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Studies on Sulphamethoxazole Solid Dispersions and their Tablets

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Several insoluble drugs when prepared as solid dispersions showed improved solubility and dissolution. Techniques of melting and melt-solvent methods were used to prepare solid dispersions to enhance the solubility of poorly soluble sulphamethoxazole. Solid dispersions of various compositions were prepared using mannitol as carrier. An improvement in the solubility and dissolution rates of sulphamethoxazole from solid dispersions was observed. Solid dispersions of sulphamethoxazole-mannitol in the proportion of 1:2 prepared by melting and melt solvent method were developed into tablet dosage forms by both wet granulation and direct compression methods. The solid dispersion tablets were evaluated and compared with some of the sulphamethoxazole-trimethoprime conventional tablets available commercially (only sulphamethoxazole was estimated). Solid dispersion tablets of melt solvent method prepared by direct compressable method have shown highest dissolution rate.

Solid dispersion techniques can be used to increase the dissolution and absorption of several insoluble drugs[1,2]. Number of insoluble drugs have been shown to improve their dissolution character when converted to solid dispersions[1,3-7]. To date some reports on formulation of these systems have appeared[2,8-16]. So far there are only few reports in the literature on the dissolution study of solid dispersion tablet dosage forms and their comparison with similar tablets prepared by physical mixture or its conventional dosage forms[17,18].

Sulphamethoxazole (SMZ) is a widely used antibacterial agent and it is poorly soluble in water[19]. Since the dissolution rate of a drug from a surface is affected by the carrier in solid dispersion, the carrier has an ultimate influence on the dissolution of the dispersed drug. Therefore, highly water soluble mannitol was used as carrier in this study. SMZ-mannitol solid dispersions were prepared by melting (I) and melt-solvent (H) methods. These solid dispersions were characterised and formulated as tablets using wet granulation (WG) and direct compression (DC) techniques. Such tablets were subjected to quality control tests and were evaluated for dissolution.

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MATERIALS AND METHODS:

Sulphamethoxazole IP obtained from Siris Ltd., Hyderabad, Mannitol IP from Unicorn Organics Ltd., Warangal, Erndex from Edward Mendell (Europe) Ltd., England and starch from Rajaram Maij Products, Rajnandgaon, MP. Talc and magnesium stearate were obtained from S.D. Fine Chemicals, Mumbai. All other materials used are of AR grade.

Preparation of solid dispersions:

Solid dispersions containing sulphamethoxazole-mannitol in the proportions of 1:1,1:2,1:4,1:6,1:8 and 1:10 were prepared by melting and melt-solvent methods. Using the melting method. Solid dispersions were prepared by melting the physical mixture of SMZ and mannitol on a sandbath[1]. The fusion temperature is controlled and found to be between 165-175°. The molten mixture was immediately cooled and solidified in an ice bath with vigorous stirring. The solid

mass thus obtained was scrapped, crushed, pulverised and passed through 60/80 mesh.

In the melt-solvent method, SMZ was dissolved in acetone and the solution was incorporated into the melt of mannitol at 165° by pouring into it[20]. It was kept in an ice bath for sudden cooling. The mass was kept in a desiccator for complete drying. The solidified mass was scrapped, crushed, pulverised and passed through 60/80 mesh.

Preparation of tablets:

Solid dispersion prepared by melting and melt-solvent method were formulated into tablets by wet granulation and direct compression methods. Each time a batch of about 1000 tablets, each weighing 1.4 g with the average hardness of about 4 kg/cm^2 was prepared using cadmach single punch tablet machine.

Wet granulation method:

SMZ-mannitol solid dispersion (1.092 kg) and starch (0.07 kg) were mixed in a plastic container. To this, starch paste (0.140 kg) was added and mixed thoroughly. The wet mass was passed through a number 12 mesh. The wet granules were dried at 40° for 12 h. The dried granules were size reduced and passed through a number 16 mesh. To these granules, starch (0.07 kg), magnesium stearate (0.014 kg) and talc (0.014 kg) were added and mixed thoroughly and compressed.

Direct compression method:

The granules of SMZ solid dispersion (1.120 kg) was mixed with EMDEX (0.266 kg), a directly compressible agent and magnesium stearate (0.014 kg) and compressed to from tablets. The prepared tablets were evaluated as per the standard procedures for weight variation, disintegration[21], content uniformity[22], hardness and friability[23].

Solubility and dissolution of SMZ-Mannitol solid dispersion:

Total solubility of SMZ in water from plain, SMZ-mannitol physical mixtures and solid dispersions was measured. The powder samples representing 1 g of SMZ were added to the 500 ml of distilled water. Which was stirred continuously for 6 h. After 6 h, three samples, 1 ml each were taken and analysed for SMZ using the method reported by Bratton and Marshal[24].

Dissolution studies were performed using a dissolution tests apparatus USP XX[25]. The medium consisted of 1000 ml of distilled water maintained at 37±0.5°. The samples, SMZ pure, SMZ-mannitol physical mixture or SMZ-mannitol solid dispersions equivalent to 50 mg of pure SMZ were added to the dissolution medium. The medium was stirred with a paddle stirrer at 100 rpm. Sample (1 ml) was withdrawn from a fixed position in the vessel at intervals of 1, 2, 3, 5, 10, 15 and 30 min using specially made sampling instrument with inbuilt filters. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. The samples were analysed for SMZ. From the sample, 0.2 ml was taken and diluted to 5 ml with distilled water. To this, I ml of 0.5 N hydrochloric acid and 1 ml of 0.1% w/v sodium nitrate was added and kept for 3 min. Then, 1 ml of 0.5% w/v ammonium sulphamate was added and the solution was mixed using cyclomixer till evolution of gas ceases. After 2 min 1 ml of 0.1% w/v N-(1-naphthyl) ethylenediamine dihydrochloride was added and finally, the volume made upto 10 ml with distilled water and allowed to stand for 10 min. The absorbance was measured at 545 nm using spectrocolorimeter against blank. The percent drug released at various time intervals was calculated.

Dissolution test of tablets:

Dissolution test was carried out in USP XX dissolution apparatus[25] using 1000 ml of glass distilled water as dissolution medium. The test was carried out at 37±0.5° and at 100 rpm. The samples (1 ml) were withdrawn at the interval of 10, 20, 30, 40, 50, 60 and 90 min and replaced with the equal quantity of dissolution medium. The samples were analysed for SMZ using the procedure mentioned above. The percent release was computed at each sampling intervals. For comparison, marketed tablets of SMZ-trimethoprime of three brands coded A, B and C were also evaluated (only SMZ was estimated).

RESULTS AND DISCUSSION

Table 1 shows solubility of SMZ from physical mixture and solid dispersion expressed as percentage solubility. It is clear that the solubility of SMZ has improved considerably in solid dispersions of various compositions of melting and melt solvent methods. Melting method shows higher improvement in solubility.

The dissolution data of physical mixtures and solid dispersions prepared by melting and melt solvent methods are presented in Table 2. All physical mixtures have exhibited decreased drug release compared to control. It is evident that solid dispersions made out of melting method have shown improvement in their release over the control. Among

TABLE 1: SOLUBILITY OF SULPHAMETHOXAZOLE.

Drug-Mannitol ratio*	Plain SMZ	Physical mixture	Melting method	Melt solvent method
-	73.00	-	-	-
1:1	-	74.00	96.00	76.00
1:2	-	74.00	98.00	80.00
1:4	-	74.00	99.00	81.00
1:6	-	74.00	100.00	70.50
1:8	-	74.00	96.00	79.00
1:10	-	74.00	92.00	81.00

*Weight ratio. Percent solubility (mg/100 ml) of sulphamethoxazole in distilled water.

the various solid dispersions, 1:2 composition has exhibited higher release. In case of solid dispersions made out of melt solvent method (Table 2), 1:2 and 1:6 have shown highest release.

Time dependent changes in the rate of dissolution presented as percent improvement in dissolution of solid dispersion over the pure drug for the melting and melt solvent methods are depicted in figs. 1 and 2. These percent improvement curves seems to exhibit a specific pattern, a rising phase followed by declining phase which in some cases crossed the zero line. The rising phase is because of improvement in the intrinsic solubility of the drug due to molecular dispersion. The declining phase represents decreased solubility due to distortion of molecular aggregate structure between the drug and carrier. Such distortion can release more and more carrier molecules into the bulk, which

TABLE 2: PERCENTAGE OF SMZ RELEASED.

Time min	Pure SMZ	Physical Mixture of SMZ-Mannitol 1:1	1:2	1:4	1:6	1:8	1:10
1	40.00	41.00	42.51	30.00	38.51	20.00	25.00
2	56.00	56.00	45.04	50.00	52.52	48.00	40.32
3	66.00	66.50	60.06	67.50	63.02	56.52	50.50
5	87.00	86.00	72.07	77.50	80.53	72.00	60.92
10	91.50	93.00	84.08	85.00	91.03	80.00	65.00
15	98.00	94.68	87.08	87.52	91.03	80.00	65.00
Time min		**Solid Dispersion-Melting Method**					
1		47.00	48.04	68.00	66.52	52.00	60.00
2		62.00	82.58	82.50	91.03	80.00	85.00
3		78.00	88.58	92.50	94.58	84.00	85.00
5		88.00	99.09	95.00	94.58	84.00	85.00
10		88.00	100.0	95.00	94.58	84.00	85.00
15		88.00	100.0	95.00	94.58	84.00	85.00
Time min		**Solid Dispersion-Melt Solvent Method**					
1		52.00	67.56	55.00	70.00	72.00	75.00
2		73.00	71.32	65.00	73.52	78.10	80.00
3		78.29	80.33	70.00	94.03	84.00	99.69
5		86.00	81.00	77.50	94.53	84.00	99.69
10		91.00	87.08	77.50	94.53	84.00	99.69
15		91.00	88.59	77.50	94.53	84.00	99.69

Percentage of SMZ released (mg) from physical mixture and solid dispersions prepared by melting and melt-solvent methods.

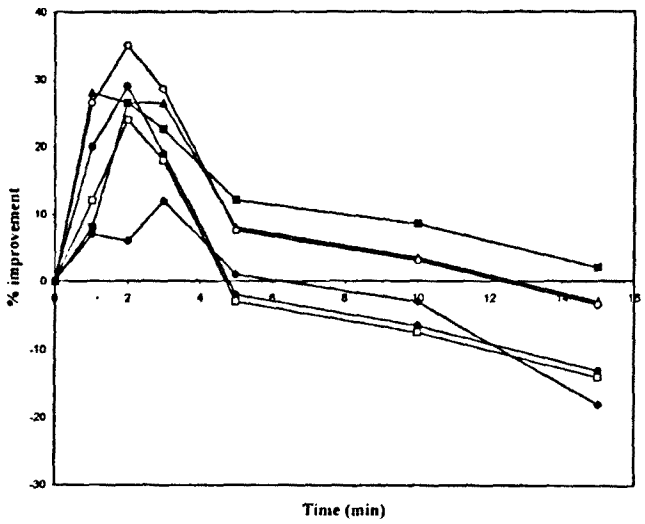

Fig. 1: Improvement in dissolution of SMZ from solid dispersions prepared by melting.
Profiles of per cent improvement in dissolution of SMZ solid dispersions prepared by melting method over that of pure SMZ. Different ratios of SMZ:mannitol used were, 1:1 (-◆-), 1:2 (-■-), 1;4 (-▲-), 1:6 (-○-), 1:8(-□-) and 1:10 (-●-).

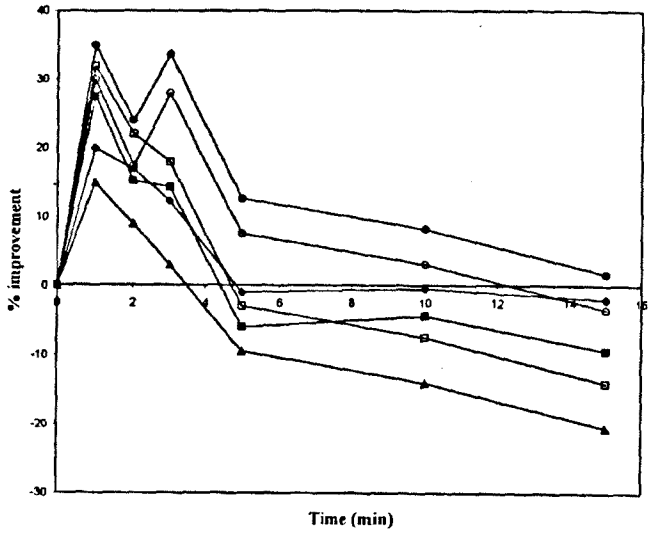

Fig. 2: Improvement in dissolution of SMZ from solid dispersions prepared by melt-solvent method.
Profiles of per cent improvement in dissolution of SMZ solid dispersions prepared by melt-solvent method over that of pure SMZ. Different ratios of SMZ:mannitol used were,1:1 (-◆-), 1:2 (-■-), 1;4 (-▲-), 1:6 (-○-), 1:8(-□-) and 1:10 (-●-).

eventually prevents further solubility of drug.

The negative effect on dissolution appears to be distortion of molecular dispersion structure which leaves an insoluble base particle and increased accumulation of carrier molecule in the bulk seems to cause a saturation by which further solubility is retarded. It is important to note that the composition 1:2 did not exhibit the negative effect.

The present investigation thus reveals marked improvement in the dissolution rate of SMZ in solid dispersions. The technique can be further explored for use in tablet formulations. Composition 1:2 (drug:carrier) appears particularly promising in this respect.

Each tablet of SMZ solid dispersion was designed to contain 400 mg of SMZ. All the seven tablet lots (four lots of SMZ solid dispersion and three lots of commercial tablets A, B and C) had more than 95% of the expected drug content (Table 3). A large difference in hardness and friability was observed in all seven lots of tablets. Three commercial tablets have shown lower friability than tablets of solid dispersions. In commercial tablets, tablet A showed maximum hardness (7 kg/cm^2) and least friability. There appears a broad correlation between friability and hardness in solid dispersion tablets.

In solid dispersion tablets prepared by melt solvent method, least friability and highest hardness was observed for tablets prepared by wet granulation method, while highest friability and lowest hardness was exhibited by tablets prepared by direct compression method indicating poor binding strength (Table 3). Wet granulation method seems to have improved binding over the tablets prepared by direct compression.

The three commercial tablets showed different disintegration times but all were within a narrow range of 1-3 min (Table 3). However, there is a large difference in disintegration times of solid dispersion tablets. Interestingly, the least disintegration time was exhibited by tablets prepared by wet granulation method. The highest was for tablet of direct compression. This is inspite of their least hardness and greater friability. These tablets were prepared with a directly compressible vehicle Endex and did not contain any disintegrant in them. In contrast to those, tablets prepared by wet granulation method contained starch as disintegrant. Thus, they have the improved disintegration over the tablets obtained by direct compression.

Dissolution profiles of three commercial tablets of SMZ and four tablets of SMZ made from solid dispersion are shown in fig. 3. Broadly, dissolution rate of solid dispersion

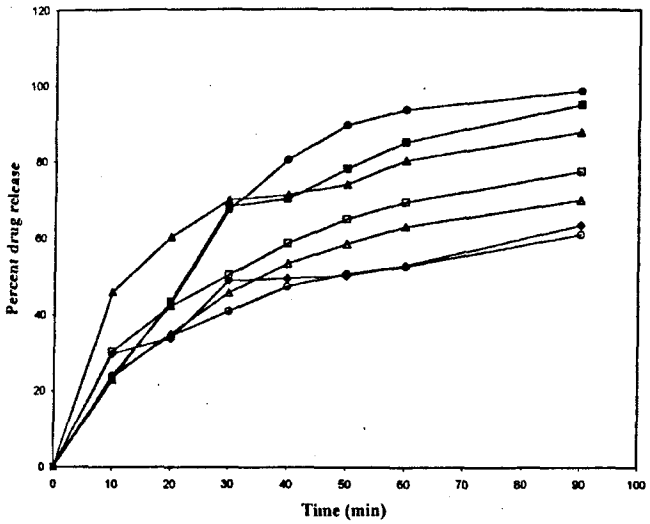

Fig. 3: Dissolution profiles of marketed and prepared solid dispersion tablets.

Dissolution profiles of marketed and solid dispersion tablets prepared by I-wet granulation (-◆-), I-direct compression (-■-), II-wet granulation (-▲-), II-direct compression (-●-), marketed tablet A (-□-), tablet B (-○-) and tablet C (-△-). Solid dispersions are prepared by I-melting method and II-melt-solvent methods, respectively.

tablets was either superior or comparable with that of commercial tablets. Among the various tablets compared, the commercial tablet B and solid dispersion tablets (melting method) prepared by wet granulation method have shown least dissolution rate. The reasons for this result are difficult to state as we have not studied granule strength and porosity of the tablets. Highest dissolution rate was for tablets prepared by direct compression method, where SMZ solid dispersion was obtained by melt solvent method.

To understand the mechanism of drug dissolution from the tablets prepared by solid dispersions, the dissolution data was plotted according to Hixson-Crowell equation[26] (figs. 4 and 5). All the four solid dispersion tablets and three commercial tablets have exhibited biphasic dissolution profiles. Such profiles were reported earlier for several tablets containing insoluble drugs. There was initial fast dissolution phase (α-phase) followed by a slow phase (β-phase) for each tablet form. From the intersection point of these two phases one can obtain critical time. Critical time (Tc) is the final time required to completely solubilize first smallest particle, which existed in the system or is being generated spontaneously by deaggregation of granules. The highest time (Tc) with fastest initial dissolution, was shown by tablets of solid dispersions prepared by directly compressible vehicle. This clearly indicates that these are the tablets possessing finest particulate net work in them. Since these tablets have higher disintegration times, it is understandable that the dissolution is occurring by microsurface errosion upto critical time.

These results reveal that for insoluble drugs where dissolution improvement is necessary, one can use solid dispersion techniques. Melt-solvent method is an equally potent solid dispersion technique and is obviously useful for

TABLE 3: EVALUATION OF MARKETED AND SOLID DISPERSION TABLETS.

Test	Marketed Tablets			Melting Method		Melt Solvent Method	
	A	B	C	Wet Granulation	Direct Compression	Wet Granulation	Direct Compression
Friability	0.196	0.164	0.12	0.302	0.461	0.296	0.404
± S.D.	0.012	0.02	0.01	0.025	0.029	0.022	0.03
Hardness (kg/cm^2)	7	4	5	4	3	6.3	3
Drug Content (mg)	401.7	398.1	399.5	392.0	390.6	395.2	396.0
±S.D.	5.0	8.0	12.5	12.5	10.0	9.4	6.9
Disintegration time (s)	110	210	80	45	720	45	480
±S.D.	5	7	5	2	10	2	7

± S.D. denotes standard deviation.

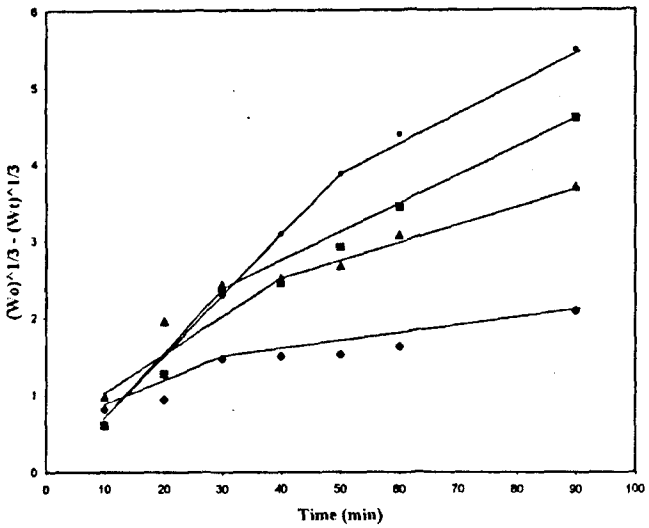

Fig. 4: Dissolution profiles of solid dispersion tablets as per Hixson-Crowell equation.

Dissolution profiles of solid dispersion tablets as per Hixson-Crowell cube root equation prepared using different methods, I-wet granulation (-◆-), I-direct compression (-■-), II-wet granulation (-▲-), II-direct compression (-●-). Solid dispersions are prepared by I-melting method and II-melt-solvent methods, respectively.

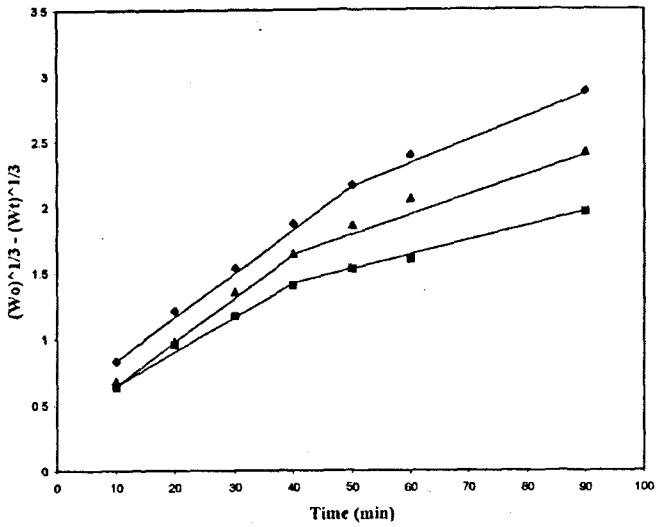

Fig. 5: Dissolution profiles of marketed tablets according to Hixson-Crowell equation.

Dissolution profiles of marketed tablets as per Hixson-Crowell cube root equation Marketed tablet A (-◆-), tablet B (-■-) and tablet C (-▲-).

thermolabile drugs.

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