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Statistical Optimization Supported Product Development of Anti-Asthmatic Multiparticulate Drug Delivery System

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A multiparticulate drug delivery system of theophylline and etophylline, two widely used anti asthmatic drugs, was developed using factorial design and the manufacturing procedure along with the drug entrapment efficiency of the microcapsules were optimized and suitable statistical models were developed.The release rate and its variation due to addition of film-modifier polyisobutylene were studied.The release was found to follow Higuchi square root kinetics.The developed formulation may be useful in prophylaxis of recurrent and nocturnal asthmatic attacks.

Abnormally high levels of air pollution in the major metros of India have brought about a spurt in respiratory diseases, especially asthma, a disease that can rarely be cured but the intensity and severity can be reduced or minimized by giving symptomatic relief by proper drug therapy. While expensive aerosol therapy is available for quick symptomatic relief of asthma and chronic obstructive pulmonary diseases (COPD), major Indian population cannot afford the cost of this therapy. Moreover, the aerosols are not so popular for self-medication among the geriatric and pediatric patients due to difficulty of usage and inadequate instructions[1]. Therefore, a need for prompt acting oral antiasthmatic medication is solicited which would concurrently give once-daily convenience. A multiparticulate drug delivery system would be the best choice for the purpose. Theophylline being sparingly water-soluble would release relatively slowly compared to etophylline. This property of the drugs may be utilized to blend the two types of microcapsules to yield a multiparticulate dosage form that will promptly give symptomatic relief from asthmatic attacks and then sustain the action for prophylaxis against recurrence, particularly towards nocturnal symptoms. Hence, in the present work an attempt has been made to design and evaluate a multiparticulate drug delivery system of theophylline and etophylline that will achieve the aforementioned objective.

#Deceased, *For Correspondence

MATERIALS AND METHODS

Theophylline I.P. and etophylline I.P. were generously donated by Indian National Drug Co. Pvt. Ltd. and Caplet (India) Ltd., Calcutta respectively. Ethylcellulose (BDH Chemicals, England) was used as the coating polymer. Polyisobutylene (PIB; National Chemicals, Baroda) was used as a film modifier. All other chemicals used were of analytical reagent grade, obtained commercially and used as such without further purification.

Preparation of the Microcapsules:

A modified emulsification solvent evaporation methodology was followed to prepare the microcapsules with acetone as the solvent for ethylcellulose and PIB, in which the drugs (300 mg in each batch) were dispersed using a magnetic stirrer at 180 rpm[2]. In this modified method, an oily continuous phase without any surfactant is used instead of aqueous phase in contrast to the original method. The suspension was then poured slowly into liquid paraffin stirred at 500 rpm. Acetone was allowed to evaporate and further stirring rigidified the

microcapsules. They were washed with petroleum ether (40° - 60° grade) and dried for 12 h.

To standardize the whole manufacturing process and to study the variation of release rate with the process and formulation variables, a composite factorial design was followed[3] (Table 1). These designs require more than two levels of factors and are effective to estimate curvature (mathematically, the response equation would be a polynomial of order 2) and give orthogonal estimates of the polynomial coefficients.

Physico-chemical Studies:

The size distribution of the particles was determined using a nest of standard ASTM sieves. The drug polymer compatibility was assessed through infra-red spectrophotometry of the drug, polymer and the prepared microcapsules using Jasco IR - 700 spectrophotometer. The surface morphology of the microcapsules were studied by using a Hitachi S-415A Scanning Electron Microscope.

The drug entrapment efficiency was studied by crushing a weighed portion of the microcapsules in a mortar, diluting and filtering after stirring for 30 min. The solution was then further diluted and drug content was determined spectrophotometrically using a Beckman DU-64 spectrophotometer employing appropriate blanks and with reference to a calibration curve.

***In vitro* Release Studies:**

The USP XXIII method for dissolution testing was followed[4]. Phosphate buffer, pH 6.6 for theophylline and pH 7.2 for etophylline was used. In both cases, USP XXIII Apparatus I was employed at 100 rpm with a dissolution medium volume of 1000 ml maintained at 37° ± 1°. Samples were withdrawn at predetermined intervals and assayed spectrophotometrically at 271 nm for theophylline and at 272 nm for etophylline.

Statistical optimization Study:

The data on the dependent parameter, drug entrapment efficiency (DEE) obtained through experimentation was subjected to multiple regression analysis and the predictor equations were used for validation of the models.

TABLE 1 : COMPOSITE FACTORIAL DESIGN FOR THE OPTIMIZATION STUDY

Polymer level (X)	PIB level (Y)	Batch No.	DEE(%) (Theophylline)	Batch No.	DEE(%) (Etophylline)
-1	-1	T1	102.20	E1	138.55
-1	0	T2	101.58	E2	125.89
-1	+1	T3	110.84	E3	125.00
0	-1	T4	91.09	E4	112.89
0	0	T5	86.74	E5	117.70
0	+1	T6	87.64	E6	121.76
+1	-1	T7	82.88	E7	89.52
+1	0	T8	80.99	E8	80.32
+1	+1	T9	83.78	E9	85.84

Coded Levels	Polymer (mg)	PIB
-1	300	0.0%
0	600	0.5%
+1	900	1.0%

TABLE 2 : CORRELATION COEFFICIENTS OF THE RELEASE KINETIC MODELS

Theophylline Microcapsules				Etophylline Microcapsules			
Batch	R_{HG}	R_0	R_1	Batch	R_{HG}	R_0	R_1
T1	0.909953	0.785193	-0.86896	E1	0.979359	0.90027	-0.9308
T2	0.928214	0.812827	-0.88873	E2	0.996038	0.943254	-0.96812
T3	0.936581	0.827694	-0.88921	E3	0.986082	0.916135	-0.94362
T4	0.985798	0.918132	-0.95405	E4	0.993923	0.935193	-0.95709
T5	0.969944	0.883686	-0.92773	E5	0.995826	0.943386	-0.96140
T6	0.946400	0.844534	-0.89370	E6	0.995612	0.942913	-0.96187
T7	0.998404	0.957453	-0.97103	E7	0.998716	0.959223	-0.97257
T8	0.997849	0.954465	-0.97095	E8	0.999355	0.967887	-0.97896
T9	0.999319	0.967924	-0.97803	E9	0.998182	0.957397	-0.97162

R = Correlation coefficient; Subscripts: HG = Higuchi model, 0 = Zero order model, 1 = First order model

RESULTS AND DISCUSSION

The microcapsules obtained were white, smooth-walled, discrete and free flowing. During preformulation study, variable volumes of liquid paraffin (15, 20 and 30 ml) were used to determine the optimum volume suitable for batch reproducibility. There were occasional aggregates in batches prepared with low volume (15 and 20 ml) of liquid paraffin. So, we used 30 ml of liquid paraffin in subsequent product development work. Due to small batch size, flow properties could not be assessed quantitatively. Granulometric analysis showed that yield of the formulations was maximum at ASTM #30 mesh size with normal distribution within the range #12 to #60 mesh.

Scanning electron microscopy of the prepared microcapsules and exhausted particles after dissolution indicated the presence of pores, but there was no alteration of shape or size of the microcapsules after dissolution, though the exhausted particles had relatively rougher surface. The number and size of the pores increased slightly after dissolution indicating the leaching or diffusion mechanism of drug release (Figure 5a and 5b).

The drug content of various batches showed that the microencapsulation technique offers at least 80% entrapment efficiency (Table 1). Release from the microcapsules predominantly followed Higuchi kinetics. However, the correlation coefficients (Table 2) of the Higuchi model and first-order model being very close in magnitude implied that a mixed-kinetics may be operational during release. The amount of polymer and the film-modifier PIB affected the release, which progressively decreased with increase in polymer level (Figures 1 and 2). At high PIB concentrations, film consolidation occurs reducing the cracks and channels in the coating. This also imparts additional hydrophobicity to the polymeric coating, thereby resisting the penetration of dissolution fluid into the active core. However, no direct relationship between PIB amount and release profile could be differentiated.

Full quadratic models with polynomial and interaction terms were developed for the drug entrapment response for theophylline and etophylline (Equation 1 and 2). The polymer and PIB levels were coded using the equation $T = [C_i - (C_{max} + C_{min})/2]/[(C_{max}-C_{min})/2]$, where T is the transformed/coded value, C_i is the actual value of the polymer/PIB level, C_{max} is the uncoded maximum polymer/PIB level and C_{min} is the uncoded minimum polymer/PIB level. This relationship can also be used to decode the required independent parameter (polymer and PIB) values from the equations generated to achieve an optimum and desired response (DEE). The coding is required to increase accuracy and reduce mathematical burden during multiple linear regression used to generate the predictor polynomial equations. The levels of the polymer and PIB were chosen based on preformulation studies so that DEE could be maximized without adversely influencing the release profile.

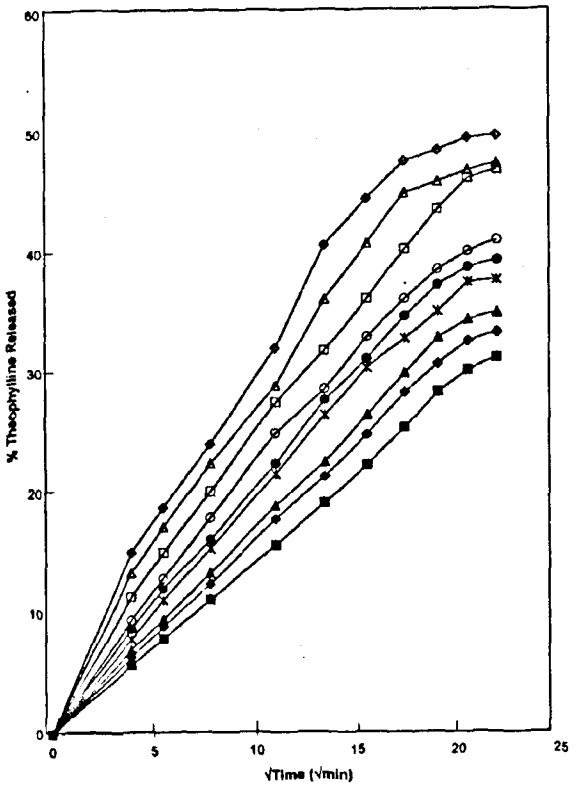

Fig. 1: Release profiles of Theophylline microcapsules

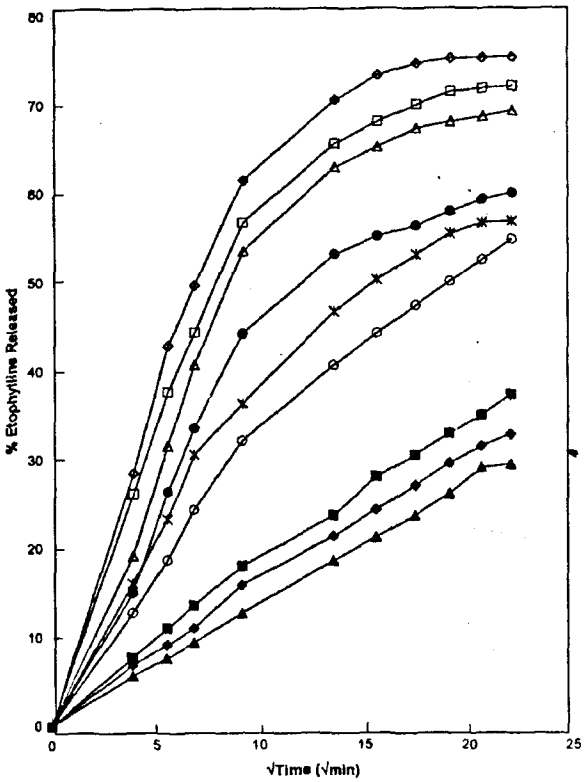

Fig. 2: Release profiles for the Etophylline microcapsules

Theophylline (Full model):

$$DEE = 86.29-11.16X+1.02Y+5.22X^2+3.30Y^2 - 1.94XY \quad (1)$$

Etophylline (Full model):

$$DEE = 114.59-22.29X-1.39Y-9.93X^2+4.29Y^2+2.47XY \quad (2)$$

[where X = polymer level & Y = PIB concentration level in the formulations]

The ANOVA study and F-value as well as R^2 (adj.) values calculated for the two equations prompted the authors to evaluate the reduced models and finally the following equations (Equations 3 and 4) were found to be statistically significant at $p<0.05$ (Tables 3 and 4).

Theophylline (Reduced Model):

$$DEE = 86.29-11.16X+1.02Y+5.22X^2+3.30Y^2 \quad (3)$$

Etophylline (Reduced model):

$$DEE = 114.59-22.29X-1.39Y-9.93X^2+4.29Y^2 \quad (4)$$

The contour diagrams for the drug entrapment efficiency response, shown in Figure 3 and Figure 4, give a better visualization of the complex relationship of DEE with polymer level (X) and PIB concentration level (Y). The equations suggest that mainly polymer effects the drug entrapment efficiency compared to PIB concentration. For both the drugs, DEE decreases progressively as polymer and PIB concentration increases. However, the DEE for etophylline is much higher compared to theophylline presumably because the latter being more lipophilic, gets lost by partitioning into the liquid paraffin which is the continuous manufacturing phase during microencapsulation. Etophylline being more water-soluble is not lost substantially into the liquid paraffin from the drug-polymer dispersion droplets. Since for a manufacturing procedure to be reproducible and predictable, the DEE should ideally be 100%, the study points out that we can take polymer level between 0.5 to 0.6 (coded values) at different PIB concentrations depending upon the release desired for etophylline. Similarly, for theophylline the polymer level required to attain 100% DEE is between - 0.95 to -0.65 (coded values) at various PIB concentrations within the range investigated.

TABLE 3 : ANOVA OF THE STATISTICAL MODELS FOR THEOPHYLLINE MICROCAPSULES

Source of Variation		Sum Squares	n	Mean Squares	F_0	P
Regression	FM*	844.9887	5	168.9977	20.09166	0.01633
	RM*	830.0118	4	207.5029	20.64146	0.00621
Error	FM	25.2340	3	8.4113		
	RM	40.2109	4	10.0527		
Total (cor.)		870.2226	8			
R^2 =	FM	0.971003		R^2 ADJ = FM	0.922674	
	RM	0.953792		RM	0.907585	

*FM = Full Model ; RM = Reduced Model

TABLE 4 : ANOVA OF THE STATISTICAL MODELS FOR ETOPHYLLINE MICROCAPSULES

Source of Variation		Sum Squares	n	Mean Squares	F_0	P
Regression	FM*	3251.97676	5	650.3954	15.6853	0.02322
	RM*	3227.62253	4	806.9056	21.6983	0.00565
Error	FM	124.395842	3	41.46528		
	RM	148.750067	4	37.18752		
Total (cor.)		3376.3726	8			
R^2=	FM	0.963157		R^2 ADJ = FM	0.901752	
	RM	0.955944		RM	0.911888	

*FM = Full Model; RM = Reduced Model

The present study throws light on how the interaction of a film-modifier, PIB and coating polymer, ethylcellulose alters the release rate and drug entrapment efficiency of two anti-asthmatic drugs, theophylline and etophylline, in the product development of a suitable prolonged release anti-asthmatic multiparticulate oral drug delivery system utilizing the concept of statistical optimization technique of factorial design. Other aspects of the dosage form like particle size and yield may also be optimized utilizing the same concept before bioavailability studies are taken up.

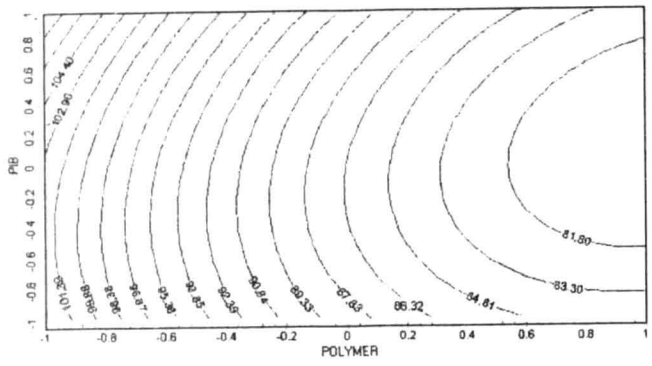

Fig. 3 : Contour Plot of Drug Entrapment Efficiency for theophylline microcapsules

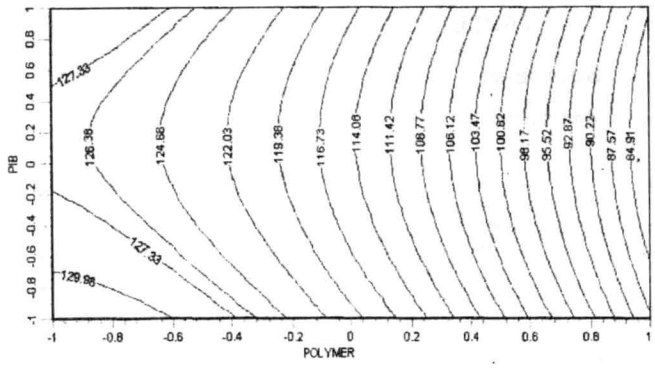

Fig. 4 : Contour Plot of Drug Entrapment Efficiency for etophylline microcapsules

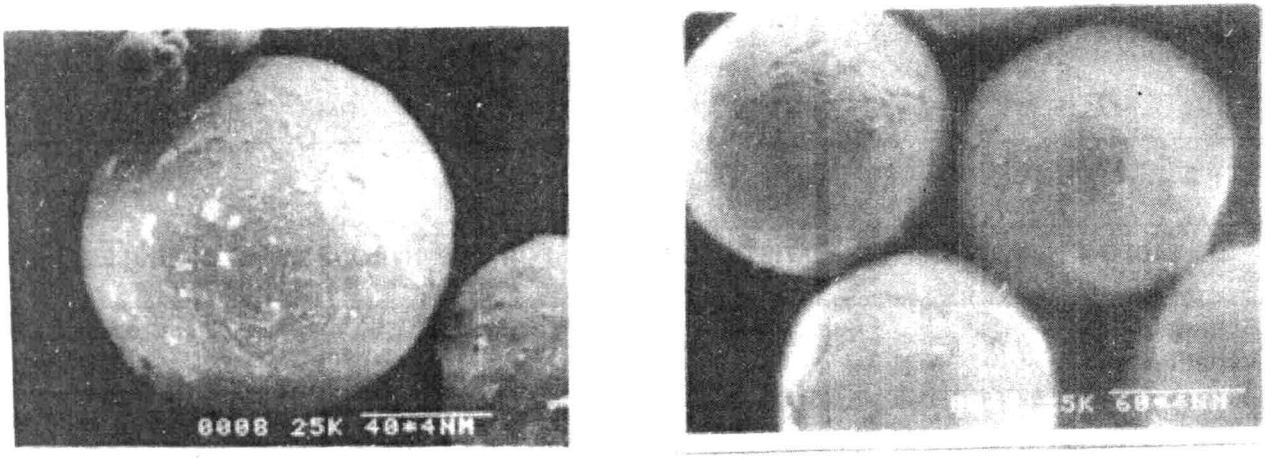

Fig. 5 : Scanning Electron Micrograph for the microcapsules (a) before dissolution [50X magnification], (b) after dissolution [75X magnification]

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