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EVALUATION OF ENHANCEMENT OF SOLUBILITY OF ASPIRIN BY SOLID DISPERSION TECHNIQUES USING DIFFERENT POLYMERS CONCENTRATION

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ABSTRACT

In the present study, the aim was to study the effect of carrier PEG 1500 & PEG 6000 on solubility and dissolution rate of aspirin. Initial studies were carried out using physical mixtures of the drug and carrier. Solid dispersions were prepared by solvent evaporation, kneading and fusion method. Aspirin was formulated as physical mixtures and solid dispersions using 1:1, 1:2, and 1:4 ratios of drug and carrier (PEG 1500, PEG 6000). Saturation solubility study for pure drug, physical mixtures and solid dispersions were carried out in pH 6.8 phosphate buffer solutions (PBS). The *In vitro* dissolution studies were carried in pH 6.8, higher *in vitro* dissolution of solid dispersions were recorded compared to their corresponding physical mixtures and the pure drug. The prepared solid dispersions were observed that increased in the saturation solubility and dissolution rate of aspirin than that of pure drug. PEG 6000 in 1:4 drug to carrier ratio by fusion method exhibited the fastest drug release as well as highest saturation solubility. The prepared solid dispersions were characterized by solubility test, FT-IR spectroscopy, DSC study. Solid dispersion prepared with PEG 6000 in 1:4 ratio by fusion method shows the presence of amorphous form confirmed by the characterization study. The study also shows that the dissolution rate of aspirin can be enhanced to considerable extent by solid dispersion technique.

KEYWORDS: Aspirin, solid dispersion, solubility, Fusion method, PEG-6000, kneading method, PEG-1500.

INTRODUCTION

Aspirin (acetylsalicylic acid, ASA) is one of the most widely used therapeutic substances due to its analgesic, antipyretic and anti-inflammatory properties. Despite the proliferation in development of new non-steroidal anti-inflammatory drugs (NSAIDs), ASA remains one of the most effective 'over-the-counter' drugs in the treatment of rheumatic diseases. Furthermore, due to its anti-thrombotic properties, ASA is now prescribed at low doses in the prevention and treatment of cardiovascular diseases, strokes and disorders associated with platelet aggregability.[1] It acts by inhibition of prostaglandin synthesis and COX-II inhibitor. Aspirin use has been shown to reduce the incidence and mortality of human cancers, especially colon cancer.[2] Orally administered aspirin requires high and frequent dosing because it undergoes extensive pre-systemic metabolism. Also, long term and chronic oral aspirin is associated with serious gastrointestinal side-effects. So, if the solubility and bioavailability of the aspirin can be increased, it will reduce the gastrointestinal side-effects.[6]

Pharmaceutical carriers, in particular, water-soluble carriers have been received an increasing attention in the pharmaceutical field because of their ability to enhance aqueous solubility, dissolution rate and bioavailbility of many poorly water soluble drugs. Polyethylene glycols (PEGs) with molecular weights of 1,500–20,000 are extensively used as water-soluble carriers for preparation of solid dispersions of many poorly water soluble drugs. This extensive use of PEGs is attributed to their numerous advantages including low melting point, rapid solidification rate, low toxicity, low costs and good solubility in water and most of organic solvents. Further, a particular advantage of using of PEGs is their high ability to solubilize many of poorly water soluble drugs. The high solubilization ability of PEGs may be due to different positive effects offered by PEGs including good wettability, local solubilization and particle size reduction. [4]

The aim of a present study was to compare solubility of aspirin alone, complexes of aspirin with PEG 6000 and PEG 1500 using different solid dispersion techniques.

MATERIALS AND METHODS

MATERIALS

Aspirin was obtained from Research-lab fine chem. Industries India. PEG 6000, PEG 1500 was purchased from S D fine-chem limited India. Methanol from S D fine-chem limited was

used. All reagents were of A.R. grade. Double distilled water was used throughout the experiment.

METHODS

I. Preparation of physical mixture (PM)

The physical mixture of Aspirin- PEG 6000 and Aspirin-PEG1500 each were prepared in 1:1, 1:2, 1:4 ratios by mixing accurately weighed amounts of drugs and various carriers with the help of a spatula in a glass mortar.[2]

II. Preparation of Aspirin-PEG6000 and Aspirin-PEG1500 Solid Dispersions

A. Preparation by kneading method (KM)

The required amount of Aspirin and carrier in 1:1, 1:2 & 1:4 ratio were wetted with sufficient volume of methanol and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through sieve no. 40 and stored in desiccators until further evaluation.[2]

B. Solvent evaporation method (SE)

SDs were prepared by dissolving accurately weighed amounts of Aspirin and carrier in ethanol. After complete dissolution of Aspirin and carrier in ethanol the solution was sonicated for 20 minutes, and then solvent was evaporated under reduced pressure at room temperature in a dessicator. Subsequently, the solid mass was ground through sieve no. 40. The sifted ground powder was kept in an oven for 48 hrs at 60 ºC. [3]

C. Fusion method (FM)

Solid dispersions (SD) were prepared by melting the accurately weighed amounts of PEG (PEG 1500 or PEG 6000) in a water bath and the drug was dispersed in the molten solution. The mixtures were stirred repeatedly, after 10 min cooled at room temperature. Solid mass obtained was passed through the sieve # 40 and stored in vacuum dessicator until use. [5]

Characterization of solid dispersions

Drug content

The drug content in each solid dispersions and physical mixture was determined by the UV spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 100 mg of Aspirin, was transferred to a 100 mL volumetric flask containing 5 mL of methanol and dissolved. The volume was made up to 100 mL with pH

6.8. The solution was filtered and the absorbance was measured after suitable dilutions by using UV-VIS spectrophotomer (SHIMADZU Corporation, Japan) at 265 nm wavelength. [9]

Saturation solubility studies

The saturation solubility of pure Aspirin, physical mixtures and solid dispersions were determined and compared with each other. The known excess samples (Aspirin solid dispersions, physical mixtures and pure Aspirin) were added to 5 ml of pH 6.8 phosphate buffer and these samples were rotated in a water bath (37 ± 0.5°C) for 48 hours. The samples were then filtered through 0.45 µm membrane filter, suitably diluted, and analyzed by UV-VIS spectrophotomer (SHIMADZU Corporation, Japan) at 265 nm wavelength. [8]

In vitro drug dissolution studies

Dissolution studies were performed in pH 6.8 phosphate buffer at 37 ± 0.5°C, using USP type-II apparatus with paddle rotating at 75 rpm. Sample of pure Aspirin, solid dispersions as well as physical mixtures, each containing 100 mg equivalent of aspirin were subjected to dissolution. At fixed time intervals, samples withdrawn were filtered and spectrophotometrically analyzed at 265 nm. [9]

FT-IR Spectroscopy

Fourier transmitted Infrared (FT-IR) spectroscopy was conducted using Shimadzu FTIR and the spectrum was recorded in the wavelength region of 4000 to 500 cm−1. The procedure consisted of dispersing a sample (drug alone or solid dispersions) in KBr (1:3 ratio) and compressing into discs by applying a pressure. The pellet was placed in the light path and the spectrum was obtained. [11]

Differential Scanning calorimetry (DSC) studies

A differential scanning calorimeter (DSC-821e, Mettler Toledo, Switzerland) was used to obtain DSC curves of pure Aspirin and solid dispersions. About 10mg of sample was weighed in a standard open aluminium pan, and scanned from 30-280 °C at a heating rate of 10 °C/minute while being purged with dry nitrogen. [3,10]

RESULTS AND DISCUSSION

Table 1: Composition and batch code of solid dispersion of aspirin with carrier

Batch code	Carrier	Ratio of drug and carrier	Method of preparation	Drug content (%)
PM 1	PEG 1500	1:1	Physical Mixture	98.92
PM 2	PEG 1500	1:2	Physical Mixture	97.84
PM 3	PEG 1500	1:4	Physical Mixture	101.16
PM 4	PEG 6000	1:1	Physical Mixture	97.17
PM 5	PEG 6000	1:2	Physical Mixture	98.22
PM 6	PEG 6000	1:4	Physical Mixture	98.64
KM 1	PEG 1500	1:1	Kneading Method	98.15
KM 2	PEG 1500	1:2	Kneading Method	97.48
KM 3	PEG 1500	1:4	Kneading Method	98.61
KM 4	PEG 6000	1:1	Kneading Method	99.29
KM 5	PEG 6000	1:2	Kneading Method	98.91
KM 6	PEG 6000	1:4	Kneading Method	99.46
SE 1	PEG 1500	1:1	Solvent Evaporation	98.47
SE 2	PEG 1500	1:2	Solvent Evaporation	101.35
SE 3	PEG 1500	1:4	Solvent Evaporation	101.44
SE 4	PEG 6000	1:1	Solvent Evaporation	99.86
SE 5	PEG 6000	1:2	Solvent Evaporation	100.24
SE 6	PEG 6000	1:4	Solvent Evaporation	99.57
FM 1	PEG 1500	1:1	Fusion Method	101.16
FM 2	PEG 1500	1:2	Fusion Method	100.85
FM 3	PEG 1500	1:4	Fusion Method	101.46
FM 4	PEG 6000	1:1	Fusion Method	99.54
FM 5	PEG 6000	1:2	Fusion Method	100.14
FM 6	PEG 6000	1:4	Fusion Method	99.89

The drug content in physical mixtures, solid dispersions with PEG 1500 & PEG 6000 as reported in Table 1 were found to be in the range of 97.17 to 101.46%. Therefore, methods used in this study appear to be applicable for the preparation of solid dispersions without affecting drug content.

Solubility Studies

The results of saturation solubility studies are given in Table 2. The solubility of pure drug in PBS (pH 6.8) was found to be 13.86 ± 0.56 mg/mL. The solubility of different solid dispersions of drug and PEG1500 was within the range 14.21 ±1.81 to 29.84 ±1.55 mg/mL. Also, the solubility of different solid dispersions of drug and PEG6000 was within the range 15.23 ±1.12 to 36.56 ±0.94 mg/mL. Maximum solubility in phosphate buffer solution was observed in fusion method 1:4 (Drug: PEG 6000) ratio 36.56 ±0.94 mg/mL when compared with that of pure aspirin (13.86 ±0.56mg/mL).

Table 2: Solubility studies of drug and solid dispersions

Batch code	Solubility(mg/mL)
Pure Drug	13.86 ±0.56
PM 1	15.17 ±1.45
PM 2	16.24 ±1.26
PM 3	19.19 ±1.89
PM 4	16.21 ±0.84
PM 5	17.52 ±0.75
PM 6	22.35 ±0.56
KM 1	15.12 ±0.98
KM 2	18.23 ±1.25
KM 3	22.56 ±1.24
KM 4	17.23 ±0.68
KM 5	21.89 ±0.65
KM 6	26.31 ±1.59
SE 1	14.21 ±1.81
SE 2	16.27 ±1.45
SE 3	17.85 ±1.36
SE 4	15.23 ±1.12
SE 5	17.56 ±0.82
SE 6	20.29 ±0.73
FM 1	19.28 ±1.25
FM 2	25.13 ±0.94
FM 3	29.84 ±1.55
FM 4	21.23 ±0.75
FM 5	30.15 ±0.85
FM 6	36.56 ±0.94

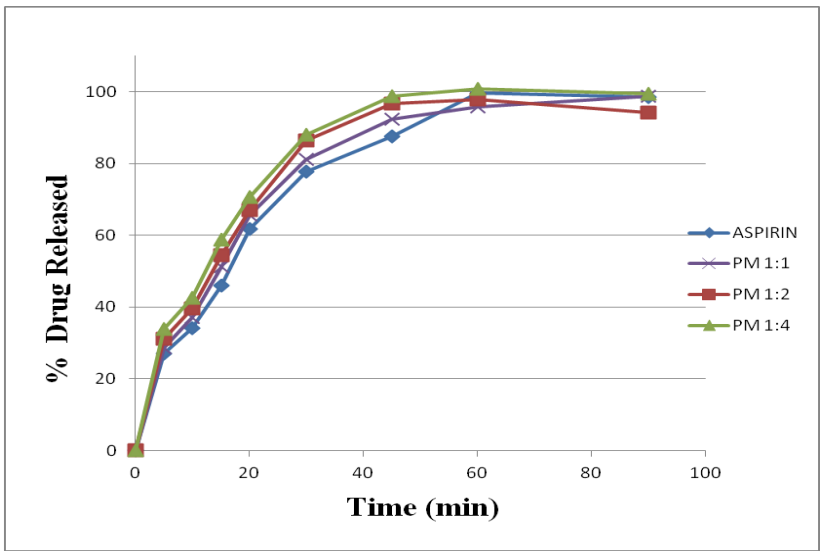

Fig 1: Percentage release of Aspirin from PM1, PM2, PM3 with pure Aspirin

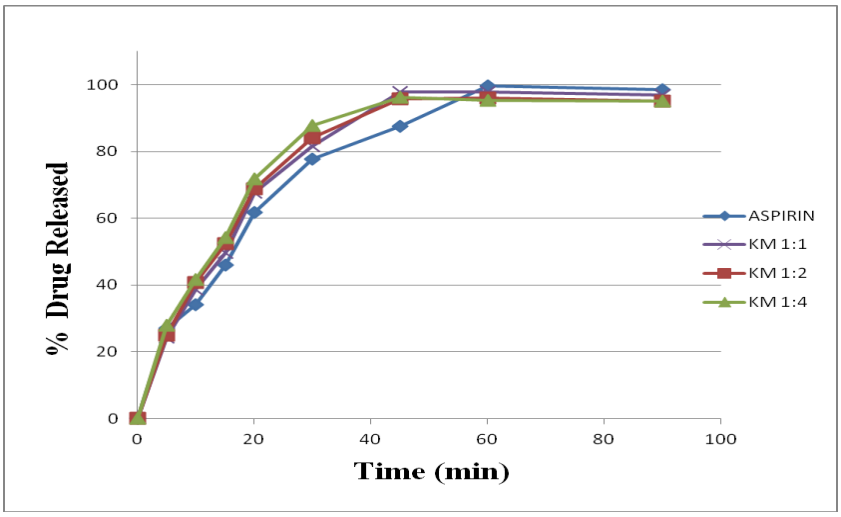

Fig 2: Percentage release of Aspirin from KM1, KM2, KM3 with pure Aspirin

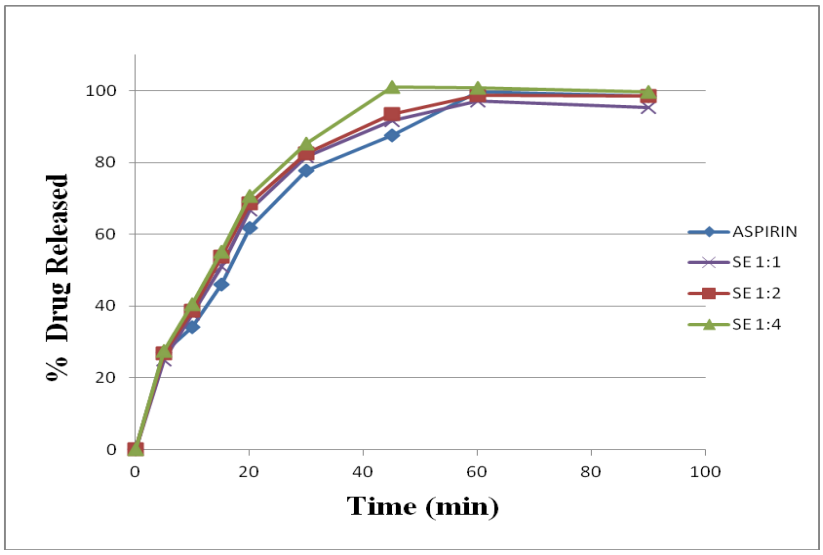

Fig 3: Percentage release of Aspirin from SE1, SE2, SE3 with pure Aspirin

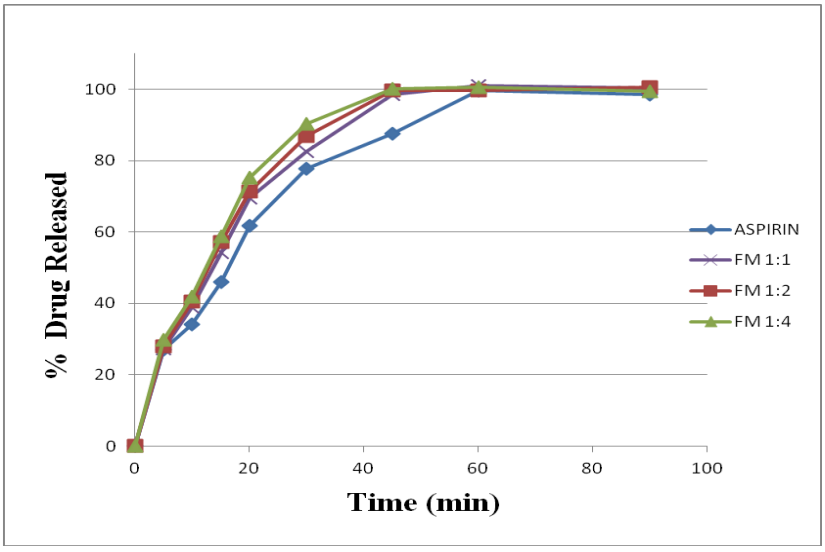

Fig 4: Percentage release of Aspirin from FM1, FM2, FM3 with pure Aspirin

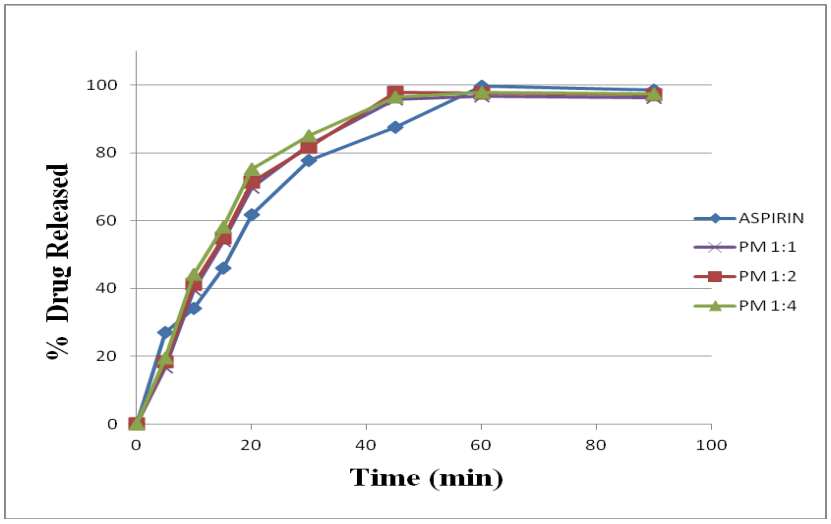

Fig 5: Percentage release of Aspirin from PM4, PM5, PM6 with pure Aspirin

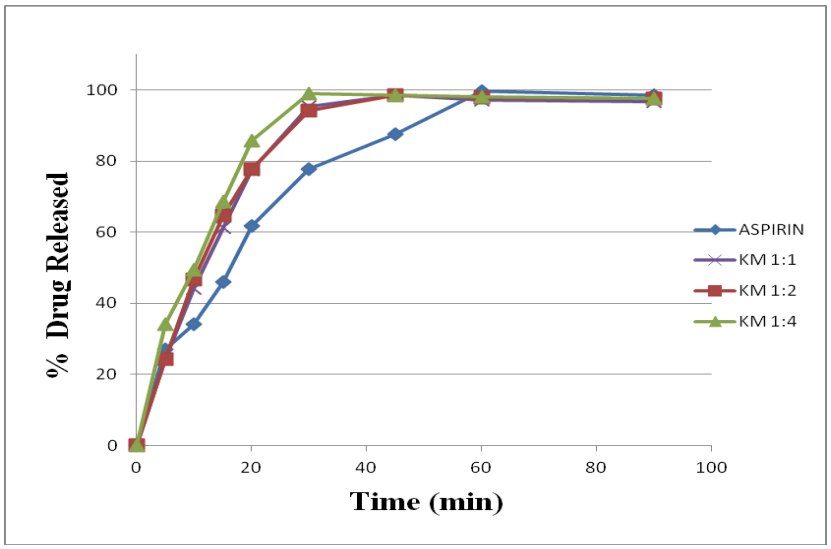

Fig 6: Percentage release of Aspirin from KM4, KM5, KM6 with pure Aspirin

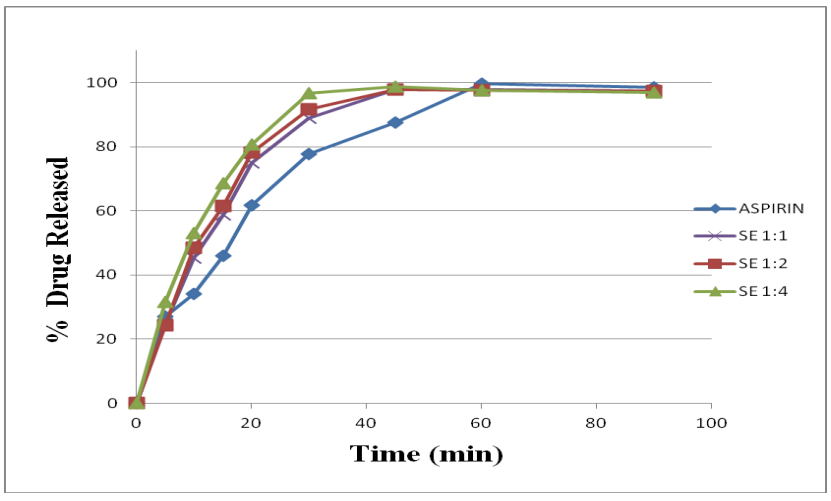

Fig 7: Percentage release of Aspirin from SE4, SE5, SE6 with pure Aspirin

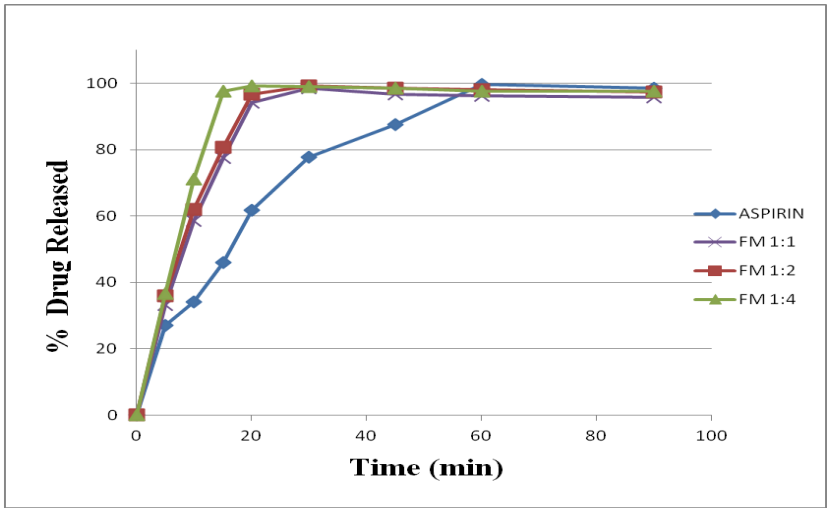

Fig 8: Percentage release of Aspirin from FM4, FM5, FM6 with pure Aspirin

In-vitro dissolution study

The dissolution profiles of aspirin for solid dispersion and physical mixture performed in 6.8 phosphate buffer were studied. The comparative cumulative release of aspirin at various time intervals from the physical mixtures and solid dispersions made by using various concentrations of PEG 1500 are shown in Fig. 1-4, as well cumulative release of aspirin at various time intervals from the physical mixtures and solid dispersions made by using various concentrations of PEG 6000 are shown in Fig 5-8. Prepared physical mixtures and solid dispersions showed improvement in dissolution characteristics. Solid dispersions With PEG 6000 showed better release profile as compared to solid dispersions with PEG 1500. In particularly, solid dispersions with PEG 6000 using fusion method showed fastest release. Hence the optimised batch FM 6 was subjected to differential scanning calorimetry (DSC) and IR analysis.

FT-IR Spectroscopy

The IR spectra of pure Aspirin and solid dispersions are shown in Fig 9&10 respectively. The IR spectra of pure Aspirin showed characteristic peaks which are shown in Table 3

Table 3: Functional groups of Aspirin from FT-IR study

Functional groups	Wave number (cm-1)
C=C (Aromatic)	1600-1400 cm-1
C=O (ester)	1750-1730 cm-1
C=O (carboxylic acid)	1725-1700 cm-1
C-O (ester/carboxylic acid)	1300-1000 cm-1
O-H (carboxylic acids)	3300-2500 cm-1

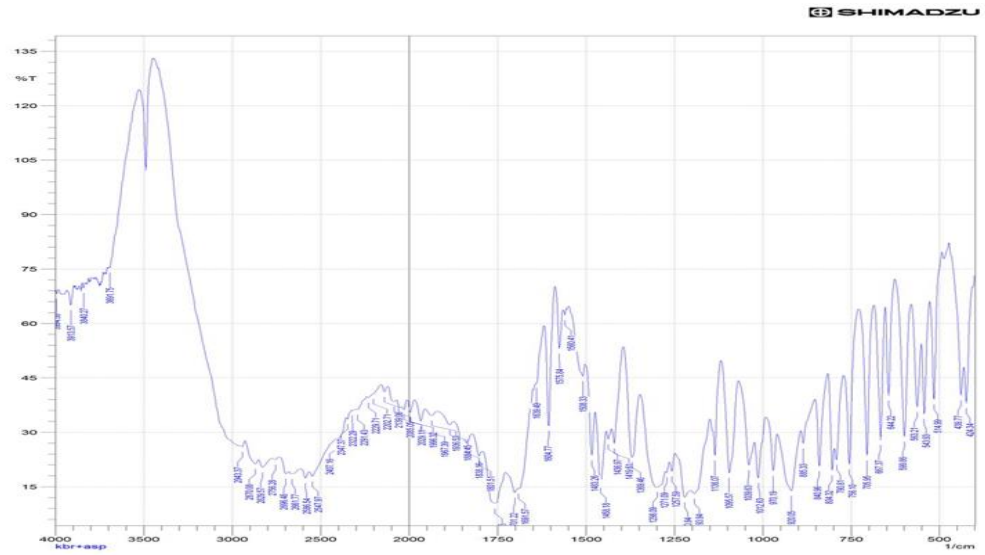

Fig 9: IR spectra of Aspirin

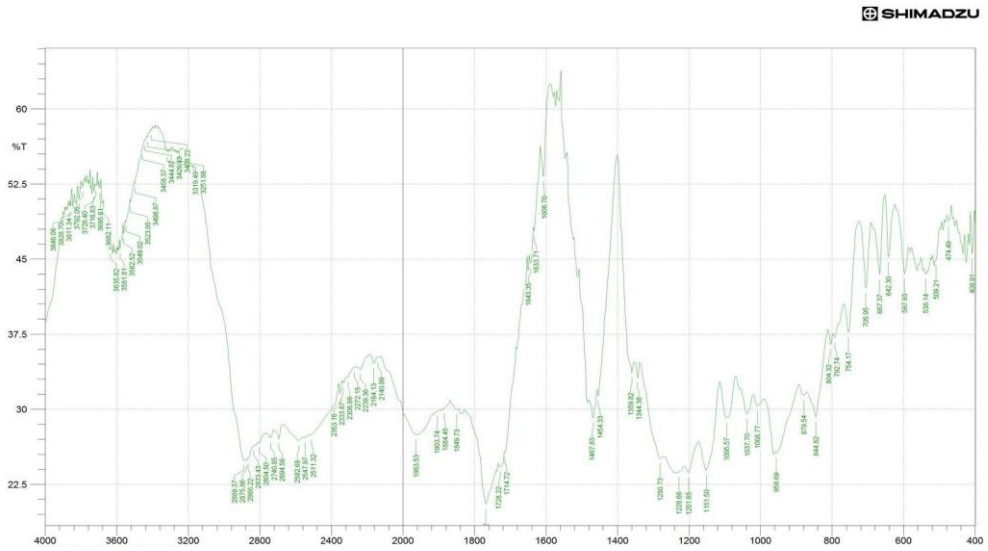

Fig 10: IR spectra of solid dispersion (Aspirin:PEG6000)

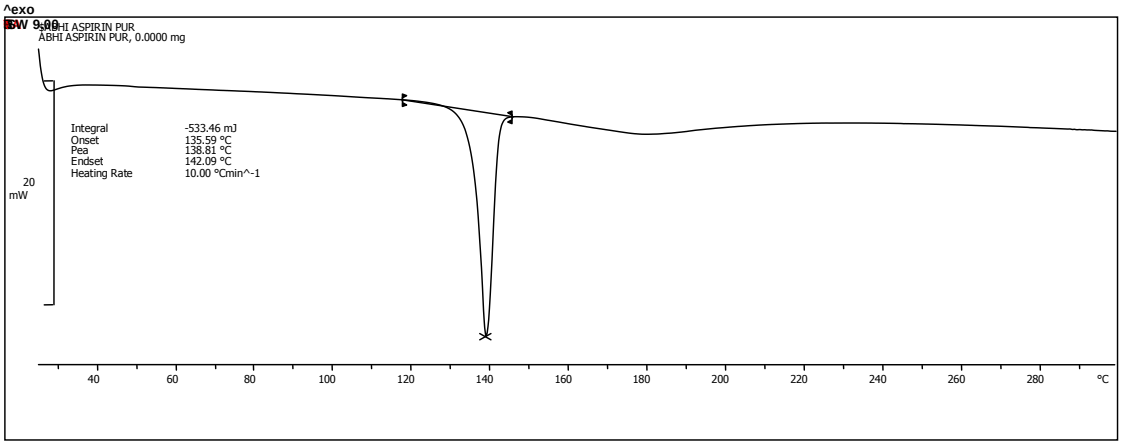

Fig 11: DSC Thermogram of pure Aspirin

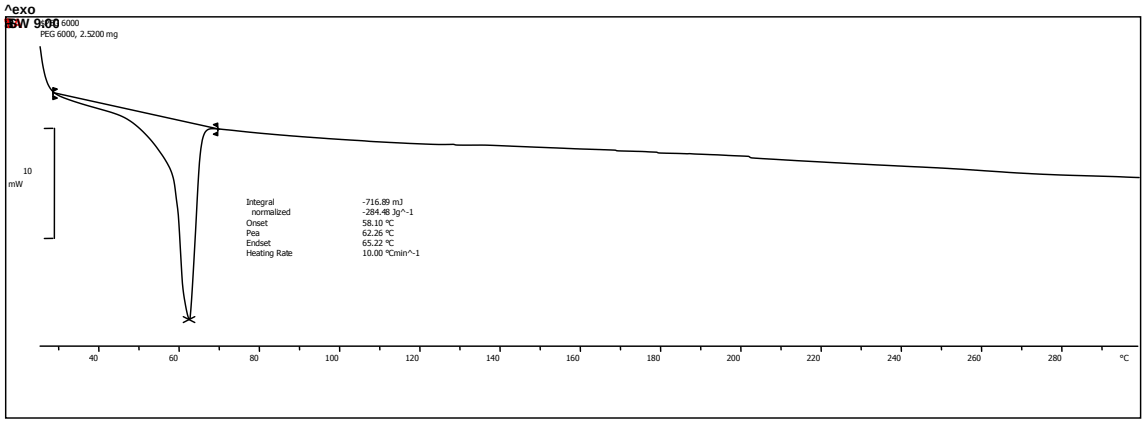

Fig 12: DSC Thermogram of PEG6000

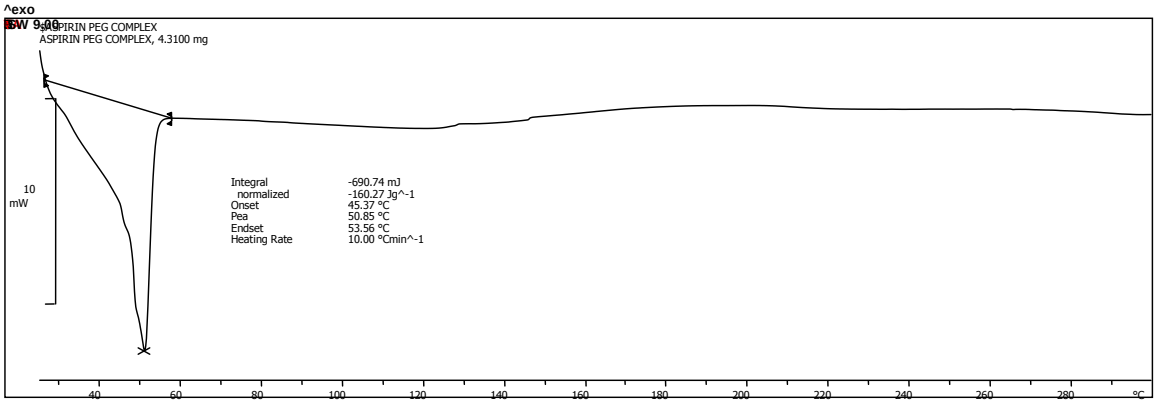

Fig 13: DSC Thermogram of Aspirin: PEG6000 (FM6)

Differential scanning calorimetry

The differential scanning calorimetry is a tool used to measure the temperature and energy variation involved in the phase transitions, which reflects the degree of crystallinity and stability of the solid state of pharmaceutical compounds. The peak size and shape of the DSC curves are useful in determining the crystallinity and stability of the drug and the carrier. The DSC curves of Aspirin, PEG 6000 and solid dispersion of Aspirin-PEG 6000 complex (FM6) were shown in figure 11, 12 and 13 respectively. The DSC curve of pure Aspirin and PEG 6000 showed apparent sharp endothermic peaks at 138.81°C and 62.26°C respectively, corresponding to its melting point. The DSC curve of solid dispersion (FM6) Aspirin-PEG 6000 Complex Prepared by fusion method showed shift in endothermic peak of PEG 6000 appeared at 50.85°C But, the sharp melting peak of Aspirin was absent in the DSC curve of the Aspirin solid dispersion, indicating absence of crystalline drug and presence of amorphous drug in the solid dispersion sample. Again, this could be attributed more uniform distribution of the drug in crust of polymer.

CONCLUSION

The prepared solid dispersions were examined to various characterizations. The solubility and dissolution studies showed there is a possibility of improved solubility of aspirin through solid dispersion with PEG 6000 by fusion method. Further, all the solid dispersions performed better than the corresponding physical mixtures. IR spectra indicated no well-defined interaction between the drug and carrier. A maximum increase in dissolution rate was obtained with aspirin: PEG 6000 solid dispersion with a weight ratio of 1:4 by fusion method. The crystallinity of the drug was reduced in solid dispersion with polymers PEG6000. Finally it could be concluded that solid dispersion of aspirin using hydrophilic polymers improved the solubility, dissolution rate and thereby enhancing its systemic availability.

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