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Research article

Formulation and evaluation of solid dispersions of an anthelmintic drug for enhancement of dissolution rate

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Key words: Solubility enhancement technique, solid dispersion, poorly water-soluble drug and Anthelmintics.

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Abstract

The purpose of present research work was to improve dissolution rate of Mebendazole which belongs to BCS II drug by enhancing its aqueous solubility using different hydrophilic carriers like PEG 6000 and Poloxamer 338. The various solid dispersion formulations were prepared by employing fusion and solvent evaporation method using different carriers. Further solid dispersion formulations were subjected to different *in-vitro* evaluation tests for solubility, drug content uniformity, drug-polymer interaction, DSC study and *in-vitro* drug release study. The results of drug content uniformity showed uniform dispersion of Mebendazole in solid dispersion formulations. To know the dispersion of drug in polymers used DSC study was carried out. The endothermic peak at 254.43°C due to Mebendazole was partially and completely disappeared in solid dispersion formulation indicating that drug was completely dispersed in formulations. *In-vitro* drug release showed 80.35% in 60minutes for the best solid dispersion formulation F3 (Mebendazole and Poloxamer 338 ratio 1:2) which was prepared using fusion method.

Introduction

An oral route of drug administration is the most preferred route of drug delivery due to convenience and ease of ingestion. A solid dosage form is a comfortable and familiar means of taking medication. Hence, a patient compliance and drug treatment is usually more effective with orally administered medications than other routes of administration [1-3].

In the present research work, Mebendazole which belongs to BCS II is the drug of choice for treating parasitic infections like Helminthiasis including Trichuriasis (whipworm infections), Ancylostomiasis (hookworm infections) and Ascariasis which mostly affect colon. The drug acts by inhibiting the polymerization of helminth β-tubulin, thus interfering with microtubule-dependent functions such as glucose uptake [4-6]. Poorly water-soluble drugs are increasingly becoming a problem in terms of obtaining the satisfactory dissolution within the gastrointestinal tract that is necessary for good bioavailability. So the aim of the proposed work was to improve the solubility and dissolution of poorly aqueous soluble drug such as Mebendazole which belongs to BCS II using solid dispersion technique.

Experimental

Materials

Mebendazole was a gift sample from Sellwell Pharmaceutics Pvt. Ltd., Indore. PEG 6000 and Formic acid was supplied from S.D. Fine Chemicals Limited, Mumbai. Poloxamer 338 was obtained from Kemwell Biopharma Pvt. Ltd.

Formulation of Mebendazole solid dispersions

The solid dispersion systems of Mebendazole were prepared with Poloxamer 338 in the ratios 1:1, 1:1.5, 1:2 and PEG 6000 in the ratios 1:1, 1:2 and 1:3. The solid dispersions were prepared by employing fusion and solvent evaporation method.

Fusion method (Melt method) [7, 8, 10-11]

The accurately weighed amount of carrier was melted in a porcelain dish and calculated amount of Mebendazole was added with thorough mixing for 1-2 minutes followed by quick cooling. Formulations prepared using fusion method is listed in table 1.

Solvent evaporation

The required amount of Mebendazole was dissolved in the solvent system, methanol: formic acid (1:1). The carrier was dispersed in the drug solution. The solvent was removed under vacuum until dry. The dried mass was pulverized and sieved through #120 and stored in desiccators until further evaluation. Formulations prepared by solvent evaporation method are listed in table 2.

Table 1. List of Formulations F1-F6

Formulation Code	Solid dispersion	Drug & Carrier ratio	Method employed
F1	Mebendazole : Polox. 338	1 : 1	Fusion method
F2	Mebendazole : Polox. 338	1 : 1.5	Fusion method
F3	Mebendazole : Polox. 338	1 : 2	Fusion method
F4	Mebendazole : PEG 6000	1 : 1	Fusion method
F5	Mebendazole : PEG 6000	1 : 2	Fusion method
F6	Mebendazole : PEG 6000	1 : 3	Fusion method

Table 2. List of Formulations S1-S6

Formulation Code	Solid dispersion	Drug & Carrier ratio	Method employed
S1	Mebendazole : Polox. 338	1 : 1	Solvent evaporation method
S2	Mebendazole : Polox. 338	1 : 1.5	Solvent evaporation method
S3	Mebendazole : Polox. 338	1 : 2	Solvent evaporation method
S4	Mebendazole : PEG 6000	1 : 1	Solvent evaporation method
S5	Mebendazole : PEG 6000	1 : 2	Solvent evaporation method
S6	Mebendazole : PEG 6000	1 : 3	Solvent evaporation method

Characterization and evaluation of solid dispersion solubility studies

The solubility measurements of Mebendazole were carried out by adding excess amount of drug (50 mg) to 20 ml of Poloxamer 338 and PEG 6000 prepared in 0.1N HCl (pH1.2) in a series of stoppered conical flasks in the concentration of 2, 4, 6 and 8%. Later, the suspensions were agitated at 37°C ± 1°C until equilibrium was achieved. Then 1 ml aliquots were filtered, diluted suitably and assayed by employing Shimadzu UV-Spectrophotometer at 287nm for Mebendazole content.

FT-IR

Compatibility of drug with other excipients was studied using Fourier Transform Infrared spectroscopy. FT-IR spectra of Mebendazole, Poloxamer 338, physical mixture and the best formulation were measured using JASCO V460 PLUS IR spectrometer by diffuse refluctance technique.

Drug content uniformity

The sample equivalent to 50 mg of Mebendazole was accurately weighed and transferred to 50 ml volumetric flask and extracted in formic acid. The volume was made up to 50 ml with 0.1N HCl. From this 1ml is subsequently diluted to 10 ml with 0.1N HCl and assayed for Mebendazole content by measuring at 287 nm using 0.1N HCl as blank. The drug content of all solid dispersion formulations is given in table 3 and 4.

Table 3. Drug content of Mebendazole in Mebendazole: PEG 6000 solid dispersions

Formulation	Drug Content (in mg)
F4	33.41
F5	36.06
F6	38.64
S4	36.64
S5	38.05
S6	40.29

Table 4. Drug content of Mebendazole in Mebendazole: Poloxamer 338 solid dispersions

Formulation	Drug Content (in mg)
F1	38.47
F2	40.82
F3	42.52
S1	40.35
S2	43.82
S3	44.47

In-vitro drug release studies

The *in-vitro* dissolution studies were performed for Mebendazole and all solid dispersion formulations using USP XXII dissolution test apparatus type II (Electro lab) maintained at 100 rpm. Mebendazole pure drug 50mg and solid dispersions system equivalent to 50mg of Mebendazole were accurately weighed and used in each test. The dissolution studies were carried out using 900 ml of buffer solutions (0.1 N HCl), maintained at 37 ± 5°C was used as dissolution media to maintain the sink condition. The release of Mebendazole was measured by withdrawing 5ml aliquot samples at regular time intervals and withdrawn volume was replaced with fresh quantity of dissolution medium [9]. The withdrawn samples were filtered through Whattman filter paper and suitably diluted with buffer assayed by using Shimadzu UV-Spectrophotometer at 287 nm. The % cumulative drug release after every time intervals was calculated and reported. The results are shown in the figures 1 and 2.

DSC study

The physical state of drug in the samples was determined by Differential Scanning Calorimetry (DSC) using SDTQ 600 V 20.9 BUILD 20, Universal V4.5ATA Instrument. Samples containing 3mg of drug were placed in the aluminium pans and heated from 0^0C to 300^0C at a heating rate of 10^0C/min under inert atmosphere flushed with nitrogen at the rate of 20 ml/min [12].

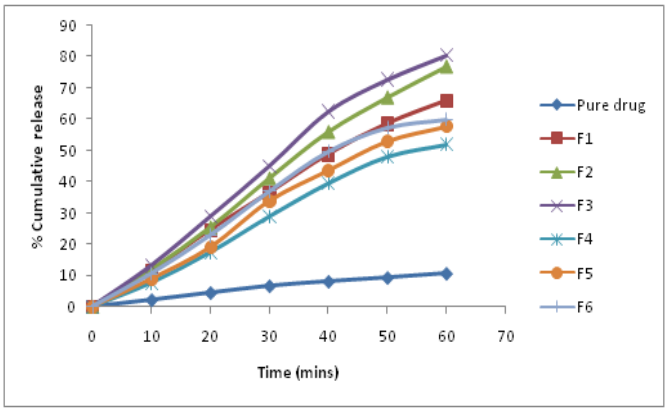

Figure1. *In-vitro* profile of formulation F1- F6.

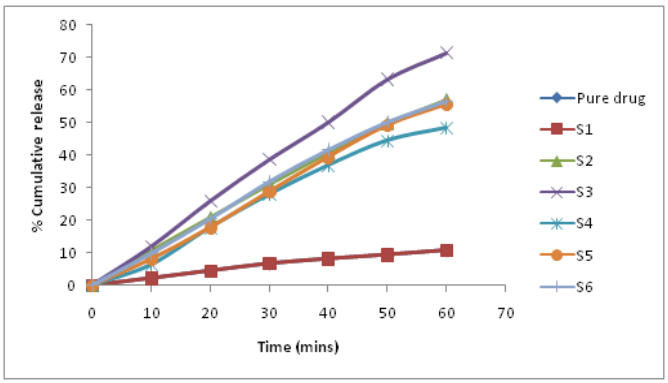

Figure 2. *In-vitro* profile of formulation S1-S6.

Results and Discussion

The effect of PEG 6000 and Poloxamer 338 on the solubility of Mebendazole was studied and results summarized in table for PEG 6000 and Poloxamer 338. The solubility of Mebendazole was found to be 0.273, 0.326, 0.371 and 0.380 mg/ml at 2%, 4%, 6% and 8% (w/v) of PEG 6000 concentration respectively. The solubility of Mebendazole was found to be 3.64, 3.92, 4.03 and 4.08 mg/ml at 2%, 4%, 6% and 8% (w/v) of Poloxamer 338 concentration respectively. The solubility studies showed that solubility of Mebendazole increased with concentrations of carrier.

To study the possible interactions between Mebendazole, PEG 6000 and Poloxamer 338, FT-IR spectra of solid dispersions was compared with the drug alone. The FT-IR spectra of Mebendazole exhibit characteristic peaks for C=O stretching at 1717.30cm^{-1}, C=C Stretching at 1595.81cm^{-1}, C-H stretching at 3021.91cm^{-1}, NH stretching at 3175.22cm^{-1}, C-O stretching at 1008.59 and C=N stretching at 1648cm^{-1}. The physical mixture showed almost the same characteristic peaks of drug indicating no interaction. In the FT-IR spectra of the best solid dispersion formulation F3, N-H stretching of amide group of the Mebendazole was shifted towards lower wavelength and the other peaks are almost the same. This indicated that overall symmetry of the molecule is not significantly affected.

The DSC graph of pure drug and the best formulation F3 is shown in figure 3 and 4 respectively. The DSC of pure Mebendazole shows sharp endothermic peak at 254.43°C due to its melting point. The best solid dispersion F3 (Mebendazole and Poloxamer 338 in the ratio of 1:2 prepared using fusion method) shows sharp endothermic peak at 55.76°C which could be due to the melting point of Poloxamer 338. The endothermic peak of Mebendazole is suppressed indicating Mebendazole would completely disperse in Poloxamer 338.

In-vitro dissolution studies of solid dispersions were compared with the pure Mebendazole in Tablet 5 and Table 6. It found that drug dissolution was generally higher in the formulations prepared using fusion method than solvent evaporation technique. Further, it was found that the drug dissolution was highest i.e., 80.35% in the formulation F3 (drug and carrier ratio was 1:2 prepared by employing fusion method) at the end of 60 minutes.

Table 5. *In-vitro* release data of formulation from F1-F6 in 0.1 N HCl

Time	Percentage Cumulative Release (% CR)						
(mins)	Pure drug	F1	F2	F3	F4	F5	F6
10	2.20	11.43	11.85	13.12	7062	8.89	10.58
20	4.49	24.57	25.42	28.81	17.37	19.06	22.88
30	6.69	36.46	41.12	44.94	28.82	33.91	36.88
40	8.14	48.78	55.99	62.35	39.44	43.69	49.63
50	9.38	58.58	67.06	72.58	47.96	53.05	57.30
60	10.74	65.90	76.94	80.35	51.83	57.78	59.90

Table 6. *In-vitro* release data of formulation from S1-S6 in 0.1 N HCl

Time	Percentage Cumulative Release (% CR)						
(mins)	Pure drug	S1	S2	S3	S4	S5	S6
10	2.20	10.58	11.85	12.70	6.35	8.04	9.74
20	4.49	20.76	25.84	27.12	17.79	17.79	20.34
30	6.69	30.95	38.58	39.43	27.97	28.82	31.79
40	8.14	40.72	50.06	51.33	36.90	39.44	41.57
50	9.38	49.66	63.24	65.36	44.56	49.23	50.09
60	10.74	56.91	71.38	74.79	48.43	55.65	56.51

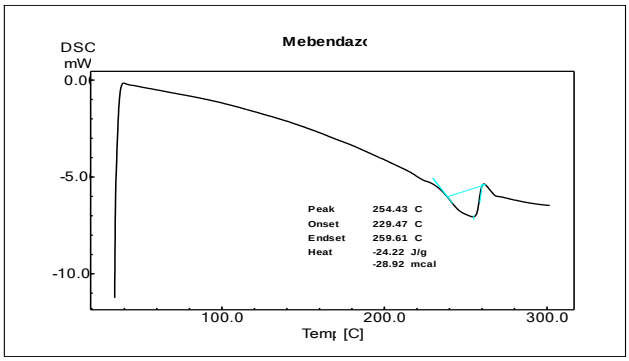

Figure 3. DSC spectra of Mebendazole (pure).

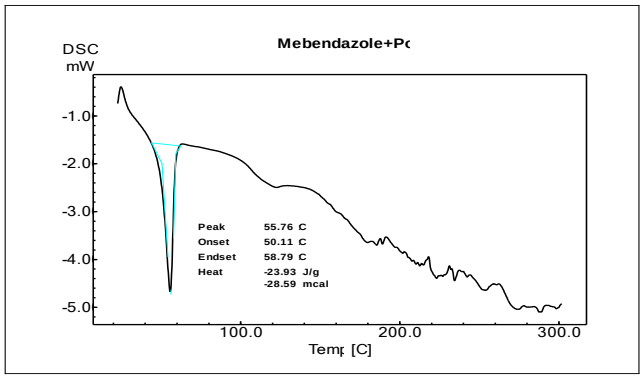

Figure 4. DSC spectra of the best solid dispersion formulation F3.

Conclusion

Using Poloxamer 338, the order of dissolution rate is 1:2 > 1:1.5 > 1:1 solid dispersion prepared using both fusion and solvent evaporation method. Similarly, for PEG 6000, the order of dissolution rate is 1:3 > 1:2 > 1:1 solid dispersion prepared by employing both fusion and solvent evaporation method. With these findings, it would be noticed that Poloxamer 338 in the best solid dispersion F3 has characteristics to form molecular dispersions with the drug molecules, hence enhancing the dissolution rate of drug and decreasing the time of drug release from the solid dispersion.

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