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Preparation and evaluation of sulfamethoxazole solid dispersion employing starch citrate-a new solubility enhancer

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ABSTRACT

Sulfamethoxazole used widely as a broad spectrum antibiotic. However, its solubility and dissolution rate is very low due to poor solubility in water. Solid dispersion technique was selected for the current research to improve solubility and drug absorption from of Sulfamethoxazole. A new solubility enhancer starch citrate was selected prepared and characterized for its solubility, viscosity, swelling index, gelling property, particle size, etc. Prepared Sulfamethoxazole solid dispersion was evaluated for drug content and *in vitro* dissolution.

Keywords: Sulfamethoxazole, Starch citrate, Solid dispersion & *In vitro* study.

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1. INTRODUCTION

Solubility is an essential parameter for drug absorption to achieve the desired pharmacological effect. Almost 90% of drugs are non-polar. These drugs are lipophilic and insoluble in water. Hence, the solubility behavior of drugs remains one of the most challenging aspects to prepare solid oral dosage forms[1]. Recently various formulations techniques are in use to improve solubility of hydrophobic drugs. Among all solid dispersion approach of delivering poorly water-soluble drugs have attracted attention as an efficient means of enhancing dissolution rates and bioavailability.[2] Solid dispersion prepared by dispensing one or more active ingredient in an inert carrier using physical mixing, solvent evaporation and kneading method at solid state. In solid dispersion there is markedly improvement of drug dissolution; wettability and enhancement of oral absorption of hydrophobic drugs take place.[3]

Sulfamethoxazole is a broad spectrum antibiotic mainly used for bacterial infections such as bacterial infection in bronchitis, prostatitis and urinary tract. It falls under BCS class II drugs which are practically insoluble in water. The present research aim is to improve the solubility and bioavailability of sulfamethoxazole by solid dispersion method employing starch citrate.

2. MATERIALS AND METHODS

2.1 Materials

Sulfamethoxazole was a gift sample from A to Z pharmaceuticals, Chennai. Citric acid was purchased from microfine chemicals. Potato starch, methanol and all other solvents of analytical grade were purchased from SD fine chem. Ltd. Mumbai. Distilled water was used throughout the experimentation.

2.2 Methods

2.2.1 Preparation of starch citrate[4, 5]:

Starch citrate was prepared by dissolving 10 parts of citric acid in 25ml of distilled water. The pH of citric acid solution was adjusted to 3.5 by adding drop wise 10M sodium hydroxide, and the volume of this solution was made up to 50 ml by adding distilled water. In the next step, 25 parts of potato starch was added to the above-prepared solution and kept for conditioning at room temperature for 16 hours. After 16 hours the mixture was dried at 60°C in a hot air oven for six hours and further dried at 60°C for 2 hours. The unreacted citric acid was removed by washing the mixture with distilled water followed by drying at 50°C which results in a removal of moisture entirely.

2.2.2 Characterization of starch citrate

The starch citrate prepared was evaluated for the following;

S. No	Parameter	Method
1	**Solubility**	Solubility of starch citrate was checked in water, aqueous buffer having pH 1.2, 4.5 and 7.4 and in organic solvents like alcohol, dichloromethane, chloroform, acetone and petroleum ether.
2	**pH**	The pH was determined by pH meter after preparing 1% w/v slurry of starch citrate.
3	**Melting point**	Melting point apparatus was used for the determination of melting point.
4	**Viscosity**	Starch citrate 1% dispersion in water was prepared and then viscosity was determined using Ostwald viscometer.
5	**Swelling index**	200 mg of starch citrate was added to water and liquid paraffin in two different graduated test tubes and mixed properly to form dispersion. Then the test tubes are allowed to stand for 12 hours to check the volume of sediment. After 12 hours, the volume of sediment was checked and recorded. $$S.I = \frac{\text{Volume of sediment in water} - \text{Volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light liquid paraffin}} \text{ X } 100$$
6	**Gelling property**	7% w/v dispersion of starch and starch citrate was prepared and then heated in a water bath at 100 ºC for 30 min, for the evaluation of their gelling property.
7	**Particle size**	By sieving method (standard sieve)
8	**Density**(g/cc)	By liquid displacement method, using benzene as liquid.
9	**Bulk density**	In a 50 ml of measuring cylinder, accurately weighed sample was taken and packing volume was noted. Loose bulk density was determined by using the formula $$\text{LBD} = \frac{\text{Mass of powder}}{Volume\ of\ packing}$$ Tapped bulk density was noted after tapping the measuring cylinder filled with sample on a plane surface. Calculated by using the formula $$\text{TBD} = \frac{\text{Mass of powder}}{Tapped\ volume\ of\ packing}$$
10	**Compressibility index**	Percentage compressibility of powder blend reflected by compressibility index. Formula for the calculation of Carr's Compressibility Index is $$\%\ \text{Carr's Index} = \frac{(\text{TBD} - \text{LBD})}{\text{TBD}} \text{ X } 100$$ Where, TBD= Tapped bulk density; LBD= Loose bulk density.
11	**Angle of repose**	Angle of repose is the maximum angle formed between the powder surface and the horizontal plane, calculated by the formula given below $$\tan\theta = \frac{h}{r} \qquad \theta = \tan^{-1}\frac{h}{r}$$ Where θ=angle of repose; h=height; r=radius

2.2.3 Preparation of solid dispersion[6]

Solid dispersion of sulfamethoxazole employing starch citrate was prepared by different three methods like physical mixing, solvent evaporation, and kneading method. In all methods, different ratios of drug and starch citrate was used. Composition of different solid dispersion is given in table 1.

Physical mixing	Solvent evaporation	Kneading method
In a clean and dry mortar, sulfamethoxazole and starch citrate was taken and mixed by spatula (in different ratio 1:1,1:2,1:3) and then through sieve no.100 blend was sieved and stored in a desicator in an airtight container.	In a clean and dry china dish, sulfamethoxazole was dissolved in methanol to get a clear solution and then starch citrate was added to form dispersion. (Starch citrate was added in different ratios 1:1, 1:2, and 1:3).Formed dispersion was heated at 50°C in order to remove the solvent. Sieved through #100 and keep in an airtight container in desicator.	In different ratios (1:1, 1:2, 1:3) sulfamethoxazole and starch citrate were taken in a mortar and mixed followed by the addition of methanol. To form thick slurry, mixture was stirred and kneaded for the evaporation of methanol. After drying at 55°C, the resultant product was pulverized, sieved and kept in a desicator for further use.

Table 1: Composition of sulfamethoxazole solid dispersion by different methods:

Formulation	Ratio	Sulfamethoxazole(g)	Starch citrate(g)
P1 Physical mixing	1:1	1	1
	1:2	1	2
	1:3	1	3
P2 Solvent evaporation	1:1	1	1
	1:2	1	2
	1:3	1	3
P3 Kneading method	1:1	1	1
	1:2	1	2
	1:3	1	3

2.2.4 Determination of drug content[7,8]

Solid dispersion equivalent to 50 mg of sulfamethoxazole was weighed and acetone was added to dissolve the drug from solid dispersion completely in a 50 ml volumetric flask and kept aside for one hour. Then the solution was filtered and 1ml was transferred to 100 ml volumetric flask and the volume was make up by 0.1N HCl and analyzed at 265nm by UV spectrophotometer.

2.2.5 *In Vitro* dissolution study[9]

To study the release of drug from prepared solid dispersion, the dissolution study was carried out using USP type II (paddle) apparatus by using 0.1N HCl as buffer at 37°C±5°C by maintaining agitation speed of 50 rpm. At different time intervals (5, 10, 15, 30, 45, 60 minutes), 5 ml of sample was taken and 5 ml buffer was replaced in the dissolution medium to maintain sink condition. The obtained sample was filtered through 0.45 micron and analyzed for sulfamethoxazole at 265nm by UV spectrophotometer.

3. RESULTS AND DISCUSSION

The starch citrate prepared was found to be white amorphous free-flowing powder. The physical and micromeritics properties of the starch citrate are given in table 2. It was insoluble in all aqueous and organic solvents tested. The pH of 1.0% aqueous dispersion was found to be 7.72.

Starch citrate exhibited good swelling in water. The swelling index was found to be 1500. All micrometric properties indicated good flow properties needed manufacturing of tablets. The density of starch citrate was found to be 0.645g/cc. The angle of repose and compressibility index showed good flow properties of starch citrate.

Solid dispersion prepared using sulfamethoxazole, and starch citrate found to be colorless, free-flowing and amorphous. The percent of sulfamethoxazole dissolved from solid dispersion obtained from *in vitro* dissolution study were given in table 3.

Table 2: Physical and micromeritics properties of the starch citrate prepared

Parameters	Observation
Solubility	Insoluble in all aqueous and organic solvents tested
pH (1% w/v aqueous dispersion)	7.72
Melting Point	Charred at 210º C
Viscosity(1% w/v aqueous dispersion)	1.01cps
Swelling index	1500
Gelling property	No gelling at 100^{0}C but formed to clear solution. Where as in the case of starch, it was gelatinized and formed gel.
Particle Size	152 µm (80 mesh)
Density	0.645g/cc
Bulk Density	0.834 g/cc
Angle of Repose	21.04^0
Compressibility Index	8.81%

Table 3: Cumulative Percent dissolved of sulfamethoxazole

Formulation/Time	5 (min)	10 (min)	15 (min)	30 (min)	45 (min)	60 (min)
F0	1.94	2.20	2.87	3.18	4.46	4.78
F1	4.25	7.60	12.76	14.16	24.46	34.94
F2	12.44	13.66	23.84	34.95	44.87	45.16
F3	12.28	32.99	43.03	48.93	53.85	55.43
F4	5.18	8.88	14.58	23.94	33.86	41.44
F5	16.44	18.76	24.14	34.29	44.51	56.68
F6	17.82	34.35	44.75	55.30	65.31	76.74
F7	12.10	23.55	35.49	45.76	55.62	67.04
F8	23.04	33.36	43.91	56.12	66.71	77.04
F9	35.42	46.39	86.42	98.66	-	-

Dissolution profile of pure drug of sulfamethoxazole (F_0) and different solid dispersion formulation employing sulfamethoxazole and starch citrate in different ratios(1:1, 1:2, 1:3) by various methods like physical mixing, solvent evaporation, and kneading method are carried out and percent drug dissolved of all formulations at different time intervals (5, 10, 15, 30, 45 and 60 minutes) was calculated. Figure 1 shows the dissolution profile of solid dispersion by various methods and figure 2 shows the dissolution profile of solid dispersion based on their different ratios. Dissolution studies indicated, that solubility of sulfamethoxazole is increased when it is formulated into solid dispersion form. In comparison to all formulations, dissolution rate was enhanced to maximum extent in 1:3 ratio by kneading method as shown in figure 3.

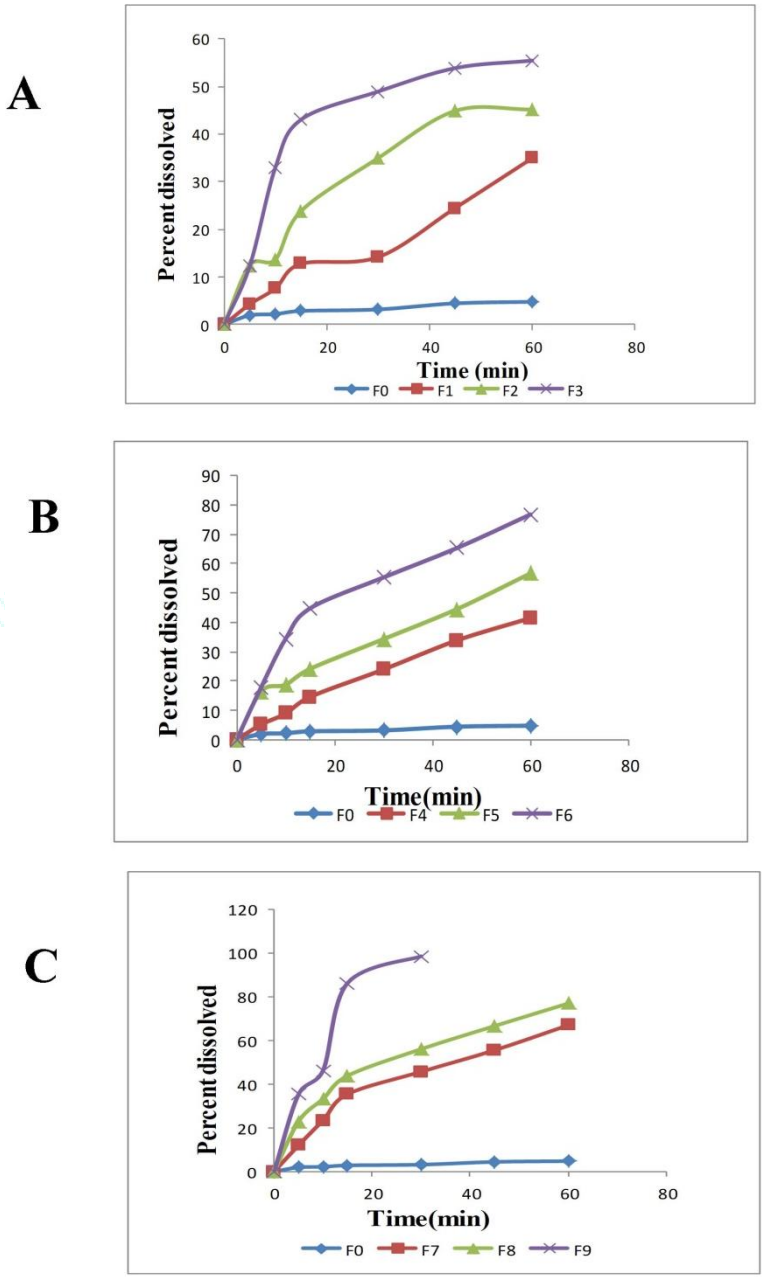

Figure 1: Dissolution profile of sulfamethoxazole solid dispersion by different methods (A: dissolution profile by physical mixing method, B: dissolution profile by solvent evaporation method, C: dissolution profile by kneading method)

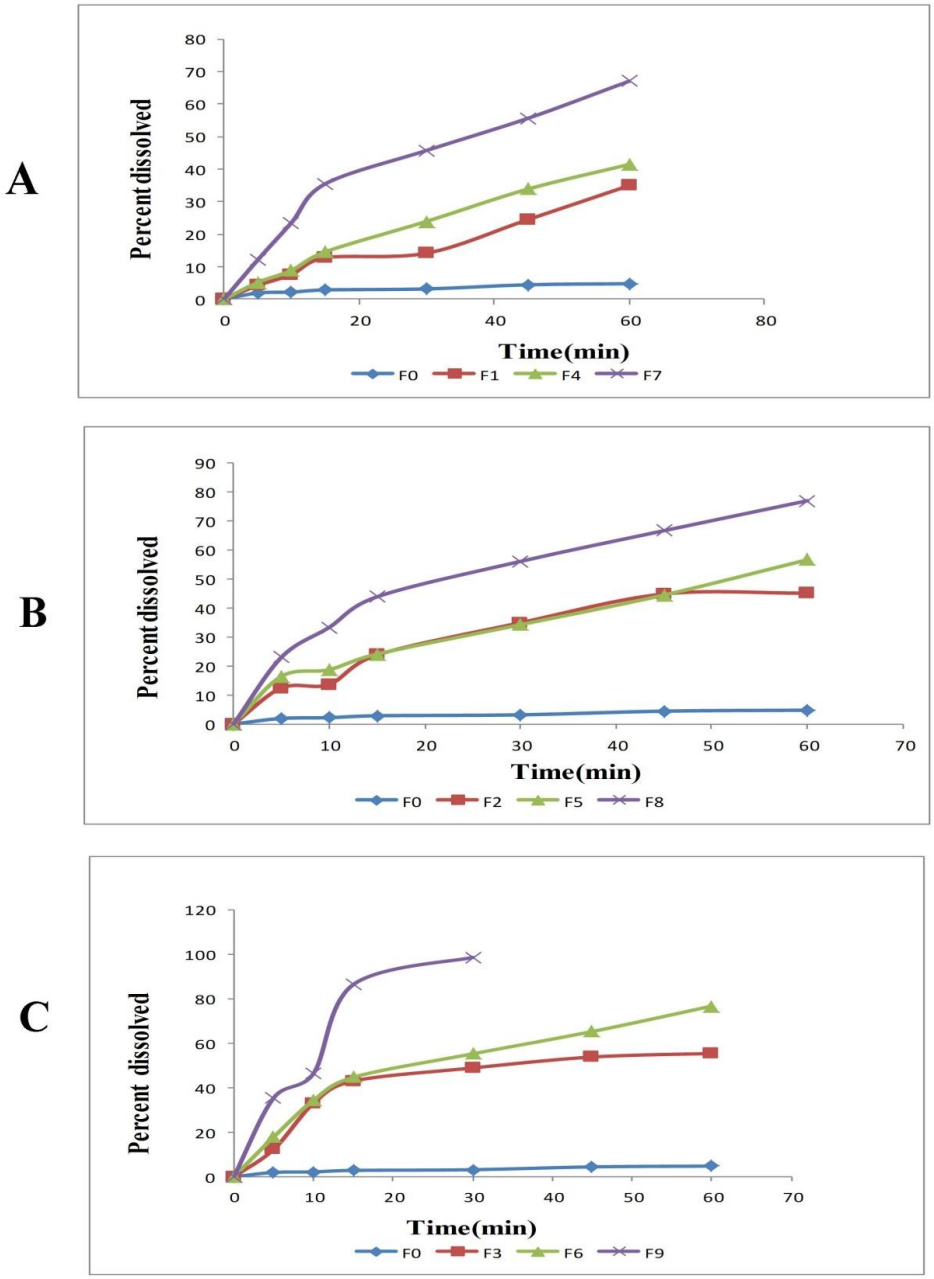

Figure 2: Dissolution profiles of sulfamethoxazole solid dispersions (A: dissolution profile of solid dispersion in 1:1 ratio, B: dissolution profile of solid dispersion in 1:2 ratio, C: dissolution profile of solid dispersion in 1:3 ratio).

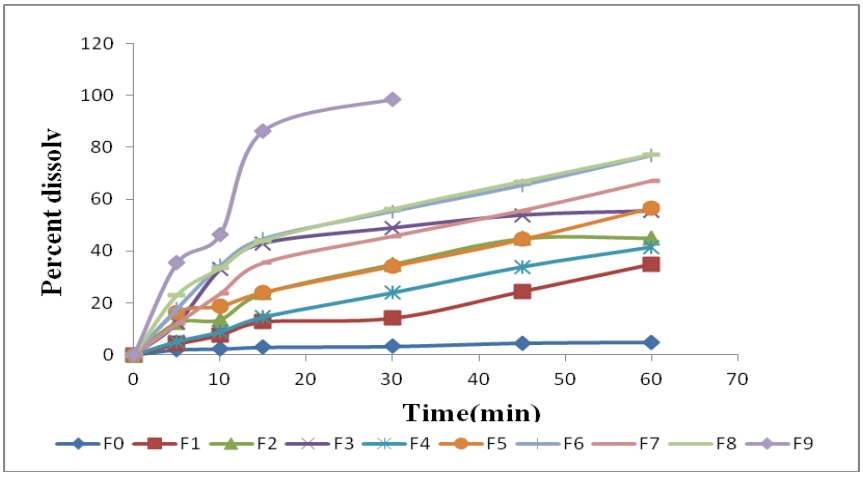

Figure 3: Dissolution profiles of sulfamethoxazole solid dispersions by different methods

4. CONCLUSION

Solid dispersion of sulfamethoxazole by employing starch citrate as solubility enhancer prepared by utilizing physical mixing, solvent evaporation and kneading method. Starch citrate used in three different ratios shows maximum solubility in formulation comprising ratio 1:3. Among methods of preparation of solid dispersion, kneading method was found to be best method as a solubility enhancer of poorly soluble drugs. Therefore, starch citrate can be used as a carrier in formulation of solid dispersion.

Financial & competing interests' disclosure

The authors confirm that this article content has no conflict of interest.

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