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Solid dispersion tablets of loratadine using locust bean gum and skimmed milk- A comparative study

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ABSTRACT

Enhancement of dissolution characteristics of poorly soluble drug loratadine by solid dispersion technique using different carriers, modified locust bean gum (MLBG) and skimmed milk (SM) is being investigated in current study. Solid dispersions (SD) were prepared by solvent evaporation technique. Various mixtures (Kneading Mixture, Physical Mixture and Co-grinding Mixture) were prepared by methods reported in literature. F1- F6 batches of SD (1:2- 1:12 ratio of drug to MLBG); SM1-SM5 batches of SD (1:2-1:10 ratio of drug to Skimmed Milk) were prepared. Solubility studies indicated 1:8 ratio (F4 batch) as the best one from MLBG batches; SM3 (1:6) batch from skimmed milk batches. FTIR studies indicated no interaction of drug to polymer. DSC, X-RD and SEM studies indicated transition from crystalline to amorphous state of drug. In vitro release studies revealed maximum dissolution in F4 and SM3 (84% and 89% in 30 min respectively) as compared to 47% in case of pure drug. Optimum solid dispersion batches F4 and SM3 were further compressed into tablets. SD Batch F4 was successfully compressed into tablets but skimmed milk SD batch SM3 showed significant chipping problems. The in vitro release from tablet batch revealed comparable dissolution characteristics (with that of SD batch F4). Therefore, MLBG solid dispersion tablets can be a convenient dosage form with enhanced dissolution characteristics; Skimmed milk solid dispersion powder SM3 showed better solubility and dissolution (as compared to MLBG); can be used as such in capsule dosage form and conversion into tablet need further exploration of dosage form development process.

Keywords: solubility; dissolution; carrier; amorphous; crystalline

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INTRODUCTION

Loratadine is a second-generation H_1 histamine antagonist, used for treatment of allergic conditions. It has structural similarity with tricyclic antidepressants, like imipramine. It belongs to (Biopharmaceutics Classification Scheme) BCS class II drugs i.e. it has poor aqueous (0.0134mg/mL) solubility and high permeability thereby exhibits low oral bioavailability (40%). Loratadine is prescribed for the symptomatic relief of hay fever (allergic rhinitis), urticaria (hives) and chronic idiopathic urticaria. It is also used to relieve various symptoms of eye and nose such as sneezing, runny nose, itchy or burning eyes (in allergic rhinitis) [1].

The low solubility of BCS class II drugs in gastrointestinal fluids leads to poor bioavailability after oral administration in spite of their good permeability. A number of techniques are being used to enhance the solubility of poorly aqueous soluble drugs such as micronization, salt formation, complexation with polymers, prodrugs, pH alteration, use of surfactants, liquisolid compacts, co-precipitation using antisolvent [2,3,4] and solid dispersions

(SD). Solid dispersion technique is most widely used and successful strategies to enhance the dissolution characteristics of poorly aqueous soluble drugs. The solid dispersions technology includes dispersion of drug in biologically inert matrix, usually with the purpose to improve the oral bioavailability [5]. This technique has been widely documented as successful strategy for enhancement of solubility of a number of drugs (irbesartan using dextrose by co-grinding method and melt fusion method; Flufenamic acid using PEG (Polyethylene Glycol) 6000 and 4000 as carriers; Indomethacin using PVP and isomalt by solvent evaporation method) [6-8].

Various natural polymers have been exploited for improving the solubility of a number of drugs (Modified gum karaya for glimepiride by solvent evaporation method, modified hupu gum for Pioglitazone HCl by solid dispersion technique) [9,10]. Skimmed milk (SM) has also been reported for solubility enhancement of a number of drugs (valsartan, atorvastatin) [11, 12]. Various research reports evidenced the improvement in the solubility of loratadine using different carrier systems e.g. use of ethyl cellulose, HPMC by spray drying technique [13]; using hydroxypropyl methylcellulose (HPMC) and polyvinyl pyrrolidone (PVP) and hydroxypropyl cellulose (HPC) by solvent casting method [14]. Present study explored the use of modified locust bean gum (MLBG) and skimmed milk (SM) as a natural carrier for dissolution improvement of the loratadine (drug substance).

MATERIALS AND METHODS

2.1 Materials

Pure drug Loratadine was generously gifted by IPZAH Pharmaceuticals Ltd, Patiala; Locust Bean Gum was gifted by Lucid Colloids Ltd, Delhi. Skimmed milk was procured from local market, Ethanol was obtained from Changshu Yangyuan Chemical, China and Hydrochloric Acid was obtained from Qualigens, Mumbai.

2.2 Methods

2.2.1 Modification and Characterization of Locust Bean Gum (LBG):

Modified locust bean gum (MLBG) was synthesized by heating LBG at 80°C on hot plate. Heating was continued until the gum turns into light brown colour. The time required for this process varies from 30-40 min. The modified gum was sieved using # 80 and evaluated for swelling index, viscosity, hydration capacity, angle of repose, density, Carr's index (CI). The procedure for above tests was same as described in literature [15].

2.2.2 Formulation of Solid Dispersions:

Solid dispersions of Loratadine (drug substance) were prepared by using MLBG via solvent evaporation method. The drug loratadine and polymer MLBG was mixed/dispersed in ethanol (25 ml) in round bottom flask and dispersion were prepared using rotary evaporator at 45-50°C and under vaccum. The five batches (F1-F5) were prepared in different ratio of drug to polymer (1:2, 1:4, 1:6, 1:8, 1:10 and 1:12).

Skimmed Milk was used as another carrier in this study and various batches (SM1-SM5) were formulated in same ratio using solvent evaporation technique. The formulation batches were first analyzed for equilibrium solubility. 1: 8 ratio (Drug:polymer) showed higher solubility and was further used to prepare other mixtures.

2.2.3 Formulation of Physical Mixture:

Precisely weighed Loratadine (100mg) and MLBG (800mg) were mixed thoroughly using spatula. The mixture was sifted through 80 # mesh and kept in air tight containers at room temperature.

2.2.4 Formulation of Co-grinding Mixture:

Loratadine (drug substance) and MLBG in ratio (1:8) were placed in the mortar and grinded properly. The mixture was then sieved through the 80 #. The mixture was kept in the air tight container at room temperature.

2.2.5 Formulation of Kneading Mixture:

Accurately weighed Loratadine (drug substance) (100mg) and MLBG (800mg) and kneaded using ethanol in mortar. The mixture was dried in the hot air oven until the attainment of constant weight. The dried weight strained through the 80 # mesh. The mixture was kept in the air tight container at room temperature.

2.2.6 Evaluation of Various Mixtures:

2.2.6.1 Equilibrium Solubility Studies:

Equilibrium solubility of different mixtures (SD, PM, KM and CGM) was determined in distilled water at 37^{o}C. For each preparation, amount equal to 10 mg of loratadine was dispersed in 50 ml of distilled water and covered each flask with aluminium foil. The flasks were placed in orbital shaking incubator for a period of 24 h at a temperature of 37±0.5^{o}C. Then, the solution was strained and the filtrate was assayed using UV spectrophotometer at 280nm.

2.2.6.2 Fourier Transform Infrared Spectroscopy:

Dried potassium bromide was mixed with 10 mg of the sample. The mixture was properly grinded using pestle and mortar. The mixture was compressed into pellets using hydraulic press. The scanning frequency range was kept in 4000 – 500 cm^{-1}. Infrared absorption spectra of Loratadine (drug substance), LBG, MLBG, SM and various mixtures (SD, KM, PM, CGM) were obtained using FTIR spectrophotometer (Spectrum 400, Perkin Elmer,USA).

2.2.6.3 Differential Scanning Calorimetry (DSC):

Thermal analysis of drug Loratadine and best batches F4 and SM3 were determined by Differential Scanning Calorimetry (DSC 60A, Shimadzu, Japan). The sample was wrapped in aluminium pan and scanning was done at temperature range from 30 to 300^{o}C and the heating rate of 10^{o}C/min in nitrogen atmosphere.

2.2.6.4 Scanning Electron Microscopy (SEM):

Loratadine (drug substance), best batch of solid dispersions (F4, SM3) and other mixtures CGM and KM were attached onto the stubs using double adhesive tape and coated with gold palladium alloy (150-200 A^{o}) using fine coat ion sputter (JEOL, JSM-6100, USA). The samples were analyzed using the scanning electron microscope for external morphological features.

2.2.6.5 X-Ray Diffraction(X-RD):

Powder X-Ray diffraction patterns were drawn using X-ray diffractometer (X'PertPro,India). The samples were examined using Ni filtered Cu (K-α) radiations, a voltage of 45 kV, a current of 40 mA. The samples were examined over 2θ range of 0-50^{o} and scan step time of 25 s.

2.2.7 Conversion into Tablet Dosage Form:

The optimized batches of solid dispersion using MLBG (F4) and using skimmed milk (SM3) were compressed into tablets (200mg) by adding various excipients (Avicel 112, talc, mannitol and magnesium stearate). Crosspovidone (CP) was also added to enhance the disintegration characteristics. The tablet formulation batches (with and without CP) were evaluated further. The composition of tablet is depicted in table 1.

2.2.8 Physicochemical Characterization of Tablets: All the standard tests for tablets (weight variation, friability, hardness and disintegration) were done as specified in reference standards. Other tests such as water absorption ratio and wetting were carried out as reported in literature.

2.2.8.1 Wetting Time:

Five rounded pieces of tissue papers of 10cm diameter were placed in a petridish (10cm diameter) containing 10 mL of Eosin dye aqueous solution. The tablet was kept on the surface of the wet tissue paper. Wetting time is the time required for water to reach upper surface of the tablet [16, 17].

2.2.8.2 Water Absorption Ratio:

The tablet was placed on a folded piece of tissue paper in a small petri dish (6mm diameter) containing 6 ml of water. The whole wetting of tablet was observed [16, 17] and wetted tablet was then weighed. Water absorption ratio (R) was determined by following equation.

$R=100(W_a/W_b)$

Where, W_b is weight of dry tablet and W_a is weight of wetted tablet.

1.2. 8.3 *In vitro* Dissolution Studies:

In vitro release of drug from tablet batch, various mixtures, marketed tablet and loratadine (drug substance) was carried out in 0.1N HCl (900 ml) at 37 ± 0.5^{o}C using USP II dissolution apparatus. The stirrer rotation speed was

kept at 50 rpm. 5ml aliquots were withdrawn at consistent intervals of 5min, 15min, 30min, 45min, 60min, 120 min and appropriate dilutions were done and assayed using UV spectrophotometer at 280 nm.

2.2.9 *In vitro* Release Kinetics*:*
In vitro kinetic models were applied to analyze the kinetics of drug release from formulations. The zero order kinetics determines the concentration independent drug release whereas first order kinetics determines that the drug release from system is dependent on concentration. The release of drug from insoluble matrix is determined using Higuchi model. The drug release mechanism from polymeric system is described using Korsmeyer-peppas equation[18].

2.2.10 Effect of Storage on Physical Properties of Tablets
The selected tablet batch T2 was kept in stability chamber at 40^{o}C and 75% RH (relative humidity) conditions for three months. The stability of prepared formulation was assessed under stated conditions of temperature and humidity by determining the physical characteristics of the tablet at specified durations (15 days, 1 month, 2 month and 3 months).

RESULTS AND DISCUSSION

3.1 Physicochemical Characterization of LBG and MLBG
Unmodified and modified form of gum was assessed for various physicochemical properties such as swelling index, angle of repose, viscosity, hydration capacity, density [(LBD) and (TBD)], Compressibility index (CI). The viscosity of the locust bean gum was found to be decreased about 3 times after modification while swelling index remained same with both LBG and MLBG. Hydration capacity indicating the tendency/capacity to retain the water was found to be almost same (Table 2). LBG and MLBG possessed good flow properties as suggested by CI and angle of repose.Good flow characteristics revealed further easy and uniform formulation development into tablets.

3.2 Evaluation of Various Mixtures
Various mixtures (PM, KM, CGM, solid dispersions using MLBG and skimmed milk) were successfully prepared in different ratios and evaluated for further studies.

1.3. 1 Equilibrium Solubility Studies
Various mixtures were evaluated for equilibrium solubility (µg/ml) in distilled water. The results are shown in the Figure 1.

Equilibrium solubility of loratadine (drug substance) in distilled water was found to be very low i.e. 2.96 (µg/ml). Mixing of drug with MLBG in solid dispersion leads to increase in solubility (F1-F4) of drug which may be due to wetting characteristics of MLBG. Further higher ratio of polymer MLBG (F5, F6) showed a decrease in the equilibrium solubility. MLBG in higher ratio caused increased viscosity of the mixture which hinders drug solubilization and thereby dissolution also. Other mixtures (PM, KM and CGM) were prepared in one ratio which is best out of all solid dispersions F4 (i.e. 1:8 ratio). No significant changes in solubility of drug were observed in case of physical mixture whereas other mixtures (Kneading mixture and Co-grinding mixture) showed increased solubility of the drug. The solid dispersions prepared with skimmed milk lead to significant improvement in solubility of loratadine in comparison to that of solid dispersions with MLBG. SM3 (1:6 ratio) batch showed maximum solubility. Skimmed milk led to decrease in crystallinity of drug which was confirmed by DSC, X-RD analysis.

3.2.2 Fourier Transform Infrared Spectroscopy (FTIR):
FTIR analysis was done to establish the presence of various functional groups. FTIR spectrum of loratadine (drug substance), LBG, MLBG, SM and various mixtures are shown in overlay diagram (Figure 2). FTIR spectrum of loratadine shows characteristic peaks at 3038 due to C-H stretching, at 1702 due to C=O of ester, 1644 due to imine linkage (C=N), 1474 due to stretching vibrations of benzene ring, 1385 due to C-N of benzene and at 996 due to aromatic ring. FTIR spectrum of MLBG showed C-O stretching at 1024.81cm^{-1}, CH_2 bend at 1432.10 cm^{-1} and C-H stretching at 2925.54 cm^{-1}. The presence of almost all characteristic peaks of drug (1703, 1647, 1473, 1435 and 1226) in spectra of all solid dispersions (particularly F4 batch) and PM, KM CGM which indicates no interaction of drug with polymer. SM 3 batch showed some characteristic peaks (1652, 1435, 1228). The presence of polymers in

the mixtures (F4 and SM3) may hide some peaks of drug and even lead to additional peaks (which are not due to any interaction between drug and polymer).

3.2.3 Differential Scanning Calorimetry
DSC thermogram of loratadine (drug substance) (Figure 3) showed sharp endothermic peak at 139.17^{o}C with enthalapy of fusion 85.89 J/g corresponding to its melting point, which specifies its crystalline nature.

DSC thermogram of solid dispersion batch F4 and SM3 (Figure 4) showed endothermic peak at 135.30^{o}C and 130.59^{o}C respectively with enthalapy of fusion 5.50 J/g and 50.30J/g respectively. Slight shift in endothermic peak of drug with decreased intensity in DSC thermograms of solid dispersions (F4 and SM3) suggested change of crystalline state to amorphous state of drug.

3.2.4 Scanning Electron Microscopy
SEM images of the loratadine (drug substance), solid dispersion batch F4 and SM3 are shown in Figure 4. The drug appeared as smooth surfaced rectangular crystalline structure while topological changes (porous surfaced particles) are observed in solid dispersion batches (F4 and SM3) indicating change in crystallinity of drug.

3.2.5 X-Ray Diffraction
The crystallinity characteristics of loratadine (drug substance) and polymer was determined by X-ray diffraction studies. The X-RD of drug, polymer and various mixtures are shown in overlay diagram (Figure 5). Loratadine showed sharp peaks of the diffraction angle of 2θ at 6.8485, 13.2871, 16.975, 24.22, and 30.88 with peak intensities of 23.06, 48.62, 100.00, 32.26 and 20.89 and the area of 124.22, 196.46, 538.80, 217.24, 140.70 respectively. Absence of some characteristic peaks or peaks with decreased intensity in diffraction patterns of solid dispersion batch F4 and other mixtures (co-grinding mixture and kneading mixture) indicates decrease in drug crystallinity in the mixture. The diffraction patterns of solid dispersion batch SM3 using skimmed milk also showed absence of characteristic peaks of drug or peaks with less intensity. This also suggests decreased crystallinity of drug in solid dispersion.

3.3 Conversion into Tablet Dosage Form:
Best solid dispersion batches F4 and SM3 were used for further compression into tablets. Two batches containing F4 solid dispersion using MLBG (T1 and T2 with and without crosspovidone respectively) and other two batches containing solid dispersion SM3 using skimmed milk (T3 and T4 with and without crosspovidone respectively). T1 tablet batch shows slight chipping during compression which was overcome by adding crosspovidone (T2 batch). T3 and T4 tablet batches were not compressed as there is significant loss of powder due to capping and chipping of tablets during compression. Therefore skimmed milk solid dispersion batches cannot be formulated into tablet dosage form. Further formulation trials are required to convert into uniform tablet dosage form. Therefore only T2 batch was used for further studies.

3.3.1 Physicochemical Characterization of Tablets:
T2 tablet batch was assessed for various standard tests (weight variation, friability, hardness, disintegration, wetting time, water absorption ratio and in vitro drug release). The results are depicted in table3. % weight variation of all tablets in the batch was within standard limits (±7.5%). The prepared tablets possessed sufficient hardness in the range of (between 2-2.5 kg/cm²) as indicated by good mechanical strength. The good mechanical resistance is shown by friability values below 1% for the tablet batch. The wetting time and disintegration time values of less than 1 min were observed. Water absorption ratio of more than 100% suggested sufficient swelling and disintegration of tablet leading to better dissolution characteristics [17].

1.4. 2 *In vitro* Dissolution studies:
In vitro release from various solid dispersions using MLBG (F1-F6), KM, PM and CGM is compared with loratadine (drug substance) (Figure 6). Drug release was found to be increased in various solid dispersions batches as compared to that of pure drug. Maximum dissolution characteristics were observed in SD batch F4 with (68% in 15 min and 100% release in 1h) suggesting (1:8 ratio)as the optimum one. The results were also in confirmation with solubility data. The drug release was decreased in F5 and F6 which may be due to the reason that higher ratio of polymer lead to viscous mixtures which further hinders the drug dissolution.PM does not show any significant change in dissolution whereas KM also leads to improved dissolution. CGM showed comparable dissolution characteristics with that of F4 solid dispersion batch. The improved dissolution of solid dispersions batches may be

due to improved wettability, decrease in particle size of drug and reduced crystallinity of drug. The decreased viscosity of MLBG led to use of gum in higher ratio in the formulation which otherwise may not be possible with LBG.

Skimmed milk batches (SM1 –SM5) also showed enhanced dissolution characteristics with maximum in SM3 (1:6) batch (Figure 7). The SM3 batch appeared better than F4 batch (as seen from drug release data) in terms of solubility as well dissolution improvement. The enhanced dissolution with skimmed milk is due to reduced particle size and conversion into amorphous state of the drug. The casein micelles formed which entrap the lipophilic drug leading to remarkable increase in solubility.

The drug release from tablet batch T2 was compared with SD batches F4, SM3, marketed tablet and pure drug (Figure 8). The results revealed that compression into tablet does not affect the release characteristics which were comparable with that of F4 solid dispersion. The presence of crosspovidone may lead to better disintegration and thereby dissolution.

3.4 *In vitro* Release Kinetics

In vitro drug release kinetics data from various mixtures suggested that release of drug from various formulations follows Koresmeyer Peppas (KP) model (highest R^2 values). The n value (0.2) of KP model suggested that drug release behavior followed power law. This suggested that no exact single release mechanism of the drug from the mixtures (Table 4) [18].

3.5 Effect of Storage on Physical Properties of Tablets

Tablet batch T2 was kept for 3 months at 40°C and 75% RH conditions to estimate effect of adverse storage conditions on physical characteristics of tablets. The results indicated no remarkable changes in the physical parameters of the tablets (Table 5). The results indicated good stability of the formulation even after stressed conditions.

Table 1: Composition of tablet batches

Ingredients	Formulation Code			
	Solid Dispersion (MLBG)		Solid Dispersion(SM)	
	T1(mg)	T2(mg)	T3(mg)	T4(mg)
SD powder(eq. to 10 mg drug)	90.5	90.5	70	70
Avicel 102	70	60	85	75
Mannitol	34.5	34.5	40	40
Talc	2	2	3	3
Magnesium Stearate	3	3	2	2
Crosspovidone (CP)	--	10	--	10
Total weight of tablet (mg)	200	200	200	200

Table2: Physicochemical characterization of LBG and MLBG

Parameters	LBG	MLBG
Swelling index (%)	288.58 ± 4.77	285.52 ± 2.37
Viscosity (cps)	1195 ± 44.22	338 ± 36.10
Hydration Capacity	2.40 ± 0.19	2.38 ± 0.16
Angle of Repose	39.56 ± 2.49	38.22 ± 2.21
Density (g/cm^3)		
LBD	0.59 ± 0.06	0.61 ± 0.02
TBD	0.60 ± 0.06	0.61 ± 0.04
CI (%)	23.47 ± 0.62	21.52 ± 0.48

Table 3: Physicochemical Characterization of prepared tablet and marketed tablet

Parameters	Tablet	Marketed tablet (Alastin)
Weight variation (mg)	198.62	199.64
Hardness (kg/cm^2)	3.0± 0.3	3.2± 0.4
Friability (%)	0.73 ± 0.04	0.62 ± 0.05
Disintegration Time (sec)	25 ± 2	28 ±3
Wetting Time (sec)	21± 2	26± 2
Water absorption ratio (%)	113.45	100.87

Table 4: R^2 values of release kinetic profiles of various formulations

Formulation	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-Peppas R^2	N
F4 solid dispersion	0.498	0.977	0.923	0.996	0.291
SM3 solid dispersion	0.467	0.806	0.932	0.991	0.275
T2 tablet batch	0.482	0.982	0.910	0.992	0.221

Table 5: Physicochemical Characterization of tablet batch T2 during stability testing

Parameter→Time↓	Weight variation(mg)	Hardness Kg/cm^2	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorption ratio (%)
15 days	196.54	2.87± 0.7	0.67±0.02	25±3	22±3	115.56
30 days	196.47	2.74 ±0.5	0.64±0.04	24±2	21±2	115.23
60 days	196.44	2.70 ±0.6	0.63±0.02	24±2	20±2	114.45
90 days	196.5	2.71 ±0.6	0.61±0.02	24±2	20±3	114.67

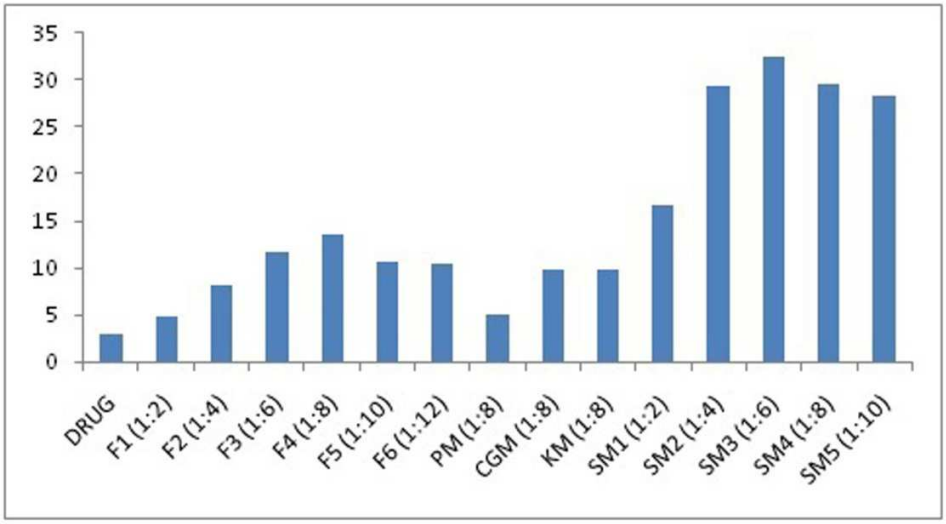

Figure 1: Comparative solubility of pure drug and various mixtures

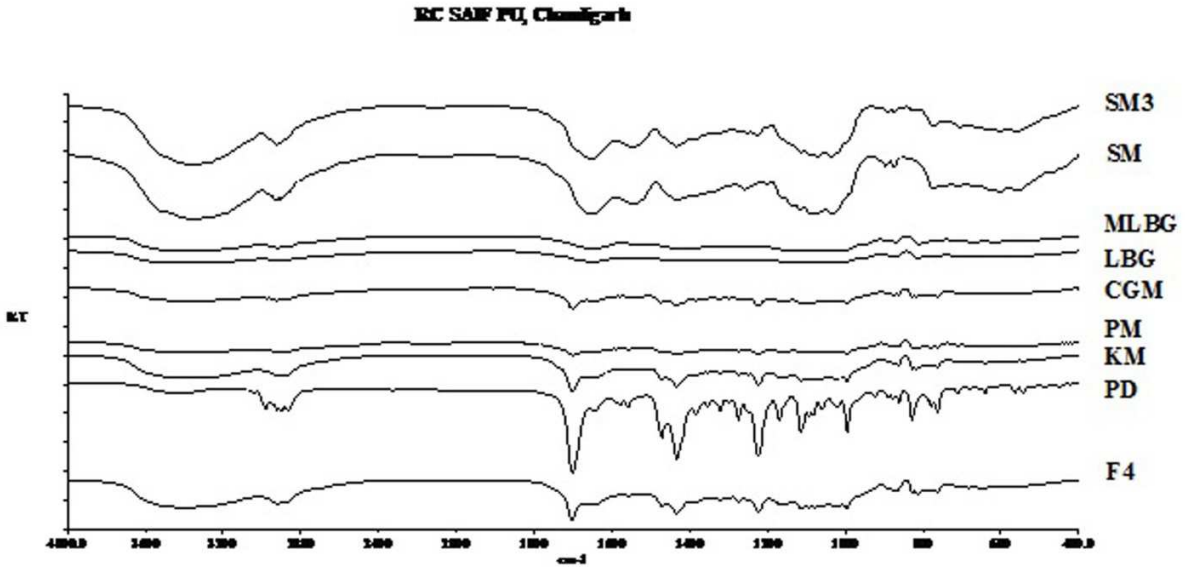

Figure 2: Overlay diagram of SM3, SM, MLBG, LBG, CGM, PM, KM, PD and F4(1:8)

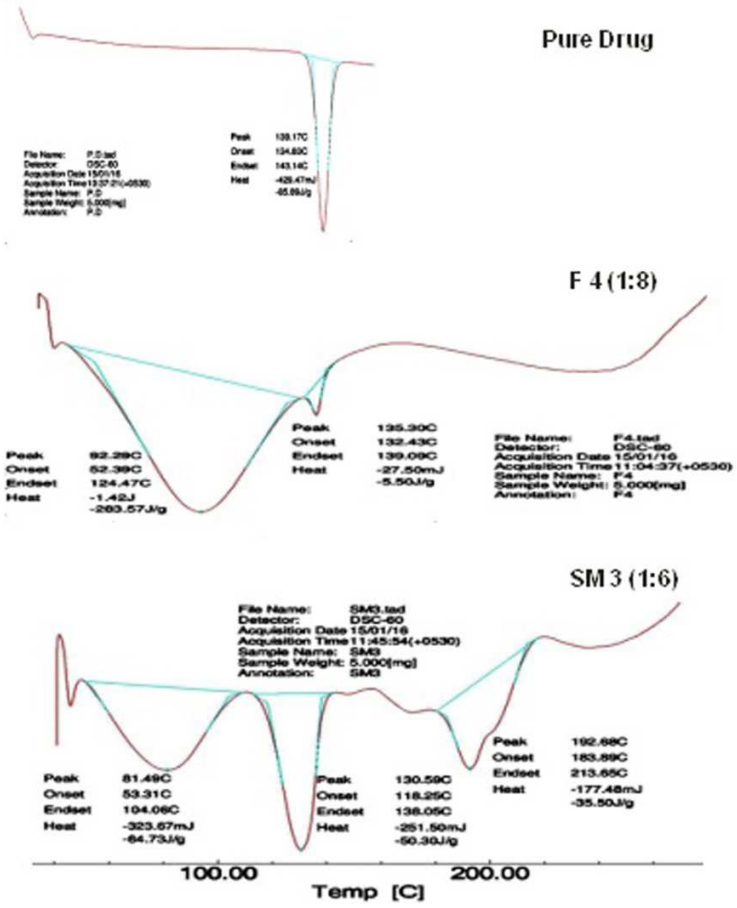

Figure 3: Overlay of DSC of pure drug, solid dispersion batch F4 and SM3

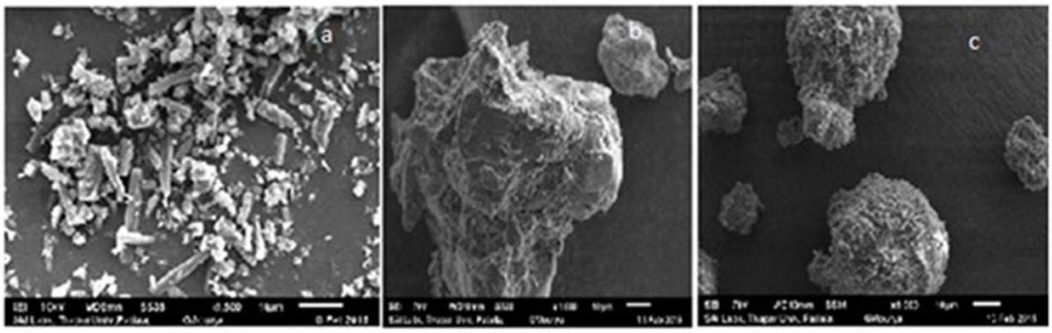

Figure4: Scanning electron micrograph of a) PureDrug b) F4 c) SM3

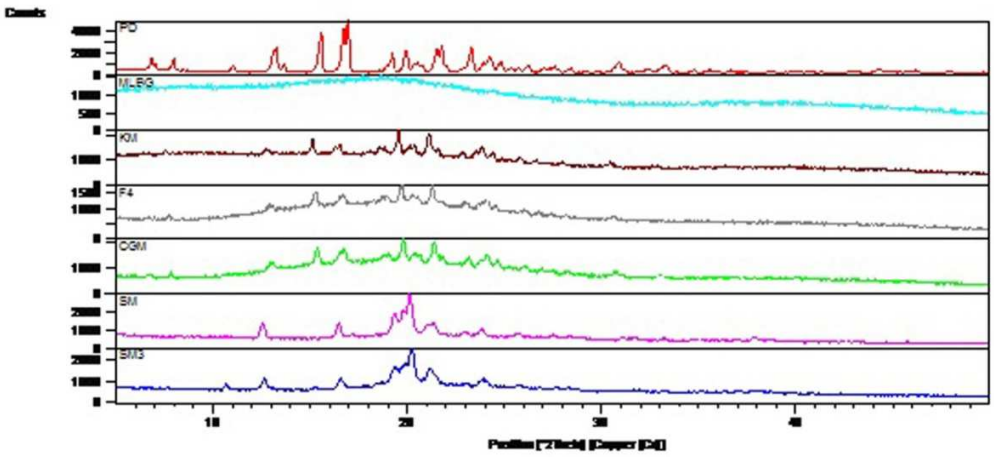

Figure 5: Overlay diagram of XRD of pure drug, MLBG, KM, F4, CGM, SM and SM3

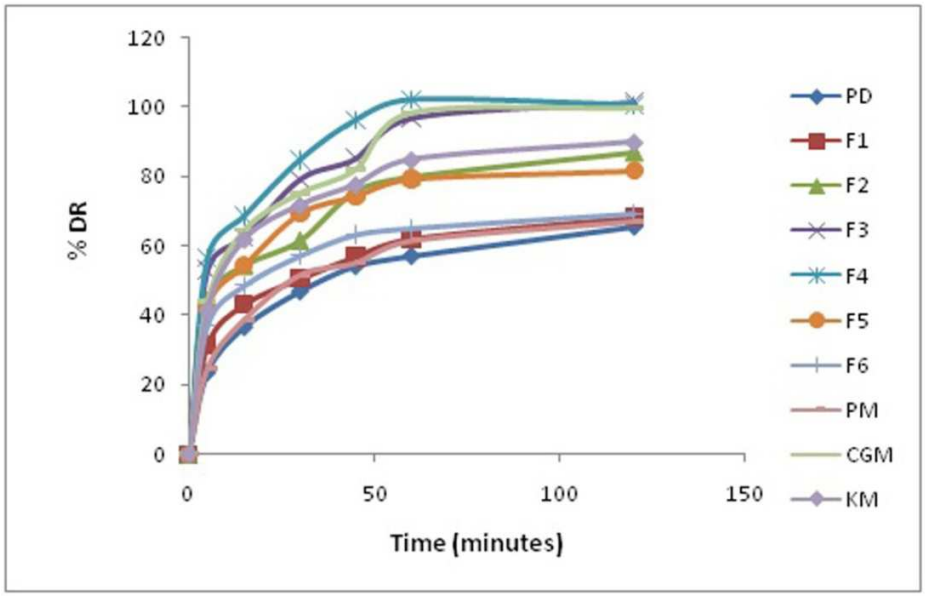

Figure 6: Comparative i*n vitro* release profile of various solid dispersions (F1-F6), PM, CGM, KM and pure drug (PD)

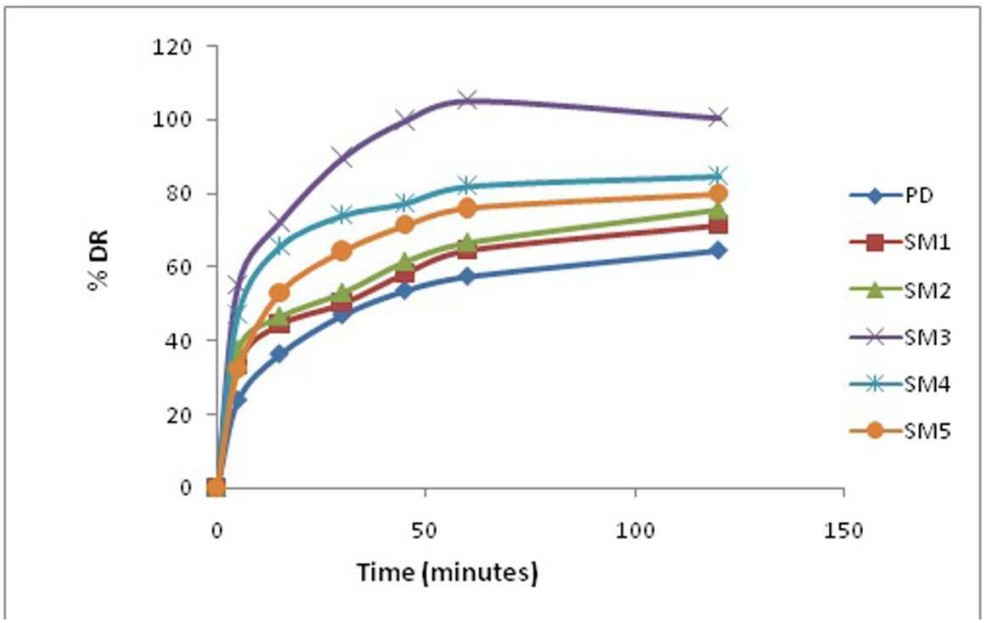

Figure 7: Comparative *in vitro* release profiles of (SM1-SM5) and pure drug

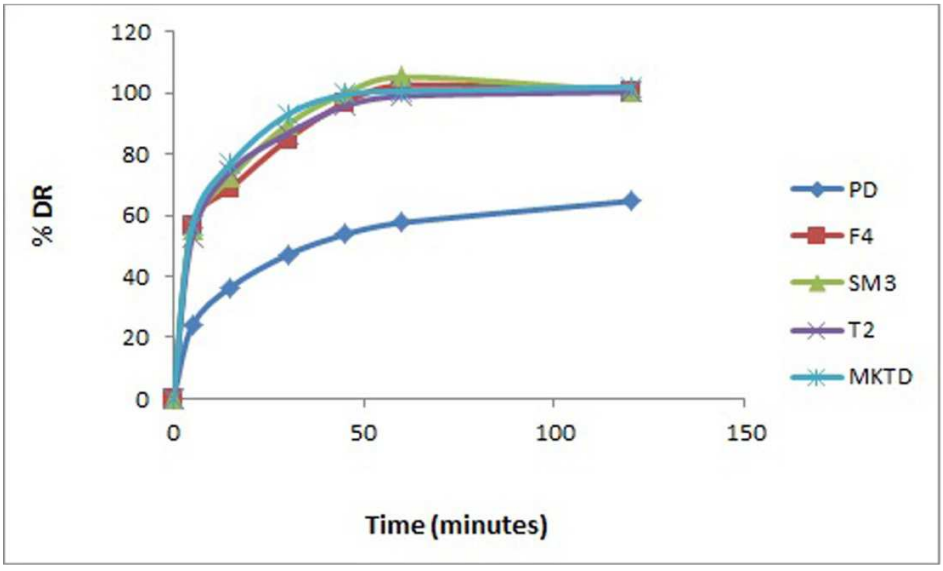

Figure 8: Comparative *in vitro* release profiles of Pure Drug, F4, SM3 batch, T2 and Marketed tablet

CONCLUSION

The potential of natural carrier MLBG and skimmed milk is being explored for the solubility enhancement of loratadine. The enhanced solubility as well as improved dissolution was due to the synergistic effect of reduced particle size of the drug during preparation of mixtures wetting ability of MLBG, and decreased drug crystallinity. Moreover, the less viscous nature of modified LBG showed encouraging results and it can be used in higher amounts as compared to unmodified LBG. However skimmed milk leads to better results in enhancement of drug dissolution which may be due to formation of casein micelles which help in emulsify the hydrophobic drug which is entrapped with in the micelles. Conversion into amorphous form of drug is the main reason for skimmed milk based

solubility enhancement of drug. However skimmed milk as a carrier does not support for formulation into tablet, therefore further development steps are required for the same.

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