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DEVELOPMENT AND CHARACTERIZATION OF TINIDAZOLE FOR ENHANCEMENT OF SOLID DISPERSION SYSTEM USING AQUEOUS SOLUBILIZING AGENT

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Abstract

The present research endeavours towards the enhancement of the solubility of tinidazole by solid dispersion technique, were prepared by solvent evaporation method and different polymers are CMC, MC and GELATIN. There was significant increase in dissolution rate of tinidazole + CMC, MC and Gelatin with different proportions are (1:1, 1:2, 1:3). Solid dispersion of tinidazole evaluated by solubility test, IR Spectroscopy, Dissolution characteristic, solid dispersion of tinidazole in polymers different ratios to improve the dissolution rate thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. . Thus, the solid dispersion technique can be successfully used for improvement of dissolution of tinidazole.

Keywords: Tinidazole, CMC, MC, Gelatin, Methanol.

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Introduction

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.[1] Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine.

Tinidazole is a synthetic antiprotozoal agent. It is 1-[2-(ethylsulfonyl) ethyl] -2-methyl-5-nitro imidazole, a second-generation 2-methyl-5-nitroimidazole. Tindamax (tinidazole) is contra - indicated in patients with hypersensitivity to tinidazole, any component of the tablet, or other nitroimidazole derivatives. Tindamax is contraindicated during the first trimester of pregnancy.

Solid dispersion technique is used to enhance the dissolution of a poorly water soluble drug. Solid

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dispersions are one of the most successful techniques to improve dissolution rate of poorly water-soluble drugs. Solid dispersions are molecular mixtures of poorly aqueous soluble solid drug with an inert hydrophilic carrier. Drug release profile from such mixtures is driven by the carrier properties. Various hydrophilic carriers employed in preparation of solid dispersions methanol. There are various methods for preparing solid dispersion which includes solvent wetting method, physical mixture, solvent evaporation method, melting method, solvent wetting method, fusion method, kneading method and super critical fluid method, etc.

Material and Method

Materials

Tinidazole Was Gift Sample From Dr.Reddy's Laboratory, Hyderabad, india. Carboxy methyl cellulose, Methyl cellulose, Gelatin purchased from Sd fine chemicals,Mumbai. Methanol all reagents and solvents used was of analytical grade.

Method

Preparation of solid dispersion by solvent evaporation method

Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the bioavailability. Tinidazole solid dispersions were prepared by using carriers (i.e. Gelatin, MC, and CMC) in proportions viz. 1:1, 1:2 and 1:3 (Drug: Carrier) by solvent evaporation method. Methanol was added to the mixture of drug and carrier and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and passed through a sieve no 60. Then the prepared formulations were stored in a desiccators until further used.

Fourier transform infrared (FTIR) spectroscopy[2]

FTIR spectra were recorded on samples prepared in potassium bromide (KBr) disks using a Shimadzu Corporation (Koyto, Japan) facilty (model - 8400S). Samples were prepared in KBr disks in a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 cm^{-1}.

Standard Calibration Curve

100 mg of tinidazole was accurately weighed and transferred into 100 mL volumetric flask, dissolved in few ml of water and the final volume was made up to 100 mL of phosphate buffer 6.8 to get a stock solution of concentration 1mg/ml. From stock solution further dilutions were made ranging from 1 µg/mL to 5 µg/mL. The absorbances of these solutions were measured at 295 nm in UV-Visible Spectrophotometer (Elico SL 150). The absorbance was plotted against concentration of as shown in (**Table no-2, fig no-1**). The method obeyed Beer's law in the concentration of 2-10 µg/ml.

Estimation of drug content.

The formulation equivalent to 100 mg of tinidazole was weighed and diluted suitably with Phosphate buffer 6.8. The absorbance was measured at 295 nm by UV Specetrophotometer, and the amount of drug in each formulation was calculated. table no-3.

Evaluation of solid dispersion

Bulk density and tapped density

Accurately weighed amount of physical mixtures were transferred to a graduated cylinder to measure the apparent volumes or bulk volume (V_b). The measuring cylinder was tapped for a fixed period of time and tapped volume (V_t) occupied in the cylinder was measured, The bulk density and tapped/true density were calculated in gram per milliliter by the following formula

a) Bulk Density=Mass/Volume

b) Tapped Density=Mass/Tapped Volume

c) Carr's index and Hausner's ratio

Angle of repose

A funnel was fixed in a stand in such a way that the top of the funnel was at a height of 6 cm from the surface. The Solid dispersions were passed from the funnel so that they formed a pile. The height and the radius of the heap were measured and the angle of repose was calculated using the equation. Results are given in table no-4.

$\varphi = \tan^{-1} (h/r)$

h = Height of the heap

r = Radiation of the heap

***In-vitro* dissolution study**

In-vitro dissolution studies were performed for all prepared formulations. The following parameters were maintained for the dissolution process

Instrument: Dissolution test apparatus.

Type: Paddle type. **Temperature:** 37±0.5°C, **rpm:** 100

Dissolution medium: Water. **Volume of medium:** 900 ml.

Sampling volume: 5 ml withdrawn at fixed time intervals and replaced with 5 ml of fresh water maintained at same temperature.

It is defined as the area under the dissolution curve between time points t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, over the same time period or the area under the dissolution curve up to a certain time, t, (measured using trapezoidal rule) expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. DE_{20} values were calculated from dissolution data and used to evaluate the dissolution rate.

Establishment of drug release kinetics model[3]

Kinetics of *In-vitro* Drug Release

To study the release kinetics of *in-vitro* drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppa

Zero order kinetics Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation: given in table no-6, fig no-6.

Q_0 n $Qt = K_0t$ Rearrangement of equation $Qt = Q_0 + K_0t$

a) First order kinetics

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation

Given in Fig no-7

$$\frac{dC}{dt} = -Kc$$

b) Higuchi model[4]

(i) Initial drug concentration in the matrix is much higher than drug solubility.

(ii) Drug diffusion takes place only in one dimension (edge effect must be negligible).

(iii) Drug particles are much smaller than system thickness; (iv) Matrix swelling and dissolution are negligible.

$$f_t = Q = A\sqrt{D(2C - C_s)\,C_s\,t}$$

Accordingly, model expression is given by the equation:

Where,

Q- is the amount of drug released in time t per unit area A, C -is the drug initial concentration, substance. Fig no-8

c) Korsmeyer Peppas model

To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyern Peppas model. Fig no-9.

$$M_t / M_\infty = Kt^n$$

The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n = 0.5, then the drug release mechanism is Fickian diffusion. If n < 0.5 the mechanism is quasi-Fickian diffusion, and 0.5 < n < 1.0, then it is non-Fickian or anomalous diffusion and when n = 1.0 mechanism is non Fickian case II diffusion, n> 1.0 mechanism is non Fickian super case II. Fig no-9.

d) Hixon Crowell model[5]

In the Hixson-Crowell cube root law, the equation can be written as follows **t**

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the system and K_{HC} is the rate constant for the Hixson-Crowell rate equation. The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles. Fig no-10.

Stability study as per ICH guidelines

An accelerated[6] stability study of SDs of best formulation prepared by solvent evaporation method was carried out at 40ºC/75%RH for a period of 3 months. An accurately weighed amount of sample was placed into glass vials with aluminum lined caps and stored in humidity chamber. The sample were removed and evaluated for drug content and dissolution studies.

Results and discussion

Determination of drug melting point

Melting point of tinidazole was observed by using capillary tube method

Table No. 01: Melting point of tinidazole

Sample name	Melting point
Tinidazole	125^0C

Analytical studies

a) Construction of calibration curve of Tinidazole

Table No. 2: Construction of calibration curve of Tinidazole

S.No.	Concentration (µg/ml	Absorbance
0	0	0
1	2	0.1371
2	4	0.2547
3	6	0.377
4	8	0.4787
5	10	0.5979

Tinidazole was estimated by UV spectro-photometric method by measuring the absorbance at 295 nm. Linearity was observed in the concentration range of 1-10 µg/ml (r = 0.9)

b) Determination of drug content

Table No. 03: Estimation of drug content of tinidazole

S.No	Formulation	Drug : carrier	Drug content (± S.D, n=3)
1	F1	1:1	96.5 ± 0.21
2	F2	1:2	99.4 ± 0.09
3	F3	1:3	97.4 ± 0.05
4	F4	1:1	98.2 ± 0.03
5	F5	1:2	97.8 ± 0.06
6	F6	1:3	98.8 ± 0.03
7	F7	1:1	96.9 ± 0.04
8	F8	1:2	99.8 ± 0.06
9	F9	1:3	97.8 ± 0.03

Actual drug content of all nine formulations were shown in the table no 7.4. The drug content of the prepared solid dispersions were found to be in the range of 96.50 – 99.89 % and it indicates good uniformity in drug content in all the formulations.

c) Detection of flow properties

Micromeritic Studies

Table No. 04: Micromeritic properties of Tinidazole & F2

Formulation	Carr's index	Hausner's ratio	Angle of repose
PD	38.14	1.611	43
F1	15.72	1.194	31.55
F2	14.97	1.185	29.36
F3	15.21	1.196	28.59
F4	13.98	1.183	26.54
F5	14.21	1.183	26.54
F6	13.93	1.175	24.97
F7	14.60	1.168	23.84
F8	15.43	1.153	20.23
F9	13.28	1.165	19.67

Flow ability of Tinidazole (pure drug) and its solid dispersions were assessed by determination of Carr's index (CI), Hausner's ratio (HR) and angle of repose. Micromeritic behaviour of the Tinidazole powder and all prepared solid dispersions were listed in the above table. The results showed that the flow ability represented in terms of Carr's index, Hausner's ratio and angle of repose was much improved compared to those of original powders (untreated Tinidazole). In case of pure Tinidazole powder could not pass through the funnel during the angle of repose experiment. The poor flow of Tinidazole could be due to the irregular shape and high fineness of the powder, which Possessed hurdles in the uniform flow from the funnel. These results are significantly different from those of untreated Tinidazole

d) *In -vitro* dissolution study

Table No. 05: Cumulative % drug release of Tinidazole by solvent evaporation method

	% Cumulative drug release								
Time	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
10	20.9± 0.02	20.73±0.04	20.54±0.07	26.36±0.04	22±0.02	27.6±0.04	24.82±0.07	24.82±0.06	27.6±0.07
20	37.13±0.07	32.01±0.03	39.45±0.02	44.46±0.06	36±0.05	33.2±0.05	50.45±0.06	58.9±0.08	43.2±0.02
30	39.27±0.02	43.27±0.01	57.54±0.04	79.73±0.05	58.9±0.06	48.9±0.06	78.9±0.04	87.36±0.05	57.36±0.03
40	40.65±0.07	48.9±0.03	75.45±0.03	90±0.03	87.36±0.05	57.36±0.07	92.36±0.04	93.01±0.04	85.82±0.06
50	-	50.82±0.04	90.51±0.05	-	94.18±0.05	80.18±0.05	-	-	95.46±0.05
60	-	-	99.31±0.04	-	-	98.76±0.05	-	-	-

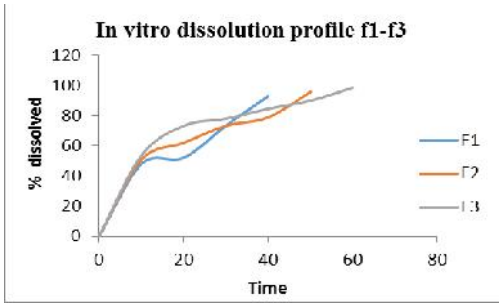

Fig. No. 01 : Dissolution profile of tinidazole-MC SDS

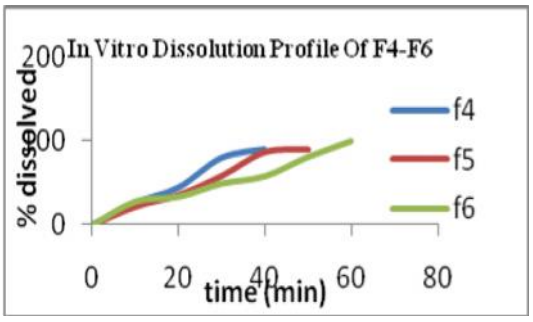

Fig. No. 02 : Dissolution profile of tinidazole- gelatin SDS

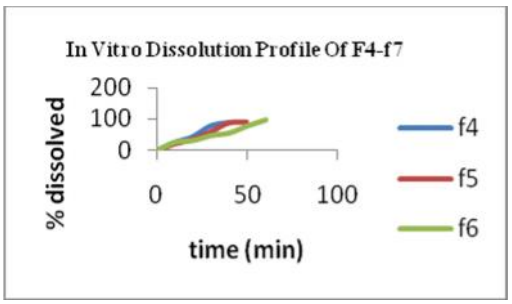

Fig. No. 03: Dissolution profile of tinidazole-CMC SD

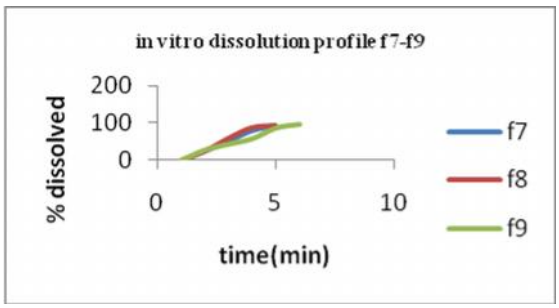

Fig. No. 04 : Dissolution profile of Tinidazole – Combinations SDS

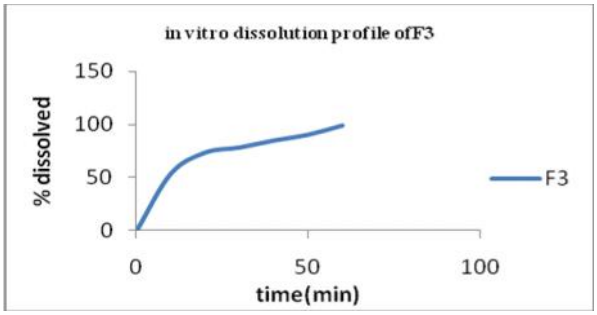

Fig. No. 05: Dissolution profile of Optimized FormulationF3

Dissolution studies were performed to compare the drug release from the solid dispersions to that of the pure drug by solvent evaporation method. The dissolution study for solid dispersions of tinidazole and pure drug was carried out for a period of 60 min in distilled water. Samples of 100 mg pure drug and equivalent weight of solid dispersion was used for dissolution study. All the experiments were carried out in triplicate average value considered.

From Figures it was clear that solid dispersions were showed that enhanced dissolution rate compared to the pure drug, solid dispersions. As concentration of carrier increases the dissolution rate of tinidazole had also increased. Solubility of solid dispersions was increased by maximizing the surface area of the drug that comes in contact with the medium. This might be due to the surface tension lowering effect of polymer to the medium, resulting in the wetting of hydrophobic drug of crystalline surface, which can be attributed to the reduction of crystalline of drug, and therefore improved release profile. From the in vitro drug release profile, it can be seen that formulation F3 containing drug and MC in the ratio of 1:3 shows higher dissolution rate compared to other formulations i.e., 98.6 % drug release in 60 min. The increase in dissolution rate was in the order of **F3**>F6>F9>F5>F8>F5>F4>F2 >F1>PD

Establishment of drug release kinetics model

Table No. 06: Cumulative drug release

Time (min)	%Cumulative drug release of	%Cumulative drug remaining	log% Cumulative drug remaining	Square root of time	log time	log % cumulative drug release	Cube root of % drug remaining
0	0	0	0	0	0		0
10	20.54	79.46	1.900149	3.162278	1	1.3126	4.57
20	39.45	60.55	1.782114	4.472136	1.30103	1.596047	4.53
30	57.54	42.46	1.62798	5.477226	1.47712	1.75997	4.45
40	75.45	24.55	1.390051	6.324555	1.60206	1.877659	4.37
50	90.51	9.49	0.977266	7.071068	1.69897	1.956697	4.24
60	99.31	1.4	0.146128	7.745967	1.77815	1.996993	4.12

a) Zero order

In zero order release kinetic model, data obtained from *in- vitro* drug release studies were plotted as cumulative amount of drug released versus time .shown in the table no-7.5

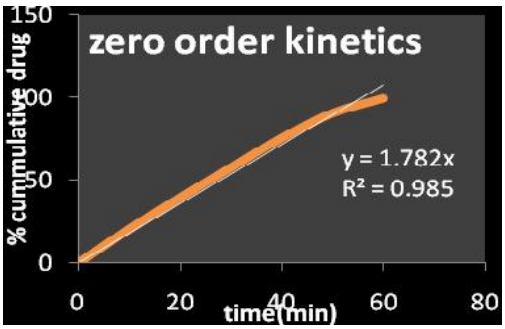

Fig. No. 06: Zero order plot of F3

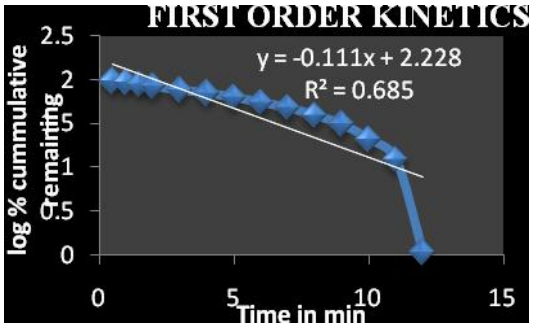

Fig. No. 07: First order plot of F3

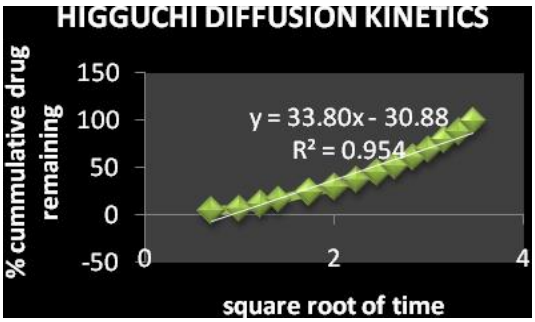

Fig. No. 08: Higuchi's plot of F3

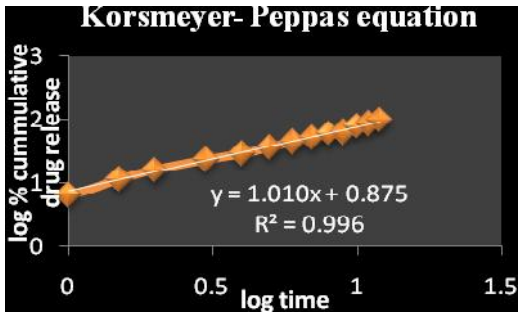

Fig. No. 09: Korsemeyer peppas plot of F3

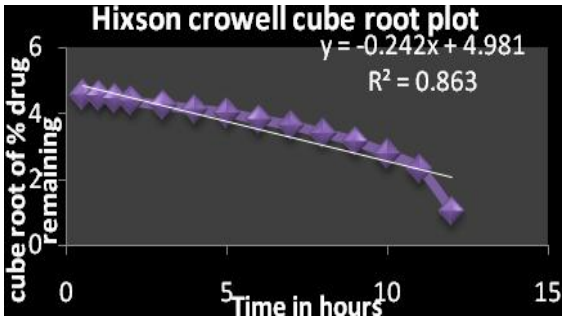

Fig. No. 10: Hixson-Crowell plot of F3

Table No. 07: R^2 values of all kinetics model

Formulations	Zero order	First order	Higuchi	Peppas	Hixson Crowell
F1	0.983	0.782	0.870	0.971	0.891
F2	0.970	0.779	0.922	0.930	0.900
F3	0.985	0.685	0.954	0.996	0.863
F4	0.841	0.920	0.880	0.969	0.969
F5	0.820	0.952	0.967	0.959	0.971
F6	0.984	0.819	0.860	0.979	0.897
F7	0.951	0.892	0.987	0.984	0.978
F8	0.979	0.827	0.944	0.900	0.922
F9	0.974	0.777	0.964	0.989	0.930

From all kinetic models data, has concluded that all formulations following mixed order kinetics

V) Stability study as per ICH guidelines

Stability studies of best formulation

Table No. 08: Stability studies of best formulation

Time (months)	Physical Appearances	Drug content (%)	Drug release (%)
0	White	98.8	101.15
1	White	98.7	100.45
2	White	98.5	99.56
3	White	98.5	99.55

Formulation F3 containing drug and MC in the ratio of 1:3 was considered as the best formulation and was subjected to different temperature and humidity conditions namely 40ºC/75%RHs for a period of 3 months. The drug content and dissolution studies were carried out at the end of 3 months. From the results of stability studies it was observed that there was only very slight variation in drug content and dissolution than actual and therefore the formulation was stable throughout the study period.

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