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Original Article

Formulation and Evaluation of Ritonavir Solid Dispersions

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Abstract: Ritonavir is an anti-retroviral agent used in the treatment of AIDS having lowest water solubility of about 0.01mg/ml, indicates class IV drug bio-pharmaceutical classification systems, make an objective to study the solubility and dissolution by solid dispersion technique. Ritonavir solid dispersions are prepared using maltodextrin and poloxamer by solvent evaporation and kneading method at 1:1 and 1:3 drug: carrier and were evaluated for drug content, solubility, saturation solubility, FTIR, XRD, DSC and *in-vitro* dissolution.

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Introduction

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints and flexibility in the design of dosage form. Thus, many of the generic drug companies are inclined more to produce bioequivalent oral drug products. The high costs and time involved in new drug development, expiry of patents for a significant number of drug molecules, ease of manufacturing and ready availability of technology to produce oral drug products are also driving the generic

pharmaceutical companies towards the development of bioequivalent oral dosage forms.

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists.

Many potential drug candidates are characterized by a low oral bioavailability. Often poor drug dissolution/solubility rather than limited permeation through the epithelia of the gastrointestinal tract and responsible for low oral bioavailability [1].

The rate and extent of dissolution of the active ingredient from any dosage form often determines the rate of extent of absorption of the drug. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first pass metabolism, presystemic metabolism and susceptibility to efflux mechanisms [2-4].

The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. When an active agent given orally, it must first dissolve in gastric and/or intestinal fluids before it can then permeate the membranes of the GI tract to reach systemic circulation.

Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. T

hus aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus *in-vivo* efficacy [5, 6]. Most useful methods to overcome the inherent difficulties associated with the formulation and development of a poorly water soluble drug is to enhance the solubility of the same. In such case, formulators endeavors toward searching for a way to improve the absorption of a drug by increasing its dissolution rate, the rate limiting step for absorption of many drugs.

Among the methods of increasing the dissolution rate, those used most are increasing the surface area by micronization, increasing the wettability of the drug by incorporation of surfactants and using different carriers to diminish electrostatic forces. Solid dispersions of drugs in different carriers to increase the dissolution rate and bioavailability of poorly soluble drugs had been studied extensively [7-10]. This provides a means of reducing particles size to nearly a molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles for quick dissolution and absorption.

Ritonavir is a human immuno deficiency virus (HIV) protease inhibitor indicated for the treatment of autoimmune deficiency syndrome (AIDS). Ritonavir is practically insoluble in water [11] and could potentially exhibit dissolution rate limited absorption. Ritonavir would exist as a dicationic species in the stomach. However, in the intestine where the pH is 5.4±7.5 [12], the molecule would be primarily unionized. The solubility of ritonavir at 37^{o}C drops from 400±10 µg/ml in 0.1 N HCl to 1±0.02 µg/ml at pH 6.8 buffer, which is consistent with the ionization of the molecule. Although the solubility of ritonavir in 0.1 N HCl is 400 µg/ml, the IDR value is only 0.03±0.001 mg/cm2/min. Compounds with IDR<0.1 mg/min/cm^2 usually exhibit dissolution rate limited absorption [13], and dissolution rates may be improved through the preparation of solid dispersions [14, 15] therefore, ritonavir is a classic candidate for solid dispersions. In the present investigation, an attempt is made to prepare and evaluate ritonavir solid dispersions using hydrophilic polymers viz., maltodextrin and poloxamer to improve solubility and dissolution properties.

Materials and methods

Materials: Ritonavir (rit) obtained as gift sample from Stride arc lab Bengaluru, India. Maltodextrin (malto) and Poloxamer (polo) were procured from Sd fine-chem. limited, Mumbai. All chemicals and solvents used were of analytical grade.

Methods

Preparation of physical mixtures (PM) and solid dispersions: Physical mixtures of ritonavir: maltodextrin and ritonavir: poloxamer at 1:1 and 1:3 ratios were obtained by mixing individual components together with a spatula and kept in desiccator for further study. Similarly, solid dispersions of ritonavir were prepared by kneading and solvent evaporation method with maltodextrin and poloxamer at 1:1 and 1:3 ratios **Table 1.**

Table 1: Formulae of ritonavir physical mixture and solid dispersions

Batches	Polymer	Ratio	Method
F1	Maltodextrin	1:1	PM
F2	Maltodextrin	1:3	PM
F3	Maltodextrin	1:1	KNE
F4	Maltodextrin	1:3	KNE
F5	Maltodextrin	1:1	SE
F6	Maltodextrin	1:3	SE
F7	Poloxamer	1:1	PM
F8	Poloxamer	1:3	PM
F9	Poloxamer	1:1	KNE

F10	Poloxamer	1:3	KNE
F11	Poloxamer	1:1	SE
F12	Poloxamer	1:3	SE

Kneading method (KNE)

The drug and excipient were weighed accordingly to the specified drug: carrier ratio and was taken in a glass mortar. The mixture was triturated slowly with ethanol for 1h take care that the damp mass was maintained throughout the trituration period. Further mass was dried under vacuum, pulverized and sieved through #120 and stored in dessicator for further study.

Solvent evaporation method (SE)

The required amount of ritonavir was dissolved in ethanol and excipient was dispersed in the drug solution. The solvent was removed under vacuum until dry. The dried mass was pulverized and sieved through #120 and stored in dessicator until further evaluation.

Evaluation

Solubility studies: Solubility of ritonavir carried out in different concentrations of maltodextrin and poloxamer solutions. A little excess amount of ritonavir dispersed in 25ml vials containing different concentrations of maltodextrin and poloxamer solutions. The sealed vials were shaken on rotary shaker for 24h at room temperature and equilibrated for 48h. An aliquot was passed through 0.45 nylon disc filter and the filtrate was suitably diluted and analyzed on UV at 210 nm.

Saturation solubility: The saturation solubility studies were carried out for pure drug, physical mixtures and solid dispersions. Weighed amount of pure drug, physical mixture and solid dispersions equivalent to 50 mg of the drug, dispersed in 25ml vials containing 20ml of 0.1N HCl. The sealed vials were shaken on rotary shaker for 24h at room temperature and equilibrated for 48h. An aliquot was passed through 0.45 nylon disc filter and the filtrate was suitably diluted with 0.1N HCl and measures the absorbance at 210 nm and estimate the ritonavir content using the calibration curve.

Drug content: In each case, physical mixture and solid dispersions equivalent to 25mg of ritonavir was accurately weighed and transferred to 100ml volumetric flask. To this add 25ml of ethanol to dissolve the ritonavir further volume was made up to 100 ml with ethanol. Filter if necessary further it was subsequently diluted with 0.1N HCl and measure the absorbance at 210nm and estimate the ritonavir content using the calibration curve.

FTIR studies: Fourier transform infrared (FTIR) spectra were recorded on a Shimadzu FTIR-281-spectrophotometer. The spectrum recorded for ritonavir, maltodextrin, poloxamer, physical mixtures and solid dispersions. Samples were prepared in KBr disks prepared with a hydrostatic press at a force of 5.2Tcm^{-2} for 3min. The scanning range was 450-4000cm^{-1} and the resolution was 1cm^{-1}.

Powder X-ray diffractometry: The powder X-ray diffraction patterns of ritonavir, maltodextrin, poloxamer and solid dispersions were recorded by using Philips X-ray powder diffractometer (model PW 1710) employing Cu-Kα-radiation. The diffractometer was run at 2.40/min in terms of 2θ angle.

Differential scanning calorimetry: The thermogram of ritonavir, maltodextrin, poloxamer and solid dispersions were recorded on Seiko, DSC 220C model (Tokyo, Japan), 10 mg of samples were sealed in aluminium pans and heated at a rate of 10oC/min from 30oC-300^{o}C.

Dissolution studies: *In-vitro* dissolution studies of pure ritonavir, physical mixture and solid dispersions were carried out in 900ml of 0.1N HCl using a USPXXI type 2 dissolution test apparatus by powder dispersed amount method (powder samples were spread over the dissolution medium). Sample equivalent to 100mg of ritonavir, speed of 50rpm and a temperature of 37^{o}C were used in each test. A 5ml aliquot was withdrawn at different time intervals, filtered using a 0.45 m nylon disc filter and replaced with 5ml of fresh dissolution medium.

The filtered samples were suitably diluted, if necessary and assayed for ritonavir content by measuring the absorbance at 210nm. The results were computed by using dissolution software PCP DISSO V3.0.

Results

The solubility of ritonavir in 0.1N HCl was found to be 2.22±0.0025 Mx10^{-3}, the solubility of ritonavir increased linearly with increase in the concentration of maltodextrin and poloxamer. The solubility profiles were given in Fig. 1 (A) and 1(B). The solubility profiles were given in **Fig. 1 (C) and 1(D).** The percentage drug content was found to be in the range of 98.04±0.0640 to 99.91±0.0023 and 98.44±0.0400 to 99.90± 0.0023 for solid dispersions prepared with maltodextrin and poloxamer respectively 97.42±0.65 and by kneading method was found to be 97.56±0.68 and 98.82±0.08 after 120 min.

The comparative FTIR spectras were given in **Fig 2.** The DSC thermograms are represented in **figure 3.** The influence of maltodextrin, and poloxamer in the possible phase transformation in ritonavir solid dispersions prepared by solvent evaporation and kneading methods at 1:3 rations were investigated through X-ray diffraction **studies (Fig. 4).**

The cumulative percentage drug release from the solid dispersions prepared at 1:1 and 1:3 with poloxamer by solvent evaporation method was found to be 95.78±0.51 and 97.42±0.65 and by kneading method was found to be 97.56±0.68 and 98.82±0.08 after 120min. The comparative

dissolution profiles were shown in **Fig 5 (A) and (B)** and dissolution parameter data in **Table 2.**

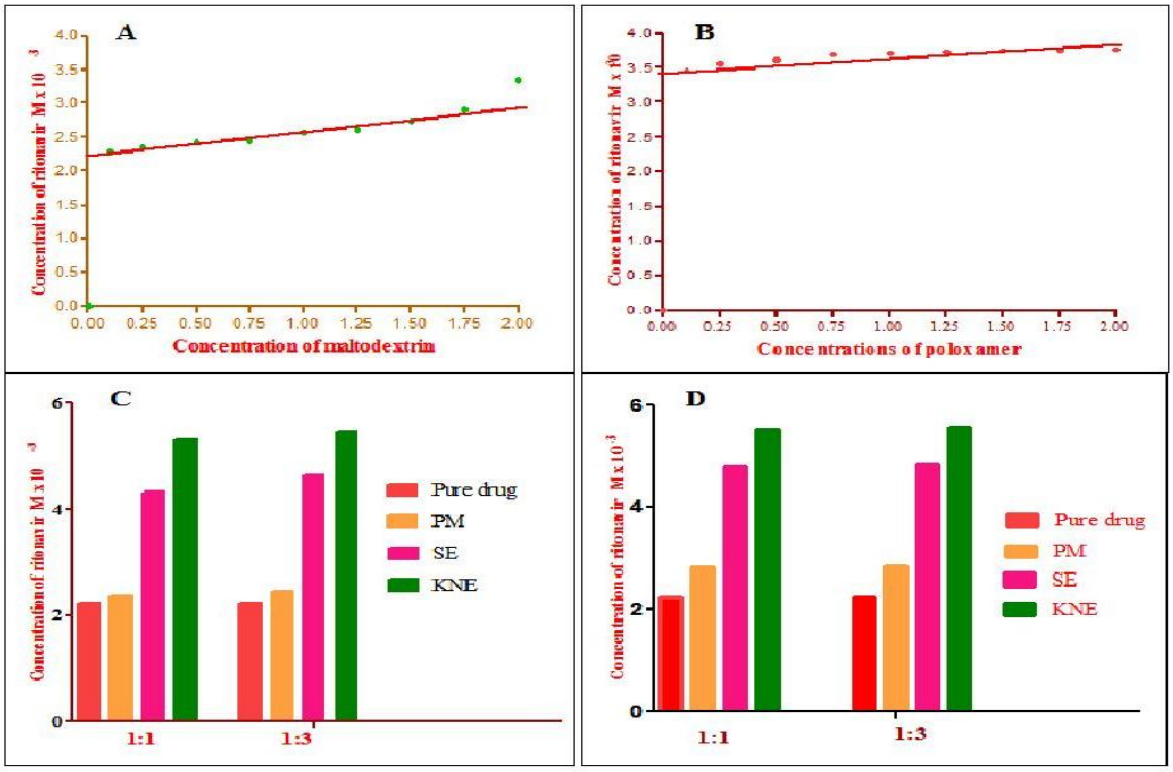

Figure 1: Solubility profile of ritonavir in: (A) Different concentrations of maltodextrin; (B) Different concentrations of poloxamer; (C) Solid dispersions prepared with maltodextrin; (D) Solid dispersions prepared with maltodextrin

Discussion

In case of physical mixture, a small increase in solubility of ritonavir was observed which can be explained due to the formation of a minimum quantity of the dispersion. In case of solid dispersions, the solubility was increased with respect to the ratio and method. In all the excipients, the saturation solubility was found to be in the order 1:3 > 1:1 and methods KNE > SE > PM > Pure drug. The coefficient of variation (CV) in the percentage drug content was less than 1% in all the batches prepared. With small SD and CV values indicates that method employed resulted solid dispersions with uniform drug content.

Ritonavir shows a characteristic carbonyl absorption band at 1703.23cm^{-1}, assigned to aromatic ketonic carbonyl stretching. In case of physical mixtures prepared with maltodextrin and poloxamer at 1:1 and 1:3, the characteristic aromatic carbonyl stretching band of ritonavir appeared shifted 1701.87cm^{-1} and 1701.57cm^{-1} with maltodextrin and 1701.66cm^{-1} and 1700.98cm^{-1} with poloxamer. Solid dispersions prepared by solvent evaporation method with maltodextrin and poloxamer at 1:1 and 1:3, the characteristic aromatic carbonyl-stretching band of ritonavir appeared shifted to1704.39cm^{-1},1705.72cm^{-1} with maltodextrin, 1708.54cm^{-1}, 1710.92cm^{-1} with poloxamer.

Solid dispersions prepared by kneading method with maltodextrin and poloxamer at 1:1 and 1:3, the characteristic aromatic carbonyl-stretching band of ritonavir appeared shifted to 1705.66cm^{-1}, 1712.54cm^{-1} with maltodextrin, 1711.90cm^{-1}, 1711.39cm^{-1} with poloxamer. Shifting of the characteristic aromatic carbonyl-stretching band of ritonavir towards lower wavelength in case of physical mixtures prepared with all the excipients and shifting towards higher wavelength in case of solid dispersion prepared by solvent evaporation and kneading method with maltodextrin at 1:1 and 1:3. These indicated that the vibrating and the bending of the ritonavir molecule were restricted due to the mild interaction at molecular level.

The X-ray diffraction pattern for ritonavir showed numerous strong distinctive peaks at 11.73^{o}, 18.34^{o}, 25.30^{o}, 32.24^{o} and 38.61^{o} at a diffraction angle of 2θ indicating high crystalline nature. The X-ray diffraction pattern for solid dispersions prepared with maltodextrin and poloxamer by solvent evaporation and kneading methods at 1:3 ratios shows a significant decrease in the degree of crystallinity, as evident by the decrement in the number of sharp distinctive peaks with respect to the excipient. The shearing force applied by

the kneading in kneading method, intimate mixing of drug solution with carrier in solvent evaporation method results nucleation and crystal growth phases, leading to formation of crystals/partial amorphization.

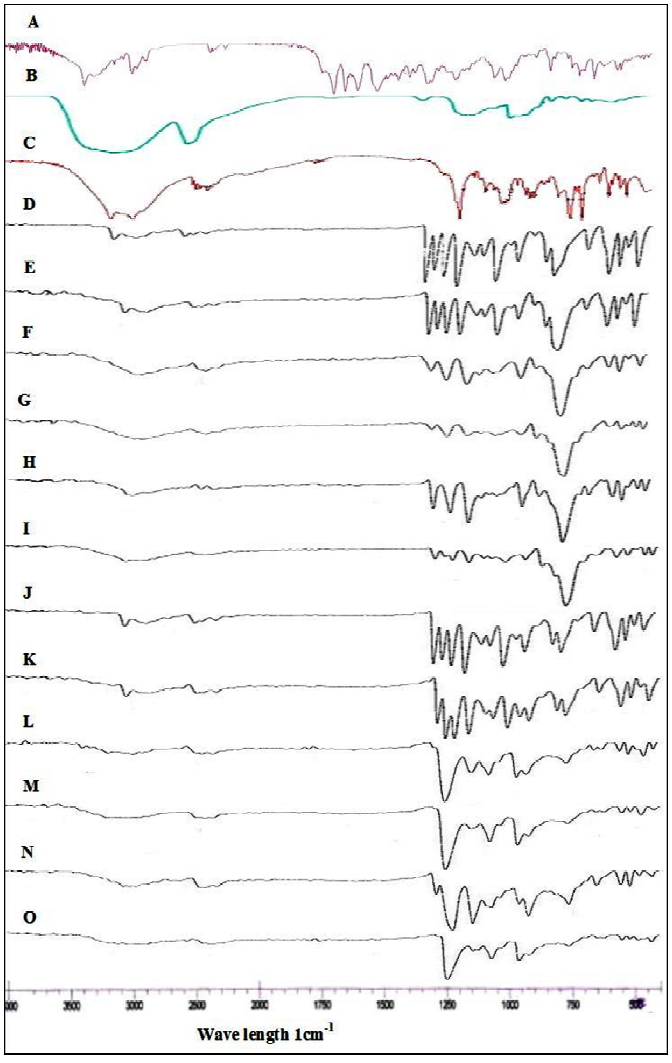

Figure 2: Comparative FTIR spectra: (A) Ritonavir; (B) Maltodextrin; (C) Poloxamer; (D) 1:1 Malto PM; (E) 1:3 Malto PM; (F) 1:1 Malto SE; (G) 1:3 Malto SE; (H) 1:1 Malto KNE; (I) 1:3 Malto KNE; (J) 1:1 Pol PM; (K) 1:3 Pol PM; (L) 1:1 Pol SE; (M) 1:3 Pol SE; (N) 1:1 Pol KNE; (O) 1:3 Pol KNE

The relative reduction in the diffraction intensities in the surface solid dispersions can be attributed to the change in orientation during the crystal growth phase. These results suggest crystallinity was modified to great extent indicate there is a possibility of mild interaction between the ritonavir and the excipient, a greater portion of solid dispersions was converted into amorphous form. These results were in coordination with by DSC studies. Ritonavir showed a sharp endothermic peak at 124.26°C with enthalpy (*ΔH*) of 195.41j/g which were near to its melting point whereas maltodextrin showed a broad melting endothermic peak at 261.32°C with enthalpy (*ΔH*) of 200.91j/g and poloxamer showed a broad melting endothermic peak at 176.23°C with enthalpy (*ΔH*) of 2.86j/g.

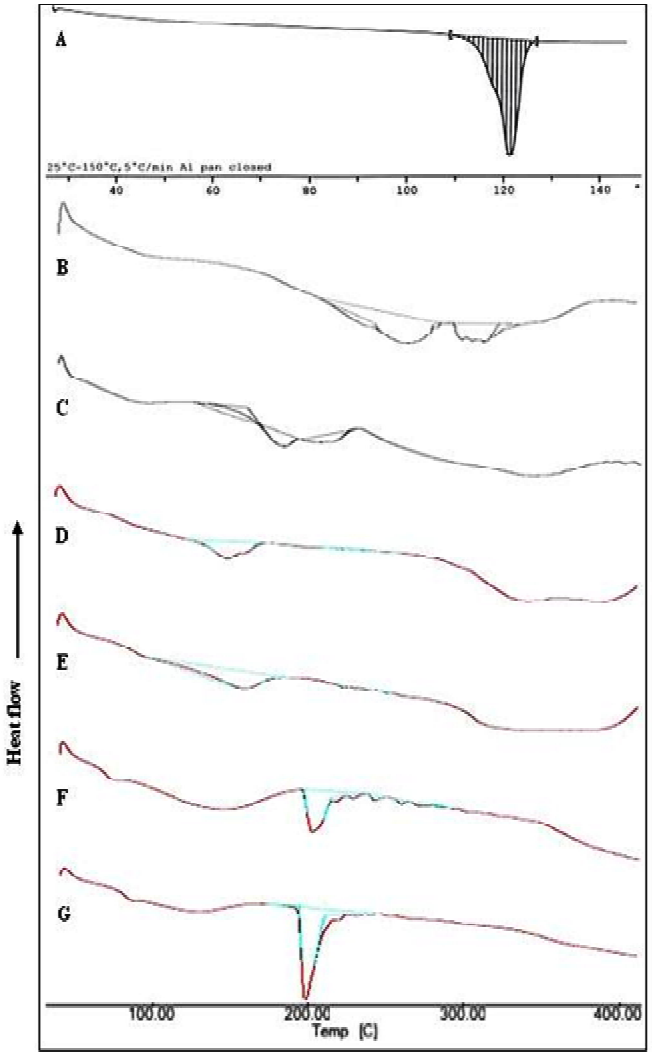

Figure 3: Comparative DSC thermograms (A) Ritonavir (B) Maltodextrin (C) Poloxamer (D) 1:3 Malto: Rit SE (E) 1:3 Malto: Rit KNE (F) 1:3 Polo: Rit SE (G) 1:3 Polo: Rit KNE

Thermogram of solid dispersions prepared by using maltodextrin at 1:3 ratio shows broad endothermic peaks of 115.59°C with enthalpy -54.09mj, 189.14°C, with enthalpy 0.01mj for solvent evaporation method whereas a sharp broad endothermic peak of 117.63°C with enthalpy -65.85mj, 164.08°C with enthalpy -0.09mj for kneading method. Thermogram of solid dispersions prepared by using poloxamer at 1:3 ratios show broad endothermic peaks of 153.84°C with enthalpy -85.60mj, 182.11°C, with enthalpy -4.00mj for solvent evaporation method whereas a sharp broad endothermic peak of 145.11°C with enthalpy -191.74mj for

kneading method. The DSC results suggest that the melting endothermic peak of ritonavir in solid dispersions prepared with maltodextrin was shifted to lower melting point whereas with poloxamer shows shifting towards higher melting point indicating possible interaction between the ritonavir with maltodextrin and poloxamer at 1:3 ratio.

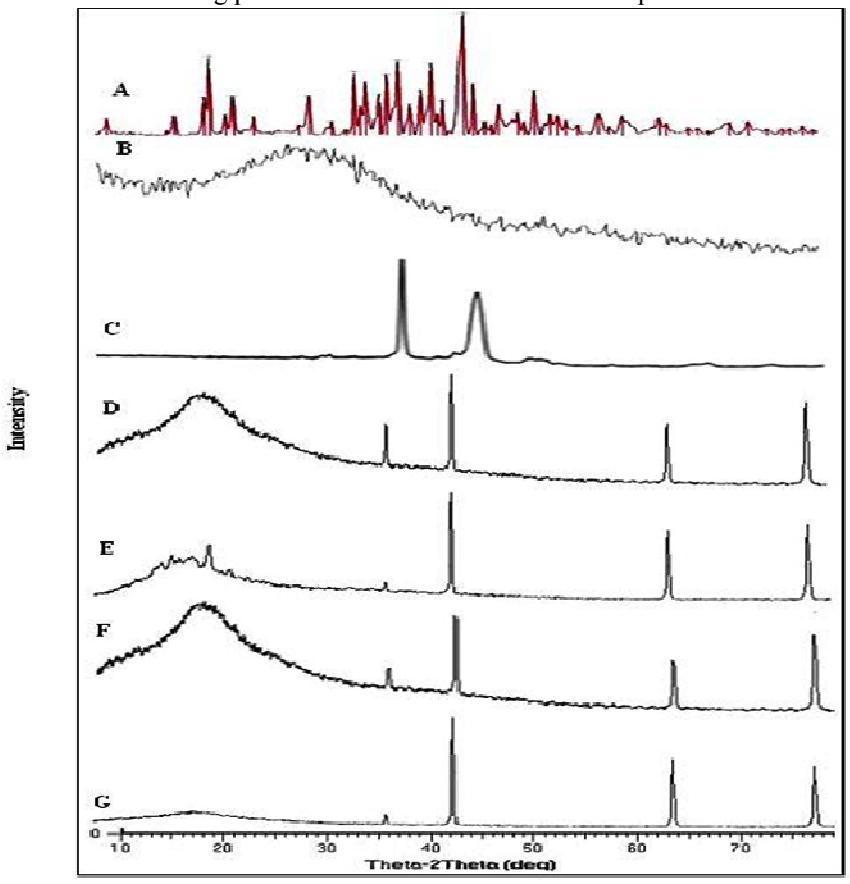

Figure 4: Comparative XRD spectras of: (A) Ritonavir; (B) Maltodextrin; (C) Poloxamer; (D) 1:3 Malto: Rit SE; (E) 1:3 Malto: Rit KNE; (F) 1:3 Polo: Rit SE; (G) 1:3 Polo: Rit KNE

Table 2: Comparative dissolution parameter data for pure drug, physical mixture and solid dispersions prepared with maltodextrin and poloxamer

Batches		DE_{60} (%)	DP_{60}	T_{50} (min)	RDR_{60}	First order rates $K_1 \times 10^2$ (min^{-1})	Hix.Crow $K_{HC} \times 10^2$ ($mg^{1/3}.min^{-1}$)
						R	R
Maltodextrin solid dispersions data							
Pure drug		5.99	11.6	120	1	0.9995	0.9996
PM	1:1	10.36	20.6	167.6	1.775	0.9961	0.9995
PM	1:3	10.98	21.7	157.8	1.870	0.9972	0.9971
SE	1:1	40.08	66.0	40.9	5.689	0.9962	0.9982
SE	1:3	42.46	69.1	38.2	5.956	0.9959	0.9978
KNE	1:1	44.44	72.6	35.3	6.258	0.9946	0.9963
KNE	1:3	46.37	75.6	33.0	6.517	0.9961	0.9953
Poloxamer solid dispersions data							
PM	1:1	11.17	21.8	157.0	1.879	0.9989	0.9978
PM	1:3	11.75	22.5	151.8	1.939	0.9996	0.9996
SE	1:1	43.40	70.5	37.1	6.077	0.9940	0.9997

SE	1:3	44.88	73.1	34.9	6.301	0.9884	0.9944
KNE	1:1	45.73	74.3	34.0	6.405	0.9806	0.9949
KNE	1:3	46.94	76.7	32.2	6.612	0.9849	0.9956

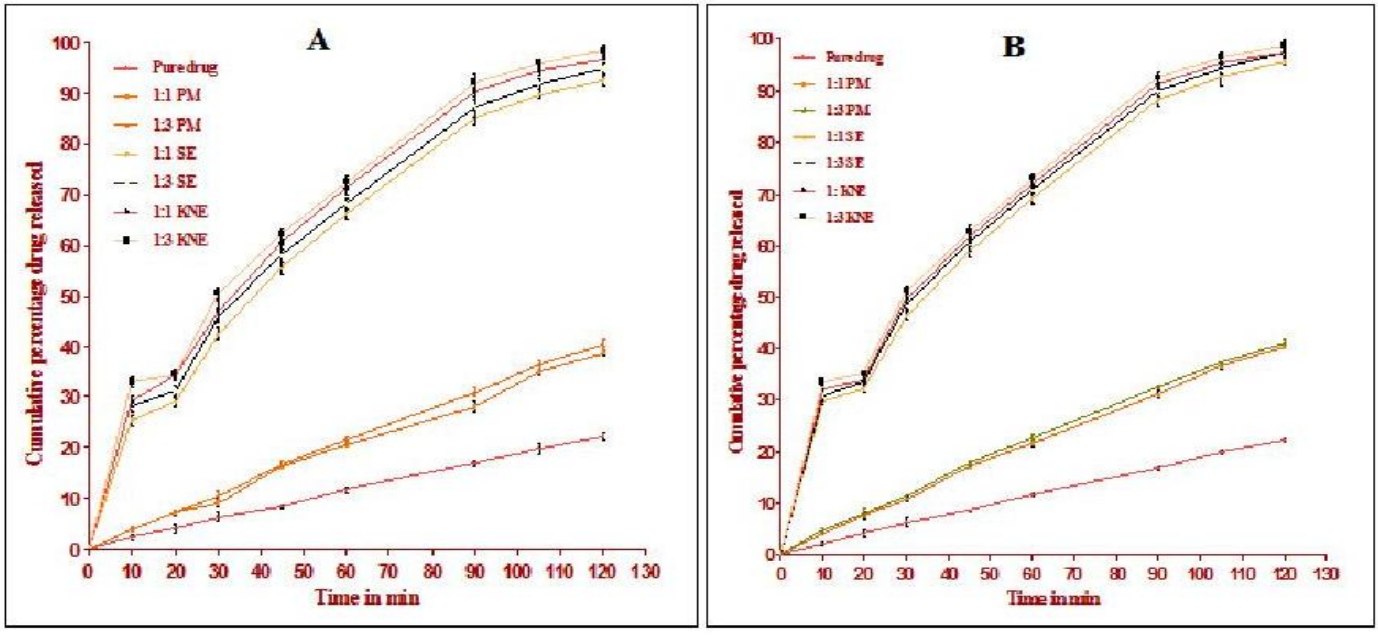

Figure 5: Comparative dissolution profiles of (A) Pure drug, physical mixtures and solid dispersions prepared with maltodextrin (B) pure drug, physical mixture and solid dispersions prepared with poloxamer

The results attributed with reduced intensity suggests decrease in crystallinity of ritonavir, these results are in support with XRD results. Overall the rank order of improvement in dissolution properties of ritonavir with different excipient is poloxamer> maltodextrin and with methods KNE > SE > PM and ratios in the order 1:3 > 1:1. One-way ANOVA was used to test the statistical significant difference between pure and prepared solid dispersions. Significant differences in the means of DP_{60} and DE_{60} were tested at 95% confidence. The DP_{60} and DE_{60} values of solid dispersions prepared by kneading and solvent evaporation method are significantly higher ($P<0.05$) when compared to DP_{60} and DE_{60} values of physical mixture and pure ritonavir.

The solid dispersions of the water insoluble drug ritonavir were successfully prepared by kneading and solvent evaporation methods using hydrophilic carriers' viz., maltodextrin, and poloxamer. The results of the dissolution rate studies indicated higher dissolution rate of ritonavir from solid dispersions when compared to ritonavir itself and the corresponding physical mixtures.

The slight increase in dissolution rate and efficiency values recorded for the physical mixture may be explained based on the solubility of the drug in aqueous hydrophilic polymeric solutions. Since the hydrophilic polymer dissolve more rapidly in the dissolution medium than the drug alone, it can be assumed that, in early stages of the dissolution process, the hydrophilic excipient molecule will operate locally on the hydrodynamic layer surrounding the particles of the drug.

In vitro release studies reveal that there is marked increase in the dissolution rate of ritonavir from all the solid dispersions when compared to pure ritonavir itself. The results further explain formulation containing 1:3 drug: carrier ratio shows higher dissolution rate compared with other ratios in all methods with both excipients. This may be attributed to the increase in drug wettability and solubilization of the drug due to hydrophilic carrier at higher concentration.

The regression coefficient (r) values model that gave higher 'r' value was considered as best fit model. The dissolution of ritonavir from all the solid dispersions followed first order kinetics and best fit model was found to be Hixson Crowell cubic root law. The DE_{30} and DE_{60} values [16] of the ritonavir: polymer kneaded solid dispersions were higher than those of the solid dispersions prepared by solvent evaporation and physical mixtures, this may be due to less crystallinity of the ritonavir in kneaded systems than that of solvent evaporation and physical mixture and solid dispersions. These results are supported and justified by XRD studies.

The *in vitro* dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with

pure ritonavir. Mechanisms involved are solubilization and improved wetting of the drug in the hydrophilic carriers rich microenvironment formed at the surface of drug crystals after dissolution rate. The crystallinity of the drug was reduced in solid dispersion formulation with carriers viz., maltodextrin, and poloxamer.

Finally, it could be concluded that solid dispersions of ritonavir using hydrophilic carriers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability.

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