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An approach to formulating an oral floating drug delivery system for dexchlorpheniramine maleate using factorial design

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The purpose of this research was to formulate and evaluate a floating tablet formulation of dexchlorpheniramine maleate (DCPM) using full factorial design. A 3^2 factorial design (nine runs) was utilized to optimize the formulation, the contents of hydroxypropyl methyl cellulose (HPMC) (X1) and Carbopol 934P (X2) being taken as independent variables and t50% (Y1), % drug release after 6 h (Y2), % drug release after 12 h (Y3), and floating lag time (FLT) (Y4) as the dependent variables. The tablets showed 99.2635 to 102.4709 of the labeled amount of dexchlorpheniramine maleate indicating uniformity of content. The tablets containing DCPM released 72.28 to 99.461% of drug at the end of 12 h by an *in vitro* release study. Hardness, friability, floating capacity, weight variation and content uniformity were also examined. In addition,the tablets were evaluated for *in vitro* release characteristics for 24 h. The optimal batch (F9) was selected by regression analysis and followed Higuchi kinetics. The drug release mechanism was found to be a complex mixture of diffusion, swelling and erosion. The floating tablets of DCPM developed may be used clinically for prolonged drug release for at least 16 hrs, thereby improving bioavailability and patient compliance.

1. Introduction

Oral drug administration is the most preferable, versatile and useful means for taking medication (Streubel et al. 2006). The idea of a floating drug delivery system (FDDS) was described in the literature in 1962 (Singh et al. 2000). Prolonging gastric retention time (GRt) is important because drugs are absorbed in the stomach or the upper part of the small intestine and thus bioavailability of a drug is improved when it is retained in the stomach for a longer time (Choi et al. 2002).

These factors resulted in the design of extended-release dosage forms with prolonged residence times, like low density systems that float in the stomach (Rouge et al. 1996), mucoadhesive systems or bioadhesion to the stomach mucosa, slower motility of the gastrointestinal tract by concurrent administration of drugs, or systems that expand by swelling or unfolding (Arora et al. 2005; Mayavanshi et al. 2008).

Dexchlorpheniramine maleate is the dextrorotatory isomer of chlorpheniramine maleate and is twice as potent as the racemic mixture. DCPM is a histamine H1-receptor antagonist. These drugs find their greatest use in the symptomatic treatment of allergic rhinitis (Verster et al. 2004). Antihistamines used in the treatment of allergy act by competing with histamine for H_1-receptor sites on effector cells. First generation drugs, developed around 1940, such as pyrilamine maleate (an ethylenediamine salt) can both stimulate and depress the CNS (Goodman et al. 2001) thus tending to produce moderate drowsiness and impairment of driving ability immediately after oral administration. After 8 h, no significant difference from placebo was found. Dexchlorpheniramine (DCPM), a propylamine used in the form of the maleate salt (DCPM, Fig. 1), is absorbed relatively slowly from the gastrointestinal tract, with peak plasma concentrations occurring about 2.5 to 6 hours after oral administration. Dexchlorpheniramine appears to undergo considerable first-pass metabolism. Bioavailability is low, values of 25 to 50% having been reported, and the biological half-life is 6.09 ± 1.0 h) (Rajua et al. 2007). It is given by mouth in doses of 2 mg every 4 to 6 hours up to a maximum 12 mg daily (Craig et al. 1997) and is useful in the acute rather than the chronic form of urticaria (Craig et al. 2004; Katzung et al. 1992).

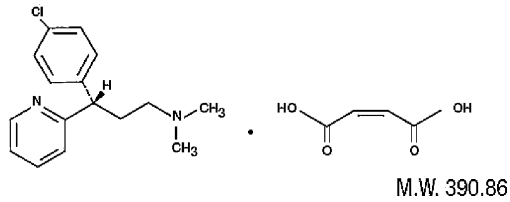

Fig. 1: Structure of dexchlorpheniramine

2. Investigations, results and discussion

Nine formulations were prepared as shown in Table 1. A 3^2 randomized full factorial design was used. In this design two factors were evaluated, each at three levels, and experimental trials were performed of all nine possible combinations. The amounts of HPMC K15 M (X1) and of Carbopol 934P (X2) were selected as independent variables. The time required for 50% drug dissolution (t50%), percentage drug release at 6 h (Q6), percentage release at 12 h (Q12) and floating lag time (FLT) were selected as dependent variables.

2.1. Evaluation of floating tablets

The results of all the physical parameters investigated of the different batches of extended release floating formulations,

Table 1: Composition of floating tablets of DCPM (all formulations have 10 mg DCPM; 50 mg sodium bicarbonate; quantum satis of MCC PH 102; 3% PVP k30; 2% magnesium stearate; 1% talc and 1% Aerosil)

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC K 15M	−1	−1	−1	0	0	0	1	1	1
Carbopol 934P	−1	0	1	−1	0	1	−1	0	1

Translation of Coded Values to Actual Values

Coded values	Actual values	
	X1	X2
−1	50	35
0	75	50
+1	100	65

*Where X1 – amount of HPMC K 15 M, and X2 - amount of Carbopol 934P

Table 2: Tablet properties of dexchlorphenaramine maleate floating tablets (values ± S.D)

Batch code	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content %	Floating lag time (sec)	Total floating time (hrs)
F1	Weight ± 2.35	4.10 ± 0.02	11.32 ± 0.006	6.31 ± 0.11	0.63	102.09 ± 2.32	22.3 ± 0.160	> 24
F2	Weight ± 1.68	4.12 ± 0.015	11.33 ± 0.015	6.55 ± 0.165	0.64	101.41 ± 0.92	20.6 ± 0.266	> 24
F4	Weight ± 3.33	4.12 ± 0.02	11.33 ± 0.01	6.55 ± 0.568	0.68	99.63 ± 1.59	17.92 ± 0.533	> 24
F4	Weight ± 1.40	4.12 ± 0.03	11.33 ± 0.02	6.50 ± 0.338	0.48	100.62 ± 2.91	21.43 ± 0.526	> 24
F5	Weight ± 3.53	4.12 ± 0.015	11.34 ± 0.021	6.84 ± 0.087	0.50	101.84 ± 1.66	16.78 ± 0.111	> 24
F6	Weight ± 1.84	4.12 ± 0.027	11.33 ± 0.01	6.37 ± 0.313	0.695	100.75 ± 2.46	12.8 ± 0.09	> 24
F7	Weight ± 0.94	4.12 ± 0.035	11.32 ± 0.0058	6.79 ± 0.161	0.51	99.73 ± 1.89	10.21 ± 0.167	> 24
F8	Weight ± 3.39	4.11 ± 0.055	11.32 ± 0.026	6.26 ± 0.166	0.68	99.46 ± 1.00	7.38 ± 0.137	> 24
F9	Weight ± 2.45	4.14 ± 0.02	11.32 ± 0.0015	6.17 ± 0.19	0.70	102.02 ± 1.81	5.6 ± 0.608	> 24

including hardness, floating lag time, total floating time, and average percentage deviation are shown in Table 2.

2.2. Pre-compression parameters

Angle of repose of all formulated blends was found to be in range of 18.49 to 23.91. The results for angle of repose (< 30) indicated good flow properties of the blend.

Carr's index was determined and found to range from 12.5% to 15.625%, Values of Carr's index below 15% indicate that flow characteristics are good, while readings above 25% indicate poor flowability.

2.3. Post-compression parameters

All the formulations from batches F1 to F9 were evaluated for thickness and diameter of tablets, measured by an ERWEKA TBH300 S apparatus (ERWEKA GmbH, Germany). The thickness of tablets prepared from formulations F1 to F9 was between 3.103 and 3.123 mm, while diameters were between 11.32 ± 0.00577 and 11.343 ± 0.021 mm.

Friability ranged from 0.4815% to 0.699%. As the results were less than 1% for all the formulations, this indicated that the tablets were mechanically stable.

All the tablets passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ± 7.5% of the weight.

Drug content of the formulations was assayed spectrophotometrically at 269 nm. The percentage of target DPCM content for F1 to F9 was found to be between 99.46 ± 1.00 and 102.09 ± 2.32%.

2.4. In vitro drug release

The performance of floating tablet formulations has been shown to be greatly influenced by physiological requirements such as food transport and gastrointestinal motility. The floating lag time was studied for all tablet formulations was studied when the tablets were undergoing the dissolution test. The lag time was found to be less than 30 s for all formulations. All the floating matrix tablet formulations contained an equal amount of gas generating agent (sodium bicarbonate). The study was performed for 24 hours and cumulative drug release was calculated at several times. Two different polymers and their combinations (Fig. 2) were used to prepare floating tablets. It was observed that the type of polymer affected the drug release model, studies for all the formulations showing controlled release of drug for 16 h, and the optimized formulation (F9) for 24 h. Drug release from formulation F1 was found to be 97.74 ± 0.74 at 16 h, while for

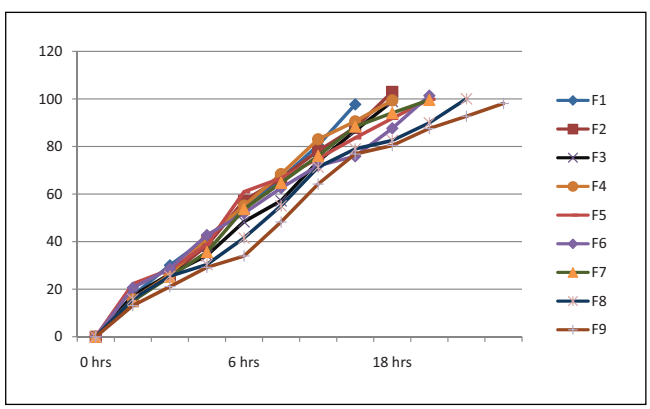

Fig. 2: *In-vitro* dissolution profile of formulations

Table 3: Fitting of release profiles to five different models (r^2 values)

	Mathematical models (Kinetics) R2 values				
	Zero order	First order	Higuchi	Hixson Crowell	Best fit model
F1	0.9743	0.8445	0.9969	0.9642	Higuchi
F2	0.9507	0.8106	0.9876	0.7447	Higuchi
F3	0.9893	0.8985	0.9886	0.917	Zero order
F4	0.9463	0.8076	0.993	0.9555	Higuchi
F5	0.9395	0.8399	0.9791	0.89	Higuchi
F6	0.934	0.8255	0.9764	0.9663	Higuchi
F7	0.9557	0.8226	0.9936	0.9556	Higuchi
F8	0.9772	0.8841	0.9872	0.7736	Higuchi
F9	0.9869	0.8917	0.9899	0.9662	Higuchi

F2, F3 and F4 it was found to be $102.95 \pm 1.44\%$, $98.98 \pm 3.2\%$ and $99.42 \pm 2.99\%$ respectively at 18 h. The release data for cumulative % drug released for formulations F5 to F9 were obtained over 20 h, the optimized formulation F9 showing drug release of $98.11 \pm 3.17\%$.

2.5. In-vitro release kinetics

In order to investigate the kinetics of drug release, the curves obtained from the data were fitted to various kinetic models such as zero order, first order, Higuchi, and Hixson Crowell. The R^2 values for each model and each formulation are shown in Table 3, as is the equation giving the best fit. For the optimized formulation, F9, the R^2 value obtained for the zero-order plot is 0.9869 and first order gave 0.8917. The relationship between drug release time and concentration of drug of the optimized formulation F9 showed best linearity in the Higuchi equation plot (Fig. 3) ($R^2 = 0.9899$), indicating the release of drug from the matrix was process dependent on the square root of time, consistent with Fickian diffusion. The dissolution data was also plotted in accordance with the Hixson Crowell equation, where the fit of the data ($R^2 = 0.9662$) showed a change in surface area and diameter of floating matrix tablets with the progressive dissolution of matrix as a function of time (Seta et al. 1988).

2.6. Statistical analysis of the drug release profile

Statistical analysis was performed using Graph with SPSS 14 software for Windows (SPSS Inc., Chicago, USA). All the parameters were determined 3 times ($n = 3$) except the pre-compression parameters. Experimental results were expressed as mean ± SD. The Shapiro–Wilk test was used to verify normality, and the Kolmogorov-Smirnov test was used to verify homogeneity of variances [Table 4]; one-way analysis of variance (ANOVA) was applied to check significant differences in means of dependent and independent variables. Statistical significance was set at $p < 0.05$.

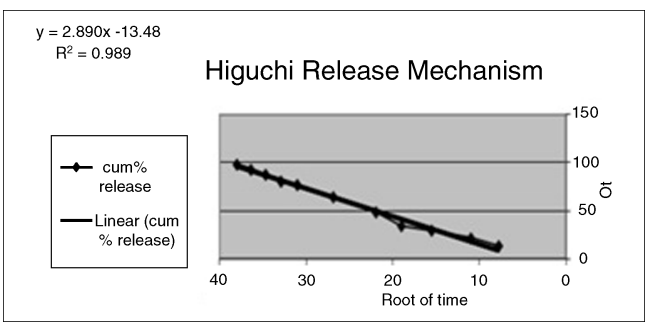

Fig. 3: Drug Release Kinetic of Higuchi Model of (F9)

2.7. Evaluation of tablet floating

In vitro floating studies in simulated gastric fluid, pH 1.2, showed good buoyancy for all the formulations at 37 °C. The tablets floated and remained floating without disintegration. The floating matrix tablets contained sodium bicarbonate as a gas-generating agent, generating CO_2 in the presence of 0.1 N HCl. The gas generated was trapped in the swollen polymer matrix and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet allowing the dosage forms to float. The tablets floated on the simulated gastric fluid for 24 h, because of the presence of internal space in the dry center of tablets (porosity) giving increased bulk volume and decreased tablet density (Ozdemir et al. 2000).

2.8. Response surface method optimization results

The results obtained from the mathematical relationships generated by SPSS 14 software for Windows_ (SPSS_ Inc., Chicago, USA) for the response variables studied are expressed in the equation

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

where Y is the dependent variable, b0 the constant of the 9 runs, and bi (b_1, b_2, b_{12}, b_{11} and b_{22}) is the regression coefficient. X1 and X2 stand for the main effects, while X_1X_2 are the interaction terms, and show how response changes when two factors are changed simultaneously. The polynomial term (X_1^2 and X_2^2) are included to investigate nonlinearity.
The regression coefficients in the regression model for each term are summarized in Table 5, and the analysis of experimental data variance (ANOVA) information is shown in Table 6.

Table 4: Cumulative % drug release for stability study of batch F9

Shapiro-Wilk			Kolmogorov-Smirnov(a)			
Sig.	df	Statistic	Sig.	df	Statistic	
.037	9	.823	.200(*)	9	.209	x1
.037	9	.823	.200(*)	9	.209	x2
.040	9	.825	.089	9	.257	Y1
.291	9	.906	.200(*)	9	.220	Y2
.935	9	.975	.200(*)	9	.150	Y3
.386	9	.919	.200(*)	9	.168	Y4

* This is a lower bound of the true significance. a Lilliefors Significance Correction

Table 5: 3^2 factorial design with corresponding responses for dependent variables

$Y1 = -0.034 + 0.03X_1 + 0.05\ X_2$
$Y2 = 90.461 - 0.20X_1 - 0.323X_2$
$Y3 = 110.07 - 0.139X_1 - 0.33X_2$
$Y4 = 48.5 - 0.25\ X_1 - 0.196\ X_2$

Batch code	Y_1	Y_2	Y_3	Y_4
	$t_{50\%}$ time required for 50% of drug release (h)	% release at 6hr (Q_6)	% release at 12h (Q_{12})	Floating lag time FLT (sec)
F1	5.35	54.47	80.55	22.3 ± 0.160
F2	5.24	57.20	78.17	20.6 ± 0.266
F3	6.38	48.38	73.76	17.92 ± 0.533
F4	5.27	55.17	83.05	21.43 ± 0.526
F5	5	61.01	74.96	16.78 ± 0.111
F6	5.8	51.95	71.97	12.8 ± 0.09
F7	5.66	53.74	76.05	10.21 ± 0.167
F8	7.32	41.55	71.34	7.38 ± 0.137
F9	8.64	33.96	64.23	5.6 ± 0.608

All the polynomial equations were found to be statistically significant ($P < 0.05$), as determined using ANOVA

2.8.1. Effect of formulation variables on time required for 50% of drug release (hours)

The model term for DCPM release at the first hour was found to be significant with a probability value over 0.05 (0.059), indicating a sufficient good fit to the linear surface model (Fig. 4).
$Y1 = -0.034 + 0.03X_1 + 0.05\ X_2 (R^2 = 0.514)$
The values of the correlation coefficient were studied, the probability value being over 0.05 (0.059), so the model term of $t_{50\%}$ for DCPM was found to be not significant, indicating that the concentration of HPMC K15 M and Carbopol 934P had no influence on the time required for 50% release of drug.

2.8.2. Effect of formulation variables on % release after 6hr (Q6)

The model term for Q6 was found to be of low significance with a probability value over 0.05 (0.103) for adequate fitting of the linear surface model (Fig. 5).
$Y2 = 90.461 - 0.20\ X_1 - 0.323X_2$ ($R2 = 0.499$)

Table 6: Analysis of ANOVA

Model	Sum of square	df	Mean square	F	Sig	
Y_1						
Regression	7.034	2	3.517	4.727	0.059[a]	a: predictors x_2, x_1
Residual	4.464	6	0.744			
Total	11.489	8				
Y_2						
Regression	299.065	2	149.533	3.403	0.103[a]	a: predictors x_2, x_1
Residual	263.664	6	43.944			
Total	562.729	8				
Y_3						
Regression	146.934	1	146.934	10.292	0.15[a]	a: predictors x_2, x_1
Residual	99.936	7	14.277			
Total	246.869	8				
Y_3						
Regression	219.474	2	109.737	24.034	0.001[b]	b: predictors x_2
Residual	27.396	6	4.566			
Total	246.869	8				
Y_4						
Regression	236.003	1	236.003	21.767	0.002[a]	a: predictors x_1
Residual	75.895	7	10.842			
Total	311.898	8				
Y_4						
Regression	287.747	2	143.873	35.743	0.000[b]	b: predictors x_1, x_2
Residual	24.151	6	4.025			
Total	311.898	8				

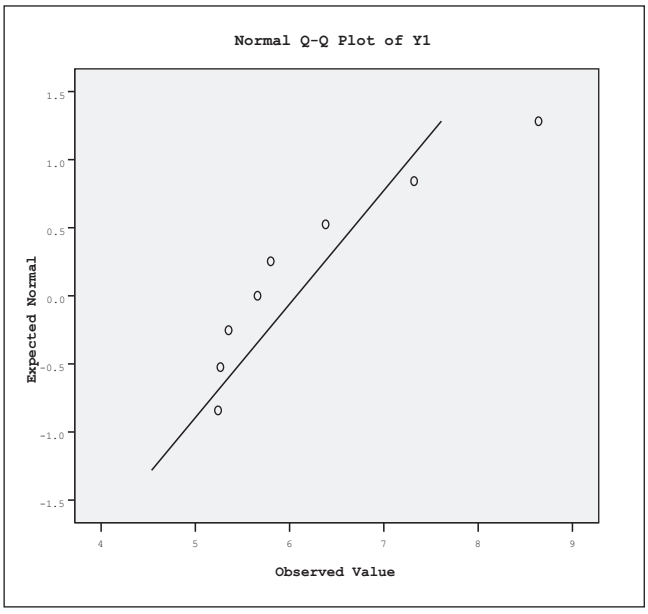

Fig. 4: Correlation between actual and predicted values for t 50% (Y1)

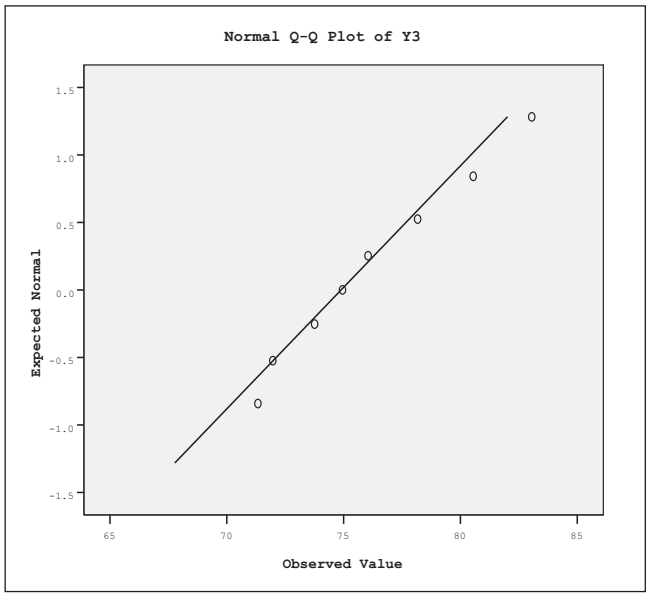

Fig. 6: Correlation between actual and predicted values for Q12 (Y3)

2.8.3. Effect of formulation variables on % release at 12 h (Q12)

In this case, the model term for release at 12 h (Q12) of the tablet was found to be significant, with a probability value of 0.015. Both the factors had a significant effect on the Q12 of the tablet. As the Carbopol 934P ratio increased, the release of drug at 12 h decreased. Similarly, as the concentration of HPMC K15 M increased the rate of release at 12 h decreased.

$Y3 = 110.07 - 0.139X_1 - 0.33X_2$ ($R2 = 0.889$)

The interaction factor X1 X2 can be studied with the help of the response surface plot (Fig. 6).

2.8.4. Effect of formulation variables on floating lag time

The model term for floating lag time was found to be very significant with an F value of 0.002, indicating adequate fitting of the quadratic model. As the amount of HPMC K15 M in the dosage form increased, the floating lag time decreased, which may be due to the formation of a gel layer with low viscosity of the polymer matrix of HPMC alone, which in turn increased the influx of water into the gel matrix and decreased the density of the floating tablet.

$Y4 = 48.5 - 0.25X_1 - 0.196X_2$ ($R^2 = 0.923$) (Fig. 7).

The factor X1 was found to be significant with regard to the response of floating lag time. The interaction factor X1 X2 could be studied with the help of the response surface plot. It was concluded that higher levels of X1 (amount of HPMC K15 M) and higher levels of X2 (amount of Carbopol 934P) favoured the preparation of floating sustained release DCPM tablets.

2.9. Stability studies

From the results of a stability study of formulation F9, it was found to be stable under accelerated conditions (40 °C/75% RH), with no change in physical appearance, drug content, floating lag time, hardness, friability, or *in-vitro* release. It was thus found that the floating tablets of DCPM (F9) were stable under these

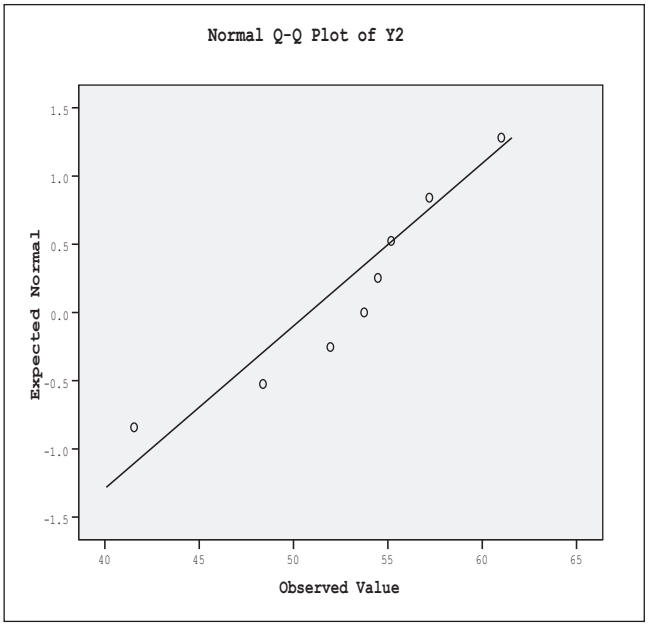

Fig. 5: Correlation between actual and predicted values for Q6 (Y2)

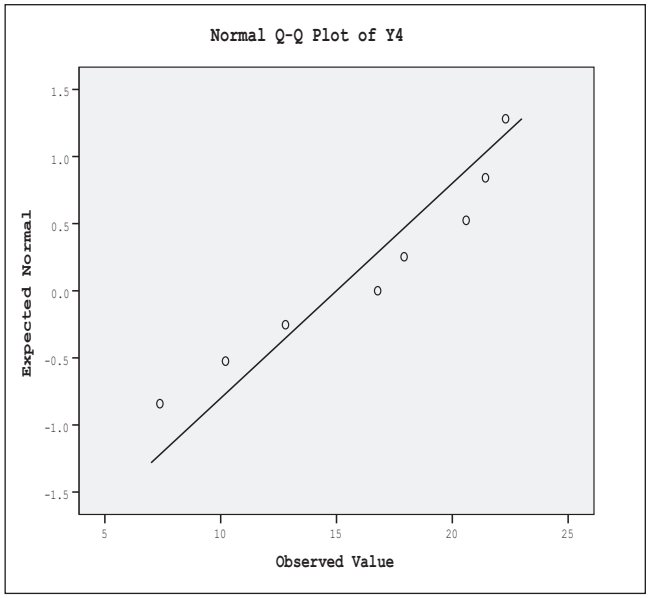

Fig. 7: Correlation between actual and predicted values for FLT (Y4)

Table 7: Cumulative % drug release for stability study of batch F9

Time (h)	Cumulative % drug release (Initial)	Cumulative % drug release (After storage at 40 °C for 3 month)
1	13.11	11.40
2	21.09	20.96
4	29.19	30.09
6	33.96	35.05
8	48.26	49.17
12	64.23	66.48
16	76.86	76.48
18	80.43	81.60
20	87.58	88.66
22	92.71	93.75
24	98.11	100.53

storage conditions for at least 90 days. Drug release of F9 aftr storage for 3 months is given in Table 7.

2.10. Conclusion

A gastro-retentive drug delivery system was successfully prepared using factorial desig, the amounts of HPMC K15 M (X1) and Carbopol 934P (X2) having a significant effect on Q12 and floating lag time. From this study, formulation F9 was selected as an optimized formulation because it gave the best results as a sustained drug release system in terms of floating for 24 h and giving the desired sustained release. Hence the floating matrix tablet prepared appears promising for the delivery of drug release over a period of 24 h, through gastric retention.

3. Experimental

3.1. Materials

Dexchlorpheniramine maleate as the model drug was obtained as a gift sample from Schering-Plough Corporation (USA), Dexchlorpheniramine maleate as a reference sample was purchased from Sinochem Ningbo Ltd, China, Hydroxypropyl methyl cellulose (HPMC K15 M), Carbopol 934P and PVP-k30 were kindly supplied by Sigma Aldrich (Germany). Sodium bicarbonate (VWR International, Haasrode Research, Leuven, Belgium) was purchased. Other excipients used were of standard pharmaceutical grade or analytical grade.

3.2. Preparation of gastro-retentive floating tablets

Nine tablet formulations were prepared by the direct compression technique using a 3^2 factorial design (Table 1). All the powders were passed through a 60 mesh sieve. The required quantity of drug and low-density polymer were mixed thoroughly. PVP K30, talc and magnesium stearate were finally added as glident and lubricant respectively. The blend was directly compressed (10 mm diameter punches) using a single-punch tableting machine (ERWEKA GmbH, D-63150 Heusenstamm, Germany). Each tablet contained 10 mg of dexchlorpheniramine maleate. Compositions of each tablet for each batch are shown in Table 1. The amounts of HPMC K15 M and Carbopol 934P in the combinations were optimized based on floating lag time, floating time and release profile after various preliminary trial batches. HPMC K15 M offers the advantages of being non-toxic and relatively inexpensive and also it can be compressed directly into matrices, so it was used in this study.

3.3. Evaluation of powder blends

The angle of repose of the powder blends was determined by the funnel method. The accurately weighed powder blend was put in the funnel. The height of the funnel was adjusted so that 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 cone was measured and angle of repose was calculated using the following equation:

$\tan \theta = h/r$

Where, h and r are the height and radius of the powder cone. (Aulton et al. 1998; Martin 2008b)

Apparent bulk density was determined by pouring the presieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as is". It is expressed in g/ml and is given by:

$BD = M/V_0$

where M is the mass of powder and V0 is the bulk volume of the powder.

Tapped density was determined by placing a graduated cylinder containing a known mass of the drug-excipient blend on a mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given by

$TBD = M/Vt$

where M is the mass of powder and Vt is the tapped volume of the powder. (Aulton et al. 1998; Martin 2008b)

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

Carr's compressibility index (%) = [(tapped bulk density-bulk density)/ × 100]/tapped bulk density

3.4. Evaluation of post-compression parameters of tablets

Twenty tablets from each batch were selected randomly after compression, weighed individually, and the average weight determined. The percentage weight variations for all formulations are shown in Table 2. All the tablets passed the weight variation test as the % weight variation was within the Pharmacopoeial limits of ± 7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The weight variation was measured using a Shimadzu auw220d dual-range semi-micro balance.

Ten tablets were tested for hardness. The hardness was measured with a hardness tester (ERWEKA TBH300 S, GmbH, Germany).

The friability of the tablet was determined using an ERWEKA Friabilator. Twenty previously weighed tablets were rotated at 25 rpm for 4 min. The weight loss of the tablets before and after measurement was calculated using the equation.

F% = ((Initial weight – Final weight)/Initial weight) × 100

Five tablets were weighed individually and powdered. The powder equivalent to the average weight of tablets was weighed and drug was extracted by 0.1 N HCl; the drug content was determined by measuring the absorbance at 269 nm after suitable dilution using a Shimadzu UV-1601 UV/Vis double beam spectrophotometer. The drug content was determined by referring to the reference (United States Pharmacopeia 2007b).

Gastro retentive tablets of DCPM formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature and at 40°C for up to 30 days. Samples were withdrawn after periods of 15 days, and 30 days and were analyzed for appearance, hardness, and friability, floating time, drug content and *in vitro* release (Liberman and Lachman 1991; ICH topic 8 2004; ICH Q1A 2003).

3.5. Floating characteristics

Floating characteristics of the prepared formulations were determined using a USP XXIII paddle apparatus (dissolution tester; Erweka, Type DT 800, Germany) under sink conditions. The dissolution medium was 500 ml of 0.1 N HCl (pH 1.2), the temperature of which was maintained at 37 ± 0.5 °C throughout the study. The time that tablets took to emerge at the water surface, called the floating lag time (FLT), and the duration of time the tablets constantly floated on the water surface, called the total floating time (TFT), were measured. The measurements were carried out for each series of tablets ($n = 6$) (Havanpatil et al. 2006; Ozdemir et al. 2000).

3.6. In vitro drug release

Drug release studies were carried out using a dissolution tester (Type DT 800, ERWEKA GmbH, Germany). The dissolution test was performed using 500 ml of 0.1N HCl (pH 1.2), at 37 ± 0.5 °C and Apparatus 2 (paddle method), with the paddle rotation speed kept at 75 rpm. Samples of 10 ml were withdrawn at, 1, 2, 4, 6, 8, 12, 16, 18, 20, 22 and 24 h. The samples were replaced by an equivalent volume of fresh dissolution medium and were filtered through a 0.45 μm membrane filter and diluted to a suitable concentration then analyzed by UV (Shimadzu UV-1601 UV/Vis double beam spectrophotometer) at 269 nm (Viana et al. 2005). The percentage drug rlease was plotted against time to determine the release profile.

3.7. *In vitro drug release kinetic studies*

In vitro release was examined by fitting the release data to various kinetic equations. The kinetic models used were zero order, first order, Higuchi and Hixson Crowell, and drug release was analysed by using the MS EXCEL statistical function to find the R^2 (correlation coefficient) values of the release profile corresponding to each model. The model with the highest correlation coefficient was considered to be the best model (Liberman and Leon Lachman 1991b; Xiaoqiang et al. 2006).

3.7.1. Zero-order release kinetics

The system where the drug release rate is independent of its concentration
$C = K_0 t$
where C is the fraction of drug release, K0 is the zero-order rate constant expressed in units of concentration/time and t is the release time.

3.7.2. First–order release kinetics

Describes the release from a system where the release rate is concentration dependent. The release rate data are fitted to the following equation:
$LogC = LogC_0 - kt/2.303$
where, C_0 is the initial concentration of the drug and K is the first order constant.

3.7.3. Higuchi release kinetics

Described the release of drug from an insoluble matrix as a process dependent on the square root of time, based on Fickian diffusion To study the Higuchi release model the release rate data are fitted to the following equation:
$Q = Kt^{1/2}$
where, Q is the percentage of drug released at time t and k is the kinetic constant.

3.7.4. Hixson-Crowell release kinetics

Describes the release from systems where there is a change in surface area and diameter of particles or tablets. To study the Hixson -Crowell release model the release rate data are fitted to the following equation:
$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t$
Where Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for the Hixson-Crowell rate equation.

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