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Development and *in-vitro* evaluation of intra gastric cefadroxil monohydrate floating tablet

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ABSTRACT

In the present investigation, an attempt has been made to increase therapeutic *efficacy to reduce the frequency of administration and improve patient compliance by developing floating* tablet *of Cefadroxil monohydrate by using various grades of hydrophilic matrix forming polymer HPMC K100M* and *HPMC K*15*M, lactose,* sodium-*bicarbonate and citric acid use as gas generating agent. A* 3^2 *factorial design was applied systematically; the amount of* HPMC K15M *(X1) and amount of HPMC K100M(X2) were selected as independent variables. The time required for 50% drug release* ($t_{50\%}$)*, percentage drug release at 12hr*(Q_{12}) *percentage drug release at 6 hr* (Q_6) *were selected as dependent variables. The* tablets *are prepared by direct* compression *method. The powder* blend *was evaluated for the bulk density, tapped density, angle of repose, compressibility index and Hausner ratio. The values indicate good flow* and *compression properties. The compressed tablets were evaluated in terms of their physical characteristics, in vitro release, buoyancy, buoyancy lag-time. All the* observations *are within the prescribed limits. . The* in vitro *data were fitted to different kinetic models.*

Key words: Cefadroxil monohydrate, Floating tablets, HPMC K100M, HPMC K15M, Buoyancy studies.

INTRODUCTION

It is evident from the recent scientific and patent literature that an increse intrest in novel drug dosage forms that are retained in stomach for a prolonged and predictable period of time. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in GI tract is to control the gastric resident time (GRT) i.e. Gastro retentive Dosage forms will provide us with new & therapeutic option[1]. An oral dosage form Floating drug delivery designed to prolong the residence time of the dosage form within the GIT[2, 3]. It is a formulation of a drug with gel forming hydrocolloids meant to remain buoyant in the stomach contents and have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration[4, 5]. The FDDS can be divided into gas-generating and non-effervescent systems.

Cefadroxil monohydrate[6, 7] is the choice of drug for urinary tract infectionand phyrangitis it has also been reported that it has only 1.5 hrs biological half life and well absorbed through stomach.This necessitated the design and development of sustained release Gastro retentive drug delivery system for Cefadroxil Monohydrate using suitable

polymers The aim of the present study is not only develop a floating system but also to release the drug in controlled fashion.

MATERIALS AND METHODS

Cefadroxil monohydrate was obtained as gift sample by Mann Pharmaceutical laboratories Ltd, Mehasana.(Gujarat) India. HPMC-K100M and HPMC-K15M were obtained as a gift sample from the Colorcon Asia Pvt. Ltd., Goa, India. All other materials and solvents used were of analytical grade.

Preparation of Floating tablets of Cefadroxil monohydrate-
The composition of different formulations of Cefadroxil floating tablets is shown in Table no.1.Effervescent Floating tablets containing Cefadroxil were prepared by direct compression using varying concentrations of different grades of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, magnesium stearate was added as post lubricant and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine using 16 mm flat punch.

Factorial Design:
A 3 randomized full factorial design was used, in this design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of HPMC K-15 (X_1) and amount of HPMC K-100M (X_2) were selected as independent variables. The time required for 50% drug(t_{50}) dissolution percentage drug release at 12 hours (Q_{12}) and percentage release at 6 hours (Q_6) Given in table no-2 were selected as dependent variable[8-10].

Evaluation of Pre Compressed Tablet Blend:
The flow properties of powder blends were characterized in terms of angle of repose, Carr index and Hausner's ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner's ratio were calculated.[11-14]

Evaluation of Cefadroxil Floating Tablets:
Tablets from all the formulations were evaluated for various properties such as hardness by Pfizer hardness tester, Friability by Roche Friabilator and weight variation by using electronic balance.

Content Uniformity:-
Twenty tablets were weighed from each formulation, powdered and equivalent to 100 mg of Cefadroxil monohydrate was taken and to which 2 ml of methanol was added and finaly the volume to 100 ml with water. The resultant solution was shaken well and filtered with whatman filter paper.Taken 1ml of resultant solution to which 1 ml of 0.1 N NaOH and 1ml of 0.005% solution of N-BromoSuccinamide was added and finaly the volume to 100ml with water. the content of cefadroxil was estimated spectrophotometrically at 238 nm[15]

In Vitro Buoyancy studies:-
In Vitro buoyancy studies was performed for all the ten formulations as per the method described by Rosa et.al[16]. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT).The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

Swelling Characteristic
Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule[17-19] the liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet. From each formulation, one tablet was weighed and placed in a dissolution test apparatus, in900 ml of enzyme free simulated gastric fluid at 37 ±0.5°C. After predetermined time interval the tablet was removed from

apparatus, blotted to remove excess water and weighed. The swelling characteristics were expressed in terms of the percentage water uptake (WU %) according to following equation

Swelling Index (S.I.) = $\{(W_t-W_o)/W_o\} \times 100$

Where, S.I. = swelling index
W_t = weight of tablet at time t
W_o = weight of tablet before immersion.

In Vitro Dissolution studies:
The *in vitro* dissolution studies was carried out in 900 ml of simulated gastric fluid, pH 1.2 (enzyme free) using USP XXII Dissolution test apparatus employing paddle stirrer. One tablet was placed inside the dissolution medium and the paddle was rotated at 100 rpm. 5ml samples were withdrawn at specific time intervals and the same volume was replaced to maintain sink conditions. The samples were analyzed for drug content against 0.1 N HClLLLL as blank spectrophotometrically at 395nm.

IR Spectral Analysis:
It was used to study the interactions between the drug, polymer and excipients. The drug and excipients must be compatible with one another to produce a product stable, efficacious and safe. Infrared spectrum of Cefadroxil was determined on Fourier Transform Infrared Spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run.

Kinetic modeling for drug release:
Analysis of drug release from swellable matrices must be performed with a flexible model that can identify the contribution to overall kinetics The dissolution profile of all the batches was fitted to various models such as zero-order[20] Higuchi ,Korsmeyer and Peppas to ascertain the kinetic modeling of drug release[21,22].

STABILITY STUDIES:
To assess the drug and formulation stability, stability studies were done according to ICH and WHO guidelines[23].Optimized formulation F1 sealed in aluminum packaging coated inside with polyethylene and various replicates were kept in the humidity chamber maintained a 45±2°C and 75±5% RH for 6 month. At the end of studies, samples were analyzed for the drug content, *in vitro* dissolution, floating behavior and other physicochemical parameters.

RESULTS AND DISCUSSION

A 3^2 factorial design was constructed to study the effect of the amount of HPMCK15M (X1) and HPMC K100M (X2) on the drug release from floating Cefadroxil tablet respectively. The dependent variables chosen were times required for 50% drug release (t_{50}), percentage drug 50% release at 12 hours (Q_{12}) and percentage drug release at 6 hours (Q_6) given in **.** A statistical model incorporating interactive and polynomial term was used to evaluate the responses.

$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X1X1 + b22X2X2$

Where, Y is dependent variable, b0 is the arithmetic mean response of the 9 runs, and b1 (b1 b2, b12, b11 and b22 is the estimated coefficient for the factor X1 the main effect. (X1 and X2) represents the average results of changing one factor at a time from its low to high values. The interaction term (X1 X2) show how the response changes, when 2 factors are changed simultaneously. The polynomial term (X_1^2 and X_2^2) are included to investigate nonlinearity. The $t_{50\%}$, Q_6 and Q_{12} , for 9 batches (F1- F9) showed a wide variation (i.e. 256-378 min, 44.48-61.56, 68.34-96.78% respectively). The2 responses of formulation prepared by 3 factorial designs are indicated in Table 2. The data clearly indicate that the t_{50} , Q_6 and Q_{12} were strongly dependent on the selected independent variables. The fitted equation relating the response $t_{50\%}$, Q_6 and Q_{12} to the transformed factors are,

$T_{50\%}=321.0+23.82X_1+10.73X_2+0.25X_1X_2-9.56X_1^2-0.56X_2^2$. ($R^2=0.8299$)

$Q6=61.56-4.38X_1-2.67X_2-2.09X_1X_2-2.67X_1^2-3.06X_2^2$. ($R^2=0.9197$)

$Q12=78.45-4.35X_1-7.24X_2-4.30X_1X_2+6.61X_1^2+1.31X_2^2$. ($R^2=0.9425$)

The values of the correlation coefficient indicate a good fit. (Fig 1, 2, 3.**)** Shows the plot of the amount of Cefadroxil (X1) and amount of HPMC K100M (X2) versus ($t_{50\%}$),(Q6) and (Q12) respectively. The data demonstrate that both X1 and X2 affect the drug release ($t_{50\%}$, Q_6 and Q_{12}). It was concluded that the low level of X1 (amount of HPMCK15M) and the higher level of X2 (amount of HPMC K100M) favor the preparation of floating sustained release Cefadroxil tablets. The high value of X1X2 coefficient also suggests that the interaction between X1 and X2 has a significant effect on t50% An increase in the concentration of HPMCK15M (X1) and amount of HPMC K100M (X2), decrease rate of release of Cefedroxil floating tablet respectively.

All the tablets of factorial design batches showed good in vitro buoyancy, having floating lag time between 32-41 sec and remaining buoyant for 12 hours.given in table-4 The bulk density of granules was found to be between 0.298 ± 0.04 to 0.367 ± 0.073 g/cm. This indicates good packing capacity of granules. Carr's index was found to be between 10.73 ± 0.03 to 16.31 ±0.10 showing good flow characteristics. Hausner's ratio low range was indicates good flowability. The angle of repose of all the formulations within the range of 28.45 ± repose of all the formulations within the range of 28.45 ±0.08 to 34.65 ± 0.12 i.e. granules were of good flow properties. The hardness of tablet was in range of 5.6± 0.21 to 6.7 ± 0.40 measured by Monsanto hardness tester. The friability was in range of 0.036 ± 0.02 to 0.061± 0.01. The values of average weight are within limit. Drug content was in range of 97.93 ± 0.62 to 98.96± 0.13 indicating good content uniformity in the prepared formulation results shown in table No-3.

The fitted equations relating the responses, Q_6, Q_{12}, $T_{50\%}$ to the transformed factor are shown in the Table No.-1The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive). Table No. 5 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Data were analyzed using Microsoft Excel.

The swelling index was calculated with respect to time. As time increase, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and HPMC K100M concentration and as HPMC K-100M and HPMC K -15 concentration increase; swelling index was increased showed in (Fig. 4).

From the dissolution study of batch F1 to F9, it was concluded that release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The drug release study was carried out up to 12 hrs. The percentage drug release from batch F1 to F9 vary from 68.34 to 96.78 %. Large concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in the retardation or decreases the drug release (F3). Dissolution profiles for all batches were shown in (Fig. 5).

Infrared absorption spectrum of Cefadroxil: IR spectrum shows all prominent peaks of Cefadroxil. IR spectrum indicated that characteristics peaks belonging to measure functional groups such as principle peaks at wave numbers 3211.17., 1757.04, 3423.88., 1267.22 and 1560.91 , The major IR peaks observed in Cefadroxil were 3211.17 (3300-3500) (C-H), 1757.04(1680 - 1760 (C=O),3423.88(3500 - 2800 (O-H), 1267.22 1220 -1020 (C-N) and 1560.91(1400 –1600) (CO-NH)

The IR spectra of physical mixture of polymers (HPMC-K100M, HPMC-K15M and cefadroxil was studied and confirmed that there is no interaction with each other. The spectra show all the prominent peaks of drug as well as polymer. IR spectrum indicated characteristics peaks belonging to measure functional groups such as principal peaks at wave numbers 3331.65, 1757.04, 1561.16, 750.12, 1269.15.cm-, The major IR peaks observed in matrices were 3331.65 (3300 – 3500) (C-H), 1757.04 (1680 – 1760) (C=O), 1561.16 (1550 – 1650) (o-H), 1269.15 (1250-1500) (C-N), 750.12 (750-900) (CO-NH). Hence it can be concluded that there were no any significant changes and behaviour in the physical mixture of cefadroxil and polymer (HPMC K15M and HPMCK100M)

All these formulations presented a dissolution behavior controlled by anomalous transport mechanism, when treated with kinetic equations and Cefadroxil release from hydrophilic binder matrices followed Fickian diffusion[24] shown in (Table 6).

In view of the potential utility of the formulation, stability studies were carried out on optimized formulation F1 at 45±2 °C and 75±5% RH for three months to assess their long-term stability. The protocols of stability studies were in compliance with the guidelines in the WHO document for stability testing of products intended for the global market. After storage, the formulation was subjected to a drug assay, floating behavior and *in vitro* dissolution studies (Table. No-7). The stability study showed no significant change after storage at 45±2°C and75±5% RH for six month.

Table No.1. Preparation of Cefadroxil floating Tablet

Batches	Ingredients (mg)					
	Cefadroxil	HPMCK 15M	HPMCK 100M	Lactose	Sod. Bicarbonate	Citric Acid
F1	500	180	40	70	70	30
F2	500	200	40	70	70	30
F3	500	220	40	70	70	30
F4	500	180	50	70	70	30
F5	500	200	50	70	70	30
F6	500	220	50	70	70	30
F7	500	180	60	70	70	30
F8	500	200	60	70	70	30
F9	500	220	60	70	70	30

Table 2: Formulation and Dissolution Characteristics of Batches in 3^2 Factorial Designs

Batch code	Coded value		$t_{50\%\ Min}$	% Drug Release at (Q_6)	% Drug Release at(Q_{12})
	X1	X2			
F1	-1	-1	256	59.46	96.78
F2	0	-1	275	57.87	90.81
F3	+1	-1	314	56.12	91.78
F4	-1	0	348	61.15	92.50
F5	0	0	342	61.56	78.45
F6	+1	0	372	51.56	78.23
F7	-1	+1	368	56.59	90.56
F8	0	+1	365	49.18	69.52
F9	+1	+1	378	44.48	68.34

Coded value	Actual value	
	X1	X2
-1	180	40
0	200	50
+1	220	60

- where X1 –amount of HPMCK15M, X2-amount of HPMCK100M,(t_{50}- time required for 50% of drug release, (Q_{12})-Percentage release at 12 hr,(Q_6)-percentage drug release at 6 hr.

Table No.3. Charecterastic of powder blend.

Batches	Parameters				
	Bulk density(gm/cc)	Tapped density(gm/cc)	Angle of repose	Compressibility index (%)	Hausner ratio
F1	0.313	0.374	34.39	16.31	1.19
F2	0.326	0.384	33.50	15.10	1.17
F3	0.367	0.412	34.65	10.95	1.12
F4	0.332	0.394	30.05	15.73	1.18
F5	0.323	0.374	27.15	13.63	1.15
F6	0.326	0.369	31.45	11.65	1.13
F7	0.326	0.361	33.12	10.73	1.10
F8	0.298	0.367	29.78	18.80	1.23
F9	0.314	0.371	28.45	15.36	1.18

Table No.4 Evaluation of Cefadroxil Floating Tablet

Batch	parameters				
	Hardness (kg/cm^3)	weight variation	Friability	Drug content	floating lagtime
F1	5.6±0.21	0.930±0.49	0.036	98.96±0.62	35
F2	5.2±0.20	0.916±0.42	0.049	97.93±1.50	39
F3	6.7±0.17	0.914±0.44	0.061	97.98±1.47	37
F4	6.9±0.20	0.914±0.38	0.061	98.23±1.61	32
F5	6.2±0.21	0.894±0.38	0.062	98.45±1.12	40
F6	6.6±0.15	0.934±0.39	0.048	98.26±0.96	35
F7	6.0±0.21	0.874±0.37	0.076	98.96±0.96	40
F8	6.7±0.12	0.914±0.26	0.061	98.49±0.84	37
F9	5.9±0.10	0.894±0.37	0.037	98.18±1.31	41

Table 5: Summary of Results of Regression Analysis

Model	T50%		Q6		Q12	
	coeficent	p-value	coeficent	p-value	coeficent	p-value
Intercept	321.0	0.0004	61.56	0.001	78.45	0.0003
X1	23.82	0.0045	-4.38	0.0005	-4.35	0.0033
X2	10.73	0.0001	-2.67	0.0068	-7.24	0.0002
X1X2	0.25	0.071	-2..09	0.0792	-4.30	0.0184
$X1^2$	-9.56	0.073	-2.67	0.0106	6.61	0.0007
$X2^2$	-0.56	0.05	-3.06	0.0054	1.31	0.2575
R^2	0.8299		0.9197		0.9425	

R2 value for Q6, Q12 and T50% are 0.9197, 0.9425 and 0.8299 respectively indicating good correlation between dependent and independent variables. The terms with P<0.05 were considered statistically significance.

Table No.6 Drug release kinetic parameter of Cefadroxil Floating Tablet

Batches	**Korsemeyer Peppas**		
	n	**R^2**	**K**
F1	0.740	0.996	0.557
F2	0.959	0.976	0.401
F3	0.995	0.995	0.542
F4	0.991	0.991	0.566
F5	0.993	0.993	0.547
F6	0.996	0.996	0.557
F7	0.995	0.995	0.562
F8	0.991	0.991	0.583
F9	0.991	0.991	0.584

Table No.7 Characteristic of optimized formulation F1

Parameters	**% Drug content**	**Hardness Kg/cm^3**	**Floating lag time(sec)**	**Total Floating time(Hrs.)**	**%Drug release**
Before storage	98.96±0..62	5.6±0.21	35	**1**2	96.78
After storage	98.87±0.78	5.6±0.11	37	**1**2	95.94

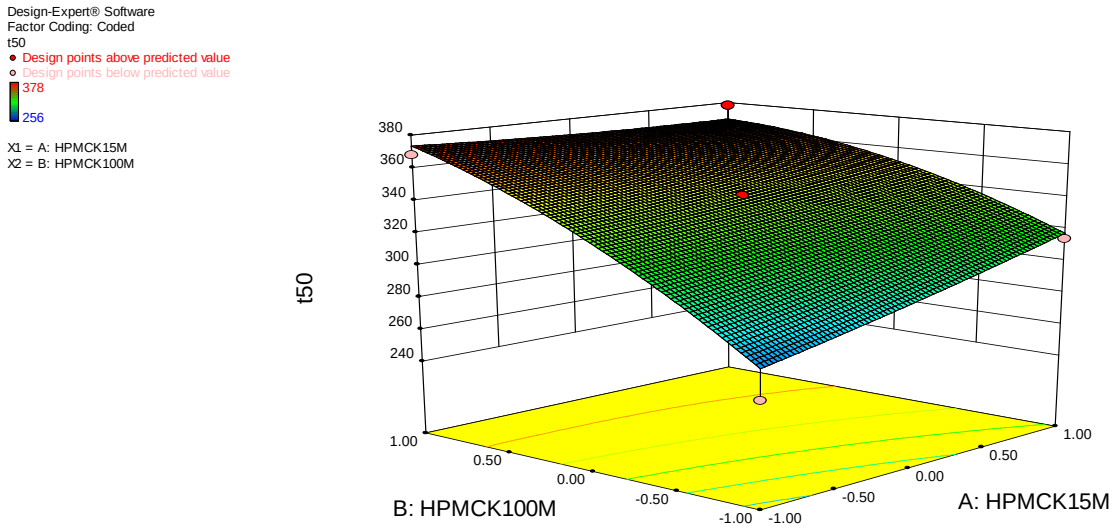

Fig.no.1 Responce surface plot for t_{50}

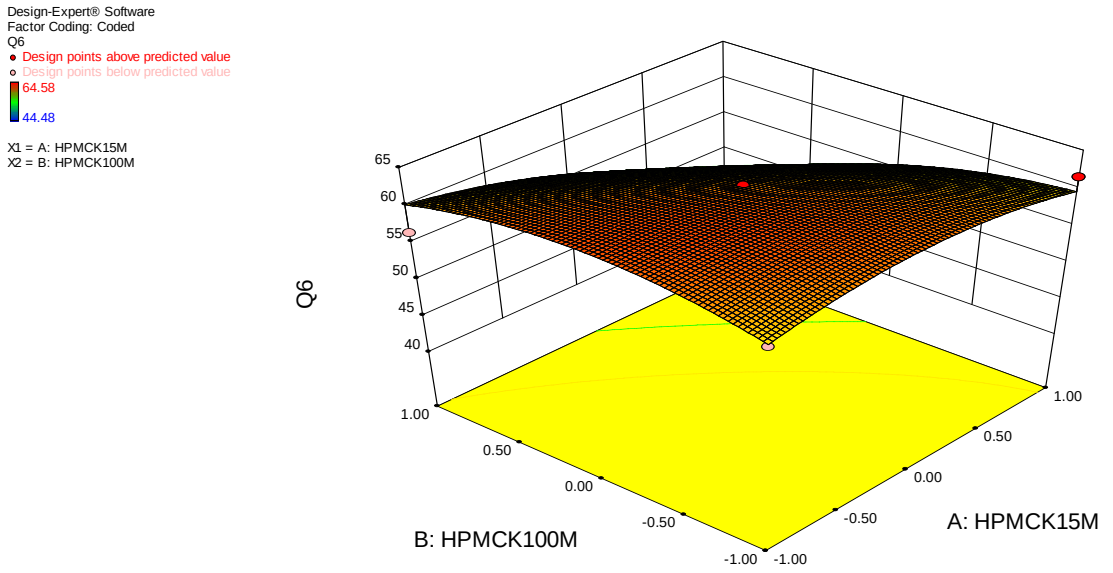

Fig.no-2 Responce surface plot for Q_6

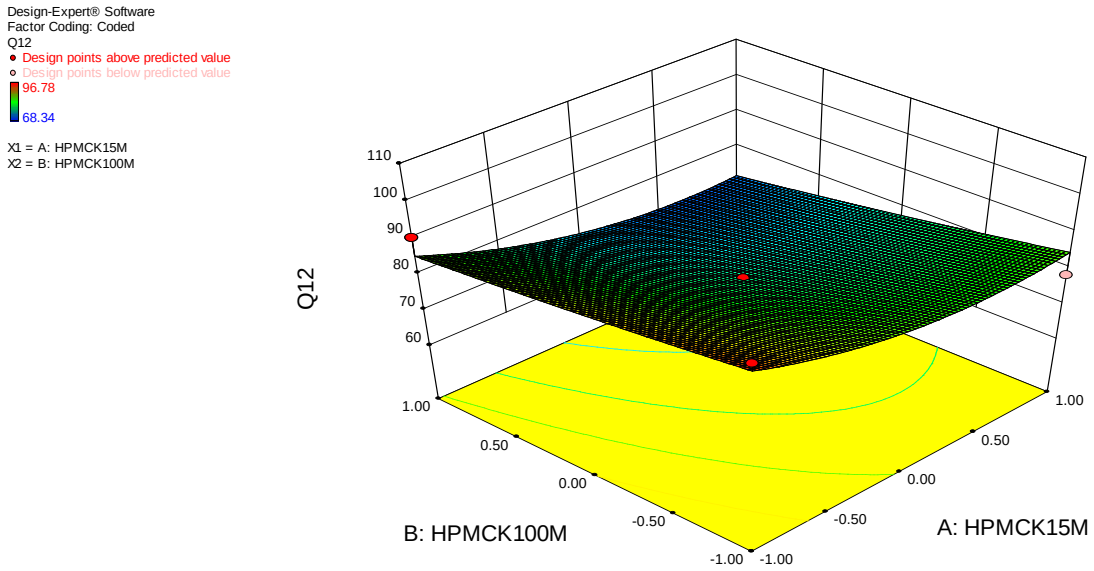

Fig.no-3 Responce surface plot for Q_{12}

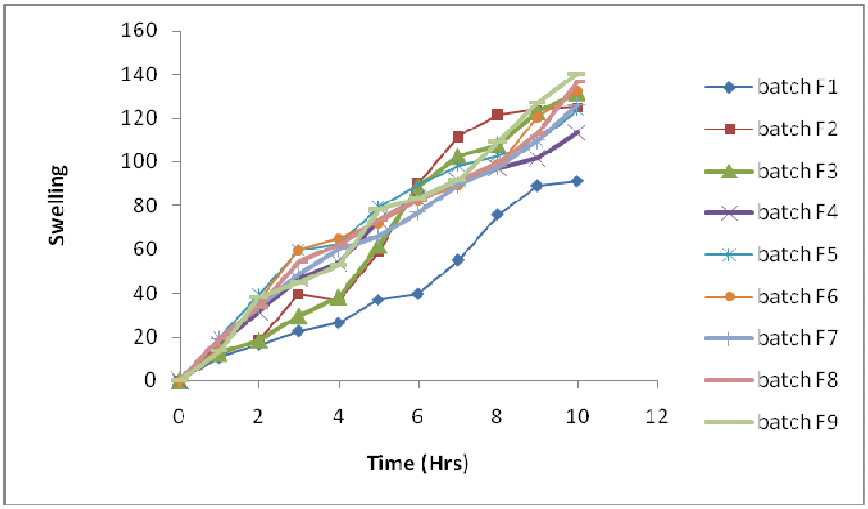

Fig.no.4-Relationship between swelling index and time

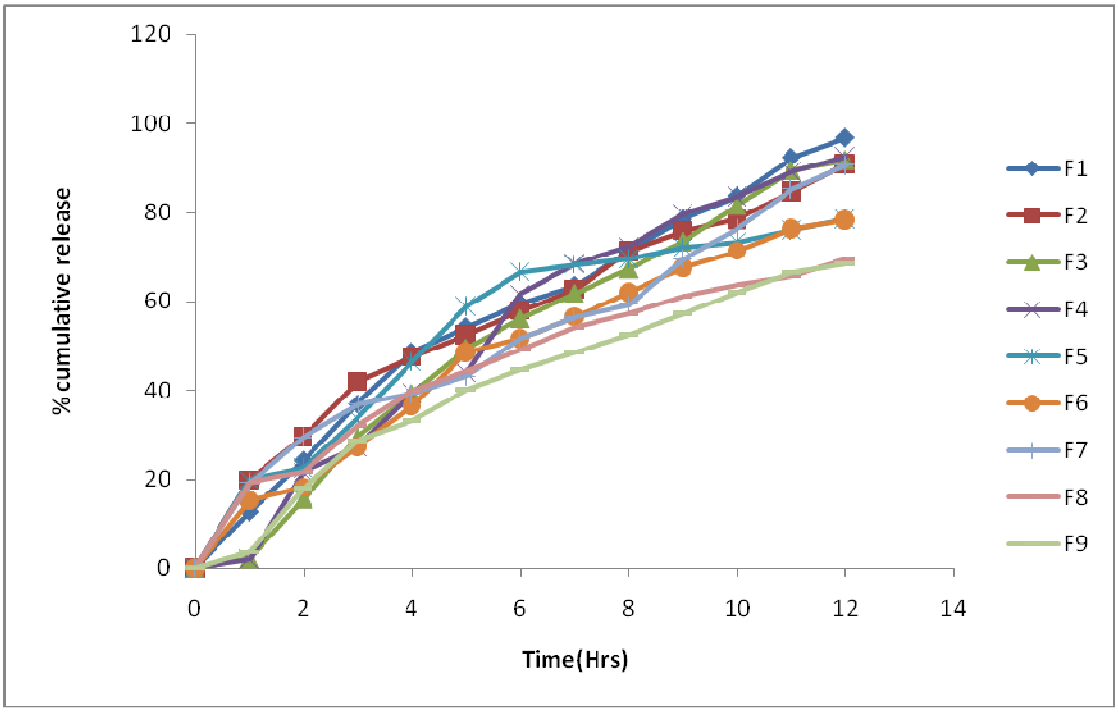

Fig.no.5-Results of % drug release Vs time

CONCLUSION

The present study was carried out to develop the floating drug delivery with controlled release of Cefadroxil monohydrate to provide an effective and safe therapy for Urinary tract infection and pharyngitis with a reduced dose and reduced length of treatment. *In vitro* dissolution studies of all tablets formulation showed controlled release of Cefadroxil monohydrate for 12 hr. by maintaining the buoyancy. Thus, results of the current study clearly indicateted a promising potential of the Cefadroxil floating system as an alternative to the conventional dosage form.

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