"FORMULATION AND IN-VITRO EVALUATION OF FLOATING MATRIX TABLET OF FUROSEMIDE FOR ORAL CONTROLLED RELEASE"

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ABSTRACT:

The aim of present study is The stomach and upper part of the small intestine are where furosemide is primarily absorbed when treating edema brought on by congestive heart failure (CHF), hepatic cirrhosis, renal impairment, and nephrotic syndrome. This narrow absorption window is responsible for furosemide's limited oral bioavailability. Floating matrix tablet were prepared by direct compression technique using different Polymer with varying concentration. all polymer and drug were passed through sieve no.80 separately. Then drug were mixed in polybag for 5 min with the polymers and other ingredients in weight proportion as mentioned in Table 13. The powder blend was then lubricated with magnesium stearate and talc, and this lubricated blend were compressed into tablets using 8-mm flat-face on a 16 stationary rotary punching tablet machine with hardness in range of 5 to 5.5 kg/cm2.

HPMC K4M and HPMC K100LV have predominant effect on drug release. HPMC K4M gives the good matrix integrity and retained drug release. HPMC K100LV along with HPMC K4M provides sustained and controlled drug release over the expected period of time. Sodium bicarbonate has predominant effect on the buoyancy lag time and also shows significant effect on drug release. In-vitro release rate studies showed that the minimum drug release was observed

KEY WORDS: Floating Matrix Tablet of Furosemide, Pre-Formulation, FORMULATION DESIGN Evaluation of blend Furosemide Tablets (Lasifru Tablet Market product), Dissolution profile comparison. comparative studies of in-vitro dissolution, Dissolution apparatus USP type-II, spectrophotometer technique.

1. INTRODUCTION

1.1 NOVEL DRUG DELIVERY SYSTEM:

Historically, oral drug administration has been the predominant route for drug delivery due to the ease of administration, patient convenience and flexibility in formulations. However, it is a well-accepted fact today that drug absorption throughout the GI tract is not uniform. Using currently utilized release technology, oral drug delivery for 12 or even 24 hours is possible for many drugs that are absorbed uniformly from GI tract. Nevertheless this approach is not suitable for a variety of important drugs characterized by narrow absorption window in the upper part of GI tract i.e. stomach and small intestine.

The design of oral sustained drug delivery systems (DDS) should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.[2]

The sustained release systems for oral use are mostly solid and based on dissolution or diffusion or a combination of both the mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these are classified as:

A. Continuous Release System:

These systems release the drug for a prolonged period of time along the entire length of GIT with normal transit of the dosage form. The various systems under this category are:

I. Dissolution sustained release systems

II. Diffusion sustained release systems
III. Dissolution and diffusion sustained release systems
IV. Ion-Exchange resins – drug complexes
V. slow dissolving salts and complexes
VI. PH –dependent formulations
VII. Osmotic pressure sustained systems
VIII. Hydrodynamic pressure sustained systems

B. Delayed Transit and Continuous Release System:
These systems are designed to prolong their residence in the GIT along with their release. Often, the dosage is fabricated to retain in the stomach and hence the drug present therein should be stable at gastric PH. Systems included in this category are:
I. Altered density systems
II. Mucoadhesive systems
III. Size-based systems

C. Delayed Release Systems:
The designs of such systems involve release of drug only at a specific site in the GIT.
The drugs contained in such system have following category:
I. Destroyed in the stomach or by intestinal enzymes
II. Known to cause gastric distress
III. Absorbed from a specific intestinal site, or
IV. Meant to exert local effect at a specific GI site.

The two types of delayed release systems are:
I. Intestinal release systems
II. Colonic release systems [3]

Oral sustained release dosage forms have been developed for the past three decades due to their various benefit characteristics which includes.4, 5

To overcome these problems and improve the efficacy of oral administration, some recent studies have reported that sustain oral drug delivery system with prolonged gastric residence time, such as floating dosage system have been proved to be advantages.

A gastrointestinal drug delivery system can be made to float in the stomach by a gelling process of hydrocolloid materials or by incorporating a floatation chamber with vaccum or gas. In this way bulk density less than that of gastric fluid is produced. However, most of the devices generating gas or gelling need time to be floated and this parameter must be checked carefully in order to prevent the dosage form from transiting in to the small intestine along with food before floating in stomach. Among the floating system, multiple unit formulation shows several advantages over monolithic ones; more predictable drug release kinetics, less chances of localized mucosal damage, insignificant impairing of performance due to failure of a few units, coadministration of units with different release profile or obtaining incompatible substances, larger margin of safety against dosage form failure.[8]

2. METHODOLOGY

The materials used in the present investigation were either AR/LR grade or the best possible Pharma grade.

2.1 MATERIALS USED

Table No.1: List of chemicals used with their grade and supplier

Sr. No.	Material	Grade	Supplier
1.	FUROSEMIDE	Pharma	Nulife pharmaceuticals, pune

2.	HPMC K4M	Pharma	Nulife pharmaceuticals, pune
3	HPMC K100LV	Pharma	Nulife pharmaceuticals, pune
3.	HPMC K15M	Pharma	Nulife pharmaceuticals, pune
4.	$NaHCO_3$	A.R	Nulife pharmaceuticals, pune
5.	Talc	A. R	Nulife pharmaceuticals, pune
6.	Magnesium stearate	A R	Nulife pharmaceuticals, pune
7.	Lactose	A R	Nulife pharmaceuticals, pune

2.2 EQUIPMENTS USED

Table No.2: Details of Equipments Used

Sr. No.	Instrument	Manufacturer
1.	Electronic Balance	Shimadzu – AW220
2.	Tablet Compression Machine	Cadmac, Ahmadabad
3.	Hardness Tester	Monsento hardness tester
4.	Friability Test Apparatus	Roche Friabilator.
5.	Tablet Dissolution Tester	Electro Lab.(USP XX IV) (TDT– 08L)
6.	UV double beam Spectrophotometer	Chemito spectrascan uv-2700
7.	FT-IR Spectrophotometer	Digilab excalibur HE-series
8.	Digital pH meter	Electrolab, Mumbai
9.	Hot Air Oven	Kami cochin, India

2.3 METHOD

PRE-FORMULATION STUDY OF FUROSEMIDE:

2.3.1 Physicochemical Property of Furosemide:

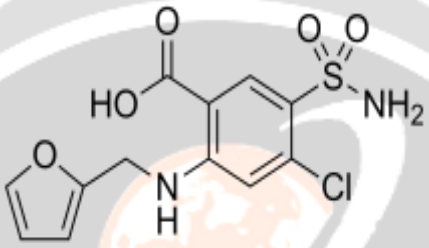
Furosemide is a high ceiling (loop) diuretics. It is used in edema and hypertension

Official status: Official in I.P., B.P. and U.S.P.

Molecular formula: $C_{12}H_{11}ClN_2o_5S$

Molecular weight: 330.745 g/mole

Structure:



Chemical Name:

4-chloro-2-(furan-2-ylmethylamino)- 5-sulfamoylbenzoic acid

Description:

Furosemide is a white to off-white crystalline powder with a bitter taste and odourless.

Melting point:

Melting point was determined by capillary method that was found 204˚c, which is within the reported value (202-206˚c).It complies with standards thus indicating the purity of the drug sample.

Solubility:

Soluble in acetone sparingly soluble in ethanol (95%)

Practically insoluble in water -

It dissolves in dilute aqueous solution of alkali hydroxides.

Very slightly soluble in cold water, diethyl ether.

Bioavailability: 43-69%

Metabolism: Hepatic and renal glucuronidation

Half life: up to 2-3 hours

Excretion: renal 66%, biliary 33%

2.3.2 Identification test:

1) U V spectra**:**

Diluted drug sample in 0.1N Hcl and UV spectrum of its obtained using a 1cm cell and examined in the range of 220 to 360nm, gives absorption maxima at 271nm.

2) I R spectra:

The IR Spectra is concordant with the reference spectrum of Furosemide (spectra No.1)

2.3.3 Preparation of standard curve of Furosemide by using U V-double beam spectroscopic method

Procedure:

Preparation of standard solution: accurately weighed 100 mg of Furosemide is dissolved and diluted to 100 ml with 0.1N HCl to get a concentration of 1000mcg/ml (SS-I).

Preparation of working standard solutions: pipette out 2 ml from SS-I and made up the volume up to 100 ml with 0.1N HCL to get a concentration 20 mcg/ml (SS-II). pipette out 1ml to 10ml of solution from SS-II in series of 10 ml volumetric flask and filled up to marking, The absorbance value of solution were measured at 271nm, against a reagent blank calibration graph was plotted with absorbance against respective drug concentration (graph No.1).

λ max=271nm

Beer's range: 1-20µg/ml

R_2=0.995

2.3.4 Interaction studies of drug and polymers.

Prior to the development of the dosage forms the Preformulation studies were carried out, Furosemide/polymers interaction were investigated by infrared spectral studies.

2.4 FORMULATION DESIGN.

Table No.3 Actual values of ingredients taken for floating tablet.

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Furosemide	40	40	40	40	40	40	40	40	40	40	40	40
2	HPMC K15M	80	120	160	-	-	-	-	-	-	-	-	-
3	HPMC K4M	-	-	-	80	120	160	-	-	-	20	40	80
4	HPMC K100LV	-	-	-	-	-	-	80	120	160	60	80	80
5	$NaHCO_3$	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
6	Lactose	87.5	47.5	7.5	87.5	47.5	7.5	87.5	47.5	7.5	87.5	47.5	7.5
7	Magnesium sterate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

8	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

*All values are taken in mg.

2.4.1 Preparation of Floating tablet

Floating matrix tablet were prepared by direct compression technique using different Polymer with varying concentration shown in table No.13 all polymer and drug were passed through sieve No.80 separately. Then drug were mixed in polybag for 5 min with the polymers and other ingredients in weight proportion as mentioned in Table 13. The powder blend was then lubricated with magnesium stearate and talc, and this lubricated blend were compressed into tablets using 8-mm flat-face on a 16 stationary rotary punching tablet machine with hardness in range of 5 to 5.5 kg/cm2 (table No.20).

Physical parameters of the tablet:

- Tablet weight : 250mg ± 05 mg
- Thickness : 3.2± 0.04 mm
- Hardness : 5.1 ± 0.5 kg/cm^2
- Friability : Not more than 1%

2.4.2 Evaluation of blend:

Evaluation of blend with the help of below parameters

Angle of Repose

Carr's Compressibility Index

Bulk Density & Tapped Density

Hausners ratio

Evaluation of floating tablets

All the prepared floating tablets were evaluated for following official and unofficial parameters.

Appearance

Thickness

Hardness

Friability

Weight variation

Drug content uniformity

Details of dissolution test:

Dissolution test apparatus : USP II

Speed	: 100±0.1 rpm
Stirrer	: paddle type
Volume of medium	: 900 ml
Aliquot taken at each time interval	: 5ml
Medium used	: 0.1N HCl
Temperature	: 37 ± 0.5 ^{0}C

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifications for stability study:

- Long term testing: 25^{0}C ± 2^{0}C /60% RH ± 5% RH for 12 months.
- Accelerated testing: 40^{0}C ± 2^{0}C /75% RH ± 5% RH for 6 months.
- Alternate testing : 30^{o}C ± 2^{0}C/65%RH± 5% RH for 12 months.

Procedure:

In the present study, stability studies were carried out at 40 ^{0}C and 75% RH for a specific time period up to 90 days for optimized formulations.

For stability study, the tablets were sealed in aluminum packaging coated inside with polyethylene. These sample containers were placed in desiccator's maintained at 75% RH.

NOTE: Saturated solution of sodium chloride at 40^{0}C yields a 75% relative humidity.

Evaluation of samples:

The samples were analyzed for the following parameters:

I. Physical evaluation:
Appearance: The samples were checked for any change in colour at every month.

Hardness: The samples were tested for hardness at every month.

II. Chemical evaluation:
Drug content: The samples were checked for drug content.

Drug release: The samples were subjected to drug release studies.

(Table No. 31, 32)

3. RESULTS

Table No. 4 comparison of functional group observed in IR spectra of Furosemide with standard spectra.

Sr. No.	Functional group	Standard IR Range (cm^{-1})	Assessment of peak (cm^{-1})

1	Aromatic C-S, stretching	750	745
2	Amine N-H, stretching	1596	1602
3	Aromatic C=O, stretching	1671	1670
4	Aromatic S=O, stretching	1322	1320
5	Halogens C-Cl, stretching	582	585
6	Aromatic O-H, stretching	781	769

Table No.5: Comparison of the peak of functional groups of Furosemide observed in IR spectra of compatibility studies

Sr No.	Functional group	Assessment of peak (cm^{-1}) of pure drug	Ranges of group
1	Aromatic C-S, stretching	750	743-760
2	Amine N-H, stretching	1596	1590-1605
3	Aromatic C=O, stretching	1671	1670-1675
4	Aromatic S=O, stretching	1322	1320-1325
5	Halogens C-Cl, stretching	582	580-585
6	Aromatic O-H, stretching	781	769-795

3.1 EVALUATION PARAMETERS:

3.1.1 Evaluation of Blend:

Table No. 6 Evaluation parameter of powder blend

Formulation Code	Angle of Repose (º)	LBD (gm/cm^2)	TBD(gm/cm^2)	Compressibility index (%)	Hausner's ratio
F1	35.53±0.45	0.375±0.006	0.479±0.025	21.42±4.47	1.27±0.07
F2	36.76±0.55	0.387±.005	0.506±0.005	23.54±1.76	1.30±0.03
F3	37.13±0.32	0.394±.009	0.504±0.007	21.75±0.62	1.27±0.01

F4	35.13±0.40	0.349±0.005	0.456±0.004	23.44±0.81	1.30±0.01
F5	36±0.26	0.366±0.004	0.482±0.004	23.98±1.69	1.31±0.02
F6	36.53±0.45	0.375±0.004	0.482±0.026	21.97±4.32	1.28±0.06
F7	33.3±0.81	0.338±0.002	0.440±0.001	23.23±0.44	1.30±0.007
F8	34.5±0.7	0.337±0.003	0.458±0.003	26.41±0.38	1.35±0.007
F9	35.13±0.25	0.353±0.005	0.470±0.002	24.92±1.42	1.33±0.02
F10	35.63±0.66	0.342±0.003	0.453±0.002	24.42±1.02	1.32±0.01
F11	35.83±0.25	0.348±0.003	0.465±0.003	25.16±0.58	1.33±0.01
F12	35.8±0.36	0.357±0.004	0.470±0.002	24.14±0.83	1.31±0.01

n=3, determinations

3.1.2 Evaluation Parameters of formulations:

Table No. 7: Evaluation parameters of formulations

Formulation code	Evaluation parameter				
	Thickness ± S.D. (mm) (n = 5)	**Hardness ± S.D. (kg/cm^2) (n = 5)**	**Friability (%)**	**Average weight variation (n=10)**	**Drug content (%)**
F1	3.21±0.01	5.22±0.03	0.47±0.005	246.3±0.35	98.73
F2	3.16±0.06	5.23±0.02	0.24±0.01	246.01±0.27	97.96
F3	3.24±0.04	5.35±0.03	0.27±0.03	246.66±0.75	98.5
F4	3.16±0.04	5.27±0.03	0.36±0.015	246.38±1.02	98.6
F5	3.26±0.06	5.32±0.02	0.36±0.03	246.25±0.39	98.23
F6	3.18±0.07	5.37±0.02	0.46±0.03	246.26±0.37	98.8
F7	3.26±0.08	5.21±0.02	0.62±0.02	246.3±0.6	97.76
F8	3.22±0.05	5.23±0.01	0.52±0.03	246.3±0.27	98.78
F9	3.28±0.07	5.28±0.01	0.48±0.03	246.2±0.39	98.16
F10	3.2±0.04	5.18±0.02	0.35±0.005	246.18±0.38	98.66
F11	3.27±0.09	5.19±0.05	0.44±0.04	246.25±0.63	98.73

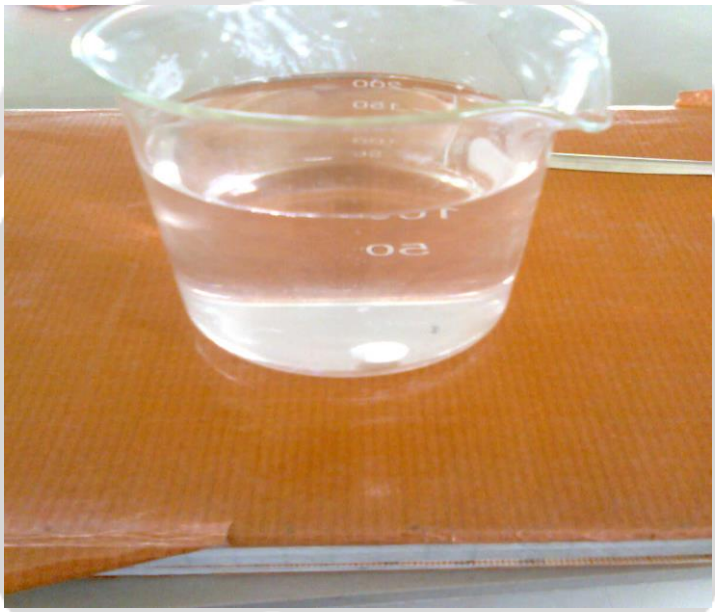
F12	3.23±0.09	5.21±0.01	0.36±0.02	246.23±0.45	97.73

Floating properties:

The tablet were placed in a 100 ml beaker containing 0.1N HCl .the time required for the tablet to rise to the surface and float was taken floating lag time. The experiment was conducted in triplicate

Figure No.1 Floating tablet buoyancy time study

A. Immediately after adding the tablet



B. After 30 sec

Table No. 8 Result of Floating Property of Furosemide tablet

Formulation code	Floating lag time (sec)	Totalfloating duration (hours)
F1	25	10
F2	50	11
F3	30	10
F4	35	12
F5	30	11
F6	25	12
F7	20	12
F8	30	12
F9	30	12
F10	35	12
F11	37	12
F12	35	12

Table No. 9: Curve fitting data of the release rate profile of formulation F1 toF6

Model		Formulation code					
		F1	F2	F3	F4	F5	F6
Korsmeyer-peppas	R	0.987	0.993	0.987	0.984	0.993	0.993
	n	0.995	1.08	1.29	1.0	1.00	1.0
Zero order	R	0.996	0.995	0.996	0.991	0.992	0.996
First order	R	0.936	0.924	0.959	0.796	0.895	0.955
Higuchi matrix	R	0.940	0.912	0.913	0.95	0.907	0.928
Best fit model		Higuchi	Higuchi	Higuchi	Peppas	Peppas	Peppas

Table No. 10 Curve fitting data of the release rate profile of formulation F7 -F12

Model	Formulation code					
	F7	F8	F9	F10	F11	F12

Korsmeyer-peppas	R	0.997	0.995	0.994	0.996	0.995	0.997
	n	0.745	0.799	0.782	0.735	0.833	0.875
Zero order	R	0.986	0.989	0.994	0.982	0.995	0.996
First order	R	0.763	0.856	0.725	0.915	0.901	0.915
Higuchi matrix	R	0.974	0.962	0.955	0.976	0.954	0.952
Best fit model		Peppas	Peppas	Peppas	Peppas	Peppas	Peppas

Table No. 11: Stability studies of optimized formulation F10:

Time	Hardness (kg/cm^2)	Drug content Uniformity (%)	% CDR
After 1 month	5.1	98.21	96.80
After 2 month	4.9	97.65	96.25
After 3 month	4.7	97.55	96.12

4. SUMMARY

Furosemide is a high ceiling (loop) diuretics, it inhibits Na^+-K^+-2Cl co transport. It is the diuretics of choice for mobilizing edema fluid.

Furosemide is considered to be absorbed in upper part of GIT (duodenal) it has 2 hours half-life and 60% bioavailability.

Therefore an attempt is made to retain the dosage form in stomach for longer period of time. This is achieved by developing Gastro retentive drug delivery system i.e. floating drug delivery system. These floating tablets mainly prepared for reduction of lag time and release the drug upto 12 hours and may also increase the bioavailability of the drugs by utilizing the drug to full extent avoiding unnecessary frequency of dosing.

For the formulation of floating tablets HPMC K15M, HPMC K4M and HPMC K100LV was used as matrix forming agent and floating enhancer. Other excipients used are sodium bicarbonate (gas generating agent), talc and Magnesium stearate (lubricating agent). Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions.

The tablets were compressed using 8 mm circular flat-headed punch and die on CADMAC multi station rotary punching machine.

The prepared floating tablets were evaluated for hardness, Weight variation, thickness, friability, drug content uniformity, buoyancy lag time, total floating time, water uptake, (swelling index),*in-vitro* dissolution studies. F10 formulation showed good floating property and a controlled drug release. Stability studies were carried out for F10 formulation, they had showed good stability when stored at accelerated stability state as per the ICH guideline and the values were within permissible limits.

It was observed that Formulations F10 retained the drug release upto 12 hrs with minimum FLT. All formulations were subjected for four different models viz. Zero order, First order, Higuchi matrix and Peppas model equations and F1 to F3 formulation best fit in Higuchi matrix model and remaining formulation are best fit into the Peppas model by giving the values of diffusional exponent (n) in the range of 0.5-0.8 that indicate the formulation had release the drug by diffusion followed by erosion mechanism.

It was revealed that polymers and sodium bicarbonate ratios had significant influence on drug release. Thus conclusion can be made that stable floating dosage form can be developed for Furosemide for the controlled release by floating tablets.

5. CONCLUSION

From the above experimental results it can be concluded that,

- HPMC K4M and HPMC K100LV have predominant effect on drug release. HPMC K4M gives the good matrix integrity and retained drug release.
- HPMC K100LV along with HPMC K4M provides sustained and controlled drug release over the expected period of time.
- Sodium bicarbonate has predominant effect on the buoyancy lag time and also shows significant effect on drug release.
- In-vitro release rate studies showed that the minimum drug release was observed in F10 formulations up to 96.86%, with less floating lag time, and the matrix integrity.
- Hence it is postulated that gastro retentive approach may improve the condition of edema associated with heart failure, and hypertension by increasing the gastric emptying time of the dosage forms. Thus the dose and dosing frequency can be reduced by this approach.
- Formulations F10 are found to be stable at accelerated stability as per the ICH guidelines for a period of 3 month.
- From the study it is evident that floating tablets of Furosemide can be formulated with various polymers to achieve gastro retention and promising controlled release of drug.
- Further detailed investigations are required to establish efficacy of these formulations.

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