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Original Article

Solid State Characterization and Miscibility of Raltegravir in Soluplus Using Solid Dispersion Technology

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ABSTRACT

Background: Raltegravir Potassium (RTGP), a BCS class II drug used in the treatment of HIV, has minimal solubility in the aqueous medium, resulting in poor bioavailability; Further, RTGP poor dissolution and limited solubility are also major factors responsible for the significant inter- and intra-patient variability in absorption following oral administration. **Objectives:** To enhance the solubility of Raltegravir potassium and its free acid using Soluplus® by solid dispersion technology. **Materials and Methods:** In the current study, Amorphous Solid Dispersions (ASDs) of RTGP and Raltegravir free acid (RTG) of 20:80% w/w with Soluplus® (SLP) were prepared using quench cooling. The prepared ASDs analyzed for homogenous single-phase formation and intermolecular interactions employing DSC, XRD, and FT-IR. The drug-polymer miscibility was calculated theoretically as well as experimentally with the aid of Hansen solubility parameter and melting point depression methods. The solubility of the ASDs was evaluated by the shake flask method. **Results:** Quench cooling yielded an RTGP-SLP and RTG-SLP homogeneous amorphous systems. DSC and XRPD results showed the complete transformation of crystalline to the amorphous phase for ASDs. Intermolecular interactions in specific hydrogen bonding were observed between the carbonyl (-C=O) group of Soluplus® and the Raltegravir -N-H moiety. RTG solubility in salt solid dispersion increases by 10.7 and 17.4 folds, respectively, compared to pure forms. Furthermore, free acid ASDs improved solubility by 8.7 and 14.1 folds, respectively, compared to their pure compounds. **Conclusion:** Salt solid dispersion showed a greater extent of miscibility and improved solubility of RTG compared to free acid solid dispersion.

Keywords: Raltegravir, Amorphous salt solid dispersion, Amorphous solid dispersion, Quench cooling, Solubility.

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INTRODUCTION

Raltegravir Potassium (RTGP) is a weakly acidic drug with low solubility /high permeability, classified as class-II according to Biopharmaceutical Classification System (BCS).[1] RTG, the first-in-type Human Immunodeficiency Virus (HIV) integrase strand transfer inhibitor, prevents viral DNA from being inserted into the human genome, thereby inhibiting HIV replication.[2] RTG is marketed as a potassium salt form to improve its dissolution and solubility properties.[3] Despite being converted to its salt form, RTGP exhibited low solubility across the various physiological pH (pH 1.2 - 0.16 mg/mL, pH 4.5 - 0.17 mg/mL and pH 6.8 - 0.48 mg/mL).[4] The low solubility of RTGP significantly impairs its dissolution properties. *In vitro* dissolution studies for RTGP revealed that less than 20% of the drug could dissolve in 2 hr in 0.1 N HCl and pH 6.8 phosphate buffer (50 mM).[5] RTGP is administered at a very high dose of 400 mg twice a day alone and 800 mg twice daily in combination with rifampin due to its low solubility and poor dissolution properties to achieve the desired therapeutic effect.[1] Currently, RTGP oral dosage forms such as chewable tablets, granules for suspension, and film-coated tablets are available on the market.[6] Further, RTGP poor dissolution and limited solubility are also major factors responsible for the significant inter- and intra-patient variability in absorption following oral administration. Such high inter- and intrapatient variability is concerning because it can lead to drug resistance in patients as a result of unintended viral replication.[7]

Drug solubility improvement is an essential area of drug delivery research for molecules like RTGP (BCS-II) due to the intrinsic difficulty of making it a successful dosage form. Many formulation techniques, such as surface modification,[8] miniaturization,[9] solid lipid nanoparticles,[10] solid dispersion,[11] and complexation,[12] have been developed in recent decades to address drug solubility issues. Amongst these methods, solid dispersion is regarded as a distinctive, economical, and feasible approach to improving drug solubility. It enables a reduction in particle size, thereby

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increasing particle wettability with increased porosity, reducing aggregation, transforming to an amorphous state, and improving drug solubility. However, physical stability remains an issue for amorphous drugs, frequently caused by higher molecular mobility.[13] Polymeric Solid Dispersions (ASDs) have been well established as one of the most effective methods for inhibiting amorphous drug crystallization and phase separation, thereby improving the physical stability of the drug due to molecular level dispersion in the polymers.[14] ASDs improve drug solubility through multiple mechanisms, including wettability, particle size reduction, intermolecular interactions, and amorphization.[15,16] Further, spray drying,[17] hot-melt extrusion,[18] freeze drying,[19] quench cooling,[20] and solvent evaporation[21] were widely used techniques to prepare ASDs. Amorphous Salt Solid Dispersion (ASSD) is a novel strategy that combines the advantages of amorphization and salt formation to improve amorphous drug physical stability, aqueous solubility, and dissolution rate. Because electrostatic interactions are stronger than hydrogen bonding interactions, salt formation with excipients or counterions stabilizes the amorphous form of a drug.[22,23] Salts can also increase drug solubility by altering the pH of the dissolution media as they dissolve. Paluch *et al*. prepared crystalline and amorphous salts of Ciprofloxacin (CIP) with succinic acid in various molar ratios. Amorphous salts improved the solubility of CIP in water compared to the crystalline succinate salts of CIP.[23] Mesallati and Tajber *et al.* prepared ciprofloxacin ASSD using succinic acid along with polymers and observed the improvement in solubility, physical stability for ASSD compared to pure forms and ASDs.[24]

In the current study, ASDs of RTGP and Raltegravir free acid (RTG) were prepared using soluplus® (SLP) as a polymeric carrier to improve the solubility of RTG. SLP was previously utilized as a polymeric matrix with various molecules to prepare ASDs, where it demonstrated enhancement in the solubility due to its ability to develop *in situ* micelles of nano dimensions.[25-29] RTGP/RTG-SLP thermodynamic miscibility was studied employing Flory Huggins theory and the solubility parameter approach. Further, the solid-state characterization of prepared ASDs was performed using DSC, FTIR PXRD techniques and evaluated the improvement in solubility.

MATERIALS AND METHODS

Materials

Raltegravir Potassium (RTGP) was offered as a gift sample by STEERLife Pvt. Ltd., Bengaluru, India. Soluplus® (SLP) was obtained from BASF, Germany as a gift sample. Acetonitrile and Methanol were acquired from Merck Life Sciences Pvt. Ltd., Mumbai, India. which are of HPLC grade. SIEMENS purification system was utilised for the Ultra-pure water installed in the lab.

Methods

Preparation of RTG solid dispersions

Accurately weighed RTGP/RTG and SLP were taken in 20:80% w/w ratio and heated up in a porcelain dish with a hot plate until a homogeneous melt formed. To induce amorphization, the melt was transferred directly to a glass desiccator and maintained for 3 hr at -80°C. The resulting ASDs was pulverized gradually with a ceramic mortar-pestle followed by sieving using a 100 m sieve before being stored in a vacuum at room temperature until characterization.

Preparation of Raltegravir Free Acid

1g of RTGP was dissolved in 20mL of water and stirred for 12-15 hr at 25-30°C. The precipitate obtained was filtered and stored for 10-12 hr in a vacuum desiccator at 45°C for further use.[30]

Analytical Technique

The samples were analyzed using a Shimadzu UV-1800 UV/Visible Scanning Spectrophotometer; The photometric mode was employed to record the absorbance of the ASDs solubility samples at 316 nm. Samples were prepared using Acetonitrile and phosphate buffer of pH 3.5 at 45:55 v/v. Further, the concentration was calculated by extrapolating the recorded values into the calibration curve of RTG.

Assay of ASDs

An assay was performed to evaluate the drug content of RTGP/RTG in the prepared ASDs. The above-mentioned analytical method was used to analyse standard and test samples. In triplicate, test samples were prepared with 10 mg ASDs powder equivalent to 10mg RTGP/RTG and dissolving it in 10 mL methanol. To obtain a 1µg/mL sample, serial dilutions were performed with 50:50 Methanol and water. The results were compared to an RTGP/RTG standard of 1µg/mL.

Solid state characterization

Differential Scanning Calorimetry (DSC)

The thermal properties of the prepared ASDs, pure RTGP/RTG, and SLP were studied using shimadzu DT-60 Differential Scanning Calorimeter. 5mg of sample was placed in a flat-bottomed aluminum pan crimpled with an aluminum lid and heated from 25°C to 300°C at 10°C/min under nitrogen flow.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR-8300 spectrophotometer (Shimadzu Co., Kyoto, Japan) was used to record the infrared spectra of the prepared ASDs, pure RTGP/RTG, over a range of 4000 to 500 cm^{-1}. The KBR disc method was used to prepare the samples.

Powder X-ray Diffraction (XRPD)

XRD assessment of the prepared ASDs, pure RTGP/RTG, and SLP was performed using a X-ray diffractometer of Rigaku miniflex -600. The current and voltage held constant at 15 mA and 40 Kilovolt (kV). The diffraction intensities were recorded by placing 20mg of sample in the sample holder and scanning in the 5-40°C (2θ) range.

Drug-polymer miscibility

Theoretically and experimentally, drug-polymer miscibility was deliberated by the Hansen solubility parameter and Flory Huggins interaction parameter approaches. The solubility parameter measures the cohesive energy or attraction between molecules in a material. The sum of dispersion forces (d), polar forces (p), and cohesive forces (h) represent the solubility parameter (δ) of the compound. It is calculated by the using the formula:

$$\delta^2 = \sqrt{\delta d^2 + \delta p^2 + \delta h^2}$$

Equation - 1

Where δd, δp, and δh are calculated using the following formulas,

$$\delta d = \frac{\sum Fdi}{Vm}$$

$$\delta p = \frac{\sqrt{\sum F^2 \mathrm{pi}}}{Vm}$$

$$\delta h = \sqrt{\frac{\Sigma Ehi}{Vm}}$$

Where Fdi, F^2pi, and Ehi are molar attraction forces of dispersive interaction, dipole-dipole interaction, and hydrogen bonding.

Flory Huggins' theory was essential in determining the free energy required to form a homogeneous phase without phase separation. It predicts the optimal drug load for the preparation of amorphous solid dispersion. The melting point depression method was used to calculate the Flory-Huggins interaction parameter (x). The following formula was used to acquire the interaction parameter, where the slope of the line can be considered for the interaction parameter value (x).

$$\left(\frac{1}{Tm} - \frac{1}{Tm^0}\right) * \frac{\triangle Hf}{-R} - In\oslash d - \left(1 - \frac{1}{m}\right)\oslash p \text{ vs} \oslash^2 p$$

Equation - 2

Where ⊘d and ⊘p are the volume fractions of drug and polymer, Tm and Tm^0 are the melting points of physical mixture of drug-polymer and pure drug. △Hf is the pure drug heat of fusion. m is the ratio of polymer chain volume to a drug molar volume

Solubility Determination

The shake-flask method was utilised to estimate the equilibrium solubility of the RTGP, RTG, and prepared ASDs. 20 mg of each above-mentioned sample was taken in a vail containing 4 mL of United States Pharmacopeia (USP) phosphate buffer pH 6.8 in triplicates; and kept in an orbital shaker at 150 RPM for 24 hr. Samples were centrifuged using Remi C24 centrifuge for 10 min at 4°C, 10000 rpm and the supernatant was collected for further analysis.

RESULTS

Assay of prepared ASDs

An assay was performed to ascertain the drug content of RTGPSD and RTGSD. RTGSD had a drug content of 90.2±1.5% w/w in the sample, whereas RTGPSD had a drug content of 86.7±1.3% w/w.

Solid state characterization

DSC

RTGP, RTG, SLP, and ASDs were analysed using DSC to examine their thermal properties. RTGP and RTG exhibited an endotherm at 276°C and 220°C (Figure 1).[31,32] Depression in the melting point was observed in the case of RTG compared to RTGP, where 56°C shift in the melting point occurred towards the lower side.

FTIR

FT-IR data from RTGP/RTG, SLP, and PM were compared to data from RTGPSD and RTGSD to assess the likelihood of intermolecular interactions between the drug and polymer. RTGP FTIR spectra showed characteristic peaks at 3174 cm^{-1}, 1670 cm^{-1}, 1625 cm^{-1}, 1521 cm^{-1}, and 1184 cm^{-1}, corresponding to N-H, C=O, C=N, C=C, and C-F stretching vibrations (Figure 2). Interestingly RTG spectra showed a shift in the peaks along with the presence of a hydroxyl band at 3585 cm^{-1}. Further, N-H, C=O, C=N, C=C, and C-F stretching vibrations in RTG spectra appeared at 3300 cm^{-1}, 1691 cm^{-1}, 1637 cm^{-1}, 1537 cm^{-1}, and 1209 cm^{-1}. The prominent peaks in the RTGP/RTG were evident in the PM with less intensity due to the phase solubility with SLP.

XRPD

The pure RTGP diffractogram showed characteristic sharp Bragg's peak at 5.66, 11.26, 12.16, 20.16, 22.22, 23.16, 25.18, and 29.82°C confirming the crystalline state of the RTGP as assisted by the DSC thermogram.[33,34] Interestingly RTG diffractogram demonstrated a shift in the peaks towards the right side compared to its potassium salt RTGP (Figure 3). It includes 7.98, 11.48, 13.54, 20.24, 22.56, 24.06, 25.36, and 30.08°C which were higher than the RTGP diffraction peaks. SLP exhibited a halo pattern in the diffractogram, which implies the amorphous nature. Further, the diffractogram of the physical mixture revealed Bragg's peaks with less intensity compared to the pure crystalline forms. A halo spectra was observed for RTGPSD and RTGSD ASDs, representing the complete conversion of the drug into an amorphous form. Hence the prepared ASDs amorphized successfully in spite of salt and free acid forms with SLP.

Solubility studies

The equilibrium solubility of RTGP, RTG, PM, RTGPSD, and RTGSD in USP pH 6.8 phosphate buffer was observed as 180.0 ± 0.6, 111.1 ± 0.4, 191± 0.5 1950 ± 9.8, and 1584 ±1.4, as shown in Figure 4. Interestingly, RTG solubility in salt solid dispersion increases by 10.7 and 17.4 folds, respectively, when compared to pure RTGP and RTG forms. Furthermore, RTGSD improved solubility by 8.7 and 14.1 folds, respectively, compared to their individual compounds.

DISCUSSION

Assay of prepared ASDs

The concentration of RTG is high in case of RTGSD compared to RTGPSD in ASDs. This trend prompted us to the previously reported thermal stability of RTGP.[35] Despite the thermolability of RTGP, this study attempted to form a solid dispersion of RTGP with SLP to examine whether SLP could offer leverage in reducing the melting point of RTGP deprived of generating thermal degradation. Because in DSC, melting endotherms were not observed for 10 and 20% w/w physical mixtures of RTGP and SLP. This observation implies the phase solubility of RTGP with SLP. Further, pure RTGP was quench cooled to investigate the thermal stability by carrying out the assay. The drug content of quench cooled pure RTGP was found to be 45%, where degradation of RTGP is confirmed (Figure 7).

DSC

Irrespective of salt and free acid forms, crystalline nature was evident from their respective thermograms. Further, the SLP thermogram revealed glass transition temperature at 72°C, consistent with the literature reports.[36] Melting events in RTGPSD and RTGSD ASDs are absent, owing to the formation of a single homogeneous amorphous phase. The thermal property of RTGP/RTG is assumed to have changed during the solid dispersion. Furthermore, this study confirms the transition of the RTGP/RTG physical state from crystalline to amorphous.

FTIR

To assess intermolecular interactions if any, the spectrum of an RTG and SLP Physical Mixture (PM) was compared to that of prepared ASDs. A peak at 3174 cm^{-1} of N-H stretching was absent in RTGPSD and RTGSD ASDs, unlike in PM. This may be attributed to the intermolecular hydrogen bonding between N-H of RTGP/RTG and C=O of SLP vinyl caprolactam and vinyl acetate moiety. Singh *et al.* 2016 used hot-melt extrusion to prepare Itraconazole/Soluplus® ASDs. Because of hydrogen bonding interactions between Itraconazole and Soluplus®, the dispersion was found to be stabilised. However, Soluplus®-rich regions were observed at the time of compression as tablets preparation was attempted with the prepared ASDs.[37] It has been demonstrated that the disruption of hydrogen bonding results in phase separation. Jog *et al.* 2016 prepared ASDs of ABT-102 model compound with Soluplus® and investigated the physical stability of ASDs. The prepared ASDs demonstrated physical stability due to strong hydrogen bonding between the -C=O function of Soluplus® and the drug's -N-H moiety.[17] Except for the disappearance of the N-H stretching peak, other characteristic peaks were broadened and attenuated in ASDs than pure RTGP/RTG due to the change in the chemical environment from crystalline to amorphous form. Nevertheless, intermolecular interactions in specific hydrogen bonding were observed for RTGPSD and RTGSD ASDs.

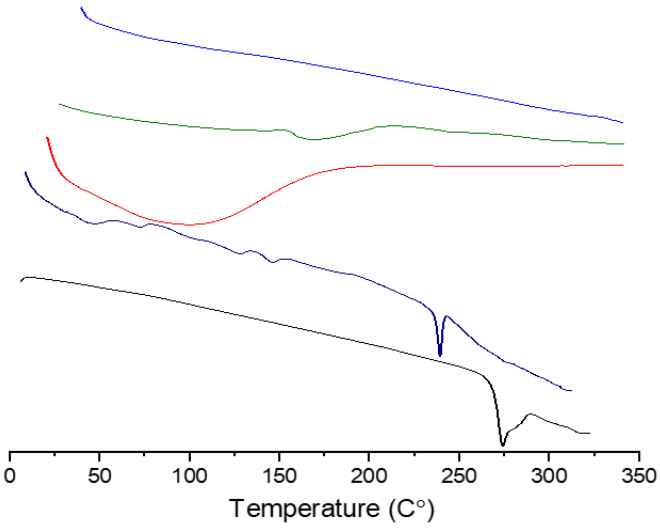

Figure 1: DSC Thermograms of RTGP, RTG, RTGPSD, and RTGSD solid dispersions.

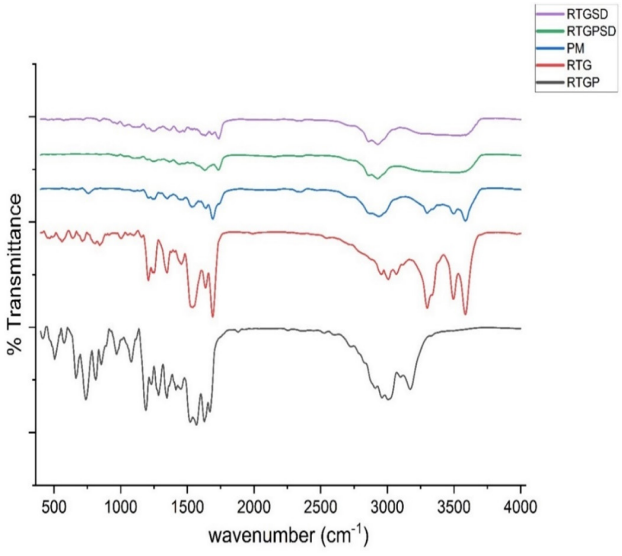

Figure 2: FTIR spectra of RTGP, RTG, PM, RTGPSD and RTGSD solid dispersions.

Table 1: Drug co-former miscibility calculation using Hasen solubility parameter method.

Sl. No	Substance	Molecular Weight (g/mol)	Density (g/cm³)	Molecular Volume (cm³/mol)	Melting Point (K)	Solubility Parameter (MPa$^{1/2}$) Hansen δh δd δp
1.	Raltegravir potassium	482.5	1.46	330.47	549.15	15.37 12.25 10.75
2.	Raltegravir	444.14	1.46	304.39	492.15	13.8 17.37 13.40
3.	Soluplus	118000	1.20	98333	-	8.6 17.4 0.3

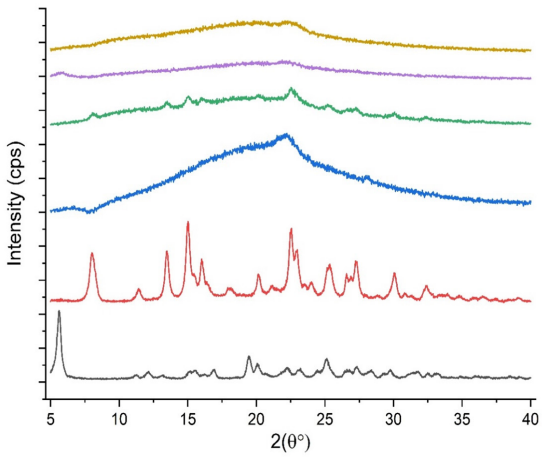

Figure 3: X-ray diffractograms of RTGP, RTG, SLP, PM, RTGPSD, and RTGSD solid dispersions..

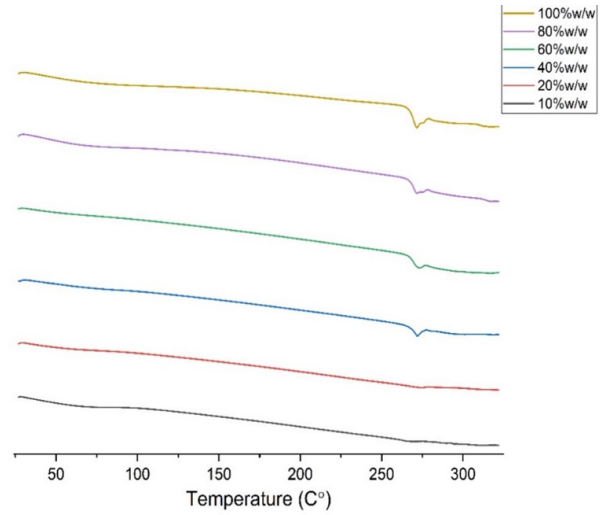

Figure 5: DSC thermograms of RTGP-SLP physical mixtures at 5 °C/min heating rate in melting point depression method.

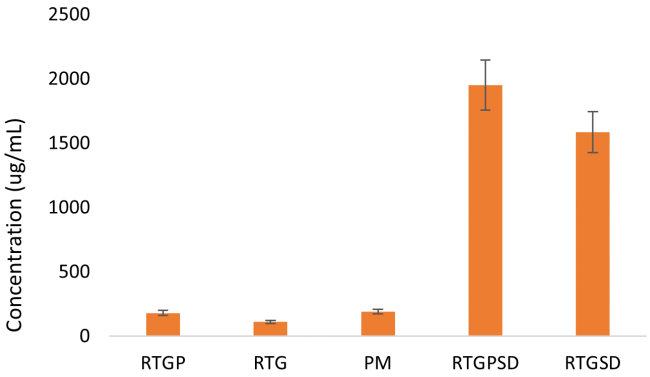

Figure 4: Equilibrium solubility RTGP, RTG, PM, RTGPSD, and RTGSD solid dispersions.

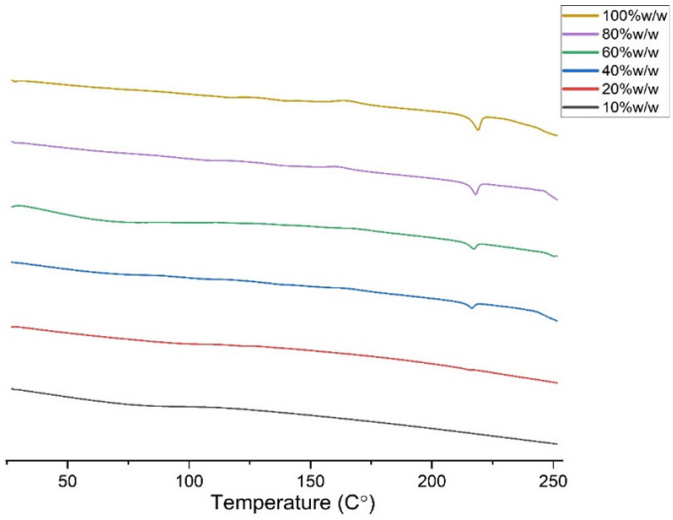

Figure 6: DSC thermograms of RTG-SLP physical mixtures at 5 °C/min heating rate in melting point depression method.

Drug-polymer miscibility

Drug-polymer miscibility is a critical parameter for rational formulation design, especially when evaluating ASDs. A thoroughly blended and molecularly disseminated drug within a polymer is well desirable. This will inhibit supersaturation-induced recrystallization or phase separation in both solid and liquid states. As a result, the phase solubility of a drug-polymer pair is essential and is determined by theoretical, computational, and experimental approaches. Theoretically, the Hansen solubility parameter was calculated for RTGP/RTG and SLP miscibility. Furthermore, the affinity for hydrogen bonding and dispersibility of RTGP -SLP are very similar compared to RTG-SLP. In

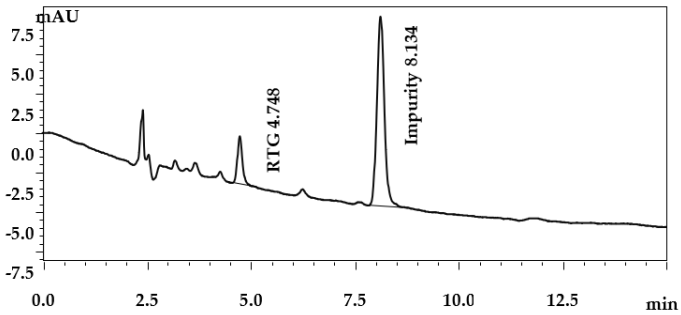

Figure 7: Chromatogram of quench-cooled RTGP with its impurity.

particular, to polar bonding affinity with SLP, RTGP showed higher affinity than the RTG form (Table 1). As a result, to some extent, the miscibility of RTGP/RTG-SLP solid dispersions can be considered.

Drug-polymer miscibility was investigated experimentally utilizing the melting point depression method through the DSC technique. (Figures 5 and 6). At higher temperatures, there is a likelihood of the thorough mixing of a drug and a polymer, resulting in the formation of a single phase. This kind of drug-polymer miscibility reduces the chemical potential of the drug, thereby rendering it a lower melting point than the pure drug. Positive and negative interaction parameters of drug and polymer indicate miscibility and phase separation. The interaction parameter (χ) was estimated in this work for both the RTGP/RTG with SLP. Both the RTGP-SLP and RTG-SLP formulations have a negative interaction parameter (χ), which include -0.184 and -0.084, implying the miscibility with SLP. Further, the RTGP-SLP system exhibited a higher negative value compared to RTG-SLP.

Solubility studies

The improvement in the solubility of RTG from the ASDs formulations can be ascribed to the conversion of crystalline to amorphous form. In particular, RTGPSD exhibited the highest solubility due to the collective effect provided by the extent of miscibility and amorphization approach. Thus, it is apparent that the salt form ASDs resulted in a substantially higher RTG solubility than the respective free acid ASDs.

CONCLUSION

ASDs of RTG salt and free acid form were successfully formulated using soluplus®, using the quench cooling technique. DSC, XRD, and FTIR were used to characterise the prepared ASDs. Drug-polymer miscibility was estimated using the melting point depression approach by employing DSC. Irrespective of physical forms RTGP/RTG negative interaction parameter (χ) was observed. Moreover, in the case of RTGP-SLP the interaction parameter (χ) was higher compared to the RTG-SLP system. Solubility of RTG was improved in both the ASDs compared to the physical mixture and pure RTG. RTGPSD demonstrated the highest improvement in the RTG solubility, followed by RTGSD.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ASSDs: Amorphous salt solid dispersion; **ASDs:** Amorphous solid dispersion; **BCS:** Biopharmaceutical Classification System; **RTGP:** Raltegravir potassium; **RTG:** Raltegravir free acid; **SLP:** Soluplus®; **RTGPSD:** Raltegravir potassium solid dispersion; **RTGSD:** Raltegravir free acid solid dispersion; **HIV-1:** Human immunodeficiency virus type 1; **GIT:** Gastrointestinal Tract; **kV:** Kilovolt; **mA:** Milliampere; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transform Infrared Spectroscopy; **XRPD:** X-ray Powder Diffraction; **UV-VIS:** Ultraviolet-Visible Spectroscopy; **USP:** United States Pharmacopeia.

SUMMARY

Raltegravir potassium, a BCS class II drug, has minimal solubility in the aqueous medium, resulting in poor bioavailability. This study emphasized studying the impact of drug-polymer miscibility on improving the solubility of Raltegravir in both salt and free acid amorphous solid dispersions. The drug-polymer miscibility was calculated theoretically as well as experimentally with the aid of Hansen solubility parameter and melting point depression methods. RTG solubility in salt solid dispersion increases by 10.7 and 17.4 folds, respectively, when compared to pure forms. Furthermore, free acid ASDs improved solubility by 8.7 and 14.1 folds, respectively, compared to their individual compounds.

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