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Research Article

Design and Development of Oral Sustained *In Situ* Gelling System of Famotidine

SB CHANDRA MOHAN*[1], N MANJUNATHA[2], KALPESH PATEL[2], MK SAMANTA[2], SHYAMALA BHASKARAN[1]

[1]Department of Pharmaceutics, Al-ameen College of Pharmacy, Bangalore-560027, INDIA

[2]Department of Pharmaceutics, JSS College of Pharmacy, Ooty-643001, INDIA

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ABSTRACT

In situ gels are capable of releasing drug in a sustained manner affording relatively constant plasma profiles. The study evaluates the potential of oral sustained delivery of famotidine with gellan gum and sodium alginate as gelling agents. Calcium ions present in the formulation helps in formation of gel when administered as oral aqueous solutions. Aqueous solutions of gellan gum and sodium alginate form gels on warming to body temperature in the presence of cations. The Famotidine a H_2 receptor antagonist, with short half life of 3 h is chosen as candidature. Different Solutions (sols) were prepared varying the concentration from 0.25 %w/v to 6.0 % w/v and 0.5 % w/v to 7.0 % w/v in case of gellan gum and sodium alginate respectively. The sols were evaluated for rheological properties using brookfield viscometer. *In vitro* release rate studies were carried out using gastric buffer (pH 1.2) for 2 h followed by acidic buffer (pH 4) for 2h and than the phosphate buffer (pH 6.8) for 2 h respectively. Diffusion studies were carried out in franz diffusion cell using cellophane membrane and water uptake studies was also done. 1.0 % w/v sols and suspensions of the polymers showed pseudoplastic flow with a satisfactory release rate following diffusion mechanism. The diffusion co-efficient was found to be 2.5488 x 10^{-7} Cm^2/Sec and 3.9648 x 10^{-7} Cm^2/Sec for gellan gum and sodium alginate formulations. The sols of gellan gum or sodium alginate results in the formation of *in situ* gel of famotidine for better treatment of ulcer.

INTRODUCTION

A conventional dosage form of Famotidine a H_2 receptor antagonist which is 8 times more potent than ranitidine, 20 times more potent than cimetidine is widely administered at night in treatment of gastric and duodenal ulcer and it acts mainly by inhibiting acid production by reversibly competing with histamine. As a conventional form it is rapidly and incompletely absorbed from gastrointestinal tract (GIT) with the bioavailability of about 43% having an elimination half life of 3 h, the treatment becomes ineffective in some cases like reflux oesophagitis, in which the acid secretion continues through out night (nocturnal acid breakthrough). In these conditions, the action of the drug has to be sustained [1].

Several techniques were being adopted to sustain the release of the drugs with the application of polymer characteristics.

Author for Correspondence:
Email: sirish_sb@yahoo.com

The *in situ* gelling system being one among them is a type of mucoadhesive drug delivery system principally capable of releasing drug molecule in a sustained manner affording relatively constant plasma profile. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH dependent and cation induced gelation. Compared to conventional controlled release formulations, *in situ* forming drug delivery systems possess potential advantages like simple manufacturing processes and ease of administration [2,3]. Even though the delivery system is widely applicable for ocular therapy, it has several advantages as a dosage form for oral administration like maximum intimate contact of the drug at the absorption site, influenced rate of absorption, ease of preparation, homogenicity of drug distribution compared to other conventional suspensions, and mucoadhesive in nature which helps in coating of the ulcer lining once the sol comes in contact with the gastric pH [4].

Thus in the present study an attempt was made to prepare a formulation of famotidine as *in situ* gel forming

drug delivery system for oral delivery using gellan gum and sodium alginate as gel forming agents. The gellan gum commercially available as gelrite is an anionic deacetylated exocellular polysaccharide secreted by pseudomonas elodea, with a tetrasaccharide repeating unit of one alpha-L-rhamnose, one beta-D-glucuronic acid and two beta-D-glucose units. It has a characteristic property of temperature dependent and cation induced gelation [5]. whereas the sodium alginate undergo gelation in presence of di- or trivalent metal ions by a co-operative process involving consecutive glucuronic residues in the alpha-L-glucuronic acid blocks of the alginate chain [6,7].

MATERIALS AND METHOD

Materials

Famotidine was gifted from M/s Torrent Pharmaceuticals Limited, Mumbai, India. Gelrite Gellan gum and Sodium alginate was obtained from M/s Sigma-Aldrich Chemicals, Bangalore. Sodium citrate and Calcium chloride ($CaCl_2$) was purchased from M/s Loba Chemie, Mumbai. Hydrochloric acid (HCl) and Sodium Hydroxide (NaOH) was procured from M/s Thomas baker chem. Ltd and M/s S. D. Fine Chem. Ltd, Mumbai respective. All the chemicals were of analytical grade.

Dose calculation

The total dose of drug (Dt) in a sustained release dosage forms [8] is calculated using the equation Dt = f(Dn+Ds) where Dn is the normal dose (20mg) and Dm is the maintenance dose which is given as DnK where K is the first order elimination rate constant (rate at which drug must be replaced for the peak plasma blood level to be maintained). With the maintenance period of t the Dm = DnKt. whereas f is the factor to adjust the amount of drug to attain the effective therapeutic blood level, which is gained by dividing the minimum effective concentration by $C_{max.}$

Drug polymer interaction studies

The drug polymer interaction studies were carried by IR peak matching technique (FTIR – 8700, M/s Shimadzu) by KBr pelletization method. The physical mixture of drug and polymers were taken in a ratio of 1:1 and mixed uniformly with demoisturized KBr (IR grade) in ratio of 1:4 respectively. The mixture was compressed to a thin transparent pellet by subjecting to hydraulic press, which is then placed in the path of IR rays using a sample holder to record the spectra.

Preparation of Sols and Suspensions

Gellan gum solutions of concentrations 0.25-6.0 % w/v were prepared by adding the gum to ultrapure water containing 0.17 % w/v sodium citrate and heated to 90°C while stirring. After cooling to below 40°C appropriate amounts of calcium chloride 0.016 % w/v was added while stirring. Famotidine (30 mg) was then dissolved in 0.1N HCl solution and added slowly to the above gum solution while stirring on a magnetic stirrer so that there was proper and homogeneous dispersion of the drug.

Sodium alginate suspensions were also prepared in a similar manner. Sodium alginate solutions of concentrations 0.5-7.0% w/v were prepared by adding the alginate to ultrapure water containing 0.25% w/v sodium citrate and heating to 60°C. After cooling to below 40°C appropriate amounts of calcium chloride 0.075 % w/v was added while stirring. Famotidine (30 mg) was then dissolved in 0.1N HCl solution and added slowly to the above alginate solution while stirring on a magnetic stirrer so that there was proper and homogeneous dispersion of the drug. The HCl was neutralized with addition of 0.1N NaOH in both the cases [9].

Rheological properties of Sols and Gels

The viscosity of the sols and gels were determined at ambient condition using DV III+, Brookfield Programmable Rheometer using 2 ml aliquot of the sample.

Effect of Polymer concentration

Eight different formulations namely G_1, G_2, G_3, G_4 and S_1, S_2, S_3, S_4 were formulated with varying drug to polymer ratio of 1:0.5, 1:1.0, 1:1.5, and 1:2.0 respectively, keeping other conditions as follows; Sodium citrate- 0.17 % w/v and Calcium chloride-0.016 % w/v for gellan gum formulation and Sodium citrate 0.25 % w/v and calcium chloride 0.075 % w/v for sodium alginate formulation.

Estimation of Drug content

The drug content of the formulations was measured by UV spectroscopic method (UV – 1700, M/s Shimadzu) at λ_{max} of 266 nm after aliquot dilution with 0.1N HCl [9].

In Vitro release studies

The formulations were taken into beaker containing 100ml of acidic buffer (pH 1.2). The gel formed is shaken in a bath incubator at 50rpm with maintenance of temperature of 37°C through out the process. At every 30 min interval the known volume of sample was withdrawn and subjected to UV spectroscopic method at a wavelength of 266nm. The sink condition of the media was maintained with replacement of fresh buffer solution [4].

Diffusion Studies

The diffusion studies were carried out using Franz diffusion cell [4]. The capacity of the donor compartment was 5 ml and the receptor compartment 100 ml. the diffusion studies were carried out in simulated gastric fluid (pH 1.2). The surface area of the membranes was 3.4618 cm^2. The donor and receptor compartment were separated by a GI mucosa of porcine. The sample was withdrawn at regular intervals from the receptor compartment and replaced with the fresh buffer. The drug concentration of the samples was determined using a spectrophotometer at a wavelength of 266 nm.

Determination of diffusion Co-efficient

Diffusion co-efficient is the ability of the drug to diffuse out through biological membranes [10-12]. and is given by the formula D = Ph/K where D is the diffusion coefficient, P is the permeability coefficient, h is the thickness of the membrane, and k is partition coefficient.

Determination of Flux and Permeability co-efficient:
The flux and the permeability co-efficient is calculated by applying below formula

$$\text{Flux} = \frac{\text{slope}}{\text{Surface area}}$$

$$\text{Partition co-efficient (P)} = \frac{\text{Flux}}{\text{Drug concentration in the donor compartment}}$$

Measurement of Water Uptake by the Gel

The *in situ* gels formed in 40 ml of gastric acid buffer (pH 1.2) were used for this study. The gel portion from the buffer was separated and the excess buffer was blotted out with a tissue paper. The initial weight of the gel taken was weighed and to this gel 10 ml of distilled water was added and after an interval of 30 minutes the water was decanted and the weight of the gel was recorded and the difference in the weight was calculated and reported [4].

RESULTS AND DISCUSSION

The dose calculation revealed that the administration dose of *in situ* gel formulation should contain 30mg of famotidine so that the plasma concentration of the drug is maintained. Keeping the dose in consideration, drug polymer interaction studies were carried out by subjecting the drug polymeric physical mixture to IR spectroscopic analysis to determine the compatibility between them. Sufficient period of time (one month) was provided for any physical reaction to take place between them by storing at ambient conditions. The peak matching technique revealed no changes in the formulations that observed for pure drug (Table 1).

Preparation of Sols and Gels

The Preliminary studies were carried out to determine the gellan gum and sodium alginate concentration necessary *in situ* gel formation with acceptable consistence for the drug delivery. At lower concentrations there was improper gellation which leads to rapid flow of the formulation and also the time required for gelation. At very high concentration gel was obtained in which the viscosity just increases and it was difficult to pour the solution, therefore the optimum concentration chosen for gellan gum and sodium alginate was 1 % w/v. The pH of the solution was neutral. The Calcium ions included in the formulation for induction of gelation were inactivated by complex formation with required quantity of sodium citrate, to maintain the fluidity. The complex will be broken in the acidic environment of stomach resulting to gel formation.

Table 1: IR Peak matching studies

Functional group	Range (cm^{-1})	Pure Drug (cm^{-1})	Gelrite mixture (cm^{-1})	Sodium alginate mixture (cm^{-1})
NH Stretch Amine group	3300-3600 Doublet	3400.3 3373.3	3400.3 3373.3	3400.2 3373.3
=C-H	3100-300	3103.3	3103.3	3105.2
C=N	1650-1590	1639.4	1639.4	1641.3
C=C	1600-1500	1596.4	1596.9	1596.9
S=O	1550-1500	1533.3	1533.3	1533.3
C-S	1250-1350	1282.6	1282.6	1284.5
C-N	1070-1170	1149.5	1149.5	1149.5

Rheological properties of Sols and Gels and the effect of polymer concentration

The Table 2 compares the Rheological properties of gels of gellan gum and sodium alginate. The values determined shows the significant difference in gel strengths of these two gels and the Fig 1 compares the shear dependency of the viscosity of the 1.0% w/v gellan and sodium alginate. The entire formulations showed shear thinning behaviour with decrease in viscosity as the shear rate increases. The low viscosity of the sols makes them suitable for oral administration which forms gels at the pH1.2 in stomach. The increase in polymer ratio enhanced the viscosity indicating the better gelling property. The Fig 1 shows the rheological behaviour of G2 and S2 formulations and the formulations showed shear thinning behaviour.

Table 2: Rheological properties of Sols and Gels

Formulation Code	Drug: Polymer ratio	Concen-tration (%)	Speed (RPM)	Viscosity *(CP)	pH
G_1	1:0.5	0.5	150	258	7.0
G_2	**1:1.0**	**1.0**	**150**	**315**	**7.0**
G_3	1:1.5	1.5	150	340	7.0
G_4	1:2.0	2.0	150	365	7.0
S_1	1:0.5	0.5	150	197	7.0
S_2	**1:1.0**	**1.0**	**150**	**238**	**7.0**
S_3	1:1.5	1.5	150	251	7.0
S_4	1:2.0	2.0	150	272	7.0

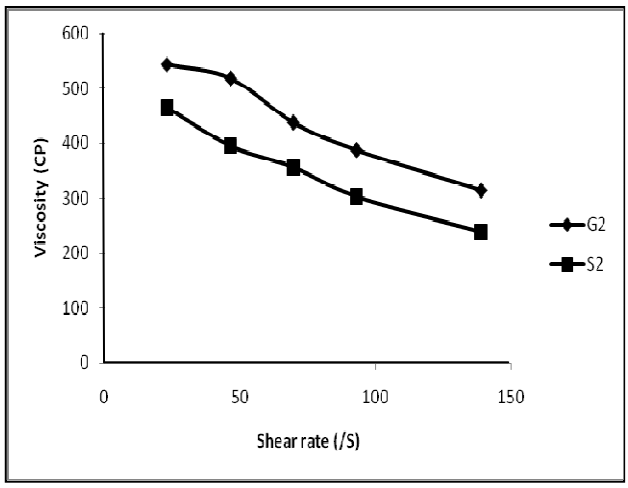

Figure 1: Rheological behaviour G2 and S2 formulations

Rheological properties of Sols and Gels and the effect of polymer concentration

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Drug content and *in vitro* release studies

UV spectroscopic analysis of one ml of all the formulation diluted with 0.1N HCl revealed that all the formulations contain more than 96% of the drug administered; the results are triplicate of analysis. Appropriate volume of gel containing 30mg of the drug was taken for dissolution, the release studies were carried for 4 h in gastric pH and then for 2h at the intestinal pH 6.8 to mimic the passage through the gastrointestinal tract. The *in vitro* results of gellan gum and sodium alginate were compared and reported in Table 3 and Fig 2 and 3. There was no discontinuity of the plots when the dissolution medium was changed from simulated gastric fluid (pH 1.2) to simulated intestinal fluid (pH 6.8) to mimic passage through the gastrointestinal tract. This occurs since there will be no change in the state of ionization of acidic drug famotidine (pKa) accompanying the pH change. Gelation of the sol in the receptor compartment is a result of hydrogen bonding of the chains by the H^+ ions that diffuse through the membrane. Although the pH of the sol is reduced as a result of the influx of H^+ ions, there is clearly sufficient ionization of the carboxylic groups of gellan for gelation to occur by this process. This process is rapid, with complete gelation of the receptor solution occurring before the time of first measurement (30 minutes after initial contact). The comparison of release rate between G1 and G2, S1 and S2 shows that the increase in polymer concentration did not retard the release which may be due to insufficient concentration of polymer to retard whereas further increase retarded the release which may be due to enhanced gel strength but the pattern of release among G3 and G4, S3 and S4 remains unclear as the rate of release from G4 and S4 is almost same as that of G3 and S3 respectively though the polymer concentration is more.

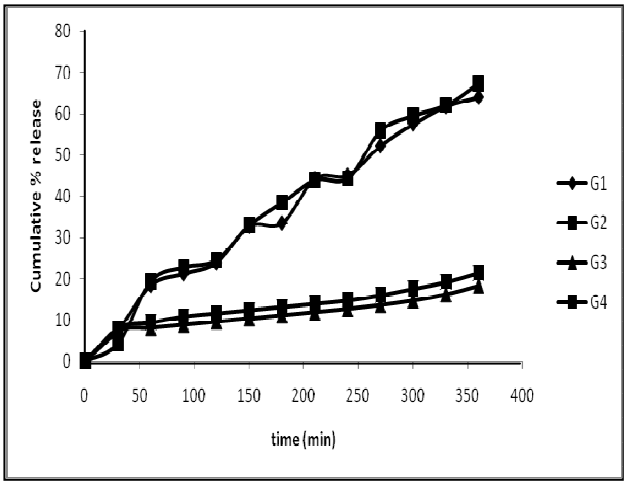

Figure 2: Comparison of in vitro release profile of gellan gum formulations

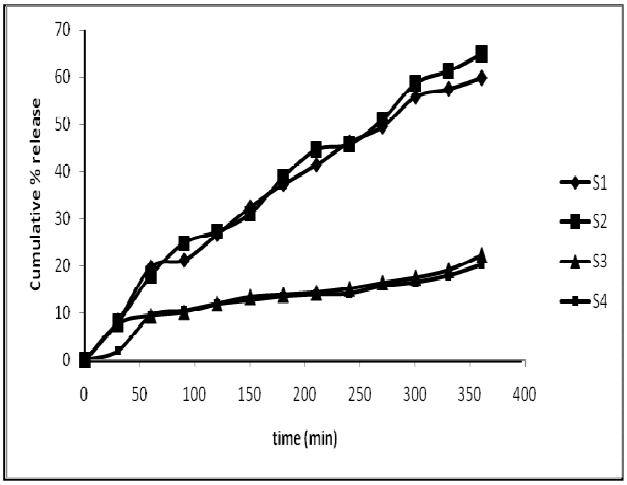

Figure 3: Comparison of in vitro release profile of sodium alginate formulations

The release studies thus reports that all the formulations are suitable for sustained delivery systems but the release rate of G3, G4, S3 and S4 was found to be too retarded because of which the administered drug may not reach the systemic circulation at high enough concentration where as the other formulations G1, G2, S1 and S2 retarded the release at desirable rate. The G2 and S2 formulations having the same rate of release as that of G1 and S1, had good gelling strength property compared to G1 and S1, which makes them the best suitable formulations for further studies.

Diffusion Studies

Once the drug gets released from the formulation into the surrounding media, it may reach systemic circulation or get excreted as such or as metabolite, for a drug to act it must reach the systemic circulation. So diffusion studies are carried to find out the amount of drug that reaches systemic circulation via diffusion through mucosal layer of the GIT. The studies were carried as discussed earlier using franz diffusion cell and diffusion co–efficient for 1% w/v gellan gum and 1% w/v Sodium alginate formulation calculated is reported as 2.5488 x 10^{-7} and 3.9648 x 10^{-7} cm^2/Sec respectively**.** The 1% w/v gellan gum having the greater D showed better diffusion of the drug compared to 1% w/v sodium alginate.

Water uptake studies

According to ficks law, the release of drug is directly associated with penetration of water into the matrix of gel. Simple weight analysis was performed which shows initial increase of water uptake followed by a decrease in same which may be due to collapse of gel structure with time. The 1% w/v gellan gum had higher water uptake compared to 1% w/v sodium alginate which may be one of the reason for better release and diffusion of the drug from gellan formulations.

Table 3: *In vitro* release studies of gellan gum and sodium alginate formulation

Time (min)	Cumulative Percentage Release (%) *							
	G1±SD	G2±SD	G3±SD	G4±SD	S1±SD	S2±SD	S3±SD	S4±SD
0	0	0	0	0	0	0	0	0
30	7.66±0.02	4.33±0.018	7.33±0.040	8±0.016	8.33±0.006	8±0.043	7.66±0.012	2±0.013
60	18.41±0.013	19.4±0.019	8.07±0.013	9.41±0.031	19.75±0.026	18.08±0.008	9.41±0.017	9.41±0.026
90	21.18±0.033	22.83±0.027	8.82±0.024	10.84±0.011	21.18±0.014	24.86±0.016	10.17±0.028	10.5±0.017
120	23.95±0.014	24.6±0.014	9.57±0.033	11.61±0.021	26.62±0.031	27.28±0.024	11.93±0.030	11.94±0.011
150	32.74±0.021	33.05±0.012	10.33±0.044	12.39±0.013	32.41±0.029	31.07±0.035	13.38±0.016	12.72±0.023
180	33.53±0.017	38.51±0.008	11.1±0.051	13.18±0.040	37.21±0.018	38.86±0.026	13.85±0.011	13.51±0.014
210	44.32±0.037	43.97±0.023	11.87±0.016	13.97±0.059	41.34±0.012	44.66±0.017	14.31±0.010	13.91±0.016
240	45.13±0.044	44.44±0.040	12.65±0.022	14.77±0.007	46.16±0.012	45.8±0.013	15.12±0.025	14.11±0.022
270	52.23±0.044	56.02±0.026	13.59±0.022	16.01±0.016	49.47±0.012	51.09±0.029	16.38±0.041	15.7±0.020
300	57.51±0.015	59.6±0.019	14.69±0.019	17.6±0.014	55.78±0.016	58.71±0.031	17.46±0.031	16.53±0.017
330	61.78±0.019	62.19±0.016	16.14±0.012	19.19±0.027	57.43±0.042	61.34±0.030	19.06±0.070	17.9±0.016
360	64.06±0.046	69.46±0.011	18.25±0.025	21.45±0.033	59.75±0.015	64.98±0.006	22.19±0.018	20.18±0.030

*n=3

CONCLUSION

The study reports that both the gellan gum and sodium alginate have the potential to form the gel *in situ* in contact with gastric pH and also have the ability of sustain the release of the famotidine beyond 6 h which is desirable for better treatment of gastric and duodenal ulcers in cases of reflux oesophagitis where acid secretion continues. With various parameters studied the 1% w/v solutions of gellan gum and sodium alginate were found ideal in formation of rigid gel at the gastric pH but gellan gum was found best among the two. With this we conclude that the administration of famotidine as *in situ* gel formulation using gellan gum will definitely improve the patient compliance especially for those suffering with reflux oesophagitis.

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