Original Article

Effect Of Binder And Superdisingrants On The Formulation & Development Of Antiviral Drug

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Abstract

AIM- The aim of the present investigation is to study the effect of binder and superdisingrants on the formulation & development of antiviral drug.

MATERIAL & METHODS- The Thiel's tube method of melting point determination in liquid paraffin was used in the present study. FTIR spectra of drug in KBr pellets were recorded at moderate scanning speed between 4000 600 cm^{-1}. UV scanning was done for RTV from 200-400nm in 0.1 N HCl containing 0.5% w/v SLS employing Shimadzu UV-1700 double beam spectrophotometer. In the present work the effect of seven commonly used binders on the dissolution rate of ritonavir from compressed tablets was studied. For the same, the following requirements were used i.e. Ritonavir, Polyvinyl pyrrolidone (Mfg: BASF, PVP K-30), Hydroxy propyl methyl cellulose, Potato starch, Gelatin, Acacia, Methyl cellulose (methoxyl content: 28-32%; viscosity: 65 cps) Sucrose, Starch paste, Talc I.P, Magnesium stearate I.P. All other materials used were of Pharmacopoeial grade.

RESULTS- The melting point of RTV was found to be 122°C. This matches with the standard melting temperature range (119-123°C) (Vijay 854), indicating the identity of the drug. UV scanning was done for RTV from 200-400nm in 0.1 N HCl containing 0.5% w/v SLS employing Shimadzu UV-1700 double beam spectrophotometer. The λ_{max} was found at 246. FTIR spectra of drug in KBr pellets were recorded at moderate scanning speed between 4000- 600 cm^{-1}. 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.

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

KEYWORDS Binder and Superdisingrants, Formulation & Development, Antiviral Drug, Ritonavir, PVP, HPMC, MC

INTRODUCTION

The Biopharmaceutical Classification System divides drugs into four classes depending on in vitro and in vivo permeability data.(Alsenz et al., 2007) Four classes of compound can be distinguished: I (high solubility, high permeability), II (low solubility, high permeability), III (high solubility, low permeability) and IV (low solubility and low permeability). Class I compounds are typical examples for waiving bioequivalence studies. In the selection process, new chemical compound with low aqueous solubility and low permeability are preferably filtered out since they might pose problems during pharmaceutical development. For class II drugs dissolution /solubility and for Class III drug permeability limits the oral drug absorption (Butler et al., 2010).

It is obvious that class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption than their ability to permeate through the intestinal epithelia. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs solid dispersion, solubilization using surfactant, the use of co-solvent, reduction of particle size, hydrotropy and the use of aqueous soluble derivatives or salts (Chavda et al., 2010; Chiou et al., 1971).

Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble Antiviral drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wet ability, bioavailability may be significantly improved. The aim of the present investigation is to study the effect of different binders and superdisintegrants on the formulation and development of Ritonavir (Leuner and Jennifer, 2007).

MATERIAL & METHODS

Equipments

Equipment	Manufacturer	M o
Digital weighing balance	Shimadzu, Delhi	AX200
USP dissolution test apparatus	Electrolab, Mumbai	TDT- 08L
UV-visible double beam spectrophotometer	Shimadzu, Delhi	UV-1700
Fourier transform infrared spectrophotometer	Shimadzu, Delhi	8400S
Differential scanning calorimeter	Mettler, Mumbai	Toledo
X-ray diffractometer	Bruker, Mumbai	D8 Advance
Digital pH meter	Elico limited, Ahmedabad	ElicoL1 612
Humidity oven	Nova Instrum Pvt. Ltd., Ahmedabad	NV-8903

Melting Point Determination

Melting point is the temperature at which pure liquid and solid exist in equilibrium. In practice, it is measured at an external pressure of 1 atmosphere. The Thiel's tube method of melting point determination in liquid paraffin was used in the present study (Löbenberg and Gordon, 2000).

FTIR Spectra

FTIR spectra of drug in KBr pellets were recorded at moderate scanning speed between 4000 600 cm^{-1}.

UV Spectrum

UV scanning was done for RTV from 200-400nm in 0.1 N HCl containing 0.5% w/v SLS employing Shimadzu UV-1700 double beam spectrophotometer. The λ_{max} was found at 246 nm.

EFFECT OF VARIOUS BINDERS & SUPERDISINTEGRANTS ON DIFFERENT PARAMETERS OF RITONAVIR FROM TABLETS

Effect of Binders

In the present work the effect of seven commonly used binders on the dissolution rate of ritonavir from compressed tablets was studied. For the same, the following requirements were used i.e. Ritonavir, Polyvinyl pyrrolidone (Mfg: BASF, PVP K-30), Hydroxy propyl methyl cellulose, Potato starch, Gelatin, Acacia, Methyl cellulose (methoxyl content: 28-32%; viscosity: 65 cps) Sucrose, Starch paste, Talc I.P, Magnesium stearate I.P. All other materials used were of Pharmacopoeial grade (Pouton, 2006).

Preparation of Ritonavir Tablets

Compressed tablets each containing 200 mg of ritonavir were prepared by conventional wet granulation method using various binders as per the formulae shown in Table.

Table 1: Formula of Ritonavir Tablets Prepared with Various Binders

Formulation

Ingredient mg/tab.	RT1	RT 2	RT 3	RT 4	RT 5	RT 6	RT 7
Ritonavir	200	200	200	200	200	200	200
Acacia	5	-	-	-	-	-	-
Sucrose	-	5	-	-	-	-	-
PVP	-	-	5	-	-	-	-
MC	-	-	-	5	-	-	-
HPMC	-	-	-	-	5	-	-
Starch paste	-	-	-	-	-	5	-
Gelatin	-	-	-	-	-	-	5
Potato starch	50	50	50	50	50	50	50
Talc	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5
Lactose up to (mg)	200	200	200	200	200	200	200

Method

The aqueous binder solution mucilage 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 (Mallappa et al., 2015).

Effect of Superdisintegrants

Disintegrants is a critical ingredient in tablets that influences the dissolution rate and bioavailability of the drug from tablets. In the present work, the effect of five superdisintegrants on the tablets qualities and dissolution rate of ritonavir from compressed tablets was studied to optimize the formulation of ritonavir tablets. The following requirements were used i.e. Ritonavir, Primogel, Croscarmellose sodium, Crospovidone, Prosolve, Modified Starch, Magnesium stearate I.P, Talc I.P (Patil and Das, 2011).

Preparation of Ritonavir Tablets

Compressed tablets each containing 100 mg of ritonavir were prepared by conventional wet granulation method using various superdisintegrants as per the formulae. All superdisintegrants except Prosolve were used at 4% concentration and Prosolve was used at 10% concentration. Acacia (2.5%) was used as binder in the form of aqueous mucilage in all the formulations.

The required quantity of medicament and other ingredients was taken in a mortar. The aqueous mucilage of binder 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. The superdisintegrants, 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.

Table 2: Formula of Tablets Prepared with Various Superdisintegrants

Ingredient (mg/tab)	Formulation				
	RT 8	**RT 9**	**RT 10**	**RT 11**	**RT 12**
Ritonavir	200	200	200	200	200
Acacia	5	5	5	5	5
Modified Starch	8	-	-	-	-
Primogel	-	8	-	-	-
Crospovidone	-	-	8	-	-
Croscarmellose	-	-	-	8	-
Sodium Prosolve Talc					
Magnesium stearate	-	-	-	-	20
Lactose up to (mg)	5	5	5	5	5
	5	5	5	5	5

Evaluation of Tablets

All the tablets prepared are evaluated for

i) Content of active ingredient
ii) Hardness
iii) Friability
iv) Disintegration time
v) Dissolution rate

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 50 ml volumetric flask and the volume was made upto 50 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 (Rani et al., 2013).

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

Melting Point Determination

The melting point of RTV was found to be 122°C. This matches with the standard melting temperature range (119-123°C) (Vijay 854), indicating the identity of the drug.

UV Spectrum

UV scanning was done for RTV from 200-400nm in 0.1 N HCl containing 0.5% w/v SLS employing Shimadzu UV-1700 double beam spectrophotometer. The λ_{max} was found at 246.

FTIR Spectra

FTIR spectra of drug in KBr pellets were recorded at moderate scanning speed between 4000- 600 cm^{-1}.

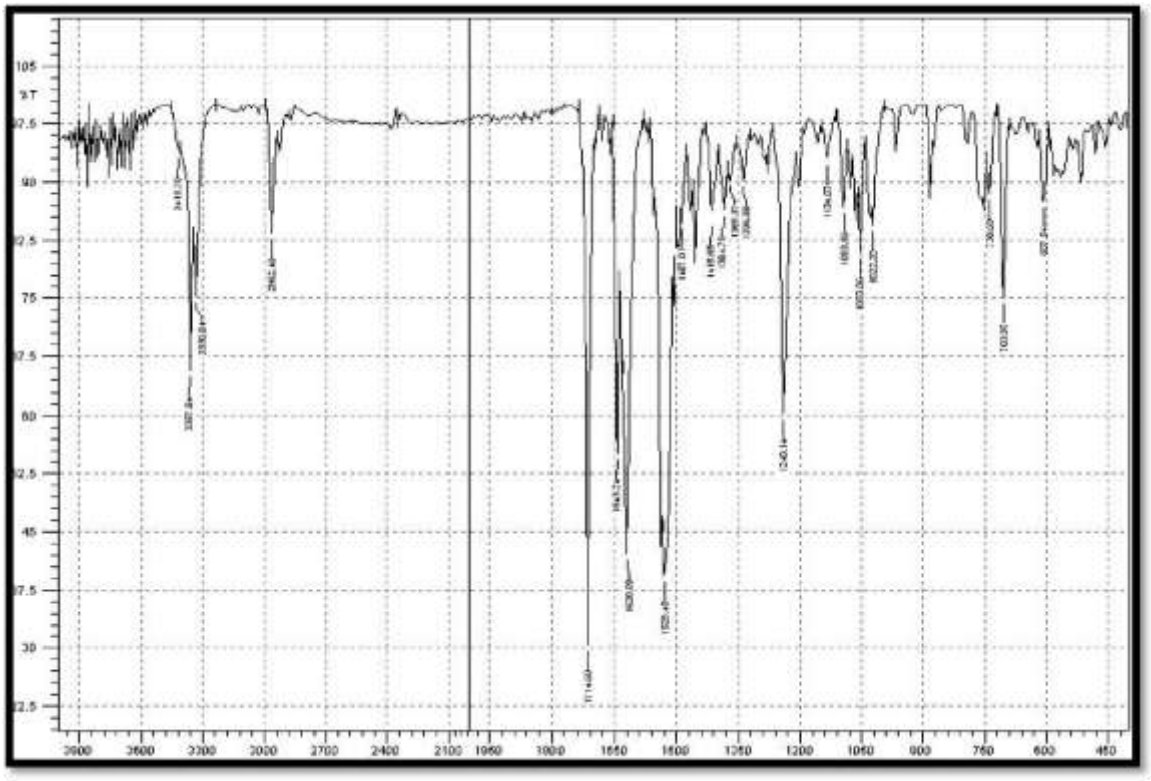

Fig. 1: FTIR spectrum of ritonavir

The functional groups present in RTV are 3357 cm^{-1}, 3330 cm^{-1} corresponding to the N-H stretching amide group, 2962 cm^{-1} corresponding to the hydrogen bonded acid within the molecule, 1714 cm^{-1} for ester linkage and 1620 cm^{-1} , 1529 cm^{-1} referring to –C=C- stretching aromatic carbons.

Effect of Various Binders on Tablet

Table 3: 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	99.3	6.4	0.91	3.6
TF2	99.6	5.2	1.25	0.7
TF3	98.4	5.6	0.98	2.3
TF4	100.3	12.3	0.46	19.2
TF5	100.7	11.7	0.54	15.6
TF6	99.4	6.9	0.97	1.4

Binders used in formulations:

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

Effect of Various Binders on Dissolution rate of Tablet

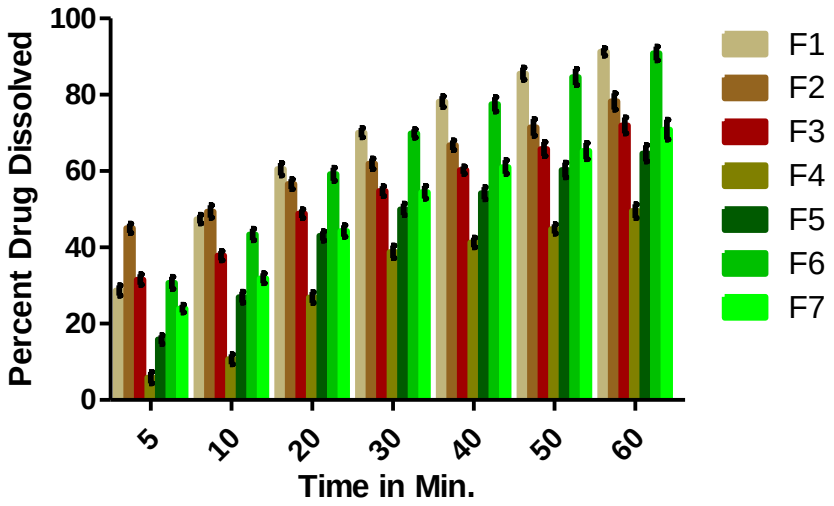

Figure 2: Dissolution Profiles of Ritonavir Tablets Formulated Employing Various Binders

Effect of Various Binders on Dissolution Parameters of Tablet

Table 4: 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	0.040	49.44	47.22± 1.3
TF2	Sucrose	0.032	47.23	49.33± 1.5
TF3	PVP	0.024	40.45	37.45±1.3
TF4	MC	0.013	19.44	10.56±1.4
TF5	HPMC	0.021	32.11	26.11±1.5

TF6	Starch paste	0.038	49.31	43.37±1.6
TF7	Gelatin	0.022	35.48	31.38±1.4

DISCUSSION

Ritonavir tablets could be prepared by wet granulation method employing the commonly used binders. 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.

The dissolution data were analyzed 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 (Reddy and Reddy, 2013).

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 would relate to the dissolution of drug from a particular formulation after 30 min and could only be compared with DE of other formulations (Shafiq and Shakeel, 2010). Summation of the large dissolution data into a single figure DE enables ready comparison to be made between a large numbers of formulations (Shukla and Patel, 2010).

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 and sucrose were found to be suitable binders for ritonavir tablets (Zhao and Feng, 2010).

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.

REFERENCES

1. Alsenz, Jochem, and Manfred Kansy. “High Throughput Solubility Measurement in Drug Discovery and Development.” Advanced drug delivery reviews 59.7 (2007): 546–567.
2. Butler, James M, and Jennifer B Dressman. “The Developability Classification System: Application of Biopharmaceutics Concepts to Formulation Development.” Journal of pharmaceutical sciences 99.12 (2010): 4940–4954.
3. Chavda, H, C Patel, and I Anand. “Biopharmaceutics Classification System.” Systematic reviews in pharmacy 1.1 (2010): 62.
4. Chiou, Win Loung, and Sidney Riegelman. “Pharmaceutical Applications of Solid Dispersion Systems.” J. Pharm Sci 60.9 (1971): 1281–1302.
5. Leuner, Christian, and Jennifer Dressman. “Improving Drug Solubility for Oral Delivery Using Solid Dispersions.” European journal of Pharmaceutics and Biopharmaceutics50.1 (2000): 47–60.
6. Löbenberg, Raimar, and Gordon L Amidon. “Modern Bioavailability, Bioequivalence and Biopharmaceutics Classification System. New Scientific Approaches to International Regulatory Standards.” European Journal of Pharmaceutics and Biopharmaceutics 50.1 (2000): 3–12.
7. Pouton, Colin W. “Formulation of Poorly Water-Soluble Drugs for Oral Administration: Physicochemical and Physiological Issues and the Lipid Formulation Classification System.” European Journal of Pharmaceutical Sciences 29.3 (2006): 278–287.
8. Mallappa, Manjanna Kolammanahalli, Rajesh Kesarla, and Shivakumar Banakar. “Calcium Alginate-Neusilin US2 Nanocomposite Microbeads for Oral Sustained Drug Delivery of Poor Water Soluble Drug Aceclofenac Sodium.” Journal of drug delivery 2015.
9. Patil, C, and S Das. “Effect of Various Superdisintegrants on the Drug Release Profile and Disintegration Time of Lamotrigine Orally Disintegrating Tablets.” African journal of pharmacy and pharmacology 5.1 (2011): 76–82
10. Rani, A Prameela, and H Wessam. “Full Factorial Design in Formulation of Lamotrigine Suspension Using Locust Bean Gum.” Int J Chem Sci 11.2 (2013): 751–760.
11. Reddy, Swetha, and Satish Reddy. “Formulation & Evaluation of Oral Disintegrating Tablets of Lamotrigine Solid Dispersions.” Iranian

Journal of Pharmaceutical Sciences 9.1 (2013): 1–12.
12. Shafiq, Sheikh, and Faiyaz Shakeel. “Stability and Self-Nanoemulsification Efficiency of Ramipril Nanoemulsion Containing Labrasol and Plurol Oleique.” Clinical Research and Regulatory Affairs 27.1 (2010): 7–12.
13. Shukla, Jill B, and Sachin J Patel. “Formulation and Evaluation of Self Micro Emulsifying System of Candesartan Cilexetil.” Int. J. Pharm. Pharm. Sci 2.4 (2010): 143–146.
14. Zhao, Lingyun, and Si-Shen Feng. "Enhanced Oral Bioavailability of Paclitaxel Formulated in Vitamin E-TPGS Emulsified Nanoparticles of Biodegradable Polymers: In Vitro and in Vivo Studies."Journal of pharmaceutical sciences 99.8 (2010): 3552-3560.