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FORMULATION AND EVALUATION OF EXTENDED RELEASE SOLID DISPERSION OF ANTIHISTAMINICS AGENT

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ABSTRACT

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs from ointment and suppository bases, and improved solubility and stability. The present investigation was aim to formulate & evaluate extended release solid dispersion of antihistaminics agent. In the current study poor solubility of Rupatadine was increase by preparing Solid Dispersion by Fusion Method using PEG 6000 in the Ratio 1:4.Optimized Solid Dispersion tablet of Rupatadine, prepared using HPMC can successfully be employed as an oral controlled release drug delivery system. Optimized Formulation F2 with optimized solid dispersion ration (1:4) reduced the frequency of Dose and also increases its water solubility.

KEY WORDS: Solid dispersion, extended release tablet.

INTRODUCTION

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid

pharmaceutical formulations. Most of drugs weakly acidic and weakly basic with poor aqueous solubility. Hence, various techniques are used for the improvement of the solubility of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy etc.[1]

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, enhanced release of drugs from ointment and suppository bases, and improved solubility and stability.

Methods of preparation of solid dispersions[2]

Various methods used for preparation of solid dispersion system. These methods are given bellow.

1. Melting method
2. Solvent method
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomeration Process
7. The use of surfactant
8. Electrospinning
9. Super Critical Fluid (SCF) technology.

MATERIALS AND METHODS

Rupatadine was a gift sample from Getz Pharmaceuticals Ltd, Mumbai. Carbopol 934P was used as a polymer. All other chemicals and reagents used were of high analytical grade.

Identification of pure drug (Rupatadine)

Pure drug has been identified by using technique like IR.[3]

An infra-red spectrophotometer for recording the spectra in the infra-red region consists of an optical system capable of providing the monochromatic light in the region of 4000 to 400 cm^{-1} and the means of measuring the quotient of the intensity of the transmitted light and the incident light.

Compatibility study

To analyze the compatibility between Rupatadine and excipients proposed to incorporate into the formulation. Rupatadine is mixed with excipients in different ratio.[4] These mixtures were kept in a 6ml glass white colour vials and packed properly. These vials are exposed to

1) Room temperature

2) 30°C / 65% relative humidity and

3) 40˚C / 75% relative humanity.

16 gm of blend is prepared which is filled in 3 vials.

Preparation of solid dispersion by fusion method[5]

Physical mixtures were melting in water bath with gradual increasing temperature up to the value necessary for the complete melting. The molten mass was rapidly cooled with constant stirring with a glass rod. The resulting solid dispersion was stored in desiccators for 24 hrs.after then the prepared solid dispersion was grounded in motor for 2min.and passed through 0.25(#60) mesh and used for further studies as shown in Table no 1.

Table 1: Formulation of Solid Dispersion.

SD composition	Drug-Polymer ratio	Formulation Code
Rupatadine: PEG 6000	1:1	F1
	1:2	F2
	1:3	F3
	1:4	F4

Solid dispersion into sustained release Rupatadine tablet

Solid dispersion into sustained release Rupatadine tablet is prepared through wet granulation method accordingly.[3] Steps like sieving, dry mixing, preparation of binder solution, granulation and drying are involved. This preparation was passed through sieve No. 20 sieve. Solid dispersion of Rupatadine, HPMC, Ethyl cellulose and MCC were mixed thoroughly in a poly bag to ensure uniform mixing with the drug for 5 minutes. 9 mg of PVP K-30 is weighed accurately and then mixed with IPA to form a binder solution which was added slowly to the dry mix to form uniform granules. The wet granules are then dried by air drying as IPA is corrosive and gets evaporated quickly. The dried samples are removed at random at regular time intervals and then passed through sieve No. 20 and lubrication was done as shown in Table 2.

Table 2: Formulation of Sustained Release Tablets.

Ingredients (300 mg)	F1	F2	F3	F4	F5	F6
Rupatadine SD equivalent to 10mg	50	50	50	50	50	50
HPMC	80	100	120	---	---	---
EC	---	---	---	80	100	120
MCC	154	134	114	154	134	114
Magnesium Stearate	8	8	8	8	8	8
Talc	8	8	8	8	8	8

Stability Study[6]

The optimized Formulation was subjected to stability studied at 40ºC under humidity conditions (75%) for a period of four week.[4] Samples were analysed for colour changes appearance, drug content and release characteristics. From the result it was observed that there was no significant change in physiochemical properties as well as in drug release profile even after storage at 40ºC for four week. It may be inferred that there was no degradation and change in the matrix system.

RESULTS AND DISCUSSION

Rupatadine was available gift Sample and Characterization of Drug and various parameters comply with reference standard. In the Identification of Rupatidine, FT-IR shows the prominent peaks of Rupatadine shown in Figure No.1 which are 3058 cm^{-1} Aromatic C-H stretch, 1448 cm^{-1} C-C Skeletal Vibration and 745, 698 cm^{-1} Mono-substituted benzene as shown in figure 1.

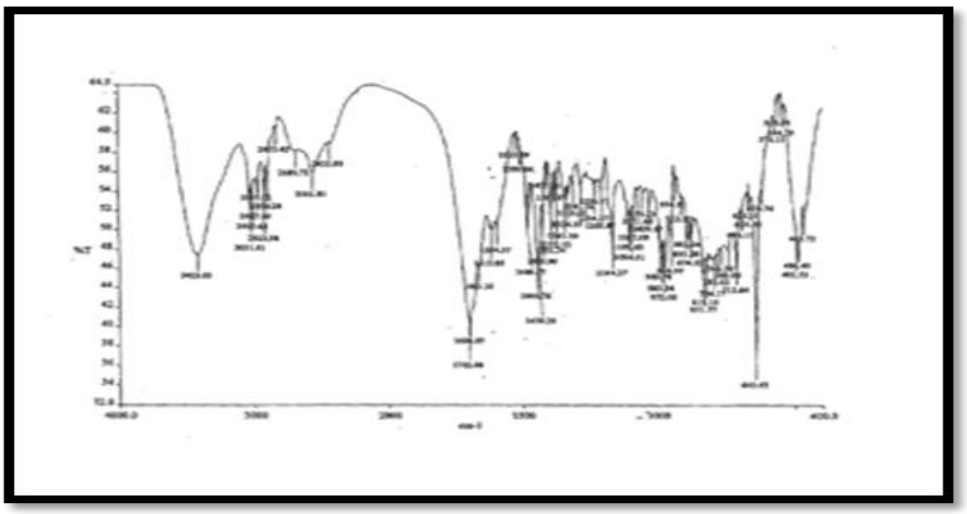

Figure 1: IR Spectra of Rupatadine Powder.

Characterization study for pure drug has been performed like Description, solubility study, Identification by FT-IR, Melting point and assay study as shown in Table No. 07.

Table 3: Characterization of pure drug.

Sr. No	Characterization	Specification	Result
1.	Description	White or creamy white crystalline powder	White crystalline powder
2.	Solubility	Soluble in DMSO, methanol, chloroform, alcohol, and slightly soluble in water.	Complies
3.	Identification by FT-IR	To match with working standard	Matches with the working standard
4.	Melting range	$105.5 – 107.5^0$ C	Complies
5.	Assay	98.0-100.5%	Complies

Preformulation testing is an investigation of physical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms. Rupatadine is mixed with excipients in different ratio. These mixtures were kept in a 6ml glass white colour vials and packed properly. These vials are exposed to Room temperature, 30°C / 65% relative humidity and 40˚C / 75%RH. 16 gm of blend is prepared which is filled in 3 vials.

Solid Dispersion was prepared by Fusion Method using PEG 6000 as a polymer in the ratio 1:1, 1:2, 1:3 and 1:4 for F1, F2, F3 and F4. *In-vitro* dissolution results for solid dispersion form shown that F4 (1:4) has 99% drug release in 60 min which is shown in Table No. 4 and Figure No. 2. Hence F4 was selected for further study.

Table 4: *In-vitro* dissolution results for solid dispersion form.

	F1	F2	F3	F4
5 min	17	20	19	**29**
10 min	28	31	30	**37**
15 min	36	37	39	**46**
20 min	44	45	46	**55**
30 min	57	59	64	**68**
45 min	63	66	71	**80**
60 min	72	79	84	**99**

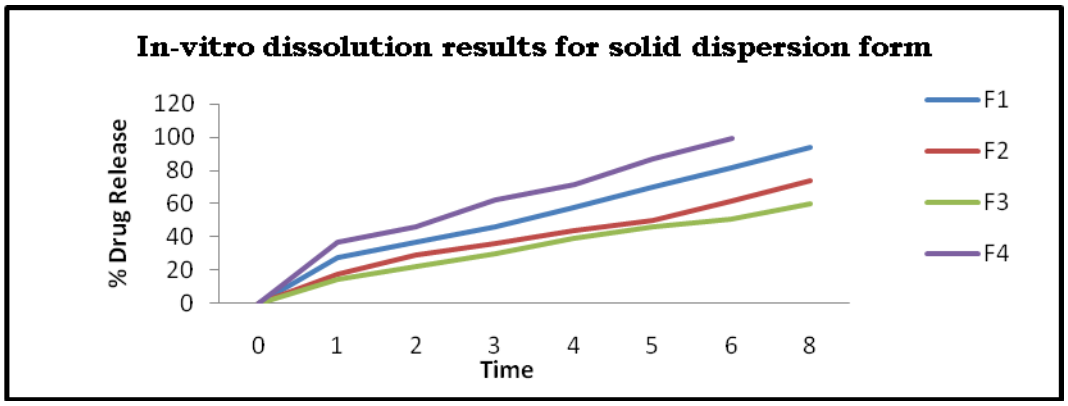

Figure 2:- In-vitro Drug Release of solid dispersion form.

Solid dispersion into sustained release Rupatadine tablet 300 mg is prepared through wet granulation method accordingly. Solid dispersion of Rupatadine, HPMC, Ethyl cellulose and MCC were mixed thoroughly in a poly bag to ensure uniform mixing with the drug for 5 minutes. 9 mg of PVP K-30 is weighed accurately and then mixed with IPA to form a binder solution which was added slowly to the dry mix to form uniform granules. The wet granules are then dried by air drying as IPA is corrosive and gets evaporated quickly. The dried samples are removed at random at regular time intervals and then passed through sieve No.20 and lubrication was done. These formulations were evaluated for the precompression and postcompression parameters as shown in table 5.

Table 5: Physical evaluation of formulated tablet batches.

Parameter	F1	F2	F3	F4	F5	F6
Thickness (mm)/± SD	4.21± 0.01	**4.16± 0.06**	4.24± 0.04	4.16± 0.04	4.26± 0.06	4.18± 0.07
Hardness (kg/cm^2)/± SD	5.22± 0.03	**5.23± 0.02**	5.35± 0.03	5.21± 0.03	5.32± 0.02	5.37± 0.02
Friability (%w/w)/± SD	0.47± 0.05	**0.24± 0.01**	0.27± 0.03	0.26± 0.05	0.36±0. 03	0.46± 0.03
Average weight variation (n=10)	300 ± 0.50	**301 ± 0.15**	299 ± 0.86	301 ± 0.15	300 ± 0.20	351 ± 0.25
Drug content (%w/v)/± SD	99.8± 0.60	**99.3± 0.57**	98.7± 0.98	99.9± 0.57	99.1± 0.65	98.0± 0.98

Drug release from Formulation F1 was found 94 at 8 hrs. Formulation F2 and F3 showed drug release slower than F1 which 96% and 78% respectively for 12 hrs. Results of drug release from Formulation F4, F5, F6 was found to be 99% for 6 hrs, 98% for 8 hrs. and 92% for 8 hrs. Respectively. Rate of percent drug release tended to decrease with increase in the content of either HPMC is shown in table 6 & figure 3.

Table 6: In-vitro drug release from blended formulation.

Time (hrs)	F1	F2	F3	F4	F5	F6
1	**28**	**18**	**15**	**37**	**29**	**24**
2	**37**	**29**	**22**	**46**	**38**	**35**
3	**46**	**36**	**30**	**62**	**49**	**43**
4	**58**	**44**	**39**	**71**	**60**	**56**
5	**70**	**50**	**46**	**87**	**72**	**67**
6	**82**	**62**	**51**	**99**	**85**	**81**
8	**94**	**74**	**60**	-	98	92
10	-	**82**	69	-	-	-
12	-	**96**	78	-	-	-

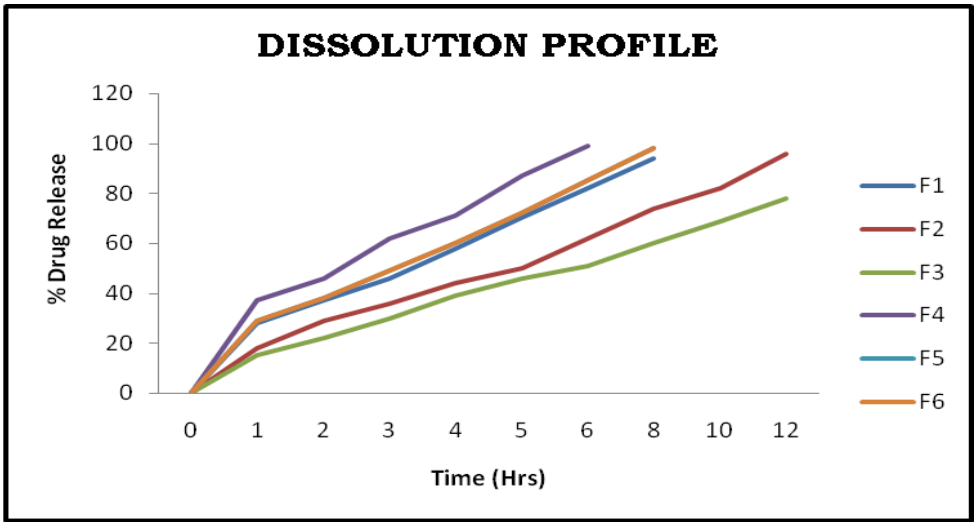

Figure 3: *In-vitro* Drug Release from Tablet.

The optimized Formulation was subjected to stability studied at 40ºC under humidity conditions (75%) for a period of four week. Samples were analysed for colour changes appearance, thickness, hardness, drug content and release characteristics. From the result it was observed that there was no significant change in physiochemical properties as well as in drug release profile even after storage at 40ºC for four week. It may be inferred that there was no degradation and change in the matrix system as shown in Table No. 19. In-vitro drug release study of formulation (F2) also done for optimized batch after stability study and found unaffected as shown in Table 7 & Figure No. 4.

Table 7: In-vitro drug release study of formulation (F2) kept for stability at 40°C / 75%RH.

Time (Hrs)	Cumulative % Drug Release				
	0 week	1 week	2 week	3 week	4 week
1	**18**	**19**	**19**	**17**	**20**
2	**29**	**28**	**30**	**27**	**31**
3	**36**	**37**	**34**	**37**	**38**
4	**44**	**45**	**48**	**44**	**46**
5	**50**	**51**	**55**	**49**	**55**
6	**62**	**61**	**64**	**61**	**64**
8	**74**	**71**	**75**	**75**	**73**
10	82	81	83	84	83
12	96	97	95	96	96

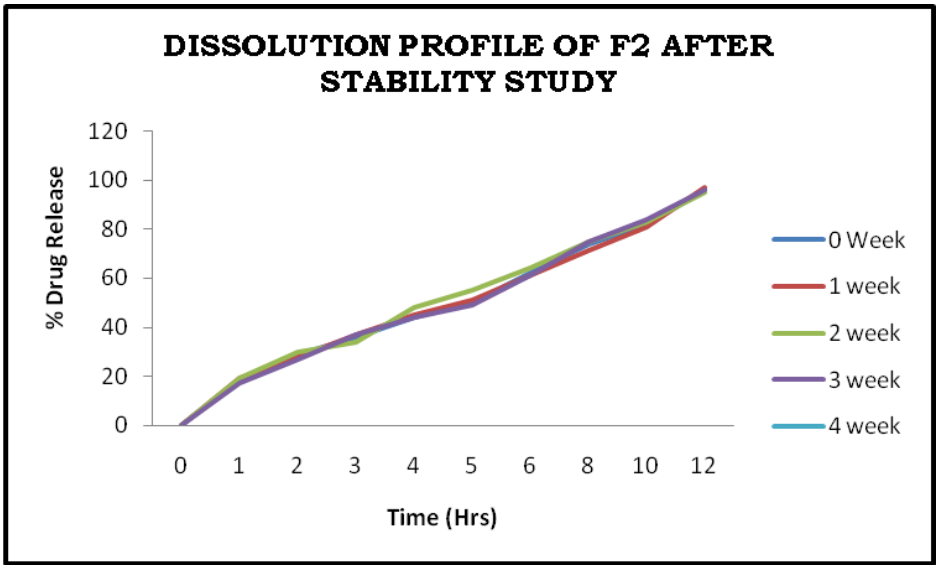

Figure 4: Comparative dissolution profile of formulation F2 before and after stability study.

CONCLUSION

In the current study poor solubility of Rupatadine was increase by preparing Solid Dispersion by Fusion Method using PEG 6000 in the Ratio 1:4.Optimized Solid Dispersion tablet of Rupatadine, prepared using HPMC can successfully be employed as an oral controlled release drug delivery system.Optimized Formulation F2 with optimized solid dispersion ration (1:4) reduced the frequency of Dose and also increases its water solubility.

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