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Research Article

Effect of Binders on the Dissolution Rate and Dissolution Efficiency of Ritonavir Tablets

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ABSTRACT
Ritonavir, a widely prescribed anti-retroviral drug, belongs to Class II under 'BCS' and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Ritonavir is practically insoluble in water and aqueous fluids. Its aqueous solubility was reported to be 2.56 mg/100 ml. As such oral absorption of ritonavir is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability. In the case of poorly soluble drugs formulation variables greatly influence their dissolution rate and bioavailability from solid dosage forms. The objective of the present work is to study the effect of seven binding agents on the tablet qualities and dissolution rate of ritonavir tablets to optimize the formulation of ritonavir tablets**.** Compressed tablets each containing 100 mg of ritonavir were prepared by conventional wet granulation method using seven binders namely acacia, sucrose, PVP, methyl cellulose, HPMC, starch paste and gelatin and the tablets were evaluated for content of active ingredient, hardness, friability, disintegration time, dissolution rate and dissolution efficiency. The binder used has significant influence on the tablet qualities and dissolution rate of ritonavir from the tablets. The order of performance of binders based on increasing dissolution rate and dissolution efficiency was acacia > starch paste > sucrose > PVP >gelatin > HPMC > MC. Tablets formulated with acacia, starch paste, and sucrose exhibited higher dissolution rates and dissolution efficiency values fulfilling all other official (IP) and GMP requirements of compressed tablets. Overall acacia, starch paste, sucrose and PVP were found to be suitable binders for ritonavir tablets.

Keywords: Ritonavir, Tablets, Binder, Dissolution rate, Dissolution Efficiency

INTRODUCTION

Many of the modern drugs belong to the Class II category under biopharmaceutical classification system[1] (BCS), which are characterized by low solubility and high permeability. These drugs are insoluble in water and aqueous fluids in the pH range of 1.0 - 7.5 and exhibit low and variable dissolution and bioavailability. There is a great need to develop technologies for these 'BCS' Class II drugs for enhancing their dissolution rate and bioavailability. The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug product development.

Ritonavir, a widely prescribed anti-retroviral drug[2-5], belongs to Class II under 'BCS' and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Ritonavir is practically insoluble in water and aqueous fluids. Its aqueous solubility was reported[6] to be 2.56 mg/100 ml. As such oral absorption of ritonavir is dissolution rate limited and it requires enhancement in solubility and dissolution rate for increasing its oral bioavailability.

The poor aqueous solubility of the drug gives rise to difficulties in the formulation of solid dosage forms such as tablets and capsules. In the case of poorly soluble drugs formulation variables greatly influence their dissolution rate and bioavailability from solid dosage forms. Though ritonavir tablets are available commercially, no work was reported on the pharmaceutical formulation aspects of ritonavir. Ritonavir tablets are official in I.P. 2010 which prescribed a dissolution rate test specification of NLT 70 % in 60 min to check the quality of commercial brands.

In the present work, the effect of seven binding agents, on the tablet qualities and dissolution rate of ritonavir tablets was studied to optimize the formulation of ritonavir tablets. Binder is a critical ingredient in tablets that influence tablet characters[7]. The effect of binding agents on the dissolution rate of poorly soluble drugs such as

hydrochlorthiazide, furosemide, nicotinic acid, aspirin, paracetamol, tolbutamide, phenylbutazone and nimesulide was reported earlier[8, 9]. In the present work the effect of seven commonly used binders on the dissolution rate of ritonavir from compressed tablets was studied.

EXPERIMENTAL

Materials

Ritonavir was a gift sample from M/s Hetero Drugs Ltd., Hyderabad. Polyvinyl pyrrolidone (Mfg: BASF, PVP K-30), hydroxy propyl methyl cellulose (having a viscosity of 50 cps in a 2% weight aqueous solution at 20°C), potato starch (Loba Chemie), gelatin (oxoid), acacia (Loba Chemie), methyl cellulose (methoxyl content: 28-32%; viscosity: 65 cps), sucrose, Talc I.P and Magnesium stearate I.P. All other materials used were of Pharmacopoeial grade.

Preparation of Ritonavir Tablets

Compressed tablets each containing 100 mg of ritonavir were prepared by conventional wet granulation method using various binders as per the formulae given in Table 1.

Method

The required quantity of medicament and other ingredients (Table 1) were taken in a mortar. Half the quantity of potato starch was added before granulation and the remaining half was added after granulation. The aqueous binder solution was added and mixed thoroughly to form dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 4 hr. The dried granules were passed through mesh No. 16 to break the aggregates. Talc (2%) and magnesium stearate (2%) were passed through mesh No. 100 onto dry granules and blended in a polyethylene bag. The tablet granules were then compressed into tablets on a rotary multi-station tablet punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 6-7 kg/sq.cm using 9 mm round and flat punches.

Evaluation of Tablets

All the tablets prepared are evaluated for content of active ingredient, hardness, friability, disintegration time, dissolution rate and dissolution efficiency.

Content of Active Ingredient

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 100 mg of the medicament was taken into a boiling test tube and extracted with 4 x 10 ml quantities of methanol. The methanolic extracts were collected into 100 ml volumetric flask and the volume was made upto 100 ml with methanol. The solution was subsequently diluted with 0.1 N hydrochloric acid and assayed for the drug content by the UV spectrophotometric method at 210 nm.

Hardness

Hardness of the tablets was tested using a Monsanto hardness tester.

Friability

Friability of the tablets was determined in a Roche friabilator.

Disintegration Time

Disintegration times were determined in Thermonic tablet disintegration test machine using distilled water as fluid.

Dissolution Rate Study

The dissolution rate of ritonavir from the tablets was studied in 900 ml of 0.1 N hydrochoric acid using Disso 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37°C ± 1°C was maintained throughout the study. One tablet containing 100 mg of ritonavir was used in each test. Samples of dissolution media (5 ml) were withdrawn through a filter (0.45μ) at different intervals of time, suitably diluted and assayed for ritonavir at 210 nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid and a suitable correction was applied for the amount of drug removed in the sample of dissolution fluid at each time. The dissolution experiments were conducted in triplicate (n=3).

RESULTS AND DISCUSSION

Ritonavir tablets could be prepared by wet granulation method employing the commonly used binders as per the formulae given in Table 1. Ritonavir content, hardness, friability and disintegration time of various tablets are given in Table 2. All the tablets were found to contain the ritonavir within 100±2% of the label claim. Hardness of the tablets was in the range 5-6.5 kg / sq.cm in all the batches of tablets except those prepared using methyl cellulose and HPMC as binders. The tablets prepared using these binders were found to be relatively harder with hardness in the range 11-12 kg/sq.cm. The percentage weight loss in the friability test was less than 1.2 with all the batches of tablets. Tablets formulated employing methyl cellulose and HPMC as binders did not fulfilled the official (IP) disintegration test of uncoated tablets. Though the tablets formulated with all other binders disintegrated within 4 min., variations were observed in their disintegration time in the range 0.5 - 4.0 min.

Table -1: Formulae of Ritonavir Tablets Prepared with Various Binders

	Formulation						
Ingredient mg/tab.	**TF1**	**TF2**	**TF3**	**TF4**	**TF5**	**TF6**	**TF7**
Ritonavir	100	100	100	100	100	100	100
Acacia	5	-	-	-	-	-	-
Sucrose	-	5	-	-	-	-	-
PVP	-	-	5	-	-	-	-
MC	-	-	-	5	-	-	-
HPMC	-	-	-	-	5	-	-
Starch paste	-	-	-	-	-	5	-
Gelatin	-	-	-	-	-	-	5
Potato starch	40	40	40	40	40	40	40
Talc	4	4	4	4	4	4	4
Magnesium stearate	4	4	4	4	4	4	4
Lactose up to (mg)	200	200	200	200	200	200	200

Dissolution characteristics of various tablets prepared are shown in Table 3 and Fig. 1. The dissolution data were analysed as per zero order and first order kinetic models. The kinetic model that fits the dissolution data was evaluated by comparing the correlation coefficient (r) values obtained in zero order and first order models. The model that gave higher (r) value is considered as the best fit model. The (r) values were found to be higher in the first order model than those in zero order models indicating that the dissolution of ritonavir from all the tablets prepared followed first order kinetics. The correlation coefficient (r) value between log percent undissolved and time was in the range 0.974 -0.999 with various tablet formulations. Dissolution efficiency (DE_{30}) values were calculated as suggested by Khan[10].

Table -2: Drug Content, Hardness, Friability and Disintegration Time of Ritonavir Tablets Formulated with Various Binders

Tablet Formulation	**Ritonavir content (mg/Tab)**	**Hardness Kg/sq. cm.**	**Friability (%)**	**Disintegration Time (min.)**
TF1	99.2	6.5	0.95	3.8
TF2	99.5	5.0	1.26	0.5
TF3	98.5	5.5	0.95	2.2
TF4	100.2	12.0	0.42	19.0
TF5	100.5	11.5	0.52	15.0
TF6	99.6	6.25	0.93	1.0
TF7	99.8	6.5	0.94	1.0

Binders used in formulations:

TF1 (Acacia), TF2 (Sucrose), TF3 (PVP), TF4 (MC), TF5 (HPMC), TF6 (Starch paste), TF7 (Gelatin).

Another parameter suitable for the evaluation of in vitro dissolution data has been suggested by Khan[10] who introduced the parameter dissolution efficiency (DE). DE is defined as the area under dissolution curve upto a certain time T expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

Dissolution Efficiency

$$(DE) = \left[\frac{\int_0^t y dt}{y100.t} \right] 100$$

The dissolution efficiency can have a range of values depending on the time intervals chosen. In any case, constant time intervals should be chosen for comparison. For example the index DE_{30} would relate to the dissolution of drug from a particular formulation after 30 min and could only be compared with DE3o of other formulations. Summation of the large dissolution data into a single figure DE enables ready comparison to be made between a large numbers of formulations.

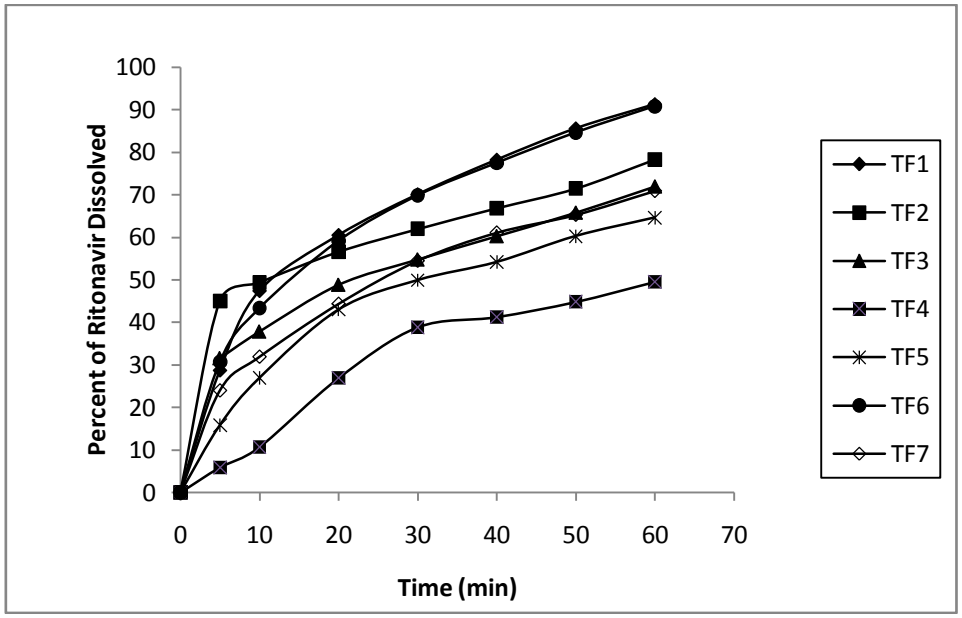

Fig. 1: Dissolution Profiles of Ritonavir Tablets Prepared using Various Binders

Table- 3: Dissolution Parameters of Ritonavir Tablets Formulated with Various Binders

Formulation	Binder Used	K_1 (min^{-1})	DE_{30} (%)	Percent Drug Dissolved in 10 min
TF1	Acacia	0.0400	49.37	47.41± 1.1
TF2	Sucrose	0.0322	49.03	49.40± 1.6
TF3	PVP	0.0264	40.14	37.84±1.2
TF4	MC	0.0163	19.08	10.67±1.3
TF5	HPMC	0.0231	32.03	26.95±1.4
TF6	Starch paste	0.0398	47.31	43.34±1.5
TF7	Gelatin	0.0262	35.82	31.90±1.3

The dissolution parameters of various tablets prepared are summarized in Tableb3. Much variation was observed in the dissolution characteristics of tablets prepared with various binders. The order of performance of binders based on increasing dissolution rate was found to be acacia > starch paste> sucrose> PVP> gelatin> HPMC> MC. The same order of performance was

observed based on the dissolution efficiency. Tablets formulated with acacia, starch paste and sucrose exhibited higher dissolution rates and dissolution efficiency values among all and these tablets also fulfilled all official (IP) and GMP requirements of compressed tablets. Overall acacia, starch paste, sucrose and PVP were found to be suitable binders for ritonavir tablets.

CONCLUSIONS

The binder used has significant influence on the tablet qualities and dissolution rate of ritonavir from the tablets.

The order of performance of binders based on increasing dissolution rate and dissolution efficiency was acacia > starch paste > sucrose > PVP >gelatin > HPMC > MC.

Tablets formulated with acacia, starch paste, and sucrose exhibited higher dissolution rates and dissolution efficiency values fulfilling all other official (IP) and GMP requirements of compressed tablets.

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