Effect of Hydrophilic Carriers for Solubility and Dissolution Enhancement of Sulfamerazine by Solid Dispersions Technique

.

ABSTRACT

Aims: The present research was carried out to investigate the effect of hydrophilic carriers in enhancing the solubility and dissolution rate of Sulfamerazine (SMZ) employing the fusion technique of solid dispersions (SD).

Methodology: SMZ is an oral antibacterial drug exhibiting a poor dissolution profile and water solubility. SD of SMZ was prepared using poloxamer 407 (PX407) and Polyethylene glycol 6000 (PEG6000) as a hydrophilic carrier by employing the fusion technique.

Results: The powder SDs were subjected for solubility, Fourier transform infrared spectrometry (FTIR), Differential scanning calorimetry (DSC), *in-vitro* dissolution profile, Scanning electron microscopy (SEM), and X-ray diffraction (XRD) study. The FTIR spectral analysis showed no significant incompatibility between drug and carriers and confirmed the presence of SMZ. From XRD and DSC, SMZ indicated the amorphous form in solid dispersion with larger specific surface area, resulting in a better *in-vitro* rate of dissolution of the drug from solid dispersions than pure drug. However, SD of PX407 (SDSMFF8) indicated higher aqueous solubility than pure SMZ. Further, SDSMFF7 showed higher *in-vitro* drug release 96.45±0.3% within 60 minutes, and pure drug (18.54±0.8%).

Conclusion: In conclusion, enhancing the solubility and dissolution of SMZ using hydrophilic carriers by solid dispersion technique provides new strategies for broadening its potential clinical application.

Keywords: Solid dispersion, Polyethylene glycol 6000, Poloxamer407, Solubility, Bioavailability.

1. INTRODUCTION

Any pharmaceutical research aims to serve society's needs by developing a suitable dosage form with high safety and efficacy with minimum undesirable effects. The technology permits economic, reliable, and reproducible large-scale production methods without new and expensive specialist equipment. In recent years, combinatorial chemistry and high-throughput screening have been employed for the drug discovery process. However, newer drug candidates found it more challenging for scientists to design dosage forms due to poor aqueous solubility. In addition, 40% of newer candidates used in pharmaceutical industries exhibit poor aqueous solubility. Thus, the solubility behavior of drugs remains one of the most challenging aspects in formulation development and complicating the delivery of poorly water-soluble drugs [1-2].

Potential drug candidates exhibited less oral bioavailability and showed lower permeation through epithelia of the gastrointestinal tract [1-3]. Solid dispersion contains particles with a high porosity, resulting in a high dissolution rate. Thus, aqueous solubility is the governing step for any therapeutically active substance showing enhanced dissolution and absorption. In addition, drug candidates with low solubility exhibited less dissolution profile and showed poor oral bioavailability [4]. Poor solubility results in low bioavailability, large inter and intra-subject variation, and significant variations in plasma drug concentrations under fed versus fasted conditions [5]. A poorly aqueous-soluble drug candidate requires more time to dissolve in GIT fluid than gastrointestinal absorption [6].

SD technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate, altered solid-state properties, and improved stability. So, the drug can be dispersed molecularly in amorphous particles (clusters) or crystalline particles [7-9].

SMZ is antibacterial, has low bioavailability (only 1 percent), and belongs to BCS (Biopharmaceutical Classification System) class II drug. SMZ inhibits dihydrofolic acid synthesis in bacteria and competes with para-aminobenzoic acid (PABA) to bind to dihydropteroate synthetase (dihydrofolate synthetase). SMZ is bacteriostatic in nature. The side effects are nausea, vomiting, diarrhea, and hypersensitivity reactions [10,11]. It is very slightly soluble in water, belongs to BCS class II and a good candidate for formulation of solid dispersion using hydrophilic carriers like polyethylene glycol (PEG6000), poloxamer (POX407), sodium caparate, caproic acid, beta cyclodextrin, PEG 4000, urea, polyvinyl pyrrolidone (PVP) K30, desoxycholic acid, citric acid and pentaerythritol etc. The solid dispersion techniques help in reducing the harmful effects. Thus, the present research aims to investigate the effect of hydrophilic carriers on enhancing the solubility and dissolution rate of SMZ by using the solid dispersion technique [12-14].

2. MATERIAL AND METHODS

2.1 Material

Sulfamerazine was purchased from Yarrow Chem Pharma, Delhi, India. Polyethylene glycol 6000, Poloxamer407 were also purchased from Yarrow Chem Pharma, Delhi, India. All reagents of A.R. grade was used of CDH (Chemical Drug House), Delhi.

2.2 Methods

2.2.1 Solubility study of SMZ in different conc. of polymer

Higuchi and Connors method was employed to determine solubility. As a result, An excessive amount of SM solubilized in the glass vial containing 20ml of PEG6000 and Poloxamer407 if different concentrations separately. The resultant samples were agitated at 37±0.5 °C for 3 days in a water bath (Remi Pvt Ltd, Mumbai) to reach equilibrium, filtered using membrane filters (0.45 µm), and the filtrate was diluted, analyzed spectrophotometrically using a UV-VIS spectrophotometer (Shimadzu 17000, Japan) at 257nm. Gibbs free energy (ΔG_o^{tr}) of transfer of SMZ from pure water to the aqueous solutions of carrier was calculated as [12,13].

$\Delta G_o^{tr} = -2.303\ RT\ Log\ (S_o/S_s)$

Where S_o/S_s: Ratio of molar solubility of SMZ in an aqueous solution of carriers with respect to water.

2.2.2 Fusion method of solid dispersion

Solid dispersions (SDs) of SMZ were prepared using the fusion method with hydrophilic carriers (Table 1, Fig.1) and melted at their respective melting point. Then, the drug was added to the molten polymer, mixed (Remi equipment, India), and cooled at room temperature to obtain a solid mass. Finally, the solidified mass was suitably crushed, sieved # 60, and stored resultant solid dispersion in a desiccator [12,13].

Table 1. Composition of various solid dispersions of SMZ.

Formulation[#]	Drug-Polymer	Ratio

SDSMFF1	D:PEG6000	1:1
SDSMFF2	D:PEG6000	1:2
SDSMFF3	D:PEG6000	1:4
SDSMFF4	D:PEG6000	1:6
SDSMFF5	D:PEG6000	1:8
SDSMFF6	D:PEG6000	1:10
SDSMFF7	D:POX407	1:1
SDSMFF8	D:POX407	1:2
SDSMFF9	D:POX407	1:4
SDSMFF10	D:POX407	1:6
SDSMFF11	D:POX407	1:8
SDSMFF12	D:POX407	1:10

#SDSMFF- Solid Dispersion Sulfamerazine Fusion Formulation

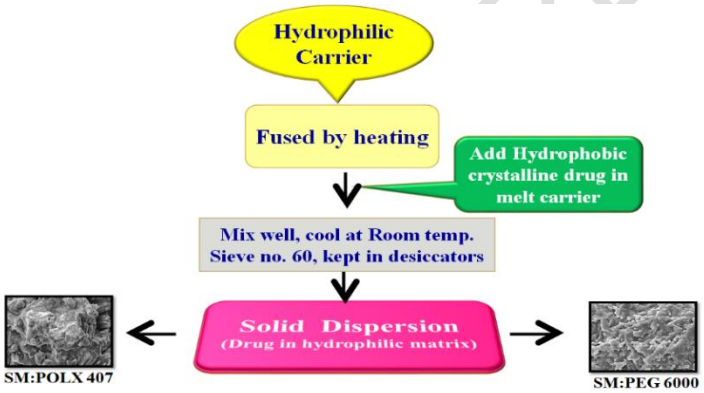

Fig. 1. Flow diagram of preparation of solid dispersion by Fusion method.

3. CHARACTERIZATION OF FORMULATIONS OF SOLID DISPERSION

3.1 Percent yield

The %age yield of prepared solid dispersion formulations gravimetrically determined based on polymer and drug recovery [12,13].
Yield (%) = [W_1 / W_2] x100 Where, W_1- Amount of SD, W_2- Total amount of drug & polymer.

3.2 Drug Content

The drug content (D.C.) of SD was analyzed by extracting SM in phosphate buffer using 25 ml methanol. The resultant preparation is transferred to a glass stopper conical flask, adjusted at pH 6.8 PBS, agitated in an orbital shaker (HICON, New Delhi, India), and sonicated in a bath sonicator (HICON 1.5L50H, New Delhi, India). This process is continued for a day, filtered using Whatman filter paper, and spectroscopically analyzed at 257nm

using UV/VIS spectrophotometer (Shimadzu UV-1700, Japan). The % drug content was calculated [12,13].
D.C. (%) = (A_c) / T_c) x 100 Where, T_c - Theoretical D.C., A_c - Actual D.C.

3.3 Surface morphology study

The surface morphology of SD was investigated by scanning electron microscopy. Solid dispersion was mounted on glass stubs was then air-dried. Then the stubs were pasted over the grid using double-sided carbon adhesive tape and sputter-coated with conductive gold-palladium. Gently placed a circular coverslip over the stub to enable even distribution of the sample suspension. They were viewed with an EVO LS 10 (Carl Zeiss, Brighton, Germany) scanning electron microscope operating at an accelerating voltage of 200 kV under a high vacuum. Then examine the particles for surface characteristics like shape, size, pores, pits, and presence of aggregation [12,13].

3.4 Solubility study of different solid dispersion

The saturated solutions of solid dispersions were made in 10 ml solvents like water shake for 12 hours and kept aside for 24 hours. Then the solutions were filtered, and the filtrate was analyzed in UV-Spectrophotometer at the respective 257 nm λ_{max} of the drug.

3.5 Micromeritics properties [12,13,15-20]

3.5.1 Angle of repose

The angle of repose (Θ) is a valuable method for calculating the flow behavior of powders. First, the angle of repose was determined using the fixed funnel method by pouring the solid dispersion formulations one by one on the surface from a fixed height (h) of 5cm. Then, the radius (r) of the pile at the base was measured at four different points and took their average for calculating the angle of repose using the following formula.
$\Theta = \tan^{-1} (h/r)$

3.5.2 Bulk Density and Tapped Density

The bulk density (BD) was determined according to the method specified in USP by pouring SD formulations one by one into graduated cylinder 50ml, and tapped density (TD) was determined by mechanically tapping 50 times, repeated three times to obtain triplicate. Thus, bulk density and tapped density were determined using the formula.
$BD = M/V_{b,}$ $TD = M / T_v$
Where, M = Mass of sample, V_b = Bulk Volume, T_v = Tapped Volume

3.5.3 Compressibility Index (CI)
Carr's index or Compressibility index (CI) of drug sample were calculated using the below equation.
Carr's Index (%) = [(TD – BD) / TD] x 100

3.5.4 Hausner's ratio (HR)

HR of microspheres was determined using formula as-
H.R. = TD / BD

3.6 Thin Layer Chromatography (TLC)

Stahl, in 1958 introduced the method for TLC based on adsorption chromatography. It is an essential analytical method used for qualitative and quantitative analysis. A rectangular glass chamber (30x15x8 cm) with a ground glass rim on which a glass lid is placed applied grease on the rim of the chamber to make the glass jar airtight. Silica gel-G was used as an adsorbent. The plates were activated in a hot air oven (110ºC) for 30 minutes and stored in a closed desiccated cabinet. The drug, physical mixture, and solid dispersion samples were dissolved in the freely soluble solvent. The spots on plates were applied using a fine capillary tube, (1mm) diameter at 1 cm. The inner wall of the chamber was lined with filter paper from all sides except the front face to maintain a saturated atmosphere. The solvent system (Ethyl acetate: Methanol (9:1)) was poured into the chamber at the height of 1 cm. Then the mouth chamber was closed with a rectangular glass plate and made airtight with grease. The chamber was then allowed for saturation and developed chromatograms. The developing solvent system was allowed to travel up to seventy-five percent of the total length of the plate and dried the plate at room temperature. Then U.V and daylight of U.V. cabinet were used to detect of the spots of samples, marked the spots, and calculated R_f (Retardation factor) value [10,21-24].

$R_f = S_d / S_l$ Where, S_d- Distance traveled by solute, S_l- Distance traveled by the solvent

3.7 Fourier transformer infrared study

Fourier-transform Infrared (FTIR) spectrum was employed to predict drug-polymer compatibility, vacuum dried for 12 h using FTIR spectrophotometer (Shimadzu FTIR IR Affinity, Japan), scanned between 4000–400 (cm^{-1}) [10,12,13].

3.8 Differential scanning calorimetry (DSC) study

DSC of drug, polymer, and their physical mixture and SD were determined using (DSC-60 Instruments, Shimadzu Corporation, Japan). 5mg sample weighed accurately and sealed hermetically. The pans are suitably heated, kept between 50°C- 300°C at 5°C per min heating rate, at atmospheric air blanket, and note down the melting point from the endothermic peak [10,12,13].

3.9 X-ray diffraction (XRD) study

X-ray diffraction analysis was carried out to determine drug and solid dispersion crystallinity (Model: PW 3710, Holland). Before scanning, the samples were triturated, converted into fine powder forms, loaded onto the diffractometer. The scanning is done from 10° to 80° at a scan rate of 0.05°/0.4 sec and notes down the intensity of peak at different theta values from diffractogram [10,12,13].

3.10 *In-vitro* drug release profile

In-vitro dissolution studies were done using phosphate buffer solution (pH 6.8, PBS), 900 ml. at a temperature of 37±0.5°C, and thermostatically controlled. Further, it is rotated at 50 rpm, employing paddle-type dissolution apparatus (United States Pharmacopeia XXIV). During the process, the 5ml sample solution was with-drawn at 5, 10, 15, 20, 30, 40, 50, and 60 minutes respectively, and supplemented with equal PBS. The diluted sample solution was thus obtained and filtered using a membrane filter, analyzed spectroscopically at 257nm [10,12,13].

3.11 Accelerated stability study

An accelerated stability study of solid dispersion was performed to investigate chemical and organoleptic properties for 90 days at 40±2°C and 75%±5% RH. In addition, SD was evaluated periodically at 0, 15, 30, 45, 60, 75, and 90 days for reporting any alteration in chemical and physical properties [25,26].

4. RESULT AND DISCUSSION

4.1 SMZ solubility at different concentrations of hydrophilic carriers

The results of solubility experiments are notably affected by the presence of POX407 compared to PEG6000 (Table 2). Further, at 18%w/v concentration of POX407 and PEG6000, the solubility of SMZ increased by 13.96 and 9.11 folds, respectively, indicating SMZ transfer from pure water to the aqueous solution of PEG 6000 and POX 407. From Fig. 2, ΔG_o^{tr} of SMZ is associated with the aqueous solubility of SMZ in the presence of PEG 6000 and POX 407. All the values are negative, indicating the spontaneous nature of the drug solubilization [12,13].

Table 2. Effect of PEG6000 and POX407 conc. on (ΔG_o^{tr}) and SMZ solubility.

PEG 6000 (%w/v)	SMZ (mg/ml) at 37 °C	$\Delta G_o^{tr\#}$ (J/Mol)	POX 407(%w/v)	SMZ (mg/ml) at 37°C	$\Delta G_o^{tr\#}$ (J/Mol)
0	0.1997	0.00	0	0.1997	0.00
2	0.3208	-145.83±0.03	2	0.3625	-183.43±0.02
4	0.4041	-216.86±0.05	4	0.4875	-274.59±0.01
6	0.4875	-274.59±0.02	6	0.5708	-323.12±0.05
8	0.6541	-365.03±0.06	8	0.7375	-401.95±0.02
10	0.7791	-418.84±0.07	10	0.9458	-478.49±0.03
12	0.9041	-464.62±0.04	12	1.1958	-550.65±0.07
14	1.2791	-571.37±0.05	14	1.4041	-600.06±0.06
16	1.4875	-617.81±0.03	16	1.8625	-686.99±0.03
18	1.8208	-680.02±0.04	18	2.7791	-810.12±0.04

#N=3±S.D.

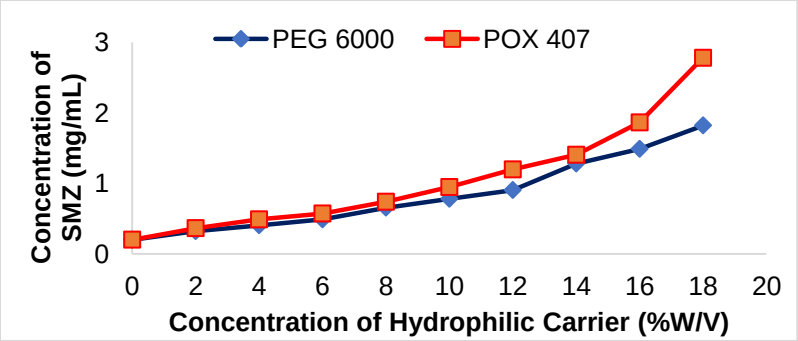

Fig. 2. Effect of PEG 6000 and POX 407 concentration on solubility of SMZ.

4.2 Percentage yield

The yield (%) of solid dispersions (SDSMFF1-SDSMFF12) was found to be 75.22±2.21 to 91.23±1.13%. Finally, SDSMEF14 showed 91.23±1.13% highest percent yield, as shown in (Table 2).

4.3 Percent drug content

The drug content (%) of various solid dispersions (SDSMFF1-SDSMFF12) was found to be 74.67±0.26 to 91.96±0.67%. But the SDSMFF8 showed the highest 91.96±0.67% drug content (Table 3).

Table 3. Drug content (%), Yield (%) of various SDs of SMZ.

Formulation[#]	Yield[#] (%)	D.C.[#] (%)
SDSMFF1	80.47±1.37	88.86±0.25
SDSMFF2	91.23±1.13	91.96±0.67
SDSMFF3	89.46±2.16	86.23±0.65
SDSMFF4	85.72±1.19	82.16±0.91
SDSMFF5	75.22±2.21	79.24±0.75
SDSMFF6	78.19±1.10	74.67±0.26
SDSMFF7	81.87±0.97	89.34±1.00
SDSMFF8	94.43±1.10	92.33±0.72
SDSMFF9	88.26±1.12	85.54±0.51
SDSMFF10	86.72±0.87	82.76±0.54
SDSMFF11	77.92±1.31	77.85±0.65
SDSMFF12	79.79±1.21	75.98±1.01

[#]N=3±S.D., SDSMEF- Solid Dispersion Sulfamerazine Fusion Formulation, D.C.- Drug Content

4.4 Solubility study of different solid dispersion

The solubility of solid dispersion formulations SDSMFF1-F6 and SDSMFF7-F12 in distilled water was found to be 447.30±0.12 to 2907.08±0.12µg/mL and 663.84±0.32 to 3294.12±0.23µg/mL, respectively. But SDSMFF8 showed the highest solubility (3294.12±0.23 µg/mL) in water i.e., 16.49 folds more in comparison to pure SMZ (199.7±0.008 µg/mL), (Table 4) [12,13].

Table 4. Solubility study of various solid dispersions and SMZ in aqueous medium.

Formulation[#]	Solubility[#] (µg/mL)
SDSMFF1	2084.45±0.09
SDSMFF2	2907.08±0.12
SDSMFF3	1473.63±0.52
SDSMFF4	1158.65±0.04
SDSMFF5	647.30±0.45
SDSMFF6	447.30±0.12

SDSMFF7	2432.31±0.21
SDSMFF8	3294.12±0.23
SDSMFF9	1960.67±0.45
SDSMFF10	1107.32±0.12
SDSMFF11	834.38±0.32
SDSMFF12	663.84±0.09
Pure SMZ	199.7±0.008

[#]N=3±S.D., SDSMFF- Solid Dispersion Sulfamerazine Fusion Formulation

4.5 Surface morphology study

SEM is employed for the determination of surface morphology. The SEM results showed that SDs particles are amorphous (Fig. 3) [12,13].

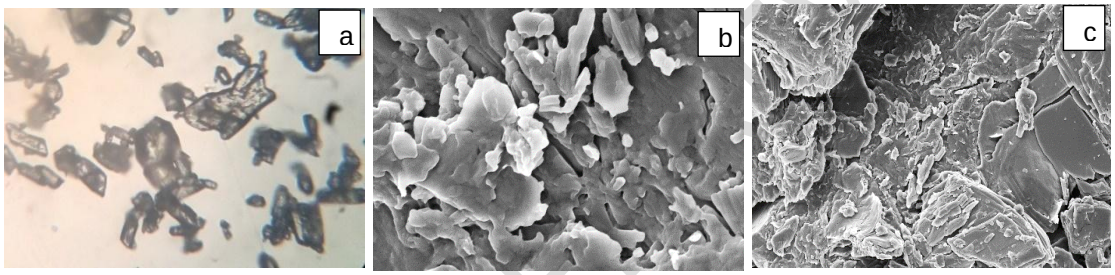

Fig. 3. (a) Photomicroscope image of pure drug, (b) SEM of SMPEG6000 Solid dispersion and (c) SEM of SMPOX407 Solid dispersion.

4.6 Micromeritics properties

The various micromeritics parameters BD, TD, HR, CI of SDSMFF1-SDSMFF12, found to be 0.327±0.04 to 0.617±0.02g/mL, 0.373±0.05 to 0.722±0.05 g/mL, 1.134±0.005 to 1.178±0.012 and 11.818±0.26 to 15.116±0.11 respectively. The angle of repose was found to be 19.34±0.41° to 34.54±0.32 (SDSMFF1-SDSMFF12). But SDSMFF8 indicates the excellent flow behavior, shown in (Table 5).

Table 5. Micromeritic parameters of various Solid dispersion of SDSMFF1- SDSMFF12 formulations.

Formulation[#]	BD (g/ml)[#]	TD (g/ml)[#]	HR[#]	CI (%)[#]	AR (^{0})[#]
SDSMFF1	0.568±0.04	0.658±0.06	1.158±0.003	13.636±0.23	23.15±0.54
SDSMFF2	0.549±0.03	0.631±0.02	1.148±0.007	12.857±0.14	21.31±0.36
SDSMFF3	0.562±0.05	0.649±0.04	1.156±0.003	13.483±0.54	26.23±0.27
SDSMFF4	0.568±0.03	0.644±0.02	1.134±0.005	11.818±0.26	28.11±0.67
SDSMFF5	0.581±0.06	0.685±0.03	1.178±0.012	15.116±0.11	31.49±0.41
SDSMFF6	0.617±0.02	0.722±0.05	1.169±0.006	14.444±0.35	34.54±0.32
SDSMFF7	0.349±0.03	0.404±0.02	1.158±0.004	13.614±0.52	21.13±0.27

SDSMFF8	0.327±0.04	0.373±0.05	1.141±0.003	12.332±0.28	19.34±0.41
SDSMFF9	0.356±0.02	0.413±0.03	1.160±0.006	13.801±0.41	24.12±0.32
SDSMFF10	0.367±0.05	0.43±0.01	1.172±0.005	14.651±0.22	29.47±0.53
SDSMFF11	0.373±0.03	0.444±0.06	1.190±0.002	15.991±0.34	33.21±0.54
SDSMFF12	0.387±0.05	0.465±0.04	1.202±0.004	16.774±0.41	37.45±0.27

[#]N=3±S.D., SDSMFF- Solid Dispersion Sulfamerazine Fusion Formulation, BD- Bulk Density, TD- Tapped Density, CI- Carr's Index, HR- Hausner's ration, AR- Angle of repose

4.7 Thin Layer Chromatography

TLC of drug, physical mixture of drug and polymer, and SDSMFF8 were found to be 0.59, 0.58, 0.57, and 0.59, respectively, which were close to standard Rf value 0.59. Thus, the result indicated there is no significant interaction between polymer and drug (Fig. 4) [10,21-24].

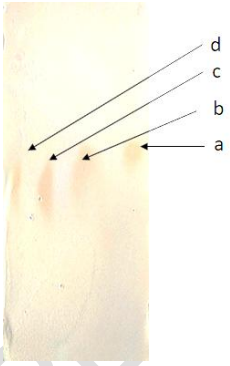

Fig. 4. TLC of pure Sulfamerazine (a), SDSMFF8, (b), physical mixture of drug and PEG6000, (c), physical mixture of drug and POX407 (d).

4.8 FTIR-spectroscopy study

The IR spectra of SDs and PMs were compared with the standard spectrum of SMZ (Fig. 5). IR spectrum showed the SO_2 group at 1344 and 1160 cm^{-1}, SDs and PMs showed band shifting towards decreased frequencies at 1325 and 1153 cm^{-1}, respectively [27]. NH asymmetric and symmetric (3490 and 3380 cm^{-1} bands of SMZ shifted towards higher frequencies 3498 and 3384 cm^{-1} in the IR spectrum of solid dispersion of SMZ. The S-N stretching group bands are located at 890 cm^{-1} in pure SMZ and solid dispersion. Significant vibrations are detected for POX407 for C–H stretching at 2,885 cm^{-1} and C–O stretching 1,109 cm^{-1} and –OH stretching at 3,350 cm^{-1}, respectively. The results show peak shifting of the SO_2 group of SMZ in the IR spectrum of SDSMFF8, indicating increased bond strength due to the stabilizing effect of the hydrogen atom of the POX407 interacting with the oxygen atoms of the SO_2 group (28). In solid-state, this indicates changes in peak spectra due to physical interaction of SMZ with POX407 complexation and hydrogen bonding. It might be expected that the hydrogen atom of NH of SMZ formed the hydrogen bond with one of the ion pairs of the oxygen atom of POX407 [12,13].

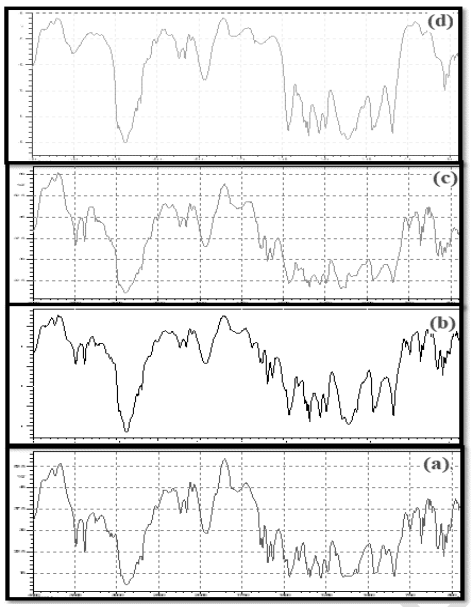

Fig. 5. FTIR spectrum of Pure SMZ (a), SDSMFF8 (b Physical mixture of SM-POX407 (c), POX407 (d).

4.9 Differential Scanning Calorimetry study

DSC analysis provides information regarding the interaction between drug and excipient and provides information of the physical properties of the sample, i.e., crystalline or amorphous nature. DSC thermogram of solid dispersion SDSMFF8 showed a sharp endothermic peak at 233.42˚C, which did not correspond to the melting point (224.15°C) of the drug **(**Fig. 6). Thermogram indicated the absence of an SMZ peak, suggesting that SMZ is entirely soluble in the liquid phase of polymer or lack of crystalline nature of the drug. The PM of SMZ and POX407 also showed no endothermic peak corresponding to SMZ. The absence of an endothermic peak of the drug in SD has also been reported by other researcher groups [29-33].

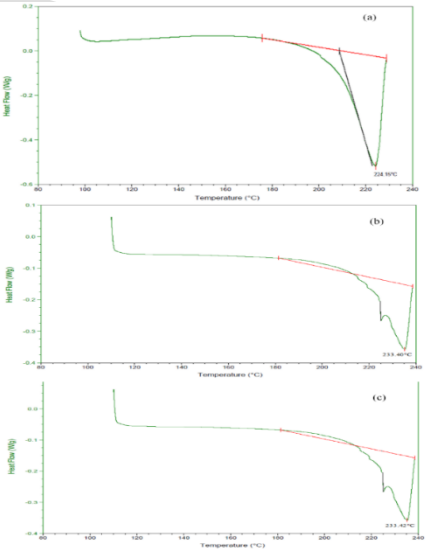

Fig. 6. DSC thermogram of SMZ, (a), Physical mixture of drug and poloxamer 407 (b), SDSMFF8 (c).

4.10 X-ray Diffraction (XRD) study

For the study of crystalline change of drugs, XRD analysis is used. The diffraction spectrum of XRD of pure SM and solid dispersion SDSMFF8, shown in Fig. 7. The diffraction spectrum of pure SMZ was crystalline in nature and showed numerous prominent characteristics peaks at 2θ of 2.38, 2.76, 2.90, 2.94, 3.05, 3.22, 3.27, 3.53, 3.67, 3.74, 3.80, 3.89, 3.95, 4.11, 4.37, 4.72, 5.14, 5.46, 6.02, 6.35, 6.76, 7.03, 7.65 and 10.72 (fingerprint region). The extent of crystallinity affects drug dissolution. An amorphous or metastable form dissolves at the fastest rate due to high energy and motion, enhancing thermodynamic properties. Changes in peaks were observed due to a significant decrease in intensities of SMZ, altering quality and crystal size. Results indicate that SMZ exits as partial crystalline or microcrystalline form in the SDs [12,13,34,35].

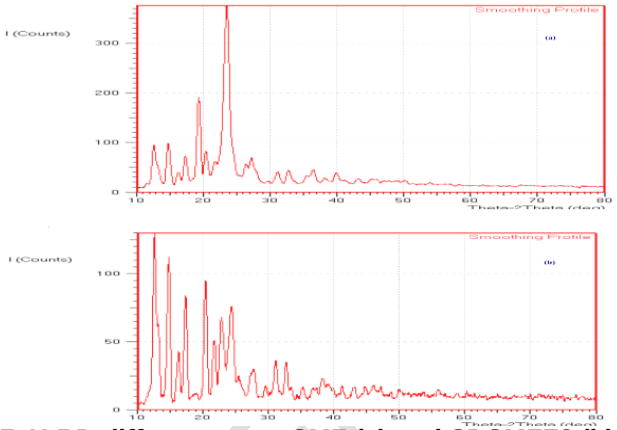

Fig. 7. X-RD diffractogram- SMZ (a) and SDSMFF8 (b).

4.11 *In-vitro* drug release profile

In-vitro drug release of various solid dispersion (SDSMFF1-F12) was found to be 29.28±0.04 to 98.45±0.03%. But the SDSMFF8 showed the highest 98.45±0.03% drug release among all solid dispersion formulations compared to pure SMZ (18.54±0.09%) within 60 min in PBS pH 6.8. It reflects the decreasing in contact angle and improving the wettability results in enhancement of bioavailability of the drug. Furthermore, the formation of the film of the hydrophilic carrier (POX407) around the drug particles results in altering the hydrophobicity of the surface of drug particles. In addition, the amorphous or partial crystalline nature of SD of SMZ enhanced the drug dissolution in comparison to pure SMZ, and the result showed in (Fig. 8 a and b) and (Table 6) [12,13,36-41].

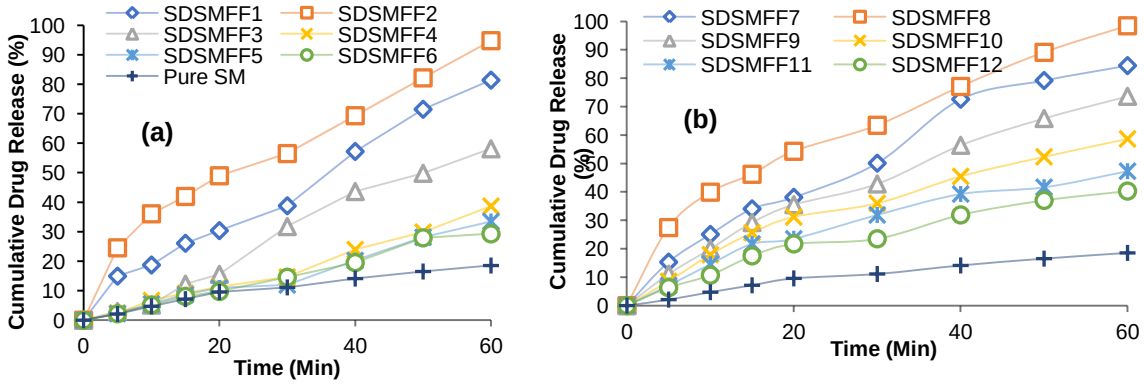

Fig. 8. *In-vitro* cumulative drug release (%) of SDSMFF1-SDSMFF6 formulations (a); SDSMFF7-SDSMFF12 formulations (b).

Table 6. Percent cumulative drug release profile of various formulations of solid dispersion.

Time (min)	Percent Cumulative Drug Release[#] (%)												
	SDS MFF 1	SDS MFF 2	SDS MFF 3	SDS MFF 4	SDS MFF 5	SDS MFF 6	SDS MFF 7	SDS MFF 8	SDS MFF 9	SDS MFF 10	SDS MFF 11	SDS MFF 12	Pure SMZ
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
5	14.96 ±0.05	24.55 ±0.12	2.96 ±0.09	2.45 ±0.10	2.22 ±0.05	2.19 ±0.07	15.33 ±0.05	27.45 ±0.09	11.05 ±0.03	8.55 ±0.06	7.05 ±0.09	6.30 ±0.03	2.11 ±0.03
10	18.72 ±0.09	36.09 ±0.17	6.12 ±0.03	5.71 ±0.11	5.55 ±0.07	5.15 ±0.05	25.05 ±0.09	39.9 ±0.07	19.95 ±0.10	17.9 ±0.09	14.55 ±0.10	10.71 ±0.04	4.72 ±0.05
15	26.08 ±0.07	41.98 ±0.06	12.24 ±0.07	9.12 ±0.09	8.64 ±0.10	8.05 ±0.04	34.05 ±0.10	46.2 ±0.03	29.2 ±0.04	25.65 ±0.03	21.70 ±0.06	17.53 ±0.09	7.15 ±0.09
20	30.38 ±0.10	48.98 ±0.09	15.56 ±0.10	11.28 ±0.05	10.94 ±0.03	9.73 ±0.09	38.12 ±0.08	54.3 ±0.07	35.5 ±0.09	31.20 ±0.13	23.50 ±0.04	21.72 ±0.10	9.57 ±0.07
30	38.80 ±0.06	56.52 ±0.11	31.76 ±0.05	14.66 ±0.07	11.95 ±0.05	14.57 ±0.08	50.12 ±0.03	63.45 ±0.10	42.8 ±0.05	36.23 ±0.02	31.91 ±0.09	23.51 ±0.04	11.13 ±0.06
40	57.23 ±0.08	69.36 ±0.07	43.64 ±0.08	23.96 ±0.11	20.26 ±0.06	19.53 ±0.02	72.61 ±0.04	77.1 ±0.09	56.4 ±0.03	45.45 ±0.04	39.25 ±0.03	31.90 ±0.13	14.12 ±0.10
50	71.53 ±0.09	82.19 ±0.08	49.84 ±0.09	29.88 ±0.10	28.14 ±0.08	27.94 ±0.10	79.21 ±0.03	89.1 ±0.13	65.83 ±0.02	52.35 ±0.09	41.65 ±0.08	37.01 ±0.02	16.52 ±0.05
60	81.43 ±0.04	94.81 ±0.21	58.14 ±0.04	38.68 ±0.05	33.47 ±0.09	29.28 ±0.04	84.45 ±0.09	98.45 ±0.03	73.63 ±0.10	58.65 ±0.03	47.32 ±0.02	40.32 ±0.09	18.54 ±0.03

[#]N=3±S.D.

4.12 Accelerated stability study

A short-term accelerated stability study for the optimized (SDSMFF8) formulation indicated no change in the physical properties such as colour and odour. The percent drug content found under acceptable limit and result showed in (Table 7).

Table 7. Accelerated stability study of SDSMFF8.

Condition	Time Period (Days)	Parameters[#]		
		Colour	Odour	D.C. (%)
Accelerated 40±2°C, 75±5%RH	0	-	-	92.33±0.3
	15	-	-	92.10±0.5
	30	-	-	91.87±0.2
	45	-	-	91.63±0.3
	60	-	-	91.35±0.4
	75	-	-	91.21±0.7
	90	-	-	91.03±0.6

(-): No change, [#]N=3±S.D.

5. CONCLUSION

Using the solid dispersion technique, the solubility and dissolution rate of SMZ increased with hydrophilic carriers (PEG6000 and POX407). POX407 enhanced 16.9 and PEG6000 9.6 times more solubility than pure SMZ. FTIR study indicated no significant and well-defined chemical interaction between hydrophilic carriers and drugs in PMs and SDs. In addition, the XRD study proved the presence of an appreciable fraction of crystallinity of SMZ with

decreased intensity in SD. However, the formation of metastable or amorphous form or drug crystallinity indicated a reduction in the aggregation of SMZ particles and enhanced dispersibility. Alteration in quality and crystal size enhanced surface activity; wettability might play a pivotal role in improving solubility and dissolution rate of SMZ in solid dispersion form and a little bit in PMs. Absence of endothermic peak in DSC thermogram of SD with POX407 explicit absence of crystalline SMZ.

ABBREVIATIONS

SMZ: Sulfamerazine; SD: Solid Dispersion; PX407: Poloxamer 407; PEG 6000: Polyethylene Glycol 6000; FTIR: Fourier Transform Infrared Spectrometry; DSC: Differential Scanning Calorimetry, SEM: Scanning Electron Microscopy, XRD: X-ray Diffraction; GIT: Gastrointestinal Tract; BCS: Biopharmaceutical Classification System: PABA: PARA-Aminobenzoic Acid; PVP: Polyvinyl Pyrrolidone; D.C.: Drug Content; BD: Bulk Density, TD: Tapped Density; HR: Hausner's Ratio; CI: Compressibility Index; TLC: Thin Layer Chromatography; PBS: Phosphate Buffer Solution; SDSMFF- Solid Dispersion Sulfamerazine Fusion Formulation; PM: Physical Mixture; AR: Angle of Repose.

COMPETING INTERESTS DISCLAIMER

Authors have no competing and conflict of interest.

REFERENCES

1. Patidar K, Soni, M, Sharma KD. Solid dispersion: Approaches, technology involved, unmet need & challenges. Drug Invent Today. 2010;2(7):13-20.
2. Kannan KK., Puratchikody A., Masilamani K, Senthilnathan B. Solubility enhancement of poorly soluble drugs by solid dispersion technique-A review. J Pharm Res. 2010;3(9):2314-2321.
3. Tong WQ. Pharmaceutical preformulation. Integrated drug development process. 2012. Accessed on September 20, 2021.
   Available: https://docplayer.net/29796687-Integrated-drug-development-process.html.
4. Vansihv SD, Rao MRP, Sonar GS, Gogad K, Borate SG. Physicochemical characterization and In-vitro dissolution of domperidone by solid dispersion technique. Indian J Pharm Educ Res. 2009;43(1):86-90.
5. Chaturvedi AK, Verma A. Solubility enhancement of poorly water-soluble drugs by solid dispersion. Int J Pharm Sci Res. 2012;3(1):26-34.
6. Mooter GVD, Weuts I, Rider TD, Blaton N. Evaluation of Inutec SPI as a new carrier in the formulation of solid dispersion for poorly water soluble drugs. Int J Pharm. 2006;3(6):1-6.
7. Ohara T, Kitamura S, Kitagawa T, Terada K. Dissolution mechanism of poorly water soluble drug from extended solid dispersion system with ethyl cellulose and hydroxypropyl methyl cellulose. Int J Pharm. 2005;3(2):95-102.
8. Verma S, Rawat A, Kaul M, Saini S. Solid Dispersion: A strategy for solubility enhancement. Int J Pharm Tech. 2011;3(2):1062-1099.
9. Chiou WL, Reigelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60(9):1281-1302.
10. Florey K. Eds. In: Analyfical Profiles of Drug Substances. 7th ed. New York and Landon: Academic Press; 2010.
11. Tripathi KD. Essential of Medical Pharmacology. 6th ed. New Delhi: Jaypee Brothers Medical Publisher Ltd; 2009.

12. Gill B, Kaur T, Kumar S, Gupta GD. Formulation and evaluation of glimepiride solid dispersion tablets. Asian J Pharm. 2010;4:1-7.
13. Sahoo SB, Murthy PN, Giradkar RP, Avari JG. Enhancement of dissolution rate of gliclazide using solid dispersions with polyethylene glycol 6000. AAPS Pharm Sci Tech. 2008;9(2):1-8.
14. Djordje P, Medarevic KK, Mitric M, Djuris J., Djuric Z, Ibric S. Dissolution rate enhancement and physicochemical characterization of carbamazepine-poloxamer solid dispersions. Pharm Dev Technol. 2016;21(3):268-76.
15. Martin A, Bustamante P, Chun AHC. Physical pharmacy: Physical chemical principles in the pharmaceutical sciences. 4th ed. New Delhi: BI Publications Pvt. Ltd.; 2005.
16. Subrahmanyam CVS. Text Book of Physical Pharmaceutics. 2nd ed. Delhi: Vallabh Prakashan; 2000.
17. Thalla S, Arsham P, Kumar YS. Formulation and evaluation of etodolac oral disintegrating tablets. Curr Trends Biotechnol Pharm. 2018;12(1):75-84.
18. Nagaraju T, Sujitha H, Krishna KM, Rajashekar M, Sathish D, Kumar YS, Rao YM. Formulation and evaluation of oral disintegrating films and tablets of candesartan cilexetil. Curr Trends Biotechnol Pharm. 2014;8(1):72-82.
19. Harrika B, Reddy VP. Formulation and evaluation of fast disintegrating zolmitriptan sublingual tablets. Curr Trends Biotechnol Pharm. 2012;6(1):84-98
20. Bhattacharyya S, Mohan RB. Design and evaluation of terbutaline sulphate immediate release tablets prepared by fluidized bed granulation technology. Curr Trends Biotechnol Pharm. 2020;14(2):156-163.
21. Gupta R, Gupta MK, Bhandari A, Gupta J. Preliminary pharmacognostical and physicochemical analysis: a poly herbomineral formulation. Int J Drug Dev Res. 2014;6(3):85-92.
22. Gupta R, Gupta MK, Bhandari A, Gupta J, Pathan IK. Preparation and standardization of polyherbomineral formulation. Int J Drug Dev Res. 2014;6(2):211-219.
23. Gupta R, Gupta MK, Bhandari A, Gupta J. Evaluation of Antitussive activity of Polyherbomineral formulation on cough reflex induced by different cough induced models in mice. Int J Drug Dev Res. 2014;6(4):280-289.
24. Gupta R, Gupta MK, Bhandari A, Gupta J. Polyherbomineral formulation: investigation of antitussive activity on cough reflex induced by different cough induced models. Int J Pharma Res Bio Sci. 2014;3(4):837-848.
25. Cartensen JT. (1995). Drug Stability: Principle and Practices. 2nd ed. New Work: Marcel Dakker; 1995.
26. ICH guidelines, Q1AR2, Stability testing of new drug substances and products, ICH harmonized tripartite guidelines. Accessed on September 15, 2021.
Available: www.ich.org
27. Özkan Y, Atay T, Díkman N, Isimer A, Aboul-Enein HY. Improvement of water solubility and in vitro dissolution rate gliclazide by complexation with b-cyclodextrin. Pharma Acta Helv. 2000;74:365-370.
28. Winters S, York P, Timmins P. Solid state examination of a gliclazide:beta-cyclodextrin complex. Eur J Pharm Sci. 1997;5:209-214.
29. Damian F, Blaton N, Naesens L, Balzarini J, Kinget R, Augustinjns P, Mooter GV. Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14. Eur J Pharm Sci. 2000;10:311-322.
30. Okonogi S, Oguchi T, Yonemochi E, Puttipipatkhachorn S, Yamamoto K. Improved dissolution of ofloxacin via solid dispersion. Int J Pharm. 1997a;156:175-180.
31. Betageri GV, Doshi HD, Ravis RW. Carbamazepine and polyethylene glycol solid dispersions: preparation, in vitro dissolution and characterization. Drug Dev Ind Pharm. 1997;23(12):1167-1176.
32. Shin SC, Kim J. Physicochemical characterization of solid dispersion of furosemide with TPGS. Int J Pharm. 2003;251:79-84.

33. Okonogi S, Yonemochi E, Oguchi T, Puttipipatkhachorn S, Yamamoto K. Enhanced dissolution of ursodeoxycholic acid from the solid dispersion. Drug Dev Ind Pharm. 1997b;23:1115-1121.
34. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci. 1997;86:1-12.
35. Valizadeh H, Nokhodchi A, Qarakhani N, Zakeri-Milani P, Azarmi S, Hassanzadeh D, Lobenberg R. Physicochemical characterization of solid dispersions of indomethacin with PEG 6000, Myrj 52, Lactose, Sorbitol, Dextrin, and Eudragit E100. Drug Dev Ind Pharm. 2004;30(3):303-317.
36. Mooter GV, Augustijns P, Blaton N, Kinge, R. Physicochemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K 30. Int J Pharm. 1988;164:67-80.
37. Saers SE, Craig DQM. An investigation into the mechanisms of dissolution of alkyl p-aminobenzoates from polyethylene glycol solid dispersions. Int J Pharm. 1992;83:211-219.
38. Dubois JL, Ford JL. Similarities in the release rates of different drugs from polyethylene glycol 6000 dispersions. J Pharm Pharmacol.1985;37:494-495.
39. Ford JL. The current status of solid dispersions. Pharm Acta Helv.1986;61:69-88.
40. Degwy MAAEAAE, Tayel S, El-Nabarawi MA, El-Rehem RTA. The effect of using two NSAIDs with different solubility on freeze drying technology. Curr Trends Biotechnol Pharm. 2013;7(4):890-903.
41. Mehta A, Vasanti S, Tyagi R, Shukla A. Formulation and evaluation of solid dispersions of an anti-diabetic drug. Curr Trends Biotechnol Pharm. 2009;3(1):76-84.