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Enhancement of dissolution of poorly soluble ritonavir drug using synthetic polymers

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ABSTRACT

Ritonavir a widely prescribed antiretroviral protease inhibitor drug belong to Class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Its oral absorption is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. In present study PEG 20000, SOLUPLUS and PLASDONE were used as carriers to enhance the dissolution of Ritonavir. Solid dispersions were prepared at 1:1, 1:2 and 1:3 ratios of drug and polymers. Solid dispersions of all the values are within the official I.P. limits. Dissolution of Ritonavir was studied in pH 1.2 in case of carriers. FT-IR was performed to identify the interaction between drug and carriers. 'r' values are higher in first order indication first order kinetics. So selected ratios were used for preparation of tablets by direct compression method. Prepared tablets were again evaluated for Drug content, hardness, friability, disintegration and dissolution characteristics. All the values were found to be within the official I.P. limits. In dissolution study 'r' values found to be first order model indicates first order kinetics. In each case tablets prepared employing carriers gave higher dissolution rates as compared to the tablets prepared using pure drug. Hence solid dispersion in polymers can be used for enhancing the solubility and dissolution of Ritonavir.

INTRODUCTION

The advent of high throughout techniques the discovery of therapeutically active new channel is taking place at a pace we never seen before. These drugs are designed to have optimal receptor binding addition of lipophilic group is favored to increase the in vitro potency. Most of these chemical compounds that are discovered have poor aqueous solubility. That fact more than 40% oh newly discovered drugs have little or no water solubility. Because of their low aqueous solubility, dissolution or release from the delivery systems became the rate-limiting step in the absorption and systematic availability. No matter how active or potentially active new molecular entity is against a particular target, if the drug is not available in solution at the site of action as a result many of the existing new molecular entity is stopped before their potential realized or confirmed. So the dissolution enhancement of poor aqueous soluble remains most challenging aspect in drug development[1].

Oral route has one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms.

For many decades, treatment of an acute disease or chronic illness has mostly accomplished by delivery of drugs to patients using conventional drug delivery system. Even today, these conventional drug delivery systems are the primary pharmaceutical products commonly seen in the prescription. Conventional oral drug products are formulated to release the active principle immediately after oral administration to obtain rapid and complete systemic drug absorption.

Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation[2].

Systemic drug absorption from a drug product consists of a succession of rate process for solid oral, immediate release drug products.

The rate process include

- Dissolution of the drug in an aqueous environment.
- Absorption across cell membranes into systemic circulation.

For drug that have very poor aqueous solubility, the rate at which the drug dissolves (dissolution) is often the slowest step and therefore exhibits a rate limiting effect on drug

bioavailability. In contrast, for a drug that has a high aqueous solubility the dissolution rate is rapid the drug crosses or permeates cell membrane is the slowest orate limiting step.

Together with the permeability, the solubility behavior of a drug is a key determinant of its oral bioavailability. They have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. Examples such as griseofulvin, digoxin, phenytoin, sulphathizole and chloramphinicol come immediately to mind. With the recent advent of high through put screening ofpotrntial therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now present one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry.

Consideration of the modified Noyes-Whitney's equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitation to oral availability[3].

MATERIALS AND METHODS

Methods of evaluation

Preformulation studies[52-54]

Preformulation testing is the first step in the rational development of dosage forms of a drug substance.

Definition

it can be defined san investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

Objective

Overall objective of prefromulaton testing is to generate information useful to the formulator in developing Tablet and Bio – available dosage forms.

Evaluation of blends

The powder blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

1. Bulk density (Db)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It expressed in g/cc and is given by

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of powder, V_0 is the bulk volume of the powder

2. Tapped density (Dt)

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2 %). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by

$$D_t = \frac{M}{V_1}$$

Where, M is the mass of powder, V_t is the tapped volume of the powder

3. Carr's index (%)

The bulk density is the measurement of weight to the volume of the sample. Tapped density is determined as the measurement of weight of the sample to the volume after tapping the measuring cylinder for 500 times from a height of 2 inches. The percentage compressibility (Carr's index) was calculated as 100 times the ratio of the difference between tapped density and bulk density to the tapped density.

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

4. Hausner's ratio

Hausner's ratio is the ratio of tapped density to bulk density. Lower the value of Hausner's ratio better is the flow property. The powder with Hausner's ratio less than 1.18, 1.19-1.25, 1.3-1.5 and greater than 1.5 indicates excellent, good, passable and very poor flow properties, respectively.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table 1: Scale of flow ability

Compressibility index (%)	Flow character	Hausner's ratio
1 – 10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25

21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
> 38	Very, Very poor	> 1.60

5. Angle of repose (θ)

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

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

Where, θ is the angle of repose
h is the height in cms
r is the radius in cms

Method

The powder mixture was allowed to flow through the funnel with its tip fixed to stand at a definite height (h) from a graph paper placed on a horizontal surface. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. A value for angle of repose ≥ 40° suggests a poorly flowing material

Table 2: Flow properties and corresponding Angle of repose

Flow property	Angle of Repose (Degrees)
Excellent	25 – 30
Good	31 – 35
Fair (aid not needed)	36 – 40
Passable (may hang up)	41 – 45
Poor (must agitate, Vibrate)	46 – 55
Very poor	56 – 65
Very, Very poor	> 66

Compressed Tablets Evaluation

1. Thickness

The thickness of the tablets was determined by using Vernier callipers. Five tablets from each formulation were used and average values were calculated.

2. Hardness test

Hardness (diametral crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The permissible limit for hardness is 3 – 5 kg/cm^3. The hardness was tested using Monsanto tester. "Hardness factor", the average of the five determinations was determined and reported.

3. Friability test

Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Five tablets were weighed collectively and placed in a chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula.

$$(W_1 - W_2)/W_1 * 100$$

Where, W_1 = weight of the tablets before test, W_2 = weight of the tablets after test.

4. Uniformity of weight (Weight variation test)

20 tablets were weighed individually. Average weight was calculated from the total weight of the tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (7.5%). The percent deviation was calculated using the following formula.

% weight variation = Individual weight – Average weight/ Average weight * 100

Table 3: Weight variation specification as per IP

Average weight of tablet	% Weight variation
80 mg or less	± 10
More than 80 mg but less than 250 mg	± 7.5
250 mg or more	± 5

6. Content uniformity

10 tablets are accurately weighed and powdered. Tablets powder equivalent to 20 mg of medicament was taken in the test tube and extracted with methanol. The methanolic extract collected into 50ml volumetric flask and volume made up to 50ml with purified buffer. The solution was subsequently diluted and assayed for drug content.

7. Disintegration

Tablet was placed in disintegration apparatus (I.P) containing 900ml of distilled water (at $37^0C \pm 2^0C$). time required for complete disingration of a Tablet was noted.

8. Dissolution Studies: Preparation of Dissolution medium

8.5ml of Hydrochloric acid was taken in a 1000ml volumetric flask and made upto 1000ml with distilled water.

Dissolution parameters

Medium : 900ml of 0.1M Hydrochloric acid.
Apparatus : USP type II (Paddle)
RPM : 75.
Temperature : $37^0C \pm 0.5^0C$.
Sampling volume : 5 ml

A sample (5ml) of the solution was withdrawn from the apparatus in diferent time intervals.Samples were replaced with fresh dissolution medium. The samples were filtered through Watmann filter paper. Measure the absorbance of the filtrate, diluted with the dissolution medium if necessary, at 210nm using UV-Spectrophotometer and using the dissolution medium as blank.

Kinetics of drug release[55-56]

The dissolution data were subjected to release kinetic study. Drug dissolution from solid dosage form has been described by kinetic models following.

Zero order equations

It describes systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fit into zero order equation.

$$Q=Q_0 - K_0t$$

Q = Amount of drug released at time 't'
Q_0 = Amountof drug released initially (often considered zero)
K_0 = Zero order conistant
A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.
Zero oder plot is derived from ploting the cumulative percent drug dissolved vs time

First order equation

The first order equation describes the releasefrom system where dissolution rate is dependent on the concentration of the dissolving species.

The dissolution data of Tablet formulation in dissolution medium that is water containing PH-1.2 hydro chloric acid buffer were plotted in accordance with the first oder equation, i.e., the logarithm of the percent remained as a fuction of time.

$$\text{Log } C = \text{Log } C_0 - k_t / 2.303$$

C_0 = Initial concetration of drug
C = Concetration of drug at time 't'
K = First order constant
t = Time

Fourie Transform – Spetroscopy

FT – IR spectra were recorded on sample prepared in potassium bromide discks using thermon electron FTIR specyrophotometer. Sample were prepared in potassium bromide discks by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}

Estimation of ritonavir
Calibration curve of ritonavir

Spectrophotometric method based on the measurement of absorbance at 210nm of U.V region in 0.1N HCl buffer of pH 1.2 was used in the study for estimation of Ritonavir.

Preparation of 0.1N HCl buffer

8.5ml of HCl was taken in 1000ml volumetric flask and it is made up to 1000ml with distilled water.

Constructioon of calibration curve of Ritonavir

50mg of Ritonavir was weighed accurately and transfer to 50ml volumetric flask and dissolve the drug in 10ml of methonal and made uptothe volume with 0.1N HCl. From this stock – I, 10ml is transfer to 100ml volumetric flask and made upto the volume by uing buffer. This is the stock – II solution. Frome the stock – II various concentration of 10, 12, 14, 16, 18, 20µg/ml were prepared. The absorbance of those dilutions was measured in SHIMADZU 1700 spectrophotometer at 210nm against blank. The absorbance of Ritonavir for corresponding concentration are given in the below table. The absorbance was plotted against concentration of Ritonavir as shown in below figure. This calibration curve was used for estimation of Ritonavir in films in the study. The liner regression analysis was carried on absorbance data points. A straight line equation (Y = mx + c) was generated to facilitate the calculation of amount of drug. Absorbance = Slope × Concentration + intercept.

Table 4: Concentration versus absorbance data for standard graph of Ritonavir

S.NO	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.311
3	12	0.364
4	14	0.419
5	16	0.485

6	18	0.539
7	20	0.599

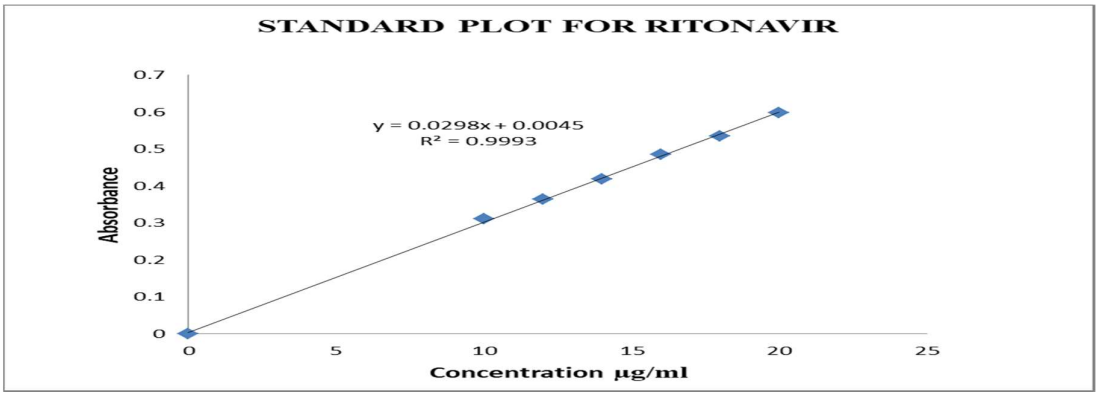

Fig 1: Standard Graph of Ritonavir in 0.1N HCl buffer

Development of formulation

Preparation of Ritonavir solid dispersion by fusion method

Fusion Method

In fusion method, carriers i.e., PEG 2000, Soluplus and Plasdone s- 630 in different ratios were taken into a porcelain dish and melting those at there melting pointes and to this Ritonavir added with thorough mixing for 1 – 2 minutes followed by quick cooling. The dried masswas pulverized and sieved through mesh 100#.

Formulation of Ritonavir solid dispersion tablets by direct compression method

All the ingredients were blended and compressed into Tablet (Ritonavir and carriers in diff. ratios of 1:1, 1:2, 1:3) on a 10station Rotary punch Tablet Compression machine. Tablet formula given in below table.

Table 5: List of Formulations

MATERIALS	F1(with out carrier)	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ritonavir	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
PEG 20000	-	-	-	-	-	-	-	100mg	200mg	300mg
Soluplus	-	-	-	-	100mg	200mg	300mg	-	-	-
Plasdone	-	100mg	200mg	300mg	-	-	-	-	-	-
Lactose	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg	100mg
Sodium Starch Glycolate	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg
Aerosil	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg	3mg
Magnesium Stearate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg

RESULTS AND DISCUSSION

Pre formulation studies

Melting point

Melting point of Ritonavir was found to be in the range of 120-123^{0}c. Which complied with the standard, indicating purity of the drug sample.

Solubility

It is freely soluble in methanol and ethanol, soluble in isopropanol and insoluble in water.

Compatability studies

Compatibility studies were performed using FT – IR spectrophotometer, the FT – IR spectrum of pure drug and physical mixture of drug and polymers were studies. The interpretation results were summarized in below table.

FTIR Spectrum of pure Ritonavir

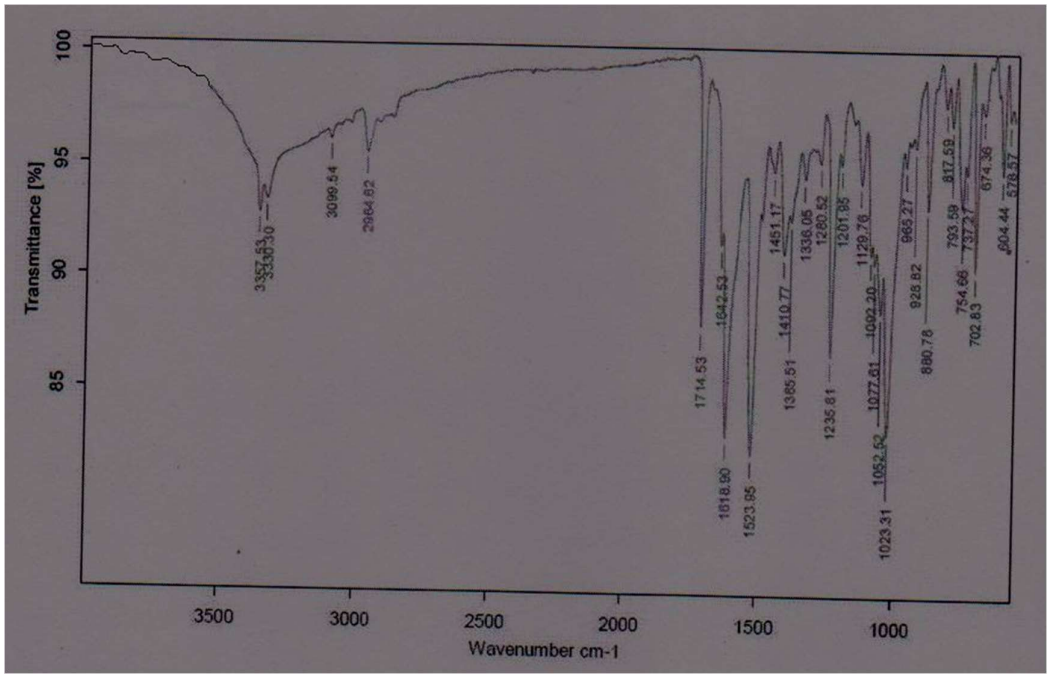

Fig 2: FTIR Spectrum of pure Ritonavir drug

FTIR Spectrum of Ritonavir with Soluplus (1:3)

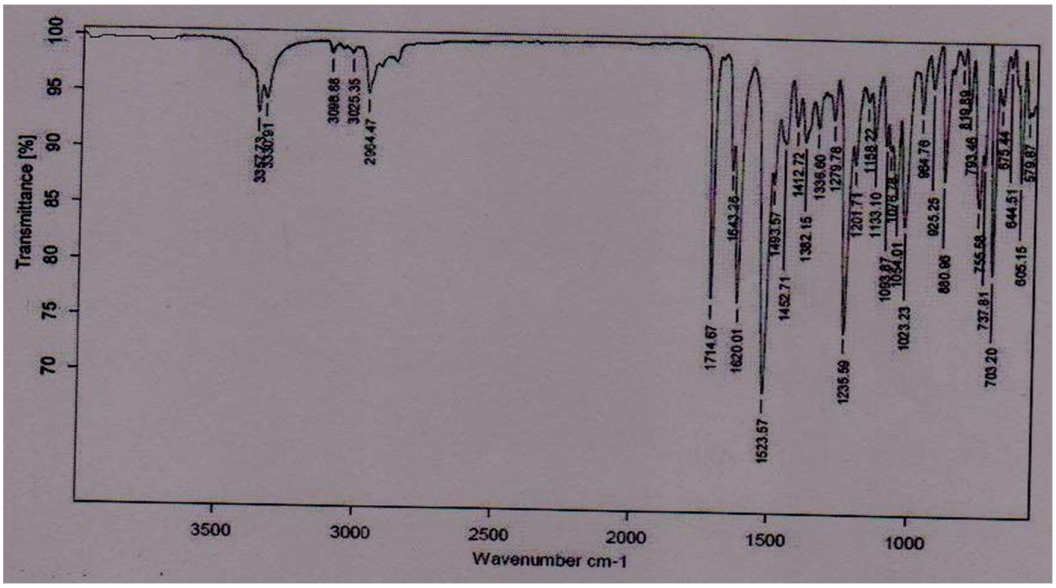

Fig 3: FTIR Spectrum of Ritonavir with soluplus

FTIR Spectrum of Ritonavir with Plasdone (1:3)

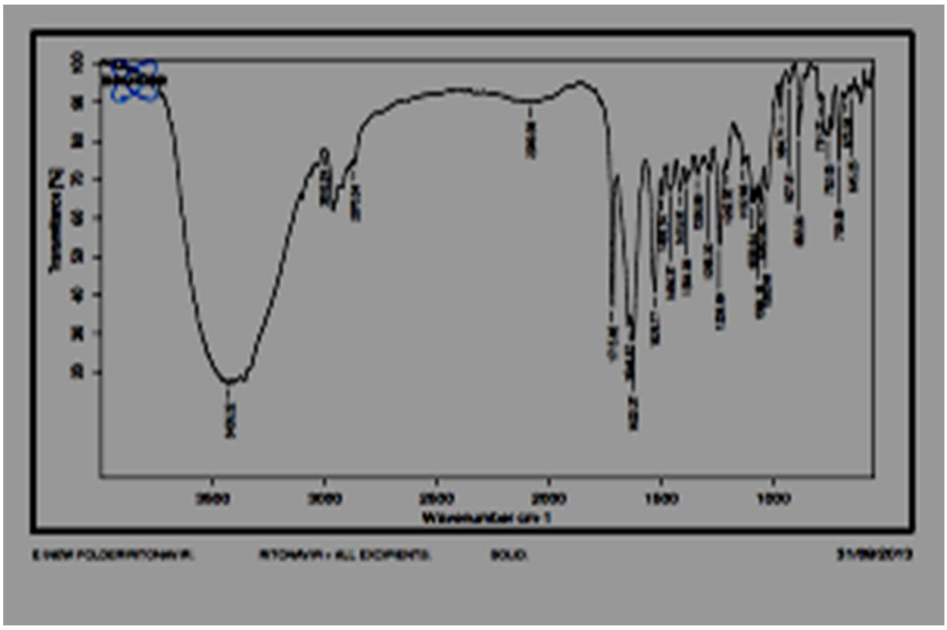

Fig 4: FTIR Spectrum of Ritonavir with Plasdone

FTIR Spectrum of Ritonavir with PEG 20000 (1:3)

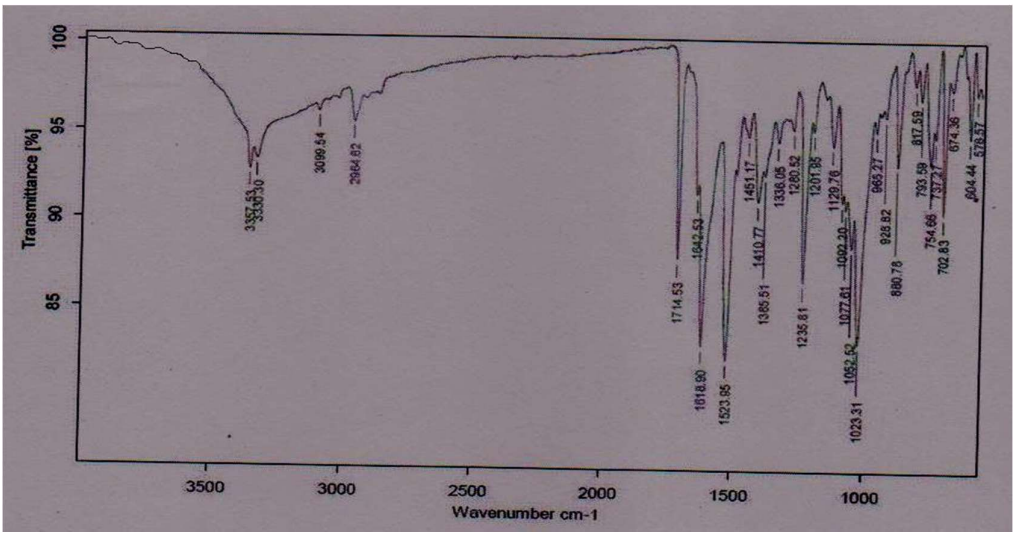

Fig 5: FTIR Spectrum of Ritonavir with PEG 20000

Pre compression studies

Different blend parameters are performed as per standard procedures and results are mentioned in the table and graphs.

Table 6: Evaluation parameters of blend

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Compressibility index (%)	Hausner's ratio
F1	0.52	0.62	27.14º	13.88	1.16
F2	0.53	0.68	29.14º	13.91	1.16
F3	0.57	0.66	25.14º	12.70	1.14
F4	0.58	0.69	28.38º	12.10	1.13
F5	0.54	0.65	29.26º	13.76	1.15

F6	0.31	0.36	26.46º	13.88	1.16
F_7	o.49	0.58	24.38^0	13.20	1.15
F_8	0.51	0.64	26.92^0	12.76	1.14
F_9	0.57	0.66	23.72^0	12.24	1.14
F_{10}	o.49	0.58	26.06^0	12.72	1.14

Post compression studies

The prepared tablet were tested for the compressed tablet parameters and the results were mentioned in the table.

Table 7: Evaluation parameters of Tablet

Tablet Formulation	Hardness(kg/cm^2)	Diameter(mm)	Thickness(mm)	Friability(%)
F_1	4.24	9.0	4.01	0.60
F_2	4.5	9.2	4.05	0.57
F_3	4.81	10.27	4.22	0.37
F_4	4.92	11.35	4.93	0.44
F_5	4.75	9.1	4.02	0.85
F_6	4.84	10.29	4.27	0.51
F_7	4.95	11.37	4.94	0.49
F_8	4.87	9.3	4.01	0.69
F_9	4.78	10.25	4.25	0.55
F_{10}	4.92	11.39	4.96	0.67

Drug Content and In vitro Disintegration Time of tablet

Table 8: Drug Content and In vitro Disintegration Time of tablet

Tests	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Drug content(mg/tablet)	99.1	98.9	99	98.6	98.8	99.2	99.1	98.6	98.9	99.3
Disintegration Time(Sec)	252	184	175	156	143	117	102	83	67	52

In – vitro Drug Release Studies

According to USP, dissolution test for Ritonavir tablet was done by using 01N HCl for 3hrs at 75 rpm using type – II dissolution apparatus.

Table 9: Percent drug release profiles

Time (mnts)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
0	0	0	0	0	0	0	0	0	0	0
10	25.45	33	35.18	35.18	31.64	39.27	43.27	28.36	37.9	41.09
20	39.27	44.36	45.18	48.63	39.27	41.18	54.09	34.9	41.18	49.36
30	41.18	46	49.27	53.63	45.54	48.27	59.54	37.72	47.54	58.9
45	45.27	48.45	52.9	54.72	50.72	55.81	65.18	43.63	58.81	67.36
60	48.27	53.71	58.63	61.54	61.81	67.27	71.45	47.81	65.54	78.45
90	51.54	55.81	59.81	63.72	66.27	78.09	83.9	54	73	89.54
120	55.81	56.36	66.63	68.09	73.63	83	88.36	60.36	80.81	95.45
150	59.45	60.72	69.63	71.63	76.09	88.72	92.27	73	91.18	100
180	61	65.16	71.18	77.18	81	90.81	99	88.9	100	--

Dissolution profile of Ritonavir formulated employing Ritonavir and solid dispersiond in different typesof polymers

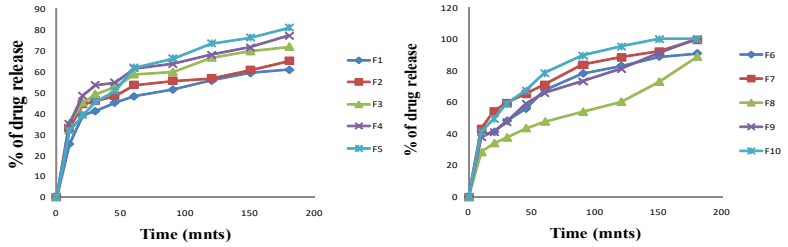

Fig 6: Dissolution profile of Ritonavir formulated employing Ritonavir and solid dispersion in different types of polymers

Dissolution Profile of Ritonavir- PEG 20000 Solid Dispersions

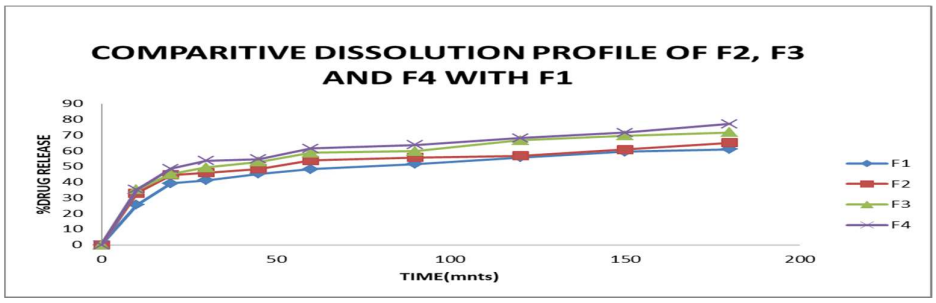

Fig 7: dissolution profile of Ritonavir –PEG 20000

Dissolution Profile of Ritonavir- Soluplus Solid Dispersions

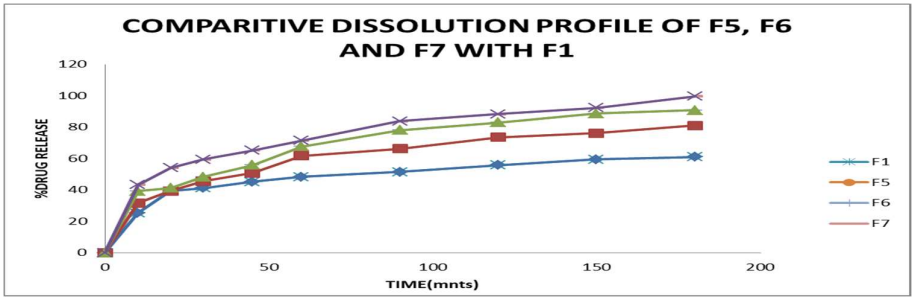

Fig 8: dissolution profile of Ritonavir – Soluplus

Dissolution Profile of Ritonavir- Plasdone Solid Dispersions

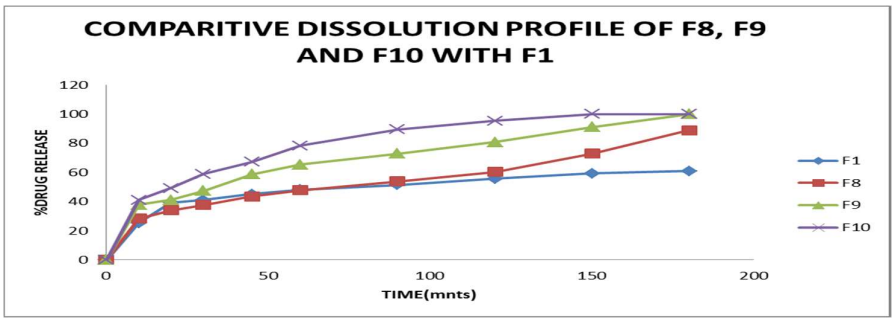

Fig 9: dissolution profile of Ritonavir – Plasdone

Zero order plot for best formulations (F9 AND F10)

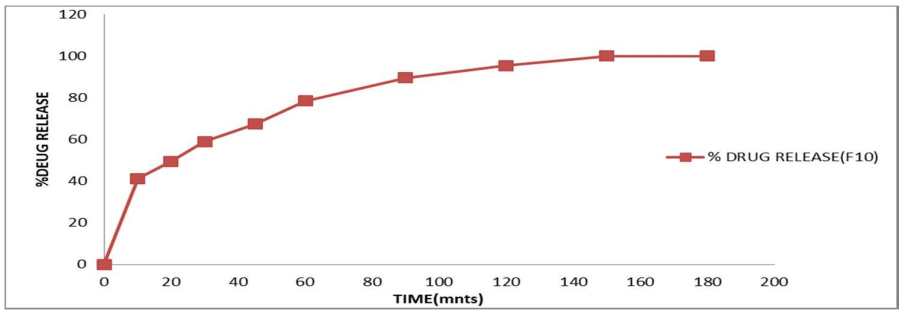

Fig 10: Zero order dissolution profile of Ritonavir best formulations

First order plot for best formulations (F9 AND F10)

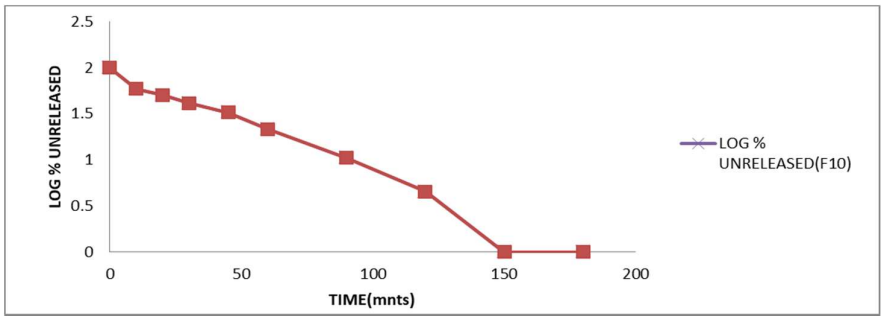

Fig 11: First order dissolution profile of Ritonavir best formulations

Table 10: The Correlation Coefficient (r) values in the analysis of Dissolution Data of Ritonavir with Synthetic polymers solid dispersions as per Zero order and First order kinetics (Fusion method)

Solid dispersion formulations	Correlation Coefficient (r)	
	Zero order	First order
F_1	0.9184	0.961
F_2	0.9457	0.994
F_3	0.9411	0.9884
F_4	0.8852	0.9569
F_5	0.9384	0.9542
F_6	0.8911	0.9912
F_7	0.9272	0.9901
F_8	0.9149	0.9747
F_9	0.8852	0.9287
F_{10}	0.9246	0.9392

DISCUSSION

Preparation of Solid dispersions of Drug with synthetic polymers

Solid dispersions can be prepared by methods such as physical mixtures, kneading, freeze drying, spray drying and co evaporation. In the present study, Fusion method was employed to prepare solid dispersion. In this case, solid dispersion were prepared at 1:1, 1:2 and 1:3 ratios of drug and different synthetic polymers (F_2, F_3, F_4 were 1:1, 1:2, 1:3 ratios respectively for PE 20000 ; F_5, F_6, F_7 were 1:1, 1:2, 1:3 ratios respectively for Soluplus and F_8, F_9, F_{10} were 1:1, 1:2, 1:3 ratios respectively for Plasdone). The solid dispersion prepared were evaluated for drug content uniformity and dissolution rate. Drug contents in various solid dispersion were found tobe within 100±5% of the theoretical amount. In each case low CV values (< 1.5%) in the percent drug content indicated uniformity of drug content in the solid dispersions prepared.

Dissolution characteristics of Ritonavir solid dispersion with three different synthetic polymers

The dissolution rate of Ritonavir from different synthetic polymers solid dispersions were studied in 0.1N HCl buffer of P^H 1.2 and compared with that of pure drug. The dissolution data of Ritonavir dispersions are given in table no.15 and the dissolution profiles are shown in figure no. 12.

The dissolution data were analyzed as per zero-order and first-order kinetics. The model that best fits the dissolution data was evaluated by calculating the correlation coefficient (r) between the two variables namely time and percent dissolved in the zero-order model and time and log percent remaining in the first order model. The correlation coefficient (r) values in the analysis of dissolution data as per zero-order and first-order kinetics are given in Table no. 16. The 'r' values were found to be relatively higher in the case of first order model in all the cases. Thus the dissolution on Ritonavir as such and from various ratios of different synthetic polymers followed first-order kinetics. The corresponding liner plots are shown in Figure no.16 for best optimized formulations.

CONCLUSION

- The present work on enhancement of dissolution rate of Ritonavir tablets by solid dispersion fusion technique utilizing PEG20000, Soluplus and Plasdone to increase the solubility of the formulation in 3hrs time period. Among all 10 formulations F_{10} formulation showed better drug release of 100% drug release at the end of 150th minute compared to other 8 formulations and plain Ritonavir formulation. So F_{10} (containing 1:3 ratio of PEG 20000) is the optimized formulation.
- Among the polymers used the role of PEG20000 is quite worthy compared to Soluplus and Plasdone in enhancing the dissolution rate.
- Drug–excipients interaction was carried out for pure drug and optimized formulations by using FTIR study. In this analysis drug-excipients compatibility interaction were not observed.
- From the 'r' value obtained from the dissolution data profile, it was concluded that the optimized formulation follow First-order release kinetics.

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