

Formulation, Optimization and *In Vitro* Evaluation of Solubility Enhanced Fast Disintegrating Tablets of Mebendazole

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Abstract

Mebendazole (MBZ) is used for the treatment of different intestinal helminthic infections (IHI) and extraintestinal helminthic infections (EIH). Due to its poor aqueous solubility and high first pass metabolism, MBZ has low bioavailability that can affect the therapeutic efficacy of the drug for EIHs. The aim of the present study is to develop solubility enhanced rapidly disintegrating tablets of MBZ with a simple and industrially feasible manufacturing process.

The influence of the selected excipients (nicotinamide (NIC), crospovidone and microcrystalline cellulose to mannitol ratio (MCC: MNTL)) on the physicochemical properties of MBZ were determined by using 32 factorial design. By using the shake flask method, NIC as hydrotropic agent enhanced solubility of MBZ more than 16 times in 40% w/v hydrotropic solution. Formulation (F8) which consisted of 5% crospovidone, 2:1 MCC: MNTL and 1 MBZ: 3 NIC hydrotropic solid dispersion (HSD) prepared by kneading method (KM1:3) had the shortest disintegration time (21 ± 1.7 sec), lowest wetting time (56 ± 3 sec) and largest crushing strength (10.25 ± 0.79 kg/cm²). These properties could be due to the binding and disintegrant properties of MCC and the disintegrant property of crospovidone. All of the formulations released more than 75% of the label claim within 20 min except formulation without NIC (F10). The rapid dissolution behavior is likely due to the formation of hydrotropic system.

Keywords: Mebendazole; Solubility enhancement; Nicotinamide; Hydrotropic solid dispersion; Fast disintegrating tablet; Optimization

Introduction

Helminthes as multicellular organisms can cause severe and even fatal human diseases [1,2]. They can be classified as intestinal helminthiasis which inhabit the human GIT and systemic helminthiasis which inhabit the liver, brain, lungs, kidneys, heart, thyroid and bone [3-5].

Anthelmintic like MBZ is a broad-spectrum drug which is effective for controlling and correct treatment of a number of nematodal and cestodal species of helminthes. It inhibits glucose uptake in the parasite resulting in glucose deficiency [4-7].

MBZ is recommended for the chemotherapy of non-surgical cases and as a supplementary treatment prior to and post-surgery of EIHs; such as alveolar and cystic hydatid disease. MBZ 40- 50 mg/kg per day for 3- 6 months have demonstrated efficacy [2,8,9]. The prolonged, high-dose therapy used in the treatment of EIHs has been associated with alopecia, hepatocellular injury and bone marrow suppression [6,10].

As MBZ is susceptible to high first pass elimination and poor water-soluble drug (BCS II), it can exhibit a number of negative clinical effects including potentially serious issues of inter-patient variability, erratic absorption (2-10% of an oral dose absorbed) and limited efficiency against tissue-dwelling helminthes [7,11]. So, it requires innovative approaches to reach a sufficiently high bioavailability when administered by the oral route [12,13].

Fast dissolving drug delivery system as a novel drug delivery system and a patient-oriented pharmaceutical preparation is designed to enhance the safety and efficacy of the drug molecule by formulating a dosage form which disintegrate or dissolve in a few seconds after placement in the mouth [14,15]. It can be administered easily to the geriatrics, pediatrics and patients suffering from dysphagia. It can bypass first pass elimination by undergoing pre-gastric absorption. This improves bioavailability of the drug and reduces dosing frequency

and dose related untoward effects [16-18].

The fast disintegrating tablets (FDTs) can be prepared using various techniques; such as tablet molding, sublimation, lyophilization, direct compression and addition of disintegrants, etc. Cost effective technologies like direct compression and disintegrant addition can be easily adapted by pharmaceutical companies [19,20].

Solubility is one of the most important parameters to achieve desired concentration of drug in systemic circulation to elicit pharmacological response [21,22]. Hydrotrophy is one of the innovative approaches as solubilization method whereby addition of large amounts of a second sparingly soluble solute [23,24]. The use of hydrotropic agents has several advantages over other solubility enhancing methods; because it doesn't require chemical modification and system emulsification, eco-friendly, independent of pH and high selectivity [25,26]. Among hydrotropes, nicotinamide (NIC) has three special advantages which make it a very attractive agent. It has FDA approval status, very low toxicity and economical [24,27,28].

MBZ is available in the forms of oral suspension (500 mg/5 mL), 100 mg tablet, 100 and 500 mg chewable tablet and administered orally [10,29]. In the present work, hydrotrophy method was used to increase the solubility of MBZ using NIC as a suitable hydrotrope and FDT was prepared from MBZ HSD using crospovidone by direct compression.

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Materials and Methods

The materials used were MBZ (SupharmaChem, India), NIC (Lonza Guangzhou Ltd, China), crospovidone (China Associate Co. Ltd, Shenzhen, China), MCC (Avicel[®] Microcellulose Weissenborn GmbH + KG, Weissenborn, Germany) and MNTL (China Associate Co. Ltd, Shenzhen, China), Whatman[®] filter paper, etc.

Calibration curve of mebendazole

As stock solution, 200 µg/mL were prepared using MBZ (10 mg) and formic acid (20 mL). This solution was made up to 50 mL and diluted to 3 -10 µg/mL solution using 0.1N HCl. They were filtered by Whatman[®] filter paper (2.5 µm) and absorbance determined using UV-VIS spectrophotometer at 286 nm using formic acid and 0.1N HCl mixture as blank. Finally, calibration curve was developed using absorbance and concentration data.

Determination of equilibrium solubility of mebendazole in nicotinamide solutions

Excess amount of MBZ was added to accurately measured 10 mL of 10, 20, 30 and 40% w/v of hydrotropic solutions in 0.1N HCl and shaken (5 rpm) on orbital flask shaker for 48 h; allowed to equilibrate for the next 48 h and centrifuged for 15 min at 2000 rpm at room temperature.

The supernatant filtered and analyzed spectrophotometrically at 286 nm against corresponding blank reagent (hydrotropic solution in 0.1N HCl). The experiment was performed in triplicate and the solubility of each preparation was estimated using calibration curve formula.

Preparation of mebendazole hydrotropic solid dispersion

By kneading technique, accurately weighed amount of MBZ and NIC were taken in a glass mortar and mixed for 5 min. Then, 99.5% methanol was added drop by drop while triturating to get slurry like consistency for 15 min. The uniform mass was dried in oven at 60°C for 4 h. The dried HSD was pulverized and passed through sieve № 60 (224 µm) and stored in screw capped glass vial until further evaluation.

In the solvent method, 99.5% methanol was used to dissolve the required amount of MBZ and NIC by continuous stirring with a magnetic stirrer for 30 min at room temperature. The paste formed was further dried in oven at 60°C for 4 h. The resulting solid dispersions was scraped, pulverized and sieved through a № 60 (224 µm) sieve and stored in screw capped glass vial at room temperature until further analysis.

Physical mixture (PM) was prepared by manually mixing MBZ and NIC of different ratios using glass mortar and pestle for 10 min

duration. Finally, the mixture was passed through sieve № 60.

Compatibility study: Fourier transform infrared spectroscopy

The compatibility between the drug and excipients used in the formulation was studied using Fourier transform infrared spectroscopy (FT-IR) (Shimadzu FTIR-8400S spectrometer, Japan). Samples of MBZ and HSD prepared by KM and PM of MBZ and crospovidone were grinded and mixed thoroughly with KBr at a 1:5 sample/KBr ratio. The KBr discs were prepared by compressing the powders at a pressure of 5 T for 5 min in a hydraulic press. The scanning range was 400 to 4000 cm⁻¹ and the resolution was 4 cm⁻¹.

In vitro dissolution tests of mebendazole hydrotropic solid dispersion

In vitro dissolution rates of pure drug and different HSDs powder were studied using USP 36/NF 31 (Type II) dissolution test apparatus. A USP Apparatus II (paddle) was set-up with a rotational speed of 75 rpm and 500 mL of dissolution medium (0.1N HCl). The temperature was maintained at 37.0 ± 0.5°C throughout the dissolution study. The amount of pure drug and HSD equivalent to 10 mg of MBZ were spread on the surface of the medium (0.1N HCl). The 5 mL sample withdrawn at predetermined time points was filtered and analyzed by UV-VIS spectrophotometer at 286 nm. The dissolution media replenished at each sampling time. All experiments were performed in triplicates and the cumulative amount of drug released from the system was estimated.

Measurement of micromeritic properties

Micromeritic properties like bulk density (pb), tapped density (pt), Hausner ratio (HR) and compressibility index (% CI) of MBZ, HSD and formulations powder blend were studied.

Seventy grams of MBZ, HSD and each formulations powder blend were carefully introduced into a 250 mL graduated cylinder and the bulk volume of the powder was noted. After 500 times tapped using a tap densitometer, the tapped volume was noted.

Preparation of solubility enhanced fast disintegrating tablets of mebendazole

Nine FDT formulations were manufactured using HSD (KM1:3) by direct compression. The composition of tablet formulations (Table 1) were HSD (KM1:3), MCC, MNTL, crospovidone, magnesium stearate, talc and colloidal silicone dioxide (cSiO₂). All ingredients were passed through mesh aperture of 224 µm. HSD prepared by KM1:3, MCC, MNTL and crospovidone were blended for 10 min. Magnesium stearate, talc and cSiO₂ were added to the blend and the final blend was lubricated for 3 min. Finally, the tablets were prepared by compression machine (punch 16/32) using suitable constant compression force.

Formulations	HSD (KM1:3) (% w/w)	Excipients (% w/w)					
		Crospovidone	MCC	MNTL	Talc	Mg stearate	cSiO ₂
F1	66.67	0	14.79	14.79	1	0.75	2
F2	66.67	0	9.86	19.72	1	0.75	2
F3	66.67	0	19.72	9.86	1	0.75	2
F4	66.67	3	13.29	13.29	1	0.75	2
F5	66.67	3	17.72	8.86	1	0.75	2
F6	66.67	3	8.86	17.72	1	0.75	2
F7	66.67	5	12.29	12.29	1	0.75	2
F8	66.67	5	16.39	8.19	1	0.75	2
F9	66.67	5	8.19	16.39	1	0.75	2

Table 1: Compositions of solubility enhanced fast disintegrating 600 mg MBZ tablet formulations.

Characterization of formulated tablets

The tablets were evaluated according to the USP 36/NF 31; based on hardness, friability, disintegration time, wetting time and *in vitro* dissolution rate evaluation criteria. Six tablets were randomly taken from each formulation and tablet hardness was measured by using hardness tester.

Tablet friability was determined by taking previously weighed 10 tablets in friabilator and rotated at 25 rpm for 4 min. The tablets were taken out, dusted and reweighed. The percentage friability of the tablets was calculated.

Six tablets from each formulation were randomly selected and placed in a disintegration apparatus filled with 900 mL of distilled water kept at $37 \pm 2^\circ\text{C}$. The time required for complete disintegration of the tablets with no palpable mass remaining in the apparatus was recorded as the disintegration time.

Three tablets of each formulation were taken and placed on Whatman[®] filter paper, folded once diametrically and placed in 8 mL water and bromophenol blue containing Petri dish (8.5 cm in diameter). The appearance of the dye on the surface of the tablet was taken as a sign for complete wetting and wetting time.

In vitro dissolution studies for the FDTs were carried out by using USP36 Type II dissolution apparatus at 75 rpm in 900 mL of 0.1 N HCl+1% sodium lauryl sulphate as dissolution medium maintained at $37 \pm 0.5^\circ\text{C}$. FDT of desired formulations was taken and placed in the vessels of dissolution apparatus. Sample of 10 mL were collected from the vessels at specified time intervals and replaced by blank medium. The sample filtered, and absorbance determined by UV-Visible spectroscopy at 286 nm. Blank experiments were also performed at 286 nm for correction. Drug concentration was calculated and expressed as drug percentage released.

Results and Discussion

Calibration curves of mebendazole

MBZ calibration curve was prepared by using formic acid+0.1N HCl as solvent and the UV-VIS spectrophotometer method. The 0.1N HCl was used because it simulates gastrointestinal/ stomach environment.

UV-Visible spectral studies of MBZ at 286 nm showed the linearity range in the concentration range of 3-10 $\mu\text{g/mL}$ (Figure 1).

Equilibrium solubility of mebendazole in nicotinamide solutions

The effect of NIC concentration on the solubility of MBZ was examined by the shake flask method. The solubility of MBZ in each preparation was determined using the formula:

\uparrow Solubility = Solubility of MBZ in hydrotropic solution/ solubility of MBZ in 0.1N HCl

Saturated solubility experiments showed that the concentration of MBZ in 0.1N HCl is notably affected by the presence of NIC (Figure 2). The solubility study diagram investigated in 0.1NHCl was positive curvature in a wide range of NIC concentrations. At 40% w/v concentration of NIC, the solubility of MBZ increased by more than 16-fold. The results were in accordance with the formation of soluble complexes between hydrotropic agents and poorly water-soluble drugs. Different studies demonstrated intermolecular interactions

between drug and NIC and wetting effect of NIC increase solubility and dissolution rate of poorly soluble drugs. The increase in solubility, however, was not a linear function of NIC concentration; suggesting the formation of higher order complexes [28,30,31].

Compatibility study: Fourier transform infrared spectroscopy

The FT- IR spectrum of 1MBZ: 3NIC prepared by KM (Figure 3A) showed characteristic peaks of MBZ at 3363.62 for N-H stretching, 1458.08 for aromatic ring stretching and 2854 for CH₃ stretching.

And, the PM of MBZ and crospovidone (Figure 3B) showed MBZ peaks near 3350 for N-H stretching, near 2850 for CH₃ stretching and at 1458.08 for aromatic ring stretching. Both KM prepared HSD and PM of MBZ and crospovidone showed the essential peaks for MBZ at 1458.08 for aromatic ring stretching. On the other hand, MBZ exhibits the broad infrared band around 2900 cm^{-1} characteristic of benzimidazole in both PM and MBZ HSD prepared by KM (Figure 3C).

According to FT- IR study results, there was no major shift in the peak positions and retention of characteristic peaks for MBZ in MBZ HSDs and MBZ + crospovidone PM. Moreover, different studies showed that other ingredients used in this study, such as, aerosil,

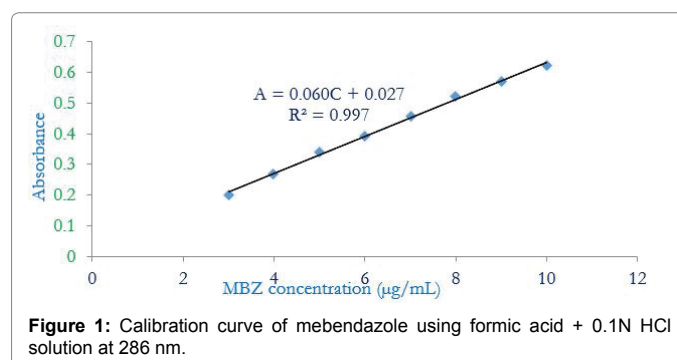


Figure 1: Calibration curve of mebendazole using formic acid + 0.1N HCl solution at 286 nm.

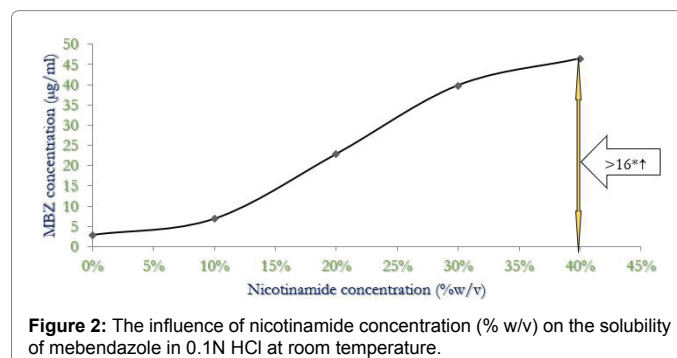


Figure 2: The influence of nicotinamide concentration (% w/v) on the solubility of mebendazole in 0.1N HCl at room temperature.

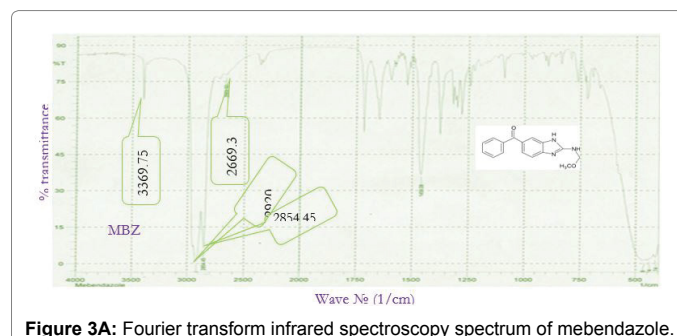


Figure 3A: Fourier transform infrared spectroscopy spectrum of mebendazole.

magnesium stearate, MCC and MNTL, are used in the conventional MBZ tablet without affecting drug therapeutic effects.

***In vitro* dissolution profiles of mebendazole hydrotropic solid dispersion**

In vitro dissolution study is the most significant evaluation parameter for any solid dosage form. MBZ alone and its' HSDs *in vitro* dissolution were carried out to determine the rate and extent of dissolution.

From the dissolution studies, depending on their drug release rate and amount within 90 min, the HSD prepared by KM had greatest dissolution rate and amount than those prepared by physical method, solvent evaporation method and MBZ alone. KM is also the safest method compared to solvent evaporation and hot melt method (Figure 4) [32].

HSD prepared by KM with the lowest amount of hydrotropic carrier (KM1:1) showed low percentages dissolved within 90 min. A similar observation of concentration dependence of NIC on improving

dissolution profile of poor water-soluble drugs was reported by Coffman, Kildsig and Evstigneev et al. [23,33]. Depending on the ratio of MBZ: NIC, there is no much difference in increment of dissolution rate and amount among KM 1:3, 1:4 and 1:5 ratio. So, HSD prepared by KM using 1MBZ: 3NIC (KM1:3) was used for developing FDT to enhance the solubility of poor water soluble MBZ.

Micromeritic properties of mebendazole hydrotropic solid dispersions and different formulations' powder blend

Powder flow properties are crucial in handling and processing operations such as flow from hoppers, mixing and compression. In recent years, the CI and the closely related HR have become simple, fast and popular methods of predicting powder flow characteristics.

Based on the results (Table 2), HSD preparation modified the % CI and HR of MBZ; indicating the improvement of flow and compressibility. The % CI values for all the formulation batches were found between $19.45 \pm 0.66\%$ to $22.96 \pm 0.25\%$; which is satisfactory for the powder flow and imply that the blends have good compressibility. HR values obtained were in the range of 1.24 ± 0.01 to 1.297 ± 0.01 ; which shows a passable flow property for the powder blend based on the USP [34].

Generally, the micromeritic properties indicated that HSDs possess improved flow and compacting properties compared to MBZ alone. Thus, MBZ HSDs would be more convenient for solid dosage form design and manufacture by direct compression.

Characteristics of tablet formulations

Preliminary experiments indicated that independent variables, such as MBZ: NIC ratio, percentage of croscopvidone and MCC: MNTL were found to be the critical factors which affect the various responses. The main response variables investigated were tablet disintegration time, hardness and *in vitro* drug release within 90 min. FDTs were prepared and examined visually that they were smooth. As tablet must show good mechanical strength in order to withstand handling during manufacturing, packaging and transportation, tablet hardness for all batches was found in the range between 6.6 ± 0.35 - 10.25 ± 0.79 kg/cm². Friability values for all the formulations were found to be in the range of 0.39- 0.66%. The results obtained were found to be within the acceptable range (<1%); indicating sufficient mechanical integrity and strength for the prepared tablets according to the USP [34].

For FDT, disintegration time is considered to be one of the important criteria in selecting the best formulation. As shown in Table 3, the *in vitro* disintegration time ranged from 21 ± 1.7 - 214 ± 4.6 sec. Wetting time was determined for all the nine formulations (Table 3), and the results revealed that the wetting time ranged from 56 ± 3.0 - 225 ± 3.6 sec. Formulation (F8), which contains 5% croscopvidone, 2:1 MCC: MNTL and MBZ: NIC (KM1:3) have the shortest disintegration time (21 ± 1.7 sec), lowest wetting time (56 ± 3.0 sec) and highest crushing strength (10.25 ± 0.79 kg/cm²). These properties could be due to the binding and disintegrant properties of MCC and the disintegration and hygroscopic properties of croscopvidone.

The *in vitro* drug release behaviors of different formulations were studied. The USP36/NF31 (2013) specification for the release of MBZ from tablets states that not less than 75% of the label claims of MBZ should be dissolved in 120 min [34]. As can be seen in (Figure 5), all the formulations released more than 75% of the label claim within 20 min except formulation without NIC. Thus, all the FDT formulation, except F10 which doesn't contains NIC, passed the USP requirement for dissolution within 20 min.

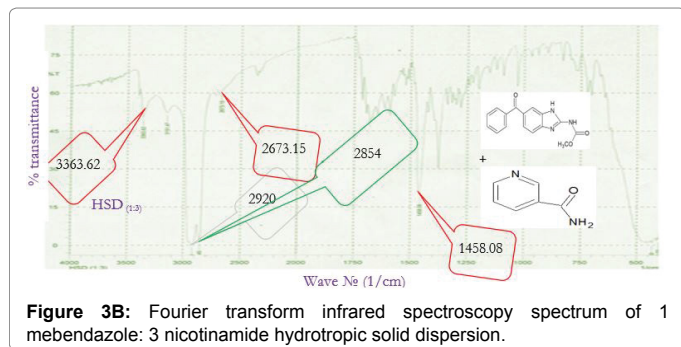


Figure 3B: Fourier transform infrared spectroscopy spectrum of 1 mebendazole: 3 nicotinamide hydrotropic solid dispersion.

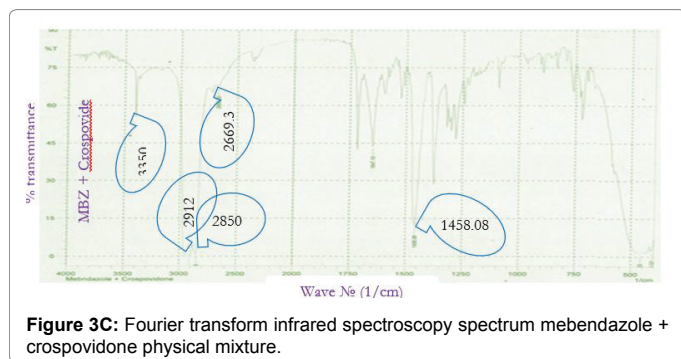


Figure 3C: Fourier transform infrared spectroscopy spectrum mebendazole + croscopvidone physical mixture.

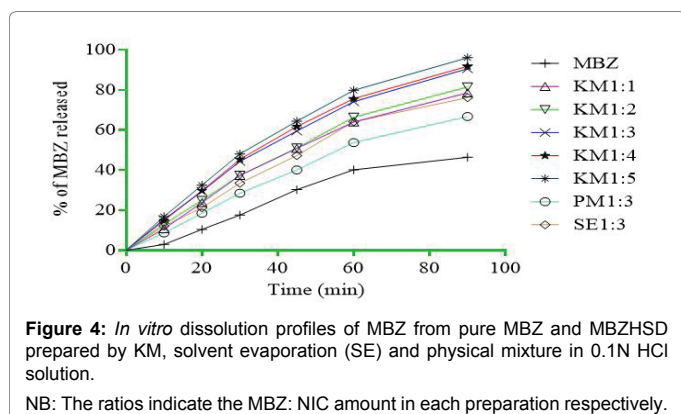


Figure 4: *In vitro* dissolution profiles of MBZ from pure MBZ and MBZHSD prepared by KM, solvent evaporation (SE) and physical mixture in 0.1N HCl solution.
NB: The ratios indicate the MBZ: NIC amount in each preparation respectively.

Formulation	pbulk (g/mL) ± sd	ptapped(g/mL) ± sd	CI (%) ± sd	HR ± sd
MBZ alone	0.22 ± 1.12	0.31 ± 0.31	29.0 ± 2.10	1.41 ± 0.23
HSD (KM 1:3)	0.48 ± 0.06	0.59 ± 0.11	16.92 ± 2.6	1.20 ± 0.06
F1	0.46 ± 0.00	0.58 ± 0.01	20.69 ± 0.70	1.26 ± 0.01
F2	0.49 ± 0.00	0.60 ± 0.02	19.45 ± 0.66	1.24 ± 0.01
F3	0.45 ± 0.01	0.59 ± 0.00	22.70 ± 0.00	1.29 ± 0.00
F4	0.46 ± 0.02	0.58 ± 0.01	20.40 ± 0.14	1.26 ± 0.00
F5	0.46 ± 0.03	0.57 ± 0.01	20.30 ± 0.27	1.25 ± 0.01
F6	0.44 ± 0.00	0.58 ± 0.03	22.96 ± 0.25	1.29 ± 0.00
F7	0.43 ± 0.00	0.55 ± 0.02	21.98 ± 0.07	1.28 ± 0.02
F8	0.43 ± 0.01	0.56 ± 0.13	22.86 ± 0.24	1.29 ± 0.01
F9	0.46 ± 0.00	0.57 ± 0.00	20.0 ± 0.15	1.25 ± 0.00

Table 2: Micromeritic properties of mebendazole alone, hydrotropic solid dispersion prepared by kneading method and powder blends.

Formulation	Hardness (kg/cm ²)	Friability (%)	Disintegration time (sec) ± sd	Wetting time (sec) ± sd	Weight variation (mg)	Drug content (%)
F1	8.00 ± 0.70	0.52	134 ± 2.5	170.7 ± 2.0	581 ± 1.44	97.2 ± 1.35
F2	6.60 ± 0.35	0.64	214 ± 4.6	225 ± 3.6	590 ± 0.72	96.7 ± 0.51
F3	9.70 ± 0.14	0.39	56 ± 4.6	125 ± 3.2	582 ± 1.25	98.0 ± 0.75
F4	8.30 ± 0.80	0.52	29 ± 2.3	80 ± 2.5	596 ± 1.20	96.5 ± 0.72
F5	9.80 ± 1.00	0.40	25 ± 0.58	65 ± 2.0	590 ± 1.23	98.5 ± 0.86
F6	6.67 ± 0.75	0.65	34 ± 0.58	85 ± 2.9	579 ± 1.02	96.7 ± 1.23
F7	8.60 ± 0.10	0.53	26 ± 0.58	75 ± 2.6	580 ± 0.87	98.2 ± 0.92
F8	10.25 ± 0.79	0.41	21 ± 1.7	56 ± 3.0	572 ± 1.33	98.2 ± 1.53
F9	6.70 ± 0.33	0.66	31 ± 3.2	70 ± 4.2	585 ± 1.43	96.3 ± 1.25

Table 3: Hardness, friability, disintegration and wetting times of solubility enhanced fast disintegrating tablets of mebendazole prepared for optimization.

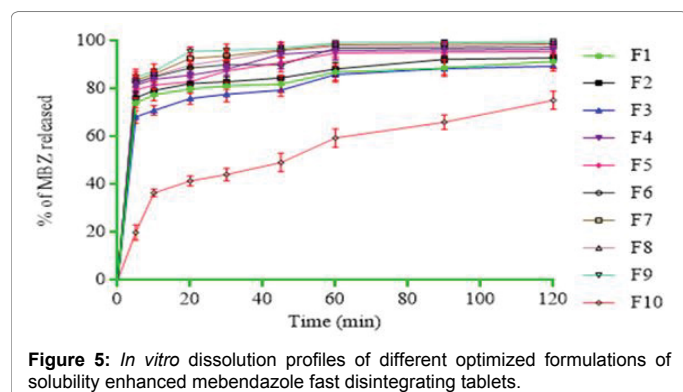


Figure 5: *In vitro* dissolution profiles of different optimized formulations of solubility enhanced mebendazole fast disintegrating tablets.

Conclusion

NIC enhanced the solubility of MBZ more than 16 times in 40% w/v hydrotropic solution. HSD powder of MBZ prepared using KM (1:3) showed the optimum *in vitro* drug release profile of MBZ. The rapid *in vitro* release behavior could be due to the fast dissolution time of NIC, together with its superior dispersibility and excellent wetting properties. The independent variables (crospovidone and MCC: MNTL) significantly affected the various responses; such as tablet hardness, disintegration time, friability and *in vitro* drug release of solubility enhanced FDTs. So, solubility enhanced FDTs of MBZ, which is suitable for paediatric, geriatric and other special population patients can be successfully developed by simple and feasible manufacturing method.

Recommendations for Further Research

- Investigate the *in vivo* drug release profile and performance of the optimized formulation;
- Determine the long-term stability study of the optimized batch in order to determine the shelf life of the product;

Perform optimized pilot scale and commercial scale production of the optimized formulation.

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