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Research Article

FORMULATION & OPTIMIZATION OF IMMEDIATE RELEASE TABLET OF RUPATADINE FUMARATE

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Abstract

The anti-allergic drug rupatadine may be slowly or incompletely dissolved in gastro intestinal tract. The rate of dissolution and bioavailability of the drug may be increased by using superdisintegrants in its immediate release tablets. In the present study the selection of proper superdisintegrants among sodium CMC, crospovidone and alginic acid was carried out to develop immediate release tablets of nateglinide. The FT-IR studies were carried out for compatibility testing between drug and excipients used in tablets. A 3^2 full factorial design was used to investigate the joint influence of 2 independent variables: amount of selected superdisintegrants, crospovidone and hardness of the tablets. The results of multiple linear regression analysis revealed that the dependent variables; disintegration time and drug release at 0.5h values are strongly dependent on the selected independent variables. The sign of coefficient of polynomial equation signified that an increase in disintegration time on decreasing the hardness of the tablets. An increase in the value of drug release at time 30 min observed on increasing the concentration of crospovidone. A checkpoint batch was also prepared to prove the validity of the evolved mathematical model. The systematic formulation approach helped in understanding the effect of formulation processing variables. Stability studies of factorial batches indicated that no significant change in appearance of the tablets, disintegration time, and percentage drug release were observed.

Keywords: - Rupatadine Fumrate,Immediate release ,factorial design.

Introduction

Among the different routes of administration, the oral route of administration continues to be the most preferred route due to various advantages including ease of ingestion, avoidance of pain, versatility and most importantly patient compliance(1). The concept of immediate release tablets emerged from the desire to provide patient with more conventional means of taking their medication when emergency treatment is required. Most of the technologies for the manufacture of immediate release tablets use superdisintegrants so that the tablet disintegrates at quickly in the stomach(2). The superdisintegrants which are employed such as crosscarmellose sodium, The superdisintegrants which are employed such as crosscarmellose sodium, sodium starch glycolate, crospovidone and alginic acid enhance the dissolution rate by lowering the disintegration time. Rupatadine is an antiallergic drug and useful in the treatment of seasonal and perennial rhinitis. Rupatadine fumarate act by two mechanisms first as H1 receptor as well as PAF antagonist.

The disintegration of the solid oral dosage form which will increase the wettability of the drug by increasing the surface area of the drug particles. This highlights the importance of proper choice of superdisintegrants i.e. crospovidone, sodium CMC, alginc acid and there consistency of performance which are of critical importance to increase the rate of dissolution and hence its bioavailability(3). There are various factors (hardness, concentration of binders, disintegrants etc.) affecting the disintegration time (DT) and rate of dissolution of the drug(4). The objective of the present study was to optimize the concentration of superdisintegrants and hardness of the immediate release tablets of Rupatadine fumarate. . Rupatadine is

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an antiallergic drug and useful in the treatment of seasonal and perennial rhinitis Rupatadine fumarate act by two mechanisms first as H1 receptor as well as PAF antagonist(5).

Materials used :

Materials	Source
Rupatadine fumarate	Hetero drugs , Baddi(gift sample)
Alginic acid	Himalaya meditech, Dehradun(gift sample)
Crospovidone	Himalaya meditech, Dehradun(gift sample)
Sodium CMC	CDH, Delhi
Sodium Saccharin	CDH, Delhi
Vanillin	Qualikem fine chemicals, Delhi
Dibasic calcium phosphate	CDH, Delhi
Magnesium Stearate	Qualikem fine chemicals, Delhi
Mannitol	Rankem , Delhi
MCC	CDH, Delhi

Instruments used:

Instruments	Source
Single punch tableting machine	Kshitij innovations ,Ambala
UV Visible spectrophotometer	Labtronics
Monsanto hardness tester	Kshitij innovations ,Ambala
Friability testing apparatus	Kshitij innovations ,Ambala
Ovens	Kshitij innovations ,Ambala
Disintegration test apparatus	Kshitij innovations ,Ambala
Dissolution test apparatus USP type 2	Electrolab
FT-IR spectrophotometer	Shimadzu

Identification of drug and compatibility studies of drug - polymers by FT-IR (Fourier transform)spectroscopy(6)

The identification of drug and drug-excipients compatibility was performed using FT-IR spectroscopy. The compatibility of the drug and formulation is an important pre-requisite for formulation. Infra-red spectrum of pure drug was also obtained individually.

Characterization of drug, polymer and their physicalmixture:

IR has been the method of choice to prove the nature and extent of interaction in polymer blends. The premise of using an IR to study polymer blends is that the mixing of the two compounds at molecular level will cause changes in oscillating dipole of the molecule. This will manifest itself as changes in frequency and bandwidth of interaction group, in the spectrum. if the drug and polymer interact then functional groups in FTIR spectra will show band shift and broadening compared to the spectra of pure drug.

Method: The FT-IR spectrum of pure drug and Physical mixture of pure drug and polymers were analyzed to check the compatibility between the pure drug and polymers using Shimadzu Fourier Transform Spectrophotometer by KBr disc method. The procedure consisted of dispersing a sample (drug alone or mixture of drug and polymers) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained

FT-IR spectra of drug and drug-excipient blends were recorded on an IR spectrophotometer (FTIR-8400S, Shimadzu, Japan) in the range of 4000-500 cm^{-1} using potassium bromide discs.

OBSERVATION OF COMPATIBILITY STUDIES (Values in wave number)

S.NO.	Combination	O-H Bonding	Alkene stretching	C=N Stretching	($N-CH_3$) Stretching	- CH_2 group	C=O stretching
1	Drug and sodium CMC	3424.76	2929.03	1695	1436	1337.69	1161.20
2	Drug & alginic acid	3421.87	2983.04	1701.29	1482.36	1328.05	1165.05
3	Drug &crospovidone	3424.76	2976.29	1696.47	1481,39	1333.83	1166.98
4	Drug & Mannitol	3400.65	2974.36	1697.43	1428.35	1391.70	1165.05
5	Drug & all Polymers	3404.51	2914.57	1698.40	1432.29	1389.77	1163.13

4. Determination λ max and Estimation of Rupatadine Fumarate(7)

Rupatadine fumarate was estimated by UV/VIS spectrophotometry in 0.1 N HCl. The *in vitro* dissolution study was also carried out in 0.1 N HCl (pH 1.2).

Preparation of stock solution:

UV spectra of Rupatadine fumarate was carried out in 0.1N HCl. Weighed quantity of the drug(100mg) was dissolved in pH 1.2 buffer and the volume made up to 100ml with the same.

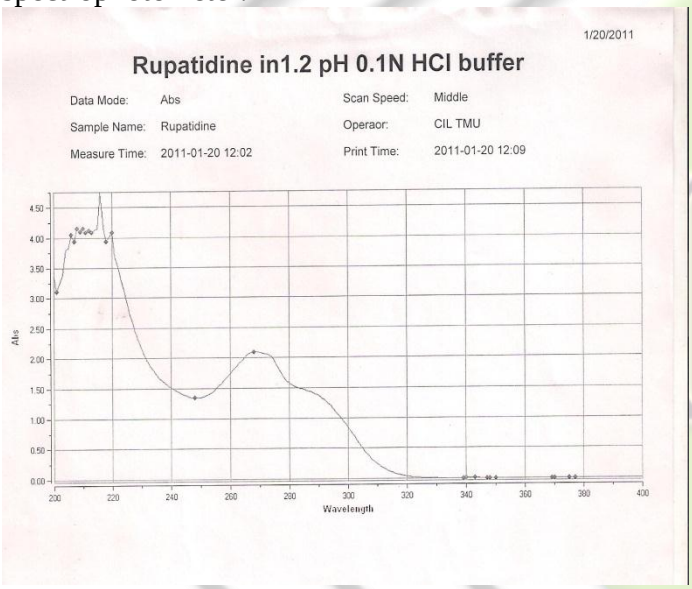
S.S I ⇒ 1000 mcg/ml.

10ml of Stock solution I was further diluted with 100ml of pH 1.2 buffer to get a working standard **S.S I ⇒ 100mcg/ml**

Aliquots of 1,2,3,4&5ml of stock solution was pipetted into 10ml volumetric flask and the volume was made upto 10ml with pH 1.2 buffer. The absorbance was measured at 268 nm against reagent blank (pH 1.2 buffer).

UV absorption maxima:

A UV spectrum was taken at 50 µg/ml concentration. The scanning was done from 200-300 nm in 0.1N HCl as blank using Labtronics double beam UV/ VIS spectrophotometer.



5. Preparation of standard curve:

From the stock solution 1,2,3,4&5 ml were transferred to 10 ml volumetric flasks and were diluted with 0.1 N HCl, up to the mark to obtain concentration 10,20,30,40 and 50 µg/ml respectively. Absorbance of each solution was measured at 268 nm. The results are mentioned in table below :

Concentration µg/ l	Absorbance
10	0.1863
20	0.4003
30	0.6142
40	0.8283
50	1.0423

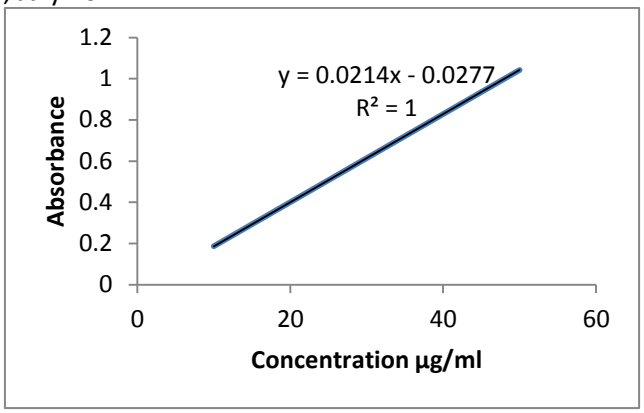


Figure 1. Standard curve of Rupatadine Fumarate

Preparation of Immediate Release Tablets(8)

The tablet consisted of Rupatidine fumarate (10 mg), mannitol, and Sodium saccharin, flavours, magnesium stearate, dibasic calcium phosphateÂ and various concentration of microcrystalline cellulose and superdisintegrants (10mg).The weight of tablets in each batch was kept constant. All the batches of tablets were prepared by direct compression using single punch machine. Effect of variables like types of superdisintegrant, concentration of superdisintegrant on various tablet properties and vitro dissolution characteristics were studied and discussed(9).The composition of the preliminary and factorial design batches is shown in Tables 1 and 2 respectively.

Evaluation of powder blend and tablets

The prepared granules were evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner ratio. The prepared tablets were evaluated for weight variation, friability, hardness, thickness and DT.

Table.1. Results of Preliminary Batches of Immediate release Tablets of Rupatadine fumarate.

Formulation*	T-1	T-2	T-3	T-
Rupatadine fumarate	10	10	10	10
Sodium CMC (mg)	-	10	-	-
Crospovidone (mg)	-	-	10	-
Alginic acid (mg)	-	-	-	10
Mannitol (mg)	120	120	120	12
MCC (mg)	62	52	52	52
Disintegration time				
Drug release at 0.5 h				

All batches contained sodium saccharin (2mg), vanillin (2mg), dibasic calcium phosphate(2mg), magnesium stearate (2mg) . Hardness of all batches was 5 kg/cm^2

Full factorial design

A 3^2 randomized full factorial design was used to optimize the variables in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations[14 -16]. The percentage (2, 4 and 6) of crospovidone (X_1), and hardness (3, 5 and 7 kg/cm^2) of tablets (X_2), were selected as independent variables. The DT and percentage of drug release at 0.5 h ($DR_{0.5h}$) were selected as dependent variables(12).

Table. 2. 3^2 Full Factorial Design Layout*.

Batch Code†	Variable Levels in		Dissolution	DT
		X_2	% drug	DT
F-1	-1	-1	67.83	158.67
F-2	-1	0	61.7	179.33
F-3	-1	1	54.9	193.33
F-4	0	-1	99.8	33
F-5	0	0	94.33	39.67
F-6	0	1	91.4	53.67
F-7	1	-1	99.99	17.331
F-8	1	0	99.8	19.67
F-9	1	1	99.9	30
Check	***0.47***	***0.5***	99.9	22.15

Codes values	Actual value	
	X_1	X_2
-1	8	3
0	10	5
1	12	7

*X_1, indicates amount of crospovidone (mg); X_2, Hardness of the tablets (kg/cm^2) and DT, disintegration time (seconds).

†All batches contained sodium saccharin (2mg), vanillin (2mg), dibasic calcium phosphate(2mg), magnesium stearate (2mg).

Table. 3. Calculations for Testing the Model in Portions*.

	For % of dissolution at 0.5h				
	DF	**SS**	**MS**	**F**	**R^2**
Regression					
FM	5	2774.78	554.96	712.1	0.99
RM	4	2774.67	693.67	1134.	0.99
Error					
FM	3	2.34	0.78		
RM	4	2.45	0.61		
	For disintegration time				
	DF	**SS**	**MS**	**F**	**R^2**
Regression					
FM	5	43460.69	8692.1	987.	0.9994
RM	4	43456.32	10864.	1411	0.9993
Error					
FM	3	26.41	8.80		
RM	4	30.78	7.69		

*DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, Fischer's ratio; R^2, regression coefficient; FM, full model; and RM, reduced model.

Table. 4. Summary of Regression Analysis Results

For % of dissolution at 0.5h						
Respons	**bo**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
FM	95	19.25	-3.60	3.40	-	.23
RM	95.1	19.25	-3.60	3.40	-	
For disintegration time						
Respons	**bo**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
FM	41.0	-77.38	11.35	-5.50	57.	1.4
RM	42.0	-77.38	11.35	-5.50	57.	

*FM indicates full model; and RM, reduced model.

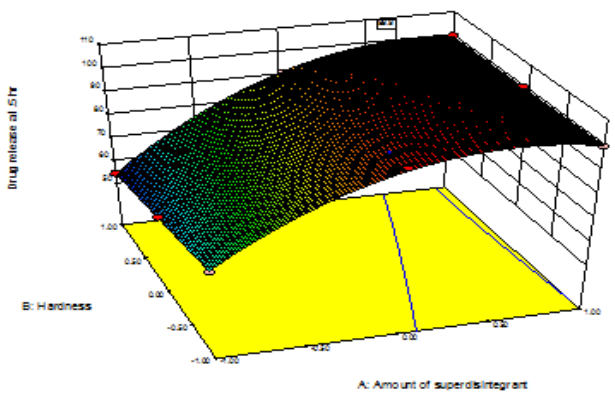


Fig. 2. Response surface plot of % of drug release at 0.5h.

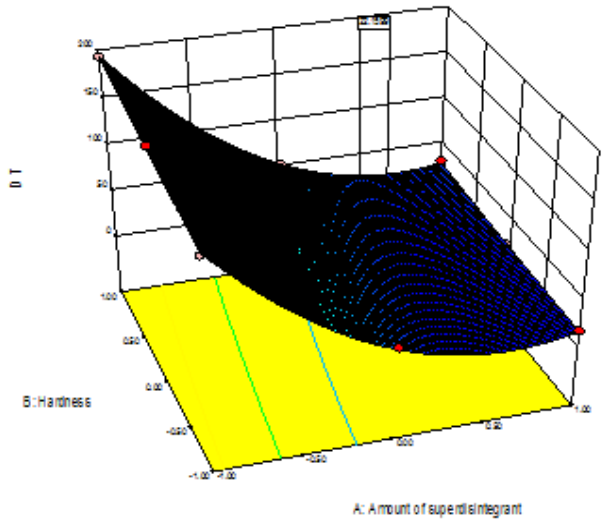


Fig.3. Response surface plot of Disintegration time (s).

Results and Discussion

There was no appearance or disappearance of peaks in the spectra of drug and excipients mixture when compared to the spectrum of pure drug in the FT-IR study. It was confirmed that excipients used for the formulation tablets are compatible with Rupatadine fumarate.

The flow properties of granules can be judged from the angle of repose, compressibility index and hausner ratio(10). The angle of repose (θ) $<30^0$ indicates free flowing material and $>40^0$ with poor flow properties. The compressibility index <10% indicates excellent flow properties and >38% with poor flow properties. The hausner ratio 1.00-1.11 indicates free flowing and >1.60 with poor flow properties(11). Values for angle of repose (θ), compressibility index (%) and hausner ratio for all prepared granules were found to be in the range of 21 to 28^0, 7.14 to 7.71, and 1.07 to 1.08 respectively, which showed that the granules were free flowing and can be used for tablet compression. Percentage of weight variation was observed within the limit of ±7.5%w/w for all the prepared tablets, which is well accepted for uncoated tablets as per USP-NFXXIV. Friability test of the prepared tablet except batch F-1 to F-3 was passed (weight loss <1%w/w) which, assumed that tablets (F-4 to F-9) formulated at higher hardness have sufficient mechanical integrity and strength.

Mannitol was selected as diluent for antiallergic drug Rupatadine fumarate by considering its advantages in terms of easy availability, cost-effectiveness, and relative moisture insensitivity. The preliminary trial batches were conducted arbitrarily without addition of superdisintegrants (T-1) and in addition with 10 mg of sodium CMC (T-2), crospovidone (T-3), and alginic acid (T-4) at 5 kg/cm^2 hardness for the selection of superdisintegrants. It was observed that the DT of T-1, T-2and T-4 were more than the acceptable limit. The results obtained from preliminary trial that the batch containing crospovidone showed less DT and more percentage of drug release at 0.5 h ($DR_{0.5h}$) than other superdisintegrants containing batches, hence crospovidone was considered for further investigation. Hardness of the tablets has impact on the DT as well as the amount of drug release from tablets so it needs to optimize. In order to investigate the influence of concentration of CCS and hardness of the tablet systematically, a 3^2 factorial design was employed in this investigation.

The amount of CCS (X_1) in tablets and the hardness of the tablets (X_2) were chosen as independent variables in a 3^2 full factorial design. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

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

Where, Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i is the estimated coefficient for the factor X_i. 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 terms (X_1X_2) showed how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The DT and $DR_{0.5h}$ for the 9 batches (F1 to F9) showed a wide variation. The data clearly indicates that the DT and $DR_{0.5h}$ values are strongly dependent on the selected independent variables. The fitted equations (full and reduced) relating the responses DT and $DR_{0.5h}$ to the transformed factor were observed. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (ie, positive or negative). The above table shows the results of the analysis of variance (ANOVA), which was performed to identify insignificant factors. The high values of correlation coefficient for DT and percentage of drug release at 0.5h indicate a good fit.

The significance level of coefficient b_{22} was found to be above than the limit in full model for DT and $DR_{0.5h}$ respectively; hence it was omitted from the full model for both the cases to generate the reduced models. The results of statistical analysis are shown in Table 4. The coefficients b_1, b_2, b_{11}, and b_{12} were found to be significant at $P<0.05$, hence they were retained in both the reduced model. The reduced model was tested in portions to determine whether the Pharm Bull., 2008,

coefficient b_{22} contributes significant information for the prediction of DT and $DR_{0.5h}$ or not. The results of multiple linear regression analysis (reduced model) reveal that, on increasing the concentration of CCS, a decrease in DT is observed; the coefficients b_1 bear a negative sign. The coefficient b_2 bear a positive sign signifies an increase in DT on decreasing the hardness (kg/cm^2) of the tablets. An increase in the value of $DR_{0.5h}$ observed on increasing the concentration of CCS (b_1 is positive) and on decreasing the hardness (b_2 is negative) of the tablets.

The response surface plot of % of CCS (X_1) and hardness of the tablets (X_2) versus DT and that versus % of $DR_{0.5h}$ are shown in Fig. 2 and 3 respectively. The response plot showed that there is a significant effect of both factors on selected response.

The model predicts required DT (as per USP limit) and $DR_{0.5}$ (99.9%) from point prediction. Though model also predicted the required response at lower concentration of crospovidone and hardness; the tablets did not get acceptable DT in lower CCS concentration and failed to pass the friability at lower hardness.

A checkpoint batch was prepared at $X_1 = 0.47$ level and $X_2 = 0.5$. From the reduced model, it is expected that the $DR_{0.5h}$ value of the checkpoint batch should be 99.9 and the value of disintegration time should be 22.15 seconds. Thus, we can conclude that the statistical model is mathematically significant.

In this study, the dissolution of Rupatadine fumarate was significantly enhanced by using crospovidone in compare with alginic acid and sodium CMC as superdisintegrants in immediate release tablet. The results of a 3^2 full factorial design revealed that the amount of crospovidone and hardness of the tablets significantly affect the dependent variables, disintegration time, and percentage of $DR_{0.5h}$ from the tablets. It is concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time. with minimum efforts.

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