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SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OF RITONAVIR BY SOLID DISPERSION TECHNIQUE

Swathi[1] and Y. Anand Kumar[1]*

[1]Department of Pharmaceutics, V.L. College of Pharmacy, Raichur, Karnataka.

***Corresponding Author: Dr. Y. Anand Kumar**

Department of Pharmaceutics, V.L. College of Pharmacy, Raichur, Karnataka.

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ABSTRACT

In this study Ritonavir a model class II drug is selected for increasing the solubility and dissolution by solid dispersion technique using skimmed milk powder. Solid dispersions were prepared by solvent evaporation and kneading method at three different ratios. The prepared solid dispersion were evaluated for solubility, drug content and *in vitro* drug release as well as interactions studies by FTIR, DSC and powder XRD. The FTIR, studies reveals there is no interaction between drug and polymer but the crystallinity was modifies to greater extent justified with XRD and DSC results. The solubility of ritonavir was increased linearly with increase in the concentration of skimmed milk powder. Overall the rank order of improvement in dissolution properties of pure ritonavir was method dependent viz., KNE > SE > PM and ratios in the order 1:3 > 1:1 > 3:1. One-way ANOVA was used to test the statistical significant difference between ritonavir and 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.

KEYWORDS: ritonavir, Skimmed milk powder, FTIR, XRD, DSC, *In vitro* dissolution.

INTRODUCTION

In recent years, the number of poorly soluble drug candidates has increased tremendously, formulation of such poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. Solubility behaviour of a drug is one of the key determinants of its oral bioavailability. 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.

In1961 Sekiguchi and Obi[1] developed the method of preparing of solid dispersions to reduce the particle size of drugs and subsequently these mixtures were studied in detail.[2-5] Generally solid dispersions of poorly water soluble drugs have revealed remarkably higher availability[6-8] due to the fact that solid dispersions combine the benefits of both a local increase in the solubility and a maximization of the surface area of the drug that comes in contact with the dissolution medium as the carrier dissolves. Traditionally, the carriers used have been water soluble or water miscible polymers such as polyethylene glycols[9], polyvinylpyrrolidone[10] or low molecular weight materials such as sugar[11] Recently other polymers have been reported such as Eudragit®[12], carbomers[13], cellulose derivatives[14], Gelucires®[15] and skimmed milk powder.[16-19]

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 and could potentially exhibit dissolution rate limited absorption. The solubility of ritonavir in 0.1 N HCl is 400 µg/ml, the IDR value is only 0.03±0.001 mg/cm^2-min. Compounds with IDR<0.1 mg/min/cm^2 usually exhibit dissolution rate-limited absorption. A variety of polymers were used to enhance the solubility of ritonavir by solid dispersion techniques.[20-23] In the present work, ritonavir solid dispersions were developed using skimmed milk. The skimmed milk is a colloidal suspension of casein micelles, globular proteins and lipoprotein particles. The principal casein fractions are α-s1, α-s2, β-casein and κ-casein. β-casein is amphiphilic and acts as a detergent molecule with surfactant property. The milk also contains whey proteins with principle fractions of β-lactoglobulin, α-lactalbumin, bovine serum albumin and immunoglobulins. These molecules were found to be

surface active with superior solubility than caseins. Different ratios of drug and carrier were formulated and evaluate the possible effects of the carrier on the drug solubility, *in vitro* dissolution and further characterized by FTIR, DSC and XRD studies.

MATERIALS AND METHODS

Materials: Ritonavir obtained as gift sample from Stride arc lab Bengaluru, India. Skimmed milk powder was prepared by conventional method. All chemicals and solvents used were of analytical grade.

Methods

Preparation of skimmed milk powder

100 ml of skimmed milk was dried in a rotary vacuum evaporator at 100 rpm, 35°C under vacuum for 6 h. The obtained powder was dried in an oven and passed through a sieve no 120 and stored in airtight container for further use.

Preparation of physical mixtures (PM) and solid dispersion systems

Physical mixtures of ritonavir: skimmed milk powder at 3:1, 1:1 and 1:3 ratios were obtained by mixing individual components together with a spatula and kept in dessicator for further study. Similarly solid dispersion systems of ritonavir were prepared by kneading and solvent evaporation method with skimmed milk powder (SKM) at 3:1, 1:1 and 1:3 ratios. The formulae were given table 1.

Table: 1 Formulae of ritonavir physical mixture and solid dispersions.

Batch code	Polymer	Ratio	Method
F-1	SKM	3:1	PM
F -2	SKM	3:1	SE
F -3	SKM	3:1	KNE
F -4	SKM	1:1	PM
F -5	SKM	1:1	SE
F -6	SKM	1:1	KNE
F -7	SKM	1:3	PM
F -8	SKM	1:3	SE
F -9	SKM	1:3	KNE

Kneaded systems (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 1 hr 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 systems (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

FTIR studies

FTIR spectra for ritonavir, skimmed milk powder, physical mixture and solid dispersions were recorded on a Shimadzu FTIR-281-spectrophotometer. Samples were prepared in KBr disks prepared with a hydrostatic press at a force of $5.2Tcm^{-2}$ for 3 min. The scanning range was $450\text{-}4000cm^{-1}$ and the resolution was $1cm^{-1}$.

Powder X-ray diffractometry

The powder X-ray diffraction patterns for ritonavir, skimmed milk powder and solid dispersions were recorded by using Philips X-ray powder diffractometer (model PW 1710) employing Cu-Kα-radiation. The diffractometer were run at 2.4^0/min interms of 2θ angle.

Differential scanning calorimetry

The thermogram for ritonavir, skimmed milk powder and solid dispersions were recorded on Seiko, DSC 220C model Differential scanning calorimeter (Tokyo, Japan). About 10 mg of samples were sealed in aluminium pans and heated at a rate of 10^oC/min from $30^oC\text{-}300^oC$.

Solubility studies

A little excess amount of ritonavir dispersed in 25 ml vials containing different concentrations of skimmed milk powder solutions. The sealed vials were shaken on rotary shaker for 24 hrs at room temperature and equilibrated for 48 hrs. An aliquot was passed through 0.45µ nylon disc filter and the filtrate was suitably diluted and analysed on UV at 210 nm.

Saturation solubility

Weighed amount of ritonavir pure drug, physical mixture and all prepared solid dispersions equivalent to 50 mg of the drug, dispersed in 25 ml vials containing 20 ml of 0.1N HCl. The sealed vials were shaken on rotary shaker for 24 hrs at room temperature and equilibrated for 48 hrs. An aliquot was passed through 0.45µ 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.

Drug content uniformity

Solid dispersions equivalent to 25 mg of ritonavir was accurately weighed and transferred to 100 ml volumetric flask. To this add 50 ml 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 210 nm and estimate the ritonavir content.

Dissolution studies

Ritonavir, physical mixture and solid dispersions were subjected for *in vitro* dissolution studies using USPXXI type 2 dissolution test apparatus by powder dispersed amount method (powder samples were spread over the dissolution medium). 900 ml of 0.1N HCl used as dissolution medium, in each case a sample equivalent to 100 mg of ritonavir, speed of 50 rpm and a temperature

of 37^{0}C were used. A 5 ml aliquot was withdrawn at different time intervals, filtered using a 0.45µm nylon disc filter and replaced with 5 ml of fresh dissolution medium. The filtered samples were suitably diluted, if necessary and assayed for ritonavir content by measuring the absorbance at 210 nm. The dissolution experiments were conducted in triplicate and the results were computed by using dissolution software PCP DISSO V3.0.

RESULTS AND DISCUSSION

The solubility of ritonavir in 0.1N HCl was found to be 2.227±0.0025 Mx10^{-3}. The solubility of ritonavir was increased linearly with increase in the concentration of skimmed milk powder figure1.

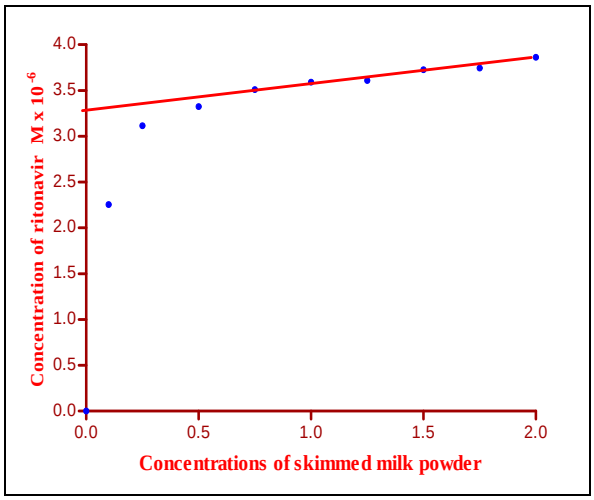

Figure 1: Solubility profile of ritonavir in different concentrations of skimmed milk powder.

In case of solid dispersions the solubility was increased with respect to the ratio and method and the saturation solubility was found to be in the order 1:3 > 1:1 > 3:1 and methods KNE > SE > PM > Pure drug figure 2.

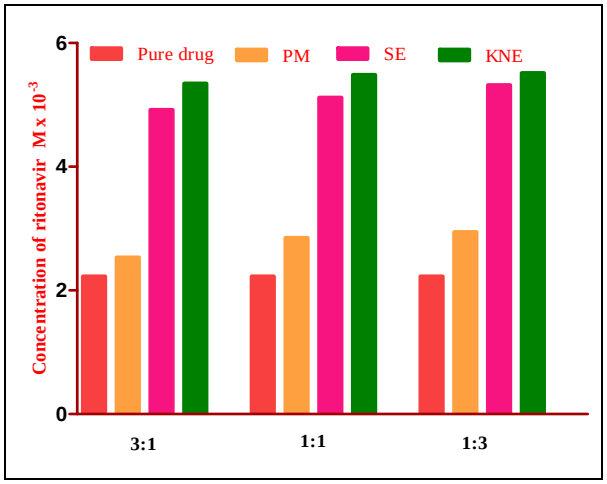

Figure 2: Saturation solubility profile of ritonavir from physical mixture and its solid dispersion systems prepared with skimmed milk powder.

The percentage drug content was found to be in the range of 98.36 ± 0.0083 to 99.88 ± 0.0040 for solid dispersions. 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.

FTIR studies

FTIR spectra of the solid dispersions were compared with the physical mixture and ritonavir figure 3. Changes or shifting of the characteristic bands of pure substances confirm the mild interaction between the drug and skimmed milk powder. Ritonavir shows a characteristic carbonyl absorption band at 1703.23 cm^{-1}, assigned to aromatic ketonic carbonyl stretching. The characteristic aromatic carbonyl-stretching band of ritonavir appeared shifted to 1702.03 cm^{-1} 1701.37 cm^{-1}, 1701.28; 1710.45 cm^{-1} 1710.55 cm^{-1}, 1712.08; 1711.90 cm^{-1} 1711.39 cm^{-1}, 1712.54 for physical mixtures, solvent evaporation and solvent evaporation at 3:1, 1:1 and 1:3 respectively. Shifting of the characteristic aromatic carbonyl-stretching band of ritonavir towards lower wavelength in case of physical mixtures and shifting towards higher wavelength in solid dispersions prepared by solvent evaporation and kneading method indicates minor interaction at molecular level.

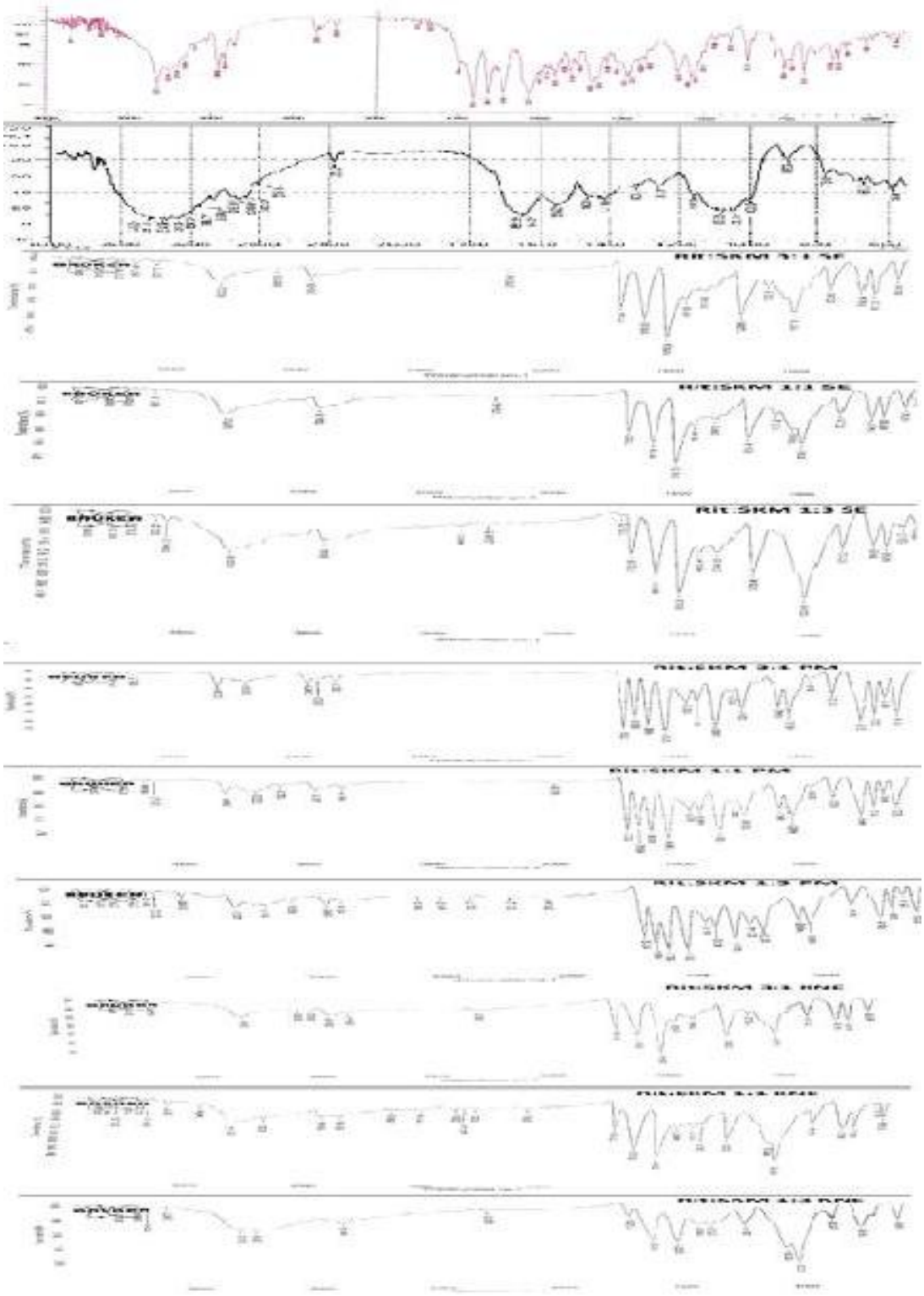

Figure 3: Comparative FTIR spectra of Ritonavir, SKM, Physical mixtures and solid dispersions.

XRD Studies

The X-ray diffraction pattern for ritonavir showed numerous strong distinctive peaks at 11.73°, 18.34 °, 25.30 °, 32.24 ° and 38.61 ° at a diffraction angle of 2θ indicating high crystalline nature. The X-ray diffraction pattern for solid dispersions 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. 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. 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. The results suggest that the crystallinity was modified to great extent indicate there is a possibility of interaction between the ritonavir and the excipient, a greater portion of solid dispersion systems was converted into amorphous form figure 4. These results were in coordination with by DSC studies.

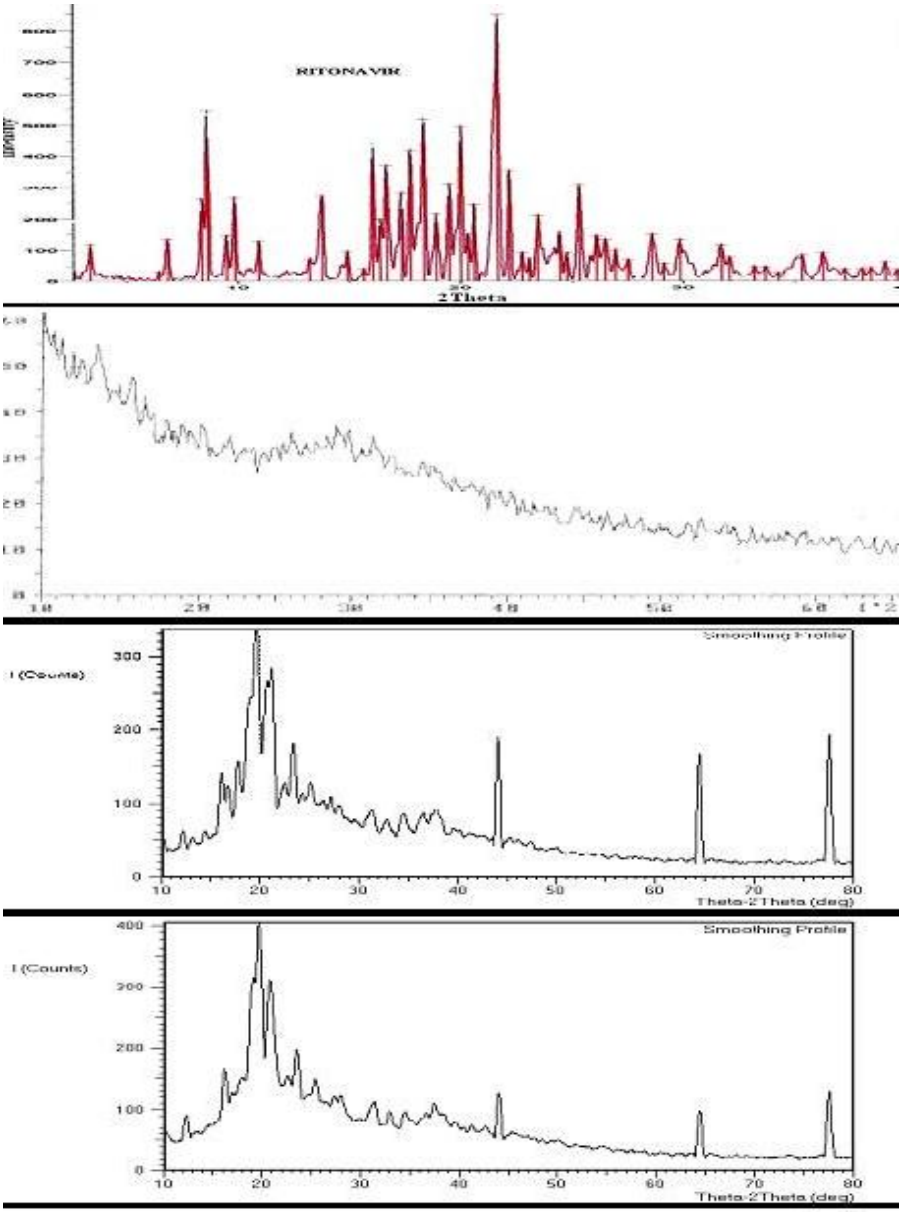

Figure 4: Comparative X-ray diffraction pattern of ritonavir, skimmed milk powder and its solid dispersions at 1:3 rations.

DSC Studies

The DSC thermograms of pure ritonavir and solid dispersions at 1:3 ratios were studied figure 5. The ritonavir showed a sharp endothermic peak at 124.26^{o}C with enthalpy (ΔH) of 195.41 J/g which were near to its melting point and skimmed milk powder showed a broad melting endothermic peak at 179.33 ^{o}C with enthalpy (ΔH) of 2.56 J/g. Thermograms of solid dispersions at 1:3 ratios shows broad endothermic peaks of 117.76 ^{o}C with enthalpy -38.96 mJ, 169.25 ^{o}C, with enthalpy -4.06 mJ for solvent evaporation method whereas a sharp broad endothermic peaks of 123.10 ^{o}C with enthalpy -1.77 mJ, 144.96 ^{o}C with enthalpy -39.73 mJ for kneading method. The DSC results suggest that the melting endothermic peak of ritonavir in solid dispersions was shifted to lower melting point indicating possible interaction between the ritonavir with skimmed milk powder at 1:3 ratio. The results attributed with reduced intensity suggests decrease in crystallinity of ritonavir, these results are in support with XRD.

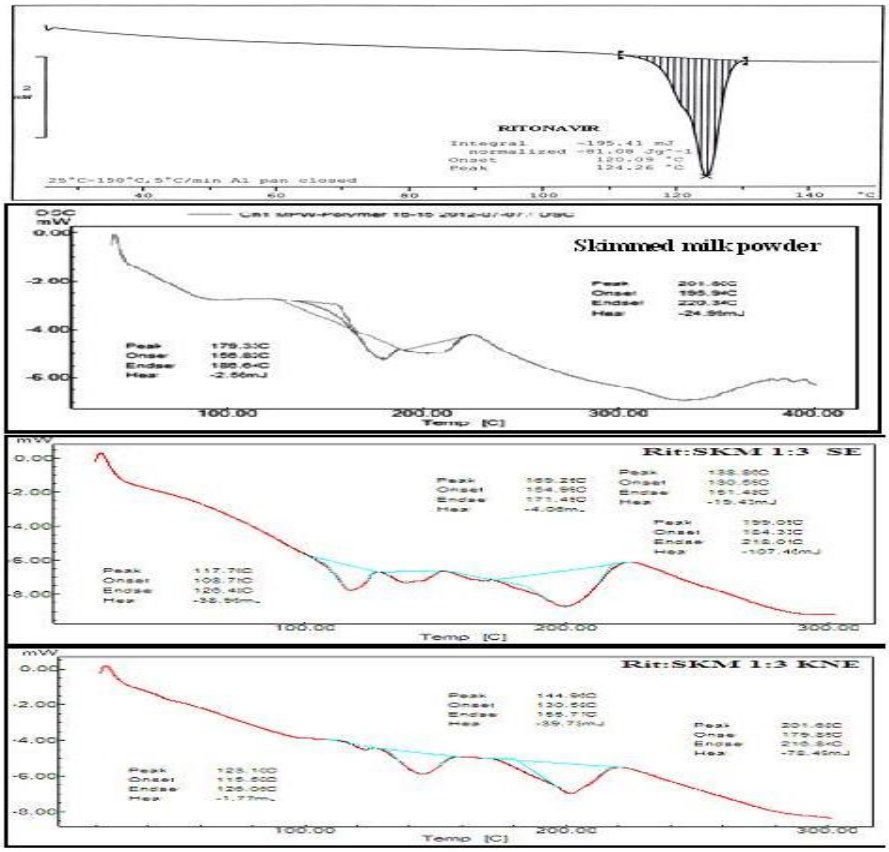

Figure 5: Comparative X-ray diffraction pattern of ritonavir, skimmed milk powder and its solid dispersions at 1:3 rations.

DISSOLUTION STUDIES

Powder dispersion amount method is used to investigate the various dissolution parameters of ritonavir, physical mixtures and its solid dispersions table 2,3. The usual method of evaluation of *in vitro* dissolution testing is the comparison of time taken for given proportions of active drug to be released into solution and parameter such as T_{50} value was often used. Alternatively the fraction of drug in solution after given time is used for comparison such as DP_{30}, DP_{60} and also relative dissolution rate at 30 min and 60 min i.e. RDR_{30} RDR_{60} were calculated to know extent of dissolution rate enhancement. Another parameter suitable for the evaluation of *in vitro* dissolution has been suggested by Khan [24] is dissolution efficiency. The dissolution efficiency can have a range of values depending on the time interval chosen. In this study DE_{30} and DE_{60} values were calculated from the dissolution data and are used for comparison table. The cumulative percentage drug release from the pure drug was found to be 22.26±0.08, whereas physical mixtures at 3:1, 1:1, 1:3 shows 35.80±0.46, 37.15±0.08 after 120 min. The cumulative percentage drug release was found to be 86.44±0.22, 90.92±1.50 and 92.70±0.66; 93.42±1.09, 96.12±1.09 and 97.71±0.93 after 120 mins at 3:1, 1:1, 1:3 by solvent evaporation method and kneading method respectively figures 6,7 and 8. 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. There is marked increase in the dissolution rate of ritonavir from all the solid dispersions when compared to pure ritonavir itself. From the *in vitro* drug release profile, it can be seen that formulation containing 1:3, drug: carrier ratios shows higher dissolution rate compared with other ratios in both methods. This may be attributed to the increase in drug wettability and solubilization of the drug due to hydrophilic carrier at higher concentration. From the regression coefficient (r) values for formulations, model that gave higher 'r' value was considered as best fit model. The 'r' values were found to be higher in the first order model indicating that the dissolution of ritonavir the solid dispersions followed first order kinetics and release of drug by erosion mechanism and dissolution limited. The DE_{30} and DE_{60} values of the kneaded solid dispersions were higher than those of the solid dispersions prepared with solvent evaporation and physical mixture, this may be due to less crystallinity of the ritonavir in kneaded systems than that of solvent evaporation and physical mixture solid dispersion systems. These results are supported and justified by XRD studies. Overall the rank order of improvement in dissolution properties of ritonavir was method dependent viz., KNE > SE > PM and ratios in the order 1:3 > 1:1 > 3:1.

Table 2: *In vitro* dissolution data of pure drug, physical mixture and solid dispersions all methods at 3:1, 1:1 and 1:3 ratios.

1	Pure drug	Physical mixture			Solvent evaporation			Kneading		
		Cumulative percentage drug released ± SD			Cumulative percentage drug released ± SD			Cumulative percentage drug released ± SD		
		3:1	1:1	1:3	3:1	1:1	1:3	3:1	1:1	1:3
10	2.01±0.15	2.11±0.31	3.11±0.09	3.62±0.09	20.71±0.71	23.62±0.74	25.97±1.15	23.47±0.87	28.53±0.46	32.14±1.13
20	4.14±0.23	6.37±0.15	6.59±0.23	6.59±0.46	24.73±0.15	27.17±0.82	29.52±0.69	31.11±0.90	33.70±1.04	33.95±1.29
30	6.35±.023	8.53±0.15	8.53±0.15	8.73±0.23	34.85±0.15	40.41±0.37	42.79±0.85	44.32±0.99	46.75±0.93	50.12±1.38
45	8.48±0.15	15.48±0.31	16.23±0.15	18.12±0.23	48.56±0.15	54.18±0.44	56.35±0.73	57.14±1.99	60.09±1.54	61.72±1.18
60	11.72±0.22	17.85±0.15	19.66±0.37	20.10±0.17	58.87±0.15	64.61±0.74	66.52±0.78	68.09±0.98	70.78±0.96	71.96±1.02
90	16.87±0.15	26.08±0.15	27.59±0.22	31.12±0.15	74.33±0.15	82.76±1.12	85.58±0.51	87.00±0.97	89.92±1.42	91.53±1.33
105	19.83±0.15	30.44±0.29	33.39±0.30	35.23±0.15	81.94±1.05	88.10±1.83	90.18±0.38	91.44±1.24	93.91±1.17	95.51±1.17
120	22.26±0.08	35.80±0.46	37.15±0.08	39.23±0.58	86.44±0.22	90.92±1.50	92.70±0.66	93.42±1.09	96.12±1.09	97.71±0.93

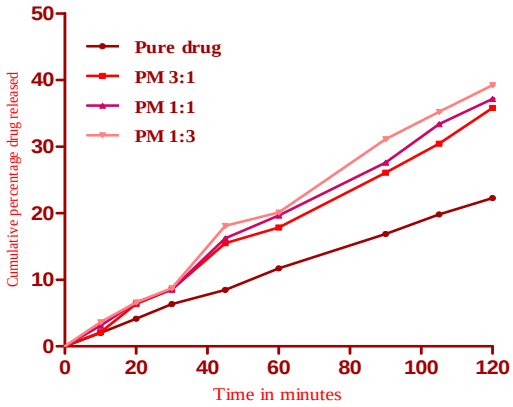

Figure 6: Comparative dissolution profiles of pure drug with physical mixture.

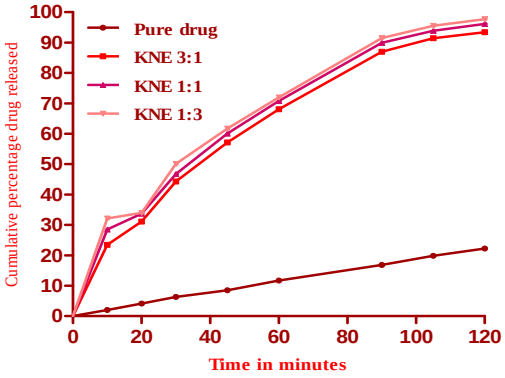

Figure 8: Comparative dissolution profiles of pure drug with solid dispersions prepared by kneading method.

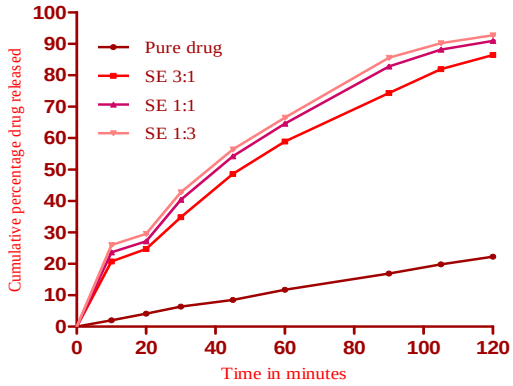

Figure 7: Comparative dissolution profiles of pure drug with solid dispersions prepared by solvent evaporation method.

Table: 3: Dissolution parameter data and model fitting values for pure drug, physical mixtures and its solid dispersions.

Batches	DE_{30} (%)	DE_{60} (%)	DP_{30}	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
Pure drug	3.21	5.99	5.9	11.6	>120	1	0.9995	0.9995
PM	4.39	9.37	9.6	18.6	>120	1.603	0.9961	0.9971
PM	4.66	9.79	10.2	19.8	>120	1.706	0.9972	0.9982
PM	4.86	10.07	10.5	20.2	>120	1.741	0.9962	0.9978
SE	20.96	34.34	32.8	57.5	49.9	4.956	0.9959	0.9963
SE	23.67	38.51	37.3	64.0	42.9	5.517	0.9946	0.9953
SE	25.63	40.57	39.2	66.6	40.5	5.741	0.9942	0.9947
KNE	25.58	41.13	40.3	68.0	39.2	5.862	0.9938	0.9955
KNE	28.54	43.99	43.3	71.9	35.9	6.198	0.9892	0.9955
KNE	30.39	45.89	45.6	74.6	33.7	6.431	0.9807	0.9950

CONCLUSIONS

The solid dispersions of the water insoluble drug ritonavir were successfully prepared by kneading and solvent evaporation methods using skimmed milk powder. 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 skimmed milk powder. One-way ANOVA was used to test the statistical significant difference between pure and prepared solid binary systems. 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 dispersion systems 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. Finally it could be concluded that solid dispersions of ritonavir using skimmed milk powder would improve the aqueous solubility and dissolution rate.

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