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Original Research Article

Enrichment of aqueous solubility and dissolution profile of mesalamine: In vitro evaluation of solid dispersion

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ABSTRACT

Purpose: The aim of the present study was to formulate solid dispersion (SD) of Mesalamine to enrich the aqueous solubility and dissolution rate. Mesalamine is used in the management of acute ulcerative colitis and for the prevention of relapse of active ulcerative colitis.

Materials and Methods: In the present study, Solid dispersion of Mesalamine was prepared by Fusion and Solvent evaporation method with different polymers. SD's were characterized by % practical yield, drug content, Solubility, FT-IR, PXRD (Powder X- ray diffractometry), SEM (Scanning electron microscopy), in vitro dissolution studies and Stability studies.

Results: The percent drug release of prepared solid dispersion of Mesalamine by fusion and solid dispersion method (FM47, FM67, SE47 and SE67) in 1:7 ratio was found 81.36±0.41, 86.29±0.64, 82.45±0.57and 87.25±1.14 respectively. The aqueous solubility and percent drug release of solid dispersion of Mesalamine by both methods was significantly increased. The PXRD demonstrated that there was a significant decrease in crystallinity of pure drug present in the solid dispersions, which resulted in an increased aqueous solubility and dissolution rate of Mesalamine.

Conclusion: The significant increase in aqueous solubility and dissolution rate of Mesalamine was observed in solid dispersion as the crystallinity of the drug decreased, absence of aggregation and agglomeration, increased wetability and good dispersibility after addition of PEG 4000 and PEG 6000.

1. Introduction

According to Chiou and Riegelman (1971), a solid dispersion is "the dispersion of one or more active ingredients in an inert carrier at solid state prepared by melting (fusion), solvent or the melting-solvent method". The carrier used has traditionally been a water soluble or water miscible polymer such as polyethylene glycol (PEG) or polyvinyl pyrrolidone (PVP) or low molecular weight materials such as urea, citric acid and mannitol. Solid dispersion is one of the approaches employed to improve dissolution of poorly soluble drugs whose absorption is dissolution rate limited. Solid dispersion (SD) technique has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water soluble drugs. The term solid dispersions have been utilized to describe a family of dosage forms where by the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability.

The oral route of drug administration is the most common and preferred method of delivery due to

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convenience and ease of ingestion. From a patient's perspective, swallowing a dosage form is a comfortable and a familiar means of taking medication. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration. Limited drug absorption resulting in poor bioavailability is paramount amongst the potential problems that can be encountered when delivering an active agent via the oral route.[1,2] Some proposed mechanisms of the solid dispersion formulations including the solubilizing effect of the carrier, decreased agglomeration and aggregation of drug particles, particle size reduction to molecular size, yielding to solid state solution within carriers and increased drug solubility via complex formation or solubilization and improved wettability.[3] Mesalamine is indicated to treat mild to moderate acute exacerbations of ulcerative colitis's in remission, particularly in patients intolerant of sulphasalazine. It is white to pinkish crystals slightly soluble in water belonging to BCS class II, 20 to 30% absorbed following oral administrations. Due to its poor flow properties as well as low solubility, it is a suitable candidate for formulating solid dispersion.[4] In case of drug that is poorly water-soluble, dissolution may be the rate limiting step in the process of drug absorption. Drugs with poor water solubility have been shown to be unpredictably and slowly absorbed compared with the drugs of higher solubility. The purpose of this study was to prepare solid dispersion by solvent evaporation and melting point method to improve the dissolution rate of Mesalamine.

The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Noyes- Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.[5,6] Chiou and Riegelman outlined 6 types of drug carrier interactions in solid-state dispersions simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates and compound or complex formation. Other factors such as increased wettability, solubilization of the drug by the carrier at the diffusion layer, and the reduction or absence of aggregation and agglomeration may also contribute to increased dissolution.[7,8]

The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented as the relatively low temperatures required for the evaporation of organic solvents.

2. Materials and Methods

Mesalamine was received as gift sample from Sun Pharma Ltd, Ahmednagar. Polyethylene glycol 4000, Polyethylene glycol 6000, Methanol, Hydrochloric acid were purchased from LobaChem Pvt. Ltd, Mumbai. The disodium hydrogen phosphate and potassium dihydrogen phosphate were obtained from SD Fine Chem limited, Mumbai, India. All other chemicals were used of analytical grades.

2.1. Preparation of solid dispersion by fusion method

Mesalamine and polymers were weighed accurately in different ratios (Table 1) and mixed for 15 min in a mortar and sieved through sieve number 100. Physical mixture was then heated on water bath upto melting point of pure drug. After melting, molten mass was dried and crushed after 24 hrs. Solid dispersion was collected for further characterization.

2.2. Preparation of solid dispersion by solvent evaporation method

Mesalamine and polymers were weighed accurately in various ratios (Table 1) and transferred to china dish containing sufficient quantity of methanol to dissolve. Methanol was evaporated on heating mantle at 40^0C. The resulting solid dispersions were stored for 24 hrs in desiccators. The mass obtained was crushed, pulverized. Finally, dispersions were passed through sieve number 100 and were stored in air tight containers till further use.[9–13]

2.3. Characterization of solid dispersion

2.3.1. Preformulation studies

In the preformulation study of drug, λ-max of Mesalamine in distilled water was found at 303 nm. Similarly Partition coefficient of Mesalamine was found to be 5.9 by shake flask method, which indicates that Mesalamine is lipophilic. So it can pass cell membrane easily once it got solubilized.

2.3.2. Percent practical yield

Percentage practical yield was calculated to know about percent yield or efficiency of method, thus it helps in selection of appropriate method for production. SDs were separately collected and weighed to determine practical yield from the following equation[14]

$$\%\ Practical\ Yield = \frac{Practical\ Mass\ (Solid\ dispersion)}{Theoretical\ Mass\ (Drug+Carrier)} \times 100$$

2.4. Solubility studies

The solubility of drug is a very important physicochemical property because it directly affects the rate of drug release from formulation into the dissolution medium, bioavailability of the drug and consequently the therapeutic efficacy of the pharmaceutical product.

Table 1: Formulation of solid dispersion

Sr. No	Polymer	Ratio	Method	Formulation code
1		1:1		FM41
2	PEG-4000	1:3		FM43
3		1:5		FM45
4		1:7		FM47
5		1:10	Fusion method	FM410
6		1:1		FM61
7	PEG-6000	1:3		FM63
8		1:5		FM65
9		1:7		FM67
10		1:10		FM610
11		1:1		SE41
12	PEG-4000	1:3		SE43
13		1:5		SE45
14		1:7		SE47
15		1:10	Solvent Evaporation	SE410
16		1:1	Method	SE61
17	PEG-6000	1:3		SE63
18		1:5		SE65
19		1:7		SE67
20		1:10		SE610

2.5. Solubility of drug and solid dispersions

An excess quantity of drug and solid dispersions was added separately to 5 ml distilled water in a volumetric flask with cap. The volumetric flasks were kept in a shaker at 37±0.5°C for 48 hours. The solutions were filtered through 0.45 μm Millipore filter and the filtrate was analyzed spectrophotometrically at 303 nm.

2.6. Detection of drug content in solid dispersions

Samples of prepared Mesalamine dispersions equivalent to 10mg of Mesalamine were accurately weighed, crushed and transferred to 10ml standard conical flask and the volume was made up to 10 ml with Phosphate buffer pH 6.8, filtered through Whatmann filter paper and absorbance was taken at 297.5 nm.[15]

2.7. Fourier transform infra red (FTIR) spectroscopy

Infra red studies was carried out to rule out interaction between drug and carrier used in formulation of solid dispersion by potassium bromide disc method using Infra red spectrophotometer (FTIR 8400S, Shimadzu, Japan). The scanning range was 500 to 4000 cm.[1]

2.8. Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry was performed to obtain suitable thermogram, using METTLER Toledo India Pvt. Ltd. The accurately weighed sample was placed in an aluminium pan and an empty aluminium pan was used as reference. The experiment was performed under Nitrogen flow, at a scanning rate 30^0C/min. in range of 50-300^0C, whilst retaining the inert atmosphere.

2.9. Powder X-ray diffraction (PXRD)

As a consequence of the importance of solid drug substance characterization, analytical tools such as X-ray diffractometry are usually employed in the pharmaceutical field. The detection of crystalline phases in mixed systems can be analyzed by powder X-ray diffraction. However, too much crystallinity causes brittleness and can decrease the solubility of the drug. The crystallinity parts give sharp narrow diffraction peaks and the amorphous component gives a very broad peak. The ratio between these intensities can be used to calculate the amount of crystallinity in the material.

2.10. Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) analyzed with 2 mg of pure drug and the solid dispersions were mounted on to the stubs using double sided adhesive tape and then coated with gold palladium alloy using fine coat ion sputter. The samples were subsequently analyzed under the scanning electron microscopy.

2.11. Dissolution studies

Dissolution studies are the most significant evaluation parameter for any solid dosage form. Dissolution study was carried out to determine the rate and extent of dissolution. The dissolution study of drug and solid dispersions was performed separately in 900ml Phosphate buffer pH 6.8 at 37ºC+0.5ºC using the USP- I Basket Type apparatus at

50 rpm. Aliquots of 10 ml from the dissolution medium were withdrawn at 5 min time interval and replenished by an equal volume of fresh dissolution medium. The samples were filtered through whatman filter paper and analyzed by UV visible Spectrophotometer by measuring absorbance at 297.5 nm.

2.12. *Stability study*

Stability studies were carried out for selected formulations as per ICH guidelines (40°C ± 2°C/75% RH ± 5% RH). The selected solid dispersions were stored in stability chamber at 40°C ± 2°C/75% RH ± 5% RH for 3 month and observed for the drug content at 1, 2, 3 months interval.

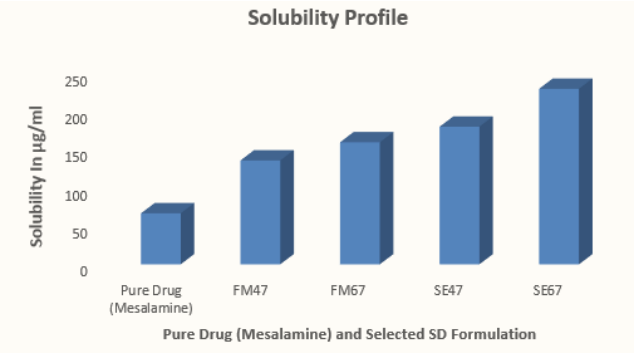

Fig. 1: Solubility of mesalamine and selected solid dispersion

3. Results and Discussion

3.1. *Solubility studies*

Solubility data indicated that 67 μg/ml of pure Mesalamine was soluble in distilled water; hence they are considered as poorly water-soluble drugs. Here the solubility of drug in fusion and solvent evaporation method containing Mesalamine and polymers is depicted in Table 2. As compared to pure drug and fusion method, the solid dispersion prepared by solvent evaporation showed highest solubility 206.47 μg/ml in distilled water. This investigation suggested that, it might be possible due to preparation of solid dispersion using varying concentration of PEG 4000 and PEG 6000 which formed eutectic mixture and hence increase aqueous solubility of Mesalamine.

3.2. *Percentage practical yield and drug content*

In all formulations, the drug content was found to be between 82% and 102% and the practical yield was found to be between 86% and 96%. All the formulations of different ratio showed the presence of high drug content and low practical yieldTable 2 which indicates that the drug is uniformly dispersed in the powder and well loaded in the formulation. The high drug content or drug loading is the function of the characteristics of polymer, drug, surfactant and cross-linking agent, etc. Since the drug is hydrophobic in nature, there was less chance of diffusion of drug away from the polymer network during preparation.[16,17] The product yield depended upon the agglomeration and sticking of polymer to blades of stirrer and to the wall of the beaker during formulation. The solvent evaporation and fusion method used in this study appears to be suitable for formulation. It has been found that there is no significant drug or polymer loss during the solvent evaporation as well as fusion method.

3.3. *Fourier transform infra red (FTIR) spectroscopy*

Infra-red spectrum of Mesalamine is shown in Figure 2. The characteristic peaks of functional groups presents in the drugs were checked and depicted in Table 3. The functional groups present in the structure of Mesalamine were identified correctly and hence the drugs was confirmed and considered for further uses.

The FTIR spectra of pure Mesalamine displayed bands at 2960 cm- 1 due to Ar-CH stretching at 1485, 1610 1446 cm-1 due to –C=C stretching, at 2600 cm-1 due to COOH stretching. The spectra also showed bands at 1750 cm-1 due to C=O stretching, at 3356 cm-1 due to NH_2 stretchingand 3486 cm-1 due to OHstretching Figure 2. The infrared spectrum of physical mixture of Mesalamine with PEG 4000 and PEG 6000 is shown in Figures 3 and 4 respectively. From the spectrum it was observed that chemical groups Ar-CH stretching, –C=C, COOH, NH_2 stretching, OH stretching and C=O bending were found with the same wave number as that of Mesalamine Figure 2. The result with the FTIR indicates that there was no significant change in the principle peaks in pure drug.

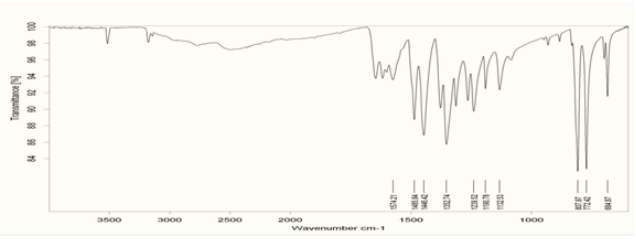

Fig. 2: FTIR Spectrum of mesalamine

3.4. *Powder X-ray diffraction (PXRD)*

The XRD diffractogram of Mesalamine and SDs are presented in figure 5, figure 6 and figure 7. The XRD spectra of Mesalamine showed various sharp and intense peaks at 89°, 111°, 199°, 221°, and 232.1° at a diffraction angle range of 5–50°, suggesting that Mesalamine was present in the crystalline form. The diffraction pattern of Mesalamine-SDs (SE47 and SE67) presented the complete

Table 2: Solubility, % practical yield and % drug content of solid dispersion

Sr. No.	Formulation code	Ratio	Method	Solubility (μg/ml)	% practical yield	% Drug content
1	FM41	1:1		98.41	89	91.77
2	FM43	1:3	Fusion	102.12	88	86.47
3	FM45	1:5	Method	128.1	93.5	88.93
4	FM47	1:7		136.46	94.4	91.01
5	FM410	1:10		130.23	90.66	90.31
6	FM61	1:1		101.36	88.5	87.02
7	FM63	1:3	Fusion	113.3	94.48	90.54
8	FM65	1:5	Method	124.3	96.5	92.64
9	FM67	1:7		160.32	92.66	91.55
10	FM610	1:10		122.6	94.66	85.73
11	SE41	1:1		112.2	86.5	95.04
12	SE43	1:3	Solvent	133.7	88	91.79
13	SE45	1:5	Evaporation	153.5	90.5	101.9
14	SE47	1:7	Method	180.74	93	83.12
15	SE410	1:10		196.72	93.6	82.09
16	SE61	1:1		112.32	93.5	86.9
17	SE63	1:3	Solvent	141.21	96	85.03
18	SE65	1:5	Evaporation	148.31	94	90.06
19	SE67	1:7	Method	230.47	95	94.29
20	SE610	1:10		179.35	97	105.1

Table 3: IR interpretation of mesalamine

Sr. No.	Compound	Frequency (cm^{-1})	Type of vibration
1.	Mesalamine	2960 (w)	Ar-CH str
		1485, 1610 1446, (s)	C=C
		2600 (b)	COOH str
		1750 (s)	C=O str
		3356 (m)	NH_2str
		3486 (m)	OH $_{str}$

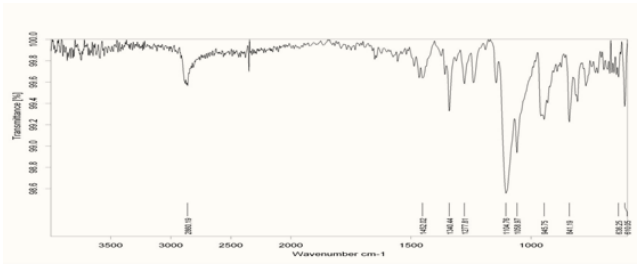

Fig. 3: FTIR Spectrum of SE47

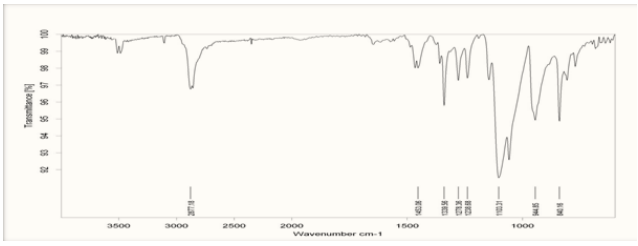

Fig. 4: FTIR Spectrum of SE67

disappearance of the characteristic peaks of Mesalamine. The disappearance of the characteristic peaks suggested that Mesalamine is completely dispersed in the PEG 4000 and PEG 6000 carrier and converted to the amorphous state. Only the characteristic peaks of the carrier were observed in the Mesalamine-SDs, which suggested the absence of any physical interaction between Mesalamine and PEG. However, there are some intense peaks observed at angles other than drug specific angles, which were because of the crystalline nature of the solid dispersion formers.

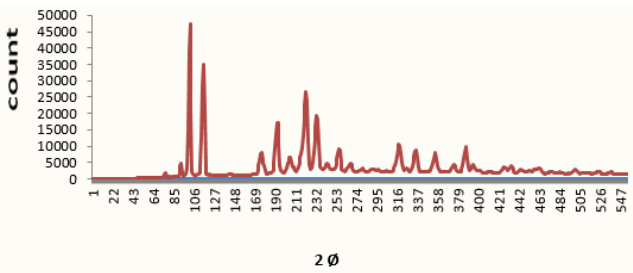

Fig. 5: X-ray spectrum of mesalamine.

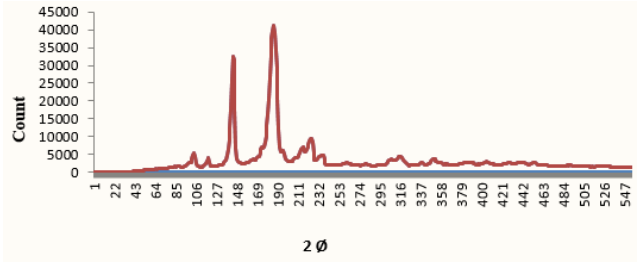

Fig. 6: X-ray spectrum of solid dispersion (SE47)

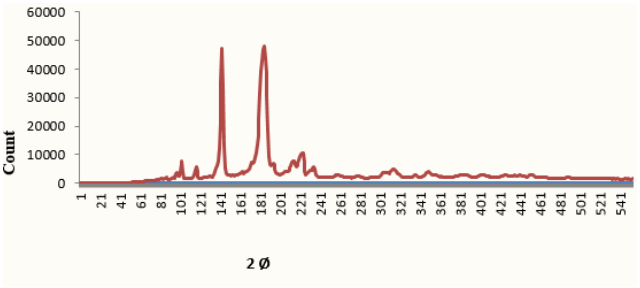

Fig. 7: X-ray spectrum of solid dispersion (SE67)

3.5. Scanning electron microscopy

SEM photographs for pure drug and selected solid dispersion (SE47 and SE67) is shown in Figures 8, 9 and 10 respectively. The drug crystals seemed to be smooth-surfaced, irregular in shape and size. In case of Solid dispersions, it was difficult to distinguish the presence of drug crystals. The drug surface in solid dispersion seems to be more porous in nature. Solid dispersions appeared as uniform and homogeneously mixed mass with wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymers. SEM picture images suggested that the surface properties of Mesalamine were lost during solvent evaporation and the formation of effective solid dispersion systems. These findings demonstrated that the drug was thoroughly mixed in the carriers with the negligible loss of little crystallinity.

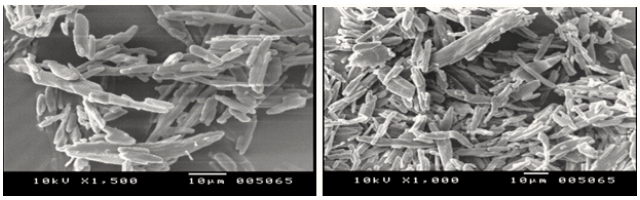

Fig. 8: SEM of mesalamine.

3.6. Dissolution study

Dissolution studies were performed to compare the drug release from the solid dispersions, to that of the pure drug. The dissolution study was carried out for a period of 60 min in pH 6.8 Phosphate buffer. The drug release data obtained from selected solid dispersions FM47, FM67, SE47 and SE67 are tabulated inTable 4. It shows the cumulative percent drug released as a function of time for all formulations. The cumulative percent drug released after 60 min was depicted in Table 4. In vitro studies reveal that there is marked increase in the dissolution rate of Mesalamine from all the solid dispersions when compared to pure Mesalamine itself. From the in vitro drug release profile, it can be seen that all the selected formulations containing Mesalamine with PEG 4000 and PEG 6000 showed higher dissolution rate as compared with pure drug. The graphical presentation of dissolution profile of solid dispersion of Mesalamine over the period of 1 hr is shown inFigure 11.

Maximum drug released up to 10min was 55.32±1.2% with drug-carrier ratio (FM67). While over the period of 60 min, maximum drug was released from all selected formulations. This was might be due to absence of aggregation and agglomeration with crystalline drug, water-soluble carrier increased wetability and good dispersibility and conversion of drug to amorphous state. Less viscosity

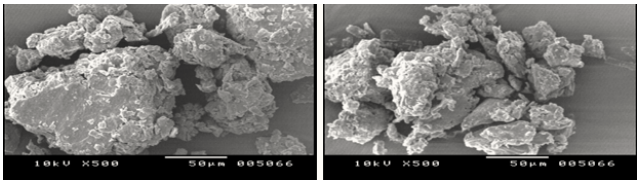

Fig. 9: SEM of solid dispersion (SE47)

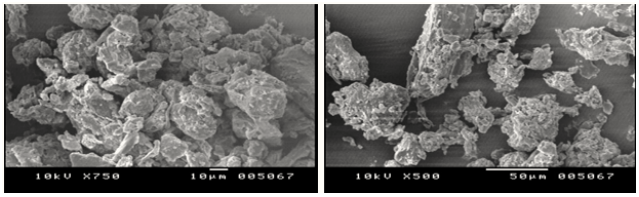

Fig. 10: SEM of solid dispersion (SE67)

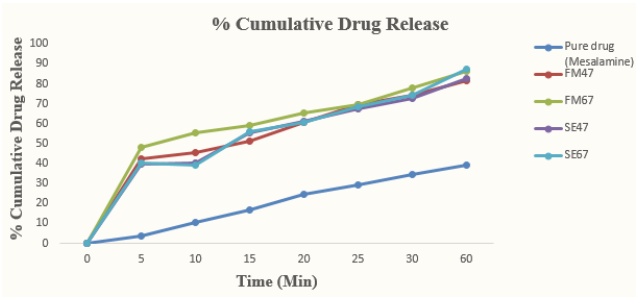

Fig. 11: In-Vitro dissolution profiles of mesalamine and SDs prepared by fusion and solvent evaporation method in phosphate buffer pH 6.8 at 37±0.5°C.

Table 4: Dissolution study data of mesalamine and selected solid dispersion

Sr. No.	Time (min)	% cumulative drug release*				
		Pure drug (Mesalamine)	FM47	FM67	SE47	SE67
1.	0	0	0	0	0	0
2.	5	3.9±0.25	42.17±0.23	48.36±0.74	39.53±0.45	40.36±0.52
3.	10	10.7±0.85	45.3±0.53	55.32±1.2	40.23±0.85	39.32±0.42
4.	15	16.9±0.45	51.53±0.48	59.13±0.58	55.23±1.65	56.23±1.32
5.	20	24.6±0.68	60.81±0.23	65.28±0.48	61.45±0.35	60.56±0.85
6.	25	29.3±0.15	69.81±0.25	69.71±0.69	67.25±0.65	68.45±1.48
7.	30	34.7±0.95	74.48±0.35	78.16±0.77	72.51±0.78	74.55±1.25
8.	60	39.4±0.14	81.36±0.41	86.29±0.64	82.45±0.57	87.25±1.14

* All values are expressed as mean ± SD, n=3

Table 5: Stability study data of Formulation

Formulation code	Parameters	Storage at 40°C+2°C			
		0 Month	1 Month	2 Month	3 Month
FM47	% Drug content	91.01	90.88	90.56	90.30
FM67	% Drug content	91.55	90.77	90.37	90.20
SE47	% Drug content	83.12	83.00	82.77	82.44
SE67	% Drug content	94.29	94.19	93.77	93.22

and good water holding capacity of carrier helps to dissolve the drug rapidly by increasing free kinetic energy. The graphical presentation of % cumulative drug release is shown inFigure 11. The literature reveals that the solvent evaporation method of solid dispersion solubilizes the drug and carrier in molecular level. Hence form eutectic mixture and increased solubility of poorly water soluble drug.

Kim et al. and Vilhelmsen et al. reported that the second generation solid dispersions were made using amorphous carriers, which are mostly polymers,[18,19] whereas the first generation solid dispersions were made using crystalline carriers. These form thermodynamically stable crystalline solid dispersions.[19] In the 1960s, it was reported that amorphous solid dispersions were more effective than crystalline solid dispersions due to their thermodynamic stability.[20,21] Also Lloyd et al. and Pokharkar et al. demonstrated that drugs with low water solubility have higher solubility when they are in amorphous state rather than in crystalline state.[22,23] Theoretically, a certain amount of energy is demanded for breaking up the crystal lattice during the dissolution process if the drug is in its crystal state.[24] However, amorphous drugs do not need such energy,[25] making the drug more easily released.[26] This improved drug release rate ultimately promotes drug's bioavailability, making solid dispersions more ideal for administrating hydrophobic oral drugs.[24] From the result, it was evident that using second generation polymer and its different percentage of concentration in solid dispersion is an advanced approach for immediate and prolonged release of poorly soluble drug than by using first generation polymer in solid dispersion which has immediate release. Moreover, in optimized condition/using third generation polymer (which include additional surface active properties e.g. inulin, inutec SP1, compritol 888 ATO, gelucire 44/14,poloxamer 407, etc.,) in the preparation of solid dispersion may be an advance technology for controlled release of poorly soluble drug than microsphere. Also, due to its easy preparation, solid dispersion would be one of the exciting frontiers of controlled release drug delivery systems.[27,28] Kim et al. reported some commercial applications of solid dispersion formulation using second generation polymer such as HPMC, PEG20000, PVP etc.[24]

3.7. Stability studies of the formulation

Solid dispersions showed maximum solubility and drug content were selected for stability studies. Selected formulations were stored at 40°C ± 2°C/75% RH ± 5% RH for a period of 3 months. Formulation was evaluated at periodical intervals of 1 month for drug content. Drug loss was minor as observed after a month study. From the stability studies of the selected batch it was found that the solid dispersions remained stable even after exposing to stress conditions of temperature.

4. Conclusion

In the present study it was demonstrated that Mesalamine solid dispersions can be effectively produced by processing via fusion and solvent evaporation method with enhanced solubility and dissolution rate. PEG 4000 and PEG 6000 combinations were selected and stable SD systems were developed successfully. Utilization of PEG 4000 and PEG 6000 offers excellent possibilities to develop stable amorphous solid dispersion. Furthermore, this Mesalamine incorporated solid dispersion gave higher dissolution and solubility values compared to the pure Mesalamine drug.

In vitro drug release studies of all selected formulations exhibited a cumulative release of almost 90% within 60 min. FTIR spectrum revealed that no chemical interaction occurred between the drug and excipients used in the formulation. Scanning electron microscopy studies suggested the conversion of crystalline Mesalamine to an amorphous form. The dissolution rate and solubility of Mesalamine solid dispersions was improved significantly using PEG 4000 and PEG 6000.

5. Source of Funding

None.

6. Conflict of Interest

None.

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