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Design and characterization of pentoxifyllinepharmacosomes by solvent evaporation method

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ABSTRACT

Aim

The objective of the present investigation is to formulate the Pentoxifyllinepharmacosomes using 3^2 factorial design technique.

Methods

Pentoxifylline is drug of choice for treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs and is a BCS class II drug. Pentoxifyllinepharmacosomes were prepared by solvent evaporation method using variable concentrations of Lecithin. The formulation design is developed by altering the concentrations of Pentoxifylline and Lecithin in a fixed ratio and considered as independent variables assigned X_1 and X_2 respectively. Whereas, the time required to release 10% ($t_{10\%}$), 50% ($t_{50\%}$), 75% ($t_{75\%}$), and 90% ($t_{90\%}$) are considered as the dependent variables. The design developed total 9 formulations which were formulated and evaluated as per the pharmacopoeial tests.

Results

The results reveal that the developed formulations are in the pharmacopoeial limits. Further, the formulations are subjected to *in-vitro* drug release studies through kinetic modeling which ultimately lead to the development of slope, intercept and regression coefficient. The resultant is implied for the generation of various polynomial equations for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ drug release which confirms the optimized formulation as F1.

Conclusion

Based on the results it can be concluded that the best optimized formulation is F1 and follows first order kinetics. Further, Higuchi kinetics reveals that the formulation follows non-Fickian diffusion anomalous transport (n= 0.723)

Keywords: 3^2 factorial design, Claudication, Lecithin, Variables.

INTRODUCTION

In the recent years investigators are much focused on the development of various novel drug delivery systems that can be able to deliver the drug to the targeted site and at a predetermined rate[1]. Although numerous drug delivery systems are available to meet the desired criteria a special focus is made to accomplish the requirement through incorporation of drug in a carrier system or altering the structure of the drug at molecular level or controlling the drug input into the bio environment for distribution[2,3]. The current drug delivery strategies are focused on the incorporation of carriers or chemical deactivation for depicting the safety and efficacy of the dosage form[4]. In order to meet the above criteria various pharmaceutical carriers came into existence of which a particular colloidal carrier type known a colloidal carrier system which includes microspheres, nanoparticles, polymeric micelles, and vesicular systems such as liposomes, transferosomes, niosomes, proniosomes, pharmacosomes, virosomes etc[5]. Of these vesicular systems, pharmacosomes are colloidal dispersions of drug that are covalently bounded to lipids and possess unique advantages over liposomes and niosomes such as high drug incorporation, minimum drug leakage, reduced cost, incorporation of hydrophilic and hydrophobic drugs etc[6,7]. The surface interaction of drug with lipid is the criteria for development of pharmacosomes. Any drug possessing active hydrogen can be esterifies to a lipid with or without spacer units resulting in the formation of amphiphilic compound and facilitate cell wall, tissue, and membrane transfer in the organisms and thereby enhancing the bioavailability, pharmacokinetic and pharmacodynamics properties of the drug[8,9]. Apart from these they should be specially focused on certain properties such as size, entrapment efficacy, amphiphilicity, active drug loading and stability for its precision and selectivity. The present investigation deals with the design and formulation of Pentoxifylline, which is a BCS class II drug and is widely preferred for decreasing the muscle aches, cramps, and pain during exercise, including walking, that occur with intermittent claudication[10]. The selection of Pentoxifylline for the present investigation is due to its profound pharmacokinetics which undergoes complete absorption on oral administration and undergoes first pass metabolism which leads to the appearance of metabolites in the plasma very soon on dosing. The peak plasma levels of the compound is attained with in 1 hour and apparent plasma half lives vary from 0.4 to 0.8 hours and the apparent plasma half live of metabolites vary from 1 to 1.6 hours[11]. Therefore, the necessity for alteration in dosing frequency and most possibly the demand for change in dosage form is recommended to meet the patient acceptability. The investigation is carried out with a fixed ratio of drug: lipid using a three square factorial technique to trace out the optimized formulation an meet the required specifications.

MATERIALS AND METHODS

Materials

Pentoxifylline was obtained fromYarrow pharmaceuticals, Ahmedabad, India.Lecithin was obtained from Yarrow chemicals, Ahmedabad, India. Dichloromethane (A.R) was obtained from Finar chemicals, Mumbai, India.

Drug Profile and Rationality for Experimental Design

The present investigation is focused on the Pentoxifylline pharmacosomes that can generate a sustain release effect and can ultimately enhance the pharmacokinetic parameters of the drug. Pentoxifylline is basically designed for decreasing the viscosity of systemic circulation, improving erythrocyte flexibility, exhibiting dose related hemorrheological effects and for enhancing the tissue oxygenation in specific diseased conditions such as peripheral arterial disease [12]. The insight on various pharmacokinetic parameters of Pentoxifylline reveals that the drug gets completely absorbed through oral route and generates peak plasma levels and its corresponding metabolites in 1hour. The plasma half life of Pentoxifylline is 0.4 to 0.8 hours and its corresponding metabolites vary from 1 to 1.6 hours [13]. Therefore, a suitable formulation that can enhance the pharmacokinetic parameters is to be designed and the current investigation is focused on the above criteria through a specific design that meets the above requirements.

In order to fulfill the current strategy, various response surface methodologies (RSM) utilizing a polynomial equation are preferred. Now a days various RSM's such as factorial design, central composite design, Box-Behnken design, and D-optimal design are available for successfully carrying out the investigation. Apart from these, the RSM is employed only when a few significant factors are involved in optimization and demands less time and experimentation trials. Hence, The RSM's can be more economical and effective than the traditional methods of formulation design [14].

The investigation on Pentoxifyllinepharmacosomes outlines the optimization of Pentoxifylline and lecithin concentration that exhibits a profound effect on the release characteristics of the drug. Among the above mentioned RSM's a 3^2 factorial design is employed for the investigation of the effect of two independent variables i.e. Pentoxifylline and lecithin on the dependent variables such as such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ which refers to the time required for the drug to release 10%, 50%, 75%, and 90% from the dosage form.

Formulation Development of PentoxifyllinePharmacosomes

The factorial design is a statistical optimization technique that allows the optimization of key factors and helps in assessing the interaction between the specific factors. The design consists of selection of factors their responses[15,16]. As described above, the design involves selection of dependent variables such as drug and lecithin concentration and independent variables such as $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ from the formulation. In addition, the significance was tested at 95% confidence interval ($P < 0.05$) and the development of polynomial equations for $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ is performed using step-wise backward linear regression analysis.

As a part of exploration, total nine formulations were generated using 3^2 factorial design at three different levels of factor X1 which stands for Pentoxifylline and another three levels for factor X2 which stands for lecithin at a concentration of 400mg, 200mg and 100mg. Finally the results were evaluated to trace out the combined effects of both factors X1 and X2 to select the best formulation required to achieve the desired quality attributes.

Preparation of Pentoxifyllinepharmacosomes

The current investigation involves preparation of pharmacosomes through solvent evaporation method in which the equimolar ratios of drug and lipid were taken in a round bottomed flask and refluxed for 1 hour. The resultant is evaporated under vacuum at 40ºC in an rotary evaporator and the dried residue is collected in and placed in desiccator for overnight for the absorption of moisture[17,18].

Experimental Design

The current research employs three square factorial design for the optimization of drug: lecithin concentration in which X1 is designated as drug concentration and X2 is designated as lecithin concentration. Therefore, three levels were selected in the experimental design such as "+1" for higher concentrations i.e. 400mg, "0" for intermediate concentrations i.e. 200mg, and "-1" for lower concentrations i.e. 100mg as shown in table 1 for reference.

Table 1: Experimental design Layout

Formulation code	X1	X2
F1	1	1
F2	1	0
F3	1	-1
F4	0	1
F5	0	0
F6	0	-1
F7	-1	1
F8	-1	0
F9	-1	-1

Where, X1 stands for the drug concentration and X2 stands for lecithin concentration.

Table 2: Formulation chart for the preparation of Pentoxifyllinepharmacosomes

Formulation Code	Pentoxifylline (mg)	Lecithin(mg)	Dichloromethane (ml)
F1	100	100	20
F2	100	50	20
F3	100	25	20
F4	50	100	20
F5	50	50	20
F6	50	25	20
F7	25	100	20
F8	25	50	20
F9	25	25	20

CHARACTERIZATION OF PENTOXIFYLLINE PHARMACOSOMES

Preformulation Studies

The Preformulation studies is considered as primary and crucial step in drug development and is defined as the investigation of physiochemical properties of drug when present alone or its compatibility in combination with excipients. The primary objective of Preformulation studies lies in generating information for justifying the safety, efficacy and stability of the dosage form which is quite useful for the formulator in dosage form design [19].

Identification Studies

Identification of drug

The procured sample was analyzed for IR spectral analysis and the same was compared with the IR spectrum of the standard Pentoxifylline.

Method for drug identification

The drug identification is performed using FTIR spectrophotometer in which 1-3mg of the sample is admixed with 100mg of potassium bromide and grounded to a fine powder using motor and pestle. The resultant blend is converted to a transparent disc using a pellet press and the generated pellet is subjected for FTIR analysis [20].

Determination of Melting point

The melting point is determined using open capillary method in which a thin walled capillary tube of 10-15cm is selected and loaded with the drug sample. The capillary tube is sealed at both ends and placed in the melting point apparatus. The temperature is gradually raised and the point at which the sample melts is recorded as the melting point of the substance [20].

Determination of solubility

Nearly 10mg of drug is added to the 5ml phosphate buffer pH 6.8 and subjected for magnetic stirring in a water bath maintained at 37±0.5ºC for 2hrs. The samples were withdrawn at regular intervals of tome and filtered through 0.45µ whatman filter paper, suitably diluted and analyzed through UV spectrophotometer at 277nm[20].

Compatibility studies

The current strategy is significant in Preformulation for estimating the compatibility between the drug and excipient whose interaction can impact on stability and bioavailability of the drug and in turn affects the safety and efficacy of the dosage form. The drug and excipient compatibility is analyzed using FTIR spectroscopy which incorporates the preparation of potassium bromide pellets using pellet press. The principal procedure for the preparation of pellets include admixing the required quantity of powered sample with 5 times the quantity of KBR and the resultant blend is grounded well using mortar and pestle. The finely powdered blend is introduced in a stainless steel die and pressed between the anvils at a pressure of 50 pounds. The spectrum is recorded at a wave length between 4000^{-1} to 400^{-1} cm [20].

Preparation of Calibration curve Preparation of stock solution

For the preparation of calibration curve 100mg of drug is dissolved in 100ml of dichloromethane to obtain a concentration of 1000µg/ml (stock solution I) and from that nearly 10 ml of the solution is pipetted out and diluted with 100ml of

dichloromethane to obtain a concentration of 100µg/ml (stock solution II)

Determination of λ max

From the stock solution, the specific concentrations of the drug are prepared and scanned between 200-400nm and a sharp peak was observed at 277nm which confirms the specified wavelength.

Preparation of calibration curve

From the stock solution B, 0.5, 1, 1.5, 2, 2.5, and 3ml is pipette out and diluted to 10ml with dichloromethane to get the concentration of 5, 10, 15, 22, 25, and 30µg/ml respectively and the resultant are measured at 277nm.

CHARACTERIZATION OF PHARMACOSOMAL FORMULATION

Preformulation studies

As a part of the Preformulation studies the drug and the excipients used in the formulation were subjected to FTIR study to evaluate the incompatibilities between the drug and excipients. The results reveal that the formulation doesn't exhibit any interaction between the drug and the excipients there by effecting the safety and efficacy of the dosage form.

Determination of drug content

The current evaluation study involves determination of drug content in Pentoxifylline – lecithin complex which involves incorporation of accurately weighed quantity of dosage form to volumetric flask containing 100ml of phosphate buffer pH 6.8. The volumetric flask is stirred continuously for 24 hrs and suitable dilutions were made and analyzed spectrophotometrically at 277nm[21].

Determination of entrapment efficacy

The entrapment efficacy test is performed to separate the unentrapped drug from the formulation using exhaustive dialysis method. The study involves incorporation of measured quantity of dosage form to the dialysis tube for which the egg membrane is securely attached to one side, and the dialysis tube is suspended in a 100ml phosphate buffer pH6.8 maintained at room temperature on a magnetic stirrer. As the procedure follows, the unentrapped drug gets separated through the egg membrane and at every hour the whole medium (100ml) is replaced with a fresh medium for nearly 9-12hrs until the absorbance indicates a constant reading which confirms that no more drug is available in unentrapped form. Further, the solution is diluted with a suitable quantity of buffer and the drug entrapment is estimated by UV spectrophotometric method at 277 nm. The entrapment efficiency is calculated by the following equation [21]:

$$\% \text{ drug entrapped} = \frac{\text{Total amount of drug} - \text{unentrapped drug}}{\text{Total amount of drug}} \times 100$$

In-vitro drug release studies

The in-vitro drug release studies are performed using USP dissolution apparatus (basket type), using phosphate buffer pH 6.8. The procedure involves filling the dissolution apparatus with 900ml phosphate buffer pH 6.8 maintained at 37±0.5ºC and a50rpm. The specified quantities of pharmacosomes are added to the dissolution apparatus and run for 10hrs during which 10ml of sample is withdrawn in every hour and continued up to 10hrs. Meanwhile, the withdrawn quantity of the sample is replaced with the similar quantities of fresh medium and the collected samples were filtered and analyzed using UV spectrophotometer [22].

RESULTS AND DISCUSSION

The compatibility studies are generally preformed prior to the formulation studies which include performance of IR spectroscopy for pure drug and excipients as shown in the figures. The IR spectrum generates a characteristic peak at specific wave length whose analysis reveals the drug-excipient compatibility. The current IR spectrum of

Pentoxifylline signifies no change in its chemical integrity.

Melting point

The melting point of the drug was performed using open capillary method which specified the melting point as 106ºC and complies with the IP standards which indicates the purity of sample.

Solubility studies

The solubility of Pentoxifylline in various solvents was analyzed and found that the drug is soluble in water, chloroform, methanol, dichloromethane. The current studies are quite helpful in analytical method development of drug and drug release studies.

Table 3: Determination of drug content and entrapment efficacy

Formulation Code	Drug Content	Entrapment efficacy
F1	97.4	98.67
F2	91.6	94.25
F3	89.1	92.54
F4	94.5	96.89
F5	97.0	98.37
F6	87.2	94.26
F7	88.3	92.72
F8	90.8	92.57
F9	96.9	98.24

The prepared pharmacosomes were evaluated for drug content, Entraptment efficiency and the corresponding results were shown in table 3.The drug content was determined at 277nm using phosphate buffer pH 6.8 and exhibits maximum for 1:1 ration of drug: lecithin i.e. for F1 (97.4), F5 (97.0), and F9 (96.9). Therefore, the results on drug content reveals that the drug loading decreased with the increase in concentration of lipid to drug and F1 is considered as the optimized formulation as it exhibits higher drug content and entrapment efficacy (98.67) in comparison to F5 (98.37) and F9 (98.24).

In-vitro drug release studies of Pentoxifyllinepharmacosomes

The in-vitro drug release studies were performed in USP dissolution apparatus type (basket), using phosphate buffer pH 6.8 as a dissolution media. The drug release studies were mainly affected by drug: lipid concentration which was further subjected to zero order, first order, Higuchi model, and Korsemeyer-Peppas model for establishing the mechanism of drug release and its kinetics from the pharmacosomes. In connection to the above, when the data was subjected to zero order and first order kinetics, it exhibited a linear relationship and generated high R^2 values for first order when compared to the zero order which reveals that the formulation follows a first order kinetics.

Further, the data generated through Higuchi model reveals linearity and R^2 values are in the range of 0.942 to 0.984, which reveals that the drug follows diffusion mechanism. Further, the kinetic data fitted to Korsemeyers-Peppas model exhibits "n" values in the range 0.723 to 0.907 (>0.5 and < 1) which indicates non-fickian diffusion (anomalous drug transport). Polynomial equations were derived for all the dependent variables and the corresponding response surface plots were developed using sigmaplot®V12 trial version. The surface response plots are depicted for kinetic parameters $t_{10\%}$, $t_{50\%}$, $t_{75\%}$, and $t_{90\%}$ and the corresponding are tabulated in table 5. The polynomial equations generated for 3^2 factorial designs can be explained as follows:

$Y=b_0 + b_1X_1 + b_2X_2 + b_12X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$

where Y is dependent variable, $b_0$is average response of 9 trails, and $b_1$is estimated coefficient for X_1. The main effects ($X_1$and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction 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. Simultaneously the polynomial equations were developed for dependent variables such as

Y_1= 1.153 + $0.07X_1$-$0.095X_2$-$0.06X_1X_2$-$0.07X_1^2$ - $0.045X_2^2$ ($t_{10\%}$)

Y_2 = 7.028 + $0.353X_1$-$0.89X_2$+$0.07X_1X_2$-$0.256X_1^2$ -$0.156X_2^2$ ($t_{50\%}$)

Y_2 = 8.904 + $0.426X_1$-$1.07X_2$+$0.187X_1X_2$-$0.173X_1^2$ +$0.056X_2^2$ ($t_{75\%}$)

Y_4 = 11.787 + $0.506X_1$-$1.076X_2$+$0.122X_1X_2$-$0.313X_1^2$ -$0.253X_2^2$ ($t_{90\%}$)

The positive sign for coefficient of X_1 in the above mentioned polynomial equations indicate that as the concentration of lecithin increases the simultaneous release of the drug decreases accordingly there by producing a sustained release effect of the drug. Therefore, the appropriate ratio of lecithin: pentoxifylline can be selected through alterations in X_1 and X_2 levels. In connection to the above, the response plots for kinematic parameters reveal the effect of independent variables on dependent variables which confirms the optimized formulation as F1 depicting 1:1 ratio of drug: lecithin.

Table 4: Statistical parameters

Formulation Code	Zero Order	Higuchi	Korsemeyer-Peppas	
	r^2	r^2	n^2	r^2
F1	0.951	0.979	0.723	0.979
F2	0.955	0.984	0.739	0.985
F3	0.974	0.975	0.737	0.991
F4	0.982	0.971	0.733	0.994
F5	0.994	0.956	0.784	0.972
F6	0.980	0.942	0.907	0.988
F7	0.993	0.955	0.792	0.973
F8	0.991	0.948	0.768	0.964
F9	0.994	0.962	0.827	0.998

Where r^2 = correlation coefficient

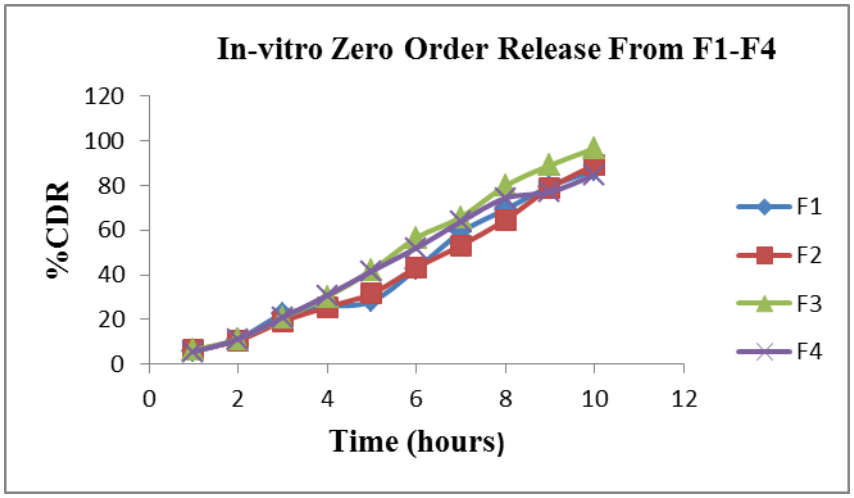

Fig. 1 In-vitro drug release studies for zero order from F1 to F4

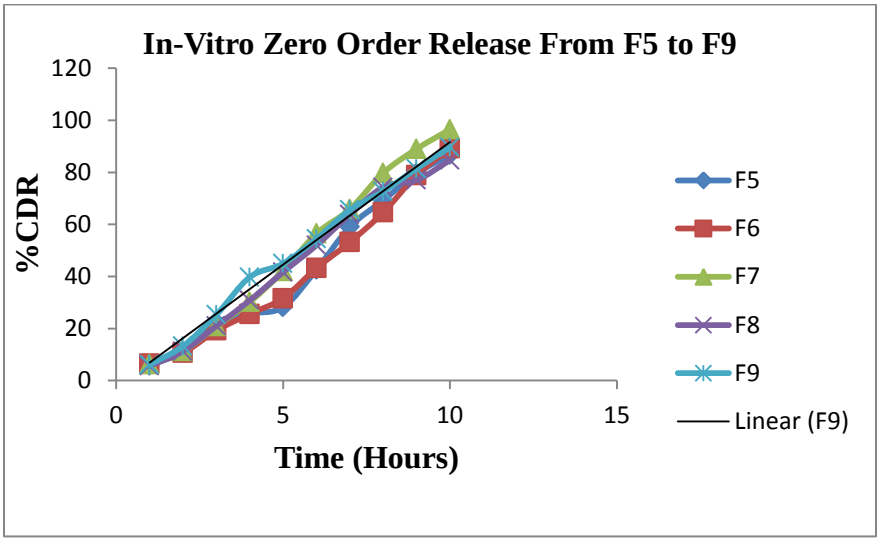

Fig.2 In-vitro drug release studies for zero order from F5 to F9

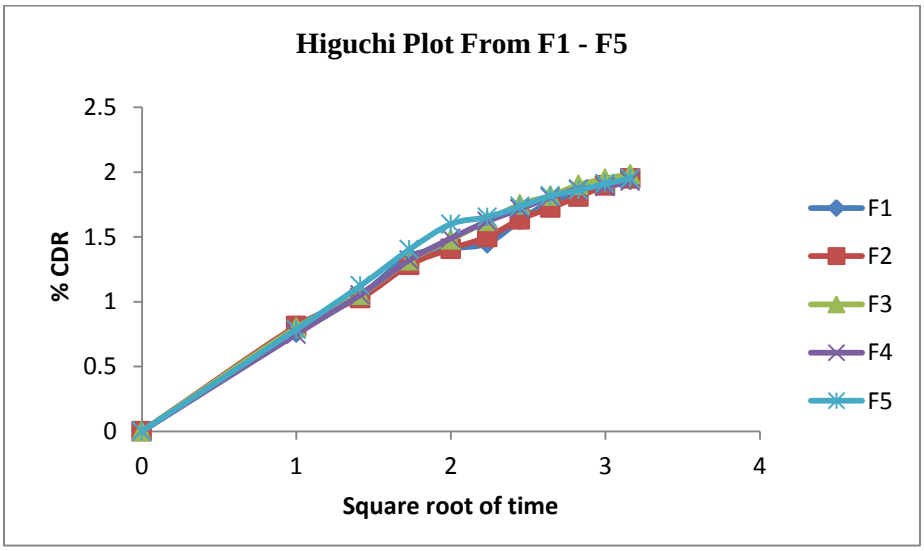

Fig. 3 Higuchi plot for the formulations F1-F5

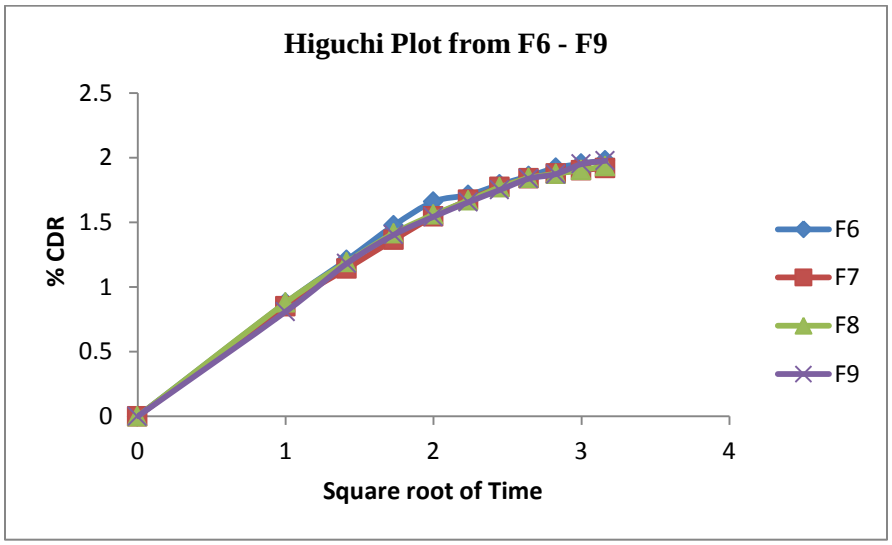

Fig. 4 Higuchi plot for the formulations F6-F9

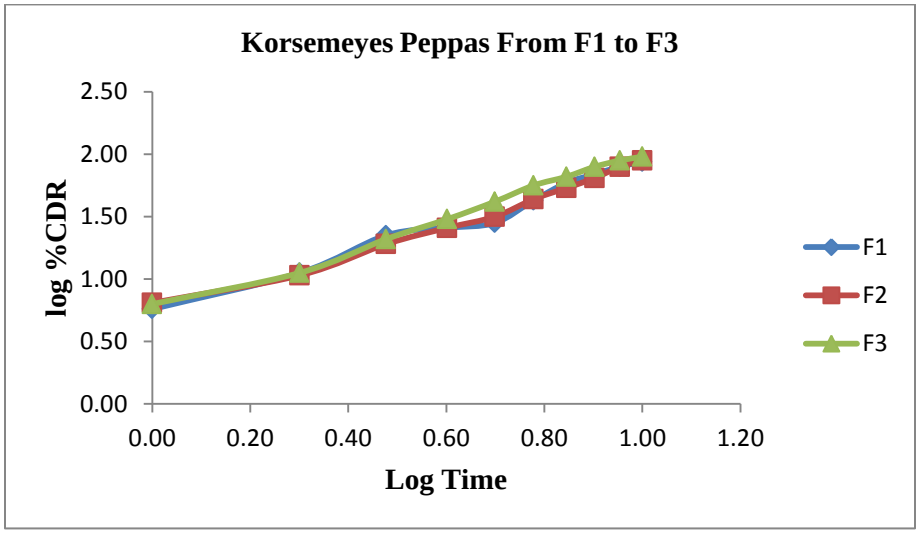

Fig. 5 Korsemeyespeppas plot for the formulations F1-F3

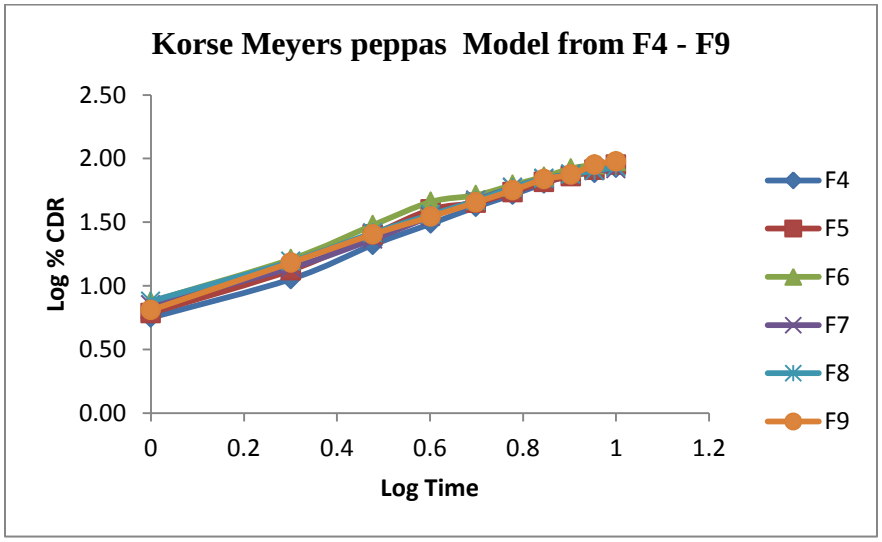

Fig. 6 Korsemeyespeppas plot for the formulations F4-F9

Table 5: Dissolution parameters for pentoxifylline

Formulation Code	$t_{10\%}$	$t_{50\%}$	$t_{75\%}$	$t_{90\%}$
F1	1.04	6.32	8.42	11.05
F2	1.25	7.59	9.32	12.45
F3	1.32	7.98	10.08	13.07
F4	1.03	6.12	7.63	10.75
F5	1.28	7.62	9.45	12.56
F6	1.29	7.86	9.98	12.68
F7	1.06	5.82	7.51	10.08
F8	1.02	6.19	7.83	10.86
F9	1.09	7.76	9.92	12.59

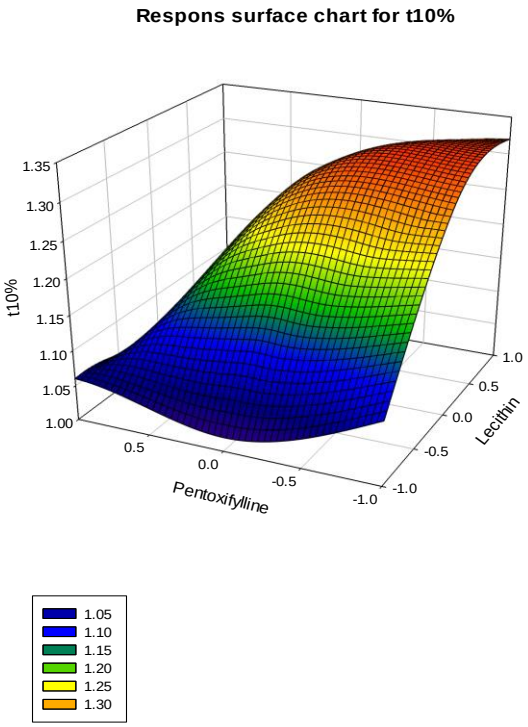

Fig. 7 Response surface chart for t10%

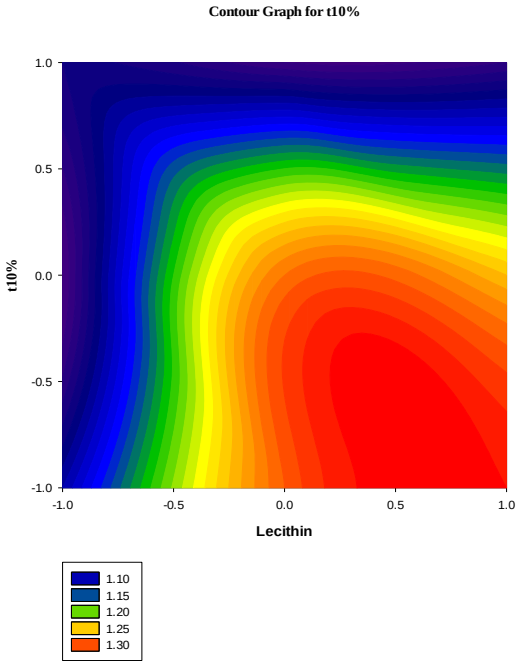

Fig. 8 Contour graph for t10%

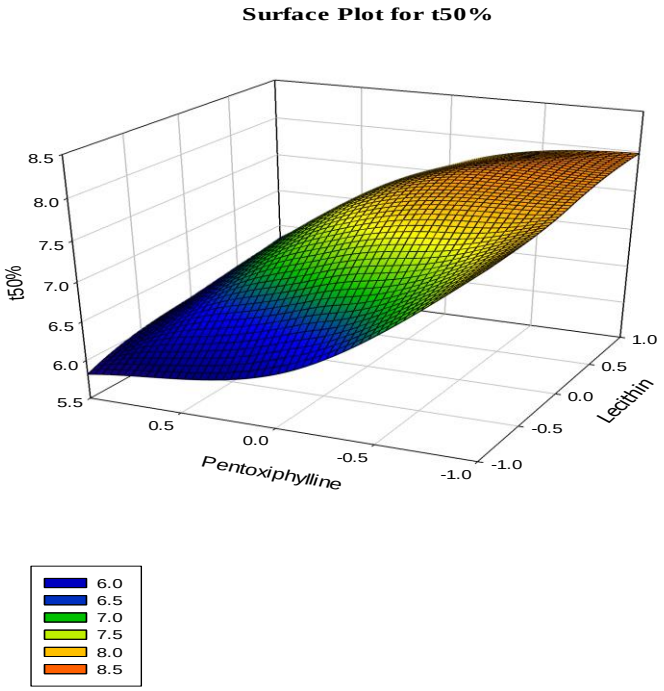

Fig. 9 Response surface chart for t50%

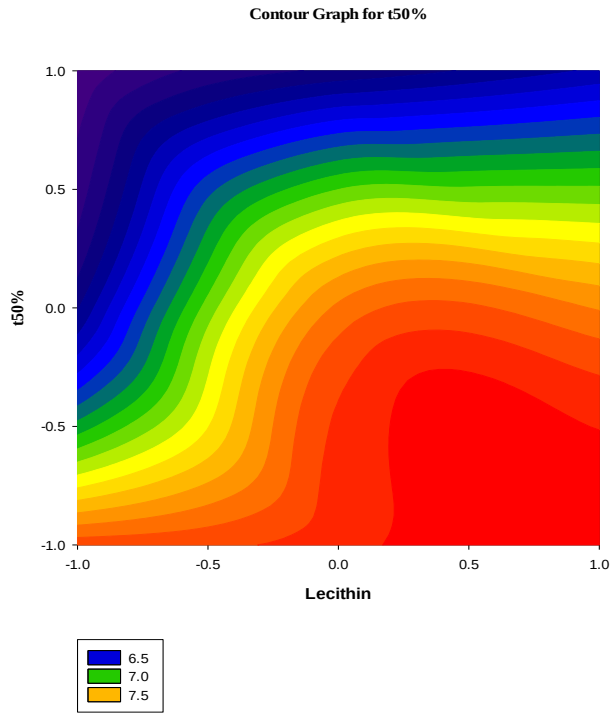

Fig. 10 Contour graph for t50%

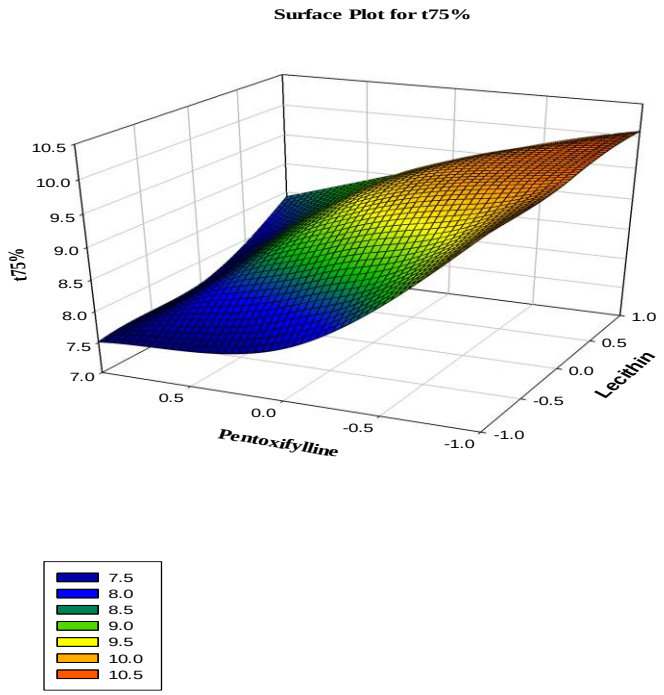

Fig. 11 Response surface chart for t75%

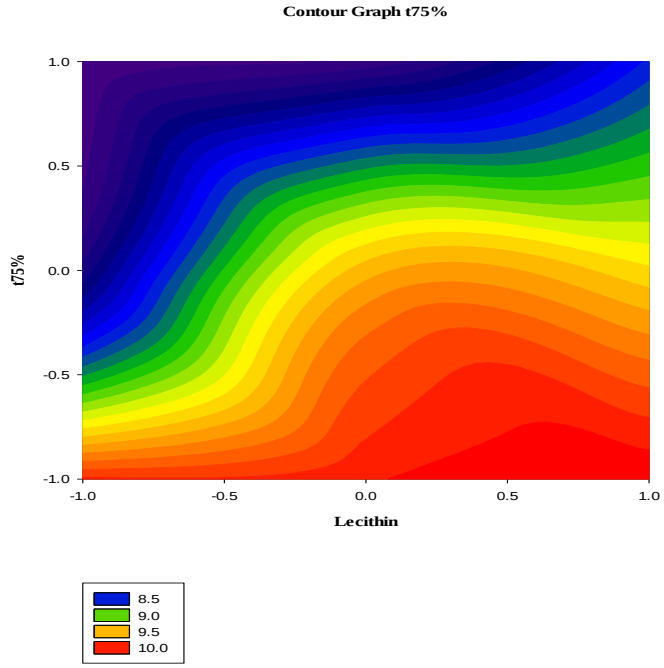

Fig. 12 Contour graph for t75%

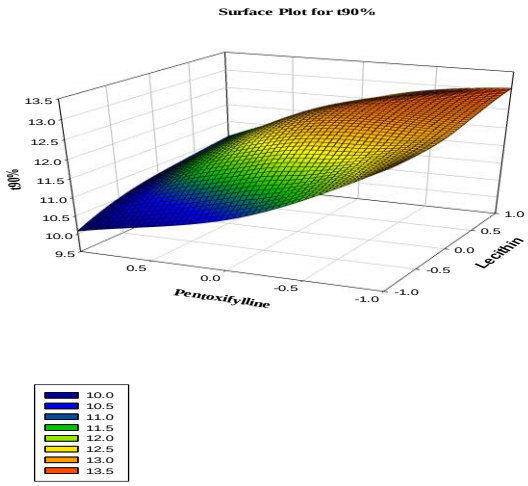

Fig. 13 Response surface chart for t90%

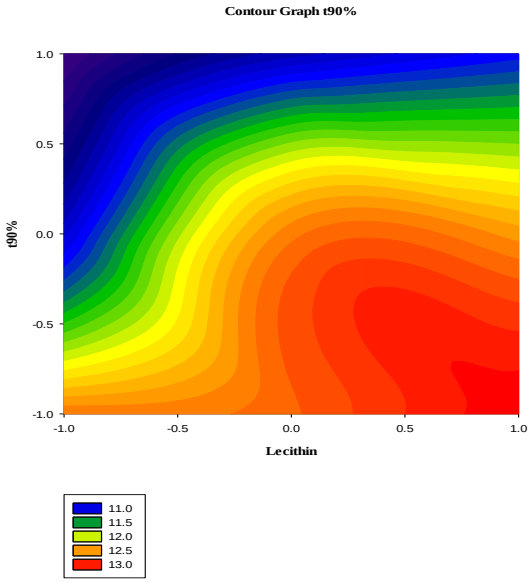

Fig. 14 Contour graph for t90%

CONCLUSION

The current study is instigated to reveal the effect of lecithin on the release of Pentoxifylline with the help of 3^2 factorial design technique. From the results it can be confirmed that the release of drug is inversely proportional to concentration of lecithin and show a sustained release effect. Further the results reveal F1 as the optimized formulation which follows non-Fickian diffusion, first order release type and can be enhance the patient compliance by decreasing the dosing frequency and reduces the cost of formulation.

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