Academic Sciences Asian Journal of Pharmaceutical and Clinical Research

Vol 5, Issue 3, 2012 ISSN - 0974-2441

Research Article

DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE FLOATING DRUG DELIVERY SYSTEM FOR TIZANIDINE HYDROCHLORIDE AND ITS *IN-VIVO* GAMMA-SCINTIGRAPHIC STUDIES USING TC-99M TRACER

NAVJOT SINGH[1],ANIRBANDEEP BOSE*[2], RAKESH K MISHRA[3], VIVEK JAIN [1],SANJAY DHAKAR[1], DILEEP BHARATI[1]

[1]Nri Institute of Pharmacy,Bhopal-462021,India ,[2].Particle design research group/non-destructive biomedical and pharmaceutical research centre,Universiti Teknologi MARA, 42300 Puncak alam,Selangor,Malaysia,[3]Brain Science Research Laboratory, Faculty of Pharmacy, Universiti Teknologi MARA, 42300, Puncak Alam, Selangor, Malaysia .E-mail: anirbandeep@gmail.com

Received: 13 February 2012 , Revised and Accepted: 2 May 2012

ABSTRACT

This purpose of this investigation was to develop a gastroretentive drug delivery system for tizanidine hydrochloride. Floating tablets of tizanidine hydrochloride (THC) were prepared employing hydroxypropyl methyl cellulose (HPMC) as encapsulant using wet granulation technique. The floating tablets were evaluated for angle of repose, tapped density, bulk density, hardness, drug content, and friability. The drug and polymer interaction was evaluated by Fourier transform infrared spectroscopy (FTIR). The floating lag time and floating time of the tablets were evaluated. The gastroretentive activity of the floated tablet of THC has been evaluated in vitro as well as in-vivo using gamma scintigraphy technique in healthy human volunteers. The effect of polymer concentration, polymer viscosity and type of diluent on drug release profile was investigated. The physicochemical properties of the floating tablets were found to be sufficient. It was observed that concentration of HPMC plays a key role in controlling the in vitro drug release profile of all the studied formulations. It was found that increase in HPMC concentration retards the release of the drug from the formulation. The in vivo study by gamma scintigraphic in human volunteers by Tc 99M has shown that the floating tablet of THC can maintain its integrity under harsh gastric conditions in the human stomach. The results shows that this THC floating tablets can be used as sustained release formulations.

Key Words:

INTRODUCTION

The oral route is the most convenient route for administering different protein, drugs and bioactive agents. The gastroretentive drug delivery systems (GTDDS) can assist in improving the oral bioavailability of various pharmaceutical drugs that have an absorption window in a particular region of gastrointestinal (GI) tract [1]. The design of new oral controlled drug delivery system should be aimed towards achieving maximum pharmacological action of the drugs on targated site. However, the development process uses to encounter several physiological difficulties, such as inability to restrain and localize the DDS with desirable regions of GI tract and large variation in the gastric emptying process [2]. This variability in turn may lead unpredictable bioavailability and times to achieve peak plasma levels, since majority of the drugs are absorbed in upper part of small intestine [3]. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa.[4,5,6] Thus small intestinal transit time is an important criterion for drugs that are incompletely absorbed. Among the various approaches, the floating drug delivery systems offer the most convenient and effective; approach to achieve increased gastric residence time and sustained drug release compared to the other methods [7]. 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 swell able polymers and inclusion of gas generating agents, sodium bicarbonate and citric or tartaric acid [8].Tizanidine hydrochloride is an orally administered prokinetic agent that facilitates or restores motility throughout the length of the gastrointestinal tract.Tizanidine hydrochloride is very less absorbed from lower intestine tract though it is well absorbed from the stomach.The short comings of tizanidine hydrochloride is its lower bioavailability and its short half life time.So Tizanidine is the drug which is suitable for Floating drug delivary.

MATERIALS AND METHOD

Materials

Hydroxypropyl methyl cellulose (HPMC) was purchased from Colorcon, Asia Ltd, Goa, India. Dicalcium phosphate, MCC, andlactose were procured from Emcure pharmaceutical Ltd, Pune, India. Tizanidine hydrochloride was received as a kind gift from Glenmark pharmaceutical Ltd, Nasik, Maharashtra, India.

FORMULATION DEVELOPMENT

Preparation of Matrix Tablets

The matrix tablet contains uniform mixture of drug, polymer and other excipients including gas-generating agent. The tablets were prepared by wet granulation technique. Weighed quantities of drug, polymer, diluent and sodium bicarbonate as given in a Table.3 were mixed properly in a mortar. Weight granulation was made by using 7.5 % ethanolic solution of Polyvinyl Pyrolidone. Wet mass was passed through sieve (16 #) and prepared granules were air dried and kept in desiccators for 1 day. Dried granules were again passed through sieve (40 #). Granules before few minutes of compression were mixed with talc and magnesium stearate in amber colored bottle. The well-mixed granules equivalents to 250 mg were compressed using a sixteen-station rotary tablet compression machine. Hardness of tablets was kept constant at 6-7 kg/cm^2. Formulation F1 to F15 indicates matrix tablets with diameter 10 mm; the effect of matrix tablet diameter on floating lag time, swelling characteristics and *In vitro* drug release rate was studied.

Table 1: Formulation of matrix tablets.

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
HPMC K4M	10	15	20	25	30	-	-	-	-	-	-	-	-	-	-
HPMC K15M	-	-	-	-	-	10	15	20	25	30	-	-	-	-	-
HPMC K100M	-	-	-	-	-	-	-	-	-	-	10	15	20	25	30
DCP	38.6	33.6	28.4	23.6	18.6	38.6	33.6	28.4	23.6	18.6	38.6	33.6	28.4	23.6	18.6

- All batches contained 6 mg of drug, 35 % sodium bicarbonate, 12 % stearic acid,
- 1 % magnesium stearate and 1 % talc.
- *All ingredients were taken in percentage milligrams of tablet weight.

CHARACTERIZATIONS

Infrared Spectroscopy

The polymer and drug were subjected to IR analysis with Fourier transform infrared spectrophotometer, Model-8400S, Make-Shimadzu. The KBr disks were prepared as a blank and the wavelength selected was 400-4000 cm^{-1}.

Swelling Characteristics

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of 0.1 N HCl at 37 ± 0.5 ^{0}C. The tablets were removed periodically from dissolution medium. After draining free water these were measured for weight gain, thickness and diameter. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation,

$$WU\ \% = \frac{\text{Wt. of swollen tablet} - \text{Initial wt. of the tablet}}{\text{Initial wt. of the table}} \times 100$$

EVALUATION OF GRANULES

Angle of Repose

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of angle of granules on the paper. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation:

$$\tan \theta = H / R$$

Therefore; $\theta = \tan -1 (H / R)$

Flow Rate

Flow rate of a powder has been defined as the rate at which the particular mass emerges through the orifice of funnel of a suitable diameter. The flow rate for granules of each formulation was determined by pouring accurately weighed quantities of granules in funnel with an orifice of 8 mm diameter. The time required for the complete granule mass to emerge out of the orifice was recorded using a stopwatch. The flow rate was calculated from following equation:

$$\text{Flow Rate} = \frac{\text{Weight of granules}}{\text{Time in seconds}}$$

Bulk Density

The bulk density was obtained by dividing the mass of a powder by the bulk volume in cm^3. The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no.20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$D_f = M / V_p$$

Where D_f is bulk density and M is the weight of samples in grams and V_p final volumes of granules in cm^3.

Tapped Density

The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm^3. The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no.20, is carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface 100 times from a height of 1inch.The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

$$D_o = M / V_p$$

Where, D_o is bulk density M is weight of samples in grams and V_p is final tapped volumes of granules in cm^3.

Carr's Index

An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:

$$\%\ \text{Compressibility} = \frac{D_f - D_o}{D_f} \times 100$$

Where,
D_f = Fluff or Poured bulk or bulk density
D_o = Tapped or Consolidated bulk density

EVALUATION OF TABLETS

A. *In vitro* Evaluation

. Tablet Thickness and Diameter:[9]

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using digital vernier callipers.

Tablet Hardness: [9]

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Friability: [9]

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\%\ \text{loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Uniformity of Weight

Weigh 20 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in Table.2 and none deviates by more than twice that percentage.

Table 2: IP Standards of Uniformity of weight.

S.No	Avg.wt.of tablet	% of deviation
1	80mg or < 80	10
2	>80 to < 250mg	7.5
3	>250 or more	5

Uniformity of content: [10]

This test was applicable to tablets that contain less than 10 mg or less than 10 % w/w of active ingredient. Content of active ingredient in tablets and capsules, taken at random, was determined. Crush tablets and powder equivalent to weight of tablet dissolved in 0.1 N

HCl. Drug content was calculated by measuring absorbance at wavelength 320 nm.

The tablet comply with the test if not more than one of the individual values thus obtained was outside the limits 85 to 115 % of the average value and none is outside the limits 75 to 125 % of the average value. If two or three of the individual values are outside the limits 85 to 115.5 of the average value and none is outside the limits 75 to 125 %, repeat the determination using another 20 tablets. The tablet comply with the test if in the total sample of 30 tablets not more than three of the individual values are outside the limits 85 to 115 % and none is outside the limits 75 to 125 % of the average value.

Floating Lag Time: [11, 12, 13]

This test was performed in beaker containing 100 ml 0.1 N HCl as a testing medium maintained at 37^0C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Floating Time: [11, 12, 13]

Floating time was the time, the tablet floats in dissolution medium (including floating lag time).

***In vitro* dissolution studies**

The release rate of Tizanidine hydrochloride from floating tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5^0C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 8 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper no. 41. Absorbance of these solutions was measured at 320 nm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

***In vivo* Evaluation**

Gastrointestinal retentivity test - Gamma Scintigraphy:

Gamma scitigraphic technique was used for investigating the *In vivo* gastric retention of the samples. Four healthy volunteers of age group 23-26 years having weight range of 60-70 kg were selected. ^{99}mTc 0.1 milli curve was used as radioactive nuclei. It was uniformly mixed with the final tablet blend and compressed using KBr hydraulic press at suitable pressure. The volunteers were asked to swallow these tablets with water after taking light breakfast in the morning. One hour after swallowing the tablets, volunteers were asked to lye down in supine position on the sliding table. An image was recorded by using gamma camera (low energy high resolution colorimeter integrated to ENTEGRA work station) by moving the table under the camera. Images were recorded at an interval of 1, 2, 4 and 6 hrs.

RESULTS AND DISCUSSION

FORMULATION DEVELOPMENT

Preparation of Matrix Tablets.

While designing gastro retentive drug delivery system, two mechanisms generally used were low density and gas generation. A low-density drug delivery system could be achieved by using HPMC in polymeric delivery system. HPMC has been widely used as low density hydro colloidal system.[32] In the trial study *In vitro* release of drug from tablet formulations were studied to determine optimum concentration of gas generating agents and hydrophilic matrix to entrap the gas. As concentration of sodium bicarbonate decreases, the floating lag time increases. Thus, sodium bicarbonate (80 mg per tablet) was essential to achieve optimum in vitro buoyancy.

Our preliminary observations suggest that tablets containing 5-10% HPMC were able to float in the dissolution medium for only a few hours during dissolution studies. In contrast, at higher HPMC level (10-30%), the tablets were able to sustain their floatation in the dissolution medium throughout the dissolution study over 12 hours. Therefore in this study relatively wide range of HPMC (10-30 %) has been selected in order to obtain the optimum HPMC loading level. Dicalcium phosphate was selected as a diluents because of its insolubility in water which may further contribute in the sustain release property of a tablet.[14]

Floating Lag Time

The values of buoyancy lag time for different batches were given in table below. The buoyancy lag time of tablets depend on amount of sodium bi carbonate involved in co_2 formation. For floating system the ideal matrix or coating materials should be highly permeable to dissolution media in order to initiate rapid generation of co_2 and should be permeable for co_2 to promote floating. Gerogiannis V.S and et al[26] studied the polymers of floating drug delivery system. The study reveals that selection of high molecular weight and less hydrophilic grades of polymers seen to improve floating characteristics. He also reported the use of different soluble additives along with HPMC to modify floating characteristics and drug release. Formulation F1 to F15 (10mm diameter) showed buoyancy lag time ranges from 0.55 ± 0.10 to 4.00± 0.15 min. Results indicate that FLT was found to be decreased with increase in the concentration of HPMC with in all tablet formulations.

Table3:Floating Lag Time of Floating Formulations.

S.No	Batch	FLT
1	F1	4.00 ± 0.15 Min
2	F2	2.00 ± 0.25 Min
3	F3	2.00 ± 0.09 Min
4	F4	1.55 ± 0.10 Min
5	F5	2.00 ± 0.02 Min
6	F6	1.50 ± 0.20 Min
7	F7	2.00 ± 0.10 Min
8	F8	2.00 ± 0.20 Min
9	F9	2.30 ± 0.30 Min
10	F10	3.00 ± 0.20 Min
11	F11	1.00 ± 0.02 Min
12	F12	0.55 ± 0.10 Min
13	F13	1.00 ± 0.10 Min
14	F14	0.55 ± 0.10 Min
15	F15	1.00 ± 0.09 Min

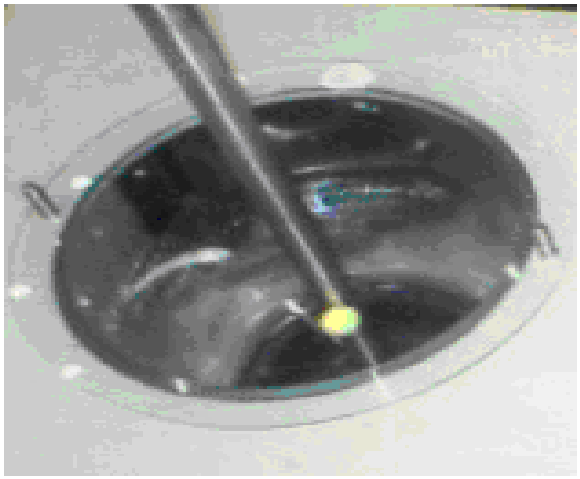


Fig 1: Floating tablet.

Floating time

Floating time was found to be depending on HPMC content HPMC was swelling polymer and degree of gelling and get strength determines its buoyancy. ***Zhenping wel and et al***[15] reported that on contact with the dissolution medium hydrocolloid in the test medium reacted with sodium bicarbonate from tablet inducing co_2 formation in the tablets. Because the gas generated was trapped in and protected by gel formed by hydration HPMC. This expansion keeps the whole tablet buoyant on the surface of the test medium as long as possible. Matrix tablets showed floating time over 12 hrs.

Swelling characteristics

The percentage water up take of the formulations F1 to F15 ranges 98.73 to 198.00%.The percentage water up take was found to be improved by increased concentration of HPMC in formulation.

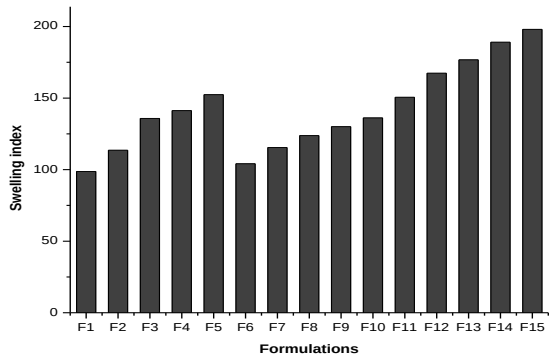


Fig 2: Swelling index of different formulation.

IN VITRO DRUG RELEASE STUDY

Effect of Polymer concentration

Matrix floating tablets were prepared by using three viscosity grades of HPMC. Almost 15 formulations were prepared by using five different concentrations of each viscosity grade of HPMC. Batches F1 to F5 (10 to 30%) were formulated to study the effect of HPMC K4M concentrations; whereas F6 to F10 (10 to 30%) were formulated to study the effect of HPMC K15M concentrations. In the batches F11 to F15 (10 to 30%) HPMC K100M was used in various concentrations. The figures 3, 4, 5 shows the Tizanidine hydrochloride cumulative percentage released graphed verses time for the different Tizanidine hydrochloride floating tablet formulations, all formulations tested showed sustained release pattern of drug over 8 hours with varying cumulative percentage release.

As expected the drug release was dependent on the concentration of HPMC in all formulations. In the batches F1 to F5, formulation F1 showed all 101.97% release and formulation F5 showed 57.75% release in 8 hours. In the batches of HPMC K15M, formulations F6, F7, F8, F9 and F10 showed 90.17, 88.23, 79.92, 60.87, 51.35% drug released in 8 hours dissolution studies respectively. T. Formulations F11 to F15 showed 91.75, 86.15, 71.51, 56.05, and 41.42% drug released respectively. In all formulations it was observed that the release rate of drug was a function of HPMC K4M, HPMC k15M and HPMC K100M content. An increase in the polymer concentration, induce a decrease in the release rate. High concentration of HPMC resulting in the more gel formation and forms a gelatinous barrier, which may retard the drug release in the formulations F5, F10 and F15 (i.e.30% HPMC concentration). Ratio of HPMC in the matrix was the key factor in controlling the drug release in all formulations. As seen from figures 3,4, 5 the higher the ratio of HPMC, slower the drug release was observed.

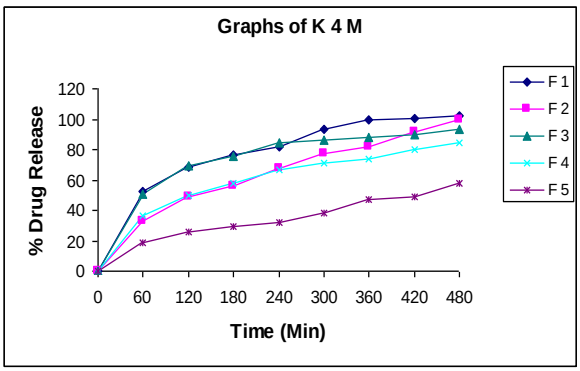


Fig3: Percentage of drug release at different time interval (F1 to F5)

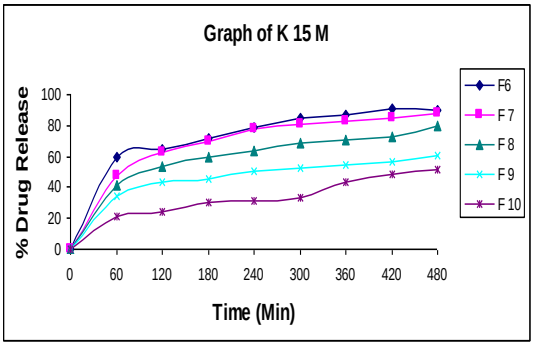


Fig4: Percentage of drug release at different time interval (F6 to F10).

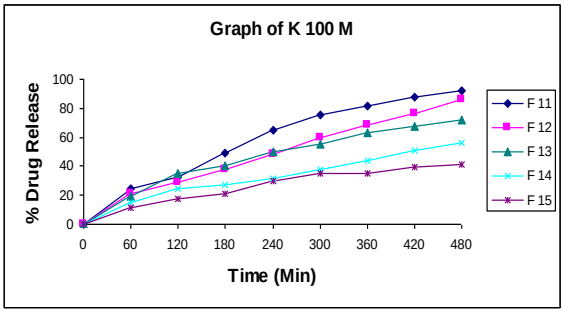


Fig 5: Percentage of drug release at different time interval (F11 to F15)

In Vivo Gastro Retentivity

A variety of techniques like string technique, Endoscopy, Radio telemetry, Roentogenography and Gamma scintigraphy were used for monitoring the *In vivo* behaviour of the oral dosage forms. As compared to other techniques gamma scintigraphy is the most widely used non-invasive technique for studying the *In vivo* behaviour of oral dosage forms under normal physiological conditions.

Selection of radioisotopes of gamma scintigraphy[7]:

The most commonly used radionuclides to correlate gastro intestinal behavior of the dosage forms with pharmacokinetic parameters i.e. correlation of the location of the dosage forms in a certain region of the GI tract to maximum plasma concentration were Technetium – 99 m (Tc – 99) and Indium 111 (In – 111). Tc – 99 m was the most widely used radionuclide in nuclear medicine. It has a very short half-life of 6 hrs and emits photons but not particulate radiation (â rays harmful to tissues). It is inexpensive and readily available in generator form or commercially as an aqueous solution. Tc – 99 m possesses most of the characteristics of an ideal radionuclide and hence found widespread applications in nuclear and in pharmaceutical formulation development. The level of radioactivity used in Gamma scintigraphy was very low and it gives a radiation dose participating subjects, which was well below the maximum permissible dose. Gamma scintigraphy was safe and always preferred over previous methods like X-rays as gamma scintigraphy gives very little radiation exposure to the participating subjects.

Thus for our work we have selected gamma scintigraphy for studying the gastric residence of Tizanidine hydrochloride tablets by using Tc-99 as radioactive isotope. The gastric retention studies of the formulation F11 was carried out in three healthy human volunteers. Fasting conditions were maintained for 12 hrs before study. When tested for 6 hrs, the gamma scintigraphy outputs have shown that the tablets maintained matrix integrity, indicating no effect of gastric conditions on the gelling properties of tablets. This effect was identical to *In vitro* studies. The gamma scintigraphy outputs were shown in fig.6, 7 and 8.

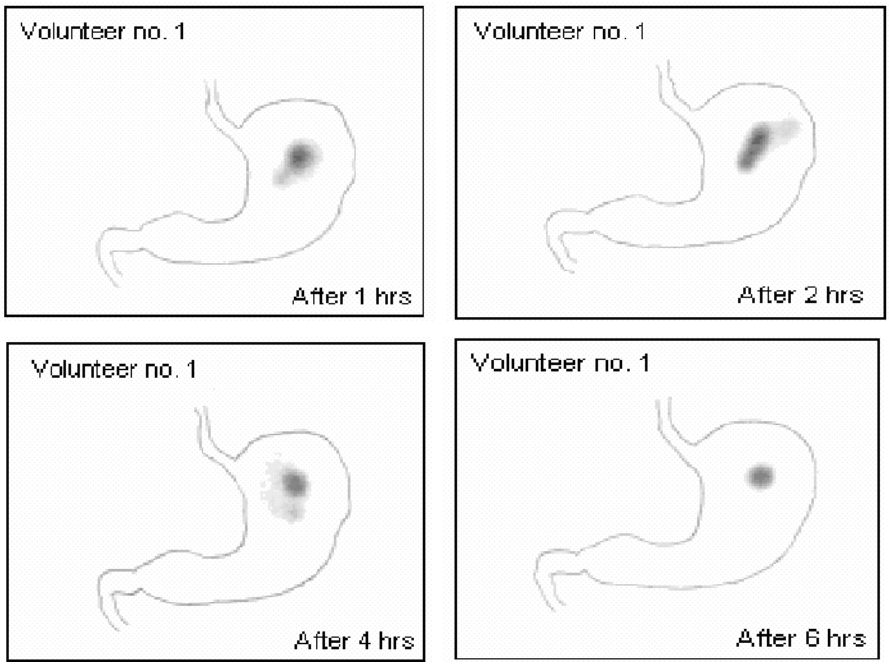


Fig. 6: Gammascintigraph images of volunteer no.1.

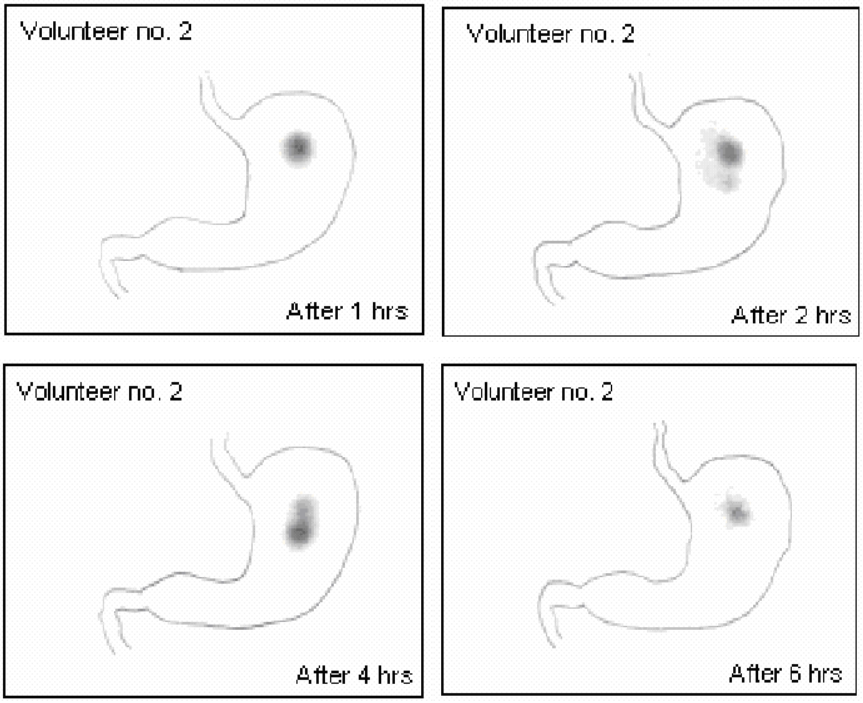
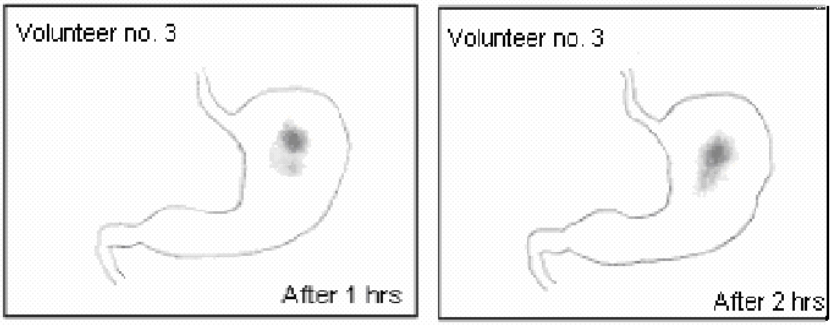


Fig. 7: Gammascintigraphs of volunteer no.2.



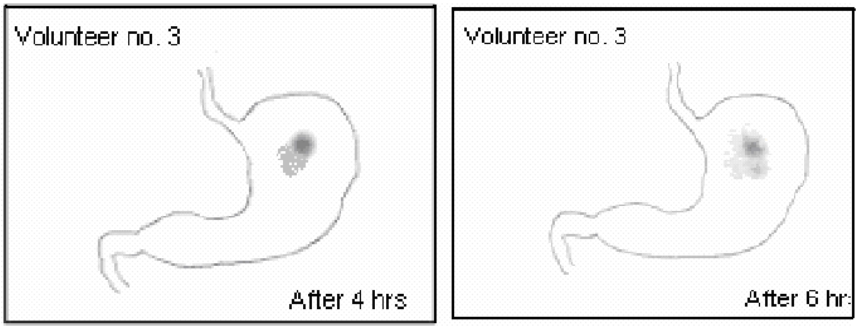


Fig.8: Gammascintigraphs of volunteer no. 3

CONCLUSIONS

The Tizanidine floating tablet formulation shows a sustained dissolution pattern in different formulation using the HPMC polymers. The tablets are well formulated and its swelling index indicate its good floating ability. Gamma scintigraphic technology reveals that the final formulation was floated for several hours.

REFERENCES

1. Chein Y W. *Novel Drug Delivery Systems*. 2nd Edn. Published by Marcel Dekker. Inc. New York. 1992; 50:1-139.
2. Singh, B.N., Kim, K.H. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Controlled Release, 2000, 63, 235-259.
3. N. Rouge, P. Buri, E. Doelker, Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery, Int. J. Pharm., 136 (1996), pp. 117–139
4. A M. Pharm. Thesis by Dhumal R. *Studies On Gastroretentive Drug Delivery System For Cefuroxime Axetil*.. B V D U Poona College of pharmacy. University of Pune. Pune; 2001-02.
5. 5.Brahmankar D M, Jaiswal S B. *Biopharmaceutics and Pharmacokinetics a treatise*. Reprint of 1st Edn. Published by Jain M K. Vallabh Prakashan. Delhi. 2003; 335 – 371.
6. 6.Hirtz J. The git absorption of drugs in man: a review of current concepts and methods of investigation. Br J Clin Pharmacol. 1985; 19:77S-83S.
7. A. J. Moes, Gastroretentive dosage forms, *Crit. Rev. Ther. Drug Carrier Syst.* 10 (1993) 143–195.
8. Thomas W L, Robinson J R. *Remington: The Science and Practice of Pharmacy*. 20th Edn. Vol. I. A.R.Gennaro (Ed). Lippincott Williams and Wilkins publication. 2000; 903-929.
9. Aulton M E. *Pharmaceutics: The Science of Dosage Form Design*. 2nd Edn. Published by Livingstone C. Elsevier science Ltd. 2002; 315-320.
10. *Indian Pharmacopoeia.* Government of India. Ministry of Health and Family Welfare. Published by the controller of Publications. Delhi. Vol. II. 1996; 736.
11. 11.Mazer N, Abisch E, Gfeller J C, Laplanche R, Bauer- Feind P, Cucala M, LuKachich M, Blum A. Intra gastric behavior and absorption kinetics of a normal and floating modified release capsule of Isradipine. *J Pharm Sci*. 1988; 8: 647-657.
12. 12.Singh B N, Kim K H. Floating drug delivery systems: An approach to Oral Controlled Drug Delivery via Gastric Retention. *J Contr Rel.* 2000; 63: 235-259.
13. 13.Atyabi F, Sharma H L, Mohammad H A H, Fell J T. *In vivo* evaluation of novel gastric retentive formulation based on ion exchange resins. *J Cont Rel.* 1996; 42: 105-113.
14. 14. Lachman L, Liberman H A, Kanig J L. *The Theory And Practice Of Industrial Pharmacy*. Varghese publishing house. Mumbai. 3rd Edn. 1990; 296-302.
15. 15.Basak S C, Rao K N, Manavalan R, Rao P R. Development and Invitro evaluation of an oral floating matrix tablet formulation of Ciprofloxacin. *Ind J Pharm Sci.* 2004; 66(3):313-316.
16. 16. Dave B S, Amin A F, Patel M M. Gastroretentive drug delivery system of Ranitidine Hydrochloride: Formulation and *In vitro* evaluation. *AAPS Pharm Sci Tech.* 2004; 5(2): Article 34.
17. Govindrajan G, Muttusamy K, Reddy M S, Ravi T K. Formulation and evaluation of floating hollow microspheres of Lansoprazole. *Ind J Pharm Sci.* 2004; 66(4): 486.