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ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of Miconazole Nitrate Solid Dispersions for Dissolution Rate Enhancement

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ABSTRACT

Solid Dispersions of miconazole nitrate (MN), with a water soluble polymer (PVP) and a super disintegrant namely, crospovidone (CP), were prepared by common solvent and solvent evaporation methods employing methanol as solvent. Solid Dispersions prepared were evaluated for dissolution rate and dissolution efficiency in comparison to the corresponding pure drug miconazole nitrate. Solid dispersions of miconazole nitrate showed a marked enhancement in dissolution rate and dissolution efficiency. The order of increasing dissolution rate was observed with increase in crospovidone ratio. At 1:4 ratio of miconazole nitrate-CP a 2.26 fold increase in the dissolution rate of miconazole nitrate was observed. The solid dispersions in combined carriers gave much higher rates of dissolution than super disintegrants alone. MN-CP-PVP solid dispersion gave a 3.47 fold increase in the dissolution rate of miconazole nitrate. Superdisintegrants alone or in combination with PVP could be used to enhance the dissolution rate of poorly soluble drug miconazole nitrate.

Keywords: Miconazole nitrate, Solid Dispersions, Dissolution rate, Solubility, Polyvinyl pyrrolidine, crosspovidone

INTRODUCTION

Miconazole nitrate (MN) is a broad-spectrum antifungalagent that has been extensively applied forthe management of dermal, buccal , and vaginal candidiasis. Several buccal drug delivery devices containing miconazole nitrate were developedsuch as chewing gum,oral gel and bioadhesivebuccal tablets. Gelcontaining miconazole nitrate are currently used. However since the drug does not persist in the oral cavity, gels have to be applied several times a day [1].

The present study aims at enhancing the dissolution rate of Miconazole nitrate. In the present investigation solid dispersions were prepared by employing common solvent and solvent evaporation methods. Studies were carried out on miconazole nitrate with an objective of enhancing their dissolution rates and bioavailability. Water dispersible superdisintegrants, a new class of tablet excipients were evaluated as carriers, alone and in combination with PVP, for enhancing the dissolution rate and bioavailability of Miconazole nitrate [2].

MATERIALS AND METHODS

Miconazole nitrate was obtained as a gift sample from Pranami drugs (P) LMT Ankleshwar. Methanol and all other materials used were of pharmacopoeial grade and were procured from commercial sources.

Preparation of solid dispersions

Preparation of solid dispersions employing soluble carriers (PVP):

Solid Dispersions of Miconazole nitrate were prepared by common solvent method employing methanol as solvent for miconazole nitrate solid dispersions. The required quantities of drug and carrier were weighed and dissolved in the corresponding solvent in a round bottom flask to get a clear solution. The solvent was then removed by evaporation under reduced pressure (vacuum) at 600^0 C with constant mixing. The mass obtained was crushed pulverized and shifted through mesh no.100. Solid dispersion was prepared in the ratio of drug carrier namely 8:2 [4-6].

Preparation of solid dispersions employing superdisintegrants [10]:

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Solid dispersions of MICONAZOLE NITRATE (MN) in super disintegrant crospovidone were prepared by solvent evaporation method. A Therequired quantity of MN was dissolved in methanol to get a clear solution in a dry mortar. The super disintegrant crospovidone(passed through 120 mesh) was then added to clear drug solution and dispersed. The solvent was removed by continuous trituration.Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 500^0 C for 4 hours in a oven. The product was crushed, pulverized and shifted through mesh no.100.In each case solid dispersions in the super disintegrant were prepared at three different ratios of drug excipient namely 1:1, 1:2 and 1:4 respectively [8,10] .

Preparation of solid dispersions employing combined carriers [12]:

The required quantities of drug and water soluble carrier (PVP) were dissolved in the solvent to get a clear solution in a dry mortar. The super disintegrant was then added to the drug solution and dispersed. The solvent was then evaporated by continuous trituration. Trituration was continued until a dry mass was obtained. The mass obtained was further dried at 500 C for 4 hours in an oven. The product was crushed, pulverized and shifted through mesh N0. 100. Various solid dispersions prepared with their composition are listed in (**Table 1**).

Estimation of Miconazole nitrate:

A spectrophotmetric method based on the measurement of absorbance at 220 nm in phosphate buffer pH 7.4 was used in the present study for the estimation of miconazole nitrate 4. The method was validated for reproducibility, accuracy, precision and linearity by analyzing six individually weighed samples of miconazole nitrate. The stock solution of miconazole nitrate was subsequently diluted to a series of dilution containing 5, 10, 15, 20 and 25*μg/ml* of solution, using phosphate buffer of pH 7.4. The absorbance of these solutions was measured in UV-VIS spectrophotometer (Chemitto 2600) .The method obeyed Beer's law in the concentration of 0-25*μg/ml*. The absorbances are listed in (**Fig 2).**

Infrared spectroscopy:

Fourier transformation infrared spectra were obtained with a resolution of 2cm-1 from 4000 to 500cm-1. KBr pellet method was employed to detect chemical interaction between drug and polymers and results were given in (**Fig 1**).

Estimation of Miconazole nitrate solid dispersions prepared:

From each batch, 4 samples of 50 mg each were taken and analyzed for the drug miconazole nitrate. 50 mg of dispersions were weighed into a 100 ml volumetric flask. Methanol was added and mixed the contents thoroughly to dissolve the drug from the dispersion. The solution was then filtered and collected carefully into another 100ml volumetric flask. The solution was made up to volume with the solvent. The solution was suitably diluted with appropriate dissolution fluid and assayed at 220 nm for Miconazole nitrate. The results are given in (**Table 2**).

Dissolution Rate Studies on Solid Dispersions:

Dissolution rate of Miconazole nitrate were studied using an USP-IIeight Station dissolution rate test apparatus (Electro Lab). Paddle stirrer at a speed of 50 rpm and temperature of 37.0 ± 10C were used in each test. Drug or solid dispersion of drug equivalent to 100 mg of Miconazole nitrate was used in each dissolution rate test. Samples of dissolution medium phosphate buffer pH 7.4 (5ml) were withdrawn through a filter (0.45 μ) at different time intervals, suitably diluted, and assayed for miconazole nitrate. The dissolution experiments were conducted in triplicate [13,16]. The results are given in (**Table 3**).

Analysis of dissolution data of solid dispersions as per Hixson crowell's cube root law:

The dissolution data of miconazole nitrate and their solid dispersions were also analyzed as per Hixson-Crowell's5 cube root equation.Hixson-Crowell introduced the concept of changing surface area during dissolution and derived the "cube-root law" to nullify the effect of changing surface area and to linearize the dissolution curves. Hixson-Crowell's cube root law is given by the following equation;

$$(Wo)^{1/3} - (Wt)^{1/3} = Kt,$$

Where Wo is initial mass and Wt is the mass remained at time't'.

[17] The cube root equation is applicable to the dissolution of mono disperse powder consisting of uniform sized particles. A plot of $(Wo)^{1/3} - (Wt)^{1/3}$ versus time will be linear when dissolution occurs from mono disperse particles of uniform size. Hixson-Crowell plots of the dissolution data were found to be linear with all solid dispersions. This observation indicated the drug dissolution from all the solid dispersions is occurring from discretely suspended or deposited (mono disperse) particles. This might have also contributed to the enhanced dissolution rate of the solid dispersions. The correlation coefficient (r) values of the first order release model are found to be (0.9075 to 0.9940) slightly higher when compared to the

Hixson-Crowell's cube root model. Hence the release of drug from the preparations followed predominantly first order kinetics compared to Hixson-Crowell cube root law. Another parameter suitable for evaluation of *in vitro* dissolution has been suggested by Khan6 by paramter Dissolution efficiency (DE). DE is defined as the area under the dissolution curve up to a certain time 't' expressed as percentage of the area of the rectangle described by 100% dissolution in the same time [18-20] .

$$Dissolution\ Efficiency\ (DE) = \left[\frac{\int_0^t y.dt}{Y_{100}t}\right] \times 100$$

The index DE30 would relate to the dissolution of drug from a particular formulation after 30 minutes and could be compared with DE30 of other formulations. Summation of the large dissolution data into a single figure DE enables ready comparison to be made between a large numbers of formulations. First order dissolution rate constants (K1) calculated from the slopes of the first order liner plots, dissolution efficiency (DE30) values, T_{50} (time for 50% dissolution) and percent dissolved in 10 minutes are given in (**Table 5**).

RESULTS AND DISCUSSION

All the dissolution parameters given in Table 2 indicated rapid and higher dissolution of miconazole nitrate from all solid dispersions when compared to miconazole nitrate pure drug. Miconazole nitrate-PVP (8:2) solid dispersion gave rapid and higher dissolution than the pure drug. A 1.20 fold increase in the dissolution rate of miconazole nitrate was obtained with this solid dispersion when compared to pure drug. Water dispersible super disintegrants gave much higher enhancement in the dissolution rate of miconazole nitrate than water soluble carriers. Solid dispersions of super disintegrants gave rapid and higher dissolution of miconazole nitrate when compared to pure drug as well as its solid dispersion in water soluble PVP. In each case, the K1 and DE30 values were increased as the concentration of carrier (super disintegrant) in the solid dispersion was increased. At1:4 ratio of MN:CP, the order of increasing dissolution rate with various super disintegrants was 1:4>1:2>1:1. A 2.26 fold increase in the dissolution rate of miconazole nitrate was observed with miconazole nitrate-CP (1:4) solid dispersion. All the solid dispersions in combined carriers gave much higher rates of dissolution, several times higher than the dissolution rate of pure drug. PVP combined super disintegrants gave higher dissolution rates than super disintegrants alone. MN-CP-PVP solid dispersion gave a 3.47fold increase in the dissolution rate of miconazole nitrate whereas solid dispersion of miconazole nitrate in CP alone (MN-CP 1:4 solid dispersion) gave only 2.26 fold increase. Thus combination of super disintegrants with water soluble carrier PVP resulted in a greater enhancement in the dissolution rate of miconazole nitrate.

Table1: Various solid dispersions and their composition

S. No	Composion		
	Drug	**Carriers**	**SD code**
1	Miconazole nitrate(8)	PVP(2)	MN-PVP, 8:2
2	Miconazole nitrate(1)	CP(1)	MN-CP, 1:1
3	Miconazole nitrate(1)	CP(2)	MN-CP, 1:2
4	Miconazole nitrate(1)	CP(4)	MN-CP, 1:4
5	Miconazole nitrate(1)	CP(3.2) PVP(0.8)	MN-CP-PVP

Table 2: Miconazole nitrate content of various solid dispersions prepared

S.No	SD code	Percent MN content (x ± s.d.,)
1	MN-PVP 8:2	79.5 ± 0.74 (0.93)
2	MN-CP 1:1	49.3 ± 0.38 (0.7)
3	MN-CP 1:2	32.5 ± 0.20(1.01)
4	MN-CP 1:4	19.8 ± 0.41 (1.26)
5	MN-CP-PVP	19.6 ± 0.19 (0.98)

Table3: Dissolution Rate Studies on Solid Dispersions

S.No	Time (min)	Percent Miconazole nitrate dissolved (x ± s.d., n = 3)					
		MN(F1)	**MN-PVP 8:2(F2)**	**MN-CP 1:1(F3)**	**MN-CP 1:2(F4)**	**MN-CP 1:4(F5)**	**MN-CP-PVP(F6)**
1	5	12.39±0.63	21.75±1.88	24.11±1.85	28.81±0.93	33.51±1.67	53.79±1.85
2	10	18.66±0.38	26.22±1.67	29.67±1.89	35.36±1.86	39.81±0.77	58.61±2.22
3	20	24.2±0.56	31.41±1.86	39.07±1.86	40.93±1.67	46.37±1.85	64.55±2.43
4	30	28.83±0.69	36.98±1.85	44.51±1.70	46.86±2.23	53.54±1.66	69.12±1.48
5	45	32.25±0.71	40.94±2.04	51.07±2.61	53.41±2.03	61.08±1.69	77.78±1.67
6	60	36.05±0.54	46.01±1.70	56.26±1.66	59.85±1.13	68.50±1.90	84.58±1.49

Table 4: The correlation coefficient (r) values in the analysis of dissolution data of Miconazole nitrate solid dispersions as per zero order, first order and HixsonCrowell cube root models

S.No	Solid dispersion	Correlation coefficient (r) value		
		Zero order	**First Order**	**Hixson crowell**
1	Pure drug	0.9875	0.9940	0.9920
2	MN -PVP8:2	0.8763	0.9075	0.9061
3	MN -CP 1:1	0.8957	0.9422	0.9300
4	MN -CP 1:2	0.8707	0.9369	0.9150
5	MN -CP 1:4	0.8725	0.9401	0.9273
6	MN -CP PVP	0.7805	0.9684	0.8846

Table 5: Dissolution parameters of Miconazolenotrate and its solid dispersions in superdisintegrants

S.No	Solid dispersion	Dissolution Parameter			
		T_{50} (min)	% Dissolved in 10 min	DE_{30} (%)	K_1 (min^{-1})
1	Miconazole nitrate	>60	10.63	19.60	0.0072
2	MN-PVP8:2	43	26.29	31.87	0.0121
3	MN-CP1:1	40	30.69	35.09	0.0128
4	MN-CP 1:2	26	34.89	39.91	0.0163
5	MN-CP 1:4	4.10	58.61	56.65	0.0250
6	MN-CP-PVP	>60	26.20	26.81	0.0087

Fig 1(a): FTIR of Miconazole nitrate

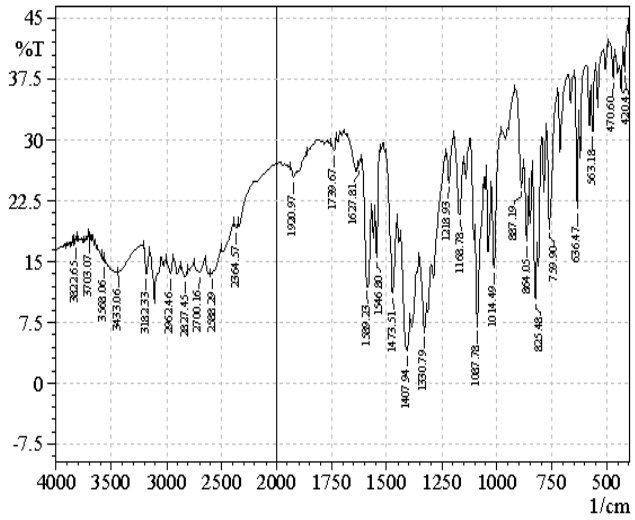


Fig 1(b): FTIR of MN -PVP8:2

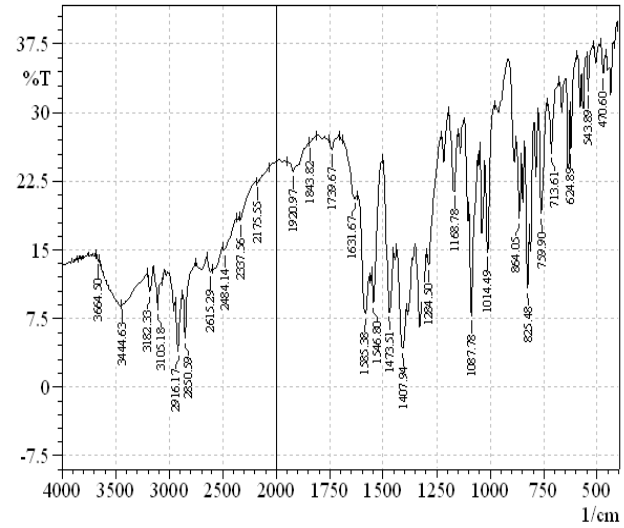


Fig1(c): FTIR of MN-CP 1:2

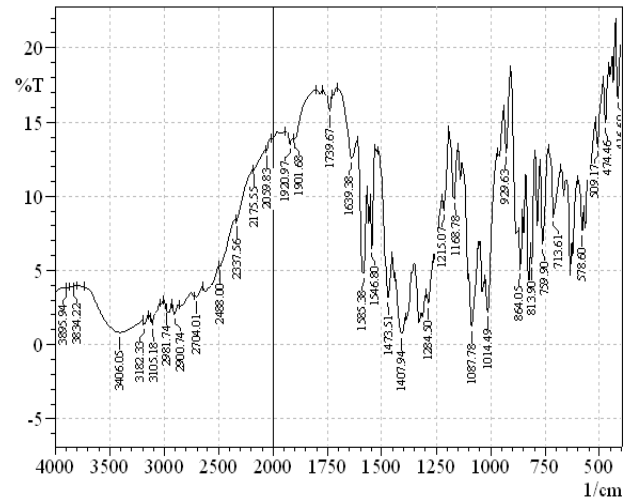


Fig 2: Calibration curve of miconazole nitrate

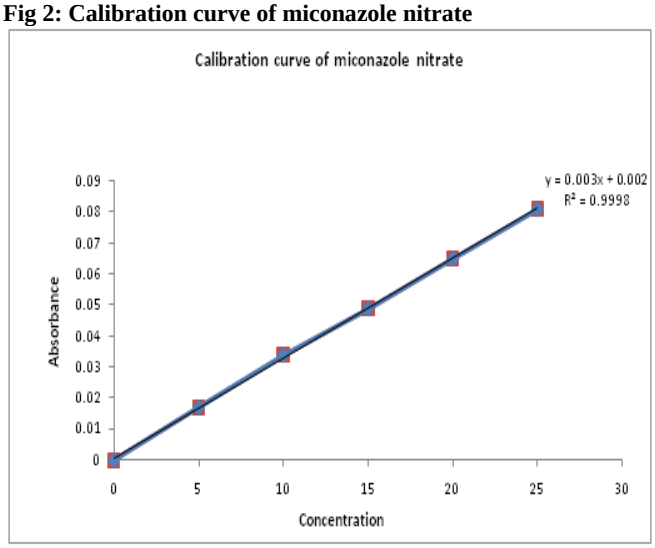
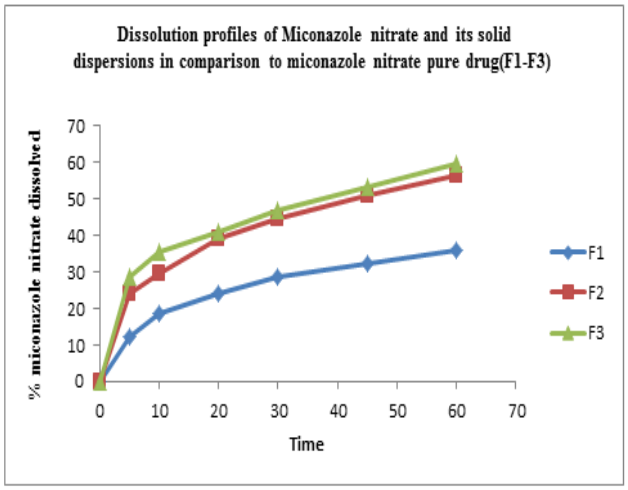


Fig 3: Dissolution profiles of Miconazole nitrate and its solid dispersions in comparison to miconazole nitrate pure drug



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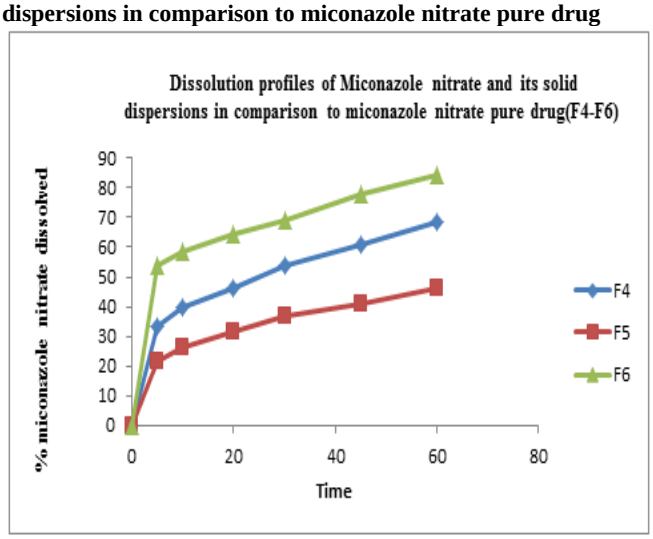

CONCLUSION

Thus super disintegrant cross povidone was found to be useful as a carrier in miconazole nitrate solid dispersions alone and in combination with PVP to enhance their solubility, dissolution rate and dissolution efficiency.

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