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Research Article

Studies on Engineered Crystals of Aceclofenac for Improved Characteristics and Drug Delivery

Adison Fernandes[1,*], R.V Keny[1], Seishin Fernandes[2]
Goa College of Pharmacy, Panjim, Goa, India

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Abstract

In this study Crystal engineering and particle design of the drug aceclofenac for improved in *vitro* availability were studied. Effect of polymers like HPMC LV 60, PVP K-90 PEG 4000 along with its concentration in solvent acetone, on the drug release was studied. The crystallization technique used in this study is the solvent change method. Blank crystals as well as polymer engineered crystals were prepared by the above mentioned method and these engineered crystals were then characterized and evaluated by various methods like SEM, XRD, particle size analysis, DSC etc. The blank crystal and the polymer engineered crystals showed a change in the external appearance of the crystal, as compared to the tabular shape of the pure drug crystal. The aqueous solubility and the *in vitro* availability of the engineered crystals were enhanced. This enhancement was attributed to the decrease in the particle size of the crystals and better wettablilty of the crystals due to the presence of polymer on the external surface of the crystals. The compatibility of drug with the excipients and the process were confirmed by IR studies and DSC studies. Thus by solvent change method and use of polymer along with the solvent, crystals habit modification were obtained thus affecting the micrometric properties and the rheological properties, without leading to polymorphic change.

1. INTRODUCTION

Solubility of a drug has been playing a major part in drug liberation, absorption and as final result in its bioavailability. The successful delivery and absorption of any drug depends on its dissolution rate. More over drug with low aqueous solubility, the bioavailability is dependent on its aqueous solubility and it serves as a rate limiting or rate controlling step in the drug bioavailability. 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 spondysis. It exhibit low water solubility which in turn affects its dissolution rate. It shows almost 100% drug release after 3 hours, however efforts are made to increase the rate of *in vitro* dissolution. In this research efforts are made to improve its water solubility and other rheological properties of the drug and thus an enhancement in the rate of dissolution profile of the drug[1, 2, 6, 7].

2. MATERIALS AND METHODS

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.

Corresponding Author:
Adison Fernandes
Assistant Professor,
Goa College of Pharmacy, Panaji –Goa.
Email: adison.fernandes@gmail.com
Contact no.: +91-9970371512

2.1 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 engineered crystals of Aceclofenac. Crystallization of aceclofenac is carried out from Acetone, under the influence of polymeric additives HPMC LV-50, PVP K-90 and PEG4000. Besides studying the effect of polymer on the crystal properties, an attempt is also made to study the effect of two different concentrations of the polymer.

Specific polymer solution was prepared in the concentration of 0.1% and 0.2% in 500ml of distilled water. The three blade stirrer was immersed in the beaker containing the polymeric solution and speed of 750 rpm was set. The drug were dissolved completely in the solvent of choice i.e. Acetone. 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 to distilled water containing no polymeric additive [3, 4, 8, 9]. The assembly used for preparing the engineered crystals is shown in figure 1.

The products were then recovered by filtration through whatmaan no 1 filter paper and dried in air. Total seven batches of engineered crystals were prepared as shown by the Table no 1.

2.2 Evaluation and Characterization of engineered crystals of aceclofenac

2.2.1 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. This was done for all the seven batches[1].

2.2.2SEM 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 engineered crystal samples selected for SEM were of 0.1% concentration. These 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].

2.2.3 *In-Vitro* Dissolution Studies

Dissolution studies on the pure drug, blank crystals as well as polymer engineered 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).

2.2.4 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). The engineered crystal selected for XRD analysis were those which are with 0.2% concentration, along with pure drug and blank engineered crystal[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.

2.2.5 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}. Engineered crystal showing best *in vitro* dissolution result were subjected to Infra red Analysis.

2.2.6 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 engineered crystals with best *in vitro* 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.

2.2.7 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 engineered crystals with best *in vitro* dissolution were selected for particle size Analysis. The size distributions 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].

2.3 Stability studies

Polymer engineered crystals with best *in vitro* dissolution were selected for stability studies. Stability analysis was carried out by subjecting the batches of the polymer engineered 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 were selected for studies[1].

3. RESULTS AND DISCUSSIONS

3.1 Aqueous Solubility Analysis

The polymer engineered crystals showed an increase in the aqueous solubility as compared to the pure drug (Table 2). This improved aqueous solubility can be due to the better wettablilty of the drug due to the presence of 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. Polymer engineered crystals prepared by PVP K-90 in concentration of 0.2% showed significant increase in aqueous solubility as compared pure drug.

3.2 SEM Analysis

The SEM results of the engineered 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 engineered 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.

3.3 *In-vitro* Dissolution studies

The best *in vitro* dissolution profile was showed by engineered crystals with polymer concentration of 0.2% by PVP K90. The blank engineered crystals showed almost same or little better in-vitro dissolution profile (Table 3), whereas the polymer engineered crystals showed an enhancement in the dissolution profile as compared to pure drug (Table 4 & Graph no 1,2,3 and 4). The pure drug of Aceclofenac showed 92% *in vitro* drug release at the end of 3 hours whereas the entire polymer engineered crystals showed *in vitro* drug release of 100% before 3 hours. Among all the polymer engineered crystals, those crystals prepared with PVP K90 with 0.2% concentration exhibited significant enhancement in the dissolution profile 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 polymer coat on crystals, particle size reduction and also decrease in the crystallinity of the drug.

3.4 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 engineered 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 engineered 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.

3.5 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 engineered 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.

3.6 Particle size Analysis

The particle size result obtained for the engineered crystals specially those with PVP K 90 polymer 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.
Also higher concentration polymer of 0.2% showed much decrease in the particle size as compared to less concentration polymer. It has been reported that the particle size is proportional to the inverse of surfactant concentration. In other words an increase in the surfactant concentration shows a decrease in the particle size of the drug as seen in this study.

3.7 Differential Scanning Analysis (DSC)
The thermogram obtained from the DSC analysis for the engineered 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.

3.8 Stability studies
The stability studies on the engineered 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 the best dissolution profile in each polymer. (Table no 6).

Table 1: Formulation codes

Drug	Solvent	Polymer	Concentration	Formulation code
Aceclofenac	Acetone	--	--	F1
Aceclofenac	Acetone	HPMC LV-50	0.1%	F1a
Aceclofenac	Acetone	HPMC LV-50	0.2%	F1b
Aceclofenac	Acetone	PVP K90	0.1%	F1c
Aceclofenac	Acetone	PVP K90	0.2%	F1d
Aceclofenac	Acetone	PEG 4000	0.1%	F1e
Aceclofenac	Acetone	PEG 4000	0.2%	F1f

Table 2: Aqueous solubility analysis

Samples	Absorbance at 275nm	Concentration (mcg/ml)
Pure drug	0.154	5.768
F1	0.237	8.876
F1a	0.313	11.723
F1d	0.342	12.809
F1c	0.352	13.184
F1d	0.418	15.655
F1e	0.249	9.079
F1f	0.255	9.266

Table 3: Dissolution profile of pure drug and blank engineered crystals of aceclofenac

Time in minutes	Cumulative percentage drug release	
	Pure drug	F1
15	32.63	25.29
30	44.24	40.29
45	55.74	53.69
60	63.61	63.16
75	72.78	79.24
90	75.05	81.42
105	78.45	84.77
120	86.35	86.80
135	88.93	90.15
150	89.83	92.85
165	90.99	94.88
180	94.25	98.23

Table 4: Dissolution profile of polymer engineered crystals of aceclofenac

Time in minutes	Cumulative percentage drug release						
	Pure drug	F1a	F1b	F1c	F1d	F1e	F1f
15	32.63	38.5	42.7	52.2	54.3	38.1	53.5
30	44.24	56.6	85.5	81.4	79.2	56.7	66.4
45	55.74	68.7	90.9	85.3	90.9	73.3	72.8
60	63.61	86.8	94.0	90.9	96.6	82.2	90.0
75	72.78	89.1	95.7	96.6	97.4	90.0	94.2
90	75.05	93.8	96.5	97.4	98.9	94.8	96.5
105	78.45	96.4	98.3	98.9	--	96.8	97.5
120	86.35	98.2	--	--	--	97.9	98.9
135	88.93	--	--	--	--	98.6	--
150	89.83	--	--	--	--	--	--
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
F1c	68.92	29.295-149.27
F1d	61.83	23.717-107.11

Table 6: Results of Stability studies

Time in minutes	Cumulative percentage drug release		
	F1b	F1d	F1f
15	42.21	55.32	53.57
30	80.29	80.21	66.62
45	90.26	89.57	74.92
60	93.92	93.26	92.12
75	95.62	97.52	94.62
90	96.82	98.92	97.43
105	98.92	--	99.32
120	--	--	--
135	--	--	--
150	--	--	--
165	--	--	--
180	--	--	--

Figure 1: Assembly used for preparing Formulations

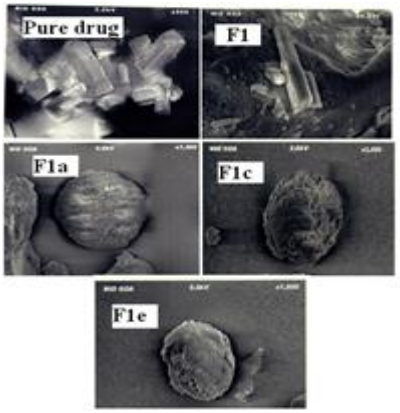


Figure 2: SEM of pure drug and formulations (F1, F1a, F1c and F1e)

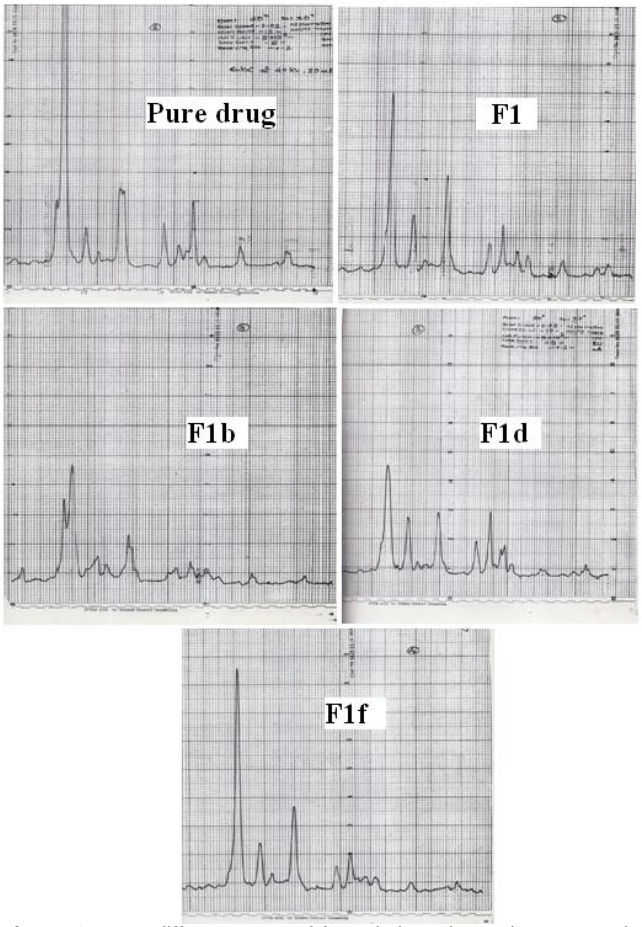
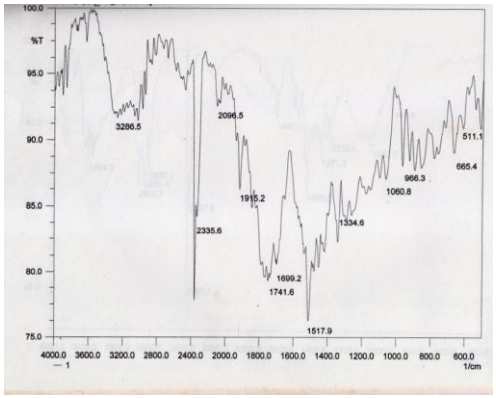
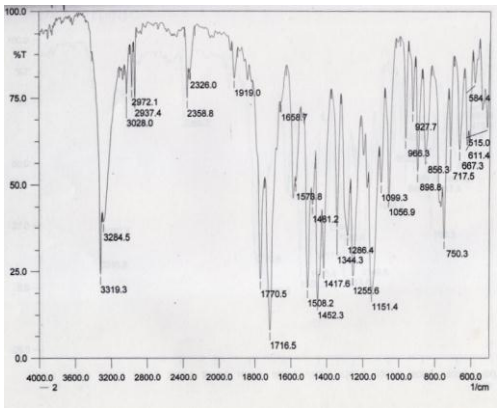


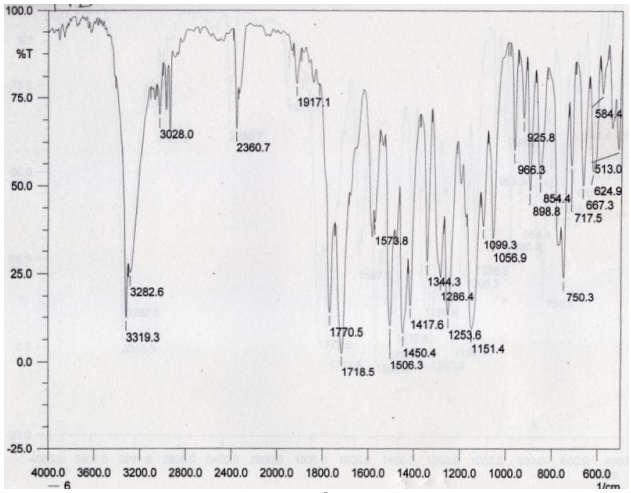
Figure 3: XRD diffratrograms of formulations (pure drug, F1, F1b, F1d and F1f)



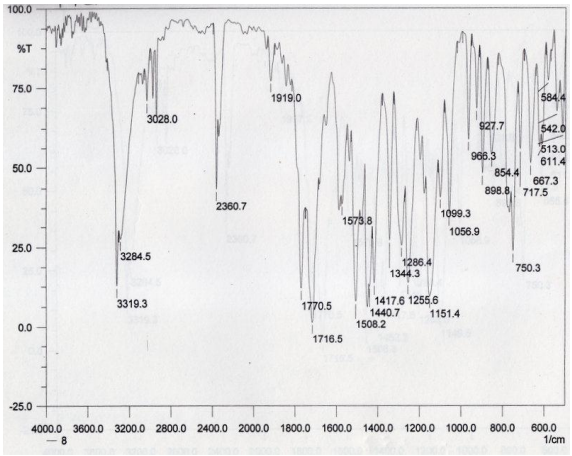
Pure drug



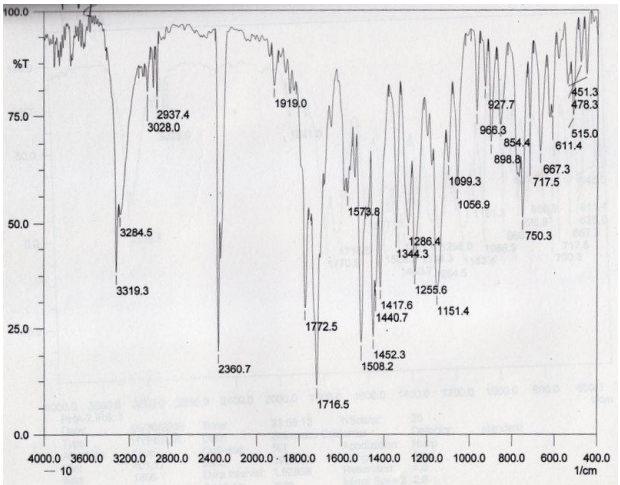
F1



F1b

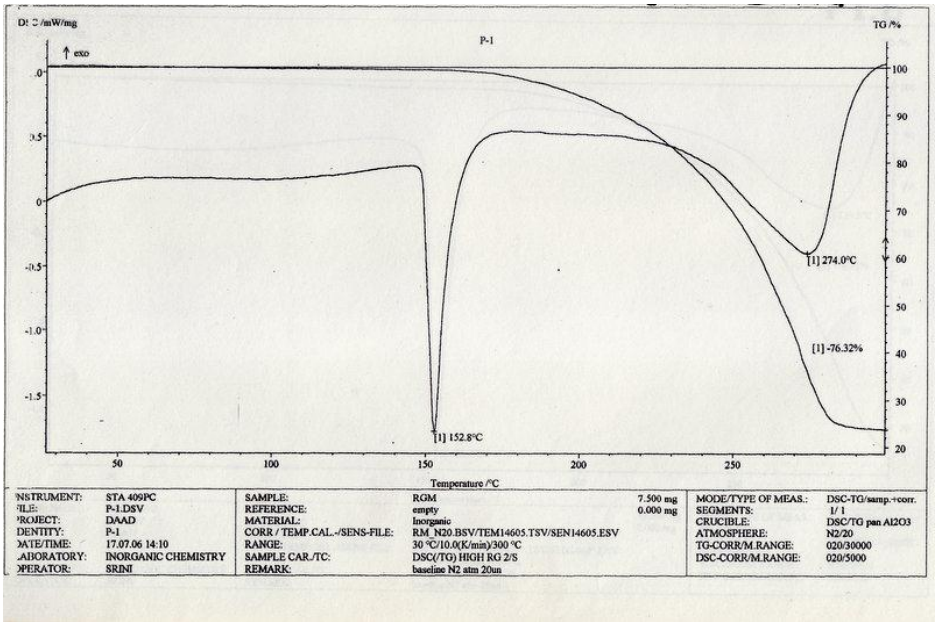


F1d

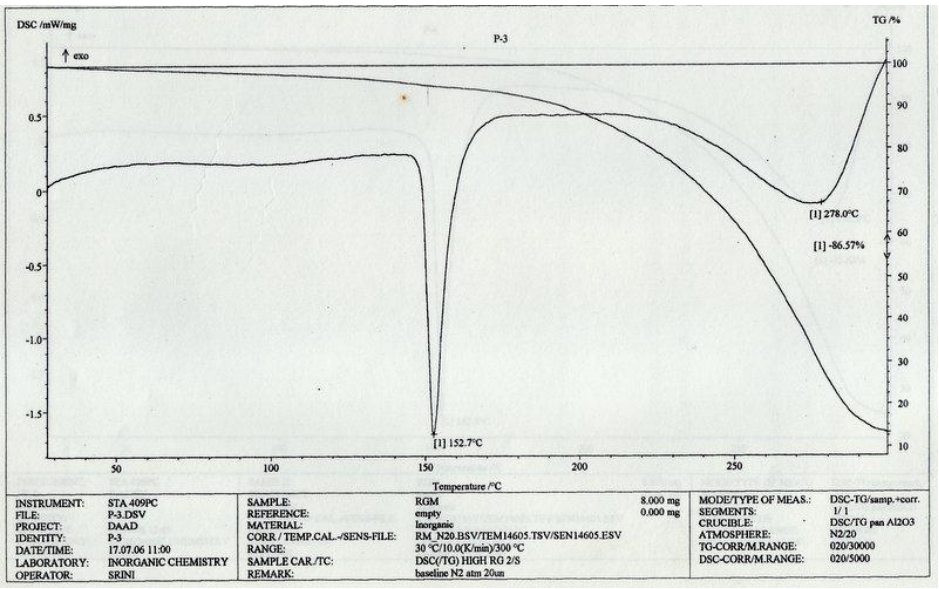


F1f

Figure 4: IR spectra of pure drug and formulations (F1, F1b, F1d and F1f)

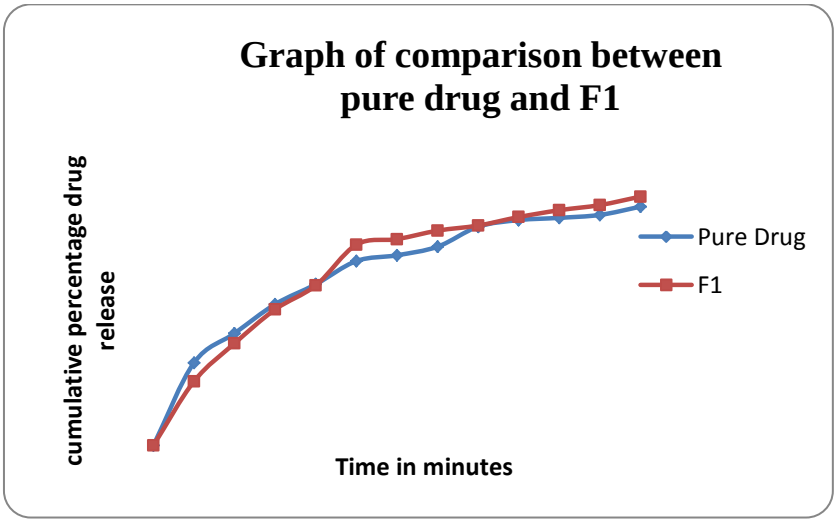


Pure drug

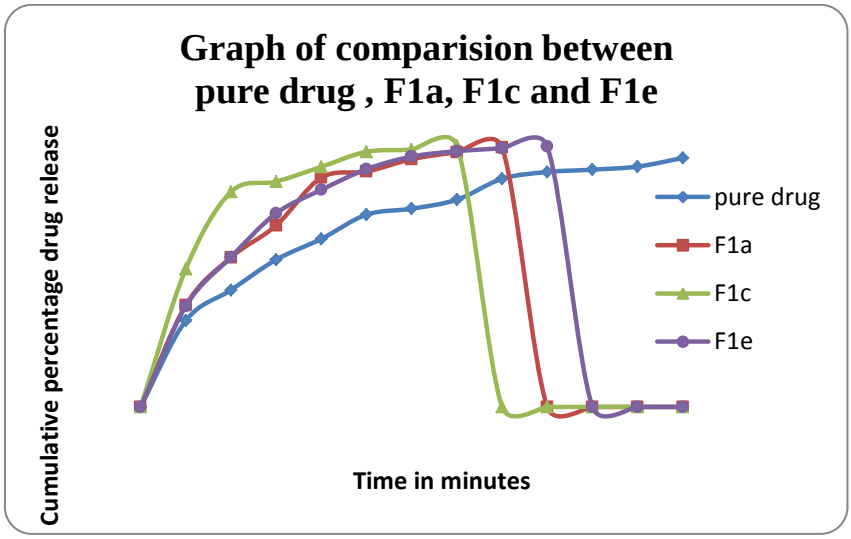


F1d

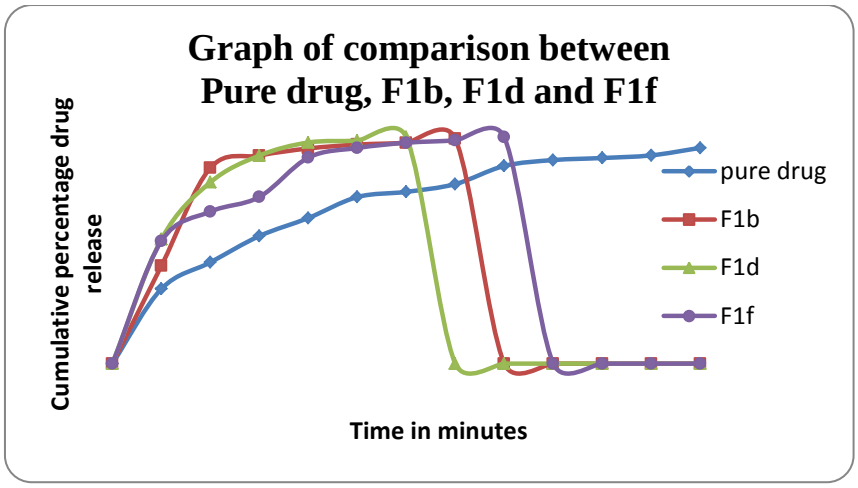
Figure 5: DSC thermogram of Pure drug and formulation (F1d)



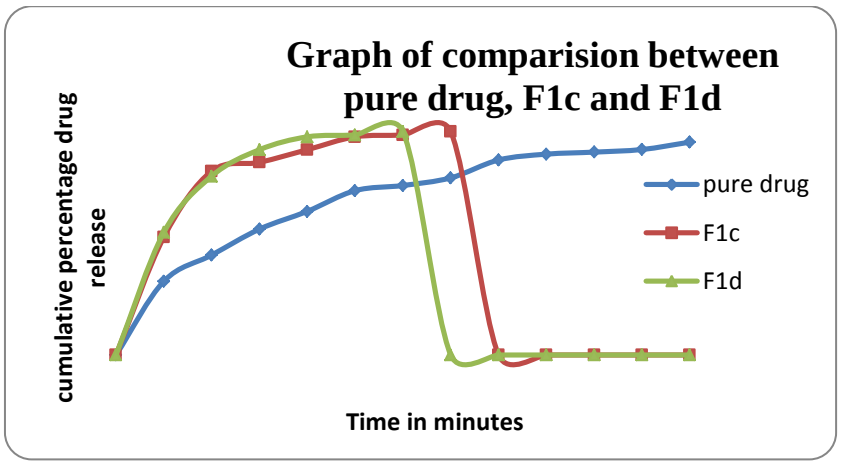
Graph 1: Graph of comparison between pure drug and F1



Graph 2: Graph of comparison between pure drug, F1a, F1c, and F1e



Graph 3: Graph of comparison between pure drug, F1b, F1d, and F1f



Graph 4: Graph of comparison between pure drug, F1c, and F1d

4. 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. Thus 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.

5. ACKNOWLEDGEMENTS

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