GASTRORETENTIVE DOSAGE FORMS BY FLOATING DRUG DELIVERY SYSTEMS

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ABSTRACT:

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of muco-adhesion, floatation, sedimentation, expansion, modified shape system, or by the simultaneous administration of pharmacological agent that delay gastric emptying.

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options

KEYWORDS: gastro retentive dosage form (GRDF), gastric residence time (GRT),oesophagitis, Floating drug delivery systems

INTRODUCTION

GASTRORETENTIVE DOSAGE FORM (GRDF) [1,2]:

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS).

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of muco-adhesion, floatation, sedimentation, expansion, modified shape system, or by the simultaneous administration of pharmacological agent that delay gastric emptying.

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as –

1. This application is especially effective in 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 overcome this problem, erodible, gastro-retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.
2. GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the sub-mucosal tissue of

stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

GRDFs can be used as carriers for drugs with so-called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides, and Tetracyclines etc.) are taken up only from very specific sites of the GI mucosa

BIOLOGICAL ASPECTS OF GRDFS:

ROLE OF GI TRACT [3]:

STOMACH:

The stomach is J-shaped organ located in the upper left hand portion of the abdomen, just below the diaphragm. It occupies a portion of the epigastria and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area very little absorption takes place from the stomach. It provides barrier to the delivery of drugs to small intestine.

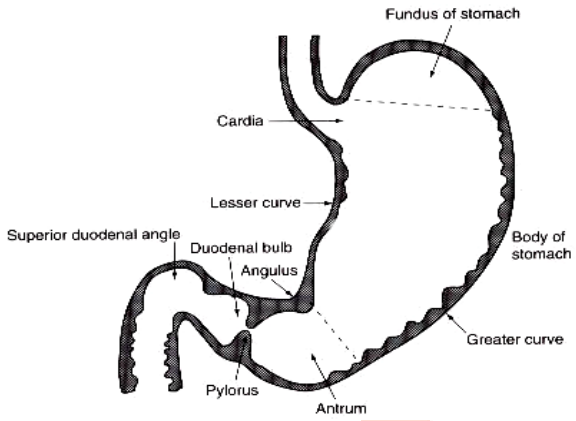


Fig.1: Anatomy of Stomach

The stomach is divided into three anatomical regions. i) Fundus ii) Body and iii) Pylorus (or antrum). The proximal stomach consisted of Fundus and body, which serves as a reservoir for ingested materials, whereas the distal region (Pylorus) is the major site of mixing motions, acting as a pump to propel gastric contents for gastric emptying. Gastric emptying occurs both in fasting as well as fed states.

The GI tract is always in a state of continuous motility. There are two modes of motility pattern. (a) The digestive mode and (b) Inter-digestive mode. In case of fasted state an inter-digestive series of electrical events occurs in cyclic manner both through stomach and small intestine every 2-3 hr. This electrical activity is termed as inter-digestive myoelectric cycle.

Table: 1. Phases of gastric emptying cycle.

PHASE	ACTION
Phase I	Period of no contraction.
Phase II	Period of intermittent contraction.
Phase III	Period of regular contractions at the maximal frequency that migrate distally.
Phase IV	Period of transition between phase III and phase I.

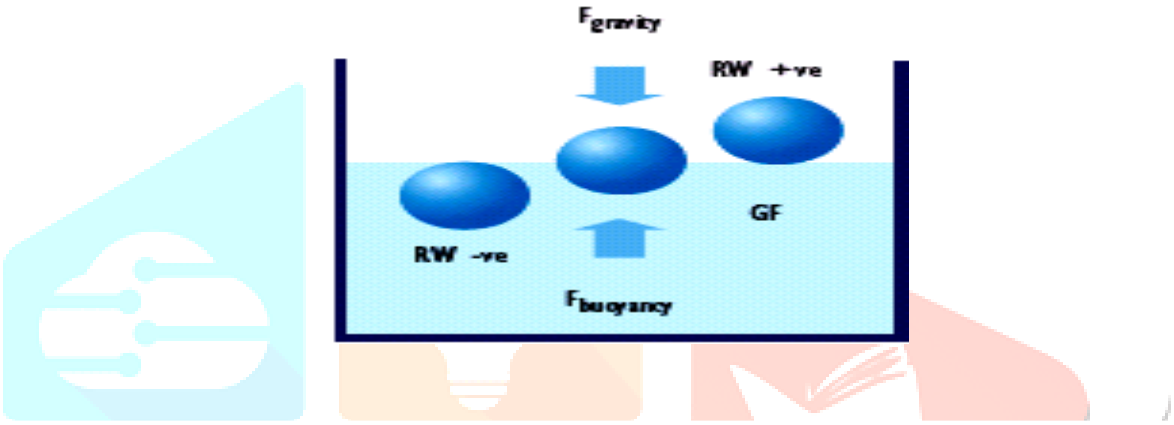
Phase III has a Housekeeping role and serves to clear all indigestible materials from the stomach and small intestine. Consequently, a controlled-release gastrointestinal drug delivery system must be capable of resisting the house keeping action of phase III. Studies revealed that in the fed state, the gastric emptying rate is slowed since the onset of MMC is delayed. It can be concluded that feeding results in a lag time before onset of gastric emptying cycle.

TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS) [4]:

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system.

fter release of drug, the residual system is emptied from the stomach. This result in an increased GRT and a better control of the fluctuations in plasma drug concentration However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus (fig: 2) operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations

Fig: 3. Diagrammatic representation of RW apparatus



GF: **gastric fluid**

RW or **F**= F buoyancy - F gravity

= (Df - Ds) gV

Where,

RW = total vertical force

Df = fluid density,

Ds = object density, V = volume;

g = acceleration due to gravity

development of FDDS, which are:

A. Effervescent System, and
B. Non- Effervescent System.

I. EFFERVESCENT SYSTEM [05,06]:

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.

These effervescent systems further classified into two types.

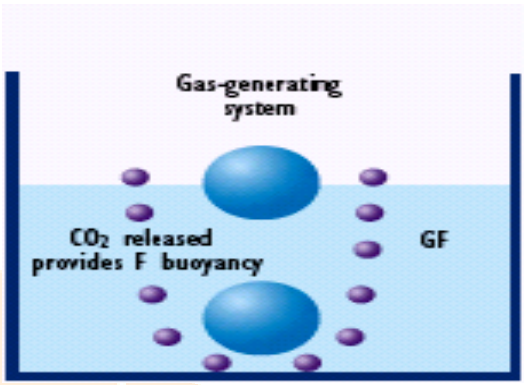
- Gas Generating systems

- Volatile Liquid/Vacuum Containing Systems.

A) Gas Generating Systems:

1. Intra Gastric Single Layer Floating Tablets or Hydrodynamically Balanced System (HBS): These are as shown in Fig. 4 and formulated by intimately mixing the CO_2 generating agents and the drug within the matrix tablet. These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the gastric emptying rate 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.

Fig 2. Intra Gastric Single Layer Floating systems.



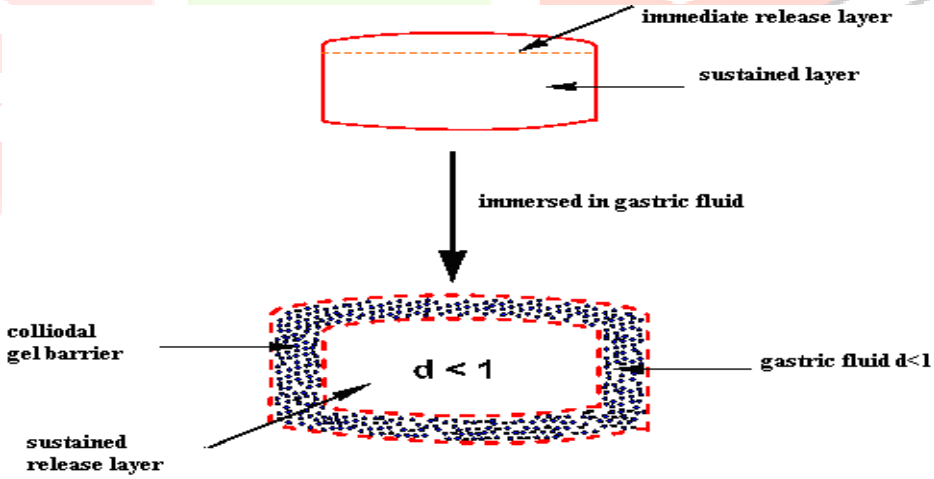
GF: Gastric Fluid

2. Intra Gastric Bilayer Floating Tablets:

These are also compressed tablet as shown in Fig: 5 and containing two layer i.e.,

i. Immediate release layer and
ii. Sustained release layer.

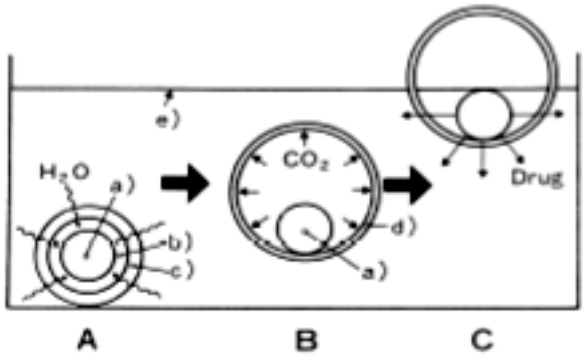
Fig 3. Intra Gastric Bilayer Buoyant Tablet.



3.Multiple Unit type floating pills:

These systems consist of sustained release pills as 'seeds' surrounded by double layers (fig: 3). the inner layers consist 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 pills like balloons, which float as they have lower density. This lower density is due to generation and entrapment of CO_2 within the system.

Fig 4. A multi-unit oral buoyant dosage system.



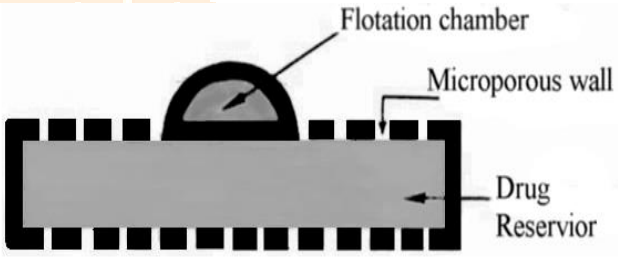
Stages of floating mechanism: (A) penetration of water; (B) generation of CO_2 and floating; (C) dissolution of drug. Key: (a) conventional SR pills; (b) effervescent layer; (c) swellable layer; (d) expanded swellable membrane layer; (e) surface of water in the beaker (37^0C).

B) Volatile Liquid / Vacuum Containing Systems [07]:

1. Intra-gastric Floating Gastrointestinal Drug Delivery System:

These systems 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 microprous compartment, as shown in Fig. 7.

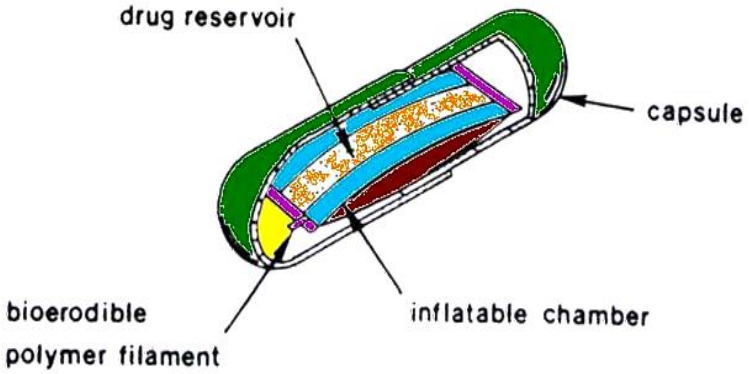
Fig : 5. Intra Gastric Floating Gastrointestinal Drug Delivery Device



2. Inflatable Gastrointestinal Delivery Systems:

In these systems an inflatable chamber is incorporated, which contains liquid ether 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.

Fig 6. Inflatable Gastrointestinal Delivery System



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 the stomach. The drug continuously released from the reservoir into the gastric fluid. This system is shown in Fig. 8.

3. Intragastric Osmotically Controlled Drug Delivery System:

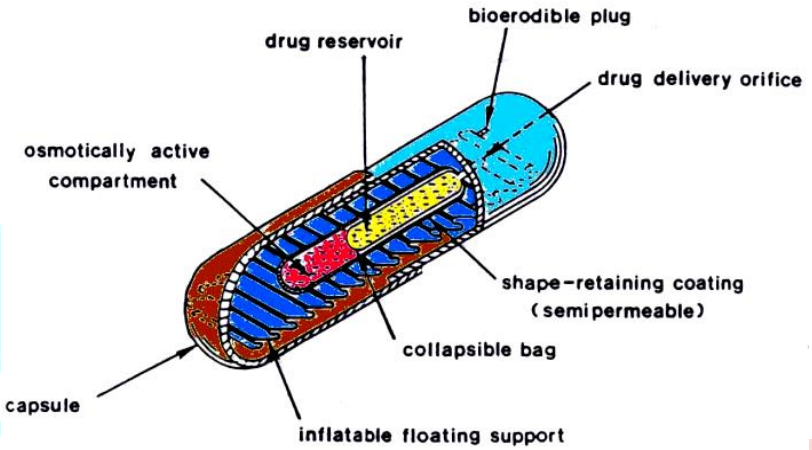
It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a biodegradable capsule. In the stomach, the capsule quickly disintegrates to release the intragastirc osmotically controlled drug delivery device. The inflatable support inside forms a deformable 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 vapor 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 in turn forces the drug reservoir compartment to reduce its volume and activate the drug reservoir compartment to reduce its volume and activate the drug release of a drug solution formulation through the delivery orifice.

The floating support is also made to contain a bio-erodible plug that erodes after a predetermined time to deflate the support. The deflated drug delivery system is then emptied from the stomach. This system is shown in Fig. 9

Fig: 7. Intragastric Osmotically Controlled Drug Delivery System

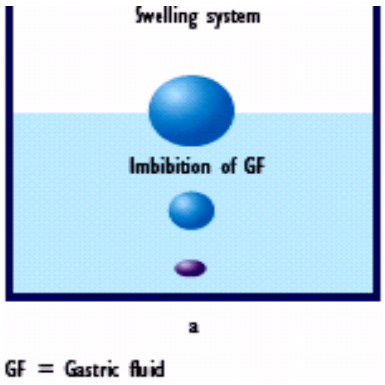


II. NON-EFFERVESCENT SYSTEMS [08]:

This type of system, after swallowing, swells unrestrained via imbibitions of gastric fluid to an extent that it prevents their exit from the stomach. These systems may be referred to as the 'plug-type systems' since they have a tendency to remain lodged near the pyloric sphincter. 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. The air trapped by the swollen polymer confers buoyancy to these dosage forms.

Other approaches reported in the literature are hydro dynamically balanced (HBS) systems developed by Sheth and Tossounian, 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

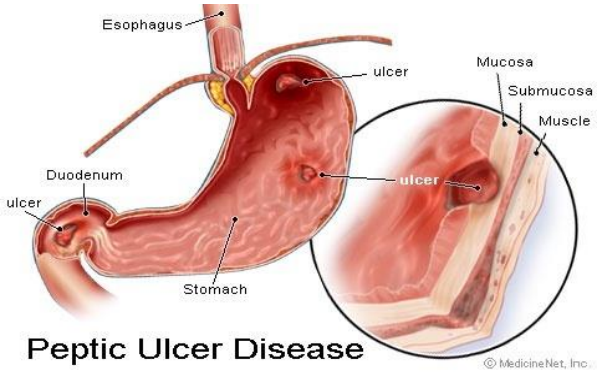
Fig 8. swelling systems



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

PEPTIC ULCER:

A peptic ulcer is a hole in the gut lining of the stomach, duodenum, or esophagus. A peptic ulcer of the stomach is called a gastric ulcer; of the duodenum, a duodenal ulcer; and of the esophagus, an esophageal ulcer respectively. An ulcer occurs when the lining of these organs is corroded by the acidic digestive juices which are secreted by the parietal cells of the stomach.



Figure–9 Diagram showing different types of ulcers

Table no: 02. pH Conditions of GIT (To match optimized value in biological fluid)

Region	pH (Fasted)	Resident time
Mouth	5.8-7.4	< 1 min
Esophagus	1-5	0.25-3 hrs
Stomach	1.5-3.5	1– 5 hrs
Small intestine	5.5-7.8	3-4 hrs
Duodenum	2.4 –6.8	> 5 hrs
Jejunum	6.0 – 7.0	1 – 2 hrs
Ileum	6.5	2 – 3 hrs
Large intestine	6.2-7	< 8-30 hrs
Colon	8	15 – 48 hrs

Causes of peptic ulcer:

1. For many years, excess acid was believed to be the major cause of ulcer disease. Accordingly, treatment emphasis on neutralizing and inhibiting the secretion of stomach acid. While acid is still considered significant in ulcer formation, the leading cause of ulcer disease is currently believed to be infection of the stomach by a bacterium called "Helicobacter pylori" (H. pylori).
2. Another major cause of ulcers is the chronic use of anti-inflammatory medications, commonly referred to as NSAIDs (Non Steroidal Anti-Inflammatory Drugs), including aspirin.
3. **FORMULATION OF FLOATING TABLETS:**

The formulation of floating tablets involves the different methods. The most common method used is the direct compression where the ingredients are and polymers are directly mixed in increasing order of their weights and

were directly compressed in order to get tablets. The other methods such as wet granulation technique, melt solidification, wet granulation technique can also be used to formulate the floating tablets.

4. METHODS OF PREPARATION [09]:

MELT GRANULATION TECHNIQUE:

It is a process by which the pharmaceutical powders are agglomerated by using a meltable binder and no water or organic solvents are required for granulation. Because there is no drying step, the process is less time consuming and uses less energy. Granules were prepared in a lab scale high shear mixer, using a jacket temperature of 60 0c and an impeller speed of 20000 rpm.

MELT SOLIDIFICATION TECHNIQUE:

This process involves emulsification of the molten mass in the aqueous phase followed by its solidification by chilling. The carriers used for this technique are lipids, waxes, polyethylene glycols. Drug is incorporated into these carriers to achieve controlled release.

DIRECT COMPRESSION TECHNIQUE:

Involves compressing tablets directly from powdered material without modifying the physical nature of the material itself. Direct compression vehicles or carriers must have good low and compressible characters these properties are imparted by predisposing these vehicles to slugging, spray drying or crystallization. Most commonly used carriers are dicalcium phosphate,trihydrate, tricalcium phosphate etc.

WET GRANULATION TECHNIQUE:

Wet granulation process involves the wet massing of powders, wet sizing or milling and drying. Wet granulation forms the granules by binding the powders together with an adhesive instead of compaction. The wet granulation technique employs a solution suspension or slurry containing a binder which is usually added to the powder mixture however the binder may be incorporated dry into the powder mix and the liquid may be added by itself. The method of introducing the binder depends on its solubility and on the components of the mixture since, in general, the mass should merely be moist rather than wet or pasty, and there is a limit to the amount of solvent that may be employed. Once the granulating liquid has been added mixing continues until a uniform dispersion is attained and all the binder has been activated. After sufficient blending, now the wet mass is made to undergo wet screening by passing through a hammer mill or oscillating granulator equipped with screens having large perforations. Now the wet material undergoes drying and the dried mass is said to undergo dry screening or dry milling and the granules now obtained now undergo compression.

EFFERVESCENT TECHNIQUE:

The floating chamber of the drug delivery system can be filled with inert gas [CO2] by the effervescent reaction between organic acid [citric acid] and bicarbonate salts.

RATIONALE BEHIND FLOATING DRUG DELIVERY SYSTEMS

TABLE 3

CATEGORY	DRUG	RATIONALE-HALF LIFE	RATIONALE-BIOAVAILBILITY
Anti-hypertensive	Diltiazem Hcl Atenolol	3-4 hours 6-7 hours	40% 50%
Anti-ulcer drugs	Ranitidine Hcl Famotidine	2.5-3 hours 2.5-4 hours	50% 20-66%

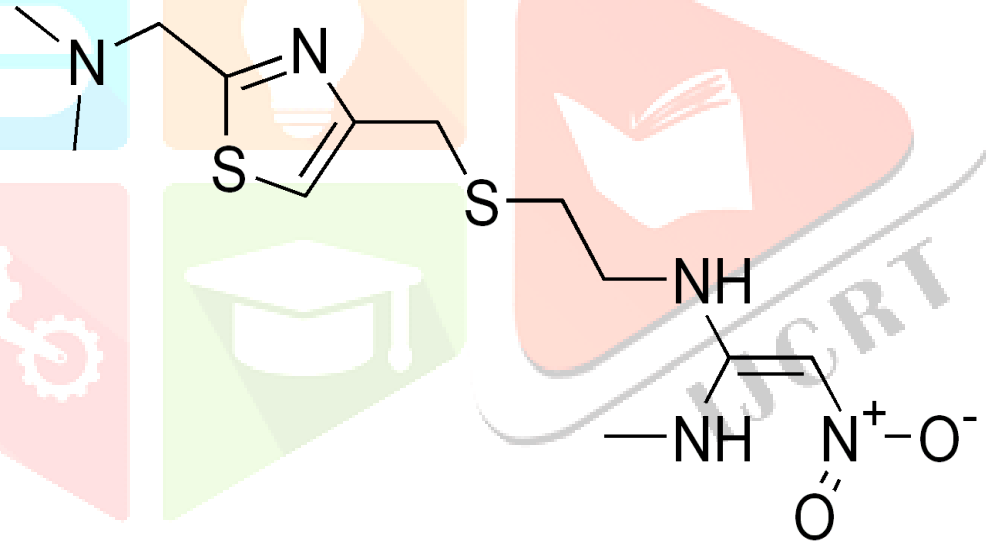
	Nizatidine Omeprazole Lansoprozole Rabeprozole	1-2 hours 1 hour 1-1.5 hours 1-1.5 hours	60-70% 50% 80% 52%
Anti diabetics	Glipizide Rosiglitazone Metformin	3-5 hours 3-4 hours 6.2 hours	50% 50% 40%

DRUG PROFILE

NIZATIDINE:

Nizatidine is a histamine H2 receptor antagonist with low toxicity that inhibits gastric acid secretion. The drug is used for the treatment of duodenal ulcers.

STRUCTURE:



METABOLISM:

Hepatic. Less than 7% of an oral dose is metabolized as N2-monodes-methylnizatidine, an H2-receptor antagonist, which is the principal metabolite excreted in the urine. Other likely metabolites are the N2-oxide (less than 5% of the dose) and the S-oxide (less than 6% of the dose).

LIST OF CHEMICALS

S.NO.	MATERIALS	MANUFACTURES / SUPPLIERS
1	NIZATIDINE	Dr. Reddy's Labs, Hyderabad.

2	HPMC 15 cps	Loba Chemie, Mumbai
3	XANTHAN GUM	Loba Chemie, Mumbai
4	CARBOPOL 940	Indian Research Products, Chennai
5	ETHYL CELLULOSE	Loba Chemie, Mumbai
6	SODIUM BICARBONATE	Loba Chemie, Mumbai
7	TARTARIC ACID	S.D. fine chem. Ltd.
8	MAGNESIUM STEARATE	Loba Chemie, Mumbai
9	LACTOSE	Loba Chemie, Mumbai

FORMULATION OF FLOATING TABLETS (EFFERVESCENT TECHNIQUE):

Following formulations were prepared usingdifferent polymers and effervescent agents by direct compression technique. (Total weight: 400 mg).

TABLE: 4

INGREDIENTS(mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7
Nizatidine	75	75	75	75	75	75	75
HPMC 15cps	200	-	-	100	-	100	50
Carbopol 940	-	200	-	100	100	-	75
Xantan Gum	-	-	200	-	100	100	75
Ethyl cellulose	20	20	20	20	20	20	20
$NaHCO_3$	50	50	50	50	50	50	50

Tartaric acid	50	50	50	50	50	50	50
Lactose	4	4	4	4	4	4	4
Magnesium stearate	1	1	1	1	1	1	1

STANDARD CALIBRATION CURVE OF NIZATIDINE:

Standard Curve of Nizatidine was determined by plotting absorbance (nm) versus concentration (µg/ml) at 242 nm. The results obtained are as follows: -

Table 5. Standard curve of Nizatidine

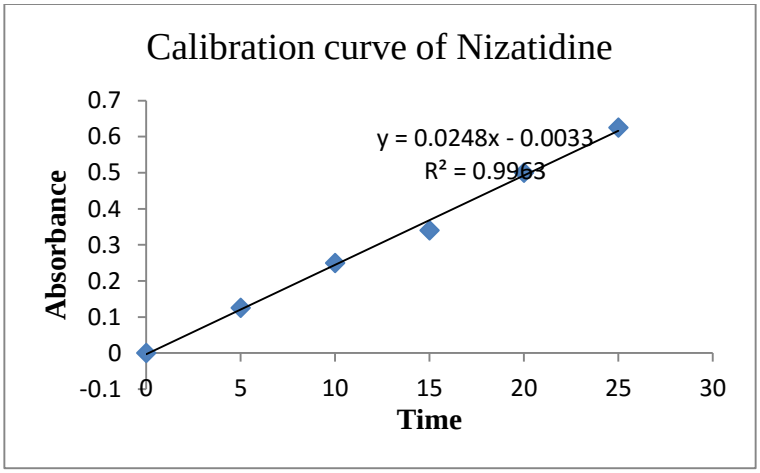
S. NO.	CONCENTRATION (µg/ml)	ABSORBANCE (242 nm)
1.	0	0
2.	5	0.125
3.	10	0.250
4.	15	0.340
5.	20	0.500
6.	25	0.625
Slope		0.024
Regression		0.996

The linear regression analysis was done on absorbance data points.
A straight-line equation *was* generated to facilitate the calculation of amount of drug. The equation is as follows.

(Y = mx+c)

Where ***Y***= Absorbance, ***m*** = slope, ***x*** = Concentration, ***c*** = Intercept.

Fig.9. STANDARD CURVE OF NIZATIDIE IN 0.1N HCl



Drug Content Uniformity:

The percentage drug content for F1 to F7 was found to be in the range of 96.38% to 98.32 % of Nizatidine. The results are shown in Table 7.

Table.6: Drug content uniformity of formulations

S.No	FORMULATIONS	DRUG CONTENT (%)
1	F1	97.92
2	F2	96.38
3	F3	98.32
4	F4	97.44
5	F5	97.70
6	F6	97.36
7	F7	97.00

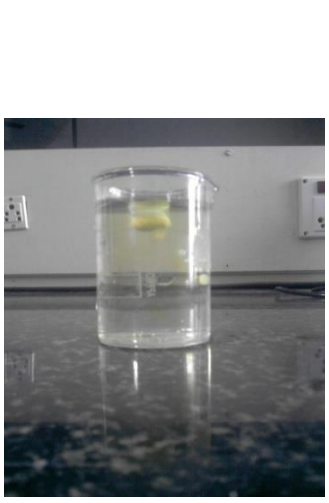
Buoyancy Study:

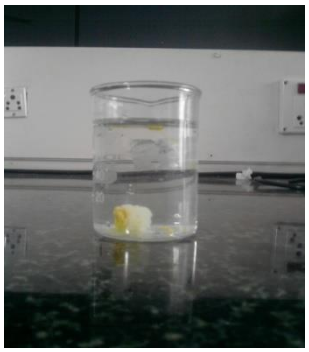
Buoyancy studies were performed using 0.1 N Hcl as medium. All formulations shown the satisfactory results

Table.7: Buoyancy lag time, Total floating time of formulations

PARMETER	F-1	F-2	F-3	F-4	F-5	F-6	F-7
BUOYANCY LAG TIME(min)	2.50	3.08	0.50	2.83	1.26	1.18	2.66
FLOATING TIME(min)	225	345	417	346	322	357	283

FIG.10: BUOYANCY / FLOATING TEST
(In Simulated Gastric Fluid)





At Initial Time

After 4 Hours

After 6 Hours

Swelling Study:Swelling study was performed on all batches (F1 to F7) for 3 hrs. The results of swelling index are shown in Table 8and swelling index against time (hrs) was plotted as shown in Fig. 10.

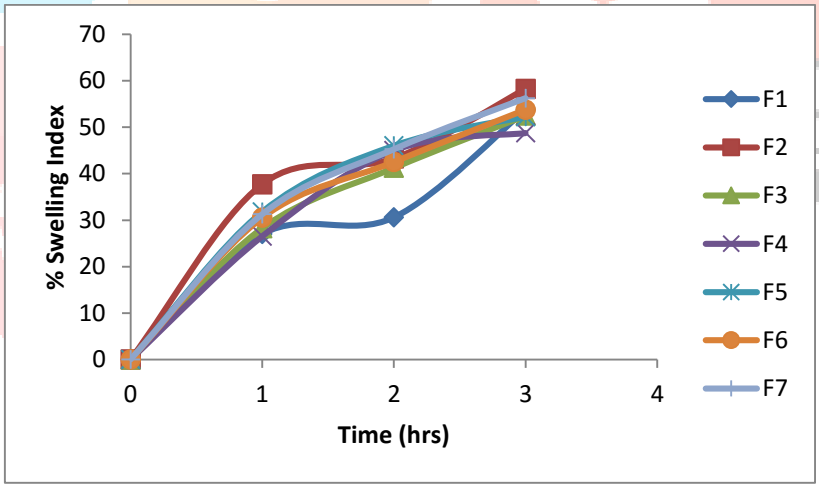
In the present study, the least swelling index (48.75%) was found for F4 containing HPMC and Carbopol 940. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability.

The percentage water uptake of the formulations ranged from 48.75 to 58.75 %.

Table.8: Swelling index of tablets of batch F1 to F7

TIME (In Hrs)	SWELLING INDEX (%)						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	27.00	37.71	28.25	26.50	31.75	30.50	31.25
2	30.56	43.25	41.25	45.00	46.00	45.50	45.25
3	53.75	58.75	52.50	48.75	52.25	53.75	56.25

Fig.11: Swelling index of formulations



In vitro drug release Studies:

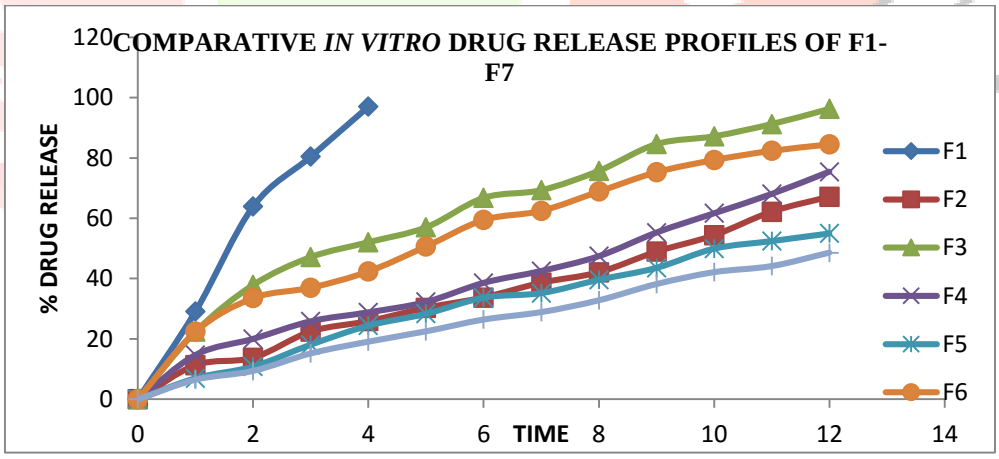
All the seven formulations F1 to F7 are subjected to *in vitro* release studies in 900 ml 0.1N Hcl (pH 1.2) using dissolution apparatus, at 50 rpm at 37±0.5˚C, and the results are recorded as shown in Tables 09 and the comparative drug release of F1-F7 was shown in fig 11.

Table.9: Comparative *In vitro* Release data for F1-F7.

TIME (In Hrs)	Cumulative % of Drug release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	29.160	11.324	22.411	14.698	6.985	22.411	6.503

2	63.934	13.759	37.887	20.034	10.857	33.549	9.410
3	80.467	22.467	47.131	25.863	18.112	36.998	15.215
4	97.036	25.891	52.056	28.813	24.419	42.382	19.106
5	-	30.287	56.992	32.251	28.330	50.671	22.523
6	-	33.729	66.759	38.589	33.695	59.461	26.429
7	-	38.624	69.317	42.531	35.216	62.484	28.898
8	-	42.083	75.737	47.445	39.632	68.889	32.818
9	-	48.925	84.580	55.263	43.576	75.307	38.193
10	-	54.336	87.177	61.651	49.939	79.330	42.134
11	-	62.168	91.224	68.054	52.459	82.396	44.155
12	-	67.126	96.245	75.434	54.985	84.505	48.590

Fig.12: COMPARATIVE *IN VITRO* DRUG RELEASE PROFILES OF F1-F7.



DRUG RELEASE KINETICS:

The regression coefficient (R^2) values of release data of all formulations obtained by curve fitting method for zero-order, first-order, and Higuchi and Krosmeyer-Peppas model are reported in Table 16.

The *in vitro* release data were fit into best – fit model using PCP-DISSO version-3.02 software and the data was recorded in the table 42.The R^2 values of zero order kinetics ranged from 0.918 – 0.988 for formulations F1 – F7. The values for first order kinetics for F1 – F7 ranged from 0.919 – 0.997. The values for Higuchi model ranged between 0.949 – 0.994. The values for Hix-crow model ranged between 0.0916- 0.998 and the values for Peppas model ranged between 0.983-0.997. All formulations showed Diffusion coefficient less than 1($n < 1$).

Table.10: Kinetic values obtained from different plots of F1- F7

Formulation	Zero order plot		First order plot		Higuchi plot		Hix-crow plot		Korsemeyer Peppa's plot			Possible mechanism of drug release
	R^2	K	R^2	K	R^2	K	R^2	K	R^2	K	n	
F-1	0.983	26.2	0.932	-0.71	0.975	45.3	0.9836	-0.15	0.986	31.0	0.86	Peppas model
F-2	0.986	5.60	0.978	-0.08	0.949	16.03	0.988	-0.02	0.987	9.64	0.73	Zero order model
F-3	0.974	9.25	0.919	-0.21	0.994	27.12	0.916	-0.05	0.991	23.9	0.56	Higuchi model
F-4	0.982	6.28	0.968	-0.09	0.954	18.03	0.982	-0.27	0.983	12.7	0.65	Peppas model
F-5	0.988	4.94	0.997	-0.06	0.959	14.18	0.997	-0.01	0.997	6.85	0.85	First order model
F-6	0.918	8.24	0.994	-0.15	0.994	24.61	0.989	-0.04	0.994	21.6	0.55	First order model
F-7	0.994	4.18	0.996	-0.05	0.950	11.94	0.998	-0.01	0.996	5.96	0.83	Hix-crow model

k= release rate constant

n= diffusion coefficient.

CURVE FITTING METHOD FOR OPTIMISED FORMULA:

Most of the formulations follow the Peppas and First order model. For the optimized formulation F3, the R^2 value of Higuchi 0.9942 (nearer to 1) is dominant than the other models which indicates drug release depended on the square root of Time. Different release models for F-3 were shown in fig 13-17.

Fig.13: Zero order plot for F-3

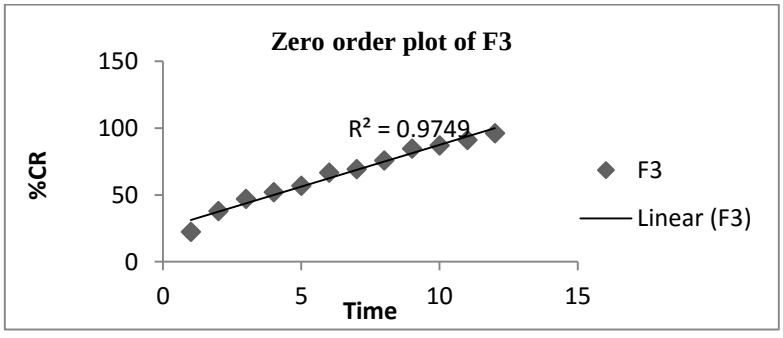


Fig.14: First order plot for F-3.

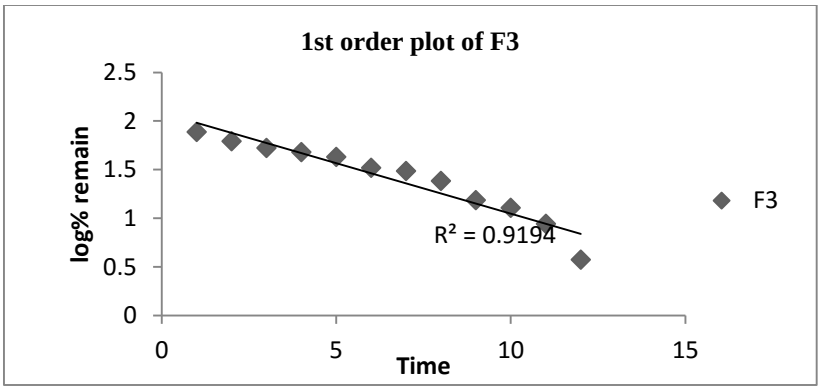


Fig.15: Higuchi plot for F-3

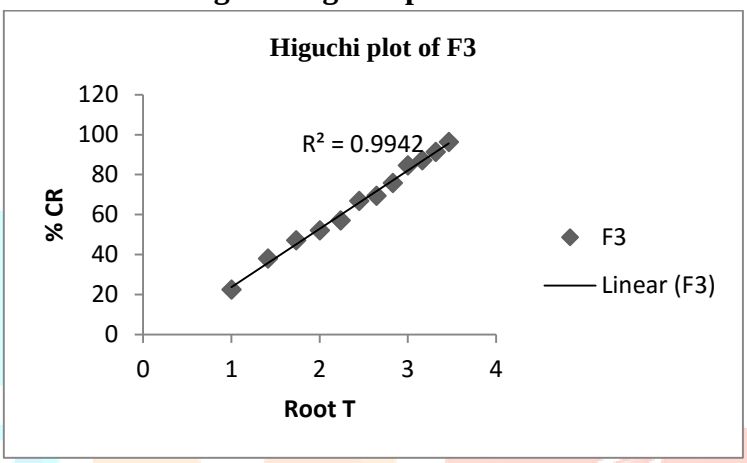


Fig.16: Hix crowell plot for F-3

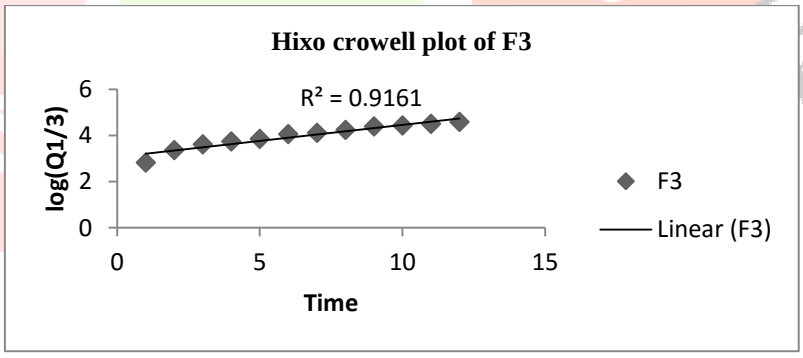
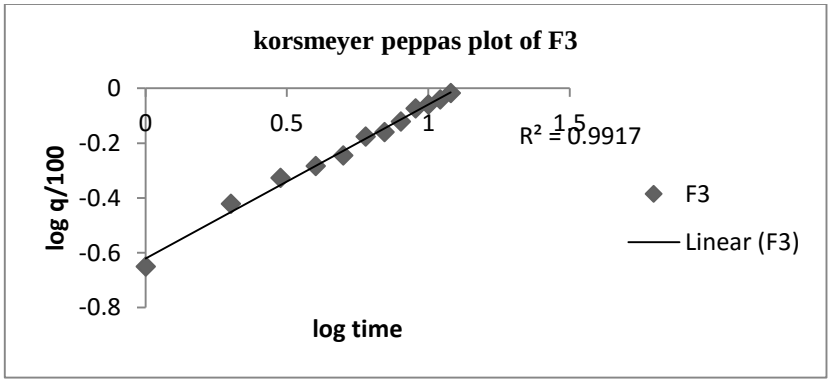


Fig.17: Korsmeyer peppas plot for F-3



Stability Study Conditions: 40 ± 2^0C/ 75 ± 5 % RH.

Time	color	Evaluation parameters		
		Hardness (kg/cm2)	**Drug content uniformity (%)**	**% CDR**
0 month	Half white	5.2	98.32	96.245
1 month	Half white	5.2	98.29	96.194
2 month	Half white	5.2	98.28	96.191
3 month	Half white	5.1	98.24	96.189

DISCUSSION:

The present work was undertaken with an objective to develop a floating drug delivery system, evaluate its various physicochemical properties, investigate the release kinetics, and optimize the release pattern of the delivery systems for effective management of peptic ulcer using a model drug Nizatidine. The rationality of the work has been discussed in introduction.

Any formulation development work has to be proceeded by pre-formulation studies There is a need for selection of excipients, which are compatible with the drug and among themselves and also physiologically safe and biocompatible. Preliminary idea about the behavior of the dosage form formulated, using the selected ingredients and their singular and collective effect on the physicochemical and pharmaceutical properties of the dosage form also needs to be generated during this phase. Accordingly to develop the floating drug delivery system of Nizatidine, it was first subjected to compatibility study using its characteristic I.R. spectra. There was no discernible shift/disappearance/appearance of peaks in drug-polymer combined spectra that indicated good-polymer compatibility (Fig.12-18).

The standard calibration curve was prepared, which exhibited linear relationship between drug concentration and UV absorbance in 0.1 N HCl (Figure 19).

The Direct Compression technique was chosen for manufacturing of the tablets with drug within the polymer, which gives adequate release retardation with hydrophilic polymers. The tablets were found to be floating completely for prolonged period of time (at least 5 hours)

Various formulations were prepared with different polymers (HPMC 15cps, Carbopol 940 and Xanthan gum). It was found that tablets formulated with the Xanthan gum polymer are showing better dissolution, drug content and floating characteristics compared to other polymers investigated.

The kinetic investigation of the release profile gave us useful insight into the mechanism of drug release from the tablets. The release did not show any burst effect or lag time,(except F1) which is indicative of a homogeneous drug distribution in the polymer matrix. The dissolution data was subjected to regression analysis and were fitted to kinetic models, viz., Zero order, First order, Hixon- Crowell, Peppas and Higuchi. It was found that most of the formulations followed First order and Peppas release

Therefore, the objective of design and development of a floating drug delivery system of Nizatidine was completely achieved. This formulation of Nizatidine has several advantages compared to the conventional tablets. Being a floating drug delivery system, the drug would be completely released in the stomach so that the drug in solution form would slowly reach the upper part of small intestine leading to complete absorption. Theoretically, this means the bioavailability of Nizatidine may be improved, thereby giving clinicians a chance to reduce the required dose. The drug administration may be done with or without food, but with a glassful of water to provide suitable floating capability. Further, survey of public literature has shown that there has been no such attempt to optimize an economically viable tablet based Nizatidine sustained release floating drug delivery system, although, according to our opinion this type of delivery system has immense potential to improve pharmacokinetics and pharmacodynamics of the drug.

Finally, this optimized system of formulations can provide further formulations as per clinical requirements, tailor-made for individualized therapy.

CONCLUSION

Nizatidine is a safe and efficacious candidate of choice for treatment of peptic ulcer. However, due to limited bioavailability and half life unrelated to hepatic metabolism, the dosing frequency is high and hence has less patient compliance.

Keeping in view these limiting factors, in achieving optimum therapy with Nizatidine, a sustained release floating drug delivery system in the form of floating tablets were developed using widely accepted and physiologically safe excipients. Experimental design yielded the formulations with desired drug release.

- The floating tablet formulation of Nizatidine F1 containing HPMC 15 cps has released the 97% of drug within 4 hrs and it follows Peppas pattern of drug release. The tablet has been disintegrated totally within 3 hrs.
- The floating tablet formulation of Nizatidine F2 containing Carbopol has released 67% of drug at the end of 12 hrs but having less floating time. It follows Zero order pattern of drug release.
- The floating tablet formulation of Nizatidine F3 containing Xanthan gum has released 96% of the drug at the end of 12 hrs release having a higher floating time of 7 hrs when compared with the other formulations and it follows Higuchi pattern of drug release.
- The floating tablet formulation of Nizatidine F4 containing combination of HPMC and Carbopol has released 75% of drug at the end of 12 hrs having an optimum floating time and it follows Peppas pattern of drug release.
- The floating tablet formulation of Nizatidine F5 containing combination of Carbopol 940 and Xanthan gum has released 55% of drug at the end of 12 hrs which is very low when compared to other formulations and it follows First order of drug release.
- The floating tablet formulation of Nizatidine F6 containing combination of HPMC and Xanthan gum has released 84% of drug at the end of 12 hrs having a floating time of around 6 hrs and it follows First order release pattern.
- The floating tablet formulation of Nizatidine F7 containing combination of HPMC, Carbopol and Xanthan gum has released 48% of drug at the end of 12 hrs having a very slow drug release but having a floating time of about 5 hrs which is less when compared to formulations fromF2-F6. It follows Hix-Crowells release pattern.
- The following is the order upon the comparison of the drug release profiles at the end of 12 hrs.

F3>F6>F4>F2>F5>F7.

- The following is the order upon the comparison of the Floating time

F3>F6>F4>F2>F5>F7>F1.

- The following is the order upon the comparison of the Swelling index.

F2>F5>F7>F6>F3>F4>F1.

- The following is the order upon the comparison of the Drug content.

F3>F1>F5>F4>F6>F7>F2.

SUMMARY

In this work an attempt was made to formulate a gastro-retentive floating drug delivery system containing Nizatidine as a model drug using effervescent technique.

The main objective of formulating the dosage form was to improve the gastric residence time, which in turn increased the bioavailability of Nizatidine. The dosage form was made as floating matrix tablet dosage form, which released the drug in sustained manner with enhanced gastric residence time, which helps to avoid plasma fluctuation. The frequency of dosing may be less or same, but the gastro-retentive dosage forms will alter beneficially the absorption profile of the active agent, thus enhancing its bioavailability, and hence therapeutic response.

Formulations with different polymers were prepared. It was found that most of the formulations followed First order kinetics and Peppas. Because of wide range of release, it was expected that a suitable combination of the formulations would provide the desired target release profile. Hence, utilizing the experimental design concept, an effective FDDS has been developed for Nizatidine in the form of Tablets to optimize therapy of peptic ulcer, with minimal expenditure of time, resources and labor.

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