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SOLUBILITY AND DISSOLUTION ENHANCEMENT OF ACECLOFENAC BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Aceclofenac an analgesic and anti-inflammatory drug used in treatment of Osteo arthritis, rheumatoid arthritis and ankylosing spondylitis. Aceclofenac solid dispersions were prepared using hydrophilic polymers such as polyethylene glycol-4000, polyethylene glycol-6000 and Polyvinyl Pyrrolidone in the ratio of 9:1, 7:3 and 1:1 by solvent evaporation technique. The prepared formulations were evaluated for number of parameters like solubility, drug content uniformity, drug-polymer interactions, differential scanning calorimetry, X-ray diffractogram study showed the reduced number of peaks and decrease intensity of the peaks in the formulations, this suggests that the crystalline nature of the drug was converted to amorphous form, which is the reason for the higher solubility, faster dissolution rate and improved bioavailability of the drug when it is formulated in the form of solid dispersion. Drug Aceclofenac and its various formulations were subjected to scanning electron microscopy studies. The results showed the conversion of crystalline nature of the drug to amorphous form, which indicates enhanced solubility, dissolution rate and bioavailability of the drug. The *in vitro* release study was carried out on plain pure drug Aceclofenac and various solid dispersion formulations by employing pH 6.8 phosphate buffer as a dissolution medium. This shows an increased release of the drug from the dispersions in comparison to pure Aceclofenac drug. *In vitro* data of all formulations was subjected to first order plots, the graphs plotted were fairly linear and the 'r' values of all the formulations were very close to one, indicating the release mechanism followed first order kinetics.

Keywords: Analgesic, Ankylosing spondylitis, Dispersion.

INTRODUCTION

The number of sparingly soluble active pharmaceutical ingredients (API) has risen sharply in recent years and the formulation of such entities presents greater challenges to formulation pharmacists. As a matter of fact, more than 40% of new chemical entities are insufficiently soluble to allow for acceptable dosage formulation. In the last decade, competition in the pharmaceutical area has revolved around improving physicochemical properties of drugs and improving formulations to give the patient a better product¹.

The knowledge of Biopharmaceutical Classification System (BCS) included in the guidelines of the U.S. food and drug administration, can be utilized by the formulation scientists for developing an optimized dosage form². Along with the permeability, the dissolution of drug in gastrointestinal fluid is a key factor in the determination of its oral bioavailability³. Drug dissolution from oral solid dosage forms depend on the release of a drug from the dosage form and subsequent solubilization of drug particles in physiological fluid⁴.

For poorly soluble, the rate of oral absorption is often controlled by the dissolution rate in the Gastro intestinal tract. Therefore together with the permeability, the solubility and dissolution behavior of a drug are key determinants of its oral bioavailability^{5,6}. There have been numerous efforts to improve drug dissolution rate. These include, (a) reducing particle size to increase surface area, thus increasing dissolution rate of drug; (b) solubilization in surfactant systems; (c) formation of water-soluble complexes; (d) use of pro-drug and drug derivatization such as a strong electrolyte salt forms that usually have higher dissolution rate; and (e) manipulation of solid state of drug substance to improve drug dissolution i.e. by decreasing crystallinity of drug substance through formation of solid solutions⁷. The most common method is increasing the surface area of the drug by micronization. But, in practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tableted. This phenomenon was attributed to the agglomeration tendency of micronized, poorly soluble, hydrophobic drugs, which

results in a decreased effective surface area for dissolution.

By many estimates up to 40 percent of new chemical entities discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs⁸.

Aceclofenac is aceclofenacum (O-(2, 6-dichloroaniline) phenyl] acetate glycolic acid ester, 2-(2, 6-dichloroaniline) phenyl acetoxyacetic acid. Aceclofenac is a NSAID. It is used in the management of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. Aceclofenac when taken orally shows gastrointestinal disturbances such as GI discomfort, nausea, diarrhea. In some patients peptic ulceration and severe gastrointestinal bleeding may also occur.

Solid dispersion technology can be used to improve the in vitro and in vivo dissolution properties of dissolution dependent poorly water soluble drugs. PEG 4000, PEG 6000 and PVP have been reported to be used for increasing the solubility of a poorly soluble drugs¹⁰. The usual dose of aceclofenac is 100 mg given twice daily by mouth. The initial dose should be reduced to 100 mg daily in patients with hepatic impairment. Its low solubility makes it a suitable candidate for solid dispersion systems.

Materials and Method

Aceclofenac was obtained as a gift sample from Cipla Pharmaceutical Ltd. Mumbai India. Polyethylene glycol 4000, Polyethylene glycol 6000 was gift sample from Loba Chemie Pharmaceutical Pvt. Ltd. Mumbai India. PVP K30 were supplied by MIDC Pharmaceutical Ltd. Tarapur India. Concentrated hydrochloric acid, sodium hydroxide were supplied by NICE Chemical Pvt. Ltd. Cochin India. Disodium Hydrogen Phosphate, Methanol were supplied by Merck Pvt. Ltd. Mumbai India.

Preparation of solid dispersions by Solvent Evaporation method

(i) Preparation of aceclofenac – PEG 4000 solid dispersion

Weighed quantity of aceclofenac and PEG 4000 was dissolved in ethanol solvent to get a clear solution. The solvent was evaporated at room temperature. The mass obtained was pulverized and sifted through mesh no. 100 and stored in closed airtight container.

(ii) Preparation of aceclofenac -PEG 6000 solid dispersion

Weighed quantity of PEG and aceclofenac was dissolved in ethanol to get a clear solution. The solvent was evaporated at room temperature. The mass obtained was pulverized and sifted through mesh no: 100 and stored in closed airtight container.

(iii) Preparation of aceclofenac – PVP solid dispersion

Weighed quantity of PVP and aceclofenac was dissolved in ethanol to get a clear solution. The solvent was evaporated at room temperature. The mass obtained was

pulverized and sifted through mesh no: 100 and stored in closed airtight container. Table 1 showing Various Solid Dispersions Prepared by Solvent Evaporation method

RESULT AND DISCUSSION

Preformulation studies

Organoleptic Properties: The sample drug Aceclofenac was found to be white crystalline through visual inspection which is in accordance with I.P

Solubility: The solubility of aceclofenac was determined in different solvents. The drug was found to be more soluble in organic solvents.

Melting point: Melting point of the sample drug aceclofenac was found to be 149 °C which is in accordance with IP.

Partition Coefficient: The partition coefficient of aceclofenac was determined in n-octanol: distilled water and log P value was found to be 3.65

Interference of Additives / Compatibility Testing: The above results of UV spectroscopic analysis indicated that there was no chemical interaction between the drug and the additives as the respective formulation (Drug and Polymer combination) exhibited absorption nearly similar to those of the pure drug sample (Table 2 showing Interference of Additives)

Ultraviolet Absorbance spectra: Mention in Graph 1 & Table 3 Showing Standard Curve of Aceclofenac in Phosphate Buffer pH 6.8

FT-IR Spectrum of Aceclofenac: FT-IR Spectra of Aceclofenac was recorded. The characteristic peaks due to pure Aceclofenac at 667.32, 1291.25 1717.49, 1771.50, 1291 for C-H bending, C-N Stretching, C=O Str., due to polynuclear aromatic ring, secondary aromatic, carboxylic group, esters to group respectively, which is shown in Table-4.

Differential scanning calorimetry (DSC) of Aceclofenac

: The DSC thermo gram shows that when the drug aceclofenac was taken to study its properties at higher temperature it has exhibited the melting endotherm at onset 152.51 °C and peak at 158.92 °C (Fig 1-4)

Drug Content Uniformity:

The Aceclofenac solid dispersions prepared were evaluated for the uniform dispersion of the drug throughout the formulation and the results of the study were shown in table. The drug was dispersed in the range of 96.48 % to 98.90 %. So, the results suggest that the drug was uniformly dispersed throughout the formulations prepared. (Table 5)

X-Ray Diffractograms of Aceclofenac and its Formulations:

The pure drug Aceclofenac and some selected formulations such as F3, F6 and F9 were subjected to X-ray diffraction studies and they were shown in figure-00 respectively. The X-ray diffractogram of pure drug Aceclofenac shows more number of intense and sharp peaks, whereas the other diffractograms like formulation F3, F6 and F9 shows lesser number of peaks. The results showed that the numbers of peaks were reduced and also the intensity of the peaks was also decreased in the formulation diffractograms. The results suggests that the crystalline nature of the drug was converted to amorphous form, which is the reason for the higher solubility, faster dissolution rate and improved bioavailability of drug when it is formulating in the form of solid dispersions. (Fig 5-8)

Scanning Electron Microscopy:

The pure drug Aceclofenac and its various formulations were subjected to scanning electron microscopy studies. The Aceclofenac pure drug shows crystalline nature of the drug in its microphotographs, whereas in case of its formulations, the crystalline nature of the drug is get converted to amorphous form to maximum extent as shown in photograph. This converting crystalline property of a drug into amorphous form by preparation of solid dispersion is the one of the reason in enhancing its solubility, dissolution rate and bioavailability of the drug.

(Fig 9-12)

In-Vitro Drug Release Studies

The Aceclofenac pure drug and its various formulations prepared were subjected to in vitro drug release studies and the release data were shown in the table-00 and the data was plotted for cumulative percent release versus time (release plots) and also for log percent drug remaining versus time (first order plots). The Aceclofenac pure drug and its formulation with polyethylene glycol-4000 (F1, F2 and F3) shows 9.11%, 77.20%, 80.40% and 85.30% of drug release respectively at the end of one hour. Similarly the Aceclofenac formulations with polyethylene glycol-6000 (F4, F5 and F6) show 80.50 %, 85.90 and 87.40 of drug release respectively at the end of one hour. Similarly Aceclofenac formulations with polyvinyl pyrrolidone (F7, F8 and F9) release 80.10%, 82.10% and 80.06% respectively. In all the cases, the first order plots were found to be fairly linear and the 'r' coefficient value for pure drug Aceclofenac and its formulations with polyethylene glycol-4000 i.e., F1, F2 and F3 were 0.8133, 0.9935, 0.9928 and 0.9974 respectively. The same 'r' value for polyethylene glycol-6000 formulations i.e. F4, F5 and F6 were 0.9661, 0.9910 and 0.9772 respectively. Similarly the 'r' coefficient values for PVP formulations (F7, F8 and F9) were 0.9835, 0.9943 and 0.9904 respectively. So the regression data of first order plots indicates that the drug was released by first order kinetics.(Graph 2-7)

Table 1: Various Solid Dispersions Prepared by Solvent Evaporation method

Formulation code	Solid Dispersions	Drug –carrier ratio
F1	Aceclofenac-PEG 4000	9:1
F2	Aceclofenac-PEG 4000	7:3
F3	Aceclofenac-PEG 4000	1:1
F4	Aceclofenac-PEG 6000	9:1
F5	Aceclofenac-PEG 6000	7:3
F6	Aceclofenac-PEG 6000	1:1
F7	Aceclofenac-PVP	9:1
F8	Aceclofenac-PVP	7:3
F9	Aceclofenac-PVP	1:1

Table 2 : Interference of Additives/Compatibility Testing

Formulation	Absorbance of solutions			Interference Yes / No
	Polymer blend with drug	Placebo	Pure drug	
Aceclofenac-PEG 4000	0.065	0.003	0.062	No
Aceclofenac-PEG 6000	0.066	0.001	0.062	No
Aceclofenac-PVP	0.065	0.004	0.062	No

Table No 3 Standard Curve of Aceclofenac in Phosphate Buffer pH 6.8

S. No	Concentration (µg/ml)	Absorbance (275 nm)
1.	0	0
2.	10	0.060
3.	20	0.107
4.	30	0.175
5.	40	0.210
6.	50	0.281

7.	60	0.322
8.	70	0.375
9.	80	0.421
10.	90	0.458
11.	100	0.523

$R^2 = 0.996$, $Y = 0.005x$

Table No - 4 Characteristic peak ranges of Aceclofenac

S. No.	Transition	Ranges (cm ⁻¹)	Drug
1.	C = O str	1740 – 1680	1717.49
2.	C = O Str	1800 – 1725	1771 .50
3.	C – N Str.	1350 – 1280	1291.25
4.	C – H bend	900 – 625	667.32

Table No.5: Drug Content Uniformity of Aceclofenac

Formulation Code	Percentage Drug Content			Mean percent drug content ± SD
	I	II	III	
F1	96.90	95.26	98.15	96.77 ± 0.0072
F2	98.68	94.90	96.42	96.66 ± 0.0040
F3	96.57	97.89	95.00	96.48 ± 0.0032
F4	96.52	98.63	98.89	98.01 ± 0.0030
F5	97.63	95.31	98.26	97.06 ± 0.0015
F6	96.63	99.12	97.57	97.77 ± 0.0015
F7	97.00	98.68	95.94	97.20 ± 0.0017
F8	92.63	98.90	98.68	96.63 ± 0.0020
F9	98.40	99.68	98.63	98.90 ± 0.0030

Fig. 1: DSC Thermogram of Pure Aceclofenac

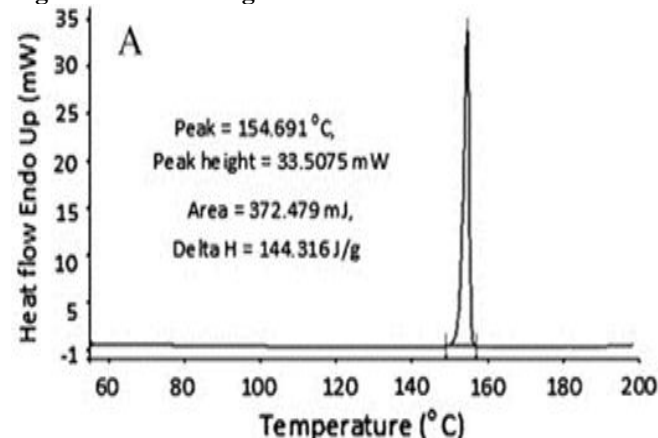


Figure 2: DSC Thermogram of PEG 4000

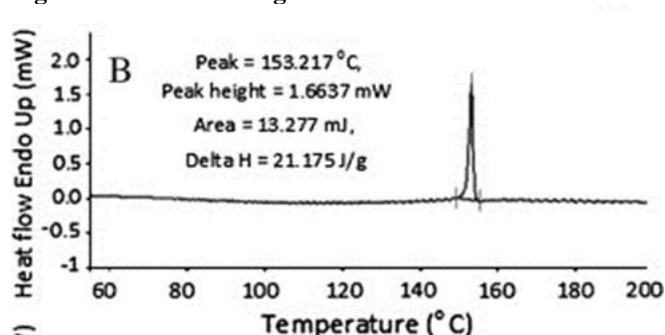


Fig. 3: DSC Thermogram of PEG 6000

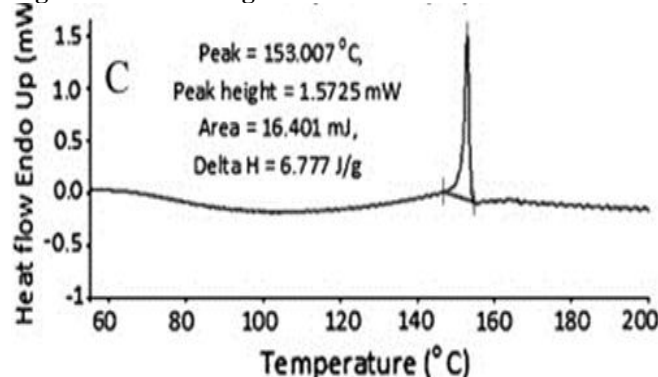


Fig. 4: DSC Thermogram of PVP

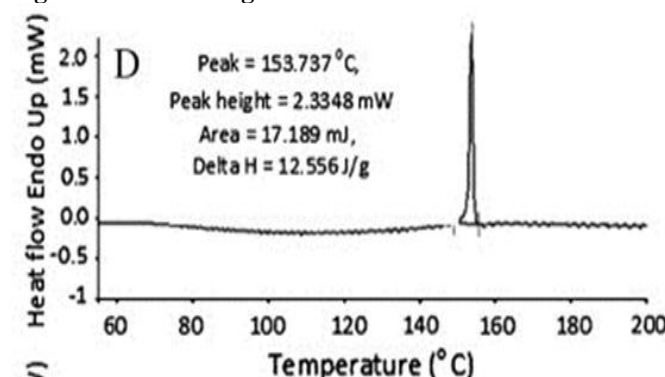


Figure 5: X-Ray Diffractogram of Aceclofenac Pure Drug

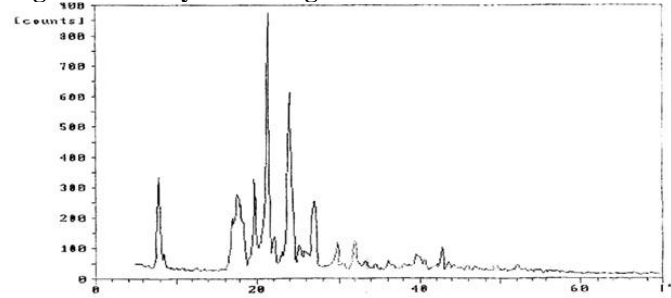


Figure 6: X-Ray Diffractogram of Aceclofenac Solid Dispersion with PEG 4000(1:1)

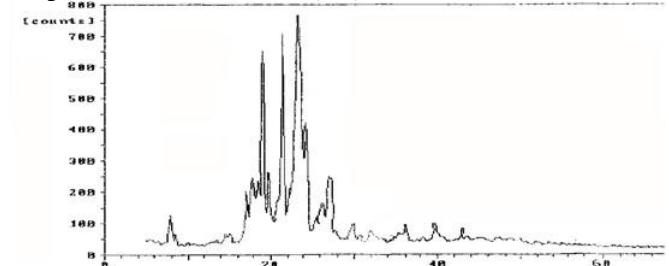


Figure 7: X-Ray Diffractogram of Aceclofenac Solid Dispersion with PVP (1:1)

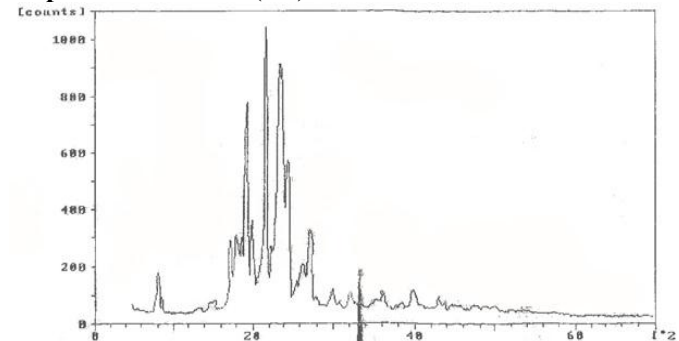


Figure 8: X-Ray Diffractogram of Aceclofenac Solid Dispersion with PEG 6000(1:1)

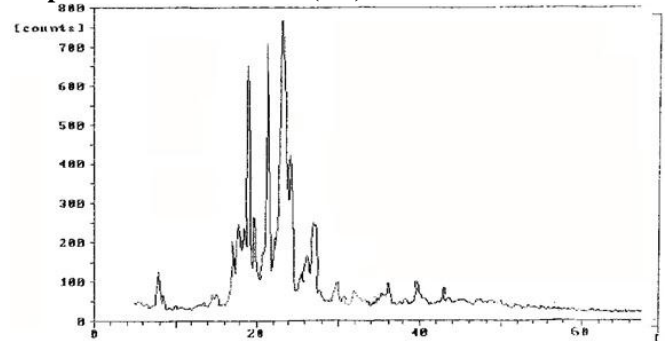


Figure 9: Scanning electron micrographs of Aceclofenac Pure Drug

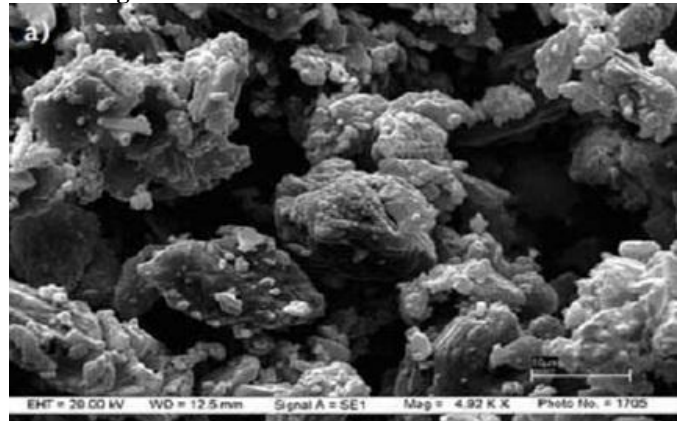


Figure 10: SEM Photograph of Aceclofenac Solid Dispersion with PEG-4000

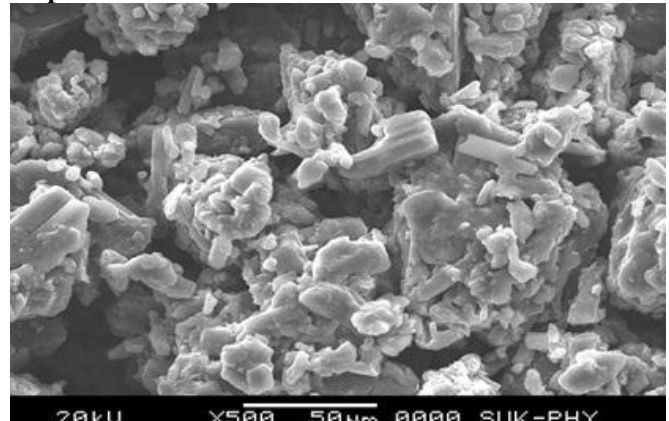


Figure 11: SEM Photograph of Aceclofenac Solid Dispersion with PVP

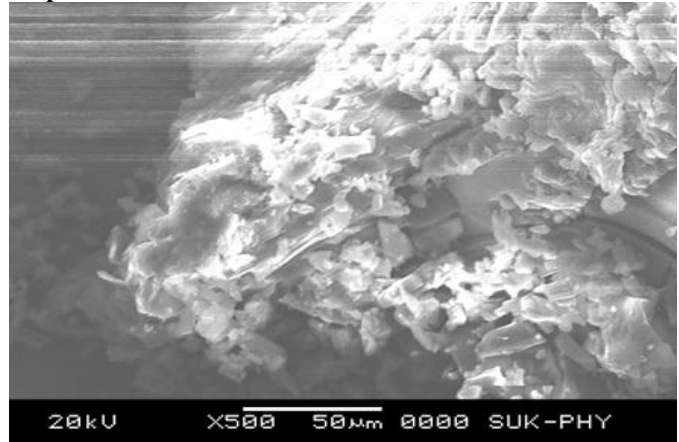
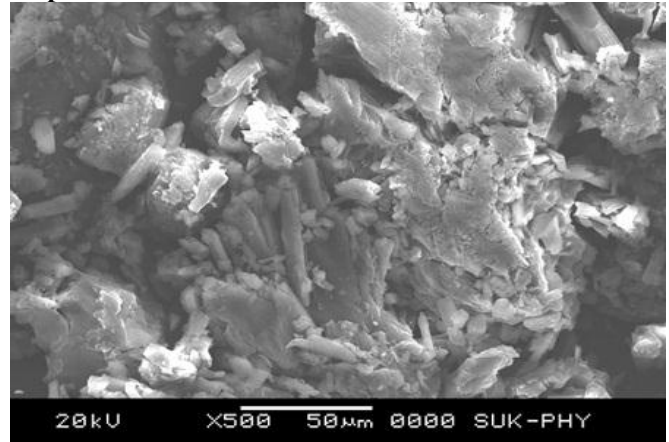
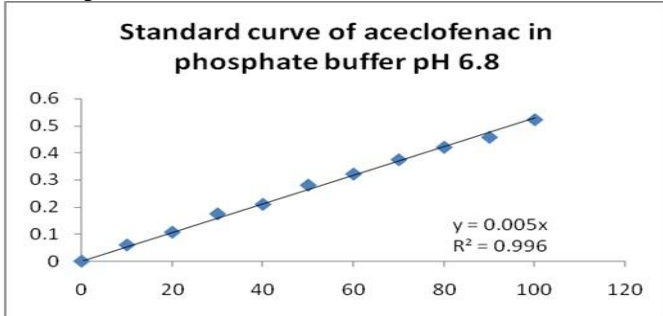


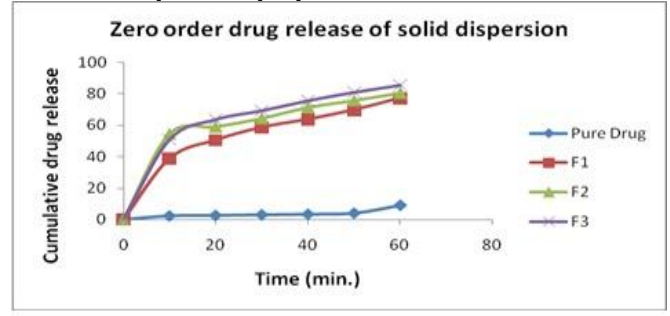
Figure 12: SEM Photograph of Aceclofenac Solid Dispersion with PEG-6000



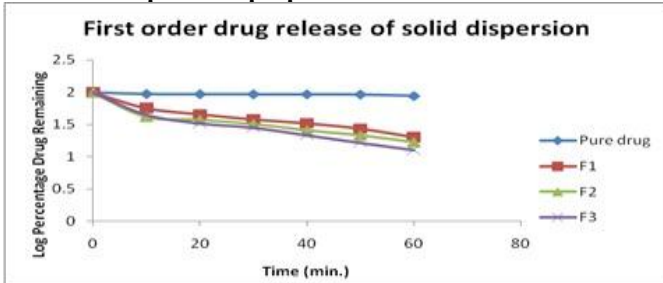
Graph 1: Standard Curve of Aceclofenac in Phosphate Buffer pH 6.8



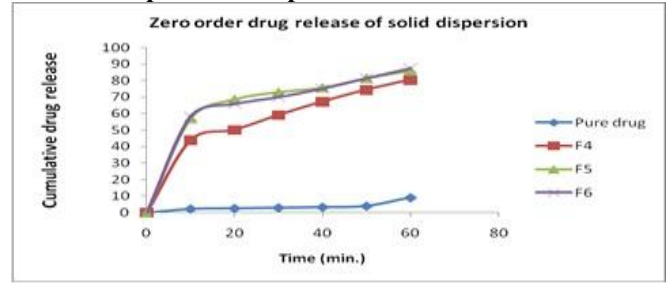
Graph 2: Zero order plots of Aceclofenac Pure Drug and it's Solid Dispersions prepared with PEG-4000



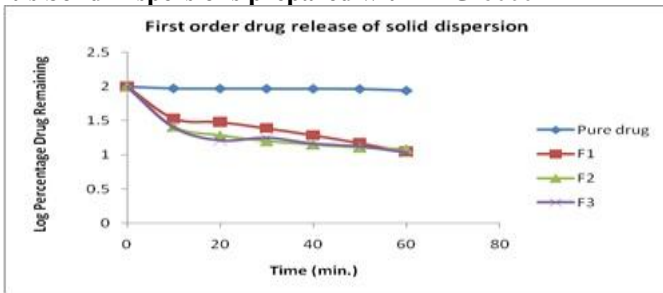
Graph 3: First order plots of Aceclofenac Pure Drug and it's Solid Dispersions prepared with PEG-4000



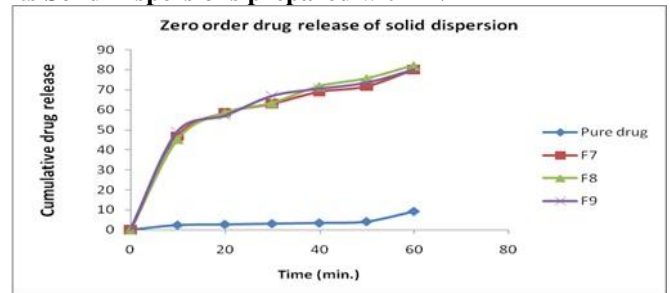
Graph 4: Zero order plots of Aceclofenac Pure Drug and its Solid Dispersions Prepared with PEG-6000



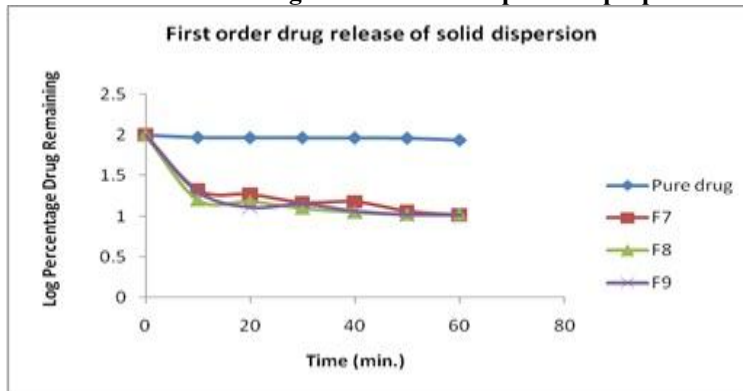
Graph 5: First order plots of Aceclofenac Pure Drug and it's Solid Dispersions prepared with PEG-6000



Graph 6: Zero order plots of Aceclofenac Pure Drug and its Solid Dispersions prepared with PVP



Graph 7: First order plots of Aceclofenac Pure Drug and it's Solid Dispersions prepared with PVP



CONCLUSION

In the present research work, Aceclofenac solid dispersions were prepared using hydrophilic polymers such as polyethylene glycol-4000, polyethylene glycol-6000 and Polyvinyl Pyrrolidone in the ratio of 9:1, 7:3 and 1:1 by solvent evaporation technique. The prepared formulations were evaluated for number of parameters like solubility,

drug content uniformity, drug-polymer interactions, differential scanning calorimetry, X-ray diffraction, scanning electron microscopy, in vitro drug release study. The concept of formulating solid dispersions of Aceclofenac containing hydrophilic polymers offers a suitable and practical approach in serving desired objective of higher solubility, faster dissolution rate and improved

bioavailability of drug. The pure drug Aceclofenac and its various formulations were subjected to scanning electron microscopy studies. The results showed the conversion of crystalline nature of the drug to amorphous form, which indicates enhanced solubility, dissolution rate and bioavailability of the drug. The *in vitro* release study was carried out on plain pure drug Aceclofenac and various solid dispersion formulations by employing pH 6.8 phosphate buffer as a dissolution medium. This shows an increased release of the drug from the dispersions in comparison to

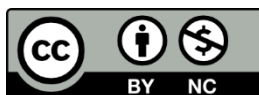
pure Aceclofenac drug. *In vitro* data of all formulations was subjected to first order plots, the graphs plotted were fairly linear and the 'r' values of all the formulations were very close to one, indicating the release mechanism followed first order kinetics.

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