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Research Article

FORMULATION AND EVALUATION OF FLOATING TABLETS OF TIZANIDINE HYDROCHLORIDE

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ABSTRACT
The objective of the present investigation was to develop floating matrix tablets of tizanidine hydrochloride for prolongation of gastric residence time in order to overcome its low bioavailability (34–40%) and short biological half life (4.2 h). Tizanidine hydrochloride floating tablets were prepared by the direct compression method, using different viscosity grades of hydroxypropylmethylcellulose (HPMC K4M and K15M). Tizanidine hydrochloride is an orally administered prokinetic agent that facilitates or restores motility throughout the length of the gastrointestinal tract. Tablets were evaluated for various physical parameters and floating properties. Further, tablets were studied for in-vitro drug release characteristics in 12 hours. Drug release from floating matrix tablets was sustained over 12 h with buoyant properties. DSC study revealed that there was no drug and excipient interaction. Based on the release kinetics, all formulations best fitted the Higuchi, first-order model and non-Fickian as the mechanism of drug release. The optimized formulation (F9) released 75% of drug at the end of 10 hours by in-vitro release study.
Keywords: Tizanidine hydrochloride, Gastroretentive drug delivery system, Floating tablets

INTRODUCTION

Effective gastroretentive drug delivery systems (GRDDS) depend upon the factors such as the gastric emptying process, gastrointestinal transit time of the dosage form, drug release from the dosage form and the site of drug absorption. Rapid GI transit leads to incomplete drug release from the dosage form in the absorption zone. This led to the development of GRDDS. Several approaches cited in the literature[1-4] include mucoadhesion, swelling or expansion, modified shape systems, floatation, gastric emptying delaying devices[5] or simultaneous administration of gastric emptying delaying drugs. Among the various approaches, the floating drug delivery systems offer the most effective, simple and practical approach to achieve increased gastric residence time and sustained drug release compared to the other methods[4]. Based on the mechanism of buoyancy, non-effervescent and effervescent technologies have been utilized in the development of floating drug delivery systems (FDDS). Non effervescent systems commonly use gel-forming or highly swellable cellulose type hydrocolloids. Effervescent systems utilize swellable polymers and inclusion of gas generating agents, i.e., sodium bicarbonate and citric or tartaric acid[6].

Tizanidine hydrochloride is an imidazoline derivative, which acts as agonist on centrally located α2 receptors and this leads to myotonolytic effects on skeletal muscle. It is structurally and pharmacologically similar to clonidine and other α2-adrenergic agonists. The correct mechanism of tizanidine in decreasing muscle tone and frequency of spasm is not clearly understood. About 53% to 66% of the dose administered is being absorbed through the gastrointestinal tract after oral administration and the peak plasma concentration is reached within 1 to 2 h. Bioavailability of tizanidine is about 34% to 40% and half-life is 2.5 h. The drug is widely distributed throughout the body and 30% of drug binds to plasma proteins. It undergoes rapid and extensive first pass metabolism in the liver (approximately 95% of a dose), leading to the oxidation of the imidazoline moiety, aromatic system, and the sulfur atom. Tizanidine is least absorbed from the lower part of the gastrointestinal tract and better absorbed from the stomach. The main limitations of the therapeutic effectiveness of tizanidine hydrochloride is its low bioavailability (30–40%), short biological half life (4.2 h) and the fact that it undergoes first pass metabolism. Thus, tizanidine hydrochloride is a candidate for the development of GRDDS. In the present study, the details of formulation development and

evaluation of effervescent floating tablets of tizanidine hydrochloride are described.

MATERIALS AND METHODS

Tizanidine hydrochloride was a gift sample from Sun Pharma Pvt. Ltd, India. Hydroxypropyl methylcelluloses (HPMC K4M and K15M) were gift samples from Danmed Pharmaceuticals, India. Microcrystalline cellulose was obtained from Aurabindo Laboratories, India. Sodium bicarbonate and magnesium stearate were purchased from S.D. Fine Chem. Ltd, India. All other chemicals used were of analytical grade.

Methods

Tizanidine hydrochloride floating tablets were prepared by direct compression method using different viscosity K-grade HPMC polymers such as K4M and K15M. The powder mixture containing drug, polymers (HPMC K4M and HPMC K15M) and other excipients including talc 1% as lubricant was blended thoroughly in mortar and pestle and passed through sieve no. 100. Then the mixture was compressed using 8mm flat faced punch on Cemach 12 station tablet compression machine. Ten formulations were prepared and coded them F1 to F10. The detail of composition of each formulation is given in Table 1.

EVALUATION

Angle of repose

Angle of repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (Q) was calculated using the formula.

$Q = \tan^{-1} (h/r)$

Bulk density

Apparent bulk density (p_b) were determined by pouring the blend in to a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated using the formula.

$p_b = M/ V_b$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend were measured. The tapped density (ρ_t) was calculated using formula.

$\rho_t = M/ V_t$

Compressibility index

The simplest way for measuring of free flow of powder was compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (I) was calculated as follows.

$I = V_0 - V_t/V_O \times 100$

Where,Vo is the bulk volume and Vt is tapped volume.

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by the following method.

Hausner ratio = ρ_t/ρ_d

Where, ρ_t tapped density and ρ_d bulk density lower hausner ratio.

Weight variation

Twenty tablets were selected randomly from each formulation and weighed individually using an electronic balance to check the weight variations as per pharmacopoeia.

Friability

Friability of the tablets was determined using Roche friabilator.

Hardness

Hardness of the tablets was measured using Monsanto tester.

Thickness

Ten tablets were taken from each formulation and their thickness was measured using digital vernier calipers.

Drug content estimation

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to the average mass of one tablet was added in 100 ml 0.1N HCl, followed by sonicating for 2 hours. The drug content was estimated by recording absorbance at 319 nm using a UV-Visible spectrophotometer.

In-vitro buoyancy studies

The *in-vitro* buoyancy was determined by floating lag time, as per the method described by Rosa et al [7]. The tablet was placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface for floating was defined as the floating lag time and total duration of time the tablet remained buoyant was defined as total floating time.

In-vitro drug release studies

The release of tizanidine hydrochloride from floating tablets was studied using a USP type II paddle dissolution apparatus (Electro Lab, India). The dissolution test was performed using 900 ml 0.1N HCl maintained at 37±0.5°C and a rotation speed of 50 rpm. Aliquots of 5 ml were collected at predetermined time intervals, filtered through a 0.45mm membrane filter and replenished with an equivalent volume of fresh dissolution medium. Drug content in the samples was determined at 319 nm after suitable dilutions[8].

Drug release kinetics

The rate and mechanism of drug release was analyzed by fitting the dissolution data into several mathematical models, zero-order, first-order, Higuchi and Peppas[9–12]. Dissolution profiles were compared with the similarity

factor using the theoretical release profile as a reference[13-14].

Differential scanning calorimetry (DSC)

The physicochemical compatibilities of the drug and excipients used were tested by performing DSC analyses of pure drug and optimized formulation (F9). DSC curves of the samples were obtained with a differential scanning calorimeter (DSC, Perkin Elmer, USA). 2- 4 mg of sample was placed in an aluminum pan and then crimped with an aluminum cover. Heating and cooling rates were 10 and 250°C, respectively.

RESULTS AND DISCUSSION

The present study was aimed at not only to improve the release of drug, tizanidine hydrochloride in the acidic pH, but also to release the drug in controlled fashion. Also, to make the formulation remain in the stomach for longer period of time, gastroretentive dosage form was designed, to make the therapy more effective. The shape of the tablets of all formulations was round and flat with no visible cracks. The granules of different formulations were evaluated for angle of repose, compressibility index, and drug content. The results of angle of repose ($26^0.74'$ to $29^0.36'$) indicate reasonably good flow property of granules. The compressibility index values in the range of 11.2% to 15.9% (< 25) were shown in Table 2. Physical characteristics of the formulated tablets were shown in Table 3. To avoid processing variables, all batches were produced under similar conditions. The mean hardness of the tablets was 4.2±0.6 kg cm^{-2}, average mass variation was 182 ± 4 mg, mean thickness was 3.3±0.4 mm and friability ranged from 0.5 to 0.7%. The content uniformity of the tablets was 98.9±2.3%. Whitehead *et al* [16] had demonstrated good correlation between in vitro and in vivo buoyancy of floating dosage forms. Their results showed that increasing concentration of sodium bicarbonate decreased the floating lag time. In this study, penetration of water into tablets with low viscosity HPMC K4M was slow, causing delayed gel formation and subsequent increase in the floating lag time and decreased total floating duration (< 8 hours) compared to the tablets prepared with K15M and K4M. F9 showed the best floating lag time of 120±5. With the exception of formulations F1 to F5, all the formulated tablets were buoyant for more than 12 hours. The DSC curves of pure drug and optimized formulation (F9). A sharp endothermic peak was observed at 290.1°C, indicating the melting point of tizanidine hydrochloride. In the DSC thermogram of optimized formulation, the peak was observed at 284.7°C. This finding clearly indicates there was no interaction between the drug and excipients used in the formulation. By using pharmacokinetic parameters of tizanidine hydrochloride, the theoretical drug release for a 12 hours dosage form was calculated. An effective drug plasma concentration was maintained when the sustained release formulation released the required quantity of drug with predetermined kinetics. To achieve this, floating tablets should be formulated so that they release the drug in a predetermined and reproducible manner. The release of tizanidine hydrochloride from floating tablets was analyzed by plotting the cumulative percent drug release against time. The in-vitro drug release studies revealed that formulations F1 to F5 using HPMC K4M the drug release after 6 hours was 97%, 92%, 86%, 85% and 75% , respectively, were able to sustain the drug release for 8 hours, respectively were shown in Table 4 and Figure 1. Floating lag time was 125 to 140 seconds; total buoyancy was > 12 hours and tablet integrity was poor for HPMC K4M formulations. Drug release profiles of formulations F6 to F10 using HPMC K15M the drug release after 10 hours was 92%, 86%, 82%, 75% and 79% respectively were shown in Table 5 and Figure 2. Formulation F8 underwent swelling and erosion, resulting in faster drug release. In F9, 75% of HPMC K15M was sufficient to sustain the drug release for 12 hours. It was observed that when the polymer concentration was increased, the drug release rate decreased. Formulation F9 matched the theoretical release profile and floating lag time of 120 seconds; for these reasons, F9 was considered the best among all the formulations. This variation was considered to be due to different polymer concentrations. Release of the drug was faster with lower viscosity grades of HPMC (K4M) due to lower gel strength, less entanglement and smaller diffusion path length compared to higher viscosity grades of HPMCs. In all the formulations, polymer concentration greatly affected the release of the drug. The drug release rate was inversely proportional to the polymer concentration present in the matrix.

The results of kinetic models for tizanidine hydrochloride release from floating matrix tablets. The coefficient of determination (R^2) was used as indicator of the best fitting for each of the models considered. The results revealed that all formulations of floating matrix tablets fitted best the Higuchi[9] (0.9220), zero order (0.9220) and first order models[10] (0.9888). To explore the mechanism of drug release, the results of in-vitro data were fitted into the Korsmeyer and Peppas equation (Mt / M_ = ktn, where Mt/M is the fraction of drug released at infinite time, k is the kinetic constant and *n* is the diffusional exponent indicative of the mechanism of drug release)[11, 12] characterizing the transport mechanism. The value of n = 0.74, indicating release governed by the non-Fickian diffusion mechanism. The optimized

formulation was selected based on the similarity factor (f2)[14] value, when compared with the theoretical release profile, was found to be 75%, which was higher than for other formulations.

CONCLUSION

The present study was conducted to develop an effervescent floating drug delivery system using two different grades of hydroxypropylmethylcellulose (HPMC K4M and K15M) in different concentrations. Optimized formulation F9 showed an excellent buoyant ability and a suitable drug release pattern. This could be advantageous in terms of increased bioavailability of tizanidine hydrochloride. The developed gastroretentive drug delivery system provides advantages of ease of preparation and sustained drug release for 12 hours.

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TABLE 1: FORMULATIONS OF TIZANIDINE HCl FLOATING TABLET

Ingredients	F 1	F2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10
Tizanidine hydrochloride	10	10	10	10	10	10	10	10	10	10
HPMC K4M	70	60	50	40	30					
HPMC K15M						70	60	50	40	30
Sodium bicarbonate	36	36	36	36	36	36	36	36	36	36
MCC	58	68	78	88	98	58	68	78	88	98
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4
Total Weight (mg)	180	180	180	180	180	180	180	180	180	180

TABLE 2: EVALUATION OF GRANULES

Formulations	Angle of Repose (Q)	Compressibility Index (%)	Hausner Ratio
F1	28^0. 70’	12.3	1.15
F2	29^0. 32’	15.9	1.19
F3	27^0. 64’	12.8	1.13
F4	28^0. 10’	15.7	1.17
F5	28^0. 46’	12.4	1.14
F6	27^0. 90’	11.2	1.13
F7	26^0. 74’	12.3	1.18
F8	28^0. 76’	12.3	1.15
F9	29^0. 36’	15.9	1.19
F10	27^0. 60’	12.8	1.13

TABLE 3: EVALUATION OF TIZANIDINE HCl FLOATING TABLETS

Formulations	Weight (mg)	Hardness (kgs)	Friability(%)	Thickness (mm)	Drug Content (%)	Floating Lag Time (sec)	Floating Time (hours)
F1	180.8±0.74	4.2±0.3	0.75±0.11	3.35±0.2	99.0±1.2	125	>12
F2	185.6±0.33	4.5 ± 0.3	0.72±0.15	3.36±0.2	98.02±3.2	128	>12
F3	184.7±0.14	3.8±0.2	0.74±0.21	3.36±0.2	98.2± 2.5	132	>12
F4	180.9± 0.28	4.4±0.2	0.70±0.45	3.36±0.2	97.28±3.1	140	>12
F5	182.3±1.14	4.2±0.6	0.68±0.1	3.35±0.2	99.12±0.5	132	>12
F6	184.6±0.85	4.4±0.7	0.58±0.05	3.36±0.2	99.06±0.9	130	>12
F7	180.4±1.01	3.6±0.1	0.64±0.12	3.34±0.2	97.07±3.5	142	>12
F8	184.1±0.52	4.2±0.4	0.63±0.11	3.35±0.2	98.01±3.4	138	>12
F9	184.2±0.34	3.8±0.2	0.59±0.14	3.34±0.2	98.01±0.8	120	>12
F10	180.1±0.48	4.2±0.4	0.62±0.21	3.46±0.2	100.2±2.4	148	>12

TABLE 4: IN-VITRO DRUG RELEASE STUDIES OF FLOATING TABLETS WITH HPMC K4M POLYMER

TIME (hours)	F1	F2	F3	F4	F5
0.5	22.1 ± 0.6	20.3 ± 1.2	19.4 ± 2.1	16.8 ± 2.5	10.7 ± 1.3
1	36.8 ± 2.1	29.4 ± 3.1	29.7 ± 1.3	25.8 ± 2.8	22.1 ± 1.2
2	54.8 ± 1.3	50.4 ± 2.6	48.7 ± 2.6	36.5 ± 3.6	28.2 ± 2.6
3	75.4 ± 2.3	59.6 ± 1.8	55.6 ± 3.2	49.8 ± 2.1	56.1 ± 3.2
4	81.3 ± 1.3	74.8 ± 1.6	72.5 ± 2.4	67.7 ± 2.4	64.1 ± 1.5
6	97.1 ± 2.5	92.0 ± 3.1	86.1 ± 3.5	85.1 ± 1.2	75.1 ± 1.9

Mean ± SD, *n* = 3.

TABLE 5: IN-VITRO DRUG RELEASE STUDIES OF FLOATING TABLETS WITH HPMC K15M POLYMER

TIME (hours)	F 6	F 7	F 8	F 9	F10
0.5	14.8 ± 2.5	12.9 ± 3.6	15.4 ± 2.1	8.1 ± 1.5	10.3 ± 1.5
1	22.7 ± 2.3	20.8 ± 2.5	23.3 ± 1.6	16.2 ± 2.4	18.8± 0.8
2	29.6 ± 2.6	33.7 ± 1.6	28.7 ± 1.5	22.5 ± 1.6	26.7 ± 3.4
3	45.9 ± 1.4	41.6 ± 2.5	38.6 ± 0.6	36.8 ± 3.4	42.8 ± 2.5
4	59.5 ± 2.6	63.2 ± 3.6	52.5 ± 2.6	48.0 ± 4.5	51.1 ± 2.6
6	74.7 ± 3.6	68.0 ± 1.8	66.3 ± 2.6	60.9 ± 2.6	63.8 ± 2.4
8	83.4 ± 4.5	79.7 ± 3.7	75.1 ± 2.7	68.1 ± 3.6	72.4 ± 3.5
10	92.1 ± 2.3	85.8 ± 4.5	81.6 ± 3.4	74.8 ± 4.5	79.4 ± 2.1

Mean ± SD, *n* = 3.

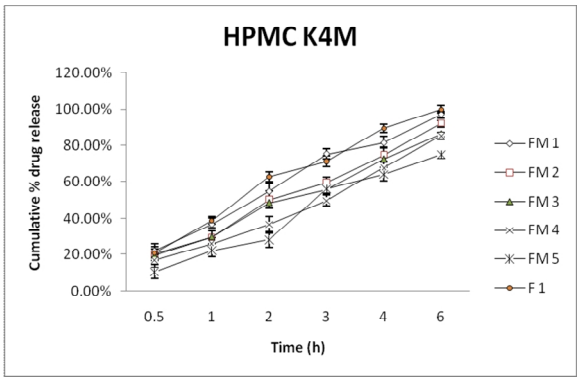

FIGURE 1: COMPARATIVE DRUG RELEASE PROFILE OF HPMC K4M FORMULATIONS (F1 TO F5)

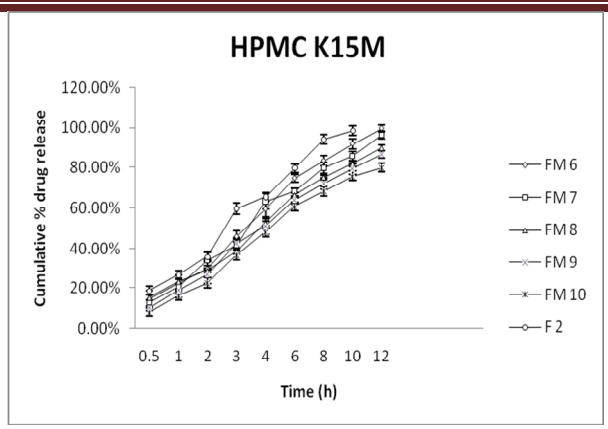

FIGURE 2: COMPARATIVE DRUG RELEASE PROFILE OF HPMC K15M FORMULATIONS (F6 TO F10)

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