International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.7, pp 207-217, 2017

Solubility Enhancement of Loratadine by Solid Dispersion Techniques

Kundawala AJ*[1], Patel PH[2]

[1]IndukakaIpcowala College of Pharmacy, New VallabhVidyanagar, 388121, Anand, Gujarat, India.
[2]A.R. College of Pharmacy & G.H. Patel Institute of Pharmacy, Vallabh Vidyanagar-388120, Anand, Gujrat, India.

Abstract : The present work was undertaken to enhance the solubility of a poorly soluble drug, Loratadine (LRD), using solid dispersion approach. Loratadine, a Class II drug, is a second generation antihistaminic agent, which is used in treatment of allergic conditions like allergic rhinitis and urticaria. Phase solubility study was performed using various concentration of β-Cyclodextrin, Poloxamer 407, PVP K30 and PEG 6000. Solid dispersions were prepared with above carriers in various ratios by kneading method, solvent evaporation method and fusion method. Characterization of the solid dispersion systems were performed, Fourier Transform Infrared (FTIR) spectroscopy and differential scanning calorimetry (DSC), powder X-ray diffractometry (XRD) and Scanning Electron Microscopy (SEM). And solid dispersions were evaluated for drug content, saturation and pH solubility study. The phase solubility studies data indicated that highest solubility was obtained with 10 %w/v of β-CD solution. All the solid dispersions showed superior dissolution as compared to pure Loratadine. However, solid dispersion with β-CD product exhibited highest, the 430 fold, solubility compared to other carriers employed. Solid dispersion of Loratadine showed increased solubility that will further assist in oral dosage forms especially with faster dissolution properties.
Key words : Loratadine, β-Cyclodextrin, solid dispersion, solubility studies.

Introduction

Oral bioavailability of drugs is affected by a variety of factors which influence their absorption from the gastrointestinal tract. Drug dissolution is a critical determinant factor for absorption which is influenced by the solubility of the drug in the gastrointestinal fluids. The limited dissolution rate arising from low solubility frequently results in the low bioavailability of orally administered drugs[1,2].The bioavailability of BCS class II drugs is likely to be dissolution rate limited. But due to their high permeability, the BCS class II drugs have been on focus for solubility enhancement researches in the recent times and several formulation approaches for this class of compounds has been developed[3]. So, formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

Many drugs suffer inadequate therapeutical efficiency due to the absorption limitation. Many approaches like prodrug, size reduction, complexation, micros emulsion, micronization, micelle formation, nano technologies and solid dispersion etc has been adopted for enhancement of silubility. Solid dispersion being economical and simple, considered as one of the successful strategies to overcome solubility of poorly soluble

drugs. It is a method that alter the solid state at the particleor molecular level and involves a physical change in the drug[4,5]. The solid dispersion method is one effective approach to achieve ideal therapy for drugs with low aqueous solubility by incorporating them into a water soluble polymer matrix. The solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic, and advantageous[6]. Mohan *et al*. developed SD of oxcarbazepine using PEG 6000 as hydrophilic carrier with melting technique, not only improved the drug dissolution characteristic but also inhibited crystallization during storage[7].Gorajana *et al.* developed and characterized cefuroxime axetil SD using hydrophilic carriers PEG 4000. SD formulations were found to have a higher dissolution rate comparatively to pure cefuroxime axetil. The enhancement of dissolution rate of SD by PEG 4000 may be caused by increased wettability, solubility, and reduction in particle size[8].Cyclodextrins are large molecules with a number of hydrogen donors and acceptors and they do not penetrate lipophilic membranes. In pharmaceutical field, cyclodextrins are versatile, crystalline complexing agents that have ability to increase the solubility, bioavailability and stability of API, mask the color and taste of the drugs and also can prevent gastrointestinal and ocular irritation[9].Kolasinac N et al prepared desloratadine tablet using solid dispersion with poloxamer and concluded that higher poloxamer ratio in SDs and higher compression force results in a significant decrease of the drug dissolution rate, which can be attributed to the lower porosity of the tablets and more pronounced bonding between poloxamer particles[10].

Loratadine is a second-generation tricyclic H_1 antihistamine, marketed for its non-sedating properties. H_1 antihistamines prevent and suppress the responses to histamine or allergen in the nose and conjunctivae, thereby eliminating such symptoms as itching, congestion, tearing and sneezing[11,12]. Loratadine is a BCS class II drug with dissolution- or solubility-limited absorption which represents a rate-limiting step in its absorption. Thus loratadine faces reduced and variable bioavailability. Due to limited oral bioavailability the drug may suffer a reduced therapeutic efficacy.

The aim of the present study was to improve the solubility of Loratadine by employing various solid dispersion techniques and evaluate the effect of the different polymers on the physicochemical properties of Loratadine in the binary mixtures. Solid dispersions are prepared using four different carriers (β-Cyclodextrin, PVP-K30, PEG 6000 and Poloxamer407) by kneading method, solvent evaporation method and fusion method for different drug to polymer ratio.

Material and method

Materials:

Loratadine (LRD) was kindly provided by Cadila Pharmaceuticals Ltd. India. β-Cyclodextrin (β-CD) was provided by Mercury Lab. Pvt. Ltd., Baroda, India. Poloxamer 407 was purchased from Sigma Eldrich Ltd. PVP K30 and PEG 6000 were purchased from SD Fine Chemicals, Mumbai. All other reagents used are of analytical grade.

Phase solubility study (Higuchi Connors method)

Phase solubility studies were performed according to the method described by Higuchi and Connors.[13] An excess amount of LRD was placed into 25 ml volumetric flasks containing concentrations of polymer (2%, 4%, 6%, 8% and 10% of each of β- CD, Poloxamer 407, PVP K-30 and PEG 6000) and volume made up by distilled water. The suspensions were kept on orbital shaking incubator at 100 rpm for 48 hr at 37 ± 0.5°C. Supernatant was withdrawn and filtered through whatman filter paper. The filtrate was analyzed by UV spectrophotometer at the wavelength of 274 nm after suitable dilutions with 0.1 N HCl. All Solubility studies were performed in triplicate (n=3).[14]Plot of solubility vs concentration of polymer was prepared and slope was studied. Increase in the solubility by each polymer was recorded and compared.

The value of the apparent stability constant, *Ks*, for drug–carrier combinations was computed from the phase-solubility profiles, as described by,

$$K_s = \frac{\text{Slope}}{\text{Intercept}(1 - \text{slope})}$$

The Gibbs free energy of transfer (ΔG°tr) values provides the information about whether the reaction condition is favorable for drug solubilization in the aqueous carrier solution. Negative gibbs free energy values indicate favorable conditions. The Gibbs free energy of transfer (ΔG°_{tr}) of LRD from pure buffer solution to the aqueous solution of carrier was calculated as follows.

$$\Delta G^{o}_{tr} = -2.303\mathbf{RT}\left(\frac{\log S_0}{S_s}\right)$$

Where S_o / S_s is the ratio of the molar solubility of LRD in aqueous solutions of carrier to that of the same medium without carrier. R is gas constant, its value is 8.31 JK^{-1} and T is temperature in Kelvin[15].

Method of preparation of solid dispersion:

Solid dispersions of Loratadine were prepared by kneading, solvent evaporation and fusion method with four hydrophilic polymers showed in Table 1.

Table 1: Method of preparation of LRD solid dispersions

Methods	Polymers	Ratios
Kneading	β-CD	1:1, 1:2, 1:3
	PVP-K30	1:1, 1:3, 1:5
Fusion	Poloxamer 407	1:1, 1:3, 1:5
	PEG 6000	1:1, 1:3, 1:5
Solvent evaporation	β-CD	1:1, 1:2, 1:3
	PVP-K30	1:1, 1:3, 1:5
	Poloxamer 407	1:1, 1:3, 1:5
	PEG 6000	1:1, 1:3, 1:5

Kneading method

Drug and polymer were accurately weight and place in glass mortar. Polymer was wetted in a glass mortar with ethanol- water 50% (v/v) solution until a paste was obtained (about 30% of the total weight of polymer and LRD). The required amount of LRD was then slowly added and the slurry was kneaded for about 45 min. Further, the product was dried under vacuum for 24 hrs and stored in a desiccator over fused calcium chloride[16,17].

Fusion method

Drug was added to molten carrier at 60°C, with continuous stirring for 15 min until a homogenous dispersion was formed. The dispersion was allowed to solidify at room temperature and then pulverized and sieved. The resulting solid dispersion was stored in a desiccator until use[18].

Solvent evaporation

Accurately weighed quantities of polymers were added to the solutions of LRD in absolute ethanol. The solutions were stirred and the solvents were allowed to evaporate at room temperature. The obtained solid dispersions powder was dried in a tray dryer at 65ºC for 10 min, and then screened through sieve no.18. The solid dispersions powder was stored in a closed container away from light and humidity until use.[19, 20].

Evaluation of Loratadine solid dispersion

Estimation of drug content

Solid dispersions containing 10 mg equivalent of LRD was taken and dissolved in 100 ml volumetric flask and the volume was made up to the mark with 0.1 N HCl. Then solution was filtrated through whatman filter paper and drug content was determined by taking absorption at the wavelength of 274 nm. The analysis performed in triplicate. Actual drug content was calculated for all batches using the equation:

$$\textbf{Drug content } \% = \frac{amount\ of\ drug}{theoritically\ amount\ of\ drug} * 100$$

Saturation solubility study

An excess amount of solid dispersion was dispersed in glass bottles containing 10 ml of distilled water subjected to shaking on orbital shaker for 24 hours at 37°C± 0.5^0C. After 24 hours the dispersion was centrifuged at 3000 rpm for 15 min. The resulting solution was then filtered through a whatman filter paper. Suitable aliquots of filtrate wereprepared by appropriate dilution and drug content was determined by taking absorbance at 274 nm in UV spectrophotometer. Solubility of solid dispersion was compared with pure drug solubility. All procedure was performed in triplicate.

pH–solubility study in phosphate buffer pH 6.8

In the present study, the effect of pH on the solubility of solid dispersion was evaluated. The solid dispersion was suspended in phosphate buffer solution, pH 6.8. The suspensions was shaken for 48 hrs using the orbital shaker at 25±0.5℃. The pH of the suspension was noted. Suitable aliquots of filtrate were prepared by appropriate dilutionand drug content wasdetermined by taking absorbance at 274 nm in UV spectrophotometer. Solubility of solid dispersion was compared with pure drug solubility. All procedure was performed in triplicate.

Solid state characterization of Loratadine solid dispersion:

Fourier Transform Infrared Spectroscopic Study

FTIR study was carried out by KBr disc method in which the drug sample was mixed with KBr and pellets were made applying pressure by the hydraulic press, which were then analyzed in FTIR (Spectrum GX, Perkin Elmer). All the spectra were scanned between 400 to 4000 cm^{-1} at a resolution of 4 cm^{-1}.

Differential scanning calorimetric analysis

The thermal behavior of LRD and solid dispersions were determined using differential scanning calorimeter (Pyris-1 DSC, Perkin Elmer). DSC runs were conducted over heating range of 50 to 300^0Cat heating rate of 10^0C /min under nitrogen atmosphere.

X-ray diffraction studies

X-ray diffraction was performed with computer-controlled Xpert MPD (Philips, Holland) diffractometer with an X-ray Source of Cu target X-Ray tube with 2º θ. The study was carried out at room temperature. The diffractograms were analyzed using the JCPDF database for the powder diffractometry program.

Scanning electron microscopic analysis

The surface morphology of the layered sample was examined by using JEOL (JSM-6380LV) SEM. The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs. These sample stubs were coated with a thin layer of platinum. The samples were examined by SEM and photographed under various magnifications with direct data capture of the images onto a computer.

Results and discussion:

Phase solubility study

The phase solubility diagrams at 37℃ were obtained by plotting the apparent equilibrium solubility of the LRD against polymer concentrations. Data for solubility of LRD in different concentrations of all carriers is presented in Table 2. It can be observed that the apparent solubility of LRD increased linearly as a function of polymers concentration over the entire concentration range studied. This pattern of increasing solubility by

increasing the amount of carrier was quite similar for all the four carriers studied. Linearity was characteristic of A_L-type system (Higuchi and Connors, 1965) and suggested that water soluble complex was formed in solution.

Table 2: Phase solubility study of LRD in different carriers (n=3)

Concentration of carrier (%w/v)	B-CD (mg/mL)	Poloxamer 407 (mg/mL)	PVP K-30 (mg/mL)	PEG 6000 (mg/mL)
2	0.958 ±0.099	0.3504 ± 0.073	0.125 ±0.122	0.0099 ± 0.043
4	3.160 ±0.037	0.5708 ± 0.062	0.175 ± 0.079	0.0095 ± 0.067
6	4.130 ±0.052	0.7416 ± 0.09	0.268 ± 0.087	0.0135 ± 0.085
8	4.781 ±0.086	0.8916 ± 0.083	0.369 ± 0.065	0.0199 ± 0.045
10	6.123 ±0.064	1.2504 ± 0.077	0.405 ± 0.060	0.0179 ± 0.026
Derived parameters of phase solubility study				
Type of curve	A_L	A_L	A_L	A_L
K_S (mg/mL)	6.03	0.96	0.94	0.21
r^2	0.9553	0.9743	0.9791	0.799

Maximum augmentation of solubility was observed with β-CD. In particular, the formation of intermolecular hydrogen bonds between the carbonyl group present in LRD and carboxyl group of dimer cyclic structure which could explain the mechanism of increased solubility of LRD.

The stability constant (K value) for β-CD, Poloxamer 407, PVP K-30 and PEG 6000 was found to be 6.03, 0.96, 0.94, 0.21 mg/ml respectively. These result showed that K value of β-CD was maximum while PEG 6000 has least capacity to form stable complex with drug.

The phase solubility diagram for different carrier system is shown in Figure 1. β-CD (10%), Poloxamer (10%), PVP K-30 (10%) and PEG 6000 (8%) increase the solubility of Loratadine 1550, 312, 101, 44 fold respectively. The enhancement in solubility might be due to hydrophilic nature of polymer or reduction in interfacial tension between hydrophobic drug and hydrophilic vehicle.

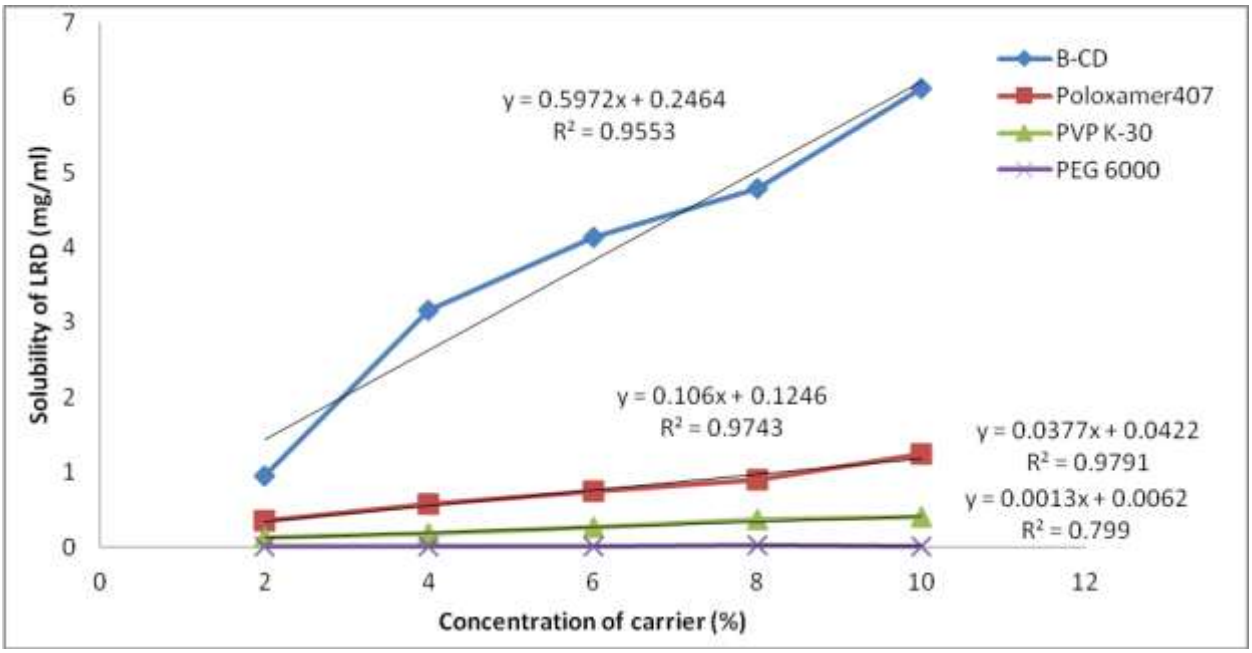

Figure 1: Phase solubility study of LRD in different carriers

Gibbs free energy

The thermodynamic parameters associated with the aqueous solubility of LRD in presence of polymers are shown in Table 3.Among the different carrier for solubility enhancement studied, β-CD was found to have greater potential to solubilize LRD. This difference in the potential of carriers is attributed to difference in surface activity of the individual carriers and ultimately altering the wettability to drug.

Table 3: Gibbs free energy of LRD-carrier systems

Gibb's free energy ($J\ K^{-1}Mol^{-1}$) at 37°C				
Concentration of Carrier (%w/v)	**β-CD**	**Poloxamer 407**	**PVP K-30**	**PEG 6000**
2	-13281.2	-10791.1	-2946.67	-2345.83
4	-17336.8	-11955.6	-6579.66	-2239.57
6	-17891.5	-12673.4	-7631.06	-3144.97
8	-18358.2	-13563.8	-8619.39	-4144.75
10	-18959	-14482.8	-9226.06	-3871.84

Evaluation of LRD solid dispersion

Drug content in each of the solid dispersionprepared wasfound to be in the range of 97.13-100.4%.

Saturation solubility study

The pure LRD possesses a very low solubility in water (0.004mg/ml). In contrast, solubility of solid dispersion increased significantly with drug: polymer ratio demonstrating that the incorporation of hydrophilic polymers like β-Cyclodextrin, PVP K-30, Poloxamer 407 and PEG 6000 was effectively enhances the LRD solubility. As the concentration of polymer increased, the saturation solubility of drug was gradually increased. All solubility data are given in Table 4.

Table 4: Saturation solubility of LRD solid dispersions (n=3)

Polymer	**β-CD (µg/ml)**		**PVP K-30 (µg/ml)**		**Poloxamer 407 (µg/ml)**		**PEG 6000 (µg/ml)**	
Ratio	**KND**	**SE**	**SE**	**KND**	**FM**	**SE**	**FM**	**SE**
1:1	616± 12	574±12	268± 12	282± 07	441± 08	324± 18	95.2± 4	85.6± 6
1:2	1150±09	742±13	355± 19	310± 16	366± 11	271± 13	116.8± 9	121.4± 13
1:3	1720±22	1391± 21	--	--	--	--	--	--
1:5	--	--	542± 18	622± 20	258± 13	188.6± 06	244.8± 18	214.8± 17

KND= Kneading method, SE= Solvent evaporation, FM= Fusion method

Table 5: pH solubility profile of LRD solid dispersions

Polymer	**B-Cyclodextrin**		**PVP K-30**		**Poloxamer 407**		**PEG 6000**	
Ratio	KND	SE	SE	KND	FSN	SE	FSN	SE
1:1	478	379	129	156	256	275	52	65
1:2	932	490	274	260	147	141	60	71
1:3	1493	659	--	--	--	--	--	--
1:5	--	--	431	482	105	123	127	132

KND= Kneading method, SE= Solvent evaporation, FM= Fusion method

Solubility study of SDs in phosphate buffer, pH 6.8

LRD has very low solubility in alkaline medium and moderate in acidic medium, so pH solubility profile of solid dispersion was evaluate to determine LRD solubility in alkaline medium. LRD is practically insoluble at alkaline pH but results of pH solubility study shows increased solubility of solid dispersion in pH

6.8. So, from the results of solubility studies it was found that solid dispersion was effectively enhances the LRD solubility at alkaline pH.

Characterization of Loratadine solid dispersion

Fourier Transform Infrared Spectroscopic study

FTIR spectra of LOR shows following characteristic peaks at 1703 cm^{-1} (C=O stretching), 1580 and 1560 cm^{-1} (C=C stretching), (C=N stretching), 1227 cm^{-1} (C–O stretching), 1117 cm^{-1} (C–Cl stretching). FT–IR spectra of LRD: β-CD showed additional absorption bands at 3424 cm–1 (for O–H stretching vibrations), 2930 cm–1 (for C–H stretching vibrations) and 1159 cm–1, 1086 cm–1 (C–H, C–O stretching vibration). The difference spectra of the solid dispersion were practically identical to the spectrum of pure LOR, indicating complex formation between LOR and β-CD.

FTIR spectra of Poloxamer 407 solid dispersion showed all the characteristic peaks of LRD and carrier. It was observed that LRD was molecularly dispersed with the carriers and there was no additional incompatible reactions found between them. FTIR spectra of LRD and solid dispersions with β-CD, Poloxamer 407were shown in Figure 2, 3 and 4, respectively.

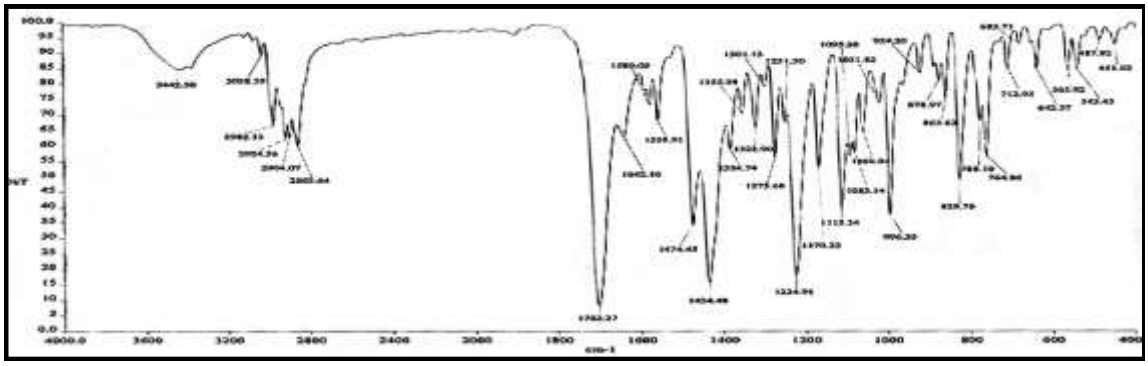

Figure 2: FTIR Spectrum of Loratadine pure drug LRD

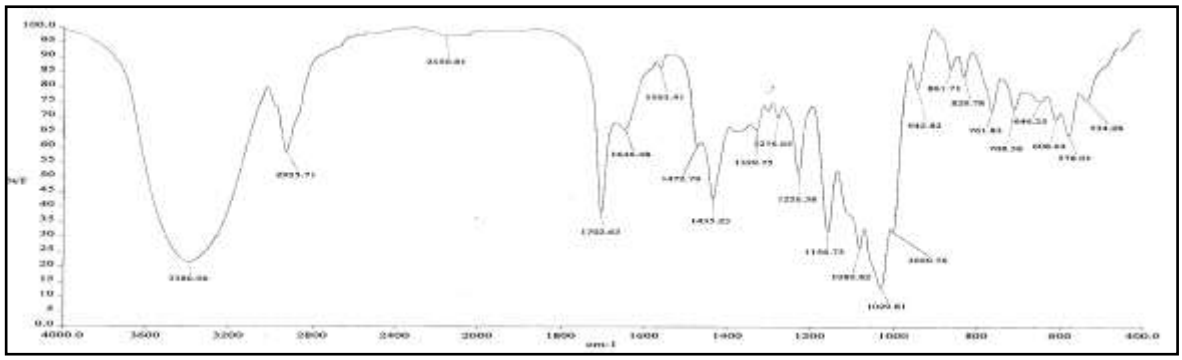

Figure 3: FTIR spectra of LRD: β-CD complex

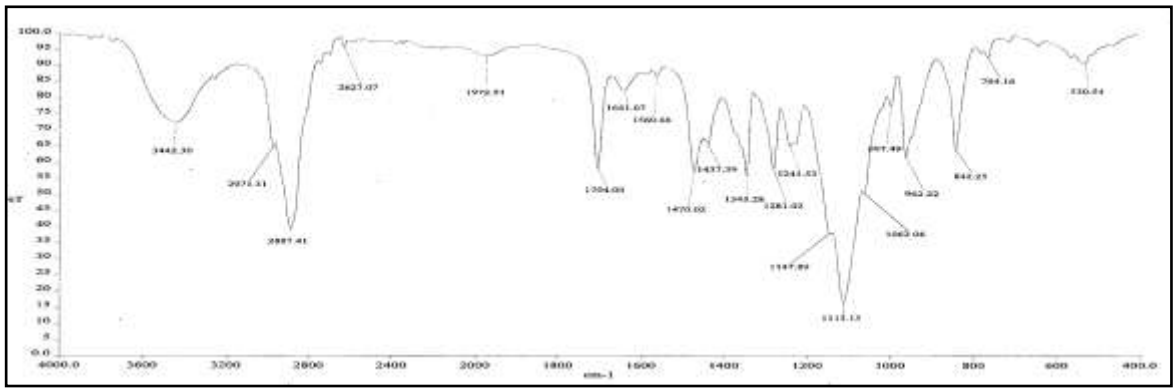

Figure 4: FTIR spectra of LRD: Poloxamer 407 dispersion

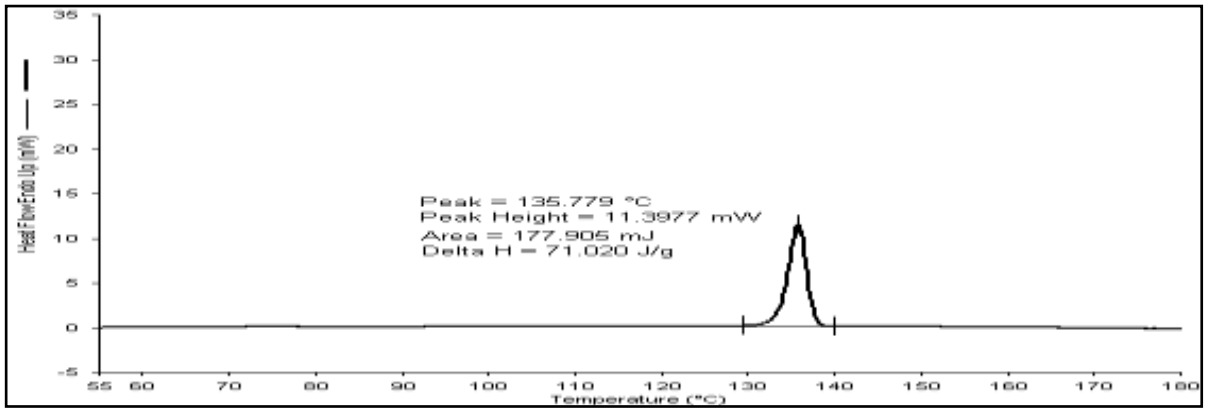

Figure 5: DSC thermogram of LRD

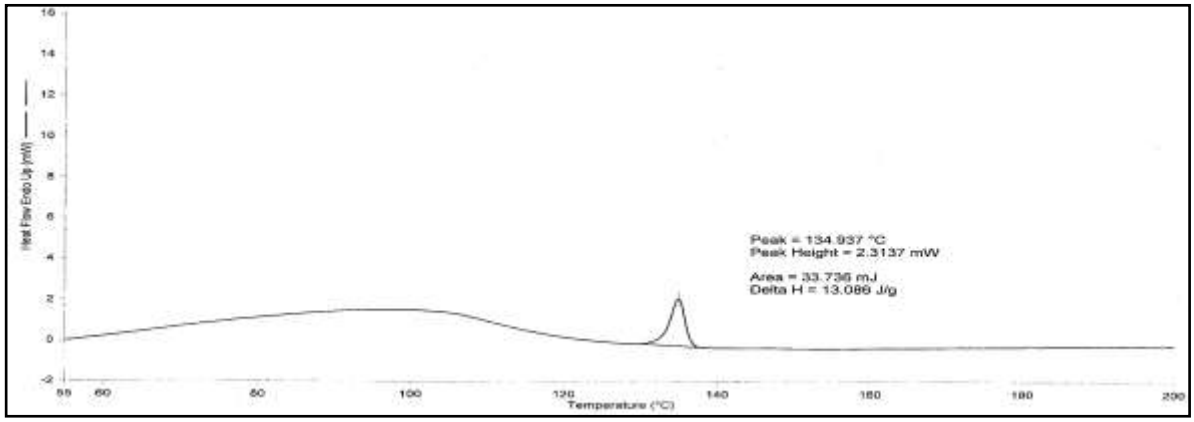

Figure 6: DSC thermogram of LRD: β-CD complex

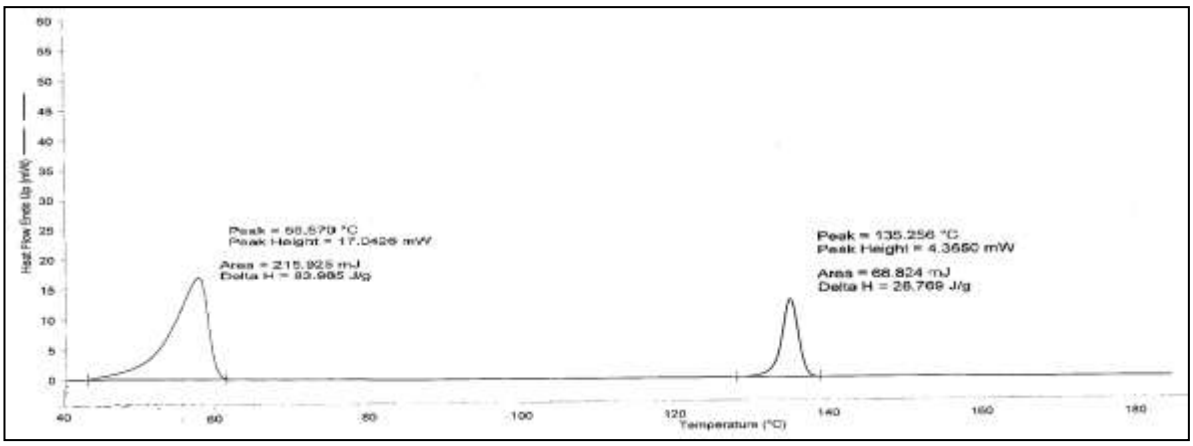

Figure 7: DSC themogram of LRD: Poloxamer dispersion

Differential scanning calorimetry (DSC) study

DSC thermograms of LRD solid dispersion were shown in Figure 5, 6 and 7. The DSC thermogram of Loratadine was typical of crystalline anhydrous substance, exhibiting a sharp endothermic peak at 135.779℃ corresponding to the melting point of the drug as shown in Figure 5. In LRD: β-CD thermogram shows broad endotherm ranging from 70 to 100°C due to presence of moisture content in β-CD and LRD peak at 134.03℃. Poloxamer dispersion thermogram shows poloxamer 407 peak at 56.67°C and LRD peak at 135.25℃.

All solid dispersions thermogram shows significant change in the peak area of thermogram. The peak area is directly proportional to amount of LRD present. The lesser peak area in thermogram represents less amount of LRD available in inclusion complex.

X-ray diffraction (XRD) study

XRD diffraction pattern of LOR and its solid dispersions were shown in Figure 8 and 9.The X-Ray diffraction pattern of LRD exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. The β-CD inclusion complex (Figure9) and Poloxamer dispersion of LRD (Figure 8) showed less intense and highly diffused peaks of drug which was very poor in reflections which testified to a reduced ordering of crystal lattice. In the prepared dispersions, reduction in crystallinity of the drug as compared to pure sample reflecting that the drug was dispersed in the polymer. The charge in crystallinity of the complexation might responsible for increase solubility of LRD.

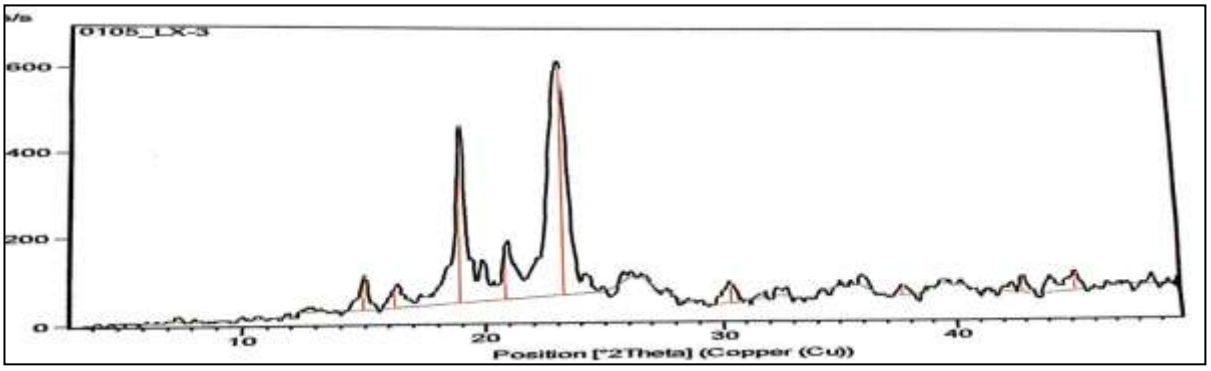

Figure 8: XRD spectrum of LRD: Poloxamer 407 dispersion

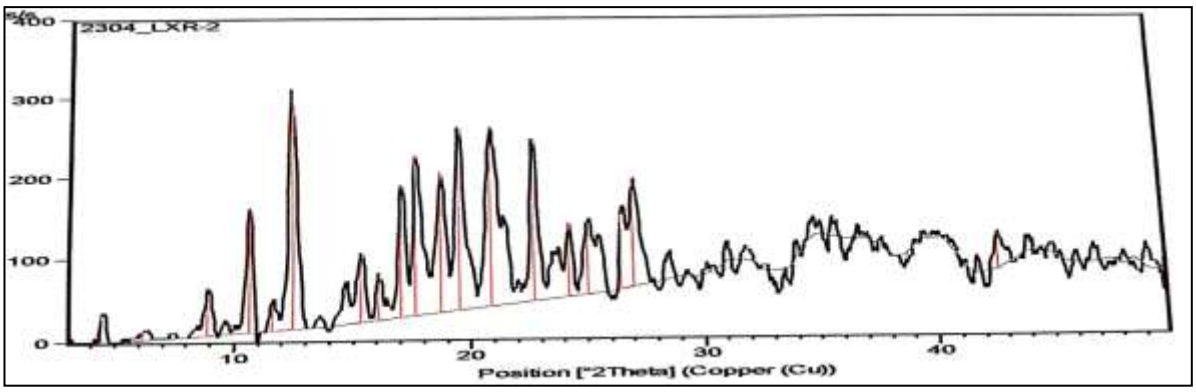

Figure 9: XRD spectrum of LRD: β-CD complex

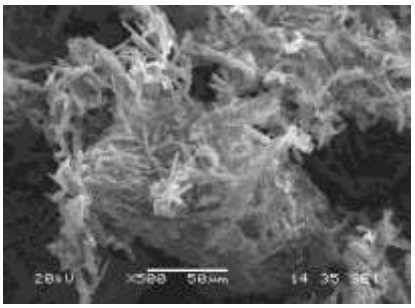

Figure 10: SEM picture of pure LRD

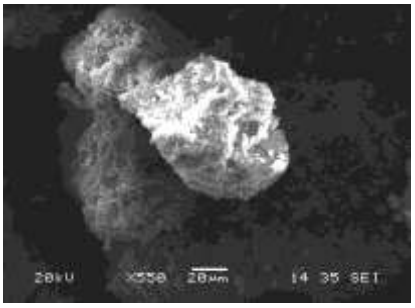

Figure 11: SEM picture of LRD: β-CD Complex

Scanning electron microscopy

SEM study indicated (Figure 10) that pure drug particles were irregular in shape, while the Solid dispersion of the LRD and β-CD showed a homogeneous dispersion indicating that the LRD molecules were dispersed uniformly in carrier matrices of solid dispersion prepared by Kneading method at 1:3 molar ratios, assuming amorphous solid dispersion state. (Figure 11)

Conclusion

Loratadine is practically insoluble drug (0.004mg/ml) which is very less and hence in order to increase solubility, solid dispersion approaches were employed to improve the water solubility of LRD. Solubility of LRD was enhanced by preparing solid dispersions with four hydrophilic carriers using kneading, solvent evaporation and low temperature fusion method. The solubility studies have showed that there is a possibility of improved solubility of LRD through solid dispersion with hydrophilic carriers compared with pure drug. A maximum increase in saturation solubility (1.720mg/ml) was obtained with LRD: β-CD Complex with a molar ratio of 1:3 prepared by kneading method. The results from this work suggested that the preparation of LRD solid dispersion by kneading method using β-CD as a hydrophilic polymer carrier could be a promising approach to improve solubility and absorption rate of LRD.These results show that solid dispersion is a promising approach for developing LRD drug products.

References

1. ZerroukN, Chemtob, Arnaud P,Toscani S and Dugue J., In vitro and in vivo evaluation of carbamazepine-PEG 6000 solid dispersions, Int. J. Pharm., 2001, 225, 49–62.
2. Szabados-NacsaÁ, Siposa P.,Martinek T.,Physico-chemical characterization and in vitro/in vivo evaluation of loratadine:dimethyl-β-cyclodextrin inclusion complexes, J. Pharm. and Biomedical Analysis, 2011, 55, 294–300.
3. Onoue S, Kojo Y., Aoki Y., Physicochemical and pharmacokinetic characterization of amorphous solid dispersion of tranilast with enhanced solubility in gastric fluid and improved oral bioavailability, Drug MetabPharmacokinet, 2012, 27, 379–387
4. Khadka P., Jieun R., Kim H, Kim I, Kim J.T., Kim H., Cho J.M., Yun G., Lee J., Pharmaceutical particle technologies : an approach to improve drug solubility, dissolution, and bioavailability, Asian J Pharm science, 2014, 9, 304-316.
5. Vasconcelos T., Sarmento B. and Costa P., Solid dispersions as strategy to improve oral bioavailability of poor water soluble Drugs, Drug Discovery Today, 2007, 12, 1068-1075.
6. Torrado S., Preparation, dissolution and characterisation of albendazole solid dispersions,Int J pharm., 1996, 140, 247-50.
7. Mohan A., Madhavi M., Jyosthna P., Preparation, *in vitro* and *in vivo* characterization of solid dispersions of oxcarbazepine using melting technique, Pharm Innov J., 2015,3,99–103.
8. Gorajana A., Rajendran A., Yew L.M., Dua K., Preparation and characterization of cefuroxime axetil solid dispersions using hydrophilic carriers. Int J Pharm Investig. 2015, 5,171–8.
9. Singh A., Worku Z.A., Van den Mooter G., Oral formulation strategies to improve solubility of poorly water-soluble drugs, Expert Opin Drug Deliv, 2011, 8, 1361-1378.
10. Kolasinac N., Kachrimanis K., Homsek I., Grujic B., Duric Z., Ibric S., Solubility enhancement of desloratadine by solid dispersion in poloxamers, Int. J. Pharm., 2012 436,(1-2),161-70.
11. Www.drugbank.ca/drugs/db00455
12. Www.drugs.com/mtm/loratadine.html
13. Higuchi T., Connors K.A., Phase-solubility techniques, Adv. Anal. Chem. Instrum., 1965,4, 117–210.
14. MukneA.P. and NagarsenkerM.S., Triamterene β-cyclodextrin systems: preparation, characterization and in vivo evaluation, AAPS, 2004, 5, 19–24.
15. Costa p., Modeling and comparison of dissolution profiles, Eur. J. Pharm. Sci. 2001, 13, 123–133.
16. Patel H.M., Shah S. A.,Preparation and characterization of etoricoxib β- Cyclodextrin complexes prepared by the kneading method,Acta Pharm, 2007, 57, 351–359.
17. Dahiya S., Dissolution enhancement of aceclofenac by alpha cyclodextrin complex, J. Pharm. Research, 2006, 5, 99-103.
18. Ali W., Williams A.C., Rawlinson C.F., Stochiometrically governed molecular interactions in drug: Poloxamer solid dispersions." International Journal of Pharmaceutics, 2010, 391, 162–168.
19. Kim E.J., Chun M.K., Jang J.S., Preparation of a solid dispersion of felodipine using a solvent wetting method." Eur. J. Pharm.Biopharm., 2006, 64, 200–205.
20. Abdul JaleelO.W., Abdulrasool A.A., GhareebM.M., Preparation and Characterization of Orally Disintegrating Loratadine Tablets from PVP Solid Dispersions,Int J Pharm Sci, 2010, 2(3), 759-770.

*****