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Research Article

Optimization of Theophylline Sustained Release Tablets Using 3^2 Full Factorial Design and Response Surface Analysis

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ABSTRACT

The present investigation describes the influence of the high substituted hydroxypropyl cellulose (HPC-H) and guar gum on release behavior and kinetics of theophylline sustained release tablets using 3^2 full factorial design. The amounts of Guar Gum (X1) and HPC-H (X2) were selected as an independent variables and drug release at 1hr (Q_1) and at 8hr (Q_8) and time required for 50% drug release ($T_{50\%}$) were selected as a dependent variable. Theophylline tablets were prepared by direct compression method using HPC-H with Guar Gum as release retardant in different proportions and MCC as directly compressible filler-binder. The parameter optimized using 3^2 factorial designs. The tablets of all batches were evaluated for various evaluation parameters. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Regression analysis and response surface analysis were performed for dependent variables. The FTIR study was carried out for drug excipient compatibility Studies. The initial release was sufficiently higher in all formulations thus ruling out the need to incorporate a specific loading dose. Thus, the use of suitable polymer combinations that could provide initial higher release and release extension up to 12 hr. It was observed that type and ratio of polymer had significant influence on Q_8, without significant influence on Q_1 and $T_{50\%}$. Mathematical treatment of the *in vitro* drug release data suggests that, the drug release of all the formulations followed Korsmeyer-peppas model, the release exponent n<0.5 indicate that drug diffuses through the polymeric matrix by a Fickian (case I) diffusion mechanism.

INTRODUCTION

Drug delivery in conventional dosage forms often suffers from the drawbacks of repeated drug administration and large fluctuations in drug blood levels. The frequency with which a rapidly absorbed and distributed drug must be given in a conventional dosage form is dependent upon intrinsic properties of the drug, viz. elimination half-life ($t_{1/2}$). [1]

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action including improved therapeutic effect, increased patient compliance by reducing dosing frequency and decrease in incidence and /or intensity of adverse effect by a constant blood concentration. [2]

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Theophylline, and its derivatives have long been used for their bronchodilator properties in the management of asthma and chronic obstructive pulmonary disease (COPD) [3]. This drug has a great variability in clearance (elimination half life 3-4 hr, adults 6-12 hr) and also has a narrow therapeutic range (7.5-20 µg/ml). Once or twice daily administration of controlled release preparations in patients with COPD is recommended and improves patient compliance. Hence, the objective of this work was to investigate the release of theophylline from tablets prepared with Guar Gum and HPC-H as matrix material.

Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules into a matrix in slowly disintegrating or inert porous material containing a hydrophilic rate controlling polymer [4, 5, 6]. Matrix systems are widely used in oral controlled drug delivery because of their flexibility (which results in obtaining desirable

drug release profile), cost effectiveness and broad regulatory acceptance [3, 7]. Cellulose ethers such as hydroxypropyl cellulose(HPC), hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC), copolymers of acrylic-methacrylic acid (Eudragits) such as Eudragit RL and RS and some natural gums like Guar Gum and xanthan gum are widely used hydrophilic polymers as release retardant. [3, 8]. Guar gum a polysaccharide derivative with glycoside linkage has been used as matrix former for controlled release of isoniazide [9] and diltiazem [10]. In case of formulation with HPC, there was an initial higher release in stimulated gastric fluid (SGF) followed by zero order release profile in stimulated intestinal fluid (SIFsp) for rifampicin. The initial release was sufficiently higher for rifampicin from HPC thus ruling out the need to incorporate a specific loading dose [11].

So the purpose of this research was to prepare matrix gastro retentive tablet of theophylline using different ratio of hydroxypropyl cellulose (HPC-H) and guar gum and applied the different dissolution model to study the drug release mechanisms and kinetics. A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e. The amounts of HPC-H and guar gum on the dependent variables, i.e. Q_1, Q_8, $T_{50\%}$ (% drug release after 1, 8,hours and time required to release 50% drug respectively).

MATERIALS AND METHODS

Materials

Theophylline and hydroxypropyl cellulose (HPC) were received as a gift sample from Torrent research center, gandhinagar, India. Guar gum was received as a gift sample from H.B. Gum India Pvt Limited, Kalol, India. Microcrystalline cellulose and magnesium stearate were obtained from S. D. fine-chem. ltd., Mumbai, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Preparation of theophylline tablets

Tablets were prepared by direct compression method. MCC was used as directly compressible filler-binder to increase the compressibility and flow of the ingredients. 1% magnesium stearate was used as a lubricating agent. Before use, all the ingredients pass through 80 # sieve and mixed thoroughly. Finally the 1% magnesium stearate was added as a lubricating agent and mixed for 2 minutes. The powder mixer was compressed in 12 mm diameter flat punches using a multi punch tablet compression machine (Cad mach, Ahmadabad, India).

Evaluation of tablets

All prepared matrix tablets were evaluated for uniformity of weight [12] and assay [13] as per I.P. method. Friability was determined using Roche friabilator. Hardness was measured by using Pfizer hardness tester. [14].

In vitro dissolution studies

The *in vitro* dissolution study of theophylline tablets was performed using USP apparatus (model TDT-08T, Electrolab, Mumbai, India) fitted with paddle (50 rpm) at $37^0C \pm 0.5^0C$ using SGF (pH 1.2; 900 mL) as a dissolution medium for the first 2 hour, followed by SIF pH 6.8 phosphate buffer solutions for further 10 hour.. At the predetermined time intervals, 10-mL samples were withdrawn, filtered through a 0.45μm membrane filter and assayed at 270 nm using a Shimadzu UV 1800 double-beam spectrophotometer (Shimadzu, Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

Preliminary screening

The preliminary screening was performed to optimize total amount of polymer in the formulation. Tablets were prepared using varying amount (30% and 40%) of polymer (Guar Gum and HPC 20:20, 15:25, 10:20 and 5:25) as shown in Table 1. Tablets prepared with varying amount of polymer were tested for *in vitro* drug release study.

Optimization of variables using 3^2 full factorial designs

A 3^2 randomized full factorial design was used in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The amounts of GUAR GUM (X1) and HPC-H (X2) were selected as independent variables in 3^2 full factorial design, while Q_1, Q8 and $T_{50\%}$ (% drug release after 1, 8,hours and time required to release 50% drug respectively) were taken as dependent variables. The formulation layout for the factorial design batches (F_1-F_9) is shown in Table 2.

Table 1: Formulation of theophylline sustained release tablet using different amount of polymer

Name of Ingredient	Quantity in percentage (%)			
	P1	**P2**	**P3**	**P4**
Theophylline	40	40	40	40
Guar Gum	20	15	10	5
HPC-H	20	25	20	25
MCC	20	20	30	30
Q_8	47.08	53.98	71.03	82.86
Q_{12}	56.29	69.29	79.91	90.53

HPC-H and MCC indicate high substituted hydroxypropyl cellulose and microcrystalline cellulose respectively. Q_8 and Q_{12} are the percentage drug release after 8 and 12 hours respectively. All formulation containing 1% magnesium stearate of total weight. All ingredients are in percentage (%). Weight of tablet is 505 mg of each.

Table 2: 3^2 Full Factorial Design Layouts

Batch Code	Variable level in coded form		Q_1	Q_8	$T_{50\%}$
	X_1(%)	**X_2 (%)**			
F-1	-1	-1	60.84	92.52	0.31
F-2	-1	0	44.41	82.74	1.69
F-3	-1	1	36.73	82.86	2.22
F-4	0	-1	57.17	89	0.41
F-5	0	0	45.75	78.58	3.35
F-6	0	1	41.81	64.70	4.25
F-7	1	-1	54.41	80.96	0.52
F-8	1	0	49.26	71.23	1.34
F-9	1	1	37.56	65.51	2.13

Coded Values	Actual Values	
	X_1 (%)	**X_2 (%)**
-1	5	20
0	6	22.5
1	7	25

X_1 and X_2 indicates the amount of Guar Gum and HPC-H respectively.
Q_1, Q_8 and $T_{50\%}$ percentage drug release after 1 and 8 hour and time required for 50% drug release, respectively.

Response surface analysis

Two dimensional (2-D) contour pot and three dimensional (3-D) surface response plots where constructed based on the model polynomial function using SIGMA PLOT 10.0 TRIAL VERSION. These plots are very useful to see interaction effect on the factor of the response.

Drug release kinetics study

The dissolution profile of all batches were fitted to various models such as zero order, first order [15], Higuchi, [16] Hixon Crowell,[17] Korsemeyer and Peppas,[18] to ascertain the kinetic of drug release. The method described by Korsemeyer and Peppas was used to describe mechanism of drug release.

Fourier transforms infrared spectroscopy

Fourier transform infrared (FTIR) spectrum of Theophylline and a physical mixture of theophylline with other excipients were recorded using KBr mixing method on FTIR instrument available at central instrument laboratory of the institute (FTIR-1700, Shimadzu, Kyoto, Japan).

RESULTS AND DISCUSSION

Results of preliminary screening

Four batches (P_1, P_2, P_3 and P_4) as shown in Table 1 were prepared using different amount of polymer Guar gum (%): HPC (%) was 20:20, 15:25, 10:20 and 5:25. Formulations P_1, P_2, P_3 and P_4 were subjected to in vitro dissolution study. The % drug release after 8 and 12 hour is shown in Table 1. Batch P_4 released the drug in controlled manner (90.53 CPR in 12hr as shown in Fig. 1) while in batch P_1, P_2 and P_3, due to the higher amount of polymer it released only 56.29%, 69.29% and 79.91% drug in 12hr respectively which is not acceptable for the optimum formulation.

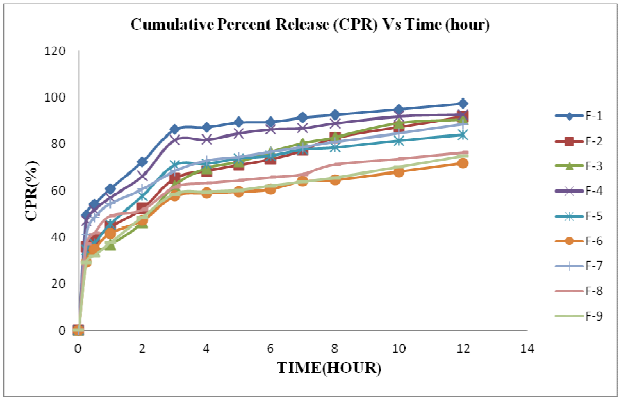

Figure 1: Comparision of the Cumulative Percentage Release of Factorial Batches

Full factorial design

A statistical model incorporating interactive and poly nominal terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2 + b_6X_1^2X_2 + b_7X_1X_2^2$$

Where, b_0 is the intercept representing the arithmetic average of quantitative out come of 9 runs b_1 to b_8 are the coefficient computed from the observed experimental value of Y & X_1, X_2 are the coded level of the independent variable.

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high values. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2, X_2^2, $X_1^2X_2$ and $X_1X_2^2$) are included to investigate nonlinearity. The dissolution profile for 9 batches showed a variation (i.e., initial 1 hr release ranging from 36.73% to 60.84% and drug released after 12 hr ranging from 71.91% to 97.5%). The data indicate that the release profile of the drug is strongly dependent on the selected independent variables. The fitted equations relating the responses, Q_1, Q_8, $T_{50\%}$ to the transformed factor are shown in the Table 2. The 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 5 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Data were analyzed using Microsoft Excel.

R^2 value for Q_1, Q_8 and $T_{50\%}$ are 0.9922, 0.9970, 0.9951 respectively indicating good correlation between dependent and independent variables. The terms with $P<0.05$ were considered statistically significance. The significance levels of the coefficients in the Q_1 and $T_{50\%}$ were found to be insignificance at $P>0.05$ hence do not contribute significance information to the prediction of Q_1 and $T_{50\%}$.

Factorial equation for Q_1

Concerning Q1, the results of multiple linear regression analysis showed that both the coefficients b_1 and b_2 bear a negative sign. It is possible that at higher polymers concentration, THP is trapped in smaller polymer cells and it is structured by its close proximity to the polymer molecules. So, increasing the amount of the polymer in the formulations increased the time it took for the drug to leave the formulation and retard release of drug into the medium.

$$Q_1 = 47.167 - 2.425\ X_1 - 7.68\ X_2 - 1.815\ X_1X_2 - 1.0416\ X_1^2 + 1.613\ X_2^2 - 2.56\ X_1^2X_2 + 3.82\ X_1X_2^2$$

The Q_1 for all the batches F1 to F9 varied from 36.73% to 60.84% (Table 2) showed good correlation coefficient as **0.9922**. Results of the equation indicated that both the concentration of the X_1 and X_2 were responsible for the Q_1 but X_2 have more effect to control the release.

Factorial equation for Q_8

The amount of drug released after 8 hrs is also important parameters for prominent drug release from sustained release matrix formulation. The Q_8 for all the batches F1 to F9 varied from 64.7% to 92.52% (Table 2) showed good correlation coefficient as **0.9970**. Therefore, increasing the concentration of either HPC-H or Guar Gum is expected to decrease the drug release and the HPC-H has more retardant effect. Such delay in drug release may be because of the release rate is conditioned by the concentration of the polymer.

$Q_8 = 77.25 - 5.755X_1 - 12.15X_2 - 1.4475X_1X_2 + 1.8766X_1^2 + 1.7416X_2^2 + 5.8725 X_1^2X_2 - 1.4725X_1X_2^2$

Factorial equation for $T_{50\%}$

The time taken to 50% amount of drug released is also important parameters for prominent drug release from sustained release matrix formulation. The **$T_{50\%}$** for all the batches F1 to F9 varied from 0.31 to 4.25 (Table 2) showed good correlation coefficient as **0.9951**.

$T_{50\%} = 2.206 + 0.175 X_1 + 1.925 X_2 + 0.1 X_1X_2 - 1.2816 X_1^2 - 0.4716 X_2^2 - 1.07 X_1^2X_2 - 0.23X_1X_2^2$

Physical Evaluation

The physical appearance, tablet hardness, friability, weight variation, and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 3. Tablet hardness was found to be good (5.2 ± 1.20 to 6.9 ± 0.89 kg/cm^2) depending on the compression force applied. In the present study, the percentage friability for all the formulations was found below 1% indicating that friability (%) is within the acceptable limits. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets of more than 250 mg is ±5%. The average percentage deviation of all tablet formulations was found to be within above limit, and hence all formulations passed the test for uniformity of weight as per official requirement. Good uniformity in drug content was found among different batches of the tablets, and the percentage of drug content was more than 98 %, which indicates that by direct compression we can get a good quality of theophylline matrix tablets.

Kinetic modeling of dissolution data

The dissolution profile of all batches were fitted to various models such as zero order, first order , Higuchi, Hixon Crowell, Korsemeyer and Peppas (Table 4). In case of the controlled or sustained release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms. Formulation containing swelling polymers show swelling as well as diffusion mechanism because the kinetic of swelling include relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to rubbery state. The diffusion exponent n is the indicative of mechanism of drug release from the formulation. For a swellable cylindrical (tablet) drug delivery system, When n<0.5, the drug diffuses through the polymeric matrix by a Fickian (case I) diffusion mechanism. For 0.5<n<0.85, an anomalous (non-Fickian) transport occurs i.e. the release is ruled by both diffusion of the drug and dissolution of the polymer. n=0.85 indicates case II transport and n> 0.85 indicates super case II transport release mechanism.[20],[21] The value of diffusion exponent n for all factorial formulations is less than 0.5 (Table 4) indicating the drug diffuses through the polymeric matrix by a Fickian (case I) diffusion mechanism.

Response Surface Analysis

Two dimensional (2-D) contour plot and three dimensional (3-D) surface response plots were constructed. Fig. 2, 3 represent surface response plot and contour plot for Q_1 respectively, they exhibit that Q_1 nonlinear fashion, as increasing amount of Guar Gum and HPC-H lead to linearity. It is also shows that HPC-H has comparative greater influence on response variable than Guar Gum.

Fig. 4 & 5 represent the influence of Guar Gum and HPC-H at Q_8. Contour plot for drug release at 8 hrs shows that somewhat linear fashion and with increase of Guar Gum and HPC-H content turn to nonlinearity. However, the effect of HPC-H is more compare with that of Guar Gum in the selected range of concentration.

Fig. 6, 7 exhibits that time to 50% drug release ($t_{50\%}$) varies in the nonlinear manner. In low content of Guar Gum exhibit somewhat linear and high amount Guar Gum and the contour line turned in to nonlinear. In the high amount of HPC-H and middle amount of Guar Gum lies to ideal 50% drug release.

Fourier transforms infrared spectroscopy

FTIR spectrum of Theophylline and a physical mixture of theophylline with other excipients were recorded using KBr mixing method on FTIR shown in Fig. 8 & 9. It was observed that there were no changes in these main peaks in the IR spectra of a drug and physical mixture. The FTIR study revealed no physical or chemical interactions of theophylline with excipients.

Table 3: Results of factorial design batches (F1-F9)

BATCH	Assay (%) (n=10)	Friability (%) (n=10)	Hardness (Kg/cm²) (n=10)	Average Weight(mg) (n=20)
F-1	97.62	0.27	6.4 ± 0.60	495.74 ± 2.81
F-2	103.5	0.42	5.8 ± 1.00	511.45 ± 2.65
F-3	100.7	0.31	6.1 ± 0.50	504.09 ± 2.00
F-4	96.52	0.48	5.3 ± 1.20	493.62 ± 3.50
F-5	102.1	0.20	6.9 ± 0.89	505.23 ± 2.00
F-6	101.08	0.56	5.4 ± 0.55	497.30 ± 2.74
F-7	99.74	0.48	6.3 ± 0.98	489.60 ± 1.15
F-8	98.23	0.37	5.2 ± 1.20	493.57 ± 2.54
F-9	102.6	0.32	5.6 ± 1.50	509.03 ± 2.23

Table 4: Drug release kinetic study

Batch	Zero Order		First order		Higuchi		Hixson Crowell		Korsmeyer-peppas		
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	K_{KP}	n	R^2
F-1	0.264	0.838	0.014	0.807	0.063	0.909	0.155	0.941	10.34	0.075	0.95
F-2	0.227	0.959	0.025	0.923	0.051	0.988	0.153	0.991	15.56	0.177	0.992
F-3	0.183	0.924	0.031	0.875	0.042	0.972	0.166	0.977	12.47	0.261	0.983
F-4	0.261	0.849	0.015	0.819	0.062	0.917	0.127	0.922	12.60	0.086	0.955
F-5	0.261	0.865	0.018	0.823	0.061	0.929	0.097	0.918	18.57	0.143	0.959
F-6	0.359	0.927	0.018	0.897	0.082	0.966	0.066	0.951	52.51	0.139	0.979
F-7	0.319	0.954	0.017	0.930	0.072	0.988	0.109	0.985	12.60	0.093	0.995
F-8	0.383	0.950	0.016	0.929	0.086	0.978	0.071	0.969	50.21	0.104	0.980
F-9	0.305	0.917	0.021	0.871	0.07	0.958	0.076	0.948	34.44	0.168	0.971

Table 5: Summary of Results of Regression Analysis

	Q_1		Q_8		$T_{50\%}$	
	Coefficients	**P-value**	**Coefficients**	**P-value**	**Coefficients**	**P-value**
Intercept	47.167	0.021	77.25	3.74	2.206	0.04401
X_1	-2.425	0.353	5.755	0.01641	0.175	0.8386
X_2	-7.68	0.123	-12.15	0.00375	1.925	0.126
$X_1 X_2$	-1.815	0.337	1.4475	0.11124	0.1	0.8690
X_1^2	-1.0416	0.614	1.8766	0.5844	-1.2816	0.1886
X_2^2	1.613	0.477	1.7416	0.6071	-0.4716	0.4408
$X_1^2 X_2$	-2.56	0.397	5.8725	0.02339	-1.07	0.3677
$X_1 X_2^2$	3.82	0.285	1.4725	0.2485	-0.23	0.8272
$X_1^2 X_2^2$	-3.19	0.7143	3.2125	0.0453	-0.886	0.3426
R square	0.99223		0.9970		0.9951	

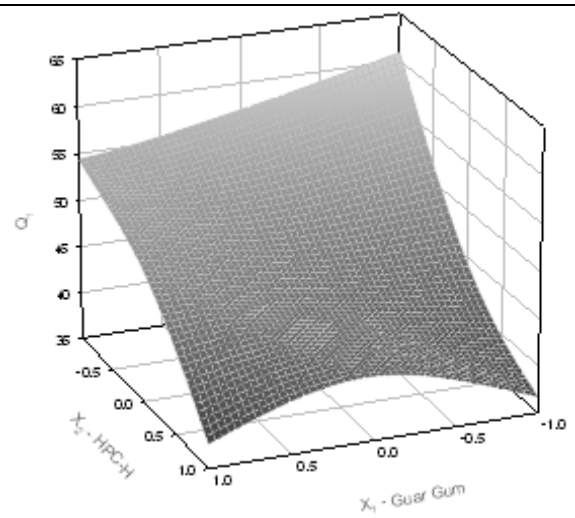

Figure 2: Response surface plot for drug release after 1 hour (Q_1)

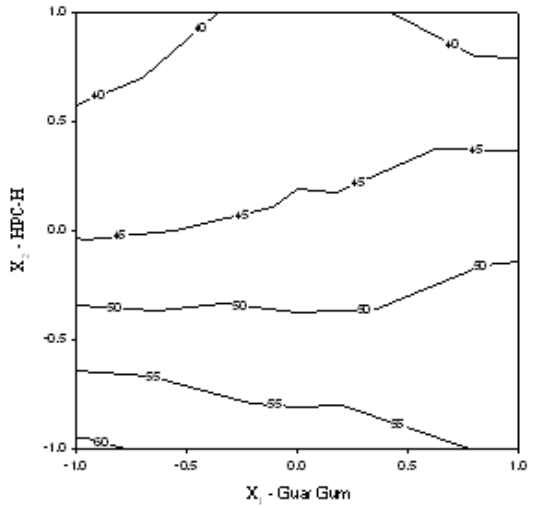

Figure 3: Contour plot for drug release after 1 hour (Q_1)

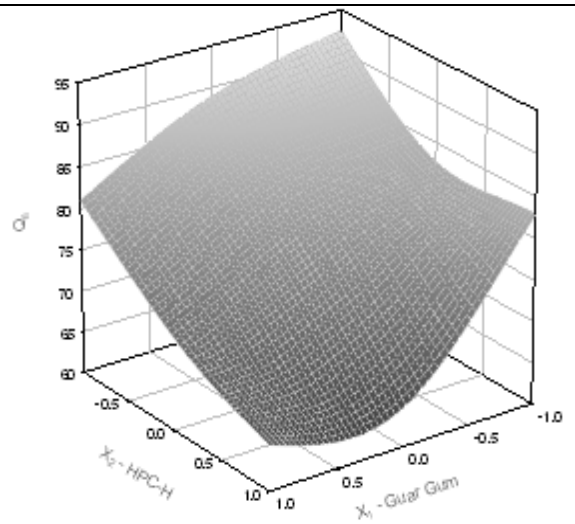

Figure 4: Response surface plot for drug release after 8 hour (Q_8)

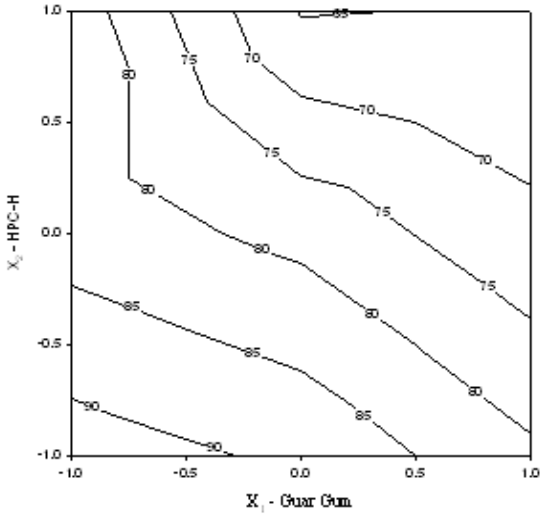

Figure 5: Contour plot for drug release after 8 hour (Q_8)

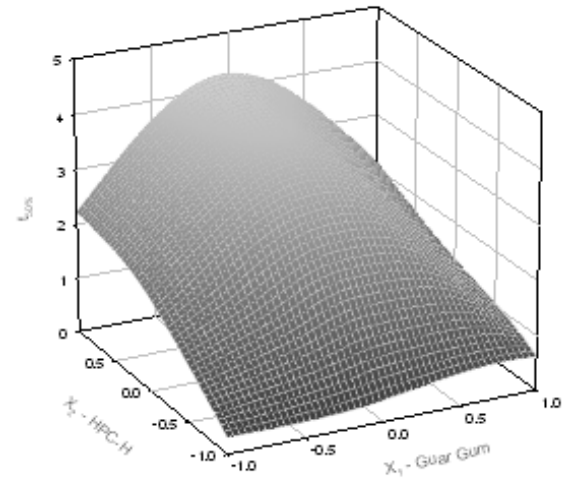

Figure 6: Response surface plot for time required for 50% drug release ($t_{50\%}$)

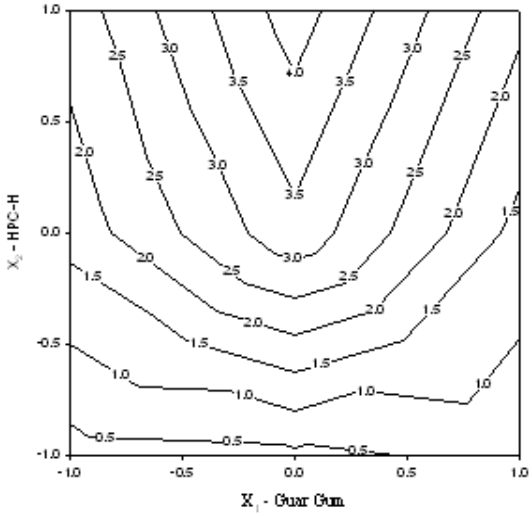

Figure 7: Contour plot for time required for 50% drug release ($t_{50\%}$)

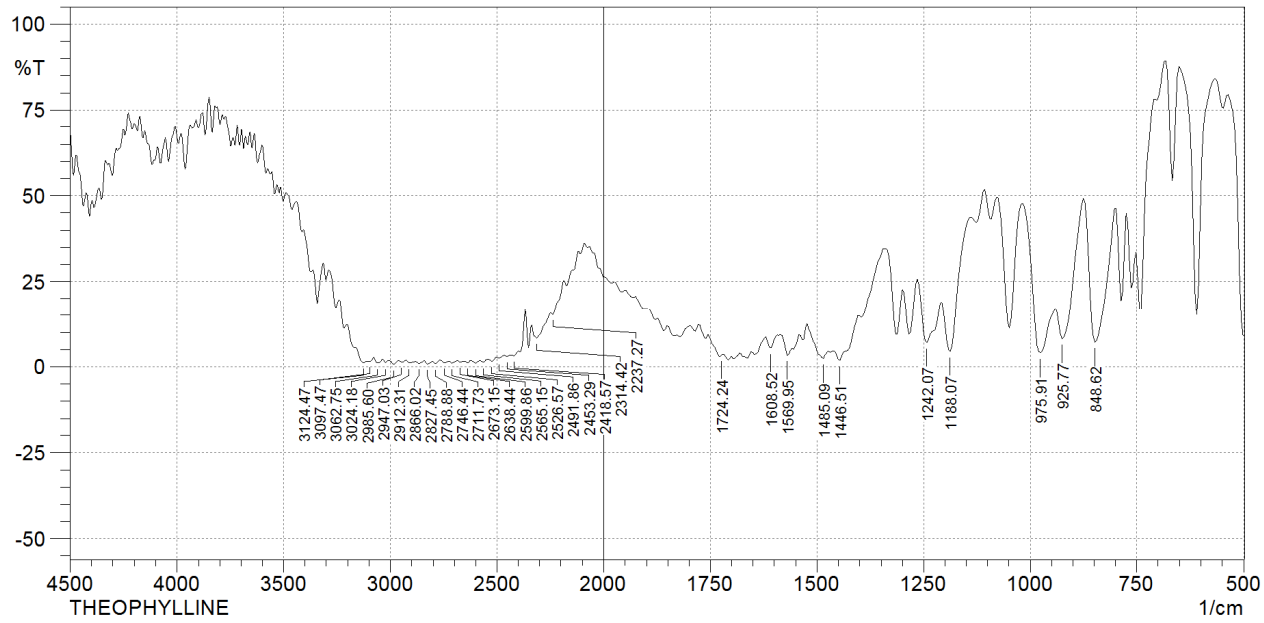

Figure 8: FTIR spectrum of Theophylline

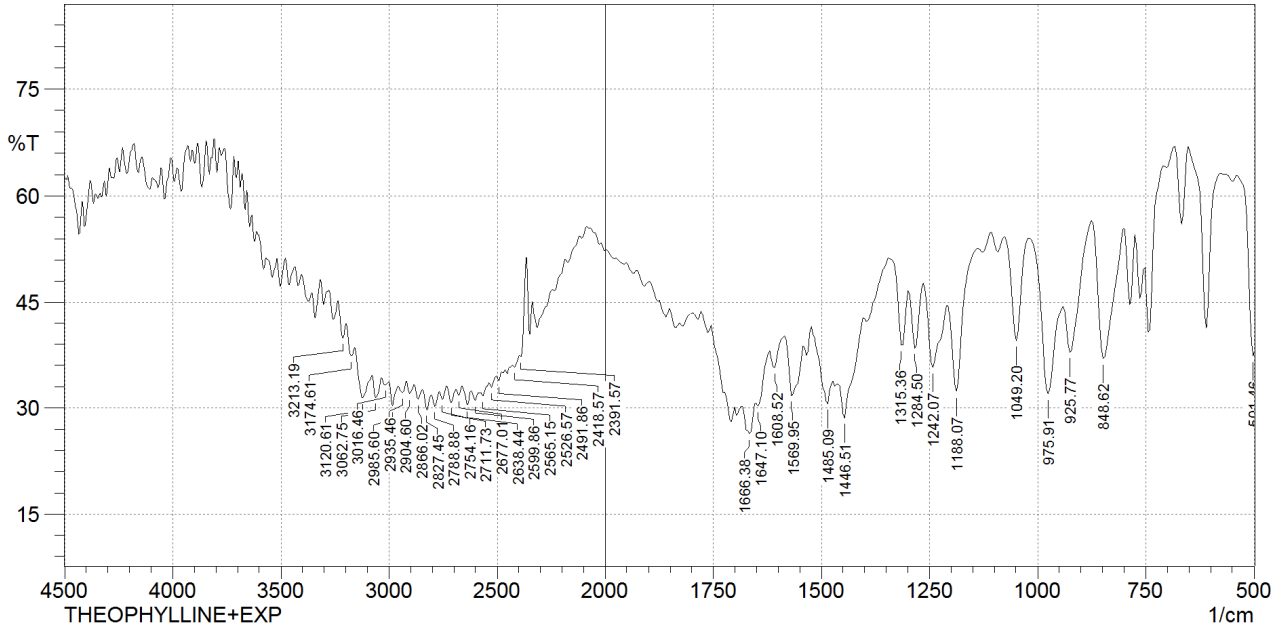

Figure 9: FTIR spectrum of physical mixture of Theophylline and other excipients

CONCLUSION

Formulation and evaluation of SR matrix tablets containing theophylline using combination of guar gum and HPC-H was found to be potential, cost effective and satisfactory *in vitro* release studies. The initial release was sufficiently higher in all formulations thus ruling out the need to incorporate a specific loading dose and release the drug in a sustained manner for prolonged time and thereby accompanying some of the benefits like reduction in total dose, frequency of administration, dose related side effects and better patient compliance. It was concluded that by adopting a systematic formulation approach, an optimum point could be reached in the shortest time with minimum efforts.

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