ORIGINAL RESEARCH ARTICLE

Enhancement of Solubility and Dissolution Rate of Trandolapril Sustained Release Matrix Tablets by Liquisolid Compact Approach

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Abstract

Trandolapril (TLP), is an antihypertensive agent, administered orally. It is having low oral bioavailability (4–9%) due to poor aqueous solubility, it undergoes CYP3A4 mediated hepatic first-pass metabolism. Liquisolid compact (LSC), the technique has the potential to improve the oral bioavailability by increasing solubility and dissolution rate of poorly water-soluble drugs. In the present work, TLP LSCs were prepared with polyethylene glycol-400 as a vehicle, Avicel, Neusilin as carriers and Aerosil as coating material. LSC and sustained release tablets of LSC containing hydroxypropyl methylcellulose $K_{15}M$ polymer, were prepared by direct compression method and characterized for hardness, friability, drug content and *in vitro* release studies in pH 6.8 phosphate buffer for LSC and 0N HCl for 2 h followed by pH 6.8 phosphate buffer for subsequent hours for SR LSC, using USP type-1 apparatus. Solid state characterization of TLP and TLP-LSC was examined using differential scanning calorimeter (DSC), powder X-ray diffraction (PXRD) and scanning electron microscopy (SEM) studies. Physical parameters of the prepared LSC tablets were found to be within the acceptable limits. *In vitro* dissolution studies of optimized SR LSC (F3) formulation had shown sustained drug release of 97.3 ± 2.59% in 14 h with Peppas model (r^2 = 0.981) followed by non-Fickian diffusion (n = 0.659) mechanism, whereas LSC tablets showed 94.1 ± 3.11% drug release in 120 min. DSC and XRD analysis indicated that TLP was amorphous form in LSC mixture. SEM studies revealed that TLP was adsorbed onto the surface of carrier material compared with the pure drug having needle-shaped crystal lattice. Therefore, LSC technique can improve the solubility and dissolution rate of poorly water-soluble drug such as TLP.

Key words: Carrier, coating material, differential scanning calorimeter, hydroxypropyl methylcellulose $K_{15}M$, liquisolid compacts, scanning electron microscopy, sustained release, X-ray diffraction

INTRODUCTION

A number of potential limiting factors must be overcome for the absorption of drugs through the gastrointestinal (GI) tract. These include appropriate stability and solubility in the GI fluids, permeability, and resistance to metabolism both within the enterocyte and the liver.[1] Various techniques have been employed to enhance the dissolution rate and in turn, the absorption efficiency and bioavailability of water-insoluble drugs or lipophilic medication such as pH adjustment[2] lipid-based drug delivery,[3] co-solvency,[4] conversion of crystal to amorphous form[5] and complexation technique.[6]

Several researchers have shown that the liquisolid compact (LSC) technique is the most promising method for enhancing the dissolution rate of poorly water-soluble drugs.[7,8] The liquisolid technology was described by Spiras in 2002,[9] in which liquid may be transformed into a free-flowing, easily compressible, and expressly dry powder by simple physical blending with selected excipients named the carrier and coating material. A liquid lipophilic drug can be converted into liquisolid system without being further modified.[10] On the other hand, if a solid water-insoluble drug is formulated, it should be initially dissolved or suspended in suitable

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nonvolatile solvent system to produce drug solution or drug suspension of desired concentration. Inert, preferably water-miscible organic solvents with high boiling point and a not highly viscous organic solvent system such as propylene glycol, liquid polyethylene glycols (PEG), polysorbate, fixed oils, or glycerine are best suitable as liquid vehicles.[11]

Liquisolid compaction based on powder solution technology shows promising potential in improving the dissolution rate of poorly soluble drugs (BCS Class-II). LSC technology not only enhances the drug dissolution but can be commercially viable and has industrial scale-up feasibility due to low cost and ease of handling.[12] LSCs would also sustain the drug release profiles that offer several pharmacokinetic and pharmacodynamic advantages over conventional dosage forms such as maintenance of constant therapeutic levels for a prolonged period and minimizing the fluctuations in plasma drug concentration.[13]

Trandolapril (TLP) is an esterified prodrug of the active metabolite of trandolaprilate and is a nonsulphydryl angiotensin converting enzyme inhibitor. It is used for the treatment of hypertension and heart failure.[14] TLP have poor oral bioavailability (4–9%; BCS-II) due to poor aqueous solubility and also undergo extensive first-pass metabolism. Therefore, enhanced solubility and dissolution rate, which will ultimately, increases absorption and improvement in oral bioavailability was key factor for TLP. Hence, the objective of the present investigation was to formulate the LSCs of TLP to improve the solubility and dissolution rate. Further, converting the TLP LSC into sustained release LSC by admixing the hydroxypropyl methylcellulose (HPMC) $K_{15}M$ for prolonged drug release, which can increase bioavailability, reduce the oral dosage required to achieve the same effect.

MATERIALS AND METHODS

Trandolapril is obtained as a gift sample from the Hetero Drugs Ltd., Hyderabad, India. HPMC $K_{15}M$ is a gift sample from Orchid Pharma, Chennai, India. Avicel pH 102, Aerosil and PEG-400 purchased from Himedia, Mumbai, India. Neusilin was obtained as gift sample from Fuji Chemical Industry Co. Ltd., Japan.

Solubility studies

Solubility measurements were performed according to the method of Higuchi and Connors.[15] Solubility studies of drug was performed in different pH media (0.1N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer) and different nonvolatile solvents that is, Polysorbate 80, Labraphil, and PEG-400 using shake flask method. An excess amount of drug was added to 10 mL of each pH media and nonvolatile liquid in separate vials. The vials were sealed, and the mixture was vortexed for 10 min in order to facilitate proper mixing of the drug with the vehicles and subjected to shaking on the incubator shaker for 48 h at 25°C. After this period, the solutions were filtered through 0.45 µm membrane filter and supernatant was separated and analyzed for drug content by ultraviolet (UV) spectrophotometer (SL-159, Elico, India). The determinations were carried out thrice for each sample and its mean along with standard deviation (SD) was reported.

Application of mathematical model to design liquisolid compacts

To calculate the amount of carrier and coating material and to maintain acceptable flowability and compressibility, the mathematical model described by Spireas and Sadu 1998[16] was used. In this study, PEG-400 was used as liquid vehicle, Avicel pH 102, Neusilin and Aerosil 200 were used as the carrier and coating materials, respectively. Flowable liquid retention potential (φ value) of powder excipients was used to calculate the required ingredient quantities for the preparation of LSC. Therefore, carrier to coating ratios (R) and liquid load factors (L_f) of the formulations are related as follows:

$$L_f = \varphi_{ca} + \varphi_{co}\,(1/R) \quad (1)$$

Where, φ_{ca} and φ_{co} are the values of carrier and coating materials, respectively and they are constant. Liquid load factor (L_f) is defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system.[17]

That is,

$$L_f = W/Q \quad (2)$$

Where, W is amount of drug in liquid vehicle;

Q is weight of the carrier powder.

The ratio R of powder is defined as,

$$R = Q/q \quad (3)$$

Where, R is the ratio between the weights of carrier (Q) and coating (q) materials.

Precompression studies

Flowability of liquisolid powder admixtures prior to compression were evaluated using parameters such as Carr's index, angle of repose, and Hausner's ratio, flow properties were calculated using fallowing equations.

Angle of repose

The fixed funnel method was employed to measure the angle of repose (θ), and it was calculated using the following formula,[18]

$\theta = \tan - 1h/r$

Carr's compressibility index

The compressibility index (Carr's index) is a measures the tendency of a powder to be compressed.

Carr's index (%) = [(tapped density − bulk density) × 100]/ tapped density

Hausner's ratio

Hausner's ratio = tapped density/bulk density

Preparation of liquisolid compacts of trandolapril

For the preparation of LSCs of TLP, a nonvolatile solvent is chosen for dissolving or dispersing the drug. Liquisolid powders containing PEG-400 as the liquid medicament, Avicel pH 102, Neusilin as carrier (and Aerosil as coating material. Desired quantities of solid drug and PEG-400 were accurately weighed and then heated with constant stirring, until a homogeneous drug solution was obtained; the resulting hot liquid medications (W) were incorporated into calculated quantities of carrier and coating materials. During the first stage, the system was blended at an approximate mixing rate. In the second mixing stage, the liquid/powder admixture was spread evenly as a uniform layer on the surfaces of the mortar and allowed to stand for 5 min by which liquid medicament to be absorbed onto the interior of the powder particles. In the third stage, the powder was scraped off from the mortar surfaces by means of an aluminum spatula [Table 1]. Further, SR tablets of LSC TLP was prepared by adding the HPMC $K_{15}M$ to this mixture and blended with mortar and final mixture is blended with magnesium stearate and talc. This blend was compressed into tablets by direct compression technique using 16 station rotary tablet compression machine (Riddi, Ahmadabad, India) with 8 mm concave punches [Table 2].[19]

Determination of/angle of slide

This experiment was designed to measure the flowable liquid retention potential (φ-value) for carrier materials (Avicel pH 102 and Neusilin, φ_{Ca}), and coating material (Aerosil, φ_{Co}). The φ-value of a powder is the maximum amount of given nonvolatile liquid that can be retained inside bulk powder while maintaining acceptable flowability, whereas L*f* is the mass ratio (w/w) of the liquid medication to the carrier powder in the liquisolid formulation. For this purpose, each admixture containing liquid medicament, carrier, coating material were placed on a shiny metal plate, the plate was then tilted until the admixture slides. The angle formed between the plate and the horizontal surface, at which admixture slides were measured as angle of slide (θ). The flowable liquid retention potential was calculated using the following equation:

φ-value = weight of nonvolatile liquid/weight of carrier or coating material

Each admixture has specific φ-values which were determined. The φ-value that corresponds to an angle of slide of 33° was reported to represent the flowable liquid retention potentials of powder admixtures.

Evaluation of compressed tablets

Friability test

Friability was determined using Roche Friabilator. Ten tablets were weighed (W) and placed in the friabilator and then operated at 25 rpm for 4 min. The tablets were then reweighed (W_o), it was expressed in percentage. The difference in the two weights is used to calculate friability.

Friability = (1 − initial weight of tablet W/final weight of tablet W_o) × 100

Hardness

Prepared tablets were tested for hardness using Monsanto hardness tester. It is expressed in kg/cm^2. Six tablets from each formulation were tested for hardness and reported as mean ± SD.

Table 1: Composition of TLP LSC formulations

Formulation code	Liquid vehicle	Drug (mg)	Liquid vehicle (mg)	L_f=W/Q	*R*=Q/q	Avicel pH 102 (mg) (Q)	Neusilin mg (Q)	Aerosil 200 mg (q)	Sodium starch glycolate (mg)	Tablet weight (mg)
F1	Polyethyleneglycol-400	5	60	0.426	10.8	152.36	-	14.1	15	246
F2		5	60	0.757	8.08	-	85.8	10.61	15	176
F3		5	60	0.571	8.82	113.69	-	12.89	15	206
F4		5	60	0.899	8.04	-	72.27	8.98	15	161
F5		5	60	0.277	9.11	234.21	-	25.7	15	339
F6		5	60	0.678	5.81	-	95.75	16.42	15	192

LSC: Liquisolid compact, TLP: Trandolapril

Table 2: Liquisolid compact formulations containing HPMC $K_{15}M$

Formulation code	HPMC $K_{15}M$ (mg)	Total tablet weight (mg)
F1	50	296
F2	50	226
F3	50	256
F4	50	211
F5	50	389
F6	50	242

HPMC: Hydroxypropyl methylcellulose

Content uniformity

Ten tablets were weighed and powdered, and 5 mg equivalent weight of TLP was accurately weighed and transferred into a 100 mL volumetric flask. Initially, 10 mL of methanol was added and shaken for 10 min. Then, the volume was made up to 100 mL with pH 6.8 phosphate buffer. The solution is filtered through 0.22 µ filter, diluted suitably, and analyzed spectrophotometrically at 220 nm using UV-visible spectrophotometer.

In vitro drug release studies for trandolapril liquisolid compact and SR-trandolapril liquisolid compact

The developed TLP LSCs and sustained release LSC tablets were subjected to release studies using USP Type I dissolution apparatus at 75 rpm with a constant temperature at 37°C ± 0.5°C. Dissolution medium used was pH 1.2 (900 mL) for first 2 h and pH 6.8 phosphate buffer (900 ml) for next remaining hours for SR and pH 6.8 phosphate buffer for TLP LSS. The samples were withdrawn (5 mL) at different time interval and replaced with an equivalent amount of fresh medium. After filtration through 0.22 µ filter, the concentration of TLP was determined UV spectrophotometrically at 220 nm. Conventional SR-TLP tablets release studies were also carried out in the same manner.

Mathematical model fitting of in vitro drug release

In vitro release data of the SR TLP LSC tablets were fit into different equations and kinetic models to explain the release kinetics of TLP from SR LSC tablets. The kinetic models[20,21] used were zero order equation, first-order equation, Higuchi and Korsmeyer-Peppas models. Regression coefficients (R^2) and release exponents (n) calculated through various models. Release data were analyzed using the well-known semi-empirical equation shown as equation (4):

$$Mt/M\infty = ktn \quad (4)$$

Where $Mt/M\infty$ is the fractional releasing of the drug; t denotes the releasing time; k represents a constant, incorporating structural and geometrical characteristics of the SR tablets; and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, $n = 0.5$; for zero-order release (Case II transport), $n = 1$; and for super case II transport, $n > 1$.

Solid state characterization

Differential scanning calorimeter

Differential scanning calorimeter (DSC) analysis of TLP pure drug and LSC mixture were performed using Perkin Elmer DSC (DSC 4000, USA). Pure drug sample, optimized LSC mixture (approx. 8 mg) were heated in aluminum pans within a heating range of 40–200°C[22] and at a rate of 10°C/min using dry nitrogen as the effluent gas, empty aluminum pan is used as reference.

Powder X-ray diffraction

Powder X-ray diffractometer (PXRD) (XRD-6000, Shimazdu, Japan) was used for diffraction studies. Powder XRD studies were performed on the samples by exposing them to nickel filtered CuKα radiation (40 kV, 30 mA) and scanned from 2° to 70°, 2 θ at a step size of 0.045° and step time of 0.5 s. Samples used for PXRD analysis were pure drug, and optimized LSC formulation.[23]

Scanning electron microscope

Surface morphology, particle shape of samples were analyzed by scanning electron microscope (SEM) (Hitachi, Japan) studies. The samples were first adhered to the carbon-coated metallic stub. This was sputter coated with platinum coating machine and mounted on SEM for surface analysis. Imaging was carried out at acceleration voltage of 30 kV.[24]

RESULTS AND DISCUSSION

Solubility study of trandolapril

Solubility data of TLP in various pH media and liquid vehicles are shown in Table 3. From the results, the solubility of drug was increased (8.88 ± 0.57 µg/mL in pH 1.2) with increased pH up to the pH 6.8 phosphate buffer (88.84 ± 2.51 µg/mL). Hence, TLP was highly soluble in pH 6.8 phosphate buffer than other media, and this buffer was used as dissolution media for *in vitro* release studies.[25] After separating the supernatant, it was diluted initially with methanol and further with pH 6.8 phosphate buffer. Among all liquid vehicles, drug has high solubility in PEG-400, it indicates that drug was molecularly dispersed uniformly.

Measuring angle of slide for determination of flowable liquid retention potential

The values of φ_{Ca} and φ_{Co} for liquid vehicles were used to calculate L*f*. The lowest liquid load factor was obtained for

Avicel, and accordingly, the amount of carrier was higher than other formulations. The highest liquid factor was obtained for Neusilin.

$L_f = \varphi_{ca} + \varphi_{co} (1/R)$

$L_f = 0.57 + 3.95 (1/8.82) = 0.51$

Based on this equation, L_f is calculated using different R values.

Liquisolid compact of TLP was prepared with Avicel (F1, F3 and F5) and Neusilin (F2, F4 and F6) as carrier material, each with three different concentrations. Further, TLP LSC and SR LSC tablets were prepared by direct compression method. Depending on the excipient ratio (R) of the powder substrate, an acceptably flowing and compressible liquisolid system can be obtained only if a maximum liquid load on the carrier material is not exceeded.

Flow properties of liquisolid compact

Powder flowability is one of the critical parameter in the compressibility of drug molecule with high dose. Angle of repose, Carr's index and Hausner's ratio of the prepared LCS are showed in Table 4. From the results the angle of repose values below the 25°, Carr's index 11.3 ± 0.45–16.8 ± 0.81 and Hausner's ratio 1.35 ± 0.01–1.98 ± 0.04. Hence, the LCS powder was free-flowing.

Table 3: Solubility data trandolapril in various pH media and liquid vehicles

Media/Vehicle	Solubility (µg/mL)
Media	
0.1N HCl	8.88±0.57
pH 4.5 acetate buffer	27.74±0.82
pH 6.8 phosphate buffer	88.84±2.51
pH 7.4 phophate buffer	23.72±0.83
Vehicle	
PEG-400	26.28±1.05
Polysorbate 80	11.55±1.22
Labraphil	4.39±0.95

Table 4: Characterization of powder mixtures of LSC

Formulation code	Angle of repose	Car's index	Hausner's ratio
F1	17.5±1.66	13.6±0.57	1.82±0.02
F2	23.8±1.08	15.3±0.42	1.74±0.01
F3	19.6±1.23	14.38±0.67	1.70±0.01
F4	25.7±2.92	12.9±0.39	1.64±0.03
F5	16.0±0.98	16.8±0.81	1.98±0.04
F6	21.58±2.21	11.3±0.45	1.35±0.01

LSC: Liquisolid compact

Evaluation of trandolapril liquisolid compact and SR trandolapril liquisolid compact tablets

The data of physical parameters such as hardness, content uniformity, friability of all the formulations (both TLP LSC and SR tablets) are enclosed in Table 5 and Table 6. All the parameters lie within the limits according to IP. The hardness was maintained as 4.0 ± 0.52–5.2 ± 0.38 kg/cm^2 and 4.0 ± 0.78–4.9 ± 0.35 kg/cm^2 in all the formulations of TLP LSC and SR tablets, respectively. The friability of all the formulations falls in the acceptable limit. The content uniformity was found to be in acceptable pharmacopeial limits (IP).

In vitro release studies

In vitro drug release from LSCs and SR LSC are shown in the Figures 1 and 2. In TLP LCS tablets, the drug present on the surface of the carrier material dissolves after exposure to dissolution medium, this leads to initial burst release of the drug, this burst release may act as loading dose. From the Avicel containing formulations, drug release was continued for 120–160 min (F1-96.55 ± 1.22% in 140 min, F3-94.1 ± 3.11% in 120 min and F5-90.1 ± 2.63% in 160 min) whereas with Neusilin it was continued for 100–120 min. Similarly, drug release from bulk was found to be 51.37 ± 2.34% in 160 min. This increase in the dissolution rate of

Table 5: Physical characterization of conventional TLP LSC tablets

Formulation code	Hardness kg/cm^2	Friability (%)	Percentage drug content
F1	4.0±0.52	0.35±0.02	97.8±1.27
F2	4.3±0.67	0.41±0.03	96.2±1.06
F3	5.2±0.38	0.28±0.02	95.4±0.95
F4	4.6±0.48	0.56±0.14	96.8±0.83
F5	4.3±0.44	0.46±0.01	98.2±1.39
F6	4.8±0.67	0.3±0.02	97.5±1.15

TLP: Trandolapril, LSC: Liquisolid compact

Table 6: Physical characterization of SR TLP LSC tablets

Formulation code	Hardness kg/cm^2	Friability (%)	Percentage drug content
F1	4.4±0.44	0.52±0.05	95.5±1.79
F2	4.1±0.97	0.64±0.06	94.7±0.66
F3	4.0±0.78	0.59±0.03	96.8±1.67
F4	4.9±0.35	0.48±0.09	95.8±0.98
F5	4.3±0.62	0.55±0.10	97.6±1.93
F6	4.7±0.71	0.62±0.04	98.5±1.75
F7	5.3±1.03	0.59±0.05	99.1±2.03

TLP: Trandolapril, LSC: Liquisolid compact

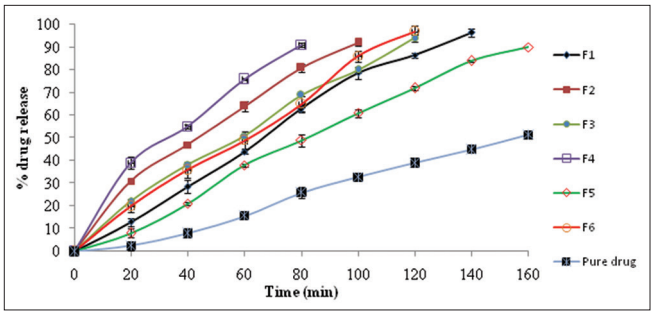

Figure 1: *In vitro* dissolution profiles of conventional trandolapril liquisolid compact tablets (mean ± standard deviation)

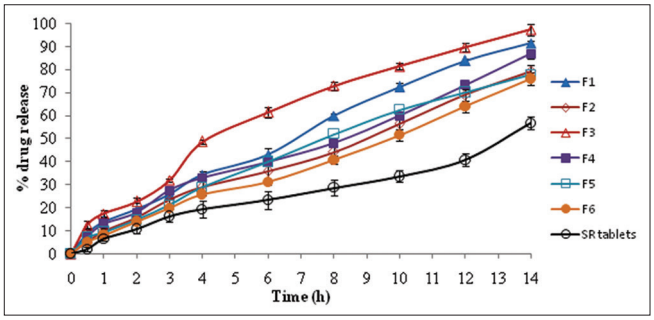

Figure 2: *In vitro* drug release profiles of trandolapril sustained release liquisolid compact tablets (mean ± standard deviation)

LSC formulation was due to the increased wettability and surface availability of drug to the dissolving medium as drug is molecularly dispersed within a water-miscible solvent like PEG 400 when compared with pure drug.

From the SR TLP LSCs, F1, F3 and F5 formulations showed more retarding drug release of 91.39 ± 2.16%, 97.3 ± 2.59% and 77.69 ± 3.11% during 14 h. Formulation with higher amount of the Avicel (F5) showed a decrease in the initial burst release than other (F1 and F3), as the concentration of Avicel increases the drug release retarded. Formulations containing Neusilin F2, F4 and F6 showed release of 79.23 ± 1.24, 86.71 ± 2.02 and 75.99 ± 2.11%, respectively. From this, the concentration of Neusilin increases the release of drug decreased but, compared with Avicel drug release was found to be lower. Further, *in vitro* release of SR TLP tablets showed 56.72 ± 3.16% in 14 h. The sustained action of TLP from the SR LSC was due to the concentration and swellable nature of the HPMC $K_{15}M$ polymer responsible for the release retardation of the drug release from the LSCs. From the dissolution profiles, all LSC formulations significantly sustain drug dissolution compared to conventional tablets, thus optimized F3 formulation showing 97.3 ± 2.59% drug release in 14 h, which is more sustained than other LS formulations. The amount of Neusilin was required less to absorb the same amount of liquid vehicle than Avicel, which lowered the total weight of tablet. From the kinetic modeling, release of SR LSC of TLP tablets followed Peppas model (r^2 value 0.981) with nonfickian diffusion mechanism (n value more than 0.5) [Table 7].

Table 7: Regression coefficient (R^2) values of SR TLP LSC tablets

Formulation	R^2 values of SR TLP LSC tablets				
	Zero order	First order	Higuchi	Peppas	
				R^2 value	n value
F1	0.992	0.945	0.957	0.99	0.723
F2	0.992	0.954	0.949	0.995	0.796
F3	0.958	0.928	0.98	0.981	0.659
F4	0.987	0.916	0.953	0.992	0.773
F5	0.991	0.99	0.96	0.988	0.773
F6	0.993	0.947	0.933	0.994	0.809
SR tablets	0.969	0.936	0.922	0.963	0.898

LSC: Liquisolid compact, TLP: Trandolapril

From the above results, formulation of conventional TLP LSC into SR dosage forms advantageous for prolonged drug release, further beneficial in reducing the frequency of administration and was also reported earlier by Javadzadeh *et al*., 2008 and Elkordy *et al*., 2012.[19,24]

Mechanisms of enhanced drug release from the liquisolid systems might be due to an increased surface area of drug available for release; an increased aqueous solubility of the drug; an improved wettability of the drug particles and formation of a complex between the drug and excipients or any changes in crystallinity of the drug.[26]

Solid state characterization

The potential precipitation is dependent on the solubility of the drug in the solvent and the degree of saturation of the drug solution or interaction between components. It has been shown that polymorphic changes of the drug are important factors that may affect the dissolution rate and bioavailability.[28] Therefore, polymorphic changes of TLP in liquisolid formulations are essential to study. The most traditional method for the differentiation of crystalline changes of TLP and TLP LSC is with DSC and PXRD.

Differential scanning calorimetry

Differential scanning calorimetry analysis was used to determine the crystalline nature and incompatibility of the drug with excipients used in the formulation development. DSC thermogram of TLP showed a sharp endothermic peak at 121.32°C corresponding to its melting point, this sharp endothermic peak indicates the crystalline nature of drug [Figure 3]. Absence of endothermic peak of the TLP in LSC formulation, indicating that the drug is solubilized and molecularly dispersed within LSC mixture. This could be the reason for enhanced drug dissolution rate from LSCs. This was further confirmed by powder XRD studies.

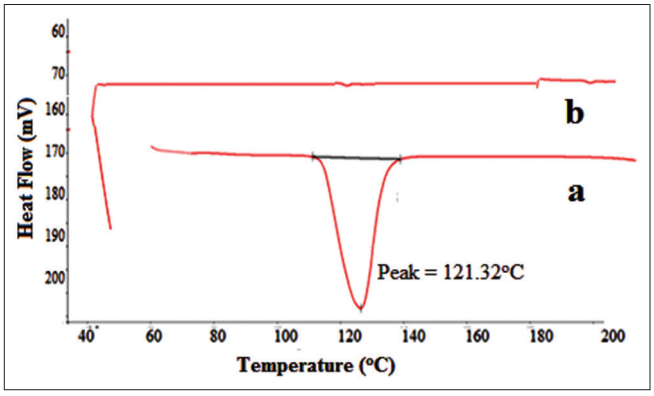

Figure 3: Differential scanning calorimeter thermograms of (a) pure drug, and (b) optimized (F3) liquisolid mixture

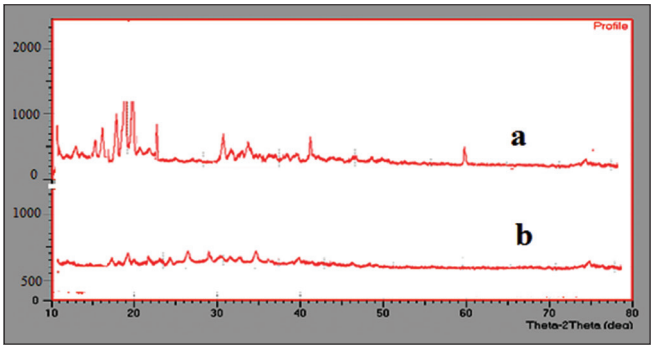

Figure 4: (a) X-ray diffractograms of pure drug, (b) and liquisolid compact mixture

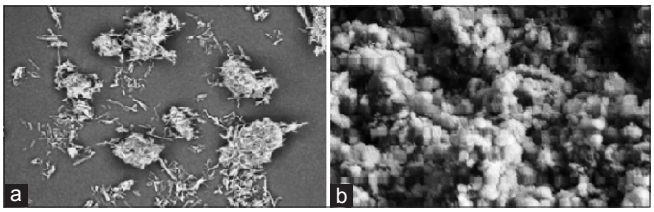

Figure 5: Scanning electron microscopy images of (a) pure drug, and (b) optimized formulation

Powder X-ray diffraction studies

Powder X-ray diffraction studies also used for the characterization of crystalline state of drug and physical mixtures. TLP exhibited high-intensity peaks at 15°, 16°, 18°, 20°, 23° and 31°[29] But, the distinctive peaks of drug in LSC mixture was disappeared, indicating that the drug was dissolved molecularly in LSC mixture. This also suggests that TLP was in amorphous state in the LSC mixture [Figure 4] and might be resulted in dissolution rate.[30]

Scanning electron microscope

Scanning electron microscope images of TLP showed the needle-shaped crystals indicating the crystalline nature of the drug. SEM photomicrograph of optimized LSC mixture (F3) shows that the drug particles are entrapped/adsorbed onto the surface of the carrier material. This surface modification ensures that the decrease in crystallinity of the drug particle [Figure 5].

CONCLUSION

Liquisolid compacts technique can be effectively used for the preparation of sustained release tablets of TLP with PEG-400 was used as liquid vehicle. DSC and XRD analyze that TLP was in amorphous form in the LSCs. LSCs were prepared with PEG-400 could be useful formulation to enhance the solubility and the *in vitro* dissolution rate of TLP, solubilization effect of hydrophilic carriers results in the increased wettability. SEM images suggest that alteration of the surface properties of the drug particles. LSCs of TLP can be a promising approach for sustaining the drug release up to 14 h, which was achieved by admixing the HPMC $K_{15}M$ polymer. Solubilization of drug in liquid vehicle and increased wettability by hydrophilic carrier material of LSCs could improve the dissolution rate and thus enhancing the oral bioavailability.

REFERENCES

1. Kawabata Y, Wada K, Nakatani M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. Int J Pharm 2011;420:1-10.
2. Jain A, Ran Y, Yalkowsky SH. Effect of pH-sodium lauryl sulfate combination on solubilization of PG-300995 (an anti-HIV agent): A technical note. AAPS PharmSciTech 2004;5:e45.
3. Müller RH, Mehnert W, Sven G. Solid lipid nanoparticles (SLN) for controlled drug delivery - A review of the state of the art. Eur J Pharm Biopharm 2000;50:161-77.
4. Tirucherai GS, Mitra AK. Effect of hydroxypropyl beta cyclodextrin complexation on aqueous solubility, stability, and corneal permeation of acyl ester prodrugs of ganciclovir. AAPS PharmSciTech 2003;4:E45.
5. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev 2007;59:617-30.
6. Wen X, Tan F, Jing Z, Iiu Z. Prepration and study of the 1:2 inclusion complex of carvedilol with R – cyclodextrin, Simeoni. J Pharm Biomed Anal 2004;34:517-23.
7. Javadzadeh Y, Musaalrezaei L, Nokhodchi A. Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. Int J Pharm 2008;362:102-8.
8. Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). Int J Pharm 2007;341:26-34.
9. Spireas S. US Patent 6423339B1; 2002.

10. Spireas S, Sadu S, Grover R. *In vitro* release evaluation of hydrocortisone liquisolid tablets. J Pharm Sci 1998;87:867-72.
11. Spiras S, Bolton SM. Liquisolid Systems and Methods for Preparing Tsame. United States Patent 5,968550;1999.
12. Spiras S, Bolton SM. Liquisolid Systems and Methods for Preparing Tsame. United States Patent 6,096337;2000.
13. Kulkarni SD, Bakliwal SR, Rane BR, Pawar SP, Gujarathi NA. Evaluation of liquisolid compacts using response surface methodology. Int J Drug Deliv 2012;4:427-33.
14. Peters DC, Noble S, Plosker GL. Trandolapril. An update of its pharmacology and therapeutic use in cardiovascular disorders. Drugs 1998;56:871-93.
15. Higuchi T, Connors KA. Phase solubility techniques. Adv Anal Chem Instrum 1965;4:117-212.
16. Spireas S, Sadu S. Enhancement of prednisolone dissolution properties using liquisolid compacts. Int J Pharm 1998;166:177-88.
17. Tayel SA, Soliman II, Louis D. Improvement of dissolution properties of Carbamazepine through application of the liquisolid tablet technique. Eur J Pharm Biopharm 2008;69:342-7.
18. Hegde RP, Rheingold JL, Welch S, Rhodes CT. Studies of powder flow using a recording powder flowmeter and measurement of the dynamic angle of repose. J Pharm Sci 1985;74:11-5.
19. Javadzadeh Y, Musaalrezaei L, Nokhodchi A. Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. Int J Pharm 2008;362:102-8.
20. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydro-matrices and other factors may be responsible. Int J Pharm 1983;15:25-35.
21. Peppas NA. Analysis of Fickian and non-Fickian drug matrix tablets with respect to the compression force release from polymers. Pharm Acta Helv 1985;60:110-1.
22. Ford JL, Mann TE. Fast-Scan DSC and its role in pharmaceutical physical form characterisation and selection. Adv Drug Deliv Rev 2012;64:422-30.
23. Vogt FG, Williams GR. Advanced approaches to effective solid-state analysis: X-ray diffraction, vibrational spectroscopy and solid-state NMR. Am Pharm Rev 2010;13:58-65.
24. Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: *in vitro* and *in vivo* evaluation. Eur J Pharm Biopharm 2008;69:993-1003.
25. Saeedi M, Akbari J, Morteza-Semnani K, Enayati-Fard R, Sar-Reshteh-Dar S, Soleymani A. Enhancement of dissolution rate of indomethacin: Using liquisolid compacts. Iran J Pharm Res 2011;10:25-34.
26. Elkordy AA, Essa EA, Dhuppad S, Jammigumpula P. Liquisolid technique to enhance and to sustain griseofulvin dissolution: Effect of choice of non-volatile liquid vehicles. Int J Pharm 2012;434:122-32.
27. Abdou HM, editor. Dissolution, Bioavailability and Bioequivalence. Easton, Pennsylvania: Mack Pub. Co.; 1989. p. 53-72.
28. Javadzadeh Y, Siahi MR, Asnaashari S, Nokhodchi A. An investigation of physicochemical properties of piroxicam liquisolid compacts. Pharm Dev Technol 2007;12:337-43.
29. Bader T. Polymorphic and Pseudo Polymorphic forms of Trandolaprilate, Pharmaceutical Compositions and Methods for Production and use. United States Patent No. US7943655B2.
30. Sanjeev RG, Ravindra J. Formulation and characterization of atorvastatin calcium liquisolid compacts. Asian J Pharm Sci 2010;5:50-60.

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