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Research Article

ENHANCEMENT OF DISSOLUTION RATE OF KETOCONAZOLE BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. In the present investigation, an attempt were made to improve the solubility and dissolution rate of a poorly soluble drug, Ketoconazole by solid dispersion method using mannitol, polyethylene glycol (PEG) 4000 and polyethylene glycol 6000, polyvinyl pyrrolidone K-30, ß-cyclodextrin as carrier. Solid dispersion of Ketoconazole was prepared by fusion, solvent evaporation, melt solvent and kneading method. In vitro release profiles of all Solid dispersions were comparatively evaluated and also studied against pure Ketoconazole. Faster dissolution was exhibited by F10, Solid dispersion containing 1:1 ratio of drug : ß-cyclodextrin by Solvent evaporation method. The prepared Solid dispersions were subjected for percent practical yield, drug content, infra red (I.R.) spectroscopic studies and differential scanning calorimetry (DSC). FT-IR spectra revealed no chemical incompatibility between drug and ß-cyclodextrin. Drug - polymer interaction were investigated using differential scanning calorimetry (DSC).

Keywords: Ketoconazole, Solid dispersion, Mannitol, PEG - 4000, PEG - 6000, PVP K-30, ß-cyclodextrin.

INTRODUCTION

Poorly water-soluble drugs present many difficulties in the development of pharmaceutical dosage forms due to their limited water solubility, slow dissolution rate and low bioavailability. Solid dispersions have been widely reported as an effective method for enhancing the dissolution rate and bioavailability of poorly water soluble drugs.[1] The dissolution rate is directly proportional to solubility of drug.[2] The term 'solid dispersion' refers to the dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by the fusion, solvent evaporation and melt solvent methods.[3] The release mechanism of drug from a variety of solid dispersions depends on the physical properties of carriers as well as drug substances and preparation methods.[2]

Ketoconazole was used as a model drug, which is an anti-fungal agent with topical and systemic action that can be incorporated into several pharmaceutical forms.[4] It is a recent synthetic triazole antifungal agent used in the treatment of superficial and systemic fungal infections such as, tinea corporis, tinea cruris, tinea manus and tinea pedis caused due to Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum canis and for the treatment of seborrheic dermatitis.[5] Due to its dissolution and absorption properties, Ketoconazole is classified in the Biopharmaceutics Classification Scheme as a class II drug, since it has a high permeability, but a solubility in aqueous media which is insufficient for the whole dose to be dissolved in the gastro-intestinal fluids under normal conditions.[6]

The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Ketoconazole by preparing Solid dispersion with various water soluble polymers such as mannitol, polyethylene glycol-4000, polyethylene glycol-6000, polyvinyl pyrrolidone K-30, and ß-cyclodextrin.

The prepared Solid dispersions were evaluated for % practical yield, drug content, in- vitro dissolution rate studies and interactions between the drug and polymer using IR spectral studies and differential scanning calorimetry.

MATERIALS

Ketoconazole was received as gift sample from FDC Limited, Raigad, India. Mannitol, Polyethylene glycol 4000 LR, and Methanol (sd fine-chem. Limited, Mumbai), Polyvinyl pyrrolidone K-30, ß-cyclodextrin (Hi-Media Laboratories Pvt. Ltd., Mumbai), Polyethylene glycol 6000 (Loba Chem. Pvt. Ltd., Mumbai) were procured from commercial sources. All other chemicals and reagents used in this study were of analytical grade.

METHODS

Preparation of solid dispersions

Solid dispersions were prepared by mixing various polymers and different methods as shown in Table-1.

Physical mixture

Physical mixtures were prepared by mixing the appropriate amount of Ketoconazole and polymer in mortar and pestle and pass through sieve # 60.[7]

Fusion method

Accurately weighed amount of PEG-4000, and PEG-6000, were melted in a porcelain dish at 80-85°C and to this calculated amount of Ketoconazole were added with though mixing for 1-2 min followed by quick cooling.[8] It were kept in a dessicator under vacuum for 24 hrs. Then, solid dispersion formulations were pulverized using a porcelain mortar and pestle. The pulverized powder were classified using the sieve # 60.[9]

Solvent evaporation method

The drug and the excipients were dissolved in sufficient volume of methanol with continuous stirring. The solvent was then completely evaporated at 40-45°C with continuous stirring to obtain dry granules.[8] The resulting solid dispersion were stored in airtight container till further use.

Melt solvent method

Accurately weighed amount of Ketoconazole was dissolved in chloroform (10 ml) and the solution was incorporated into the melt of different polymer by pouring slowly into hot melt with vigorous stirring. The melt was cooled immediately and the mass was kept under vacuum in a dessicator for 24 hrs. The solidified mass scrapped, crushed, pulverized and passed through 60/80 mesh.[10]

Kneading method

ß-cyclodextrin was added to the mortar, and small quantities of 50% V/V ethanol were added while triturating to get slurry like consistency. Then slowly the drug was incorporated into the slurry, and trituration was continued further for 1 hr. The slurry was then air dried at 25°C for 24 hrs. Pulverized, and passed through sieve # 100 and stored in a dessicator over fused calcium chloride.[11]

Table 1: Formulation ingredients, preparation method of Ketoconazole solid dispersions

Batch Code	Composition	Method	Ratio
F1	Ketoconazole + Mannitol	Physical mixture	1:1
F2	Ketoconazole + PEG 4000	Physical mixture	1:1
F3	Ketoconazole + PEG 6000	Physical mixture	1:1
F4	Ketoconazole + PVP – K30	Physical mixture	1:1
F5	Ketoconazole + ß-cyclodextrin	Physical mixture	1:1
F6	Ketoconazole + Mannitol	Solvent evaporation method	1:1
F7	Ketoconazole + PEG 4000	Solvent evaporation method	1:1
F8	Ketoconazole + PEG 6000	Solvent evaporation method	1:1
F9	Ketoconazole + PVP – K30	Solvent evaporation method	1:0.1
F10	Ketoconazole + ß-cyclodextrin	Solvent evaporation method	1:1
F11	Ketoconazole + PEG 4000	Fusion method	1:1
F12	Ketoconazole + PEG 6000	Fusion method	1:1
F13	Ketoconazole + PEG 4000	Melt solvent	1:1
F14	Ketoconazole + PEG 6000	Melt solvent	1:1
F15	Ketoconazole + ß-cyclodextrin	Kneading method	1:1

Evaluation of ketoconazole solid dispersions

Percent practical yield (PY) [12]

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

PY (%) = [Practical Mass (Solid dispersion) / Theoretical Mass (Drug + Carrier)] × 100

Drug content [13]

The Physical mixture and solid dispersion equivalent to 25 mg of model drug were taken and dissolved separately in 25 ml of methanol. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were determined at 223 nm by UV-visible spectrophotometer. The actual drug content was calculated using the following equation as follows:

% Drug content = Actual Ketoconazole content in weight quantity of solid dispersion/ Theoretical amount of Ketoconazole solid dispersion x 100

In-Vitro dissolution study [14]

Dissolution studies were performed assuring sink condition according to the paddle method (USP) using USP XXIII apparatus type-II (electrolab TDT-O9T). The dissolution medium was 900 ml 7.4 pH phosphate buffer kept at 37°C ± 0.5°C. The solid dispersions containing 100 mg of Ketoconazole was taken in a muslin cloth and tied to the rotating paddle kept in the basket of dissolution apparatus, the paddle was rotated at 100 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed

spectrophotometrically at 223 nm using Shimadzu-1700 UV-visible spectrophotometer. The samples withdrawn were replaced by fresh buffer solution. Each preparation was tested in triplicate and then mean values were calculated.

Infrared spectroscopy (IR) [15]

FT-IR spectra of pure Ketoconazole, ß-cyclodextrin, with its solid dispersions were obtained by Perkin-Elmer FT-IR spectrophotometer using potassium bromide (KBr) pellets. KBr pellets were prepared by gently mixing the sample with KBr (1:100). The sample was scanned from 4,000 to 400 cm^{-1}.

Differential scanning calorimetry (DSC) [16]

Thermal analysis of Ketoconazole, ß-cyclodextrin, and the solid dispersion were carried out using differential scanning calorimetry method. Samples were examined using a Shimadzu TGA- 50 DSC instrument. Samples equivalent to approximately 8 mg Ketoconazole were placed in aluminum pans and heated from 40 to 250°C with a heating rate of 10°C/min.

RESULTS AND DISCUSSION

Solid dispersions of Ketoconazole were prepared by different methods using carriers like mannitol, PEG-4000, PEG-6000, PVPK-30, and ß-cyclodextrin. In the present work, total 15 formulations were prepared and their complete composition is shown in Table-1. All the Solid dispersions prepared were found to be fine and free flowing powders.

Percent practical yield

The results of percent practical yield studies are shown in Figure 1. The % Practical yield of the prepared solid dispersions was found to be in the range of 85.50 - 96.05% . The maximum yield was found 96.05% in F10 formulation.

Drug content

The actual drug content of all the 15 formulations are shown in Figure 2. The drug content of the prepared Solid dispersions were in the range of 86.64 - 100.40% indicating the application of the present methods for the preparation of Solid dispersions with high content uniformity. The maximum % drug content was found 100.40% in F10 formulation.

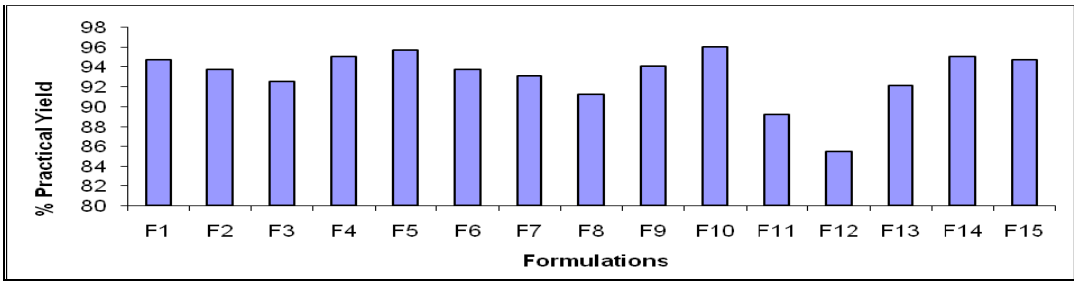

Fig. 1: Percent Practical Yield of Different Formulation of Ketoconazole Solid dispersions

In vitro dissolution study

Drug release from solid dispersions and physical mixture was faster than pure drug, Figure 3 & 4 are the plots of cumulative percent drug released as a function of time for different formulations.

Cumulative percent drug released after 80 minutes were 41.50, 47.28, 41.77, 48.35, 56.44, 85.50, 91.19, 92.86, 88.17, 98.48, 84.97, 87.64, 89.86, 87.82, and 90.13 for F1 to F15 formulations respectively, while it was 40.61% in 80 minutes for pure drug Ketoconazole.

In vitro release study revealed that there was a marked increase in the dissolution rate of Ketoconazole from all solid dispersions when compared to pure Ketoconazole. From the in-vitro drug release profile, it can be seen that formulation F10 containing ß-cyclodextrin (1:1 ratio of drug : ß-cyclodextrin) shows higher dissolution rate compared with other formulations. The increase in dissolution rate was in the order of ß-cyclodextrin > PEG-6000 > PEG-4000 > Mannitol > PVPK-30.

Infrared spectroscopy (IR)

IR spectroscopic studies were conducted to determine possible drug: carrier interactions. IR spectra of pure drug Ketoconazole, ß-cyclodextrin, and Ketoconazole with its Solid dispersion were obtained which shows all the characteristic peaks of Ketoconazole and carrier was present in the Solid dispersion, thus indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion. The result of IR study shown in Figure 5.

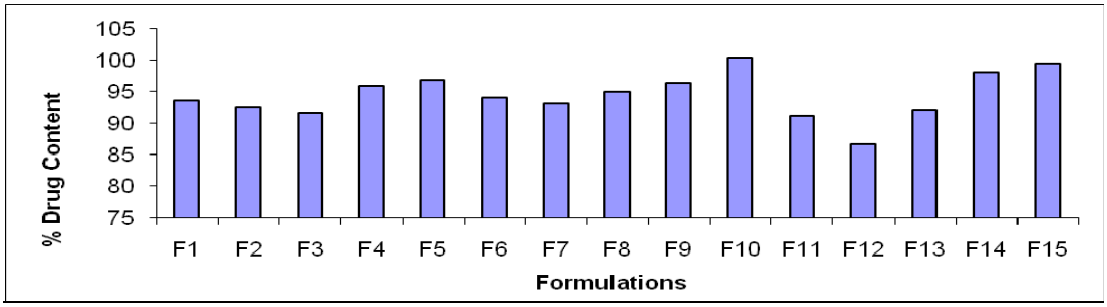

Fig. 2: Percent drug content of different formulation of Ketoconazole solid dispersions

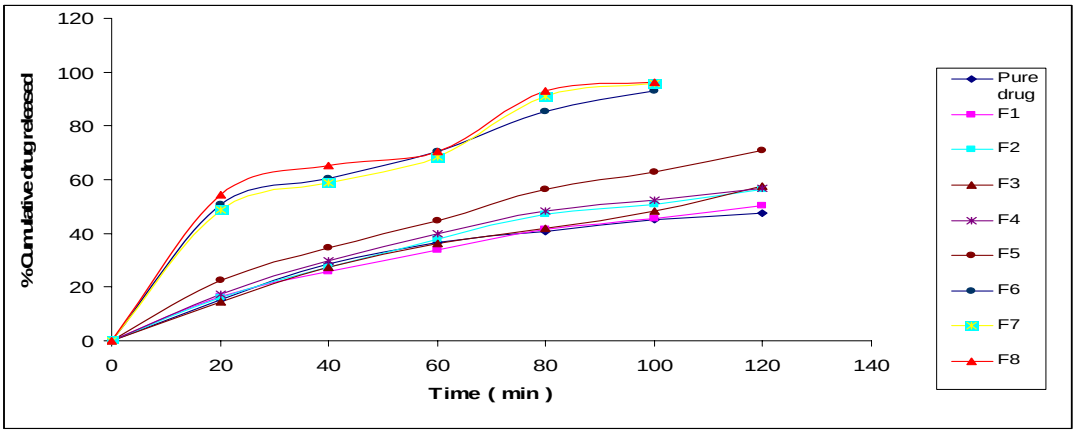

Fig. 3: In-Vitro Dissolution Profile of Pure drug and solid dispersions

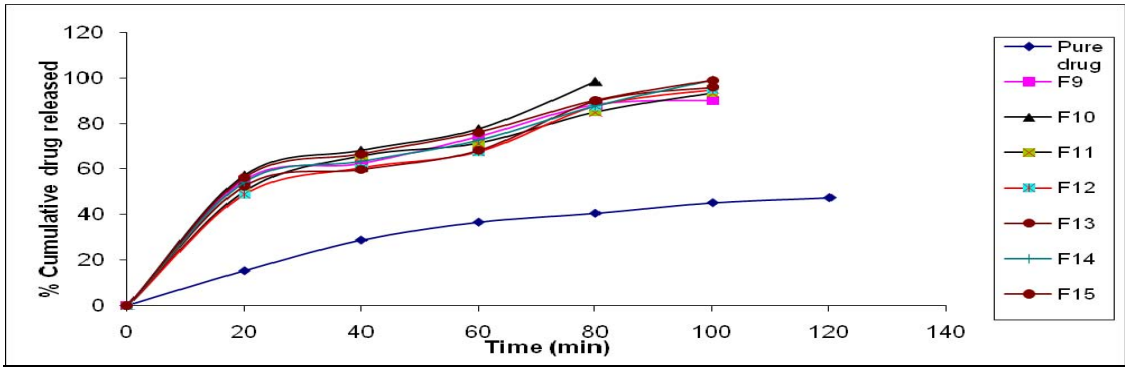

Fig. 4: In-Vitro Dissolution Profile of Pure drug and solid dispersions

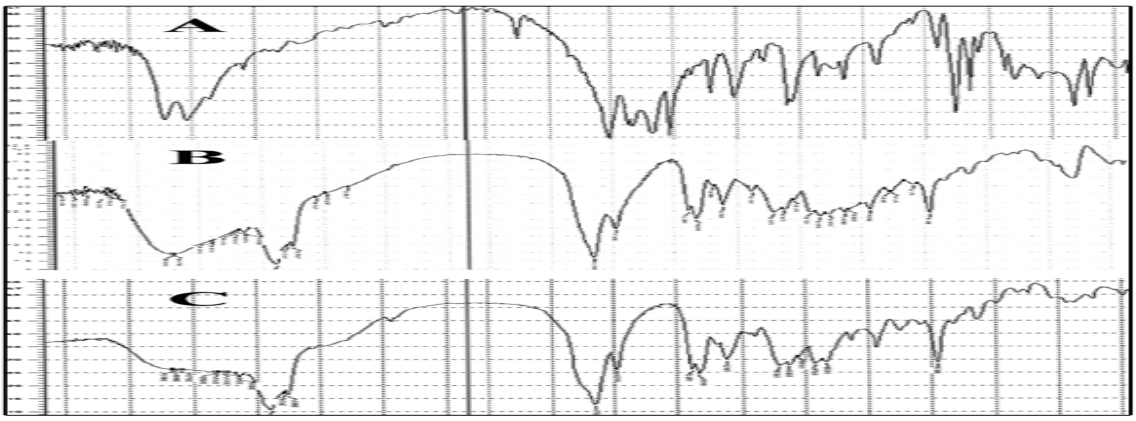

Fig. 5: IR spectra of pure drug and formulation. A = Ketoconazole (Pure drug), B = ß-cyclodextrin, C = F10 (Ketoconazole: ß-cyclodextrin, 1:1, solvent evaporation method)

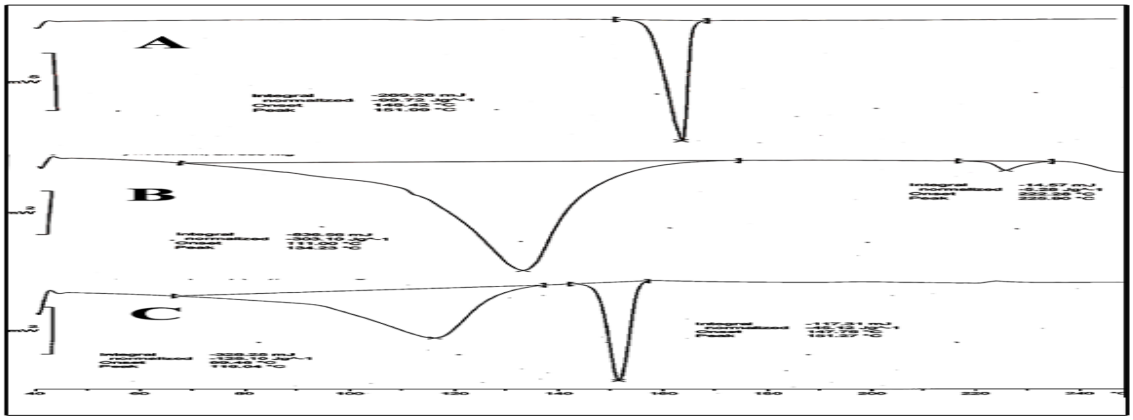

Fig. 6: DSC thermogram of A = Ketoconazole, B = ß-cyclodextrin, C = F10 formulations

Differential scanning calorimetry

The thermal behavior of the ß-cyclodextrin inclusion complexes was studied using differential scanning calorimetry in order to confirm the formation of solid inclusion complexes. When guest molecules are incorporated in the ß-cyclodextrin cavity or in the crystal lattice, their melting, boiling, and sublimation points usually are shifted to a different temperature or disappear within the temperature range in which the ß-cyclodextrin lattice is decomposed. The DSC shows sharp endothermic fusion peak at 151.27˚C, which is corresponding to the melting point of Ketoconazole. (Figure 6)

CONCLUSION

The objective of the present study was to improve the solubility and dissolution behaviour of the poorly soluble drug, Ketoconazole by solid dispersion technique using mannitol, PEG-4000, PEG-6000, PVPK-30, and ß-cyclodextrin as carrier. The solvent evaporation method of preparing solid dispersions was found to be satisfactory as it produced good product with high drug content. Out of the 15 formulations prepared formulation F10 showed marked increase in the solubility as well as the dissolution when compared to pure drug. The IR study showed no signs of interactions of the drug with the carrier. Thus it can be concluded that the solubility of the poorly soluble drug, Ketoconazole can be improved markedly by using solid dispersion technique and the carrier ß-cyclodextrin has increased the dissolution of the drug without any interaction.

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