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Amalgamation of solid dispersion and adsorption technique

A case study of ritonavir

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Abstract The objective of present investigation was to improve dissolution of ritonavir (RTV), a BCS Class II drug. Amalgamation of solid dispersion and melt adsorption technology was utilized for developing the formulation. Solid dispersion adsorbate (SDA) was prepared using combination of Lutrol F127, Transcutol HP and Labrasol as carriers and Neusilin as an adsorbent and flow inducer. The concept of design of experiments (DoE) was used in identifying the critical formulation factors. The optimised SDA was characterised by Fourier transform infrared spectroscopy, differential scanning calorimetry, thermogravimetric analysis and X-ray diffraction studies. From the results obtained, it can be concluded that improvement in dissolution of RTV was due to hydrogen bonding of drug with Neusilin, micellar solubilisation of drug in carrier, improved wettability and reduction in the crystallinity. The dissolution efficiency value of optimised SDA is 41.68 % at 10 min time point which is three times the release of untreated drug. Convolution modelling was employed to get a predicted plasma drug concentration time profile.

Keywords Ritonavir · Solid dispersion adsorbate · Neusilin · Lutrol F127 · Transcutol HP · Labrasol · Dissolution

Introduction

More than 81 % of the best-selling pharmaceutical products today are administered by the oral route [1]. Due to advances in combinatorial chemistry and high throughput screening, more than 40 % of the newly discovered active pharmaceutical ingredients (API) exhibit high lipophilicity and often high activity, but poor water-solubility [2–4]. As a result, drug dissolution into gastrointestinal (GI) tract fluids, which is recognized as a prerequisite for absorption into the systemic blood stream, has become a major challenge for oral drug delivery. To assist successful oral drug development, in vitro dissolution testing has emerged as a potential performance test to evaluate development potential of new APIs and drug formulations [5]. The Biopharmaceutics Classification System (BCS) classifies APIs into four basic groups according to their solubility and permeability [6]. Increased risk for successful drug product development can be considered with BCS class II and IV APIs, which are usually quite lipophilic and, thus, sparingly water soluble. For BCS class II drugs, oral absorption is predominantly limited by their (a) inability for the whole dose to be dissolved in the GI aqueous contents or (b) too slow dissolution rate. Generally, the bioavailability of a BCS class II drug is rate-limited by its dissolution, so that even a small increase in dissolution rate sometimes results in a large increase in bioavailability. Therefore, an enhancement of the dissolution rate of the drug is thought to be a key factor for improving the bioavailability of BCS class II drugs [4, 7]. Various techniques have been used to improve dissolution rates of poorly water-soluble drugs which include solid dispersion, micronization, lipid-based formulations, melt granulation, direct compaction, solvent evaporation, co-precipitation, adsorption, ordered mixing, liquisolid compacts, inclusion complexation, steam-aided granulation, etc. [8, 9].

Solid dispersion is the most widely used technique because of promises it offers in the bioavailability enhancement of poorly water-soluble drugs, low cost and

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industrially feasible [10]. Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared my melting, solvent or melting-solvent method [11]. However, the process can be individualized depending on the interaction between drug and carrier. Poor compressibility, scale up, requirement of large amount of carrier and poor stability are the main problems associated with this technique [12]. The third generation solid dispersions (solid dispersions with surfactant) may overcome some of the problems. Complete drug dissolution can be achieved from solid dispersion by using surface active carrier [13]. The solid dispersion can be adsorbed onto a suitable adsorbent to form a free flowing powder.

Ritonavir (I) (RTV), [5S-(5R*,8R*,10R*,11R*)]-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, is a novel protease inhibitor. It is used for treatment of acquired immunodeficiency syndrome (AIDS) and it belongs to BCS Class—II [14–16]. Different approaches have been worked by various investigators to improve dissolution properties, which might lead to decrease in variation in bioavailability demonstrated by pure RTV [17].

Recently, poloxamers, a group of non-ionic surfactants, have been reported to improve the dissolution of poorly water-soluble drugs from solid dispersions [10, 18]. Lutrol F127 (Poloxamer) has been successfully utilized to enhance the dissolution rate of poorly water-soluble drugs [18]. Neusilin® was used in the present investigation as an adsorbent. It exhibits high specific area, increased surface adsorption, porosity, anticaking and flow enhancing properties. These features of Neusilin allow formulators to explore solid dispersion technology to improve bioavailability and overcome problems associated with processing and stability of poorly water-soluble drugs. Neusilin has silanol groups on its surface, which make it a potential proton donor as well as acceptor. The hydrogen bonding potential of silanol in the local environment on silica surfaces is well documented [12, 19–22].

In the present work, amalgamation of solid dispersion and melt adsorption technology was utilized to prepare solid dispersion adsorbate (SDA) of RTV in order to improve its dissolution rate [12, 23]. The drug dissolution properties from SDA were studied and compared with untreated RTV. Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), thermogravimetric analysis (TG) and X-ray diffraction analysis (XRD) were used to characterize the solid dispersions. The concept of design of experiment was used since it is an integral part of quality by design (QbD).

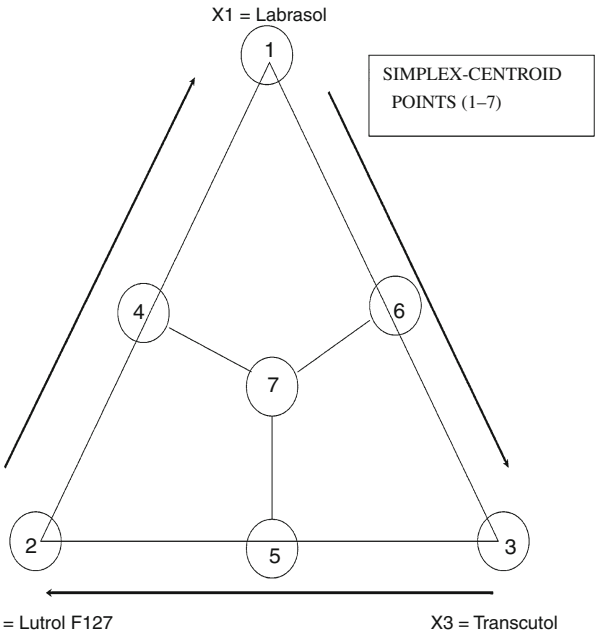

Fig. 1 Simplex lattice design

Materials and methods

Materials

Ritonavir (RTV) was received as a gift sample from Torrent Research Centre (Gandhinagar, India). Lutrol F127, Transcutol and Labrasol were kindly gifted by BASF Ltd. (Mumbai, India). Neusilin US2 was procured from Gangwal Chemicals Ltd. (Mumbai, India). All other reagents used were of analytical grade.

Preparation of solid dispersion adsorbate and physical mixture

The drug to Neusilin to carrier ratio was fixed at 1:2:4 on the basis of outcome of preliminary trials. For Lutrol F127-RTV adsorbate (LT-RTV), RTV was added to melt of Lutrol F127 at 60 °C and mixed. After properly dispersing the drug, Neusilin was added and stirred until the blend was converted into a free-flowing powder form. In case of Transcutol and Labrasol (excipients in liquid form), the drug was dispersed in the excipient at ambient condition and then the drug dispersion was adsorbed onto the Neusilin to make Transcutol-RTV adsorbate (T-RTV) and Labrasol-RTV adsorbate (L-RTV), respectively. The solid dispersion adsorbates (SDA) were passed through 40# sieve to obtain free-flowing powder of uniform size. Simultaneously, physical mixture of drug and Neusilin in a ratio of 1:4 was also prepared by co-grinding.

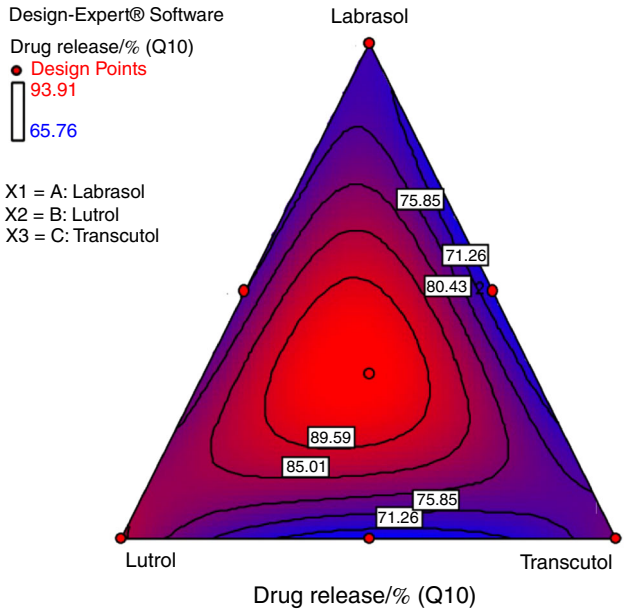

Fig. 2 Effect of formulation variables on percentage drug release in 10 min (Q10)

Simplex lattice design

A simplex lattice design was adopted to study the effect of the carriers, alone as well as in combination, on the drug release rate. In this design, three factors were evaluated by changing their concentrations simultaneously while keeping their total concentration constant. The simplex lattice design for a three-component system (X1, X2 and X3) is represented by an equilateral triangle in two-dimensional space (Fig. 1). The amount of Labrasol (X1), Lutrol F127 (X2) and Transcutol (X3) was selected as independent variables. The percentage drug release at 10 min (Q10) was selected as a dependent variable.

Statistical analysis

The statistical analysis of the results was performed by multiple regression analysis using Microsoft Excel. To graphically demonstrate the influence of each factor (independent variable) on the response (Q10), the response surface plot was generated using Design Expert 7.0.11 (State Ease, Inc., Minneapolis) demo version software. The outcomes of regression analysis are shown in Figs. 2 and 3.

Percentage yield and in vitro drug dissolution study

The percentage yield was calculated for each type of SDA. Drug release studies were performed in triplicate using paddle apparatus. Dissolution studies were carried out in 900 mL of 0.5 % SLS in 0.1 N HCl at 37 °C at 50 rpm. Physical mixture and untreated drug (equivalent to 100 mg drug) were also tested for dissolution behaviour. 10 mL of sample was withdrawn at 10, 15, 30, 45 and 60 min and replaced with the fresh dissolution medium. The solutions were filtered through Whatmann filter paper (0.22 μm) and assayed spectrophotometrically at 246 nm. The results are depicted in Fig. 4.

Dissolution efficiency

Dissolution efficiency (DE) was calculated using the Eq. 1 [24], where y is the percentage of dissolved drug. DE is then the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, $y100$, over the same time period. The dissolution efficiency for untreated drug, formulated products and checkpoint batch was calculated.

$$DE = \frac{\int_{t1}^{t2} y.dt \times 100}{y100.(t2 - t1)} \quad (1)$$

Physicochemical characterisation

FT-IR

FT-IR spectra of RTV and LT-RTV adsorbate were obtained using Shimadzu Biorad FT-IR system (Kyoto, Japan). Each sample was dispersed in dry potassium bromide (5 mass % of sample), ground well in mortar and pestle, and disc was prepared at a pressure of 1,000 psig. The disc was placed in the FT-IR sample holder, and IR spectra, in absorbance mode, were recorded in the spectral region 4,000–500 cm^{-1} using the resolution 1 cm^{-1}.

DSC study

The melting behaviour of RTV, Lutrol F127 and LT-RTV adsorbate were evaluated. Samples were sealed in aluminium pans and scanned from 30 to 200 °C at a heating rate of 10 °C min^{-1} in an atmosphere of nitrogen gas.

TG

The TG curves were obtained for RTV, LT-RTV and Lutrol F127. The conditions used in the experiments were as follows: nitrogen atmosphere at a flow rate of 50 mL min^{-1} and heating rate of 10 °C min^{-1} from 50 to 600 °C.

XRD study

The physical characterisation of RTV, LT-RTV and Lutrol F127 were subjected to XRD analysis using Philip's X-ray diffractometer. The experiment was carried out at 25 °C

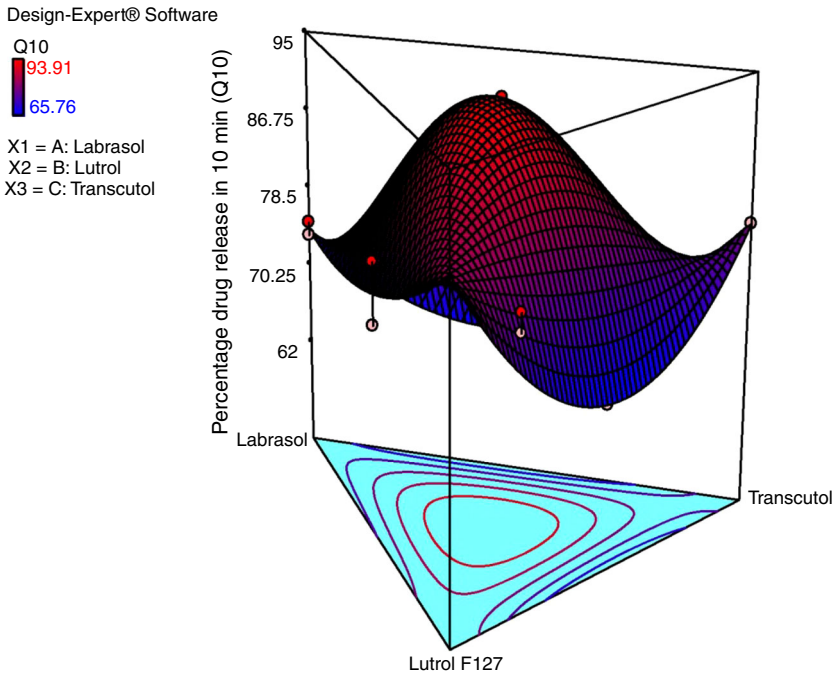

Fig. 3 Three dimensional response surface plot for percentage drug released in 10 min (Q10)

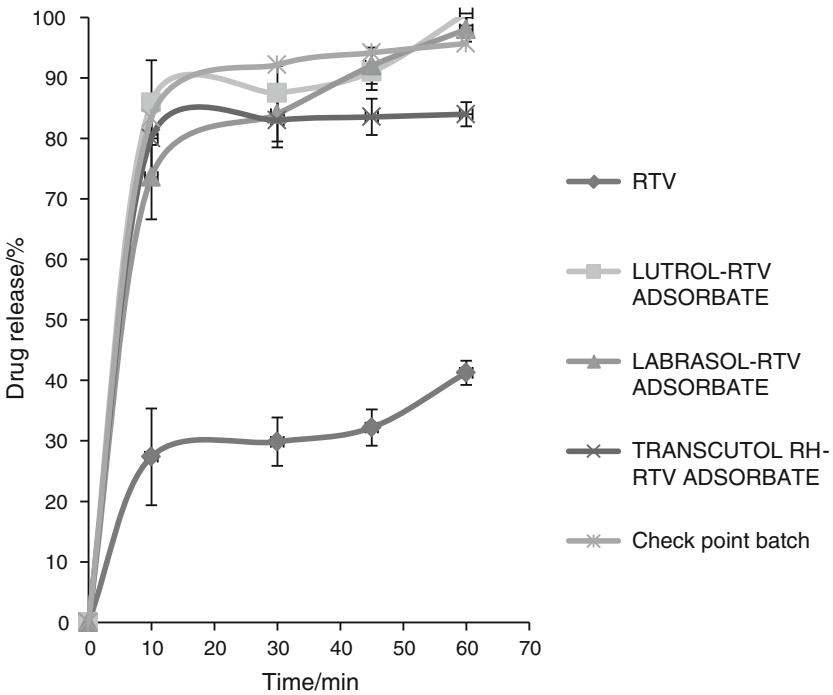

Fig. 4 The dissolution profile of RTV, prepared formulations and check point batch

under the following conditions: scanning angle ranged from 0 to 50 of 2θ, voltage—30 kV and current—40 mA.

Convolution modelling

One of the vital tests for a formulation developed at the R&D department of any pharmaceutical company is to achieve expected performance of the dosage form in vivo. Selection of a bio-batch has to be done intelligently so that failure is not seen in pilot or full scale in vivo testing. The in vitro drug dissolution data of checkpoint batch were merged with the reported pharmacokinetic parameters of RTV such as V_d, F, K_a and K_{el} to predict plasma drug-concentration time profile. A method for back calculation in Wagner Nelson approach was adopted [25]. The PK parameters for RTV are $V_d = 221227$ mL, $K_{el} = 0.1199\ h^{-1}$ and $K_a = 0.4332\ h^{-1}$.

The results were compared with the reported literature values [26].

Stability study

Stability study was performed according to ICH guidelines for 3 months. The final formulation was kept at 45 °C and 75 % RH conditions maintained in stability chamber. Dissolution study as well as DSC was carried out at the end of 3 months period to check inhibition of reversion of RTV to crystalline form.

Results and discussion

Preliminary studies were carried out to select suitable carrier. Neusilin was selected as an adsorbent owing to its good adsorptive capacity. The ratio of RTV to adsorbent (1:2) was fixed after evaluating the flow property. Ritonavir was dispersed in different hydrophilic carriers like Lutrol F127, Labrasol and Transcutol, to obtain SDA.

FDA prefers the use of concept of quality by design (QbD) in formulation development while evaluating the ANDA applications. Hence, the help of simplex lattice design, a subset of design of experiments, was adopted. There were two primary objectives: (1) To identify the critical variables that may influence the dissolution behaviour of RTV and (2) To identify the design space. The outcome of DOE can be of help in technology transfer and also in planning control strategy.

Simplex lattice design

The amount of hydrophilic carriers such as Labrasol, Lutrol F127 and Transcutol, respectively, was selected as independent variables (IV). The design layout and outcome of study are shown in Table 1. The actual and coded value is depicted in Table 2. A statistical model incorporating seven interactive terms was used to evaluate the response. The dependent variable (DV), percentage of drug released in 10 min (Q10), ranged from 67 to 93. The wider range of response indicates that the selected IV's exhibit effect on DV. Further data analysis is therefore warranted.

The relationship between the IV and DV can be expressed by Eq. 2.

$$Q10 = b1X1 + b2X2 + b3X3 + b12X1X2 + b23X2X3 + b13X1X3 + b123X1X2X3 \quad (2)$$

where, Q10 is the dependent variable and bi is the estimated coefficient for the factor Xi. The main effects (X1, X2 and X3) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2, X2X3, X1X3 and X1X2X3) show how the response changes when two or more factors are simultaneously changed. The statistical analysis of the simplex lattice design batches was performed by multiple linear regression analysis using Microsoft Excel. The data clearly indicate that the value of Q10 is strongly dependent on the independent variables. The statistically non-significant terms were eliminated from full model to obtain a valid reduced model, which is expressed by Eq. 3.

$$Q10 = 73.6\ X1 + 85.89\ X2 + 80\ X3. \quad (3)$$

The value of R^2 was calculated as 0.9959. Based on the results of regression analysis, it can be concluded that 99 % variability in the dependent variable is explained by the model. The Fisher's ratio (F value) was found to be 0.00938 ($P = 0.0093$). The results of analysis of variance (ANOVA) indicate that at least one of the selected independent variables has influenced the dependent variable. The main effects are statistically significant as indicated by Eq. 3 and therefore may be considered as critical formulation variables. The interaction terms have insignificant effect on the response variable as P value is greater than 0.05. The three main effects have almost similar numerical coefficients (73–86). Each of the IV's can be considered as critical since the value of coefficient is far greater than zero.

Table 1 Composition of simplex lattice design batches and response

Batch code	Transformed fraction of variables			Dependent variable
	X1	X2	X3	Q10/% ± SD
NR1	1	0	0	73.6 ± 2.3
NR2	0	1	0	85.89 ± 3.4
NR3	0	0	1	80 ± 3.2
NR4	0.5	0.5	0	72.15 ± 2.1
NR5	0	0.5	0.5	67.72 ± 3.6
NR6	0.5	0	0.5	65.76 ± 3.8
NR7	0.33	0.33	0.33	93.91 ± 1.3
NR8	0.5	0.5	0	78.87 ± 3.2
NR9	0	0.5	0.5	87.79 ± 3.2
NR10	0.5	0	0.5	72.58 ± 3.4

X1 amount of Labrasol, *X2* amount of Lutrol F 127, *X3* amount of Transcutol, *Q10* drug release/% in 10 min, *SD* standard deviation, $n = 3$

Table 2 Actual and coded values of design batch

Coded value	Actual value		
	X1/mg	X2/mg	X3/mg
1	400	400	400
0	0	0	0

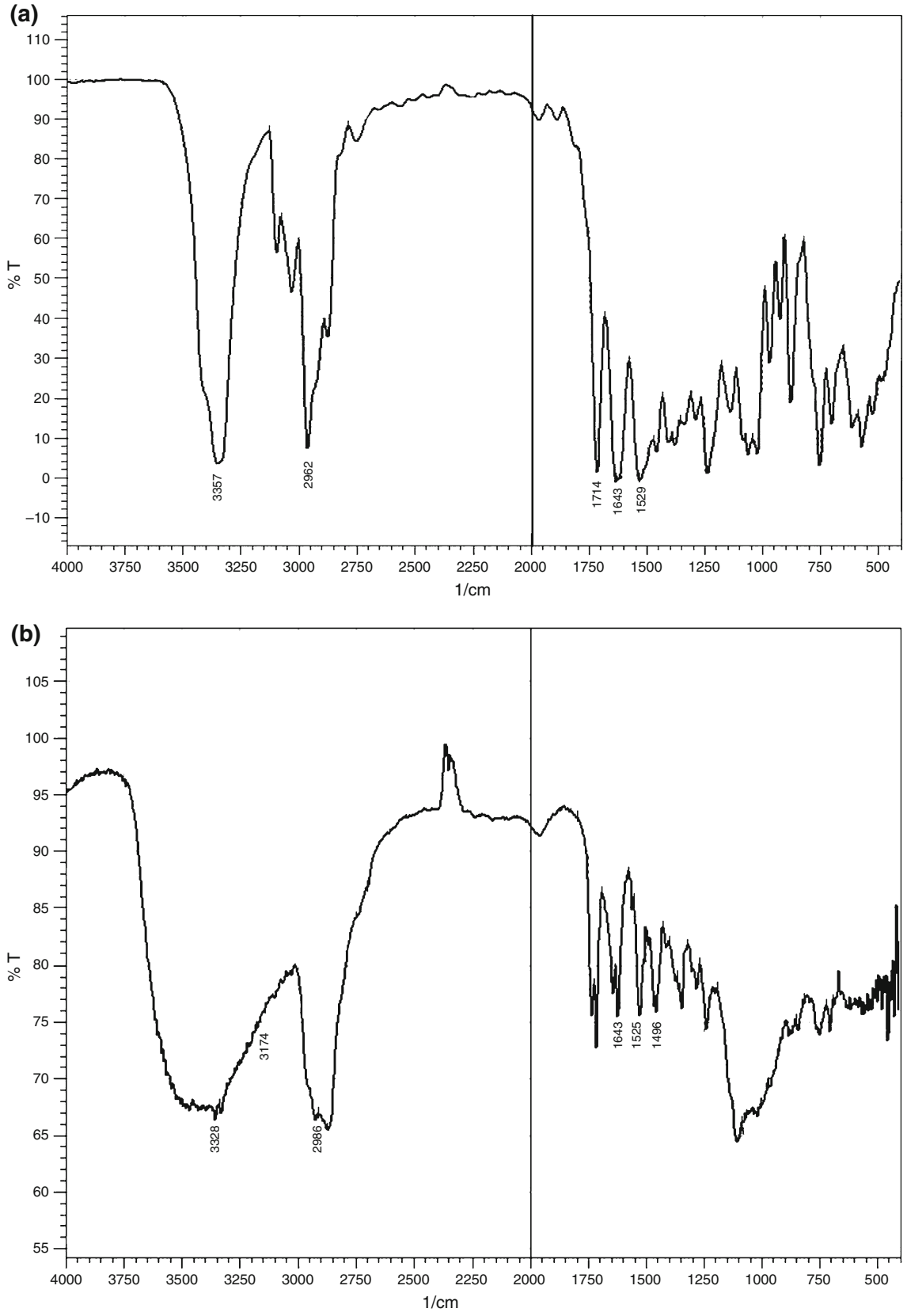

Fig. 5 The infrared spectrum of **a** RTV, **b** LT-RTV adsorbate

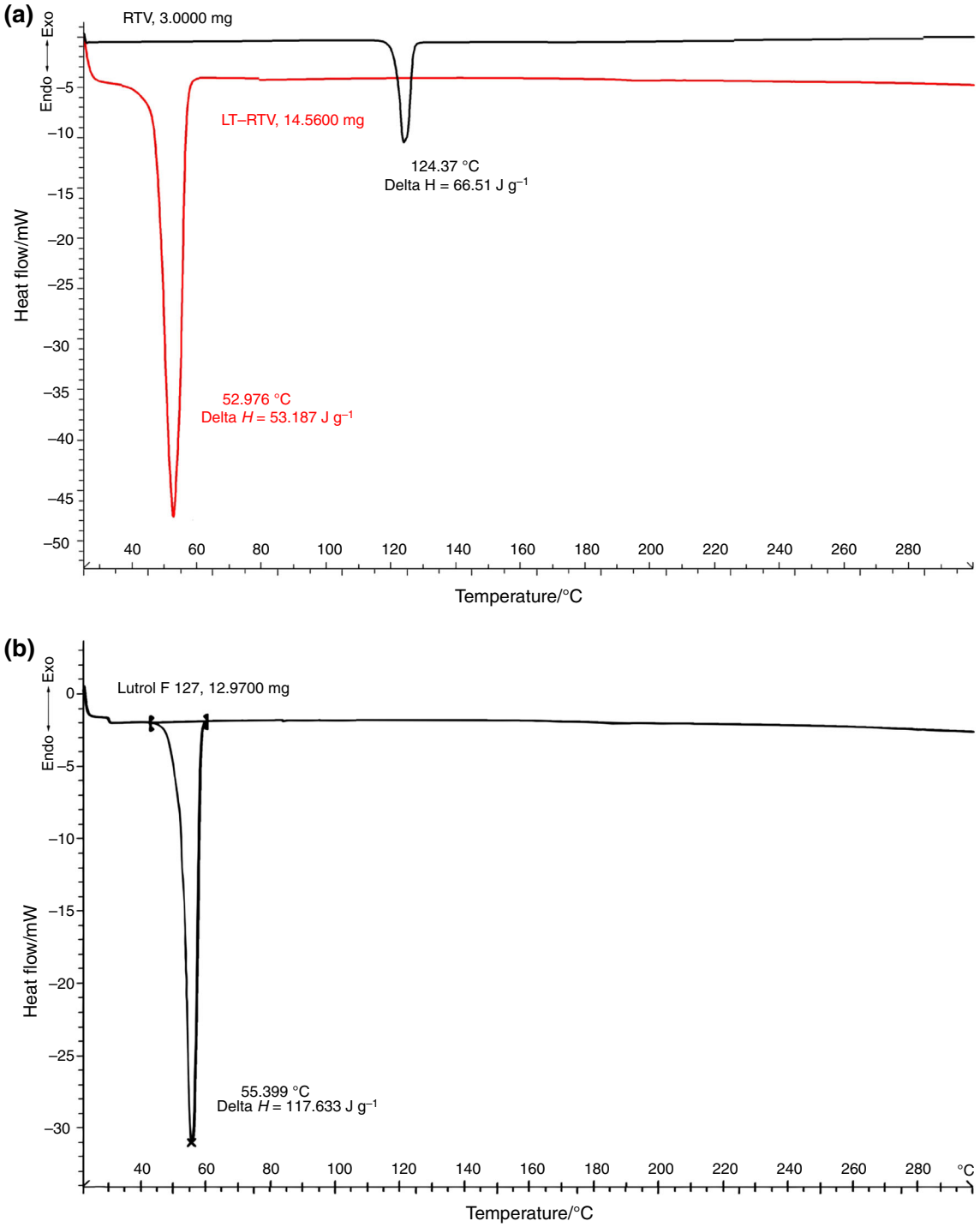

Fig. 6 DSC scan of **a** overlay of RTV and LT-RTV adsorbate **b** Lutrol F127

A checkpoint batch was prepared in order to validate the mathematical model shown in Eq. 3. Combination of all the three carriers was used keeping in view the amount of each excipient within IIG (Inactive Ingredient Guide) limits. The checkpoint batch contained Labrasol (70 mg), Lutrol F127 (110 mg), Transcutol HP (220 mg), Neusilin (200 mg) and RTV (100 mg). The calculated value of percentage drug release in 10 min was 80.5 % while practically observed value was 83 % from the check point batch. Thus, the model has reasonably good predictive ability.

One of the important considerations in industry is the percentage yield of adsorbate containing drug and excipients. The percentage yields were found to be 95, 90 and

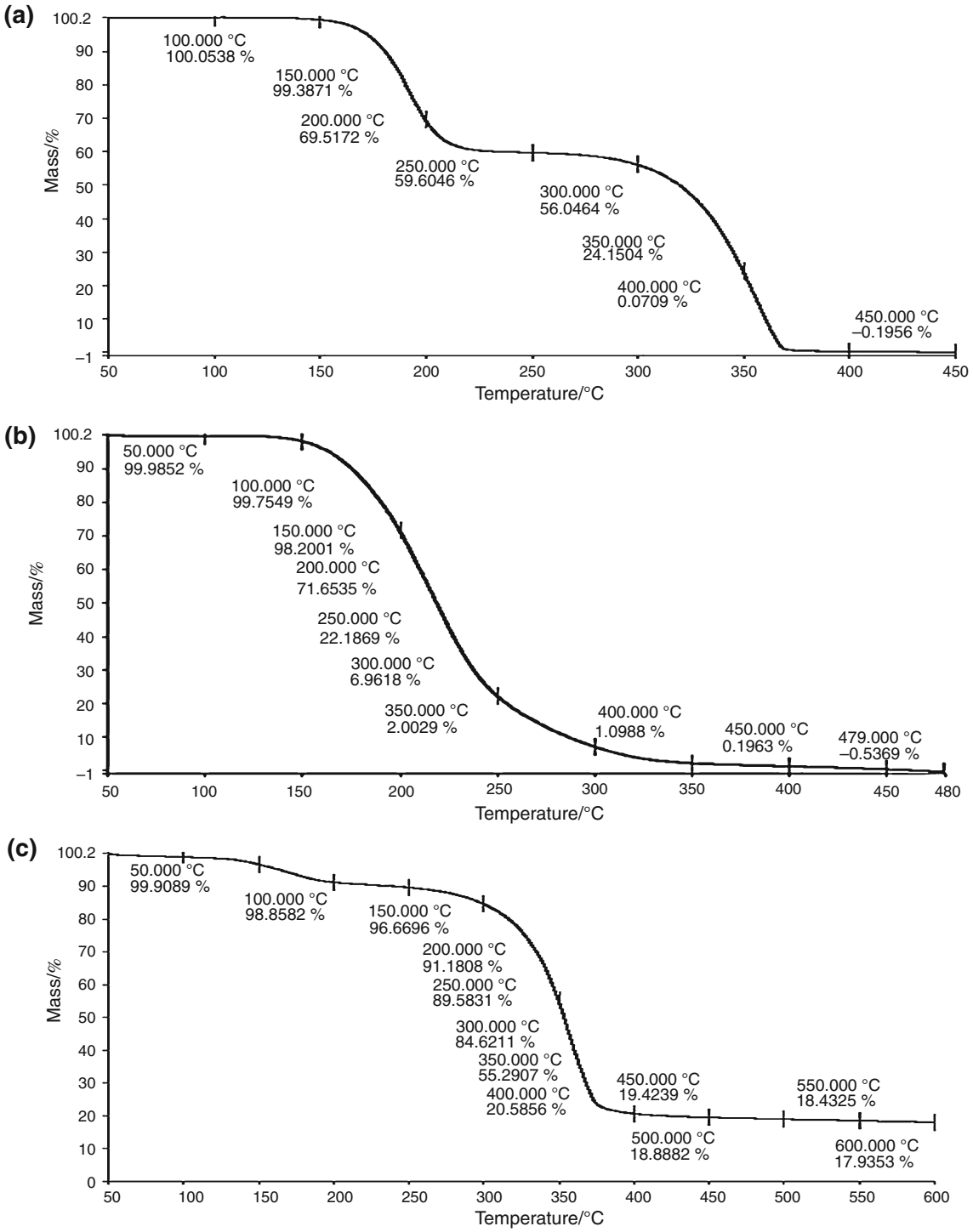

Fig. 7 TG curve of **a** RTV **b** Lutrol F127 and **c** LT-RTV adsorbate

70 %, respectively, for Lutrol-RTV, Transcutol-RTV and Labrasol-RTV. It is worthwhile to note that liquid excipients resulted in less yields as compared to meltable excipient.

The dissolution criteria for RTV were set as >70 % release in 10 min as per the CDER Report of Clinical Pharmacology/Biopharmaceutics review [16]. The formulation of Labrasol does not match the set criteria of >70 % release of RTV at 10 min so it was not considered further for formulation development. Highest drug release was seen with Lutrol-RTV adsorbate (about 86 % in 10 min) while Transcutol-RTV adsorbate showed 80 % drug

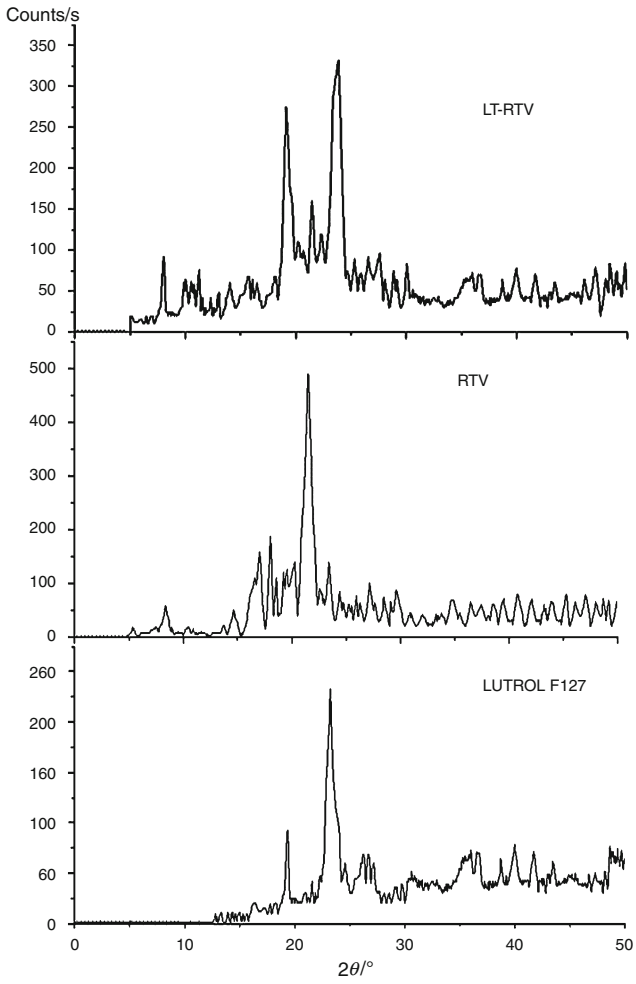

Fig. 8 The X-ray diffraction pattern of LT-RTV, RTV and Lutrol F127 adsorbate

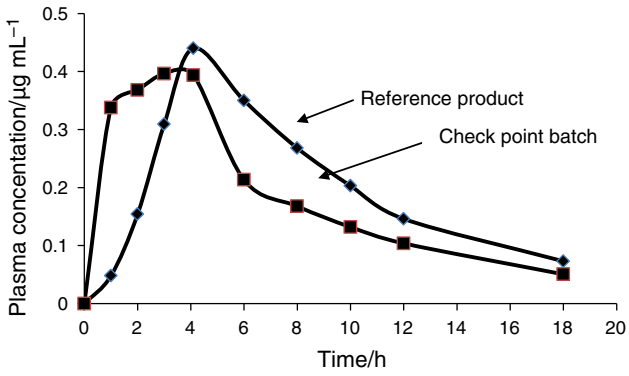

Fig. 9 Plasma concentration profile of check point batch and reference product

release in 10 min. Based on % yield and dissolution study, Lutrol-RTV adsorbate (Batch NR2) was selected for further characterization. The dissolution profile of prepared batches is shown in Fig. 4.

Table 3 Comparison of AUC, Cmax, Tmax of formulated batch with reported value [26]

Parameters	Calculated value for test product	Reference product
AUC_{0-t}/μg h mL^{-1}	3.43	3.67
$AUC_{0-\infty}$/μg h mL^{-1}	3.63	3.77
C_{max}/μg mL^{-1}	0.4	0.44
Approx. T_{max} h^{-1}	4	4.1

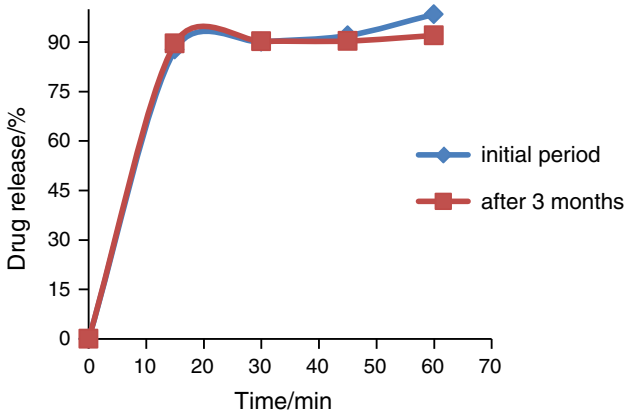

Fig. 10 Dissolution profile of LT-RTV batch before and after 3 months

Similarity factor is used for comparing two drug formulations. If the drug formulations are more than two, the comparison can be done using dissolution efficiency. Dissolution efficiency of untreated drug, Lutrol-RTV adsorbate, Transcutol-RTV adsorbate, Labrasol-RTV adsorbate and checkpoint batch was found to be 13.68, 42.94, 40, 36.8, 41.68 %, respectively, at 10 min time interval. Thus, the formulated products show threefold increase in the drug release compared to untreated drug. At the time point of 60 min, the dissolution efficiency of untreated drug, Lutrol-RTV adsorbate, Transcutol-RTV adsorbate, Labrasol-RTV adsorbate and checkpoint batch was found to be 20.62, 41.99, 50.33, 49, 47.83 %, respectively.

The FT-IR spectrum of RTV (Fig. 5) showed characteristic peaks at 3,357 cm^{-1} (secondary amine peak), 2,962 cm^{-1} (–CH_3– stretching), 1714 cm^{-1} (ester group), 1643 cm^{-1} (carbonyl ester peak) and 1529 cm^{-1} (–C=C– stretching aromatic carbons). The spectrum of solid dispersion adsorbate of RTV with Lutrol F127 shows shifting of peak from 1,643 cm^{-1} to 2,160 cm^{-1} and 2,248 cm^{-1}. It indicates complexation of Mg^{+2} and Al^{+3} with the carbonyl group. It transfers its lone pair of electrons to the metal ions so –C=O– is converted to –CO– which indicates π to π* transition. The –CO– group is weaker compared to –C=O– group so there is shifting of peak. Ester carbonyl group remains intact. There is possibility of intra hydrogen

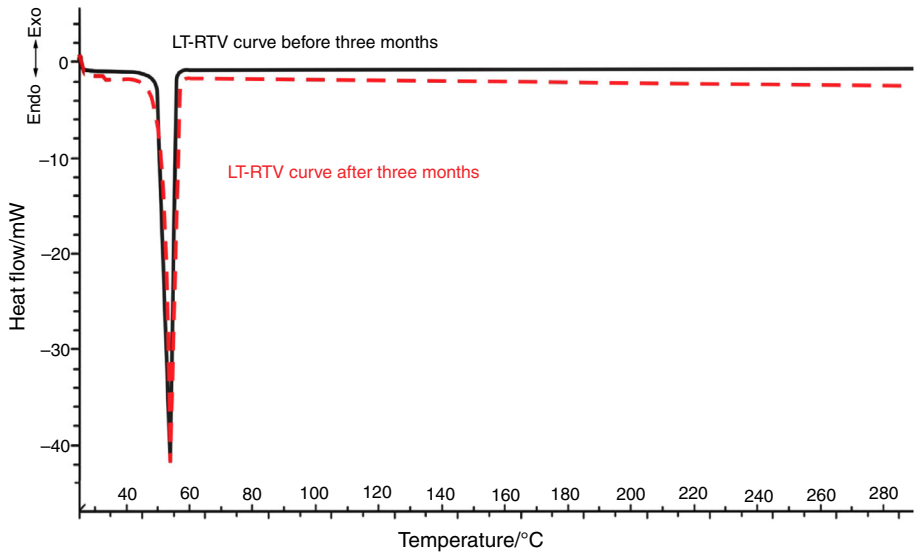

Fig. 11 DSC scan of LT-RTV adsorbate before and after 3 months

bonding with –NH– group which decreases the sharpness of peak of secondary amine and converts to tertiary amine. In case of adsorbate LT-RTV, an additional band of $–CH_2–$ stretching is seen at 2,986 cm^{-1} while in T-RTV, –OH– stretching is seen at 3,400–3,000 cm^{-1}. The other groups remain intact. It can be concluded that there is no interaction between drug, carrier and adsorbent. Also, hydrogen bonding between silanol group of Neusilin and RTV is seen, which is one of the factors responsible for the increase in the dissolution rate [21].

DSC curve of RTV, Lutrol F127 and the LT-RTV adsorbate was recorded. The DSC curve of RTV gives an endothermic peak corresponding to its melting point at 124.37 °C with an enthalpy value (ΔH) of 66.5 J g^{-1}. DSC curve of pure Lutrol F127 shows an endothermic peak corresponding to its melting point at 55.39 °C with an enthalpy value (ΔH) of 117.633 J g^{-1}. DSC curve of SDA has an endothermic peak near 52.97 °C with an enthalpy value (ΔH) of 53.187 J g^{-1}. Thus, the peak of carrier is seen intact, and endothermic peak corresponding to the melting point of the drug at 124.37 °C disappeared. This result indicates the formation of a monotectic system where the melting point of the carrier is unchanged in the presence of drug [27]. Also, the change in value of ΔH, compared to the pure drug, indicates the association between carrier and drug, indicating formation of SDA. The results are displayed in Fig. 6. Thus, formation of SDA results in improved drug dissolution due to solubilizing effect of carrier, improved wetting and reduction in crystallinity of drug [18].

In TG, the change in the experimental mass is measured as the temperature is increased at a predetermined rate. Percentage mass remaining of the compound is plotted against temperature (T). The TG curve of RTV, Lutrol F127 and LT-RTV adsorbate is shown in Fig. 7. Mass loss of 0.613, 1.8 and 3.34 % was observed for RTV, Lutrol F127 and LT-RTV adsorbate, respectively, at 150 °C [28]. Also as temperature is further increased to 200 °C, there is sudden loss in % mass of RTV and Lutrol F127 while loss in % mass of LT-RTV adsorbate is gradual and less. This indicates thermal stability of developed formulation against chemical induced degradation.

X-ray diffraction study was carried out for the RTV, Lutrol F127 and LT-RTV. Sharp and intense peaks at 2θ of 21.51° and 18.13° were observed in the diffraction spectrum of RTV indicating crystallinity. On the other hand, LT-RTV adsorbate showed the distinct broad peak that is observed in amorphous and highly disordered material which corresponds to diffraction pattern of Lutrol F127. The characteristic peak of ritonavir in adsorbate was less intense, indicating a decrease in the crystallinity of drug. The number of major peaks in LT-RTV SDA is three while for RTV the number increases to eighteen. This also indicates the decrease in the crystallinity of drug in SDA. This reduction of crystallinity may explain the higher drug release profile of SDA compared to RTV [29]. The results are shown in Fig. 8.

The purpose of carrying out dissolution test is not completed, until the analyst provides the simulated plasma drug level curves derived from dissolution results. Thus, from the results of convolution study as shown in Fig. 9 revealed faster onset of action and a quicker drug release rate of the formulated product. The bioavailability parameters were also comparable of the formulated product with the reference drug product as shown in Table 3.

Dissolution stability study of LT-RTV adsorbate performed at the end of 3 months revealed no change in the dissolution pattern. *t* test paired for two samples of means was performed to confirm these observations. *t* calculated (0.449) was less than t tabulated (2.776), thus the change

was found insignificant, and the release pattern remains the same on storage. Thus, the prepared formulation remains stable and there is no conversion of amorphous form back to crystalline form on storage. The dissolution profile is shown in Fig. 10. DSC study carried out after 3 months period confirms this result as no endothermic peak of RTV is observed. Only endothermic peak of Lutrol F127 is seen at 57.18 °C (Fig. 11).

Conclusions

Ritonavir, Neusilin and Lutrol F127 forms solid dispersion adsorbate in the ratio of 1:2:4. In vitro dissolution studies showed that 83 % of drug was released in 10 min which matches the required criteria of greater than 70 % drug release in 10 min [16]. Threefold increase in dissolution, compared to untreated drug (Ritonavir), was seen. The enhancement in dissolution may be due to hydrogen bonding between the drug and Neusilin, micellar solubilisation of drug in carrier, improved wettability and reduction in crystallinity. Inhibition of reversion of amorphous form to crystalline form is the main advantage of this technique. The result indicated that the solid dispersion adsorbate is a promising approach for the dissolution enhancement of ritonavir and can be used for the development of suitable solid dosage form for commercialization. The excipients were used within the limits permitted by IIG, and the current concept of QbD was adopted in the study. The formulation can be taken up for further studies in industry since the needs of industry and FDA were kept in mind while planning the study.

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