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RESEARCH ARTICLE

Formulation Development and Evaluation of Doxofylline Sustained Release Tablets

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Formulation Development And Evaluation Of Doxofylline Sustained Release Tablets

SUMMARY

The main objective of present research investigation is to formulate the sustained release tablet of Doxofylline using 3^2 factorial design. Doxofylline, an anti-Asthmatic agent, belongs BCS class-III agent. The SR tablets of Doxofylline were prepared employing different concentrations of HPMC K100M and Chitosan in different combinations by Direct Compression technique using 3^2 factorial design. The concentration of Polymers, HPMC K100M and Chitosan required to achieve the desired drug release was selected as independent variables, X_1 and X_2 respectively whereas, time required for 10% of drug dissolution ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) were selected as dependent variables. Totally nine formulations were designed, Formulated and are evaluated for hardness, friability, thickness, % drug content, In-vitro drug release. From the Results it was concluded that all the formulation were found to be with in the Pharmacopoeial limits and the In-vitro dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept, slope & regression coefficient were calculated. Polynomial equations were developed for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, t90%. Validity of developed polynomial equations were verified by designing 2 check point formulations (C_1, C_2). According to SUPAC guidelines the formulation (F_4) containing combination of 10% HPMC K100M and 15% Chitosan, is the most similar formulation (similarity factor f_2= 64.501, dissimilarity factor f_1= 6.862 & No significant difference, t= 0.23001) to marketed product (DOXOLIN). The selected formulation (F_4) follows Zero order, Higuchi's kinetics, and the mechanism of drug release was found to be Non-Fickian Diffusion anomalous Super Case-II Transport (n= 0.963).

Key Words: *Doxofylline, 32 Factorial Design, Sustained Release Tablet, HPMC K100M ,Chitosan, SUPAC,*

Doksofilin Sürekli Salım Tablet Formülasyonu Geliştirme ve Değerlendirme

ÖZET

Bu araştırma makalesinin temel amacı, 3^2 faktöriyel tasarım kullanarak Doksofilin'in sürekli salım tablet formülasyonunu geliştirmektir. Doksofilin, astıma karşı kullanılan, BCS sınıf III'e ait bir bileşiktir. Doksofilin'in SR tabletleri, 3^2 faktöriyel tasarım kullanılarak direk basım tekniği ile farklı konsantrasyonlarda HPMC K100M ve kitozan kullanılarak farklı kombinasyonlarda hazırlanmıştır. İstenen ilaç salımını sağlamak için gereken HPMC K100M ve kitozan polimerlerin konsantrasyonu, ilaç çözünmesinin %10'u ($t_{10\%}$), %50 ($t_{50\%}$), %75 ($t_{75\%}$) 'i ($t_{50\%}$) olmak üzere bağımsız değişkenler X_1 ve X_2 olarak seçilmiştir ve %90 ($t_{90\%}$) bağımlı değişken olarak seçilmiştir. Dokuz formülasyon tasarlanmış, formüle edilmiş ve sertlik, ufalanabilirlik, kalınlık, % ilaç içeriği, in-vitro ilaç salımı değerlendirilmiştir. Sonuçlara bakıldığında, tüm formülasyonların Farmakope limitleri içinde olduğu bulunmuştur ve tüm formülasyonların in-vitro çözünme profilleri farklı kinetik modellere uydurulmuş, kesişim, eğim ve regresyon katsayısı gibi istatistiksel parametreler hesaplanmıştır. Polinomiyal denklemler $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$ için geliştirilmiştir. Geliştirilmiş polinom denklemlerinin geçerliliği, 2 kontrol noktası formülasyonu (C_1, C_2) tasarlayarak doğrulanmıştır. SUPAC kılavuzlarına göre, %10 HPMC K100M ve %15 kitozan içeren formülasyon (F_4) pazarlanmış ürüne (DOXOLIN) en benzer formülasyondur (benzerlik faktörü f_2 = 64.501, farklılık faktörü f1 = 6.862 ve anlamlı fark yok, t = 0.23001). Seçilen formülasyon (F_4) sıfırıncı derece kinetik, Higuchi kinetiği ve ilaç salım mekanizması Non-Fickian Diffüzyon Super Case II Transport olarak bulunmuştur (n = 0.963).

Anahtar Kelimeler: *Doksofilin, 32 Faktöriyel Tasarım, Sürekli Salım Tableti, HPMC K100M, Kitozan, SUPAC,*

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INTRODUCTION

Tablets are the most popular oral solid formulations available in the market and are preferred by patients and physicians alike. There are many reasons for this, not the least of which would include acceptance by the patient and ease of administration. In case for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages (Swati Jain et al., 2014). However, when administered orally, many therapeutic agents are subjected to extensive presystemic elimination by gastrointestinal degradation and/or first pass hepatic metabolism as a result of which low systemic bioavailability and shorter duration of therapeutic activity and formation of inactive or toxic metabolites (R. Ruben Singh., 2014).

Sustained release (SR) tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs (Raghavendra Kumar Gunda et al., 2015). Sustained release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i. e., concentration dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving sustained release delivery (Lachmann et al., 1991; Bankar GS et al., 1996; Raghavendra Kumar Gunda et al., 2015).

Sustained release tablet allowing a 2 fold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a prompt release dosage form (J. N. Suresh Kumar et al., 2015). Sustained release products provide advantage over immediate release dosage form by optimising biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drug. Sustained release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration.

The use of polymers in controlling the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Over many years, numerous studies have been reported in the literature on the application of hydrophilic polymers in the development of SR matrix systems for various drugs (Raghavendra Kumar Gunda ., 2015).

Since the early 1950s, the application of polymeric materials for medical purposes is growing very fast. Polymers have been used in the medical field for a large extent (Raghavendra Kumar Gunda et al., 2015). Natural polymers remain attractive primarily because they are economic, readily available, be capable of chemical modifications, non-carcinogenicity, mucoadhesivity, biodegradable, biocompatible, high drug holding capacity and high thermal stability and easy of compression (Prakash P et al., 2011). This led to its application as excipient in hydrophilic drug delivery system. The various natural gums and mucilages have been examined as polymers for sustained drug release in the last few decades for example; guar gum, tragacanth gum, xanthan gum, pectin, alginates, Chitosan etc. In the development of a sustained release tablet dosage form. Availability of wide variety of polymer and frequent dosing interval helps the scientist to develop sustained release product. cellulose derivatives such as carboxymethyl cellulose (CMC), sodium carboxy methyl cellulose(SCMC), hydroxyproyl cellulose (HPC), and hydroxypropyl methyl cellulose (HPMC) have been extensively studied as polymer in the sustained release tablet formulations. These polymers are most preferred because of its cost effectiveness, broad regulatory acceptance, non-toxic and easy of compression. Some factors like molecular size, diffusivity, pKa-ionization constant, release rate, dose and stability, duration of action, absorption window, therapeutic index, protein binding, and metabolism affect the design of sustained release formulation. The future of sustained release products is promising in some area like chronopharmacokinetic system, targeted drug delivery system, mucoadhesive system, particulate system that provide high promise and acceptability.

Oral sustained release dosage form by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms (Raghavendra Kumar Gunda ., 2015). The selection of the drug candidates for sustained release system needs consideration of several biopharmaceutical, pharmacokinetic and pharmacodynamic properties of drug molecule (Rhodes C.T et al., 2003).

In the present study, a sustained release dosage form of Doxofylline has been developed that makes less frequent administering of drug.

Doxofylline, a new generation methyl xanthine derivative used to treat Asthma, belongs BCS class-III agent. It acts by inhibiting Phosphodiesterase there by producing Bronchodilator activity . It has decreased affinity towards A_1, A_2 receptors (P. Praveen kumar

et al., 2014). After oral administration, shows peak plasma level within one hour. Absolute Bioavailability is 62.59% protein binding about 48%. Less than 4% of oral dose excreted unchanged in Urine (Kaushik P et al., 2012). The poor aqueous solubility and wettability of Doxofylline give rise to difficulties in the design of pharmaceutical formulations and led to variable oral bioavailability. Thus, there is a need to increase rate of dissolution. Hence, the study was carried out to formulate and evaluate sustained release dosage form of Doxofylline as a model drug and had an aim that final batch formulation parameters should shows prolong drug release.

It is an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, response surface methodology (RSM) utilizing a polynomial equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. Response surface methodology (RSM) is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating sustained release dosage forms (Raghavendra Kumar Gunda ., 2016).

Hence an attempt is made in this research work to formulate sustained release (SR) tablets of Doxofylline using HPMC K100M and Chitosan . Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties.

Large scale production needs more simplicity in the formulation with economic and cheapest dosage form.

A **3^2** full factorial design was employed to systematically study the drug release profile . A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e the amounts of HPMC K100M and Chitosan on the dependent variables, i.e. $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (Time taken to release 10%,50%,75%,90% respectively).

MATERIALS AND METHODS

Materials used in this study were obtained from the different sources. Doxofylline was a gift sample from Aurobindo pharma Ltd, Hyderabad, India. HPMC K100M, Chitosan were procured from Merck Specialities Pvt.Ltd , Mumbai. Micro crystalline cellulose, PVP K30 were procured from Loba Chemie Pvt.Ltd, Mumbai. Other excipients such as magnesium stearate, Talc were procured from S.D. Fine Chem. Ltd., Mumbai.

Formulation Development of Doxofylline Sustained Release Tablets:

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses (Raghavendra Kumar et al., 2015; Raghavendra Kumar et al., 2016).

A selected three level, two factor experimental design (3^2 factorial design) describe the proportion in which the independent variables HPMC K100M and chitosan were used in formulation of Doxofylline sustained release (SR) Tablets. The time required for 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$) and 90% ($t_{90\%}$) drug dissolution were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for Final Equations. Polynomial equations were developed for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, $t_{90\%}$, (step-wise backward Linear Regression Analysis).

The three levels of factor X_1 (HPMC K100M) at a concentration of 5%, 10%, 15%. three levels of factor X_2 (Chitosan) at a concentration of 5%, 10%, 15%.(% with respect to total tablet weight) was taken as the rationale for the design of the Doxofylline SR tablet formulation. nine Doxofylline sustained release tablet formulations were prepared employing selected combinations of the two factors i.e $\mathbf{X_1}$, $\mathbf{X_2}$ as per 3^2 Factorial and evaluated to find out the significance of combined effects of $\mathbf{X_1}$, $\mathbf{X_2}$ to select the best combination and the concentration required to achieve the desired prolonged/ sustained release of drug from the dosage form.

Preparation of Doxofylline Sustained Release Tablets:

Doxofylline SR Tablets were prepared by Direct Compression method. Composition of each Tablet was shown in Table 2. All ingredients were collected and weighed accurately and passed through sieve no 60. They were mixed uniformly in a polybag or triturate for 15 minutes. magnesium stearate was added and then again blend for 5-6 minutes, Blend was subjected to compression by using 8 station rotary tablet punching machine (Minipress, RIMEK, Ahmedabad) using 12 mm circular punches and same hardness used for required number of tablets. Compressed

tablets were examined as per official standards and unofficial tests. Tablets were packaged in well closed light resistance and moisture proof containers.

Experimental Design:

Experimental design utilized in present investigation for the optimization of polymer concentration such as, concentration of HPMC K100M was taken as X_1 and concentration of Chitosan was taken as X_2. Experimental design was given in the Table 1. Three levels for the Concentration of HPMC K100M were selected and coded as -1= 5%, 0=10%, +1=15%. Three levels for the concentration of Chitosan were selected and coded as -1= 5%, 0=10%, +1=15%. Formulae for all the experimental batches were given in Table 2 (A. A. Kharia et al., 2010).

Table 1: Experimental design layout

Formulation Code	X_1	X_2
F_1	1	1
F_2	1	0
F_3	1	-1
F_4	0	1
F_5	0	0
F_6	0	-1
F_7	-1	1
F_8	-1	0
F_9	-1	-1
C_1	-0.5	-0.5
C_2	+0.5	+0.5

Table 2: Formulae for the preparation of doxofylline sustained release tablets as per experimental design

Name of Ingredients	Quantity of Ingredients per each Tablet (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Doxofylline	400	400	400	400	400	400	400	400	400
Microcrystalline Cellulose pH-102	48	68	88	68	88	108	88	108	128
PVP K30	20	20	20	20	20	20	20	20	20
HPMC K 100M	60	60	60	40	40	40	20	20	20
Chitosan	60	40	20	60	40	20	60	40	20
Magnesium Stearate	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
Total Weight	600	600	600	600	600	600	600	600	600

Evaluation of Doxofylline Sustained Release Tablets:

Hardness

The hardness of the tablets was tested by diametric compression using a Monsanto Hardness Tester. A tablet hardness of about 2-4 kg/cm² is considered adequate for mechanical stability.

Friability

The friability of the tablets was measured in a roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_0) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %

Friability (%) = [(Initial weight- Final weight) / (Initial weight)] x 100

Content Uniformity

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or more than 115% of the labelled drug content can be considered as the test was passed.

Assay

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 100 mg was dissolved in 100ml of phosphate buffer pH 6.8, followed by stirring. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 263 nm using phosphate buffer pH 6.8 as blank.

Thickness

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.

***In-vitro* Dissolution Study**

The *In-vitro* dissolution study for the Doxofylline sustained release tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of 0.1 N HCl as dissolution medium for first two hours followed by phosphate buffer pH 6.8 at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 263 nm using UV -Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

Kinetic modeling of drug release:

The dissolution profile of all the formulations was fitted in to zero-order, first-order, Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release (Higuchi., 1963; Peppas., 1985).

RESULTS AND DISCUSSION:

Sustained release tablets of Doxofylline were prepared and optimized by 3^2 factorial design in order to select the best combination of different polymers, HPMC K100M, chitosan and also to achieve the desired prolong/sustained release of drug from the dosage form/ Formulation. The two factorial parameters involved in the development of formulations are, quantity of HPMC K100M & chitosan as independent variables (X_1, X_2), and *In vitro* dissolution parameters such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ & $t_{90\%}$ as dependent variables. Totally nine formulations were prepared using 3 levels of 2 factors and all the formulations containing 400 mg of Doxofylline were prepared as a sustained release tablet dosage form by direct compression technique as per the formulae given in Table 2.

All the prepared tablets were evaluated for different post compression parameters, drug content, mean hardness, friability, mean thickness as per official methods and results are given in Table 3. The hardness of tablets was in the range of **4.25±0.15-4.52±0.4 Kg/cm².** Weight loss in the friability test was less than **0.54%**. Drug content of prepared tablets was within **acceptance range only**. Results for all Post-compression parameters were tabulated or summarised in Table 3. *In-vitro* dissolution studies were performed for prepared tablets using 0.1 N HCl for first two hours followed by phosphate buffer pH 6.8 as a dissolution media at 50 rpm and temperature 37±0.5°C. The *In-vitro* dissolution profiles of tablets were shown in Fig.1-4 (Kinetic Plots) and the dissolution parameters were summarised in Table 4. Cumulative % drug release of factorial design formulations F_1-F_9 at 12Hr were found to be in the range of **85.94-99.535%**. From the result it reveals that the release rate was higher for formulations containing Low level of HPMCK 15M compared with other Formulations containing Higher level, due to High concentration of polymer drug may have entrapped within a polymer matrix causing a decrease in rate of drug release. variable concentrations of chitosan produce modified release properties but high retardation of drug release also not advisable. Therefore, required release of drug can be obtained by manipulating the composition of HPMC K100M and chitosan.

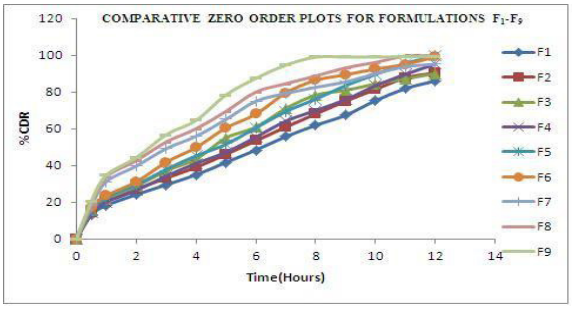

Fig.1 Comparative Zero Order Plots for F_1-F_9

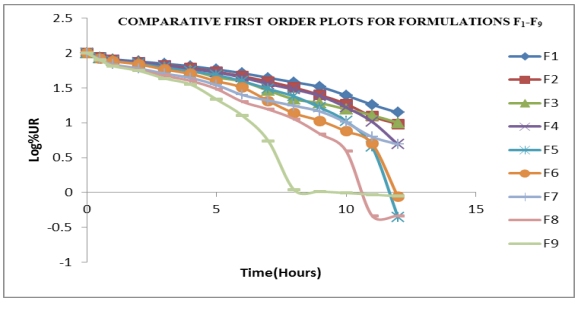

Fig.2 Comparative First Order Plots for F_1-F_9

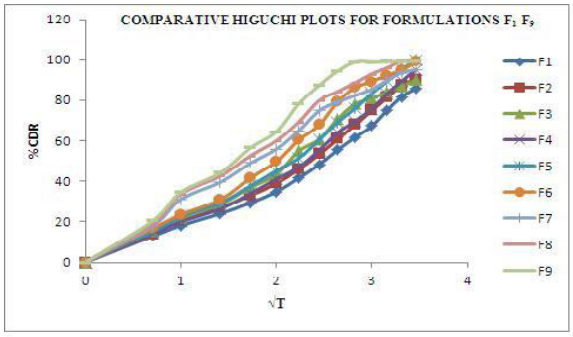

Fig.3 Comparative Higuchi Plots for F_1-F_9

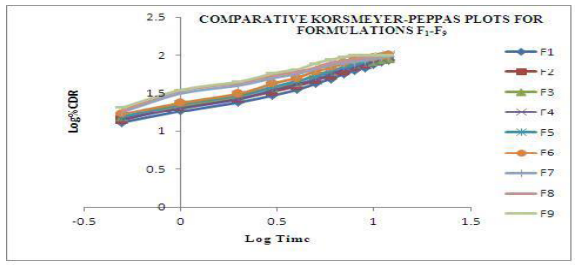

Fig.4 Comparative Korsmeyer-Peppas Plots for F_1-F_9

Table 3: Post-compression parameters for the formulations

S.No	Formulation Code	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Weight Variation (mg)	Drug Content (%)
1	F_1	4.45±0.11	3.75±0.15	0.54±0.03	599.0±0.14	98.73±0.46
2	F_2	4.35±0.05	3.8±0.13	0.51±0.025	598.90±0.31	98.995±0.52
3	F_3	4.25±0.15	3.65±0.12	0.51±0.03	599.15±0.30	98.38±0.32
4	F_4	4.5±0.21	3.75±0.15	0.53±0.025	600.09±0.01	99.29±0.41
5	F_5	4.42±0.5	3.81±0.14	0.5±0.02	600.80±0.02	99.55±0.35
6	F_6	4.31±0.20	3.65±0.26	0.51±0.025	601.05±0.10	98.94±0.36
7	F_7	4.52±0.40	3.70±0.14	0.525±0.025	598.95±0.16	99.44±0.36
8	F_8	4.43±0.20	3.75±0.16	0.495±0.02	598.85±0.10	99.71±0.32
9	F_9	4.30±0.5	3.61±0.15	0,505±0.025	599.10±0.21	99.09±0.41

Table 4: Regression analysis data of 3^2 factorial design formulations of doxofylline

S. NO	Formulation Code	KINETIC PARAMETERS											
		ZERO ORDER			FIRST ORDER			HIGUCHI			KORSMEYER-PEPPAS		
		a	b	r	a	b	r	a	b	r	a	b	r
1	F_1	8.133	6.661	0.995	2.030	0.064	0.974	8.160	25.069	0.981	1.235	0.608	0.988
2	F_2	9.940	7.093	0.993	2.045	0.077	0.972	7.798	26.878	0.985	1.282	0.600	0.991
3	F_3	13.259	7.229	0.979	2.019	0.082	0.994	6.048	27.968	0.992	1.325	0.591	0.994
4	F_4	9.793	7.373	0.994	2.077	0.090	0.948	8.594	27.914	0.985	1.284	0.612	0.992
5	F_5	11.600	7.806	0.992	2.195	0.138	0.872	8.232	29.723	0.989	1.326	0.604	0.994
6	F_6	14.919	7.942	0.977	2.140	0.137	0.942	6.482	30.813	0.992	1.365	0.595	0.994
7	F_7	21.330	7.140	0.955	2.005	0.102	0.992	0.421	28.483	0.997	1.448	0.513	0.995
8	F_8	23.137	7.572	0.951	2.179	0.178	0.938	0.782	30.291	0.996	1.477	0.513	0.994
9	F_9	26.457	7.708	0.923	2.108	0.200	0.967	2.533	31.381	0.983	1.507	0.508	0.988

F_1 to F_9 are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope.

Much variation was observed in the $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ due to formulation variables. Formulation F_4 containing 40 mg of HPMC K100M, 60 mg of Chitosan showed promising dissolution parameter (**$t_{10\%}$= 0.508 h, $t_{50\%}$ = 3.343 h, $t_{75\%}$ = 6.686 h, $t_{90\%}$ = 11.108 h**). The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures (A. A. Kharia et al., 2010). As the increase in viscosity results in a corresponding decrease in the drug release, which might be due to the result of thicker gel layer formulation (Dortunc B et al., 1997).

The *In -vitro* dissolution data of Doxofylline SR tablet formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4 and plots shown in Figs 1-4. It was observed

from the above that dissolution of all the tablets followed zero order kinetics (Except F_3, F_9 due to Low concentration of Chitosan) with co-efficient of determination (R^2) values above **0.923 (0.923-0.995)**. The values of r of factorial formulations for Higuchi's equation was found to be in the range of **0.981-0.997**, which shows that the data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from **1.235-1.507** that shows Non-Fickian diffusion mechanism anomalous Super case-II Transport. Polynomial equations were derived for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ values by backward stepwise linear regression analysis using **PCP Disso** software and Response surface plots were constructed using **SIGMAPLOT V13** software. The Response surface plots were shown in Fig.5-8 for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ using X_1 and X_2 on both the axes respectively. The dissolution data (Kinetic parameters) of factorial formulations F_1 to F_9 were shown in Table 5.

Table 5: Dissolution parameters of doxofylline sustained release tablets 3^2 full factorial design batches

S.NO	FORMULATION CODE	KINETIC PARAMETERS			
		$t_{10\%\ (Hrs)}$	$t_{50\%\ (Hrs)}$	$t_{75\%\ (Hrs)}$	$t_{90\%\ (Hrs)}$
1	F_1	0.719	4.728	9.455	15.710
2	F_2	0.591	3.886	7.771	12.912
3	F_3	0.561	3.690	7.380	12.262
4	F_4	0.508	3.343	6.686	11.108
5	F_5	0.331	2.180	4.360	7.244
6	F_6	0.334	2.197	4.394	7.301
7	F_7	0.448	2.946	5.892	9.789
8	F_8	0.258	1.695	3.390	5.632
9	F_9	0.228	1.502	3.004	4.991

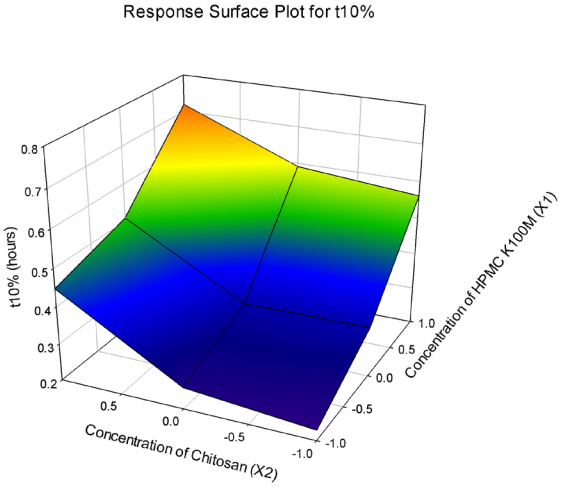

Fig.5 Response surface plots for $t_{10\%}$

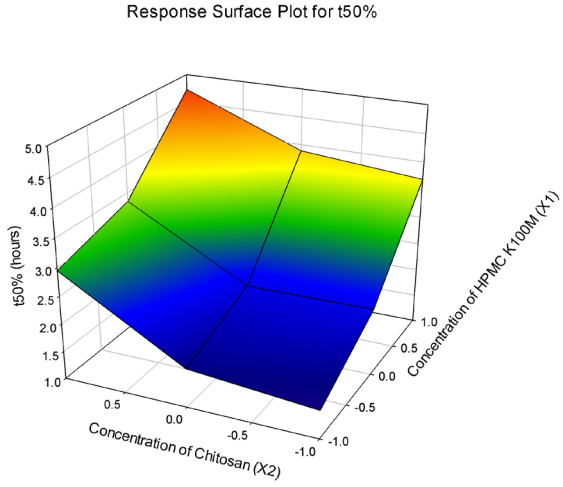

Fig.6 Response surface plots for $t_{50\%}$

Table 6: Dissolution parameters for predicted and observed values for check point formulations

FORMULATION CODE	PREDICTED VALUE				ACTUAL OBSERVED VALUE			
	$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)})$	$t_{90\%\ (h)}$	$t_{10\%\ (h)}$	$t_{50\%\ (h)}$	$t_{75\%\ (h)})$	$t_{90\%\ (h)}$
C_1	0.352	2.312	4.624	7.683	0.355	2.324	4.659	7.689
C_2	0.600	3.943	7.886	13.105	0.628	3.957	7.892	13.113

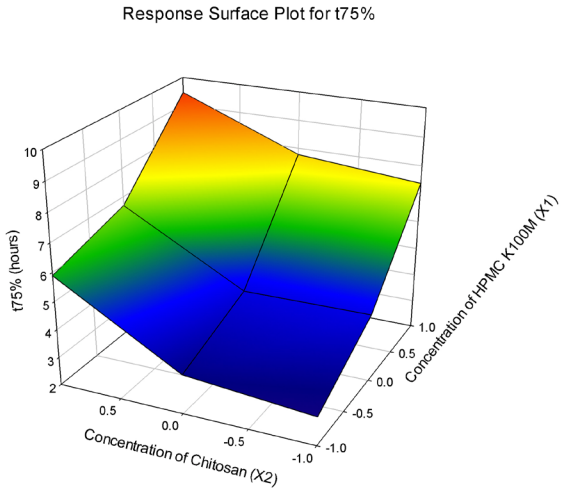

Fig.7 Response surface plots for $t_{75\%}$

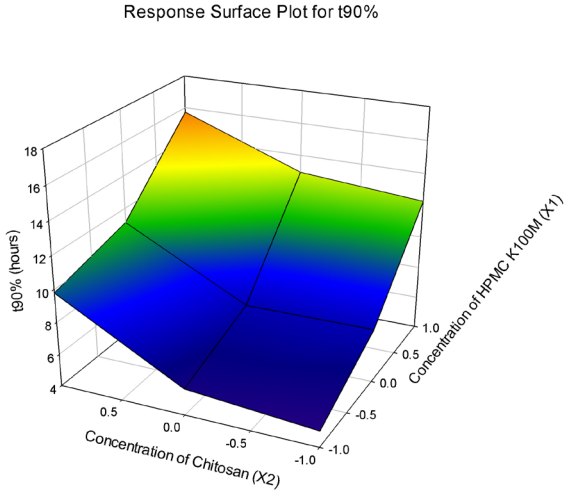

Fig.8 Response surface plots for $t_{90\%}$

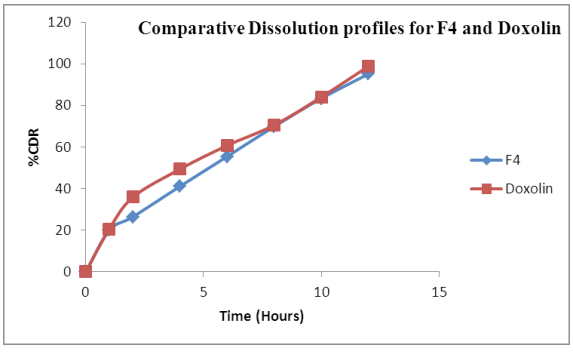

Fig.9 Comparative dissolution profiles for F4 and Doxolin

Polynomial equation for 3^2 full factorial designs is given in Equation

$$\mathbf{Y= b_0+b_1 X_1+b_2 X_2+b_{12} X_1X_2+b_{11} X_1^2+b_{22} X_2^2\ldots}$$

Where, Y is dependent variable, b_0 arithmetic mean response of nine batches, and b_1 estimated co-efficient for factor X_1. The main effects ($\mathbf{X_1}$ and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate non-linearity. Validity of derived equations was verified by preparing Two Check point Formulations of Intermediate concentration(C_1, C_2).

The equations for $t_{10\%}$, $t_{50\%}$ $t_{75\%}$ and $t_{90\%}$ developed as follows,

Y_1= 0.442+0.156X_1+0.092X_2-0.016X_1X_2+0.077 X_1^2+0.073X_2^2 **(for $t_{10\%}$)**

Y_2= 2.907+1.027X_1+0.605X_2-0.102 X_1X_2+0.501 X_1^2+0.481 X_2^2 **(for $t_{50\%}$)**

Y_3= 5.815+2.053X_1+1.209X_2-0.203 X_1X_2+1.0 X_1^2-0.962 X_2^2 **(for $t_{75\%}$)**

Y_4 = 9.661+3.412X_1+2.01X_2-0.338 X_1X_2+1.67 X_1^2+1.598 X_2^2 **(for $t_{90\%}$)**

The positive sign for co-efficient of X_1 in Y_1, Y_2, Y_3 and Y_4 equations indicates that, as the concentration of HPMC K100M increases, $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ value increases. In other words the data demonstrate that both X_1 (amount of HPMC K100M) and X_2 (amount of Chitosan) affect the time required for drug release ($t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$). From the results of dissolution rate study it can be concluded that increase in the amount of the polymer leads to decrease in release rate of the drug and drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. The Dissolution parameters for predicted from the polynomial equations derived and those actual observed from experimental results are summarised in Table 6. The closeness of Predicted and Observed values for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$ indicates validity of derived equations for dependent variables. The response surface plots were presented to show the effects of X_1 and X_2 on $t_{10\%}$, $t_{50\%}$, $t_{75\%}$ and $t_{90\%}$. The final best (Optimised) formulation (F_4) is compared with marketed product (**DOXOLIN**) shows similarity factor (f_2) 64.501, difference factor (f_1) 6.862 (There is no significant difference in drug release because t_{cal} is<0.05) Comparative dissolution profile for best formulation and marketed product shown in fig 9.

CONCLUSION

The present research work envisages the applicability of Polymers such as HPMC K100M and Chitosan in the design and development of sustained release tablet formulations of Doxofylline utilizing the 3^2 factorial design. From the results of *In vitro* dissolution studies it was clearly understand that as the retardant (HPMC) concentration increases the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired sustained release of the drug for longer periods. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be Non-Fickian Diffusion, Zero order release type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation $\mathbf{F}_4$ may be used once a day administration in the management of Asthma, COPD and to reduce the risk of Respiratory Problems. This may improve the patient compliance by reducing the dosing frequency. which will ultimately improve the therapeutic outcome. We could be able to minimize the per oral cost of the Formulation.

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ABBREVATIONS AND SYMBOLS USED

SR	- Sustained Release
HPMC	- Hydroxy Methyl Propyl Cellulose
BCS	- Biopharmaceutical Classification System
Kg	- Kilo Gram
Cm	- Centi Meter
%	- Percentage
mg	- milli gram
ml	- milli litre
%CDR	- Percentage Cumulative Drug Release
UR	- Un Released
Min	- Minute
^{o}C	- Degree Centigrade
mm	- milli meter
$t_{1/2}$	- Half Life
$t_{10\%}$	- Time taken to release 10% drug from dosage form
$t_{50\%}$	- Time taken to release 50% drug from dosage form
$t_{75\%}$	- Time taken to release 75% drug from dosage form
$t_{90\%}$	- Time taken to release 90% drug from dosage form