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ENHANCEMENT OF DISSOLUTION RATE OF ACECLOFENAC USING HYDROPHILIC CARRIERS BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

The main objective of this study was to investigate the effect of various hydrophilic carriers on the dissolution behavior of aceclofenac. Solid dispersion was prepared using Poly Vinyl Pyrrolidone (PVP), Mannitol or Urea as hydrophilic carriers by kneading and physical mixing methods. The micromeritic properties, Fourier transform infra-red (FTIR) spectroscopy, percentage practical yield, drug content, wettability and *in vitro* drug releasewere evaluated. The Solid dispersion was prepared in 1:1, 1:3 and 1: 5 weight ratios of the drug to carrier. FTIR studies showed that there was no interaction between the drug and carrier. *In vitro* release profiles of all Solid dispersions (F1 to F18) were comparatively evaluated and also compred with pure Aceclofenac. Among the Solid dispersions, F15 (1:5) using PVP showed minimal wetting time of 13 seconds and maximum drug release of 93% compared with the other formulations. So, the solid dispersion containing PVP (1:5) by kneading method my offer suitable formulation because of its faster drug release among all formulations and low wetting time. The development of solid dispersion of Aceclofenac could be a promising approach to enhance its dissolution rate and wetability property, which may subsequently minimize the variation in its bioavailability.

KEYWORDS: Solid dispersion, Aceclofenac, Kneading method, Polyvinyl pyrrolidone, Mannitol, Urea.

INTRODUCTION

The oral route of administration is the most common and preferred method of delivery due to convenience and ease of ingestion. Even though the oral drug route is preferred, it can be problematic for number of reasons the most significant contributors being poor aqueous solubility and or poor membrane permeability of the drug molecule which results into poor bioavailability after oral administration (Abdul Hasan Sathali A., *et al* 2013 and Appa Rao B., *et al* 2010). Solid dispersions traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water soluble drugs. Molecular dispersion of the drug in polymeric carriers may lead to particle size reduction and surface area enhancement, which result in improved dissolution rates **(**Sarifulislam Howlader Md., *et al* 2012 and Deshmukh D B., *et al* 2010).

Aceclofenac is an anthranilic acid derivative and acts as an anti inflammatory drug. Aceclofenac binds the prostaglandin synthetase receptors COX-1 and COX-2 inhibiting the action of prostaglandin synthetase. The symptoms of pain are temporarily reduced, thus produce beneficial therapeutic effects. It is mainly used in the treatment of rheumatoid arthritis. According to their Biopharmaceutical Classification System (BCS), Aceclofenac belongs to class II compound having poor aqueous solubility and high permeability (Brahmankar D M., *et al* 2009). Therefore, solid dispersion technology may offer suitable approach to improve the poor solubility of Aceclofenac and subsequently reduces the variation on its bioavailability and difficulties in its solid formulation.

The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of Aceclofenac by preparing solid dispersions. Kneading and physical mixing methods with various water-soluble carriers such as PVP, Urea and Mannitol were investigated. The prepared solid dispersions was tested for practical yield (%), drug content, infrared (IR) spectroscopic and *in vitro* dissolution behavior.

2. MATERIALS AND METHODS

Aceclofenac was obtained from Madras Pharmaceuticals, Chennai. PVP, Mannitol, Urea & ethanol were obtained from Loba Chemie, Mumbai. All other chemicals used were of analytical grade.

2.1 Calibration Curve of Aceclofenac

A standard curve was prepared with different concentrations (1 to 10µg/ml) using pH 6.8 phosphate buffer solution. The absorbance of these solutions were measured at 274nm by UV- spectrophotometer. This standard curve was used to measure the concentration of the drug release from the formulation during the *in vitro* dissolution studies. (Abdul hasan sathali *et al.*, 2012).

2.2 Fourier Transform Infra red spectroscopic studies

FTIR Spectroscopic study was carried out to check the compatibility between drug and carrier. The spectrum of Aceclofenac (pure drug) and physical mixtures were recorded using Fourier transform infrared spectrometer (Spectrum RX-1 Perkin-Elmer, German). Samples were prepared using KBr (Spectroscopic grade) discs by means of hydraulic pellet press at a pressure of five tons for 30 seconds at a resolution of $4cm^{-1}$ (Irin Dewan., *et al* 2012).

2.3 Preparation of Solid dispersion

Solid dispersion was prepared by using different carriers PVP, Urea or Mannitol in different drug: carrier weight ratios of 1:1, 1:3, 1: 5 by kneading and physical mixing methods.

The various compositions of drug and hydrophilic carriers with their formulation code (F1 – F18) were listed in Table 1.

2.3.1 Kneading method

A mixture of drug (Aceclofenac) and carriers (PVP, Urea and Mannitol) in different ratios (1: 1, 1: 3 and 1: 5) were wetted with solvent (ethanol and water (1: 1 ratio) and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under room temperature for 24 hrs. Dried powder was scrapped, crushed, pulverized and passed through sieve No. 40 and stored in a desiccator. (Rabi Narayan Panigrahy., *et al* 2014).

2.3.2 Physical mixing method

A mixture of drug and carriers were prepared by mixing the different ratios (1: 1, 1: 3 & 1: 5) drug and carriers (PVP, Urea and Mannitol) in a glass mortar. Solid mass is pulverized and passed through sieve No. 40 to get uniform sized particles, and stored in desiccators until further use. (Shobit Kumar *et al* 2011 and Subhashish Debnath *et al*., 2013).

2.4 Micromeritic studies: All the formulations were evaluated for bulk density, tapped density, angle of repose, Compressibility index & Hausner's ratio.

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder.

It is measured by pouring the solid dispersion into a measuring cylinder and initial weight is noted. This initial volume is called the bulk volume. (Ankit gupta *et al.*, 2014),

$$\text{Bulk density} = \frac{\text{Mass of solid dispersion (gm)}}{\text{Bulk volume (ml)}}$$

Tapped density

It is determined by placing a graduated cylinder, containing a known mass of solid dispersion. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping is continued until no further change in volume is noted. (Aulton M E *et al*., 2002),

$$\text{Tapped density} = \frac{\text{Mass of solid dispersion (gm)}}{\text{Tapped volume (ml)}}$$

Angle of Repose

The angle of repose was determined using funnel method. Funnel that can be fit vertically with stand at 2cm height. Appropriate quantity of solid dispersion was poured into funnel and a conical pile height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ), calculated using the formula, (Ganesh Chaulang *et al*., 2008 and Veena G., *et al* 2011),

$$\tan\theta = h/r$$

$$\theta = \tan^{-1} h/r$$

Where, θ= Angle of repose.

h= height of pile (cm).

r = radius of pile (cm).

Carr's index (or) % compressibility

Carr's index is also known as % compressibility. It indicates the powder flow properties. (James W *et al*., 2006). It is expressed in percentage and is given.

$$\text{Carr's index} = \frac{\text{Tapped density - Bullk density}}{\text{Tapped density}} \times 100$$

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow (Aulton M E *et al.*, 2002). It is calculated by the following formula,

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower Hausner ratio (>1.25) indicates good flow.

Higher Hausner ratio (<1.5) indicates poor flow.

1.25-1.5 indicates normally improves flow.

2.5 Determination of Percentage practical yield: (Harinath More N *et al.*, 2007)

The % practical yield of all the prepared formulations were found out using

$$\text{Practical yield} = \frac{\text{Practical mass (solid dispersion)}}{\text{Theoretical mass (drug + carrier)}} \times 100$$

2.6 Determination of drug content

Solid dispersion equivalent to 10 mg of Aceclofenac was weighed accurately and dissolved in 10 ml of methanol, diluted with phosphate buffer pH 6.8 and absorbance was measuredat λmax =? nm by UV-spectrophotometer. (Kul Karni Parthasarathi Kesava rao *et al.*, 2012 and Mohammed Jafar *et al.*, 2010).

$$\% \text{ drug content} = \frac{\text{Sample absorbance}}{\text{Standard absorbance}} \times 100$$

2.7 Determination of wettability

Aceclofenac solid dispersions were placed in a sintered glass funnel plunging into beaker containing water such that the surface of water in the beaker remains at the same level of formulation in the funnel. Methylene blue and amaranth powder, layered uniformly on the surface of various formulations in the funnel and the time required for wetting methylene blue and amaranth powder was measured. (Venkateshkumar Krishnamoorthy *et al.*, 2011).

***2.8 In vitro* dissolution studies**

Dissolution study was carried out by using USP rotating basket apparatus (Type I) for 1 hour, with a stirring rate of 100 rpm. As per IP specifications, Phosphate buffer pH 6.8 used as dissolution medium (900 ml) and temperature was maintained at 37±0.5ºC. Solid dispersions equivalent to 100 mg of Aceclofenac was filled in hard gelatin capsules used for dissolution studies. Samples (5ml) were collected at regular interval of time (10,20,30,40,50,60 min).

The same volume of fresh buffer solution was replaced into the dissolution jar after each sample withdrawl. Similarly, dissolution test was conducted for the physical mixtures and pure drug. The absorbance of the samples was measured using Ultraviolet (UV) spectrophotometer at 274nm after suitable dilution using appropriate blank. (Abdul hasan sathali *et al.*, 2013, Shivalingam M R *et al*., 2013 and Ankit gupta *et al.*, 2014).

3. RESULTS

The λ_{max} of Aceclofenac was determined by scanning the 10µg/ml of the drug solution in phosphate buffer solution pH 6.8 by UV-spectrophotometer. It showed the λ_{max} of 274 nm. Plot of absorbance against concentration in phosphate buffer solution pH6.8 was shown in Figure 1.

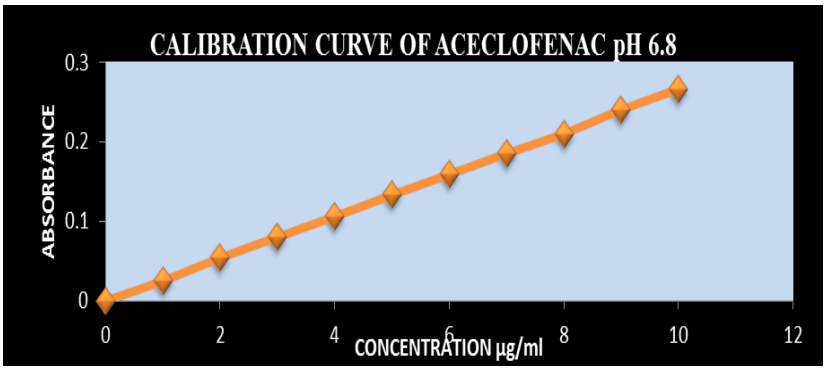

Figure: 1 Standard Curve of Aceclofenac.

FTIR spectrum of Pure Aceclofenac showed sharp characteristic peaks at 3900.20, 3566.50, 3547.21, 3028.34, 1919.31, 1770.71, 1760.70, 1506.46, 1344.43, 1253.77, 964.44, 750.31, 667.39 cm^{-1} were shown in Figures 2-8.

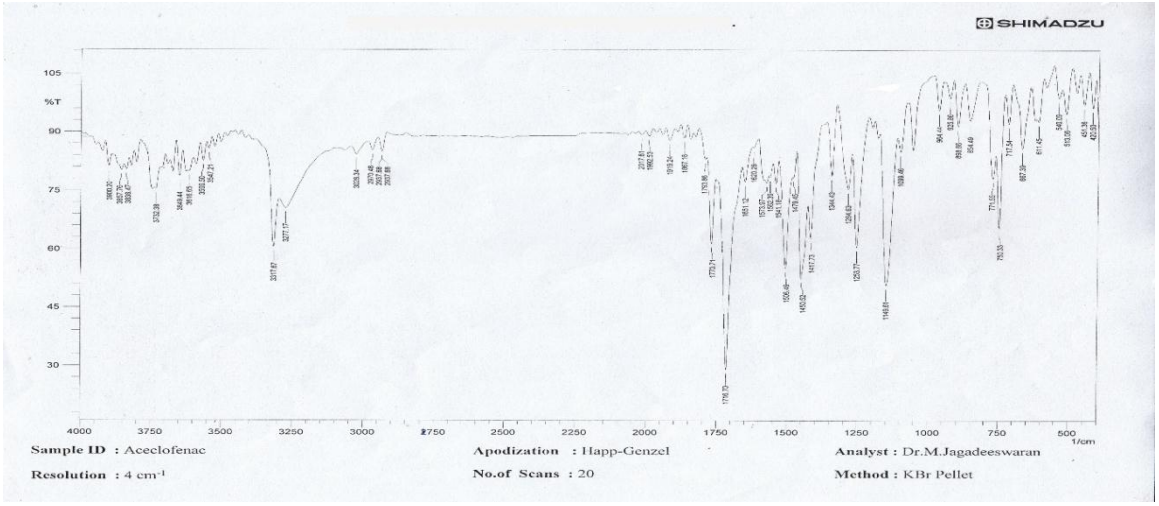

Fig: 2 Ftir Spectrum of Aceclofenac.

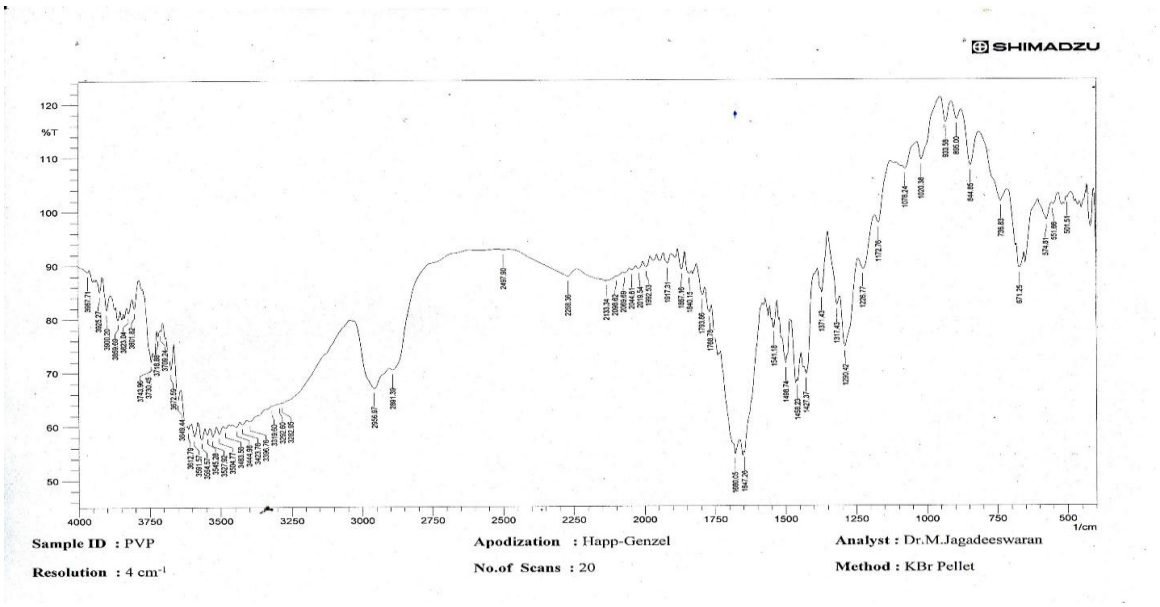

Figure: 3 Ft Ir Spectrum of Pvp.

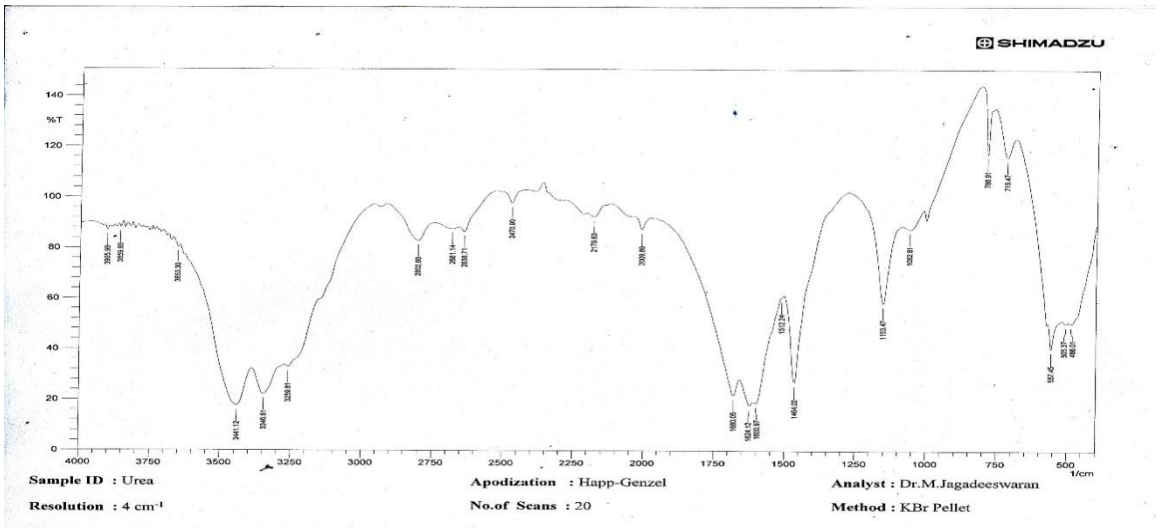

Figure: 4 FTIR Spectrum of urea.

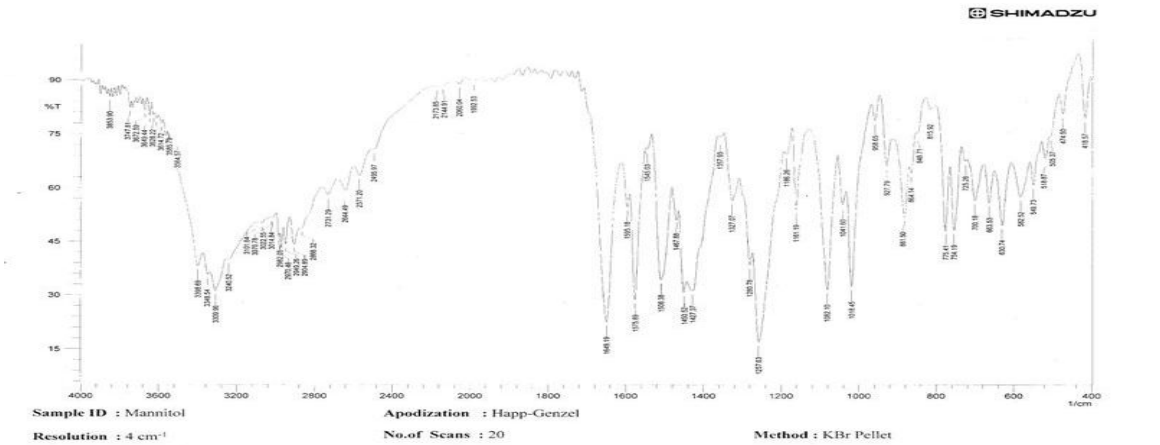

Figure: 5 FTIR Spectrum of mannitol.

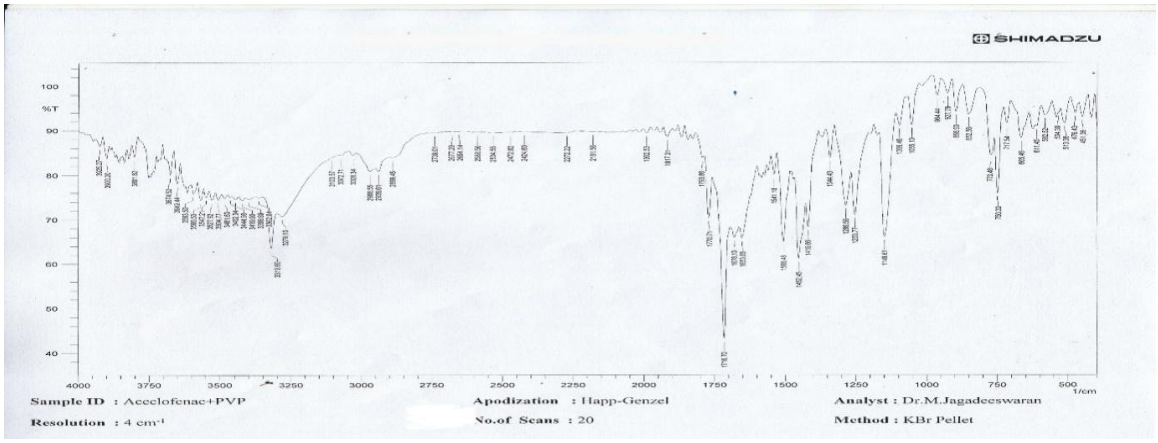

Fig: 6 Ftir Spectrum of Aceclofenac + Pvp.

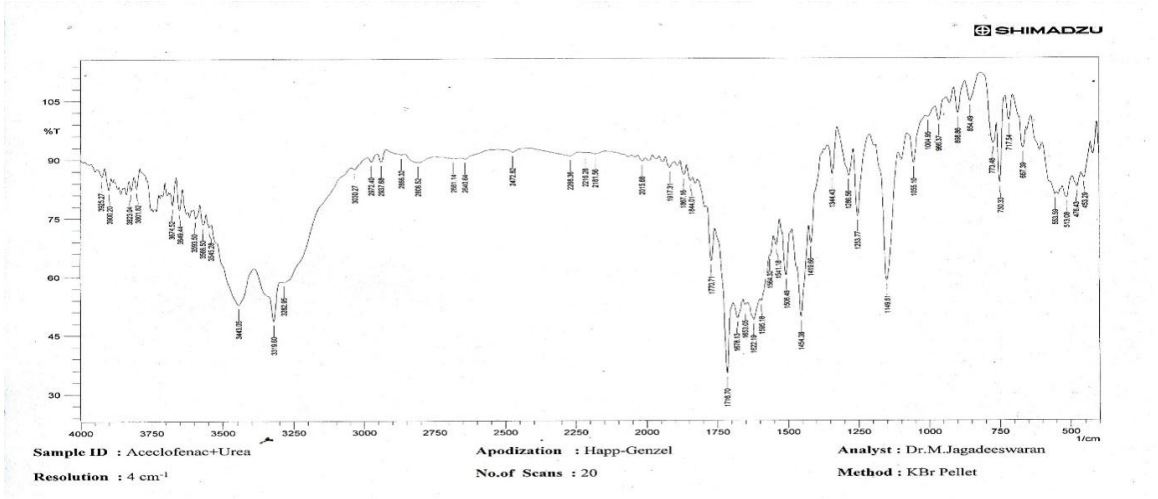

Figure: 7 FTIR Spectrum of Aceclofenac + urea.

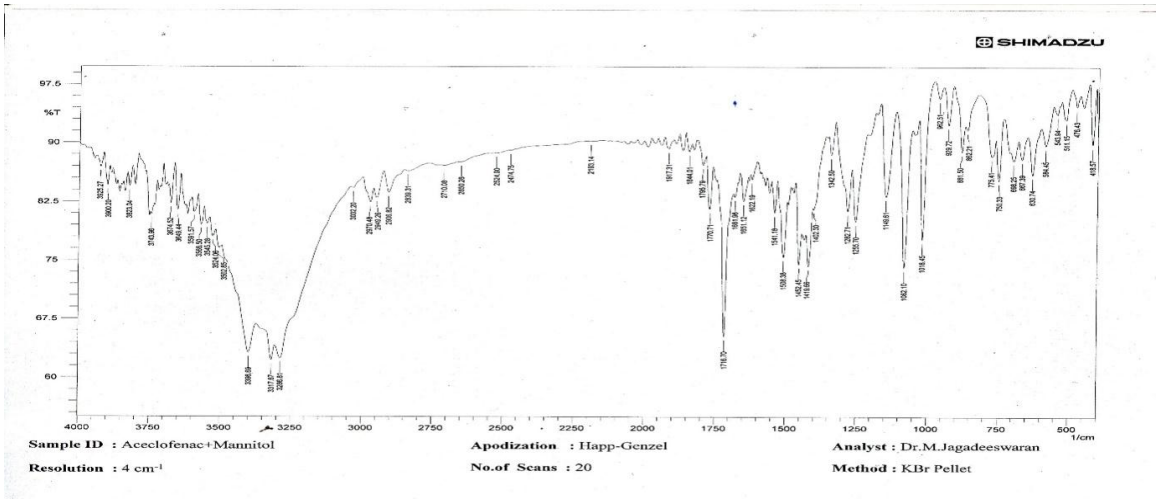

Figure: 8 FTIR Spectrum of Aceclofenac + mannitol.

Eighteen formulations were prepared using carriers (PVP, Mannitol & Urea) in different ratios by Kneading and Physical mixing methods were shown in Table 1.

Table 1: Compositions of Prepared Aceclofenac Solid Dispersions (1 Gm Aceclofeanc Is Ued In Each Experiment).

S. No	Formulation Code	Drug: Carrier Ratio		Carrier			Technique Used
				Urea	Mannitol	PVP	
1	F1	1:1		1gm	_	_	Kneading method
2	F2	1:3		3gm	_	_	
3	F3	1:5		5gm	_	_	
4	F4	1:1		1gm	_	_	Physical mixing method
5	F5	1:3		3gm	_	_	
6	F6	1:5		5gm	_	_	
7	F7	1:1		_	1gm	_	Kneading method
8	F8	1:3		_	3gm	_	
9	F9	1:5		_	5gm	_	
10	F10	1:1		_	1gm	_	Physical mixing method
11	F11	1:3		_	3gm	_	
12	F12	1:5		_	5gm	_	
13	F13	1:1		_	_	1gm	Kneading method
14	F14	1:3		_	_	3gm	
15	F15	1:5		_	_	5gm	
16	F16	1:1		_	_	1gm	Physical mixing method
17	F17	1:3		_	_	3gm	
18	F18	1:5		_	_	5gm	

All the prepared formulations were evaluated for bulk density, tapped density, angle of repose, compressibility index & Hausner ratio and the results were shown in Table 2. The results obtained for the %drug content, %particle yield and wettability studies were shown in Table 3.

Table 2: Micrometric Evaluation of Aceclofenac Solid Dispersion.

S.No	Formulation code	Bulk density(gm/ml)	Tapped density (gm/ml)	Carr's index	Hausner ratio	Angle of repose
1.	F1(1:1)	0.42	0.62	32.25%	1.4761	$21^{0}81^{1}$
2.	F2(1:3)	0.53	0.68	22.05%	1.2830	$23^{0}49^{1}$
3.	F3(1:5)	0.53	0.70	24.28%	1.3207	$23^{0}72^{1}$
4.	F4(1:1)	0.39	0.53	26.41%	1.358	$22^{0}05^{1}$
5.	F5(1:3)	0.47	0.48	2.083%	1.0212	$23^{0}44^{1}$
6.	F6(1: 5)	0.43	0.46	6.521%	1.0697	$26^{0}28^{1}$
7.	F7(1:1)	0.40	0.49	18.36%	1.1750	$21^{0}47^{1}$
8.	F8(1:3)	0.45	0.48	6.25%	1.0666	$22^{0}68^{1}$
9.	F9(1:5)	0.46	0.54	14.81%	1.1739	$23^{0}62^{1}$
10.	F10(1:1)	0.34	0.37	10%	1.0882	$19^{0}70^{1}$
11.	F11(1:3)	0.36	0.51	29.4%	1.4166	$24^{0}88^{1}$
12.	F12(1:5)	0.33	0.44	25%	1.3333	$29^{0}42^{1}$
13	F13(1:1)	0.41	0.5	18%	1.2195	$18^{0}70^{1}$

14	F14(1:3)	0.43	0.49	12.24%	1.1395	$18^{0}80^{1}$
15	F15(1:5)	0.42	0.49	14.28%	1.1666	$20^{0}70^{1}$
16	F16(1:1)	0.39	0.48	18.75%	1.2307	$21^{0}70^{1}$
17	F17(1:3)	0.4	0.41	2.43%	1.025	$21^{0}44^{1}$
18	F18(1:5)	0.41	0.47	12.76%	1.1463	$23^{0}64^{1}$

Table 3: % Practical Yield, Drug Content & Wetting Time of Aceclofenac Solid Dispersion.

S. No	Formulation Code	% Practical Yield	% Drug Content	Wetting Time(Seconds)
1.	F1(1:1)	95	97.17	20
2.	F2(1:3)	94	97.44	17
3.	F3(1:5)	94.5	96.15	14
4.	F4(1:1)	95	96.66	45
5.	F5(1:3)	96.6	97.69	36
6.	F6(1:5)	94.5	96.66	30
7.	F7(1:1)	94	96.92	25
8.	F8(1:3)	93.3	95.89	21
9.	F9(1:5)	93	98.46	17
10.	F10(1:1)	94	95.12	47
11.	F11(1:3)	93	95.64	38
12.	F12(1:5)	95	98.46	33
13	F13(1:1)	93	97.22	17
14	F14(1:3)	94	97.12	15
15	F15(1 :5)	95	94.22	13
16	F16(1:1)	93	94.3	39
17	F17(1:3)	92	96	30
18	F18(1:5)	93	94	21
19	Pure drug	-	-	99

In vitro dissolution study was performed for all the formulations and the results were shown in Figure 9-14.

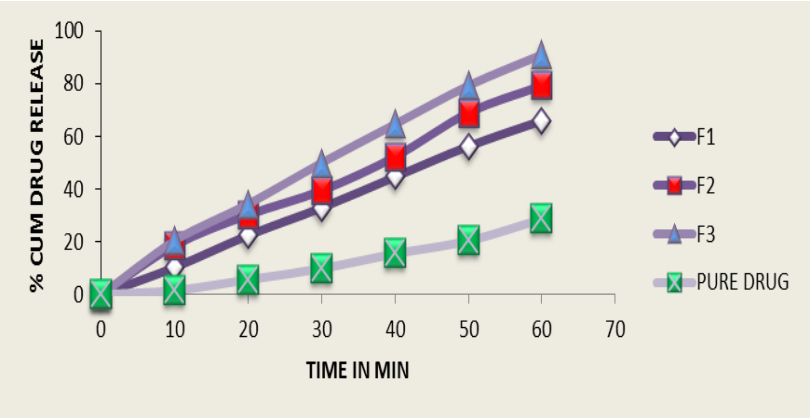

Figure: 9 Comparison of *in vitro* drug release profile of aceclofenac solid dispersion using urea (Kneading Method).

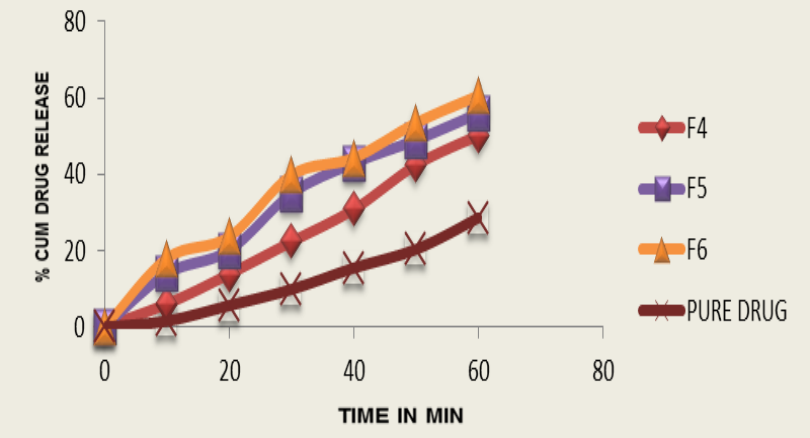

Figure: 10 Comparison of *in vitro* drug release profile of physical mixing using urea (Physical Mixing Method).

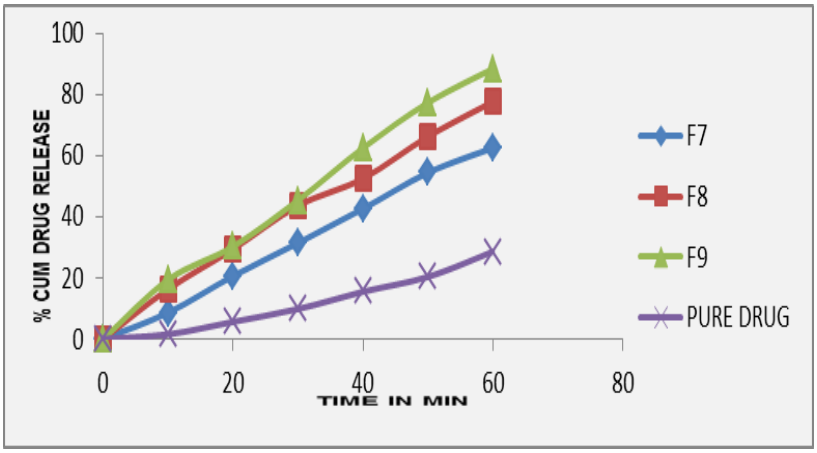

Figure: 11 Comparison of *in vitro* drug release profile of aceclofenac solid dispersion using mannitol (Kneading Method).

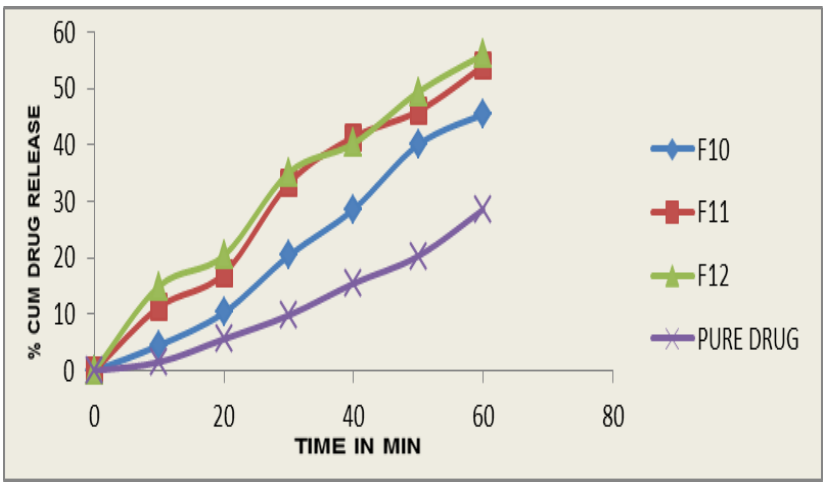

Figure: 12 Comparison of *in vitro* drug release profile of aceclofenac soliddispersion using mannitol(Physical Mixing Method).

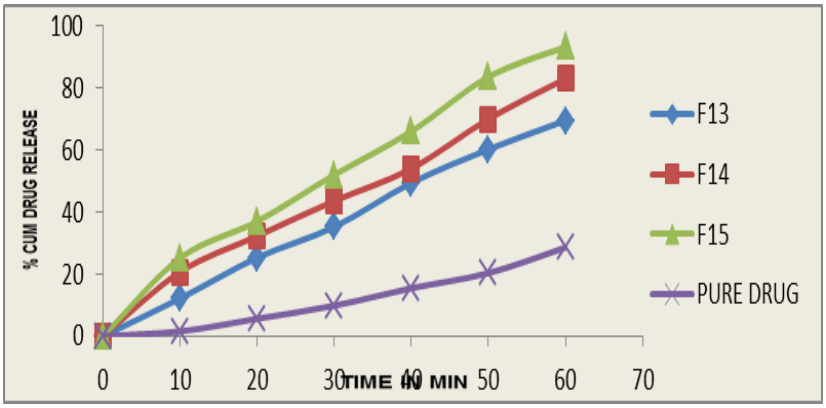

Figure: 13 Comparison of *in vitro* drug release profile of aceclofenac solid dispersion using PVP (Kneading Method).

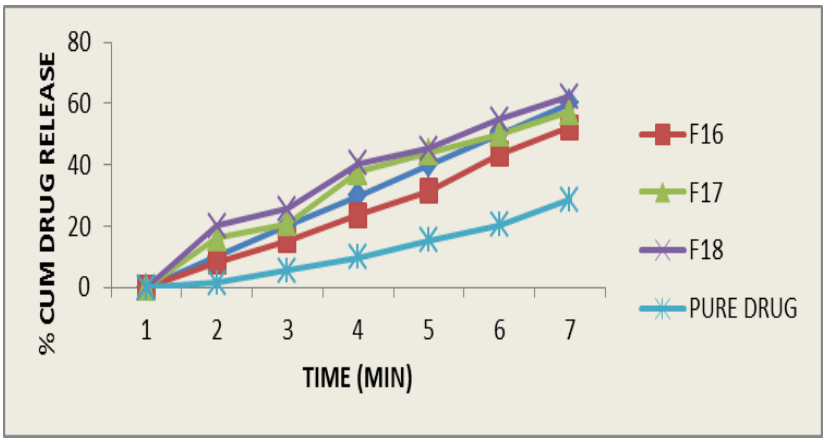

Figure: 14 Comparison of *in vitro* drug release profile of aceclofenac solid dispersion using PVP (Physical Mixing Method).

From the results, it was observed that, among the three carriers, PVP was found to have greater release rate than Mannitol and Urea.

PVP > Mannitol > Urea

The increase in dissolution rate of the drug in prepared solid dispersions by both the Physical mixing and Kneading methods were obtained because of the enhanced wettability and hydrophilic nature of the carriers in the formulations. The best formulation was selected based on the results obtained from the wettability and *in vitro* release studies.

DISCUSSION

From the FTIR spectral studies, it was suggested that there was no interactions between the drug and polymer.

There was no considerable loss in the yield during the process & the drug distribution was uniform all the formulations**.** Among all the formulations, minimum mean wetting time (13 seconds) was observed for the dispersion containing PVP prepared by kneading method.

In vitro dissolution studies showed that there was marked increase in the dissolution rate of Aceclofenac from all the solid dispersions when compared with pure drug. From the *in vitro* drug release profile, it could be seen that formulation F15 containing PVP (1:5 ratio of drug: carrier) showed higher dissolution rate 93% at 1 hour, so it was considered as the best formulation**.** The dissolution rate of Aceclofenac was found to be increasing in the following order.

Pure drug < Physical mixing < Kneading

This may be due to the presence of water soluble carrier, which fastens wettability and dissolution of the drug by decreasing the drug particle size in the course of the solid dispersion preparation.

CONCLUSION

The solid dispersions of a poorly water soluble drug (Aceclofenac) via kneading and physical mixing methods were used in order to improve the solubility.

The objective achieved and the result suggested that kneading method can be employed successfully for improvement of dissolution profile and solubility of solid dispersions of poorly water soluble drug.

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