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Amorphous solid dispersions of ritonavir by melt-quenching: A quality by design approach

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***Abstract*---**Ritonavir is crystalline solid which is very slightly soluble in water yet having high dose. This condition necessitates enhancement of solubility before developing into dosage forms. Melt-quenching is recently exploring technique for developing amorphous solid dispersions (ASDs) for crystalline drugs to with a hydrophilic carrier to enhance solubility. ASDs have a drawback of poor thermodynamic stability which needs to be considered. The current work was aimed to develop ASDs for Ritonavir with improved solubility yet thermodynamically stable. Quality by design (QbD) was employed to elucidate the effects of the carrier, plasticizer and cooling temperature on the solubility and stability of the prepared ASDs. Differential scanning calorimetry (DSC) and X-ray diffraction (X-RD) analysis were performed to investigate the physical state of Ritonavir and the stability of the ASDs upon storage. These results illustrated the effects of the factors on the solubility and stability were significant at $p< 0.05$. Statistical optimization was performed to identify the best combination of the factors to obtain ASDs with maximum solubility and stability. ASDs prepared with Soluplus as carrier at 50% w/w, Poloxamer 188 as plasticizer 15% w/w at6.81^{o}C temperature were found to have desired solubility and stability.

***Keywords*---**ritonavir, melt-quenching, amorphous solid dispersions, quality by design, statistical optimization.

Introduction

Globally 70 million people were affected with HIV so far; among them more than 50% people were died. Initially HIV used to treat with one drug therapy for short

period mortality reduction, later shifted to two-drug therapy for better mortality benefit; unfortunately, two-drug therapy also achieved only short-term benefit. Now a day's three drug therapy is most widely accepted approach due to less mortality when compared to previous therapy. Currently 29 therapeutic moieties were approved for HIV therapy among them Ritonavir was one of the most potent CYP3A4 inhibitor ever described, initially 600mg daily dose was used for survival benefit (Eckhardtet al., 2017). Ritonavir is a highly lipophilic crystalline drug exhibiting extremely low aqueous solubility (Lawet al., 2004) and high permeability belongs to the BCS Class-II. Absorption of Drugs in GIT takes place only when drug is dissolved in GI fluids which pose a major problem for the drugs with poor aqueous solubility. Numerous approaches have studied to enhance solubility of Class-II drugs thereby enhancing bioavailability like particle size reduction which includes form micronization to production of nanoparticulate substances, β cyclodextrins, salt formation etc., all these methods suffer their own disadvantages (Raghuveeret al., 2020a; Raghuveer et al., 2020b; Sinha et al., 2010). Ritonavir suffers from poor aqueous solubility due to lipophilic nature and due to its crystallinity. Solid dispersions may be one of the best formulation strategies for Ritonovir because they can convert crystalline drug into more soluble amorphous form, this high solubility of amorphous form may be attributed lack of energy requirement to break the crystalline lattice of crystalline form (Paudwalet al., 2019).

FDA approvals for products containing solid dispersions were accelerated in the recent years makes solid dispersion as an important formulation strategy for solubility enhancement. Solid Dispersions are defined as dispersion of amorphous drug in a solid matrix i.e hydrophilic polymer where drug is dispersed in molecular state. Commercially Solid dispersions were produces by three methods. For drug which are possessing low melting point melt extrusion method will be more suitable. If the drug exhibit high melting point and low solubility in organic solvents co-precipitation method will be best choice. For drug soluble in any volatile solvent preferable method will be spray drying(Huanget al., 2014). All these methods include an organic solvent which may not be environmentally friendly, and presence of residual solvent may lead to several complications like reduction in shelf life (Shiet al., 2018). When compared crystalline solids amorphous solid dispersions possess high entropy and Gibbs free energy which makes them easily soluble when compared to crystalline solids. But these properties will also make them thermodynamically unstable, this stability issues responsible for conversion of ASDs into crystalline form upon storage. To successfully formulate ASDs there is an immense need to modify processing methods or materials which can impart thermodynamic stability (Costa et al., 2019). Quench cooling or melt cooling method is one of the most promising and less explored method for the preparation of ASDs in scalable manner and with more thermo dynamic stability and as this method does not require any volatile organic solvent or any sophisticated instrument. This technique of producing ASDs involves only careful control and monitoring temperatures (D'Angeloet al., 2018).

Current research was aimed to develop Ritonavir ASDs (RASDs) by exploring the suitability of melt-quench method for its solubility enhancement. For the preparation of ASDs a hydrophilic carrier along with a plasticizer were utilized to

study their ability in producing stable ASDs. Highly reported statistical tool quality by design (QbD) using Design Expert software was utilized to conduct present work (Srikaret al., 2019) in such a way that the influence of carrier, plasticizer and processing temperature on solubility and stability of the prepared RASDs were studied. Further, optimization was performed to identify the best combination of the factors to achieve RASDs with maximum solubility and stability.

Materials and Methods

Materials

Ritonavir was a gift sample from M/s EASAI Pharma Technology Pvt. Ltd., Visakhapatnam Soluplus, Poloxamer 188 and Starch citrate were procured from commercial sources. All other materials used were of pharmacopeial grade.

Development of Ritonavir ASDs
QbD aspects

The target quality of the ASDs to be developed is to have high solubility and high thermodynamic stability. Thermodynamic stability of the ASDs can be expressed based their conversion rate into crystalline compounds which ultimately result in decreased solubility. So, the change in the solubility of the ASDs upon storage is compared with their initial solubility which is in this experiment expressed as solubility change ratio (SCR). So, initial solubility (S0) and SCR were taken as the responses to indicate the quality of the ASDs. Concentration of Soluplus as hydrophilic carrier (Factor A), concentration of Poloxamer 188 (Factor B) as the plasticizer and the cooling (quenching) temperature (Factor C) were taken as the independent factors. Box-Behken design (BBD) was used to develop Ritonavir ASDs. The combinations of the factors with their levels according to the BBD were shown in the Table 1.

Preparation of RASDs

RASD's were prepared by using melt-quench method. Ritonavir 1gm was taken in a polythene bag to it corresponding weights of Soluplus and P-188 were added and mixed thoroughly till the maximum possible homogeneous mixture was obtained. Enough of this mixture was taken in a China dish and heated in a hot plate until all the materials present in the mixture were completely melted with occasional mixing using a glass rod. Molten mixture was immediately cooled down at 30^0C (air cooling), at 0^0C (in freezer which is precooled and maintained at 0^0C), or -30^0C (in freezer which is precooled and maintained at -30^0C) as per respective formulation. Time required for complete solidification will depends on temperature conditions and formulation composition, once complete solidification occurred, RASDs were milled, passed through sieve for uniform size distribution and stored in air sealed containers. (Mistry, P et al., 2017, D'Angelo, A et al., 2018)

Table 1: Combination of the factors with their levels for developing ASDs of Ritonavir

Formulation code assigned	Levels of the factors			Results* of the Responses		
	A: Soluplus conc. (% w/w)	B: P-188 conc. (% w/w)	C: Cooling Temp (Cel)	R1: Initial Solubility (S_0, mg/mL)	Solubility after 6 months (S_6, mg/mL)	R2: Solubility change ratio (SCR)
RASD1	35.00	5.00	-30.00	0.94 ± 0.05	0.39 ± 0.04	0.59 ± 0.02
RASD2	20.00	10.00	-30.00	0.99 ± 0.08	0.43 ± 0.06	0.57 ± 0.03
RASD3	50.00	10.00	-30.00	1.21 ± 0.14	0.72 ± 0.10	0.41 ± 0.01
RASD4	35.00	15.00	-30.00	0.97 ± 0.10	0.65 ± 0.04	0.33 ± 0.03
RASD5	20.00	5.00	0.00	0.48 ± 0.03	0.29 ± 0.05	0.40 ± 0.07
RASD6	50.00	5.00	0.00	0.76 ± 0.06	0.58 ± 0.07	0.24 ± 0.03
RASD7	35.00	10.00	0.00	0.92 ± 0.11	0.79 ± 0.09	0.14 ± 0.01
RASD8	20.00	15.00	0.00	0.85 ± 0.04	0.76 ± 0.08	0.11 ± 0.05
RASD9	50.00	15.00	0.00	1.19 ± 0.09	1.12 ± 0.11	0.06 ± 0.02
RASD10	35.00	5.00	30.00	0.42 ± 0.06	0.33 ± 0.06	0.22 ± 0.03
RASD11	20.00	10.00	30.00	0.37 ± 0.05	0.32 ± 0.04	0.13 ± 0.01
RASD12	50.00	10.00	30.00	0.63 ± 0.05	0.56 ± 0.07	0.11 ± 0.04
RASD13	35.00	15.00	30.00	0.52 ± 0.07	0.49 ± 0.06	0.06 ± 0.01

* Expressed in Mean ± Standard deviation for n = 3

Characterization of the prepared RASDs
Percentage yield

Prepared RASDs were evaluated for percentage yield (Liw et al., 2022) using the following formula

$$\%\ yield\ = \frac{\text{Weight of RASD obtained}}{\text{Weight of the solids taken}}\ X\ 100$$

Differential Scanning Calorimetry (DSC) Analysis

DSC analyses were performed to investigate physical state of Ritonavir in pure state and prepared RASDs. Pure Ritonavir and Prepared RASD samples were

carefully weighed and sealed in aluminum pans with lids using empty pan as a reference.Samples were heated at a rate 10^{o}C from 20^{o}C to 400^{o}C and the spectra were recorded(Yu et al., 2020).

X-Ray Diffraction (X-RD) analysis

XRD is one of the most efficient ways to determine crystallinity of the powder. Samples of pure Ritonavir and prepared RASDs after storage were dried, grinded and passed through 80 mesh then subjected to XRD analysis. Samples were scanned at range of 0^{o} to 90^{o} (2θ angle) with scanning rate 2^{o}/min[19] and the spectra were recorded(Huanget al., 2019).

Drug content

100 mg Ritonavir equivalent prepared RASDs were taken in 50ml volumetric flask, added 40ml of methanol to it and mixed thoroughly. The contents were repeatedly warmed in a hot batch while mixing to dissolve the drug in solvent. the solution was made up to volume with methanol and assayed for drug content after suitable dilution. (Srikaret al., 2013)

Solubility

The solubility was determined by adding excess amount of solid (pure Ritonavir or RASDs initially or RASDs after storage) into 10ml of water, then kept in orbital shaker for 24 h at 37^{0}C and 100rpm. The samples were filtered and analyzed for Ritonavir content in UV spectrophotometer at 240nm.

Stability

RASDs prepared from different rapid cooling temperatures, were placed in stability chambers maintained at 40^{0}C and 75% RH for 6 months. After 6 months, the samples were withdrawn and characterized for Drug content, XRD analysis, and solubility studies to determine the changes in crystallinity. Solubility differences between RASDs initial (S_0) and after stability study (S_6) calculated. Difference between these solubilities in relative to initial solubility was taken as SCR. Higher value in SCR indicates significant change in solubility which indicates lesser stability in RASDs(Khodaverdiet al., 2012).

Results and Discussion

Yield

Prepared RASDs using various rapid cooling temperatures have shown satisfactory results with yields in the range of 85.3 – 93.4%. These results indicate suitability of experimental methods and conditions to obtain significantly good amount of product with minimal loss.

Drug content

Drug content results were shown in table, indicated ranges from 96.8 to 102.7 %. These results prove us that drug was miscible with carrier and plasticizer during melting and homogeneity of the dispersion was maintained even after cooling.

DSC analysis

The DSC spectrums of Ritonavir, RSADs prepared by quenching method at different rapid cooling temperatures were given in Figure 1. A sharp endotherm at 126^{o}C was observed in pure Ritonavir spectrum (RTV1 spectrum) which may be corresponding to melting point of crystalline Ritonavir (Sathigariet al., 2009). In the other three spectra RTV2, RTV3 and RTV4 of the RASDs prepared at cooling temperatures -30^{o}C, 0^{o}C and 30^{o}C, the endotherm corresponding to crystalline RTV was not observed. This observation designated that the crystalline RTV was converted into amorphous form during the melt-quenching. Further, a small endotherm at around 98oC was in these three spectra. This might be due to the extended glass-transition temperature (T_g) of Poloxamer 188. The T_g of Poloxamer is around 60oC but an increase in T_g upon melt-quenching indicates its conversion into amorphous form (Shoormeijet al., 2018). These DSC results clearly designated that upon melt-quenching, the resulted solid dispersion was in amorphous form and thus these can be called as ASDs. From this we can attribute that melt-quenching technology successfully converted crystalline form irrespective of quenching temperatures, this phenomenon may enhance the solubility of Ritonavir (Hurleyet al., 2020).

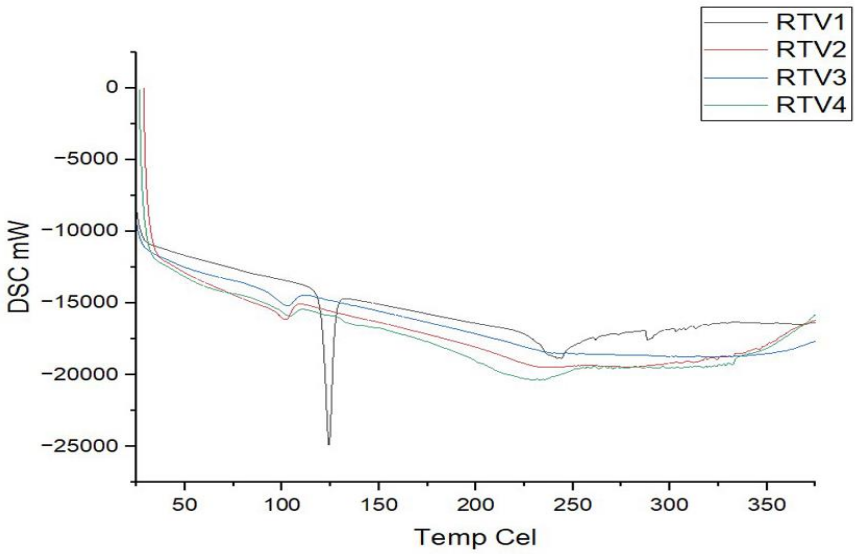

Figure 1: DSC spectra of pure Ritonavir (RTV1); RASDs prepared at -30^{o}C (RTV2); RASDs prepared at 0^{o}C (RTV3); and RASDs prepared at 30^{o}C (RTV4)

Solubility

Prepared RASDs, immediately after production were subjected to solubility studies and results were shown under S_0 in Table 1. S_0 values of the prepared RASDs were found to be higher than pure crystalline Ritonavir which was obtained as 0.068 mg/mL. Effect of the selected factors was determined with the Design of experiment software on S_0 as one of the responses. The factors have exerted liner effect on S_0 and the regression equation between this solubility and the factors was obtained as

$S_0 = +2.24 + 0.85* A + 0.58* B – 0.73* C$

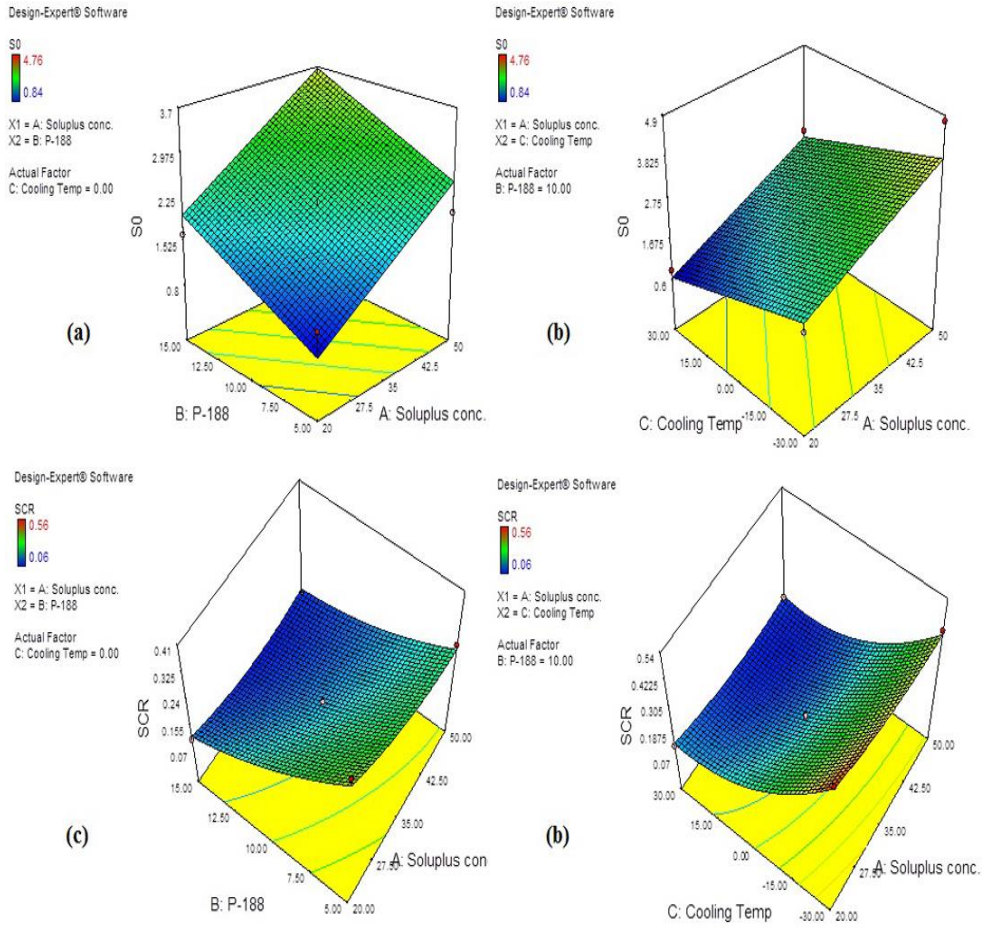

Figure 2: 3D-surface plots showing the effects of (a) the factors A and B on S_0; (b) the factors A and C on S_0; (c) the factors A and B on SCR; and (d) the factors A and C on SCR

Influences of all the factors are shown in Figure 2(a) and 2(b). Positive effect of factor A was fond on solubility, as solubility enhanced with the increase in concentration of Soluplus, which may be designated to hydrophilic nature of compound. Enhanced concentration of this carrier may impart more

hydrophilicity and reduced crystallinity of the drug there by enhancing solubility of Ritonavir(Liu et al., 2020). Factor B also exerted positive effect on the initial solubility, S_0. This could be attributed to capacity of Poloxamer 188 to improve wettability by decreasing interfacial tension between drug and water and its hydrophilicitywhich can enhance the solubility (Szafraniecet al., 2019). In contrary to Factors A and B, Factor C exerted negative effect on solubility. When the temperature provided for quench cooling decreases, solubility was found to be enhanced. This higher solubility may be designated to formation of more random amorphous forms of drug due to rapid solidification of molten drug when exposed to -30^0C. In case of solidification at $+30^0$C, more time could be taken for solidification results in ordered solidification of drug causing possible crystallinity, if any with less amorphous state(Hurley et al., 2020). This suggested that quenching at relatively higher temperature produced ASDs with less solubility.

Stability and Solubility change ratio

From the previous results even though we can state that ASDs can be used to enhance the solubility of crystalline drugs, they possess serious issues with their low thermodynamic stability. Upon aging these ASDs may develop crystallinity due to their higher molecular flexibility in glassy state. Recrystallization rate of ASDs depends on numerous factors like plasticizer stabilization effect, rate of cooling provided for solidification etc. This instability of ASDs leads to decrease in solubility upon aging. Thus, composition of ASDs and the processing conditions play a crucial role in maintaining stability of ASDs during their shelf-life(Bhujbalet al., 2021), while their instability leads torecrystallization which decreases solubility of drug (Shi et al., 2019). In this present research work SCR (solubility change ratio) was utilized to represent instability of prepared RASDs. If RASDs prone for recrystallization, it will result in reduced solubility. Extent of recrystallization can be studied with extent of solubility reduction, hence higher SCR ratio indicates lesser stability of ASDs

SCR results of RASDs are shown in Table 1. In order to investigate the effect of factors on the SCR as the second response, these results further subjected to DoE analysis and found that factors exhibited quadratic effect on the SCR. The regression equation depicting the quadratic regression between the factors and the SCR was obtained as

$$SCR = +0.15 - 0.046^* A - 0.1^* B - 0.17^* C + 0.030^* AB + 0.023^* AC + 0.018^* BC + 0.030^* A^2 + 0.030^* B^2 + 0.11^* C^2$$

Negative effect exerted by all three factors A , B and C on the SCR that the SCR decreased as level of factors increases and hence increase in thermodynamic stability of ASDs. The influence of all the factors on the SCR was shown as contour plots in Fig 2(c) and 2(d). Free energy of recrystallization will be reduced by presence of any carrier with drug in its amorphous form. Presence of Soluplus in high concentration might decrease the free energy to greater extent which lead to lesser degree of recrystallization during the storage (Liuet al., 2020), hence lesser SCR values were observed indicating more stability. In case of factor B i.e. with the concentration of Poloxamer 188, similar effect but with higher degree

was observed. This effect maybe attributed to the plasticizing nature ofPoloxamer 188 which can stabilize the amorphous state of any solid by reducing thermodynamic free energy (Lauer et al., 2018). So, increasing the concentration of Poloxamer 188 can result in greater stability of the ASDs which was designated by lesser SCR values.

Quenching temperature, the factor F was found to reduce the SCR and thus enhance stability. Rate of cooling at which molten mixture subjected to quneching will also affect Thermodynamic stability of RASDs. Quenching at lower temperatures results in faster solidification of the molten solid which leads to poorly ordered amorphous state with has higher free energy(Hurleyet al., 2020). So, the RASDs solidified at -30^0C were found to have maximum SCR which indicate least stability. This could be attributed to high free energy which leads to crystallization of drug during storage leading to decrease in solubility. Whereas the RASDs solidified at 30^{o}C might be more ordered with least free energy. So, even though the initial solubility of these RASDs was relatively lesser they maintained the solubility due to more stability thus exhibiting lesser SCR values. The X-RD analysis of the RASDs after six months storage at accelerated stability conditions were also supported these interferences.

XRD analysis

The XRD spectrums of pure Ritonavir and the RASDs are shown in Figure 3(a) to 3(e).Crystalline nature of the Ritonavir can be observed from presence of sharp high intense (more than 1000 counts) peaks in XRD spectrum of the pure Ritonavir (shown in Figure 3(a)). But, in the spectrum of the RASDs taken immediately after preparation, the intensity of the peaks(only around 400 counts) werefound to be greatly reduced. This may be accorded to melt-quench technique that method was successful in converting crystalline Ritonavir to almost amorphous form(Hurley et al., 2020). These results were also correlated with DSC analysis. Later, the RASDs stored for 6 months at accelerated conditions. After storage, the RASDs were again analyzed by X-RD. The obtained spectra are illustrated in Figure 3(c) to 3(e) for the RASDs prepared at –30^{o}C, 0^{o}C and +30^{o}C respectively.

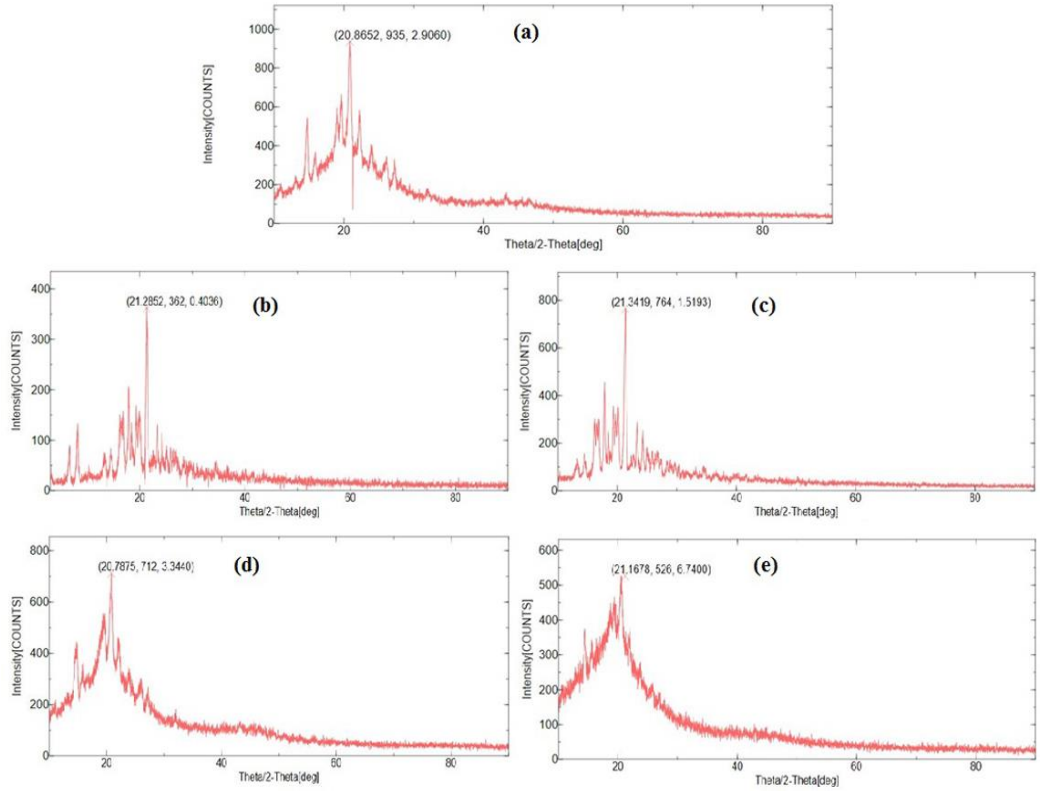

Figure 3: X-RD spectra of (a) pure Ritonavir; (b) RASDs before storage; (c), (d) and (e) are the X-RD spectra taken after storage for 6 months of the RASDs prepared at –30°C, 0°C and +30°C respectively.

After storage, the RASDs prepared at –30°C exhibited relatively more intense peaks in their X-RD spectra (Figure 3(c)) than the corresponding RASDs prepared at 0°C and 30°C orderly.Rapid quenching at lower temperatures (–30°C) could result the RASDs with more entropy and free energy which resulted higher initial solubility but they undergo higher degree of recrystallization upon storage which eventually reduce the solubility. Whereas, slow quenching at relatively higher temperature (+30°C) resulted in ASDs with relatively lesser entropy and lesser free energy. So, though the initial solubility was relatively lesser, they lesser degree of recrystallization and greater stability and so could retain the solubility with lesser SCR values.

Design validation and Optimization

The chosen BBD for the development of RASDs and the regression models for both the responses had to be validated for their suitability and significance so as to proceed for the optimization. For the first response S_0, the factors were found to have liner influence and this linear model as well the factor effects on the S_0 were found to be significant at $p< 0.05$ by Analysis of variance (ANOVA) as showed in Table 2. For the second response SCR, the factors influence was obtained as quadratic regression model. This model and the main factors effects were found to be significant at $p< 0.05$ by Analysis of variance (ANOVA) as

showed in Table 3. Further, the normal plots of residuals for both the responses as showed in Figure 4(a) and 4(b) illustrated a linear order without any sigmoid shape. This designated that the observed response values did not require any transformation for statistical analysis. These results confirmed that the selected BBD and the models were significant enough to proceed for the optimization.

Table 3: ANOVA test results of response surface linear model for initial solubility (R1)

Source	SS[a]	Df[b]	MSS[c]	F value	p-Value	Inference[d]
Model	12.71	3	4.24	16.68	0.0005	Significant
A: Soluplus conc.	5.76	1	5.76	22.69	0.0010	Significant
B: P-188	2.67	1	2.67	10.51	0.0101	Significant
C: Cooling Temp	4.28	1	4.28	16.85	0.0027	Significant
Residual	2.29	9	0.25			
Cor Total	14.99	12				

Note: [a]-Sum of Squares; [b]-Degrees of Freedom; [c]-Mean Sum of Squares; [d]-p-Value less than 0.05 indicates model terms are significant

Table 4: ANOVA test results of response surface quadratic model for the SCR (R2)

Source	SS[a]	Df[b]	MSS[c]	F value	p-Value	Inference[d]
Model	0.38	9	0.042	41.71	0.0054	Significant
A: Soluplus conc.	0.017	1	0.017	16.97	0.0259	Significant
B: P-188	0.086	1	0.086	85.40	0.0027	Significant
C: Cooling Temp	0.24	1	0.24	236.08	0.0006	Significant
AB	$3.6x10^{-3}$	1	$3.6x10^{-3}$	3.57	0.1552	
AC	$2.025x10^{-3}$	1	$2.025x10^{-3}$	2.01	0.2514	
BC	$1.225x10^{-3}$	1	$1.225x10^{-3}$	1.21	0.3509	
A^2	$2.057x10^{-3}$	1	$2.057x10^{-3}$	2.04	0.2485	
B^2	$2.057x10^{-3}$	1	$2.057x10^{-3}$	2.04	0.2485	
C^2	0.029	1	0.029	28.69	0.0127	Significant
Residual	$3.025x10^{-3}$	3	$3.025x10^{-3}$			
Cor Total	0.38	12				

Note: [a]-Sum of Squares; [b]-Degrees of Freedom; [c]-Mean Sum of Squares; [d]-p-Value less than 0.05 indicates model terms are significant

Optimization was performed with the desirability of obtained ASDs maximum solubility and minimum SCR (maximum stability) as per the desired target quality. The resultant desirability and overlay plots given by the Design expert software is presented in Figure 4(c) and 4(d). The yellow color region in the overlay

plot indicates the design space, within which any combination of the factors would yield RASDs with maximum solubility and minimum SCR with a desirability of 0.859 (85.9%). One such combination of the factors as identified by the software was taken and RASDs were prepared at this combination and studied for the S_0 and SCR values. The factors combination, predicted values of the responses and the observed values of the responses were shown in the Table 4. These results indicated that experimentally observed response values were correlated with those of the predicted values as they were within the 95% confidence intervals (CI) region of the predicted values. This designated that the suggested combination of the factors as the best optimized combination of the selected factors to prepare RASDs with maximum solubility and stability.

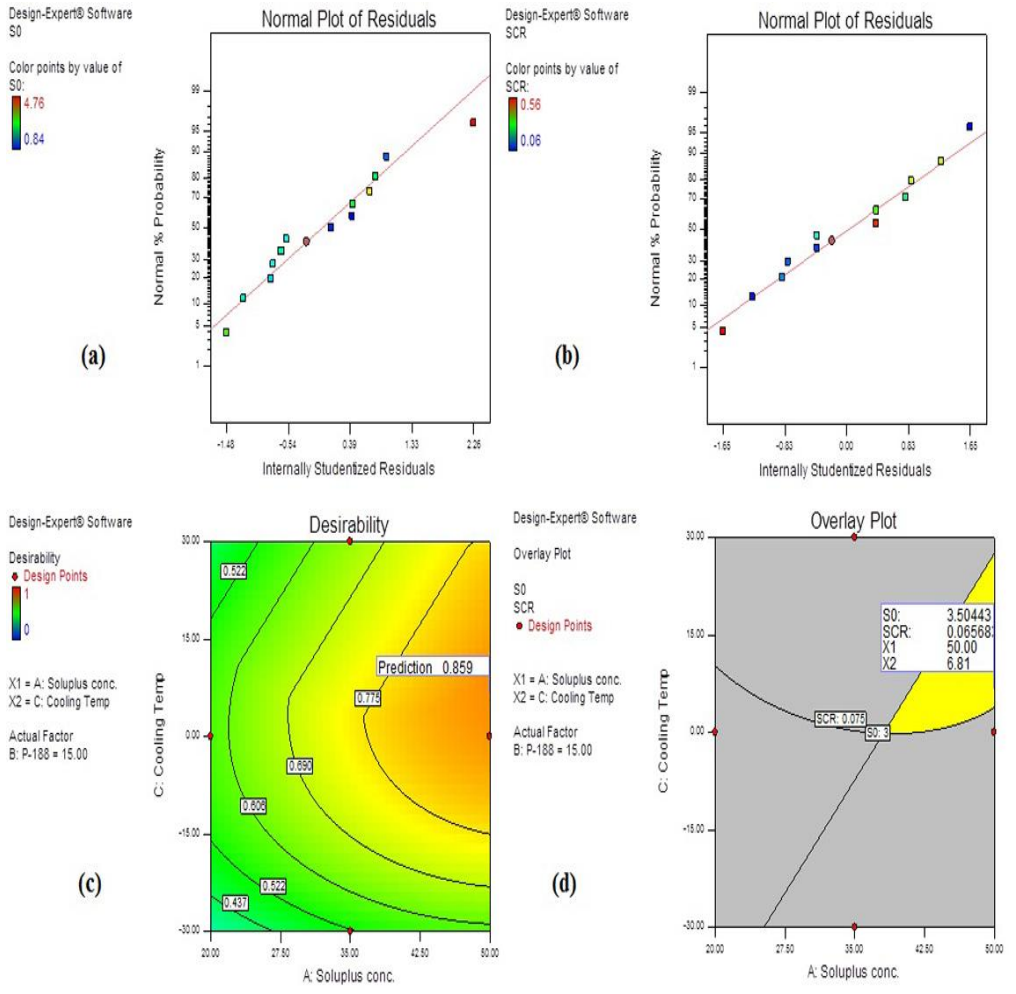

Figure 4: (a) and (b) Normal plots of residuals for the responses S_0 and SCR; (c) and (d) Desirability plot and Overlay plot obtained after optimization.

Table 5: Comparison of the predicted and observed values of the responses for the optimized ASDs of Ritonavir

Factors combination	Responses	Predicted values	95% CI low	95% CI high	Observed values
A: Soluplus conc. (50% w/w) B: P-188 (15% w/w) C: Cooling Temp (6.81°C)	R1: S_0 (mg/mL)	3.51	2.85	4.16	**3.39**
	R2: SCR	0.065	0.023	0.15	**0.071**

Conclusion

Development of ASDs for bioavailability enhancement of BCS class-II drugs is one of the best promising scalable and easy technique. But, stability of prepared ASDs is the major challenge as they prone for recrystallization upon storage. In the current work, Ritonavir ASDs prepared by melt-quench method and the effect of carrier, plasticizer and cooling temperature on stability and solubility of prepared ASDs were studied. QbD approach was adopted using Design Expert software. Box-Behnken design was used to study the effects of the factors on the selected responses. All the three factors carrier, plasticizer and cooling temperature were found to show significant effect on solubility and stability among them cooling temperature and plasticizer has shown profound effect on stability. The RASDs prepared at higher concentration of the Poloxamer 188 and at slow rate of cooling were found to be more stable and retain the improved solubility even after storing at accelerated stability testing conditions.

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