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Formulation and evaluation of Sulfamethoxazole solid dispersions

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ABSTRACT
Sulfamethoxazole (SM) is frequently used in diverse bacterial infections. However, its poor aqueous solubility limits its therapeutic action. Therefore, an attempt has been made in this study to improve its dissolution and solubility through solid dispersion (SD) approach. SD of SM was prepared using either polyvinyl pyrrolidone k-30 (PVP K-30) or Polyethylene glycol 6000 (PEG-6000) by kneading method. Different SD formulations were prepared by kneading the SM with PVP K-30 at 1:5, 1:7.5 1:10, 1:12.5 and 1:15 (w/w) ratios (F1-F5). Similarly, SM and PEG-6000 was kneaded at 1:1, 1:3 and 1:5 ratio to prepare the SD (F6-F8). The prepared SD of SM either with PVP K-30 or with PEG-6000 were evaluated for percent yield, drug content and the saturation solubility. Furthermore, the prepared SD was evaluated for bulk density, tapped density, angle of repose and carr's index. The prepared SD blends possess suitable micrometrics characteristics. These SD (F1-F8) were then manually filled into the hard gelatin capsule (#0) and in-vitro dissolution studies was performed and compared with control formulation (FCO). The percentage yield was of SD prepared with PEG-6000 was highest and was found to be 94.34 % as compared to that of PVP K-30 which was 89.86 %. Similarly, the formulations with PEG 6000 were found to be more superior in enhancing the dissolution of SM by releasing more than 95 % drug just in 45 minutes over PVP K-30. The SD prepared with PEG-6000 were more promising as compared to PVP K-30 warrant further evaluation in future studies.
Key-Words: Solid-Dispersion; PVP K-30; PEG-6000; dissolution.

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INTRODUCTION

The Orally administered dosage forms are still the most successful type of dosage forms as they offer high patient compliance. But, many of newly marketed drugs have low water solubility, therefore limiting their therapeutic efficacy [1]. Drug possessing low solubility show limited bioavailability, further if the drug has additional low permeability this situation becomes even more critical. The drug with low solubility and high permeability are known as BCS Class II drug, whereas drugs having both low solubility and permeability are referred to as BCS Class IV drugs [2]. Recently, solid dispersion (SD) has been employed for tackling the issue of poor drug solubility [3][4]. The solubility enhancement by SD approach is achieved by improving the wettability of hydrophobic drug by the dissolution fluids. This enhances the drug dissolution and further its biological absorption [5]. In our previous studies we found that SD can be used to enhance the dissolution of poorly water soluble domperidone (BCS Class II drug) [6][7].

SM is an anti-bacterial compound (sulfonamide) frequently used in treating various infections Figure 1. It restricts the production of Folic acid in the microorganisms (required for DNA synthesis in bacteria). SM works as a competitor for p-amino benzoic acid (PABA) in the production of dihydrofolate [8]. However, SM show poor aqueous solubility (BCS Class II) and therefore its therapeutic action is limited [9].

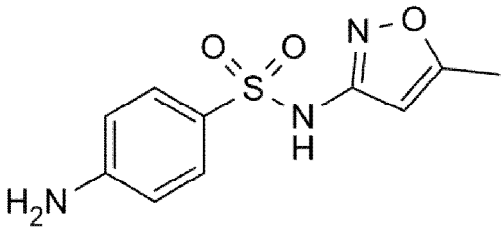

Fig. 1: Structure of Domperidone

In past years numerous attempts have been made for enhancing the dissolution rate and solubility of SM using different polymers like β-Cyclodextrins (CDs) [10][11], starch citrate [12], dendrimers [13]. A recent report by Altamimi et al. 2018 discussed that PEG-6000 could enhance the solubility of SM [14]. Therefore, our attempt in this study is to assess if PVP K-30 and PEG-6000 can increase the solubility of SM using SD approach by kneading method.

MATERIAL AND METHODS

Materials

Sulfamethoxazole was purchased from Yarrow Chem. Pvt. Ltd. India. PVP K-30 and PEG-6000 was purchased from CDH (P) Ltd, India. All other reagents used were of A.R. grade.

Preparation of physical mixtures

The weighed amount of drug is mixed with the corresponding amount of polymer either PVP K-30 or PEG 6000 in a proportion of 1:5, 1:7.5 1:10, 1:12.5 and 1:15 (w/w) and 1:1, 1:3 and 1:5 (w/w). Drug and polymer physical mixture are prepared by slightly grinding drug and carriers in mortar for 2 min at the required drug/polymer ratio, then the powder is passed through a 250 µm mesh collected, and stored in a closed container away from the light and humidity until further use [15].

Preparation of SD

The solid dispersions were prepared using the physical mixtures prepared by kneading with a solution 50 % hydro-alcoholic to a sufficient quantity to maintain a slightly moist consistency (about 10% of weight). After 20 min of kneading, the product was placed in an industrial oven at 50° C for 16 h. The dried product was sieved through a 250 µm mesh and placed in a vial and stored in airtight glass desiccators [16].

EVALUATION OF SD

Determination of Percent Yield

Percentage of practical yield is calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid Dispersions are collected and weighed to determine practical yield (PY) from the following equation[17].

$$\% \mathbf{PY} = \frac{\textbf{Practical mass (solid dispersion)}}{\textbf{Theoretical mass (Drug+Carriers)}} \mathbf{x100} \quad \ldots\ldots\ldots\ldots\ldots \mathbf{eq.\ (i)}$$

Drug Content

Solid dispersions equivalent to the amount of drug are weighed accurately and dissolved in 10ml of ethanol. The solution is filtered, diluted suitably and drug content is analyzed at 270 nm by UV Spectrophotometer [15].

Saturation solubility studies

The solubility of solid dispersions was determined using a 24-hour shake flask method. Equivalent amount of solid dispersions were weighted and transfer in volumetric flask and added 10 ml phosphate buffer pH 6.8. After 24 hrs the samples with sufficient dilutions were analyzed spectrophotometrically [18].

SM-SD BULK AND FLOW PROPERTIES ASSESSMENT

Bulk density

The bulk density value includes the volume of all of the pores within the sample. An accurately weighted quantity of solid dispersion (M) was transferred into measuring cylinder and initial volume (V) was measured. The bulk density was calculated by using following formula [19].

$$\textbf{Bulk Density} = \frac{\textbf{Mass}}{\textbf{Bulk Volume}} \ldots\ldots. \mathbf{eq\ (ii)}$$

Tapped Density

The tapped density, or absolute density, of a sample excludes the volume of the pores and voids within the sample. An accurately weighted quantity of granules/powder (M) transferred into measuring cylinder. The cylinder then allowed to tap on to a bulk density apparatus for 100 times. The height of tapped granules/powder is measured (V), then the tapped density calculated by using following formula [19].

$$\textbf{Tapped Density} = \frac{\textbf{Mass}}{\textbf{Tapped Volume}} \ldots\ldots\ldots \textbf{eq (iii)}$$

Carr's index and Hausner's ratio

The Carr's index and the Hausner's ratio determined by measuring both the bulk density and tapped density of the prepared dispersion, the standard values have been tabulated in the table 4 and 5. The Carr's index and Hausner's ratio calculated as follows [19].

$$\textbf{Carr}'\textbf{s Index} = \frac{\textbf{Tapped Density} - \textbf{Bulk Density}}{\textbf{Tapped Density}} \textbf{x100} \ldots. \textbf{eq (iv)}$$

$$\textbf{Hausner}'\textbf{s Ratio} = \frac{\textbf{Tapped Density}}{\textbf{Bulk Density}} \ldots\ldots. \textbf{eq (v)}$$

Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose (Θ). Angle of repose is defined as the maximum angle possible between the surface a pile powder and horizontal plane. The angle of repose was determined by fixed funnel method to access the flow property of granules. The diameter of the cone (d) and the height (h) of the pile will be noted. From the diameter, radius (r) was calculated. The angle of repose (Θ) was calculated by using following formula [20].

$$\boldsymbol{\theta = \tan -1 \frac{h}{r}} \ldots\ldots.. \boldsymbol{eq\ (vi)}$$

PREPARATION OF SD CAPSULES

The SD formulation prepared with either of the polymers (F1-F8) were incorporated into the hard gelatin capsules (size # 0) manually.

***In-vitro* dissolution studies SD**

The in vitro dissolution studies are studied in USP XXXIII Electrolab six basket dissolution apparatus (Type II) using phosphate buffer 6.8 pH at 37±5°C rotation speed of 50 rpm. Formulations were added to the dissolution medium. At appropriate time intervals, 5 ml of the mixture was withdrawn and filtered through cellulose acetate membrane (0.45 µm). The initial volume was maintained by adding 5 ml of fresh dissolution medium. The removed samples were assayed for drug content at 270 nm by UV spectrophotometer (Shimadzu UV-1800) [21].

RESULTS AND DISCUSSION

Percent yield and drug content

Solid dispersions of Sulfamethoxazole were prepared with PVP-K30 and PEG-6000 using kneading method. Percentage yield and percent drug content of all formulations was determined and it was found that percentage practical yield, percentage drug content in the range of 84.45%-89.86 % for formulation with PVP-K30 and 86.49%-94.34% with PEG-6000 whereas the percent drug content varied in the range of 85 % -99.28 % for PVP K30 and 89.11%-99.20 % for PEG 6000 table 1.

Saturation Solubility

The results indicated that as the ratio of polymer was increased the saturation solubility of drug was increased in a direct relation and the results have been given in table 1.

Table 1: Result of percent practical yield, drug content and saturation solubility

Formulation Code	% Practical Yield	% Drug Content	Saturation Solubility (µg/ml)
F1	84.45	85.00	90.00
F2	88.39	88.34	92.23
F3	89.00	92.02	95.00
F4	89.45	98.23	100.29
F5	89.86	99.28	105.23
F6	86.49	89.11	95.45
F7	92.35	86.88	99.98
F8	94.39	99.20	104.94

Mean ± SD, *n* = 3.

Bulk and flow properties of prepared dispersions

The result of bulk and flow properties data suggested that almost all the prepared SD can be filled into the capsules. The data for the studies have been given in table 2.

Table 2: Bulk and flow properties of prepared solid dispersion of Sulfamethoxazole

Formulation Code	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of Repose
F1	0.516	0.579	11	1.122	28.89
F2	0.49	0.525	6.66	1.071	31.66
F3	0.516	0.543	5.00	1.052	36.42
F4	0.554	0.582	4.76	1.05	37.56
F5	0.539	0.566	4.8	1.049	37.63
F6	0.510	0.569	10.36	1.11	27.87
F7	0.514	0.529	2.83	1.02	30.23
F8	0.526	0.556	5.39	1.05	33.23

In-vitro dissolution study

The in vitro dissolution profiles of the drug SM, various solid dispersions in capsule using PVP K30 and PEG-6000 in phosphate buffer (pH = 6.8) for 60 minutes are shown in Figure 2, 3 and the data is given in table 3. All of the solid dispersion samples showed improved dissolution of SM as compared to control formulation devoid of any polymer. The enhancement of dissolution is mainly attributed due to amorphous nature of the dispersion which in turn might have the increased surface area of drug exposed, thereby leading to increased wettability. Furthermore, the SD prepared with PEG-6000 have shown substantial enhancement of dissolution over formulations with PVP-K30 figure 2 and 3.

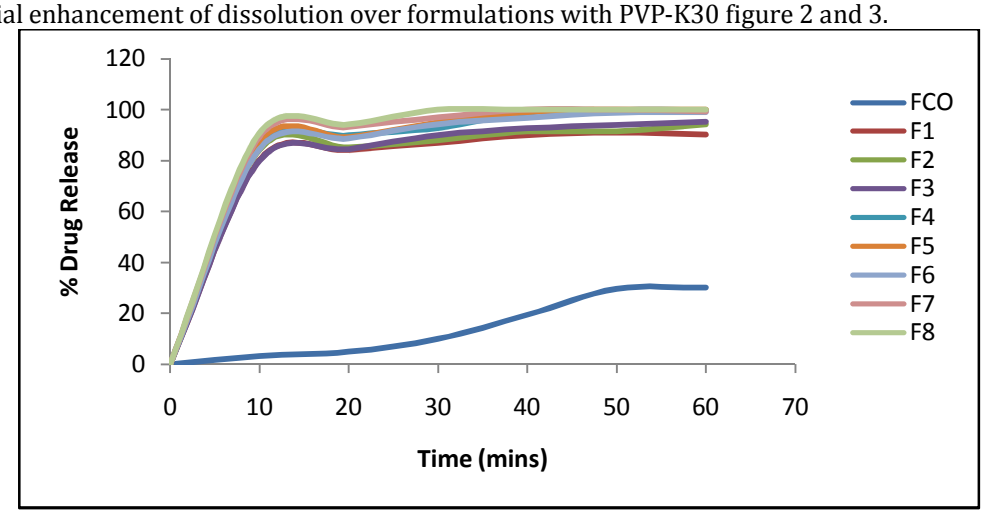

Fig. 2: Percent drug release of solid dispersion formulations with PVP K-30 (F1-5), FCO (Control formulation)

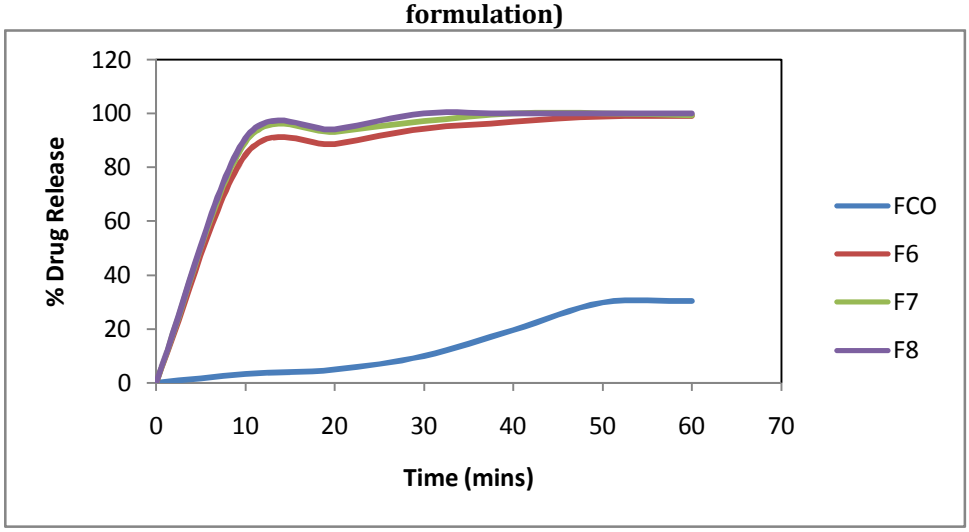

Fig. 3: Percent drug release of solid dispersion formulations with PEG-6000 (F6-F8), FCO (Control formulation)

Table 3: Dissolution data for solid dispersion formulation (F1-F8), FCO represents control formulation.

Time (mins)	FCO	F1	F2	F3	F4	F5	F6	F7	F8
10	3.23	80.18	84.18	79.9	85.18	87.18	84.56	89.18	90.67
20	4.99	84.15	85.15	84.5	89.99	89.15	88.78	93.15	94.15
30	10	86.97	87.97	90	92.97	94.97	94.45	96.97	99.97
40	19.56	90	91.34	92.7	98.99	98.98	96.89	99.96	99.98
50	29.78	91.02	91.49	94	99.97	99.99	98.99	99.99	99.99
60	30.33	90.23	94.23	95.2	99.99	99.99	99.23	99.23	99.99

CONCLUSION

This study was an attempt to address the poor solubility and dissolution of Sulfamethoxazole (BCS Class IV) drug and it can be concluded by the study that both the polymers with increase in concentration could increase the solubility and dissolution of the drug. Moreover, formulations with PEG 6000 were found to be more superior in enhancing the drug dissolution by releasing more than 95 % of drug in 45 minutes over PVP K-30 as only formulation F4 and F5 could release 95 % of drug in 45 minutes. Hence, SD based on PEG-6000 can be further evaluated for the delivery of poorly soluble drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest either financial or non-financial.

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