



SOLUBILITY AND DISSOLUTION ENHANCEMENT OF SULFASALAZINE BY SOLID DISPERSION TECHNIQUE.

D. M. Shinkar,* A. N. Patil² and R. B. Saudagar³

^{1,2}*Department of Pharmaceutics, R.G.Sapkal College of Pharmacy, Anjaneri, Nashik-422213. Maharashtra, India.

³Department of Pharmaceutical Chemistry, R.G. Sapkal College of Pharmacy. Anjaneri, Nashik-422213. Maharashtra, India.

*Corresponding Author: Prof. D. M. Shinkar

Department of Pharmaceutics, R.G.Sapkal College of Pharmacy, Anjaneri, Nashik-422213. Maharashtra, India.

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ABSTRACT

The solubility behavior of drug remains one of the most challenging aspects in formulation development. Most NCE are poorly water soluble, drug not well absorbed after oral administration. Solid dispersion is an increasingly important approach to enhance dissolution rate and solubility of poorly water soluble drug. Sulfasalazine is derivative of mesalazine. Sulfasalazine and its metabolite 5-aminosalicylic acid (5- ASA) are poorly absorbed from gut so its main mode of action is believed to be inside the intestine. It exhibits slow GI absorption rate and inter individual variation of its bioavailability. Thus solubility enhancement and dissolution enhancement of sulfasalazine from its dosage form is an important issue for its *in vivo* bioavailability and therapeutic efficacy. It was planned to improve the solubility of sulfasalazine by using polymer like Gelucire 50/13. Different ratio were employed as 1:1, 1:3, 1:5 and Solid dispersion were prepared by Solvent evaporation method, Physical mixture and Kneading method. Preformulation study was done before going to formulation in that melting point, solubility and compatibility study was done. The prepared solid dispersion also evaluated for percentage yield, percent drug content. Solubility study was done in water. Solid dispersion also characterized by FTIR, DSC, PXRD. *In-vitro* dissolution study was done in pH6.8 phosphate buffer using USP dissolution test apparatus type II.

KEYWORDS: Solid dispersion, Sulfasalazine, Gelucire 50/13, BCS Class 2 drug.

INTRODUCTION^[1,2,3]

Sulfasalazine is a sulfa drug. It is a derivative of mesalazine. It is formed by combination of sulfapyridine with salicylate by an azo bond. It can be abbreviated by SSZ. Sulfasalazine and its metabolite 5-aminosalicylic acid (5- ASA) are poorly absorbed from gut so its main mode of action is believed to be inside the intestine. Sulfasalazine is used for the treatment of inflammatory bowel disease, including ulcerative colitis and Crohn's disease. Sulfasalazine can reverse the scarring associated with cirrhosis of the liver. Myofibroblasts cells contribute to scar tissue in a diseased liver; these cells also secrete proteins that prevent the breakdown of the scar tissue. Sulfasalazine retard this secretion. It also helps in healing cirrhosis of the liver⁴.

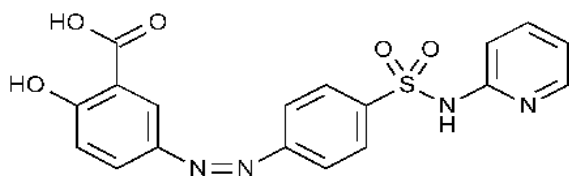
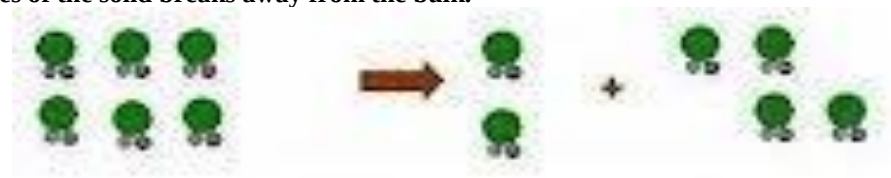


Fig 1: Structure of sulfasalazine.

Solid dispersion, which was introduced in the early 1970s, is essentially a multi-component system, having drug dispersed in hydrophilic carrier(s) by different methods. In solid dispersion systems, a drug may exist as an amorphous form in polymeric carriers and this may result in improved solubilities and dissolution rates as compared with crystalline material. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during dissolution process and drug solubility and wettability may be increased by surrounding hydrophilic carriers. The present study aims to enhance the aqueous solubility and dissolution rate of carvedilol through formation of solid dispersions of carvedilol and gelucire 50/13 in different molar proportions viz. 1:1 and 1:2 (drug:carrier) by using various techniques, physical mixing, melting method and solvent evaporation method thereby to improve its oral bioavailability.

Mechanism of solubilization**Step- I Holes opens in the solvent****Step-II Molecules of the solid breaks away from the bulk.****Step-III The freed solid molecule is integrated into the hole.****Fig no 2: Mechanism of Solubilisation****MATERIALS AND METHODS**

Sulfasalazine was provided by Glenmark Pharmaceutical Ltd, Nashik, India and Gelucire 50/13 from Glenmark Pharmaceutical Ltd., Sinnar, India as a gift sample. All other chemicals and reagents were used of analytical grade.

Phase Solubility Study^[4,5]

Solubility measurements were performed according to Higuchi and Connors method. An excess amount of the drug was added to 10 ml volumetric flask containing 1%, 3%, 5%, 7%, 9% aqueous solution of Gelucire 50/13. The samples were shaken for 48 hours at room temperature $25 \pm 1^\circ\text{C}$ on an orbital shaker incubator. After 48 hours of shaking to achieve equilibrium, 5 ml of aliquots were withdrawn after 1 hour and filtered immediately using membrane filter (0.45μ). The filtered samples were diluted suitably and assayed for absorbance at 359 nm using UV/Visible spectrophotometer (Shimadzu 1800). Solubility studies of physical mixtures, solid dispersion and Kneading method were also performed in same manner. Three determinations were carried out for each sample to calculate the solubility of sulfasalazine.

Preparation of Solid dispersion

The solid dispersion was prepared by using Gelucire 50/13 as a hydrophilic carrier. Different drug and polymer ratios were employed as 1:1, 1:3, 1:5 and prepared by Solvent evaporation method, Physical mixture method and Kneading method.

a) Solvent evaporation method

Solid dispersions were prepared using a SE method. Drug & polymers (Gelucire 50/13) were dissolved in methanol in different ratio & the solutions were made

homogeneous by continuous stirring and solvent was evaporated by subjecting the solution with constant stirring at 70 to 80°C till complete evaporation of solvent. The obtained SD's were dried and subsequently pulverized by triturating in pestle mortar and screened through 60 mesh sieve and stored in desiccator till further evaluation.

b) Physical Mixture method

Solid dispersions were prepared using a PM method. Drug & polymers (Gelucire 50/13) were weighed and transferred to mortar and mix it using pestle. The Physical mixture was sieved through 60 mesh and stored in desiccator till further evaluation.

c) Kneading Method

A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved and stored in desiccator till further evaluation.

Characterization of Prepared solid dispersion^[6,7,8,9,10]**1. Drug Content**

About 10 mg drug equivalent of SD was weighed accurately and transferred to 100 ml volumetric flask. From this stock solution ($100 \mu\text{g/ml}$), 1 ml was withdrawn and further diluted up to 10 ml with PBS pH(6.8). This solution was used for the assay for drug content by UV spectrophotometer at 359 nm. Concentration of drug in stock solution was calculated by using calibration curve and from which percent drug content was calculated.

$$\% \text{ Drug Content} = \frac{W_a}{W_t} \times 100 \dots \dots \dots (2)$$

Where,

W_a = Actual drug content,
 W_t = Theoretical drug content.

2. Fourier Transform-Infra Red Spectroscopy

FT-IR spectra of plain SSZ and solid dispersions with carrier by using Fourier transform infrared spectrophotometer. Solid dispersion were then scanned using FT-IR spectra of mixture were compared with that of plain drug for change or shift in any principle peak of spectra of plain drug.

3. Production Yield

The production yield of solid dispersion was calculated using the weight of final product after drying with respect to the initial total weight of the drug and carrier used for the preparation of solid dispersion. Percent production yield were calculated as per the formula mentioned below,

$$Py = \frac{W_o}{W_t} \times 100 \dots \dots \dots (1)$$

Where,

P_y = Product yield,

W_o = Practical mass (solid dispersion)

W_t = Theoretical mass (carrier + drug)

4. Solubility Studies

The solubility of Sulfasalazine, Physical Mixture and Solid dispersion was determine in distilled water. The solubility of drug and solid dispersion were determined by taking 10 mg drug, equivalent quantity of solid dispersion and added them in 20 ml of distilled water, in 25 ml vials. The samples were kept at equilibrium for a period of 72 hrs. in incubator at $37 \pm 0.5^\circ\text{C}$ with occasional shaking. The supernatant collected from vials was filtered through Wattman filter paper and analyzed by UV- Visible Spectrophotometer at wavelength of 359 nm. All experiments were conducted in triplicate ($n=3$) and tabulated.

5. Powder X-Ray Diffraction

PXRD analysis was done by irradiating the samples with monochromatized Cu $K\alpha$ radiation ($1.506 \text{ \AA}$) and analyzed between 3° and 60° (2θ) employing a Bruker AXS D8 Advance Diffractometer with Lynx Eye Detector. The step was at rate of 0.020° with step time of 32.8 sec. The diffractogram was produced by using Diffrac plus Software.

6. Differential Scanning Calorimetry

The powdered sample (3 mg) was hermetically sealed in aluminum pans and heated at a constant rate of $10^\circ\text{C}/\text{min}$, over a temperature range of $50\text{--}300^\circ\text{C}$ with nitrogen low rate of $30 \text{ ml}/\text{min}$. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale.

7. Dissolution Studies of Solid Dispersion

The *in vitro* dissolution study of SD was carried in USP Apparatus 2. Samples equivalent to 500 mg of SSZ was hold in muslin cloth and then added to 900 ml of phosphate buffer pH 6.8 at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. 5 ml aliquots were withdrawn at time interval of 5, 15, 30, 45, 60 min and filtered through Whatman's (No. 41) filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analyzed spectrophotometrically at 359 nm. Cumulative percentage of labeled amount of drug released was calculated.

RESULT AND DISCUSSION

Phase solubility study

The solubility of sulfasalazine in distilled water was found to be 0.034 mg/mL. The increase in solubility was linear ($r^2 = 0.964$) with respect to the increase weight fraction of the Gelucire50/13 indicating the solvent properties of Gelucire50/13 for the drug, giving AL type solubility diagrams (Fig: 2). At 3% concentration of Gelucire50/13, the increase in solubility was around 24 fold compared with pure drug. This increase in solubility of sulfasalazine can be probably explained due to the wettability of sulfasalazine in the presence of Gelucire50/13. Recently, the increased effect of Gelucire was observed for the solubility.

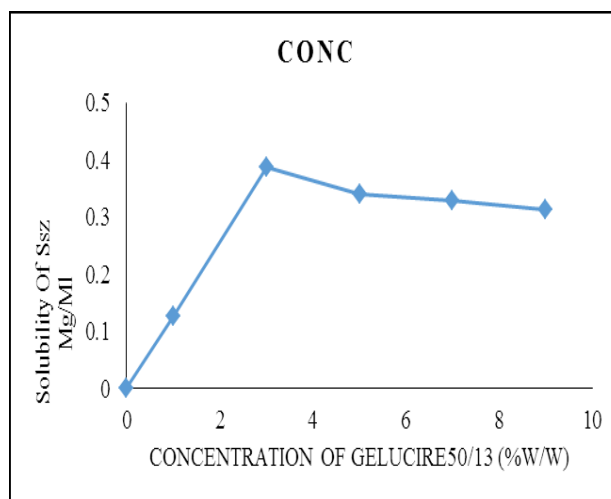


Fig 3: Phase Solubility Studies.

Drug Content

The selected ratios were subjected to the determination of drug content. The drug content in the selected ratios were found to be in range of 85 to 97%. Almost negligible loss of drug may have occurred probably because preparation of combinations was confined to the very small area of mortar. The results of drug content (%) are shown in table 1.

Table No 1: Percent Drug content

Sr. No.	Formulation Code	Drug	Polymer	Ratio	Drug Content (%)
1.	SE 1	SSZ	Gelucire50/13	1:1	88.25±0.039
2.	SE 2	SSZ	Gelucire50/13	1:3	99.06±0.048
3.	SE 3	SSZ	Gelucire50/13	1:5	91.01±0.221
4.	PM2	SSZ	Gelucire50/13	1:3	93.16±0.048
5.	KM 2	SSZ	Gelucire50/13	1:3	93.41±0.23

Production Yield

The production yield of solid dispersion prepared by solvent evaporation method was found to be 85%. Any loss in yield can be attributed to the product remaining

adhered to the walls of the mortar which could not be retrieved. The production yield of PM and Kneading method given below.

Table no 2: Determination of Production Yield.

Sr.no	Formulation code	Ratio	Percentage yield
1.	SE 1	1:1	73 %
2.	SE 2	1:3	84 %
3	SE 3	1:5	86 %
5	PM 2	1:3	86 %
8.	KM 2	1:3	85%

FT-IR Study

The characteristic FTIR spectra of Sulfasalazine, Gelucire50/13, SE2, PM 2, KM 2 were shown in Fig. 3. Sulfasalazine alone showed characteristic bands belonging to SO₂ NH at (1124). C=O at 1674 cm⁻¹. Gelucire 50/13 showed peaks at 2818 cm⁻¹ (-O-H

stretching). The characteristic peaks of sulfasalazine and Gelucire 50/ 13 were observed in both solid dispersion and its corresponding physical mixture. This suggests that there is no significant interaction between the drug and carrier.

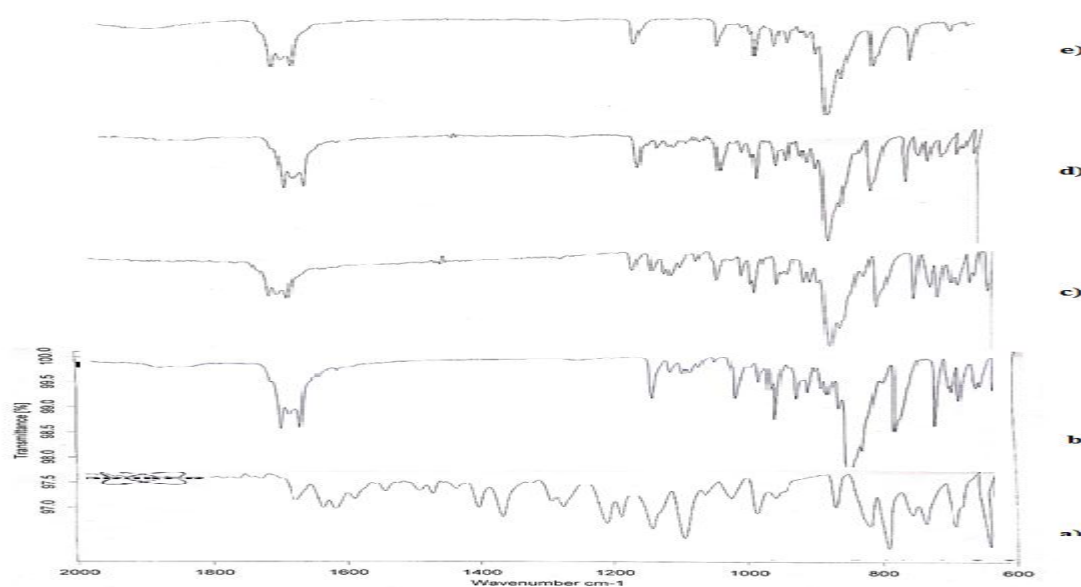


Fig no. 4: FT-IR Spectra of a) Drug SSZ b) Solvent evaporation method c) Physical mixture method d) Kneading method e) Pure Gelucire50/13 Ratio 1:3.

Differential Scanning Calorimetry

Drug-polymer specific interactions are thought to be of particular importance and needed to be analyzed by using Differential Scanning Calorimetry. Differential scanning calorimetry studies were carried out in order to evaluate ability of the polymer to stabilize amorphous form of drug in SD. DSC thermograph of SSZ is shown

in figure 4 which shows melting endotherm at 238.85⁰c i.e. melting point and amorphous state of drug. DSC thermograph of SSZ:Gelucire50/13 (SE) is shown in figure 4 indicating formation of stable crystalline SD investigated by decline in melting endotherm of Gelucire50/13 from 50.41⁰c to 63.27⁰c and increase in melting endotherm of SSZ from 220.05⁰c to 240.0⁰c.

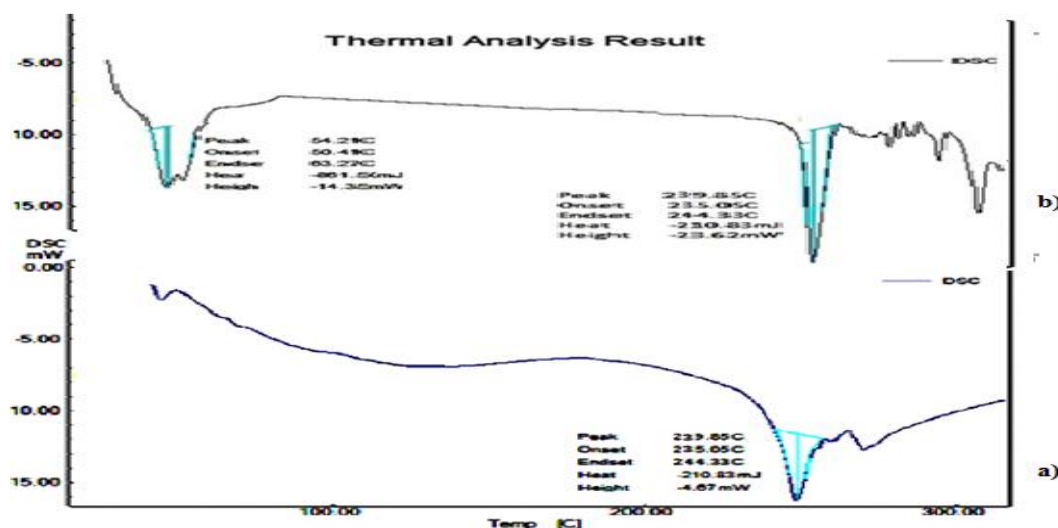


Fig 5: DSC thermograph of a) Pure SSZ b) SD by Solvent evaporation

PXRD Studies

The SD was studied for prediction of crystallinity. The PXRD Pattern of SSZ is shown in Figure 5. Based on the diffractogram it can be suggested that SSZ is present in its amorphous form since it exhibits several well defined peaks at a diffractogram angle of 2θ . The strong peak at 2θ of 21.39 was highly intense peak with 100% intensity indicating presence of amorphous SSZ.

SSZ: Gelucire50/13 (SE) Figure 5, XRD diffraction pattern revealed that the functional peak of SSZ was of low intensity and showing characteristic peak of Gelucire50/13 in the solid dispersion at 2θ of 22.628 indicating presence of SSZ in crystalline state within the gelucire.

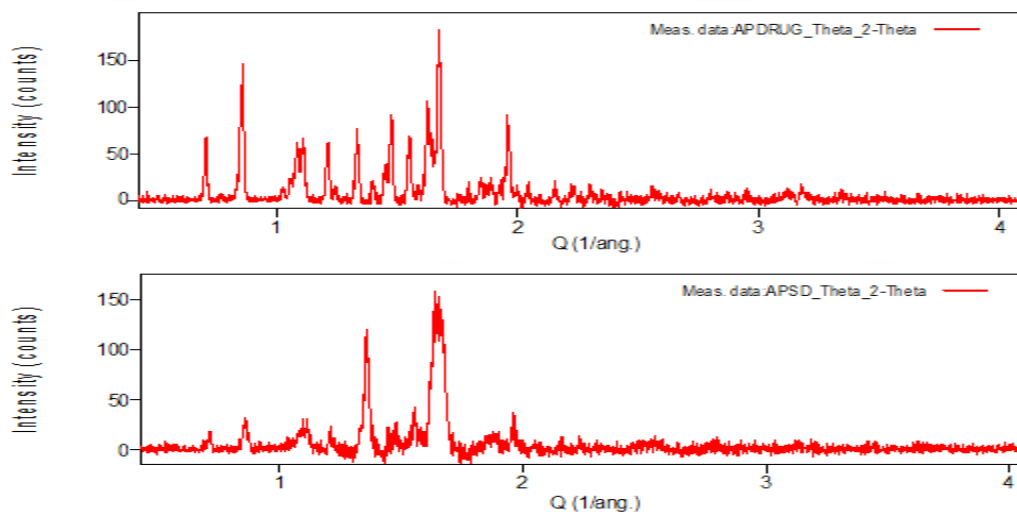


Fig 6: PXRD Studies of a) Pure Drug b) SD by Solvent evaporation.

Dissolution Study

The *in vitro* dissolution study of SD was carried in USP Apparatus 2. Samples equivalent to 500 mg of SSZ was hold in muslin cloth and then added to 900 ml of phosphate buffer pH 6.8 at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. 5 ml aliquots were withdrawn at time interval of 5, 15, 30, 45, 60 min and filtered through Whatman's (No. 41) filter paper. An equal volume of fresh dissolution medium was replaced to maintain the volume of dissolution medium. The filtered samples were analyzed

spectrophotometrically at 359 nm. Cumulative percentage of labeled amount of drug released was calculated. The *in-vitro* dissolution profiles of the drug and solid dispersion are shown in (Table 3) & Figure 6. Drug exhibited a slow dissolution, suggesting that its absorption would be dissolution rate limited, whereas solid dispersion showed a marked enhancement in dissolution rate. Thus, dissolution up to 99.22% was recorded with solid dispersion in 60 min.

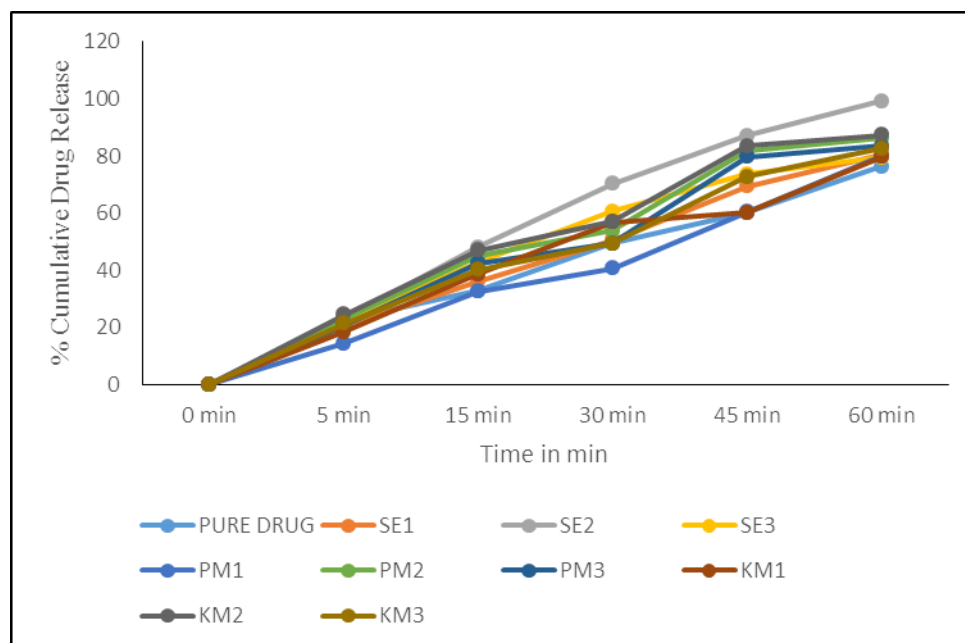


Fig no. 7: Dissolution Profile of Pure Drug and Solid dispersion

CONCLUSION

The results of this study were able to conclude that the formulation of Sulfasalazine solid dispersions markedly improves the solubility and dissolution characteristics. At 3% concentration of Gelucire50/13 the increase in solubility was around 24 fold compared with pure drug. FTIR spectroscopy studies showed no well-defined interaction between Sulfasalazine and Gelucire 50/13. The DSC thermograms of SDs of carvedilol with Gelucire 50/13 showed the transformation of Sulfasalazine from a crystalline to an amorphous state, this was supported by XRD studies. Gelucire50/13 is good carrier for solubility and dissolution enhancement.

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