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Research Paper

FORMULATION AND BIOPHARMACEUTICAL EVALUATION OF FUROSEMIDE LOADED GASTRO RETENTIVE TABLET

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The current work was carried out to design the floating drug delivery system to reduce side effects, boost action prolongation, decrease the frequency of administration, and cost-effective. The floating drug delivery (FDD) as furosemide-containing non-effervescent tablets (Furosemide) prepared by the direct compression method by using the different polymers like HPMC K4M, K15M and K100M and effervescing agents sodium bicarbonate. The formulations were evaluated on different parameters like thickness, hardness, friability etc. The prepared tablets were determined floating parameters like swelling index and in-vitro buoyancy test and estimated the mechanism of the drug release rate kinetics of the dosage form, the data were supported with zero-order, first-order, Higuchi, and Korsmeyer-Peppas release model. The drug release from the floating tablets was found to be non fickian diffusion obeying zero-order kinetics.

Key Words: Floating Drug Delivery System, Gastro Retentive Tablet, HPMC K4M, Furosemide.

INTRODUCTION

In the near past, the people who involve research in pharmaceutical corporations have developed more refined and robust medicines. These medicines have the specific ability to liberate their bioactive components at the correct time, location and secure concentration, that is, administer perniciousness. Definition of DDS as given through the National Institute of Health (USA) is, "formulation of a device that enables the introduction of therapeutic substances into the body and improves efficiency and safety by controlling the rate, time and place of release of drug in the body". Accustomed DDSs do have limitations that include unfair bioaccessibility, after effects, less capacity of loading drug, fluctuating of Plasma of the levels of the drug, less rectifying action and scarcity of deliverance of the objective [1]. Circulation of the drugs by these systems to the cells is non-selective, that may result in severe outcome for example repercussions, multiple drug resistance (MDR) and reduction in drug's concentration at the destined location [2].

Oral drug delivery system

The use of oral path is continuously increasing to deliver therapeutic chemicals because of its low cost and easy administration that ultimately leads to increased levels of patient's consent. Of all the systems of drug delivery that are available commercially, more than half belong to

this type of delivery system[3]. The main aim of the drug Delivery System that is controlled orally should be higher prediction and also that bioavailability of the drug should be increased. The oral managed discharge formulations are developed keeping in mind that the drug is released slowly in the gastrointestinal tract and a stagnant concentration of a drug is maintained in the serum for a longer period. To lengthen gastric retentiveness, it is very important to have control over GRT as this facilitates keeping the controlled discharge system in the stomach for a prolonged time in a manner well predictable [4]. The Delivery system in which the release of drug is controlled has many advantages like the activity of period for less half-life drugs is enhanced; after-effects are eliminated; dose frequency is reduced; drugs are wasted less; therapy works optimally and last but not the least good at patient's consent. To develop an oral controlled Drug Delivery System successfully; one should have a proper understanding of the following three factors, through,

- The physicochemical nature of the medicine
- Physiology and anatomy of GIT, and
- Attributes of dose forms

Gastrointestinal Retention- Gastro-retentive systems may remain in the gastric area for many hours and hence lengthen the residing period of medicines in the gastric significantly. An increase in the period of gastric retentiveness enhances the bioavailability, lowers the wastage of drugs and increases the solubility of drugs whose solubility is less in an environment of large pH value. It is also applicable for localized drug delivery to the proximal small intestine and stomach. Gastro retentiveness facilitates in providing higher attainability of newer commodities along with fresh therapeutically scopes and extraordinary advantages for sicks.[5,6]

For successful modulation of the gastrointestinal transfer timing of a system of delivery of the drug via floating Drug Delivery System (FDDS) for maximum consumption of medicine in Gastro intestine and delivery at the particular site, one should have good basic knowledge of anatomic as well as physiological attributes of the human GIT.[7] Floating drug delivery systems have less volume density concerning gastric liquids and hence remain buoyant inside the gut and do not affect the gastric vacancy pace for a lengthened time. Meanwhile, the system floating over the gastric components, the medicine is slowly discharged at the required pace by the system. When the medicine is released, the Residue of the system is thrown out of the gut. For the system to keep floating, incorporation of a floating chamber containing air, vacuum, or inert gas, can be done

The present study aims to formulate and in-vitro evaluation of non-effervescent of Furosemide gastro retentive floating tablets and to interpret

the in-vitro dissolution studies.[8,9]

Mechanism of floating systems-

Various methodologies are used to raise the retaining time of content in the stomach. It involves the introduction of floating dosage forms (swelling, gas - creating or enlarging systems), high-density systems, mucoadhesive systems, gastric emptying retarding gadgets, modified shape systems and co-ordination of gastric emptying slowing medicines. Floating drug delivery systems (FDDS) always have volume density lesser to gastric liquids and therefore stay buoyant inside the stomach and do not have any effect over the pace of gastric emptying for a lengthened time duration, As the System remains floating over gastric components, the medicine is discharged at slow and needed pace by the system 6. The equipment performs by regularly computing the force equivalent to F (a function of time) which is a must for maintaining the gadget that is submerged. This apparatus facilitates the floating Drug Delivery System to work optimally regarding stability as well as durability of floating pressures produced to safeguard from the disadvantages of unpredictable intragastric buoyancy ability differences.[10,11]

F= F buoyancy - F gravity = (Df-Ds) gv---(1)

Here F=sum of vertical force,

Ds= density of object

Df=density of fluid,

v= volume,

g= acceleration due to gravity.

Benefits of Floating Drug Delivery System [12]

- Floating dosage forms like capsules or tablets do stay in the solution for a long period although at the alkaline pH of the intestine.
- FDDS are more beneficial for medicines that are utilized to act locally in the stomach example antacids.
- FDDS dose forms are useful in conditions of robust moves of the intestine as well as in diarrhea to have the drug floating in the stomach to get comparatively more response.
- Acidic matters like aspirin create uneasiness on the wall of the stomach when comes in touch with it, therefore; FDDS/HBS formulas may be helpful in the conduction of aspirin as well as other drugs of the same kind.
- The advantageousness of FDDS has been observed for medicines that are absorbed by the stomach for example antacids, ferrous salts.

Limitations of Floating Drug Delivery System [13]

- A fluid at a raised level is necessary for the stomach for the medicine to keep floating and perform perfectly.
- Medicines that have problems with dissolvability and stagnancy in GIT do not suit such systems.
- Drugs like nifedipine, which go through first-pass metabolism are not favorable for preparing such systems and also, drugs that create irritation to gastric mucosa are even not suiting.

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- The medicine matter that is not stable in the acidic atmosphere of the stomach is not favorable once for use in the systems.

Furosemide or Furosemide (INN) (former BAN), a loop diuretic utilized for treating cognitive cardiac failure and edema. The main location of activity of the drug is the fat climbing leg of the Loop of Henle where Furosemide impedes K+-,Na+-,2CL—cotransport and has very less action on proximal tubule is also signified. Secretion in the proximal tubule is by organic anion movement & destined at the rising Limb of the loop of henle where its action is the true luminal portion of the membrane. [14,15]

The rationality of selection of Furosemide as a model drug is that because its clinical studies demonstrated that sustained-release preparations can produce a similar diuretic effect without producing the major side effects of conventional tablets. The present study aims to formulate and in-vitro evaluation of non-effervescent of Furosemide gastro retentive floating tablets and to interpret the in-vitro dissolution studies [16]

Methodology-

Furosemide, sodium bicarbonate, and avicel ph 102 were purchase from modern lab, indore. india.

HPMC of different grade were purchased from colorcon asia pvt. ltd., other excipient like magnesium stearate andtalc were purchased from S.D. Fine Chem. ltd. in addition of this hydrochloric acid was purchased from lr s.d. fine chem. ltd.

Table No. 1: Constitution of Furosemide Floating Tablets (ingredients in mg).

Effervescent layer		Release layer		Magnesium stearate	Talc	HPMC K4M	HPMC K15M	HPMC K-100M	SCMC
Formulations	Sod. Bi-carbonate	HPMC K4M	Furosemide						
5	**40**	150	80	**5**	**5**	40	-	-	-
5	**40**	150	80	**5**	**5**	80	-	-	-
5	**40**	150	80	**5**	**5**	-	40	-	-
5	**40**	150	80	**5**	**5**	-	80	-	-
5	**40**	150	80	**5**	**5**	-	-	40	-
5	**40**	150	80	**5**	**5**	-	-	80	-
5	**40**	150	80	**5**	**5**	-	-	-	40
5	**40**	150	80	**5**	**5**	-	-	-	80

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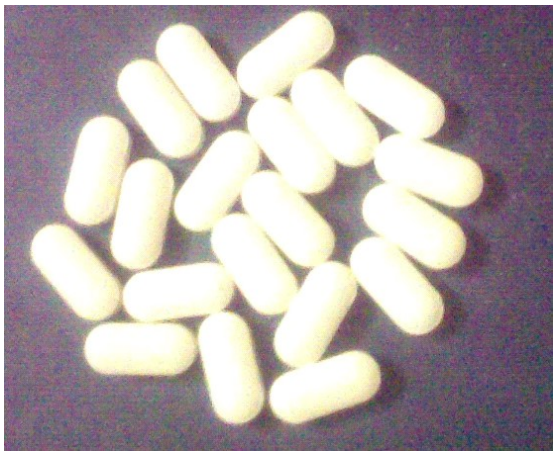

Fig. 1: Formulated Tablets of Furosemide Floating Tablets

Method of Preparation- Oral disintegrating tablets of Furosemide were prepared by using the direct compression method according to the formulae as shown in the table 1. This method involves a simple procedure of blending API with other ingredients and the resulted mixture is subjected to direct compaction. The required ingredients were blended and mixed. Then mixture was passed through sieve no 60 and finally, magnesium stearate was added as a lubricant and thoroughly mixed. Compression of lubricated granules was done by a rotary tableting machine. Tablets' weight was maintained at fixed for all formulations. [17, 18]

Evaluation Parameter of the tablet-

In tablet compression, the characterization of the flow properties of powder blends is important. The powder blends provide standardized die fill with strong flow properties and thus gives the uniform tablet weight-

Thickness- diameter and thickness of tablets were primary for the size of the tablet to be uniform. Measurement of diameter and thickness was done using vernier calipers

Hardness- To check tablet hardness, that may undergo breaking or chipping while storage, handling and transportation, this test is utilized. Given tablets were randomly chosen & the stiffness of every one tablet was evaluated by using Mmonsanto hardness tester in kilogram per centimeter square.[19]

Friability- The test of friability was done to calculate the stability and hardness instantly. Initially, 20 tablets were weighed (Wo) in Roche friabilator and put in rotating and tumbling apparatus drum. They were then made to drop through a height of 6 inches. When a hundred rotations were completed, the tablets were once more weighed (w). Loss percentage in friability (f) or weight was evaluated.[19]

Weight Variation- 20 tablets were generally and specifically chosen and weighed. The weight average was determined from the collective weight. The weight of each tablet was

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then compared to the average weight to ensure whether or not it was under acceptable limits. For 200 mg tablets, not more than two of the individual weights varied by more than 7.5 percent from the average weight and none by more than twice that amount.[20]

Drug Content- For maintaining the uniformness of wt of each one tablet that must be in the specified limit as per the Indian pharmacopeia, this test is performed. The test for content uniformity is compulsory for tablets that have a mean weight below 50 milligram. To perform this testing, twenty tablets were chosen randomly, weighed & made in powdered form. The amount of powdered tablet same as 100 milligrams of Furosemide was added in 0.1 N hydrochloric acid in hundred-milliliter volumetric flask. The sample so produced was thinned and absorbance was computed at 278 nm with the use of 0.1N HCl as blank and percentage of drug content evaluated.[21]

Determination of floating parameter-

In-vitro buoyancy test - in-vitro buoyancy estimated and the tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required the tablet to rise to the surface and float was considered as the floating lag time.[22]

Study of swelling- The swelling characteristic of a dosage form is estimated via reviewing its increase in weight or water uptake (WU). To perform this study, the dosage form is immersed in 0.1N HCl at 37 degrees centigrade and evaluating these factors at uniform intervals up to duration of 8 hrs. Water uptake was calculated in the terminology of wt gain percentage, as calculated by the following formula.[23]

$$WU = (Wt - Wo) \times 100/Wo$$

Wt = dosage form weight at time t
Wo= dosage form's initial weight.

In-vitro dissolution study- *In- vitro* dissolution was performed with the use of USP XXIV (DISSO model, M/s lab India) rotating paddle method (apparatus 2). The pace of stirring was 50 rotations per minute.0.1 N hydrochloric acid was used as a mediator of dissolution 900 milliliters and was controlled at 37+- 0.5 degree centigrade. 5 milliliter samples were taken at pre-fixed intervals of time, filtration was done and substituted with 5 milliliters of fresh agent of dissolution. The accumulated samples were diluted suitably with dissolution liquid, wherever needed and analysis was done for Furosemide at 278nm with the use of double-beam ultraviolet spectrophotometer (Shimadzu- 2000). Every dissolution review was done thrice and the average values were noted.[24]

Mechanism of the drug release rate kinetics to dissolution data- The obtained data were fitted in zero-order, first order, Higuchi, and Korsmeyer - Peppas release models to examine the mechanism of the drug release rate kinetics

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of the dosage form. [25, 26]

Zero-order release rate kinetics: To study the zero-order release kinetics the release rate data are fitted to the following equation.

F = Ko t,

Where F" is the drug release at time „t", and „Ko" is the zero-order release rate constant. The plot of % drug release versus time is linear

First-order release rate kinetics: The release rate data is, Log (100-F) = kt, A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model and kinetics: F = k t1/2, Where k" is the Higuchi constant. In the Higuchi model, a plot of % drug release versus the square root of time is linear.

Korsmeyer and Peppas release model: The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to the Korsmeyer Peppas equation. The exponent „n" indicates the mechanism of drug release calculated through the slope of the straight line. Mt/ M∞ = K

Mt/ M∞ = K tn, Where, Mt/ M∞ is the fraction of drug released at a time „t", k represents a constant, and „n" is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n=1; and for super case II transport, n > 1. In this model, a plot of log (Mt/M∞) versus log (time) is linear. Hixson-Crowell release model: Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets). (100-Qt) 1/3 = 1001/3 – KH Ct, where, k is the Hixson - Crowell rate constant.

Result and Discussion-

Standard Curve- Standard graph were plotted for furosemide 0.1N hydrochloric acid (pH 1.2) at 244nm by using various concentration of 0. 0.1, 0.2, 0.3 and 0.4 respectively.

Table No. 2: Standard graph

S.NO.	Concentration	Absorbance
1.	0	0.00±0.0000
2.	2	2 0.093±0.0031
3.	4	4 0.161±0.0025
4.	6	6 0.245±0.0020
5.	8	8 0.331±0.0030
6.	10	**0.401±0.0035**

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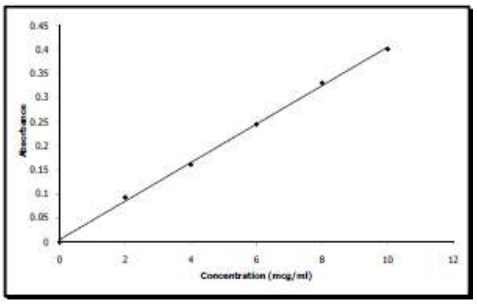

Fig. 2: Standard curve for Furosemide

FTIR Result- FTIR studies were conducted and the spectrum was recorded in the range of 6000-400cm^{-1}. No significant interaction between drug and Excipients was observed. All the spectrum i.e. drug and Excipients were concordant with that of standard IR spectra of pure drug Furosemide

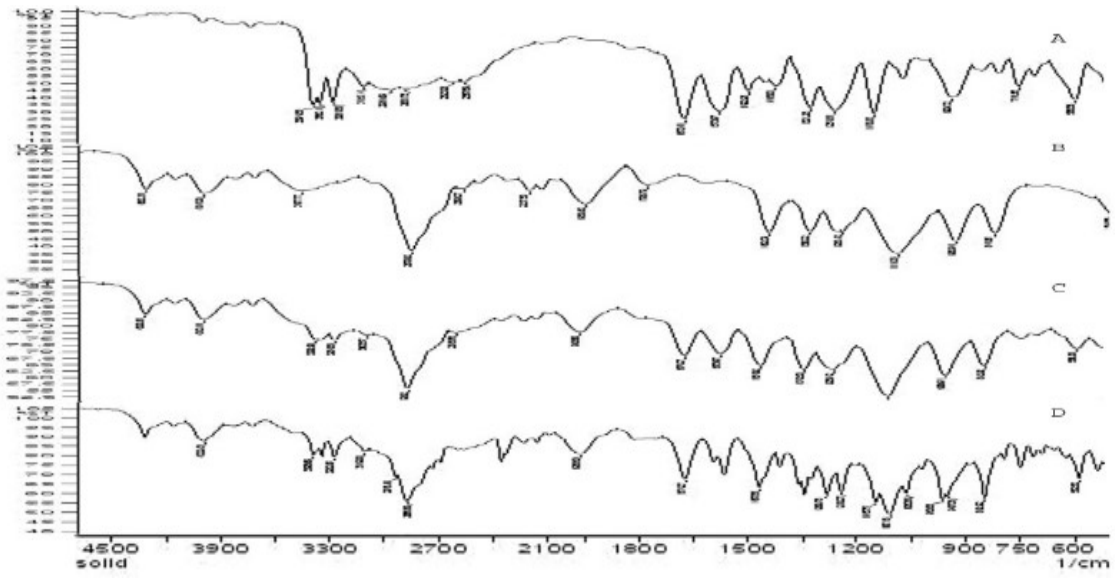

Fig 3: FTIR Spectra of Furosemide (A), PEG-6000 (B), 1:6 Solid Dispersion (C), 1:6 Physical Mixtur(D)

Evaluation of non – effervescent gastroretentive tablets of Furosemide- In this present study, evaluation parameters were performed such as weight variation, hardness, friability, thickness, drug content and floating lag time. All the formulations [F1 – F9] were complied with specifications and shown in Table 5. Among all formulations, F6 were found to be the best formulation because it is stabilized for six months Result of *In-vitro* dissolution of solid dispersion and physical mixture shown in table no. 4.0

Evaluation of floating Characteristics- Formulated swimming tablets of Furosemide work calculated for its floating characteristic like total floating period, floating lag period and swelling index. Composed tablets were also estimated for mean hardness, weight, friability, thickness and drug content. The outcomes are mentioned in table no 5.0.

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Table No 3: Evaluation of Tablet Parameters

Formulation Code	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	4.7±0.015	4.5±0.5	0.35±0.05	555.2±1.4	99.79±0.12
F2	4.6±0.013	4.7±0.4	0.43±0.06	552.6±1.7	99.49±0.03
F3	4.7±0.017	4.6±0.7	0.35±0.04	555.5±0.6	99.91±0.17
F4	4.7±0.016	4.5±0.5	0.37±0.05	556.2±1.5	100.02±0.03
F5	5.8±0.014	4.5±0.2	0.46±0.07	657.3±1.3	98.88±1.02
F6	5.7±0.013	5.3±0.6	0.55±0.04	653.5±0.3	100.07±0.02
F7	5.7±0.016	4.4±0.5	0.47±0.05	652.6±0.7	99.99±0.95

Table No.4: *In-vitro* dissolution of solid dispersion and physical mixture

S. N0.	Time (min) %	Cumulative drug dissolved		
		Furosemide	1:6 SD	1:6 PM
1.	0	0	0	0
2.	5	8.49±0.017	55.45±0.016	14.03±0.014
3.	15	14.36±0.014	77.24±0.029	17.03±0.028
4.	30	19.24±0.037	85.39±0.034	27.74±0.013
5.	60	24.13±0.024	93.36±0.014	28.02±0.011
6.	120	27.44±0.012	98.44±0.025	36.22±0.034

Table No 5: Estimation of floating characteristics

S.NO	Formulation Code	Floating Lag Time (sec)	Total Floating Time (hr.)	Swelling Index (%)
1.	F1	122	24	222.84
2.	F2	186	26	217.06
3.	F3	164	28	204.86
4.	F4	154	24	232.78
5.	F5	226	26	257.25
6.	F6	227	22	323.05
7.	F7	202	27	296.65
8.	F8	234	25	263.32

Kinetics of drug release: The outcomes of data of dissolution were put to different drug release Kinetic equations. The drug release kinetics of R values attained for formulations F1, F2, F3 for talc, HPMC and sodium CMC are given in table no 6 ,7and 8. Higuchi matrix, first order, zero order and Korsemeyer-peppas are also tabulated.

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Table.no.6: Correlation coefficients (r values) of release kinetics of Furosemide.

FORMULATION	Zero order	First order	Higuchi Matrix	Peppas	
				r	N
MARKETED	0.991	0.921	0.986	0.994	0.905
FG1	0.976	0.899	0.999	0.984	0.754
FG2	0.983	0.925	0.987	0.987	0.676
FG3	0.977	0.938	0.991	0.994	0.771

FDDS made from various concentrations of Talc

Table.no.7:. Correlation coefficients (r values) of release kinetics of Furosemide

FORMULATION	Zero-order	First-order	Higuchi Matrix	Peppas	
				R	N
MARKETED	0.991	0.925	0.984	0.991	0.903
FS1	0.995	0.924	0.981	0.994	0.834
FS2	0.984	0.907	0.974	0.995	0.825
FS3	0.986	0.734	0.986	0.999	0.791

FDDS made with various concentrations of SODIUM CMC

Table.no.8: .Correlation coefficients (r values) of release kinetics of Furosemide

FORMULATION	Zero order	First order	Higuchi Matrix	Peppas	
				R	N
MARKETED	0.994	0.926	0.984	0.992	0.903
FH1	0.991	0.911	0.966	0.969	0.706
FH2	0.995	0.906	0.984	0.994	0.957
FH3	0.991	0.917	0.959	0.975	0.801

FDDS made from various concentrations of HPMC K15M

Conclusion- The present research, by using different hydrophilic polymers to achieve in vitro floating tablets, is the gastro retentive non-effervescent floating matrix formulation of Furosemide. In order to achieve gastro retentive floating drugs, the inclusion of non-effervescent ingredient is used as accumulation was rather important. Different concentrations of gel-

forming polymers such as HPMC K100M, K15M and HPMC K4M were used to formulate the tablets and all the formulations were found to have their physical chemical properties within the specified official requirements. The profiles of in vitro disintegration of all the produced formulas of FDDS of Furosemide were observed to prolong the discharge of medicine over a duration of 7 to 12 hours and the discharge of drug retarded with decrement in a concentration of polymer. Comparing all formulations, FDDS formulation of FG3 was regarded as a perfect formula that possessed 99.8 7% of medicine discharge in 12 hrs, having a floating lag duration of 130 secs along with a floating period of 24 hrs.

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