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SOLUBILITY ENHANCEMENT OF LORATADINE BY SOLID DISPERSION TECHNIQUE AND FORMULATIONS OF FAST DISSOLVING TABLETS

BALJEET SINGH*, SEEMA SAINI, NARESH SINGH GILL

Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, S.B.S. Nagar, Punjab-144533, India.

Keywords:

Solid dispersion, Solubility enhancement, Loratadine, Guar gum

For Correspondence:

BALJEET SINGH

Department of Pharmaceutics, Rayat Institute of Pharmacy, Railmajra, S.B.S. Nagar, Punjab-144533, India

E-mail:

bsm96472@gmail.com

ABSTRACT

Loratadine is the second generation, non-sedative anti-histamine used in symptomatic relief of allergy. The main aim of the present research work was Solubility enhancement of loratadine by solid dispersion techniqueand to formulate fast dissolving tablets of Loratadine. Loratadine is a BCS Class II drug with high permeability and low solubility. As a result, solid dispersions were created to improve the drug's solubility. These were manufactured using the solvent evaporation method and two different polymers, namely Guar Gum and PEG 4000. SD4 and SD8 solid dispersions were chosen for tableting based on dissolution studies. Fast dissolving Tablets were prepared by direct compression method. In this research work, organoleptic studies, melting point determination, solubility study, absorption maxima calculation, calibration curve and FTIR studies (drug and polymers) were carried out.All the formulations F1 to F8 were subjected to in vitro release studies and formulation F8 showed maximum release 88.48% of drug in 150 sec. It can be concluded that FDTs containing Loratadine with Guar gum (F8) are superior than other tablets. As a result, the side effects associated with Loratadine's low solubility and dose can be reduced to a greater extent.

1 INTRODUCTION:

The formulation of poor aqueous soluble drugs has been a challenging aspect faced by pharmaceutical scientists and it is anticipated to amplify the solubility of such drugs, as approximately 40% or additional of the new chemical entities (NCE) existence generated through drug discovery programs are poor aqueous soluble. Also with an advent of combinatorial chemistry and high throughput screening method give rise to the no. of poor water soluble compounds.[1,2,3] This becomes point at issue for delivering these drugs by oral route, as distribution of such drugs by this route associated with minimum bioavailability and deficient of dose proportionality. This inadequate bioavailability is due to low dissolution rates offered by such drugs which are controlled by surface area that they introduce for dissolution.Consequently, improving dissolution rates is of big value which in turn leads to greater bioavailability and solubility.

Solubility is chemical property of the given substance, the solute to dissolve in particular solvent. Drug is considered to be highly soluble when highest dose of drug is soluble in ≤250 ml of water over a pH range of 1 to 7.5 and a drug is considered to be highly permeable when extent of absorption in humans is to be ≥90% of an administered dose. Extent of solubility depends upon solvent used, temperature and pressure. It can be measured at equilibrium stage, where solution becomes saturated and further increase in solute will not increase its concentration in solution. At equilibrium, there is a balance between dissolved and undissolved ions of the salt and this saturated solution is sometimes described by solubility constants.

The Biopharmaceutical classification system (BCS) is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. As for BCS class II & IV drugs, the rate-limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility, in turn, increase the bioavailability for BCS class II & IV drugs. There are various strategies to enhance solubility and dissolution rate, which are solubilisation, lyophilization, pH adjustment, salt formation, particle size reduction, complexation, solid solutions etc. Among all of these methods, solid dispersion shows potential approach to scientists right and proper to the straightforwardness of research and reproducibility of manufacturing procedure.[4,5]

FAST DISSOLVING TABLETS

Fastdissolvingtabletscameoutaswidelyaccepteddosageformsbecauseofvariousadvantages. Fastdissolvingtabletsaredesignedtodissolvefasterinsalivawithinfewseconds (less than 60 seconds) without the need for the water, resulting in the formation ofsolution or suspension which can easily slide down along the esophagus with the saliva. Toenhance the disintegration rate of dosage form in buccal cavity, super disintegrants are addedtothe formulation.[6]

The Advantages of fast dissolving tablets are conventional processing and packaging equipment'sallowthemanufacturingoftablets at low cost.[7,8]

NEED FOR SOLUBILITY ENHANCEMENT

For new chemical entities as well as generic drugs, low aqueous solubility is one of the major problems encountered. As water is solvent of choice, any drug to be absorbed at absorption site, it must be in aqueous solution. In BCS class II, drugs are highly permeable but least soluble. In this class, rate limiting steps are the release of drug from dosage form and their solubility in gastro intestinal fluid. So, it is required for class II drugs to increase their solubility to get maximum bioavailability. For orally administered drugs, solubility is most

important parameter to get desired pharmacological response.[4]

DRUG PROFILE

Loratadine: Loratadine is a piperidine histamine H1-receptor antagonist with anti-allergicproperties and without sedative effects. Loratadine blocks the H1 histamine receptor andprevents the symptoms that are caused by histamine activity on capillaries, bronchial smoothmuscle, and gastrointestinal smooth muscle, including vasodilatation, increased capillarypermeability,bronchoconstriction,and spasmodic contraction of gastrointestinal smooth muscle.[9]

2 MATERIALS AND METHODS

Loratadine was obtained as a gift sample from Theon Pharmaceuticals Ltd. PEG 4000, Guar gum, Methanol, Dextrose, Sodium hydroxide, Sodium starch glycolate, Magnesium hydroxide, MCC and Talc were obtained from S.D. Fine-Chem. Ltd. Mumbai.

3 PREFORMULATION STUDIES

Preformulation is the branch of Pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance. Prior to the development of any dosage form, it is essential that certain fundamental physical and chemical properties of drug powder are determined. It is necessary to determine purity of API before formulation of any dosage form. Such studies give directions for the development of formulation and selection of various excipients. The interaction between the drug components and the excipients used in the formulation are generally included in the study resulting in intelligent selection of excipients.[10] In this research work, organoleptic studies, melting point determination, solubility study, absorption maxima calculation, calibration curve and FTIR studies (drug and polymers) were carried out.

Calibration curve of Loratadine was made using phosphate buffer pH 6.8. The drug was analyzed spectrophotometrically (SHIMADZU UV-VIS 1700) at 274 nm.

4 PREPARATION OF SOLID DISPERSION (SD)

The SD was prepared by solvent evaporation method. Weighed amount of drug was dissolved in 20 ml of methanol. Then polymers were added in varying ratio's (D: P) 1:1, 1:2, 1:3, 1:4 respectively. Methanol was completely evaporated by drying at 50°C for 5-25 min to obtain dry mass. The resultant mass was passed through 44 mesh sieve and stored in desiccators until used for further evaluation.[11]

Table 1: Formulation batches of Loratadine solid dispersion

Formulations	Ratio	Drug+ Polymer
SDI	1:1	Loratadine + PEG 4000
SD2	1:2	
SD3	1:3	
SD4	1:4	
SD5	1:1	Loratadine + Guar gum
SD6	1:2	
SD7	1:3	
SD8	1.4	

Preparation of Fast dissolving Tablets (FDTs) containing Solid dispersion by Direct Compression method

The SD formulation which showed maximum dissolution rate was selected to formulate FDTS.TheSDequivalentto10mgofLoratadine wastaken.Thenitwasmixedwithdirectlycompressible diluents and superdisintegrants and Dextrose in the mortar pestle. Magnesiumstearateandtalewerepassedthroughsieveno.60andmixedwiththeinitialmixture inthemortarpestle followed by compression of the blend (table 2).

Table2: Composition of FDTs containing solid dispersion

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
SD with PEG 4000(1:4)	25	25	25	25	-	-	-	-
SD with Guar Gum(1:4)	-	-	-	-	25	25	25	25
Sodiumstarch glycolate	4	6	-	-	4	6	-	-
Croscarmellosesodium	-	-	4	6	-	-	4	6
Magnesiumstearate	2	2	2	2	2	2	2	2
Dextrose	50	50	50	50	50	50	50	50
Talc	2	2	2	2	2	2	2	2
Microcrystallinecellulose	117	115	117	115	117	115	117	115

5 EVALUATION OF SOLID DISPERSION

Solubility Studies of Various Solid Dispersions

Loratadine loaded solid dispersions equivalent to 10mg were weighed and transferred to four flasks containing 50 ml of distilled water. The samples were agitated at 80 rpm in thermostated shaking water bath at 37 + 0.5°C for 8 hours. The supernatant solutions were filtered through whatmann filter paper. The filtrate was diluted and absorbance was measured using UV Visiblespectrophotometer.Themaximumsolubilitywasobtainedin SD4andSD8.Thesolubilitydataofvarious solid dispersions in distilled water is givenintable3.

Table 3: Solubility Data of SD of Loratadine in Distilled Water

Formulation Code	Solubility of SD in Distilled Water (ug/ml)
SD1	250 ± 0.56
SD2	270 ± 0.42
SD3	272 ± 0.66
SD4	320 ± 0.41
SD5	252 ± 0.52
SD6	275 ± 0.35
SD7	289 ± 0.46
SD8	325 ± 0.65

Table 4: Calibration curve of Loratadine in Phosphate buffer pH 6.8

S.No.	Concentration(µg/ml)	Absorbance
1.	**0**	0
2.	**2**	0.18
3.	**4**	0.27
4.	**6**	0.35
5.	**8**	0.48
6.	**10**	0.68
7.	**12**	0.83
8.	**14**	0.94

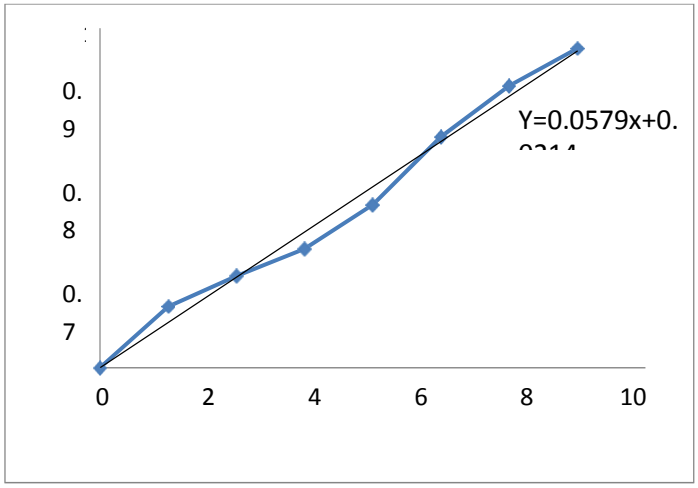


Figure 1: Standard Curve of Loratadine in Phosphate buffer pH 6.8

FOURIER TRANSFORM INFRARED RADIATION (FTIR) ANALYSIS

The FTIR analysis is the most powerful technique for qualitative identification by means of spectral comparison with that of an authentic sample and verification of the presence of functional group in an unknown molecule. The FTIR spectra of pure drug and polymer i.e. Guar Gum, PEG 4000 is shown in figure 2, 3, and 4 respective.

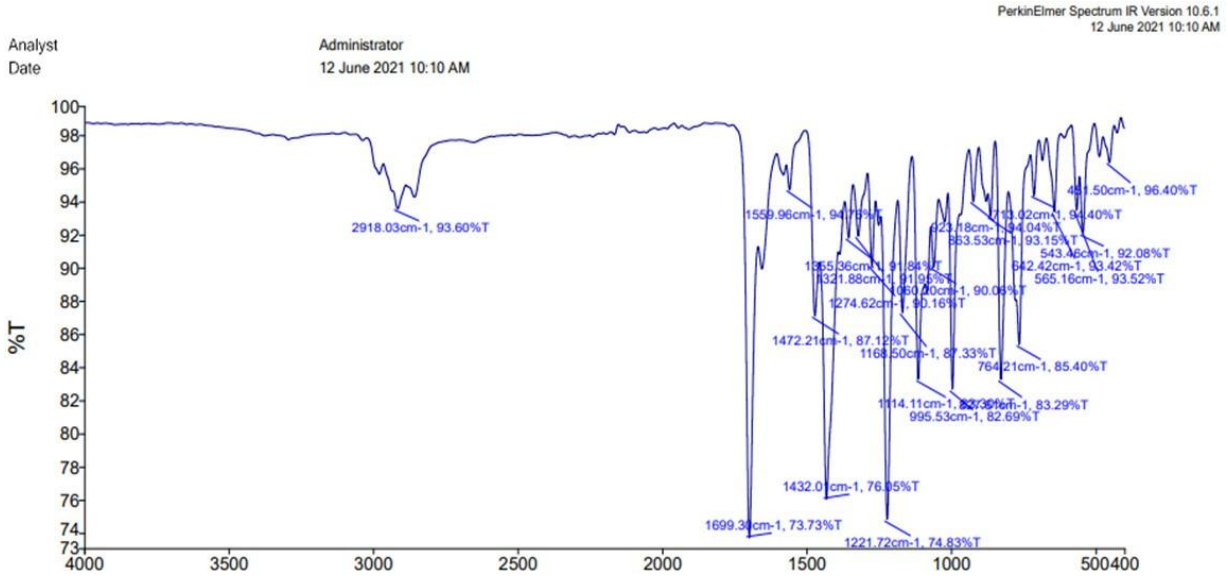


Figure 2: FTIR spectrum of Loratadine

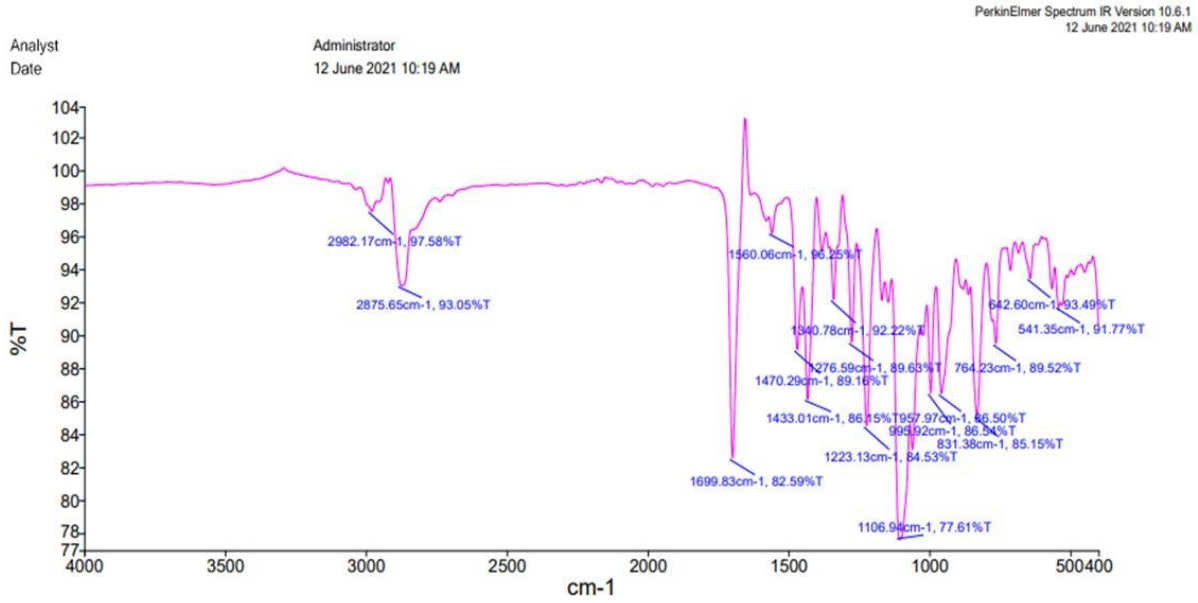


Figure 3: FT-IR of mixture Loratadine+PEG4000

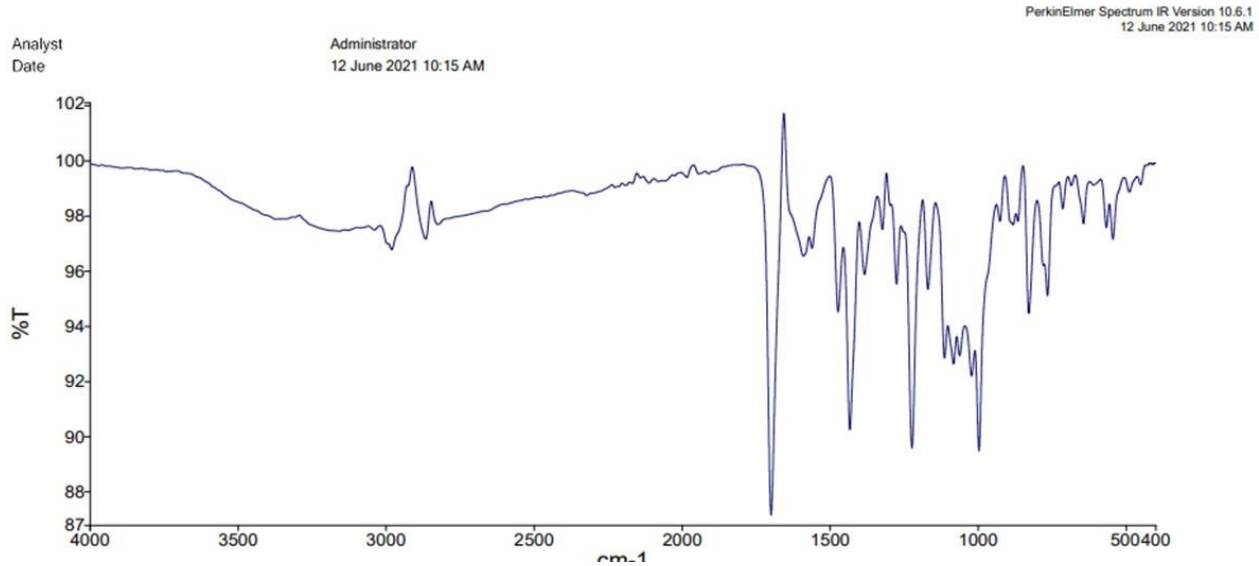


Figure4:FT-IR spectrum of Mixture Loratadine+GuarGum

Percentage yield

Percentage yield of the solid dispersions was determined after drying. The yield obtained was in the range of 66.7 - 91.2% as shown in table 5. The maximum percentage yield was obtained in SD4 (PEG4000) and SD8 (Guar Gum) with 89.57% and 91.2% drug release respectively.

Drug Content

Maximum drug content was obtained in SD4 (PEG 4000) and SD8 (Guar Gum) solid dispersionwhich is as shown in table 5. It indicates that the drug is uniformly dispersed in the powder formulation. Therefore,themethodusedinthisstudyappear stobereproducibleforthepreparationofsolid dispersion.

Table 5: Evaluation Parameters of Loratadine solid dispersion

Solid Dispersion	Percentage Yield (%)	Drug Content(%)
SDI	66.7	92.02±0.04
SD2	81.89	91.34±0.18
SD3	85.5	91.11±0.16
SD4	89.57	93.46±0.22
SD5	76.6	92.4±0.07
SD6	83	92.16±0.02
SD7	86.4	93.04±0.13
SD8	91.2	96.84±0.35

*All readings were in triplicate (n=3)

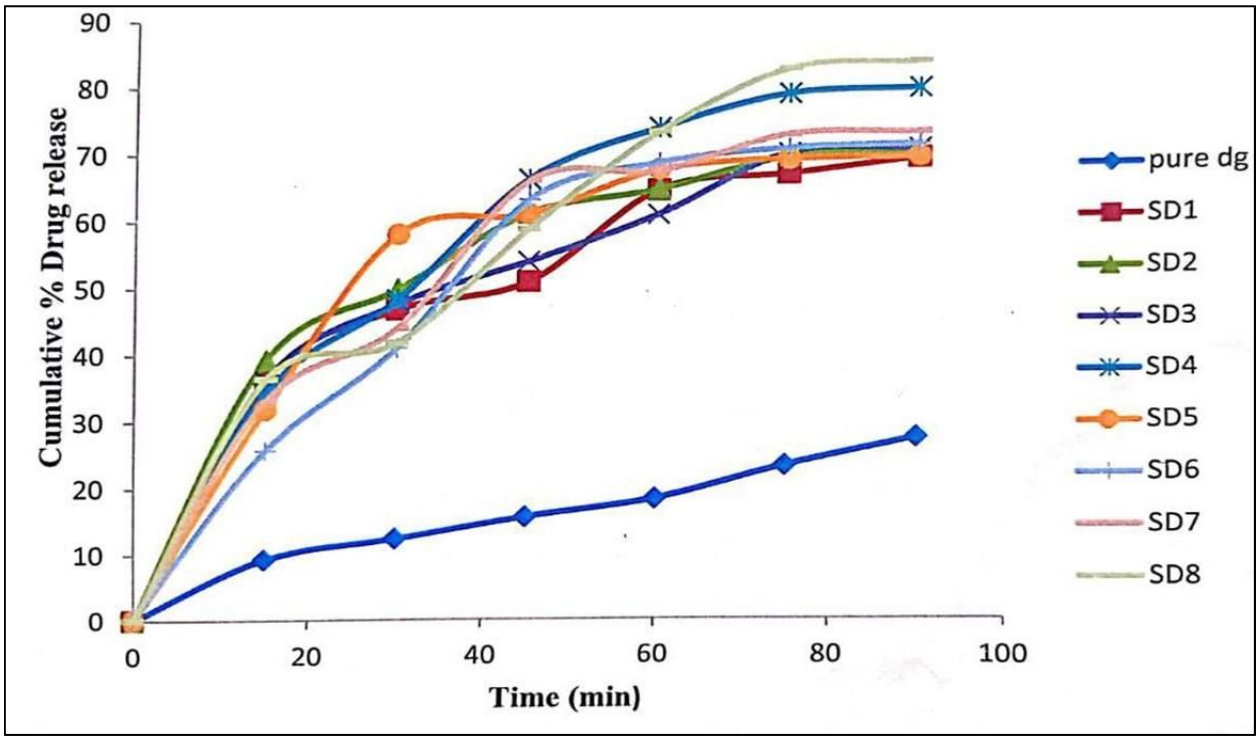
In vitro dissolution studies of Loratadine pure drug and solid dispersion

The results of dissolution studies revealed that maximum amount of drug released was obtained in SD4 (PEG 4000) and SD8 (Guar Gum) solid dispersion with 75.32% and 83.34% respectively in 90 min, where as the pure drug released maximum 27.34% of drug in 90 min. The cumulative % drug released at a is shown in table 6 and graph is shown in figure 5.

Table 6: In vitro Drug Release Data of various Solid dispersions and pure drug

Time (min)	Pure drug	Cumulative % drug release							
		SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8
0	0	0	0	0	0	0	0	0	0
15	9.23	36.56 ± 0.16	39.49 ± 0.33	36.25. ± 0.62	34.52 ± 0.24	31.96 ± 0.20	25.71 ±0.08	33.26 ± 0.56	36.54 ± 0.07
30	12.32	47.11 ± 0.23	50.22 ± 0.15	47.96 ± 0.46	48.68 ± 0.13	58.53 ± 0.31	41.35 ± 0.12	44.32 ± 0.24	42.13 ± 0.34
45	15.56	51.37 ± 0.34	61.72 ± 0.22	54.43 ± 0.11	66.87 ± 0.27	61.59 ± 0.44	63.76 ± 0.37	66.65 ± 0.28	59.33 ± 0.23
60	18.20	65.28 ± 0.21	65.35 ±0.14	61.54 ± 0.25	74.61 ± 0.55	68.34 ± 0.24	69.37 ± 0.53	68.14 ± 0.19	74.03 ± 0.16
75	23.17	67.56 ± 0.03	70.17 ± 0.19	70.69 ± 0.42	74.66 ± 0.16	69.76 ± 0.13	71.42 ± 0.28	73.54 ± 0.03	80.45 ± 0.04
90	27.34	69.78 ± 0.43	70.89 ± 0.73	71.16 ±0.32	75.32 ± 0.31	69.89 ± 0.06	71.87 ± 0.05	73.67 ± 0.08	83.34 ± 0.01

*All readings were in triplicate (n=3)



6 Evaluation of FDTs

Initially all the formulations blends were evaluated for various pre-compression parameters to access the flow properties. The observations are tabulated.

Table 7: Data of pre-compression parameters

Formulation code	Angle of repose (θ) ±SD	Bulk density (g/cc) ± SD	Tapped density (g/cc) ± SD	Carr's Index (%± SD	Hausner's ratio ± SD
F1	24.3±0.11	0.391± 0.27	0.413±0.23	14.01±0.75	1.03±0.12
F2	28.65±0.07	0.402±0.12	0.433±0.17	15.60±0.42	1.02±0.65
F3	20.6±0.05	0.382±0.35	0.406±0.04	13.51±0.33	1.04±0.27
F4	22.73±0.01	0.418±0.24	0.523±0.41	12.73±0.22	1.04±0.06
F5	27.10±0.24	0.368±0.22	0.478±0.35	15.16±0.01	1.02±0.15
F6	26.49±0.11	0.434 ±0.05	0.502±0.26	13.23±0.17	1.031±0.17
F7	24.12±0.46	0.397± 0.26	0.452±0.02	14.35±0.08	1.076±0.43
F8	24.67±0.54	0.471± 0.06	0.568±0.04	12.28±0.04	1.06±0.04

*All readings were in triplicate (n=3)

Table 8: Observations of different post-compression parameters of FDTs

Formulation code	Weight variation test (mg) ± SD	Thickness (mm) ± SD	Hardness (kg/cm²) ± SD	Friability (%) ± SD
F1	148.96±0.01	3.18±0.12	4.54±0.13	0.393±0.08
F2	149.61±0.04	3.88±0.13	5.04±0.12	0.433±0.14
F3	151.03±0.03	4.09±0.11	4.16±0.13	0.922+0.05
F4	150.32± 0.04	3.92±0.12	4.38±0.14	0.521±0.12
F5	148.36±0.01	3.85±0.12	4.70±0.11	0.507±0.04
F6	149.94±0.13	3.91±0.14	4.76±0.14	0.425±0.09
F7	149.59±0.01	4.19±0.25	5.74±0.03	0.758±0.12
F8	150.07±0.03	3.93±0.03	4.52±0.04	0.514± 0.02

*All readings were in triplicate (n=3) and SD =Standard Deviation

Table 9: Observations of evaluation parameters of FDTs

Formulation code	Wetting time (sec) ± SD	Water absorption ratio(%) ± SD	In vitro dispersion time(sec) ± SD	Disintegration time (sec) ± SD	% drug content ±SD
F1	34±0.06	87.48±0.12	25±0.15	32±0.15	96.02± 0.11
F2	22±0.09	89.47±0.14	23±0.11	31±0.09	97.33±0.46
F3	36±0.12	88.05±0.06	26±0.05	33±0.16	96.36±0.32
F4	19±0.04	98.36±0.16	21±0.12	27±0.02	97.72±0.02
F5	26±0.07	94.65±0.19	24±0.02	30±0.12	96.05±0.12
F6	29±0.11	96.93±0.13	23±0.16	25±0.07	96.16±0.18
F7	26±0.14	95.22± 0.12	22±0.05	31±0.19	96.42±0.02
F8	18±0.05	98.10±0.01	20±0.03	24±0.03	97.81±0.01

*All readings were in triplicate (n=3) and SD =Standard Deviation

In vitro Dissolution study of FDTs

The formulation F4 (PEG 4000) SD released 79.21% of the drug whereas the formulation F8 (Guar Gum) SD released 88.48 % of drug in 150 sec. On the basis of drug release, formulation F8 containing croscarmellose sodium as superdisintegrant released drug at a faster rate. Therefore, formulation F8 was selected as the best formulation. In vitro drug release study data is shown in table 10 and a graph between cumulative % drug release versus time is shown in figure 6.

Table 10: Data of Cumulative % Drug release in phosphate buffer pH 6.8

Time (sec)	Cumulative % Drug Release							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
15	5.85±0.12	7.93±0.11	6.92±0.04	12.57±0.10	9.59±0.34	10.12±0.03	11.25±0.02	12.78±0.05
30	13.8±0.16	19.38±0.50	14.88±0.09	23.84±0.15	16.34±0.23	23.28±0.28	24.63±0.03	26.64±0.04
45	23.98±0.09	27.88±0.32	29.03±0.12	36.94±0.17	29.16±0.11	37.67±0.19	38.70±0.35	39.18±0.18
60	36.6±0.44	43.42±0.15	48.12±0.16	48.61±0.14	46.21±0.25	49.84±0.15	55.32±0.02	56.04±0.03
75	45.12±0.03	46.88±0.12	59.15±0.05	59.36±0.34	55.12±0.02	56.21±0.37	69.83±0.26	70.24±0.32
90	51.26±0.13	53.68±0.43	68.25±0.36	69.84±0.09	62.54±0.05	63.18±0.56	75.36±0.06	78.29±0.02
105	65.61±0.38	69.87±0.58	69.92±0.03	77.20±0.05	67.28±0.27	69.24±0.17	76.24±0.05	84.02±0.37
120	70.19±0.25	75.05±0.23	77.10±0.13	79.08±0.09	72.12±0.03	76.16±0.27	79.04±0.04	88.12±0.57
135	70.34±0.16	75.17±0.21	78.61±0.38	79.13±0.44	74.62±0.37	76.28±0.04	79.14±0.26	88.24±0.65
150	70.79±0.35	75.37±0.05	78.92±0.06	79.21±0.13	74.93±0.03	76.89±0.01	79.18±0.36	88.48±0.01

*All readings were in triplicate (n=3)

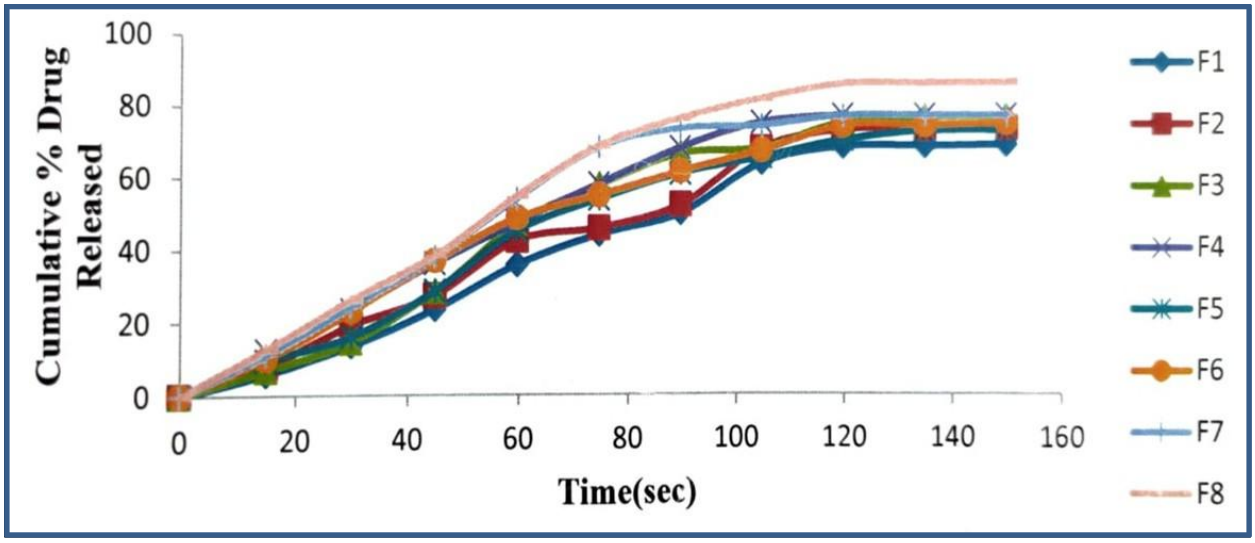


FIGURE 6: Graph showing Cumulative % Drug Release from FDTs

Stability study of Formulation(F8)

The stability study of formulation (F8) was carried out at 40°C / 75% RH for two months. The tablets were wrapped in the aluminium foil and stored in a stability chamber at accelerated conditions. The drug content was checked at regular time intervals of 15, 30, 45 and 60 days respectively and was evaluated for physical appearance. The results of drug content are shown in table 11 and the graph between drug content and time intervals is shown in figure7.

Table11: Drug Content data during Stability Study:

Time(days)	Accelerated Conditions(40±2°C/75±5%RH)	
	Physical Appearance	**Drug Content**
0	+	97.81±0.06
15	+	96.43±0.11
30	+	96.24±0.07
45	+	95.52±0.03
60	+	95.03±0.16.

(+)indicates no change in physical appearance

There was no significant change in physical appearance, Drug content at the end of two months.

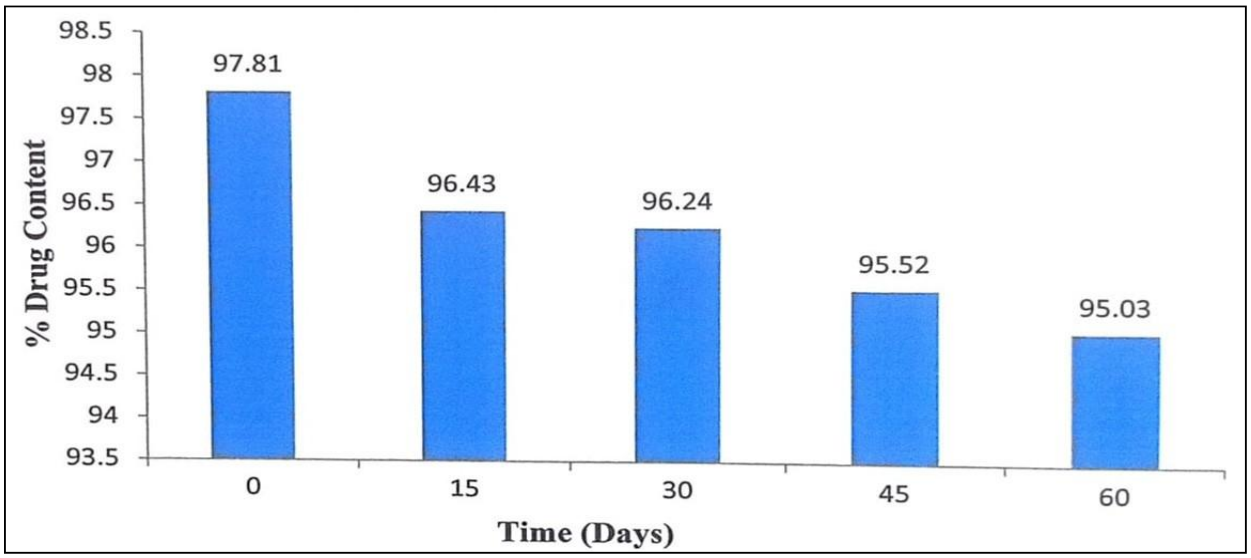


Figure 7: Stability Study of Formulation (F8) at regular time intervals

7 RESULT &CONCLUSION

In the present research work, an attempt was made to enhance the solubility of Loratadine by Solid Dispersion Technique and to formulate fast dissolving tablets of Loratadine. Solid dispersions were prepared to improve the solubility of the drug. They were prepared by solvent evaporation method using two different polymers i.e. Guar Gum and PEG 4000.The SD4 and SD8 has better solubility than other SD tablets. On the basis of dissolution studies SD4 and SD8 solid dispersions were selected for tableting. Eight formulations of fast dissolving tablets were prepared. All the formulations F1 to F8 were subjected to in vitro release studies and formulation F8 showed maximum release 88.48% of drug in 150 sec. It can be concluded that the FDTs containing Loratadine with Guar gum (F8) is better than tablet for getting better therapy. Hence, side effects associated with the low solubility and the dose of Loratadine can be minimized to a greater extent.

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