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Solubility Enhancement of Aspirin by Solid Dispersion Method

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ABSTRACT

Aspirin (Acetyl Salicylic Acid) is one of the most widely used analgesic drug. Aspirin is poorly soluble in water and causes gastrointestinal (GI) irritation. Solubility enhancement of poorly aqueous soluble drugs is an important aspect of formulation development. The objective of the study is to increase the solubility by Solid Dispersion Method and to compare dissolution of pure drug and solid dispersions. The present study is an attempt to enhance the solubility of aspirin by Physical Mixture and Fusion (Melt) Method using Aspirin and Polyethylene Glycol 6000 as carrier in the ratio of 1:1, 1:2, 1:3 and 1:4. The complex of Aspirin with Polyethylene Glycol 6000 shows enhanced solubility than the pure drug and the complex can also reduced the gastrointestinal irritation. The drug carrier interaction study was carried out by Fourier Transform Infrared Spectroscopy (FTIR). The FTIR study suggested no interaction between drug and carrier of Solid Dispersion. The dissolution rate studies were performed in phosphate buffer pH7.4 and the dissolution rates were found to be in the following order: Fusion (Melt) Method > Physical Mixture > Pure drug (Aspirin).

1. INTRODUCTION [1, 2, 3]

Aspirin (Acetyl Salicylic Acid) is one of the most widely used therapeutic substances due to its analgesic, antipyretic and anti-inflammatory properties. Despite the proliferation in the development of new non-steroidal anti-inflammatory drugs (NSAIDs), aspirin remains one of the most effective "over-the-counter" drugs in the treatment of rheumatic diseases. Furthermore, due to its anti-thrombotic properties, aspirin is now prescribed at low doses in the prevention and treatment of cardiovascular diseases, strokes and disorders associated with platelet aggregability. 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. 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 aspirin can be increased, it will reduce the gastrointestinal side-effects.

Solid dispersion is an approach widely used for the enhancement of solubility of poorly water soluble drugs. The concept of solid dispersion was introduced by Sekiguchi and Obi. In solid dispersion method, the drug is dispersed in extremely fine state in an inert water-soluble carrier in the solid state. A number of freely water-soluble materials such as citric acid, bile acids, sterols and related compounds and polymers like Polyvinylpyrrolidone and Polyethylene Glycols were used as carriers for solid dispersions. By this approach, the dissolution rate and bioavailability of poorly soluble drug can be increased.

2. MATERIALS AND METHODS:

The active drug used in the present study is Aspirin and the polymer used is PEG 6000. All other chemicals used are of analytical grade.

3. PREPARATION OF PHOSPHATE BUFFER 7.4[4]

Accurately weighed 50 mg of monobasic potassium phosphate and 39.1 ml of 0.2N sodium hydroxide were dissolved in 200 ml of distilled water.

4. PREPARATION OF CALIBRATION CURVE IN PHOSPHATE BUFFER pH 7.4[5]

Accurately weighed amount of Aspirin equivalent to 100mg was dissolved in small volume of 0.01M HCl, in 100 ml volumetric flask and the volume was adjusted to 100 ml with 7.4 pH phosphate buffer and further dilutions were made with 7.4 pH phosphate buffer. A series of standard solutions containing Beer's Lambert's range of concentrations of Aspirin was prepared and absorbances were measured at 234nm against reagent blank. All spectral absorbance measurement was made on Shimadzu 1800 UV-visible spectrophotometer.

Table 1: Standard Calibration Curve in Phosphate Buffer pH 7.4

Concentrations (µg/ml)	**0**	**5**	**10**	**15**	**20**	**25**	**30**
Mean Absorbance	0.00	0.762	1.209	1.837	2.305	2.866	3.675
±S.D	0.00	0.32	0.041	0.057	0.085	0.36	0.41

Results are mean of three determinations.

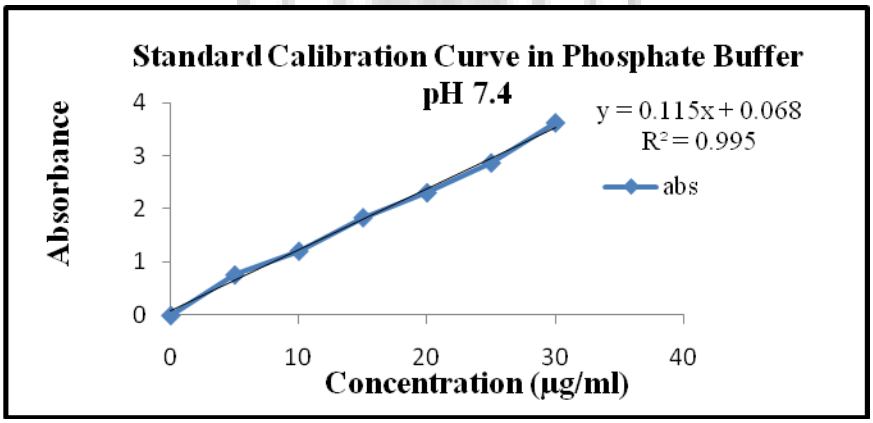

Figure 1: Standard Calibration Curve in Phosphate Buffer pH 7.4

5. METHODS OF PREPARATION OF ASPIRIN-PEG 6000 COMPLEX: [6,7,8]

5.1. Physical Mixture:

Physical mixtures were prepared by mixing the appropriate amount of Aspirin and Polyethylene Glycol 6000 of different ratio in pestle and mortar and sieved through sieve #60. The mixtures were prepared in ratio 1:1, 1:2, 1:3, 1:4 & named as F1, F2, F3, F4 respectively.

5.2. The Fusion (Melt) Method:

Accurately weighed amounts of carrier Polyethylene Glycol 6000 is placed in an aluminium pan on a hot plate and liquefy, with constant stirring, at a temperature of about 60^{o}C. An accurately weighed amount of active drug Aspirin is incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture is heated until a clear homogeneous melt is obtained. The pan is then removed from the hot plate and allowed to cool at room temperature. The mixture was prepared in ratio 1:1, 1:2, 1:3, 1:4 & named as F5, F6, F7, F8 respectively.

6. EVALUATION OF ASPIRIN-POLYETHYLENE GLYCOL 6000 SOLID DISPERSION

6.1. FTIR Study

Samples of pure drug Aspirin, polymer Polyethylene Glycol 6000, Physical Mixture and Fusion Mixture complex of drug and polymer were analysed for FTIR studies by using Shimadzu analytical FTIR machine and KBr pellets. Graphs are shown as below:

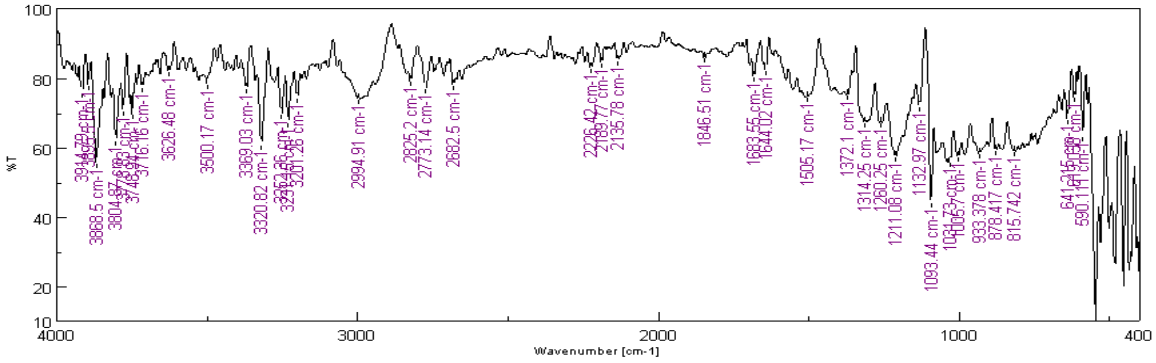

Figure 2 (a): Pure Drug

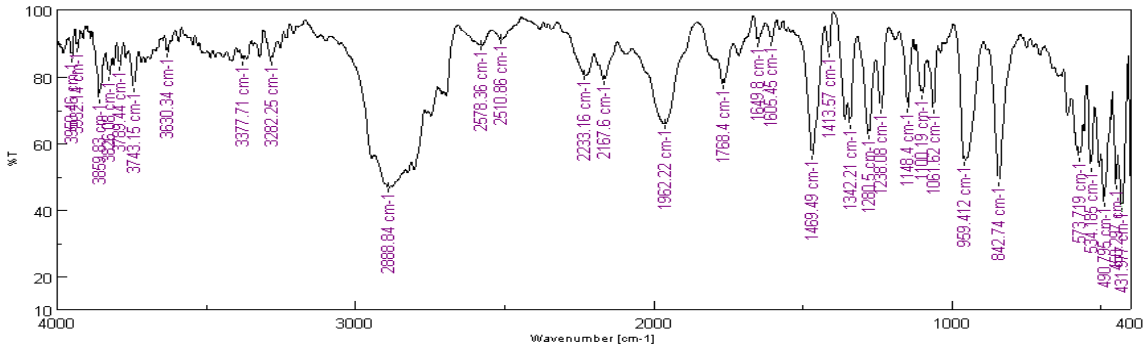

Figure 2 (b): Pure Polymer

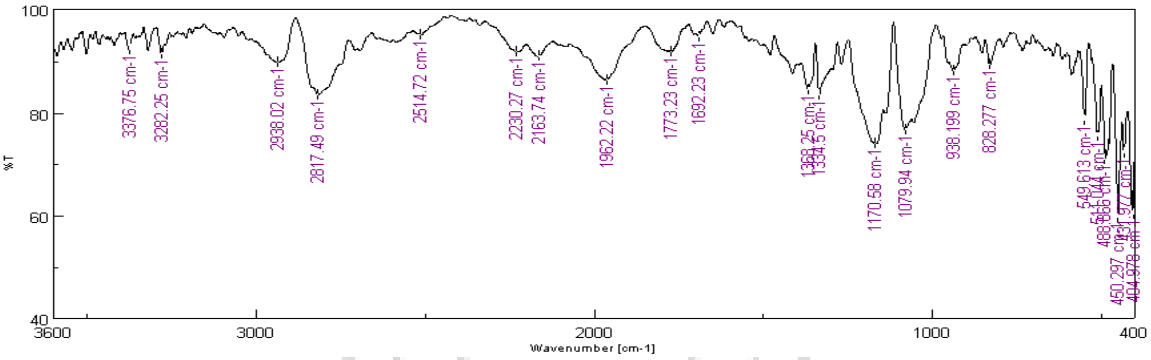

Figure 2 (c): Physical Mixture of Drug and Polymer

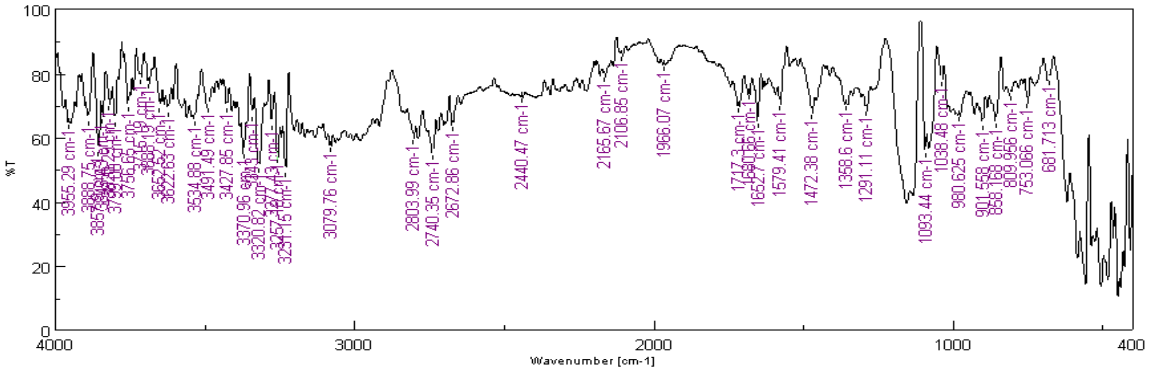

Figure 2 (d): Fusion Complex of Drug and Polymer

6.2. Dissolution Study and Observations

Dissolution studies were performed assuring sink condition according to the paddle method (USP) using USP XXIII apparatus type-II (Electro lab TDT-O9T). The dissolution medium was 900 ml 7.4 pH phosphate buffer kept at 37˚C ± 0.5˚C. The drug containing 100mg of Aspirin was taken in a muslin cloth and tied to the rotating paddle kept in the basket of dissolution

apparatus, the basket was rotated at 100 rpm. Samples were withdrawn at specified time intervals and analyzed spectrophotometrically at 234nm using Shimadzu-1800 UV-visible spectrophotometer; the samples withdrawn were replaced by fresh buffer solutions. Each preparation was tested in triplicate and then mean values were calculated.

Dissolution profile of pure drug and all formulations is shown below:

Dissolution Profile of Pure Drug:

Table 2: Dissolution Profile of Aspirin Pure Drug

Time (min.)	Abs. (nm)	Conc. in 900ml In mg.	% drug release	% drug remain
0	0.000	0.000	0.00	0.00
10	0.062	0.310	3.10	96.9
20	0.069	0.853	8.53	91.47
40	0.066	0.620	6.20	93.8
60	0.070	0.931	9.31	90.69
80	0.073	1.163	11.63	88.37

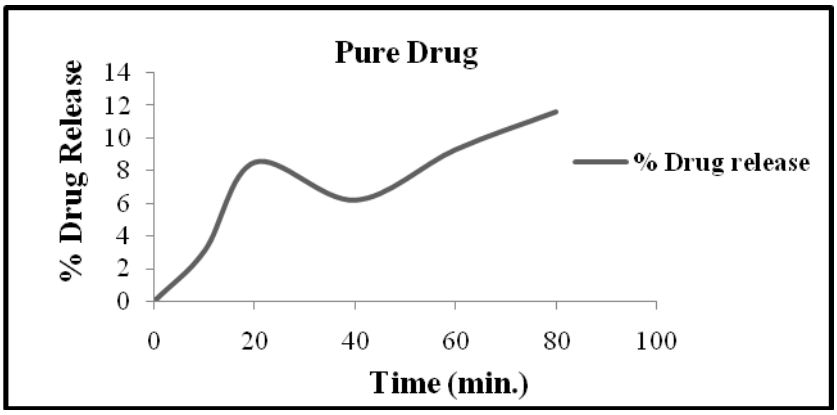

Figure 3: Dissolution Study of Pure Drug Aspirin

Dissolution Profile of Formulations Prepared by Physical Mixture Method

Table 3: Dissolution Profile of Solid Dispersions Prepared by Physical Mixture Method

Time (min.)	% Drug Release			
	F1	F2	F3	F4
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
10	6.90 ± 0.029	21.71 ± 0.044	56.63 ± 0.082	50.43 ± 0.11
20	9.30 ± 0.030	23.27 ± 0.057	58.96 ± 0.120	51.98 ± 0.10
40	19.35 ±0.033	24.82 ± 0.049	59.74 ± 0.110	54.31 ± 0.09
60	21.77 ± 0.025	27.15 ± 0.062	60.51 ± 0.070	53.53 ± 0.12
80	22.50 ± 0.023	28.70 ± 0.066	61.29 ± 0.090	55.08 ± 0.07

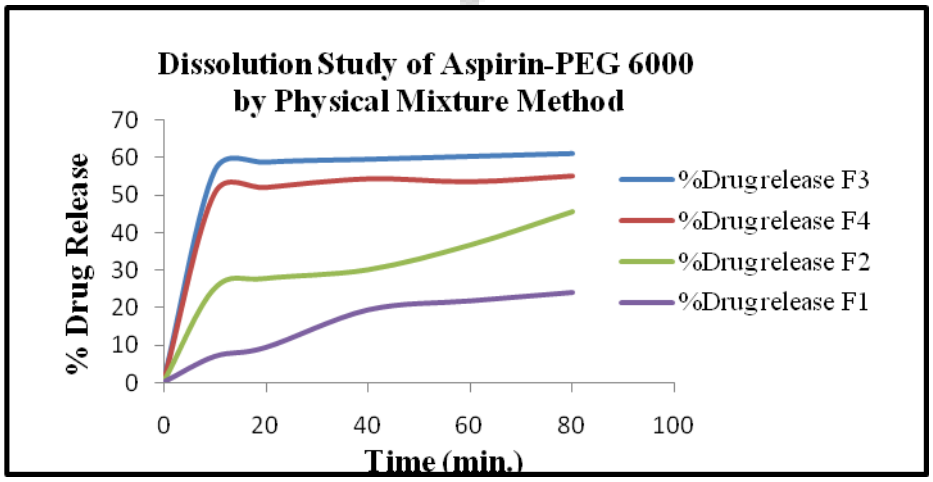

Figure 4: Dissolution profile of Solid Dispersions Prepared by Physical Method

Dissolution Profile of Formulations Prepared by Fusion (Melt) Method

Table 4: Dissolution Profile of Solid Dispersions Prepared by Fusion (Melt) Method

Time (min.)	% Drug Release			
	F5	F6	F7	F8
0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
10	10.86 ± 0.085	26.00 ± 0.120	93.87 ± 0.08	91.55 ± 0.170
20	13.40 ± 0.080	28.83 ± 0.080	94.65 ± 0.10	90.77 ± 0.092
40	23.45 ± 0.092	32.35 ± 0.091	96.68 ± 0.14	92.32 ± 0.085
60	25.60 ± 0.073	42.30 ± 0.069	96.68 ± 0.09	93.10 ± 0.142
80	31.12 ± 0.054	46.64 ± 0.088	96.68 ± 0.06	94.65 ± 0.097

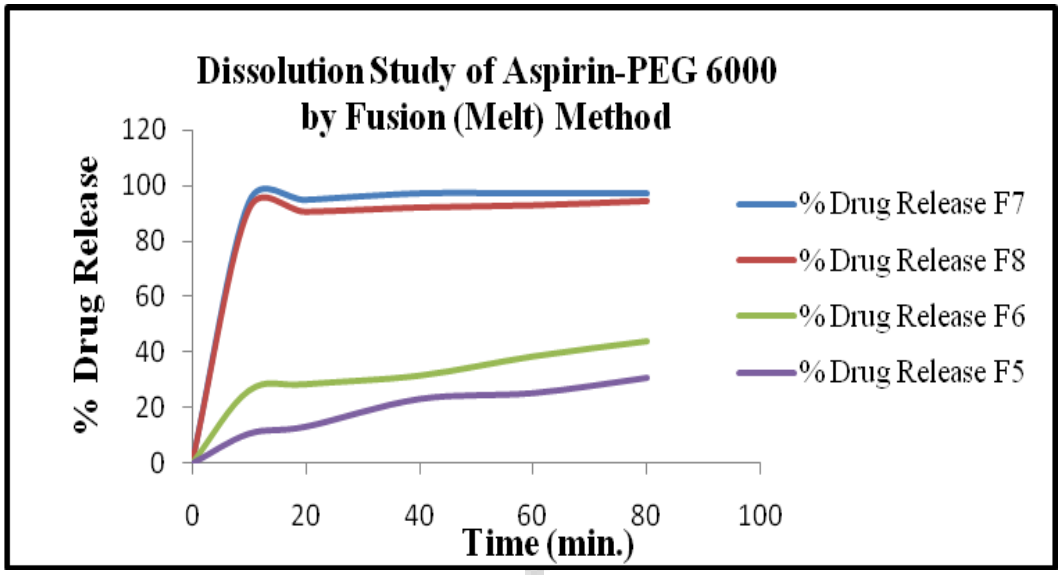

Figure 5: Dissolution Study of Solid Dispersions Prepared by Fusion (Melt) Method.

6.2.4. Comparative Dissolution Study:

To choose the best Solid Dispersion Method, the dissolution of pure drug Aspirin and Solid Dispersions by Physical Mixture Method (F3) and Fusion (Melt) Method (F7) were compared.

Table 5: Comparison of % Drug Release of Pure Drug Aspirin, and SDs From Physical Mixture Method (F3) and Fusion (Melt) Method (F7)

Time (min.)	% drug release		
	Pure drug	F3	F7
0	0.00	0.00	0.00
10	3.10	56.63	93.87
20	8.53	58.96	94.65
40	6.20	59.74	96.68
60	9.31	60.51	96.68
80	11.63	61.29	96.68

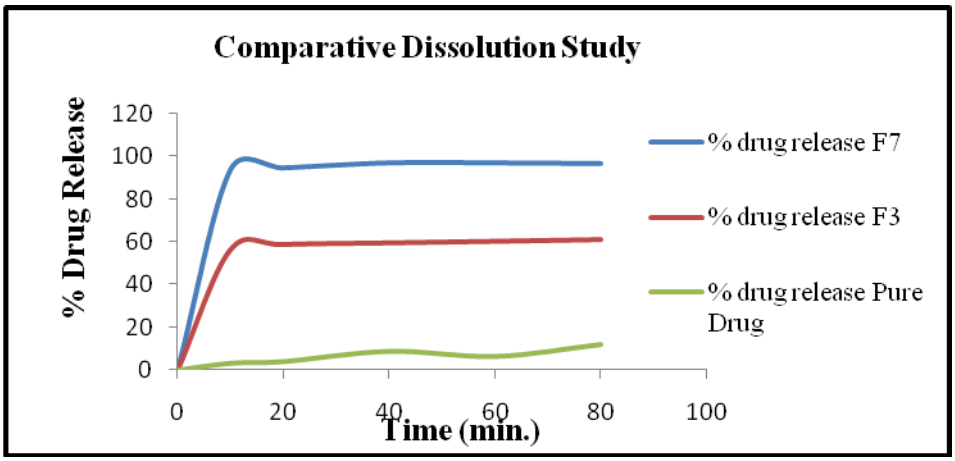

Figure 6: Comparative Dissolution Study i.e. Pure Drug, F3 and F7.

7. RESULTS AND DISCUSSION

Aspirin is poorly soluble in water and causes gastrointestinal (GI) irritation. In the present study, the attempt was made to enhance the solubility of Aspirin which will reduce the GI irritation and will also show the better bioavailability. The solubility of Aspirin was enhanced by Solid Dispersion Method i.e. Physical Mixture Method and Fusion (Melt) Method with the Polyethylene Glycol 6000 polymer.

Previously reported spectrophotometric methods of analysis of Aspirin obeys Beer-Lambert's Law in working range in Phosphate Buffer pH 7.4.

Solid Dispersions of the drug Aspirin and polymer Polyethylene Glycol 6000 was prepared by Physical Mixture Method and Fusion (Melt) Method in ratios 1:1, 1:2, 1:3 and 1:4 (Drug: Polmer). The Solid Dispersion prepared by Physical Mixture Method were F1, F2, F3 and F4 and Fusion (Melt) Method were F5, F6, F7 and F8. The Solid Dispersions of Aspirin-Polyethylene Glycol 6000 was evaluated for FTIR and *in-vitro* dissolution study.

The drug Aspirin was taken for the FTIR study. In IR spectra, the frequency for OH- stretch was observed at 3320.82 cm^{-1} and broad peak was observed at 2994.9 cm^{-1} and for C=O stretch was found at 1683.85 cm^{-1}.

The polymer taken in this study is PEG 6000 which contains OH group and peak was observed at 2888.84 cm^{-1} and in complex complete broad peak was observed at 3079.76 cm^{-1} of OH stretch. Hence, none of the functional group absorption is not affected.

IR studies indicated that no chemical interaction between drug and polymer took place during the preparation of Solid Dispersions of Aspirin and PEG 6000.

The *in-vitro* dissolution study of the pure drug and Solid Dispersions prepared by Physical Mixture Method and Fusion (Melt) Method was studied. The percentage drug release after 80 min. was 11.63%, 61.29%, 96.68% for pure drug Aspirin, F3 and F7 Solid Dispersion Formulations.

In Solid Dispersion prepared by Physical Mixture Method, F3 formulation showed better percentage drug release than the F1, F2 and F4 formulations.

In Solid Dispersion prepared by Fusion (Melt) Method, F7 Formulation showed better percentage drug release than F5, F6 and F8 formulations.

From the *in-vitro* dissolution study, the percentage drug release from the Solid Dispersion prepared by Physical Mixture Method and Fusion (Melt) Method were better than the Pure Drug Aspirin. The F7 formulation showed higher percentage drug release than the F3 formulation and pure drug Aspirin.

The Solid Dispersion prepared by Fusion (Melt) Method showed faster drug release than the Physical Mixture Method because of stronger and intimate complexes formed by Fusion (Melt) Method.

8. CONCLUSION

- Solid dispersion of Aspirin was prepared by Physical Mixture Method and Fusion (Melt) Method using carrier PEG 6000 in four different ratios (1:1,1:2, 1:3 & 1:4,) (Drug: Polymer ratio).
- The formulations are fine, free flowing and easy to prepare.
- The dissolution studies showed that the carrier PEG6000 used in the formulation enhanced the *in-vitro* dissolution of Aspirin from the solid dispersion formulation than that of the pure drug and formulations.

- Out of all formulations prepared, the formulation F7 showed better release of Aspirin than the formulation of F3 i.e the formulation prepared by Fusion (Melt) Method gives better drug release than the Physical Mixture Method.
- Also, it indicates that an increase in the polymer concentration may increase the dissolution rate.
- In Physical Mixture Method, ratio 1:3 i.e. F3 formulation showed better drug release than other formulation.
- In Fusion (Melt) Method, ratio 1:3 i.e. F7 formulation showed higher drug release.
- But further increase in Polymer concentration did not show any increase in dissolution. Hence, ratios up to 1:4 were prepared.
- Hence from overall study, it is concluded that the solid dispersion prepared by the Fusion (Melt) Method showed better drug release than the Physical Mixture Method and also PEG6000 can be effectively used in the enhancement of dissolution.

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