EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 8
589-596
Year: 2020

FORMULATION AND CHARACTERIZATION OF FLOATING MATRIX TABLETS OF TIZANIDINE HYDROCHLORIDE

[1]*Bhambar Kunal V. and [2]Dr. Pande Shrikant D.

[1]MGV's Pharmacy College, Panchavati, Nashik, Maharashtra, India.
[2]Vidyabharati College of Pharmacy, Amravati, Maharashtra, India.

***Corresponding Author: Bhambar Kunal V.**
MGV's Pharmacy College, Panchavati, Nashik, Maharashtra, India.

Article Received on 19/06/2020 **Article Revised on 10/07/2020** **Article Accepted on 31/07/2020**

ABSTRACT
Tizanidine Hydrochloride used in the control of spasticity, which is indicated in muscle pain as muscle relaxant. Tizanide Hydrochloride is crystalline powder. Tizanidine hydrochloride stimulates adrenergic receptors in the central nervous system, inhibiting presynaptic release of norepineprine and increasing the inhibitory effect on alpha motor neurons and motor reflexes. In the present investigation, efforts were given to develop a sustained release floating matrix tablets of Tizanidine Hydrochloride. Gastro retentative drug delivery system improve the pharmacotherapy of the stomach itself through local drug release leading to high drug concentrations at the gastric mucosa, which sustained over a long period of time. Floating matrix tablets were prepared by direct compression method using sodium bicarbonate and citric acid as gas forming agents. HPMC K100M and Ethyl cellulose were used in the formula to retard drug release. Floating matrix tablets were evaluated for different quality attributes. In vitro drug release showed that polymer percentage is enough to extend the release of the drug for at least 12 hr. The dissolution curve shows that formulation TF-6 shows maximum drug release 89.57 % at the end of 12 hours while TF- shows least 68.22%.

KEYWORDS: Ethyl Cellulose, Floating Matrix Tablets, HPMC K100M, Tizanidine Hydrochloride.

INTRODUCTION[7,8]
Conventional drug dosage form requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. These problems were overcome by sustained release systems. Gastro retentative drug delivery is one of the approach to retard the drug release and to retain the dosage form in stomach region. It improves drug absorption, because of increased gastric retention time and more time spent by the dosage form at its absorption site. Absorption of the Tizanidine Hydrochloride is absorbs rapidly in stomach and through whole GI tract. Tizanidine Hydrochloride acts as an agonist on Alpha-2 adrenergic receptor sites and it relieves symptoms of muscle spasticity. Tizanidine Hydrochloride has a biological half-life of 3 to 4 hours so it requires three-times a day dosing. Hence attempt was made to develop Tizanidine Hydrochloride floating matrix tablets to improve all characteristics.

MATERIAL AND METHODS
Tizanidine Hydrochloride was purchased from Blue Cross Pharmaceuticals, Nasik, India. HPMC K100M, EC was procured from Molychem, Mumbai. All other reagent and materials were of analytical grade.

Formulation of Tizanidine Hydrochloride Floating Matrix Tablets[3]
The direct compression technique was followed to manufacture the Tizanidine Hydrochloride tablets for all batches containing Tizanidine Hydrochloride. Sodium bicarbonate was passed through # 36 sieves. Magnesium stearate and Citric acid 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 using 10-station rotary press using Round shaped punches. Punches measuring 11.2 mm diameter were used for compression of the tablets. Formula for preparation of floating matrix tablets shown in table no-1.

Table 1: Formulation of Tizanidine Hydrochloride floating Matrix tablets.

	Formulation Code								
	Quantities (mg)								
Ingredients	**TF-1**	**TF -2**	**TF -3**	**TF -4**	**TF -5**	**TF -6**	**TF -7**	**TF -8**	**TF -9**
Tizanidine Hydrochloride	8	8	8	8	8	8	8	8	8
HPMCK100M	120	110	110	100	120	100	120	100	110
Ethyl cellulose	120	120	110	120	100	100	110	110	100
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Citric acid	25	25	25	25	25	25	25	25	25
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	5	5	5	5	5	5	5	5	5
Total weight	330	320	310	310	310	290	320	290	300

Evaluation of Tizanidine Hydrochloride floating tablets[1,2,8]

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 and in-vitro dissolution profile.

Organoleptic Properties

The prepared tablets were evaluated visually for cracks, depressions, pinholes, colour and polish.

Dimensions

Thickness of the tablets was measured using vernier calipers.

Hardness test

The hardness was tested using Monsanto tester. "Hardness factor", the average of the six determinations, was determined and reported.

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.

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

Friability test

Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. It was rotated at a rate of 25 rpm. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. 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. 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 λ_{max} 240 nm against blank as reference.

In vitro buoyancy studies

The tablets were placed in a 100 ml beaker containing 0.1 N 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.

Water uptake study (determination of swelling index)

The swelling index of the tablets was determined in distilled water at room temperature. The water uptake study of the tablet was done using USP II dissolution apparatus. The medium used was distilled water, 900 ml, rotated at 100 rpm. The medium was maintained at 37 ± 0.5 ^{0}C throughout the study. After every hour up to 12 hours, the tablets were withdrawn, blotted to remove excess water, and weighted. The swelling characteristics of the tablets were expressed in terms of water uptake(WU) as,

$$\% \text{ WU} = \frac{\text{Weight of the swollen tablet- Initial weight of the tablet}}{\text{Initial weight of the tablet}} \times 100$$

FT-IR Spectroscopy

The FT-IR spectrum of formulation TF-6 was recorded using FTIR spectrophotometer (Shimadzu 84005) using KBr pellet technique.

Differential Scanning Calorimetry (DSC)

DSC analysis of formulation TF-6 was performed using

Shimadzu-Thermal Analyzer DSC 60 on 2-5mg samples. Samples were heated in an open aluminium pan at a rate of 10°C/min conducted over a temperature range of 30 to 300°C under a nitrogen flow of 2 bar pressure.

In vitro dissolution study

In vitro drug release study of the samples was carried out using USP – type I dissolution apparatus (Basket type). The dissolution medium, 900 ml of simulated gastric fluid (with out enzyme), was placed into the dissolution flask maintaining the temperature of 37 ± 0.5 ^{0}C and rpm of 100. One Tizanidine Hydrochloride matrix tablet was placed in each basket of the dissolution apparatus. The apparatus was allowed to run for 12 hours. Samples measuring 5 ml were withdrawn after every 1 hour up to 12 hours manually. During sampling, samples were filtered. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were analyzed at 319 nm using 0.1 N HCl as blank. The cumulative percentage drug release was calculated using PCP Disso v3 software.

Kinetics of in-vitro drug release

To study the in-vitro drug release kinetics, data was applied to kinetic models such as zero order, first order, Higuchi, Hixson Crowell and Korsmeyer- Pappas.

Stability study for TF6

Stability studies of formulation TF6 was done as per ICH guidelines. In which the formulation was stored at 45^{0}c and 75%RH for 90 days and evaluated for physical changes, hardness, friability, drug content and percentage drug release.

RESULT AND DISSCUSSION

All the prepared floating matrix tablets were white in color having smooth surface. The thickness of all the formulations was varies with drug:polymer ratio it ranges from 5.0-5.5 mm. The weight variation test was carried out as per official method and the average percentage deviation of all the formulation was found to be less than 5%. It was found that all batches shows percent drug content more than 95 %. The tablet hardness of all the formulations was determined and it was found in the range 6.9-7.1 kg/cm^2. Another measure of tablet hardness was the friability. Compressed tablets that lose less than 1 % of their weight are generally considered acceptable. For all formulation tried here the weight loss was less than 1 % hence acceptable. All the formulations TF-1 to TF-9 floats within one minute but TF-6 takes minimum time as it contains minimum amount of polymers**.** All the formulations remains buoyant for more than20 hours. Swelling index was performed for optimized formulation (TF-6) complete swelling of tablet takes place at the end of 8 hours after that the weight of tablet was decreased. The FTIR spectrum of TF-6 exhibited characteristic signals which confirms identity and purity of dosage form. The absorption bands shown by TF-6 are characteristic of the groups present in the molecular structure of Tizanidine Hydrochloride .The DSC curve of Tizanidine Hydrochloride profiles a sharp endothermic peak at 278°C corresponding to its melting. The shift in melting point was observed due to entrapment of drug within polymers. Drug release studies were made to determine whether the release of the drug is slow enough for at least 12 hr. The dissolution curve shows that formulation TF-6 shows maximum drug release 89.57% at the end of 12 hours while TF-5 shows least 68.22%. In order to determine the release model which best describes the pattern of drug release, the in-vitro release data were fitted to zero order, first order, Hixson crowell, krosmeyer peppas and diffusion controlled release mechanism according to simplified Higuchi model. The preference of a certain mechanism was based on the correlation coefficient r for the parameters studied, where the highest correlation coefficient is preferred for the selection of mechanism of release. The highest r value was obtained for krosmeyer peppas model, so swelling followed by diffusion and erosion was the predominant release mechanism for floating matrix tablets. The value of release exponent n, obtained from Krosmeyer equation was greater than 0.5 for all nine formulations TF1-0.869, TF2-0.846, T3-0.687, TF4-0.761, TF5-0.987, TF6-0.845, TF7-0.834, TF8-0.642 and TF9-0.723 indicate non -fickian transport.

Organoleptic Properties

All the prepared matrix tablets were white in color having smooth surface.

Table 2: Evaluation of tablets parameters.

Formul-ation Code	Thickness (mm)	Hardness (Kg/cm^2)	Weight variation			Friability (%)	Drug Content (%)
			Avg Wt (mg)	Maximum % deviation			
				(+Ve)	(-Ve)		
TF1	5.4±0.14	7.2±0.20	330	+0.28	-0.25	0.38±0.11	99.65±0.31
TF2	5.3±0.35	7.3±0.40	320	+0.75	-0.26	0.43±0.23	99.21±0.28
TF3	5.5±0.27	7.3±0.43	310	+0.65	-0.78	0.38±0.16	99.11±0.56
TF4	5.3±0.34	7.2±0.36	310	+0.75	-0.59	0.35±0.11	99.31±0.26
TF5	5.4±0.43	7.4±0.46	310	+0.56	-0.86	0.38±0.17	99.61±0.35
TF6	5.2±0.29	7.3±0.45	290	+0.76	-0.82	0.47±0.17	99.10±0.31
TF7	5.0±0.32	7.3±0.08	320	+0.45	-0.66	0.48±0.12	99.59±0.25
TF8	5.2±0.15	7.3±0.19	290	+0.76	-0.68	0.34±0.16	99.66±0.27
TF9	5.3±0.20	7.1±0.07	300	+0.83	-0.85	0.47±0.16	99.38±0.46

Determination of buoyancy lags time

Table 3: Determination of buoyancy lag time of Floating Matrix tablets of Tizanidine Hydrohloride.

Formulation code	TF-1	TF -2	TF -3	TF -4	TF -5	TF -6	TF -7	TF -8	TF -9
Time (second)	36	54	34	44	36	29	41	42	38

Determination of duration of buoyancy

Table 4: Determination of duration of buoyancy time of Floating Matrix tablets of Tizanidine Hydrohloride.

Formulation code	TF-1	TF -2	TF -3	TF -4	TF -5	TF -6	TF -7	TF -8	TF -9
Time (Hours)	23	22	21	22	23	21	22	23	23

(Initial Time) (Time 15 Sec.) (Time 29 Sec.)

Fig.1: Floating Lag Time of Tizanidine Hydrocloride Floating Matrix Tablet TF6.

Water uptake study (Determination of swelling index)

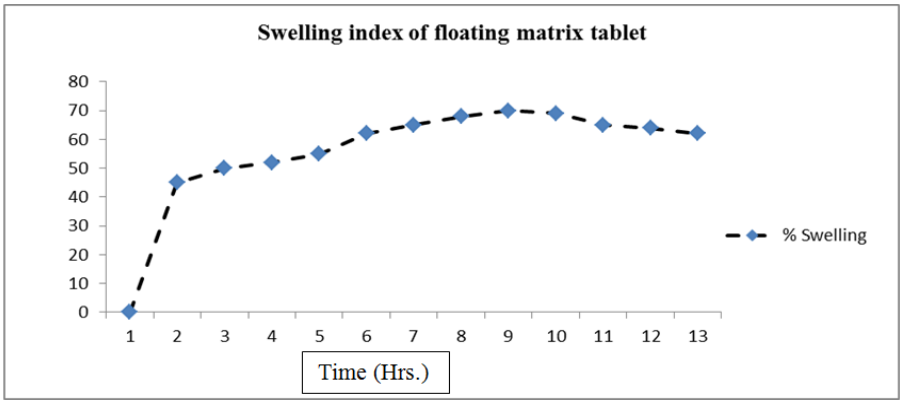

Fig. 2: Swelling index of formulation (TF-6).

FTIR of Floating Matrix Tablet TF-6

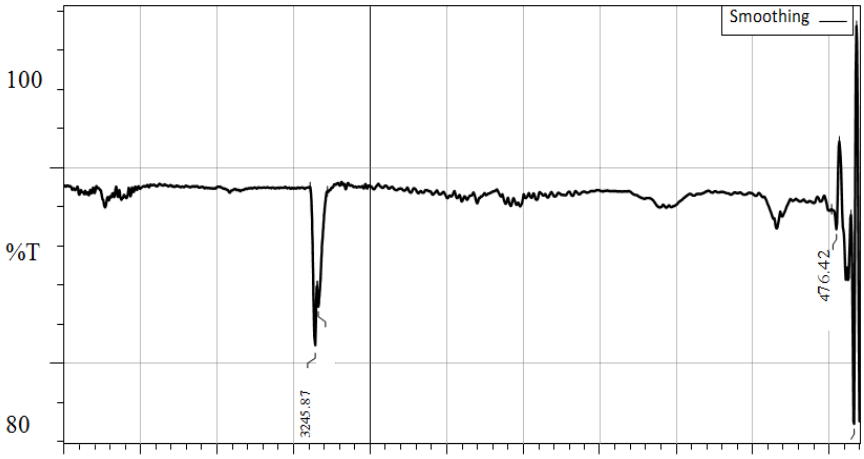

Fig. 3 FTIR of floating Matrix Tablet TF6.

Table 5: FTIR floating Matrix Tablet TF6.

Peak observed (cm^{-1})	Interpretation
2827.74	C-H stretching (aliphatic)
2978.19	C-H stretching (aromatic)
1643.90	C=N stretching
1666.55	N-H stretching

Differential Scanning Calorimetry (DSC)

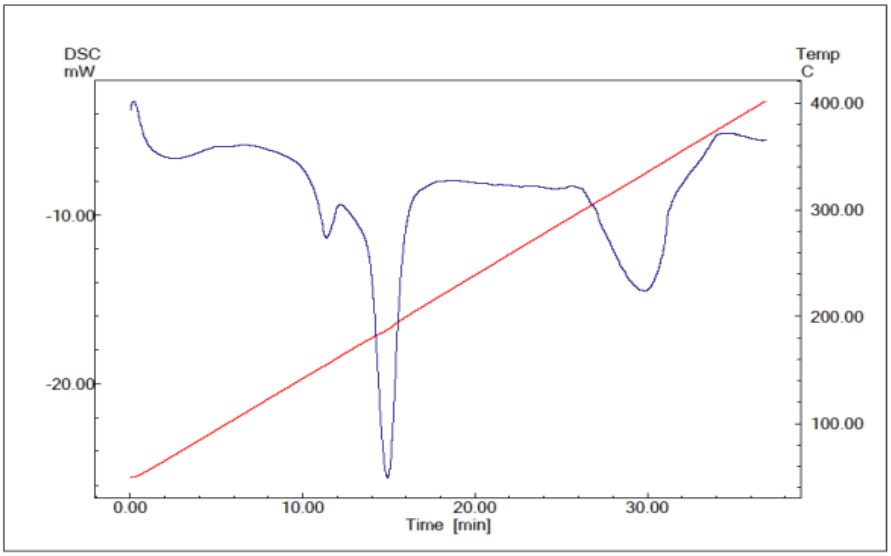

Fig. 4: DSC of TDDS T3.

Dissolution Profile of Floatinf Matrix Tablets of Tizanidine Hydrochloride

Table 6: Cumulative % drug released profile of Tizanidine Hydrochloride floating matrix tablets.

Time (Hours)	Cumulative % release (mean ± S.D.)								
	Formulation code								
	TF-1	TF -2	TF -3	TF -4	TF -5	TF -6	TF -7	TF -8	TF -9
1	10.29 ± 0.52	11.63 ±0.68	10.62 ±0.51	11.62 ±0.55	9.31 ±0.86	11.09 ±0.91	9.62 ±0.57	11.96 ±0.87	10.54 ±0.84
2	14.55 ±0.74	15.84 ±0.54	16.84 ±0.34	18.45 ±0.98	16.57 ±0.52	19.57 ±1.24	13.52 ±0.94	18.57 ±0.38	14.62 ±0.67
3	19.68 ±0.65	20.65 ±0.67	19.65 ±0.86	24.68 ±1.27	19.62 ±0.99	26.67 ±0.92	18.62 ±0.31	27.34 ±0.50	20.57 ±0.91
4	25.69 ±0.97	27.22 ±0.68	26.63 ±0.39	29.59 ±1.36	23.13 ±0.96	33.78 ±0.31	26.36 ±0.25	34.52 ±0.41	26.74 ±0.42
5	30.74 ±0.77	30.33 ±0.56	29.38 ±0.81	38.64 ±0.98	24.68 ±1.61	39.44 ±0.59	29.76 ±0.56	39.41 ±1.19	32..88 ±1.14
6	36.34 ±0.89	34.31 ±0.60	31.82 ±0.51	42.09 ±1.20	25.39 ±4.33	45.89 ±0.48	26.42 ±0.67	43.54 ±1.06	37.64 ±1.43
7	39.65 ±0.49	38.57 ±0.99	36.56 ±0.36	46.15 ±0.97	29.15 ±0.64	52.54 ±0.94	30.94 ±0.69	48.63 ±0.78	48.46 ±0.63
8	45.78 ±0.67	41.23 ±0.32	39.28 ±0.54	53.88 ±0.92	34.56 ±0.94	58.28 ±0.54	34.34 ±0.49	52.64 ±0.69	51.67 ±0.85
9	49.62 ±0.67	46.75 ±0.39	45.98 ±0.36	58.56 ±1.56	39.34 ±0.55	64.58 ±0.56	37.96 ±0.65	58.67 ±1.58	54.68 ±1.07
10	58.62 ±0.89	53.38 ±0.44	53.45 ±0.56	65.63 ±0.84	49.56 ±0.59	69.64 ±0.56	48.11 ±0.31	62.09 ±0.84	59.64 ±0.45
11	61.57 ±0.98	59.38 ±0.33	60.89 ±0.61	69.68 ±0.68	55.64 ±0.98	78.55 ±2.01	56.34 ±0.26	69.63 ±1.94	68.46 ±0.46
12	70.68 ± 0.54	69.54 ±0.67	70.54 ±0.46	79.94 ±0.67	68.22 ±0.67	89.57 ±0.45	68.74 ±0.33	78.34 ±0.67	77.92 ±0.29

Kinetic treatment of Tizanidine hydrochloride floating matrix tablets

Table 7: Kinetic treatment of prepared Tizanidine Hydrochloride floating matrix tablets.

Formulation Code	Coefficient of determination (r^2)					Korsmeyer plot n (release exponent)
	Zero order	First order	Higuchi square root	Hixson Crowell Cube Root	Korsmeyer plot	
TF1	0.994	0.959	0.994	0.978	0.946	0.869
TF2	0.982	0.937	0.982	0.960	0.956	0.846
TF3	0.975	0.914	0.975	0.942	0.957	0.687
TF4	0.992	0.948	0.992	0.976	0.927	0.761
TF5	0.939	0.860	0.939	0.892	0.950	0.987
TF6	0.993	0.955	0.993	0.981	0.996	0.845
TF7	0.935	0.855	0.935	0.889	0.930	0.834
TF8	0.983	0.958	0.983	0.979	0.896	0.642
TF9	0.992	0.941	0.992	0.970	0.935	0.723

Combined model graph (zero order, first order, higuchi model, Hixson Crowelland krosmeyer-peppas model) for Tizanidine Hydrocloride floating matrix tablets

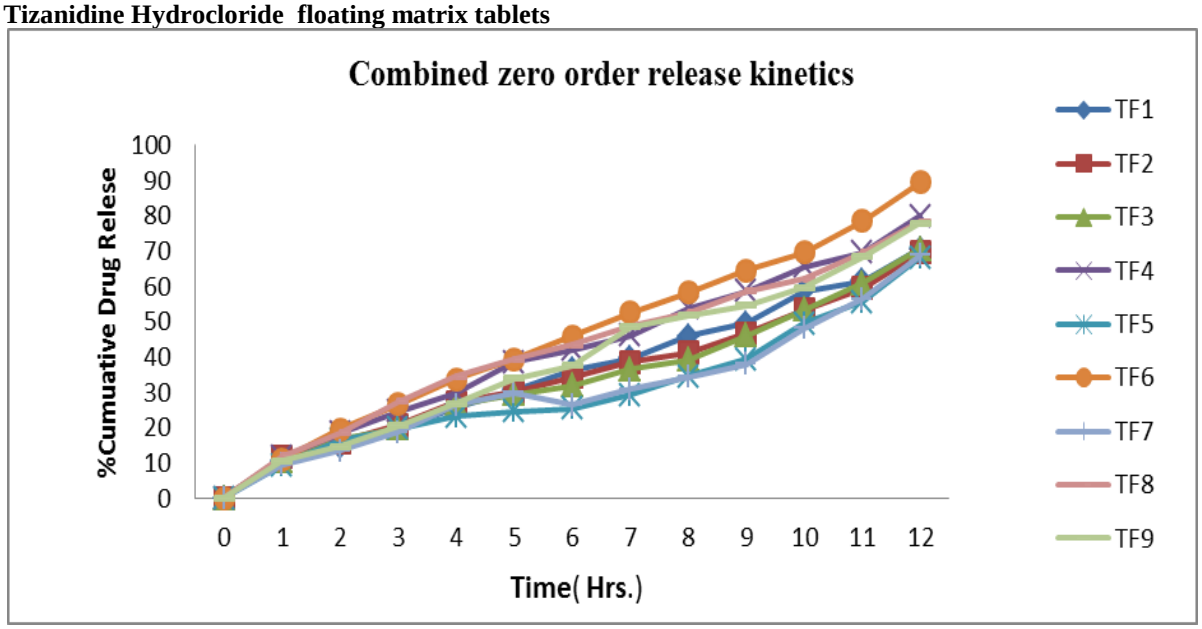

Fig. 5: Combined zero order graph of Floating Matrix Tablets.

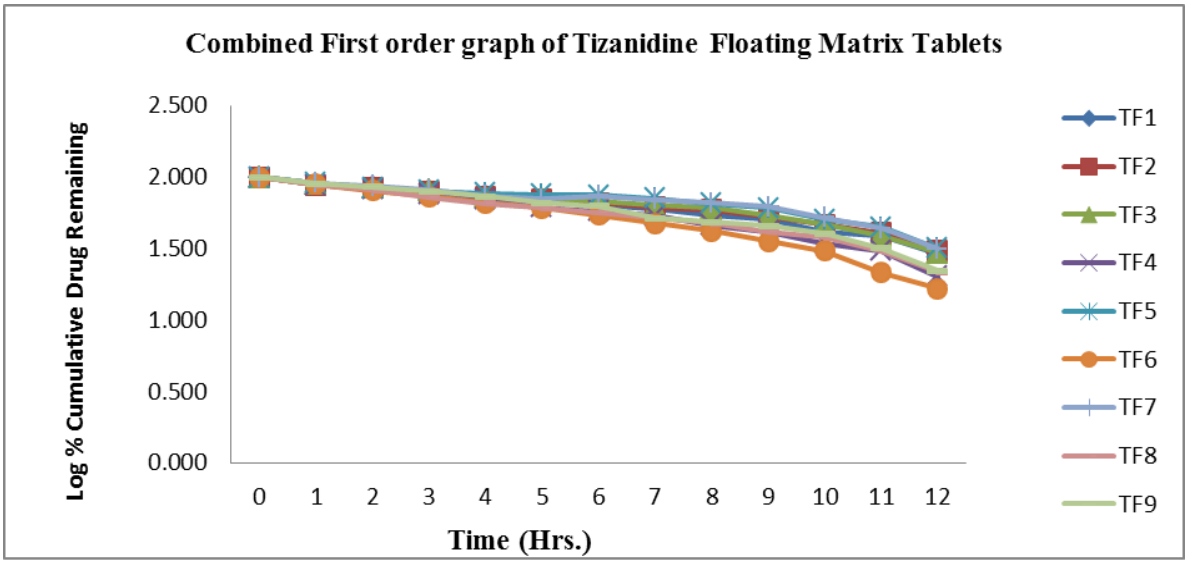

Fig.6 Combined first order graph of Floating Matrix Tablets.

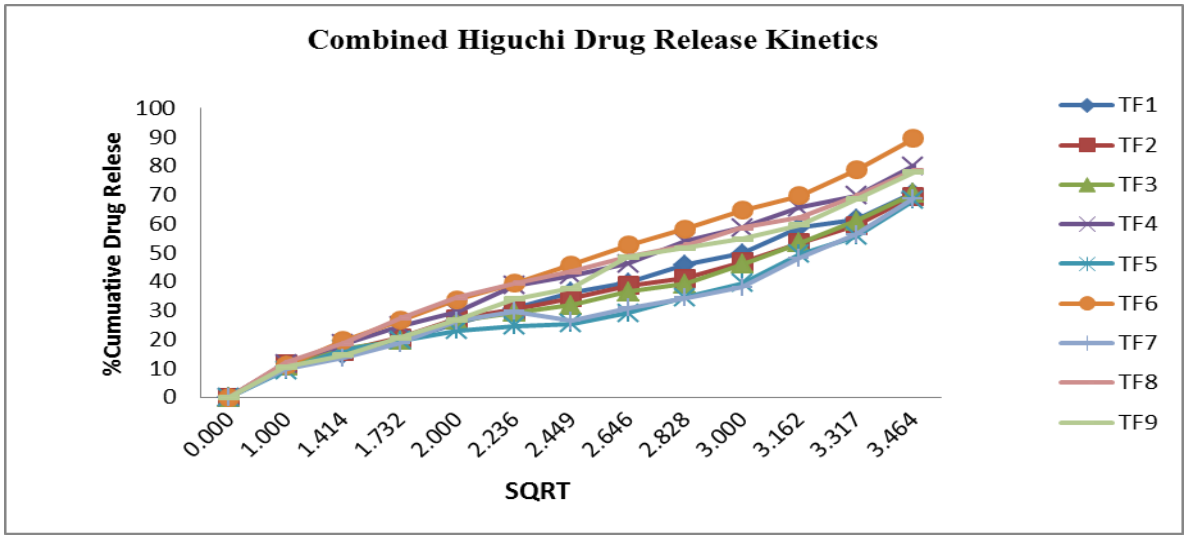

Fig. 7: Combined Higuchi graph of Floating Matrix Tablets.

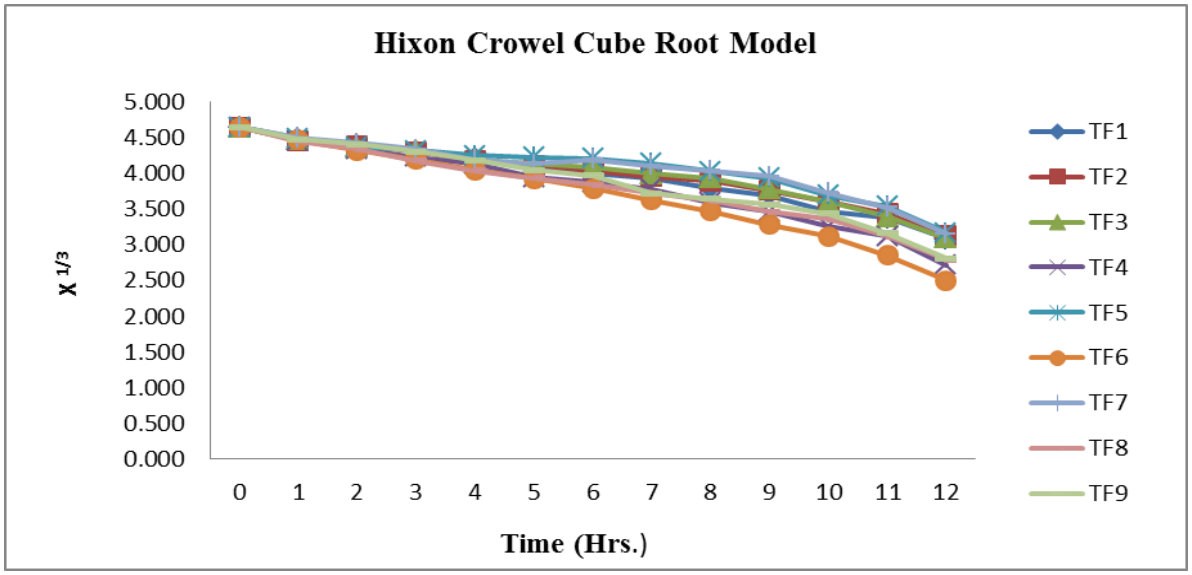

Fig.8: Combined Hixson Crowell graph of Floating Matrix Tablets.

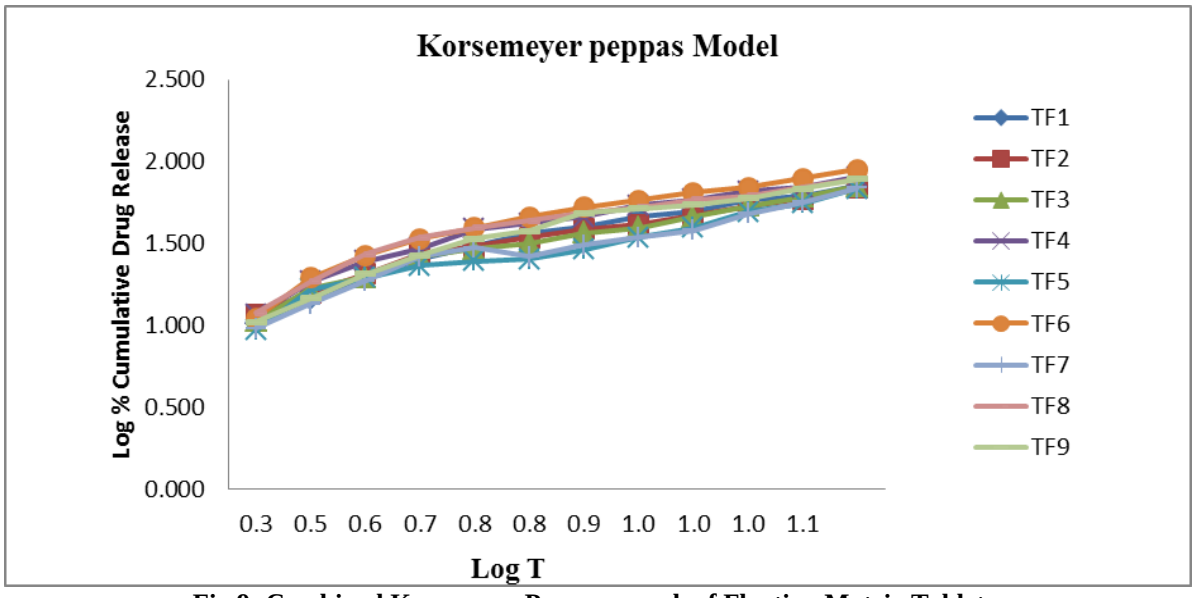

Fig.9: Combined Korsmeyer Peppas graph of Floating Matrix Tablets.

Stability Study

Table 8: Stability study of Floating Matrix Tablet(TF6).

Formulaton Code	Colour	Odour	Drug Content	friability	Cumulative % release
TF 6	White	No Odour	99.10±0.18	0.45±0.17	89.78%±0.18

CONCLUSION

Floating lag time for all Tizanidine Hydrchloride floating matrix tablets was within 1 minute and total floating time was more than 20 hours. For floating matrix tablets, the formulation TF-6 shows highest drug release as contains minimum amount of polymers and TF-5 shows lowest drug release. For floating matrix tablets, according to 'r' value, Korsmeyer-Peppas model was the best suited for drug release i.e. diffusion phenomenon but n value obtained from Korsmeyer-Peppas equation was within 0.5 <n> 1.0 which indicates anamolous releases. So the actual mechanism of drug release was swelling or rearrangement of polymers followed by diffusion and erosion.

ACKNOWLEDGEMENT

The Authors are thankfull to Blue Cross Pharmaceuticals,Nashik, India for providing the sample of Tizanidine Hydrochloride. Author also thankful to Shri S. D. Pande Sir and K.K. Tapar Sir for providing laboratory facility at Vidyabharati College of Pharmacy. Amaravati.

REFERENCES

1. Ferdous Khan, Md.Shaikhul Millat lbn Razzak, In, Prepration and In vitro Evaluation of Theophylline Loaded Gastro retentive Floating Tablets of METHOCEL K4M. J.Pharm Sci., 2008; 65-70.
2. Tanwar Y.S, Rana A.C, In, Formulation and Evaluation of Famotidine Floating Tablets. Current Drug Delivery, 2007; 4: 51–55.
3. Prajapati S.T, Patel L.D, Patel D.M, In, Studies on Formulation and In Vitro Evaluation of Floating Matrix Tablets of Domperidone. Indian Journal of Pharmaceutical Sciences, 2009; 19–23.
4. Sungthongjeen S, Sriamornsak P, In, Design and evaluation of floating multi-layer coated tablets based on gas formation. European Journal of Pharmaceutics and Biopharmaceutics, 2008; 69: 255–263.
5. Li S, Lin S, In, Statistical Optimization of Gastric Floating System for Oral Controlled Delivery of Calcium. AAPS Pharm Sci Tech., 2001; 2: 1–12.
6. Robles L.V, Martínez IJ, In, Sustained delivery of captopril from floating matrix tablets. *International Journal of Pharmaceutics*, 2008; 362: 37–43.
7. Shah S.H, Patel J.K, Patel N.V, In, Stomach Specific Floating Drug Delivery System A Review. International Journal of Pharm Tech Research, 2009; 623–633.
8. Singh BN, Kim KH. Floating drug delivery systems: An approach to Oral Controlled Drug Delivery via Gastric Retention. J Contr Rel., 2000; 63: 235-59.

Books

1. USP NF, Vol. 2, 2009, The official compendia of standards, 4th edition, The United States Pharmacopeial convention, 320-324.
2. Scan C Sweet man, Martindale The complete drug Reference, Thirty four edition, Published by the Pharmaceutical press, 1616-1618.
3. Lachman, L., Liberman, H.A., Kanig, J.L., In., The Theory and Practice of Industrial Pharmacy, 3rd Ed., Varghese Publishing House, Bombay, 1987,416-418, 430-453.