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Research Article

Design and *In Vitro* Evaluation of Gastro Retentive Sustained Release Tablets of Tizanidine Hydrochloride

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ABSTRACT

Gastro retentive sustained release formulation of tizanidine hydrochloride based floating technology was developed and evaluated. The developed formulation is equivalent to commercial marketed product in view of its *in vitro* release. The developed formulation has an additional advantage like less steps of manufacturing procedure and is therefore economical. All of which made the procedure easily amenable to mass production using conventional tablet machines. Tizanidine hydrochloride floating tablet formulations were prepared with different compositions using different grade of polymers. Finally, one optimized formula for floating tablet was selected and studied in detail. The effect of formulation variables namely different polymers and concentration of polymer were studied. Tizanidine hydrochloride release was inversely proportional to the polymer concentration. Drug release from the developed formulations was dependent on the agitation intensity and hardness of tablet. Tizanidine hydrochloride release from the developed floating formulation follows first order and diffusion is found to be the main mechanism of drug release. The manufacturing procedure was found to be reproducible and formulations were stable after one month of accelerated stability studies.

INTRODUCTION

Conventional dosage forms, which are prompt release in nature, have been used from decades for the treatment of acute and chronic diseases. The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release, but also to prolong the presence of the dosage form in the stomach or the upper small intestine until the drug is completely released in the desired period of time [1]. Recently, several technical advancements have been made which results in new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and / or targeting the delivery of drug to a tissue. Sustained release pharmaceutical dosage forms may offer one or more advantages over conventional (immediate release) dosage forms of the same drug.

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Sustained release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidences of adverse drug reactions. Ideally, a sustained release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio. One of approach is gastro retentive drug delivery systems which target the drug release in stomach for those drugs which are absorbed from the stomach or specific site of action[2.] Gastro retentive drug delivery devices are primarily controlled release drug delivery systems, which gets retained in the stomach for longer period of time, thus helping in absorption of drug for the intended duration of time. This in turn improves bioavailability, reduces drug wastage, and improves solubility of drugs that are less soluble at high pH environment. It also helps in achieving local delivery of drug to the stomach and proximal small intestine. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs[3].

The drug chosen for the present investigation was Tizanidine hydrochloride. It is effectively used in the treatment of management of spasticity, indicated in muscle pain as muscle relaxant. Tizanidine hydrochloride approximately 30% bounds to plasma proteins and is metabolized by the primary cytochrome P_{450} isoenzyme involved is CYP1A2, the metabolites of tizanidine are not known to be active. Tizanidine hydrochloride has a biological half-life of 1 to 4.3 hours and bioavailability is 40%. Its daily oral dose is 6-12 mg/day in divided doses [4]. In the present investigation, efforts were made to develop a gastro retentive sustained floating formulation of tizanidine hydrochloride for the treatment of spasticity.

MATERIALS AND METHODS

Tizanidine hydrochloride was obtained from Lincoln pharmaceutical ltd., Ahmadabad. HPMC-K15M and HPMC-K100M were obtained from the Coral Pharmaceuticals, Ahmedabad. HPMC-K4M was obtained from Signet Chemicals, Japan. All the polymers received were of pharmaceutical grade and were used as received. Other materials and solvents used were of analytical grade. Distilled water was prepared in laboratory using all glass distillation apparatus.

Manufacture of tizanidine hydrochloride floating tablets

The direct compression technique was followed to manufacture the Tizanidine hydrochloride tablets for all batches [Table 1] containing Tizanidine hydrochloride. Sodium bicarbonate was passed through # 36 sieves. Magnesium stearate and Talc were passed through # 60 sieves. Weighed amounts of drug as well all other ingredients were transferred into polythene bag and blended for 10 minutes. The blend was compressed on 16-station rotary press using Round shaped punches. Punches measuring 32 x 9 mm were used for compression of the tablets.

Drug–excipients compatibility studies (FT-IR)

The pure drugs and excipients were subjected to IR studies alone and in combination. Pure drugs / pure excipients / combination of drugs excipients were mixed with 100 mg of potassium bromide. Mixing can be effected by thorough grinding in smooth mortar. The mixture was sending for IR sample holder and analyzed by FTIR. The spectra were run from 600 cm^{-1} to 4000 cm^{-1} wave number.

Evaluation of Powder Blend

Angle of repose

The angle of repose of Tizanidine hydrochloride powder was determined by funnel method (Reposogram) [5]. Accurately weighed Tizanidine-hydrochloride powder was taken in a funnel. Height of the funnel was adjusted in such a ways that tip of the funnel just touches the apex of the heap of the Tizanidine powder. The powder was allowed to flow through the funnel freely onto the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation;

$$\tan \theta = h / r$$

Where, *h* = height of the powder cone and
r = radius of the powder cone

Bulk density

Loose bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is [6].

Tapped density

Tapped density was determined by USP method II tablet blend was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula

$$Dt = M/Vb$$

Where, M = Weight of powder taken;
Vb = tapped volume.

Compressibility index and Hausner ratio

This was measured for the property of a powder to be compressed; as such they are measured for relative importance of interparticulate interactions. Compressibility index was calculated by following equation;

$$\text{Compressibility index (\%)} = \frac{(TBD - LBD)}{TBD} \times 100$$

Where, LBD = Loose bulk density,
TBD = Tapped bulk density

Evaluation of Tablets

The tablets were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight variation, hardness, friability and drug content.

Table 1: Formulation of Tizanidine hydrochloride Gastro retentive sustained release Tablets

Ingredients	F1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Tizanidine hydrochloride (mg)	6.87	6.87	6.87	6.87	6.87	6.87	6.87	6.87	6.87
Sodium bicarbonate (mg)	28	28	28	28	28	28	28	28	28
HPMC K4M (mg)	14	28	42	-	-	-	-	-	-
HPMC K15(mg)	-	-	-	14	28	42	-	-	-
HPMC K100 (mg)	-	-	-	-	-	-	14	28	42
Magnesium stearate (mg)	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Talc (mg)	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
Quinoline yellow (mg)	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
DCP (mg)	85.53	71.53	57.53	85.53	71.53	57.53	85.53	71.53	57.53
Total Weight (mg)	140	140	140	140	140	140	140	140	140

Table 2: Evaluation of powder blend of Tizanidine hydrochloride

SL. No	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose (θ)	Compressibility (%)
F1	0.556	0.667	24.78	16.67
F2	0.571	0.690	26.46	17.14
F 3	0.526	0.645	25.36	18.42
F 4	0.513	0.606	22.38	15.38
F 5	0.526	0.625	24.75	15.79
F 6	0.476	0.571	25.57	16.67
F 7	0.476	0.588	21.37	19.05
F 8	0.488	0.588	29.33	17.07
F 9	0.476	0.571	25.46	16.67

Table 3: Evaluation of Tablets of Tizanidine hydrochloride

SL. No	Floating lag time (Sec.) *	Hardness (kg/cm^2) **	Friability (%) *	Uniformity of weight, mg***	Drug content (%) *	Thickness (mm) **
F1	49 ± 4.36	5.75 ± 0.29	0.548 ± 0.15	140.05± 4.36	98.08 ± 1.19	2.63 ± 0.036
F2	36 ± 6.56	5.75 ± 0.47	0.549 ± 0.11	140.06±0.31	98.98 ± 2.29	2.64 ± 0.026
F 3	25.33 ± 1.53	5.67 ± 0.35	0.40 ± 0.04	140.02±0.20	100.44 ± 2.06	2.643 ± 0.02
F 4	46.66 ± 3.2	5.58 ± 0.29	0.38 ± 0.08	140.1±0.228	98.88 ± 0.96	2.613±0.028
F 5	38.33 ± 9.07	5.5 ± 0.23	0.355 ± 0.12	140.12±0.35	98.44 ± 0.41	2.645 ± 0.021
F 6	24 ± 2	5.67 ± 0.20	0.309 ± 0.04	140.09±0.34	100.44±0.27	2.637 ± 0.04
F 7	42.33±4.51	5.75 ± 0.24	0.356±0.072	140.07 ± 0.27	99.88 ± 1.92	2.604 ± 0.029
F 8	35.67±3.21	5.9 ± 0.235	0.378±0.11	140.03 ± 0.25	98.98 ± 0.82	2.625 ± 0.02
F 9	20 ± 1.73	6 ± 0.235	0.357±0.072	140.06 ± 0.27	100.44 ± 0.82	2.579 ± 0.016

*Each value was an average of three determinations; ** Each value was an average of six determinations; ***Results of one batch

Appearance

The tablet should be free from cracks, depressions, pinholes etc. The color and the polish of the tablet should be uniform on whole surface. The surface of the tablets should be smooth.

Dimensions

The dimensions of the tablets are thickness and diameter. The tablets should have uniform thickness and diameter. Thickness and diameter of a tablet were measured using vernier calipers. These values were checked and used to adjust the initial stages of compression.

Uniformity of weight

Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (± 7.5%). The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{average weight}}{\text{Average weight}} \times 100$$

Hardness

Hardness was measured using Pfizer hardness tester, for each batch six tablets were tested.

Friability

Twenty tablets were weight and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula.

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where, W_1 = weight of the tablets before test

W_2 = weight of the tablets after test

Content uniformity

Twenty tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately average weighed amount of tablets triturate was taken for analysis [7]. Samples were transferred to different volumetric flasks and were diluted up to the mark using 0.1 N HCl. The content was shaken well and kept for 30 minutes for dissolving the drug completely. The mixtures were filtered and appropriate dilutions were made. The drug content in each tablet was estimated at 320 nm.

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time as per the method described by the Samip et al. The tablets were placed in a 100 ml beaker containing 0.1 N HCl Solutions at 37 ± 0.5^0C. The time required for the tablet to rise to the surface and float was determined as floating lag time [8].

In vitro drug release studies

In vitro drug release study of the samples was carried out using USP – type II dissolution apparatus (Paddle type). The dissolution medium, 500 ml of simulated gastric fluid (without enzyme), was placed into the dissolution flask maintaining the temperature of 37 ± 0.5 ^{0}C and rpm of 100. One Tizanidine hydrochloride floating tablet was placed in each basket of the dissolution apparatus. The apparatus was allowed to run for 24 hours. Samples measuring 10 ml were withdrawn after every 1, 2, 4, 6, 8, 10, 12, 14, 18, and 20 hours using auto sampler. During sampling, samples were filtered through 10 µm filter which was in inline with auto sampler. The fresh dissolution medium (37^{o}C) was replaced every time with the same quantity of the sample. Collected samples were analyzed at 320 nm using 0.1 N HCl as blank. The cumulative percentage drug release was calculated [9].

Curve fitting analysis

Mathematical models, zero-order, first-order, Higuchi & Peppas were applied to analyze the release rate mechanism and pattern.[10]

Influence of different parameters on drug release

a) Effect of agitational intensity

It is necessary to check that the effect of agitational intensity on the drug release. To study the effect of agitational intensity (rpm) of the dissolution medium Release study was carried out at rotational speeds of 50, 75, and 100 rpm. Cumulative percentage drug release was calculated.

b) Effect of hardness of the tablet

It is necessary to see, whether the hardness of the tablets effects on the drug release or not. For

this study three types of tablets were prepared, with same powder blend and having same physical parameters but different hardness i.e. 6 kg/cm^2 (standard), less than 4 kg/cm^2 (less hardness) and more than 8 kg/ cm^2 (high hardness).

Swelling behavior and water uptake study

Swelling behavior and water uptake studies of Tizanidine hydrochloride tablets (F 9) was studied in de-ionized water. A 20 no. mesh screen was placed at the bottom of dissolution flask. A Tizanidine hydrochloride tablet was placed on the mesh to allow the hydration of tablet throughout its surface. A paddle was introduced and operated at 50 rpm. The tablet was removed along with mesh at different time intervals. The weight and swelling of tablet were determined. Percent water uptake and percent axial swelling were determined using the following equations.

$$\% \text{ Water uptake (weight gain)} = \frac{100 \text{ (wet weight-dry weight)}}{\text{Dry weight}}$$

$$\% \text{ Axial swelling} = \frac{100 \text{ (swollen thickness-original thickness)}}{\text{Original thickness}}$$

Stability study

Tizanidine hydrochloride gastro retentive tablets of optimized formulation (F9) were packed in aluminum-aluminum blister (Alu-Alu blister packing).The packed tablets were placed in stability chamber maintained at 40 $\pm$ 2 ^{o}C and 75 $\pm$ 5% RH for 1 month as per ICH guidelines [11]. The samples were withdrawn after one month and were observed for changes in parameters such as change in color, appearance of spots, bad odor, roughness, and any kind of microbial or fungal growth. Samples were also evaluated for drug content, floating lag time, and *in vitro* drug release.

RESULT AND DISCUSSION

In the present study, Tizanidine hydrochloride gastro retentive tablets were prepared by using HPMC-K100M, HPMC-K15M, and HPMC-K4M by direct compression technique. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. The data obtained of pre-compression parameters are shown in [Table 2].

The characteristic absorption peaks of tizanidine hydrochloride were obtained at 3246.31 cm^{-1}, 3072.71 cm^{-1}, 1640.46 cm^{-1}, 1608.69 cm^{-1}, 1288.49 cm^{-1} and 675.11 cm^{-1}.The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

Tablets were evaluated for pharmacopoeial and nonpharmacopoeial (industry specified) tests and were found to be within the prescribed limits. The data obtained of post-compression parameters such as floating lag time, Duration of floating, hardness, friability, weight variation, uniformity of content, thickness, diameter are shown in [Table 3]. The hardness was found to be in the range of 5.5 to 6 kg/cm^2 in all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations the friability value is less than 1% and meets the IP (Indian Pharmacopoeia) limits. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weight of all the tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, polymers and excipients. The percentage drug content of all the tablets was found to be between 98.08 ± 1.19 % and 100.44 ± 0.82 % of Captopril, which was within the acceptable limits.

Drug release profiles from formulations are shown in figure 1. Perusal to the figure 1 indicates drug release with in 6 hrs, due to insufficient concentration of HPMC K4M. Therefore in formulation F2 the concentration of HPMC K4M was increased. But, F2 also had shown drug release up to 8 hrs only. So, it concluded that still concentration of HPMC K4M is insufficient to get desire drug release. Therefore, in formulation F3 higher concentration of HPMC K4M was used and it shown drug release up to 10 hrs. Based on above experience it concluded that HPMC K4M is not suitable to get desired drug release as compared to marketed formula. That's why in further batches high viscosity grade of HPMC were tried.
In the formulations F4 and F5, and F6 an attempt was made by using HPMC K15M to get the required release rate. In the formulation F4 had shown drug release up to 8 hrs, due to insufficient concentration of HPMC K15M. There for in formulation F5 the concentration of HPMC K15M was increased but formulation F5 also

shown drug release up to 10 hrs only. So, it concluded that still concentration of HPMC K15M is insufficient to get desire drug release. Therefore, in formulation F6 much higher concentration of HPMC K15M was used and it shown drug release up to 12 hrs. Based on above experience it concluded that HPMC K15M is not suitable to get desired drug release as compared to marketed formula. Still there was a need for further improvement to achieve the target.

In the formulation F7, F8 and F9 HPMC K100M were added replacing HPMC K15M of the above formulation. F7 showed the drug release up to 8 hrs, due to insufficient concentration of HPMC K100M. There for in formulation F8 the concentration of HPMC K100M was increased but F8 also shown drug release up to 10 hrs only. So, it concluded that still concentration of HPMC K100M is insufficient to get desire drug release. Therefore, higher concentration of HPMC K100M was used in formulation F9 and it shown drug release up to 14 hrs as compared to marketed formulation which is shown in figure 2. It also shown good similarity factor (82.77) when it was compared to marketed formulation drug release.
To study the effect of agitation intensity on the release of tizanidine hydrochloride, the tablets of the batch 9 were subjected to the dissolution studies at different rpm (50, 75, and 100 rpm). The data of the drug release profile of batch F9 tablets at different rpm conditions are shown in Figure 3. The cumulative percentages of tizanidine hydrochloride released in 14 hours were 90.06, 96.46, and 100.03 for 50, 75, and 100 rpm, respectively. A perusal to Figure 3 showed there is a slight increase in the drug release with the increase in rpm. It could be because, when the rotational speed of the apparatus was increased, the integrity of the gel layer was decreased, and the release of drug was increased.

In order to verify effect of hardness on drug release dissolution studies were conducted on tablets having three different kinds of hardness (4 kg/cm^2, 6 kg/cm^2 and 8 kg/cm^2). Tablets of batch F9 were considered for this study. Dissolution studies were carried out using USP dissolution apparatus II and results were shown in Figure 4. The cumulative percentage of tizanidine hydrochloride released in 1 hour, were 25.07 %, 19.86 %, and 15.7 % and 100.05%, 97.61, and 90.7 after 12 hrs for tablets with 4, 6, and 8 kg/cm^2 hardness respectively. When compared to tablets of 6 kg/cm^2 hardness, dissolution profile of tablets of 8 kg/cm^2 was decreased. It could be because of decrease in porosity with increased hardness. Further increase in compression force did not alter the release profiles. This may be due to no significant change in porosity. As tablets with hardness of 6 kg/cm^2 were showing good floating lag time and also drug release profiles similar to marketed product. So, hardness 6 kg/cm^2 was considered as suitable hardness.

Perusal to Figure 5 indicates that HPMC has undergone swelling with the simultaneous release of the drug. HPMC swell immediately with complete swelling in 8 hrs. About 85% drug was released at the end of 8 hrs and erosion process might have initial attributing gradual decrease in percent swelling after 8 hrs. As described by Siepmann *et al* diffusion of drug significantly depends on water content of the tablet. This may be because the mobility of 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 of the system. This higher water content could predict the higher penetration of the gastric fluid in to the tablet leading to faster carbon dioxide generation and thus reducing the floating lag time. Consequently, faster and higher swelling of the tablet led to increase in dimensions of the tablet leading to increase the diffusion pathways and thus decreasing diffusion rates. So the drug release was found to be high initially and then gradually decreased. Complete release of drug was obtained in 14 hrs.

Tizanidine hydrochloride floating tablets were prepared with different formula for optimized formulations that show f_1 and f_2 in prescribed limits when using commercially available marketed sustained release products as reference standards. The average f_1 and f_2 values of optimized formulation were found to be 2.94 and 82.77 for floating tablets respectively. The release of tizanidine hydrochloride from developed formulations was considered to be first order The Higuchi's equation showed R^2 = 0.9858 and also when the data was fitted in to Korsmeyer et al equation it showed R^2 = 0.9725 with slope (n) value of 0.604 which is more than 0.5 and less than 1. Thus, Non-Fickian diffusion of the drug was the main mechanism for drug release for the optimized formulation. Formulation was found to be reproducible and stable for one month under accelerated stability condition.

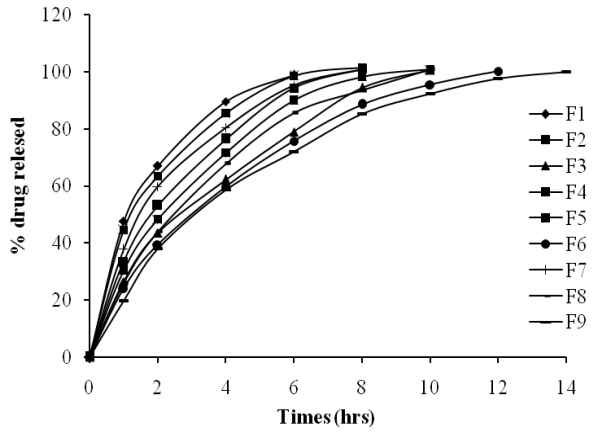

Figure 1: Comparison of *in vitro* release of Tizanidine hydrochloride from formulation F1 toF9

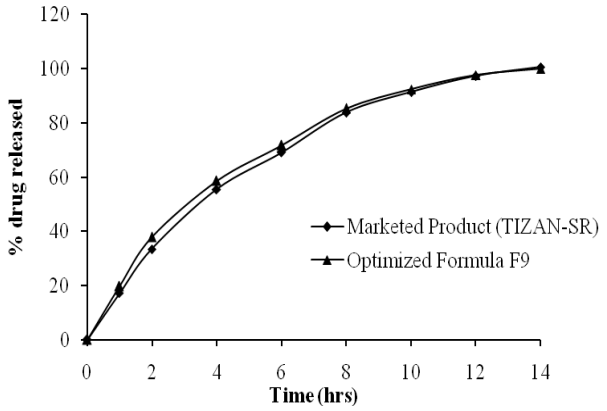

Figure 2: Comparison of *in vitro* release of Tizanidine hydrochloride optimized formulation F9 with Marketed Product (TIZAN-SR)

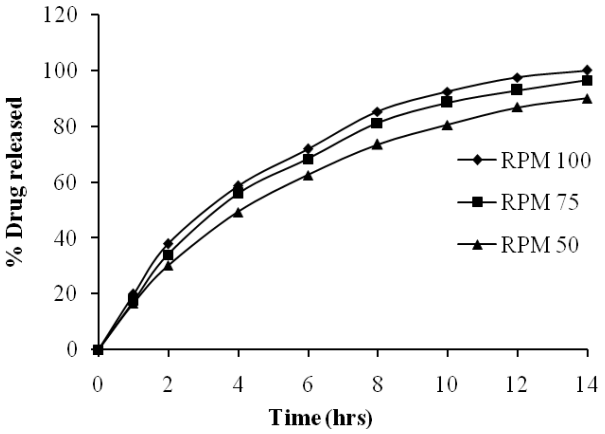

Figure 3: Comparison of *in vitro* release of tizanidine hydrochloride from tablets of optimized formulation F9 at different rotational speeds

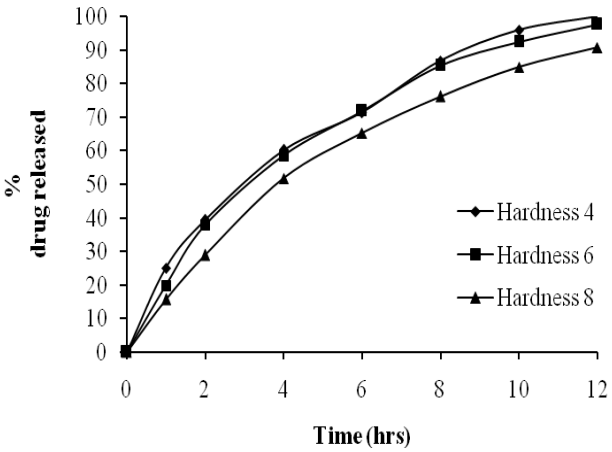

Figure 4: Comparison of *in vitro* release of tizanidine hydrochloride from tablets optimized formulation F9 of different hardness

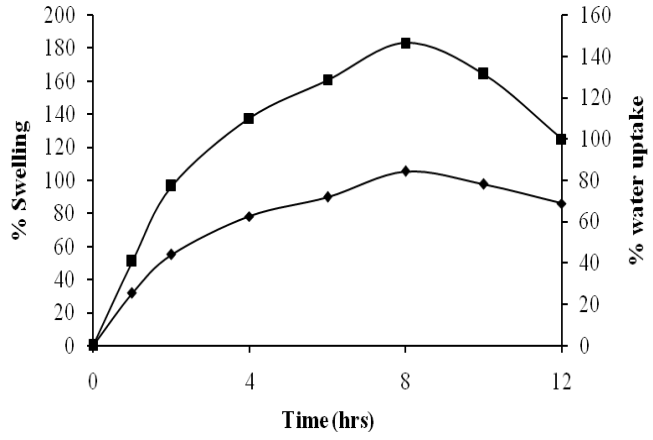

Figure 5: The percent swelling and water uptake of tizanidine tablet optimized formulation F9

(A) After 0 hrs

(B) After 20 sec

(C) After 6 hrs

(D) After 14 hrs

Figure 6: Floating properties of gastro retentive Captopril matrix tablets (Formulation F9) (A)After 0 hr, (B) After 20 sec, (C) after 6 hrs, (D) After 14 hrs

CONCLUSION

Floating tablets of tizanidine hydrochloride were successfully prepared using HPMC K100 by direct compression method. The tablets were evaluated for pharmacopoeial and non-pharmacopoeial (industry specified) tests. Based on the results, formulation F9 was identified as better formulation amongst all formulations for floating tablets. Tablets of formulation F9 passed all official and unofficial quality control tests. Drug release from the developed formulation follows first- order kinetics. *In vitro* release profiles of optimized formulations of tizanidine hydrochloride floating tablets (F9) was found to be similar to that of commercial marketed product.

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