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PREPARATION AND EVALUATION OF TERNARY MIXING ITRACONAZOLE SOLID DISPERSIONS BY SPRAY DRYING METHOD

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Abstract

The present study aims to experiment the solid dispersion of poorly water soluble drug itraconazole as model drug by spray drying method with the use of PEG/HPMC polymer blends, the influence of polymer compatibility on the degree of molecular dispersion of itraconazole solid dispersions are prepared by ternary mixing and polymer blends are also evaluated for DSC, XRD and in vitro dissolution testing. Thermal analysis of DSC and XRD graphs were analysed to evaluate the status of glass transition state ternary solid dispersion phases. Among the formulations with 15/85 (w/w) PEG/HPMC ratio was found better amorphous nature in relation with invitro release.

Introduction

The current status of scientific development also get highly variable oral bioavailability of drugs due to low solubility and or dissolution rate in the gastrointestinal absorption of many new drugs. Even though there are many methods intended to solve the problem in which the formulation of solid dispersion is one of the ideal methods to experiment. The solid dispersions as a dispersion of one or more active ingredients in an inert carrier or matrix, prepared by the melting, solvent, or melting solvent method [1]. The increase in dissolution rate and solubility provided by solid dispersions can be explained by the mechanisms described by the Noyes–whitney equation [2]. A significant particle size reduction can be obtained by manufacturing solid dispersions and in many cases the drug is molecularly dispersed in the carrier. Conversion of the physicochemical state of the drug, e.g. from crystalline to amorphous, as well as solubilization and supersaturation by the carrier, can cause an increase in the kinetic solubility and the dissolution rate [3].

Itraconazole is a potent synthetic triazole antifungal drug with activities against broad spectrum of fungal species [4,5]. It has a molecular formula $C_{35}H_{38}C_{l2}N_8O_4$, molecular weight of 705.64, and is a weak basic drug, possessing extremely low water solubility (*S*~1 ng/ml at neutral pH and *S*~ 6ng/ml at pH 1), and p*K*a of 3.7 [6]. The mechanism of action of this compound is similar to all other azole antifungals. It inhibits cytochrome P450 of the fungi and thus interferes in sterol biosynthesis in cell membrane, leading to cell death [7]. According to the biopharmaceutics classification system, itraconazole is an extreme example of a class II compound meaning that its oral bioavailability is determined by dissolution rate in the GI tract [8,9,10].

Although the use of solid disperse technique for solubility enhancement of itraconazole has been reported by several authors [11], there are only two main methods for the solid dispersion preparation: solvent casting and melt extrusion. Solid state transformations of the crystalline drug to polymorphic modifications or to the amorphous state might lead to an increase in

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its apparent solubility [12]. It is known that in solid dispersions with PEG the drug tends to reside in the amorphous domains of the carrier [13].

The objective of present study to formulate and investigate the feasibility to enhance the dissolution rate of itraconazole by using solid dispersions.

Materials

Crystalline Itraconazole (M/s Signet chemicals, Mumbai). Hydroxypropyl methylcellulose 2910 E5,Dow (Mumbai) India. Polyethyleneglycol 6000, va-sudha chemicals, India. Methanol was HPLC grade and other reagents were analytical grade.

Methods

Spray drying

Ternary dispersions of Itraconazole are prepared with blends of PEG 6000 and HPMC (Table 1) in Buchi mini spray dryer B191 (Buchi, Flawil, Switzerland). The powders were spray dried from a 5% solution of the powder blend in methanol or methylene chloride (50/50), the inlet temperature was set at 80 ºC and the outlet temperature varied from 50 to 35 º C. The aspirator was set at 100%, the pump 45%, air flow 800 L/h.

Table 1 Composition Of Polymer Mixing Ration And Ternary Solid Dispersions

Polymer Mixing ratio	Ternary Solid Dispersions	
10 / 90 (w/w) PEG / HPMC	20% itraconazole in 10 / 90 (w/w) PEG / HPMC	40% itraconazole in 10 / 90 (w/w) PEG / HPMC
15 / 85 (w/w) PEG / HPMC	20% itraconazole in 15 / 85 (w/w) PEG / HPMC	40% itraconazole in 15 / 85 (w/w) PEG / HPMC
20 / 80 (w/w) PEG / HPMC	20% itraconazole in 20 / 80 (w/w) PEG / HPMC	40% itraconazole in 20 / 80 (w/w) PEG / HPMC
25/ 75 (w/w) PEG / HPMC	20% itraconazole in 25/ 75 (w/w) PEG / HPMC	40% itraconazole in 25/ 75 (w/w) PEG / HPMC
30/70 (w/w) PEG / HPMC	20% itraconazole in 30/70 (w/w) PEG / HPMC	40% itraconazole in 30/70 (w/w) PEG / HPMC

Differential scanning calorimetry (DSC)

Thermal analysis of itraconazole, the physical mixtures of PEG/HPMC, and the solid dispersions ere carried out using differential scanning calorimetric method, (Shimadzu TGA-50 DSC instrument, Shimadzu Corporation, Japan). Samples equivalent to approximately 8mg itraconazole were placed in aluminum pans and heated from 25 to 200 ºC with a heating rate of 10°C/min.

X-ray diffraction

X-ray diffraction was analysed for HPMC, PEG and Itraconazole separately, then with binary polymer mix and ternary solid dispersion using ,Philips PW 170 system, Philips USA with Cu-$K_{2\alpha}$ radiation (40KV, 30 mA, scan speed 1º/Min)

In vitro release study

In vitro drug release was carried out using an USP 24 Type 2 dissolution testing apparatus (paddle method). 0.4% HCl used as the dissolution media. Paddle speed of 100 rpm and at 37±0.5ºC.Samples equivalent 100 mg itraconazole were added directly into the dissolution medium. The dissolution process was monitored for 2 hr 30 mins and samples were withdrawn after 30, 60, 90,120 and 150 mins and dissolution medium was replaced with an equal volume of the same fresh medium.

Results and Discussion

Differential scanning calorimetry (DSC)

The differential scanning calorimetric was performed individually with drug, polymer blends and solid dispersions (figure 1). The sharp endothermic peaks were observed for itraconazole pure drug and PEG 6000. In the presence of PEG 6000 melting peaks were between 55ºC and 65ºC, indicating the presence of separate crystalline phase separately. The physical mixture of polymer mixture also showed endothermic deviation as appearance of a transition. These have bound change in the transition temperature, peak shape and area by virtue of solid dispersion of ternary mixing. The dissolved transition levels of the DSC graphs of spray dried ternary solid dispersion were found to be effective in amorphous condition, when compared to crystalline nature existed in the PEG and itraconazole.

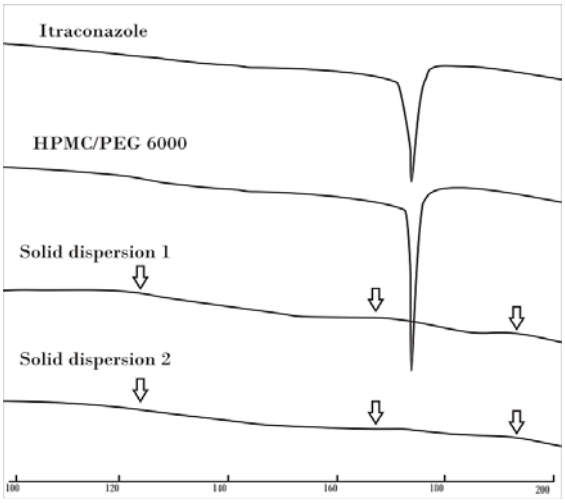

Figure: 1 DSC Overlay Graphs

X-ray diffraction

The XRD study of PEG and HPMC polymer blend compatibility on the degree of molecular dispersions was observed with itraconazole solid dispersion polymer blend, the PEG concentration in HPMC from 5-30% were prepared and subjected to XRD. The X ray diffraction peaks were indicating the presence of crystalline phase (figure 2). A diffrectrograph overlay of HPMC/PEG/Itraconazole is shown in figure 2. The clearly visible sharp diffraction peaks of itraconazole, PEG and HPMC were reduced when they prepared as ternary solid dispersion to form amorphous condition from the partial crystalline nature of materials.

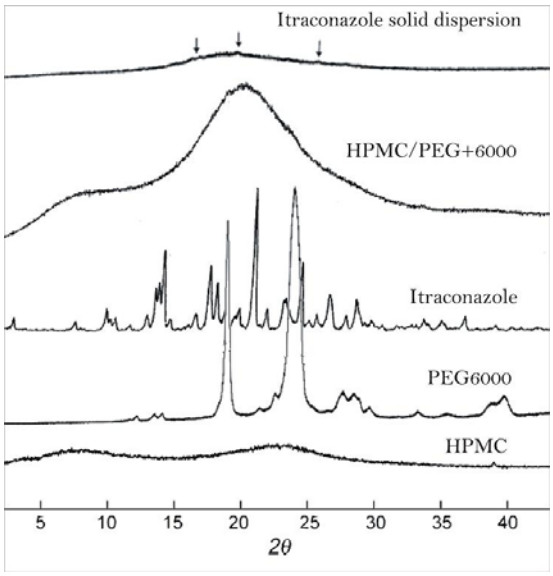

Figure: 2 XRD over lay graphs

In vitro release study

The dissolution profiles of the samples containing 20% of itraconazole in 15/85 (w/w), 20/80 (w/w) and 25/75 (w/w) PEG 6000/HPMC blends shown in Fig. 3. For all samples with 20% of itraconazole dissolution profile was maintained around 95 to 100%, which agrees with the fact that in all of these samples itraconazole was completely amorphous. Series of samples containing 40% of itraconazole in 15/85 (w/w), 20/80 (w/w) and 25/75 (w/w) PEG 6000/HPMC 2910 E5 blends shown in Fig. 3. Dissolution profile was maintained about 50 to 60%. The release was observed when a decrease with ternary solid dispersion mixers was found due to different degrees of crystallinity.

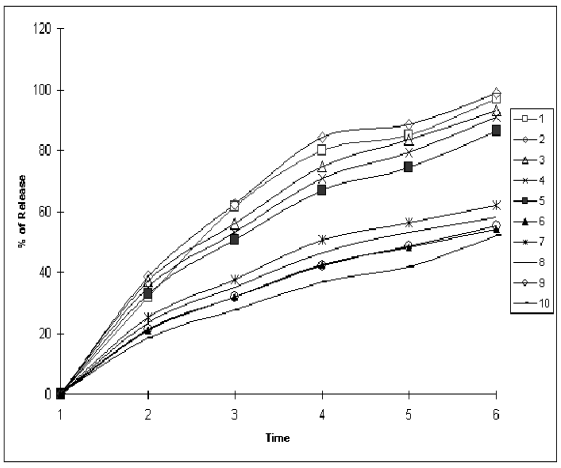

Figure 3: dissolution release of itraconazole solid dispersions

Conclusion

The current study of widely prescribed drug itraconazole a poorly soluble drug, to enhance dissolution rate and bioavailability through the solid dispersion was successfully prepared by Spray drying method. Prepared solid dispersion was evaluated for drug physical state of the drug, drug – carrier interactions, dissolution rate. The addition of itraconazole with polymer blend of PEG and HPMC was effective with respect to the concentration of drug polymer ratio. The ternary preparation solid dispersion containing 20% itraconazole with 10-15% of PEG and HPMC 85-90% dissolution was found to be around 95%. 40% itraconazole with 10-15%PEG and 85-90% HPMC dissolution release was found to be 40-60%, the results of the investigation revealed the usefulness of the PEG/ HPMC as efficient carriers for enhancing the dissolution rate and oral bioavailability of poorly soluble drugs.

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