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RESEARCH ARTICLE

PREPARATION AND CHARACTERIZATION OF SELF EMULSIFYING SOLID DISPERSIONS OF MEBENDAZOLE TO IMPROVE SOLUBILITY

Ayesha Pervaiz[1], Muhammad Asad Saeed[2], Maham Anwar[1], Ujala Mansoor[1], Ushna Shabbir[1], Maryam Khalid[1]*

[1]Faculty of Pharmacy, University of Lahore, Pakistan, [2]Faculty of Pharmacy, University of Central Punjab, Lahore, Pakistan.

*** Corresponding author's email:** asad.saeed@ucp.edu.pk
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ABSTRACT

Background: In drug development process, poor aqueous solubility is one of the challenging factors. To design an oral dosage form, poor bioavailability is the major challenge. **Objectives**: The aim of this study was to improve the solubility of mebendazole (MBZ) by formulating solid dispersion (SDS) and self-emulsifying solid dispersions (SESDS). Mebendazole is an BCS class II drug having low solubility and can ultimately lead to poor absorption and low bioavailability. **Methodology:** Physical mixture and kneading method were employed to enhance the solubility of MBZ and prepare SDS and SESDS using poloxamer-188 as the hydrophilic carrier. Soybean oil, sodium lauryl sulfate (SLS) and Transcutol-P were used as oil, surfactant, and cosurfactant, respectively. Eight formulations were designed to formulate SDS by varying the ratios of MBZ and Poloxamer-188 (1:1, 1:2, 1:3 and 1:4). All formulations were evaluated for solubility studies, and a formulation that showed maximum enhanced solubility was selected to prepare SESDS of mebendazole. All of the prepared formulations were characterized by Fourier transform infrared spectroscopy, X-ray diffraction, thermogravimetric analysis, differential scanning calorimetry, and scanning electron microscopy to check chemical interactions, crystallinity, thermal stability, drug entrapment and morphological changes, respectively. **Results:** The results show that SDS and SESDS improved solubility compared to that of a pure drug. However, SESDS prepared using kneading methods showed the highest drug solubility (6.61 folds) as compared to pure drug. **Conclusion:** The study concluded that solubility of MBZ improved due to increased wettability, hydrophilicity of carrier and reduced crystallinity.

Keywords: Mebendazole, Solid dispersions, Self-emulsifying, Solid dispersions, Mebendazole, Transcutol-P

INTRODUCTION

Bioavailability depends on many factors including solubility. At site of absorption aqueous solution of drug is required to achieve pharmacological response. Poor solubility often leads to low oral bioavailability and high doses of drug especially for class II drugs of biopharmaceutical classification system (BCS) (1). Different factors affect the solubility of drug molecules such as particle size, nature of solute and solvent, temperature, pressure, molecular size (2), polarity, and polymorphs (3). All those issues can be resolved by solubility enhancement techniques (Physical modification, Chemical modifications, and Miscellaneous techniques). Physical modification is the main method that include modification of crystal habit like polymorphs, amorphous form and co-crystallization, particle size reduction by making nanosuspension or drugs dispersion in different carriers i.e. solid dispersion, solid solutions and different cryogenic techniques (1). All of these techniques are important but solid dispersion is one of the best strategy to improve drug solubility (4).

Self-emulsifying drug delivery system (SEDDS) have reported the usefulness of oil or lipid base preparations for augmenting the solubility and bioavailability of poor water-soluble drugs. These preparations generally include either solutions of drug in tri-glycerides or complex mixture of drug, triglyceride (oil), surfactant, co-surfactant and co-solvents to solubilize the drug. Depending on the composition of formulation and sizes they are described as self-emulsifying drug delivery system (SEDDS), self-micro-emulsifying drug delivery system (SMEDDS) and self-nano-emulsifying drug delivery system (SNEDDS) (5). SEDDS formulation includes the solubilization of hydrophobic drug in mixture of oil and surfactant and then dispensed as a bulk liquid for incorporation or filled into soft capsules of gelatin. Problem associated with liquid state of SEDDS is the delectability of oily liquid and filling of oil into soft capsules of gelatin during early stage of development. These are the aspects which are disadvantageous for the commercialization of these products (6).

Solid SEDDS are the semi-solid or solid preparations at room temperature that can be transformed into powders or other dosage forms of solid. They usually combine the advantages of self-emulsifying drug delivery system (SEDDS) i.e. improved or augmented solubility and bioavailability with that of solid dosage forms i.e. high stability, low cost fabrication, better patient compliance and high reproducibility (6). Self-emulsifying solid dispersion is an effective strategy to augment the solubility of hydrophobic drugs with solubilizers and polymers. It is a reasonable way to enhance surface area, improve wettability, lessen agglomeration and transform the drug into amorphous state resulting in increased solubility. Melting method is one of the conventional strategies to formulate SESDS (7). Different SEDDS were prepared for various drugs such as fenofibrate to enhance the dissolution of drug (6), clopidogrel napadisilate (8), ezetimibe (9), itraconazole (10), revaprazan (11), isradipine (12), and erlotinib (anticancer drug) (13). Some commercially available clinically approved solid dispersions are Griseofulvin,

Isotretinoin, Nilvadipine, Cyclosporine, Everolimus, Tipranavir, Nimodipine, and Amprenavir (14).

Mebendazole (MBZ) is an essential drug that was used as a anthelmintic drug in clinical and veterinary treatment (15). Chemical name of MBZ is methyl-5-benzoyl benzimidazole-2-carbamate (16) belongs to benzimidazole class and it is broad spectrum anthelmintic drug (17). Its molecular formula and molecular weight is $C_{16}H_{13}N_3O_3$ and 295.30 g/mole respectively (18), with an melting point of 288.5 $^{\circ}$C (19). It has poor aqueous solubility or practically insoluble in water and freely soluble in formic acid (20). MBZ belongs to class II of BCS (21). MBZ causes selective and irreversible inhibition of glucose and other nutrients uptake in vulnerable helminths. This inhibition results in endogenous glycogen depletion in helminths. It does not prevent glucose uptake in mammals. It causes degenerative changes in the absorptive cells of cestodes and in the intestine of nematodes. The primary anthelmintic effect of MBZ is the degeneration of cytoplasmic microtubules in the intestinal and absorptive cells (21). In this study we aimed to enhance or improve the solubility and oral bioavailability of poorly water-soluble drug by preparing SDS with hydrophilic carrier matrix and SESDS with oil, surfactant, co-surfactant and carrier.

MATERIALS & METHODS

Materials

Mebendazole was received as a generous gift from Wilsons Pharmaceuticals Pvt. Ltd. Pakistan, poloxamer-188, sodium lauryl sulphate and methanol were purchased from Sigma Aldrich, Germany, transcutol-P from Merck KGaA, Darmstadt, Germany, soybean oil, dimethyl sulphoxide from Labscan Asia Co. Ltd, Bangkok Thailand). All the chemicals were of analytical grade.

Methods

Preparation of Solid Dispersions (SDS)

Different ratios of SDS of MBZ were prepared by using Poloxamer-188 by physical, kneading and fusion methods as shown in Table 1.

Table 1. Formulation Design for SDS

Sample code	Mebendazole (g)	Poloxamer-188(g)
PM 1:1	1.5	1.5
PM 1:2	1.0	2.0
PM 1:3	1.0	3.0
PM 1:4	0.8	3.2
KM 1:1	1.5	1.5
KM 1:2	1.0	2.0
KM 1:3	1.0	3.0
KM 1:4	0.8	3.2
FM 1:1	1.5	1.5
FM 1:2	1.0	2.0
FM 1:3	1.0	3.0
FM1:4	0.8	3.2

- PM; Physical mixture, KM; Kneading method, FM; Fusion method

Preparation of Self-Emulsifying Solid Dispersions (SESDS)

SESDS were prepared using MBZ (drug), Poloxamer-188 (polymer), SLS (surfactant), Transcutol P (co-surfactant) and soybean oil (oil phase). These were prepared in different ratios as mentioned in Table 2.

Table 2. Formulation design for SESDS

Formulation	Mebendazole	Poloxamer-188	SLS	Transcutol-P	Soybean oil
S-PM 1	1.0	4.0	2.5	2.0	0.5
S-PM 2	1.0	4.0	3.5	1.0	0.5
S-KM 1	1.0	4.0	2.5	2.0	0.5
S-KM 2	1.0	4.0	3.5	1.0	0.5

- S-PM; SESDS Physical mixture, S-KM; SESDS Kneading method

EVALUATION OF PREPARED FORMULATIONS

Calibration Curve

Stock solution of MBZ was prepared in Dimethyl sulphoxide (DMSO) by dissolving 5mg of drug in 50ml of solvent. Further dilutions of 6µg/ml, 8µg/ml, 10µg/ml, 12µg/ml, 14µg/ml, 16µg/ml, 18µg/ml and 20µg/ml were prepared from stock solution. All the dilutions were evaluated spectrophotometrically at 320nm utilizing Shimadzu-1800 UV-Visible spectrophotometer. Calibration curve was constructed between different concentrations versus absorbance. Regression equation was obtained and used for quantification of drug.

Solubility Studies

Solubility study of pure drug and formulations was determined by adding surplus amount of them in glass test tubes having 10 ml of distilled water to obtain saturated solution. Sealed tubes were placed in thermo-statically controlled orbital shaker (shaking incubator S 1990 R) for 24 h at 37 ± 0.5 ºC and operated at 150 rpm. After that, samples were taken out from shaker and were filtered through syringe filter of 0.45µm. The filtered samples were evaluated spectrophotometrically at 320nm utilizing Shimadzu 1800 UV-Visible spectrophotometer. Concentration of drug and formulations were calculated from the regression equation obtained from calibration curve (22).

Fourier Transform Infrared Spectroscopy

FTIR spectra of pure drug (MBZ), poloxamer-188, SLS, Transcutol-P, Soybean oil, SDS and SESDS were performed at room temperature using FTIR spectrophotometer in the range of 650-4000cm^{-1}. All of these spectra were recorded in percentage (%) transmittance. Samples were placed on the surface KBr disc and FTIR spectra were measured (23). It has been used effectively for finding the different bonding arrangements and crystal packing in various organic compounds (24).

X-Ray Powder Diffractometry (XRPD)

XRPD analysis was performed for pure drug, poloxamer-188, SLS, SDS and SESDS with X-Ray Diffractometer (JDX-3532 JEOL, Japan). Instrument was calibrated by using silicon reference standard and analysis was performed at ambient temperature. Diffractograms were obtained by using Cu Kα radiations at a resolution of 0.03° 2θ. The tube voltage and amperage were 40 kV and 30 mA, respectively (25). Each solid substance has a distinctive XRPD pattern, which can be used for its recognition (20).

Thermogravimetric Analysis (TGA)

Thermograms of pure MBZ, poloxamer-188, SLS, SD and SESDS were obtained by using Thermogravimetric Analyzer 50H, Shimadzu Japan. 10mg of each sample was taken in Platinum pan and heated at the rate of 10 ^{o}C min^{-1} from room temperature to 600^{o}C under Nitrogen gas stream with flow rate of 20ml/min (26). TG thermograms are the graphical representation of change in mass of a substance with time or temperature and thermal stability of materials (27).

Differential Scanning Calorimetry (DSC)

The DSC thermograms of pure MBZ, poloxamer-188, SLS, SD and SESDS were executed by utilizing DSC instrument. About 4-5mg of sample was placed in aluminum pan and scanned between the temperature ranges from 25 ^{o}C- 300 ^{o}C under the nitrogen gas purging with flow rate of 20ml/min (28, 29). It is used to measure the temperature at which thermal events happen i.e. glass transition temperature T_g (30), melting point, recrystallization and amount of crystalline material (31).

Scanning Electron Microscopy (SEM)

The surface and morphological characteristics (32) of pure drug, Poloxamer-188, SLS, SD and SESDS were studied by using SEM, Perkin Elmer, USA. Scanning electron micrographs of all the samples were taken at resolution of 0.5µm, 1µm, 5µm, 10µm and 50µm and at the magnification of X500, X1000, X2500, X5000, X10000 and X30000.

RESULTS & DISCUSSION

Standard Calibration Curve of Mebendazole (MBZ)

The stock solution of pure drug (MBZ) was made by dissolving 5mg of drug in 50ml of DMSO solution. Different concentrations of MBZ were made from this stock solution i.e. 6µg/ml, 8µg/ml, 10µg/ml, 12µg/ml, 14µg/ml, 16µg/ml, 18µg/ml and 20µg/ml. All the dilutions were evaluated spectrophotometrically at 320nm and standard calibration curve was plotted (Figure 1).

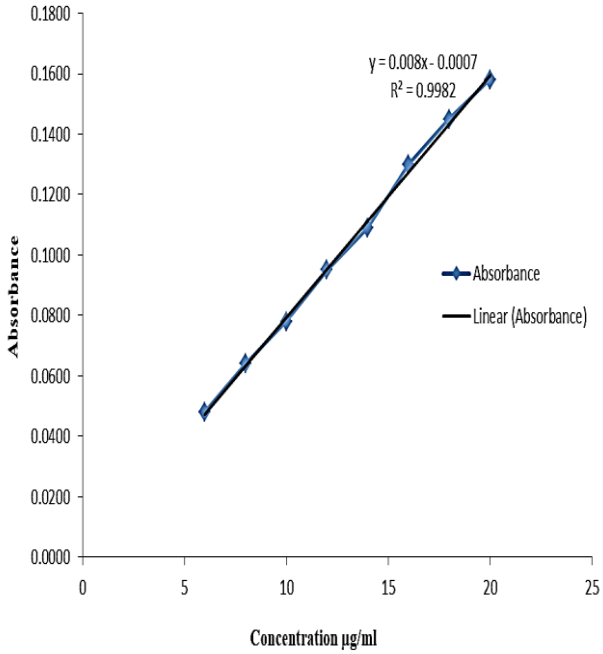

Figure 1. Calibration curve of MBZ in distilled water

Solubility Studies

The solubility of pure drug and formulations were calculated according to the regression equation. The solubility of pure drug was 8.21µg/ml in distilled water. The solubility of solid dispersions was increased and highest increase was seen in formulation KM 1:4 (4.15 folds) then FM KM 1:4 (3.51 folds) and PM KM 1:4 (1.79 folds) as presented in Figure 2. All formulation exhibited improved solubility as compared to pure drug. The dispersion of pure drug in polymer results in the reduction of particle size of drug which results in increase in the wettability and eventually solubility. This improved in solubility of poor water soluble drug MBZ

was supported by the results of XRPD i.e. change in crystalline status of drug (33). The results of solubility showed agreement with the earlier reported study for etoricoxib-poloxamer 188 SDS (34).

SESDS exhibited greater solubility as compared to pure drug and SDS. In Figure 3, increase in solubility of SESDS prepared by physical mixing such as S-PM 1 and S-PM 2 was 38.59µg/ml (4.69 folds increment) and 47.09µg/ml (5.73 folds increment) as compared to pure drug. SESDS prepared by kneading method i.e., S-KM 1 and S-KM 2 also exhibited increased solubility i.e., 51.71µg/ml (6.29 folds) and 54.34µg/ml (6.61 folds) than pure drug. The order of enhancement in solubility was similar to SDS (KM > PM). Results showed that surfactant (SLS) and co-surfactant (Transcutol-P) played an important role in increasing the solubility of drug. The maximum increase in solubility was exhibited by kneading method S-KM 2. This result was supported by XRPD results where SESDS exhibited loss of crystallinity and improved solubility as compared to SDS (35). The solubility studies results depicted that the solubility of mebendazole was improved by the preparation of SDS.

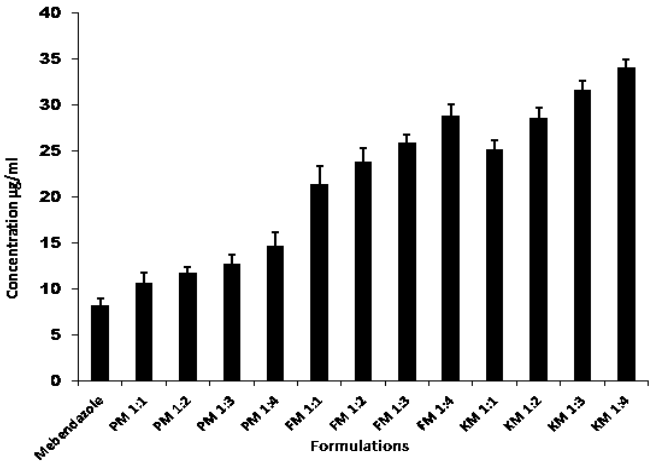

Figure 2. Solubility of SDS in distilled water

The ascending order of method with increased solubility was Physical mixture < Fusion method < Kneading method. SESDS containing additional surfactant (SLS), co-surfactant (Transcutol-P) and oil (Soybean oil) exhibited more increase in solubility as compared to SDS. The Kneading method exhibited higher solubility as compared to Physical mixture in SESDS.

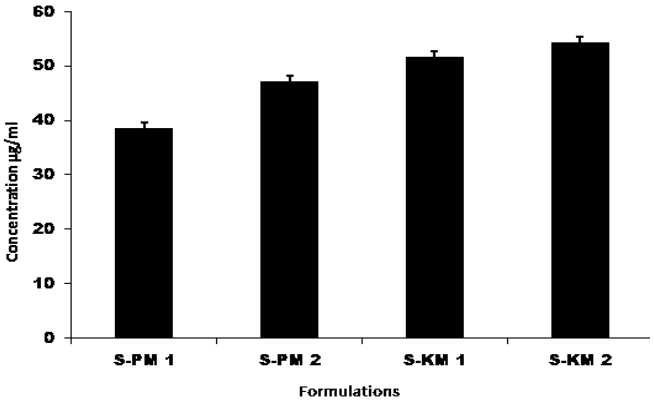

Figure 3. Solubility of SESDS in distilled water

Fourier Transform Infrared Spectroscopy (FTIR)

To identify the different polymeric forms of mebendazole (MBZ), Infrared spectroscopy has appeared as a preferable method (36). It has also been used effectively for finding the different bonding arrangements and crystal packing in various organic compounds (24). The FTIR spectrum of Drug (A), Poloxamer-188 (B), Transcutol-P (C), and Soybean oil (D). was presented in Figure 4.The FTIR spectrum of MBZ showed characteristic peaks at 3369.5cm^{-1} (N-H stretching) and at 1729.5cm^{-1} (stretching vibration of C=O group) which is of amide band as reported earlier (15). This FTIR spectrum also showed the bands at 3056.4cm^{-1} and 2998.8cm^{-1} (aromatic C-H stretching), 2948.3cm^{-1} (CH_3 stretching), 2661cm^{-1} (C-H stretching), 1636.3 (C=O ketone stretching), 1591.6cm^{-1} (Aromatic C=C /C=N stretching), 1528.2cm^{-1} (Amide II Band), 1457.4cm^{-1} (aromatic ring stretching), 1323.3cm^{-1} (CH_2 deformation) , 1259.8cm^{-1} (Amide III Band) , 1226.3cm^{-1} (Amide IV Band) , 1192.7cm^{-1} (CH_2 wagging) , 1118.2cm^{-1} (CH_2 wagging) , 1088.4cm^{-1} (C-O stretching) , 1012cm^{-1} and 887.1cm^{-1} (C-H in-plane deformation) , 827.5cm^{-1} (C-H out-of-plane deformation) , 797.5 (CH_2 rocking) and 704.5cm^{-1} (N-H out-of-plane deformation). These values represented the active material was MBZ and these values were comparable to the earlier reported literature (24, 37). FTIR spectrum of poloxamer 188 showed the characteristic peak at 2885cm^{-1} (C-H stretch aliphatic) and at 1344.1cm^{-1} (in-plane O-H bending), comparable to the previously reported data which also showed the band at 1099.2cm^{-1} representative of C-O stretching and is exactly identical to earlier reported value by Sharma, *et al.*, (38). FTIR spectrum of sodium lauryl sulphate (SLS) showed characteristic peak of SO_2 stretching at 1213cm^{-1} (asymmetric) and at 1082cm^{-1} (symmetric). It also showed the bands at 2914cm^{-1} (aliphatic C-H stretching) and at 2847cm^{-1} which is for long-chain fatty alkyl group of surfactants. These values were comparable to the earlier reported values by Ng, Lee *et al.*, 2016 (39). FTIR spectrum of Transcutol-P showed characteristic band at 3434.6cm^{-1} was due to OH stretch and peak at 2873.41cm^{-1} indicated the methylene stretch. Characteristic peaks of CH_3 and CH_2 scissoring was observed at 1454.1cm^{-1} and 1351.85cm^{-1} respectively. It also showed the band at 1108.9cm^{-1} (C-O stretching) and at 1064.5cm^{-1} (O-H bending) confirming the presence of Transcutol-P as reported previously by Pireddu, *et al.*, 2018 (40). FTIR spectrum of soybean oil showed peaks at 3012.3cm^{-1} (=C-H) carbon-carbon double bond stretch, at 2927.41cm^{-1} and 2857.98cm^{-1} (C-H) saturated stretch of carbon-carbon bond, 1745.26cm^{-1} (C=O) stretch of carbonyl functional group and at 1160.9cm^{-1} (C-O-C) stretch of ester functionality. All these bands showed the agreement with the presence of soybean oil with little variation (41).

The FTIR spectrum of SD by kneading, showed the combination of bands of MBZ and poloxamer 188 with reduced peak intensities and minor shift in frequencies of bands. No change was observed in characteristic bands at 3369.5cm^{-1}, 1729.5cm^{-1} and 1457.4cm^{-1} for N-H stretching, C=O stretching (Amide) and aromatic ring stretching respectively. Only reduction in the intensities of band was observed (38).

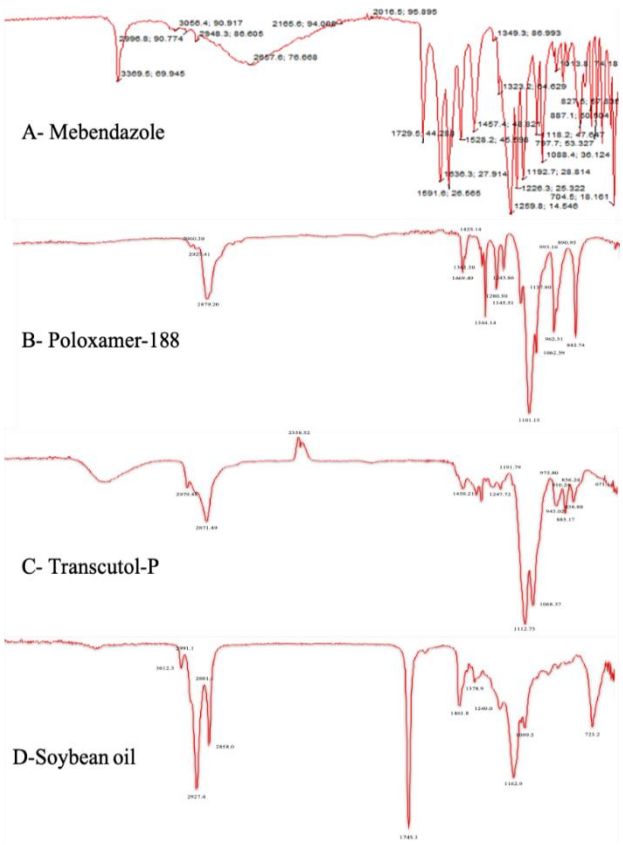

Figure 4. FTIR spectrum of Mebendazole (A), Poloxamer-188 (B), Transcutol-P (C), Soybean oil (D)

Increase in frequency of band at 1636.3cm^{-1} and 1591.3cm^{-1} to 1640.0cm^{-1} and 1595.3cm^{-1} for C=O (ketone) stretching and N=C stretching was also observed respectively. A pronounced peak at 2877.5cm^{-1} was observed in this spectrum which was not present in spectrum of pure drug. This was the peak of poloxamer 188 which got reduced to 2877.5cm^{-1} from 2883cm^{-1} (C-H stretch). As this characteristic peak of poloxamer is shifted so indicating the existence of physical interaction between drug and water soluble polymer as previously reported in SD of etoricoxib and poloxamer 188 (34). Two more intense peaks of poloxamer 188, at 1341.8cm^{-1} (in-plane O-H bend) and 1099.6cm^{-1} (C-O stretch) were observed. As this spectrum of MBZ and poloxamer 188 showing all peaks of drug with reduced intensity and all peaks of polymer with minor change indicating the possibility of inter-molecular interaction between drug and polymer as described earlier in SD of carvedilol and poloxamer 188 (38). This spectrum does not show any additional peak indicating no chemical interaction between polymer and drug (42).

In Figure 5, FTIR spectrum of SESDS by physical mixing exhibited no change in characteristic bands of MBZ at 3369.5cm^{-1} and 1729.5cm^{-1} for N-H stretching and C=O stretching (Amide) respectively. Only decline in the intensities of bands along with increase in frequency of band at 1636.3cm^{-1}, 1591.3cm^{-1} and 1457.4 to 1640.0cm^{-1}, 1595.3cm^{-1} and 1464.8cm^{-1} for C=O (ketone) stretching, N=C stretching and aromatic ring stretching was observed respectively(43). FTIR spectrum of SESDS by kneading method shown characteristic peaks of MBZ remained unchanged. They were identical to the SESDS prepared by physical mixing and were less intense as compared to pure drug. Peaks for poloxamer 188, Transcutol-P, SLS and soybean were also observed in this spectrum as in SESDS by physical mixing with minor change in frequencies. From above observations, it was concluded that significant bands of MBZ and excipients were present in these spectra and they didn't show any additional peak so there was no chemical interaction between them. Only the shift in the frequencies of bands was observed which indicate physical interaction between the excipients and drug (44).

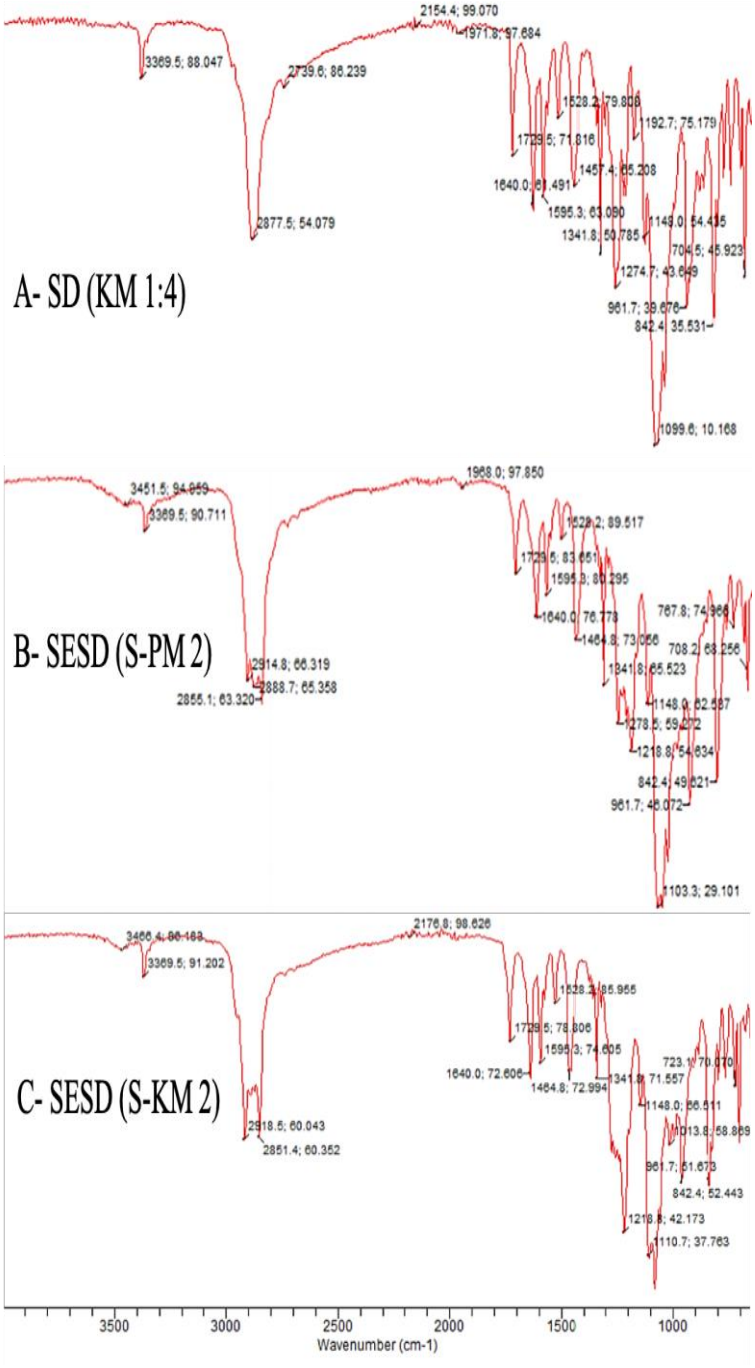

Figure 5. FTIR of A- SD (KM 1:4), B- SESD (S-PM 2), and C- SESD (S-KM 2).

Scanning Electron Microscopy (SEM)

SEM is used to investigate the shape and surface characteristics of different powder samples (17). Pure MBZ powder, polymer and SLS were examined by SEM to find any morphological changes in their shape. Pure MBZ powder (Figure 6-A) showed acicular form as previously reported by Garcia, *et al.*, 2011 (17). In Figure 6-B, poloxamer 188 showed presence of globular form as described by Sharma, *et al.*, 2013 (38). It had smooth surface with void spaces over it. In Figure 6-C, SEM of SLS particles showed irregular surface of particles that lead to the irregular SDES as represented in Figure 6-F. In Figure 6-D, SEM of SD prepared by kneading method showed absence of MBZ needle structure but presence of different shaped particles that depict both drug and poloxamer 188 has lost their original morphology. The results were supported by a previous study on carvedilol with poloxamer 188 by Sharma *et al*., 2013 (38), where surface of SD showed similarity to polymer's surface and new kind of structure was formed which revealed that drug got entrapped in the matrix of polymer and changed to partially amorphous form.

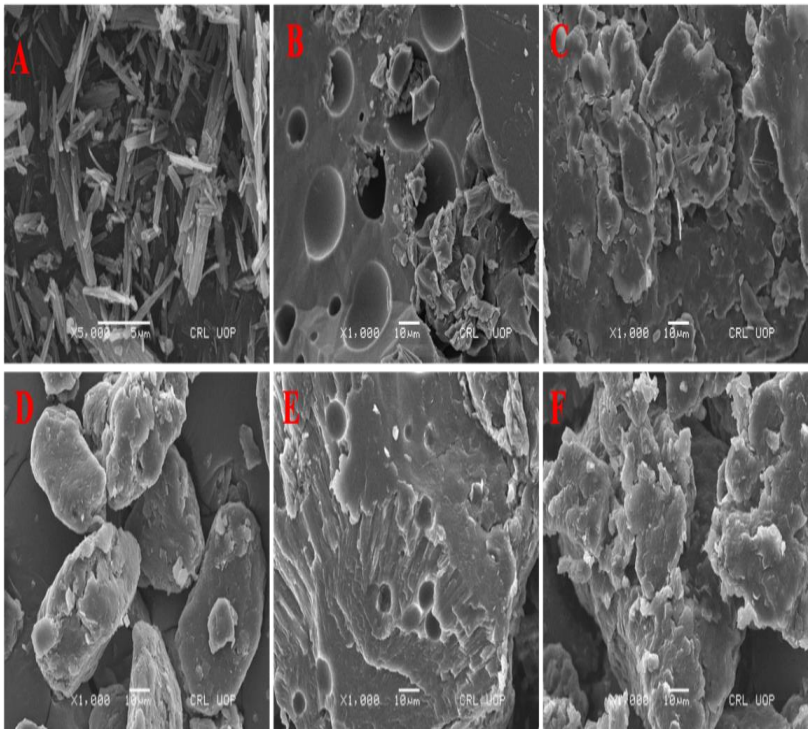

Figure 6. SEM of A- pure MBZ powder, B- poloxamer 188, C- SLS, D- SD (KM 1:4), E- SESD (S-PM 2), F- SESD (S-KM 2).

In Figure 6-E, SEM of SESD prepared by physical mixing showed irregular shape particles that exhibited rough surface. Particles were diffused and needles of pure drug were not visible which was signified with the physical interactions between drug and excipients. On higher magnification they were exhibiting smooth surface. The SEM images of SESD by kneading method (Figure 6-F) exhibited acicular shaped particles of drug were not visible and particles were exhibiting distorted surface.

The size of particle becomes small with the increased in surface area. From the results of SEM analysis, it was concluded that drug got fully dispersed in polymer matrix and results were related with a study by Rao, *et al.*, 2011 (45) where they report that, it was difficult to distinguish between the particle of polymer and drug. Overall drug, polymer and surfactant have lost their original morphology like earlier explained by Chen, *et al.*, 2008 (46).

But in SESD by kneading method, due to ruptured and smaller particle size, surface area increases due to which it will be easy for solvent to contact with particles and eventually the solubility will increase.

X-Ray Powder Diffraction (XRPD)

This technique is used to identify the changes in crystallinity of solid substances and one of the parameter accountable for increased solubility (38). Each solid substance has a distinctive XRPD pattern, which can be used for its recognition (20). Higher peak intensities of powder indicated the increased level of crystallinity. Sharp and intense peaks of MBZ revealed that it was crystalline in nature. The characteristic peaks of MBZ were at angle 2θ, degree of 7.5° and 17.2°. These characteristic peaks confirmed crystalline nature of drug (17).

Two more peaks at angle of 23.4° and 28.5° were seen. A study reported by Garcia Rodriguez, *et al.*, found similar diffractogram of drug which was identical to current study (17). Poloxamer 188 shown two distinct peaks at 19.1° and 23.5°, depict crystalline nature (38). The diffractogram of SLS exhibited a single intense peak at angle of 6.4° comparable to previously reported value (47). Characteristic peak of SLS was sharp and intense indicated that it is crystalline in nature (39). The XRPD pattern of SD (KM 1:4) showed peaks at 7.6° and 17.1° for drug with decreased count value. It exhibited the intense peaks of polymer at angle of 19.03° and 23.17°. This pattern of prepared formulation exhibited that peaks of drug remained at same position that validated the stability of drug (22). The diffractogram of recrystallized MBZ exhibited similar diffraction pattern with reduced peak intensity which indicated increase in amorphous state of drug with reduced crystallinity. This could contribute as one of the parameter for enhanced solubility (48). The diffractogram of SESD prepared by physical mixing showed peaks at angle of 19.18° and 23.6° for poloxamer 188, exhibited distinctive peak at 6.49° which was actually a peak of surfactant (SLS) (47). Due to the presence of surfactant, only a single characteristic peak of drug at 17.3° was present but with reduced intensity, which means crystallinity of drug was reduced more. Absence of various peaks of drug in the diffractogram revealed that drug has changed into less crystalline state (49). The XRPD pattern of SESD by kneading method presented the peaks at angle of 4.24°, 6.43°, 17.17°, 18.94° and 23.2°. This pattern was comparable to the pattern of

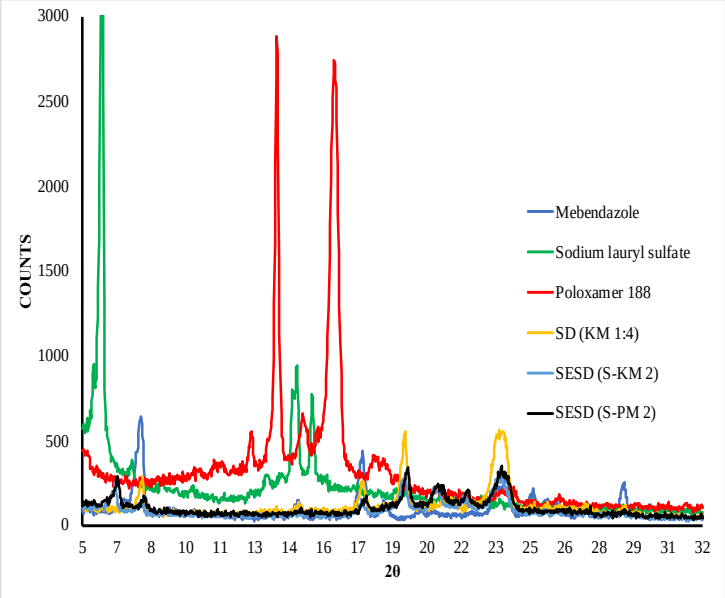

Figure 7. XRPD pattern of MBZ, Poloxamer 188, SLS, SD (KM 1:4), SESD (S-PM 2), and SESD (S-KM 2).

SESD by physical mixing. All peaks were present in this diffractogram with reduced count values as compared to SD by kneading method and SESDS by physical mixing. All other peaks of drug were absent in this diffractogram except one which is equal to 17.1°. Peak intensities got reduced which indicated that crystallinity of drug has changed but yet not completely amorphous. This could be one of the factor for increased solubility of drug (48) (Figure 7).

Thermogravimetric Analysis (TGA)

TG thermograms are the graphical representation of change in mass of a substance with time or temperature and thermal stability of materials (27, 50). Thermogram of pure drug did not show any weight loss before 200° C which confirmed the presence of MBZ as previously reported by Roque *et al.*, 2020 (51) and this is the most stable form (52). TG curve of MBZ exhibited mass loss at 244.54°C in which MBZ lost methoxy carbonyl group (-$COOCH_3$). MBZ exhibited another loss at 343.7 °C (Figure

8 A). These thermal decomposition values showed an agreement with the previously reported values (19, 53). Thermogram of poloxamer-188 exhibited loss at 270.3 °C (Figure 8 B). In SLS, loss in weight initiated at 203.85 °C and no further loss was observed after 586.93 °C (Figure 8 C). TGA of SD exhibited single step degradation which started at 383.49 °C. TG curve of SD (Figure 8 D) exhibited higher onset of degradation as compared to pure MBZ. This shift in temperature showed that both of these have different type of packing arrangements. Besides, the SD of MBZ with poloxamer-188 exhibited improved thermal stability as compared to pure drug as previously reported by Xiangjun *et al.,* 2021 in SD of celecoxib with aerosil and poloxamer-188 (54). TG curve of SESD prepared by physical mixing (Figure 8 E) showed degradation in two steps. The first mass loss occurred at 253.6 °C followed by the mass loss at 385.2 °C. Thermogram of SESD prepared by kneading method (Figure 8 F) also exhibited two steps degradation at 265.15 °C and final mass loss occurred at 397.38 °C. From above observations, it was concluded that the onset of degradation temperature increased in both formulations as compared to pure drug depicting improved thermal stability. Comparison of both SESD formulations revealed that SESD prepared by kneading method was more thermostable than by physical mixing. TGA results of pure drug, excipients and formulations are documented in Figure 8.

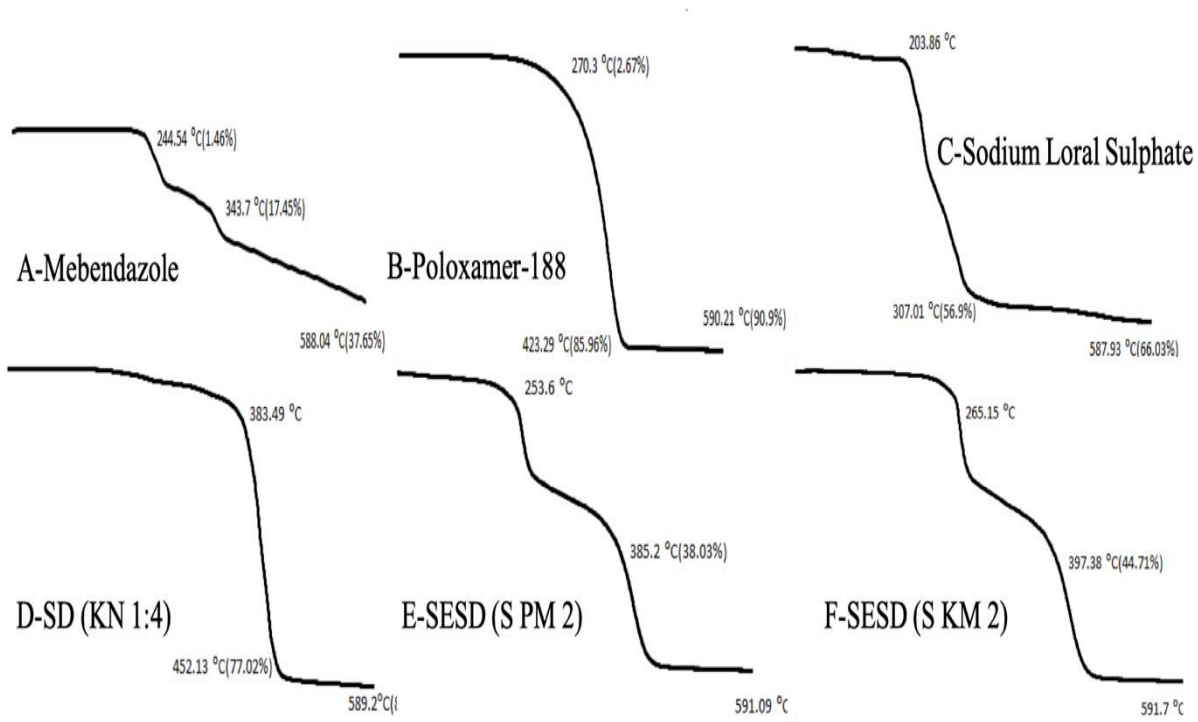

Figure 8. TG curve of drug, poloxamer-188, SLS, SD (KN 1:4), SESD (S-PM 2), SESD (S-KM 2).

Differential Scanning Calorimetry (DSC)

This technique is used to assess the flow of heat in to and out of materials as a function of temperature & time (55). It is used to measure the temperature at which thermal changes happen such as glass transition temperature (Tg) (30), melting point, recrystallization and amount of crystalline material (31). In Figure 9, DSC thermogram of pure MBZ didn't show any change till 200 °C, which showed the thermal stability and confirmed that it is the polymorph A of MBZ (24). This scan of pure MBZ exhibited two endothermic peaks. The first endothermic peak occurred at 248.49 °C. The second endothermic peak at 315.8 °C exhibited the melting of pure MBZ. Those results were similar to a study which reported that pure sample is polymorph A of MBZ (24). These results were similar with a previous reported study where slight change was observed (56). Poloxamer-188 exhibited the sharp endothermic melting peak at 53.93 °C and results were comparable to previously reported value by Xie *et al.*, 2009 & Shah *et al.*,2012 (57, 58).

DSC of solid dispersion (SD) containing MBZ and poloxamer-188 showed that all peaks of pure drug had disappeared but one endothermic peak was still present at 53.3 °C, which was the melting peak of poloxamer-188 at slightly lower temperature which revealed that the drug is miscible in the carrier (38). Disappearance of all peaks of drug except the peak of carrier, revealed the formation of complex between drug and carrier. These findings were in agreement with the previously reported studies (29, 59).

DSC of SESDS formulated using physical mixing showed the endothermic peak at 52.26 °C, and endothermic peak at 239.76 °C, both represent peak of poloxamer-188 and drug, respectively. Melting peak of pure drug was not seen in this thermogram and confirm that drug has been completely entrapped into the polymeric mesh and changed into partially amorphous form (13). DSC thermogram of SESD by kneading method showed the melting endothermic peak of poloxamer-188 at slightly lower temperature at 49.08 °C which showed the miscibility of MBZ in excipients (38). An endothermic peak of drug at 249.24 °C was also seen, which was the not the melting peak of pure drug. An endothermic peak at 99.69 °C was present, this was the peak of SLS (60). Presence of all the carrier peaks except the characteristic melting peak of pure drug revealed that most of the crystalline drug has changed into amorphous form (12). The results of DSC concluded that melting peak of MBZ was absent in all prepared formulations and confirm drug existed in amorphous form (49), the results of XRPD were also supported this where intensity of peaks reduced and straight line showed amorphous nature of formulations.

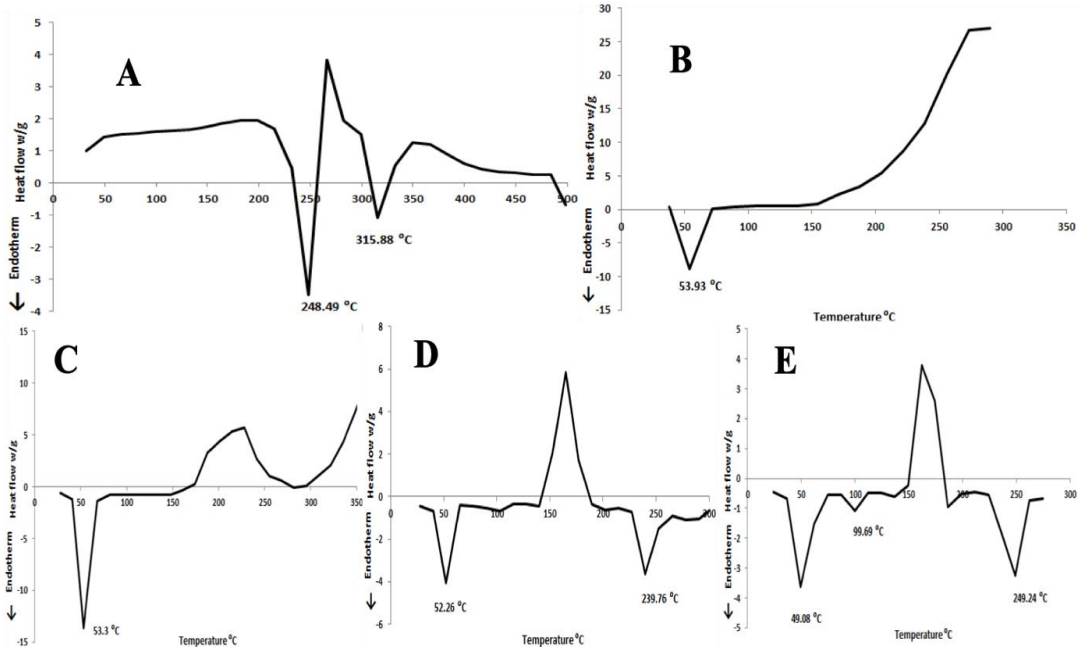

Figure 9. DSC thermogram of A- pure MBZ, B- poloxamer-188, C- SD (KM 1:4), D- SESD (S-PM 2), and E- SESD (S-KM 2)

CONCLUSION

The aim of this study was to improve the solubility of Mebendazole by preparing SDS and SESDS by changing drug to polymer ratios employing physical mixing, kneading method and fusion method. The results depicted that increased solubility was observed in all the prepared formulations. The descending order for increased solubility in SDS was Kneading method 1:4 (4.15 folds) > Fusion method 1:4 (3.51 folds) > Physical mixture 1:4 (1.79 folds) as compared to pure drug. As the kneading method (1:4) of SD exhibited higher solubility so this method and ratio was used to fabricate SESDS. Solubility study was performed on SESDS which exhibited increased solubility as compared to SDS. The order of increase in solubility was Kneading method (6.61 folds) > Physical mixing (5.73 folds). The higher solubility of SESDS is due to the combined effect of carrier, surfactant, co-surfactant and oil used in it. Increased solubility was overall result of bonding interactions between drug and excipients, reduced crystallinity, and complete entrapment of drug in polymeric matrix. Fabricated SESDS also proved to be more thermostable in comparison to Pure drug.

Future Prospects

Fabricated SESDS can be formulated in suitable solid oral dosage form and dissolution studies along with kinetic modelling can be performed to explore the possible dissolution mechanism.

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None

DECLARATIONS

Authors' Contributions

MAS contributed to study concept; MA and AP contributed to study design, data collection. UM contributed in data analysis and interpretation. US & MK did the literature review and critically reviewed the manuscript. All the authors read and approved the final manuscript.

Ethical Approval

Not applicable

Conflict of Interest

The author declared no conflict of interest among them.

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