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FORMULATION AND *IN- VITRO* EVALUATION OF TIZANIDINE HCL FLOATING TABLET

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ABSTRACT

The present study was carried out with an objective to prepare and optimized floating tablet of Tizanidine HCl using combination of natural and synthetic polymer. Tizanidine HCl is use as muscle relaxant to treat spasm, cramping and tightness of muscle. Drug is maximum absorbed from stomach and least absorbed from the lower part of GIT having short biological half life 2.5 hr. It is prefer to take 2-3 times a day therefore overcome dosing frequency by preparing floating tablet of Tizanidine HCl that provide sustained drug release and better patient's compliance. The present research work describes the affect of the combined ratio of xanthan gum and HPMC K100M and different diluents. The polymer to copolymer ratio (X1) and different diluent (X2) were selected as independent variables, while time required for 50% drug release (t_{50}), time required for 90% drug release (t_{90}), drug release at 12 hr (Q_{12}), floating lag time, diffusion exponent (n), release rate constant (k) were selected as a dependent variables. Tablets were prepared by direct compression method & evaluated for pre-compression and post-compression parameters. Dissolution data were fitted to various models to ascertain kinetic of drug release. Regression analysis and analysis of variance were performed for dependent variables. All the batches were evaluated for the pre-compression and post-compression parameters and results of all batches complies within the limits. All formulations showed good floating lag time and total floating time more than 24 hr. Optimized batch (S6) showed 99.53% drug release at the end of 24 hrs and similarity factor (f_2= 75.59) and dissimilarity factor (f_1= 4.80) with theoretical release profile of Tizanidine HCl. Optimized formulation followed by anamolous non Fickian diffusion follow dominantly with zero order release and found to be stable after 28 days at accelerated condition. It was

showed that polymer: copolymer ratio and different diluents had a significant effect on drug release rate and floating lag time. Finally it was concluded that drug release rate retarded with increasing in polymer: copolymer ratio due to the higher the viscosity of HPMC K 100M compare to xanthan gum and also retard drug release in order of MCC>lactose>DCP.

Keywords: Tizanidine HCl, Floating tablet, Xanthan Gum, HPMC K100M, 3^2 full factorial design.

INTRODUCTION

Oral delivery of drugs is the most preferred route of drug delivery due to the ease of administration; low cost therapy, patient compliance and flexibility in formulation etc. so the design of oral control drug delivery systems should be primarily aimed to achieve more predictable and increased bioavailability. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of drug by controlling its release in the body with lower and less frequent dose. The gastro retentive drug delivery is an approach to prolong gastric residence time because these dosage forms can remain in the gastric region for long periods, thereby targeting site specific drug release in the upper gastrointestinal tract for local or systemic effects[1]. Tizanidine is drug that is use as a muscle relaxant. It is a centrally acting α-2 adrenergic agonist. It is used to treat spasm, cramping and tightness of muscle caused by medical problem such as multiple sclerosis, spastic deplegia, back pain or certain other injuries to spine or central nervous system[2]. Tizanidine hydrochloride is an orally administered prokinetic agent that facilitates or restores motility throughout the length of gastrointestinal tract. Tizanidine is least absorbed from the lower part of gastrointestinal tract and better absorbed from the stomach[3]. Thus, tizanidine hydrochloride is a candidate for the development of GRDDS. Tizanidine HCl has approximately short biological half life 2.5 hours. Tizanidine HCl is required 2-4 mg three times a day[4]. Therefore to overcome dosing frequency using floating drug delivery system.

MATERIALS

Tizanidine HCl was obtained as gift sample from JPN Pharma, Mumbai. HPMC of different grades obtained as gift sample from Colorcon Asia, Goa. Xanthan Gum and was kindly gifted from National Pharmaceutical. Guar Gum and DCP was gifted from Alembic Pharmaceutical Ltd, Vadodara. Sodium bicarbonate, microcrystalline cellulose, lactose was obtained as gift

sample from Finer Chemicals Ltd, Ahmedabad. Magnesium stearate was gifted from Acme Chemicals, Mumbai.

METHOD

Preparation of Tizanidine HCl Floating Tablets

Floating tablet containing tizanidine hydrochloride (13.68 mg equivalent to 12 mg tizanidine) were prepared by direct compression using different grades of HPMC such as HPMC K4M, HPMC K15M, HPMC K100M and natural polymers such as xanthan gum and guar gum. Sodium bicarbonate was used as gas generating agent at (10%) strength in each formulation and dibasic calcium phosphate was used as diluent in all formulation. All the ingredients were passed through # 60 mesh sieves separately. All ingredients were mixed in geometrical proportion to get a uniform mixture except magnesium stearate. Required quantity of drug and diluent were mixed then polymer and sodium carbonate were mixed together to form blend. The remaining lubricant such as magnesium stearate was then added and mixed to the above blend and final blend was compressed in to tablets using 10 station rotary tablet machine using flat punch.

Evaluation of Powder Blend and Tablet [5-11]

Drug- Excipients Compatibility Study

Drug excipient play important role in the release of drug from the dosage forms. Fourier transform infrared spectroscopy has been used to study the physical and chemical interactions between drug and the excipients used. Fourier transform infrared spectra of tizanidine HCl, HPMC K100M and xanthan gum were recorded using KBr mixing method.

Loose Bulk Density

Weigh accurately 5 gm of powder blend, and transferred in 100 ml graduated cylinder. Carefully level the powder blend without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula:

Bulk Density = Mass/ apparent volume

Tapped Bulk Density

Weigh accurately 5 gm of powder blend, and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that

provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. Tap the cylinder for 500 times initially and measure the tapped volume (V_1) to the nearest graduated units, repeat the tapping an additional 750 times and measure the tapped volume (V_2) to the nearest graduated units, if the difference between the two volumes is less than 2% then final the volume (V_2). Calculate the tapped bulk density in gm/ml by the following formula:

Tapped Density = Mass/ tapped volume.

Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the Bulk Density and Tapped Density of a powder blend and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index = Tapped Density-Bulk Density×100/ Tapped Density.

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder blend material.

Hausner's Ratio = Tapped Density/Bulk Density.

Angle of Repose

The angle of repose of powder blend powder was determined by the funnel method. The powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder blend cone was measured and angle of repose was calculated using the following Equ.

Angle of Repose **(ɵ)** = $\tan^{-1}h/r$

Where, h = Height of the powder blend cone

r = Radius of the powder blend cone

Weight Variation Test

The 20 tablets were selected at random, weighed and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 10%.

Friability

For each formulation, pre weighed tablet sample (10 tablets) were placed in the Roche

friabilator which is then operated for 100 revolutions. The tablets were deducted and reweighed. Conventional compressed tablets that loose < 0.5 to 1% of their weight are considered acceptable.

Hardness

Hardness of tablet was determined using Monsanto hardness tester.

Content Uniformity

The 20 tablets were crushed and the powder equivalent of 10 mg of drug was transferred to 100 ml of 0.1 N HC1 in volumetric flask. The solution was analyzed at 320 nm using double beam UV-Vis spectrophotometer after suitable dilution. The content of drug was calculated from calibration curve.

***In vitro* buoyancy study**

The *In vitro* buoyancy was characterized by floating lag time (FLT) and total floating time (TFT). The test was performed using USP 24 type II paddle apparatus using 900 ml of 0.1 N HC1 at 50 rpm at 37 ± 0.5°C. The time required for tablet to rise to surface of dissolution medium and duration of time the tablet constantly float on dissolution medium were noted as FLT and TFT, respectively.

***In vitro* drug release study**

The *In vitro* drug release was performed using USP 24 type II paddle apparatus in 900 ml of 0.1N HC1 at 50 rpm at 37 ± 0.5°C. The samples were withdrawn at predetermined time intervals for period of 24 hr and replaced with the fresh medium. The samples were filtered through 0.45 µm membrane filter, suitably diluted and analyzed at 320 nm using double beam UV-Vis spectrophotometer. The content of drug was calculated using calibration curve.

Kinetic model for release data [12-15]

The drug released data of all batches were fitted with desired kinetic model such as Zero order kinetic, First order kinetic, Higuchi model and Korsemeyer peppas model to ascertain the drug release. The Zero order and First order drug release. The Zero order and First order drug release explain the drug release depend on drug concentration or not. The Korsemeyer peppas model described the method of drug release and Higuchi model described the diffusional drug release.

Zero order = $Q_1 = Q_0 + K_0t$

First order = $Q_t = Q_{0e}^{-K1t}$

Higuchi model = $m= (100-q) \times t^{1/2}$

Hixon Crowell Model = $W_0^{1/3} - W_t^{1/3} = kt$

Korsemeyer peppas model = $Mt/M\alpha = K \times t^{n}$

Where Q_1 is the amount of drug dissolved in time *t*, Q_0 is the initial amount of drug in the solution, Q_t is the amount of drug dissolved in time *t*, W_0 is initial amount of drug in dosage form, W_t is remaining amount of drug in dosage form at time t, Mt/Mα is the fraction of drug release at time t and n is diffusion exponent. K_0, K_1, and k refer to the rate constant.

Statistical analysis

The statistical analysis of the factorial design batches was performed by multiple regression analysis using Microsoft Excel. Data obtained from all formulations were analyzed using statistica software and used to generate the study design and the response surface plots. Polynomial models were generated for all the response variables using Microsoft Excel. In addition analysis of variance (ANOVA) was used to identify significant effects of factors on response regression coefficients. The F value and p values were also calculated using Microsoft Excel. The relationship between the dependent and independent variables was further elucidated using response surface plots.

Similarity factor (f_2) [16-17]

To evaluate and comparison of dissolution profiles, the dissolution profiles were analyzed using similarity factor f_2. The f_2 value between 50 and 100 suggests that the dissolution profiles are similar.

Dissimilarity factor (f_1) [16-17]

The dissimilarity factor (f_1) calculates the percent difference between the two curves at each time point and is a measurement of the relative error between the two curves. The values should lie between 0-15.

Accelerated stability study [18]

The purpose of stability testing is to provide evidence on how the quality of drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test for the drug substance or a shelf

life for the drug product and recommended storage condition. The storage condition used for stability studies were accelerated condition (40^0 C ± 2^0 C / 75 % ± 5% RH). Stability study was carried out for the optimized formulations. Tablets of optimized formulation were striped packed and kept in humidity chamber on above mention temperature.

Table: 1 Formulation of preliminary trial

Formulation Ingredients (Mg)	Formulation Batch Code					
	F1	F2	F3	F4	F5	F6
Tizanidine HCl	13.68	13.68	13.68	13.68	13.68	13.68
HPMC K4 M	105	-	-	-	-	-
HPMC K15 M	-	105	-	-	-	-
HPMC K100 M	-	-	105	52.5	-	52.5
Xanthan gum	-	-	-	-	52.5	52.5
Guar gum	-	-	-	52.5	52.5	-
$NaHCO_3$	15	15	15	15	15	15
DCP	13.32	13.32	13.32	13.32	13.32	13.32
Magnesium stearate	3	3	3	3	3	3
Total weight (mg)	150	150	150	150	150	150
All formulation contain 13.68 mg Tizanidine HCl equivalent to 12 mg Tizanidine						

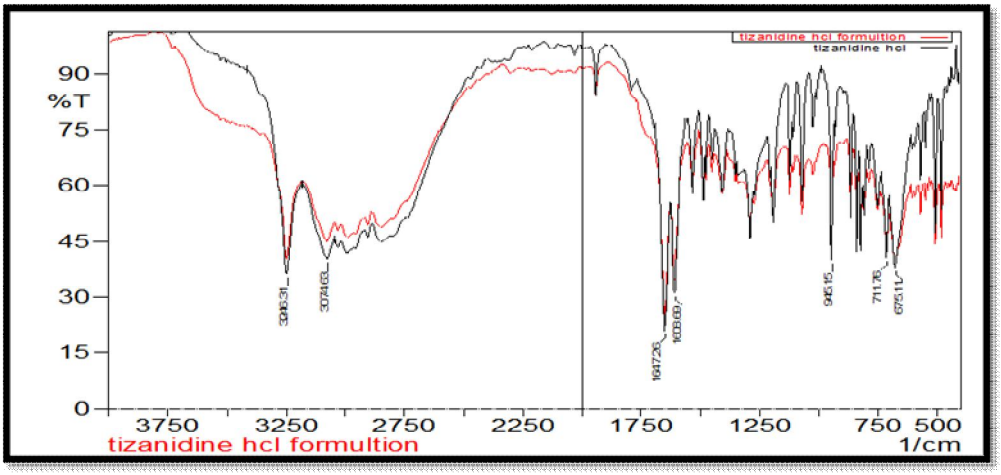

Figure 1: FTIR spectrum of Tizanidine HCl formulation

Table 2: Pre-Compression evaluation parameter of trial batches

Batch code	Bulk density (gm/ml)	Tap density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (Ɵ)
F1	0.75	0.857	12.48	1.14	25.20
F2	0.714	0.810	11.85	1.13	25.01
F3	0.652	0.75	13.06	1.15	24.90

F4	0.625	0.697	10.32	1.11	29.53
F5	0.681	0.769	11.44	1.12	29.35
F6	0.612	0.686	10.13	1.11	26.56

Table 3: Post compression evaluation parameter of trial batches

Batch code	Weight variation (mg) n=20	Hardness (kg/cm^2)*	Friability (%)	Content uniformity* (%)	Floating lag time (sec)	Total floating time (hr)
F1	139±1.3	6.5±0.22	0.69	97.22±0.35	115	13
F2	143±1.6	6.6±0.16	0.64	95.54±0.18	138	16
F3	147±2.5	6.5±0.25	0.58	99.15±0.22	150	>24
F4	136±2.9	6.7±0.2	0.86	94.25±0.34	90	15
F5	134±3.2	6.6±0.11	0.74	97.80±0.47	108	13
F6	148±2.4	6.7±0.15	0.62	97.30±0.32	87	>24

Table 4: Experimental design: Independent and dependent variables

3^2 full factorial design			
	Independent variables		**Dependent variables**
Coded value	**nthan Gum: HPMCK100M)**	**X2 (type of diluent)**	**Response(Y)**
-1	1:1	Lactose	t_{50}, t_{90}, Q_{12}, floating lag time, diffusion coefficient (n) and release rate constant (K)
0	1:2	DCP	
+1	1:3	MCC	

Table 5: Formulation of Tizanidine HCl factorial batches

Ingredients (mg)	BATCH CODE								
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**
Tizanidine HCl	13.68	13.68	13.68	13.68	13.68	13.68	13.68	13.68	13.68
Xanthan Gum	52.5	35	26.25	52.5	35	26.25	52.5	35	26.25
HPMC K100M	52.5	70	78.75	52.5	70	78.75	52.5	70	78.75
Lactose	13.32	13.32	13.32	-	-	-	-	-	-
DCP	-		-	13.32	13.32	13.32	-	-	-
MCC	-	-	-	-	-		13.32	13.32	13.32
$NaHCO_3$	15	15	15	15	15	15	15	15	15
Mg. Stearate	3	3	3	3	3	3	3	3	3
Total weight	150	150	150	150	150	150	150	150	150

Table 6: Pre-compression parameters of factorial batches

Batch code	Bulk density (gm/ml)	Tap density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (Θ)
S1	0.392	0.441	11.41	1.12	27.89
S2	0.402	0.454	11.46	1.13	28.88
S3	0.416	0.476	12.60	1.14	29.35
S4	0.405	0.461	12.14	1.13	28.73
S5	0.410	0.458	10.48	1.11	28.49
S6	0.472	0.535	11.77	1.13	29.05
S7	0.480	0.555	13.51	1.15	25.20
S8	0.431	0.504	14.48	1.16	26.56
S9	0.410	0.487	15.11	1.18	29.57

Table 7: Post compression parameter of factorial batches

Batch code	Weight variation (mg) n=20	Hardness (kg/cm^2)*	Friability (%)	Content uniformity (%)*	Floating lag time (sec)	Total floating time (hr)
S1	140±1.1	6.5±0.43	0.72	98.90±0.24	42	>24
S2	147±1.8	6.7±0.23	0.66	98.97±1.40	134	>24
S3	143±2.6	6.6±0.12	0.69	100.2±1.09	163	>24
S4	148±2.4	6.7±0.2	0.62	97.30±0.32	87	>24
S5	155±1.9	6.5±0.29	0.73	99.67±0.28	156	>24
S6	149±2.9	6.7±0.26	0.56	99.60±0.15	182	>24
S7	145±2.1	6.6±0.19	0.58	99.40±0.35	65	>24
S8	153±1.6	6.7±0.12	0.70	98.87±0.30	145	>24
S9	146±3.2	6.5±0.30	0.76	99.58±0.43	173	>24

RESULT AND DISCUSSION

Drug excipients compatibility study

Fourier transform infrared spectroscopy has been used to study the physical and chemical interactions between drug and the excipients used. Fourier transform infrared spectra of tizanidine HCl, HPMC K100M and xanthan gum were recorded using KBr mixing method. FTIR study showed that there was no interaction between drug and polymer that are shown in figure 1. So the drug and polymer were compatible with each other.

Result of Pre-Compression evaluation parameter of trial batches

The powder mixture used for tablet preparation were evaluated for pre-compression parameter like bulk density, tapped density, Carr's index, Hausner's ratio and Angle of repose are shown in table2. The bulk density was varied in the range of 0.612 gm/ml to 0.75 gm/ml, tapped density range between 0.686 gm/ml to 0.857 gm/ml. Carr's index was varied in the range of 10.13% to 13.06%, Hausner's ratio range between 1.11-1.15 and Angle of repose was varied in the range of 25.01° to 29.53°. This all parameters show good flow

property and direct compressibility.

Result of Pre-compression parameters of factorial batches

Pre-compression parameter was evaluated for factorial batches that are shown in Table 6. The values for the angle of repose were found to be in the range of 25.20° to 29.57°. This indicates good flow property of the powder blend. Compressibility index ranges between 10.48% - 15.11% indicates that the powder blend has good flow property. The values for the Hausner's ratio were found to be in the range of 1.11 to 1.18. This indicates good flow property of the powder blend. The pre-compression parameters of factorial batches showed that these were considerably good to be formulated as tablets using direct compression technique.

Result of Post compression evaluation parameter of trial batches

Post-compression parameter was evaluated for factorial batches that are shown in Table 3.All the batches showed weight variation in the range of 134 mg to 148 mg. All the batches showed hardness in the range of 6.5 to 6.7 kg/cm^2. Friability of all the batches was in the range of 0.58% to 0.86%. All the batches F1 to F6 shows drug content ranges between 94.25% to 97.80%.

Result of Post compression evaluation parameter of Factorial batches

Post-compression parameter was evaluated for factorial batches that are shown in Table 7. All the batches showed weight variation in the range of 140 mg to 155 mg. All the batches showed hardness in the range of 6.5 to 6.7 kg/cm^2. Friability of all the batches was in the range of 0.56% to 0.76%. All the batches F1 to F6 shows drug content ranges between 97.30% to 100.02%.

Result of *In-Vitro* drug release of trial batches

The result of *in vitro* drug release study is depicted in figure 2 and 3.

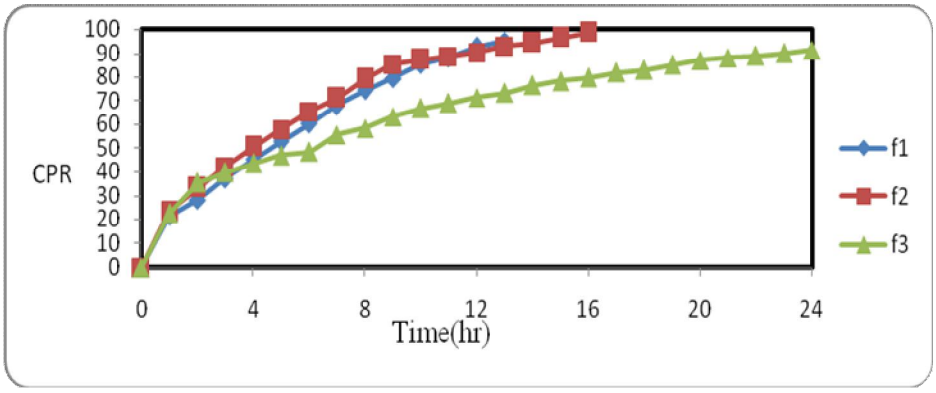

Figure 2: In-vitro drug release studies of preliminary batches of F1 to F3

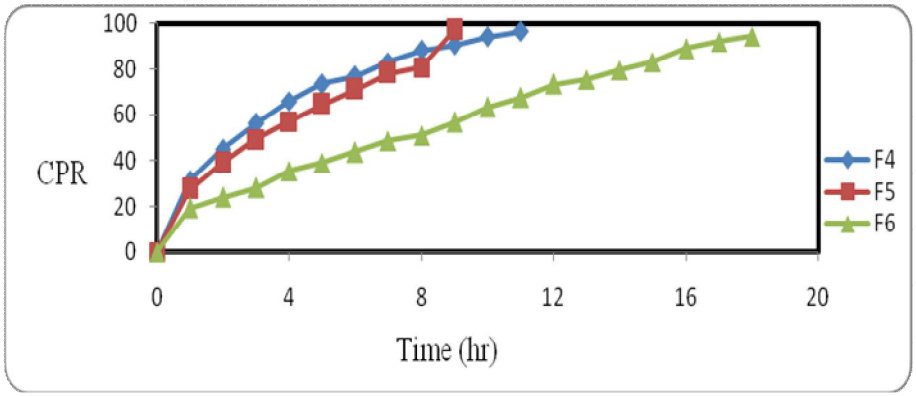

Figure 3: In-vitro drug release studies of preliminary batches of F4 to F6

From the dissolution profile it was observed that there was significant outcome of polymer grades and polymer load on drug release. All the batches exhibit initial burst release of drug due to rapid dissolution of drug from tablet surface. Formulation containing higher viscosity grade of different polymers have slower drug release rates when compared to formulation containing lower viscosity grade of polymers.

Formulation F1 contain 105 mg HPMC K4M shows release 95.11% in 13 hr. F2 contain 105 mg HPMC K15M shows release 98.49% in 16 hr. F3 contain 105 mg HPMC K100M shows release 91.36 in 24 hr. F4 contain 52.5 mg HPMC K100M and 52.5 guar gum shows release 96.52 in 11 hr. F5 contain 52.5 mg Xanthan gum and 52.5 guar gum shows release 96.99% in 9 hr. F6 contain 52.5 mg HPMC K100M and 52.5 xanthan gum shows release 94.33% in 18 hr. Results revealed that the drug release rate was decreased as viscosity of polymer increases.

All the formulations were floated. F3 formulation shows release up to 24 hr which contain 105 mg HPMC K100M due to the higher viscosity of HPMC K100M compare to HPMC K4M and K15M so it was best batch among single polymer batches and f6 formulation shows release up to 18 hr which contain 52.5 mg HPMC K100M and 52.5 mg xanthan gum. So finally, it was concluded that HPMC K100M and xanthan gum can be used in the formulation of tizanidine floating drug delivery system for further study.

Result of *In-Vitro* drug release of Post compression

The result of *in vitro* drug release study is depicted in figure 4, 5 and 6.

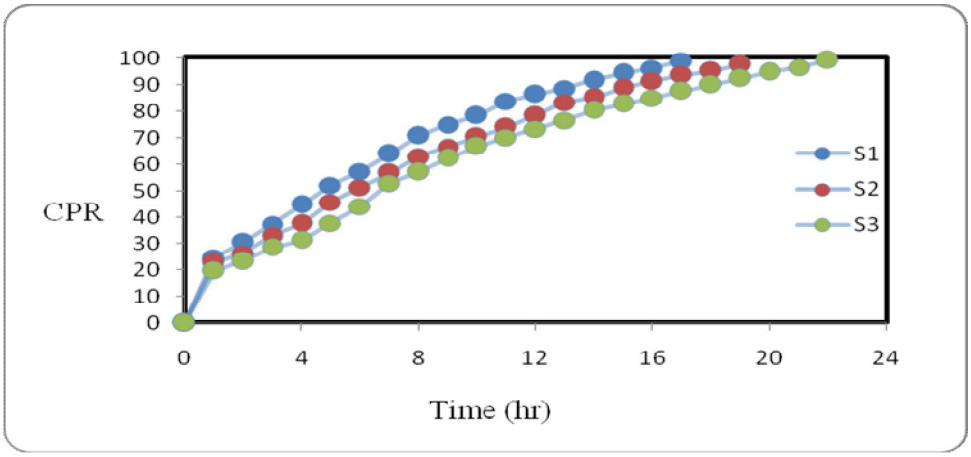

Figure 4: In-vitro Drug release studies of factorial batches of S1, S2 and S3

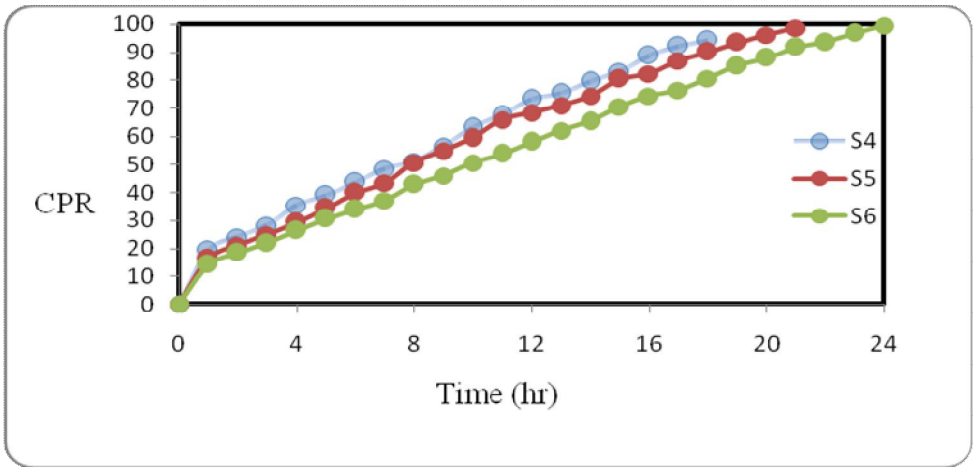

Figure 5: In-vitro Drug release studies of factorial batches of S4, S5 and S6

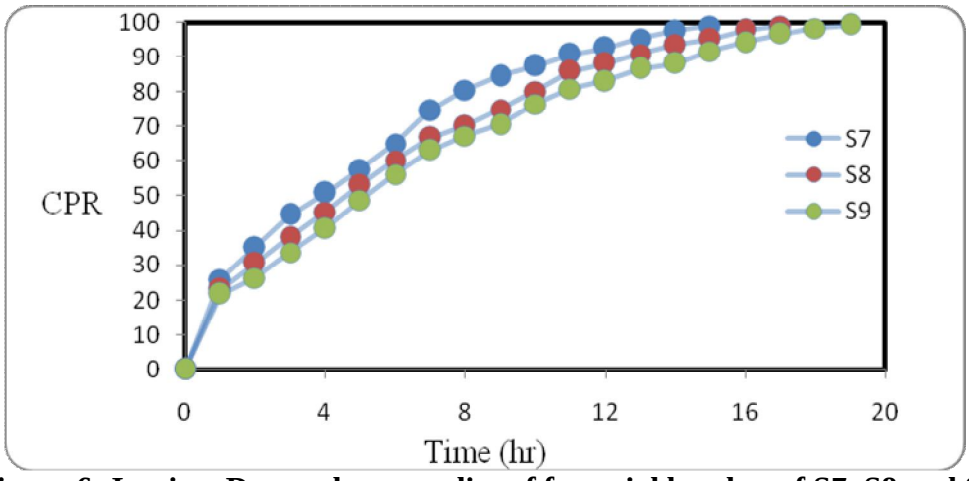

Figure 6: In-vitro Drug release studies of factorial batches of S7, S8 and S9

Formulation S1, S4 and S7 contain ratio of polymer to copolymer such as Xanthan gum and HPMC K100M such as 1:1 and diluent like lactose, dibasic calcium phosphate and microcrystalline cellulose respectively that shows drug release 98.82% in 17 hr, 94.33% in 18

hr and 99.10% in 15 hr respectively. Formulation S2, S5 and S8 contain ratio of polymer to copolymer such as xanthan gum and HPMC K100M such as 1:2 and diluent like lactose, dibasic calcium phosphate and microcrystalline cellulose that shows drug release 97.48% 19 hr, 100.07% in 22 hr and 99.13 in 17 hr respectively. Formulation S3, S6 and S9 contain ratio of polymer to copolymer such as xanthan gum and HPMCK100M such as 1:3 and diluent like lactose, dibasic calcium phosphate and microcrystalline cellulose that shows drug release 99.05 in 22 hr, 99.53 in 24 hr and 99.18 in 19 hr respectively. Results revealed that the drug release rate was decreased as viscosity of polymer increases and it could be found that among three different diluent microcrystalline cellulose exhibit faster drug release compare to lactose and dibasic calcium phosphate. Lactose shows slower drug release compare to microcrystalline cellulose and faster the drug release compare to dibasic calcium phosphate.

Dibasic calcium phosphate shows slower drug release compared to both lactose and microcrystalline cellulose hence finally it was concluded that drug containing higher polymer to copolymer ratio retard the drug release compare to lower polymer to copolymer ratio because of different effect of diluent on drug release that are in order such as microcrystalline cellulose > Lactose > dibasic calcium phosphate.

Result of statistical analysis of factorial batches

Table 8: Result of dependent variables

Batch code	Variable levels		t_{50}	t_{90}	Q_{12}	Floating lag time	n	k
	X1	X2						
S1	-1	-1	4.94	13.48	83.03	42	0.535	0.223
S2	0	-1	6.20	15.55	74.88	134	0.554	0.193
S3	1	-1	7.38	17.72	67.85	163	0.594	0.161
S4	-1	0	7.48	16.35	70.35	160	0.593	0.161
S5	0	0	8.38	17.83	66.37	169	0.649	0.133
S6	1	0	10.10	20.65	57.19	182	0.670	0.112
S7	-1	1	3.75	11.42	93.01	65	0.523	0.254
S8	0	1	4.75	13.15	84.50	145	0.548	0.220
S9	1	1	5.48	14.64	78.45	173	0.568	0.197

Full and Reduced Model for t_{50} (hr)

$Y = 8.601 + 1.131X_1 - 0.7566X_2 + 0.0783X_1X_1 - 3.236X_2X_2 - 0.1775X_1X_2$

Summary of results of regression analysis for t_{50} (hr)

Response t_{50} (hr)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	p
FM	8.601	1.131	-0.756	0.0783	-3.236	-0.1775	0.993	0.0017
P Value	2.62E-05	0.0018	0.0059	0.7025	0.0004	0.270	-	-
RM	8.653	1.131	-0.756	-	-3.236	-	0.989	2.4E-05

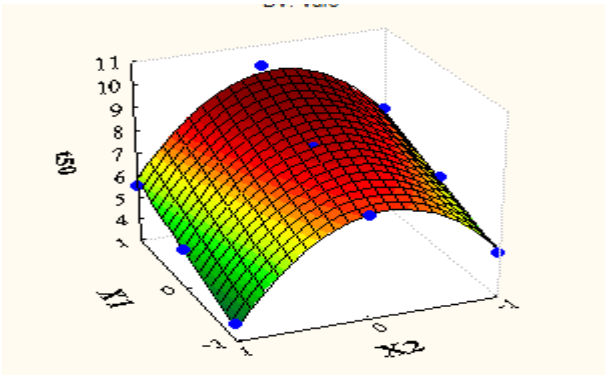

Figure 7: Response surface plot of t_{50}

Response surface plot shows that X1 as different ratio of polymer to copolymer increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so time required to release 50% of drug increase and X2 is different diluents that effect the time required to release 50% drug was highest from formulation containing MCC, intermediate from formulation containing lactose and lowest from formulation containing DCP.

Full and Reduced Model for t_{90} (hr)

$Y = 18.143 + 1.96X_1 - 1.256X_2 + 0.2X_1X_1 - 3.95X_2X_2 - 0.255X_1X_2$

Summary of results of regression analysis for t_{90} (hr)

Response t_{90} (hr)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	p
FM	18.143	1.96	-1.256	0.2	-3.95	-0.255	0.994	0.0012
P Value	5.8E-05	0.0007	0.0027	0.4618	0.0004	0.226	-	-
RM	18.276	1.96	-1.256	-	-3.95	-	0.989	2.3E-05

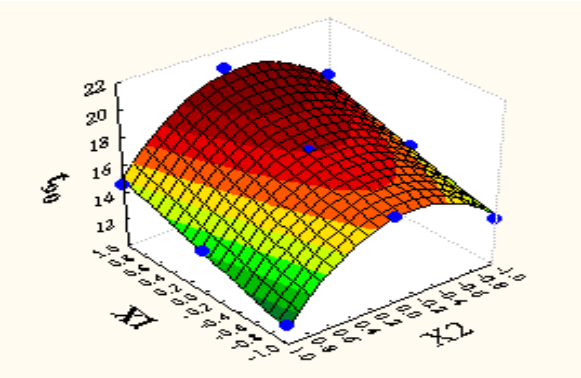

Figure 8: Response surface plot of t_{90}

Response surface plot shows that X1 as different ratio of polymer to copolymer increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so time required to release 90% of drug increase and X2 is different diluents that effect the time required to release 90% drug was highest from formulation containing MCC, intermediate from formulation containing lactose and lowest from formulation containing DCP.

Full and Reduced Model for Q12 (%)

$Y = 64.816 - 7.15X_1 + 5.033X_2 - 0.27X_1X_1 + 15.65X_2X_2 + 0.155X_1X_2$

Summary of results of regression analysis for Q12 (%)

Response Q12 (%)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	p
FM	64.816	-7.15	5.033	-0.27	15.65	0.155	0.993	0.0019
P Value	1.08E-05	0.0012	0.0036	0.812	0.0006	0.847	-	-
RM	64.636	-7.15	5.033	-	15.65	-	0.992	8.6E-05

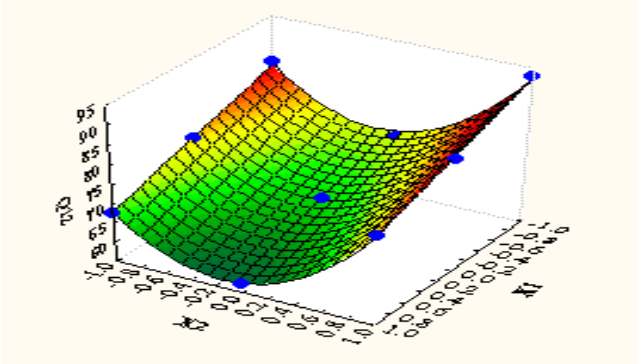

Figure 9: Response surface plot of Q12 (%)

Response surface plot shows that X1 as different ratio of polymer to copolymer increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so the drug release rate

is decrease and X2 is different diluents that effect the drug release rate was highest from formulation containing MCC, intermediate from formulation containing lactose and lowest from formulation containing DCP.

Full and Reduced Model for floating lag time (sec)

$Y = 159.22 + 54\ X_1 + 7.333X_2 - 26.33X_1X_1 - 21.33X_2X_2 - 3.25X_1X_2$

Summary of results of regression analysis for floating lag time (sec)

Response FLT (sec)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	p
FM	159.22	54	7.333	-26.33	-21.33	-3.25	992	0.0023
P Value	8.79E-05	0.0003	0.0910	0.0146	0.0257	0.4392	-	-
RM	159.22	54	-	-26.33	-21.33	-	0.854	0.00021

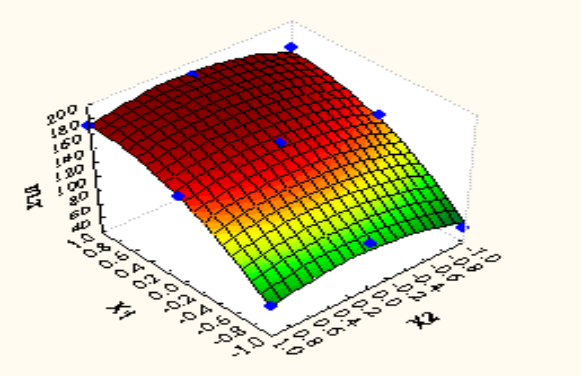

Figure 10: Response surface plot of FLT (sec)

Response surface plot shows that X1 as different ratio of polymer to copolymer increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so the floating time is increase and X2 is different diluents that effect the floating lag time was highest from formulation containing lactose, intermediate from formulation containing MCC and lowest from formulation containing DCP.

Full and Reduced Model for diffusion exponent (n)

$Y = 0.6388 + 0.0301X_1 - 0.0073X_2 - 0.0028X_1X_1 - 0.083X_2X_2 - 0.00357X_1X_2$

Summary of results of regression analysis for diffusion exponent (n)

Response n	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	p
FM	0.638	0.0301	-0.0073	-0.0028	-0.083	-0.0035	0.977	0.0111
P Value	6.4E-06	0.0091	0.239	0.7654	0.0023	0.6081	-	-
RM	0.637	0.0301	-	-	-0.083	-	0.958	7.1E

Response surface plot shows that X1 as different ratio of polymer to copolymer increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so the diffusion

exponent is increase and X2 is different diluents that effect the diffusion exponent was highest from formulation containing MCC, intermediate from formulation containing lactose and lowest from formulation containing DCP.

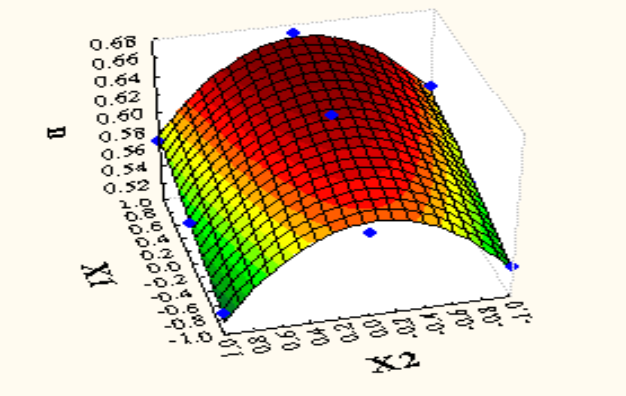

Figure 11: Response surface plot of diffusion exponent (n)

Full and Reduced Model for release rate constant (k)

$$Y = 0.1335 - 0.028X_1 + 0.0156X_2 + 0.0026X_1X_1 + 0.0726X_2X_2 + 0.00125X_1X_2$$

Summary of results of regression analysis for release rate constant (k)

Response k	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	p
FM	0.1335	-0.028	0.0156	0.0026	0.0726	0.00125	0.996	0.00057
P Value	2.7E-05	0.0004	0.0026	0.4299	0.0001	0.5889	-	-
RM	0.1353	-0.028	0.0156	-	0.0726	-	0.995	2.4E-06

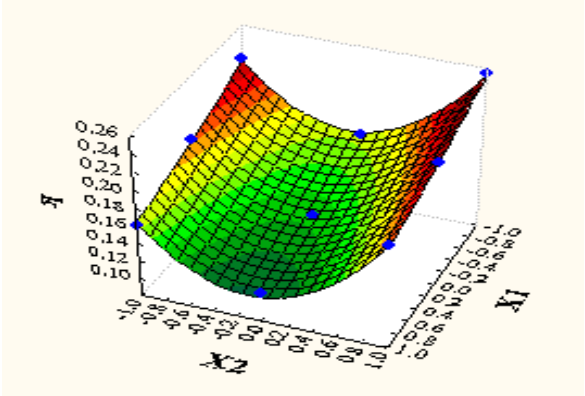

Figure 12: Response surface plot of release rate constant (k)

Response surface plot shows that X1 as different ratio of polymer to copolymer increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so the release rate constant is decrease and X2 is different diluents that effect the release rate constant was highest from formulation containing MCC, intermediate from formulation containing lactose and lowest from formulation containing DCP.

Result of kinetic modeling of dissolution data

Table 9: kinetic treatment of dissolution data

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Krosemeyer-Peppas model as evident from regression coefficients (table 9)

	S1	S2	S3	S4	S5	S6	S7	S8	S9
Zero order									
S	4.685	4.280	3.871	4.510	4.231	3.792	5.216	4.761	4.367
I	26.815	23.44	21.403	16.237	14.523	11.695	30.424	27.379	26.049
R^2	0.980	0.986	0.981	0.998	0.995	0.998	0.969	0.976	0.973
First order									
S	0.034	0.032	0.030	0.037	0.035	0.033	0.036	0.034	0.032
I	1.496	1.456	1.422	1.369	1.341	1.301	1.533	1.533	1.478
R^2	0.936	0.943	0.932	0.968	0.955	0.961	0.923	0.926	0.919
Higuchi									
S	25.604	24.451	23.701	24.695	24.955	23.618	27.183	26.128	25.225
I	-4.204	-7.350	-10.50	-13.401	-17.663	-20.246	-1.182	-4.45	-6.213
R^2	0.996	0.996	0.994	0.990	0.993	0.989	0.992	0.996	0.994
Hixon Crowell									
S	-1.561	-1.426	-1.290	-1.503	-1.410	-1.264	-1.73	-1.58	-1.455
I	24.394	25.517	26.198	27.920	28.492	29.434	23.19	24.20	24.650
R^2	-0.980	-0.986	-0.981	-0.998	-0.995	-0.998	-0.969	-0.976	-0.973
Korsemeyer and Peppas									
n	0.535	0.554	0.594	0.593	0.649	0.670	0.523	0.548	0.568
I	-0.651	-0.713	-0.792	-0.792	-0.874	-0.949	-0.593	-0.656	-0.704
R^2	0.995	0.992	0.989	0.990	0.992	0.991	0.995	0.996	0.993
S= slope, I= intercept, R^2= square of correlation coefficient, n= diffusion exponent									

Comparison of dissolution profiles for selection of optimum batch

The values of similarity factor (*f2*) for the batch S6 shown maximum f_2 value 75.59 and minimum dissimilarity factor f_1 value 4.80 as shown in Table 5.22. Hence, formulation batch S6 was considered as optimum batch.

Table 10: Similarity Factor *(f2)* and Dissimilarity factor *(f1)* for S1-S9

Batch	Similarity factor *(f2)*	Dissimilarity factor *(f1)*
S1	29.40	59.60
S2	35.62	40.99
S3	42.93	25.20
S4	42.36	30.99
S5	48.64	19.44
S6	75.59	4.80

S7	24.24	82.93
S8	28.30	62.50
S9	31.88	48.30

Result of accelerated stability study

Table 11: Result of tablet parameter of Accelerated Stability Study

Parameter	Initial	After 28 day
Hardness (kg/cm^2)	6.7	6.8
Friability (%)	0.56	0.59
Floating lag time (sec)	182	179
Total floating time (hr)	>24	>24
Drug content (%)	99.75	99.42
Similarity factor *(f2)*	75.59	77.13
Dissimilarity factor *(f2)*	4.80	4.33

CONCLUSION

The present investigation has been a satisfactory attempt to formulate and evaluate floating tablet of tizanidine hydrochloride. The floating tablet of tizanidine was prepared by direct compression method using natural polymer and synthetic polymer. Drug-excipient compatibility study was found that drug is compatible with polymer and co-excipient. All batches contain different polymer to copolymer ratio such as HPMC K100M and xanthan gum influence the release of drug formulation. The drug release was also influenced by the viscosity grade of polymer HPMC K100M and xanthan gum. As the polymer to copolymer ratio increased, the release of drug decreased due to the higher the viscosity of HPMC K100M compare to xanthan gum and it was also found that different diluents used in formulations that retard the drug release in order of MCC>lactose>DCP because of MCC gives faster drug release compare to lactose and DCP and lactose give slower drug release compare to MCC and faster drug release compare to DCP.

Different ratio of polymer to copolymer was successfully optimized by using 3^2 factorial designs. From 3^2 factorial design and graphical representation, it was finalized that batch S6 was found to be optimized batch having drug release up to 24 hr and also show good flow property, drug content and tablet floated more than 24 hr. Moreover, the dissolution profile was found to be similar with the theoretical dissolution profile having similarity factor more than 50 (*f2*=75.59) and dissimilarity factor less than 15 (*f1=4.80*) which reflects the feasibility of optimization procedure in successful development of floating tablet containing tizanidine hydrochloride using HPMC K100M and xanthan gum in combination. The

mechanism of drug release for optimized formulation S6 was found to be anomalous non fickian diffusion follow dominantly zero order release. The optimized batch was found to be stable after 28 day at accelerated condition.

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