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RESEARCH ARTICLE

FORMULATION DEVELOPMENT AND EVALUATION OF DILTIAZEM HYDROCHLORIDE GASTRO RETENTIVE FLOATING TABLETS

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ABSTRACT

The investigation was concerned with design and characterization of oral sustained release gastro retentive floating tablets of DiltiazemHCl in order to improve efficacy and better patient compliance. Present investigation was to formulate, evaluate and optimize gastro retentive tablet of DiltiazemHCl. This tablets released drug till 24 hrs due to floating mechanism of polymers. Gastro retentive floating tablets were prepared by direct compression method using various proportions of polymersHPMC K4M, HPMC K100M,Carbopol 934, Ethyl cellulose, Xanthan gum along with Sodium bicarbonatethe sustained release behaviour of the fabricated tablets was investigated. Tablets were prepared by directcompretiontechnique.Formulation was optimized on the basis of acceptable tablet properties and *in vitro* drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and low friability. All tablets but one exhibited gradual and near-complete sustained release for DiltiazemHCl (90-100%) at the end of 24 h. The results of dissolution studies indicated that formulation Dtz15 was found to be most successful as it exhibits drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on increasing polymer ratio.

Key Words: Sustained release, Gastro retentive floating, Diltiazim HCL, HPMC K100M, Carbopol 934.

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day. This results in a significant fluctuation in drug levels. The most important objectives of these new drug delivery systems are: first, it would be single dose, which releases the active ingredient over an extended period of time. Second, it should deliver the active entity directly to the site of action, thus, minimizing or eliminating side effects. To overcome the limitations of conventional drug delivery system, floating tablets have been developed. Drugs that have narrow absorption window in the gastrointestinal tract will have poor absorption. For these drugs, gastro retentive drug delivery systems offer the advantages in prolonging the gastric emptying time.

MATERIALS AND METHODS

DiltiazemHCl was gift sample from Devi's laboratories Ltd, India andHydroxypropyl methyl cellulose K4M (HPMC K4M) from Colorcon Asia Pvt.Limited, Goa, India and Hydroxypropyl methyl cellulose K100M (HPMC K100M) from Colorcon Asia Pvt. Limited, Goa, India and Carbopol 934S. D. Fine Chemicals Ltd. Mumbai, India and Ethyl cellulose Asha cellulose Pvt. Ltd, India and Xanthan gum from Otto ChemicaBiochemica Reagents, India and Sodium bicarbonate, Lactose and Hydrochloride Acid obtained from Finar chemicals, Ahmadabad, India and Micro crystalline cellulose (MCC) obtained from Acme pharmaceuticals, Kherva (Gujarat), India and Talc and Magnesium stearate obtained from S. D. Fine Chemicals Ltd. Mumbai, India.

Method forpreparation of DiltiazemHCL floating tablets

All the ingredients weigh accurately the required quantity and mix thoroughly to get uniform powder blend passed through 60 # sieve. Talc and Magnesium stearate were finally added as glidant and lubricant respectively and finally compressed with the help ofrimek mini tablet press II MT.

FORMULATION

Preliminary trials of DiltiazemHCl formulation: In present investigation attempt was made to prepare sustained (gastro retentive layer) release formulation of diltiazemHCl using different grades of HPMC, ethyl cellulose, xanthan gum and carbopol as polymers by direct compression techniques using rimek mini tablet press machine.

In preliminary study, different batches were prepared as per the composition given in Table 1. It was found that the batches Dtz3, Dtz4 and Dtz6 show the premature drug release in the initial first hour. That may be due to disintegration of the tablet before the gel formation occurs by the polymer. Batches Dtz1, Dtz2, Dtz5 and Dtz8 shows the release retardation up to some extends but that was not up to the 24 hrs. Batch Dtz7 shows the good release retardation but the drug release in the first hour is higher due to the burst release of the drug. This initial burst release may be occurs due to the rapid hydration of the polymer (HPMC K100M)which is hydrophilic in nature. While the dissolution study of batch Dtz9 shows the decrease in initial burst release of the drug and sustained effect up to 24.0 hrs having 98.88% releases at the end of 24.0 hrs. The combination of HPMC K100M and carbopol-934 forms the gel having the higher viscosity that may be responsible for the decrease in initial burst release of drug and for the sustained effect up to 24 hrs. Therefore, the composition of batch Dtz9 was selected for further work.

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Table 1: Preliminary trial formulation for DiltiazemHCl tablets

Ingredient	Batches								
	Dtz1	Dtz2	Dtz3	Dtz4	Dtz5	Dtz6	Dtz7	Dtz8	Dtz9
DiltiazemHCl	120	120	120	120	120	120	120	120	120
HPMC K4M	75	-	-	-	-	-	-	20	-
HPMC K100M	-	75	-	-	55	35	100	80	80
Ethyl cellulose	-	-	75	-	40	40	-	-	-
Xanthan gum	-	-	-	75	-	-	-	-	-
Carbopol-934	-	-	-	-	-	-	-	-	20
NaHCO3	50	50	50	50	50	50	50	50	50
MCC	100	100	100	100	100	100	100	100	100
Lactose	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Mg Stearate	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10
Total wt.	500	500	500	500	500	500	500	500	500

** All the ingredients are in mg.*

Optimization of tablet formulation using 3^2 full factorial designs: It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hours and raw materials. Traditionally pharmaceutical formulations are developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions.

The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Y_i) is measured for each trial.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \qquad (1)$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed.

A 3^2randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The design layout and coded value of independent factor is shown in Table 2 and Table 3 respectively. The factors were selected based on preliminary study. The Content of HPMCK100M (X_1) and Content of Carbopol-934 (X_2) were selected as independent variables.

The selected dependent variables are given below:

Y_1 = Cumulative percentage release (CPR) at 1hr (Q_1)
Y_2 = Cumulative percentage release (CPR) at 16hr (Q_{16})
Y_3 = Floating lag time study in seconds (FLT)

The formulations of the factorial batches (Dtz9 to Dtz17) are shown in Table 4.

Table 2: Full factorial design Layout

Batch code	X_1	X_2
Dtz9	-1	-1
Dtz10	-1	0
Dtz11	-1	1
Dtz12	0	-1
Dtz13	0	0
Dtz14	0	1
Dtz15	1	-1
Dtz16	1	0
Dtz17	1	1

Table 3: Coded values for content of HPMC K100M & content of carbopol-934

Coded value	Content of HPMCK100M (mg) X_1	Content of carbopol-934 (mg) X_2
-1	80	20
0	100	30
1	120	40

On the basis of the preliminary trials in the present study a 3^2 full factorial design was employed to study the effect of independent variables, i.e. content of HPMC K100M(X_1) and content of carbopol(X_2) on dependent variables like %drug release at 1 hr.(Q_1), %drug release at 16 hr.(Q_{16}),& floating lag time.The results clearly indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (Dtz9 to Dtz17).The fitted equations (full models) relating the responses (i.e. Q_1, Q_{16}& FLT) to the transformed factor were shown in Table 4.The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative.The values of the coefficient are shown in Table 5. and the polynomial equations can be obtained as follows by using the values of coefficient.

Table 4: Effect of Independent variable on dependent variable by 3^2 full factorial design for DiltiazemHCl

Formulation code	Independent variable		Dependent variables		
	X_1	X_2	Q_1	Q_{16}	FLT(sec.)
Dtz9	-1	-1	16.99	87.98	157
Dtz10	-1	0	15.30	87.92	168
Dtz11	-1	+1	14.45	85.19	181
Dtz12	0	-1	16.81	83.68	169
Dtz13	0	0	15.97	80.78	177
Dtz14	0	+1	13.44	79.54	180
Dtz15	+1	-1	16.80	74.51	184
Dtz16	+1	0	12.20	74.96	195
Dtz17	+1	+1	12.11	73.25	207

Table 5: Summary of regression analysis

Coefficients	Q_1	Q_{16}	FLT
b_0	15	81.68	175.55
b_1	-0.9383	-6.395	13.33
b_2	-1.7666	-1.365	9.66
b_{12}	-0.5375	0.3825	-0.25
b_{11}	-0.765	-0.6983	6.66
b_{22}	0.61	-0.5283	-0.33
R^2	0.8925	0.9871	0.9679

$Q_1 = 15 - 0.9383X_1 - 1.7666X_2 - 0.5375X_1X_2 - 0.765X_1^2 + 0.61X_2^2$ (2)
$Q_{16} = 81.68 - 6.395X_1 - 1.365X_2 + 0.3825X_1X_2 - 0.6983_1^2 - 0.5283X_2^2$ (3)
$FLT = 175.55 + 13.33X_1 + 9.66X_2 - 0.25X_1X_2 + 6.66X_1^2 + 0.33X_2^2$ (4)

Table 6: Formulation using 3^2 full factorial designs

Ingredients	Batches								
	Dtz9	Dtz10	Dtz11	Dtz12	Dtz13	Dtz14	Dtz15	Dtz16	Dtz17
DitiazemHCl	120	120	120	120	120	120	120	120	120
HPMCK10M	80	80	80	100	100	100	120	120	120
Carbopol-934	20	30	40	20	30	40	20	30	40
$NaHCO_3$	50	50	50	50	50	50	50	50	50
MCC	100	100	100	100	100	100	100	100	100
Lactose	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Mg. stearate	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10
Total weight	500	500	500	500	500	500	500	500	500

**** All the ingredients are in mg.***

EVALUATION OF BLEND:

a) Bulk density: Weight accurately the powder drug, which was previously passed through 20# sieve and transferred in 100 ml graduated cylinder. The powder was carefully level without compacting, and read the unsettled apparent volume. The apparent bulk density was calculated in gm/ml.

b) Tapped density: Accurately weighed the powder drug, which was previously passed through 20# sieve and transferred in 100 ml graduated cylinder. Initial volume was observed. The cylinder was tapped up to constant volume.

c) Compressibility index: The compressibility of the powder was determined by the Carr's compressibility index using the following formula.

$$\text{Carr's index} = \frac{[(TD - LD) \times 100]}{TD} \quad (5)$$

Where, TD-tapped density and LD-loose bulk density

d) Hausner's ratio: The Hausner's ratio is a number that is correlated to the flowability of a powder material**.**

$$Hausner's ratio = \frac{TD}{BD} \quad (6)$$

5) Angle of repose: The angle of repose of powder blend was determined by funnel method. Accurately weighed powder drug was taken in a funnel. Height of the funnel was adjusted in such ways that tip of the funnel just

touches the apex of the powder drug. The powder mix was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation;

$$\tan\theta = \frac{h}{r} \qquad (7)$$

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

Table No. 7: Physical properties of powder blend containing DiltiazemHCl

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of Repose (θ)	Hausner's ratio	Percentage compressibility
Dtz9	0.355±0.02	0.390±0.04	34.9±0.02	1.09±0.03	10.25±0.02
Dtz10	0.327±0.03	0.360±0.03	29.23±0.02	1.10±0.02	9.1±0.03
Dtz11	0.331±0.04	0.365±0.02	28.36±0.01	1.10±0.03	9.31±0.03
Dtz12	0.194±0.03	0.218±0.04	34.23±0.02	1.12±0.03	11±0.02
Dtz13	0.296±0.03	0.323±0.06	32.12±0.03	1.09±0.04	8.3±0.03
Dtz14	0.250±0.02	0.269±0.02	31.89±0.01	1.07±0.02	7.06±0.04
Dtz15	0.260±0.04	0.290±0.03	32.49±0.03	1.11±0.04	10.34±0.04
Dtz16	0.246±0.04	0.265±0.02	31.87±0.02	1.07±0.03	7.31±0.03
Dtz17	0.276±0.03	0.300±0.04	34.12±0.04	1.08±0.02	8±0.02

EVALUATION OF FORMULATED TABLET

1. Weight variation

20 tablets were selected randomly from the lot and weighed individually to check for weight variation. Weight variation specification as per I.P.

Table 8: Weight Variation Specification as per IP

Average Weight of Tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

2. Hardness

Hardness or tablet crushing strength (f_c) (the force required to break a tablet in a diametric compression) was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

3. Friability (F)

Friability of the tablet determined using Roche friabiltor. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at l height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W(initial) - W(final)}{W(initial)} * 100 \qquad (8)$$

Table 9: Physical parameters of prepared tablet containingDiltiazemHCl

Bathes	Weight variation (mg)	Hardness (kg/cm^2)	%Friability	Drug content
Dtz9	497 ± 2.78	5.7 ± 0.18	0.77±0.08	100.52±1.24
Dtz10	500 ± 2.95	5.6 ± 0.39	0.85±0.07	99.32±1.86
Dtz11	496 ± 2.58	5.8 ± 0.47	0.67±0.04	99.01±1.40
Dtz12	503 ±2.45	5.6 ± 0.35	0.87±0.03	101.09±1.96
Dtz13	496 ± 2.37	5.8 ± 0.24	0.74±0.10	99.74±1.34
Dtz14	503 ± 2.75	5.9 ± 0.14	0.86±0.09	100.57±1.21
Dtz15	500 ± 2.78	5.7 ± 0.48	0.79±0.05	100.04±1.15
Dtz16	496 ± 2.86	6.0 ± 0.34	0.95±0.03	98.75±2.32
Dtz17	502 ± 2.77	6.1 ± 0.27	0.74±0.07	97.33±3.83

All the tablet formulations showed acceptable physical parameters and complied with the in house specifications for weight variation, hardness and friability. Results are shown in Table 9. Hardness above 3 to 5 kg/cm^2 is sufficient to prevent breaking of tablets in handling as well as during packaging. Friability below 1 % prevents loss of material during handling. Weight variation is also

important consideration, which is ultimately responsible for content uniformity.

***In vitro* buoyancy studies:** *In vitro* buoyancy studies of all factorial design batches were carried out as per the procedure given before. All the different formulation has floating lag time less than 4 minutes. The pictorial results of *in vitro* buoyancy study of the best batch are shown in Figure 1. This clearly depicts the floating lag time, stable and persistent buoyancy.All the preliminary trial batches were containing different concentration of polymer blend in order to optimize content of polymer blend for desirable floating time and floating lag time.

Table 10: Floating lag time and floating time of formulation:

Parameters	Dtz9	Dtz10	Dtz11	Dtz12	Dtz13	Dtz14	Dtz15	Dtz16	Dtz17
Floating lag time(sec.)	157	168	181	169	177	180	184	195	207
Floating time (hr.)	>24	>24	>24	>24	>24	>24	>24	>24	>24

Table 10. shows floating lag time and Floating time of different formulation. Batch Dtz9, containing 16% of HPMCK100M and 4% of Carbopol shows good floating time that is more than 24 hrs and floating lag time is 157 sec. Therefore these combinations of polymers were optimized for further study. Other batches Dtz2, Dtz7 and Dtz8 also shows good floating time, which is more, then 24 hrs and also good floating lag time, which is less than 3 minutes. 3^2 factorial design (Dtz9-Dtz17) formulation showing good floating time and fast floating lag time.

Swelling index study

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water penetration.

Table 11: Swelling index study of best batch Dtz7

Time (hrs)	% Swelling index
3	75.34
6	139.57
12	182.79
15	189.34
18	197.68
24	203.77

Swelling is also vital factor to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored. The swelling index of the best batch (Dtz15) at different time intervals was mention in Table 11, which may be because of high viscosity and high water retention property of HPMC polymer.

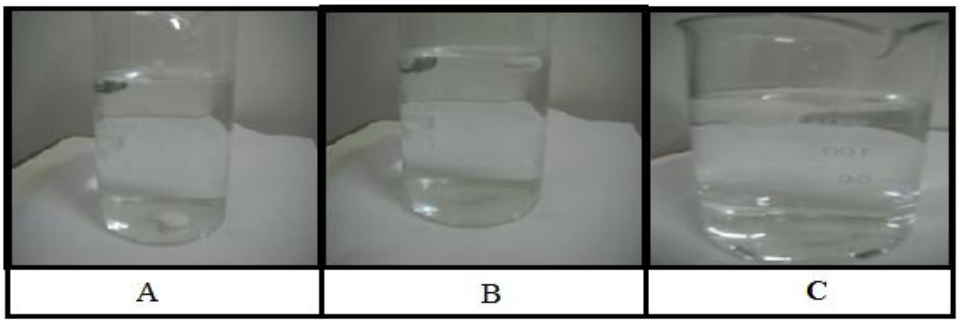

Figure 1: *In vitro* buoyancy studies

(A) Initially (B) After 184 sec. (C) After 24hrs

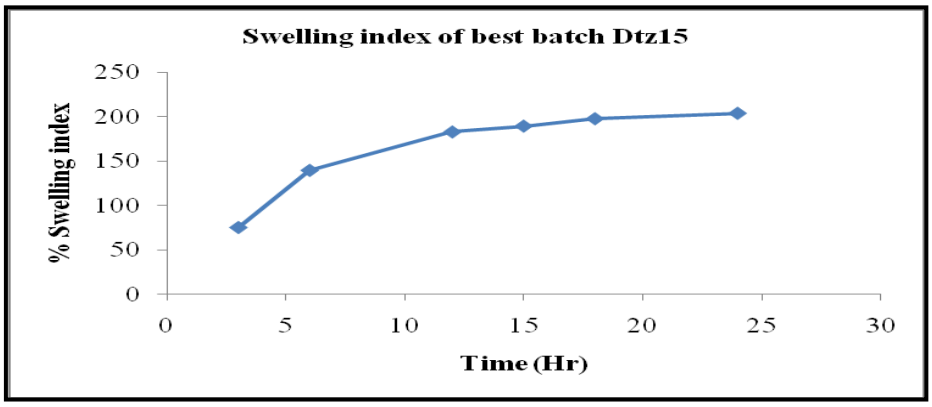

Figure 2: Swelling index of best batch Dtz15

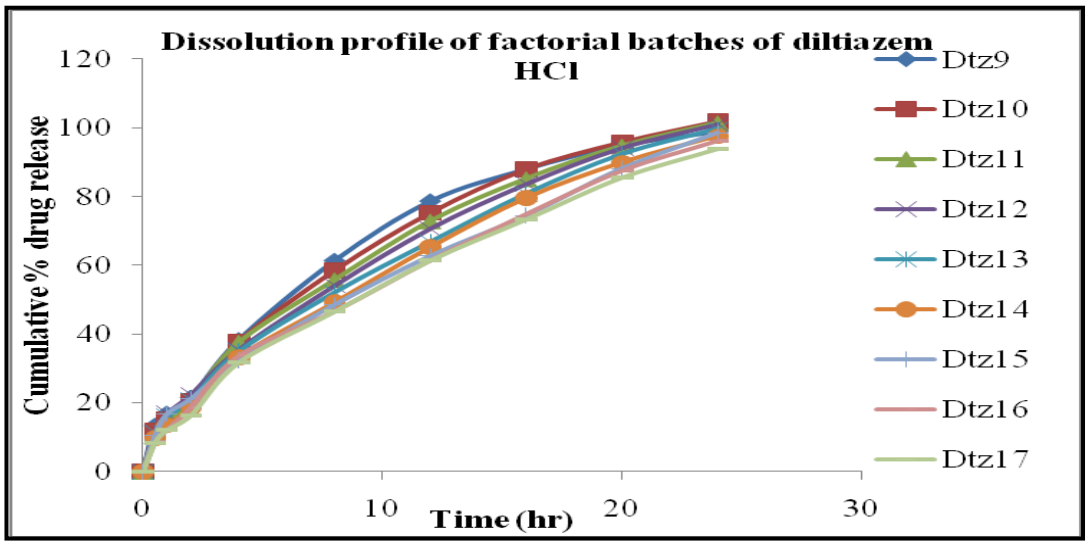

Figure 3: Drug release profile of tablet

Calculation of total dose and theoretical drug release profile

The pharmacokinetics parameters of diltiazemHCl were used to calculate a theoretical drug release profile for a 24 hrs dosage form. The immediate release dose and maintenance dose of diltiazemHCl was calculated using equation 1 & 2 and was found to be 20.66 mg. and 99.06 mg. respectively. Hence, the formulation should release 20.66 mg (17.21%) of drug in initial 1.0 hr. While in the remaining 23.0 hrs drug release should be 99.06 mg. So, every 1 hrs 4.30 mg (3.58%) of drug release till 23.0 hrs.Theoritical release profile is shown in Table 6.9.

Calculation of the loading dose:

IRD = Css × Vd × Body weight (9)

F = 20.66mg ≅21.0 mg

Calculation of Maintenance Dose (MD)

Maintenance Dose= LD Dose (1+ 0.693×t/ $t_{½}$)

(10)

= 99.06 mg ≅99.0mg

Total dose = (21 + 99) mg = 120 mg

Table 12: Theoretical release profile of sustained release layer

Time (hrs)	Theoretical release profile %	Range (%)
0	0	0
1	17.24	15-20
4	28.12	20-35
8	42.50	35-50
12	56.87	45-65
16	71.25	65-80
20	85.62	NLT 80
24	99.98	-

Comparison of dissolution profiles

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100.The dissolution profiles of products were compared using f_2. This similarity factor is calculated by following formula,

$$f_2 = 50 \log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (11)$$

Where, n is the number of dissolution time and $R_t$and T_t are the reference and test dissolution values at time t**.**

In vitro drug release profile of all batches of factorial design was compared with theoretical drug release profile. The result is shown in Table 13, which indicates that, the all the batches except the Dtz9 shows good similarity to theoretical release profile. But batch Dtz15 showed the highest f_2 among all the batches that is 74.76. The similarity between the theoretical release profile and the *in vitro* drug release profile of Dtz15 is clearly demonstrated in Figure 4.

Table 13: Similarity factor amongst the factorial batches

Formulation code	Dtz9	Dtz10	Dtz11	Dtz12	Dtz13	Dtz14	Dtz15	Dtz16	Dtz17
Similarity factor (f_2)	48.85	50.97	54.07	56.98	62.14	66.35	74.76	72.98	72.48

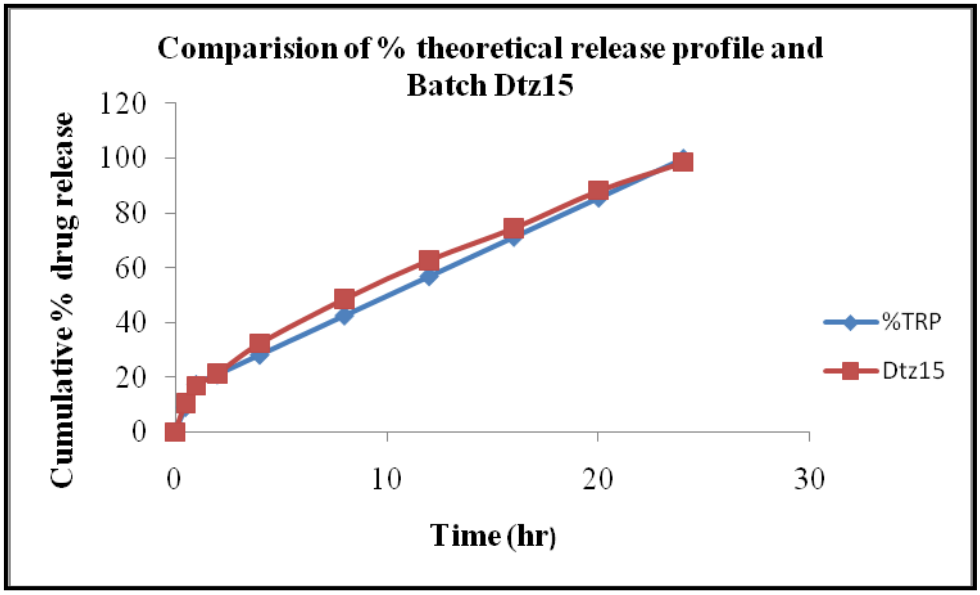

Figure 4: Comparison of theoretical drug release profile and batch Dtz15

Table 14: Comparison of check points between TRP and batch Dtz15

Check points	Theoretical value	Batch Dtz15
Q_1	17.24	16.80
Q_{16}	71.25	74.51
Q_{20}	85.62	88.18
f_2	50 - 100	74.76

The results of comparison of various check points between theoretical values and batch Dtz15 are shown in table 14. The results depicts that the batch Dtz15 shows the good fit with the theoretical values.

RESULT AND DISCUSSION

In tablet of DiltiazemHCl the loading dose, maintenance dose, and theoretical drug release profile was calculated based on pharmacokinetics data. Loading dose of DiltiazemHCl was released as a burst release from the tablet during the initial polymer hydration and the remaining drug was released up to 24 hrs as a maintenance dose.

A 3^2full factorial design was applied to systemically optimize *in vitro* drug release profile. The content of HPMC K100M(X_1) and content of carbopol (X_2) were selected as independent variables. The cumulative % drug release at1 hr (Q_1), cumulative % drug release at 16 hr (Q_{16}), floating lag time was selected as dependent variables. The result of full factorial design was indicated that the X_1 (content of HPMC K100M) and X_2 (content of carbopol) both have significant effect on *in vitro* drug release profile.

As the concentration of carbopol& conc. of HPMC K100M increases, the release of drug is retarded due to entrapment of drug molecules in the close proximity ofcarbopol& HPMC K100M. Use of HPMC K100M &carbopol was an advantageous combination for formulating gastro retentive tablet. Concentration of HPMCK100M was optimized which was 24% (120 mg). Concentration of carbopol was optimized which was 4% (20 mg). Floating lag time of all factroialbatchs was less than four minutes. From, *in vitro* dissolution study it was observed that batch Dtz15 releases 98.56 % of drug in 24 hr with floating lag time of 184 seconds. The similarity factor f_2 was applied between the in vitro drug release profile of factorial design batches and theoretical drug release profile. No significant difference was observed between desired release profile and batches Dtz10 to Dtz17. Batch Dtz15 showed highest f_2 (f_2 = 74.76) among all the batches. Data of kinetic modeling showed that drug release mechanism was best explained by higuchi plot and value of n (=0.57) indicates the anomalous transport i.e. a combined mechanism of pure diffusion and swelling-controlled drug release.

Thus it was summarized and concluded that gastro retentive tablet of diltiazemHClcan be successfully formulated with HPMC K100M and carbopol-934.

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