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FORMULATION AND *IN- VITRO* EVALUATION OF TOLPERISONE HCL BUOYANT TABLET

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ABSTRACT

The aim of present investigation was undertaken with the objective of formulating buoyant tablet of Tolperisone HCl. Tolperisone HCl is a skeletal muscle relaxant. Drug is more stable in acidic medium (pH < 4.5), and in alkaline medium (pH 4 to 7) tolperisone breaks down into 4-MMPPO [2methyl-1-(4methylphenyl)-propanone] and piperidine. Thus, the patient is exposed to an uncontrollable quantity of genotoxic agent 4-MMPPO. By preparing buoyant tablet of this drug with controlled release reduce dosing frequency, better patient's compliance and eliminate side effects. Tablets were prepared by direct compression method using Xanthan Gum and Guar Gum as a matrix forming agents to control the release of drug and Sodium bicarbonate as gas generating agent. 3^2 full factorial design was used for optimization of formulation variable. The drug: polymer ratio (X1) and concentration of sodium bicarbonate (X2) were selected as independent variables, while time required for drug release 50% (t_{50}), time required for drug release 90% (t_{90}), drug release at 12hr (Q_{12}), Floating lag time, release rate constant (*k*) and diffusion exponent (*n*) were selected as a dependent variable. Prepared tablets were evaluated for pre compression and post compression parameters. The release mechanisms were explored and explained by applying zero order, first order, Higuchi and Korsmeyer equations. Regression analysis and analysis of variance were performed for dependent variables. All the formulations were evaluated for the pre compression and post compression parameters. The evaluation results revealed that all formulations comply with the specification of official pharmacopoeias and/or standard reference. Optimized formulation (B6) showed 99.27% drug release at the end of 24 hrs and maximum similarity factor (f_2= 74.41) and minimum dissimilarity factor (f_1= 4.24) with

theoretical release profile of Tolperisone HCl. Optimized formulation followed by anomalous non Fickian release mechanism and found to be stable after 21 days at accelerated condition. It was observed that drug: polymer ratio and concentration Sodium bicarbonate had a significant effect on drug release rate and floating lag time. It was concluded that drug release rate decrease with increase in drug: polymer ratio and drug release rate increase with increase in the concentration of Sodium bicarbonate.

Keywords: Tolperisone HCl, direct compression, Buoyant tablet, Xanthan Gum, Guar Gum, 3^2 full factorial design.

INTRODUCTION

The gastro retentive drug delivery system can be retained in the stomach and assist in improving the oral control delivery of drug that have an absorption window in a particular region of the gastrointestinal tract. This system helps in continuously releasing the drug, thus ensuring optimal bioavaibility. The matrix tablet composed of drug and the release retarding material offers the simplest approach in designing of control release system. Skeletal muscle relaxants are drug that acts peripherally at neuromuscular junction or muscle fibre itself or centrally in the cerebrospinal axis to reduce the muscle tone. Centrally acting muscle relaxants are used mainly for painful muscle spasm and spastic neurological condition.[1] Tolperisone HCl causes muscle relaxation by its action on central nervous system. It also leads to membrane stabilizer and has analgesic activity. It has also been used in treatment of condition which includes dysmenorrhoea, climacteric complaints, lockjaw, and neurolatyrism. Tolperisone HCl is a "Class-I" drug according to Biopharmaceutics Classification System, possessing both high solubility and high permeability absorption characteristics. Tolperisone HCl is rapidly and completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 0.9-1.0 hours after oral dosing. Tolperisone HCl breaks down into 4-MMPPO [2 Methyl-1-(4-methyl phenyl)-propanone] and piperidine hydrochloride when undergoes into intestinal pH at 4 to 7. Thus the patient is exposed to an uncontrollable quantity of 4-MMPPO which causes genotoxicity. This problem is overcome by controlled release of tolperisone hydrochloride in the stomach at pH 1 to 2.[2] Tolperisone HCl has a short biological half life (1.5 - 2.5 hr). If it is formulated as conventional tablet it will require 150mg -450mg (2-3 times daily) in divided dosage. So it makes the tolperisone hydrochloride an ideal candidate for the control drug delivery.[3]

MATERIALS

Tolperisone HCl was obtained as gift sample from Themis Medicare Ltd, Vapi. Xanthan Gum was kindly gifted from National Pharmaceuticals. Guar Gum and Dibasic calcium phosphate (DCP) was gifted from Alembic Pharmaceutical Ltd, Vadodara. Sodium bicarbonate was obtained as gift sample from Finar Chemicals Ltd, Ahmedabad. Magnesium stearate was gifted from Acme Chemicals, Mumbai and Talc was obtained as gift sample from Lesar Chemicals Ltd, Vadodara.

METHOD

Preparation of Tolperisone HCl Buoyant Tablets

Method: Direct Compression

Direct compression was followed to manufacture the gas generating buoyant tablets of Tolperisone HCl. All the ingredients were accurately weighed and pass through sieve no. 60 before using into formulation. All the ingredients mixed except magnesium stearate and talc geometrically. Required quantity of polymer and sodium bicarbonate as gas generating agent were mixed then Tolperisone HCl is added and mixed properly then diluent is added to make up the weight. The blend obtained was then lubricated by adding magnesium stearate and talc and manually compressed on 10 station rotary tablet machine using caplet punch. The tablets were compressed to obtain hardness in a range of 6-7 Kg/cm^2.

Evaluation of Powder Blend and Tablets [4-10]

Drug-Excipients Compatibility study

Drug-excipients 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 interaction between drug and the excipients used. Fourier transform infrared (FTIR) spectra of Tolperisone hydrochloride, 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 **(Ø)** = $\tan^{-1}h/r$

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 100 mg of drug was transferred to 100 ml of 0.1 N HC1 in volumetric flask. The solution was analyzed at 261 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 261 nm using double beam UV-Vis spectrophotometer. The content of drug was calculated using calibration curve.

Kinetic model for release data [11-14]

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 = $Q_1 = Q_0 + K_0 t$

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 [15, 16]

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)

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. The f_2 value of 100 suggests that the dissolution profiles are similar. The f_2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between releases profile increases.

Dissimilarity factor (f_1)

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. For curves to be considered similar f_1 values should be close to 0.

Accelerated stability study

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 (40^0C ± 2^0C / 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: Composition of Preliminary Batches

FORMULATION INGREDIENT (mg)	FORMULATION BATCH CODE							
	F1	F2	F3	F4	F5	F6	F7	F8
Tolperisone HCl	150	150	150	150	150	150	150	150
Xanthan Gum	150	300	450	600	-	-	-	-
Guar Gum	-	-	-	-	150	300	450	600
$NaHCO_3$	90	90	90	90	90	90	90	90
DCP	495	345	195	45	495	345	195	45
Mg. Stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Talc	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total weight	900	900	900	900	900	900	900	900

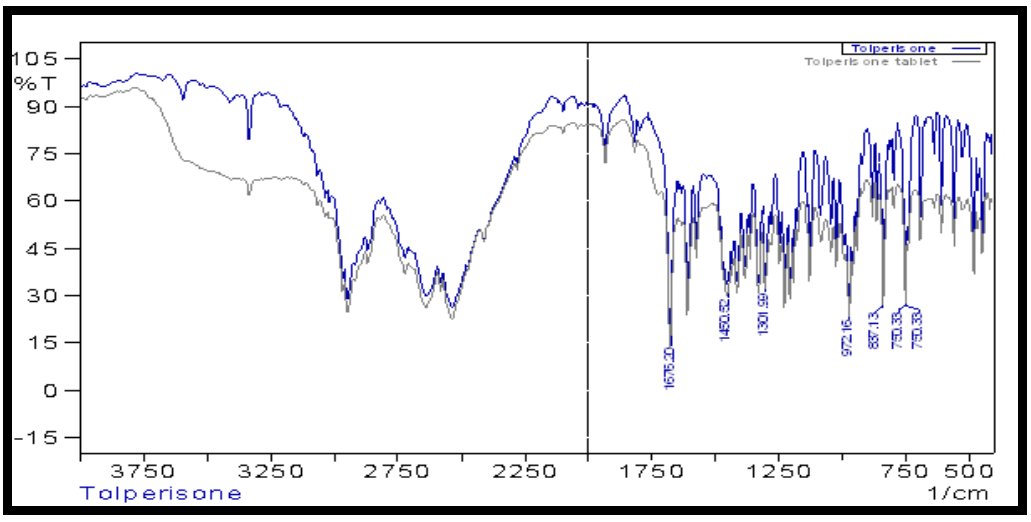

Figure 1: FTIR spectrum of Tolperisone HCl formulation

Table 2: Pre-Compression evaluation parameter of trial batches

Batch code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's Ratio	Carr's Index (%)	Angle of repose (Ɵ)
F1	0.384	0.438	1.14	12.32	27.82
F2	0.39	0.450	1.15	13.33	27.75
F3	0.370	0.413	1.11	10.41	29.42
F4	0.37	0.416	1.12	11.05	29.57
F5	0.362	0.413	1.14	12.34	28.73
F6	0.35	0.396	1.13	11.61	29.93
F7	0.36	0.40	1.12	10	27.89
F8	0.36	0.413	1.14	12.83	27.21

Table 3: Post compression evaluation parameter of trial batches

Batch	Weight variation (mg)±S.D (n=20)	Hardness * (Kg/cm^2) ± S.D	Friability (%)	Content uniformity * (%) ± S.D	Buoyancy	
					FLT (sec)	TFT (Hr)
F1	910±1.44	6.7±0.20	0.62	97.6±0.48	148	>24
F2	885±1.39	6.9±0.18	0.52	102±0.10	185	>24
F3	887±1.53	6.7±0.14	0.58	99.6±0.23	214	>24
F4	898±1.34	6.8±0.15	0.68	98.3±0.62	239	>24
F5	882±1.12	6.8±0.22	0.60	97.6±0.26	182	>24
F6	896±1.47	6.6±0.11	0.58	99.2±0.34	230	>24
F7	904±1.63	6.8±0.18	0.57	103.4±0.42	244	>24
F8	893±1.78	6.7±0.17	0.52	100.2±0.18	277	>24

Table 4: Experimental design: Independent and dependent variables

3^2 full factorial design			
	Independent variables		Dependent variables
Coded value	X1 (Concentration of Xanthan Gum)	X2 (concentration of $NaHCO_3$)	Response (Y)
-1	1:2.5	5%	t_{50}, t_{90}, Q_{12}, floating lag time, diffusion coefficient (n) and release rate constant (k)
0	1:3	10%	
+1	1:3.5	15%	

Table 5: Formulation of factorial design batches tablets

Ingredients (mg)	FORMULATION BATCH CODE								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
Tolperisone HCl	150	150	150	150	150	150	150	150	150
Xanthan Gum	375	450	525	375	450	525	375	450	525
DCP	267	192	117	224	149	74	182	107	32
$NaHCO_3$	42	42	42	85	85	85	127	127	127

Mg. Stearate	8	8	8	8	8	8	8	8	8
Talc	8	8	8	8	8	8	8	8	8
Total Weight	850	850	850	850	850	850	850	850	850

Table 6: Pre-Compression parameters of factorial batches

Batch code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's Ratio	Carr's Index (%)	Angle of repose (Ɵ)
B1	0.476	0.531	1.11	11.32	27.01
B2	0.485	0.546	1.12	11.23	24.83
B3	0.492	0.564	1.14	12.79	28.36
B4	0.480	0.540	1.12	11.11	29.57
B5	0.481	0.550	1.14	12.72	27.02
B6	0.495	0.564	1.14	12.23	23.02
B7	0.490	0.550	1.13	10.90	24.77
B8	0.500	0.568	1.13	11.97	26.11
B9	0.497	0.578	1.16	16.29	25.14

Table 7: Post compression evaluation parameter of factorial batches

Batch	Weight variation (mg) ± S.D (n=20)	Hardness* (Kg/cm^2) ±S.D	Friability (%)	Content uniformity* (%) ±S.D	Buoyancy	
					FLT (sec)	TFT (Hr)
B1	827±1.35	6.6±0.17	0.79	96.72±0.22	557	>24
B2	845±1.19	6.8±0.13	0.73	98.23±0.18	814	>24
B3	859±1.28	6.8±0.14	0.64	98.48±0.36	1189	>24
B4	844±1.15	6.7±0.23	0.76	99.45±0.27	231	>24
B5	835±1.26	6.6±0.14	0.69	99.93±0.17	264	>24
B6	853±1.26	6.7±0.21	0.61	99.89±0.09	267	>24
B7	839±1.74	6.8±0.12	0.74	98.68±0.29	178	>24
B8	841±1.24	6.6±0.15	0.67	100.82±0.25	212	>24
B9	860±1.19	6.8±0.19	0.58	100.43±0.12	236	>24

RESULT AND DISCUSSION

Drug-excipients compatibility study

Fourier transform infrared spectroscopy has been used to study the physical and chemical interaction between drug and the excipients used. Fourier transform infrared (FTIR) spectra of Tolperisone hydrochloride, 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.

Results 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, Hausner's ratio, Carr's index, and angle of repose, are shown in table 2. The bulk density was varied in the range of 0.35 gm/ml to 0.39 gm/ml, tapped density range between 0.396 gm/ml to 0.450 gm/ml, Hausner's ratio range between 1.11 - 1.15, Carr's index was varied in the range of 10 % to 13.33 % and angle of repose was varied in the range of 27.21° to 29.93°. This all parameters show good flow property and direct compressibility.

Results of Pre-Compression evaluation parameter of factorial batches

Results of Pre-Compression evaluation parameter of factorial batches are shown in table 6. Bulk density of all the factorial batches showed between 0.476 gm/ml to 0.500 gm/ml. Tapped density of all the factorial batches showed between 0.531 gm/ml to 0.578 gm/ml. The results of the Hausner's ratio of all the factorial batches (less than 1.18) and the Angle of Repose of all the factorial batches (20°-30°) reflected that the powder blend had good flow property. So the flow of prepared mass from the hopper was able to fill the die completely for compression. The Carr's index obtained was less than 17% so that showed good compressibility of mass. After the lubrication the blend ready for compression had good flow property and excellent compressibility.

Results of Post-Compression evaluation parameter of trial batches

Tolperisone HCl floating tablets were prepared and evaluated for hardness, friability and drug content uniformity. The results are shown in the table 3. All the batches showed weight variation in the range of 885mg to 910mg. All the batches showed hardness in the range of 6.7 kg/cm^2 to 6.9 kg/cm^2. Friability of the all batches showed in the range of 0.52% to 0.68%. In Friability test, the pharmacopoeia limit for friability of tablets should be less than 1% w/w. Hence, all formulations complies the friability test as per IP. All the batches F1-F8 shows drug content ranges between 97.6% to 103.4%.

Results of Post-Compression evaluation parameter of factorial batches

Results of post-compression evaluation parameter of factorial batches are shown in table 7. All the batches showed weight variation in the range of 827mg to 860mg. All the batches showed hardness in the range of 6.6 kg/cm^2 to 6.8 kg/cm^2. Friability of the all batches showed in the range of 0.58% to 0.79%. In Friability test, the pharmacopoeia limit for friability of tablets should be less than 1% w/w. Hence, all formulations complies the

friability test as per IP. All the batches F1-F8 shows drug content ranges between 96.72% to 100.82%.

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

The results of *in vitro* drug release study are depicted in figure 2 and 3.

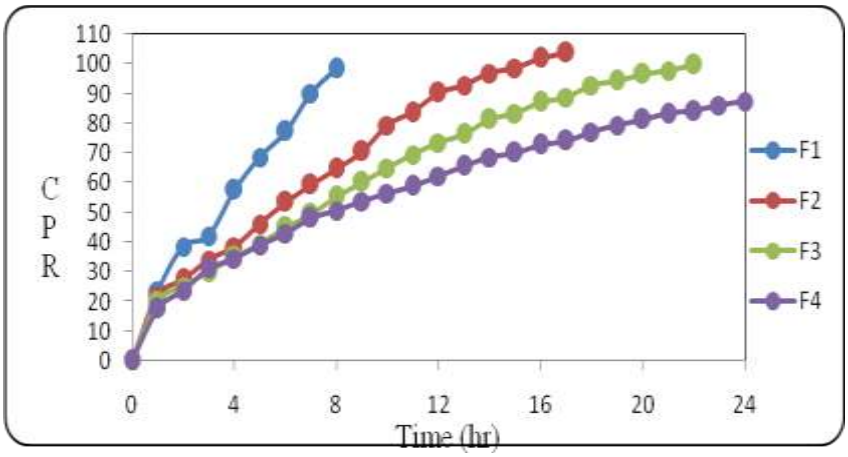

Figure 2: In-vitro Drug release studies of preliminary batches of F1 to F4

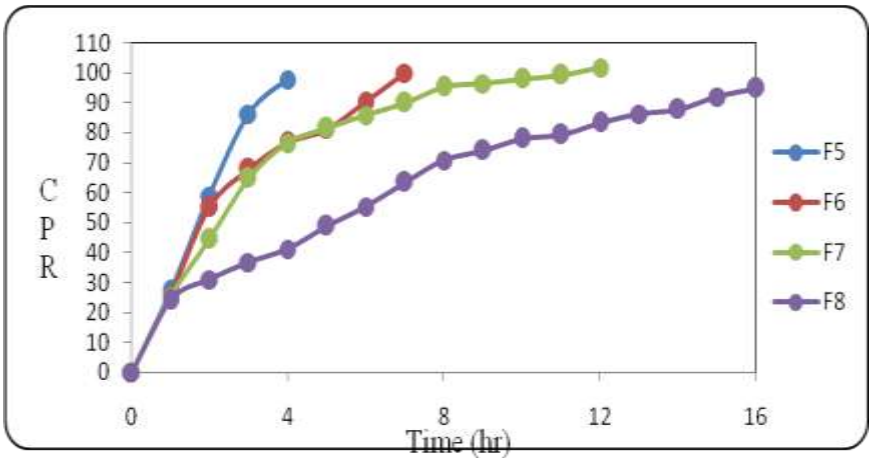

Figure 3: In-vitro drug release studies of preliminary batches F5 to F8

From the dissolution profile it was observed that there was significant outcome of different polymers and polymer load on drug release. All batches exhibit initial burst release of drug due to rapid dissolution of drug from tablet surface. Formulations containing higher viscous polymer and higher amount of polymer have slower drug release rates when compared to formulations with lower viscous polymer and lower amount of polymer. Formulation F1 contain 150 mg Xanthan Gum shows release 98.44% in 8 hr. F2 contain 300 mg Xanthan Gum shows release 102.02% in 16 hr. F3 contain 450 mg Xanthan Gum shows release 99.65% in 22 hr. F4 contain 600 mg Xanthan Gum shows release 87.46% in 24 hr. F5 contain 150 mg Guar Gum shows release 97.81% in 4 hr. F6 contain 300 mg Guar Gum shows

release 99.93% in 7 hr. F7 contain 450 mg Guar Gum shows release 101.61% in 12 hr. F8 contain 600 mg Guar Gum shows release 94.83 % in 16 hr. Results revealed that the drug release rate was decreased as polymer weight and viscosity increases. All the formulations were floated.F3 formulation shows release up to 22 hr and F4 formulation shows release greater than 24 hr which contain 450 mg and 600 mg Xanthan Gum respectively So finally, it was concluded that the concentration of xanthan gum can be required between 1:3 and 1:4 of drug to polymer ratio which can be used as relese retarding polymer in the formulation of Tolperisone HCl floating drug delivery system.

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

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

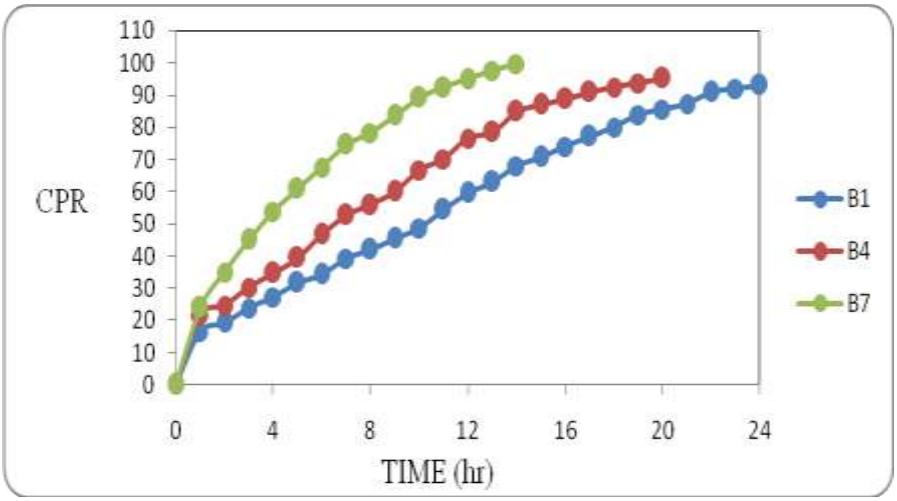

Figure 4: In-vitro Drug release studies of factorial batches of B1, B4 and B7

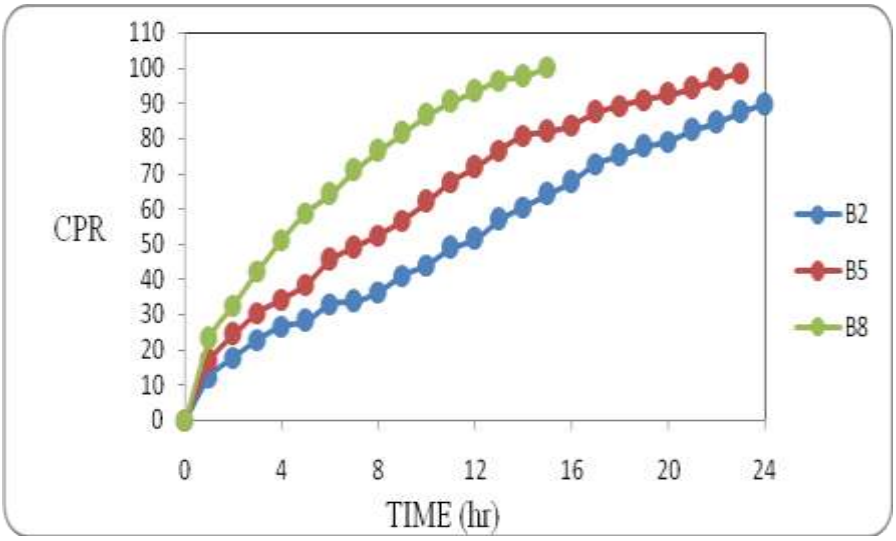

Figure 5: In-vitro Drug release studies of factorial batches of B2, B5 and B8

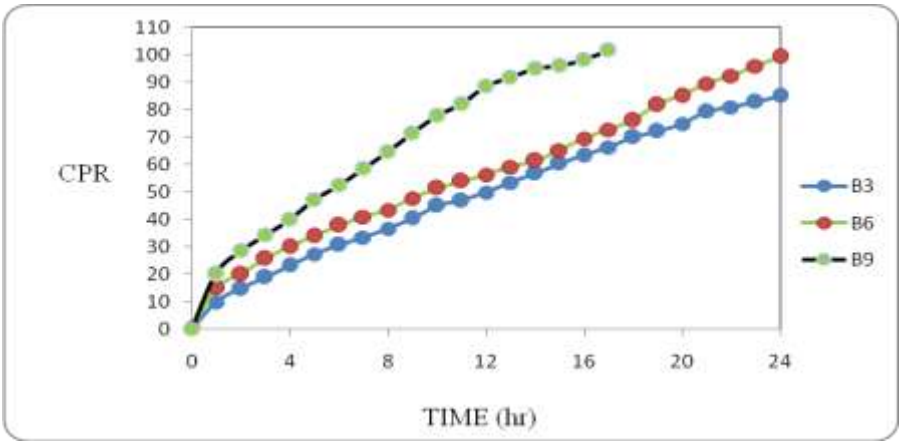

Figure 6: In-vitro Drug release studies of factorial batches of B3, B6 and B9

The formulation batches B1 to B3 contains concentration of Xanthan Gum (Drug to Polymer ratio were 1:2.5, 1:3, 1:3.5) and concentration of sodium bicarbonate was 5%. Batch B1 to B3 shows the slow drug release because of sodium bicarbonate is very low so gas generating property is very less so time for releasing the drug from matrix was high and also release rate of drug decreased as the concentration of Xanthan Gum increase.B1 release 93.02% drug at the end of 24th hr, B2 release 89.62% drug at the end of 24th hr, B3 release 85% drug at the end of 24th hr. The formulation batches B4 to B6 contains concentration of Xanthan Gum (Drug to Polymer ratio were 1:2.5, 1:3, 1:3.5) and this all batches contain 10 % sodium bicarbonate. The release of the drug was found higher as the concentration of sodium bicarbonate increase the gas generation is high when come in to contact with acid media and also floating lag time decreases as compared to batch B1 to B3 batches. B4 release 95.30% drug at end of 20th hr, B5 release 98.66% at the end of 23th hr, B6 release 99.27% drug at the end of 24th hr. Batches B7 to B9 contain concentration of Xanthan Gum (Drug to Polymer ratio were 1:2.5, 1:3 and 1:3.5) and this all formulations contain 15 % sodium bicarbonate. Batch B7 to B9 shows higher drug release rate than other batches.B7 release 99.73% drug at the end of 14th hr. B8 release 100.29% drug at the end of 15th hr. B9 release 101.60% drug at the end of 17th hr.

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 (FLT)	n	k
	X1	X2						
B1	-1	-1	10.05	21.34	56.89	557	0.622	0.126
B2	0	-1	11.35	23.12	52.2	814	0.654	0.107
B3	1	-1	12.22	24.5	49.26	1189	0.704	0.088

B4	-1	0	7	16.61	70.79	231	0.571	0.175
B5	0	0	7.61	18.46	66.17	264	0.591	0.159
B6	1	0	10.07	21.5	56.74	267	0.609	0.130
B7	-1	1	3.76	10.81	96.75	178	0.550	0.245
B8	0	1	4.26	11.89	92.75	212	0.562	0.231
B9	1	1	5.66	13.31	83.14	236	0.606	0.185

Full and reduced model for t_{50} (hr)

$Y1= 7.968 + 1.19 (X_1) – 3.323 (X_2) + 0.386 (X_1X_1) - 0.343 (X_2X_2) - 0.0675 (X_1X_2)$

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	7.968	1.19	-3.32	0.386	-0.343	-0.067	0.989	0.0035
p Value	0.0002	0.0108	0.0005	0.3658	0.4149	0.8100	-	-
RM	7.997	1.19	-3.32	-	-	-	0.982	5.55E-06

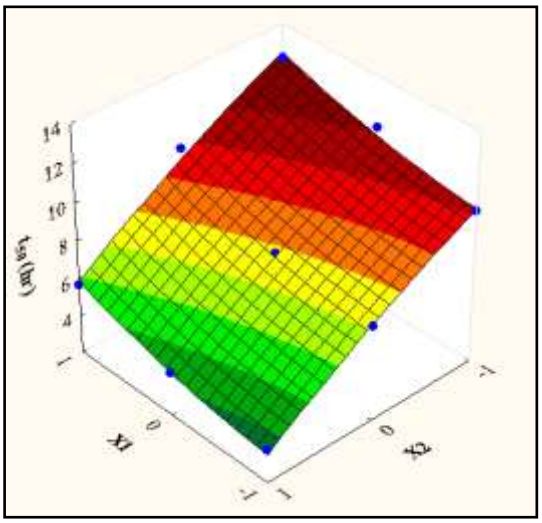

Figure 7: Response surface plot for t_{50}

Response surface plot shows that X1 as concentration of drug to polymer ratio 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 increases and X2 concentration of sodium bicarbonate increase from level -1 to 1 the more acid is penetrated in matrix so time required to release 50% of drug decreases.

Full and reduced model for t_{90} (hr)

$Y1 = 18.731 + 1.758 (X_1) – 5.491 (X_2) + 0.188 (X_1X_1) – 1.361 (X_2X_2) - 0.165 (X_1X_2)$

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	18.731	1.758	-5.491	0.188	-1.361	-0.165	0.992	0.00238
p Value	5.53E-05	0.0099	0.0003	0.7414	0.0792	0.684	-	-
RM	17.948	1.758	-5.491	-	-	-	0.973	1.95E-05

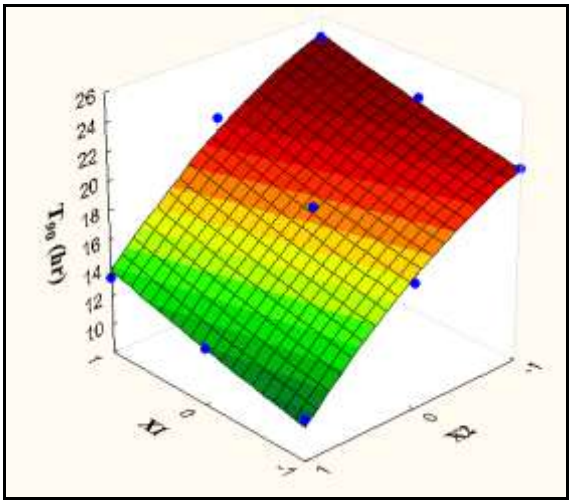

Figure 8: Response surface plot for t_{90}

Response surface plot shows that X1 as concentration of drug to polymer ratio 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 increases and X2 concentration of sodium bicarbonate increase from level -1 to 1 the more acid is penetrated in matrix so time required to release 90% of drug decreases.

Full and reduced model for Q_{12} (%)

$Y1 = 65.53 – 5.881 (X_1) + 19.048 (X_2) – 1.445 (X_1X_1) + 7.265 (X_2X_2) – 1.495 (X_1X_2)$

Summary of results of regression analysis for Q_{12} (%)

Response Q12 (%)	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2	P
FM	65.53	-5.881	19.048	-1.445	7.265	-1.495	0.996	0.0007
p Value	1.79E-05	0.0038	0.0001	0.3310	0.0101	0.1890	-	-
RM	64.566	-5.88	19.048	-	7.265	-	0.991	1.54E-05

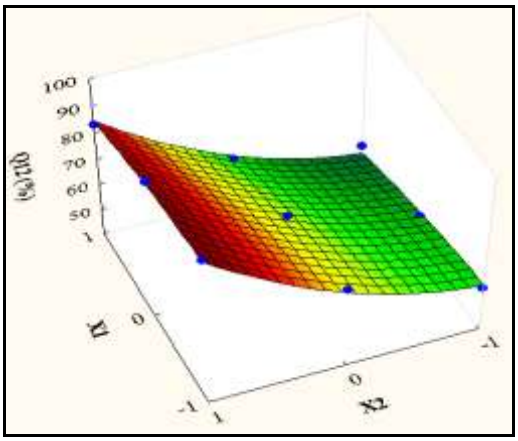

Figure 9: Response surface plot for Q_{12}

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so release rate of the drug (% drug release at 12^{th} hr) is decrease and X2 concentration of sodium bicarbonate increase from level -1 to 1 the more acid is penetrated in matrix so release rate of the drug (% drug release at 12^{th} hr) is increased.

Full and reduced model for Floating lag time (sec)

$Y1= 245.33 + 121 (X_1) – 322.33 (X_2) + 13 (X_1X_1) + 277 (X_2X_2) – 143.5 (X_1X_2)$

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	245.33	121	-322.33	13	277	-143.5	0.965	0.0211
p Value	0.0535	0.0687	0.005	0.8738	0.0347	0.0739	-	-
RM	254	-	-322.33	-	277	-	0.791	0.0090

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so floating lag time is increase and X2 concentration of sodium bicarbonate increase from level -1 to 1 the more acid is penetrated in matrix so floating lag time is decreased.

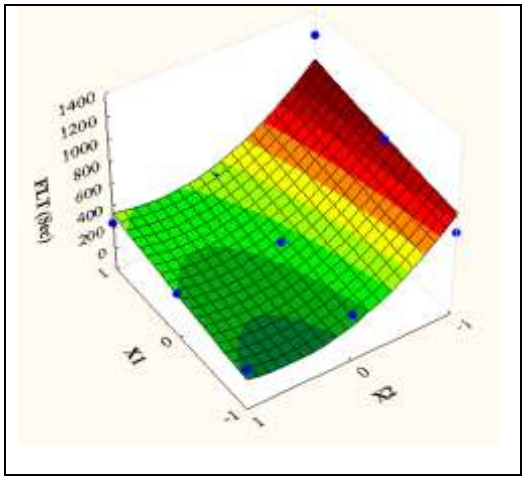

Figure 10: Response surface plot for FLT (sec)

Full and reduced model for Diffusion exponent (n)

$Y1 = 0.585 + 0.029 (X_1) – 0.043 (X_2) + 0.008 (X_1X_1) + 0.025 (X_2X_2) – 0.006 (X_1X_2)$

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	0.585	0.029	-0.043	0.008	0.025	-0.006	0.976	0.0121
p Value	8.14E-06	0.0096	0.0031	0.4124	0.0566	0.3538	-	-
RM	0.608	0.029	-0.043	-	-	-	0.887	0.0014

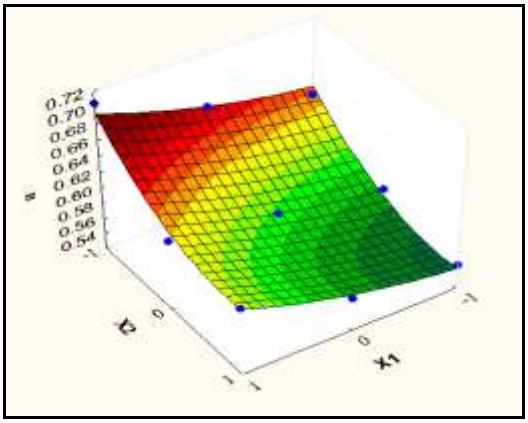

Figure 11: Response surface plot for n

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so diffusion exponent is increase and X2 concentration of sodium bicarbonate increase from level -1 to 1 the more acid is penetrated in matrix so is diffusion exponent decreased.

Full and reduced model for Release rate constant (k)

$Y1= 0.159 - 0.023 (X_1) + 0.056 (X_2) - 0.006 (X_1X_1) + 0.008 (X_2X_2) – 0.005 (X_1X_2)$

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	0.159	-0.023	0.056	-0.006	0.008	-0.005	0.995	0.0008
p Value	3.85E-05	0.0018	0.0001	0.1754	0.1080	0.1319	-	-
RM	0.161	-0.023	0.056	-	-	-	0.979	8.98E-06

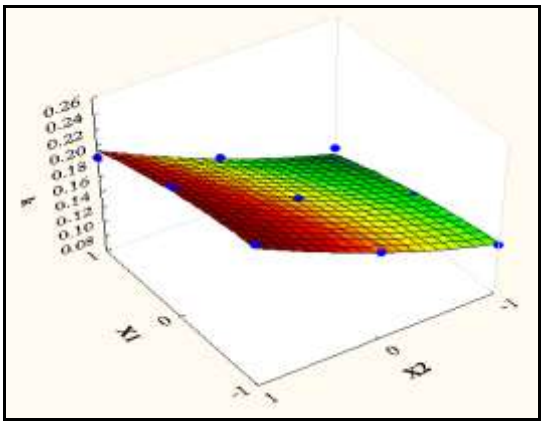

Figure 12: Response surface plot for k

Response surface plot shows that X1 as concentration of drug to polymer ratio increase from level -1 to 1 the stiff gel is formed due to increase in the gel strength so release rate constant is decrease and X2 concentration of sodium bicarbonate increase from level -1 to 1 the more acid is penetrated in matrix so is release rate constant increased.

Result of kinetic treatment of dissolution data

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

Table 9: Kinetic treatment of dissolution data

	B1	B2	B3	B4	B5	B6	B7	B8	B9
Zero order									
S	3.542	3.397	3.285	4.163	3.688	3.502	5.676	5.429	5.229
I	14.392	11.449	10.185	20.859	21.932	14.736	28.644	27.624	20.413
R^2	0.995	0.997	0.998	0.986	0.983	0.998	0.976	0.976	0.989
First order									
S	0.030	0.032	0.034	0.033	0.029	0.030	0.041	0.039	0.040
I	1.333	1.275	1.223	1.426	1.429	1.345	1.515	1.503	1.431
R^2	0.960	0.959	0.943	0.950	0.929	0.960	0.922	0.921	0.949
Higuchi									
S	22.161	21.141	20.382	24.237	23.037	21.754	28.627	28.208	28.274
I	-15.781	-17.116	-17.573	-10.164	-9.672	- 14.584	-3.615	-5.050	-13.349

R^2	0.990	0.987	0.993	0.993	0.996	0.986	0.997	0.997	0.995
Hixon Crowell									
S	-1.180	-1.132	-1.086	-1.388	-1.229	-1.167	-1.892	-1.810	-1.743
I	28.535	29.517	29.938	26.380	29.023	28.421	23.785	24.125	26.529
R^2	-0.995	-0.997	-0.998	-0.986	-0.983	-0.998	0.976	-0.976	-0.989
Korsmeyer and Peppas									
n	0.622	0.654	0.705	0.572	0.592	0.609	0.551	0.563	0.607
I	-0.898	-0.970	-1.051	-0.755	-0.798	-0.884	-0.609	-0.636	-0.732
R^2	0.988	0.992	0.998	0.988	0.997	0.994	0.998	0.998	0.996
S= slope, I= intercept, R^2= square of correlation coefficient, n= diffusion exponent									

Comparison of dissolution profiles for selection of optimum batch

Table 10: Similarity Factor *(f_2)* and Dissimilarity factor *(f_1)* for B1-B9

Batch	Similarity factor *(f_2)*	Dissimilarity factor *(f_1)*
B1	71.52	5.95
B2	69.58	5.45
B3	58.81	9.78
B4	39.82	32.08
B5	45.53	21.35
B6	74.41	4.24
B7	23.61	89.53
B8	24.89	80.06
B9	30.23	56.07

The values of Dissimilarity factor (f_1) for batches B1, B2, B3, and B6 were less than 15 compared with theoretical dissolution profile (Table 10) indicating good similarity in dissolution (Table10). The batch B6 showed minimum value of f_1 (4.24).

The values of similarity factor (f_2) for batches B1, B2, B3, and B6 were greater than 50 compared with theoretical dissolution profile (Table 10) indicating good similarity in dissolution (Table10). The batch B6 showed maximum value of f_2 (74.41).

Result of accelerated stability study

Table 11: Result of tablet parameter of Accelerated Stability Study

Parameter	Initial	After 21 day
Hardness (kg/cm^2)	6.7	6.8
Friability (%)	0.61	0.64
Floating lag time (sec)	267	273
Total floating time (hr)	>24	>24
Drug content (%)	99.89	99.76
similarity factor (f_2)	74.41	76.41
Dissimilarity factor (f_1)	4.24	3.86

CONCLUSION

The present investigation was aimed to formulate and evaluate floating tablet of Tolperisone HCl were prepared by direct compression method based on natural polymers (e.g. Xanthan Gum and Guar Gum) as matrix forming material and different concentration of sodium bicarbonate as gas generating agents.

FTIR spectroscopy indicates that the drug is compatible with the polymer. The drug content was uniform in all the formulation of the tablets prepared. Xanthan Gum retards the drug release more as compared to Guar Gum. The polymer concentration was found to influence the release of drug from the formulation. As the polymer level was increased, the release rates were found to be decrease. Amount of sodium bicarbonate has influence on floating lag time. It was found that increases in the concentration of sodium bicarbonate decrease the floating lag time and increase the drug release rate. It was found that 10% sodium bicarbonate is required to attain buoyancy.

The concentration of Xanthan Gum and sodium bicarbonate were successfully optimized by using 3^2 factorial design. From the 3^2 factorial design and different graphical representation, it was finalized that batch B6 was found to be optimized batch having drug release upto 24 hr. More ever, the dissolution profile of optimized batch B6 was found to be similar with theoretical drug release profile having similarity factor more than 50 (f_2=74.41) and dissimilarity factor less than 15 (f_1=4.24) which reflects the feasibility of the optimization procedure in successful development of floating matrix tablet containing Tolperisone HCl by using Xanthan Gum.

Various kinetic models confirmed that *in vitro* release kinetic of optimized formulation (B6) was best fitted into zero order model and Higuchi with anomalous non Fickian release mechanism. The optimized batch was found to be stable after 21 days at accelerated condition.

REFERENCES

1. Tripathi KD. Essential of Medical Pharmacology; 6th Edn; Jaypee Brothers Medical Publisher LTD, 2006, pp 339.
2. http:// www.patentbuddy.com,
   Welzig s, Rothenburger J, Kalz B, Gungl J and Gerdes K. Tolperisone hydrochloride controlled release tablet. United State Patents USP 20100249423.

3. http://www.mims.com/USA/drug/info/tolperisone
4. Chatwal GR., and Anand SK. Instrumental Method of Chemical Analysis; 5th Edn; Himalaya Publishing House, 2002, 82, pp 29-30.
5. Flese EF., Hugen TA., and Lachman L. In Preformulation; The theory and Practice of Industrial Pharmacy; 4th Edn; Varghese Publishing House, Mumbai, 1987, pp 171.
6. Wells JI., and Aulton ME. In Preformulation; Pharmaceutics The Science of Dosage Form Design; 2nd Edn; Churchill Livingstone, 2002, pp 223.
7. Cooper J., Gun C., and Carter SJ. In Powder Flow and Compaction; Tutorial Pharmacy; CBS Publishers and Distributors, 1986, pp 211.
8. Martin A. In Micromeretics; Physical Pharmacy; 4th Edn; B.I. Waverly Pvt. Limited, 1997, pp 423.
9. Indian Pharmacopoeia, Volume I, The Indian Pharmacopoeia Commission, Ghaziabad, India, 6th Edn, 2010, 192-193.
10. Patel VF, Patel NM and Yeole PG, "Studies on formulation and evaluation ranitidine floating tablets." *Ind. J. Pharm. Sci.* **2005**, *67(6)*, 703-709.
11. Coasta P, Manuel J, and Labao S. "Modelling and comparison of dissolution profiles." *Euro. J. Pharma. Sci.* **2002**, *13*, 123-133.
12. Higuchi T, "Rate of release of medicament from ointment bases containing drugs in suspension." *J. Pharm. Sci*. **1961**, *50*, 874.
13. Hixon AW and Crowell JH, "Dependence of reaction velocity upon surface and agitation theoretical consideration." *Ind. Eng. Chem*. **1931**, *23*, 923.
14. Korsemeyer RW, Ginnu R, Doelker E, Buri P and Peppas NA, "Mechanism of solute release from porous hydrophilic polymers." *J. Pharm.* **1983**, *15*, 25.
15. Costa P, "An alternative method to evaluation of similarity factor in dissolution testing." *Int. J. Pharm.* **2001**, *220*. 77- 83.
16. Moore JW and Flanner HH, "Mathematical comparison of dissolution profiles." *Pharm. Technol.* **1996**, *20(6)*, 67-74.