SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OF ACECLOFENAC BY SOLID DISPERSION TECHNIQUE

Presented By:

Khalid Bashir Mir
PhD. Research Scholar
Novel Drug Delivery Division
Deptt. of Pharmaceutical Sciences
Faculty of Applied Scs. & Tech.
University of Kashmir

Co-Authors:

Dr. Nisar Ahmed Khan
Sr. Assistant Professor
Deptt. of Pharmaceutical Sciences
Faculty of Applied Scs. & Tech.
University of Kashmir

And

Mohi Durakshan
Sheri Kashmir Ins. of Med Scs.

4th International Summit on GMP, GCP & Quality Control
OMICS International Conference series

Why do we need to go for this ?

- Because, almost 40% of the new chemical entities (NCEs) discovered nowadays, from any source face solubility problems in physiological fluids, thereby leading to poor bioavailbility.
- So, the solubility behavior of such drugs remains one of the most ambitious task in the formulation development.
- As, the solubility of drug dictates the ease with which pharmaceutical formulations can be obtained.
- Such drugs have been categorized as **BCS class II drugs, i.e., Drugs with low solubility and high permeability.**

	SOLUBILITY	PERMEABILITY
CLASS I	**High**	**High**
CLASS II	**Low**	**High**
CLASS III	**High**	**Low**
CLASS IV	**Low**	**Low**

Techniques Available To Improve Solubility Of Poorly Soluble Drugs

(I) Physical Modifications

❖ Particle size reduction	Micronization
❖ Modification of crystal habit	Polymorphs
❖ Drug dispersion in carriers	**Solid dispersions**
❖ Complexation	Cyclodextrins
❖ Solubilization by surfactants	

(II) Chemical Modifications Prodrugs

(III) Miscellaneous Methods Use of Surfactants etc.

Solid Dispersion

- **Definition**

  A solid dispersion can be defined as the dispersion of one or more active ingredients in an inert carrier matrix in a solid-state prepared by a melting /fusion, solvent evaporation, etc.

- **Mechanism of action of SDs to improve aqueous solubility**

  1. Reduction of the particle size of the incorporated drug

  2. Partial transformation of crystalline state to the amorphous state

  3. Improved wetting of the drug

  4 Reduced aggregation and agglomeration

Advantages of Solid Dispersions

In our present study, we have designed and prepared solid dispersions with enhanced solubility/dissolution rate characteristics of poorly-water soluble drugs (Aceclofenac). This type of dosage form will offer following advantages:

- **Improved bioavailability**
- **Minimum chances of under dosing**
- **Reduced fluctuations in plasma drug level**
- **More uniform drug effect**
- **Better patient compliance**

Commercial formulations of solid dispersions

(Anupama K et al., 2011)

Brand Name	Drug Name	Carrier Used	Company
GrisPeg	Griseofulvin	PEG	VIP Pharma.
Intelence	Etavirine	HP; MCC	Tibotec Pharma.
Cesamet	Nabilone	PVP	Valent Pharma.
Sporanox	Itraconazole	HPMC	Janssen Pharma.
Norvir	Ritonavir	PVP;VA	Abott Labs

Experimental Section

Physical Characterization of Aceclofenac

Nature	Crystalline powder
Color	White
Taste	Slightly bitter
Odor	Odorless

Melting point:

Observed	150 ºC	
Reported	149 to 153 ºC	**(Praveen B et al, 2011)**

Solubility practically insoluble in water at 25 ºC

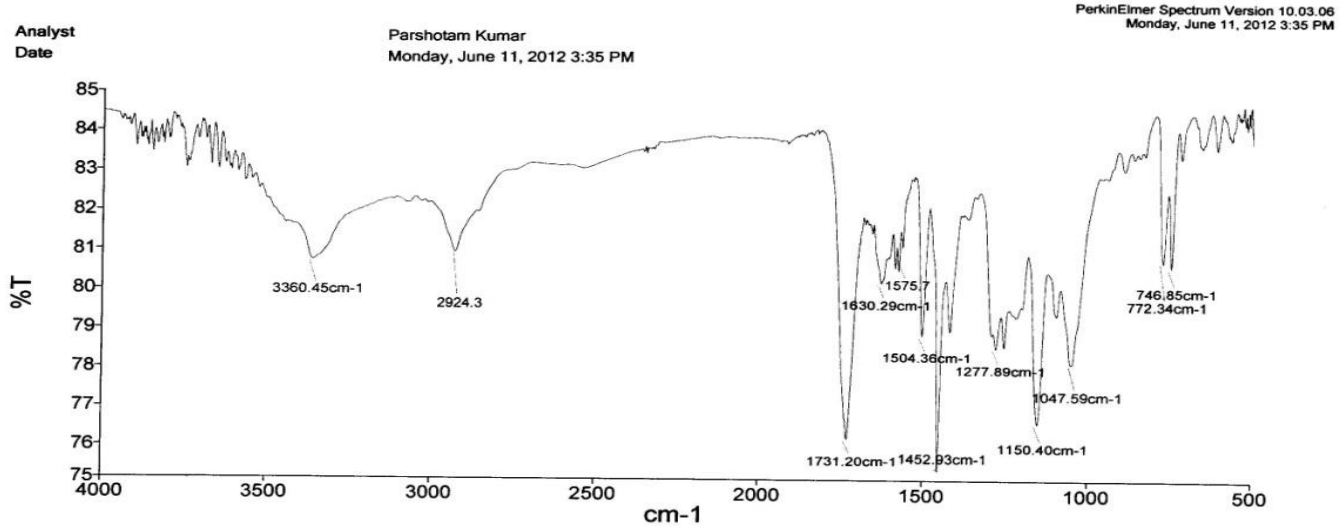
Observed	0.088 mg/ml	
Reported	0.091 mg/ml	**(Rupal J et al, 2009)**

Identification Tests

I. By IR spectral analysis of Aceclofenac

Functional groups	Absorption peaks (cm)
C=O stretching	1770.81
	1716.8
OH stretching	2970.64
CH stretching	2937.85
superimposed on OH	
stretching	
NH stretching	3319
C-Cl	669.5

IR spectrum of Aceclofenac



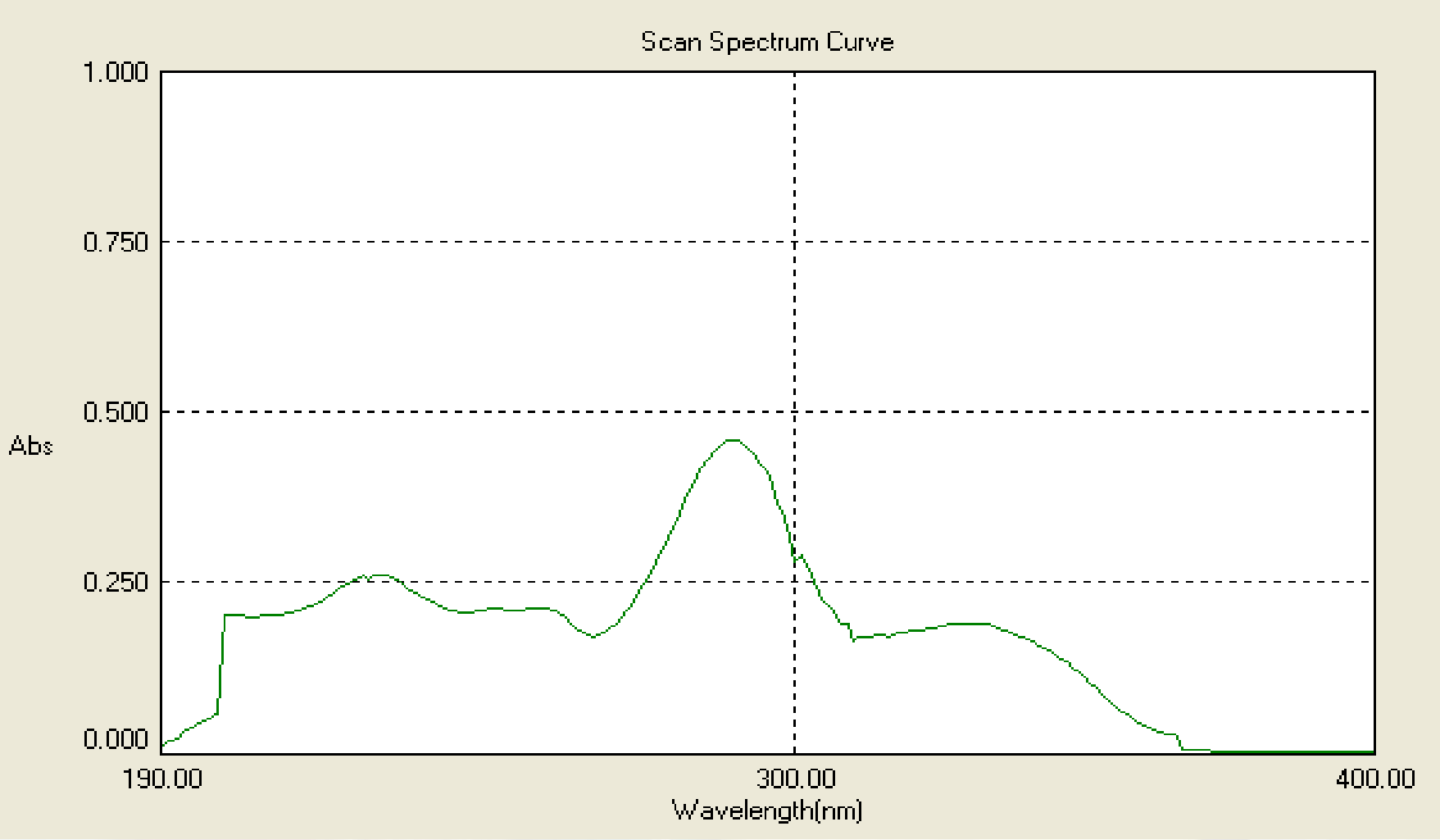
Sample Name	Description	Quality Checks
ACE-3_1	NEAT	The Quality Checks give rise to multiple warnings for the sample.

Identification Tests *(Contd.)*

II. By UV spectral analysis

	λmax	Solvent	Reference
Observed	274 nm	0.1 NHCl	
	275 nm	PB pH 7.4	
Reported	275 nm		(Praveen B et al, 2011)

UV spectrum of Aceclofenac



IDENTIFICATION TESTS (Contd.)

III. By Melting point determination: Capillary Technique

	Temperature ° C	Reference
Observed	150	
Reported	149 to 153	(Praveen B et al, 2011)

Observation

On the basis of reports from IR ,UV spectral analysis & also, from melting point determination, it was confirmed that the material was authenticated sample of Aceclofenac.

Preparation of calibration curve of Aceclofenac in 0.1 N HCl

Standard Stock Solution (100 µg/ml): 10 mg Aceclofenac in 100 ml 0. 1 N HCl

Aliquots of 0.2 to 1.2 ml of standard stock solution were transferred to a series of 10 ml volumetric flasks and volume made upto 10 ml with 0. 1 N HCl.

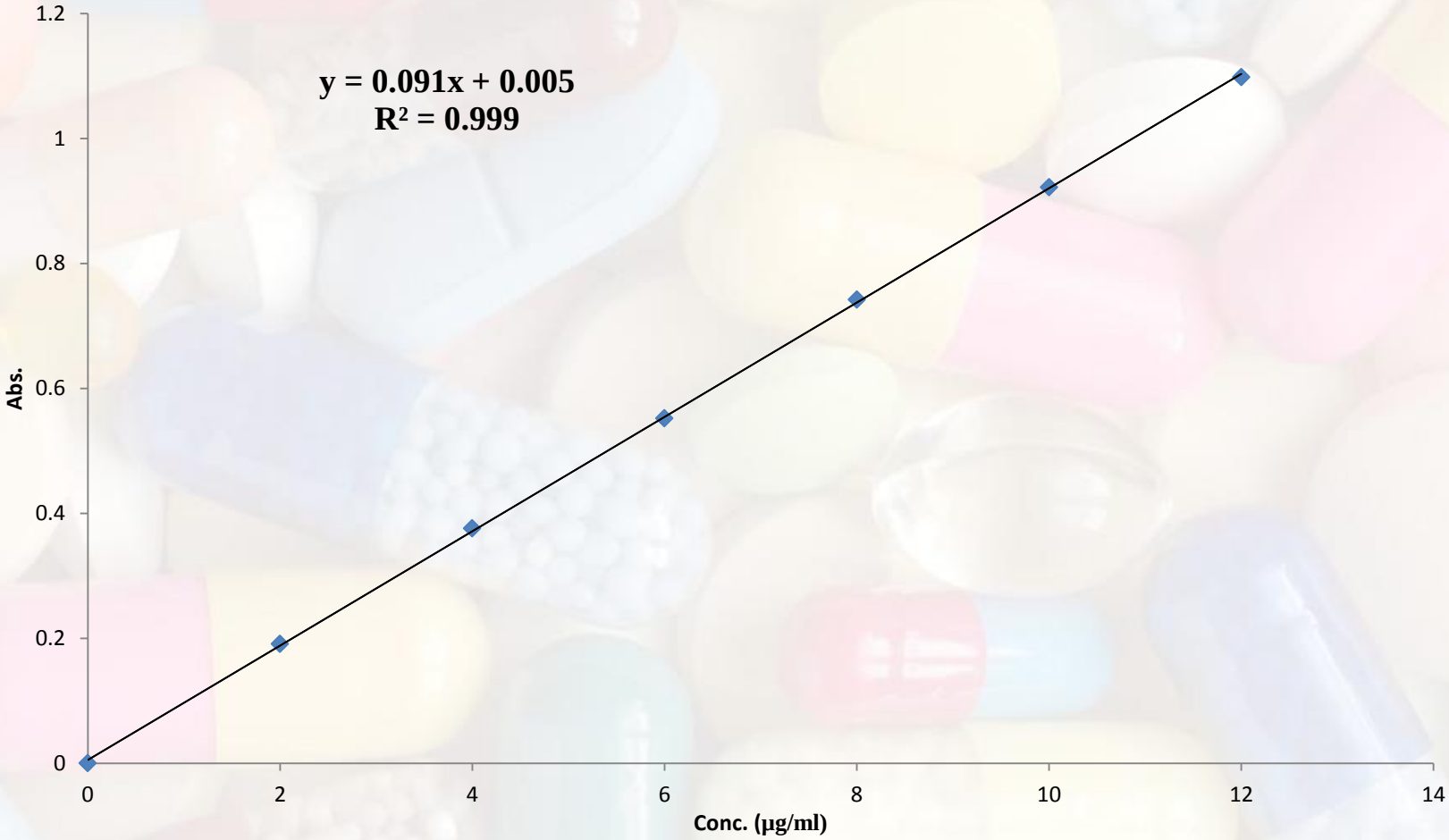
Dilutions were scanned at 274 nm against blank.

The calibration curve was plotted.

Calibration curve of Aceclofenac in 0.1 N HCl

Concentration (µg/ml)	Mean absorbance at 274 nm (n=3) ±SD	Regressed Absorbances
0	**0**	**0**
2	0.190 ± 0.012	0.188
4	0.376 ± 0.011	0.371
6	0.552 ± 0.015	0.554
8	0.742 ± 0.014	0.737
10	0.922 ± 0.013	0.921
12	1.098 ± 0.017	1.103
R^2	**0.999**	

Calibration curve of Aceclofenac in 0.1 N HCl



Preparation of calibration curve of Aceclofenac in PB pH 7.4

Standard Stock Solution (100 µg/ml): 10 mg Aceclofenac in 100 ml PB pH 7.4

Aliquots of 0.2 to 1.6 ml of standard stock solution were transferred to a series of 10 ml volumetric flasks and volume made upto 10 ml with PB pH 7.4.

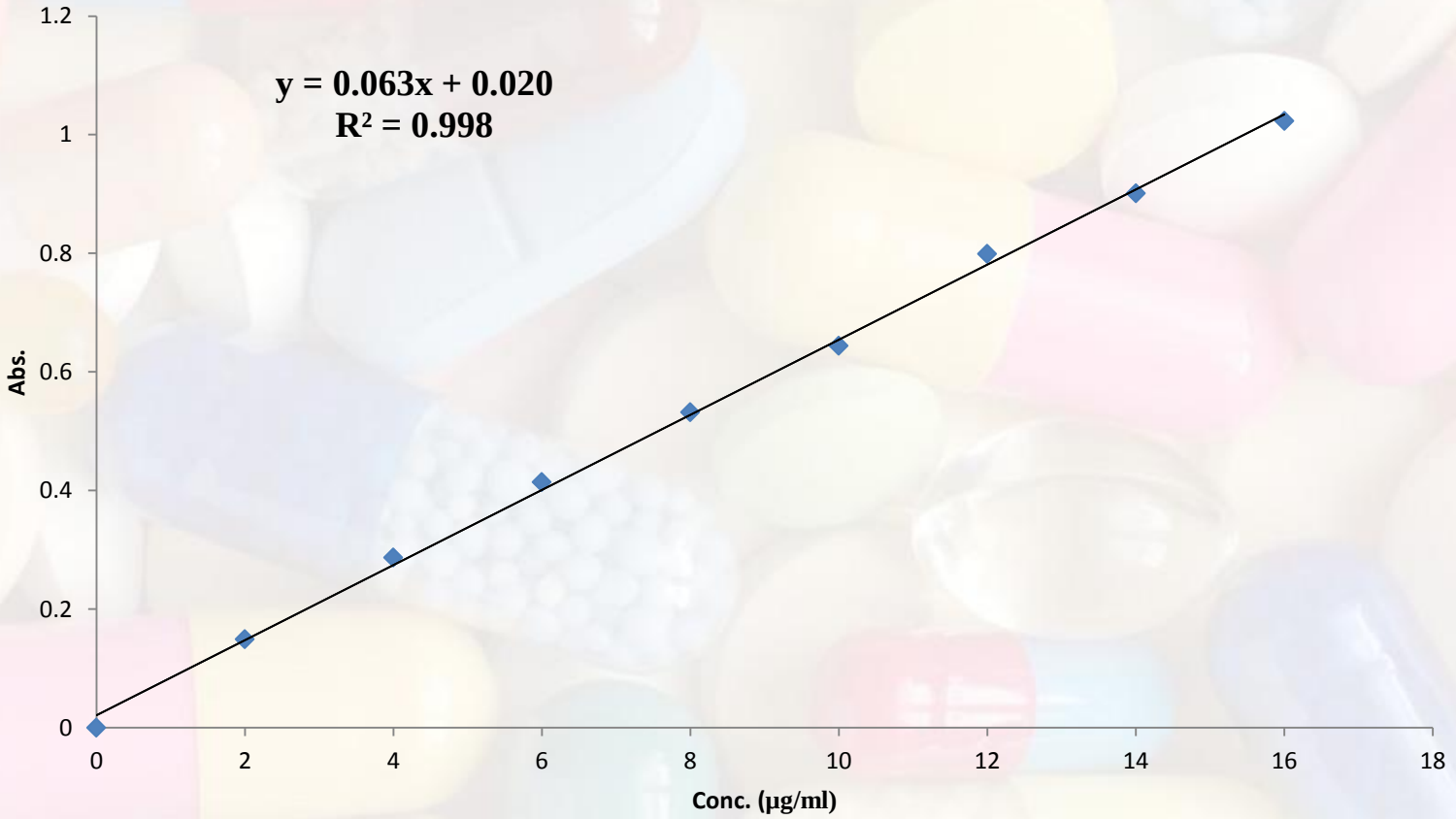
Solutions were scanned at 275 nm against blank.

The calibration curve was plotted.

Calibration curve of Aceclofenac in PB pH 7.4

Concentration (µg/ml)	Mean absorbance at 275 nm (n=3) ±SD	Regressed Absorbances
0	0	0
2	0.149 ± 0.017	0.148
4	0.287 ± 0.021	0.274
6	0.414 ± 0.011	0.401
8	0.532 ± 0.016	0.529
10	0.644 ± 0.022	0.655
12	0.799 ± 0.013	0.782
14	0.901 ± 0.017	0.908
16	1.023 ± 0.011	1.035
R^2	**0.998**	

Calibration curve of Aceclofenac in PB pH 7.4



Formulation Plan for solid dispersions of Aceclofenac

Formulation Code	Carrier Used	Amount of Carrier taken (mg)	Amount of pure Aceclofenac taken (mg)	Drug : Carrier ratio
FAC-I	PEG-4000	350	350	1:1
FAC-II		700	350	1:2
FAC-III		1050	350	1:3
FAC-IV	PEG-6000	350	350	1:1
FAC-V		700	350	1:2
FAC-VI		1050	350	1:3
FAC-VII	Urea	350	350	1:1
FAC-VIII		700	350	1:2
FAC-IX		1050	350	1:3
FAC-X	Mannitol	350	350	1:1
FAC-XI		700	350	1:2
FAC-XII		1050	350	1:3

Preparation of Solid Dispersions

By Solvent Evaporation (SE) Method

SDs of Aceclofenac with carriers in different ratios as mentioned in the formulation plan were prepared by SE method.

In this menthod, weighed quantities of individual carriers were dissolved in solvent blend ethanol & dichloromethane (1:1) & pure drug was slowly added with constant stirring. The solvent was completely removed by evaporation. The mass obtained was dried in hot air oven at 20 ºC. and. The product obtained was pulverized in mortar and then passed through sieve no. 80. The SDs obtained were kept in closed glass vials and stored in dessicator till further analysis.

Evaluation of Solid dispersions of Aceclofenac

Solubility studies

Saturation solubility studies of pure drug & SDs were conducted independently in both the solvents (0.1 N HCl & PB pH 7.4).

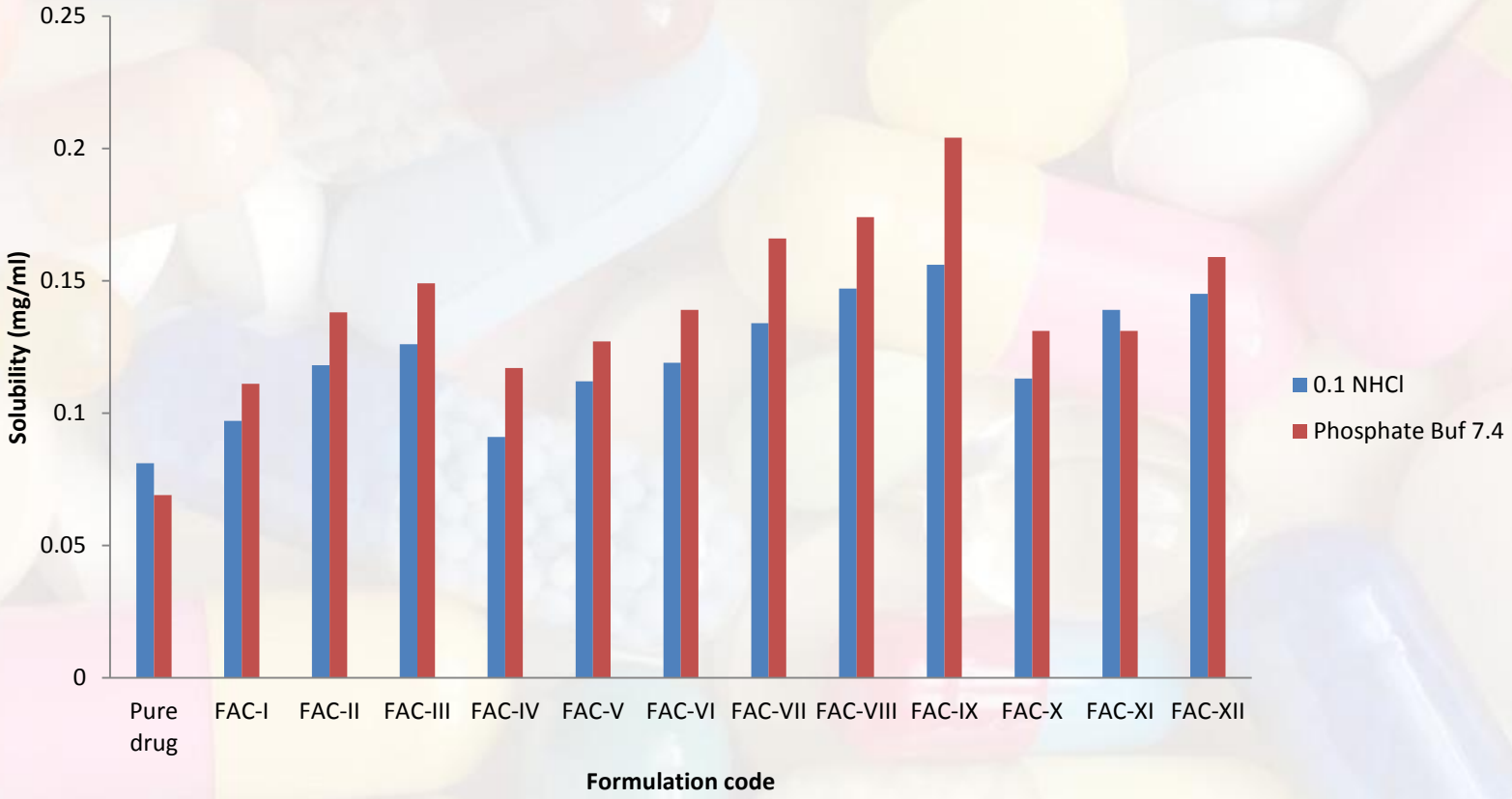
For this, excess of pure drug & SDs were taken separately in 25 ml stoppered conical flasks and the volume of solvents was kept constant to 15 ml. All the flasks were shaken at 50 rpm for 48 hours at 37 ± 0.5 ºC in orbital shaker incubator. The samples were then kept overnight for equilibration and then filtered through whatman filter paper (Grade 41). The filtrate of pure drug and each SD was diluted with 0.1 N HCl and PB pH 7.4 separately and the amount of drug was estimated spectrophotometrically at λmax 274 nm and 275 nm respectively.

(Higuchi T et al, 1965)

Comparative solubility profiles of pure drug & SDs in 0.1 NHCl & PB pH 7.4

Formulation Code	Mean solubility (mg/ml) in 0.1 N HCl (n=3) ± SD	Mean solubility (mg/ml) in PB pH 7.4 (n=3) ± SD
Pure drug	0.081 ± 0.003	0.069 ± 0.004
FAC-I	0.097 ± 0.006	0.111 ± 0.003
FAC-II	0.118 ± 0.004	0.138 ± 0.005
FAC-III	0.126 ± 0.005	0.149 ± 0.004
FAC-IV	0.091 ± 0.002	0.117 ± 0.006
FAC-V	0.112 ± 0.004	0.127 ± 0.007
FAC-VI	0.119 ± 0.002	0.139 ± 0.004
FAC-VII	0.134 ± 0.005	0.166 ± 0.005
FAC-VIII	0.147 ± 0.003	0.174 ± 0.004
FAC-IX	0.156 ± 0.001	0.204 ± 0.003
FAC-X	0.113 ± 0.005	0.131 ± 0.007
FAC-XI	0.139 ± 0.006	0.131 ± 0.004
FAC-XII	0.145 ± 0.004	0.159 ± 0.004

Comparative solubility profiles of pure drug & SDs in 0.1 NHCl & PB рң 7.4



Observation

As from the saturation solublity studies, it was observed that out of 12 SD formulations, only 4 SD formulations viz; FAC-III, FAC-VI, FAC-IX & FAC-XII showed better solubility enhancement than the pure drug and rest of the 8 SD formulations in both the solvents.

So, only 4 SD formulations viz; FAC-III, FAC-VI, FAC-IX & FAC-XII were evaluated for *in-vitro* dissolution rate studies against the pure drug.

Evaluation of Solid dispersions of Aceclofenac *(contd.)*

***In-Vitro* Dissolution studies**

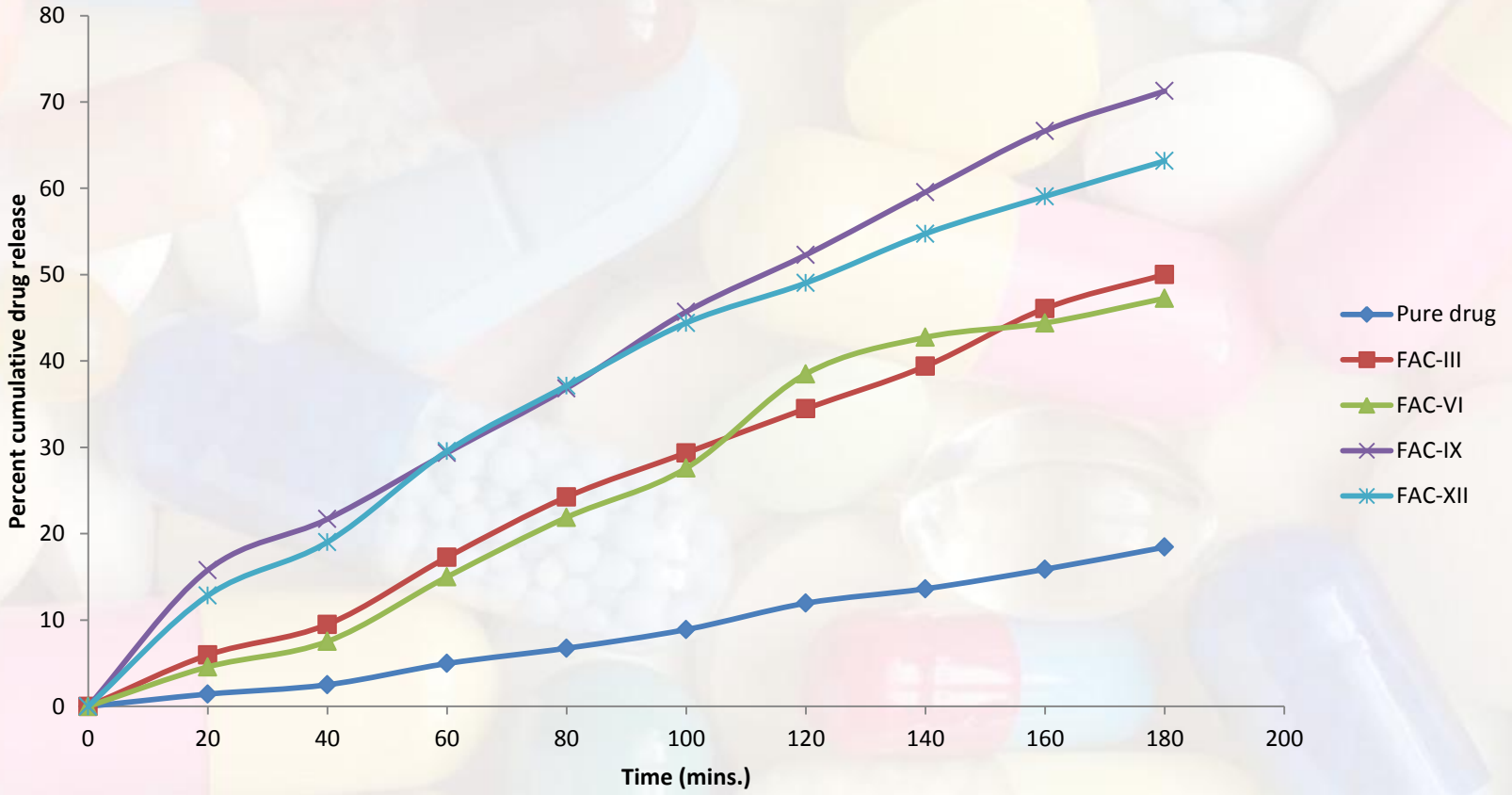
In-vitro release studies of pure drug and chosen formulations on the basis of saturation solubility studies were done in USP Paddle type-II dissolution apparatus at rpm 50 and temperature 37± 0.5 ºC using separately 900 ml of 0.1 NHCl and PB pH 7.4 as the dissolution media.

Samples (5 ml each) were withdrawn at regular time intervals. The media were replenished with 5 ml of fresh 0.1 NHCl and PB pH 7.4 each time time to maintain sink conditions. The samples were subjected to UV analysis after being suitably diluted with the respective dissolution medium. **(Higuchi T et al, 1965))**

Comparative *In-vitro* dissolution profiles of pure drug & SDs in 0.1 NHCl

Time (mins.)	Percent cumulative drug release				
	Pure drug	FAC-III	FAC-VI	FAC-IX	FAC-XII
0	0	0	0	0	0
20	1.427	5.952	4.575	15.788	12.831
40	2.509	9.493	7.526	21.691	19.031
60	4.968	17.263	15.001	29.362	29.558
80	6.739	24.247	21.886	36.837	37.132
100	8.903	29.362	27.591	45.692	44.411
120	11.952	34.476	38.509	52.283	49.034
140	13.624	39.394	42.739	59.558	54.739
160	15.886	46.083	44.411	66.641	59.069
180	18.444	50.017	47.263	71.263	63.169

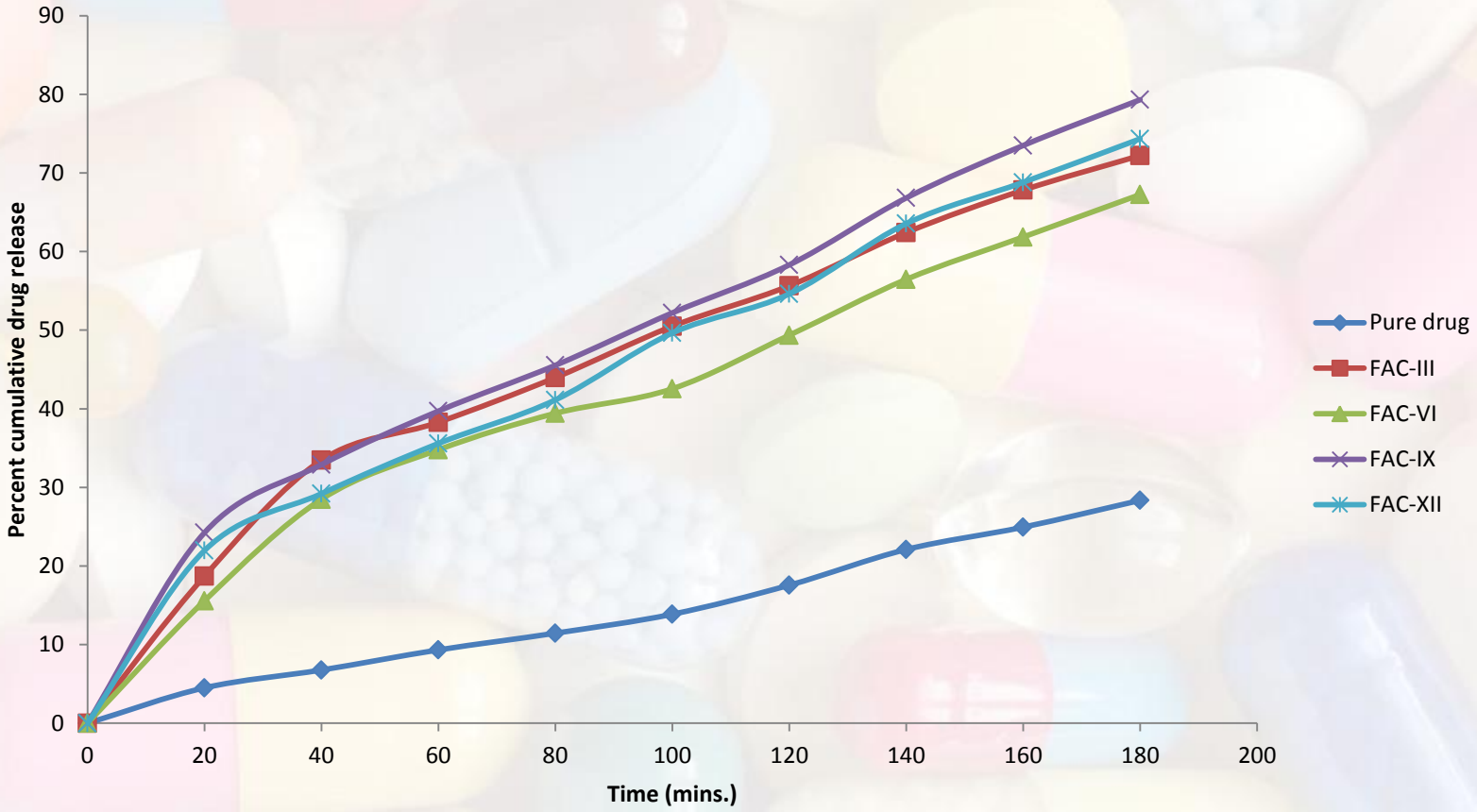
Comparative *In-vitro* dissolution profiles of pure drug & SDs in 0.1 NHCl



Comparative *In-vitro* dissolution profiles of pure drug & SDs in PB рн 7.4

Time (mins.)	Percent cumulative drug release				
	Pure drug	FAC-III	FAC-VI	FAC-IX	FAC-XII
0	0	0	0	0	0
20	4.496	18.692	15.568	24.228	21.957
40	6.767	33.455	28.486	32.887	29.196
60	9.322	38.281	34.783	39.701	35.584
80	11.452	43.961	39.417	45.521	41.121
100	13.865	50.492	42.541	52.193	49.638
120	17.556	55.632	49.354	58.297	54.606
140	22.098	62.414	56.452	66.815	63.551
160	24.938	67.808	61.846	73.486	68.802
180	28.345	72.209	67.242	79.307	74.338

Comparative *In-vitro* dissolution profiles of pure drug & SDs in PB рн 7.4



Observation

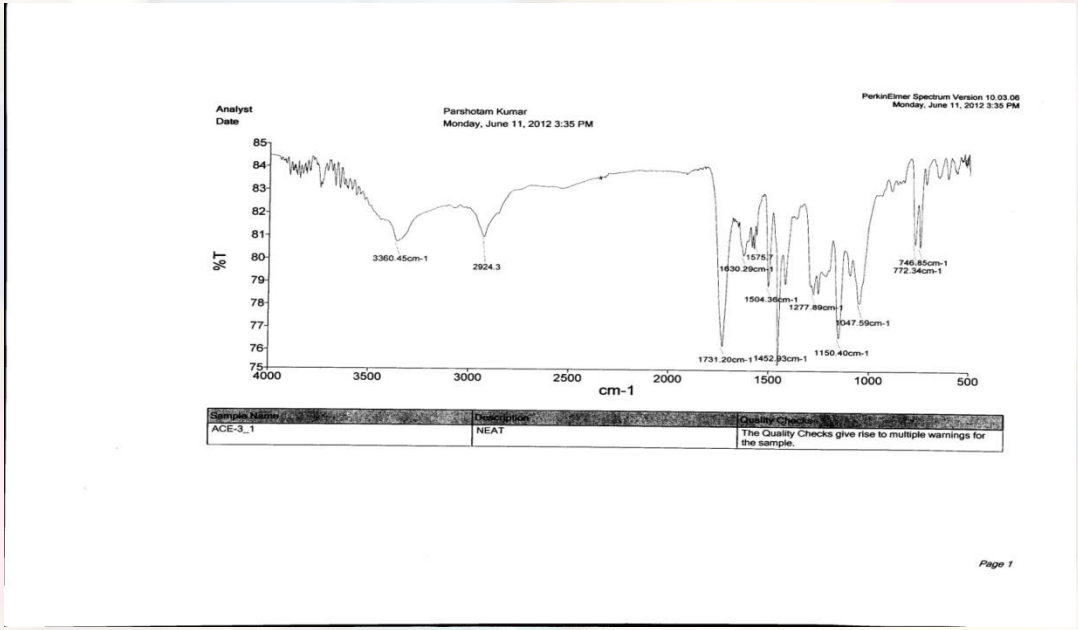
As from the *in-vitro* dissolution rat*e* studies, it was observed that all the 4 SD formulations viz; FAC-III, FAC-VI, FAC-IX & FAC-XII showed better dissolution rate enhancement than the pure drug.

So, all the 4 SD formulations were put to further characterization studies like Interaction, surface morphology; percent practical yield, percent drug content & wetting time.

Interaction studies by FTIR

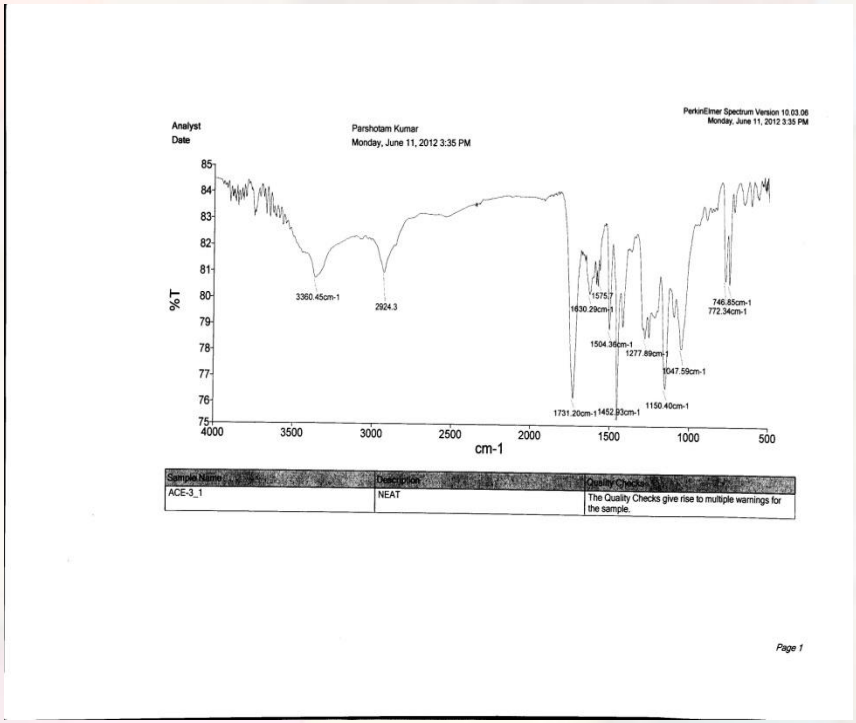
In order to ascertain that no interaction has occurred between the drug & the carriers/solvents used or due to conditions of the formulation process, the FTIR studies were carried out.

Pure (Aceclofenac)

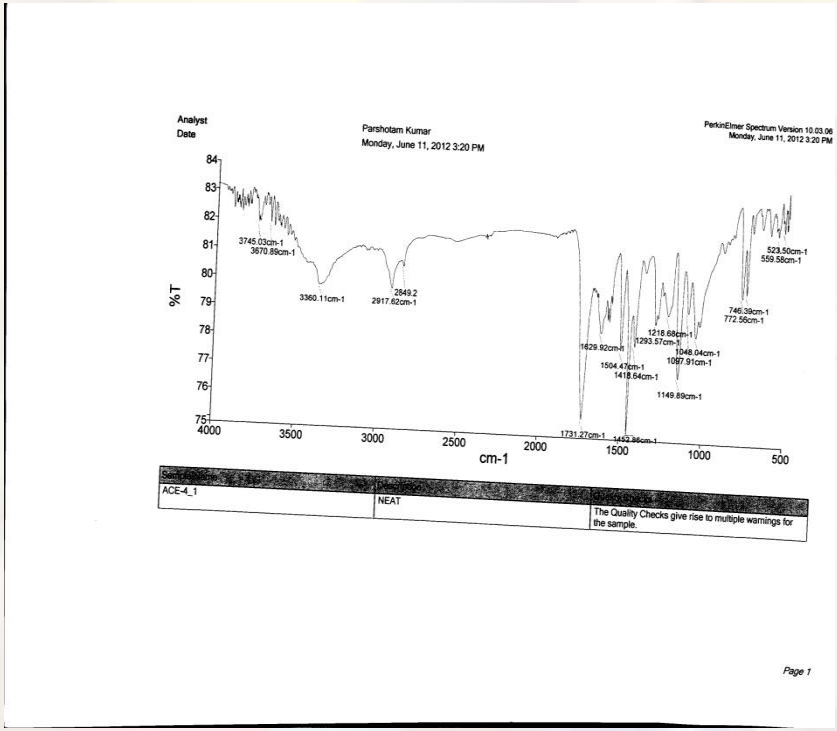


Interaction studies by IR *(contd.)*

SD (Aceclofenac + PEG-4000)

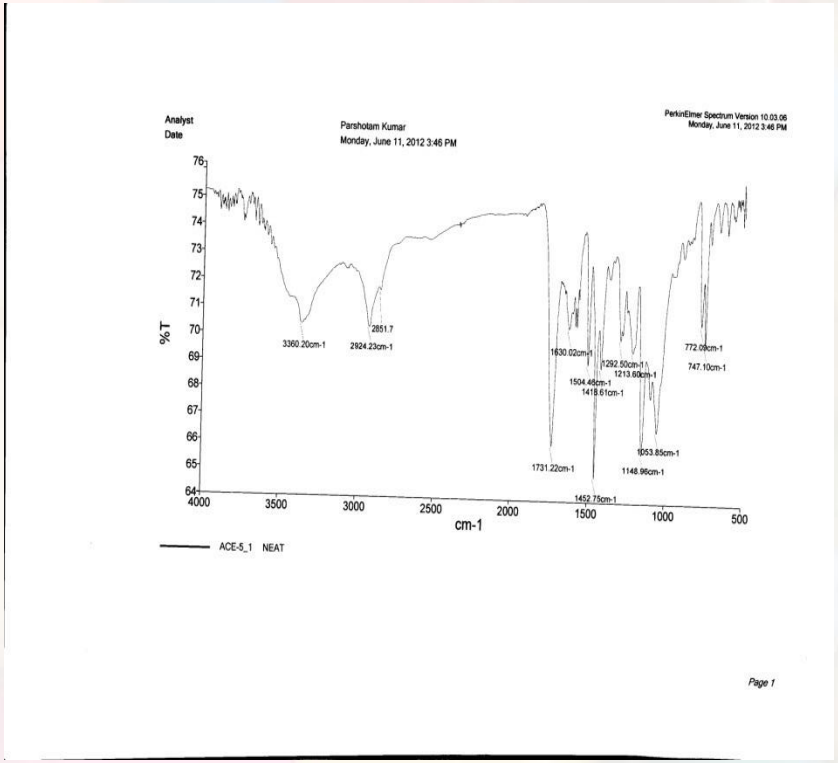


SD (Aceclofenac + PEG-6000)

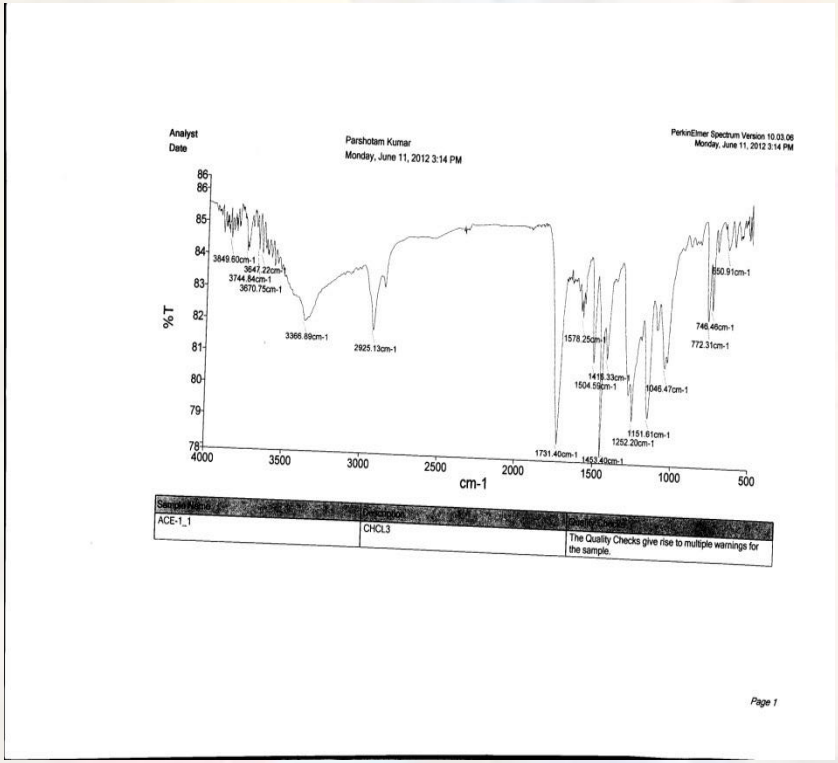


Interaction studies by IR *(contd.)*

SD (Aceclofenac + Urea)



SD (Aceclofenac + Mannitol)

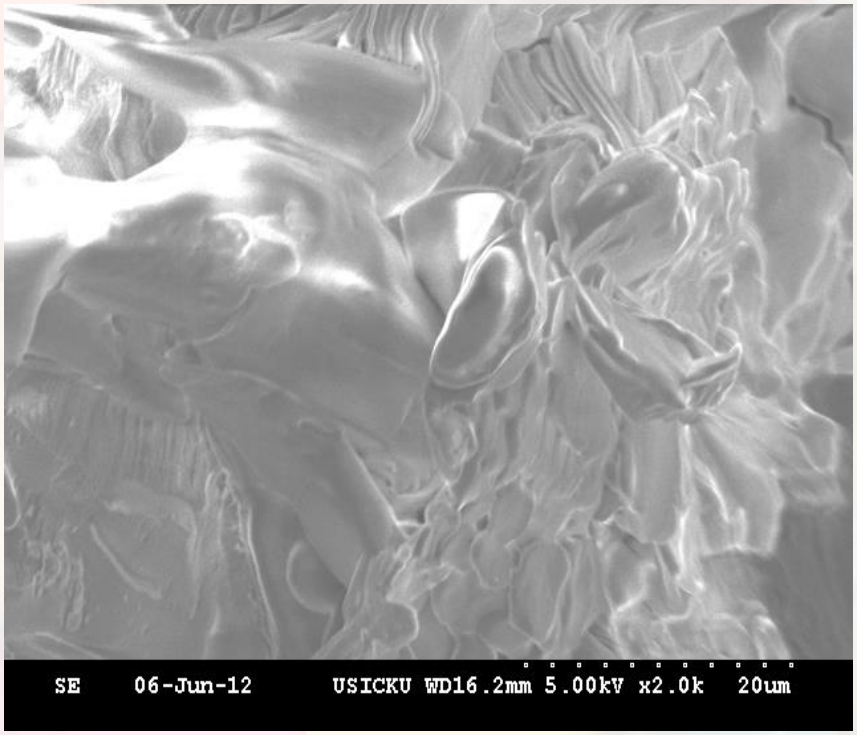


SURFACE MORPHOLOGY STUDIES BY SEM STUDIES

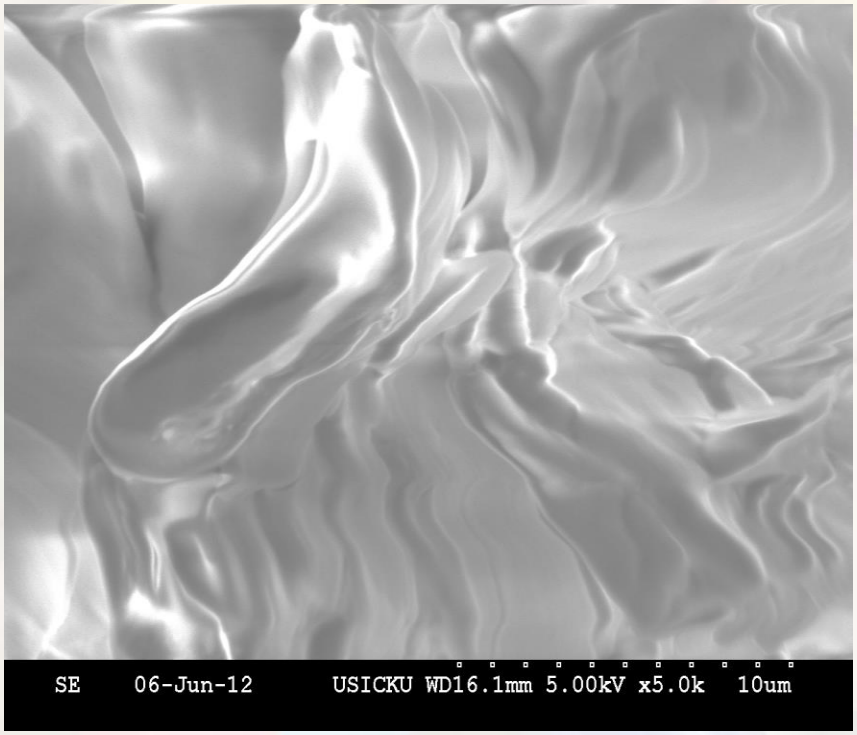
The SEM analysis was carried out using a scanning electron microscope. Prior to the examination, samples were mounted on an aluminium stub using a double sided adhesive tape and then making it electrically conducive by coating with a thin layer of gold (approximately 20 nm) in vaccum. The SEM was operated at an accelerated voltage of 5 kv and microphotographs were taken at appropriate magnification.

SEM microphotographs*(contd.)*

Pure (Aceclofenac)

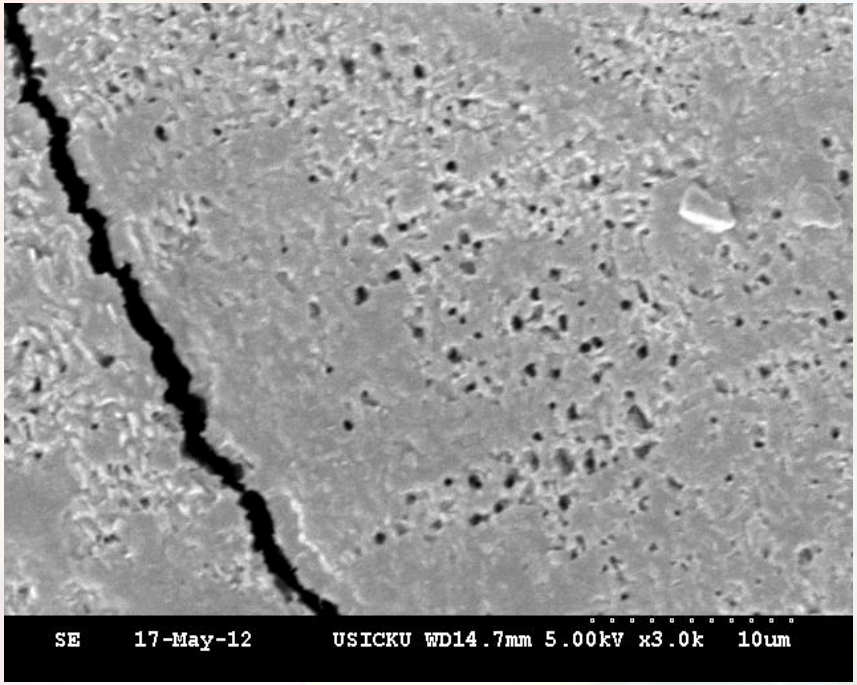


Pure (PEG-4000)

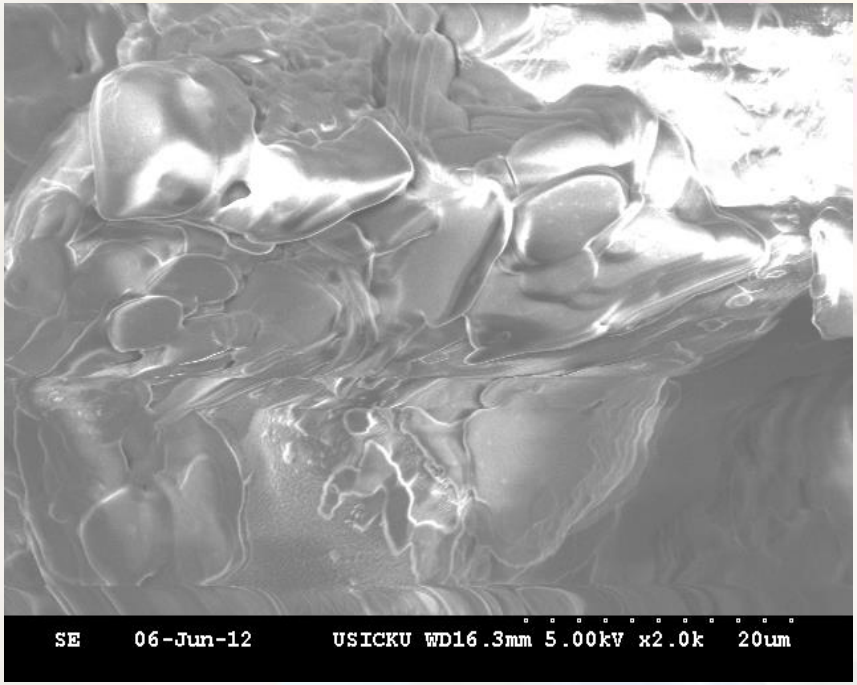


SEM microphotographs*(contd.)*

Pure(PEG-6000)

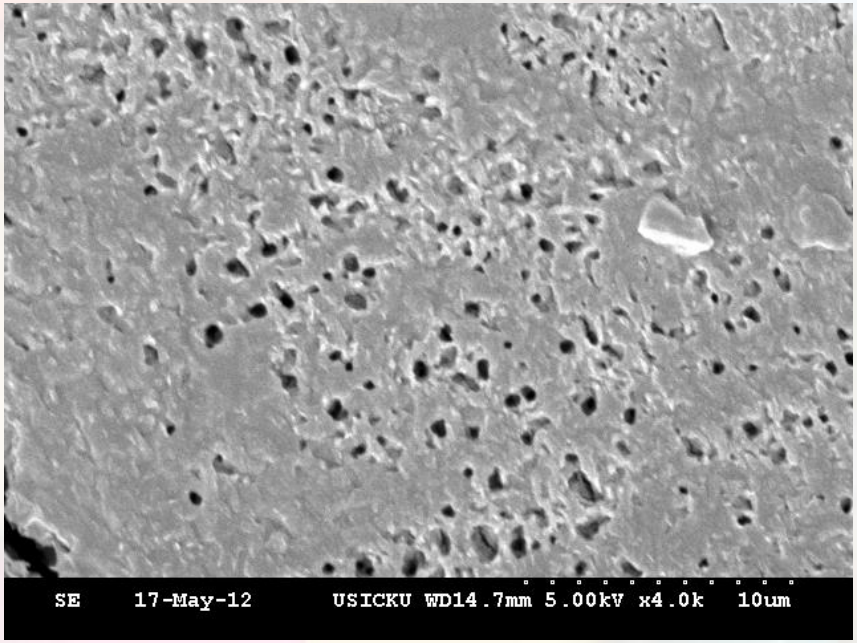


Pure (Urea)

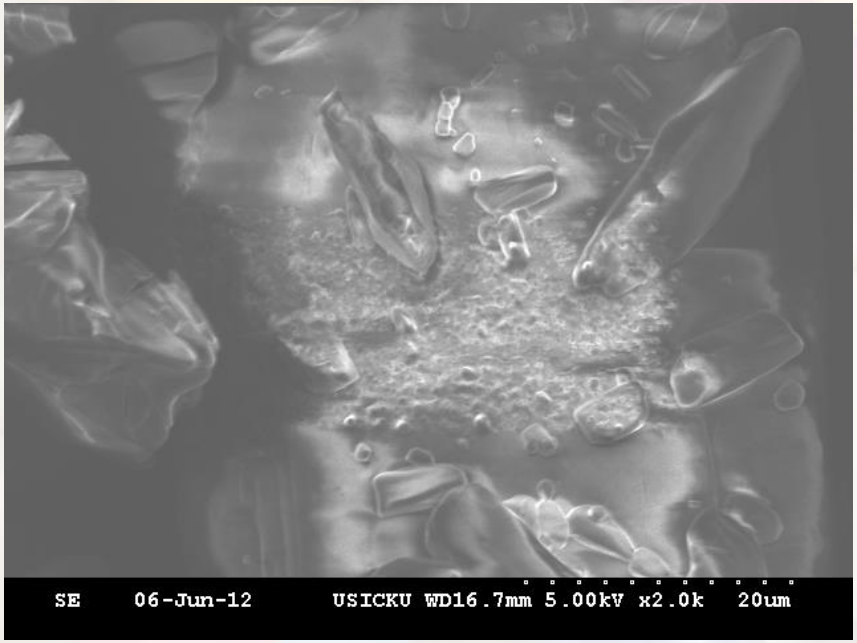


SEM microphotographs*(contd.)*

Pure (Mannitol)

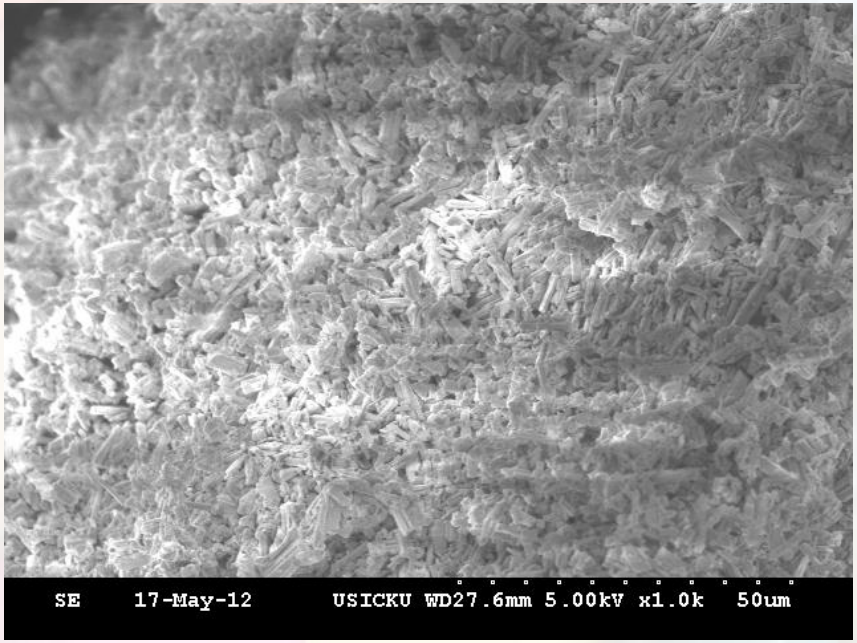


SD (Aceclofenac + PEG-4000)

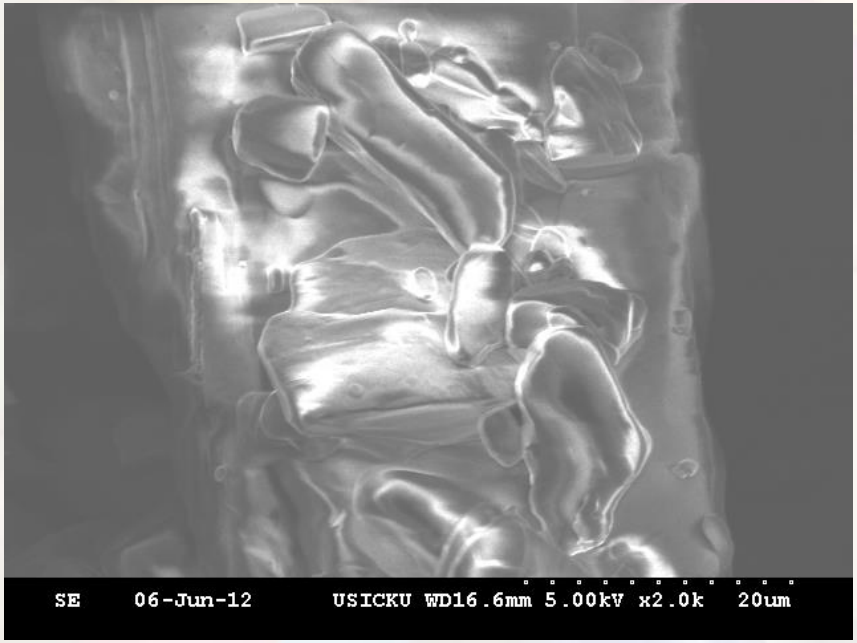


SEM microphotographs*(contd.)*

SD (Aceclofenac + PEG-6000)

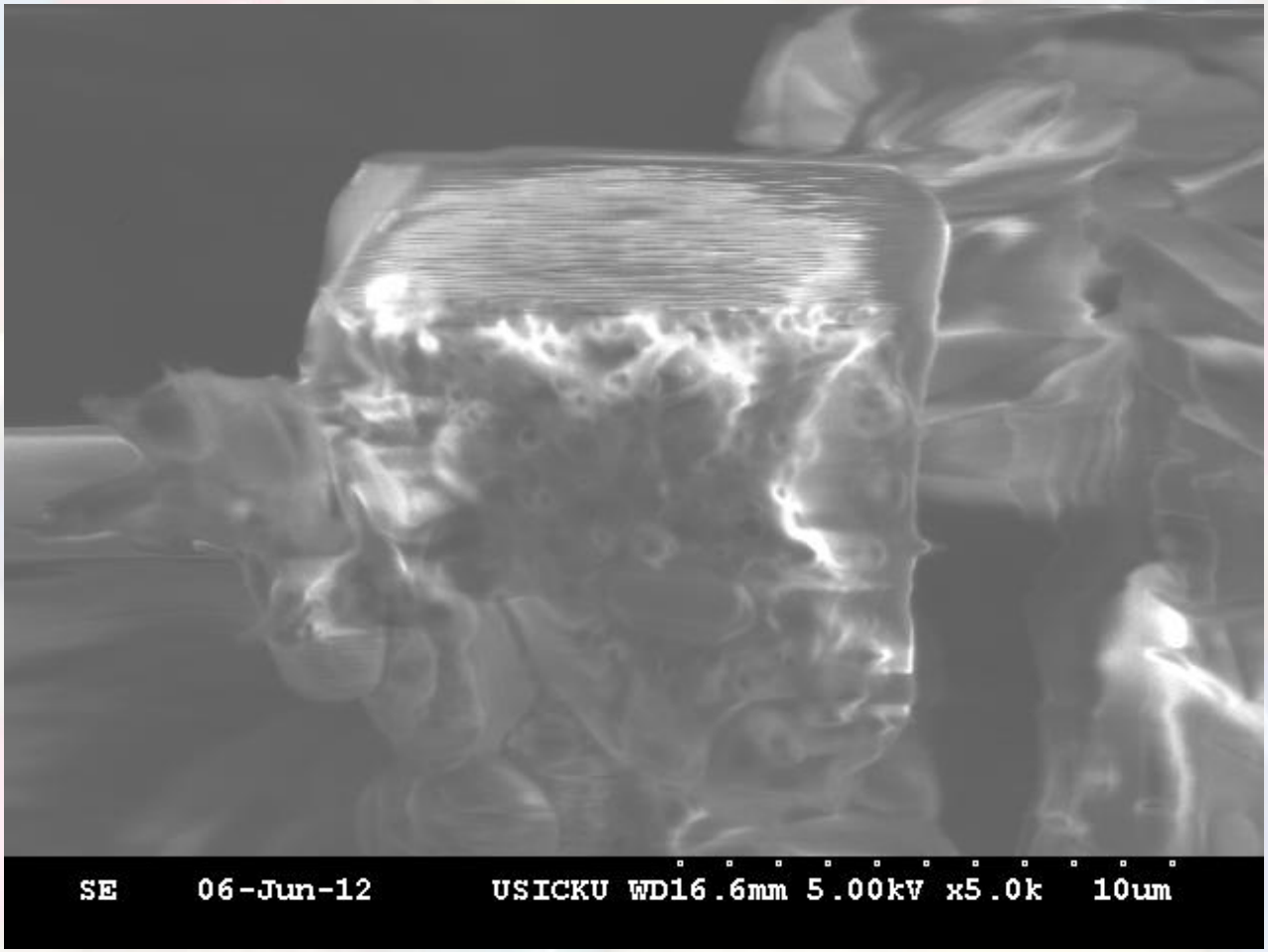


SD (Aceclofenac + Urea)



SEM microphotographs*(contd.)*

SD (Aceclofenac + Mannitol)



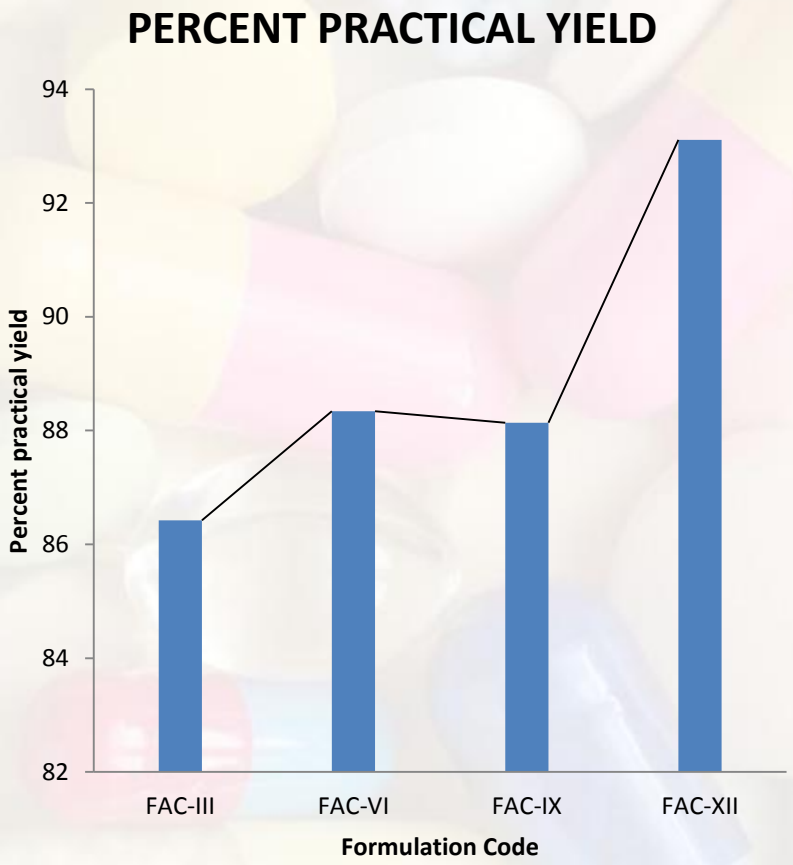
Percent practical yield

Percent practical yield was calculated to know about efficiency of a method. SDs were collected and weighed to determine practical yield (PY) from the following equation. The mean of three observations was used for drawing the conclusions

$$\text{Percent practical yield} = \frac{\text{practical mass (solid dispersion)}}{\text{theoretical mass (drug + carrier)}} \times 100$$

Percent practical yield *(contd.)*

Formulation Code	Percent practical yield (n=3) ±SD
FAC-III	86.42 ± 0.781
FAC-VI	88.34 ± 0.616
FAC-IX	88.14 ± 0.587
FAC-XII	93.11 ± 0.696



Observation

It is clear from the above data that the method adopted for preparation of SDs has better yield ranging from 86.42 to 93.11 %.

Percent Drug Content

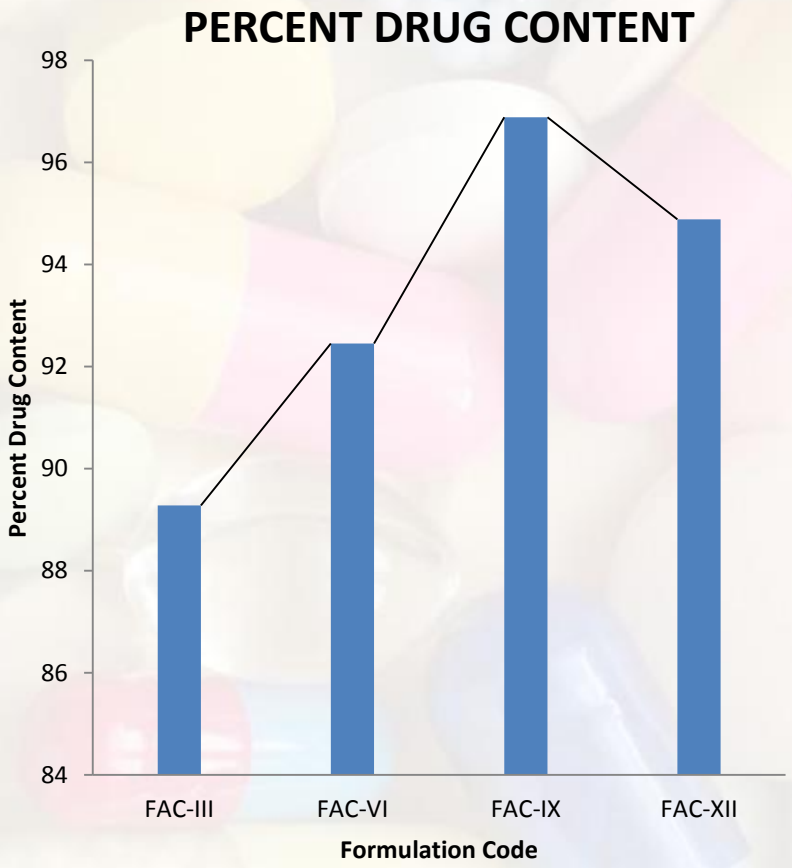
Percent Drug content was obtained by dissolving the Solid dispersions equivalent to 10 mg of Aceclofenac in the 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 275 nm by UV spectrophotometer The mean of three observations was used for drawing the conclusions.

The Actual Drug Content was calculated using the following equation as follows

$$\text{Percent Drug content} = \frac{\text{Actual amount of drug in solid dispeersions}}{\text{Theoretical amount of drug in solid dispersion}} \times 100$$

Percent Drug Content *(contd.)*

Formulation Code	Percent drug content (n=3) ±SD
FAC-III	89.28 ± 0.832
FAC-VI	92.45 ± 0.911
FAC-IX	96.88 ± 0.699
FAC-XII	94.88 ± 0.713



Observation

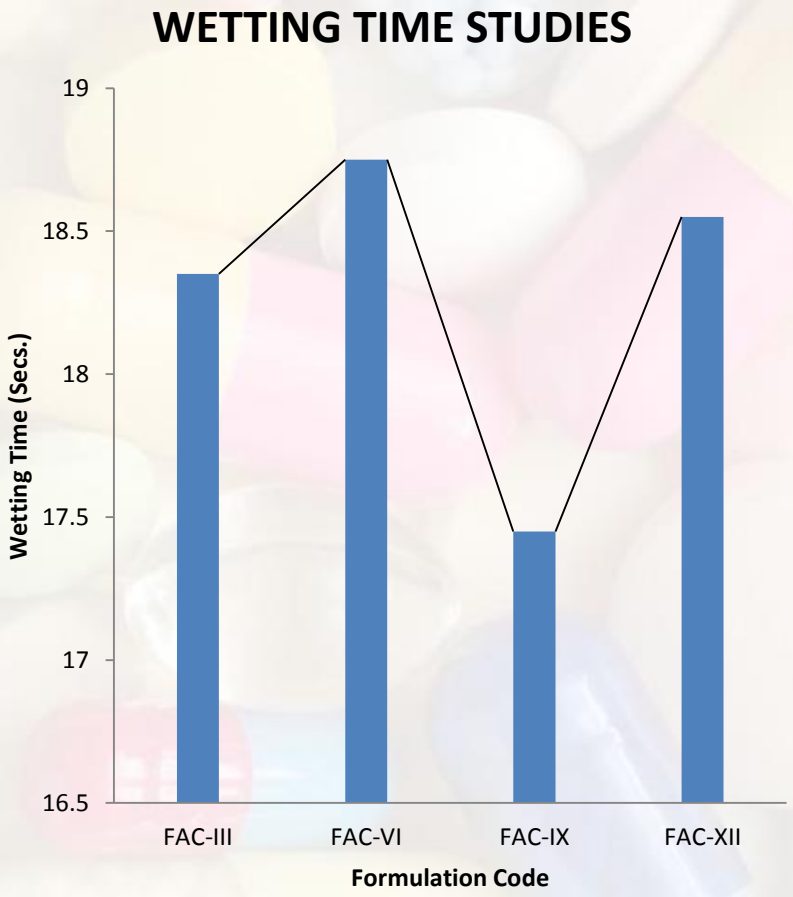
It is clear from the above data that the formulated SDs showed drug content ranging between 89.28 to 96.88 %.

Wetting Time Studies

Powdered mixture of SDs (300 mg) was placed in a sintered glass funnel with 33 mm internal diameter. The funnel was plunged into beaker containing water such that the surface of water in the beaker was at the same level as the powder or granules in the funnel. Methylene blue powder (10 mg) was layered uniformly on the surface of the powder or granules in the funnel. The time required for wetting of methylene blue powder was measured. The mean of three observations was used for drawing the conclusions

Wetting Time Studies *(contd.)*

Formulation Code	Wetting Time (Secs.) n=3 (±SD)
FAC-III	18.35 ± 0.22
FAC-VI	18.75 ± 0.28
FAC-IX	17.45 ± 0.26
FAC-XII	18.55 ± 0.24



Observation

It is clear from the above data that the formulation FAC-IX showed minimum wetting time of 17.45 secs. And the FAC-VI showed maximum wetting time of 18.75 secs.

Conclusion

This study clearly showed that addition of various hydrophillic carriers like PEG-4000, PEG-6000, Urea & Mannitol to aceclofenac improves its dissolution rate. Further, all the solid dispersions performed better than the pure drug Aceclofenac.

The present study also showed that amongst 4 hydrophillic carriers, SDs prepared with Urea in the ratio of 1: 3 (drug : carrier) proved better.

Amorphous nature of the drug in solid dispersion was confirmed by scanning electron microscopy and a decrease in enthalpy of drug melting in solid dispersion compared to the pure drug.

Results from IR spectroscopy concluded that there was no well-defined interaction between aceclofenac and carriers employed in the preparation of solid dispersions.

The solid dispersion of aceclofenac with Urea lends an ample credence for better therapeutic efficacy.

References

- **Abdelbary A et al, 2013** formulated solid dispersions of Etodolac with PEG-4000, PEG-6000, Pluronic (F-127), Gelucire (44/14 & 50/13). SDs exhibited faster dissolution rates than the intact drug. Accordingly, solid dispersion technique can be assertively considered as a promising procedure for enhanced solubility and dissolution in Etodolac.
- **Jagtap VK et al, 2012** formulated solid dispersions of Pioglitazone. The objective of this study was to design optimized solid dispersion of Pioglitazone with hydrophillic carrier Poloxamer (188) in different ratios by kneading method in an attempt to enhance solubility.
- **Poddar SS et al, 2011** prepared solid dispersions of Ritonavir. The SDs was prepared with PVP as carrier in different carrier ratios.
- **Muralidhar et al, 2010** prepared SDs of Clecoxib with PEG-6000 and PVPK30 in blend as various carrier-carriers ratios. The effect in solubilization of drug was studied with sequential enhancement of dissolution and bioavailability.

THANK YOU

khalidmir57@gmail.com