14 ± 0.6985
14.	7.00	12.67 ± 0.2589	27.92 ± 0.2121	46.93 ± 0.4259	93.00 ± 0.2563
15.	7.30	13.14 ± 0.2568	30.15 ± 0.2525	50.66 ± 0.8456	100.27 ± 0.3248
16.	8.00	14.18 ± 0.3659	32.44 ± 0.2365	54.28 ± 0.2365	99.27 ± 0.2458

* Average of three trials

Cont…

In -Vitro Drug Release data of Effervescent Tablets

Table 20: USP method

S. No.	Time (hrs)	Cumulative percentage of Drug Release *			
		ET-1	ET-2	ET-3	ET-4
		HPMC K100M	HPMC K4M	Sodium CMC	MC
1.	0.30	4.50 ± 0.2458	5.37 ± 0.1124	4.23 ± 0.4256	4.95 ± 0.4258
2.	1.00	5.63 ± 0.4475	6.90 ± 0.4896	5.06 ± 0.8975	9.41 ± 0.4896
3.	1.30	6.59 ± 0.4785	9.56 ± 0.7563	5.89 ± 0.5586	12.58 ± 0.7582
4.	2.00	7.42 ± 0.8965	11.82 ± 0.3458	7.99 ± 0.8975	14.55 ± 0.9856
5.	2.30	8.52 ± 0.2458	14.11 ± 0.8956	10.42 ± 0.2485	15.28 ± 0.5586
6.	3.00	9.48 ± 0.2214	16.48 ± 0.7458	11.21 ± 0.2145	16.97 ± 0.7789
7.	3.30	11.17 ± 0.5486	19.72 ± 0.7236	12.76 ± 0.1452	18.71 ± 0.2568
8.	4.00	12.73 ± 0.2263	23.14 ± 0.3248	14.09 ± 0.7896	19.42 ± 0.7159
9.	4.30	16.19 ± 0.5578	25.46 ± 0.3792	15.53 ± 0.5489	20.68 ± 0.2148
10.	5.00	18.17 ± 0.5689	28.61 ± 0.5486	17.08 ± 0.7596	21.91 ± 0.2248
11.	5.30	19.74 ± 0.9856	30.07 ± 0.3178	18.40 ± 0.8369	23.04 ± 0.2458
12.	6.00	22.6 ± 0.2478	31.98 ± 0.2485	19.61 ± 0.3486	24.06 ± 0.2365
13.	6.30	25.52 ± 0.4578	34.30 ± 0.4258	21.85 ± 0.9572	25.23 ± 0.5896
14.	7.00	27.37 ± 0.6352	36.42 ± 0.4159	23.22 ± 0.9425	26.63 ± 0.4785
15.	7.30	30.63 ± 0.4589	40.43 ± 0.7965	24.24 ± 0.5528	27.80 ± 0.8456
16.	8.00	32.78 ± 0.5568	43.21 ± 0.1482	27.09 ± 0.6648	30.15 ± 0.5263

* Average of three trials

STABILITY STUDIES REPORT

Table 34: NET – 7 (Methyl cellulose 60 %)

a) Temperature: $45^0C \pm 2^0C$ and RH of 75 % ± 2 %

Intervals of Testing	Appearance	Hardness (4-4.5 kg / cm2)	Floating Lag Time (< 1 min)	Drug Content (90- 110 %)
0 day	White colour, circular, flat tablets	4 kg / cm2	Float immediately	103.98
15 days	White colour, circular, flat tablets	4 kg / cm2	Float immediately	101.12
30 days	White colour, circular, flat tablets	4 kg / cm2	Float immediately	101.37
45 days	White colour, circular, flat tablets	4 kg / cm2	Float immediately	100.39
60 days	White colour, circular, flat tablets	4 kg / cm2	Float immediately	100.86
75 days	White colour, circular, flat tablets	4 kg / cm2	Float immediately	101.59
90 days	White colour, circular, flat tablets	4 kg / cm2	Float immediately	99.67

b) Temperature: Ambient Room Temp. $25^0C \pm 2^0C$

Intervals of Testing	Appearance	Hardness (4-4.5 kg / cm2)	Floating Lag Time (< 1 min)	Drug Content (90- 110 %)
0 day	White colour, circular, flat tablets	4 kg / cm2	Float immediately	101.56
15 days	White colour, circular, flat tablets	4 kg / cm2	Float immediately	100.25
30 days	White colour,	4 kg / cm2	Float immediately	101.59

15 days	White colour, circular, flat tablets	4.5 kg / cm2	1 min 20 sec	101.28
30 days	White colour, circular, flat tablets	4.5 kg / cm2	1 min 10 sec	100.99
45 days	White colour, circular, flat tablets	4.5 kg / cm2	1 min 30 sec	100.50
60 days	White colour, circular, flat tablets	4.5 kg / cm2	1 min 10 sec	98.69
75 days	White colour, circular, flat tablets	4.5 kg / cm2	1 min 40 sec	100.44
90 days	White colour, circular, flat tablets	4.5 kg / cm2	1 min 18 sec	99.25

Table 36: FB – VI (Sodium Alginate : CaCO3 1:2)

a) Temperature: 45^0C $\pm$ 2^0C and RH of 75 % $\pm$ 2 %

Intervals of Testing	Appearance	Mechanical Strength (1-1.5 kg / cm2)	Total Floating Time (> 24 hrs)	Drug Content (90- 110 %)
0 day	White colour, spherical, uniform beads	1 kg / cm2	> 24 hrs	98.65
15 days	White colour, spherical, uniform beads	1 kg / cm2	> 24 hrs	100.21
30 days	White colour, spherical, uniform beads	1 kg / cm2	> 24 hrs	101.55
45 days	White colour, spherical, uniform beads	1 kg / cm2	> 24 hrs	100.69
60 days	White colour, spherical, uniform beads	1 kg / cm2	> 24 hrs	99.23
75 days	White colour, spherical, uniform beads	1 kg / cm2	> 24 hrs	101.60
90 days	White colour, spherical, uniform beads	1 kg / cm2	> 24 hrs	102.05

b) Temperature: Ambient Room Temp. 25^0C $\pm$ 2^0C

7.	NET-7	0.2078	0.2447	16	27.05
8.	NET-8	0.2134	0.2553	17	27.50

* Average of three trials

Table 9: Preformulation Studies for the Granules of Effervescent Tablets

S.No.	Code No.	Bulk Density g / cc *	Tapped Density g / cc *	Compressibility Index (%) *	Angle of Repose (θ) *
1.	ET-1	0.2063	0.2401	15	26.85
2.	ET-2	0.2065	0.2393	14	27.29
3.	ET-3	0.1780	0.2070	14	28.07
4.	ET-4	0.1940	0.2219	13	28.12

* Average of three trials

Table 10: Evaluation of Non-effervescent Floating Tablets

S. No.	Code No.	Hardness (kg/cm^3) *	% Friability *	Thickness (mm) *	Average Weight (mg $\pm$ 7.5 %)	% Drug Content

* Average of three trials

In vitro Release data for Floating Beads

Table 22: Effect of different gas forming agents on in-vitro release of Glipizide (USP Method)

S. No.	Time (hrs)	Cumulative percentage of Drug Release *				
		FB-1 $CaCO_3$	FB-2 $MgCO_3$	FB-3 $NaHCO_3$	FB-4 Na_2CO_3	F
1.	0.30	2.42 ± 0.2256	2.20 ± 0.2356	2.33 ± 0.2453	2.22 ± 0.1245	2
2.	1.00	2.75 ± 0.4215	2.90 ± 0.8985	2.76 ± 0.1458	2.56 ± 0.2245	2
3.	1.30	3.19 ± 0.8745	3.52 ± 0.5263	3.26 ± 0.2456	3.10 ± 0.7778	2
4.	2.00	3.72 ± 0.9089	3.98 ± 0.8759	3.92 ± 0.1125	3.41 ± 0.8635	3
5.	2.30	4.17 ± 0.8652	4.42 ± 0.6682	4.29 ± 0.8965	3.78 ± 0.4263	3
6.	3.00	4.54 ± 0.4586	4.63 ± 0.5478	4.66 ± 0.8852	4.17 ± 0.5896	4
7.	3.30	4.73 ± 0.2365	4.80 ± 0.4458	4.96 ± 0.3562	4.50 ± 0.87749	4
8.	4.00	5.05 ± 0.2589	5.06 ± 0.9860	5.43 ± 0.8965	4.66 ± 0.2418	4
9.	4.30	5.50 ± 0.8896	5.40 ± 0.0986	5.66 ± 0.8759	5.05 ± 0.1448	5
10.	5.00	5.83 ± 0.7854	5.59 ± 0.7745	5.94 ± 0.2568	5.34 ± 0.8960	5
11.	5.30	6.42 ± 0.3560	5.93 ± 0.2245	6.22 ± 0.9946	5.71 ± 0.4089	5
12.	6.00	6.75 ± 0.8523	6.25 ± 0.8963	6.57 ± 0.2220	6.03 ± 0.8706	6
13.	6.30	6.94 ± 0.7485	6.53 ± 0.4862	6.86 ± 0.8845	6.32 ± 0.8904	6
14.	7.00	7.37 ± 0.4523	6.91 ± 0.7539	7.09 ± 0.7820	6.56 ± 0.5068	6
15.	7.30	8.20 ± 0.4263	7.48 ± 0.1866	7.39 ± 0.6589	6.91 ± 0.5477	7
16.	8.00	9.26 ± 0.5632	9.67 ± 0.4266	7.87 ± 0.1256	7.30 ± 0.5183	7

* Average of three trial

Table 23: Modified Beaker Method

S.No.	Time (hrs)	Cumulative percentage of Drug Release *				
		FB-1	FB-2	FB-3	FB-4	
		$CaCO_3$	$MgCO_3$	$NaHCO_3$	Na_2CO_3	
1.	0.30	0.74 ± 0.4256	0.87 ± 0.1025	0.66 ± 0.1125	0.59 ± 0.5483	0
2.	1.00	1.17 ± 0.1195	1.37 ± 0.1	1.04 ± 0.7895	0.94 ± 0.1450	0

15.	7.30	3.43 ± 0.8930	4.53 ± 0.5263	8.35 ± 0.2356	8.20 ± 0.4263	
16.	8.00	3.57 ± 0.4236	4.95 ± 0.8956	8.81 ± 0.5089	9.26 ± 0.5632	

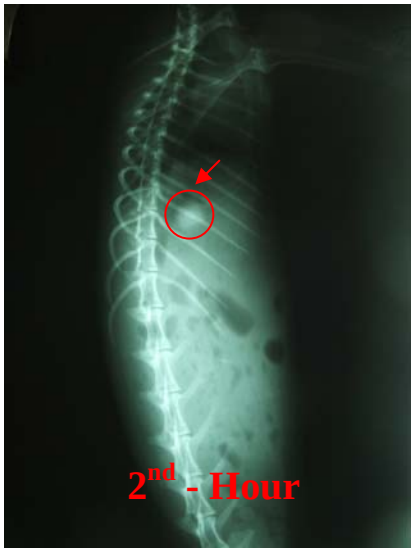
* Average of three trials

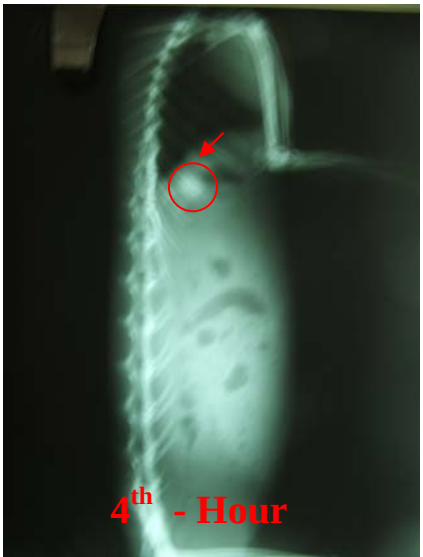
Table 25: Modified Beaker Method

S.No.	Time (hrs)	Cumulative percentage of Drug Release *				
		FB-I	FB-II	FB-III	FB-IV	
		1 : 0.25	1 : 0.50	1 : 0.75	1 : 1	
1.	0.30	0.38 ± 0.1458	0.2 ± 0.2450	0.66 ± 0.1452	0.74 ± 0.4256	0
2.	1.00	0.65 ± 0.4458	0.33 ± 0.8903	1.13 ± 0.8630	1.17 ± 0.1195	1
3.	1.30	0.92 ± 0.5689	0.56 ± 0.6403	1.69 ± 0.8459	1.59 ± 0.8906	1
4.	2.00	1.24 ± 0.5236	0.79 ± 0.7800	1.98 ± 0.5068	2.03 ± 0.5426	2
5.	2.30	1.55 ± 0.8956	1.00 ± 0.4820	2.84 ± 0.9771	2.68 ± 0.8596	2
6.	3.00	1.69 ± 0.7854	1.22 ± 0.4796	3.52 ± 0.1125	3.31 ± 0.2458	3
7.	3.30	2.12 ± 0.2568	1.54 ± 0.3596	4.34 ± 0.8236	4.32 ± 0.6593	4
8.	4.00	2.54 ± 0.8745	1.86 ± 0.4785	5.11 ± 0.2036	5.13 ± 0.8956	5
9.	4.30	2.89 ± 0.8256	2.17 ± 0.5570	5.78 ± 0.6103	5.94 ± 0.2568	6
10.	5.00	3.13 ± 0.9316	2.56 ± 0.8961	6.78 ± 0.8972	7.38 ± 0.9863	8
11.	5.30	3.63 ± 0.6653	2.92 ± 0.8430	7.63 ± 0.1036	8.32 ± 0.3346	9
12.	6.00	3.97 ± 0.5069	3.53 ± 0.5406	9.12 ± 0.8950	9.91 ± 0.8098	11
13.	6.30	4.27 ± 0.8470	3.80 ± 0.9873	9.89 ± 0.4826	11.42 ± 0.7960	12
14.	7.00	4.61 ± 0.8639	5.02 ± 0.8036	11.34 ± 0.0489	13.70 ± 0.5896	15
15.	7.30	5.12 ± 0.5069	5.93 ± 0.5403	12.29 ± 0.7895	15.80 ± 0.4520	16
16.	8.00	5.53 ± 0.3056	6.87 ± 0.6006	13.92 ± 0.4452	17.31 ± 0.1425	18

* Average of three trials

Fig. 26: IN-VIVO X-RAY PHOTOGRAPHS OF FLOATING TABLET





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