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Research Article

FORMULATION DEVELOPMENT OF RITONAVIR TABLETS CONTAINING SOLID DISPERSIONS EMPLOYING MONTMORILLONITE: DISSOLUTION RATE ENHANCEMENT

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ABSTRACT

The aim of this study was to prepare and evaluate montmorillonite (natural clay material) for enhancing the dissolution rate of drug by formulating solid dispersions of ritonavir in montmorillonite into compressed tablets. Solid dispersions of ritonavir in montmorillonite were prepared by solvent evaporation method employing various weight ratios of drug: montmorillonite such as 1:1(SD-1), 1:2(SD-2), 1:4(SD-3) and 1:7 (SD-4). Ritonavir (50mg) tablets were prepared employing ritonavir alone and it's all solid dispersions by wet granulation method and were evaluated. Prior to compression, the pre-compression parameters showed satisfactory flow properties. Post-compression parameters showed that all tablet formulations had acceptable mechanical properties. The compatibility of the drug in the formulation was confirmed by IR and DSC studies. Ritonavir tablets formulated employing its solid dispersion in montmorillonite gave rapid and higher dissolution rate and DE_{30} when compared to plain tablets. A 14, 12 and 8 fold increase in the dissolution rate (k_1) was observed with tablet formulations containing solid dispersions SD-1, SD-2 and SD-3 respectively when compared to plain tablets.

Keywords: montmorillonite, ritonavir, solid dispersions, dissolution rate.

INTRODUCTION

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.

Several techniques[1] such as micronization, cyclodextrin complexation, use of surfactants and solubilizers, solid dispersion in water soluble and dispersible carriers, use of salts, prodrugs and polymorphs which exhibit high solubility , microemulsions and self emulsifying micro and nano disperse systems have been used to enhance the solubility, dissolution rate and bioavailability of poorly soluble drugs. Among the various approaches, solid dispersions in water dispersible excipients are a simple, industrially useful approach for enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs.

Montmorillonite (MMT) clay is one of the smectite group, composed of silica tetrahedral sheets layered between an alumina octahedral sheets. MMT is natural clay; has large specific surface area; exhibits good adsorb ability, cation exchange capacity, standout adhesive ability, and drug-carrying capability. Thus, bentonite is a common ingredient as both the excipient and active substance in pharmaceutical products[2].

The objective of the present research work was to prepare drug-clay material intercalates and to investigate the possibility of improving the solubility and dissolution of ritonavir by formulating solid dispersions of ritonavir in montmorillonite into compressed tablets.

MATERIALS AND METHODS

Materials

Ritonavir was gift sample from M/s Hetero Drugs Pvt. Ltd., Hyderabad. Bentonite, acacia, magnesium stearate were supplied from FINAR reagents, Ahmedabad. Lactose and talc were supplied by NR CHEM, Mumbai. All chemicals used in the study were of analytical grade.

Methods

Purification of Montmorillonite

To obtain MMT in Na-form, 100 g of raw bentonite was dispersed in 1 L of 0.1M NaCl solution, stirred for 12 h and centrifuged. The above procedure was repeated thrice. Finally, the slurry was centrifuged and washed with de-ionized water until free from chloride ion[3]. Na-MMT was purified by sedimentation technique[4], according to the Stokes law of sedimentation. The purified MMT was obtained by dispersing 75 g of Na-MMT in 5 L de-ionized water and collecting the supernatant dispersion of particles after the pre-calculated time (10 h) at 30 ◦C. The Na-MMT slurry was dried at 100 ◦C and ground to pass through 200mesh sieve.

Estimation of Ritonavir

An UV spectrophotometric method based on the measurement of absorbance at 238 nm in 0.1N hydrochloric acid was used for estimation of ritonavir. The method obeyed Beer- Lambert's law in the concentration range of 0-10 µm/mL. When the standard drug solution was assayed repeatedly (n=6), the relative error (accuracy) and coefficient of variation (precision) were found to be 0.25% and 1.1% respectively. No interference from excipients used was observed.

Preparation of Solid Dispersions of Ritonavir in Bentonite

Solid dispersions of ritonavir and MMT were prepared in 1:1 (SD-1), 1:2 (SD-2), 1:4 (SD-3) and 1:7 (SD-4) ratios of drug: carrier by solvent evaporation method. Ritonavir (1 g) was dissolved in dichloromethane (10 mL) in a dry mortar to get a clear solution. MMT (1 g) was then added and mixed. The thick slurry was triturated for 15 min for complete evaporation of dichloromethane and then dried at 55^{0}C until dry. The dried mass was pulverized and sieved through mesh no. 100.

Preparation of Ritonavir-SD Tablets

Compressed tablets (TF1-TF5) each containing 50 mg of ritonavir were prepared by wet granulation method employing ritonavir alone and its solid dispersions (SD-1, SD-2, SD-3 and SD-4) in MMT. Lactose was used as diluent to adjust the weight of the tablet to 200 mg. acacia (2%), talc (2%) and magnesium stearate (2%) were incorporated respectively as binder and lubricants.

The tablet granules were prepared by wet granulation method and were compressed into tablets using rotary tablet machine Minipress- II (REMIK Ltd) and using 6-mm diameter concave

punches to get a tablet of 200 mg weight. In each batch 100 tablets were prepared.

Prior to compression, powder blends were evaluated for pre-compression parameters like Hausner's ratio [tapped/bulk density ratio using a tapped volumeter apparatus (Copley Scientific, UK)], Carr's compressibility index[5], and static angle of repose. To measure the angle of repose, 10 mL of powder was poured through a glass funnel onto a flat surface and the angle to the horizontal was measured. The measurements were performed in triplicate.

Differential Scanning Calorimetry

The DSC thermograms of ritonavir, MMT and mixture of ritonavir and MMT (1:1) were generated by a differential scanning calorimeter (Shiamdzu, Japan) at heating rate of 20 °C/min from 0 to 500 °C. Accurately 12 mg of sample was taken in a standard pan and placed at sample stage. Nitrogen flow was set at 50cm^3/min and the nitrogen flow rate to the chamber was 80 cm^3/min.

Drug-Excipient interaction studies

Drug, excipients and physical mixtures were subjected to IR spectral studies using FTIR spectrophotometer (BRUKER Optics Inc, Billerica MS, US).

Characterization of tablets

Physical properties of the tablets were determined according to the USP 24 methods[6]. Weight variation was performed on 20 tablets selected at random. Hardness of the tablets was measured by recording the force to fracture a tablet on a hardness tester for 6 tablets from each formulation (SCHNEUNIGER). Friability was determined using Roche friabilator for 20 tablets at 100 rpm for 4 minutes. Six tablets were tested from each formulation for disintegration time at 37 ± 0.5 °C in water (ELECTROLAB – ED-2L). For determination of drug content, a total of 10 tablets were weighed and powdered. A powder mass equivalent to 50 mg of ritonavir was weighed, dissolved in 0.1N hydrochloric acid and filtered. The filtrate was collected, diluted suitably and analyzed for the content of ritonavir by UV- Double beam spectrophotometer at 238 nm (LABINDIA® UV-3000).

In vitro release study

The *in vitro* dissolution study was carried out according to the USP 24 specifications[6] with Apparatus II (n = 6) using an Electrolab dissolution apparatus TDT-08L. The dissolution medium consisted of 900 mL of 0.1N hydrochloric acid solution maintained at 37 ± 0.5 °C and stirred at 50 rpm. Aliquot samples (5 mL) were withdrawn at predetermined intervals, filtered through a 0.45-µm membrane filter (Millipore, USA) and replaced by an equivalent volume of fresh dissolution medium. The samples were suitably diluted and the amount of the drug dissolved was analyzed spectrophotometrically at 238 nm.

RESULTS AND DISCUSSION

As montmorillonite, a chemically modified bentonite was found to be insoluble in water and has good swelling property without pasting or gelling when heated in water it is considered as a promising carrier for solid dispersions for enhancing the dissolution rate of poorly soluble drugs. Solid dispersions of ritonavir in montmorillonite were prepared by solvent evaporation method employing various weight ratios of drug: montmorillonite.

All the solid dispersions prepared were found to be fine and free flowing powders with an angle of repose in the range $19^O - 21^O$. Low C.V (< 1.0%) in the percent drug content indicated uniformity of drug content in each batch of solid dispersions prepared.

Prior to compression, the powder blends were evaluated for the most important parameters referring to flowability and compression. Table no.1 shows the pre-compression parameters of the powder blends used in the compression of ritonavir tablets. The blends were found to have passable flowability as determined by Hausner's ratio, compressibility index and angle of repose. The compressibility index ranged from 22.93 to 25 %. Compressibility index values of up to 20 % generally indicate fair flow properties in regard to compressibility-flowability correlation data. Hausner's ratio was higher than 1 and the angle of repose ranged from 19–21° for all the formulation blends. Therefore, the values of pre-compression parameters were within the prescribed limits and indicated free flow properties.

DSC studies had also been carried out in order to predict any energy level changes that might interfere with the formulations behavior. Figure 1 clearly shows that pure ritonavir showed a sharp endothermic peak at 124^0 C showing its crystalline nature. Ritonavir containing montmorillonite physical mixture showed a peak between 123 to 125^0 C. Slight difference is due to the intercalation of drug into the clay material. Intercalation of ritonavir into montmorillonite did not influence the thermal properties.

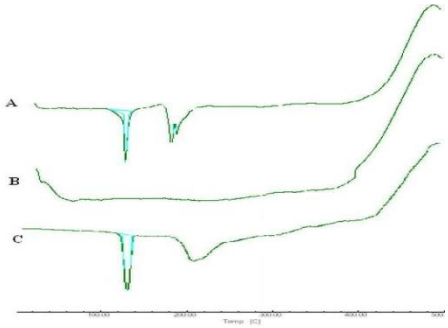

Figure 1: Differential Scanning Calorimetry. DSC thermogram of A- Ritonavir, B- Montmorillonite, C- Ritonavir and Montmorillonite physical mixture (1:1).

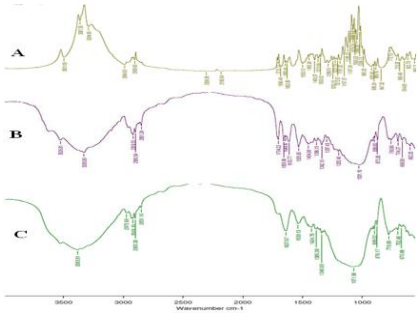

Figure 2: Fourier transforms Infrared spectroscopy. A- IR Spectra of ritonavir, B- IR Spectra of Montmorillonite, C- IR Spectra of ritonavir and montmorillonite physical mixture.

The FT-IR spectral analysis of ritonavir spectra showed characteristic absorption band at 2909.66cm^{-1} (C-H). The physical mixture of drug and montmorillonite spectra showed characteristic absorption bonds at 2900.36cm^{-1} (C-H) as shown in Figure 2. It indicates the absence of drug-excipient interactions. Data from FTIR and DSC studies shows compatibility between drug and clay material ruling out any interaction.

The feasibility of formulating ritonavir solid dispersions in montmorillonite into tablets retaining their rapid and higher dissolution rates was investigated. Ritonavir (50 mg) tablets were prepared employing ritonavir alone and its solid dispersions (SD-1, SD-2, SD-3 and SD-4) by wet granulation method and were evaluated.

The hardness test indicated good mechanical strength with non-significant differences in all formulations. All the tablets showed good mechanical resistance, as indicated by the friability test where it was less than 1 % for all tablets. Drug content was found to be consistent and almost uniform in all tablet formulations (>98 %) and no significant statistical mass variability was observed in the produced tablets. Therefore, our results, as indicated by the post-compression parameters presented in Table no.2, showed that an excellent degree of uniformity was achieved for all prepared tablet formulations. Tablets formulated employing solid dispersions

disintegrated rapidly with in 3.30 min. Tablets formulated employing ritonavir pure drug disintegrated within 5-6 min. As such all the ritonavir tablets prepared were of good quality with regard to drug content, friability, hardness and disintegration time and fulfilled the official (IP) specifications of uncoated tablets.

The dissolution data were analyzed as per zero order and first order kinetics in each case. The R^2 values were higher in the first order model than in the zero order models indicating that the dissolution of prepared ritonavir tablets followed first order kinetics with correlation coefficient 'R^2' values > 0.938. The corresponding dissolution rate (K_1) values of various products were estimated.

Dissolution of ritonavir is presented as cumulative percent released over time from tablets formulated employing its solid dispersions in montmorillonite. The dissolution parameters of the prepared tablets were given in Table 3. Ritonavir tablets formulated employing its solid dispersions in montmorillonite (TF2-TF5) gave rapid and higher dissolution rate when compared to plain (TF1) tablets. A 14, 8 and 12 fold increase in the dissolution rate (k_1) was observed with tablet formulations TF2, TF3 and TF4 when compared to formulation TF1. Thus solid dispersions of ritonavir in montmorillonite could be formulated into compressed tablets retaining their fast dissolution characteristics and fulfilling official standards.

Table 1: Pre-compression parameters of the powder blends

Formulations	Hausner's ratio	Carr's index	Angle of repose (^{0})
TF1	1.19	23.64	20.12
TF2	1.20	22.93	19.08
TF3	1.23	24.71	19.92
TF4	1.20	24.25	20.24
TF5	1.22	24.31	20.18

Table 2: Characterization of ritonavir tablets

Formulations	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (mins)	Content uniformity
TF1	201	3.3	0.49	5.86	98.26
TF2	199	3.5	0.36	3.30	98.46
TF3	199	3.4	0.56	2.50	99.02
TF4	200	3.3	0.24	3.05	99.38
TF5	198	3.2	0.37	2.10	98.36

Table3:Dissolution parameters of ritonavir tablets formulated employing ritonavir alone and its solid dispersions in montmorillonite

Formulation	r^2	K_1 (min^{-1})	Increase in K_1 (No of Folds)
TF1	0.962	0.059	-
TF2	0.986	0.845	14
TF3	0.983	0.732	12
TF4	0.939	0.477	8
TF5	0.943	0.080	-

CONCLUSION

Ritonavir tablets formulated employing its solid dispersions in montmorillonite also gave rapid and higher dissolution rate when compared to plain tablet. A 14, 8 and 12 fold increase in the dissolution rate (K_1) was observed with tablet formulations containing solid dispersions prepared at 1:1, 1:2 and 1:4 ratios respectively when compared to plain tablets. Solid dispersions of ritonavir prepared employing montmorillonite as carrier showed marked enhancement in the dissolution rate (K_1) of ritonavir. These solid dispersions could be formulated into compressed tablets retaining their fast dissolution characteristics and fulfilling official (I.P.) standards.

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DECLARATION OF INTEREST

The authors report no declarations of interest.

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