



Scholars Research Library

Der Pharmacia Lettre, 2009, 1 (2) 151-163
(<http://scholarsresearchlibrary.com/archive.html>)



ISSN 0975-5071

Formulation and evaluation of fast dissolving tablets of Rupatadine fumarate

Pushendra kumar, A. Pasupathi, Margret Chandira*, Debjit Bhowmik, Chiranjib, B. Jayakar,
+K.P.Sampath Kumar

Vinayaka Missions College of Pharmacy, Salem, Tamilnadu
Coimbatore Medical College, Coimbatore⁺

Abstract

The demand of fast dissolving tablets has been growing, during the last decade especially for geriatric and pediatric patients because of swallowing difficulties. Rupatadine fumarate is H₁ and PAF antagonist used primarily in treatment of allergic rhinitis symptoms, seasonal or perennial. Fast dissolving tablets of Rupatadine fumarate were prepared by direct compression method. The tablets were prepared by using mannitol, microcrystalline cellulose as filler, croscopovidone, croscarmillose, SSG as super disintegrants in different concentration (2-5%). Total twelve formulations 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. Optimised formulation F₄ was compared with control formulation for disintegration time and % drug release. The stability studies were performed as per ICH guidelines. The Optimized formulation (F₄) showed no significant variations for the tablets parameters and it was stable for the specified time period. It was concluded the FDT for Rupatadine fumarate can be formulated for emergency treatment of allergic rhinitis.

Key words- Rupatadine fumarate, wetting time, Fast dissolving tablets, disintegration time.

Introduction

Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) developed the following definition for an fast disintegrating tablet (FDT) as a new dosage form in 1998: A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue. Some tablets are designed to

dissolve in saliva remarkably fast, within a few seconds, and are truly fast dissolving tablets. Other tablets contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed fast disintegrating tablets as they may take up to a minute to completely disintegrate. The target population for these new fast dissolving/disintegrating dosage form have generally been pediatric, geriatric and bed ridden or disabled patients. Patients with persistent nausea, who are traveling or who have little or no access to water are also good candidates for FDDTS. In the near future, other patients populations will also be targeted. A novel application for FDDTS is in veterinary medicine, for example to avoid pilling a cat. With fast-dissolving/disintegrating dosage form increasingly available, it will be likely that prescribers will recommended such product for their non compliant patients. The ease administration of fast dissolving/disintegrating tablet, along with its pleasant taste, may encourage a patient to adhere to daily medication regimen. A major claim of these FDDTs is increased bioavailability compared to traditional tablets. Because of dispersion in saliva while still in the oral cavity, there can be pre-gastric absorption from some formulations in those case where the drug dissolve quickly. Buccal, pharyngeal, and gastric regions are all areas of absorption of many formulations. However other formulations show nearly identical plasma-concentration profile. Any pregastric absorption avoids first pass metabolism and can be a great advantage in drug that undergo a great deal of hepatic metabolism. However, if the amount of swallowed drug varies, there is the potential for inconsistency bioavailability. While the claimed increase in bioavailability is disputable, it is clear that the major advantage of these formulation is convenience. Pharmaceutical marketing is another reason for the increase in available fast-dissolving/disintegrating product. As a drug entity nears the end of its patient life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extended market exclusivity, while offering its patient population more convenient dosage form or dosing regimen. In this regard, fast dissolving/disintegrating tablet formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast dissolving/ disintegrating dosage form, leads to increase revenue, while also targeting under treated patient populations. Although the cost to manufacture these specialized dosage form exceeds that of traditional tablets, the additional cost is not being passed on to the consumer. Therefore, cost is generally not an issue when recommending these new dosage forms. This is also our objective to monitor the disintegration as well as Dissolution pattern of FDT of Rupatadine fumarate. Rupatadine fumarate is bitter in taste, thus the first step towards the formulation is to mask the bitter taste of the drug with the help of various taste masking agents. The method was simple, inexpensive, not toxic and does not affect the bioavailability and drug release time of the drug. At present, FDTs tablets of rupatadine fumarate are not available in the commercial market. ARIA (Allergic Rhinitis and its Impact on Asthma) panel reported near about 90% patient who suffering from allergic rhinitis they are also suffering from asthma. which have inability to swallow tablet. Like Pediatric and geriatric patients who face much difficulty during drug administration. . To prevent these difficulties during administration, there is need to develop rapidly disintegrating dosage form, which disintegrate and / or disperse in saliva without need of water. These tablets are known as FDTs. Thus, the aim of present investigation is to formulate and evaluate FDTs of Rupatadine fumarate.

Materials and Methods

Rupatidine fumarate is procured by Panacea Biotech Ltd Baddi., Crospovidone, Croscarmellose, Sodium starch glycolate are gifted by Signet chemical corporation Mumbai, Mannitol, Sodiam saccharin, Talc, Magnesium Stearate are procured by Loba Chemie, Cochine.

Formulation design of rapidly disintegrating tablet by direct compression using super disintegrants

The tablet consisted of Rupatidine fumarate (10 mg), mannitol, and Sodium saccharin, flavours, magnesium stearate, talc 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 multiple punch machine. Effect of variables like types of superdisintegrant, concentration of superdisintegrant on various tablet properties and vitro dissolution characteristics were studied and discussed.

Table. No. 1: Formulation composition for tablets prepared by Using Superdisintegrants-Direct compression

Name of Ingredients	Quantity (in mg)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Rupatidine fumarate	10	10	10	10	10	10	10	10	10	10	10	10
Ac-Di-Sol	4	6	8	10	---	---	---	---	---	---	---	---
Poly Plasdone	---	---	---	---	4	6	8	10	---	---	---	---
Primojel	---	---	---	---	---	---	---	---	4	6	8	10
Sodium Saccharin	2	2	2	2	2	2	2	2	2	2	2	2
Flavours	2	2	2	2	2	2	2	2	2	2	2	2
Talc	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

In the above table, three superdisintegrants have been used for the preparation of fast dissolving tablets. Ac-Di-Sol, Polyplasdone and Primojel in 2 –5 % concentration. Batch F1-F4 contain Ac-Di-Sol , F5-F8 Polyplasdone and batch F9-F12 primojel contains 2-5 % concentration of superdisintegrants.

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 .

UV absorption maxima:

A UV spectrum was taken at 80 $\mu\text{g/ml}$ concentration. The scanning was done from 200-300 nm in 0.1N HCl as blank using Elico- 164 double beam UV/ VIS spectrophotometer

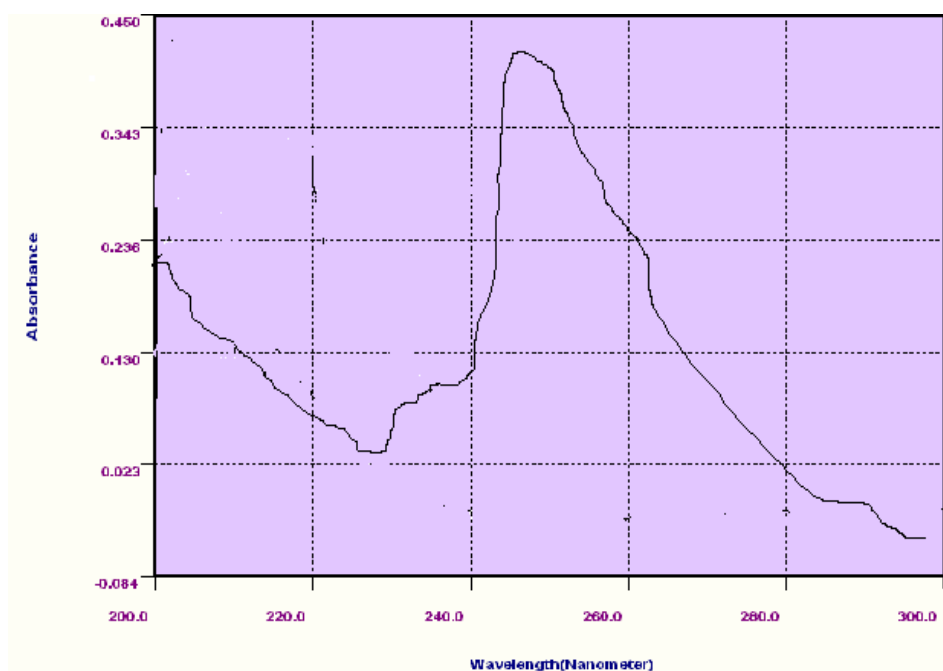


Figure. No. 1 : U.V. Spectra Of Rupatadine Fumarate

Rupatadine fumarate shown λ_{max} between 240nm to 254nm in the 0.1N HCl . As per the working standard, λ_{max} of Rupatadine fumarate is 252 nm. Thus observed λ_{max} value is identical to the theoretical λ_{max} value. This also indicated the identity and purity of the drug.

Preparation of standard curve:

From the stock solution 1, 2, 3, 4, 5, 6, 7 and 8 ml were transferred to 10 ml volumetric flasks and were diluted with 0.1 N HCl, up to the mark to obtain concentration of 10, 20, 30, 40, 50, 60, 70 and 80 $\mu\text{g/ml}$ respectively. Absorbance of each solution was measured at 252 nm.

Table. No. : 2 Standard curve of Rupatadine fumarate in 0.1N HCl at 252 nm

Standard curve of Rupatadine fumarate in 0.1N HCl at 252 nm		
S.No.	Concentration (µg/ml)	Absorbance (nm)
1	10	0.196
2	20	0.292
3	30	0.417
4	40	0.516
5	50	0.614
6	60	0.743
7	70	0.852
8	80	0.949

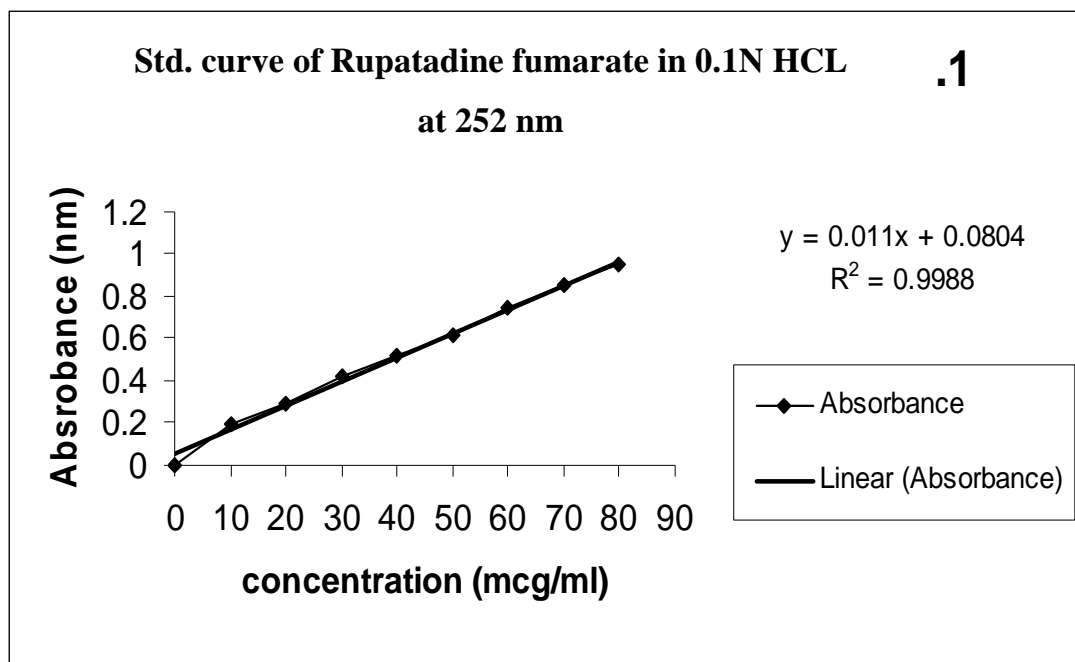


Figure. No. 2: Standard curve of Rupatadine fumarate

Evaluation of tablets prepared by direct compression technology

Low cost, direct compression method was employed to develop a rapidly disintegrating tablet with a taste and texture acceptable to patient and with sufficient structure integrity. Tablet (200 mg) were prepared from control formulation, using various concentration of superdisintegrants such as 2-5% of Ac-Di-Sol, 2-5% of polyplasdone-XL and 2-5% of primojel as superdisintegrant. The control tablet (without superdisintegrants) and tablets prepared by using Ac-Di-Sol, Polyplasdone -XL and Primojel as superdisintegrant are shown Table. no.12 and 13. Mixed blend of drug and excipients was compressed on single punch tablet machine. Tablet, each weighing 200 mg was prepared.

Weight variation

With a tablet designed to contain a specific amount of drug in a specific amount of formula, the weight of a tablet being made is routinely measured to ensure that a tablet contains proper amount of drug.

Procedure

First weight of 20 tablets was determined, from that average weight was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness and Friability

Tablets required certain amount of strength, or hardness and resistance to friability. It is necessary or important to withstand mechanical shocks of handling in manufacture, packaging and shipping.

Adequate tablet hardness and resistance to powdering and friability are necessary requisites for consumer acceptance. More recently relationship of hardness to tablet, disintegration and dissolution of drug had become apparent. Monitoring of tablet hardness is especially important for drug products that possess real bioavailability problems and or those which are sensitive to altered dissolution profile as the function of compressive force employed. Using tablet hardness tester, hardness of the tablet was checked. Using Roche Friabilator friability of the tablet was checked. This device subjects tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves. Preweighed weight of 10 tablets was placed in the Friabilator, which was then operated for 100 revolutions. Tablets were dusted and weighed. The friability was determined using following formula.

$$\text{Friability} = [(\text{Initial weight} - \text{Final weight}) / (\text{initial weight})] \times 100\%$$

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighted. Water absorption ratio, R was determined using following equation.

$$R = 100 \times \frac{W_a - W_b}{W_a}$$

Where, W_a = Weight of tablet after water absorption
 W_b = Weight of tablet before water absorption.

In-vitro dispersion time

Tablet was added to 10 ml 0.1N HCl solution, $37 \pm 2^\circ\text{C}$. Time required for complete dispersion of a tablet was measured.

Uniformity of content

The test is applicable for tablets that contain less than 10 mg or less than 10% w/w of active ingredients. The test for uniformity of content should be carried out only after the content of active ingredient in a pooled sample and tablets has been shown to be within acceptable limits of the started content. Ten tablets were taken and their content was determined by UV spectrophotometry.

Table 3: Powder properties of formulations F1-F12 containing various superdisintegrants

Super disintegrants	Formulations	Angle of repose (θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's index	Floability
Ac-di-sol	F1	28	0.28	0.35	20	Good
	F2	24	0.25	0.32	21.78	Good
	F3	26	0.27	0.34	20.58	Good
	F4	27	0.28	0.36	22.02	Good
Polyplasdone-XL	F5	28.17	0.26	0.33	21.21	Good
	F6	28.30	0.28	0.36	22.02	Good
	F7	23.96	0.25	0.34	26.47	Good
	F8	26.56	0.28	0.35	20.00	Good
Primojel	F9	28.23	0.28	0.35	20.00	Good
	F10	25.43	0.27	0.36	25.00	Good
	F11	26.64	0.25	0.34	26.47	Good
	F12	27.23	0.28	0.36	22.22	Good

In-vitro drug release:

Release of drug in vitro, was determined by estimating the dissolution profile.

Dissolution test:

Standard USP dissolution apparatus have been used to study in vitro release profile using rotating paddle. In release rate study of fast dissolving tablets of Rupatadine fumarate was carried out using the Apparatus 2 (Paddle apparatus) method. The dissolution apparatus was covered with the black colour polythine to protect the solution from light. The dissolution test was carried out using 900 ml of 0.1 N HCL, at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 2,4,6,8 and 10 minutes and withdrawn volume was replaced with fresh dissolution media.

The withdrawn samples diluted with dissolution medium and then filter it with Whatman filter paper assayed at 252 nm.

The % release of Rupatadine fumarate was calculated. The observation of different batches was shown in table no. 20 The % release of Rupatadine fumarate with respect to time for each batch, were graphically shown in Table No.19 and 20, Figure No.17-22.

Dissolution rate profile of tablet containing Ac-Di-Sol:

From table No 20 and figure No 18, it was found that 101.88% drug release was occurred within 2-6 minutes, which was very quick than control tablet. This is due to good water absorption capacity occurring with Ac-Di-Sol, which is the pivotal step in rapid disintegration and ultimately for quick release of drug from tablet.

Dissolution rate profile for tablet containing Polyplasdone –XL:

Dissolution profile for tablet prepared by polyplasdone F5, F6, F7, and F8 formulation was shown in table no. 20 and figure no. 19 from data it was observed that 99.89% drug release occurred in 2-8 minutes this may due to rapid absorption capacity and rapid disintegration.

Dissolution rate profile of tablet prepared with primojel:

From table no. 20 and figure no. 20 it was noted that 99.02% drug release was obtained within 2-10 min for all the formulation containing primojel, the slow rate of release is due to formation of viscous plugs with increase in concentration of primojel the possible reason for this slow release rate of drug are formation of viscous plugs with increase in concentration of primojel.

Table 4: Drugs release data of batch F₁ – F₁₂ using various Superdisintegrants

TIME (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
2	51.88	54.45	57.18	62.90	41.23	43.10	48.05	95.68	36.12	38.11	42.13	44.12
4	79.00	81.00	98.90	101.88	58.12	61.11	72.12	74.17	47.18	49.15	62.12	63.11
6	97.80	98.20	-	-	76.15	79.22	99.19	99.89	59.11	62.13	78.12	82.56
8	-	-	-	-	98.00	98.89	-	-	76.01	78.03	98.98	99.02
10	-	-	-	-	-	-	-	-	97.89	98.44	-	-

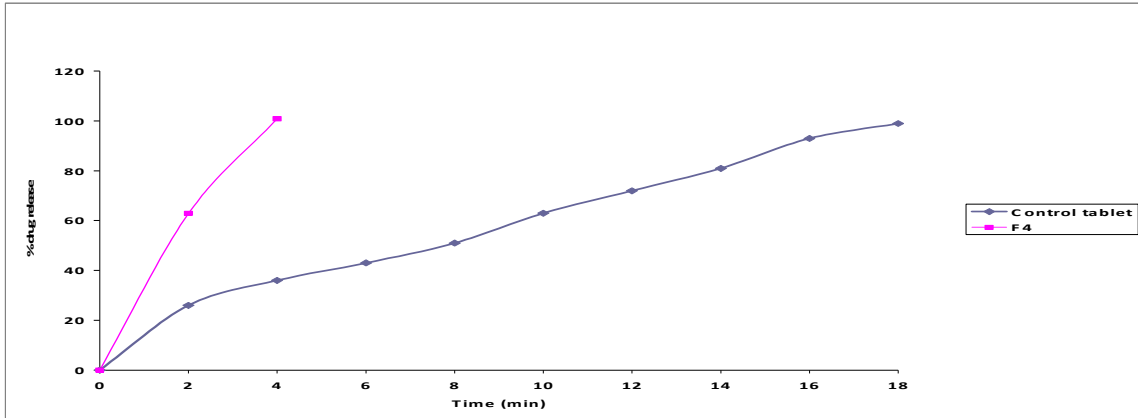


Figure. No. 3: A comparative study of In-vitro drug release of Control (C) and with optimized formulation F4 using Croscarmillose as Super disintegrant.

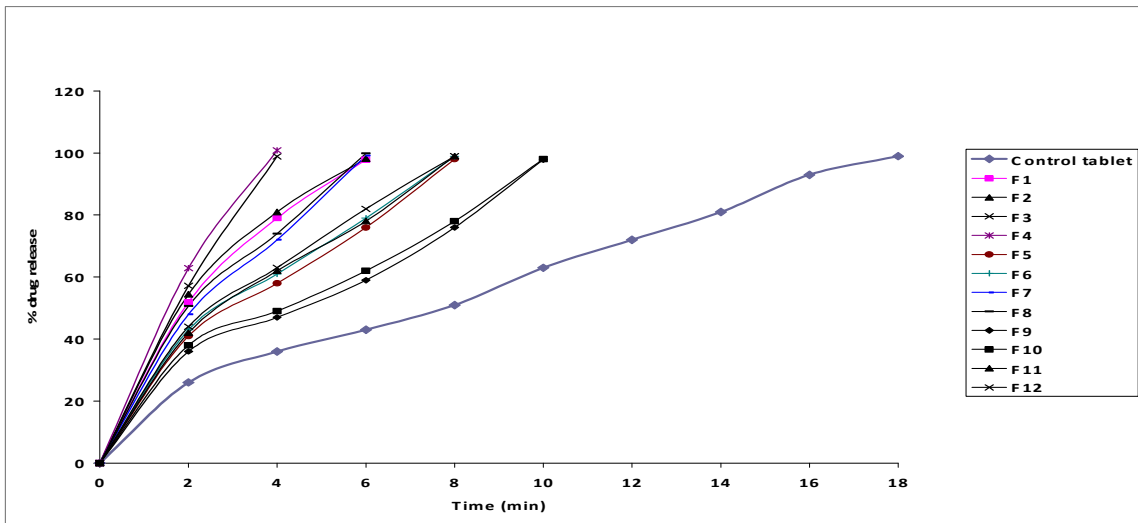


Figure. No. 4: A comparative study of In-vitro drug release of tablets using different Superdisintegrants with control tablet

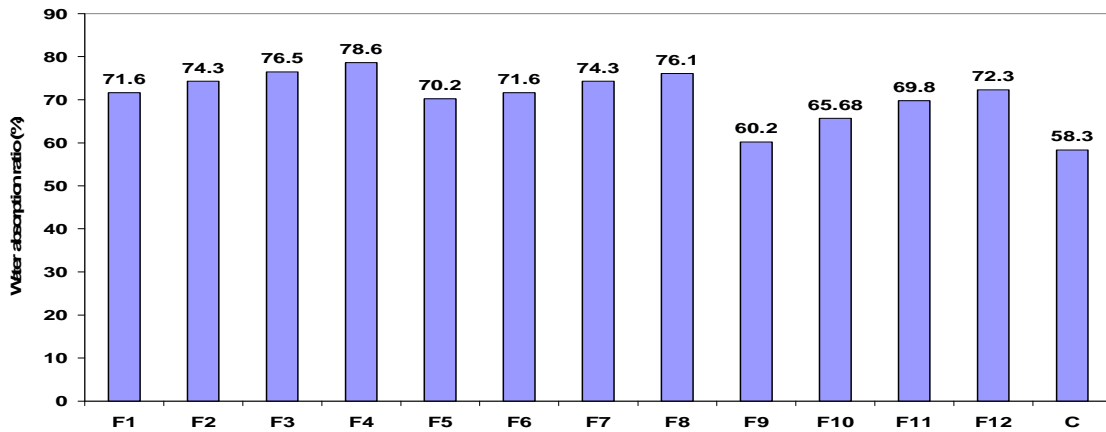


Figure. No. 5 : Column graph of Water absorption ratio of formulations F₁-F₁₂ and control tablet

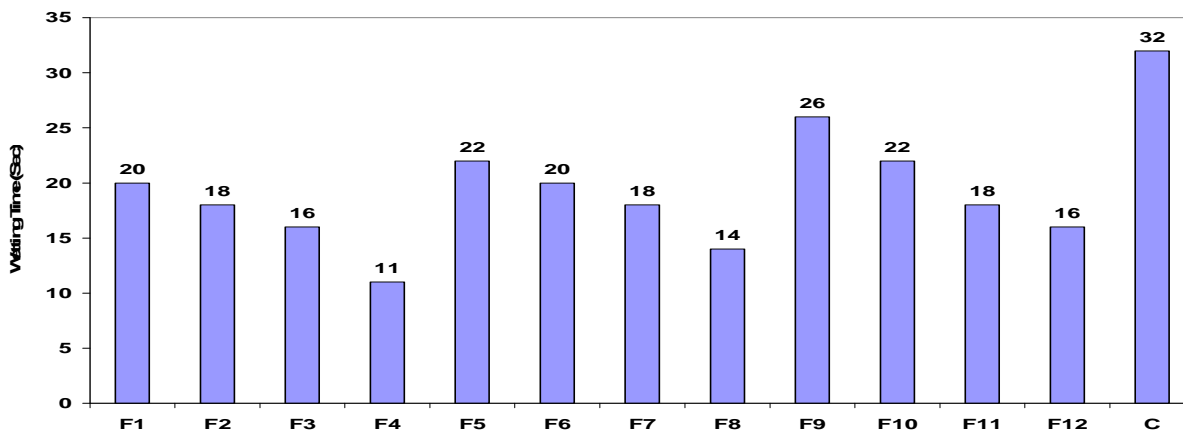


Figure. No. 6 : Column graph of Wetting time of formulations F₁-F₁₂ and control tablet

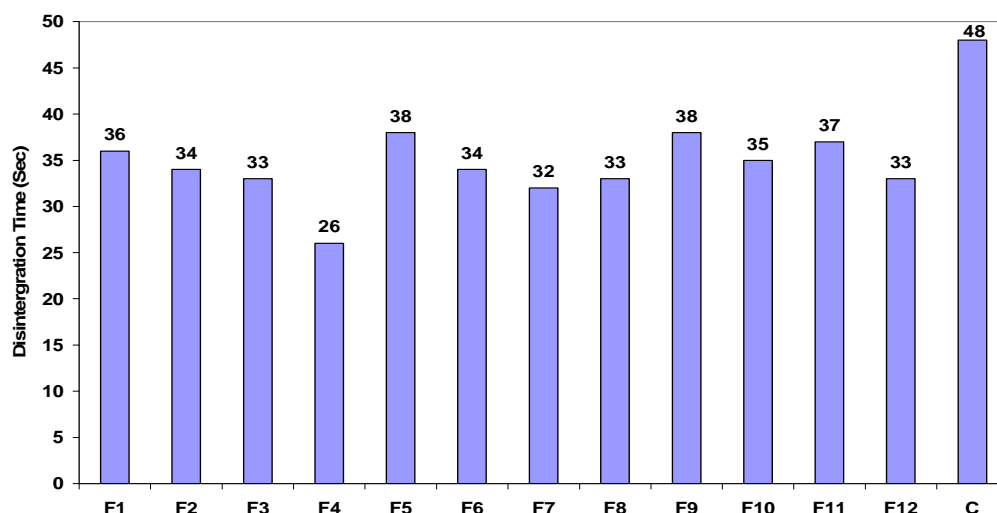


Figure. No. 7 : Column graph of Disintegration time of formulations F₁-F₁₂ and control tablet

Stability studies of fast dissolving tablets of optimized batch (F4)

It is the responsibility of manufacturers to see that the medicine reaches the consumer in an active form. So the stability of pharmaceuticals is an important criteria. Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic and toxicological specification, i.e. stability of drug is its ability to resist deterioration. 90% of labeled potency is generally recognized as the minimum acceptable potency level. Deterioration of drug may take several forms arising from changes in physical, chemical and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity.

Accelerated Stabilizing Testing:

Since the period of stability testing can be as long as two years, it is time consuming and expensive. Therefore it is essential to devise a method that will help rapid prediction of long term stability of drug.

The accelerated stability testing is defined as the validated method by which the product stability may be predicted by the storage of the product under condition that accelerate the change in defined and predictable manner.

The stability studies of formulated tablets were carried out at $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \text{RH} \pm 5\%$ at room temperature for one month. The effects of temperature and time of physical characteristics of tablet were evaluated for assessing the stability of prepared formulations.

Accelerated stability studies as per ICH guidelines:

The optimized formulation (F4) was wrapped in aluminum foils and kept in petri dish at $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \text{RH} \pm 5\%$ in humidity chamber. The stability studies were conducted after 30 and 60 days.

Table 5: Physical Characteristics of Rupatadine fast dissolving tablet of optimised Batch F₄ at Temperature ($40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \text{RH} \pm 5\%$)

Physical parameter	Formulation F4			
	0 days	15 days	30 days	60 days
Weight gain (mg)	200	200	204	204
Percent drug content%	100.3	100.3	100.1	100
Hardness (Kg/cm^2)	3.0	3.0	2.5	2.3
Disintegration time (Sec)	26	26.5	27	28.6
Wetting time (Sec)	11	11.7	13	15

Table. No. 6: Drug release % at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\%$

S.No.	Time (days)	$40^{\circ}\text{C} / 75\% \text{RH}$
1.	0	99.21
2.	30	98.23
3.	60	97.41

Conclusion

The basic idea of this investigation is to design “Fast dissolving” dosage form using Rupatadine fumarate, Rupatadine fumarate is a new selective long acting histamine H₁ receptor and platelet-activating factor (PAF) antagonist used in the treatment of allergic rhinitis. Useful for allergic urticaria conventional tablets of rupatadine required water for swallowing. Which may be un convenient 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 Polyplasdone-XL (2-5%), Ac-Di-Sol (2-5%), and primojel (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 Rotary tablet machine (cadmach machine). 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 2.0-3.5 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 superdisintegrant was more than control tablets and it was increased with increase in concentration of superdisintegrants. Out of all formulation tablet containing Ac-Di-Sol as superdisintegrant showed highest water absorption ratio than all other formulation with single use of superdisintegrant. disintegration time of all tablets was observed within fraction of second. It was found that as concentration of polyplasdone-XL and Ac-Di-Sol increases, the disintegration time decrease. for primojel, as concentration in tablet increases, disintegration time also increases, which may be because of viscous plug formation amongst all tablet, tablet containing 5% Ac-Di-Sol as superdisintegrant showed faster dissolution rate as compared to other superdisintegrants.

Tablets containing 5% Ac-Di-Sol showed 101.88% drug release within 2-6 minutes while that for tablet containing polyplasdone xl showed 99.89% drug release within 2-8 minutes. Tablet containing primojel showed 99.02% drug release within 2-10 minutes while control tablet showed 99.31% drug release in 18 minutes. In conclusion, with increase in concentration of superdisintegrant disintegration time decreases in the order of **Ac-Di-Sol < Polyplasdone-xl < primojel**. Dissolution time required is in following manner with increase in concentration of superdisintegrant in the order of

Ac-Di-Sol < Polyplasdone-xl < primojel.

Dissolution studies indicates, that tablets prepared by using superdisintegrant (Formulation F4) showed rapid dissolution as increase the concentration of superdisintegrants.

Acknowledgement

Authors are thankful to Prof.(Dr.) B.Jayakar, principal Vinayaka missions college of pharmacy, Salem, Tamilnadu, India providing all the facilities for this research Project.

References

- [1] Rathbone MJ, Hadgraft Jonathan, Rober Michael S. **2003**. Modified Release Drug Delivery Technology: Vol-126. New York: Marcel Dekker Inc, PP. 191-216.
- [2] Indurwade N.H. Rajyagru. T.H. and Nakhat P.D. **2003**, *Indian drug* 39:405-409.
- [3] B.S.Kuchekar, Atul C. Badhan, H.S. Mahajan, *Pharma Times* Vol.35, June **2003**.

- [4] Kuchekar B.S., Badhan A.C and Mahajan H.S, *Indian drugs*; **2004**. 41(10), 592-598.
- [5] Amin A.F, Shah T.J, Bhadani M.N., Patel M.M., www.pharminfo.net, 2005.
- [6] Seager H., *J.Pharm. Phamacol*, **1998**, 50, 375-382.
- [7] Heinmann H. and Rothe W., Preparation of porous tablets, US Patent No.3,885,026, 1975.
- [8] Lachmann L., Liebermann H.A and Kiang J.L., The theory and practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, Bombay, **1998**, 430-440.
- [9] Khan K.A., and Rhodes C.T, *Can. J. Pharm. Sci.*, 8; 1-5: **1973**.
- [10] Gohel M.C, Patel L.D, Murpani D, and Iyer L, *Indian Drugs*, 34; 322-326 : **1997**.
- [11] Wong D.Y, Wright P, and Aulton M.E, *Drug Dev. Ind. Pharm.* 14 ; 2109-2126: **1988**.
- [12] Whiteman M, and Yarwood, R.J, *Drug Dev. Ind. Pharm.*, 14; 1023-1040: **1988**.
- [13] Kothari.S.H, Umar V, and Banker G.S, *Int. J. Pharm.*, 232; 69-80: **2002**.
- [14] Mishra B., Panigrahi D and Baghel S., *J. Pharm. Res.*, **2005**, 4(3), 33-38.
- [15] Patel.D.M, Patel.N.M, Shah.R.R, Jogani.P.D and Balapatel.A.I; *Indian J. Pharm Sci*; **2004**. 66(5), 621-625.
- [16] Bhakaran S. and Narmada, G.V., *Indian Pharmacist*, **2002**, 1(2), 9-12.
- [17] Shah.U and Augsburger L., *Pharm. Develop. Tech.*, **2001**, 6, 419-430.
- [18] Desai S.A, Kharade S.V, Petkar, K.C and Kuchekar D.S **2006**. *Indian J. Pharm. Edu. Res* 40: 172-174.
- [19] Mishra B, Panigrahi D, Baghel S, **2005**. *Journal of pharmaceutical research* 4:33-38.
- [20] Kulkarni GT, Gowathamarajan K, Suresh B, *Ind. J. Pharm. Sci.*, **2004**, 384, 194-202.
- [21] Perissutti Beatrice, Rubessa Fulvi Moneghini Mariarosa, Voinovich Dario. **2003**, *International journal of pharmaceutics* 256, 53-63.
- [22] Mahajan H.S., Patil S.B., Gattani S.G., Kuchekar B.S, **2005**. *The pharma revire*.4 : 49-51.
- [23] Reddy L.H., Ghosh B, and Rajneesh, *Ind., J. of Pharm. Sci.*, 64(4), **2002**, 331-336.
- [24] Sreenivas S.A, Gadad A.P, Dandari P.M., Mastiholimath V.S and Patil **2006**. *Indian drug*. 43 : 35-38.
- [25] Sugimoto M, Matsubara K, Koida Y, Kobayashi M, **2001**. *Pharm dev. Technol*.6 (4) : 487-93.
- [26] Shibata Y, Yamamoto Y, Fujii M, Kondoh M, Watanabe Y, **2004**. *Chem. Pharm bull*, 52 (11) : 1394-5.
- [27] Shu T, Suzuki H, Hironaka Klto K, **2002**. *Chem pharm bull* (Tokyo). 50 (2) : 193-8.
- [28] Mukai Baku, Shuji shiraishi, Naoki Utoguchi, Makiko Fujii, Matsumoto and Watanabe Yoshiteru, **2001**, *Chem. Pham. Bull*. 49(2), 134-139.
- [29] Watanabe Y. **2001**. *Chem. Pharm bull* 49 (2) : 134-139.
- [30] Bi Y, Sunada H, Yonnezawa Y, Danjo K, Otsuka A, Iida K **1996**. *Chem Pharm Bull*, 44(11) : 2121-7.
- [31] Shirwaikar AA, Ramesh A. **2004**. *Indian J. Pharm Sci*, 66 (4) : 422-426.
- [32] Jeong SH, Fu Y, Park K. **2005**. *Expert opin drug deliv* 2 (6) : 1107-16.
- [33] Fausett, H., Gayser C and Dash A.K., **2000**. *AAPS Phar Sci Tech.*, 1 (3) 20.
- [34] Mishra B, Panigrahi D, Baghel S, **2005**. *Journal of pharmaceutical research* 4:442-449.
- [35] Silvia Kocova El Arini and Sophie dorothee Clas. **2002**, *Pharmaceutical development and technology*, 7(3), 361-371.
- [36] Khan G.M., Zhu J.B., *J.Cont. Rel.*, **1999**, 197-203.