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Formulation and evaluation of a bilayer floating drug delivery system of nizatidine for nocturnal acid breakthrough.

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RESUMEN

Objetivo: El presente trabajo tiene como objetivo desarrollar un sistema de comprimidos bicapa flotantes de nizatidina para el tratamiento de la acidosis nocturna tras comidas ricas en grasas y en casos de excesos de secreciones ácidas nocturnas relacionadas con ciclos circadianos que regulen dichas secreciones.

Métodos: La formulación comprende dos capas por comprimido. Una de ellas es de liberación inmediata y otra es de una matriz flotante. Los comprimidos bicapa se obtuvieron combinando distintos polímeros y excipientes efervescentes. Los polímeros empleados producen una estructura de gel mientras que el bicarbonato de sodio se eligió como generador de gas necesario para producir el efecto de flotación.

Resultados: Las siguientes características de los comprimidos fueron evaluadas: uniformidad de peso, resistencia a la fractura, friabilidad, contenido en principio activo, flotabilidad in vitro y velocidad de disolución. Las características físico-químicas de los comprimidos son correctas. Todos los lotes estudiados demostraron tener buenas propiedades de flotación in vitro. Los comprimidos se hincharon de forma radial y axial y en la formulación seleccionada se consiguió una liberación del 98% del compuesto activo durante 8 horas. En dicha formulación se obtuvo un tiempo inicial de latencia para obtener flotación de 25 segundos pasados los cuales comenzó a flotar y se mantuvo durante la liberación del fármaco.

Conclusiones: Se consigue un sistema de liberación bimodal con una primera fase de liberación inmediata con una acción rápida seguida de una liberación controlada útil para el tratamiento de la acidosis nocturna.

PALABRAS CLAVE: Comprimidos bicapa flotante, Sistema de gastroretención, Nizatidina, Acidosis nocturna.

ABSTRACT

Aim: The present work aims to develop a bilayer floating drug delivery system intended for release of drug to provide relief from acid secretion in response to fatty meals as well as to attenuate the ''nocturnal acid breakthrough" seen to occur in patients in response to circadian rhythm to gastric acid secretion.

Materials and Methods: The formulation comprises of a bilayer tablet with an immediate release layer and a floating matrix layer. Bilayer floating tablets of nizatidine were prepared employing different types of polymers by effervescent technique; these polymers were evaluated for their gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent.

Results: The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in-vitro* buoyancy and dissolution studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good in vitro buoyancy. The tablets swelled radially and axially during in vitro buoyancy studies. Optimized formulation released more than 98% drug in 8 h in vitro, while the floating lag time was 25 s and the tablet remained floatable throughout the studies.

Conclusions: Thus the bimodal drug release comprising of immediate release for quick onset of action followed by controlled release to attenuate the nocturnal acid breakthrough was achieved.

KEY WORDS: Bilayer floating tablets, Gastroretentive drug delivery system, Nizatidine, Nocturnal acid breakthrough.

INTRODUCTION

Nizatidine is a histamine H_2-receptor antagonist. It is widely prescribed in active duodenal ulcers, gastric ulcers, ulcerative esophagitis, gastroesophageal reflux disease, heartburn and erosive esophagitis. In active duodenal ulcer the recommended oral dosage for adults is 300 mg once daily at bedtime. An alternative dosage regimen is 150 mg twice daily. For maintenance of Healed Duodenal Ulcer the recommended oral dosage for adults is 150 mg once daily at bedtime. In Gastroesophageal Reflux Disease the recommended oral dosage in adults for the treatment of erosions, ulcerations, and associated heartburn is 150 mg twice daily. However, the recent failure of proton pump inhibitors to prevent night-time gastric acid surge (which is associated with high nocturnal histamine concentration) brings open a new door for delivery of nizatidine at specific times in relation to onset of symptom.

Normal gastric acid secretion follows a circadian rhythm with a sudden surge of gastric acidity when gastric pH level goes far below 4 for at least 1 h during the midnight. Coughing, breathlessness, heart burn, wheezing and morning phlegm are common symptoms frequently reported during this time. This pathophysiological condition is termed as nocturnal acid breakthrough (NAB). NAB is one of the main reasons of treatment failure in gastro esophageal reflux disease (GERD) compromising therapeutic goals in patients. Hence, a bed-time dosing of H2 antagonist from a bilayer floating delivery system would be a promising therapeutic regimen.

The controlled release drug delivery systems possessing the ability of being retained in the stomach are called as gastroretentive drug delivery system. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation, sedimentation, expansion, modified shape systems or by the simultaneous administration of pharmacological agents that delay gastric emptying. Nizatidine is absorbed from the upper gastrointestinal tract and it is preferentially localized in parietal cells of gastric mucosa. The short half life (1-2 h) and rapid clearance of nizatidine also suggests that it is a rationale drug for gastroretentive drug delivery. The high solubility, chemical and enzymatic stability and absorption profile of nizatidine in acidic pH values (of stomach), points to the potential of gastroretentive dosage form.

It is also reported that oral treatment of gastric disorders with an H2-receptor antagonist such as nizatidine in form of gastro retentive drug delivery promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion. The present works aims to design gastroretentive drug delivery system for nizatidine that could give site specific and bimodal controlled drug release.

MATERIALS AND METHODS

Materials

Nizatidine was received as gift sample from Lupin Research Park, Pune, India. Hydroxypropyl methylcellulose (HPMC, K4M, K15M, K100M) and Carbopol 934p were a gift sample from Colorcon Asia Private Limited; Goa, India. Crospovidone was purchased from Ana lab Fine Chemicals, Mumbai, India. Lactose and magnesium stearate were purchased from SD Fine Chemicals, Mumbai, India). All other chemicals used were of analytical grade.

Method

Preparation of bilayer tablets with floating matrix layer

Bilayer tablets consist of floating matrix layer (FML) as bottom and immediate release layer (IRL) as top layer. IRL contained: nizatidine (75 mg), crospovidone (10 mg), lactose (31.5 mg), magnesium stearate (3 mg) and color (erythrocine 0.5 mg). Ingredients of FML (table 1) were weighed, mixed homogeneously and directly compressed in a die (10 mm diameter). The bottom layer was first compressed with lower pressure, which was then followed by filling of the die cavity by the upper layer powder then final compression was done. Both the layers were identified on the basis of color since the immediate release layer had pink color and the floating matrix layer had white color. The tablets were round and flat with an average diameter of 10 ± 0.1 mm and thickness of 6 ± 0.3 mm.

Flow properties of powder blend of formulation

The flow property of powder blend (before compression) was characterized in terms of angle of repose, bulk density, tapped density and Carr's index. For determination of angle of repose (θ), the powder was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The powder was poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of the (height of the pile / radius of its base) gave the angle of repose. Powder was poured gently through a glass funnel into a graduated cylinder cut exactly to 10 mL

Table 1. Composition of Bilayer floating tablets of Nizatidine.

Ingredient (mg per tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Immediate Release Layer												
Nizatidine	75	75	75	75	75	75	75	75	75	75	75	75
Cros povidone	10	10	10	10	10	10	10	10	10	10	10	10
Lactose	31.8	31.8	31.8	31.8	31.8	31.8	31.8	31.8	31.8	31.8	31.8	31.8
Mg. stearate	3	3	3	3	3	3	3	3	3	3	3	3
Colour	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Floating Matrix Layer												
Nizatidine	75	75	75	75	75	75	75	75	75	75	75	75
Carbopol 934	70	80	90	-	-	-	-	-	-	-	-	-
HPMC K100M	-	-	-	70	80	90	-	-	-	-	-	-
HPMC K15M	-	-	-	-	-	-	70	80	90	-	-	-
HPMC K4M	-	-	-	-	-	-	-	-	-	70	80	90
Sodium bicarbonate	40	40	40	40	40	40	40	40	40	40	40	40
Lactose	52	42	32	52	42	32	52	42	32	52	42	32
Citric Acid	10	10	10	10	10	10	10	10	10	10	10	10
Mag. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Total in mg	370	370	370	370	370	370	370	370	370	370	370	370

mark. Excess powder was removed using a spatula and the weight of the cylinder with powder required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume. Bulk density (V_B) and tapped density (V_T) were calculated. Carr's index (C) was calculated according to the equation given below:

$$C = \frac{VB - VT}{VB} \times 100$$

Evaluation of floating tablets

The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester), friability using 10 tablets (Roche type friabilator, drug content, *in vitro* buoyancy[1-2], swelling index and *in vitro* dissolution studies. The results are expressed as mean ± S.D. (n=6).

***In vitro* buoyancy**

It was determined by floating lag time. The tablets were placed in a 100 mL beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

The drug content

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100 mL of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45 µm membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 313 nm using 0.1 N hydrochloric acid as blank.

Swelling index

Average weight of tablets was calculated and placed in dissolution medium containing acetate buffer pH 4.5 in dissolution apparatus, Then each tablet was removed at an interval of 0.5, 1, 2, 3, 4, 6 and 8 h, and excess water was removed by using filter paper and swelled tablets again weighted , % swelling were calculated by using following formula.

$$\% \text{ Swelling} = \frac{W2 - W1}{W2} \times 100$$

W1=Average initial wt. of tablet.

W2= Average final wt. of tablet.

Dissolution studies

Drug release from tablets was performed by using United States Pharmacopeia (USP) type II dissolution testing apparatus (Electrolab TDT-06P, Mumbai) in 900 mL of 0.1N HCl solution with agitation speed (50 rpm) at 37± 0.5°C. Samples were withdrawn at appropriate times and analyzed spectrophotometrically at 313 nm. Cumulative percentage drug release was calculated.

RESULTS

Flow properties of granules

The powder blend prepared for compression of floating

tablets was evaluated for their flow properties. The bulk density of the powder formulation was in the range of 0.31-0.37 g/mL; the tapped density was in the range of 0.36-0.44 g/mL, which indicates that the powder was not bulky. The angle of repose of drug powder was in the range of 24.11^0 - 30.64^0, which indicate good flow properties, the Carr's index was found to be in the range of 14-15, indicating that compressibility of the tablet blend is good.

Evaluation of floating tablets

Size of tablets was found to be 10 ± 0.08 mm. Thickness of tablets was found to be 6 ± 0.02 mm for all the formulations. Hardness of tablets of each formulation was measured and was found in the range of 7-8 kg/cm^2. Percentage weight loss of the tablets of each formulation was measured and was found to be less than 1% for all the formulations. Tablets from each batch showed uniformity of weight as per Indian Pharmacopeia[3] (I.P.) limits. Average weight of the tablet was found to be 370 ± 0.26 mg for all formulations. All tablets formulations showed 98.27 ± 0.63 to 101.45 ± 0.50% drug content. Tablets from each batch showed uniformity of content as per I. P. limits.

All the batches of tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid. The tablets with low-viscosity grade HPMC K4M exhibited short floating lag time and floated for longer duration as compared with formulations containing high viscosity grade HPMC (K15M, K100M) and Carbopol 934p as shown in table 2. This indicated that the molecular weight distribution or viscosity of the gel-forming polymer HPMC influenced the *in vitro* buoyancy. A combination of sodium bicarbonate (40 mg) and citric acid (10 mg) with HPMC K4M (70 mg) was found to achieve optimum *in vitro* buoyancy and floatability.

The values of swelling index of formulated tablets indicate that HPMC shows satisfactory swellability. Formulation (F10) using 70 mg polymer concentration showed maximum swelling (Figure-2) of 65% within the 1st hour itself and 209% in 8 h, which could be useful to retain tablet in the upper gastrointestinal tract as it would not be able to pass through the pylorus (diameter ≈ 1.2-1.4 cm). Figures 1 and 2 also indicate that HPMC hydrated more rapidly than Carbopol 934p in presence of 0.1N HCl.

All the formulations contain equal amount of gas generating agent (sodium bicarbonate and citric acid). The formulation F1-F3 containing (Carbopol 934p, 70-90 mg) tablets could not bear their matrix shape until 8 h and release the drug within 4 h. The drug release from HPMC K100M and HPMC K15M (F4-F9) was about (89-91%). A significantly higher rate and extent of drug release (98%) was observed from the formulations based on HPMC K4M (F10-F12).Varying amount of HPMC K4M affect the drug release[4]. The formulations containing Carbopol 934p (F1-F3) released the drug more rapidly than formulations containing HPMC. The formulations containing HPMC K100M (F4-F6) and K15M (F7-F9) sustain the drug release for longer time. Tablet formulation containing HPMC K4M (70 mg) i.e. Formulation F10 showed the desired drug release profile (98.80%) up to 8 h.

The data obtained from *In –Vitro* dissolution study were fitted into different models *viz.,* Zero order, first order and Korsmeyer's-Peppas[5-6]. In the present study diffusion exponent ranges from minimum 0.177 to maximum 0.203

Table 2. Floating lag time and total floating time.

Formulation code	Floating lag time (s)	Total floating time (h)
F1	160	2.10
F2	142	3.5
F3	120	4.09
F4	25	7.5
F5	60	8
F6	90	>8
F7	30	7.5
F8	45	7.5
F9	69	8
F10	20	>8
F11	38	>8
F12	45	>8

Table 3. Kinetics of in-vitro nizatidine release from floating tablet.

Formulation	r^2		
	Zero order	First order	Korsmeyer Peppas
F1	0.7965	0.9658	0.9892
F2	0.6852	0.9141	0.9829
F3	0.6502	0.9209	0.9932
F4	0.4189	0.8074	0.9806
F5	0.6625	0.7278	0.9885
F6	0.4825	0.6456	0.9931
F7	0.5838	0.8463	0.9845
F8	0.4944	0.8462	0.9927
F9	0.6914	0.7987	0.9926
F10	0.7894	0.8989	0.9942
F11	0.7965	0.8705	0.9786
F12	0.6852	0.8944	0.9875

Figure 1. Swelling behaviour of formulations F1- F6

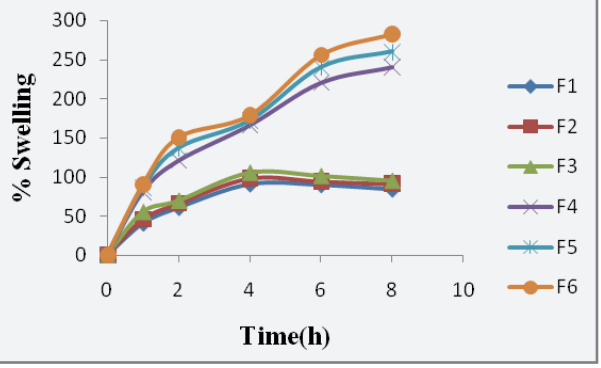
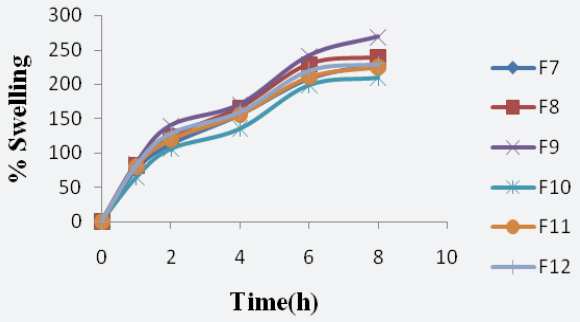


Figure 2. Swelling behaviour of formulations F7- F12.



therefore release of all formulations is mainly by Non-Fickian release. It indicates a coupling of the diffusion and erosion mechanism so called anomalous diffusion and may indicate that the drug release is controlled by more than one process. The best fit model for prepared formulation follows Korsmeyer's-Peppas model (r^2= 0.9942) and n value was found to be 0.183 which signified that release pattern of optimized batch F10 follows the Non Fickian diffusion as shown in tables 3 and 4.

DISCUSSION

As the amount of HPMC was increased, the release of drug prolonged and increasing the viscosity grade of HPMC, the release of drug was more sustained. This is due to the greater amount of gel being formed. This gel increases diffusion path length of the drug. HPMC swells by absorbing water and forms a swollen layer barrier for drug to diffuse through this layer. As proportion of HPMC in tablet is increased, thickness of the diffusion barrier layer increases. This results in reduced drug release. Higher grade of hydroxypropyl methylcellulose had higher water absorbing capacity than its lower grade counterpart. As the amount of HPMC was increased the water retaining capacity also increased which led to higher percentage of water uptake. Thickness, length and width was found to increase in swelling behavior study. Diffusion of drug significantly depends on the water content of the tablet. This may be because the mobility of the polymer chains strongly depends on the water content of the system. At high water content, polymer chain relaxation takes place with volume expansion giving high swelling to the system. Also this high water content could predict the higher penetration of the gastric fluid into the tablet leading to faster CO_2 gas generation and thus reducing the floating lag time. Consequently, faster and higher swelling of the tablet led to increase in dimensions of the tablet. The sustained release and floating tablet formulation showed Korsemeyer-Peppas model for dissolution and anomalous transport mechanism.

Table 4. Dissolution kinetics (*n=6).

Formulation	% Total Cumulative Release*	Time for Release (h)	Best Fit model	Regressio Coefficient (r^2)	N	K
F1	100.69± 0.18	3	Korsmeyer Peppas	0.9892	0.203	35.474
F2	100.42± 0.23	4	Korsmeyer Peppas	0.9829	0.180	37.647
F3	100.7± 0.53	4	Korsmeyer Peppas	0.9932	0.186	34.854
F4	89.37± 0.56	8	Korsmeyer Peppas	0.9806	0.192	25.427
F5	86.30± 0.34	8	Korsmeyer Peppas	0.9885	0.189	25.521
F6	84.91± 1.07	8	Korsmeyer Peppas	0.9931	0.183	26.457
F7	94.11± 0.34	8	Korsmeyer Peppas	0.9845	0.185	27.433
F8	92.61± 0.21	8	Korsmeyer Peppas	0.9927	0.202	25.080
F9	91.17± 0.24	8	Korsmeyer Peppas	0.9926	0.198	25.771
F10	98.80± 0.94	8	Korsmeyer Peppas	0.9942	0.183	28.110
F11	97.13± 0.87	8	Korsmeyer Peppas	0.9786	0.177	29.535
F12	95.99± 1.04	8	Korsmeyer Peppas	0.9875	0.192	27.360

CONCLUSIONS

In this study nizatidine bilayer floating gastro retentive tablets were successfully prepared by using various polymers and gas generating agent. The immediate release layer released drug within 1 h and floating matrix layer sustained release up to 8 h. The Non-Fickian transport of nizatidine from tablet was confirmed. The optimized batch F10 showed satisfactory floating as well as release characteristic.

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