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Improvement of Dissolution rate of Sulfamerazine by Solid dispersion technique

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Abstract

Background: low solubility affects dissolution leads to low bioavailability hence formulation come to less effective therefore it is required to enhance solubility in order to increase bioavailability. Sulfamerazine is a potent antibacterial drug comes in BCS class II category whose limited water solubility causes poor bioavailability.

Objective: To enhance solubility and dissolution of Sulfamerazine by using solvent evaporation method of solid dispersion.

Method: In order to get enhanced solubility of sulfamerazine (SMZ), solvent evaporation technique was adopted from solid dispersion techniques due to its easy procedure and minimum resources involved. Poloxamer 700 was used to enhance solubility of SMZ. All the required evaluation test were performed and optimized.

Result: solid dispersion of sulfamerazine was prepared and evaluated, T1 formulation was found to be better optimized formulation. All the formulations were tested for %age yield, drug content, solubility, In-vitro dissolution test whose result was found to be 62.4 ± 1.232, 87.56 ± 5.321, 0.486 ± 0.124 and 87.65 % in 8 hours respectively for optimized formulation T1.

Keywords: Solid dispersion, Solvent evaporation method, Sulfamerazine, solubility.

Introduction

Any pharmaceutical research strives to meet the demands of society by creating a dosage form that is appropriate, has a high level of safety and efficacy, and has the fewest side effects possible. The technology enables large-scale production procedures that are affordable, dependable, and reproducible without the need for brand-new, expensive specialized equipment. In recent years, high-throughput screening and combinatorial chemistry have been used in the drug development process. Scientists found it more difficult to construct dosage forms for newer medication candidates due to their poor water solubility. Additionally, water solubility is poor for 40% of newer candidates employed in the pharmaceutical industry [1]. By homogenously dissolving the solute in an appropriate solvent, solubility is a crucial factor in getting the right concentration in the systemic circulation and eliciting the desired pharmacological response [2]. The low solubility of the medicine is the main problem with the development of drug formulation. Only between 50 and 60 percent of

new chemical entities (NCEs) created by industry are somewhat soluble in water. One of the most difficult parts of medication research is improving the solubility and bioavailability of poor water soluble drugs. [3] Rapid porosity particles are present in solid dispersion, which causes a high rate of dissolution. As a result, any therapeutically active material demonstrating improved dissolution and absorption must first demonstrate aqueous solubility. Additionally, medication candidates with poor oral bioavailability and a reduced dissolution profile were identified [4]. Poor solubility causes low bioavailability, considerable differences in plasma drug concentrations between fed and fasted settings, and large inter- and intra-subject variance [5]. Poorly aqueous-soluble drug candidates take longer to dissolve in GIT fluid than they do in the stomach [6]. SMZ is an antibacterial medication that is classified as a class II BCS (Biopharmaceutical Classification System) agent and has a limited bioavailability (only 1%). In order to bind to dihydropteroate synthetase, SMZ suppresses the synthesis of dihydrofolic acid in bacteria and competes with para-aminobenzoic acid (PABA) (dihydrofolate synthetase). Bacteriostatic properties describe SMZ. Hypersensitive responses, nausea, vomiting, and diarrhoea are some of the side effects [7, 8]. It is BCS class II compliant and only very slightly soluble in water. It is a good candidate for formulation of solid dispersion using hydrophilic carriers such as polyethylene glycol (PEG6000), poloxamer (POX407), sodium caparate, caproic acid, beta cyclodextrin, PEG 4000, urea, polyvinyl pyrrolidone (PVP) K30, desoxycholic acid, citric acid, and pen Techniques for solid dispersion assist in lessening negative consequences. Therefore, the current study uses the solid dispersion technique to examine how hydrophilic carriers affect SMZ's solubility and rate of dissolution [9-11].

For scientists, creating a poorly water-soluble medication for oral administration is never easy. There are numerous methods, including particle size reduction (micronization and nanonization) to change a drug's crystal habit, manipulate its crystalline state. To make a drug dispersion, create a eutectic mixture. To complexate a drug, use a complexing agent. To create solid solutions or solid dispersions, use a self-emulsifying drug delivery system. To solubilize a substance, use surfactants. [12] Surface solid dispersion formulation aids in reducing drug agglomeration by increasing surface area, which further boosts dissolving rate [13]. Through the integration of the drug into a hydrophilic carrier system and subsequent deposition of the drug solution onto the adsorbent materials, this approach can be accomplished [14–17]. Our effort aims to produce a solid sulfamerazine dispersion and assess the degree of solubility enhancement in each carrier at various ratios.

MATERIALS AND METHODS

Materials

Drug Sulfamerazine was obtained from Yarrow Chem Pvt. ltd., Mumbai, Maharshtra; Poloxamer 407 purchased from Chemdyes Corporation Gujarat and PEG 6000 purchased from Yarrow Chem Mumbai. Other chemicals such as Sodium Hydroxide, Anhydrous Potassiumdihydrogen orthophosphate of analytical grade were purchased from CDH (Central Drug House) New Delhi, India. Solvents such as Ethanol, Methanol, Hydrochloric acid and Acetone were supplied by Astron chemicals (India) Ahmedabad.

Methodology

Solubility studies of Sulfamerazine in water: Sulfamerazine was added in 10 ml of water in beaker till access amount of drug stops dissolving and was placed on magnetic stirrer for 24 hours. After that solution was filtered through what man filter paper and filtrate solution was further suitably diluted for UV analysis. Diluted sample was subjected to UV absorbance at 253nm λmax by using UV-VIS spectrophotometer (Shimadzu 18000) and then concentration was calculated by using previously made standard curve of Sulfamerazine [18-23].

Formulation of Solid dispersion of Sulfamerazine: Solvent evaporation method was adopted to make solid dispersion of Sulfamerazine. Different ratios of drug-polymer were made in order to get optimized formulation of solid dispersion. Drug (Sulfamerazine) and Polymer (Poloxamer 407) were taken in various ratio (1:1, 1:2, 1:3) respectively and these mixture was dissolved separately in sufficient amount of methanol. Then solvent

was evaporated with continuous stirring manually. Remained portion i.e. residue of mixture was dried in desiccator at room temperature for 24 hrs. Product was obtained and further it was triturated in mortar & pestle. Then obtained fine powder of drug-polymer mixture was passed through sieve no 80 then uniform powder collected and stored in a closed container [24-28].

Evaluation of prepared solid dispersion

Percentage Yield: %age yield was determined to estimate the efficiency of the method used in development of formulation. In order to get %age yield of the formulation, following given formula was used to calculate the % yield [29].

$$\%\text{age Yield} = \frac{obtained\ amount\ of\ product}{Total\ used\ amount\ of\ drug\ and\ polymer} \times 100$$

Drug content analysis: Solid dispersion of SMZ powder was taken and weighed accurately 10 mg from each batch and separately transferred into 100ml of volumetric flask contained small amount of water for each batch. Then it was dissolved by shaking and volume was made up to 100 ml. The solution was kept for 24 hours at room temperature, and then solution was filtered and from each solution 1 ml was taken into 10 ml volumetric flask, volume was made up to 10 ml for each batch. After that absorbance was taken by using UV-VIS spectrophotometry (Simadzu 1800) at 252nm. Absorbance was fitted into standard calibration equation in order to determine concentration of the solution [24].

Solubility Studies of Solid Dispersion: Solid dispersion powder was taken and added continuously in small amount in beaker containing fixed amount of water on magnetic stirrer. Excess amount of Solid dispersion powder was added until dissolution stopped. After that it was kept for 24 hours in mixing mode. Then sample was filtered and suitably diluted in context of analyzing UV absorbance at 252 nm. Concentration was calculated using previously prepared calibration standard equation [30, 31].

In-vitro Drug release studies

Preparation of 0.1 N HCl: To make 100 ml 0.1 N HCl solution, there was 8.5 ml HCl (concentrated) solution pipette out and transferred in 100 ml volumetric flask through wall touching of volumetric flask. Before adding concentrated HCl solution into volumetric flask it was ensured that volumetric flask must be filled with small amount of distilled water [32].

Preparation of phosphate buffer of pH 7.4: As per I.P., 1.36 g of potassium dihydrogen orthophosphate anhydrous solid polymer was dissolved in 50 ml of volumetric flask, previously contained small amount of water. Another 0.4 g of NaOH pellets was dissolved in 50 ml of volumetric flask contained small volume of water. The volume was made up to 50 ml with water. Then 50 ml of 0.2 M prepared pot. Di hydrogen orthophosphate solution was transferred in 1000 ml volumetric flask then 39 ml of prepared sodium hydroxide solution was added and volume was made up to 1000 ml with distilled water. pH was checked and adjusted if needed [32].

In-vitro dissolution studies: To carry out dissolution study, USP II type dissolution apparatus was selected and all the standard parameters was kept constant like vessel was filled with 900 ml solution, temperature 37 ± 0.5°C and 50 rpm rotation. Initial for 2 hours dissolution studies was carried out in 0.1 N HCl solution then it was changed with phosphate buffer of pH 74. At every 30 minute 5 ml sample was withdrawn and replaced with fresh buffer respectively. After suitable dilution it was analyzed by UV-Vis spectroscopy at 252nm and release was calculated [24 33-36].

RESULT AND DISCUSSION

Solubility of sulfamerazine in water: From the result, it was found that solubility of SMZ in water observed 0.00401 mg/ml whereas referenced solubility of SMZ is 0.00403 mg/ml.

Evaluation of solid dispersion

%age Yield: The percentage Yield tells us the efficiency of method used in the preparations. In this method the % age Yield was found to be in the range of 56.54 -70.45% (table 1).

Table 1: %age Yield.

S. No.	Formulation	Ratio	%age Yield Mean ± SD (n=3)
1	T1	(1:1)	62.4 ±1.232
2	T2	(1:2)	58.9 ± 1.543
3	T3	(1:3)	57.5 ± 2.761

Drug Content determination: Drug content of solid dispersion formulation T1 contained 86.78 ± 3.621 which was due to Drug : Polymer ratio and as ratio was increase from 1:1 to 1:2, 1:3 then it was observed that the ratio 1:3 formulation Drug content came 26.5 ± 12.421. Hence as polymer concentration was increases, Drug content affected.

Table 2: %age Drug Content of Solid dispersions.

S. No.	Formulation	Ratio of (Drug : polymer)	% drug content
1	T1	1:1	87.56 ± 5.321
2	T2	1:2	68.54 ± 7.876
3	T3	1:3	27.54 ± 6.456

Determination of solubility of prepared Solid dispersion of SMZ: The result of the solubility analysis on T1, T2, T3 observed in distilled water that was 0.423, 0.324. 0.1576 respectively as shown in table 3. It was clearly observed that the solubility of formulations decreased as polymer concentration increase as per ratio.

Table 3: Solubility data of Solid dispersion of SMZ

S. No.	Formulation	Ratio of (Drug : polymer)	Solubility (mg/ml)
1	T1	1:1	0.486 ± 0.124
2	T2	1:2	0.2365 ± 0.278
3	T3	1:3	0.1783 ± 0.168

In-Vitro drug release profile

Release of pure drug as well as solid dispersion formulation of SMZ were studied, it was observed that the formulation T1 showed 83.65% drug release from the formulation, T2 formulation showed 65.54 % drug release and T3 showed 61.98 % drug release in 8 hours. It was cleared that solid dispersion formulations have shown better drug release in comparison with release of its pure form of drug. In drug and polymer ratio, 1:1 ratio of drug , polymer showed better result means due to solid dispersion technique i.e. solvent evaporation method causes solubility increased hence dissolution profile improved. It was found that drug release from solid dispersion and from its pure form SMZ is almost same in acidic medium but in phosphate buffer of pH 7.4, it was found that drug release form solid dispersion T1 shoed more than 80 % in 8 hours (figure 1).

Table 4: Comparative % Cumulative drug release studies.

time (h)	% Cumulative Drug Release			
	T1	T2	T3	SMZ
0	0	0	0	0
0.5	0.25	0.18	0.2	0.21
1	0.31	0.28	0.24	0.27
1.5	0.39	0.34	0.35	0.32
2	0.59	0.49	0.54	0.52
2.5	10.5	5.87	7.45	0.89
3	33.46	10.65	11.89	1.99
3.5	40.54	16.45	13.43	5.89
4	58.65	20.24	18.46	15.34
4.5	62.57	23.99	21.48	19.45
5	76.5	28.89	26.48	24.89
5.5	79.4	33.12	32.78	28.46
6	81.6	37.45	34.89	32.98
6.5	82.57	41.25	39.54	36.68
7	84.43	45.87	42.43	38.56
7.5	85.68	49.76	45.87	39.89
8	87.65	53.68	47.78	40.24

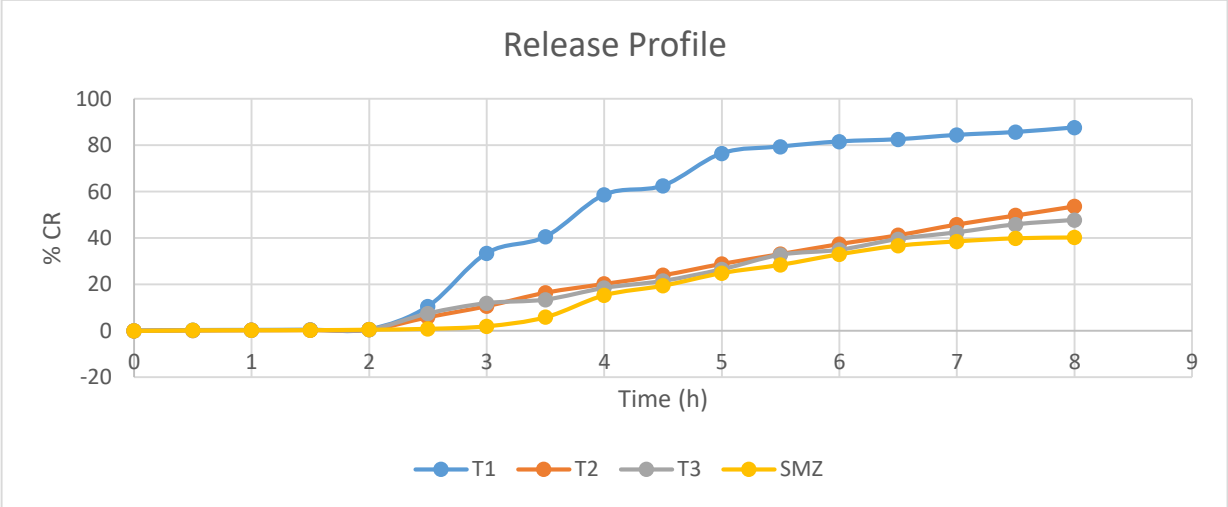

Figure 1: Comparative drug release profile of Solid dispersion T1, T2, T3 and SMZ.

CONCLUSION

In order to enhance solubility of SMZ, solvent evaporation method of solid dispersion was adopted. As pure drug sulfamerazine comes in poorly water soluble drug, result have shown solubility of SMZ was improved. There are three formulation of solid dispersion were prepared in drug polymer ratio. All the required evaluation parameters were studied for all the formulations. The highest %age yield of formulation was found to be T1 as 62.43 ± 1.232% and highest drug content was observed in formulation T1 i.e. 0.486 ± 0.124. The observed Solubility profile SMZ in water is 0.00402 mg/ml and reported was 0.00465 mg/ml at 252 nm. For improving the solubility of SMZ, solid dispersion were prepared using Poloxamer 407 (carrier) in various ratio (1:1, 1:2, 1:3). In-vitro drug release showed maximum release of drug from T1 in 8 hrs. And compared with other as well as with pure drug.

Abbreviations

SMZ: Sulfamerazine

% CR: % cumulative drug release

Conflict of Interest

There are no any conflict of interest.

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