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Research Article

Design & Evaluation of Immediate Release Tablet of Rupatadine Fumrate

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Abstract

The objective of this research was to formulate immediate release tablet of Rupatadine fumarate for rapid action. Direct compression method was adapted to prepare the tablets by using mannitol, microcrystalline cellulose as filler, crospovidone, alginic acid & sodium CMC as super disintegrants in different concentration (2-5%).Total twelve formations and one control tablet were prepared and evaluated for Hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and invitro drug release. The formulations were compared with control formulation for disintegration time and % drug release. It was concluded the immediate release tablet for Rupatadine fumarate can be formulated for emergency treatment of allergic rhinitis. FT-IR studies revealed that there was no physico-chemical interaction between Rupatadine fumarate and other excipients. All formulations are evaluated for pre-compression and post-compression parameters, wetting time, water absorption ratio. The results obtained showed that . The results indicate that the selelected batch of tablet formulation containing crospovidone provides a short DT between 40 to 22 seconds sec with sufficient crushing strength and acceptable friability.

Keywords: - : Rupatadine Fumrate,Immediate release

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. 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 quickly in stomach. Many superdisintegrants are employed such as crosscarmellose sodium, sodium starch glycolate, crospovidone and alginic acid. 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. Crosscarmellose sodium, sodium starch glycolate and crospovidone as superdisintegrants and the effectiveness of superdisintegrants has been investigated. The present investigation deals with the development of an effective and immediate release of Rupatadine having adequate hardness, low disintegration time and pleasant taste. Its insolubility in water and bitter taste makes it an ideal candidate for taste masked immediate release tablets with regards to bioavalibility.

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Materials and Instruments:

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

4. Determination λ max and Estimation of Rupatadine Fumarate

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:

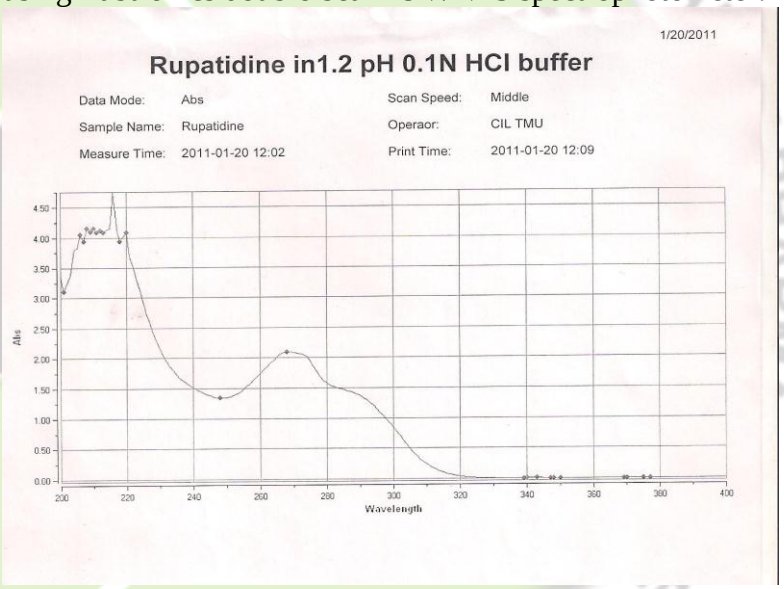
UV spectra of Rupatadine fumarate was carried out in 0.1N HCl. Weighed quantity of the drug(100mg) was dissolved in pH 1.2 buffer and the volume made up to 100ml with the same.

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:

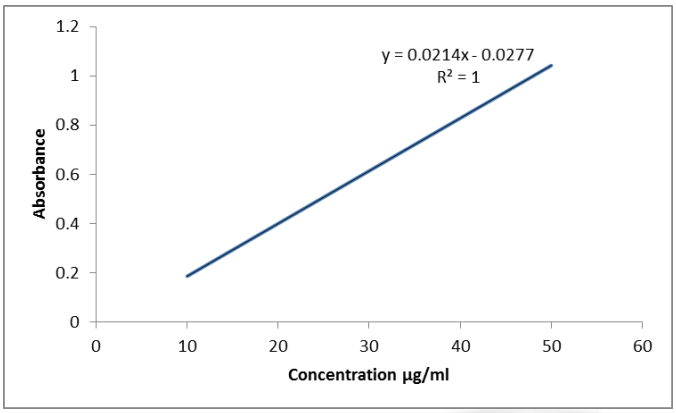
A UV spectrum was taken at 50 µg/ml concentration. The scanning was done from 200-300 nm in 0.1N HCl as blank using Labtronics double beam UV/ VIS spectrophotometer.



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



Standard curve of Rupatadine fumarate

6.Formulation design of rapidly disintegrating tablet by direct compression using superdisintegrants

The tablet consisted of Rupatidine fumarate (10 mg), mannitol, and Sodium saccharin, flavours, magnesium stearate, dibasic calcium phosphate and various concentration of microcrystalline cellulose and superdisintegrants (2%, 3%, 4%, and 5%).The weight of tablets in each batch was kept constant.

All the batches of 30 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.

Formulation composition for tablets prepared by Using Superdisintegrants-Direct compression (All quantities in mg)

Name of Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Rupatadine Fumarate	10	10	10	10	10	10	10	10	10	10	10	10
Alginic acid	4	6	8	10								
Crospovidone					4	6	8	10				
Sodium CMC									4	6	8	10
Sodium Saccharin	2	2	2	2	2	2	2	2	2	2	2	2
Vanillin	2	2	2	2	2	2	2	2	2	2	2	2
Dibasic calcium phosphate	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Mannitol	120	120	120	120	120	120	120	120	120	120	120	120
MCC	58	56	54	52	58	56	54	52	58	56	54	52
TOTAL	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation

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

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. Therefore, in preformulation study, compatibility evaluation was carried out using infra-red spectra. Infrared spectrum of formulated powder and drug in various ratios were obtained between 4000cm-1 - 400 cm-1. Infra-red spectrum of pure drug was also obtained individually.

Characterization of drug, polymer and their physical mixture:

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.

Evaluation of powder blend

In solid dosage forms the physiochemical properties of blend rules the tablet quality. The mixing step if not properly optimized can effect the characteristics of blend and thereby tablet produced. The blends were characterized by mass-volume relationship (bulk density, tapped density, Hausner's ratio, compressibility index) and flow properties (static angle of repose).

Evaluation of tablets

Tablet Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester).

Weight Variation Test

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation was calculated. IP limit for weight variation in case of tablets weighting up to 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

$$PD = (W_{avg}) - (W_{initial}) / (W_{avg}) \times 100$$

Where PD= Percentage deviation,

W_{avg} = Average weight of tablet,

$W_{initial}$ = Individual weight of tablet.

Friability

Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed 20 tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.

Drug Content

Ten tablets were powered and the blend equivalent to 5 mg of amlodipine besylate was weight and dissolved in suitable quantity of pH 1.2 solutions. Solution was filtered and diluted and drug content analyzed spectrophotometrically at 239 nm using Shimadzu Corporation, UV-1601, Japan.

Disintegration Time

The disintegration time of tablet was measured in water (37^0 C) according to USP disintegration test apparatus. Three trials for each were performed.

Wetting Time and Water Absorption Ratio

A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing 6 ml of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation,

$$\mathbf{R = 100 (W_a - W_b)/W_b}$$

Where, W_b and W_a were the weights of the tablet before and after study.

In vitro dispersion time

In vitro dispersion time was measured by dropping a tablet in a beaker containing 50 ml of Sorenson's buffer pH 6.8. Three tablets from each formulation were randomly selected and *in vitro* dispersion time was performed.

Dissolution Studies of Formulated Tablets

The dissolution of amlodipine besylate tablets was carried out in basket type dissolution apparatus. The dissolution medium, 900 ml of 0.1 N HCL was taken and temperature is maintained at 37 ± 1^0 C. The basket was rotated at 75 rpm for 30min. The sample of 10 ml was withdrawn after every 5 min. and its absorbance was measured at 268 nm**.**

Kinectic modelling The *in vitro data* was analyzed by the zero order kinetics equation as well as Higuchi's and Korsmeyer-Peppa's equation to understand the release profile and release mechanism. When a graph of the cumulative percentage of the drug released from the tablets against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration. The rate of release of the drug can be described mathematically as follows:

$$\mathbf{Rate\ of\ release = (dCs/dt) = k}$$

Where Cs = concentration of the drug present in the matrix, k = rate constant and t = time. Since

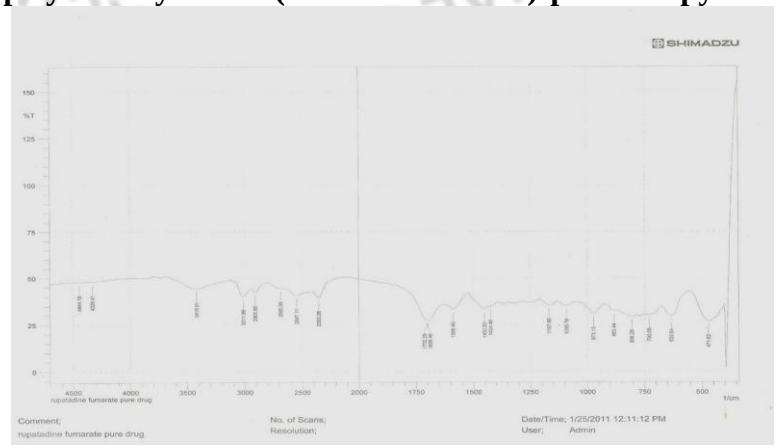
Cs is a constant, and x = amount of drug released described as dx/dt = k integration of the

equation yields x = kt + constant.

The different models, viz.-zero-order, Higuchi's equation and Korsmeyer-Peppa's equation were used to study the *in vitro* release of the immediate release tablets.

Results and discussion

Identification of drug and compatibility studies of drug-polymers by FT-IR (fourier transform)spectroscopy.



IR Spectra of Alginic acid

POSSIBLE INTERPRETATION OF SPECTRA

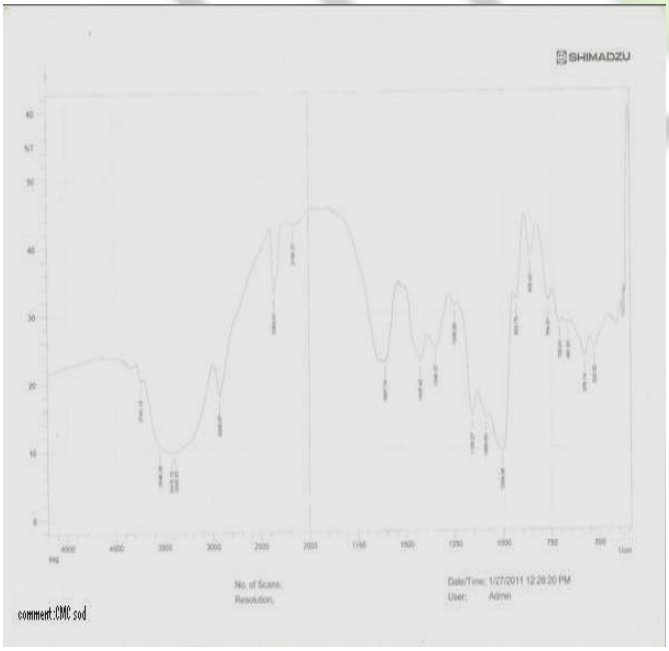
WAVE NUMBER (cm -1)	INTERPRETATION
3418.01	Hydrogen bond between OH group
2908.1	Alkene stretching
1702	C=N Stretching
1450	(N-CH_3) Stretching
1345.11	- CH_2 group
1167.5	C=O stretching

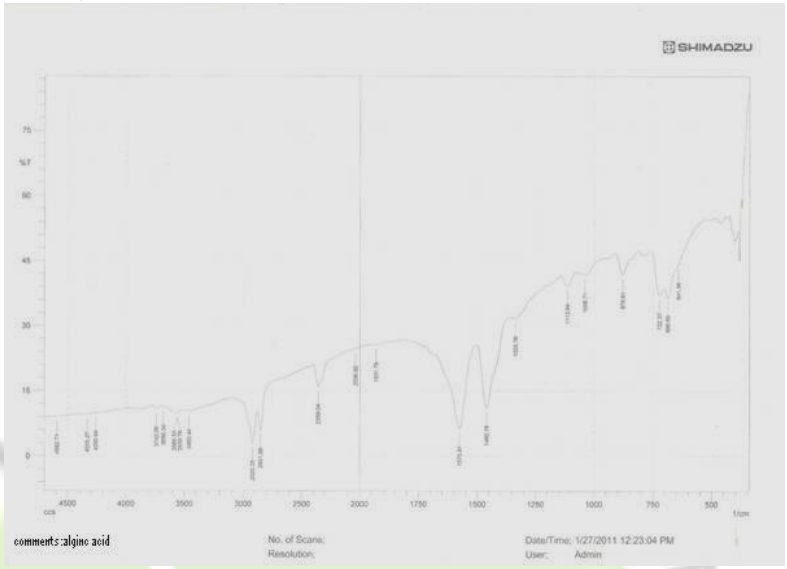
COMPATIBILITY STUDIES

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product.

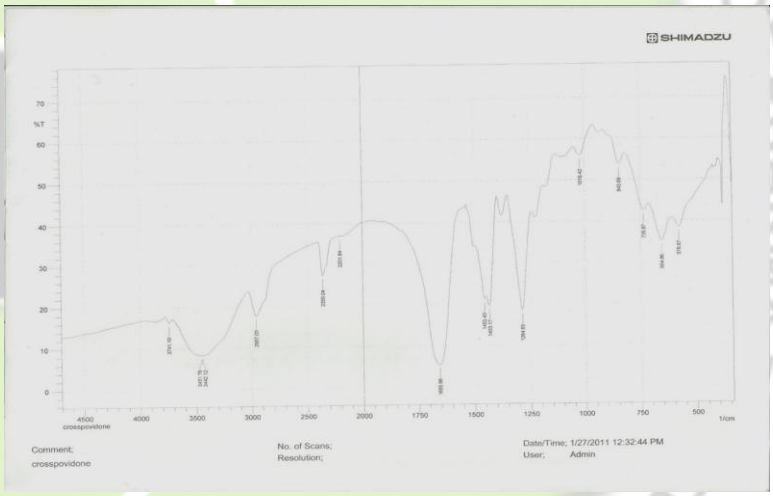
If the excipients are new and not been used in formulations containing the active substance, the compatibility studies are of paramount importance.

IR Spectra of sodium CMC

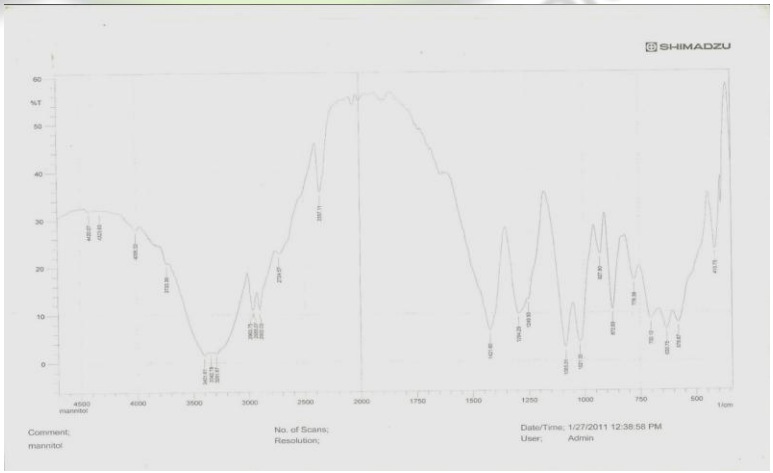




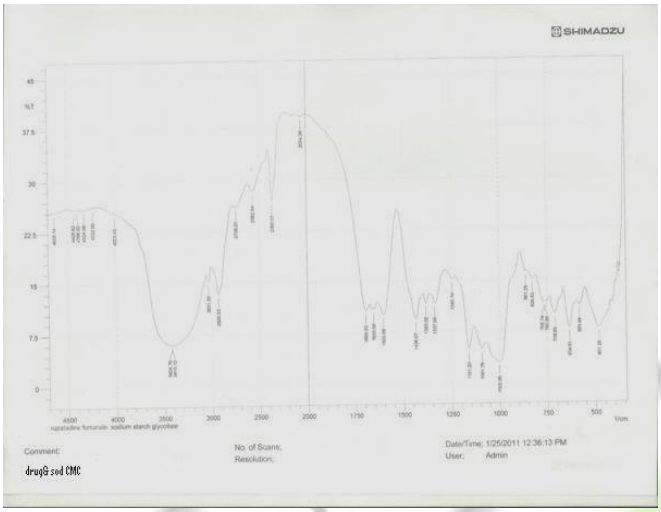
IR Spectra of crospovidone



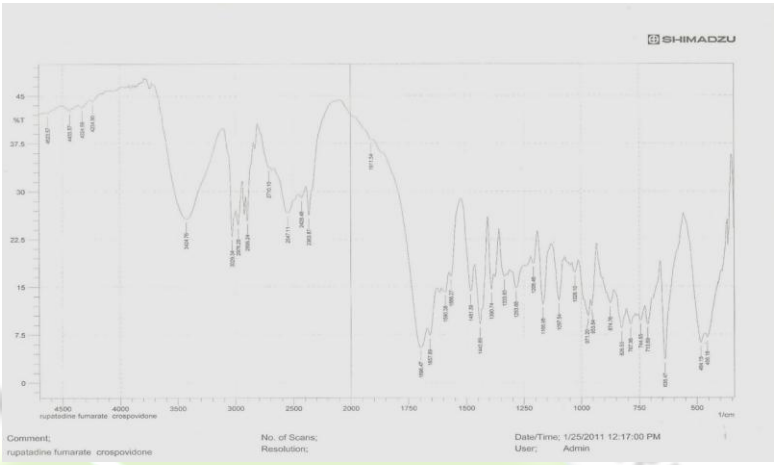
IR Spectra of Mannitol



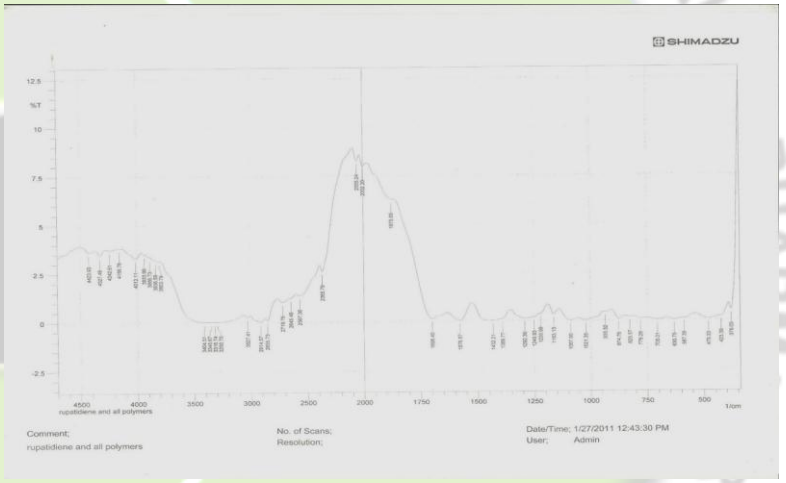
Drug and sodium CMC



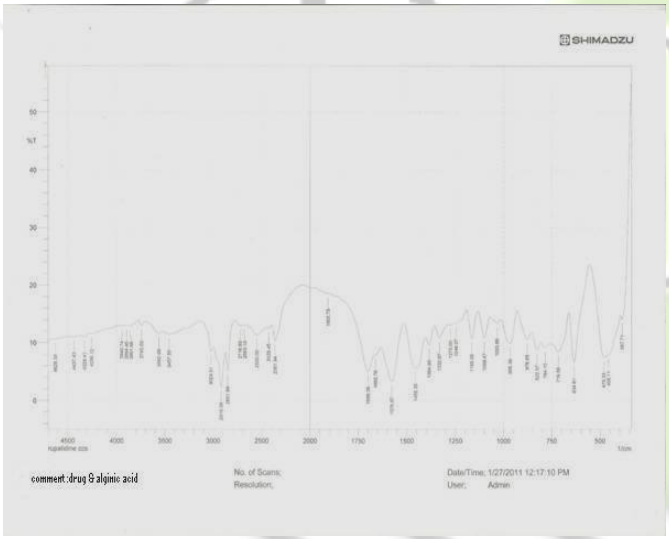
Drug & crospovidone



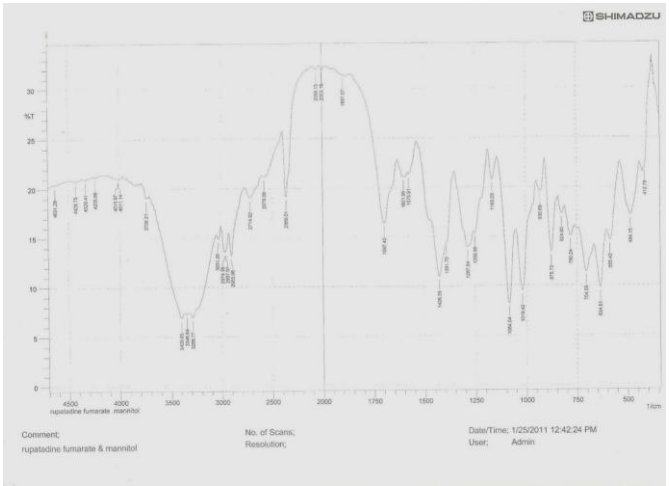
Drug & all Polymers



Drug & alginic acid



Drug & Mannitol



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

The procured sample of Rupatadine was tested for its identification. The FT-IR spectra of the physical mixture exhibited absorption peaks similar to those of the pure drug sample. The results of FT-IR analysis indicated that there was no chemical interaction between the drug and the excipients in the direct compression tablets formulation.

Evaluation of powder blend

Formulations	Bulk Density (gm/ml)	Tap Density(gm/ml)	Angle of Repose (θ)	Means Carr index	Hausner Ratio
F1	0.28	0.35	28	20	1.25
F2	0.25	0.32	24	21.78	1.28
F3	0.27	0.34	26	20.58	1.25
F4	0.28	0.36	27	22.2	1.33
F5	0.26	0.33	28.17	21.21	1.26
F6	0.28	0.36	28.30	22.2	1.28
F7	0.25	0.34	23.96	26.47	1.36
F8	0.28	0.35	26.56	20	1.25
F9	0.28	0.35	28.23	20	1.25
F10	0.27	0.36	25.43	25	1.29
F11	0.25	0.34	226.64	26.47	1.17
F12	0.28	0.36	27.23	22.22	1.28
Control	0.28	0.34	21	17.64	1.21

Evaluation of tablets

Tablet Description: The tablets descriptions found to be White, round flat, with smooth surface in both side, uncoated tablets.

Weight variation: No significant difference was observed in the weight of individual tablets form the average weight. Tablet weights of all bathes were found with in recommended IP limits, between to 120 mg to 300 mg is ± 7.5%.

Disintegrating time:

In vitro disintegration time was measured by using disintegration tester (Electrolab ED-2L) and tablet dropping in a 1000ml beaker containing 900ml of purified water which maintained at 37±0.5°C.

Mechanical strength:

Crushing strength *(Hardness)* of tablets of all batches are in between 3.5 ± 0.05 to 4 ± 0.09 (Kp)
which is acceptable limits.

Abrasion *(Friability)* of all the formulation showed % friability less than 1% that indicatesability of tablets to withstand shocks, which may encountered.

Assay

The data of uniformity of content which was performed by UV Assay, indicated that tablets
of all batches had drug content within USP limits. i.e. between 98.08 to 100.08 %.

Tabletting properties of tablets with alginic acid

Formulation properties	F1	F2	F3	F4
Weight variation	Passes	Passes	Passes	Passes
Hardness (kg/cm2)	3.5	4	3.5	3.5
Friability	0.65	0.63	0.61	0.62
Uniformity of content (%)	98.63	99.31	98.63	98.97
Water absorption ratio (%)	71.6	74.3	76.5	78.6
Wetting time	3min	2min	2min	1 min 30sec
Disintegration time	3min5sec	2min50sec	2min52sec	2min

Tabletting properties of tablets with crospovidone

Formulation properties	F5	F6	F7	F8
Weight variation	Passes	Passes	Passes	Passes
Hardness (kg/cm2)	3.5	3.5	3.5	3.5
Friability	0.82	0.61	0.63	0.61
Uniformity of content (%)	99.22	100.08	99.87	99.12
Water absorption ratio (%)	70.2	71.6	74.3	76.1
Wetting time(seconds)	36	30	20	20
Disintegration time	40seconds	36seconds	23seconds	22seconds

Tabletting properties of tablets with sodium CMC

Formulation properties	F9	F10	F11	F12
Weight variation	Passes	Passes	Passes	Passes
Hardness (kg/cm2)	4	3.5	4	3.5
Friability	0.64	0.60	0.70	0.62
Uniformity of content (%)	98.65	98.08	99.86	100.5
Water absorption ratio (%)	70.2	71.6	74.3	76.1
Wetting time(seconds)	5min	3min	3min	2min
Disintegration time	7min	6min30sec	5min42sec	3min30sec

Tabletting properties of tablets without superdisintegrants (control formulation)

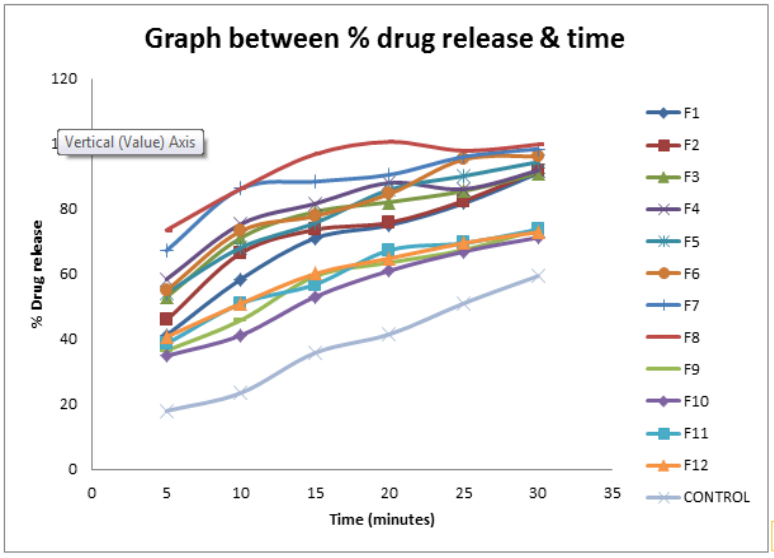
Formulation properties	Control
Weight variation	Passes
Hardness (kg/cm2)	4.5
Friability	0.64
Uniformity of content (%)	97.65
Water absorption ratio (%)	65.5
Wetting time(seconds)	7min
Disintegration time	12min

Invitro Release study

The *Invitro* release study was carried out in USP dissolution test apparatus type 2 for all batches was evaluated and % drug release was calculated.

Table showing % drug release versus time for all formulations

S. NO.	Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	Control
1	0	0	0	0	0	0	0	0	0	0	0	0		0
2	5	41.2	45.8	52.9	58.4	54.2	55.0	67.2	73.5	36.5	34.9	38.6	40.7	18.0
3	10	58.4	66.4	71.1	75.3	68.1	73.2	86.2	86.2	45.8	41.2	50.9	50.9	23.5
4	15	71.	73.6	79.1	81.6	75.7	77.8	88.4	96.8	59.3	53.0	56.8	60.1	35.8
5	20	75.	75.8	82.1	88.0	85.9	84.6	90.5	100.6	63.5	61.0	67.3	64.8	41.5
6	25	81.7	82.5	85.5	86.1	90.1	95.2	96.0	97.9	67.4	66.9	69.5	69.5	51.0
7	30	91.0	91.8	91.0	91.8	94.4	96.1	98.4	99.8	73.74	71.2	73.7	72.9	59.4



Graph between % drug release (Y-axis) and time in minutes (X - axis)

Conclusion

The basic idea of this investigation is to design immediate release tablet using Rupatadine fumarate, Rupatadine fumarate is a new selective long acting hitamine H1 receptor and platelet activating factor (PAF) antagonist used in the treatment of allergic rhinitis. Usefull for allergic urticaria conventional tablets of rupatadine required water for swallowing. Which may be inconvenient for elderly patient suffer from dysphagia and bedridden patients. Initially the standard calibration curve of Rupatadine fumarate was developed. The powder blend for all formulation containing various concentration of crospovidone (2-5%), sodium CMC (2-5%), and alginic acid (2-5 %) as superdisintegrant and control formulation (without superdisintegrant) were prepared and then evaluated for powder properties like angle of repose, bulk density, tapped density, Carr's index, Flowability. It was observed that all the formulation were having good flowability it indicate its suitability for direct compression. The tablets were prepared by direct compression using single punch Rotary tablet machine (Kshitij innovations).These tablets were evaluated for weight variation test, hardness, friability, content uniformity, water absorption ratio, disintegration time and In-vitro dissolution rate. It was observed that all the tablets passes the test for weight variation and content uniformity. Hardness of all tablets was between 3.5-4 kg/cm2 while friability below 1% showed that all the tablets have good mechanical strength it was found that water absorption ratio of tablet containing

superdisintegrants. Disintegration time required is in following manner with increase in concentration of superdisintegrant in the order of

Crospovidone>alginic acid>sodium CMC.

Dissolution studies indicates, that tablets prepared by using superdisintegrant (Formulation F8) showed rapid dissolution as the concentration of superdisintegrants was increased.

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