

Development and evaluation of a novel modified release pellet-based system for the delivery of desloratadine and pseudoephedrine hydrochloride

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Modified-release multiple unit dosage form (MRMUD) of desloratadine and pseudoephedrine hydrochloride with different release profiles were prepared. The MRMUD system consists of the immediate-release pellets containing desloratadine and sustained release pellets containing pseudoephedrine hydrochloride. The immediate and sustained release pellets were prepared by solution layering technique. A 3^2 full-factorial design was employed to optimize the sustained release formulation where in polymer ratio (Ethyl cellulose : hydroxyl propyl methyl cellulose) (X1) and % polymer coating (X2) were taken as independent variables and amount of drug release, in 0.1N HCl (Y1), after 10 hours (Y2) were taken as the dependent variables. Optimization studies were carried out using the Design Expert Software. Formulations were evaluated for *in vitro* release studies, the release data were evaluated by the model dependent (curve fitting) method using the PCP Disso software. The *in vitro* drug release followed Hixson-Crowell model and the drug release mechanism was found to be anomalous or non-fickian type. It was found that proper combination of ethyl cellulose and hydroxy propyl methyl cellulose polymer, % polymer coating and process parameters could provide sustained release of pseudoephedrine hydrochloride for a period of 12 hours.

Key words: 3^2 factorial design, desloratadine, ethyl cellulose, HPMC, modified-release multiple-unit dosage form, Pseudoephedrine hydrochloride, solution layering technique

INTRODUCTION

The oral drug delivery systems are classified broadly into single-unit dosage forms (capsules or tablets) and multiple-unit dosage forms or pelletized dosage forms (pellets or pellets in capsules or tablets).^[1] Although closely similar drug release profiles can be obtained with both single-unit and multiple-unit dosage forms, pellets offer several added therapeutical advantages.^[2] The pellets spread uniformly throughout the gastrointestinal tract. They are also found to empty gradually from the stomach with less intra and inter individual variations, thus giving better predictability for an administered dose. In contrast, the gastric emptying of a single unit dosage form is at random and with inherently large intra and intersubject variations.^[3] With the use of pellets, the risk of high local drug

concentrations and toxicity associated with the intake of locally restricted tablets can also be avoided.^[4] Premature drug release from enteric-coated tablets in the stomach, potentially resulting in drug degradation or gastric mucosal irritation, can also be reduced with the coated pellets owing to their rapid transit time. The better distribution of pellets in the gastrointestinal tract could also improve the bioavailability of the drug they contain, leading to a possible reduction in drug dose and adverse effects. The risk of dose dumping from pellets is equally divided, and it is less likely that the pellets are disrupted.^[5] Incomplete drug release of the preparation is less likely to happen. Inter and intra individual variations in the bioavailability caused for instance by food effects are also reduced. Furthermore,

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modified-release profiles can be obtained by simply mixing pellets with different release characteristics.^[1] With regard to final dosage form, pellets can either be placed into hard gelatin capsule (multiple-unit capsule) or compressed into tablets (multiple-unit tablets).

It has been documented that combination of antihistamines with nasal decongestant is better therapy for the treatment of allergic rhinitis. Thus a multiple unit system containing desloratadine and pseudoephedrine hydrochloride is more effective in relieving the symptoms of allergic rhinitis than either component alone.^[6-8]

In the light of the aforementioned need, it is necessary to develop modified release multiple-unit dosage form containing two drugs with different release profiles using desloratadine and pseudoephedrine hydrochloride. This study is aimed to avail the potential therapeutic advantages of pellets over single unit dosage form. The study might be novel in the sense that no documented study was found on the development of modified release pellet-based system for the delivery of an antihistamine and a decongestant.^[9,10]

MATERIALS AND METHODS

Materials

Desloratadine (Micro Labs Pvt Ltd.), Pseudoephedrine hydrochloride (Embio Limited.), non-pareils seeds (M.B. Sugars & Pharmaceuticals Ltd.). All other chemicals and reagents were of analytical grade.

Methods

Preparation of immediate release pellet formulations

Seal coating on base materials

Polymer seal coating was given on non-paeril seeds (Sugar sphere 18-20#) using Insta coat R & D coater. Polymer used for seal coating was HPMC. Here seal coating was done because of uniform surface available for drug loading. Solution of HPMC in isopropyl alcohol: methylene chloride (1:1) as a solvent with talc as a glidant.^[10,11]

Drug coating on seal-coated pellets

Drug coating was performed on seal-coated pellets along with binder hydroxy propyl methyl cellulose (HPMC) and polyvinyl pyrrolidone (PVP K-30). Here, binder was used because drug particles can stick to the seal-coated pellets and make a uniform drug coating on seal-coated pellets and appropriate amount of drug to be contained in to selected quantity of pellets. Drug coating on seal-coated pellets was done by solution of desloratadine in solvent with binder in Insta R & D coater [Table 1].

Film coating on drug-coated pellets

Polymer used for film coating was Instacoat universal. Talc was added for reducing the static charge in to pellets. By

adding talc in to spraying solution, evaporate during spraying and stick to the pellets and remove the static charge of pellets during spraying and drying.^[11]

Preparation of sustained-release pellet formulations

Seal coating on base materials: Polymer used for seal coating was HPMC. Seal coating was done on non-pareil seeds as a core material, using Insta R & D coater. Solution of HPMC in Isopropyl alcohol: methylene chloride (1:1) as a solvent with talc as a glidant.

Drug coating on seal-coated pellets

Drug coating was performed on seal-coated pellets along with binder HPMC and PVP K-30. Solution of pseudoephedrine hydrochloride in solvent with binder is processed in Insta R & D coater. Coating parameters followed are given in Table 1.

Polymer coating on drug-coated pellets

A full-factorial design was used in the present study. A study in which there are 2 factors with 3 levels is called a 3² factorial design. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations [Table 2]. The two independent variables selected were in polymer ratio (Ethyl cellulose: hydroxyl propyl methyl cellulose) (X1) and % polymer coating (X2). HPMC, being hydrophilic is more permeable to water so it promotes release of drug. Ethyl cellulose is hydrophobic, retards drug release being less permeable to water. Hence, the combination of a release promoting and retarding polymers was used to obtain sustained drug release. Triethyl citrate (TEC) use as plasticizer and talc as a glidant. The nine formulations 3² randomized formulated as per the experimental design [Table 3].^[12]

In vitro dissolution studies

In vitro release of pellet formulations was investigated by the USP apparatus I (Basket method) the release medium was 1000 ml 0.1N HCl solution at 37±0.5°C and the rotating speed of the apparatus was set to 50 rpm for all formulations (pellets) for 1 hour then dissolution media was replaced by 7.5 pH 0.1 M phosphate buffer. At certain time intervals, 5 ml of samples were withdrawn and immediately same amount of fresh medium was added [Table 4a-b].

Kinetics analysis of drug release

To analyze the mechanism of drug release from the dosage form, the *in vitro* dissolution data were fitted to zero order,

Table 1: Coating parameters

Conditions	Coating parameters
Non-paerils seeds	50 gm
Pan speed	35 rpm
Pump speed	1 rpm
Spray rate	1.5 ml/min
Atomizing air pressure	2 – 3 lb/inch ²
Inlet temperature	55°C

Table 2: A 3² full factorial design and level of independent variables

Formulation code	Coded values		% Release in 0.1N HCl	Q ₄	Q ₆	Q ₁₀
	X1	X2				
F1	-1	-1	31.01±0.14	68.14±0.43	87.12±0.49	101.39±0.92
F2	-1	0	29.16±0.10	68.14±0.43	87.12±0.49	102.67±0.87
F3	-1	+1	27.59±0.19	68.14±0.43	87.12±0.49	101.14±0.93
F4	0	-1	25.83±0.04	68.14±0.43	87.12±0.49	102.57±0.98
F5	0	0	23.61±0.25	68.14±0.43	87.12±0.49	101.63±0.82
F6	0	+1	21.66±0.17	68.14±0.43	87.12±0.49	98.84±0.79
F7	+1	-1	19.90±0.15	68.14±0.43	87.12±0.49	86.41±0.78
F8	+1	0	18.98±0.25	68.14±0.43	87.12±0.49	84.92±0.82
F9	+1	+1	18.05±0.18	68.14±0.43	87.12±0.49	84.93±0.76
Coded values	Actual values (%)					
	X1	X2				
-1	70:30	10				
0	80:20	15				
+1	90:10	20				

Q₄, Q₆, Q₁₀: % cumulative drug release in 4, 6, 10 hours, Mean±SD; n = 3

Table 3: Formulation of factorial design batches

Ingredients*	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Polymer ratio	70:30	70:30	70:30	80:20	80:20	80:20	90:10	90:10	90:10
Ethyl cellulose	70	70	70	80	80	80	90	90	90
HPMC	30	30	30	20	20	20	10	10	10
TEC	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
IPA:MC	100	100	100	100	100	100	100	100	100
% Coating	10	15	20	10	15	20	10	15	20

*Quantity in %; HPMC: Hydroxy propyl methyl cellulose; TEC: Triethyl citrate; IPA:MC- Isopropyl alcohol; Methylene chloride

first order, Matrix model, Hixson Crowell model, and Korsmeyer and Peppas model by using PCP Disso software and the model with the higher correlation coefficient was considered to be the best mode.^[13]

Statistical analysis

The effect of formulation variables on the response variables were statistically evaluated by using a commercially available software package Design-Expert (Stat-Ease, Inc.). The design was evaluated by best fit model, which bears the form of equation:

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2 \quad (1)$$

Where, Y is the dependent variable, b₀ is the arithmetic mean response of the nine runs, and b_i (b₁, b₂, b₁₂, b₁₁ and b₂₂) is the estimated coefficient for the corresponding factor X_i (X₁, X₂, X₁₂, X₁₁, and X₂₂), which represents the average results of changing one factor at a time from its low to high value. The interaction term (X₁X₂) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X₁² and X₂²) are included to investigate nonlinearity.^[14]

Scanning electron microscopy

Scanning electron photomicrographs of pellets were taken.

To understand changes in the surface morphology, the topography of pellets was analyzed with help of scanning electron microscopy. A small amount of pellets was spread on glass stub. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber. The scanning electron photomicrograph was taken at the acceleration voltage of 10 kV, chamber pressure of 0.6 mm Hg, with original magnification 3500. Pellet surfaces were evaluated after coating.

RESULTS AND DISCUSSION

Immediate-release desloratadine pellet formulations

The release profiles of immediate-release pellets formulation is shown in Figure 1.

Sustained-release pseudoephedrine hydrochloride pellet formulations

In vitro drug release studies

In 3² full factorial design, various factors were studied using all the possible combinations, as it was considered to be most efficient for estimating the influence of individual variables (main effects) and their interactions, using minimum experimentation [Figure 2]. From the dissolution profile, it

was concluded that batches F1-F3 of the ratio 70:30 released drug from 101.14 % to 101.39% for up to 10 h, respectively. Batches F4-F6 of the ratio 80:20 released drug from 98.84% to 102.57% up to 10 h, respectively, and F7-F9 of the ratio 90:10 released drug from 84.93% to 96.41% up to 10 h, respectively [Table 4].

Kinetics of drug release

Different kinetic models were studied from dissolution profile of the different formulations of pseudoephedrine hydrochloride sustained-release pellets as shown in Table 4. The model was calculated based on the value of co-efficient of regression closest to 0.9999. Out of a total of nine formulations, F1, F2, F3, F4 followed the first order kinetic. Formulations F5, F6, F7, F8, and F9 followed Hixson Crowell model.

In order to know the drug release mechanism the data was further analyzed by Korsmeyer Peppas equation and the value of N , i.e., release exponent was calculated. The N values were found to be between 0.42 and 0.50. Formulations F1, F2, F3, and F4 indicated that the formulations followed Fickian diffusion. Formulations F5, F6, F7, F8, and F9 indicated that the formulations followed anomalous transport.

Statistical analysis by design expert software

The cumulative % of drug release, in 0.1N HCl (Q_1), after 10 haves (Q_{10}) for the nine batches (F1-F9) showed a wide variation (i.e., 18.05-31.01%, and 84.93-101.39%, respectively). The responses of the formulations prepared by 3^2 factorial design batches are shown in Table 1. The data clearly

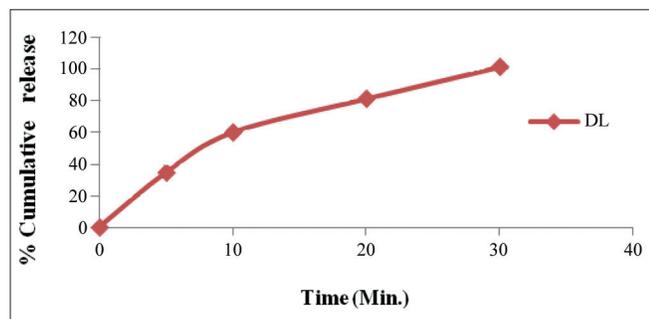


Figure 1: Dissolution profile of desloratadine formulation

indicates that the Q_1 and Q_{10} values are strongly dependent on the selected independent variables. The fitted regression equations relating the responses Q_1 and Q_{10} are shown in the equations, respectively. The equation conveyed the basis to study of the effects of variables.

The regression coefficient values are the estimates of the model fitting. The r^2 was high indicating the adequate fitting of the linear model.

Effect of formulation variables on Q_1

Final equations in terms of coded factors:

$$Q_1 = +23.86 - 5.14*A - 1.57*B \quad (2)$$

The linear model for Q_1 was found to be significant. When the polymer ratio, % coating increases, the corresponding Q_1 is decreased. The relationship between the variables was further elucidated using response surface plot [Figure 3].

Effect of formulation variables on cumulative % of drug release at 10h (Q_{10})

Final equation in terms of coded factors:

$$Q_{10} = +101.55 - 8.16*A - 0.91*B - 0.31*A*B - 7.55A^2 - 0.64B^2 \quad (3)$$

The quadratic model for the amount of release at 10 haves was found to be significant. An increase polymer ratio and % coating caused decrease in the amount of drug release at 10 haves (Q_{10}). The relationship between the variables was further elucidated using response surface plot [Figure 4].

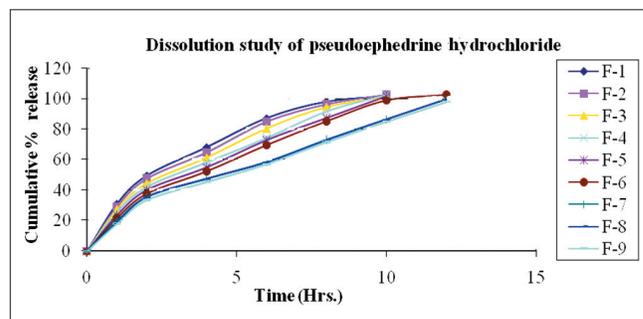


Figure 2: Dissolution profile of formulation F1-F9

Table 4: Dissolution kinetics for formulations

Formulation No.	Zero order	First order	Matrix	Hixson-crowell	Korsemayer-Peppas	
	R ²	N				
F1	0.8926	0.9546	0.9494	0.9429	0.7812	0.42
F2	0.9181	0.9578	0.9489	0.9545	0.8076	0.45
F3	0.9196	0.9717	0.9617	0.9631	0.8540	0.49
F4	0.9413	0.9747	0.9601	0.9735	0.8446	0.50
F5	0.9542	0.9752	0.9623	0.9785	0.8907	0.53
F6	0.9565	0.9854	0.9702	0.9855	0.9258	0.57
F7	0.9658	0.9720	0.9626	0.9805	0.9247	0.54
F8	0.9628	0.9721	0.9605	0.9794	0.9101	0.53
F9	0.9730	0.9754	0.9641	0.9846	0.9416	0.57

ANOVA study

The coefficients of X1 and X2 were found to be significant at $P < 0.05$; hence confirming the significant effect of both the variables on the selected responses. Increasing the

concentration of the polymer ratio resulted in the decrease in the release. Similarly, the increase in % polymer coating resulted in decrease in the drug release. Overall both the variables caused significant change in the responses.

Table 4a: Cumulative drug release from Desloratadine pellets

Time (Min.)	% Cumulative release
5	34.73±0.14
10	60.16±0.45
20	81.51±0.10
30	101.71±0.09

It was found to be near one indicating good estimation of the coefficient. Similarly, Ri-squared was near to zero which led to good model. The model F value calculated was 404.15 and 185.93 for Q_1 , and Q_{10} , respectively, which implied the models were significant. The values of Prob>F were less than 0.05, which indicated model terms were significant [Table 5].

Table 4b: Cumulative percent drug release

T	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	31.01 ±0.14	29.16±0.10	27.59 ±0.19	25.83±0.04	23.61±0.25	21.66±0.17	19.90±0.15	18.98 ±0.25	18.05±0.18
2	49.53±0.23	47.68±0.16	44.53 ±0.30	42.22±0.32	40.18±0.24	37.68±0.14	35.64±0.34	34.25±0.20	33.61±0.45
4	68.14±0.43	64.90±0.34	61.47 ±0.38	58.32±0.45	55.08±0.41	52.39±0.30	47.57±0.43	45.72±0.40	45.44±0.44
6	87.12±0.49	84.99±0.52	80.53 ±0.58	74.22±0.43	72.92±0.54	69.58±0.47	58.45±0.56	57.61±0.56	57.15±0.54
8	97.92±0.63	96.42±0.65	94.55 ±0.79	91.59±0.71	87.33±0.75	85.10±0.65	73.00±0.69	72.53±0.64	71.70±0.71
10	101.39±0.92	102.67±0.87	101.14±0.93	102.57±0.98	101.63±0.82	98.84±0.79	86.41±0.78	84.92±0.82	84.93±0.76
12	-	-	-	-	-	102.46±0.89	99.61±0.96	98.21±0.87	97.85±0.97
24	-	-	-	-	-	-	-	100.92±1.20	102.23±1.32

T: Time (Haves.); Mean±SD; n = 3

Table 5: Summary of ANOVA table for dependent variables from a full factorial design

Source of variation	Sum of square	DF	Mean square	F ratio	P value summary	
					Value	Significant
Q_1						
Linear model	173.27	2	86.63	404.15	<0.0001	Yes
Polymer ratio	158.41	1	158.41	739	<0.0001	Yes
% Coat	14.85	1	14.85	69.29	<0.0001	Yes
Q_{10}						
Quadratic model	601.66	5	120.33	185.93	<0.0001	Yes
Polymer ratio	399.19	1	399.19	616.81	<0.0001	Yes
% Coat	4.97	1	4.97	7.68	0.027	Yes
Polymer ratio ²	157.29	1	157.29	243.04	<0.0001	Yes

DF: Degree of freedom

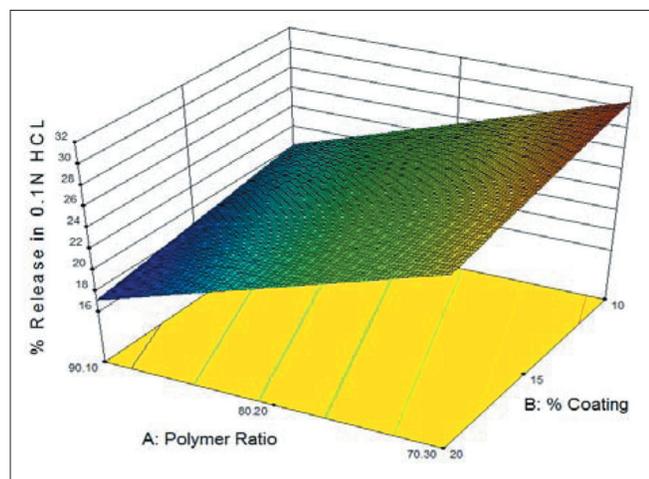


Figure 3: Response plot of Q_1

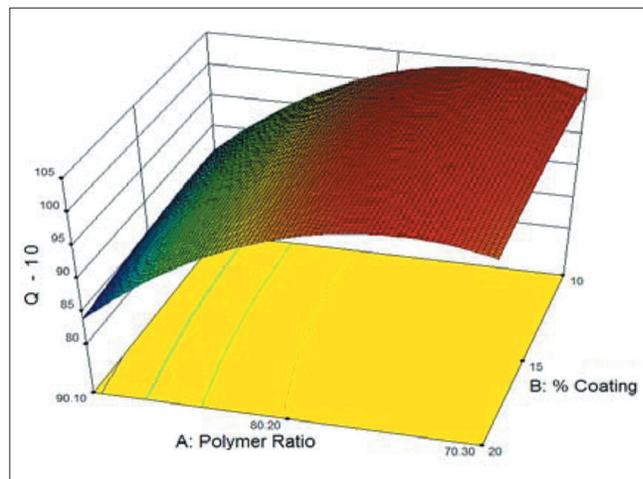
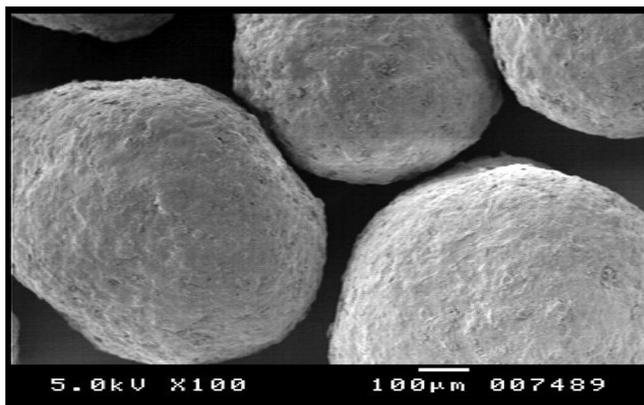


Figure 4: Response plot of Q_{10}

Table 6: Predicted and experimental values for optimized formulation

Responses	Predicted values	Experimental values	% Error
% Release in 0.1N HCl	17.61±0.11	17.96±0.24	1.98
Q ₁₀ (%)	84.72±0.19	85.13±0.14	0.48

Mean±SD; n = 3

**Figure 5:** SEM photograph of polymer coated pellets.

Optimization

A multiple response optimization approach was considered more useful and suitable for optimizing the release properties of dosage form. To optimize response with different targets, a multi-criteria decision approach, like a numerical optimization technique by the desirability function was used to generate the optimum settings for the formulation. The variables were optimized for the response Y1, Y2, and the optimized experimental parameters were set by targeting the drug release to minimum. Solutions were found with a desirability of 1. The solution having the highest desirability was composed of polymer ratio (90:10) and 18.60% polymer coating. The new optimized combinations were prepared according to the predicted model and evaluated for the responses. The results [Table 6] showed a good relationship between the experimented and predicted values, which confirms the practicability and the validity of the model.

Morphology of pseudoephedrine hydrochloride-coated pellets (SEM)

Coated pellets having the smooth surface and porous in nature, which allows penetration of dissolution media and allow passage of drug which may responsible for sustained release [Figure 5].

CONCLUSION

Modified release multiple unit dosage form (MRMUD) was developed successfully containing immediate release

pellets of desloratadine and sustained-release pellets of pseudoephedrine hydrochloride. A 3² full-factorial design was performed to study the effect of formulation variables on *in vitro* release properties by applying a computer optimization technique. The mechanism of the drug release from the optimized formulation was confirmed as non-fickian diffusion or anomalous transport, where water diffusion and polymer rearrangement have an essential role in the drug release. The statistical approach for formulation optimization is a useful tool, particularly in simultaneously evaluating several variables. The observed responses were in close agreement with the predicted values of the optimized formulations, demonstrating the feasibility of the optimization procedure in developing sustained release formulation.

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