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Research

Evaluating the neonatal formulation of famotidine in a live setting

Golla Anjali Yadav*, Jhancy Laxmi bai, V. Algarswamy

MNR college of Pharmacy Sangareddy, affiliated to Osmania University, Hyderabad, Telangana.

*Author for Correspondence: Golla Anjali Yadav
Email: gollaanjali11@gmail.com

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Abstract

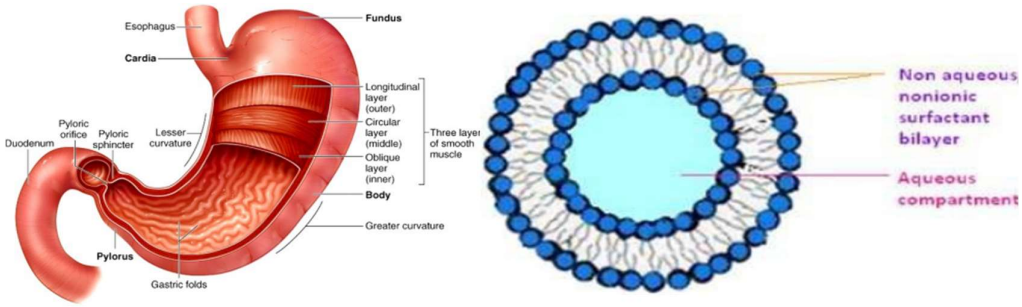
Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is bedilled with several physiological difficulties 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. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.These considerations have led to the development of a unique oral controlled release dosage form with gastro retentive properties. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner, the drug could be supplied continuously to its absorptions in the upper gastrointestinal tract. Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine.

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,niosomeshave 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.



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. While the system is floating on the gastric contents the drug is released slowly at the desired rate from the system. This results in an increased GRT and a better control of fluctuations inplasma drug concentration. The device must have sufficient structure to form a cohesivegel barrier, it must maintain an overall specific gravity lower than that of gastric contents(1.004-1.010)and it should dissolves lowly enough to serve as a drug reservoir.

Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, 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. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose[(1)]. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem[(2)].

These considerations have led to the development of a unique oral controlled release dosage form with gastro retentive properties. After oral administration, such a DF would be retained in the stomach and release the drug there in a controlled and prolonged manner, the drug could be supplied continuously to its absorptions in the upper gastrointestinal tract [(3)]. Gastro retentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestine[(4)].

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.

Evaluation parameters offdds

Floating time: The test for floating time is usually performed in simulated gastric fluid or 0.1mole.lit^{-1} HCl maintained at 37°C, by using USP dissolution apparatus containing 900ml 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 the nanalyzed for the irdrug content after an appropriate dilution.

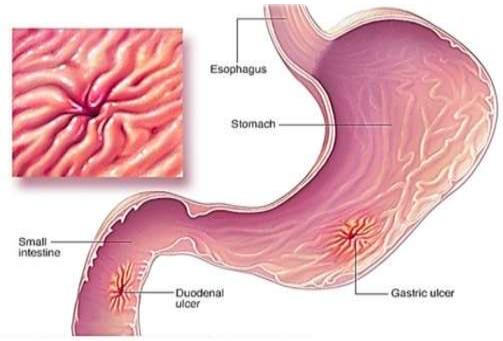
Stomach ulcer

Stomach ulcers, also known as gastric ulcers, are open sores that develop on the lining of the stomach. Ulcers canal so occur in part of the intestine just beyond the stomach– these are known as duodenal ulcers. Both stomach and duodenalulcers are sometimes referred to as pepticulcers. Here the term "stomach ulcer" will be used, although the information applies equally to duo denal ulcers.

Pepticulcers 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

Famotidineisahistamine H2 receptorantagonist that inhibits stomach acid production. It is commonly used in the treatment of peptic ulcer disease and gastro esophageal reflux disease.

GenericName: Famotidine,

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

Empirical Formula: C8H15N7O2S3Solubility- Freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.pKa-12.4.

MATERIALS AND METHODS

Famotidine, HPMCK4M, HPMCK15M, HPMCK100M, Beeswax Sodium bicarbonate, Talc, Magnesium stearate, Lactose(monohydrate), Electronic balance, FTIR spectrophotometer, UV/Visible spectrophotometer Dissolution Apparatus (USP) Vernier, Caplier Friability test apparatus ap Density Apparatus, P^Hmeter, Tablet compression machine, Tablet, Hardness tester.

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(innm)on X-axis and Y-axis respectively.

S.no.	Concentration(inµg/ml)	Absorbance(innm)
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	

Formulation and development of famotidine

INGREDIENTS (inmg)	FORMULATIONBATCHES							
	F1	F2	F3	F4	F5	F6	F7	F8
Famotidine	40	40	40	40	40	40	40	40
HPMCK4M	0	30	0	0	30	30	0	30
HPMCK15M	0	0	30	0	30	0	30	30
HPMCK100M	0	0	0	30	0	30	30	30
$NaHCO_3$	20	20	20	20	20	20	20	20
Beeswax	30	30	30	30	30	30	30	30
Lactose	98	68	68	68	38	38	38	8
Magnesium stearate	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6
Averageweight	200	200	200	200	200	200	200	200

Steps involved informulation

Sieving. Melting mixing granulation, compression

Evaluation of formulated tablets offamotidine[20]

All the formulated sustained release tablets were evaluated for following official and unofficial parameters.

Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of twenty tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in none deviate by more than twice the percentage shown.

RESULTS AND DISCUSSIONS

Preformulation studies

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

Test	Specifications/limits	Observations
Colour	Whitetopaleyellow	Whitepowder
odour	Odourless	Odourless

The result complies as per specifications.

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

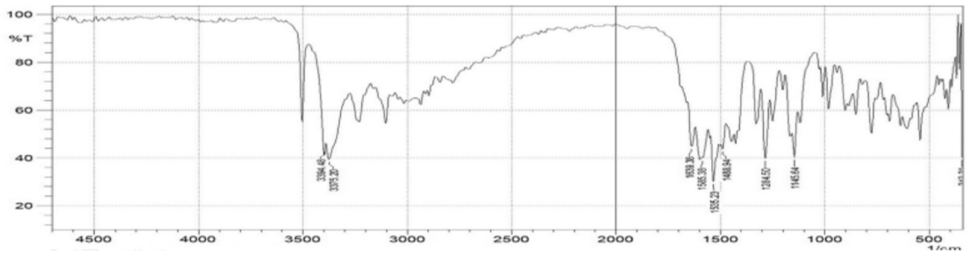
Melting point: It was determined as per procedure.The results were tabulated below.

Material	Melting point range	Result
Famotidine	163.5°C	$163\ ^0$c

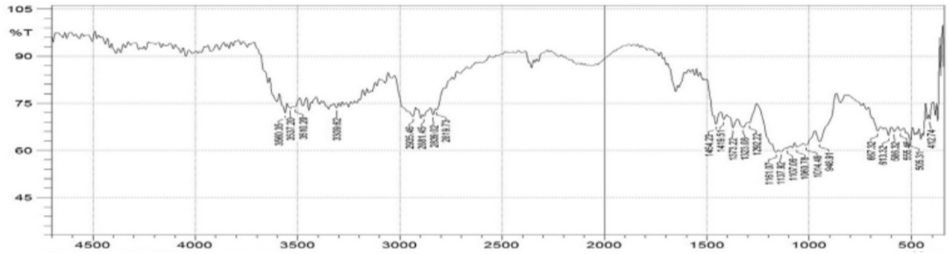
The result indicates that the Famotidine drug was pure one.

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	After1 monthat		Compatibl
		40^0C/75%RH	60^0C	
Drug	Whitepowder	Nochange	Nochange	Yes
Drug+HPMC K4M	White powde	Nochange	Nochange	Yes
Drug+HPMC K15M	White powde	Nochange	Nochange	Yes
Drug+HPMC K100M	White powde	Nochange	Nochange	Yes



FTIR of Famotidine



Evaluation of granules
Showing results of angle of repose, bulk and tapped density, Carr's index, Hausner ratio

Batchno.	Angle ofrepose(^{0})	Bulkdensity(gm/ml)	Tappeddensity (gm/ml)	Carr'sindex(%)	Hausnerratio
F1	26º32'	0.2891	0.3503	14.04	1.21
F2	24º64'	0.2845	0.3394	15.68	1.22
F3	28º59'	0.2924	0.3349	11.94	1.13
F4	26º12'	0.2875	0.3446	13.96	1.16
F5	23º62'	0.2862	0.3420	15.13	1.19
F6	24º74'	0.2677	0.3214	13.92	1.15
F7	24º77'	0.2743	0.3242	15.42	1.19
F8	26º56'	0.2847	0.3177	10.38	1.11

The angle of repose for the formulations F1-F8 was found to be in the range 23^0.62'to 28^0.59'showsgood flow. Compressibility index for the formulations F1-F8 found between 10.38% to 15.6% indicating that the blend has good flow property for a 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% (below5%) complying with the Pharmacopoeial standards. The friability of the tablets are in the range o f0.18% to 0.34% (below1%) 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

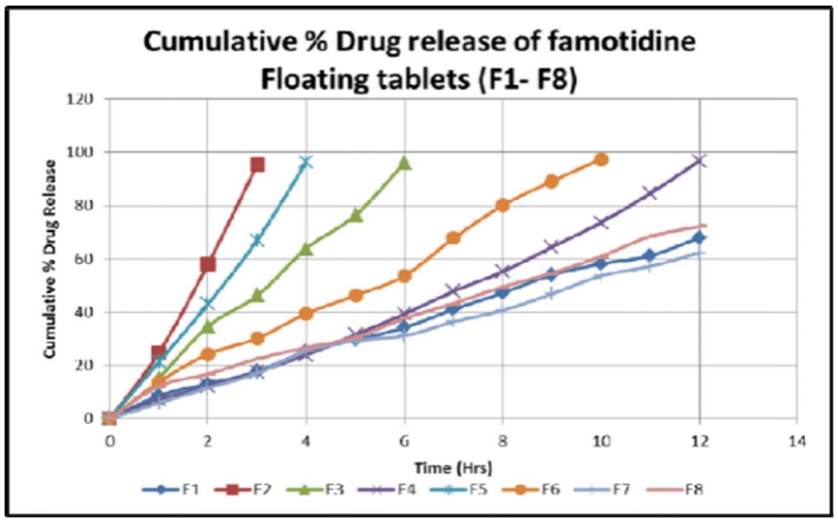
The thickness of the formulations was found to be in the range of 5.1±0.01 to 5.5±0.01 mm. The hardness of the tablets was found to be in the range of 6.2 to 7.5 kg/cm^2 indicating satisfactory mechanical strength.

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, all formulations showed buoyancy up to 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%releaseatthe end of 12th hour, hence F1 have chosen as best formulation.

Drug Release Kinetics

Time (Hr)	cumulative %drug released	%drugremaining	Square root time	LogCumu %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

Regressionco-efficientofF10

Formulation	Regressions efficient(R^2)value			
	Zero-order	First order	Higuchi	Korsmeyer –Peppas (nvalue)
Famotidinetables	0.9955	0.7328	0.9684	0.84(0.8274)

SUMMARY

The present study involves the formulation and evaluation of gastro retentive 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 there is 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 up to 12 hrs.,

which is formulated with HPMCK100M.

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 of absorption. 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. There by 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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