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FORMULATION AND DEVELOPMENT OF MUCOADHESIVE TABLET OF DILTIAZEM HYDROCHLORIDE

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ABSTRACT

Mucoadhesive tablets of diltiazem hydrochloride were formulated as matrix tablets employing, polyethylene oxide (Polyox) and hydroxypropylmethylcellulose (HPMC) and were investigated for mucoadhesion and drug release behavior. Tablets formulated using different viscosity grades of Polyox showed the drug release decreased with viscosity of Polyox increased. Tablet prepared with Polyox alone were slowly eroded and were dissolved completely within 6-10 hours. The mucoadhesive strength of the matrices increased with increase in polymer content. When HPMC was incorporated, the tablets remained intact and provided slow release of diltiazem for over 12 hr. A 3^2 full factorial design was conducted to optimized the formulation. The kinetic modeling study of all batches was shown anomalous pattern of drug release. The drug was released by both erosion and diffusion mechanism. Thus the developed formulation can be suitable for targeted delivery of diltiazem in upper part of GI tract where the absorption of diltiazem is more confined.

KEYWORDS

Mucoadhesive tablet, Diltiazem hydrochloride, polyox, optimization, Ex vivo mucoadhesion.

INTRODUCTION

Diltiazem hydrochloride is a calcium channel blocker, which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension.[1] It has a short biological half-life of about 3.5 hrs[2] and is rapidly eliminated. Because of its low oral bioavailability (38 %)[3] and short biological half-life attempts have been made to develop sustained release (SR) products with extended clinical effects and a reduced dosing frequency.[4] As diltiazem hydrochloride (DTZ HCL) is a highly water-soluble drug, its formulation into SR products is rather difficult. There are a few reports on the formulation of oral controlled release products of diltiazem employing coated beads,[5] pan coating,[6] microencapsulation[7] and complexation[8] techniques. In the present investigation mucoadhesive tablets of diltiazem were formulated employing Polyox and HPMC as mucoadhesive materials. These materials are reported[9,10] to have good mucoadhesive properties. Polyethylene oxide (Polyox) is among various hydrophilic polymers that, in presence of water, control the release of the active moiety either by swelling or by swelling / erosion by forming a hydrogel. The adjustment of polymer concentration, viscosity grade and addition

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of different types and levels of excipients to the polymer matrix can modify the kinetics of drug release.[11] Mucoadhesive polymers prolong the residence time of the dosage form in the gastro-intestinal tract and hence they are more suitable as matrix material for oral controlled release.[12] Also, these mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in high drug flux through the absorbing tissue.[13] Therefore in the present investigation, the influence of various grades and concentration of Polyox and also the effect of HPMC on performance of mucoadhesive properties and drug release from the matrix tablets were studied.

MATERIALS AND METHODS

Diltiazem hydrochloride was a gift sample from Cadila Healthcare Ltd, (Ahmedabad, India). HPMC K4M and K100M were kindly supplied by Alembic Pharmaceutical, (Vadodara, India.) Polyox was obtained from Dow chemical company, (California, USA). All other ingredients were purchased from S. D. Fine Chemicals, Mumbai, India.

1. Estimation of diltiazem

An Ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 237 nm in water was used for the estimation of DTZ HCL. The method obeyed Beer's law in the concentration range of 0-20 µg/ml. When a standard drug solution was assayed repeatedly (n=6) the relative error (accuracy) and relative standard deviation (precision) were found to be 0.9% and 1.2% respectively.

2. Compatibility study of drug and polymers

The drug- polymers compatibility study of DTZ HCl with the polymers, Polyox 303 and HPMC K100M was done by using DSC and FTIR.

3. Formulation of mucoadhesive matrix tablets for preliminary screening

Tablets were prepared by direct compression technique. DTZ HCl was mixed with the required components except talc and magnesium stearate by geometric mixing. Then the powders blend with talc and lubricated with magnesium stearate and manually compressed on 10 station rotary tablet press using 11 mm standard flat face punch. The tablets were compressed to obtain hardness in range of 5-6 Kg/cm^2. The composition of tablets for preliminary screening is depicted in Table 1.

Table 1
Composition of formulated batches for preliminary screening

Ingredients (mg)	Batch Code					
	P1	P2	P3	P4	P5	P6
DTZ HCl	60	60	60	60	60	60
PolyoxN60K	50			70		
Polyox 301		50			70	
Polyox 303			50			70
DCP	84	84	84	64	64	64
Talc	4	4	4	4	4	4
Mg. stearate	2	2	2	2	2	2
Total	**200**	**200**	**200**	**200**	**200**	**200**

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4. To evaluate the effect of HPMC on drug release studies, HPMC K15M and HPMC K100M were incorporated with polyox.

Table 2
Composition of tablets for effect of HPMC

Ingredients (mg)	Batch Code			
	PH1	PH2	PH3	PH4
DTZ HCl	60	60	60	60
Polyox 303	60	60	40	40
HPMC K15M	10		30	
HPMCK100M		10		30
DCP	34	34	34	34
Talc	4	4	4	4
Mg. stearate	2	2	2	2
Total	**200**	**200**	**200**	**200**

5. Optimization of formulation using 3^2 full factorial design

A 3^2 randomized 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. $Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2$

The factors were selected based on preliminary study described as above. The X_1 is content of Polyox 303 (%) and X_2 is Content of HPMC K100M (%) was selected as independent variables. The time required for 50% drug release (t_{50}), time required for 80% drug release (t_{80}), and mucoadhesion strength were selected as dependent variables. The formulations of the factorial batches (PF1 to PF9) are shown in Table 3.

Table 3
Composition of tablets for factorial design batches

Batch Code	Coded level		Actual value	
	X_1	X_2	X_1	X_2
PF1	-1	-1	20	8
PF2	-1	0	20	10
PF3	-1	1	20	12
PF4	0	-1	25	8
PF5	0	0	25	10
PF6	0	1	25	12
PF7	1	-1	30	8
PF8	1	0	30	10
PF9	1	1	30	12

X_1 is content of Polyox 303 (%) and X_2 is Content of HPMC K100M (%), Talc (2%) and magnesium stearate (1%), DCP quantity sufficient

6. Physical parameters of mucoadhesive tablets

Compressed tablets were evaluated for weight variation, hardness and friability according to USP XXIV.[14] Hardness of the tablets was tested using a Monsanto hardness tester (M/s Campbell Electronics, Mumbai, India.). Friability of the tablets was determined in a Roche friabilator (M/s Campbell Electronics, Mumbai, India).

7. In vitro drug release study

The *in vitro* drug release of matrix tablets was performed using USP XXIV paddle apparatus (Type-II) using 900 ml of 0.1 N HCl at 100 rpm at 37 ± 0.5^0C. The samples were withdrawn at predetermined time intervals for period of 12 hrs and replaced with the fresh medium. The samples were filtered through 0.45 µm membrane filter, suitably diluted and analyzed at 237 nm using double beam

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UV/Vis spectrophotometer. The content of DTZ HCl was calculated using calibration curve.[15]

8. *Ex Vivo* Mucoadhesion study

Ex Vivo Mucoadhesion Time:The *ex vivo* mucoadhesion time was performed (n = 3) after application of the tablet on freshly cut rat stomach mucosa. The fresh rat stomach mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of 0.1 N HCl (pH 1.2) and pasted to the rat stomach mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was tied with paddle of USP XXIV Type-II apparatus. The test was performed with 900 ml of the 0.1 N HCl (pH 1.2) at 37°C ± 1°C. After 2 minutes, a 100 rpm stirring rate was applied to simulate the stomach environment, and tablet adhesion was monitored for 12 hours.[22] The time for the tablet to detach from the rat stomach mucosa was recorded as the mucoadhesion time.[16]

Ex Vivo Mucoadhesive Strength:A modified balance method was used for determining the *ex vivo* mucoadhesive strength. A double pan physical balance was taken and both the pans were removed. The left pan was replaced with a brass wire. The right pan was replaced with a lighter pan. In the left pan polypropylene block was placed. Fresh rat stomach mucosa was obtained from a dissected rat and used within 2 hours. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with 0.1 N HCl pH 1.2 at 37°C. The left side pan was placed in the beaker contained 0.1 N HCl and kept at 37 ± 1^0 C.[16] The tablet was taken and attached to upper polypropylene cylinder and rat stomach was attached on the lower polypropylene block. A preload weight of (30gms) was placed on the left pan of the balance for 10 min. The weights were then removed slowly and weights were added slowly in increasing order to the right pan till the patch separates from the mucosal surface. The weights required for complete detachment of the film from mucosal surface was noted. Average of three determinations was calculated and applied standard deviation.

9. Optimization data analysis

The polynomial equations for 3^2 factorial design were established on the basis multiple regression analysis. Also the 3-D response surface graphs were constructed in the design expert software.

10. Kinetic modeling and mechanism of drug release

The release data obtained were fitted to zero order,[17] first order,[18] Higuchi,[19] Korsmeyer-Peppas[20] equations to determine the corresponding release rate and mechanism of drug release from the mucoadhesive tablets.

RESULTS AND DISCUSSIONS

Compitibility study of drug and polymers

Figure 1 shows DSC thermograms of the pure DTZ HCl and the physical mixture of DTZ HCl with the polyox and HPMCK100M. The DSC analysis of pure DTZ HCl showed a sharp endothermal peak at 213.04^{0}C, corresponding to drug's melting point. The DSC analysis of the physical mixtures of the drug and polymers revealed a negligible change in melting point of DTZ HCl in the presence of polymer mixture studied.

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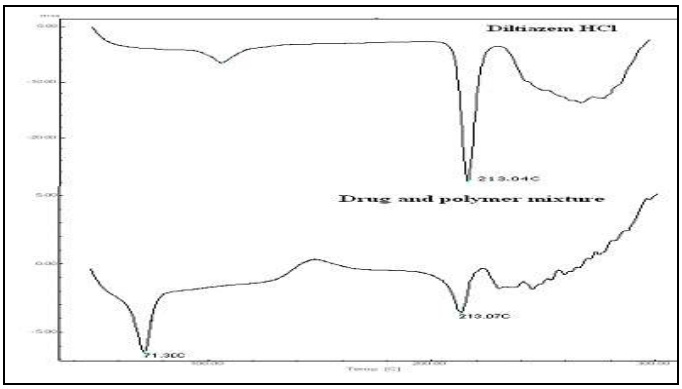

Fig 1. ***DSC spectra for drug polymer compatibility***

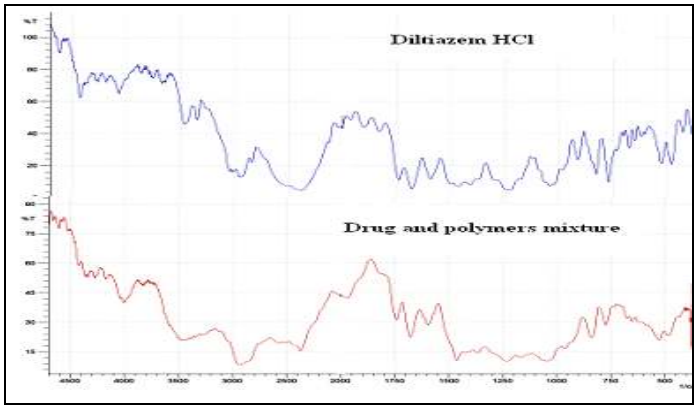

Fig 2. ***FTIR spectra for drug polymer compatibility***

The FTIR spectra of DTZ HCl and physical mixture of DTZ HCl with the polyox and HPMCK100M are shown in Figure 2. It suggested that there was no interaction between the drug and polymers because principle peaks of drug polymer mixture were nearly similar to that of pure drug. Thus DSC and FTIR analysis results suggest that the drug and polymers are compatible.Preliminary screening for ptimization of mucoadhesive tablets.The formulations of preliminary screening were evaluated for harmacotechnical parameters and in vitro dissolution profile.The results of pharmacotechnical parameters of tablets for preliminary screening are depicted in Table 4. Tablets of each batch had complied the assay, weigt variation and friability test according to USP XXIV.

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Table 4
Results of physical parameters for preliminary screening

Batch code	Assay (%)	Average weight (mg) (n =20)	Friability (%)	Hardness (Kg/cm^2)
P1	98.64	198 (1.4)	0.16	5.7
P2	98.32	199 (1.5)	0.14	5.9
P3	101.39	202 (1.6)	0.25	6.0
P4	100.75	200 (2.8)	0.29	5.8
P5	101.44	200 (1.4)	0.24	5.8
P6	100.47	200 (1.6)	0.16	6.1
Value in parenthesis indicates standard deviation				

It was observed that release of drug was dependent on content and molecular weight of polyox. Increasing the molecular weight of polyox leads to decrease in release of drug from matrices might be due to stronger gel layer formation.

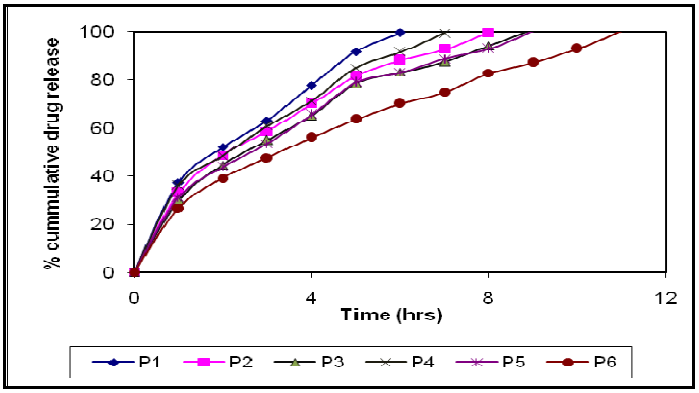

Fig 3. ***Dissolution profiles of tablets for preliminary screening***

It was observed that on increasing polymer level in matrices, it leads to decreased release of DTZ HCl. It was reasoned that increasing polymer content in tablets leads to formation of tightly swollen gel layer, which are less prone to erosion and gave slower release rate. Similar kind of observation was also reported by Di-Colo and co-workers. They reported that the release of drug was slower on increasing level of Polyox. The formulations prepared by using Polyox 303 could not extend the drug release to 12 hrs (Batch P6). So, in further study HPMC K15M and HPMC K100M were added in different concentration with Polyox 303 to retard the release of DTZ HCl.

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Effect of HPMC on drug release profile

To retard the release of DTZ HCl, HPMC K15M and HPMC K100M were incorporated with polyox. From results of pharmacotechnical parameters of tablets it was found that HPMC retard the drug release in the formulation of polyox without affecting the physical parameters of tablet. The results are depicted in Table 5. Tablets of each batch had complied the assay, weight variation and friability test according to USP XXIV.

Table 5

Results of evaluation of tablets for influence of HPMC

Batch Code	Assay (%)	Average weight (mg) (n =20)	Friability (%)	Hardness (Kg/cm^2)
PC1	99.54	202 (1.6)	0.21	5.4
PC2	100.66	201 (1.1)	0.14	6.1
PC3	101.87	201 (2.6)	0.18	6.0
PC4	99.95	200 (1.8)	0.27	5.8
Value in parenthesis indicates standard deviation.				

The results of drug release profile are shown Figure 4. The results obtained from preliminary trials indicated that above certain threshold value of molecular weight of polyox, the resultant gel layer formation do not contributed significantly for drug release from matrices. Hence based on above results, HPMC had explored for the further study, as it was reported to have some mucoadhesive properties which may assist in prolonging gastric retention of tablet. Tablets were also prepared by changing the content of HPMC to study the influence of polymer level on performance of matrix tablets.

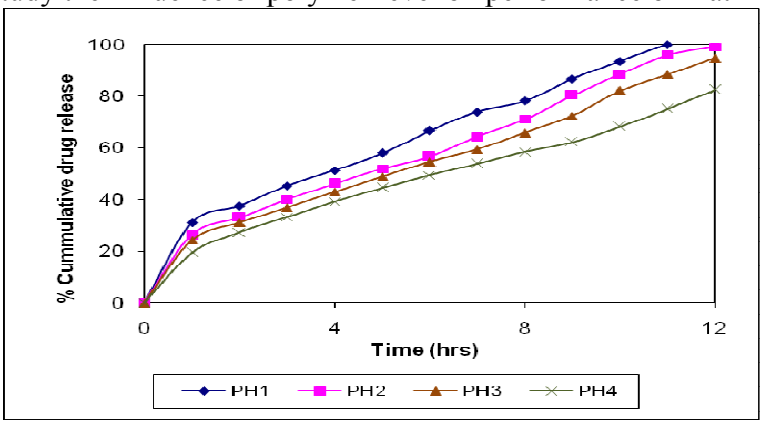

Fig 4. ***Dissolution profiles of tablets for influence of HPMC***

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From the results, it was observed that the content and viscosity of HPMC both affect on drug release of formulations. In batch PH1 and PH2, the drug release was found around 100% at the end of 12 hrs. Batch PH2 extend the drug release more promptly than PH1 therefore HPMC K100M was selected for the further study.Optimization of formulations by 3^2 full factorial design.

Table 6

Results of evaluation of tablets for factorial design batches

Batch Code	Assay (%) (n = 20)	Hardness (Kg/cm^2)	Friability (%)
PF1	100.24	5.6	0.34
PF2	98.90	5.9	0.22
PF3	99.60	6.3	0.12
PF4	99.95	6.2	0.31
PF5	100.45	5.9	0.23
PF6	99.75	5.6	0.42
PF7	99.60	5.8	0.42
PF8	101.08	5.8	0.38
PF9	101.24	5.6	0.31

In the present investigation, content of Polyox 303 (X_1) and content of HPMC (X_2) were selected as independent variables. The time required for 50% (t_{50}) and 80 % (t_{80}) drug release, and *ex vitro* mucoadhesion strength was selected as dependent variables.

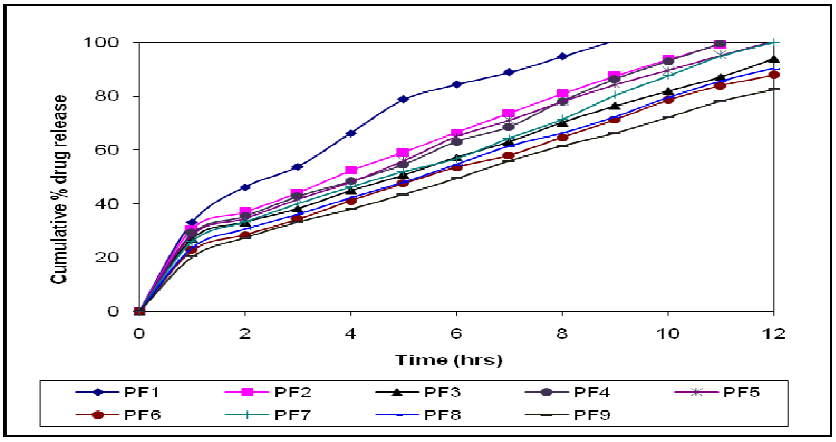

Fig 5. ***Dissolution profiles of tablets for factorial design batches***

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In the preliminary screening it was found that the content of polyox 303 and content of HPMC K100M had significant influence on DTZ HCl release kinetics from hydrophilic matrices. Therefore, the effect of content of Polyox 303 and content of HPMC K100M on drug release from mucoadhesive matrix tablets was statistically evaluated using 3^2 full factorial design. The results of evaluation of tablets are depicted in Table 6. Tablets of all batches had desire physical properties and were complied the assay, hardness and friability test according to USP XXIV. In the present study polyox 303 was used as a mucoadhesive polymer because of its dual properties as matrix forming agent and mucoadhesion property. Because it binds with the mucus layer of the stomach and enabling the dosage form to retain in the stomach. In vitro drug release study showed that the content of polyox 303 and HPMC K100M increased the drug release decreased. From the results of dissolution profile, it was found that polyox 303 at low level was unable to extend the release for the period of 12 hrs (batch PF1 and PF2) but the higher level of HPMC K100M with low level of polyox 303 showed 93% drug release at 12 hrs.
In the batches PF8 to PF9, the drug was release around 90% at the end of 12 hrs. So it was observed that the higher level of polyox and HPMC retard the drug release. Tablets of batches PF5 and PF7 showed around 100% drug release at the end of 12 hrs.The results of *ex vivo* mucoadhesion time and *ex vivo* mucoadhesive strength for factorial design batches are shown in Table 6.12. The total *ex vivo* mucoadhesion time all batches was found to be more than 12 hrs except batches PF1 to PF4. The low mucoadhesion time was due to the less content of polyox 303. The mucoadhesive strength of all formulations was increased with increasing the content of polyox 303.

Table 7

Results of dependent variables for factorial design batches

Batch code	t_{50}	t_{80}	*Ex vivo* mucoadhesion strength (gm)
PF1	3.04	6.04	24.72
PF2	4.19	7.98	27.94
PF3	5.16	9.58	31.18
PF4	4.46	8.25	43.15
PF5	4.53	8.56	44.46
PF6	5.75	10.30	47.04
PF7	4.93	8.99	56.92
PF8	5.53	10.02	58.13
PF9	6.27	11.14	62.04

The results of time required to release 80% of drug (t_{80}), time required to release 50% drug (t_{50}) and *ex vivo* mucoadhesion strength, showed wide variation among nine batches (Table 7). From results of multiple regression analysis, it was found that both factors had statistically significant influence on all

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dependent variable (P<0.05, Table 8). The high value of multiple correlation co-efficient clearly indicates that the response are strongly dependent on factors studied (Table 8).
The results of time required to release 80% of drug (t_{80}), time required to release 50% drug (t_{50}) and *ex vivo* mucoadhesion strength, showed wide variation among nine batches (Table 7). From results of multiple regression analysis, it was found that both factors had statistically significant influence on all dependent variable (P<0.05, Table 8). The high value of multiple correlation co-efficient clearly indicates that the response are strongly dependent on factors studied (Table 6.14).

Table 8

Multiple regression analysis for dependent variables

Coefficient of Regression	Dependent variables		
	***Ex vivo* mucoadhesion strength (gm)**	**t_{50}**	**t_{80}**
b_0	44.44	4.79	8.905
b_1	15.541	0.723	1.091
b_2	2.578	0.791	1.29
b_{12}	-0.335	-0.195	-0.347
b_{11}	-1.395	-0.06	-0.078
b_{22}	0.665	0.185	0.196
r^2	0.9987	0.9693	0.9728
P	0.00014	0.0176	0.0148

Factorial equations for dependent variables are shown below.

Mucoadhesion strength $= 44.44 + 15.541X_1 + 2.578X_2 - 0.335X_1X_2 - 1.395X_1^2 + 0.665X_2^2$

$\mathbf{t_{50}} = 4.79 + 0.723X_1 + 0.791X_2 - 0.195X_1X_2 - 0.06\ X_1^2 + 0.185X_2^2$

$\mathbf{t_{80}} = 8.90 + 1.091X_1 + 1.29X_2 - 0.347X_1X_2 - 0.078X_1^2 + 0.196X_2^2$

Factorial equations for mucoadhesion strength depicted that effect of X_1 (content of Polyox 303) is more significant than X_2 (content of HPMC K100M) on mucoadhesion strength of tablets. As increase in content of Polyox 303 caused increase in the value *ex vivo* mucoadhesive strength. This observed effect may be explained by assuming that as polymer levels in the matrices increases; it had stronger gel layer formation because the particles had more intimate contact with mucus layer. Factorial equations for t_{50} and t_{80} depicted that both the variable X_1 (content of Polyox 303) and X_2 (content of HPMC K100M) had significant effect on t_{50} and t_{80}. As increase in content of Polyox 303 and HPMC K100M the t_{50} and t_{80} decrease.

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Figures 6 shows influence of content of polyox 303 and content of HPMC K100M on t_{80} and t_{50}. It was observed that as polymer level increases, the release rate was decreased and mucoadhesive strength increased. Increasing polymer level in matrices increases the tortuosity, and at the same time will increase the possibility of interaction between molecules of DTZ HCl and swollen Polyox 303 particles. Increase in polymer level leads to formation of tightly swollen gel layer due to more intimate contact between the particles of Polyox, which decrease the mobility of insoluble drug particles in swollen matrices leads to decreased drug release. So the overall result showed that the medium level of Polyox 303 and HPMC K100M was selected to optimized drug release to 12 hrs and mucoadhesive strength.

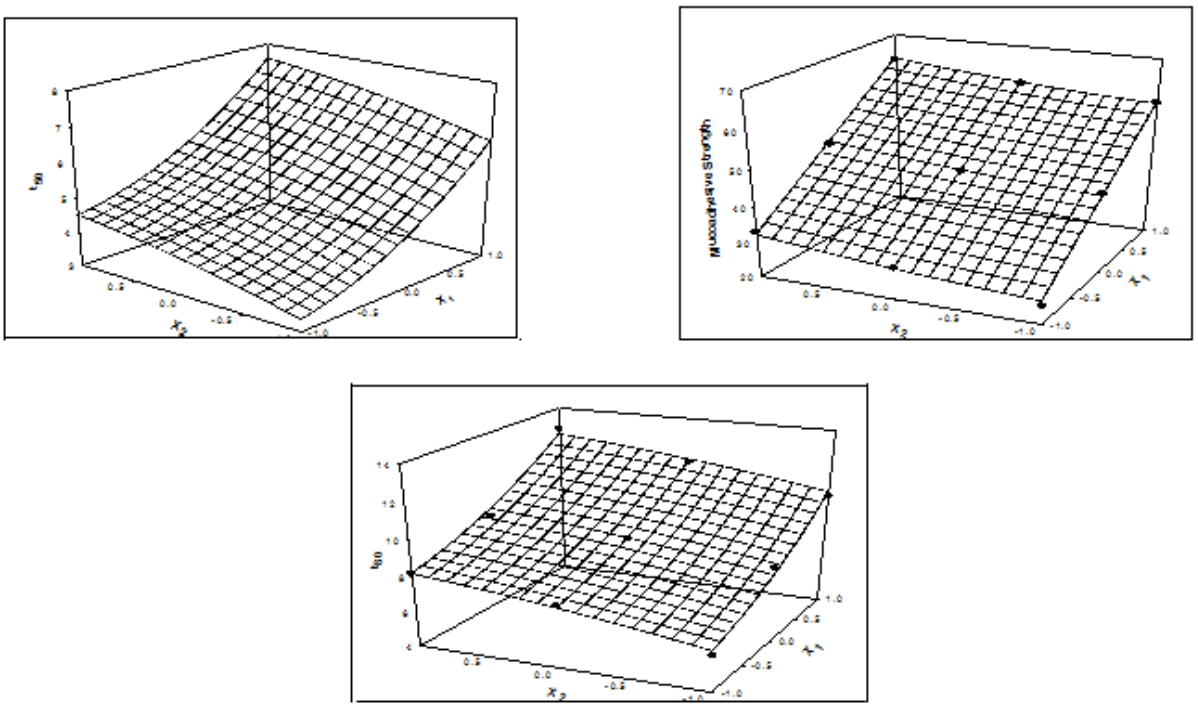

Fig6.*Surface plot to depict the influence of content of Polyox 303 (X_1) and content of HPMC (X_2) on mucoadhesive strength, particle size t_{50} and t_{80}*

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Kinetic treatment of dissolution profiles

The dissolution profiles obtained were treated with zero order, first order, higuchi, Korsmeyer and Peppas equations to get kinetic parameters.

Table 9

Result of model fitting of factorial batch

Batches	Zero order		First Order		Higuchi	Korsemeyer peppas	
	K	r^2	k	r^2	r^2	N	r^2
PF1	10.01	0.920	0.129	0.910	0.992	0.519	0.992
PF2	7.91	0.956	0.115	0.967	0.981	0.515	0.974
PF3	6.78	0.964	0.108	0.973	0.974	0.523	0.968
PF4	7.93	0.966	0.120	0.980	0.985	0.533	0.964
PF5	7.45	0.963	0.111	0.956	0.986	0.542	0.976
PF6	6.59	0.974	0.117	0.962	0.977	0.574	0.977
PF7	7.38	0.973	0.115	0.974	0.969	0.558	0.969
PF8	6.68	0.971	0.115	0.965	0.978	0.557	0.977
PF9	6.15	0.974	0.117	0.957	0.973	0.578	0.984

It can be concluded from the table 9 that Korsemeyer and peppas model fit the best for all the batches as correlation coefficient value for all the batches were more than 0.9. This is followed by zero order, higuchi and first order equation. From the n value it can be seen that all the batches follow anomalous pattern of drug release. This can be supported by the good fit of zero order and higuchi equation. The drug was released by both erosion and diffusion of the drug from the tablet matrix.Selection of optimized batches.The results of comparision of dissolution profile with theoretical drug release are shown in Table 6.16From the results of factorial design, it was found that batches PF5, PF6 and PF7 give around 99% drug release at the end of 12 hr. The mucoadhesion time for these batches was more than 12 hrs. Also the mucoadhesion strength was around 45 gm. So the dissolution profiles of these batches were compared with theoretical release profile using similarity factor (f_2). The f_2 value of batches PF5 and PF7 were found above 50. But the f_2 value for batch PF5 and PF7 was 65.31 and 53.67 respectively, so batch PF5 was selected as best batch as compare to other batches. The *ex vivo* mucoretention test of optimized batch PF5 confirms the mucoadhesion to the rat stomach mucous membrane was more than 12 hrs.

CONCLUSION

Study was mainly focused on investigating influence of molecular weight and content of Polyox along with different grade of HPMC using factorial design statistically. Tablets of all batches had desired mucoadhesive characteristics with stable matrix integrity. The content of Polyox 303 and content of HPMC K100M both had significant influence on dependent variable studied. It was found that content of polyox had dominating role as mucoadhesive and drug release controlling factor, but using blends with HPMC K100M one can tailor the desire drug release

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from hydrophilic matrices. The kinetic modelling of all batches can be seen that they follow anomalous pattern of drug release. This can be supported by the good fit of zero order and higuchi equation. The drug was released by both erosion and diffusion of the drug from the tablet matrix. Thus the developed formulation can be suitable for targeted delivery of DTZ HCl in upper part of GI tract where the absorption of DTZ HCl is more confined.

ACKNOWLEDGEMENTS

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