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Research Article

COMPARATIVESTUDY OF POLYMER MODIFIEDCRYSTALS OF ACECLOFENAC

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ABSTRACT

In this research study various polymer modified crystals of aceclofenac were compared for its *in vitro* availability and other characteristics. Role of polymer like HPMC LV 60, PVP K-90 and PEG 4000 in acetone, DMSO and methanol on the drugs characteristics and release were compared. The role of individual polymer and solvent on the release of drug is also evaluated. The solvent change method was used to prepare the modified crystals of aceclofenac. Blank crystals of aceclofenac were also prepared and compared with the polymer modified crystals. Modified crystals of aceclofenac were characterized and evaluated by various methods like SEM, XRD, particle size analysis, DSC etc. The modified crystals showed a change in the external appearance of the crystal, as compared to the tabular shape of the pure drug crystal. The modified crystals prepared from PVP K-90 and using acetone as solvent showed higher *in vitro* availability as compared to the other crystals. Also the various results revealed that crystals obtained from PVP K-90 and using acetone as solvent has good micrometric and rheological properties.

Keywords: Modified crystals, *in vitro* availability, aceclofenac, solvent change method.

INTRODUCTION

Solubility of a drug has always been a rate limiting factor for its final bioavailability as it plays an important part in drug liberation and absorption. In fact the dissolution rate of the drug determines the effectiveness of drug delivery and absorption. More over for drugs with low aqueous solubility the bioavailability depends upon its aqueous solubility. Thus increasing the oral bioavailability of poorly water soluble drugs is considered to be one of the major challenges in the area of formulation development studies.There are several methods available for enhancing the dissolution of poorly water soluble or insoluble drugs such as micronization, microcyrstallisation, solid dispersions and precipitation techniques with an inert carrier, and solvent dispersion method.

Aceclofenac, a phenylacetic acid derivative is a novel NSAID related to Diclofenac. It is used in the management of osteoarthritis, rheumatoid arthritis and ankylosis spondylis. It exhibit low water solubility which in turn affects its dissolution rate. It shows almost 100% drug release after 3 hours. Various studies are done to increase the drug *invitro*availability of the drug by using various solubilization techniques.In our earlier studies polymer engineered aceclofenac crystals were obtained using polymer PVP K-90 with two different concentrations and using acetone as solvent by solvent change method and its characteristics were studied in terms of drug delivery. However in this study efforts are madeto comparethe*invitro* dissolution profile of the drug with the modifiedcrystals prepared from various polymers anddifferent solvents. Also the role of particular polymer and the solvent on drug release is studied and subsequent effect on drug characteristics[1, 2, 6, and 7].

MATERIALS AND METHODS

MATERIALS

A gift sample of Aceclofenac was received from Amoli Organics Ltd Mumbai. Gift sample of PVP K90 was received from Centaur Pharmaceuticals Goa. Gift sample of HPMC LV-50 and PEG 4000 was received from Colorcon Asia Pvt. Ltd Goa. All the other materials used were of Analytical grade.

METHODS

Preparation of engineered crystals of aceclofenac

In the present work Solvent Change method has been adopted for the preparation of blank as well as polymer modified crystals of Aceclofenac. Crystallization of aceclofenac is carried out from Acetone, Dimethylforamide and Methanol under the influence of polymeric additivesHPMC LV-50, PVP K-90 and PEG4000. Besides studying the effect of polymer on the crystal properties, the role of polymer and solvent on *in vitro* availability is also studied.

Specific polymer solution was prepared in the concentration of 0.2% in 500ml of distilled water. The three blade stirrer was immersed in the beaker containing the polymeric solutions and speed of 750 rpm was set. The drug was dissolved completely in the solvent of choice. While stirring, the drug solution was added to the beaker containing polymeric solution. The stirring were continued for 45 minutes. Blank crystals of Aceclofenac were prepared by adding the drug solution in particular solvent to distilled water containing no polymeric additive. The assembly used for preparing the modified crystals is shown in figure 1. The products were then recovered by filtration through whatmaan no 1 filter paper and dried in air[3, 4, 8, and 9]. Totaltwelvebatches of modified crystals were prepared as shown by the Table no 1.

Evaluation and Characterization of modified crystals of aceclofenac

Aqueous solubility Analysis

Aqueous solubility was determined by adding excess amount of drug 50mg to 10ml of distilled water taken in a 50ml stoppered conical flasks and were shaken using a rotary shaker at room temperature for 24 hours. Aliquots were withdrawn and filtered through whatmaan no 1 filter paper. The filtrate was analyzed for Aceclofenac at 275nm[1]. This was done for all the batches.

SEM analysis

The scanning electron microscope is used to study the surface morphology of the sample. It has been a very powerful tool in studying the changes in the particle shape and surface topography of the drug sample. The effect of particle shape on the dissolution rate of sparingly soluble drug is also studied. Photomicrographs of the crystals were taken using the Joel model JMS- 5800 electron scanning microscope. The sample were mounted on sample snubs with doubled sided adhesive tape, vacuum coated with gold and photomicrographed at suitable magnification. The SEM photomicrograph gives a three dimensional image of the sample[10].

In-Vitro Dissolution Studies

Dissolution studies on the pure drug, blank crystals as well as polymer modified crystals of aceclofenac were carried out using XXI dissolution rate apparatus employing basket method. A sample equivalent to 20mg of Aceclofenac was placed in 900ml dissolution media (Phosphate buffer pH 7.4) stirred at 75 rpm at a temperature of 37±1 ^{o}C[1].A 10ml Aliquot of dissolution medium was withdrawn at different intervals of time, filtered through a whatmaan No 1 filter paper and assayed spectrophotometrically at 275nm using the UV spectrophotometer (CHEMISTO).

XRD Analysis

Every crystalline drug gives a characteristic unique diffractogram. These diffractograms are used to assess the crystallinity of different batches produced and to study any possible change in the solid state of the drug crystals (amorphization).Diffractograms of the modified crystalwhich showed greater *in vitro* release in particular solvent and polymer,along with pure drug and blank modified crystal were obtained[10]. X-ray studies were carried out using XRD COPMPACT 3K powder X-ray Diffractogram using CuKα radiation, at voltage of 30KV and a current of 20 mA. The formulated batches were scanned over a 2θ range of 10 to 30 ^{0}C with a scanning range of 0.02^{o} per minute.

Infra red Spectral Analysis

These studies are useful in studying the characteristic peaks of the functional groups present in the drug as well as to study the compatibility of the drug with the other formulation excipients. By spectral matching technique the identity of the samples can be confirmed. Also identification of the impurities can be done since impurity will give additional peaks than that of the drug[1, 10.] The IR spectra of the batches were taken using an IR spectrophotometer SHIMADZU with scanning range of 400-4000cm^{-1} and resolution was 4 cm^{-1}.Polymer modified crystal showing best *invitro*dissolution result in each polymer and solvent were subjected to Infra red Analysis along with blank crystals.

Differential Scanning Calorimetry

DSC studies is done to evaluate the possible interaction between the drug and the excipients and to assess possible modification of the solid state of the drug i.e. transformation from crystalline form into an amorphous one or into a different polymorphic form. Also the

thermal behavior of the pure drug and the samples were studied by DSC analysis[1, 10]. DSC analysis is found to be useful in studying the effect of the surfactants on the drug properties.
Polymer modified crystals with best *invitro* dissolution were selected for DSC analysis. DSC analysis was carried out using the STA 409PC DSC-TG. 2 to 8 mg of the sample was heated in open aluminum cells at the rate of 10^{o}C/min between 30 to 300 ^{o}C temperature ranges under a nitrogen flow of 20ml/min.

Particle size Analysis
According to Noyes-Whitney equation the dissolution rate linearly depends on the surface area. Thus by reducing particle size one or more orders of magnitude increase in dissolution rates can be achieved. Polymer modified crystals with best *invitro* dissolution were selected for particle size Analysis. The size distribution of the samples were studied using Dynamic Laser Scattering Particle Size Analyzer (Malvern Particle Size Analyzer). Appropriate amount of sample was suspended in water and placed in a small volume cell, a self contained cell with a miniature stirrer motor and agitator. It was possible to record the particle size i.e. Average diameter of the crystals, percentage of the crystal oversize /undersize and the size distribution of the crystal samples[1].

Stability studies
Polymer modified crystals with best *invitro* dissolution were selected for stability studies. Stability analysis was carried out by subjecting the batches of the polymer modified to room temperature for 3 months. Selection of the batches for studies was made based on the in-vitro dissolution data. Those with good dissolution profile in each polymer and solvent were selected for studies[1].

RESULTS AND DISCUSSIONS

Aqueous Solubility Analysis
The polymer modified crystals showed an increase in the aqueous solubility as compared to the pure drug and blank crystals(Table 2). This improved aqueous solubility can be due to the better wettablilty of the drug due to the presence of the particular polymer coat on the external surface of the crystals, also it may be due to the particle size reduction as shown by particle size analysis. Polymermodified crystals prepared by PVP K-90 in acetoneshowed significant increase in aqueous solubility as compared pure drug and other modified crystals.

SEM Analysis
The SEM results of the modified crystals showed crystal modification which is seen as change in the external appearance of the crystals (Figure 2).
Photomicrograph of the pure drug and the formulated batches revealed the changes in particle shape and surface topography. The blank crystals showed change in the outer appearance as compared to the pure drug. Spherical shapes of the polymer modified crystals were found to be a very important consideration in terms of the flowability and packability of the drug. SEM studies thus indicated that the polymer has formed a coating over the individual particle thus resulting in the formation of spherical particles with improved properties as revealed from later studies.

In-vitro Dissolution studies
The best *in vitro* dissolution profile was showed by modified crystals with polymer PVP K90 and acetone as solvent. The blank modified crystals showed almost same or little better in-vitro dissolution profile (Table 3),whereas the polymer modified crystals showed an enhancement in the dissolution profile as compared to pure drug (Table 4). The pure drug of aceclofenac showed 92% *in vitro* drug release at the end of 3 hours whereas the entire polymer modified crystals showed *in vitro* drug release of 100% before 3 hours.Among all the polymer modified crystals in particular solvent, those crystals prepared with PVP K90 exhibited enhancement in the *in vitro* availability of the drug.
The significant enhancement of the *in vitro* release can be attributed to improved wettablilty of the drug by reducing the interfacial tension caused by the particular polymer coat on crystals, particle size reduction and also decrease in the crystalline of the drug.

XRD studies
The sharp peaks in the diffractogram of the pure drug suggested that the drug is crystalline in nature as shown in figure 3. X-ray Diffractogram of blank modified crystals precipitated only showed a slight reduction in the crystal lattice as compared to the pure drug.Whereas the X-ray diffraction pattern of polymer modified crystals showed a significant reduction in the peaks, with disappearance of some of the drug peaks. This indicates decrease in the crystallinity of the pure drug (figure 3).Therefore an enhancement in the solubility of the drug may be attributed to a decrease in the crystallinity of the drug.

Infra Red Spectral Analysis

The infra red spectrum obtained helped to access the effects of crystallization process and the crystallization environment on the drug and the possible interaction of the drug with the excipients. IR spectrum of the polymer modified crystals of Aceclofenac and the blank crystals obtained from acetone correlate with the spectra of the pure drug ranging from 400 to 4000cm^{-1} i.e. they show all the characteristic peaks of the pure drug, thereby indicating no significant interaction between the drug, polymer and the solvents(figure 4).

The Changes in the intensity of the peaks are seen in some IR spectra which could be due to the effect of the solvents or due to the absorption of the polymers used in the study. Thus IR studies revealed the compatibility of the drug with the excipients employed in the micro crystallization.

Particle size Analysis

The particle size result obtained for the modified crystals especially those with PVP K 90 polymer in acetone showed a decrease in the particle size as compared to the pure drug (Table 5).These crystals were selected due to its better aqueous solubility. This particle size reduction is related to the solubility and in terns to its dissolution profile.

Differential Scanning Analysis (DSC)

The thermogram obtained from the DSC analysis for the modified crystals showed a melting endotherm similar or close to 152.8 ^{o}C which the melting endotherm is shown by the pure drug of aceclofenac (figure no 5). The slight difference in the melting endotherm of the polymer engineered crystals was probably because of the presence of polymer, solvent and the reduced particle size. Thus the crystallization process or the crystallization environment factors did not have any effect on the thermal behavior of the drug. Thus showing its compatibility with the process parameters.

Stability studies

The stability studies on the modified crystals after storing for a period of 3 months in a storing condition showed that the product does not undergo any degradation on storage and hence expected to maintain its integrity during storage with reasonable shelf life. The batches selected were those showing best dissolution profile in each polymer and solvent. (Table no 6).

CONCLUSION

From the study it was concluded that the present technique can be used to significantly modify the crystal habit of a drug particle which in turn can increase its bioavailability, which can also be applied to other water insoluble drugs. The crystals obtained from polymer PVP K90 in acetone showed better *in vitro* availability as compared to pure drug and other modified crystals. It may be concluded that PVP K-90 is an ideal polymer as compared to other polymers and acetone as the ideal solvent as compared to other solvents which are responsible for enhancing the in *vitro* availability. Also the spherical crystals obtained during the process of microcyrstallisation revealed a positive contribution of its rheological characteristics specially the flowability and compressibility of the drug leading to the possibility of preparing directly compressible tablets especially in the development of more efficacious formulation and novel technique.

ACKNOWLEDGEMENTS

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Table 1: Formulation codes

Drug	Solvent	Polymer	Concentration	Batch code
Aceclofenac	Acetone			F1
Aceclofenac	Acetone	HPMC LV-50	0.2%	F1a
Aceclofenac	Acetone	PVP K90	0.2%	F1b
Aceclofenac	Acetone	PEG 4000	0.2%	F1c
Aceclofenac	Dimethylformamide			F2
Aceclofenac	Dimethylformamide	HPMC LV-50	0.2%	F2a
Aceclofenac	Dimethylformamide	PVP K90	0.2%	F2b
Aceclofenac	Dimethylformamide	PEG 4000	0.2%	F2c
Aceclofenac	Methanol			F3
Aceclofenac	Methanol	HPMC LV-50	0.2%	F3a
Aceclofenac	Methanol	PVP K90	0.2%	F3b
Aceclofenac	Methanol	PEG 4000	0.2%	F3c

Table 2: Aqueous Solubility Analysis

Samples	Absorbance at 275nm	Concentration (mcg/ml)
Pure drug	0.154	5.768
F1	0.237	8.876
F1a	0.342	12.809
F1b	0.418	15.655
F1c	0.255	9.266
F2	0.210	7.865
F2a	0.254	9.513
F2b	0.320	11.985
F2c	0.230	8.520
F3	0.190	7.116
F3a	0.238	8.914
F3b	0.250	9.363
F3c	0.210	7.865

Table 3: Dissolution Profile of Pure Drug and Blank Crystals of Aceclofenac

Time in minutes	Cumulative percentage drug release			
	Pure drug	F1	F2	F3
15	32.63	25.29	25.31	24.06
30	44.24	40.29	39.65	41.57
45	55.74	53.69	53.82	47.87
60	63.61	63.16	63.87	53.96
75	72.78	79.24	68.20	61.53
90	75.05	81.42	71.06	64.42
105	78.45	84.77	77.42	68.20
120	86.35	86.80	82.41	77.62
135	88.93	90.15	86.88	89.60
150	89.83	92.85	92.35	90.31
165	90.99	94.88	96.64	93.21
180	94.25	98.23	97.04	95.81

Table 4: Dissolution Profile of Polymer modified Crystals of Aceclofenac

Time in minutes	Cumulative percentage drug release									
	Pure drug	F1a	F1b	F1c	F2a	F2b	F2c	F3a	F3b	F3c
15	32.63	42.7	54.3	53.5	34.5	52.2	46.4	38.4	44.2	32.2
30	44.24	85.5	79.2	66.4	53.0	61.2	58.2	49.5	50.5	47.2
45	55.74	90.9	90.9	72.8	64.0	79.2	70.2	54.6	59.5	52.5
60	63.61	94.0	96.6	90.0	80.8	86.4	76.3	69.8	74.2	60.2
75	72.78	95.7	97.4	94.2	88.4	90.8	82.8	71.2	79.8	67.5
90	75.05	96.5	98.9	96.5	92.6	93.7	88.6	74.2	89.2	74.8
105	78.45	98.3	--	97.5	96.0	97.7	92.3	81.4	93.5	82.5
120	86.35	--	--	98.9	98.6	99.0	94.3	88.5	96.2	89.4
135	88.93	--	--	--			95.5	93.2	98.2	94.4
150	89.83	--	--	--			98.2	98.1		98.4
165	90.99	--	--	--						
180	94.25	--	--	--						

Table 5: Particle size distribution of Crystals

Sample	Average diameter	Size distribution
Pure drug	71.323	28.895-158.97
F1	70.873	30.258-159.57
F1a	61.83	23.717-107.11

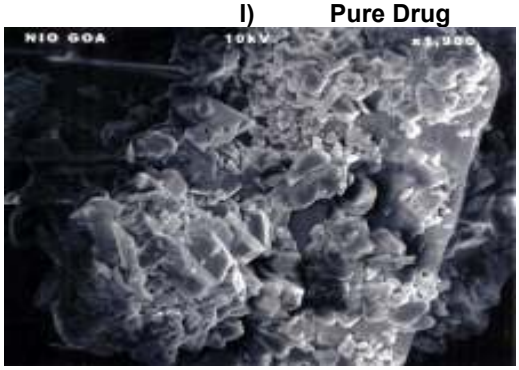
Table 6: Stability studies

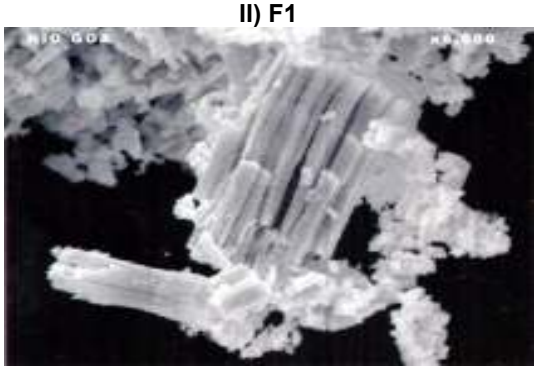
Time in minutes	Cumulative percentage drug release		
	F1b	F2b	F3b
15	55.3	35.2	44.3
30	80.2	52.0	52.6
45	89.5	63.9	58.9
60	93.2	82.8	66.2
75	97.5	87.3	78.2
90	98.9	94.2	86.9
105		97.2	92.9
120	--	99.0	94.6
135	--	--	98.9
150	--	--	--
165	--	--	--
180	--	--	--

Fig. 1: Assembly used for preparing Formulations

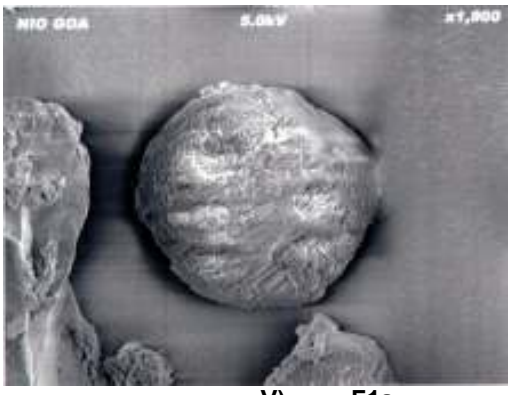
I) Pure Drug

II) F1

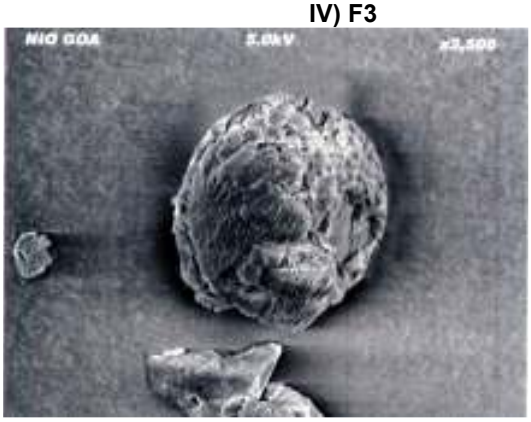




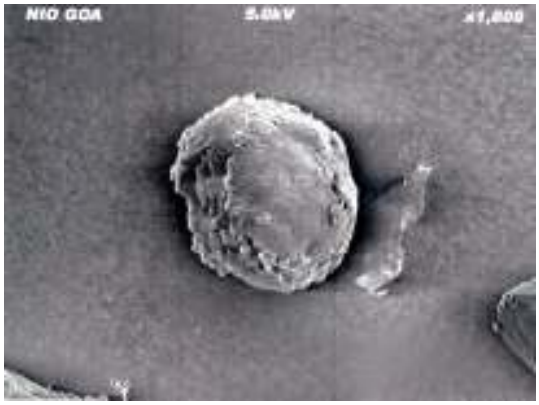
III) F2



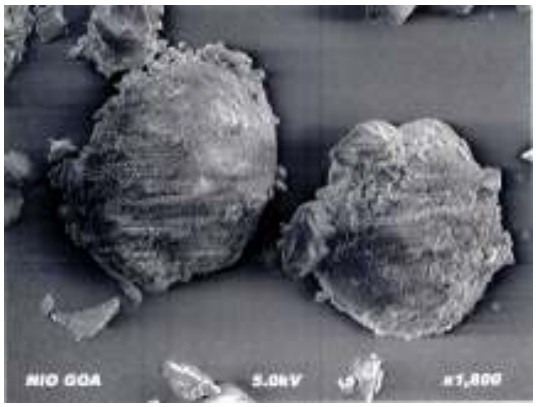
IV) F3



V) F1a

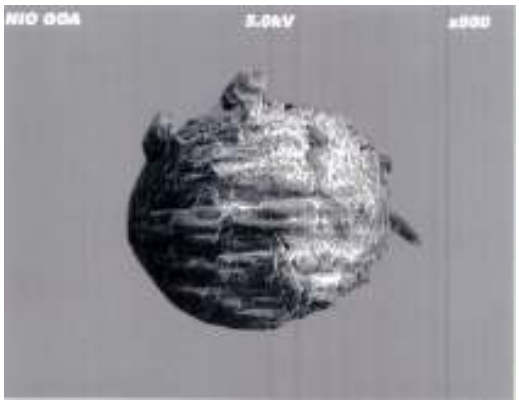


VI) F1b

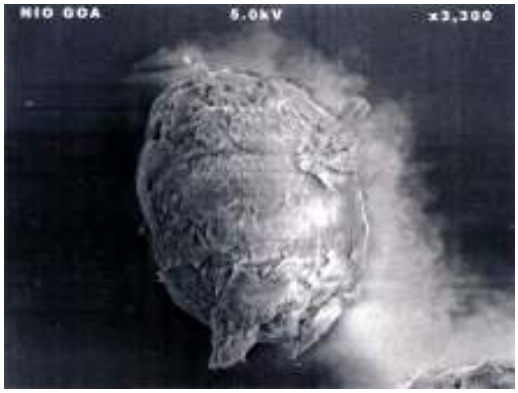


VII) F1c

VIII) F2a



IX) F2b



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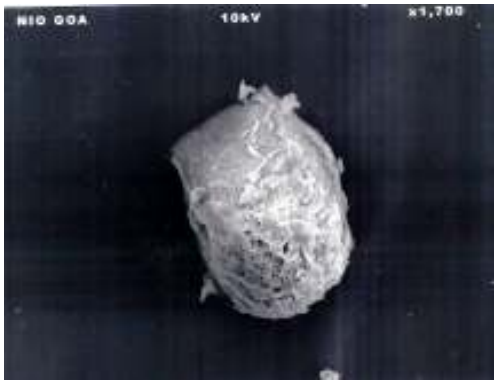
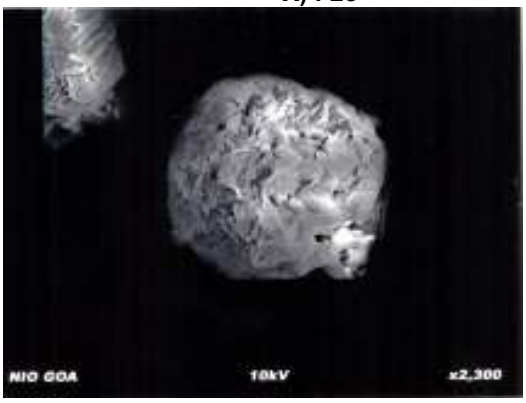
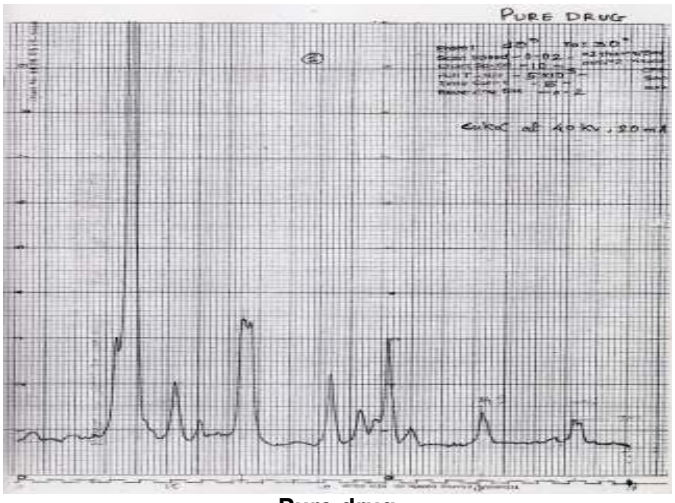




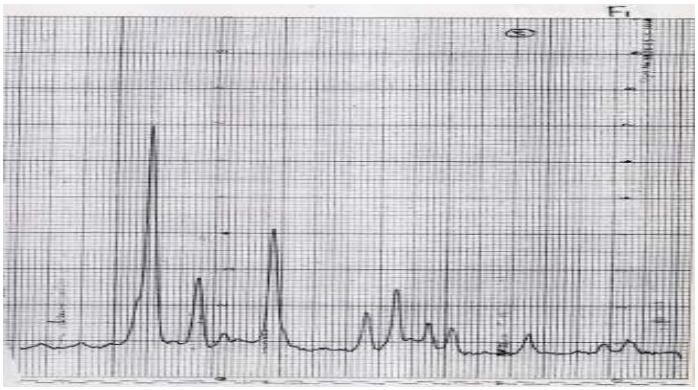
XI) F3a XII) F3b

XIII) F3c

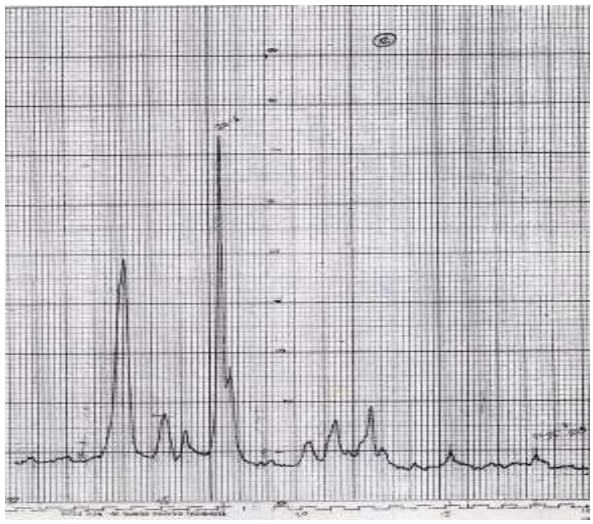
Fig. 2: SEM of formulations



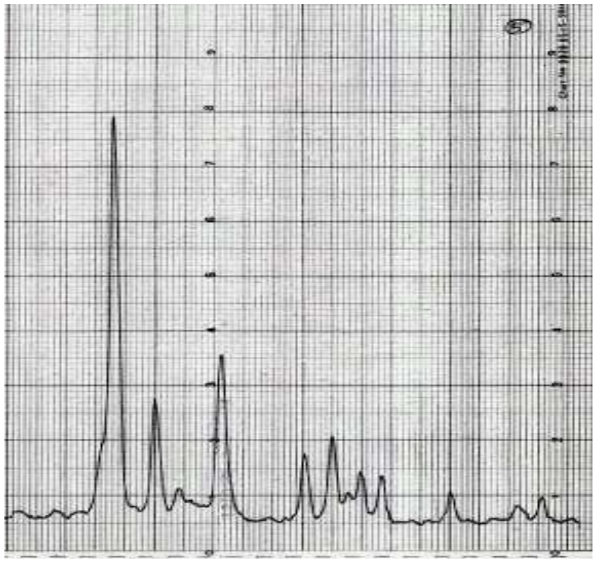
Pure drug



F1



F2



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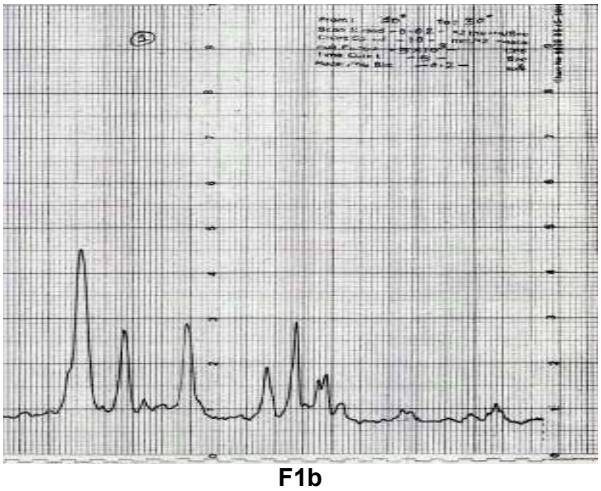
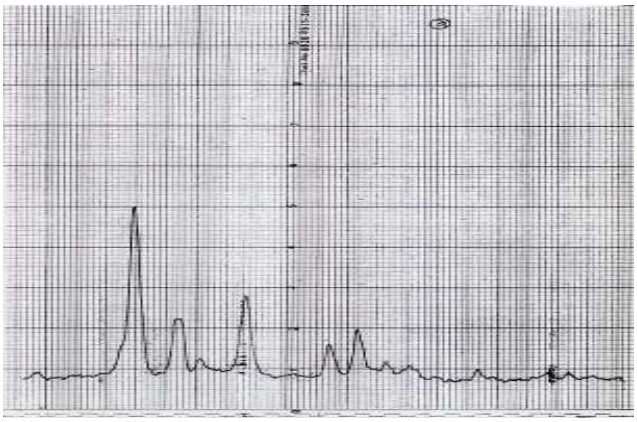
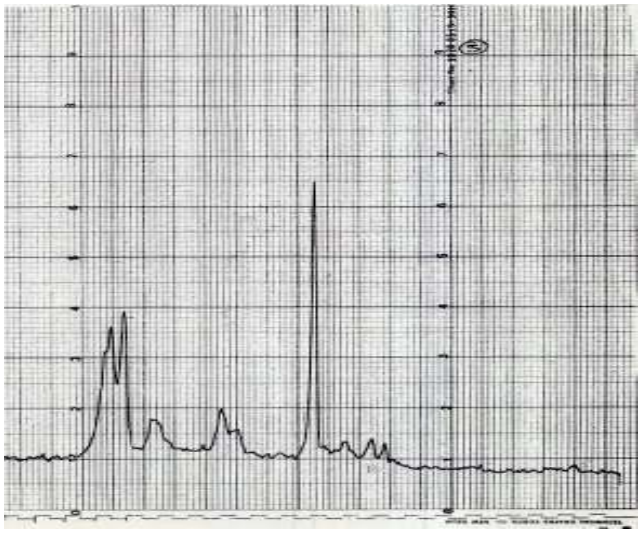


F1b

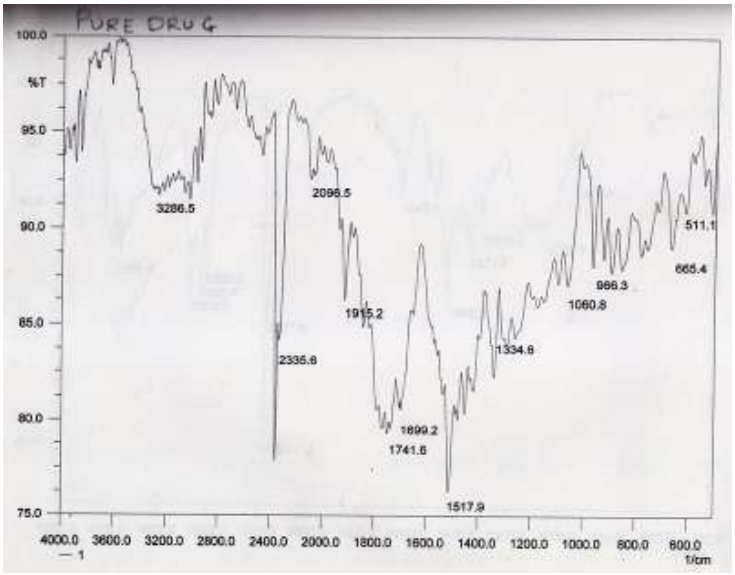


F2b

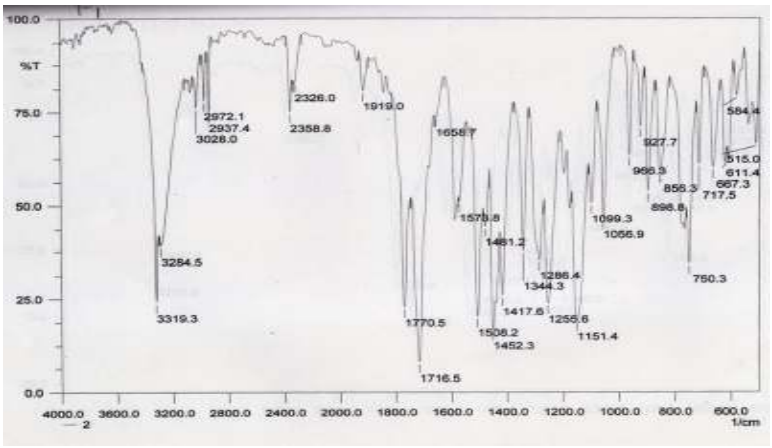


F3b

Fig. 3: XRD Diffractograms of formulations (pure drug, F1, F2, F3, F1b, F2b and F3b)



Pure drug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667.3
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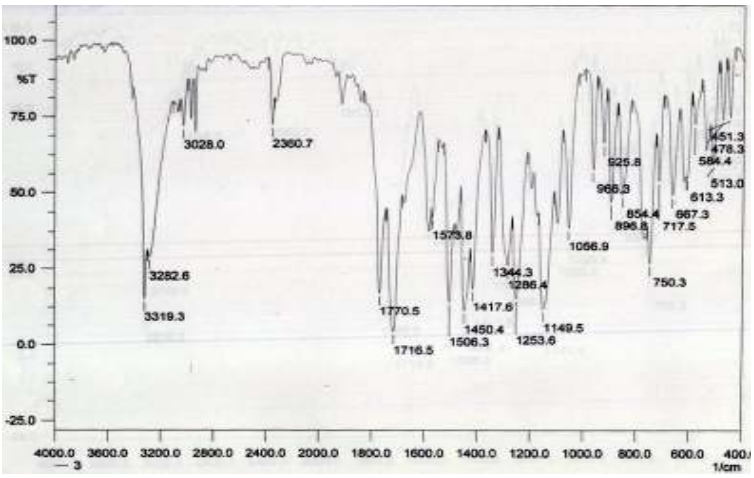
1/cm

F1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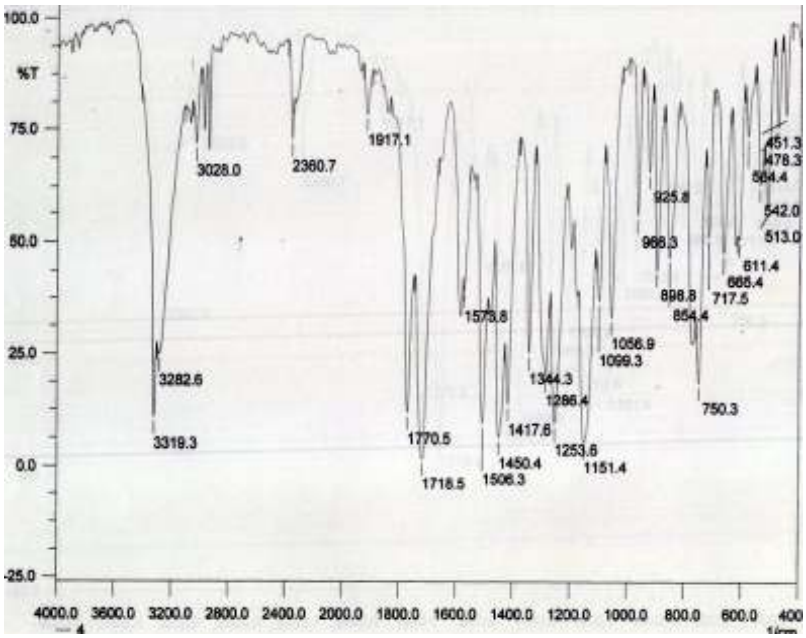
1573.8
1506.3
1450.4
1417.6
1344.3
1286.4
1253.6
1149.5
1056.9
925.8
966.3
854.4
896.8
750.3
667.3
717.5
584.4
513.0
513.3
4000.0 3600.0 3200.0 2800.0 2400.0 2000.0 1800.0 1600.0 1400.0 1200.0 1000.0 800.0 600.0
1/cm

F2


100.0
%T
75.0
50.0
25.0
0.0
-25.0
3028.0
2360.7
1917.1
3282.6
3319.3
1770.5
1718.5
1573.8
1506.3
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1344.3
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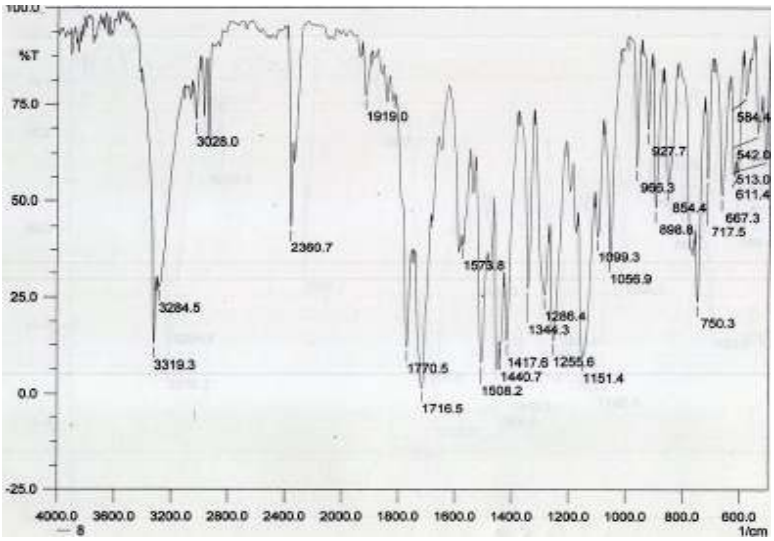
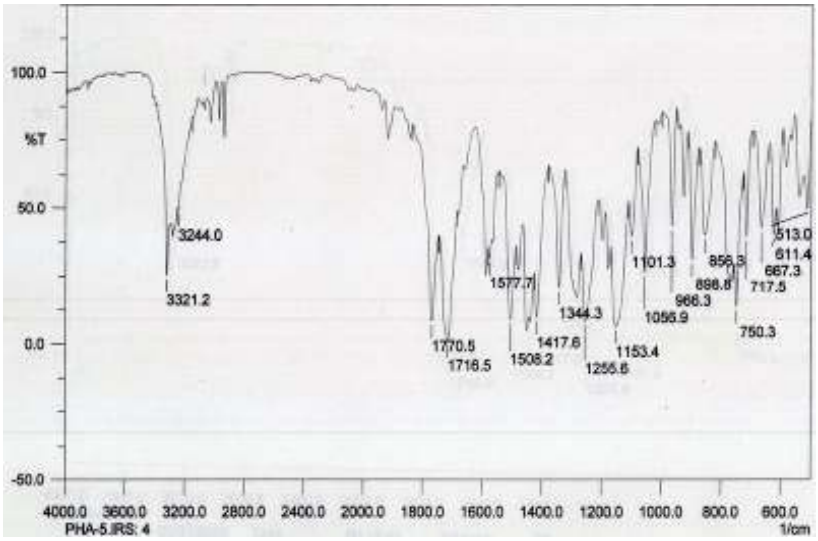
4000.0 3600.0 3200.0 2800.0 2400.0 2000.0 1800.0 1600.0 1400.0 1200.0 1000.0 800.0 600.0

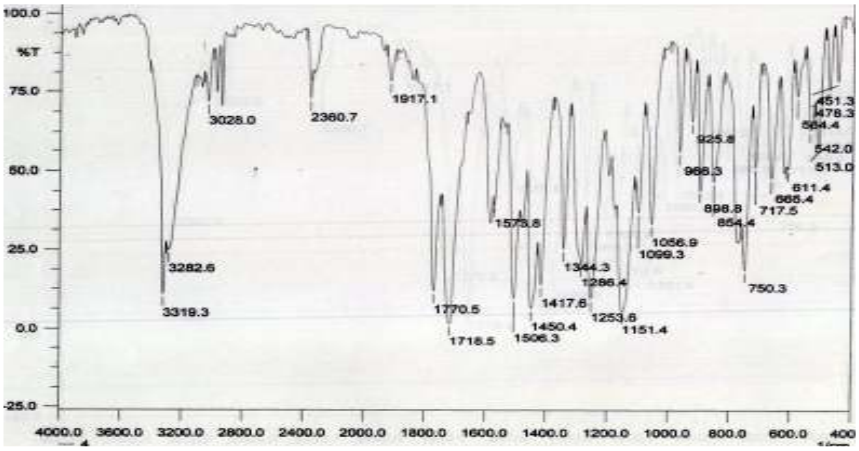
F3



F1b

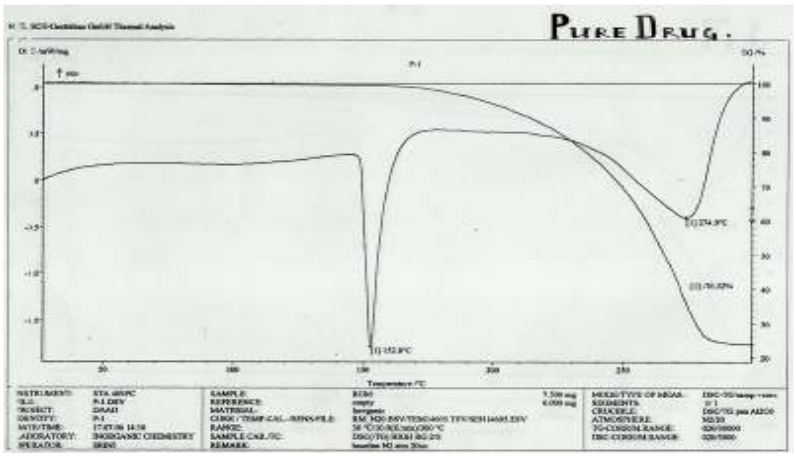


F2b

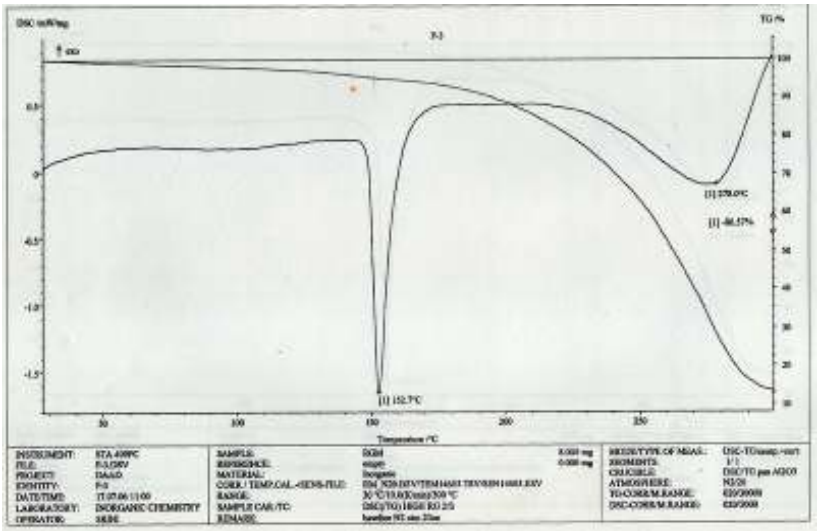


F3b

Fig. 3: IR spectra of formulations (pure drug, F1, F2, F3, F1b, F2b and F3b)

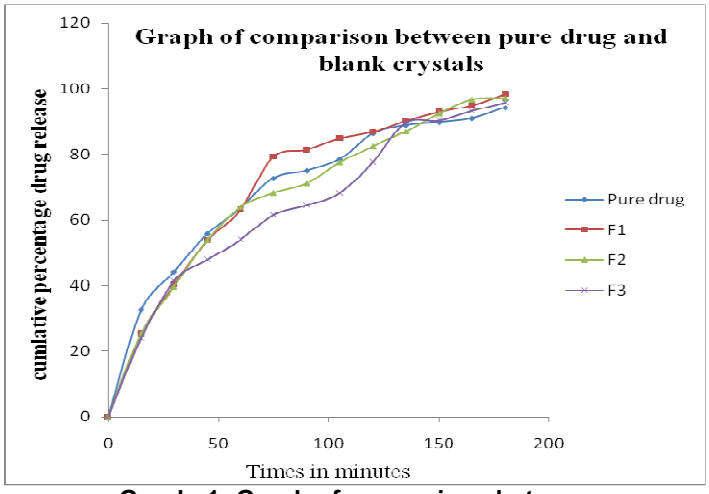


Pure drug

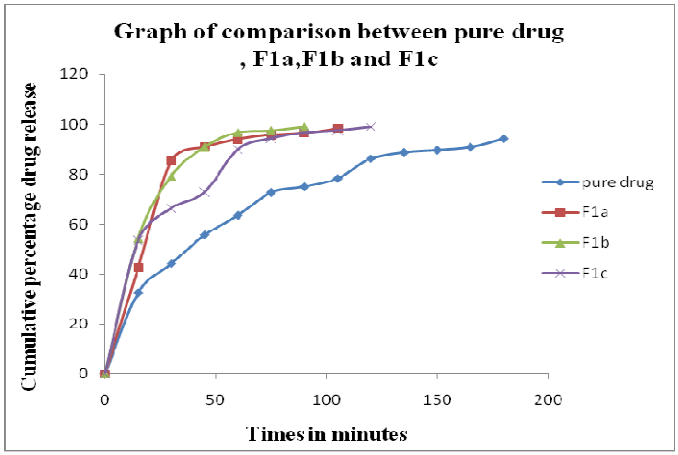


F1b

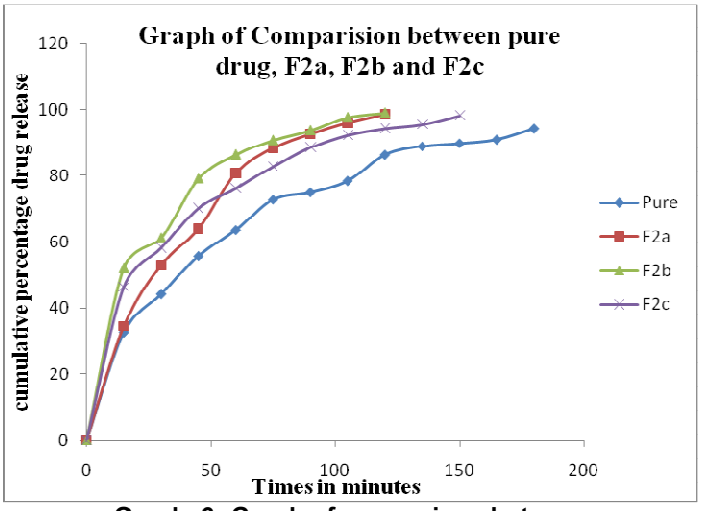
Fig. 4: DSC thermogram of pure drug and F1b



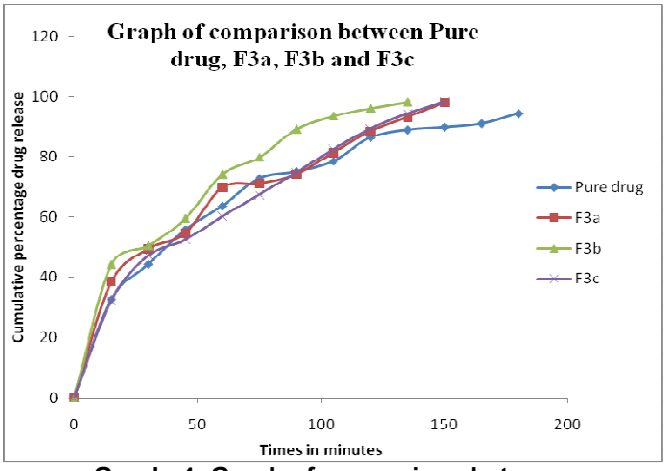
Graph. 1: Graph of comparison between pure drug and blank crystals



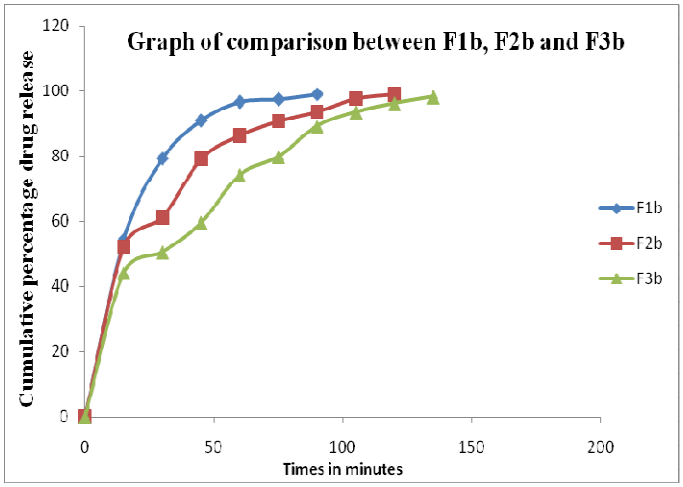
Graph. 2: Graph of comparison between pure drug, F1a, F1b, and F1c



Graph. 3: Graph of comparison between pure drug, F2a, F2b, and F2c



Graph. 4: Graph of comparison between pure drug, F3a, F3b and 3c



Graph. 5: Graph of comparison between F1b, F2b and F3b

REFERENCES

1. Modi AA and Tayade PT. Formulation of fast dissolving tablets of Valdecoxib Controlled Release Society. Indian chapter 2004;57.
2. Labhaswar V, Deshmukhn SV and Dorle AK. Studies on Crystalline forms of Ibuprofen. Drug Development and Industrial Pharmacy. 1993;19(6).
3. Loftsson T and Frioniksdottir H. The influence of water soluble polymers and pH on hydroxypropyl β Cyclodextrin complexation of drug. Drug Development and Industrial Pharmacy. 1996;22(5):401.
4. Jiao YY and Hoffmann M. Preparation and Characterization of Heparin-loaded polymeric microparticles. Drug development and Industrial pharmacy. 2002;28(8):1033.
5. Rasenack N and Muller BW. Properties of Ibuprofen crystallized under various conditions; a comparative study. Drug development and industrial pharmacy. 2002;28(9):1077.
6. Hu J and Johnston KP. Nanoparticle engineering processes for enhancing the dissolution rates of poorly water soluble drugs. Drug development and industrial pharmacy. 2004;30(3):233.
7. Sjostron B and Bent Kronberg. A method for the preparation of submicron particles of sparingly water soluble drug by precipitation in oil and water emulsion. Influence of the emulsifier, the solvent and the drug substance. Journal of Pharmaceutical Sciences. 1993;82(6):579-583.
8. Nokhodchi A and Dinarvand R. Crystal modification of Phenytoin using different solvents and crystallization techniques. International Journal of Pharmaceuticals. 2003;9250(1-2):9.
9. Pawar AP and Paradkar AR. Spherical crystallization of Celecoxib, Drug Development and Industrial Pharmacy. 2002;28(10):1231.
10. Skoog, Holler and Nieman. Principles of Instrumental Analysis, 5th edition, 294, 380, and 805.