WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.647
Volume 6, Issue 5, 945-950 Research Article ISSN 2278 – 4357

SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG TINIDAZOLE BY SOLID DISPERSION TECHNIQUE

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Article Received on
06 March. 2017,

Revised on 26 March 2017,
Accepted on 16 April 2017

DOI: 10.20959/wjpps20175-9101

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ABSTRACT

Tinidazole is nitro imidazole derivative, anti-parasitic drug against protozoan infection. It is used as tissue amoebic ides for both intestinal and extra intestinal amoebiasis. It has broad spectrum cidal activity against protozoa including giardia lamblia many anaerobic bacteria such as fragilis, fusobacterium, clostridium perfrigens, and helicobacter pylori. But as it is BCS class–II Drug, Dissolution from its dosage form is too low and rate limiting step in absorption of drug. The present study was aimed to increase the solubility of the poorly water soluble drug (Tinidazole) by using hydrophilic polymers (PEG 6000 and Mannitol). Solid dispersions were prepared by hot melt method. Phase solubility study, *in-vitro* dissolution of pure drug, physical mixtures and solid dispersions were carried out. PEG and Mannitol were found to be effective in increasing the dissolution of Tinidazole in solid dispersions when compared to pure drug. FT-IR spectroscopy studies were carried out in order to characterize the drug and solid dispersion.

KEY WORDS: Solid dispersion, Bioavailability, PEG 6000, Mannitol, Hot melt method.

INTRODUCTION

Poorly water soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability.[1] and nearly 40%of new chemical entities currently

being discovered are poorly water-soluble drug.[2] Based upon their permeability characteristics, the bio pharmaceutics classification system(BCS) classifies such drugs in two major classes i.e. Class II and IV.[3] The oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of these methods and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.[4]

Tinidazole is 1-[ethanesulphonyl)ethyl]-2-methyl-5-nitro-1H-imidazole, Molecular weight 247.269 g/mol is white or almost yellow crystalline powder, odorless, tasteless., M.P 126-128 ºC. It is slightly soluble in water, practically in soluble in most organic solvent; soluble in dilute.

There are several reports available on solid dispersions of pharmaceuticals with Polyethylene glycol which revealed that with increase in PEG content, crystallization was inhibited while solubility was enhanced. Mannitol It is freely soluble in Water (182 g/L at 25°); slightly soluble in Alkalis and Ethanol, practically insoluble in Ether and Glycerine.[5]

EXPERIMENTAL

Materials

A gift sample of Tinidazole was received from Badar Pharmaceuticals, PEG 6000 and Mannitol was obtained from S.D. fine chemical (India).

METHODS

Physical mixture of Tinidazole

Physical mixtures of Tinidazole at three different mass ratios (1:1, 1:2, and 1:3) were prepared. The mixtures were passed through a sieve no. 40. The prepared mixtures were then filled in glass bottles, sealed and stored in a desiccator until further use.[6]

Solid dispersion of Tinidazole

A mixture of drug and polymers in three different mass ratios are melted at a particular temperature in a china dish and the drug is then dispersed into the molten mixture with a

constant stirring. The molted mixture is then poured and cooled immediately to obtain the formed dispersion. The resulting mixture was sieved through a sieve no. 40 and stored in a dessicator until further evaluation.

Drug content

The drug content in each solid dispersion and physical mixture was determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 50 mg of Tinidazole, was transferred to a 100 ml volumetric flask containing 0.1N HCL. The solution was filtered through 0.45 mm membrane filter paper and from the same solution 1ml was diluted and the absorbance was measured at 275 nm.[7]

Phase Solubility Studies

The phase solubility studies were carried out according to the method reported by Higuchi and Connors. Excess amount of Tinidazole was added to the screw capped vials containing 20 ml of aqueous carrier solution (PEG 6000 and Mannitol) at various concentrations and placed on a rotatory shaker and agitated at room temperature for 48 hours. After equilibrium, the solutions were carefully filtered through Whatman No.41 filter paper and after appropriate dilution; solutions were analyzed at 275 nm by using UV- visible spectrophotometry.

Dissolution study

The dissolution study of pure drug, physical mixture and solid dispersion was carried out by using USP dissolution apparatus (type II) at 100 RPM at temperature of 37 ± 0.5°C using 900 ml volume of ml pH 1.2 and pH 7.4 used as the medium, equivalent 50 mg of drug were taken. Samples of 1 ml were withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analyzed spectrophotometric at 275 nm and the drug release was determined.[8]

RESULT AND DISCUSSION

The phase solubility studies were performed to determine stoichiometric proportions of Tinidazole and carriers- PEG 6000 and Mannitol. The effects of polymers concentration at room temperature on solubility are shown in Figure 1.

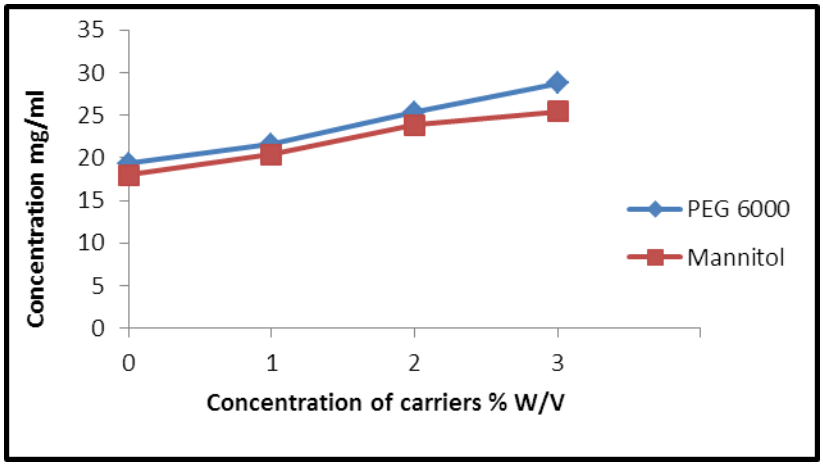

Figure 1: Results of Concentration of Carriers on Solubility of Tinidazole

The plot of drug solubility against polymer concentrations at room temperature indicated a linear relationship between drug and polymer solution. Both the type show AL type of plot i.e. the solubility of Tinidazole increased with increasing carrier concentration.

Dissolution of the pure drug, physical mixtures as well as solid dispersions of Tinidazole with PEG 6000 (equivalent to 50mg) was tested in acidic buffer (pH 1.2) and phosphate buffer (pH 7.4) for a period of 60 minutes. Dissolution of the pure drug, physical mixture and solid dispersion prepared by hot melt method in ratio of 1:3 was found to be 34.63 %, 45.63% in 60 min.and 101.80% in 40 minutes in acid buffer medium. Pure drug and physical mixtures shows almost same release, whereas the solid dispersion (1:3) shows 100% drug release in one hour. The solid dispersion prepared using ratio 1:1 and 1:2 showing corresponding drug releases that is 79.29% and 88.49% in 60 minutes as shown in fig 2.

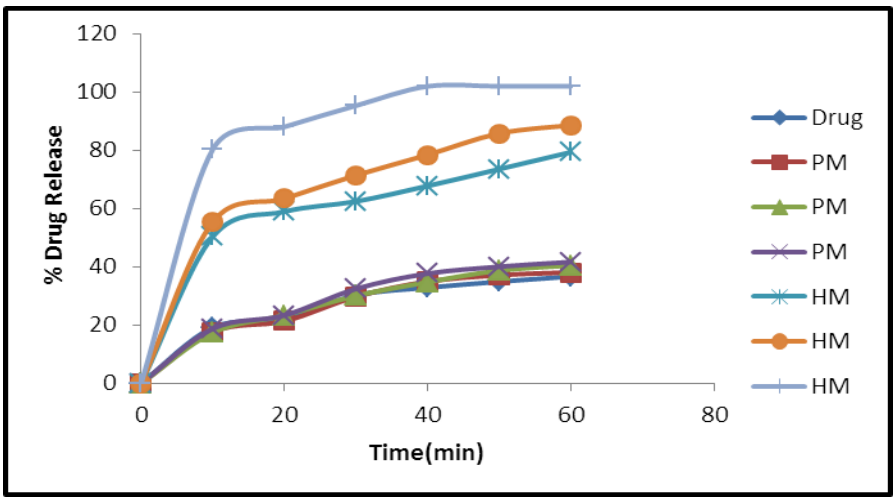

Figure 2: In-vitro Dissolution Profile of Tinidazole, PM and HM with PEG 6000 in pH 1.2

Similar study was carried out by preparing solid dispersion of Tinidazole with the Mannitol, the dissolution of pure drug, its physical mixture and solid dispersion prepared by hot melt method are 32.63%, 34.87% in 60 minutes and 100.99 % in 50 minutes respectively. The solid dispersion prepared in 1:3 ratio show the higher drug release in 50 minutes corresponding to other ratios that is 1:1and 1:2 which are 74.54%,81.50% in 60 minutes respectively in pH 1.2 as shown in Figure 3.

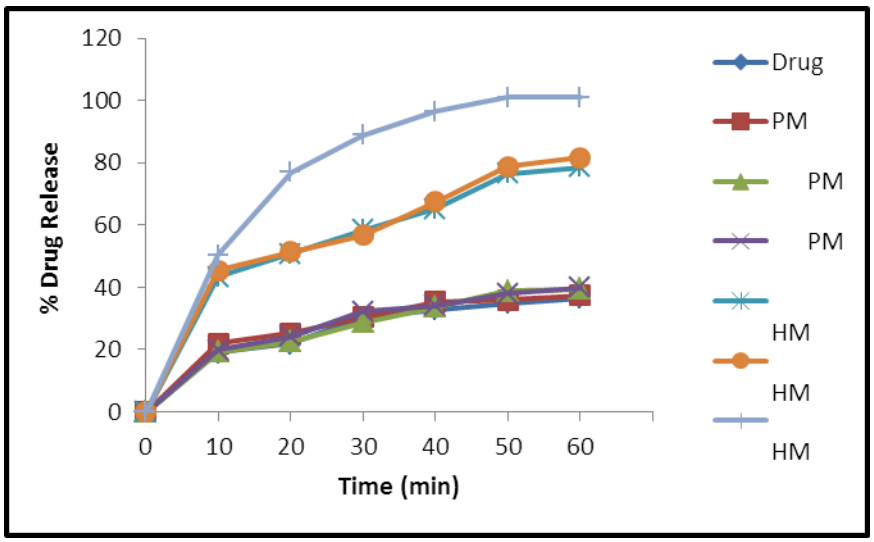

Figure 3: *In-vitro* Dissolution Profile of Tinidazole, PM and HM with Mannitol in pH 1.2

The drug content of physical mixture and solid dispersion prepared with PEG 6000 and Mannitol are shown in table no.1

Table no. 1 Analysis of Drug Content in PM and SD

	Drug Content
PM (PEG 6000)	95.25±0.34
SD (PEG 6000)	103.50±0.73
PEG6000(Mannitol)	93.38 ±0.03
SD (Mannitol)	99.92± 0.11

CONCLUSION

Increasing the drug carrier ratio from 1:1 to 1:3 improved drug release profiles observed in for all Formulations in case of Hot melt method with PEG 6000 and Mannitol but the drug release rate was higher in 1:3 ratio for both the polymers. The drug release was found to be better in solid dispersions prepared with PEG 6000 as compared to those prepared with Mannitol.

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