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Research

Evaluating the neonatal formulation of famotidine in a live setting

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Abstract

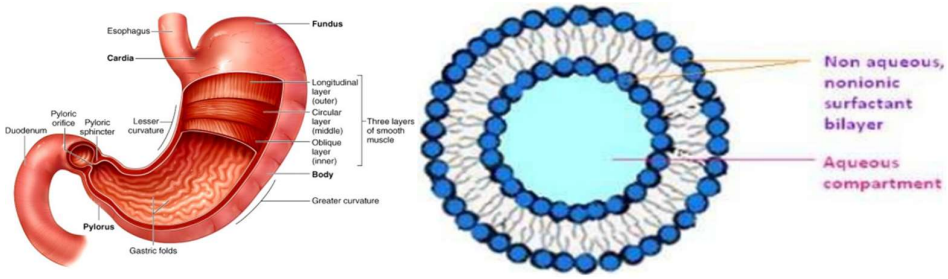
Evaluating the Neonatal Formulation of Famotidine in a Live Setting Dosage forms that can be retained in the stomach are called gastro retentive drug delivery system(GRDDS).GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site.
Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease ofadministration, patient compliance and flexibility in formulation. However, this approach is be dilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility.
Gastro retention helps to provide better availability of new products with suitable therapeutic activity and substantial benefits for patients. This mode of administration would best achieve the known pharmacokinetic and pharmacodynamic advantages of CR-DFs of these drugs.

Keywords: Evaluation, Neonatal Formulation, Famotidine, Control release

INTRODUCTION

Niosomes are lamellar structures that are microscopic in size. They constitute of nonionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. The surfactant molecules tend to orient themselves in such a way that the hydrophilic ends of the non-ionic surfactant point outwards, while the hydrophobic ends face each other to form the bilayer. Controlled release drug products are often formulated to permit the establishment and maintenance of any concentration at target site for longer intervals of time. One such technique of drug targeting is niosomes. Niosomes are microscopic lamellar structures formed on admixture of a nonionic surfactant, cholesterol and diethyl ether with subsequent hydration in aqueous media. They behave in vivo like liposomes prolonging the circulation of entrapped drug and altering its organ distribution. Niosomal drug delivery has been studied using various methods of administration including intramuscular, intravenous, peroral and transdermal. In addition, as drug delivery vesicles, niosomes h ve been shown to enhance absorption of some drugs across cell membranes, to localize in targeted organs and tissues and to elude the reticuloendothelial system. Niosomes has been used to encapsulate colchicines, estradiol, tretinoin, dithranol, enoxacin and for application such as anticancer, antitubercular, anti-leishmanial, anti-inflammatory,

hormonal drugs and oral vaccine.



There are images to four types of secretary epithelial cells that cover the surfaceof the stomach and extended down into gastric pits and glands: Mucous cells: secrete alkaline mucous that protects epithelium against shear stress and acid.

Parietal cells: secrete hydrochloric acid. Chief cells: secrete pepsin, a proteolytic enzyme. G cells secrete the hormone gastrin. The contraction of gastric smoothmuscle serves two basic functions.

Floating Drug Delivery System: 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. Whilethe system is floating on the gastric contents the drug is released slowly at the desired ratefrom the system. This results in an increased GRT and a better control of fluctuations in plasma drug concentration. The device must have sufficient structure to form a cohesive gel barrier, it must maintain an overall specific gravity lower than that of gastric contents (1.004-1.010) and it should dissolve slowly enough to serve as a drug reservoir.

Bi-layer Floating Tablets: A bi-layer tablet contain two layer one immediate release layer which releases initial dose fromsystem while the another sustained release layer absorbs gastric fluid, forming an impermeable colloidal gelbarrier on its surface, and maintain a bulk density ofless than unity and thereby it remains buoyant in the stomach[21].

Formulation ingridients of floating dosage forms

Following types of the ingredients can be incorporated in to floating dosage form,

Hydrocolloids: Inert fatty materialsRelease rate accelerantsRelease rate retardantBuoyancy increasing agentsLow density material

Miscellaneous Hydrocolloids: Suitable hydrocolloids are synthethics, anionic or non ionic like hydrophilic gumes, modified cellulose derivatives. E.g. Accasia, pectin, agar, alginates, gelatin, casein, bentonite, veegum, MC, HPC, HEC, and Na CMC can be used. The hydrocolloids must hydrate in acidic medium i.e. gastric fluid is having Although the bulk density of the formulation may initially be more than one, but when gastric fluid is enter in the system, it should be hydrodynamically balanced to have a bulk density of less than one to assure buoyancy.

Inert fatty materials: Edible, pharmaceutical inert fatty material, having a specific gravity less than one can be added to the formulation to decrease the hydrophilic property of formulation andhence increases the buoyancy. Example: Purified grades of beeswax, fatty acids, long chain alcohols, glycerides, and minaral oils can be used.

Evaluation parameters of FDDS

FLOATING TIME: The test for floating time is usually performed in simulated gastric fluid or 0.1 mole. Lit^{-1} HCl maintained at 37°C, by using USP dissolution apparatus containing 900 ml of 0.1 molar HCl as the dissolution medium. The time taken by the dosage form to float is termed as floating lag time and the time for which the dosage form floats is termed as the floating or flotation time.

DRUG RELEASE: Dissolution tests are performed using the dissolution apparatus. Samples are withdrawn periodically from the dissolution medium with replacement and then analyzed for their drug content after an appropriate dilution.

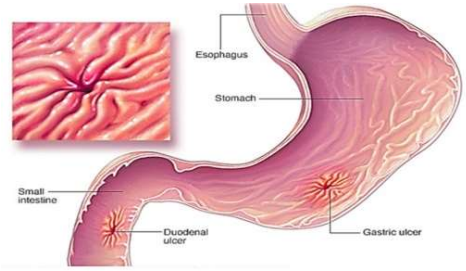
Stomach ulcers

Stomach ulcers, also known as gastric ulcers, are open sores that develop on the lining of the stomach. Ulcers can also occur in part of the intestine just beyond the stomach – these are knownas duodenal ulcers. Both stomach

and duodenal ulcers are sometimes referred to as peptic ulcers. Here the term "stomach ulcer" will be used, although the information applies equally to duodenal ulcers.
Peptic ulcers include:

Gastric ulcers that occur on the inside of the stomach

Duodenal ulcers that occur on the inside of the upper portion of your small intestine (duodenum)



Drug profile: foamatidine
Famotidine, is a histamine H2 receptor antagonist that inhibits stomach acid production.It is commonly used in the treatment of peptic ulcer disease and gastroesophageal reflux disease.

Generic Name: Famotidine
Chemical Name:3-[({2-[(diaminomethylidene)amino]-1,3-thiazol-4-yl}methyl)sulfanyl]-N'-sulfamoylpropanimidamide

Empirical Formula: $C_8H_{15}N_7O_2S_3$

Physical and Chemical Properties Molecular weight - 337.449 g/mol, Color – White to pale yellow crystals, Nature -Crystalline powder, Odour- Odourless, Melting point- 163.5 °C, Solubility- Freely soluble in glacial acetic acid, slightly soluble in methanol, veryslightly soluble in water, and practically insoluble in ethanol. pKa - 12.4.

MATERIALS AND METHODS

S.NO.	MATERIALS	SUPPLIER
1.	Famotidine	Molecules India Pvt.Ltd.
2.	HPMC K4M	Sooriyan pharmaceuticals., chennai
3.	HPMC K15M	Sooriyan pharmaceuticals., chennai
4.	HPMC K100M	Sooriyan pharmaceuticals., chennai
5.	Bees wax	Fine Chem, industries.
6.	odium bicarbonate	Fine Chem, industries.
7.	Lactose(monohydrate)	Standard chemicals
8.	Magnesium stearate	Advance labs
9.	Talc	Fine Chem, industries.

List of instruments used

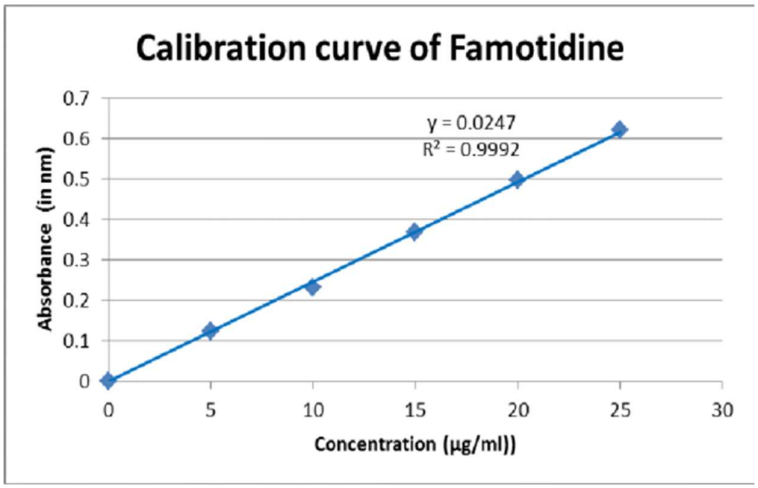
S.No.	INSTRUMENTS	MANUFACTURER
1	Electronic balance	Shimadzu Corporation, AW220&BX6205
2	FTIR spectrophotometer	Shimadzu Co UV-1700
3	UV/Visible spectrophotometer	Lab India UV 3000
4	Dissolution Apparatus(USP)	Electro lab Pvt. Ltd.
5	Tablet Hardness tester	Monsanto Hardness tester
6	Friability test apparatus	Roche Fribilator
7	Tap Density Apparatus	Erweka Pvt.Ltd
8	P^Hmeter	Systonic 335
9	Tablet compression machine	Proton Multipress
10	Vernier Caplier	Digimatic

Calibration curve of fomatidine

The absorbance of the prepared stock solutions was measured at 266 nm in an UV spectrophotometer. Plot a graph between concentration (in µg/ml) vs absorbance (in nm) on X-axis and Y-axis respectively.

S.no.	Concentration(in µg/ml)	Absorbance (in nm)
1.	0	0.000
2.	5	0.123
3.	10	0.233
4.	15	0.369
5.	20	0.497
6.	25	0.621
Slope	0.0247	
R^2	0.9992	

Calibration curve of Famotidine



Formulation and development of famotidine

INGREDIENTS (in mg)	FORMULATION BATCHES							
	F1	F2	F3	F4	F5	F6	F7	F8
Famotidine	40	40	40	40	40	40	40	40
HPMC K4M	0	30	0	0	30	30	0	30
HPMC K15M	0	0	30	0	30	0	30	30
HPMC K100M	0	0	0	30	0	30	30	30
$NaHCO_3$	20	20	20	20	20	20	20	20
Bees wax	30	30	30	30	30	30	30	30
Lactose	98	68	68	68	38	38	38	8
Magnesium sterate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Average weight	200	200	200	200	200	200	200	200

RESULT AND DISCUSSION

Preformulation studies

Organoleptic properties:The tests were performed as per the procedure. The results were tabulated below.

Test	Specifications/limits	Observations
Colour	White to pale yellow	White powder
odour	Odourless	Odourless

The result complies as per specifications.

Physical properties

Angle of repose: It was determined as per procedure. The results were tabulated below.

Material	Angle of repose
Famotidine	27.14^0

The results show that the drug having poor flow.

Bulk density and tapped density

It was determined as per procedure. The results were tabulated below.

Material	Bulk density(gm/ml)	Tapped density(gm/ml)
Famotidine	0.48	0.44

Powder compressibility

It was determined as per procedure. The results were tabulated below.

Material	Compressibility index	Hausner's ratio
Famotidine	11.27	1.44

Melting point

It was determined as per procedure. The results were tabulated below.

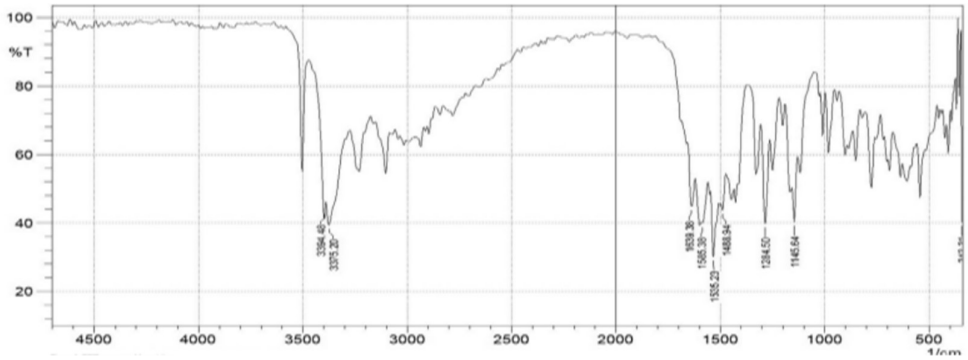
Material	Melting point range	Result
Famotidine	163.5 ° C	163 ^{0}c

The result indicates that the Famotidine drug was pure one.

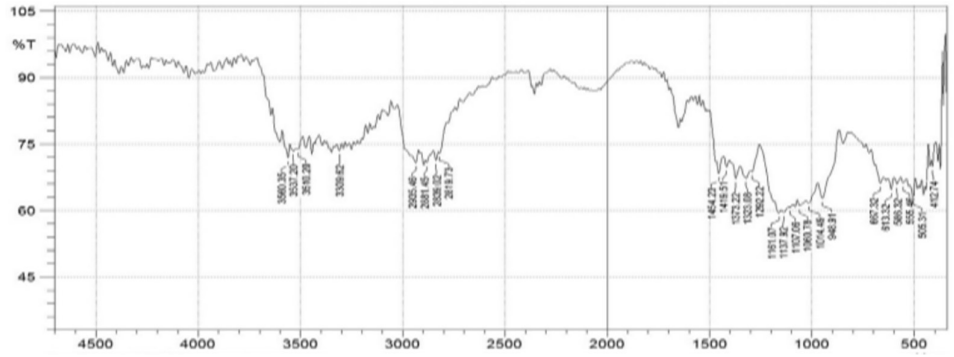
The FT-IR peaks were observed that there is no change in the spectrum representing that there is no interaction between the drug and polymers and other excipients. These peaks play a vital role with respect to drug release.'

Drug-excipient compatibility

Drug + Excipients	Initial	After 1 month at		Compatible
		40^0C/75%RH	60^0C	
Drug	White powder	No change	No change	Yes
Drug + HPMC K4 M	White powder	No change	No change	Yes
Drug + HPMC K15 M	White powder	No change	No change	Yes
Drug + HPMC K100 M	White powder	No change	No change	Yes



FTIR of Famotidine



Evaluation of granules

Results of angle of repose, bulk and tapped density, Carr'sindex, hausner ratio

Batch no.	Angle of repose(^{0})	Bulkdensity (gm/ml)	Tappeddensity (gm/ ml)	Carr's index(%)	Hausner ratio
F1	26 º 32'	0.2891	0.3503	14.04	1.21
F2	24º 64'	0.2845	0.3394	15.68	1.22
F3	28º 59'	0.2924	0.3349	11.94	1.13
F4	26º12'	0.2875	0.3446	13.96	1.16
F5	23º 62'	0.2862	0.3420	15.13	1.19
F6	24º74'	0.2677	0.3214	13.92	1.15
F7	24 º 77'	0.2743	0.3242	15.42	1.19
F8	26 º 56'	0.2847	0.3177	10.38	1.11

The angle of repose for the formulations F1-F8 was found to be in the range23^0.62' to 28^0.59' shows good flow.Compressibility index for the formulations F1-F8 found between 10.38% to15.6% indicating that the blend has good flow property for compression.

Evaluation of famotidine tablets
weight variation and friability

Batch no.	Weight variation	Friability	Content uniformity
F1	± 1.52	0.23	99.65
F2	±2.37	0.34	99.74
F3	± 1.87	0.21	98.34
F4	± 1.41	0.27	99.44
F5	±1.86	0.18	100.38
F6	±2.56	0.28	99.96
F7	±2.35	0.29	99.47
F8	±1.93	0.19	99.35

The weight variation of the above tablets are in the range of ± 1.23 to 3.09%(below 5%) complying with the pharmacopoeial standards.the friability of the tablets are in the range of 0.18 % to 0.34% (below 1%)complying with the pharmacopoeial standards.The content uniformity of the tablets are in the range of 99.37 to 100.38% complying with the pharmacopoeial standards.

Thickness and hardness

Batch no.	Thickness(mm)	Hardness(kg/cm^2)
F1	5.2±0.01	6.2
F2	5.1±0.02	7.1
F3	5.3±0.01	6.5
F4	5.1±0.03	6.9
F5	5.2±0.01	6.3
F6	5.3±0.04	7.2

F7	5.5±0.01	7.5
F8	5.3±0.01	6.4

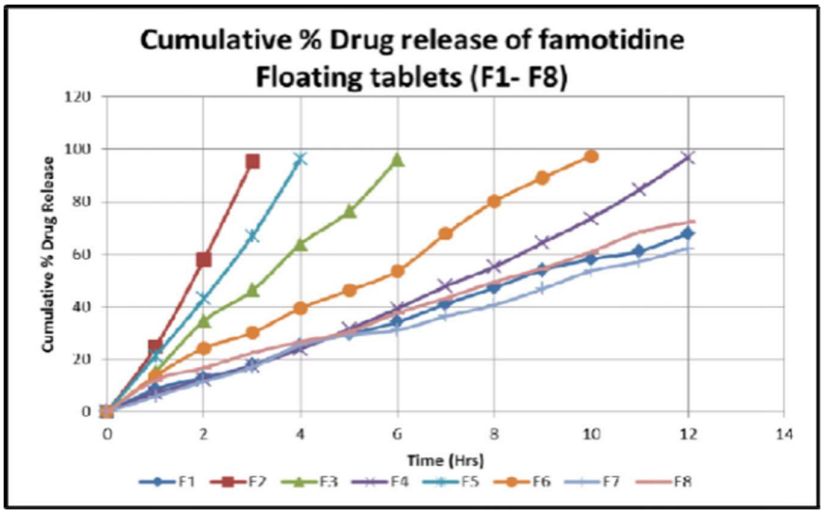
The thickness of the formulations was found to be in the range of 5.1±0.01 to5.5±0.01 mm. The hardness of the tablets was found to be in the range of 6.2 to 7.5 kg/cm^{2}indiacting a satisfactory mechanical strength.

Batch no.	Buoyancy lag time	Total buoyancy time(hrs)
F1	624	15
F2	96	3
F3	90	6
F4	84	12
F5	171	5
F6	63	10
F7	44	15
F8	39	14

From the results formulations F1, F4, F7, F8 shows good buoyancy,allformulations showed buoyancy upto 12 hrs.

***In-vitro* release profile**

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	8.65	24.79	15.13	7.24	21.32	13.76	5.91	12.25
2	13.12	58.12	34.67	12.09	43.13	24.27	11.64	16.79
3	17.75	95.39	46.21	17.62	67.08	30.14	17.08	22.47
4	25.34		63.90	23.98	96.34	39.51	25.42	26.75
5	29.59		76.39	31.56		46.24	29.32	30.54
6	34.23		96.14	39.34		53.69	31.13	37.67
7	41.09			47.87		67.76	36.41	43.34
8	47.23			55.23		80.09	40.69	49.50
9	53.98			64.42		89.13	46.86	54.71
10	58.14			73.7		97.43	53.63	60.92
11	61.17			84.54			57.20	68.43
12	67.91			96.78			62.32	72.19



From the in-vitro dissolution study of all formulations, formulation F1 gave84% release at the end of 12th hour, hence F1 have choosen as best formulation.

Drug release kinetics

Time (Hr)	cumulative % drug released	% drug remaining	Squareroot time	log Cumu %drug remainining	log time	log Cumu % drug released	% Drug released
0	0	100	0.000	2.000	0.000	0.000	100
1	7.24	92.76	1.000	1.967	0.000	0.860	7.24
2	12.09	87.91	1.414	1.944	0.301	1.082	4.85
3	17.62	82.38	1.732	1.916	0.477	1.246	5.53
4	23.98	76.02	2.000	1.881	0.602	1.380	6.36
5	31.56	68.44	2.236	1.835	0.699	1.499	7.58
6	39.34	60.66	2.449	1.783	0.778	1.595	7.78
7	47.87	52.13	2.646	1.717	0.845	1.680	8.53
8	55.23	44.77	2.828	1.651	0.903	1.742	7.36
9	64.42	35.58	3.000	1.551	0.954	1.809	9.19
10	73.7	26.3	3.162	1.420	1.000	1.867	9.28
11	84.54	15.46	3.317	1.189	1.041	1.927	10.84
12	96.78	3.22	3.464	0.508	1.079	1.986	12.24

Regression coefficient of F10"

Formulation	Regression coefficient (R^2) value			
	Zero-order	First order	Higuchi	Korsmeyer – Peppas (n value)
Famotidinetables	0.9955	0.7328	0.9684	0.84 (0.8274)

N value = 0.8274

The regression coefficient values and n values show that the drug releasesfollow Non - Fickian release.

SUMMARY

The present study involves the formulation and evaluation of gastroretentive drug delivery of Famotidine tablets. This type of drug delivery helps to retain the drug in the stomach. The swelling property of the formulation helps to retain the drug in the stomach, by swelling to such an extent so that cannot pass out of the stomach. Preformulation studies which include Organoleptic properties, Bulk and Tapped densities, Carr's index, Hausner's ratio, Melting point, P^H , Solubility, were carried out are as per IP specifications. Drug-excipient compatibility studies were performed which shows that thereis no interaction between drug and polymers. Evaluation studies have been performed for tablets include friability, hardness, weight variation, content uniformity, buoyancy studies are as per IP specifications. Drug release studies have been performed by using 0.1N Hcl for 12 hrs. These studies have shown that the formulation F1 gave better drug release upto 12 hrs. which is formulated with HPMC K100 M.

CONCLUSION

Floating tablets with sustained release characteristics offer critical advantages such as, site specificity with improved absorption and efficacy. This technology can be inculcated to various medicaments which have stomach as the major site ofabsorption. Moreover, floating mechanism doesn't require any complex technology and hence, easy to adopt. Hence, it can be employed in various developmental studies based on requirement. Drugs that have poor bio-availability because of their limited absorption to the upper gastrointestinal tract can be delivered efficiently into FDDS. Thereby maximizing their absorption and improving their absolute bioavailability. The floating concept can also be utilized in the development to treating various diseases. Buoyant delivery system considered as a beneficial strategy for the treatment of gastric and duodenal cancers.

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