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Solid dispersions: A tool for improving the solubility and dissolution of metronidazole

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Abstract

Metronidazole is a broad spectrum antibiotic. It is sparingly soluble in water but has oral bioavailability of 93-95%. So solid dispersions (SDs) containing metronidazole was prepared in different ratios (1:1, 1:2 and 1:5) and using different carriers like dextrose, citric acid, polyethylene glycol (PEG-4000) and polyvinylpyrrolidone (PVP). Fusion or melting method was used for SD containing dextrose and citric acid and Solvent evaporation method was used for SD containing PVP and PEG-4000. The solubility studies revealed that solubility of metronidazole was enhanced to manifolds. Best result was exhibited when drug carrier ratio is in the order of 1:5>1:2>1:1. Among the different carriers, the solubility and dissolution was increased to maximum in case of PVP and PEG and almost 100 % drug released within 1 hour. The development of solid dispersions was further confirmed by DSC and XRD.

Keywords: Solid Dispersions; polyvinylpyrrolidone (PVP); Metronidazole

Introduction

Metronidazole, an anti-amoebic drug, is a prototype nitroimidazole derivative. It has broad spectrum of activity and acts by disrupting the DNA's helical structure, thereby inhibiting the bacterial nucleic acid synthesis and eventually results in bacterial cell death. It is active against protozoa, including Giardia Ismblia, anaerobic bacteria like helicobacter pylori, streptococci, spirochetes etc. Metronidazole is sparingly soluble in water but has oral bioavailability of 93-95%. It is extensively metabolized by liver. The work presented deals with enhancing the solubility of metronidazole by solid dispersion approach. Since the solid dispersions are easy to prepare, less time consuming, also the carriers used here are cheap and easily available [1].

Materials and Method

Metronidazole was purchased from Alembic Pharmaceuticals Ltd (India). Dextrose, polyvinyl pyrrolidone (PVP), citric acid, polyethylene glycol-4000 (PEG), ethyl alcohol, acetone, chloroform were purchased from S.D. Fine Chemicals Ltd. (India). All other chemicals and reagents are of AR grade.

Preparation of Solid Dispersions of Metronidazole

The solid dispersions of metronidazole with PVP and PEG-4000 were made by Solvent Evaporation method [2]. The physical mixtures of metronidazole with carriers (PVP and PEG-4000) in molar ratios of 1:1, 1:2 and 1:5 were added to the common solvents (chloroform+acetone in 1:1 ratio). The solvent was evaporated in water bath at 40^0Cwith continuous stirring. The resultant residue was dried in vaccum for 3 hours and stored in dessicator for overnight. The dried mass was grinded and passed through sieve no.44.

The solid dispersions of metronidazole with citric acid and dextrose were made by Melting method [1]. The physical mixtures of metronidazole with carriers (citric acid and dextrose) in molar ratios of 1:1, 1:2 and 1:5 were taken in preheated china dish and heated until melted, thereby dispersing the drug in molten carrier. The molten mass was then cooled immediately by putting the mass on ice. The resultant residue was dried in vaccum for 3 hours and stored in desiccators for overnight. The dried mass was grinded and passed through sieve no.44.

Characterization of Solid Dispersions

Physical Appearance

The prepared solid dispersions were analyzed for their colour and appearance using simple microscope.

Solubility Studies

The saturation solubility studies of different solid dispersions were determined. Excess of solid dispersions were taken in conical flasks and placed on mechanical shaker for 24 hours, until

equilibrium is reached. The solubility was then analyzed using UV-VIS spectrophotometer (LABINDIA UV 3000) at λmax of 276 nm, by making suitable dilutions.

Dissolution Studies

In-vitro dissolution studies of metronidazole and the various solid dispersions were performed on USP Type II (Labindia DS 8000) Dissolution Test Apparatus in 0.1M HCl with a constant temperature of 37^0C and a speed of 50 rpm. Aliquotes were withdrawn at predetermined time intervals, and absorbance was measured at 276 nm, using UV-VIS spectrophotometer [10].

X-ray powder diffraction

(XRPD): X-ray powder diffraction (XRPD) patterns were recorded on an X-diffractometer (Phillip PW 1130/00 diffractometer, Netherland), employing Cu K_radiation source operating at 30 mA and 40 kV. Samples were scanned from 6 to 40 2θ at a scanning rate of 0.02 2θ s^{-1}[6].

Differential Scanning Colorimetry

DSC curve for pure metronidazole and their various solid dispersions (in different ratios) were taken and were compared [6].

Result and Discussions

Various solid dispersions were analyzed for their physical appearance as shown in Table1.

Table1: Physical appearance of various solid dispersions.

S. No.	Solid Dispersions	Appearance
1	Drug + PVP complex	Glassy and orange in color
2	Drug + PEG complex	waxy and off-white in color
3	Drug+Citric acid complex	granular and pale in color
4	Drug + Dextrose complex	granular and off-white in color

Dextrose and citric acid they results in the precipitation of drug in amorphous/granular form in SD. While the PVP and PEG results in the formation of glassy and waxy solid mass [12]. Saturation solubility study was performed for various solid dispersions and was compared with the solubility of pure drug as shown in Table 2.

Table 2: Solubility data for various solid dispersions of Metronidazole

S.No.	Solid Dispersions	Method of Preparation	Solubility (μg/ml)	Increase in solubility (in folds)
1	MTZ-dextrose 1:1 SD	Fusion/melting	1046.88	2
2	MTZ-dextrose 1:2 SD	Fusion/melting	968.013	2
3	MTZ-dextrose 1:5 SD	Fusion/melting	1767.265	4
4	MTZ-Citric acid 1:1 SD	Fusion/melting	3223.319	7
5	MTZ-Citric acid 1:2 SD	Fusion/melting	3453.201	8
6	MTZ-Citric acid 1:5 SD	Fusion/melting	4139.423	10
7	MTZ-PVP 1:1 SD	Solvent Evaporation	19983.098	46
8	MTZ-PVP 1:2 SD	Solvent Evaporation	34271.028	79
9	MTZ-PVP 1:5 SD	Solvent Evaporation	75490.65	147
10	MTZ-PEG 1:1 SD	Solvent Evaporation	4722.046	11
11	MTZ-PEG 1:2 SD	Solvent Evaporation	5970.605	14
12	MTZ-PEG 1:5 SD	Solvent Evaporation	106513.667	245

From solubility studies, it was found that among different carriers, PVP & PEG showed the maximum increase in solubility. This was probably due to the increased wettability, dispersibility and solubilization effect of polymers and surfactants. The solubility and dissolution rate increases as the amount of carrier increases (1:5>1:2>1:1). The solubility and dissolution also increases (Table 3) in case of dextrose and citric acid, because the solid dispersions result in the precipitation of drug in amorphous form, with decreased particle size. The dissolution rate was enhanced due to high surface area of the solid dispersions [12].

Further the carrier material also retards any agglomeration of particles, additionally sometimes solid dispersions results in metastable state, which has high solubility and hence faster dissolution rate.

Also, the presence of a small amount of soluble carrier in the crystalline lattice of the poorly soluble drug may also produce a dissolution rate faster than the pure compound with similar particle

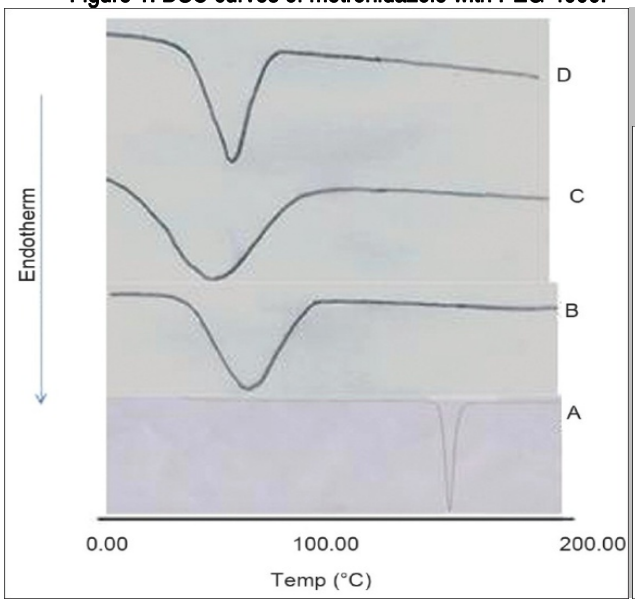
Table 3: Dissolution data for various solid dispersions of metronidazole

Time (min)	Percentage Drug Release												
	MTZ	MTZ-dextrose SD			MTZ-citric acid SD			MTZ-PVP SD			MTZ-PEG SD		
		1:1	1:2	1:5	1:1	1:2	1:5	1:1	1:2	1:5	1:1	1:2	1:5
10	13.71±2	13.81 ±2	25.56 ±2	50.54 ±3	21.32 ±3	49.27 ±1	53.36 ±2	93.99 ±1	96.99± 2	99.1 ±4	26.98 ±2	80.01 ±3	72.9±1
20	24.7 ±3	25.6± 1	36.5± 3	66.5± 3	33.7± 2	63.2± 2	68.4± 3	99.39 ±2	99.79± 1	99.9 ±3	40.2± 1	93.4± 3	85.23± 2
30	38.3 ±2	40.13 ±3	52.2± 1	78.2± 2	49.4± 3	75.5± 3	79.8± 2	99.88 ±3	99.987 ±1	99.9 ±3	57.6± 3	99.57 ±3	97.5±3
40	47.1 ±3	51.2± 2	59.4± 4	88.9± 3	56.8± 2	85.5± 2	9.7±3	99.88 ±2	99.987 ±4	99.9 ±2	62.8± 2	99.89 ±2	99.51 ±3
50	55.8 ±2	57.8± 2	69.88 ±2	96.8± 2	69.8± 2	92.9± 4	97.15 ±5	99.88 ±2	99.987 ±3	99.9 ±2	75.3± 3	99.9± 3	99.898 ±4
60	72.3 ±1	75.1± 4	80.13 ±3	98.45 ±3	80.1± 1	97.7± 2	99.18 ±3	99.88 ±2	99.987 ±3	99.9 ±2	83.7± 3	99.9± 3	99.89± 2

size. This may be due to a small number of the neighboring drug molecules holding the dissolving drug molecule after the rapid dissolution of neighboring water soluble carrier [19].

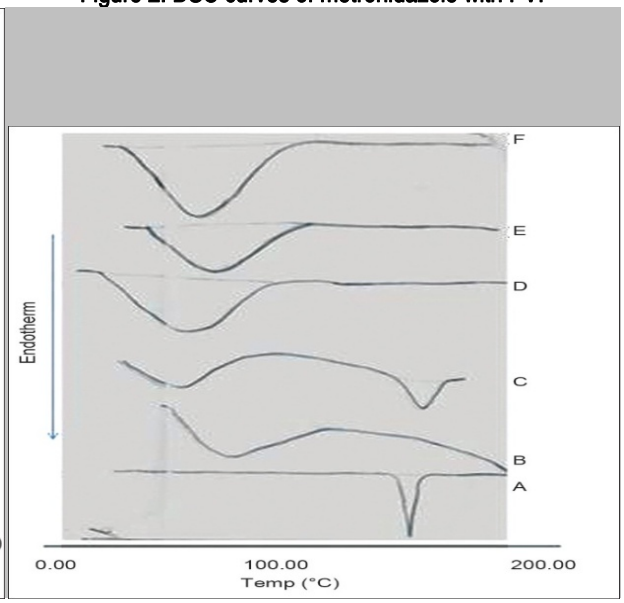
Also, there is usually a relatively strong chemical bonding between the solute and the solvent in solid solution, while the lattice energy in the glass solution is expected to be much less because of its similarity with the liquid solution. Similarly the dissolution rate from an amorphous or glassy solid is usually faster than crystal form of same chemical identity. Therefore, if everything is equal, then the dissolution rate of drugs in the glass solution should be theoretically faster than that in the solid solution. Apart from the predicted reasons, combination and miscellaneous mechanisms also exists.

Figure 1: DSC curves of metronidazole with PEG-4000.



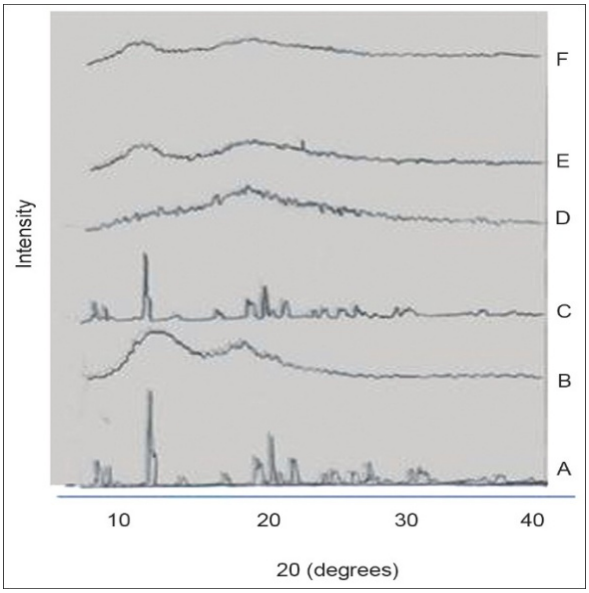
(A) Pure MTZ (B) 1:1 MTZ-PEG SD
(C) 1:2 MTZ-PEG SD (D) 1:5 MTZ-PEG SD

Figure 2: DSC curves of metronidazole with PVP



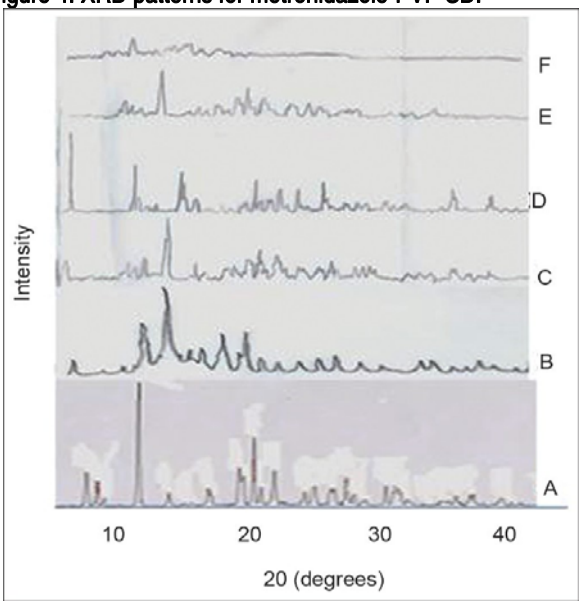
(A) Pure MTZ (B) Pure PVP
(C) Physical mixture (D) 1:1 MTZ-PVP SD
(E) 1:2 MTZ-PEG SD (F) 1:5 MTZ-PEG SD

Figure 3: XRD patterns for metronidazole-PEG SD.



(A) Pure MTZ (B) Pure PEG
(C) Physical mixture (D) 1:1 MTZ-PEG SD
(E) 1:2 MTZ-PEG SD (F) 1:5 MTZ-PEG SD

Figure 4: XRD patterns for metronidazole-PVP SD.



(A) Pure MTZ (B) Pure PEG
(C) Physical mixture (D) 1:1 MTZ-PVP SD
(E) 1:2 MTZ-PVP SD (F) 1:5 MTZ-PVP SD

The DSC and XRD data were also taken to confirm the formation of solid dispersions and also to know the mechanism of solubility and dissolution enhancement. This further confirms the amorphization and dispersibility of drug within the carrier matrix.

Conclusions

Thus from the above study we can conclude that water soluble carriers can be extensively used for their potential for improving the solubility of sparingly and poorly soluble drugs, which can further results in improving the bioavailability of many drugs.

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Authors Contribution

SS supervised the students for the preparation and analysis of complexes. BS worked on the preparation of manuscript. KM prepared and analyzed the MTZ-Dextrose complexes, ML worked on MTZ-Citric acid complexes, NK on MTZ-PVP complexes and SM on MTZ-PEG complexes.

Conflict of interest

The authors have no conflict of interest.

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