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Design and Optimization of a Multiparticulate Gastroretentive Dosage Form For Better Control Of Gastric Acidity

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Abstract:

The concept of multiunit gastroretentive microspheres can be utilized to provide a more reliable and long lasting release of drug in the stomach for local and systemic action. The floating microspheres beneficially alter the absorption of drug, thereby enhancing bioavailability. Famotidine, being a poorly bioavailable drug due to reasons unrelated to hepatic metabolism, is ideally suited to be delivered through a controlled release floating multiunit dosage form for slow release in the stomach and subsequent complete absorption in the intestine. In the present study, non aqueous solvent evaporation technique was employed to develop polymethylmethacrylate (PMMA) microspheres of famotidine. All formulation development trials leading to the successful batches have been disclosed. They were characterized physic-chemically including *in vitro* floating and drug release studies. Microspheres followed either zero-order or higuchi kinetics in drug release. They were floating for > 8 hours in simulated gastric juice. A 5-component simplex mixture design was followed to simulate the blend of microspheres required to optimize the drug release profile as per the pharmacokinetic need. Statistical optimization helped in achieving the desired target release by predicting the optimum blend to be 9:12:79 %w/w of microspheres having drug-polymer ratios (1:1):(1:2):(1:2.5) respectively, which was validated experimentally. A high similarity factor of 77% was achieved with the drug release from developed blend of microspheres in comparison to the target release profile. Hence, a statistically designed formulation development study could optimize the product in short time with minimal wastage of resources.

Key words: Famotidine, Floating drug delivery, Microspheres, Peptic ulcer, Polymethylmethacrylate (PMMA), Solvent evaporation

Introduction:

Peptic ulcer is one of the most common chronic diseases in the world afflicting ca. 4.6 million people according to WHO reports. About 1.83% of the total population is affected according to reports of US Census Bureau International Database 2004. About 3000 people die each year as a result of peptic ulcer disease in United States [1]. Peptic ulcer is the disorder of the upper gastro intestinal tract that results when gastric acid, bacteria, drugs or other assaults cause breaks or sores in mucosa, the moist tissue that lines the stomach, duodenum and other areas of gastrointestinal tract. Gastric hyperacidity is one of the main causes of peptic ulcer [2].

World wide accepted clinical therapy of acid peptic disease is based on histamine H_2 receptor antagonists. The four H_2 receptor antagonists currently available on market are Cimetidine, Ranitidine, Famotidine, and Nizatidine. Out of these drugs famotidine is the most widely used and accepted drug for the treatment of peptic ulcer. Famotidine is having fewer side effects than the other congeners and it does not appear to exhibit antiandrogenic activity or affect the hepatic clearance of other drugs [2-4].

Famotidine is having low bioavailability (40%), so there is a continued effort to improve the pharmaceutical formulation of famotidine in order to achieve an optimized therapy. These efforts mainly focus on CR/SR of the drug including the sophisticated gastroretentive systems [3,5-7]. The best form of CR formulation for famotidine should slowly release the drug in the stomach for gradual absorption in intestines [8]. The slow but complete drug release in the stomach is expected to increase bioavailability of the drug as well as lower GI side effects and dose. Of the

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various technologies for gastroretentive dosage forms [8], the floating drug delivery systems (FDDS) are most widely investigated since they are most promising dosage form to achieve reproducibility in a wide spectrum of biological condition. Single unit FDDS are, however, comparatively less reliable and may be irreproducible in their effect owing to their all or none emptying process. [9,10] Multiunit floating dosage forms are characterized by a high reproducibility of release due to plurality of release profile, relatively large surface and short diffusion path of the drugs [11-16].

With these considerations, in this paper, an attempt has been made to report design, development and evaluation of CR multi unit FDDS of famotidine for better management of peptic ulcer. Mainly our attempt has been to achieve a sufficiently prolonged drug release at par with the pharmacokinetics need while providing a floating time of > 8 hours [17]. Formulation development time and resource wastage was minimized through adoption of experimental design methodology, particularly a simplex mixture design.

Materials and Methods:

Materials:

Famotidine was obtained a gift samples from Microlabs, Cadila Healthcare Ltd and Sun Pharmaceutical Industries Ltd. Polymethylmethacrylate was purchased from Himedia Laboratories Pvt. Ltd, Mumbai. Ethyl cellulose(18-22 cps) was purchased from SD fine Chem. Ltd, Mumbai. All other chemicals and reagents were of analytical grade. Water used was semi quartz distilled.

Physicochemical studies:

The drug was characterized for melting point and UV spectrum in 0.1 N HCl. The λ_{max} was found at 266.2 nm. IR spectra of pure drug, polymer (PMMA) and their 1:1 mixtures were obtained between 4000-600 cm^{-1} to identify any potential drug interaction (data not shown). The quantitation of the drug was done spectrophotometrically using PharmaSpec UV 1700 (Shimadzu, Japan) spectrophotometer at 266.2 nm.

Preparation of floating microspheres:

Microspheres containing famotidine as the core material were prepared by non-aqueous solvent evaporation method [18]. Polymethylmethacrylate (PMMA) was dissolved in Acetone and drug was mixed to the slurry at various ratios. The drug-polymer slurry was slowly introduced into 30 ml of liquid paraffin while being stirred at 1200 rpm using a mechanical stirrer (Remi) at room temperature. Stirring was continued for 2 hours and allowed the solvent to evaporate completely and the microspheres were collected by filtration .The microsphers were washed repeatedly with aliquots of petroleum ether (40^{o}-60^{o} C) until free from oil. The collected microspheres were dried for one hour at room temperature and subsequently stored in a desiccator over fused calcium chloride until further study.

Microspheres with a size range of 251-1000 micrometer were collected and weighed. The yield of the product was calculated as follows-

% yield = (Actual weight of product / Total weight of polymer and drug) x 100

Particle size analysis:

Size distribution was determined by sieving the microparticle using a nest of standard BSS sieves [19].

Determination of drug entrapment efficiency (DEE):

Microspheres equivalent to 100 mg drug were taken for evaluation. It was estimated by crushing the microsphers with aliquot amounts of 0.1 N HCl repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume made up using 0.1 N HCl. The solution was filtered and then spectrophotometric absorbance was measured after suitable dilutions at

266.2 nm against appropriate blank. The amount of drug entrapped in the microspheres was calculated. The entrapment efficiency of the microencapsulation was determined using the formula

DEE = (Amount of drug actually present / Theoretical drug load expected) x 100

In vitro drug release study:

This study was carried out for all the batches and for the pure drug in dissolution test apparatus USP type II [20]. Medium used was 900 ml of 0.1 N HCl. 100 mg of pure drug was taken for the dissolution studies and microspheres equivalent to 100 mg of the pure drug were used. The tests were carried out for 8 hours at 50 rpm at 37±0.5 ^{o}C. 1 ml of the aliquot was withdrawn at different predetermined intervals and filtered and equal volume of fresh medium was replenished to the dissolution vessel to maintain sink conditions. The solution was analyzed for the drug content spectrophotometrically at 266.2 nm against suitable blank There trials were carried out for all the products and the average SD and SEM values were calculated.

In vitro evaluation of floatation study:

This study was carried out using 0.1 N HCl (with 0.2% Tween 20) as a dispersing medium. Microspheres were spread over the surface of 500 ml of dispersing medium at 37± 0.5^{o}C. Agitation was maintained with a paddle rotating at 100 rpm**.** The microspheres which were floating after 8 hours was collected and weighed after drying. The % of microspheres floating after 8 hours was calculated as follows-

% floating microspheres = (weight of floating microspheres/initial weight of added microspheres) x 100

Surface Topography (SEM) study:

The morphology of microspheres both before and after dissolution was examined by scanning electron microscopy at an angle of incidence of 90^{o} with accelerating voltage of 20KV after gold coating.

Theoretical in vitro release profile:

To compare the prepared formulation, there was no pharmacopoeal reference data of famotidine controlled release formulation. Therefore, theoretical in vitro release profile was calculated from pharmacokinetics of the drug as follows assuming a twice daily administration**.**

Statistical Evaluation and Comparison of release profiles [21]

To adopt the dissolution testing, the pharmaceutical scientist has performed comparisons of dissolution profiles. Many of these methods of comparisons have often been qualitative or semi-quantitative. The FDA guidance documents, SUPAC IR and MR, suggest that dissolution profiles may be compared using the following equation:

$$f_{2=} 50 \text{ x } \log\{[1+1/n\sum(R_t-T_t)^2]^{-0.5} \text{ x } 100\}$$

Where, f_2 is the similarity factor, R_t and T_t are % drug released at each time point for the reference and test formulations respectively.

Preliminary formulations:

Different formulations of microspheres were prepared with different polymers and different drug to polymer ratios varying from 1:1 to 1:5 (Tables 2 & 3) and subsequently evaluated for the optimization of effective drug-polymer ratio on drug release investigation.

Optimization strategy for the formualation [22]

Based on preliminary studies, the effect of polymer loading on drug release profile was determined. Then a simulation of release from blends of microspheres was carried out following a 5-component simplex mixture design. Best two formulation blends were investigated for closeness of release and % error in comparison with predicted as well as

pharmacokinetic target was ascertained, based on which the final formulations were selected.

Results and Discussion:

In the present study, a multiparticulate floating drug delivery system of famotidine was developed with PMMA as the rate controlling polymer. The formulations were evaluated for various physicochemical properties, floating ability, release kinetics and finally the release pattern of the delivery system was optimized using an experimental design.

The melting point, UV and IR spectra of the drug were conforming to pharmacopoeial standards [21]. Further, there was no discernible shift/disappearance /appearance of peaks in drug-polymer combined spectra that indicated good drug-polymer compatibility. Hence, polymethylmethacrylate (PMMA) was found suitable for development of the FDDS.

The non-aqueous emulsification solvent evaporation technique [23] was found to yield suitable famotidine loaded PMMA microparticles with adequate flow properties, drug entrapment and release profile that varied with drug-polymer ratio. Particles were found to be composed of a thick polymer coat with hollow core. Commensurate with the structure, the microparticles were found to float for at least 8 hours in water and 0.1 N HCl (Table 4).

Due to the absence of pharmacopoeial specifications and marketed product for famotidine extended release formulation, we have calculated theoretical in vitro release profile to set the target for drug profile shown Table 1. The conventional tablet released whole of its drug content with in fifteen minutes (data not shown). During the preformulation stage PMMA was found to influence the drug release, particle size and drug entrapment characteristics of the microspheres. Higher level of the PMMA yielded microspheres with high drug content probably due to polymer loss at high viscosity level.

The kinetics of the release profile gave us useful insight into the mechanism of drug release from the microspheres. The dissolution data was subjected to regression analysis. It was found that most of the formulation followed zero-order release. All investigated formulations showed adequate floatability at least upto 8 hours and hence did not need further adjustments.

The formulations PM1 – PM5 exhibited wide range of release both above and below the target profile depending on the polymer load. It was expected that a suitable combination of the developed formulation could be useful to achieve the target release profile. This was achieved by developing blend simulation of microparticles as per a 5-component simplex mixture design. The regression analysis and subsequent ANOVA of the design generated models, which were used to optimize the release profile and predict the desired blends of microspheres that would closely match the target profile (Table 5). We optimized the desired blends of microspheres using a trial version of Design Expert Software (v.6.0.6) [24] to yield the optimum blend of microspheres fulfilling the target characteristics.

It was found that two blends of microspheres named as formulations PM 6 (blend #1) and PM 7 (blend #2) were showing closest match with target release profile (Tables 6 & 7 and compare with Table 1).

It was found that the observed values of each parameters optimized was very close to the target and predicted values with difference of < 10%. A further indication of the success of the optimization procedure could be obtained by a look at the f_2 values of formulations PM6 and PM7, namely 77.13 and 74.64 respectively (Table 6). Hence, the release was finally optimized. Figure 1 depicts the closeness of fit among the optimized and target release profiles.

Table 1. Dissolution Target values

Time (hr)	1	2	3	4	5	6	7	8
%CDR	10.2	20.39	30.58	40.78	50.97	61.17	71.36	81.56

Table 2. Preliminary formulations at a glance

CODE / Composition	F1	F2	F3	F4	F5	F5	F6	F7	F8	F9	F10	F11
Famotidine (mg)	250	250	250	250	250	500	250	250	250	250	500	500
PMMA (mg)	250	250	250	250	250	500	--	500	250	500	250	250
Ethylcellulose (mg)	--	--	--	--	--	--	250	--	--	--	--	--
Acetone (ml)	10	10	10	--	6	10	10	10	6	--	6	6
Methanol (ml)	--	--	--	10	--	--	--	--	--	--	--	--
Liquid paraffin(ml)	20	25	30	30	30	30	30	30	25	--	25	30
Di-chloromethane (ml)	--	--	--	--	6	--	--	--	6	8	6	6
PVA (mw 1,25,000) (%)	--	--	--	--	--	--	--	--	--	0.5	--	--
Water (ml)	--	--	--	--	--	--	--	--	--	30	--	--

Table 3. Formulations with different Famotidine-PMMA ratios

Composition	PM1(1:1)	PM2(1:2)	PM3(1:3)	PM4(1:4)	PM5(1:5)
Famotidine (mg)	250	250	250	250	250
PMMA (mg)	250	500	750	1000	625
Acetone (ml)	12	14	14	14	14
Liquid Paraffin (ml)	30	30	30	30	30

Table 4. Product characteristics of preliminary formulations

Product code	Product yield (%)	DEE (%)	Mean Particle size (µm)	% floating (after 8 hour)
F1	85.11	82.26	467.66 ±76.06	82%
F2	80.24	81.26	446.24±64.27	89%
F3	87.36	82.36	443.62±72.59	92%
F4	66.24	20.60	660.40±66.43	60%
F5	87.36	89.90	554.30±64.10	85%
F6	66.61	79.50	475.20±86.65	82%
F7	86.60	88.23	473.56±74.15	99%
F8	44.65	76.60	680.20±61.63	80.40%
F9	20.42	06.00	250.40±87.27	Dissolved
F10	42.36	52.34	543.20±73.40	62.20%
F11	63.20	56.72	525.40±79.32	60.44%
PM1	88.93	85.33	412.69±81.07	99.53%
PM2	86.60	88.33	357.56±92.63	99.00%
PM3	98.90	88.88	453.73±62.26	96.57%
PM4	90.63	90.80	420.20±71.58	95.2%
PM5	88.23	89.33	452.66±79.41	92.46%

Table 5. Simulated optimum formulation blends

Blend	Component formulations					% CDR at different time (mins)									
#	PM1	PM2	PM3	PM4	PM5	15	30	60	120	180	240	300	360	420	480
1	0.09	0.12	0.00	0.00	0.79	2.40	5.10	10.77	21.98	30.64	40.52	50.05	59.72	65.94	72.32
2	0.08	0.16	0.00	0.00	0.76	2.39	5.10	10.74	21.99	30.63	40.61	50.13	59.76	65.96	72.34
3	0.06	0.22	0.00	0.00	0.72	2.38	5.10	10.70	22.01	30.61	40.74	50.26	59.83	65.98	72.36
4	0.13	0.00	0.04	0.00	0.82	2.45	5.14	10.98	22.03	30.80	40.21	49.77	59.52	65.90	72.20
5	0.03	0.35	0.00	0.00	0.62	2.35	5.11	10.64	22.08	30.60	41.08	50.58	60.02	66.05	72.42
6	0.02	0.40	0.00	0.00	0.58	2.35	5.11	10.62	22.11	30.59	41.19	50.69	60.07	66.07	72.44
7	0.01	0.42	0.00	0.00	0.57	2.34	5.11	10.61	22.12	30.60	41.24	50.74	60.10	66.08	72.45
8	0.13	0.18	0.00	0.00	0.70	2.54	5.38	11.34	22.60	31.20	41.29	50.73	60.31	66.51	72.79
9	0.08	0.23	0.12	0.00	0.57	2.38	5.1	10.79	22.03	30.69	40.43	50.05	59.5	65.76	71.98
10	0.00	0.54	0.10	0.00	0.36	2.31	5.10	10.58	22.14	30.60	41.17	50.76	59.90	65.88	72.11

Table 6. Release data comparison of optimized formulation with target

Time (hr)	%CDR				
	Target	PM6*	Difference	PM7**	Difference
1	10.20	10.65	0.45	10.35	0.15
2	20.39	23.34	2.95	20.71	0.32
3	30.58	30.74	0.16	30.66	0.08
4	40.78	42.23	1.45	41.04	0.26
5	50.97	51.69	0.72	51.02	0.05
6	61.17	61.16	0.01	61.43	0.26
7	71.36	69.82	1.54	68.53	2.83
8	81.56	76.45	5.11	74.81	6.75
f2 value		77.13		74.67	

*PM6 [PM1:PM2:PM5 = 9:12:79 %w/w]

**PM7 [PM1:PM2:PM5 = 8:16:76 %w/w]

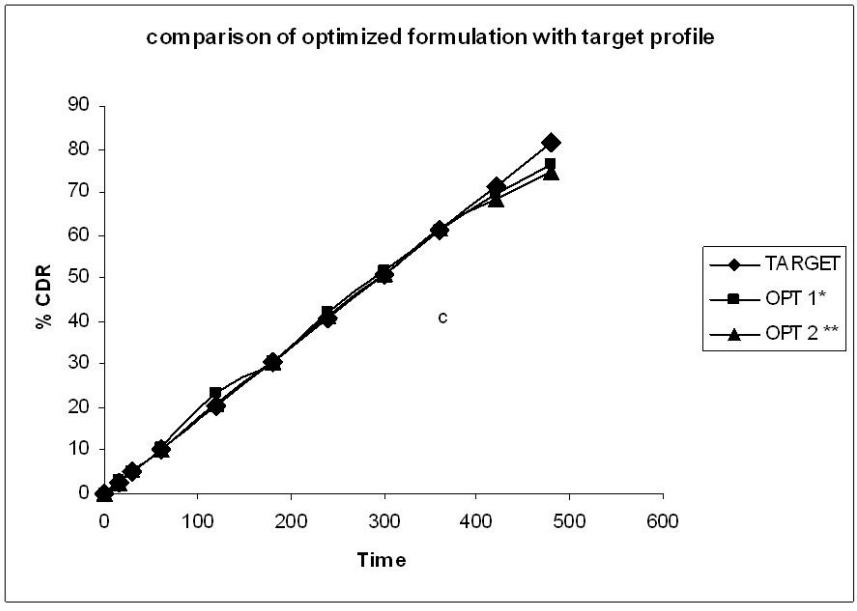

Figure 1. Comparison of release profiles of optimized formulations with target profile (Opt 1 = PM6 & Opt2 = PM7)

Therefore, the objective of designing and development of a floating multiunit delivery system of famotidine was adequately achieved. Being a floating drug delivery system, the drug would be completely released in the stomach. The drug administration may be done with or without food, but with a glassful of water to provide suitable floating capability.

Conclusion:

Peptic ulcer has attracted very wide attention of the medical and paramedical fraternity. Famotidine is a front line drug used for treatment of peptic ulcer. It is safe and efficacios drug for the treatment of peptic ulcer. Based on these considerations, floating drug delivery system in the form of floating microspheres were developed using widely accepted and physiological safe excipients and using technically simple, quick and reproducible methodologies. Experimental design supported simulation from developed formulations and subsequent optimization techniques yielded the desired formulation with drug release comparable to the theoretical profile calculated from pharmacokinetics of the drug with the added benefit of flotation mediated gastric retention. The optimization could be achieved with minimal time and resources. Therefore, the optimized multi unit floating famotidine delivery system is expected to provide the clinician with a new choice of an economical, safe and efficacious regimen in the management of peptic ulcer disease.

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