



Design and Development of Crystallo-co-agglomerates of Ritonavir for the Improvement of Physicochemical Properties

Fizikokimyasal Özelliklerin İyileştirilmesi için Ritonavirin Kristalo-Koaglomeratlarının Tasarımı ve Geliştirilmesi

© Nilesh M. MAHAJAN^{1*}, © Ashwini D. MALGHADE¹, © Nitin G. DUMORE¹, © Raju R. THENGE²

¹Dadasaheb Balpande College of Pharmacy, Department of Pharmaceutics, Maharashtra, India

²Dr. Rajendra Gode College of Pharmacy, Maharashtra, India

ABSTRACT

Objectives: The aim of the present study was to obtain CCA of ritonavir to improve the solubility, dissolution rate, and other physicochemical properties.

Materials and Methods: Ritonavir agglomerates were prepared using the CCA technique. Acetone-water containing HPMC K-15, PEG-6000, PVP K-30 was used as the crystallization medium. The agglomerates were evaluated for saturation solubility, micromeritic properties, yield, and drug content. The agglomerates were also characterized using FTIR, DSC, XRPD and SEM.

Results: The growth of particle size and the spherical form of the agglomerates resulted in the formation of products with good flow and packing properties. The improved compaction properties of the agglomerated crystals were due to the fragmentation that occurred during compression. DSC and XRD studies showed that ritonavir particles crystallized in the presence of HPMC, PEG-6000, PVP K-30 and diluents did not undergo structural modifications. The solubility and dissolution rate of ritonavir agglomerates were improve compare to pure ritonavir.

Conclusion: CCA was successfully applied to improve the physicochemical properties of ritonavir.

Key words: Crystallo-co-agglomeration, solubility, dissolution, ritonavir

ÖZ

Amaç: Bu çalışmanın amacı, çözünürlük, çözünme hızı ve diğer fizikokimyasal özelliklerini iyileştirmek için ritonavirin CCA'larını elde etmektir.

Gereç ve Yöntemler: Ritonavir aglomeratları, CCA tekniği kullanılarak hazırlandı. Kristalizasyon ortamı olarak HPMC K-15, PEG-6000, PVP K-30 içeren aseton-su kullanıldı. Aglomeratlar, doyumluk çözünürlüğü, mikromeritik özellikler, verim ve etkin madde içeriği açısından değerlendirildi. Aglomeratlar ayrıca FTIR, DSC, XRPD ve SEM kullanılarak karakterize edildi.

Bulgular: Aglomeratların partikül büyüklüğünün ve küresel formunun büyümesi, iyi akış ve paketlenme özelliklerine sahip ürünlerin oluşumu ile sonuçlandı. Aglomere olmuş kristallerin iyileşmiş sıkıştırma özellikleri, sıkıştırma sırasında meydana gelen parçalanmadan kaynaklanmıştır. DSC ve XRD çalışmaları, HPMC, PEG-6000, PVP K-30 ve seyrelticilerin varlığında kristalleşen ritonavir partiküllerinin yapısal modifikasyonlara maruz kalmadığını gösterdi. Ritonavir aglomeratlarının çözünürlüğü ve çözünme hızı, saf ritonavir ile karşılaştırılır derecede gelişti.

Sonuç: Ritonavirin fizikokimyasal özelliklerini iyileştirmek için kristalo-koaglomerasyonu başarıyla uygulanmıştır.

Anahtar kelimeler: Kristalo-koaglomerasyon, çözünürlük, çözünme, ritonavir

*Correspondence: E-mail: nmmahajan78@gmail.com, ORCID-ID: orcid.org/0000-0002-2928-0769

Received: 29.06.2017, Accepted: 07.09.2017

©Turk J Pharm Sci, Published by Galenos Publishing House.

INTRODUCTION

Crystal engineering is the design and synthesis of molecular solid-state structures with desired properties, based on an understanding and exploitation of intermolecular interactions.¹ The two main strategies currently in use for crystal engineering are based on hydrogen bonding and coordination complexation.² With advances in power technology, different attempts have been made to design primary and secondary particles of substances for several applications. Enlargement of particle size is an important process in the manufacturing of tablets that imparts some degree of functionality to particles such as improvements in flowability, solubility, dissolution, micromeritic, compression, and compressibility properties. Different techniques for enlargement of particle size are important tools for modifying primary and secondary properties of pharmaceutical substances.³ Nowadays, several new techniques combining granulation and crystallization are being developed to improve particle properties. There are various conventional processes used to enlarge particle size and involve the wider acceptability, but recently, non conventional techniques of particle size enlargement have been developed including extrusion-spheronization, melt solidification, melt granulation, melt extrusion, and spherical crystallization. These techniques are advantageous because of the lower number of unit operations and are economical in terms of processing cost, and depend on the desired properties of enlarged particle and physico-chemical properties of drug and excipients.⁴ Crystal engineering design techniques are widely used in pharmaceutical industries to modify primary (e.g., particle size, shape, crystal habit, crystal form, density, porosity, dust generation) as well as secondary (e.g., flowability, compressibility, compatibility, consolidation, reduced adhesion of formulation to the processing equipment, reduction in air entrapment during processing) properties of pharmaceuticals. In particular, improvement in the efficiency of the manufacturing process and a high degree of particle functionality can be achieved by these techniques.⁵ Crystallo-

co-agglomeration (CCA) is a novel particle engineering technique, which aggregates crystals of drugs in the form of small spherical particles using excipients and solvents to develop an intermediate material with improved micromeritic and mechanical properties, solubility, and dissolution. The rate of dissolution of the drug from the agglomerates or compacts thereof can be improved and modified by using suitable excipients during the process of preparation of agglomeration.⁶ The present work reports a CCA technique used to prepare agglomerates of ritonavir, an antiviral drug, the crystalline form consisting of long needles, which otherwise has low bulk density, very poor flow property as well as compressibility, and very low solubility in water, which makes direct compression difficult. Excipients to be incorporated in the formation of agglomerates should have an affinity toward the bridging liquid. Talc, due to its hydrophobicity, undergoes preferential wetting with bridging liquids and is a suitable excipient for incorporation in agglomerates. Apart from talc, various hydrophilic and hydrophobic polymers have been used to study their effect on physicochemical and physicomachanical properties.

MATERIALS AND METHODS

Ritonavir was obtained as a gift sample from Emcure Pvt. Ltd, Pune, hydroxypropyl methyl cellulose (HPMC) K-15, polyethylene glycol (PEG)-6000 polyvinylpyrrolidone (PVP) K-30, talc, acetone and dichloromethane were purchased from Lobachem, Mumbai, India. All the solvents used were of analytical grade.

The study was approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (registration number: 1426/PO/Re/S/11/CPCSEA, 01.08.2016)

Preparation of CCA

Different agglomerates were prepared of the compositions shown in Table 1. Ritonavir agglomerates were prepared using a three solvent system comprising acetone: dichloromethane:

Table 1. Formulation of batches of crystallo-co-agglomerates of ritonavir

Sr. no	Material used Batches	A-1	A-2	A-3 1%	B-1	B-2	B-3	C-1	C-2 0.75%	C-3
		0.5% w/v g/mL	0.75% w/v g/mL	w/v g/mL	0.5% w/v g/mL	0.75% w/v g/mL	1% w/v g/mL	0.5% w/v g/mL	w/v g/mL	1% w/v g/mL
1	Ritonavir	1	1	1	1	1	1	1	1	1
2	PEG-6000	0.5	0.75	1	--	--	--	--	--	--
3	PVP K-30	--	--	--	0.5	0.75	1	--	--	--
4	HPMC K-15	--	--	--	--	--	--	0.5	0.75	1
6	Talc	0.3	0.35	0.4 g	0.3	0.35	0.4	0.3	0.35	0.4
7	Tween 80	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
8	Dichloromethane	2	2	2	2	2	2	2	2	2
9	Acetone	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
10	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone, HPMC: Hydroxypropyl methyl cellulose

water (acetone as good solvent, dichloromethane as bridging liquid and water as bad solvent, respectively). Polymers were dissolved in a vessel in a sufficient amount of distilled water. Then, talc and Tween 80 were added under stirring conditions at 600 rpm maintained at 10°C. Ritonavir was dissolved in acetone. The latter solution was added immediately to the dispersion containing dissolved polymer under constant stirring conditions (600 rpm) and kept at room temperature. The stirring was continued for 20 min and the bridging liquid dichloromethane was added dropwise to obtain agglomerates, which were then set aside overnight. Then obtained agglomerates were filtered and dried. Three batches (A-1, A-2, A-3, B-1, B-2, B-3, C-1, C-2, C-3) were prepared by changing the concentration of excipients (0.5, 0.75 and 1 % w/v).

Characterization of agglomerates

Saturation solubility studies

To evaluate the increase in the solubility of agglomerates, saturation solubility measurements were conducted. An excess amount drug or agglomerates was added to a 50 mL conical flask containing distilled water. The system was agitated on a rotary shaker for 48 h at 100 rpm, maintained at room temperature, and filtered. The filtrate was suitably diluted and analyzed at 201 nm using an ultraviolet (UV) visible spectrophotometer (UV-1800, Shimadzu, Japan).⁷

Micromeretic study

The flow properties of agglomerates were determined in terms of angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The angle of repose was determined using the fixed funnel method, whereas Carr's index and the Hausner ratio were calculated from bulk and tapped densities. The Hausner ratio was taken as a ratio of tapped density to bulk density.

Angle of repose

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between the surface of pile of powder or granules and the horizontal plane.

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

$$\theta = \tan^{-1} h / r$$

Where, θ = angle of repose, h = height of heap, r = radius of base of heap circle.

Method: A funnel was fixed at a height approximately 2-4 cm over a platform. The drug powder was slowly passed along the wall of funnel till the tip of the formed powder cone just touched the tip of the funnel stem. The angle of repose was then determined by measuring the height of the cone of powder and the radius of the circular base of the powder heap.⁸

Compressibility index and Hausner's ratio

In recent years, the compressibility index and the closely-related Hausner ratio, which are simple and quick, have

become the most popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and Hausner's ratio are determined by measuring both bulk density and the tapped density of agglomerates.⁹

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

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

Production yield (%)

The production yields were calculated as the weight percentage of the final product after drying, with respect to the initial total amount of ritonavir and polymer used for the preparations.⁸

$$\text{Production yield \%} = \frac{\text{Practical mass (CCA)}}{\text{Theoretical mass (polymer+drug)}} \times 100$$

Drug content

Ten milligrams of agglomerates were accurately weighed in a 100 mL volumetric flask and the volume was adjusted to 100 mL with methanol (100 µg/mL), serving as a test solution. Standard solution was sonicated for 5 min and analyzed at 238 nm using a UV spectrophotometer.¹⁰

Fourier-transformation infrared (FTIR) spectroscopy

The study was conducted with an intention to check the compatibility of polymers such as HPMC K-15M, PEG-6000, and PVP K-30 with ritonavir. Also, it helps to check the suitability of polymer for the preparation of agglomerates. FTIR spectra were obtained using a Shimadzu FTIR spectrometer (Thermo Fisher, Japan). The samples of pure drug and physical mixture such as Ritonavir and HPMC K-15, PEG-6000, PVP K-30 were prepared. The scanning range was kept from 4000 to 500 cm⁻¹⁸.

Scanning electron microscopy (SEM)

The surface morphology of the optimized formulations was studied using a SEM (JSM 6390, JEOL) operated at an accelerating voltage of 10 kV and obtained micrographs were examined at different magnifications.¹¹

X-ray diffraction (XRD) of powder

The X-ray powder diffraction (XRPD) patterns were recorded on the XRD (PW 1729, Philips, Netherland). The samples were irradiated with monochromatised Cu K- α radiation (1.542Å) and analyzed between 10-50° 2 θ . The voltage and current used were 30 kV and 30 mA, respectively. The range and chart of speed were CPS and 5 mm/2 respectively.¹¹

Differential scanning calorimetry (DSC)

The thermal behavior of the drug-loaded agglomerates was studied using a differential scanning calorimeter (Mettler Toledo) at a heating rate of 10°C/min. The measurements were performed at a heating range of 20-250°C under nitrogen atmospheres.¹¹

Dissolution studies

The dissolution rate studies were conducted in 900 mL of pH 6.8 phosphate buffer (simulated intestinal fluid) at 50 rpm and maintained at $37 \pm 0.5^\circ\text{C}$ in a dissolution apparatus (Model ElectroLab Dissolution tester USP TDT-08L) using the paddle method. One hundred milligram equivalent quantity agglomerates were added to the dissolution medium and the samples were withdrawn at appropriate time intervals up to 90 mins. The samples were immediately filtered through a $0.45\text{-}\mu\text{m}$ membrane filter, suitably diluted, and analyzed spectrophotometrically at 201 nm. The data obtained from dissolution studies were statistically validated.¹²

RESULTS AND DISCUSSION

Ritonavir was crystallized from acetone-water and agglomerated with diluents. In this process, the crystallization of the drug was performed by the addition of a solution to the anti-solvent phase (water). Acetone served as good solvent and the bridging liquid and aqueous phase as the non-solvent. The saturation solubility of prepared agglomerate with HPMC K-15 showed the highest solubility compared with pure ritonavir, as shown in Table 2.

The spherically agglomerated crystals, produced in yields generally within the range 55-80% (Table 2), were produced simultaneously as crystallization was completed. As both phases (acetone and aqueous) contained the diluents, then it is likely that it was distributed both inside the agglomerates (intragranularly) and outside the agglomerate (extragranularly), attached to the surface.

Micromeritic of agglomerates

The micromeritic properties, such as flowability of agglomerates, are shown in Table 2. It shows that the flowability represented in terms of the angle of repose, Carr's index and Hausner's ratio of agglomerates was much improved compared with those of the original drug. Statistical analysis showed that the angle of repose and Carr's index for both agglomerates reduced significantly in comparison with the original drug. The Hausner's ratio for both agglomerates was found to be less than 1.52, indicating improvement in their flow properties. The poor flow properties of pure ritonavir might be attributed to it being amorphous in nature. These findings proved that the flowability of agglomerates was preferably improved as compared with the pure drug.

Morphology of agglomerates

An SEM examination confirmed that the starting material was markedly smaller in particle size than any of the treated crystals. Similar results were obtained in other studies using CCA procedures for other drugs. Ritonavir exhibits platy crystal habit, which was distributed at CCA formation. Prominent changes were observed with formulation C-1 as compared with A-1 and B-1. Although all formulations showed formation of agglomerates in the SEM images in Figure 1A-D, as evident from the adherence of the polymer and talc on to the crystal surface of drug.

FTIR spectroscopy

The FTIR spectra of samples are shown in Figure 2A-D. There was no considerable change in the positions of characteristic absorption bands and bonds of various functional groups present in the drug. This observation clearly suggests that the

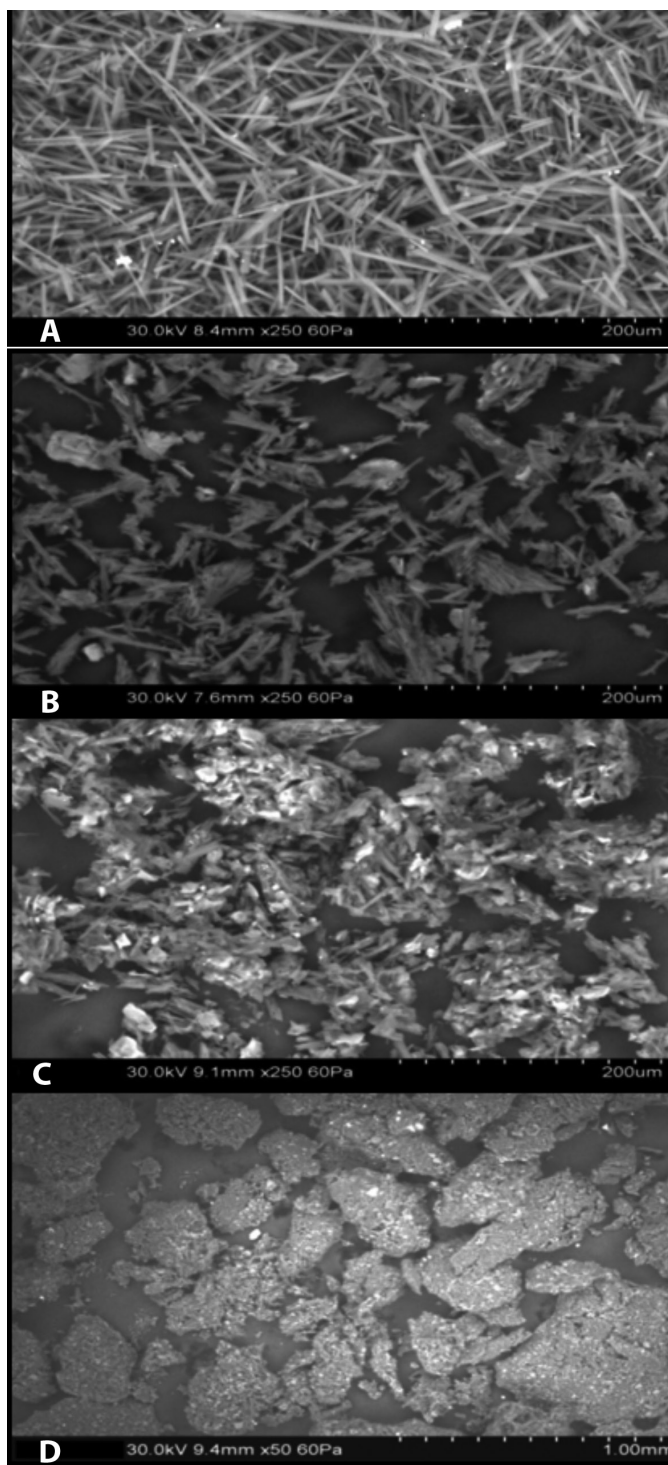


Figure 1. A) Scanning electron microscopy of pure drug (ritonavir). B) Scanning electron microscopy of crystallo-co-agglomeration of formulation A-1. C) Scanning electron microscopy of crystallo-co-agglomeration of formulation B-1. D) Scanning electron microscopy of crystallo-co-agglomeration of formulation C-1

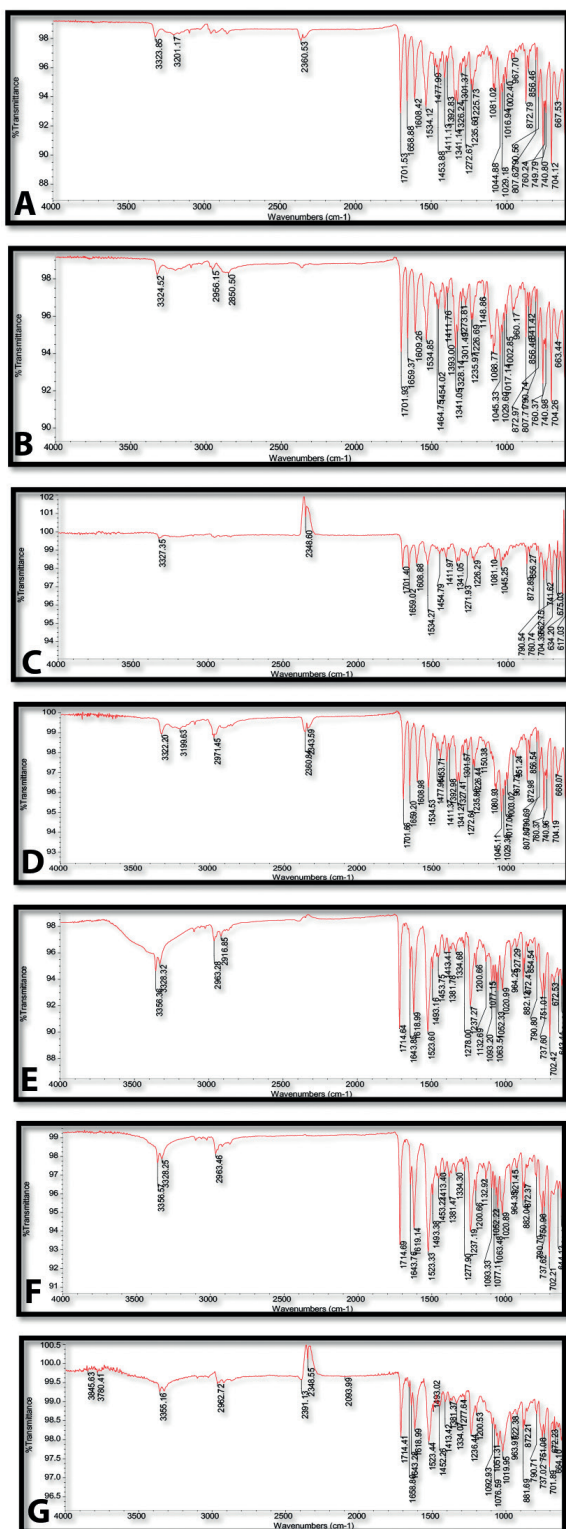


Figure 2. A) Fourier-transformation infrared spectrum of pure drug (ritonavir). B) Fourier-transformation infrared spectrum of physical mixture (polyethylene glycol-6000: ritonavir). C) Fourier-transformation infrared spectrum of physical mixture (polyvinylpyrrolidone K-30: ritonavir). D) Fourier-transformation infrared spectrum of physical mixture (hydroxypropylmethylcellulose K-15: ritonavir). E) Fourier-transformation infrared spectrum of formulation A-1. F) Fourier-transformation infrared spectrum of formulation B-1. G) Fourier-transformation infrared spectrum of formulation C-1

drug remained in its normal form with no prominent change in its characteristics, even in its physical mixture and formulation. The results of the FTIR spectra indicated the absence of any well-defined interaction between drug, diluents, and polymer, as shown in Table 3.

XRD

XRD is a powerful technique for determining the presence of polymorphs, crystal habit modification in drug crystals, and generation of new crystal forms during CCA. Every crystalline solid phase has a unique (XPRD) pattern, which can form the basis for its identification. The XRPD pattern in the $10\text{-}80^\circ$, 2θ range showed that the diffraction peaks, characteristics of ritonavir were detectable in crystalline sample i.e. CCA sample, Figure 3A-D, suggesting that the particles crystallized in the presence of polymers, and talc did not undergo structural changes or modification. However, the difference in the relative intensities of their peaks and some new identification peaks over an extended range may be attributed to the difference in the crystallinity or particle size of the sample.

DSC

DSC can be combined with XRPD to determine the polymorphic composition of pharmaceutical powders, if two or more polymorphs are present. The uniformity of crystalline structure in all batches was confirmed by the DSC. All the formulations, irrespective of the polymer and concentration used, showed a sharp melting endotherm that started at $120\text{-}121^\circ\text{C}$ with a flat baseline, which indicated that the material was not degraded by hydration, salivation or any crystalline changes. Also, it shows no interaction of drug with polymers during crystalline changes. There was no appreciable change in the melting endotherm of CCA compared with that of pure drug. The DSC results (Figure 4A-G) also revealed little amorphization of ritonavir when prepared in the form of agglomerates with HPMC K-15, PEG-6000, and PVP K-30. This is evident by a decrease in the enthalpy changes of agglomerates when compared with that of pure drug (ritonavir) -408.25 mJ/mg and that for CCA of formulation of A-1, B-1 and C-1 were -27.75 mJ/mg, -32.1818 mJ/mg and -49.77 mJ/mg, respectively.

Dissolution rate

The dissolution rate of pure ritonavir and its agglomerates are shown in Figure 5. The dissolution rates of the agglomerates were significantly different from pure ritonavir. Dissolution rate enhancement of ritonavir agglomerates were due to the presence of polymers, which may improve the wettability of the drug. The agglomerates with HPMC K-15, PVP-K30, and PEG-600 had 95.70%, 93.00%, and 89.22% drug release compared with pure drug, 55.64%.

CONCLUSIONS

CCA of ritonavir with different hydrophilic polymers such as PEG-6000, PVP K-30, and HPMC K-15 showed an improvement in the solubility, dissolution rate, and flowability as compared with pure drug. Solid state characterization of drug and CCA showed satisfactory results; FTIR proved compatibility, SEM

Table 2. Evaluation parameters of crystallo-co-agglomerates of ritonavir

Batches	Saturation solubility (mg/mL)	Hauser's ratio	Carr's index	Angle of repose (°)	Drug content (% w/w)	Production yields (%)
Pure drug	0.040	1.52	34	30.39	---	---
A-1	0.202	1.12	11	22.58	75	66.66
A-2	0.221	1.09	8	23.02	79.82	69.23
A-3	0.239	1.09	8	23.02	79.98	55.80
B-1	0.175	1.20	18	19.29	84.96	69.40
B-2	0.200	1.10	9	19.64	95.71	62.19
B-3	0.203	1.13	11	19.29	95	55.54
C-1	0.245	1.19	16	25.12	81	78.33
C-2	0.252	1.07	7	21	95	64.61
C-3	0.255	1.18	15	21.65	95.1	60.23

Table 3. Interpretation of FTIR spectra

Material	Peak (cm ⁻¹)	Functional group	Physical mixture			Formulation code		
			PEG-6000 + ritonavir	PVP K-30 + ritonavir	HPMC K-15 + ritonavir	A-1	B-1	C-1
Ritonavir	704.12	C-S stretching vibration	704.26	704.39	704.19	702.40	702.58	702.21
	790.56	C-C stretching vibration	790.74	790.54	790.96	790.87	790.73	790.51
	1235.60	C=O bending vibration	1235.97	1226.29	1235.88	1235.79	1235.19	1235.19
	1411.13	C-NH ₃ stretching vibration	1411.76	1411.97	1411.37	1411.80	1411.31	1411.07
	1658.88	C=C stretching vibration	1658.33	1659.02	1659.20	1643.32	1658.20	1659.07

PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone, HPMC: Hydroxypropyl methyl cellulose, FTIR: Fourier-transformation infrared

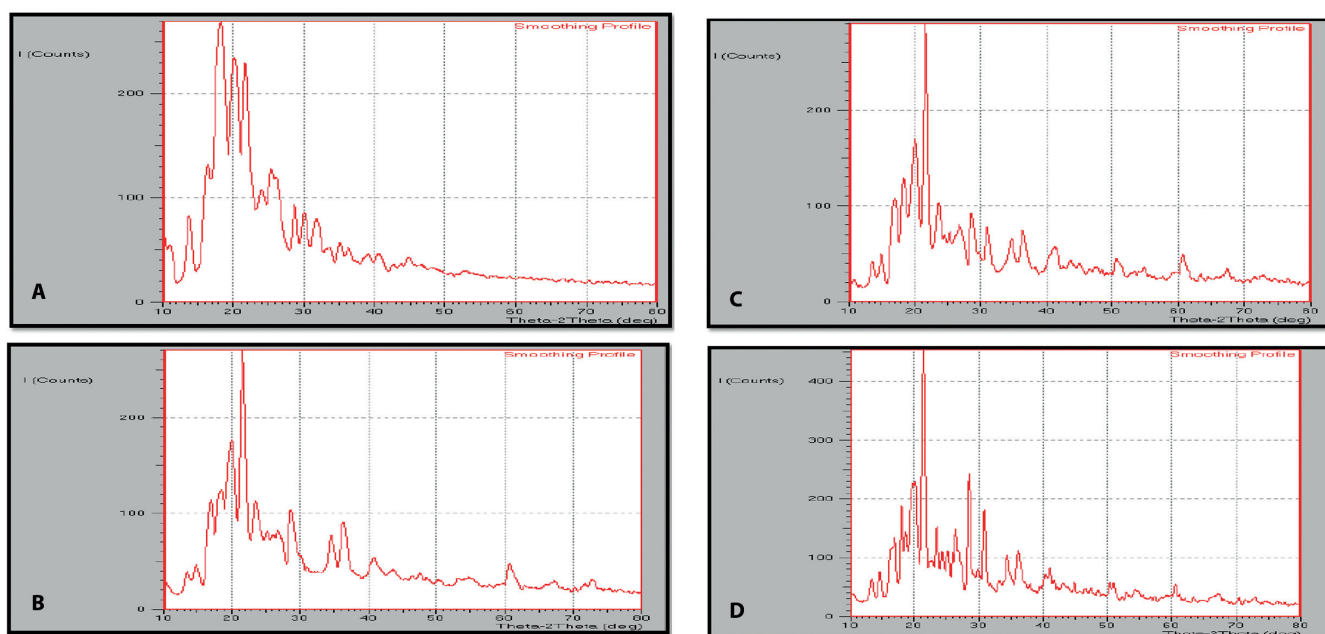


Figure 3. A) X-ray diffraction pattern of ritonavir. B) X-ray diffraction pattern of formulation A-1. C) X-ray diffraction pattern of formulation B-1. D) X-ray diffraction pattern of formulation C-1

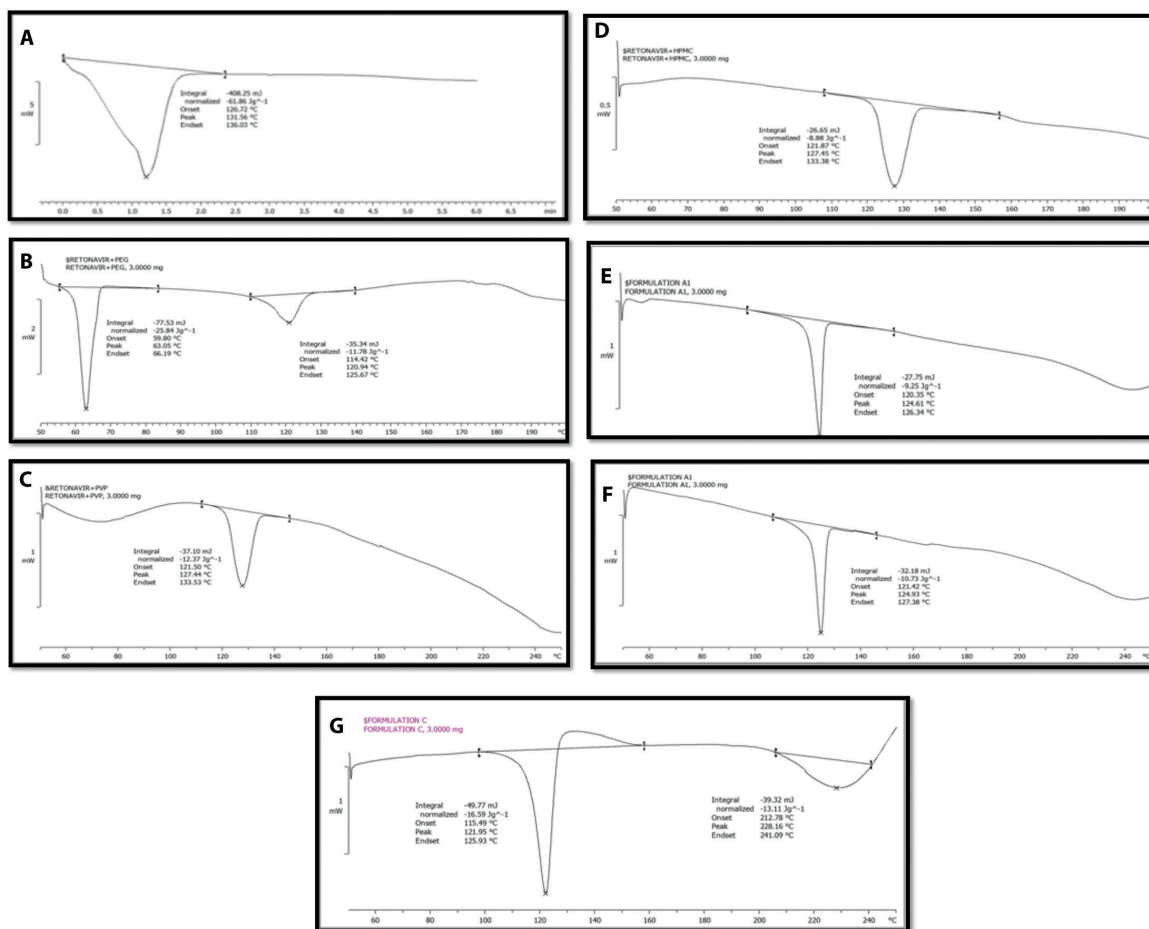


Figure 4. A) Differential scanning calorimetry spectra of ritonavir. B) Differential scanning calorimetry spectra of physical mixture ritonavir + polyethylene glycol-6000. C) Differential scanning calorimetry spectra of physical mixture (ritonavir + polyvinylpyrrolidone K-30). D) Differential scanning calorimetry spectra of physical mixture (ritonavir + hydroxypropylmethylcellulose K-15). E) Differential scanning calorimetry spectra of formulation A-1. F) Differential scanning calorimetry spectra of formulation B-1. G) Differential scanning calorimetry spectra of formulation C-1

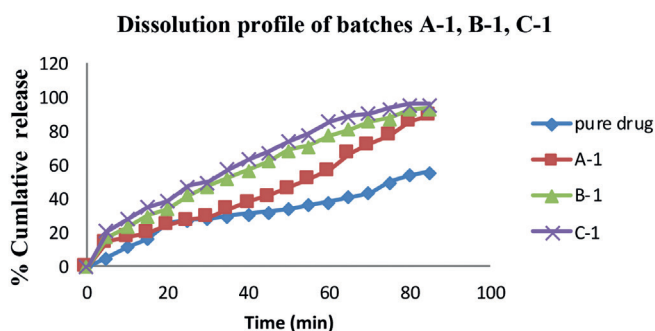


Figure 5. Dissolution profile of agglomerates and pure drug

showed enlarged size with signs of porosity, XRD proved crystallinity, and DSC showed thermal evaluation. The altered size and shape of CCA indicated modified crystal habit, which could be responsible for the dramatic improvement in flowability, solubility, and dissolution properties of ritonavir. CCA of ritonavir is an alternative and effective approach for improvement in the physicochemical and micromeritic properties of ritonavir.

ACKNOWLEDGEMENTS

The authors are thankful to Emcure Pvt. Ltd (Pune) for providing gift sample of ritonavir and also to the Principal and Management of Dadasaheb Balpande College of Pharmacy, Nagpur for providing the research facility.

Conflict of Interest: No conflict of interest was declared by the authors.

REFERENCES

- Xin Ding, Tuikka M. Halogen bonding in crystal engineering. *Recent Adv crystallography*. 2012;143-168.
- Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredient to improve solubility and dissolution rates. *Adv Drug Del Rev*. 2007;59:617-630.
- Chaturvedi A, Sharma PK, Bansal M. A review on recent advancement in crystallo-co-agglomeration. *Adv Bio Res*. 2011;5:273-281.
- Paradkar AR, Pawar AP, Jadhav NR. Crystallo-co-agglomeration: A Novel Particle Engineering Technique. *Asian J Pharm*. 2010;4:4-10.
- Garala K, Patel J, Patel A, Raval M, Dharamsi A. Influence of excipients and processing conditions on the development of agglomerates of

- racecadotril by crystallo-co-agglomeration. *Int J Pharm Investig.* 2012;2:189-200.
6. Genikal B, Rajendra A. Formulation of crystallo-co-agglomerates of naproxen; study of effect of polymers on drug release. *Int J Pharm.* 2013;5:852-864.
 7. Jolly CM, Lekshmi P, Constantine I, Bijin EN, Valsalakumari J, Pramod K. Crystallo-co-agglomeration: an innovative technique for size enlargement and improved flow properties of powders. *J Mater Sci.* 2013;1:1-14.
 8. Thenge RR. Crystal Modification of Aceclofenac by Spherical Crystallization to Improve Solubility Dissolution Rate and Micromeritic Properties. *J Pharm Res.* 2012;5:974-977.
 9. Hardik KP, Sangvi K. A review on spherical agglomeration for improvement of micromeritic properties and solubility. *Int J Pharm.* 2013;3:570-579.
 10. Shashank A, Pakash GS, Sanjav J. Particle design of meloxicam-disintegrant agglomerates for fast dissolution and direct compression crystallo-co-agglomeration technique. *Int J Pharm Sci.* 2012;1:289-297.
 11. Palermo PJ. In *Handbook of Modern Pharmaceutical Analysis*. In: Ahuja S, Scypinski S, eds. Academic Press, San Deigo. USA; 2001:243-244.
 12. Tapas A, Kawtikwar P, Sakarkar D. An improvement of micromeritic properties and dissolution behaviours of carvedilol spherical agglomerates crystallized in presence of Inutec SP1. *Turk J Pharm Sci.* 2012;9:101-112.