

Dissolution Enhancement of Raltegravir by Hot Melt Extrusion Technique

Ahmed S. Abdul Jabbar^{*,1}

^{*}Department of Pharmaceutics, College of Pharmacy, University of Basrah, Basrah, Iraq.

Abstract

The objective of the study to develop an amorphous solid dispersion for poorly soluble raltegravir by hot melt extrusion (HME) technique. A novel solubility improving agent pladone s630 was utilized. The HME raltegravir was formulated into tablet by direct compression method. The prepared tablets were assessed for all pre and post-compression parameters. The drug- excipients interaction was examined by FTIR and DSC. All formulas displayed complying with pharmacopoeial measures. The study reveals that formula prepared by utilizing drug and pladone S630 at 1:1.5 proportion and span 20 at concentration about 30mg (trail-6) has given highest dissolution rate than contrasted with various formulas of raltegravir.

Keywords: Hot melt extrusion, Raltegravir, Pladone S630.

زيادة معدل التحلل لعقار الرالتيجريف بواسطة تقنية الصهر الحار القاذف

احمد سامي عبد الجبار^{*,1}

^{*} فرع الصيدلانيات ، كلية الصيدلة ، جامعة البصرة ، البصرة ، العراق .
الخلاصة

الهدف من هذه الدراسة تطوير التشتت الصلب غير المتبلور لعقار الرالتيجريف قليل الذوبان بواسطة تقنية الصهر الحار القاذف. مادة البلاسدون س ٦٣٠ استخدمت كماده معززه للذوبانية. اقراص الرالتيجريف المحضرة بواسطة تقنية الصهر الحار القاذف تحضر بواسطة الكبس المباشر. تم تقييم الاقراص المحضرة لجميع الاختبارات قبل وبعد الكبس. كذلك تم التحقق من وجود اي تفاعل بين العقار والمواد المضافة. النتائج اثبتت ان جميع الاقراص المحضرة هي ضمن المعايير المتضمنة في دساتير الادوية. وجد ان الصيغة ٦ (١:١.٥) بلاسدون س ٦٣٠ و ٣٠ ملغم من السبان ٢٠) هي من افضل الصيغ المحضرة لأنها تمتلك اعلى واسرع معدل تحلل مقارنة مع الصيغ الاخرى. الكلمات المفتاحية : تقنية الصهر الحار القاذف, رالتيجريف, بلاسدون س ٦٣٠.

Introduction

The oral route is the most widely recognized and favored rout for drug administration because of its suitability and simplicity to ingestion. At the point when medication given orally in solid dosage form like tablet, capsules; at first will undergoes dissolution in the GI fluid before absorption⁽¹⁾. For various poorly soluble medications bioavailability is constrained by the dissolution rate. Therefore, numerous techniques were developed to enhance solubility of poor water soluble medications⁽²⁾.

The absorption of drug from solid dosage forms generally occurs when dissolved drug was transport of the across the gastrointestinal membrane⁽³⁾.

In the biopharmaceutical classification system (BCS) medications are sorted on the basis of aqueous solubility and membrane permeability. Numerous poor water soluble medications come to II and IV according to BCS classes⁽⁴⁾. The medication solubility is straightly relative to its dissolution rate and subsequently solubility is an important parameter of a medication for

assurance of its absorption and dissolution and bioavailability. Parameters, for example, particle size, salt form, solubility, wettability, complexation, polymorphism and so forth influence the rate of dissolution⁽⁵⁾. Aqueous solubility of a medication is a potential factor to assess the oral bioavailability of orally administered poorly water soluble medications. The adjustment in the dissolution profile of these lipophilic medication particles without changing the molecular structure could be conceivable by several methods utilized to improvement medication candidate's aqueous solubility⁽⁶⁾. Many techniques such as particle size decrease, solid dispersion, crystal modification, lipid based system, pH adjustment can be used to enhance solubility⁽⁷⁾. Glass solution is made when at least two components are totally miscible in molten state and cooled to form amorphous one phase system. Melt extrusion studies were conducted to improve dissolution rate and bioavailability of medication, controlling/modifying release of medication and masking bitter taste of medication.

¹Corresponding author E-mail: ahmed_1983_sami@yahoo.com

Received: 12/10/2017

Accepted: 1/1/2018

Benefits of melt extrusion include using small tool economic technique and scale up resilience, solvent free fabricating, high mixing aptness and simply controlled route parameters. While disadvantage includes thermal route (medication/polymer stability), flow properties of polymers are necessary to processing, limited number of polymers and melt technique process could not be resorted to heat sensitive materials because of high temperature contained⁽⁸⁾.

Raltegravir is an antiretroviral medication (Figure 1), utilized to treat with HIV infection. Raltegravir chemically known as is *N*-[(4-Fluorophenyl) methyl]-1, 6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[(5-methyl-1, 3, 4-oxadiazol-2-yl) carbonyl] amino] ethyl]-6-oxo-4-pyrimidinecarboxamide. It targets integrase, an HIV enzyme that integrates the viral genetic material into human chromosome. It is a climacteric step in the pathogenesis of HIV. Raltegravir is categorized as a BCS class II compound, i.e. high permeability and low solubility at physiological pH. Its pKa is 6.3⁽¹¹⁾.

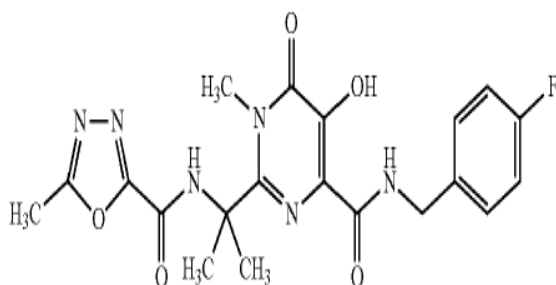


Figure 1. Chemical structure of raltegravir

Materials and Method

Materials

Raltegravir was supplied by Pharmatrain, Hyderabad. Plasdone S 630, Sskillet 20, Aerosil, Croscarmellose sodium, Hydroxy propyl cellulose, MCC pH 112, Lactose monohydrate, Sodium steryl fumarate, Magnesium stearate and Banana powder were found from S.D. Fine chemicals limited, Hyderabad. All chemicals utilized were of analytical reagent grade.

Methods

Saturation solubility

Solubility of raltegravir was evaluated in 0.1N HCl, acetate buffer (pH 4.5), phosphate buffer (pH 6.8) and distilled water. An extra amount of medication was added to 50 ml conical flask and was saved under shaking for 72 hrs in

the Rotary shaker. Saturated solution was filtered cross 0.45 μ membrane filter. Absorbance of filtered solutions was examined and amount of medication solubilized was computed.

Standard calibration curve of raltegravir in distilled water

Standard stock solution: A stock solution comprising 1000 μ g/ml of pure drug was prepared by dissolving 100 mg of raltegravir in enough water to get 100 ml solution in a volumetric flask.

Serial dilutions: Ten milliliters of the stock solution was further diluted to 100 ml with water. Aliquots of 0.5, 1.0, 1.5, 2.0 and 2.5 ml of diluted stock solution were pipette out into 10 ml volumetric bottles. The volume was made up to the sign with water. These dilutions give 5, 10, 15, 20, and 25 μ g/ml concentration of raltegravir individually. The absorbance was evaluated in the UV-Visible spectrophotometer at 315 nm utilizing purified water as blank and the concentration vs. absorbance was graphed.

Preparation of raltegravir immediate release tablets by using hot melt extrusion technique

Ten batches of immediate release raltegravir tablet were prepared depending on different drug to polymer proportion by hot melt technique as shown in table 1. Raltegravir, plasdone S630, aerosil crossed through 30 mesh sieve and granulated in rapid blender granulator with span 20 for 3 minutes. Pass this intra granular blend cross hot melt extruder at 100°C, 115°C, 130°C and 135°C zones. Then extrudes were powdered utilizing co-mill at 15000 rpm. Except sodium steryl fumarate, all extra granular blends sieve cross 30 mesh and blended for 10 mints. Sodium steryl fumarate is going cross 60 mesh and blended all mixture for 5 mints then compressed into tablet.

Table 1. HME raltegravir immediate release tablet composition

Ingredient	Trail-1	Trail-2	Trail-3	Trail-4	Trail-5	Trail-6	Trail-7	Trail-8	Trail-9	Trail-10
INTRAGRANULAR										
Raltgravir	400	400	400	400	400	400	400	400	400	400
Plasdone S 630	0	200	400	600	600	600	600	600	600	600
Span 20	30	30	30	30	50	30	30	30	15	30
Aerosil	10	10	10	10	10	10	10	10	10	10
Croscarmellose Sodium	10	10	10	10	10	10	10	10	10	10
EXTRAGRANULAR										
Croscarmellose Sodium	30	30	30	30	30	60	90	60	60	60
Hydroxy Propyl Cellulose	10	10	10	10	10	10	10	20	10	10
Microcrystalline Cellulose	105	105	105	105	105	105	105	105	105	75
Sodium Stearyl Fumarate	15	15	15	15	15	15	15	15	15	15
Total Weight	610	810	1010	1210	1230	1240	1270	1250	1225	1210

All amounts given in above table are in milligram

Characterizations of Hot Melt Extrudates

FT-IR spectroscopic analysis

Medication polymer reactions were considered by FT-IR spectroscopy. Ten milligrams of raltegravir and mixture of medication and polymer were weighed and combined correctly with potassium bromide uniformly. A small amount of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR- spectrum of the pellet from 450-4000cm⁻¹ was read taking air as the reference and collating to study any interference.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed utilizing DSC-60 (Shimadzu, Tokyo, Japan) calorimeter to ponder the thermal behavior of drug alone and mixture of drug and polymer. The testers were warmed in closed aluminum pans under nitrogen stream (80ml/min) at a scanning level of 10 degree centigrade/minute from 25 to 450 degree centigrade. Empty aluminum pan was utilized as reference.

Micromeritic Properties of Pre-Compressed Powder

Flow properties measurement of the various batches pre-compressed powder was evaluated by defining their angle of repose utilizing fixed-base cone method. A glass funnel was secured with its tip situated at fixed height (h) above chart paper put on a horizontal surface. The

sample was tapped cross the funnel until the apex of the conical pile touched to the funnel tip. The heap height and radius was evaluated [12]. The angle of repose (tan θ) was calculated using the equation;

$$\text{Angle of repose}[\theta] = \tan^{-1}(h/r)$$

h = funnel height, r = radius of circular base created by the granules on the ground.

Bulk and tapped densities measurement of the pre-compressed powder were assessed by using the bulk density apparatus. Known weights of formulated granules were moved into a 50cc graduated measuring cylinder. The cylinder was stable on bulk density device and the timer knob was put for 500 tapings. Then, the initial bulk volume and last volume after 500 tapings were noted⁽¹³⁾. The respective densities of various batches of granules were computed by utilizing the following formulas;

$$\text{Bulk density [gm /ml]} = \frac{\text{Mass of the sample (g)}}{\text{Bulk volume (ml)}}$$

$$\text{Tapped density [gm /ml]} = \frac{\text{Mass of the sample (g)}}{\text{Tapped volume (ml)}}$$

Compressibility index or Carr's index value of pre- compressed was computed according to the following equation; Compressibility index or

Carr's index value of pre-compressed was computed according to the following equation;

$$\text{Carr's index (CI\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio of pre-compressed powder was calculated by collating the tapped density to the bulk density by utilizing the equation;

$$\text{Hausner's ratio} = \text{Tapped density} / \text{Bulk density}$$

Evaluation of Immediate Release HME Raltegravir Tablets

Weight variation, hardness and friability

The uniformity of weights of tablets was examined according to the method cited in USP [14]. Weighed 20 tablets individually in an electronic balance and their average weight were computed;

$$\text{Average weight (gm)} = \frac{\text{Total of the tablets}}{20}$$

For each formulation, the hardness of 10 arbitrarily chosen tablets was examined utilizing a Pfizer hardness tester. The tablet hardness or crushing strength was evaluated in kg/cm².

The percentage of friability was evaluated by utilizing Roche friabilator. Ten or twenty tablets from each batch were weighed and placed in the plastic chamber. The chamber rotated for 4 minutes or 100 revolts. After 100 revolts tablets were moved from the chamber and reweighed [15]. The percentage of weight loss or friability was examined by the following formula;

$$\text{Friability (\%)} = \frac{\text{Loss in weight of tablets}}{\text{Initial weight}} \times 100$$

Content uniformity

Five tablets of each batch were weighed and powdered. The amount of the powder equal to 10 mg of raltegravir was dissolving in 100 ml of water comprising 10 ml of methanol. The resulting solution was moved into a locked funnel bottle and the bottle was shaken for interval of 12 h by utilizing a mechanical shaker at room temperature. The following day it was stirred for 15 minutes. The solution was filtered, later suitable dilution; the medication content in the filtrate was examined at 315nm utilizing UV- Visible spectrophotometer ⁽¹⁶⁾.

In-vitro drug release studies

Various batches of raltegravir compressed tablet was subjected to estimate drug release in the

water up to 60 minutes by utilizing dissolution test device USP XIII paddle type, 50 rpm in 900 ml dissolution medium (what media) and maintained at 37 ± 0.5 °C. Samples (5ml) were withdrawn at interval time of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 60 minutes time interval. After each sampling, equal volume of the medium was substituted with similar volume of fresh medium. The tester was filtered cross 0.45μ membrane filter and diluted with suitable dilution with respective medium. Then estimate the raltegravir concentration in the solution by utilizing UV-Visible spectrophotometry measured at 315 nm. The absorbance of the samples was evaluated at various time intervals and the concentration, amount of medication released and the percentage of medication released were computed ⁽¹⁷⁾.

Results and Discussion

Saturation solubility

The saturation solubility of raltegravir in different media illustrated in the table 2. The results show increase in solubility of raltegravir with increasing pH. It is likely that the drug obtains a negative charge at higher pH by deprotonating of the hydroxyl group at the 5 position of the 6-oxo-1,6-dihydropyrimidine ring. This negative charge would result in increasing the solubility of the drug in aqueous buffer ⁽¹⁸⁾.

Table 2. Saturation solubility of raltegravir

Media	Saturation solubility (mg/ml)
0.1 N HCl	0.031
Acetate buffer (pH 4.5)	0.049
Phosphate buffer (pH 6.8)	0.18
Distilled water	0.31

Construction of standard calibration curve of raltegravir in distilled water

The absorbance of the solution was evaluated at 315nm, utilizing UV spectrometer with water as blank. Figure 3 of absorbance vs. concentration was plotted which indicated in compliance to Beer's law in the concentration range 5 to 25 μg/ml.

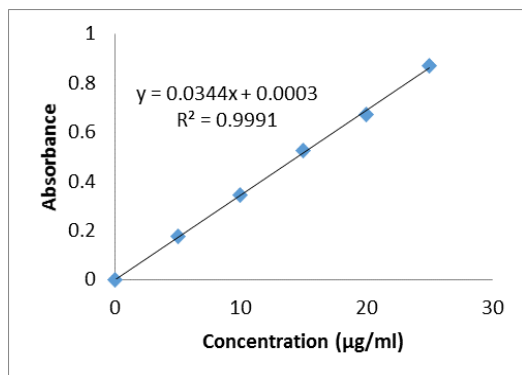


Figure 3. Calibration curve for raltegravir in distilled water

Micromeritic properties of pre-compressed powder blends

Powder blends of various formulations were evaluated for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. From table 3; all the formulas powder blends illustrate angle of repose (<40) demonstrating fair flow properties due to rise of bonding between microcrystals of medication and diluent⁽¹⁹⁾.

The bulk and tapped density values were found in the suitable range demonstrating good pack capability. Compressibility index and Hausner's ratio values are found in the range of 7.27 to 10 and 1.08 to 1.11 individually. This specifies that the prepared powder blends having better compressibility and good flow properties⁽²⁰⁾.

Table 3. Powder flow properties of (trial 1 –trial 10)

Formulations	Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index	Angle of Repose
Trail-1	0.80	0.89	1.11	10.00	30
Trail-2	0.77	0.83	1.08	7.69	28.23
Trail-3	0.80	0.89	1.11	10.00	30.02
Trail-4	0.73	0.78	1.08	7.27	27.81
Trail-5	0.77	0.83	1.08	7.69	27.42
Trail-6	0.75	0.82	1.08	7.55	28.13
Trail-7	0.78	0.85	1.09	7.84	28.87
Trail-8	0.74	0.82	1.10	9.26	29.12
Trail-9	0.78	0.85	1.09	7.84	28.91
Trail-10	0.80	0.87	1.09	8.00	28.63

Post compression studies

Table 4; shows that the weight difference of the tablets perceived within pharmacopeia limit submitted lower than $\pm 5\%$ w/w of stander deviation from the average. Hardness of the formulated tablets was found within suitable range of 8.0 to 12 kg/cm². Friability values were

found to be lower than 1% in all prepared formulations and though to be reasonable [20]. The content of raltegravir existent in the formulated tablets was detected in the range of 98.25 to 101.27 %. Trial 6 show best post compression parameters.

Table 4. Post compression parameters of raltegravir HME tablets

Formulations	Weight Variation	Hardness kg/cm ²	Disintegration Time (Min.)	Friability	Content Uniformity
Trail-1	Pass	8	12	0.281	99.13
Trail-2	Pass	8.5	17	0.146	98.61
Trail-3	Pass	8.5	16	0.432	100.03
Trail-4	Pass	10	14	0.318	98.25
Trail-5	Pass	9	12	0.516	99.57
Trail-6	Pass	10.5	10	0.125	101.25
Trail-7	Pass	11	10	0.314	100.57
Trail-8	Pass	12	14	0.264	100.63
Trail-9	Pass	12	13	0.468	99.15
Trail-10	Pass	12	16	0.312	99.87

FT-IR spectroscopy

For assessing any conceivable chemical interactions between the medication and polymers, FTIR spectra of raltegravir, physical mixture, and HME formulations were observed. IR spectrum of raltegravir introduced typical peaks at 1675.7, 1072.2, 3149.5, 1632.0, and 1270 according to C=N and C=C, C-N and C-O, N-H, (Figure 4). As illustrated in figure 5 and 6, the spectra of physical mixture and HME formulations are analogous. The raltegravir skeleton stretching vibrations are not impacted by the polymer adding, assuming no reactions between the polymer and medication in the physical and HME mixtures. Plasdone S-630 has two groups (=N- and C=O) that could possibly create hydrogen bond with raltegravir in the HME

formulations. The carbonyl group is more promising for hydrogen bonding and intermolecular interactions than the nitrogen atom due to steric hindrance (Figure 7). For HME formulations, the N-H stretching bands broadened and the band intensity reduced, demonstrating specific degree of reactions between the proton donating group (-NH) of raltegravir and the proton accepting group (C=O) in the Plasdone S-630 polymer. This states that the drug was molecularly dispersed in the polymers or in drug loaded formulations thus thereby demonstrating the absence of any interactions.

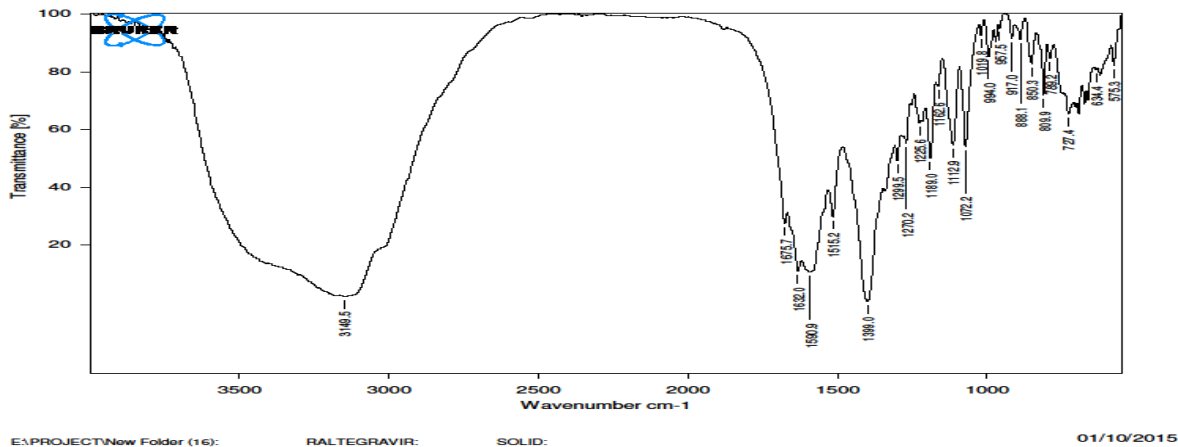


Figure 4. FTIR spectra of raltegravir

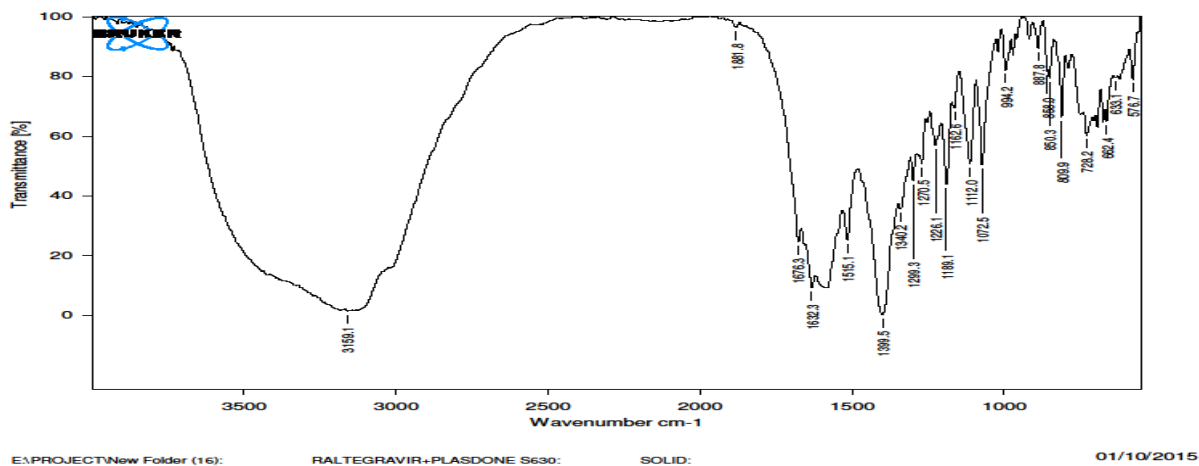


Figure 5. FTIR of physical mixture

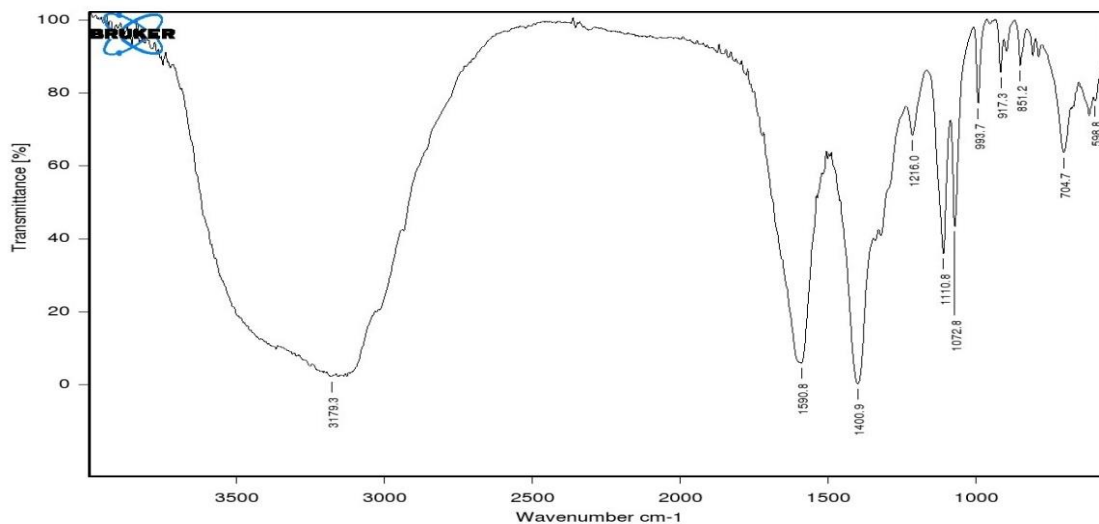


Figure 6. FTIR spectra of raltegravir HME best formulation (Trial 6)

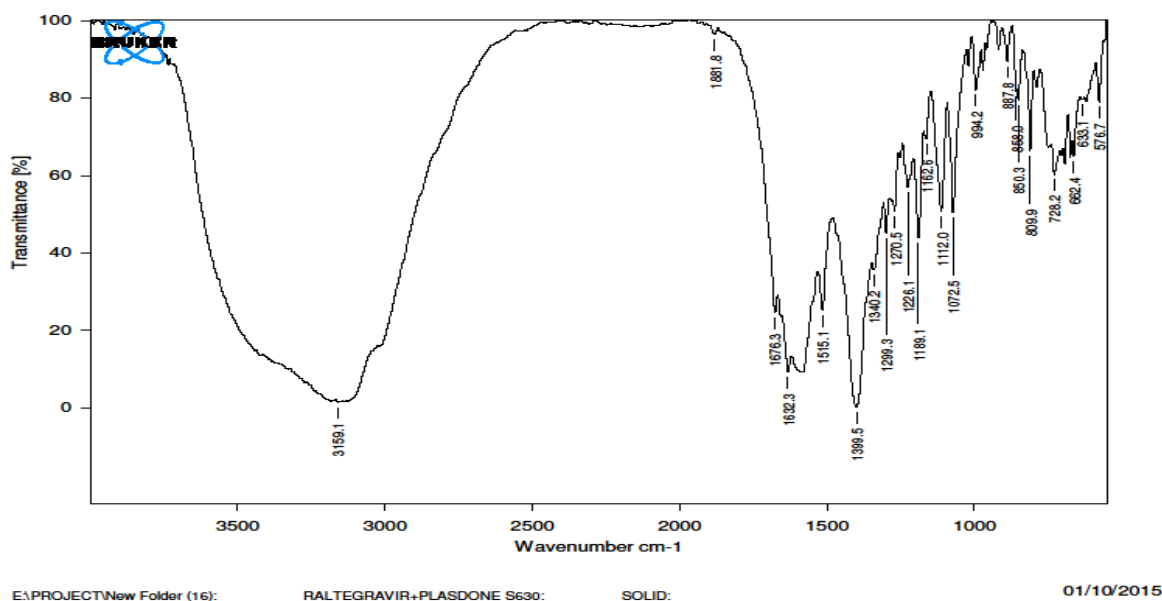


Figure 7. FTIR spectra of raltegravir and Plasdane S630

Differential scanning calorimetry (DSC)

DSC thermogram of raltegravir, illustrated sharp endothermic melting point at 277°C (Figure 8). Thermograms of raltegravir HME (Figure 9) illustrated a little, slightly wide endotherm that specified the reduced crystallinity of raltegravir. This might be because of interaction of drug and

polymer in DSC pan during heating ramp. On heating polymer gets melted far before drug's melting point so drug starts interacting with rubbery polymer. When temperature rises to melting point of drug, drug has already been solubilized into molten polymer and hence exhibits broad melting endotherm⁽²¹⁾.

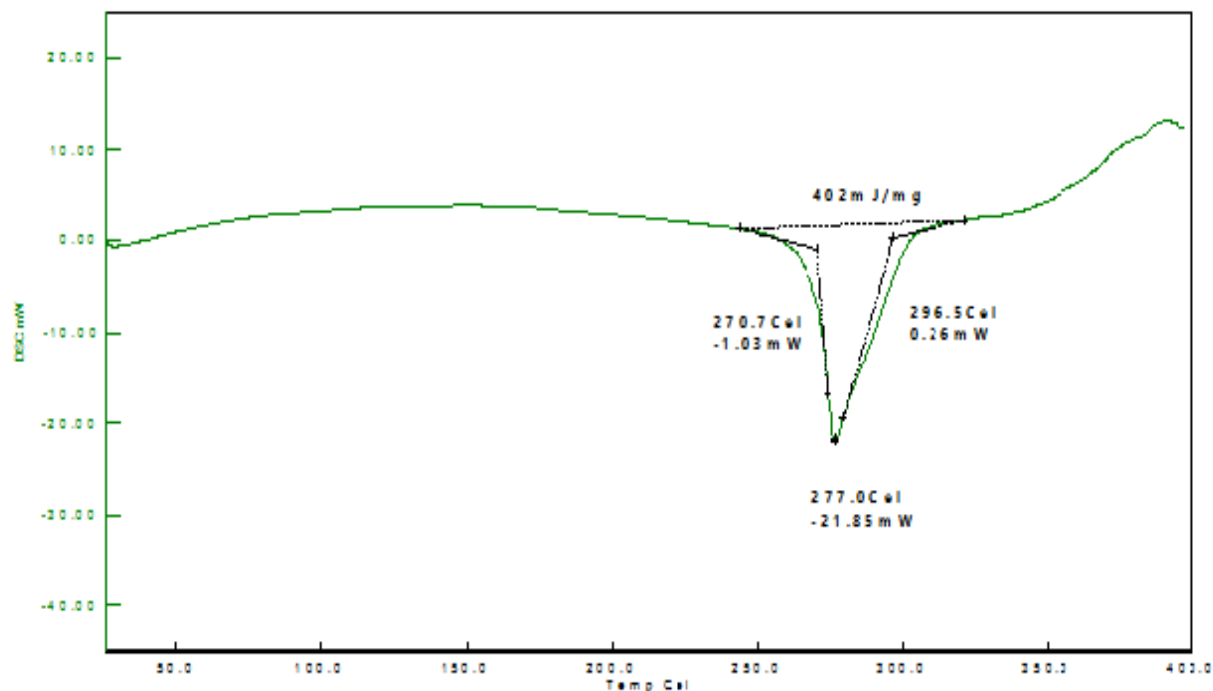


Figure 8. DSC spectrum of raltegravir

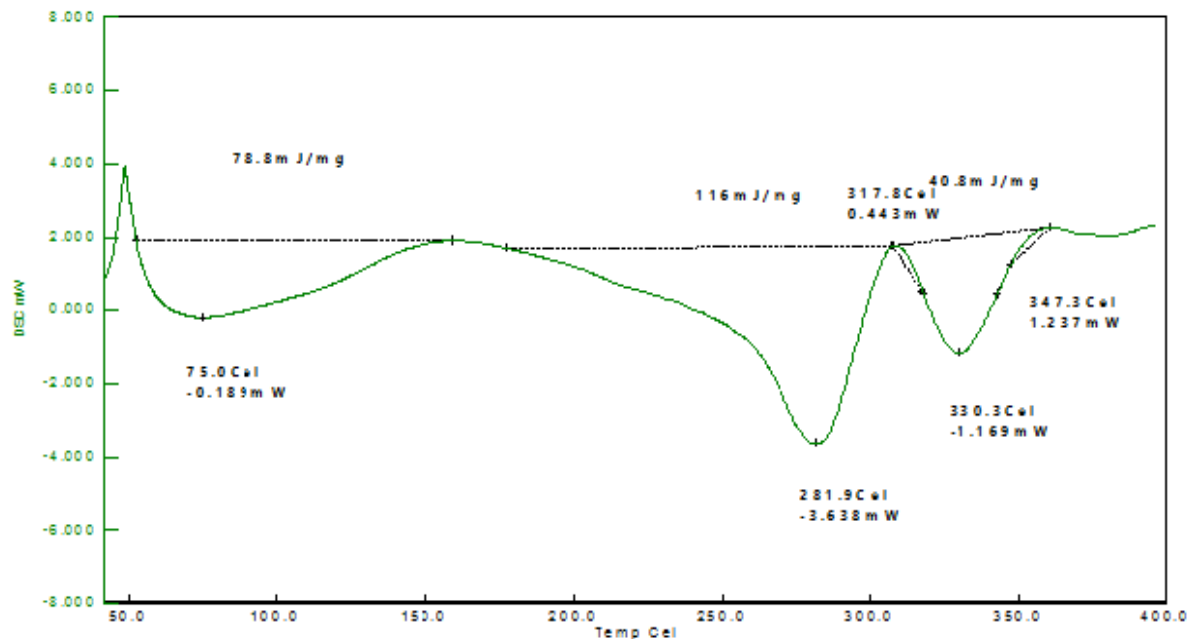


Figure 9. DSC spectrum of raltegravir HME

Dissolution studies

High dissolution rate in the HME formulation state is accredited to the amorphous case of the medication (some of drug exist in amorphous state) that present a lesser thermodynamic barrier to dissolution and the creation of a glassy solution where the medication

is molecularly dispersed in the polymer. The higher apparent solubility and increase in dissolution rate for amorphous materials is well recognized and has been widely known. The improvement in solubility is the result of the disordered structure of the amorphous solid ⁽²²⁾.

Raltegravir hot melt extrudes tablet illustrated noticeably higher dissolution - more than 80 % release in 45 min (Figure 10 and 11). Improvement in dissolution is because of reducing in crystallization of raltegravir in hot melt extrudes. Additional solubilizing agent Plasdane S-630 raises the dissolution of raltegravir by improving its wettability. The drug solubility and dissolution rate were not improved by simple physical mixing with the polymer. Higher apparent medication solubility and improved dissolution profiles are accredited to the amorphous nature of raltegravir where it is molecularly dispersed in the polymer matrix ⁽²³⁾.

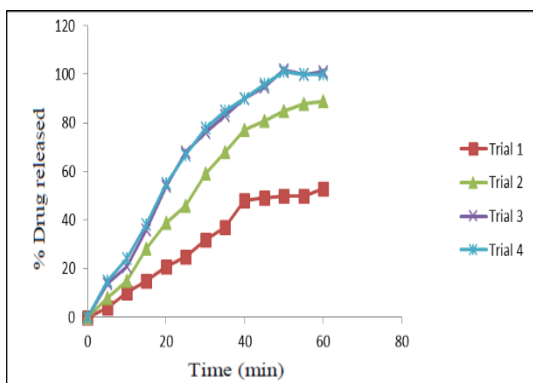


Figure 10. In-vitro drug dissolution profiles (Trial 1- Trial 4)

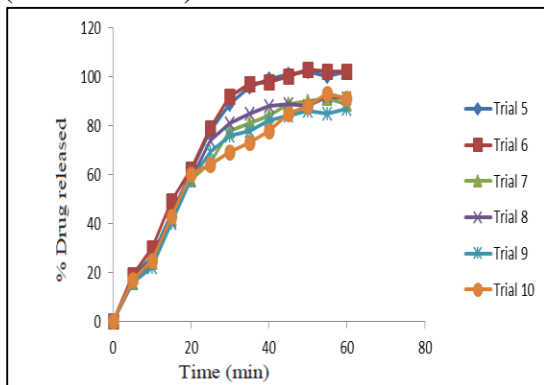


Figure 11. In-vitro drug dissolution profiles (Trial 5- Trial 10)

Conclusion

Solubility of raltegravir can be improved by HME technology which is one of the methods of solid dispersion. DSC and FTIR study approves the decreased crystallinity raltegravir in solid dispersion with Plasdane S-630. All HME formulations shows better enhancement in dissolution rate. Increasing in polymer amount decreases the crystallinity of medication due to higher possibility of creation of the dispersion rather than solid dispersion.

References

- Reddy, T.A., S. Srinivasan, K. Kavitha, R. Kumar and J. Singh. Review on: better solubility Enhancement of Poorly Water Soluble Drugs. *International Journal of Inventions in Pharmaceutical Sciences*, 2013; 1(4): 267.
- Vemula, V.R., V. Lagishetty and S. Lingala. Solubility Enhancement Techniques. *International Journal of Pharmaceutical Sciences Review and Research*, 2010; pp: 41-42.
- Kumar, P. and C. Singh. A Study on Solubility Enhancement Methods for Poorly Water Soluble Drugs. *American Journal of Pharmacological Sciences*, 2013; 1(4): 67.
- Pawar, A.R. and P.D. Chaudhary. Novel Techniques for Solubility, Dissolution Rate and Bioavailability Enhancement of Class II and IV drugs. *Asian Journal of Biomedical and Pharmaceutical Sciences*, 2012; 2(13): 9-14.
- Wairkar, S.M. and R.S. Guard. Solid Dispersions: Solubility Enhancement Technique for Poorly Soluble Drugs. *International Journal of Research in Pharmaceutical and Biomedical Sciences*, 2013; 4(3): 847.
- Saharan, V.A., V. Kukkar, M. Kaia and M. Gera. Dissolution Enhancement of Drugs. *International Journal of Health Research*, 2009; 2(2): 108.
- Chaudhary, M.D, R.O, Sonawane, L. Zawar, S. Nayak and S.B Bari. Solubility and Dissolution Enhancement of Poorly water Soluble Glimepiride by Using Solid Dispersion. Technique. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2012; 4(5): 534-539.
- Rauwendael CH. *Polymer Extrusion*, Hanser Publishers, München (1986) 20-25.
- Kruder GA. Extrusion. In: *Encyclopedia of Polymer Science and Engineering* Vol. 1, 2nd ed. John Wiley & Sons Inc., New York (1985) 571-631.
- Crowley MM, Zhang F, Repka MA, Thumma S, Upadhye SB, Battu SK, McGinity JW. Martin C. *Pharmaceutical Applications of Hot Melt Extrusion: Part I. Drug Dev Ind Pharm*, 2007; 33(9):909-926.
- www.ema.europa.eu/docs/en_GB/document_library/.../WC500037408.pdf
- Martin Alfred, *Physical Pharmacy* 4th Edition B.I. Waverly Pvt. Ltd., New Delhi, 1991; 760.

13. Indian Pharmacopoeia, Ministry of Health and Family Welfare, Government of India, 1996; II: 328-32.
14. Subrahmanyam CVS, Text Book of Physical Pharmaceutics, second edition, Vallabh Prakashan, New Delhi, 2000; 85.
15. Sharma S, et al, . Formulation of fast dissolving tablets of Promethazine Theoclate. *Trop J PharmRes.* , 2010; 9 (5): 489- 497.
16. Ravikiran N. Design and evaluation of orodispersible tablet of piroxicam using different superdisintegrants. *Journal of Drug Formulation & Research*, 2010; 349-374.
17. Fahmy R.H., Kassem M.A. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: in vitro and in vivo evaluation. *Eur. J. Pharm. Biopharm*, 2008; 69: 993– 1003.
18. Cattaneo D, et al. Inter- and Intra-patient Variability of Raltegravir Pharmacokinetics in HIV-1-Infected Subjects. *J. Antimicrob. Chemother*, 2011; 67:460–464.
19. Hou, H., Sun, C.C. Quantifying effects of particulate properties on powder flow properties using a ring shear tester. *Journal of Pharmaceutical Sciences*, 2008; 97 (9), 4030-4039.
20. Shangraw R.F. Compressed tablets by direct compression, second ed., in: Lieberman H.A., Lachman L., Schwartz J.B. (Eds.).
21. Vavia P *et al.* Preparation of Oxcarbazepine Solid Dispersion by Hot Melt Extrusion for Enhanced Dissolution: Downstream Processing to tablets. *American Journal of PharmTech Research*, 2013; 3(1): 557-569.
22. Hancock BC, Parks M. What is the true solubility advantage for amorphous pharmaceuticals *Pharm Res*, 2000; (4):397–404.
23. Ritesh Fule *et al.*, Solubility and dissolution rate enhancement of lumefantrine using hot melt extrusion technology with physicochemical characterization. *Journal of Pharmaceutical Investigation*, 2013; 43:305-321.