INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

DOI: https://dx.doi.org/10.33289/IJRPC.9.3.2019.970

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF APREMILAST BY RECRYSTALLIZATION TECHNIQUE

Hemanth Palepu, Sai Prasanna Prathipati,

Karthik Uppalapati and TP. Rao*

KVSR Siddhartha College of Pharmaceutical Sciences
Vijayawada, Andhra Pradesh, India.

ABSTRACT

The aim of present study was to enhance the solubility and dissolution rate of apremilast by recrystallization technique. In the present investigation, apremilast, a poorly soluble drug was recrystallized using various organic solvents. The recrystallized products obtained were characterized by analytical techniques such as (FT-IR) Fourier Transform Infrared Spectroscopy, X-Ray Diffraction (X-RD), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM) and subjected to in-vitro dissolution studies. Apremilast tablets were prepared by direct compression technique using selected recrystallized products and their drug release profile was compared with the marketed formulation. The results obtained from the above studies confirmed the change in crystal form of the drug apremilast. From the dissolution studies, the solubility and dissolution rate of recrystallized product in acetonitrile (APM-ACN) was found to be superior when compared to pure APM and similar results were obtained with the tablet formulation consisting of APM-ACN (formulation F2) which was high compared to marketed formulation. Finally, it can be concluded that a simple and effective method such as recrystallization can be employed to enhance the solubility and dissolution rate of poorly soluble drugs.

Keywords: Apremilast, Recrystallization, Solubility and Dissolution.

INTRODUCTION

Oral route of drug administration is the most significant and convenient method of administering a drug. Orally administered drugs completely absorb only when they possess optimum solubility in gastric medium and such drugs are assumed to project good bioavailability. The solubility and dissolution properties of drugs play an important role for their development into an oral dosage form. In this aspect, the aqueous solubility of any therapeutically active substance is a considerable attribute as it governs dissolution, absorption and thus the in vivo efficacy of the drug product.

The simple and most preferred choice for increasing the release rates of poorly soluble drugs is by improving their solubility through formulation approaches. The considerable approaches for the enhancement of solubility & dissolution rate include particle size reduction; modification of crystal habit (Recrystallization); complexation; solid dispersion technique etc. Crystallization is a (natural or artificial) process of formation of crystals from a uniform (or) homogeneous solution. The crystal habit of a drug is considered as an important variable in pharmaceutical manufacturing. These crystals can be modified by recrystallizing the drug in different ways, which effects its physicochemical properties such as melting point, solubility, flowability, tabletability and dissolution profile.

Recrystallization method is also simple and inexpensive enough for scaling up to a commercial level. It reduces time and cost by enabling faster operation with less machinery and fewer personnel. Hence, this technique was employed in the present experiment, for the enhancement of solubility and dissolution properties of a poorly soluble drug.

Apremilast is a novel, oral small molecule inhibitor of type-4 cyclic nucleotide phosphodiesterase (PDE-4) that works intracellularly to modulate a network of pro- and anti-inflammatory mediators. It is a medication used for the treatment of certain types of psoriasis and psoriatic arthritis. It may also be useful for other immune system related inflammatory diseases. APM being classified as a class IV drug by the BCS classification, possess low solubility and low permeability. It is practically insoluble in water and aqueous buffers, irrespective of pH range; soluble in lipophilic solvents such as acetone, acetonitrile, dichloromethane, methyl ethyl ketone, methylene chloride and tetrahydrofuran. The low solubility of APM influences the dissolution and absorption of the drug. The change in the crystal form of the drug may help in achieving the desired dissolution rates. Hence, in the present investigation, the solubility and dissolution rate of apremilast was improved by recrystallizing with various organic solvents.

MATERIALS AND METHODS

MATERIALS

Apremilast was obtained as a gift ample from Mylan Laboratories (Visakhapatnam, India). Apremilast tablets (Aprezo, reference formulation) was purchased from local market. Lactose monohydrate was obtained from Loba Chemie, Mumbai. Starch was obtained from Qualigens fine chemicals. Sodium starch glycolate was obtained from Yarrow chem products, Mumbai. Magnesium stearate from Rasayan Laboratories, Gujarat. Microcrystalline cellulose from Indian Research Products, Chennai and Talc from Otto Chemie Pvt Ltd., Mumbai. The various solvents used were of analytical grade and procured from various suppliers.

Method of preparation

Analytical method for the estimation of Apremilast

The analytical method used for determination of Apremilast is UV Spectrophotometric method. In the present study, Apremilast peak was observed at 230nm in UV Spectrophotometry.

Preparation of stock solution

Weighed accurately about 10 mg of Apremilast and dissolved it in few mL of methanol in a 10 mL volumetric flask and the volume was made up with methanol.

Preparation of Calibration Standards

For the estimation of Apremilast , the stock solution was subsequently diluted to get a series of dilutions 2, 4, 6, 8 and 10 µg/mL of solution using pH 6.8 sodium phosphate buffer and the absorbance was measured at 230 nm (UV-VIS spectrophotometer, SL-120, Elico) against pH 6.8 sodium phosphate buffer as blank. The calibration curve was shown in figure 1.

Preparation of samples by recrystallization technique

Method for Recrystallization

In the present study, recrystallization technique was employed to change the crystal habit of Apremilast to increase its solubility. The various solvents used for recrystallization were given in Table 1. In this method, 15ml of the solvent was taken in a petri dish, placed it on a heating mantel and the temperature was maintained at 45°C. Care should be taken not to reach the boiling point of the solvent and uniform temperature should be maintained for best results. The drug was added gradually with constant stirring until it forms a super saturated solution. The resultant product was cooled slowly at room temperature, dried at 40°C for the complete evaporation of the solvent. The recrystallized product was passed through #80 sieve and stored in a well-closed glass container for further use.

Physicochemical characterization of Apremilast and its recrystallized products

Fourier Transform Infrared Spectroscopic (FT-IR) Analysis

The samples were analyzed using an FTIR spectrometer (Bruker, Germany). Spectra were measured over the wave number range of 4000-500 cm^{-1} at a resolution of 1.0 cm^{-1}. The powder sample was simply placed on to the ATR crystal (Attenuated Total Reflection method) and the sample spectrum was collected. The sample was then cleaned from the crystal surface and the accessory was ready to collect additional spectra. ATR method is fast & less complicated than KBr pellet method and requires a very small amount of sample.

X-Ray Diffraction (X-RD) Analysis

The samples were analyzed using XRD-7000 X-Ray Diffractometer (Shimadzu, Japan) using Cu-kα line as X-Ray radiation (λ= 1.54 Å) at 40 kV & 30 mA power. X-Ray diffraction patterns were collected over the 2θ angle with in the scan range of 10°- 80° and a scan rate of 4°/min. The position and intensities of diffraction peaks were considered for the evaluation of crystallinities of pure APM and its recrystallized products.

Differential Scanning Calorimetry (DSC) Analysis

DSC analysis for the samples was carried out using DSC–60 Differential Scanning Calorimeter (Shimadzu, Japan). The samples of pure APM and its recrystallized products were accurately weighed & placed on the aluminum pan. The thermal behavior of the samples was investigated by heating them at a temperature rate of 4°C/min over a temperature range of 40-302 °C under an inert atmosphere flushed with nitrogen gas at a rate of 50 mL/min.

Scanning Electron Microscopy (SEM) Analysis

Scanning Electron Microscopy is widely used to study the morphology and surface topography of the powders. The samples were examined by placing them on a stub of metal with adhesive, coated with 40 - 60 nm of metal such as Gold/Palladium under a reduced pressure (60% vacuum) and observed at different magnifications. Some of the frequently observed crystal habits are given below.

In-vitro Dissolution studies for APM recrystallized products

In-vitro dissolution studies of apremilast-recrystallized products were carried out in 900 mL of 25mM pH 6.8 Sodium Phosphate buffer as dissolution medium using USP Type-II (Paddle) Dissolution Rate Test Apparatus (DISSO 8000, LAB INDIA) with agitation speed of 75 rpm. The temperature was maintained constantly at 37 ± 0.5°C. 5mL aliquots were withdrawn at specific time intervals (5, 10, 15, 20, 30, 45 & 60 min) and filtered using a 0.45µ nylon disc filters and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted and analyzed at 230nm using UV-Visible Elico SL120 spectrophotometer. Dissolution experiments were conducted in triplicate.

Formulation and Evaluation of Apremilast Tablets

In the present investigation, tablets containing Apremilast recrystallized products (equivalent to 30mg of pure apremilast) were prepared by direct compression method as per formulae given in the Table 2. Microcrystalline cellulose (MCC) was used as direct compressible vehicle, Lactose monohydrate (LMH) and Starch as diluents, Sodium starch glycolate (SSG) as super disintegrant, Talc and Magnesium stearate as glidant and lubricants respectively.

Method of Preparation - Direct compression

About 30mg of recrystallized APM was accurately weighed, added the other excipients to it and mixed thoroughly. Finally, talc and magnesium stearate were added and blended for 2 min. These blends were compressed with a 10mm punch to a hardness of 3kg/cm² by using a Cadmach single stage tablet compression machine. The prepared tablets were stored in an airtight container and evaluated for the post-compression parameters in triplicate.

Evaluation of Pre-compression properties of powder blends

Pre-compression testing is the first step in the rational development of dosage forms. It can be defined as an investigation of physicochemical properties of the drug substance alone and combined with excipients. The use of pre-compression parameters maximizes the chances of formulating an acceptable, safe, efficacious and stable product. The following pre-compression parameters were studied for the drug apremilast.

Bulk density

Bulk density was determined by pouring gently about 20gms of sample through a glass funnel into 20ml graduated cylinder. The volumes occupied by the samples were recorded. The bulk density was calculated as

Bulk density = weight of powder (g) / bulk volume (ml).

Tapped density

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted, and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density was calculated by using the following formula.

Tapped density = weight of powder (g) / tapped volume (ml)

Angle of Repose

The angle of repose is used to characterize the flow property of the powder blends. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. It is the maximum possible angle between surface of pile of powder or granules and the horizontal plane.

$$Angle\ of\ repose\ (\theta) = \tan^{-1}(h/r)$$

where,

r = radius of the heap
h = height of the heap.

Compressibility Index and Hausner's ratio

In recent years, the Compressibility Index (Carr's Index) and Hausner's ratio have become the fast, simple and popular methods for predicting powder flow characteristics. The Compressibility Index has been proposed as an indirect measure of the bulk density, size and shape, surface area, moisture content and cohesiveness of the materials.

Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of the powder.

Compressibility Index (I) = 100*[Tapped density – Bulk density / Tapped density]

Hausner's Ratio (H) = [Tapped density / Bulk density]

Drug – Excipient compatibility studies

FT-IR Analysis

The FT-IR studies were carried out to characterize the drug-excipient compatibility. The spectra were recorded over the range of 4000-500 cm^{-1} by using ATR method. These studies helps us to investigate the possibility of any chemical interaction between the recrystallized product and other excipients.

Evaluation of Post-compression parameters for Apremilast Tablets

The compressed tablets were evaluated for post-compression parameters such as drug content, uniformity of weight, friability, hardness, and disintegration time and dissolution properties.

Uniformity of weight of tablets

About 10 tablets were selected at random from each batch and weighed individually. The average weight and standard deviation of 10 tablets was calculated. The batch passes test for weight variation if not more than two of the individual tablets weight deviate from the average of the tablets.

Hardness

The hardness of the Apremilast tablets was measured with a Monsanto Hardness Tester (M/s Campbell Electronics, model EIC-66, India). Three tablets from each batch were tested for hardness and the results were reported.

Friability

From each formulation, about 10 tablets were selected at random and recorded their initial weight. Placed the tablets in a Roche Friabilator (M/S Campbell Electronics, India) and were subjected to 100 rotations at 25rpm. After the completion of 100 rotations, the tablets were dusted and recorded their final weight; the loss in weight indicated the friability. The formula for calculating friability is *%F = W1-W2 / W1 * 100 where*, 'W1' & 'W2' are the initial and final weights of the tablets.

Disintegration Test

In-vitro disintegration time for tablets was determined using disintegration test apparatus as per IP specifications. Two tablets from each formulation were placed in each tube of the disintegration apparatus containing 900ml of pH 6.8 phosphate buffer. Temperature was maintained at 37±0.5 °C. The time taken (in sec) for complete disintegration of the tablet with no palpable mass remaining in the apparatus was recorded.

In-vitro Drug release studies

In-vitro dissolution studies of apremilast tablet formulations were carried out in 900 mL of 25mM pH 6.8 Sodium Phosphate buffer as dissolution medium using USP Type-II (Paddle) Dissolution Rate Test Apparatus (DISSO 8000, LAB INDIA) with agitation speed of 75 rpm. The temperature was maintained constantly at 37 ± 0.5°C. 5mL aliquots were withdrawn at specific time intervals (5, 10, 15, 20, 30, 45 & 60 min) and filtered using a 0.45µ nylon disc filters and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted and analyzed at 230nm using UV-Visible Elico SL120 spectrophotometer. Dissolution experiments were conducted in triplicate. The drug release profiles of the formulated products were compared with the release profile of the marketed formulation. The dissolution data was fitted into model dependent methods like First order plots, in order to elucidate the drug release kinetics.

RESULTS AND DISCUSSIONS

Physicochemical characterization of Apremilast and its recrystallized products

FT-IR Spectroscopic Analysis

In order to study the possibility of any interaction of Apremilast with the solvents used, the samples were analyzed using Fourier Transform Infrared (FT-IR) Spectroscopy. If the drug and solvent would interact, then functional groups in the FT-IR spectra would show band shift and broadening in peaks. The FT-IR spectra obtained from various samples can simply regarded as the superposition of peaks of pure drug and solvents. Therefore, no interaction was observed between the drug and solvents. The

IR spectra of pure APM and its recrystallized product (APM-ACN) is illustrated in figure 2.

X-RD Analysis

The pure drug and selected APM recrystallized product (APM-ACN) were subjected to X-RD studies in order to investigate the crystallographic properties. The X-RD diffraction patterns of pure APM shows characteristic intense peaks at 11.29°, 17.80°, 26.49°. Whereas, in case of the recrystallized product in acetonitrile (APM-ACN) these peaks were absent or less intense and newer peaks were observed at 23.10°, 23.92°, 24.52°. The results indicated that the crystallinity of APM was affected by recrystallization method. The differences in the intensity of the existing peaks and the appearance of new peaks is an indication of change in crystal nature of the drug (APM) or its conversion into an amorphous form which depends upon the solvent used. The X-Ray diffraction patterns of the pure APM and its recrystallized products were given in figure 3.

DSC Analysis

Differential Scanning Calorimetry (DSC) is one of the widely used techniques for the characterization of crystals. DSC was performed in order to study the changes in crystal nature depending on its melting point. The results obtained from the thermograms shows an endothermic peak at 155.62 °C for the pure APM whereas the recrystallized product (APM-ACN) possessed a peak at a low melting point indicating the change in the crystal form of apremilast. The DSC thermograms of the recrystallized APM in acetonitrile along with the pure APM were shown in figure 4.

SEM Analysis

The Scanning Electron Microscopy (SEM) studies were carried out to assess the effect of recrystallization on the surface morphology (shape & size) of Apremilast. The SEM images of the pure APM and its recrystallized product showed irregular shaped crystals with different particle sizes, which infers that recrystallization, had not affected the morphology of the compound. The SEM photographs of pure APM & its recrystallized products (APM-ACN) were shown in figure 5

In-vitro Dissolution studies for Apremilast and its recrystallized products

The In-vitro Dissolution studies were performed to analyze the solubility and dissolution rates of recrystallized APM products and compare these results with that of the pure Apremilast. The in-vitro dissolution studies were performed for all the samples using 25mM pH 6.8 Sodium phosphate buffer as the dissolution medium to assess the various dissolution properties such as the percent drug release at 10 min (DP_{10}), 60 min (DP_{60}), $t_{50\%}$ and first order rate constants. The release profiles were shown in figure 6 and data was given in table 3

From the in-vitro dissolution data, it was clear that the APM recrystallized product with Acetonitrile (APM-ACN) showed a clear and remarkable increase in the dissolution rate when compared to the pure drug and other recrystallized APM products. The order of the dissolution rates of the APM recrystallized products was as follows

APM-ACN > APM-IPA > APM-THF > APM-DCM > APM-ETA > Pure APM > APM-ACE > APM- METH > APM-ETH.

Formulation and Evaluation of Tablets with Recrystallized APM products

From the results obtained in the above section, the APM recrystallized products with acetonitrile and Isopropyl alcohol were selected for the preparation of a tablet formulation.

All the formulations were subjected to pre-compression parameters to determine the type of flow and drug-excipient compatibility studies to assess the interaction of drug with the other excipients and the results were given in the Table 4. The formulated tablets were evaluated for the post-compression parameters like hardness, friability, disintegration time and the data was given in Table 5.

In-vitro Drug release data of Apremilast formulations

The in-vitro dissolution data of the tablets clearly portrays a remarkable increase in the dissolution rate of formulation F2 when compared to the other formulations. The drug release from F2 at 60 min was found to be 99%. A 1.34 fold increase in the drug release was observed when compared to the marketed formulation. The dissolution rates of various formulations were in the order of F2 **> F1 > F4 > F3 > MF**.

CONCLUSION

Apremilast, a drug with low solubility and low permeability was recrystallized using various organic solvents to improve its solubility and dissolution rates. The recrystallized products were subjected to physicochemical characterization and in-vitro dissolution studies. APM recrystallized product in acetonitrile (APM-ACN) was found to possess superior dissolution properties when compared

to its pure drug, which proves that the enhancement of solubility and dissolution properties of poorly soluble drugs can be achieved by recrystallizing the drug under suitable conditions. The formulation F2 (consisting of APM-ACN) showed high dissolution rate when compare to the marketed formulation.

ACKNOLEDGEMENTS

Authors are highly thankful to Siddhartha Academy of General and Technical Education, Vijayawada for providing necessary facilities to carry out this research work.

Table 1: Solvents used and Apremilast recrystallized products

Solvents	Amount of Drug Taken	Vol. of the solvent	Temp. (°C)	Sieve No.	Sample Code
Methanol	Suitable Qty.	15ml	45°C	#80	APM-METH
Ethanol	Suitable Qty.	15ml	45°C	#80	APM-ETH
Isopropanol	Suitable Qty.	15ml	45°C	#80	APM-IPA
Acetone	Suitable Qty.	15ml	45°C	#80	APM-ACE
Dichloromethane	Suitable Qty.	15ml	45°C	#80	APM-DCM
Acetonitrile	Suitable Qty.	15ml	45°C	#80	APM-ACN
Ethyl acetate	Suitable Qty.	15ml	45°C	#80	APM-ETA
Tetrahydrofuran	Suitable Qty.	15ml	45°C	#80	APM-THF

Table 2: Formulae for tablets containing Apremilast recrystallized products

Ingredients (mg/tab)	F1	F2	F3	F4
APM - ACN	30	30	-	-
APM - IPA	-	-	30	30
Micro Crystalline Cellulose	56	56	56	56
Starch	35	-	35	-
Lactose Monohydrate	-	35	-	35
Sodium Starch Glycolate	75	75	75	75
Magnesium Stearate	2	2	2	2
Talc	2	2	2	2
Total Wt. (mg)	200	200	200	200

Table 3: In-vitro dissolution properties of pure APM and its Recrystallized products

Recrystallized products	Disso profile at 10 min (DP_{10}) (%)	Disso profile at 60 min (DP_{60}) (%)	$t_{50\%}$ (min)
Pure APM	9.49	45.51	> 60
APM-METH	7.36	32.54	> 60
APM-ETH	6.54	31.47	> 60
APM-IPA	13.08	56.08	41
APM-ACE	13.31	34.67	> 60
APM-DCM	10.91	50.09	60
APM-ACN	8.62	68.01	39
APM-ETA	8.02	47.89	> 60
APM-THF	24.05	55.79	49

Table 4: Pre-compression studies for Apremilast tablet formulations

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose (°)	Carr's Index	Hausner's Ratio
F1	0.529 ± 0.01	0.579 ± 0.008	25.83 ± 0.40	7.30 ± 0.79	1.07 ± 0.01
F2	0.522 ± 0.10	0.571 ± 0.003	26.43 ± 0.46	8.57 ± 1.68	1.09 ± 0.02
F3	0.597 ± 0.06	0.637 ± 0.004	28.96 ± 0.29	6.32 ± 0.46	1.06 ± 0.05
F4	0.577 ± 0.40	0.655 ± 0.007	27.69 ± 0.33	11.87 ± 1.28	1.13 ± 0.01

Table 5: Post-compression studies for Apremilast tablet formulations

Formulation	Mean Weight ± % Variation	Hardness (Kg/cm^2)	Friability (%)	Disintegration Time (sec)
F1	200.00 ± 2.64	3.03 ± 0.05	0.61 ± 0.03	81.66 ± 1.52
F2	200.33 ± 0.57	3.03 ± 0.15	0.59 ± 0.01	79.33 ± 1.57
F3	201.66 ± 1.52	2.86 ± 0.05	0.58 ± 0.05	91.33 ± 2.08

F4	203.33 ± 2.51	3.06 ± 0.15	0.61 ± 0.01	80.66 ± 0.57

Table 6: In-vitro dissolution properties of formulated and marketed products

Formulation	Disso profile at 5 min (DP_5) (%)	Disso profile at 20 min (DP_{20}) (%)	Disso profile at 60 min (DP_{60}) (%)	$t_{50\%}$ (min)	$t_{90\%}$ (min)
F1	54.37	63.76	97.39	4.5	50
F2	71.76	99.09	99.09	3	10
F3	41.71	60.30	83.03	10	> 60
F4	42.26	59.33	90.12	13	60
MF	10.97	44.96	73.27	23	> 60

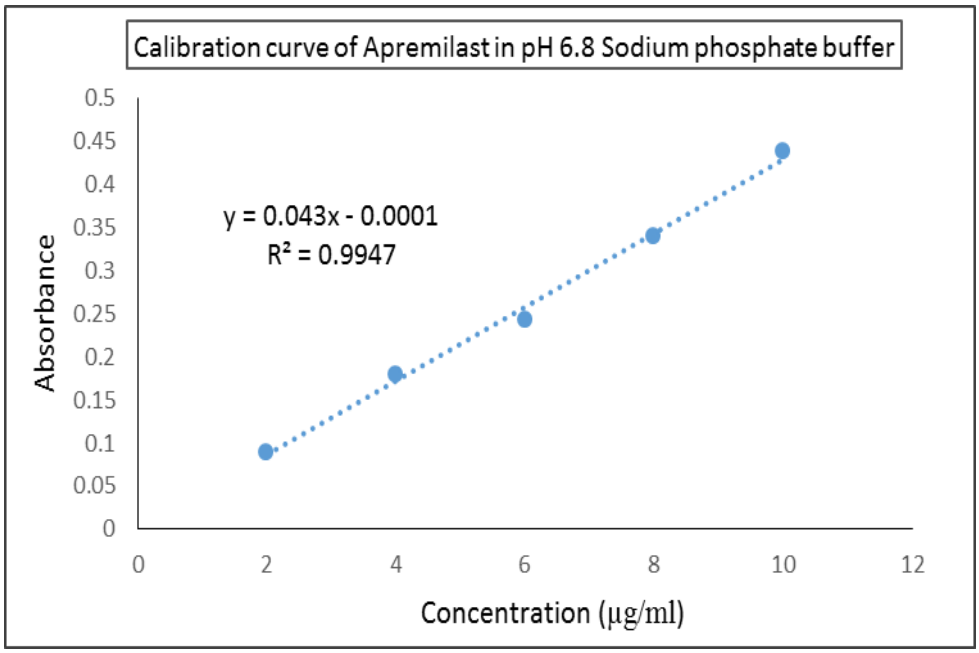
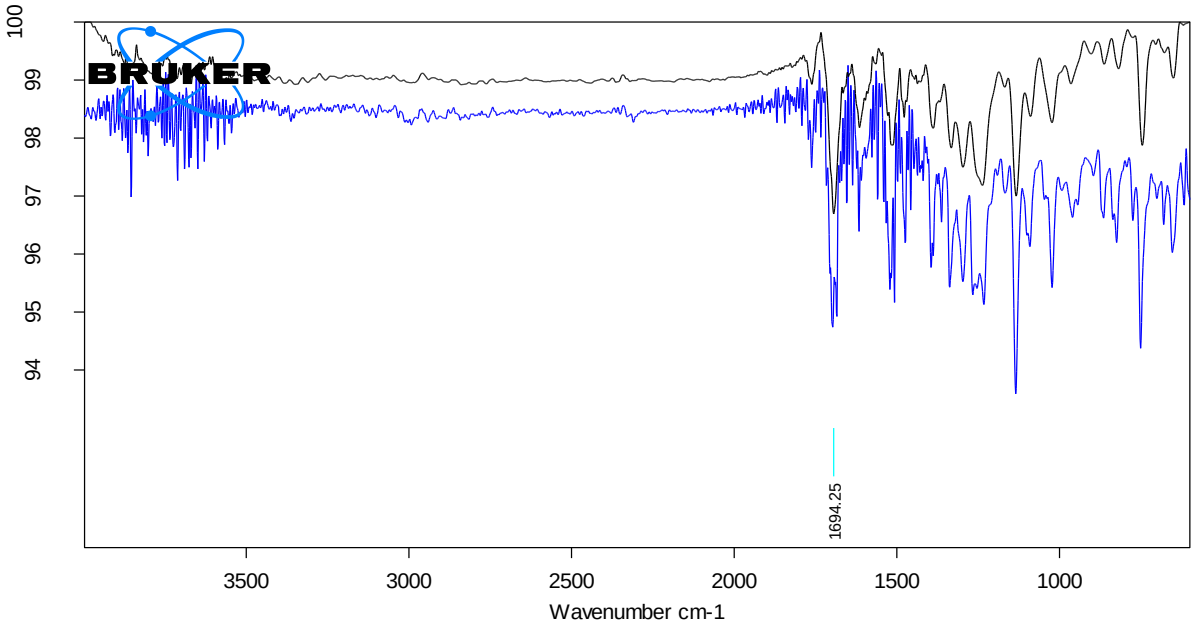


Fig. 1: Calibration curve for Apremilast in pH 6.8 Sodium phosphate buffer



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C:\OPUS_7.0.129\MEAS\BAP-W0.520	G	Instrument type and / or accessory	7/26/2019

Fig. 2: FT-IR spectrum overlay of pure APM & APM-ACN

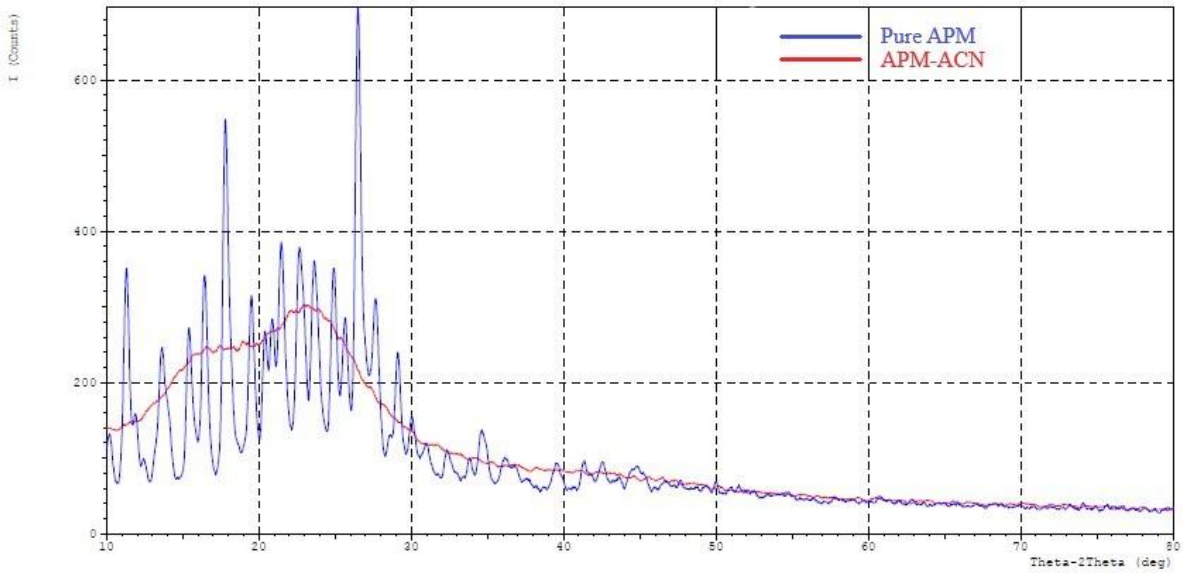


Fig. 3: X-Ray diffractogram overlay of pure APM & APM-ACN

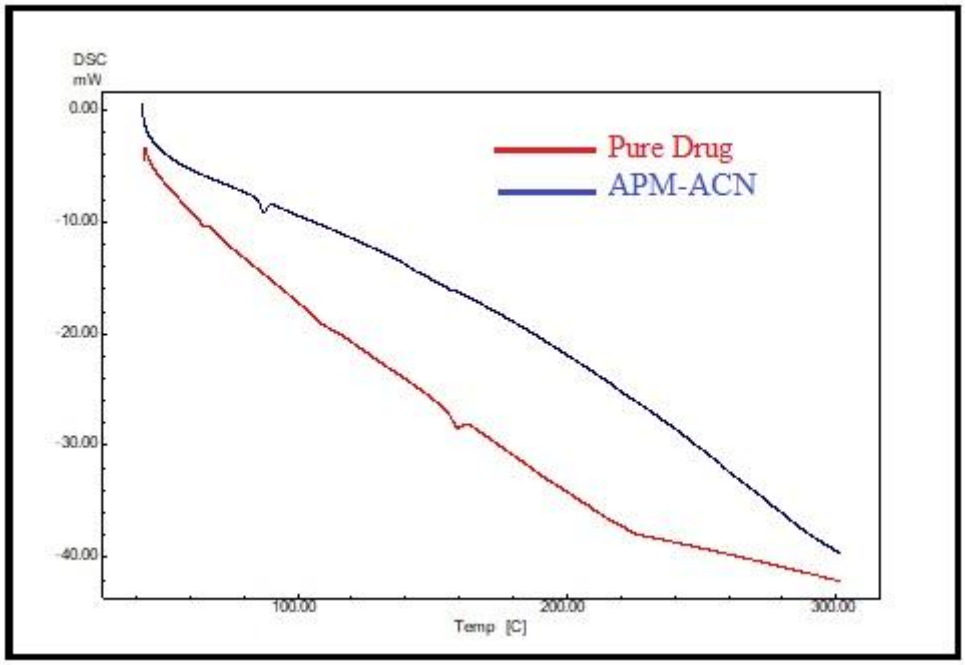
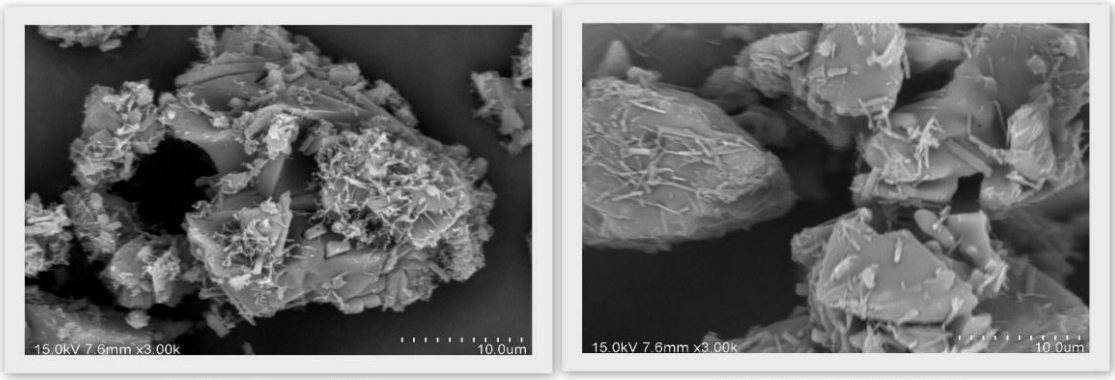


Fig. 4: DSC thermogram of pure APM and its recrystallized product APM-ACN



a) SEM of pure APM *b) SEM of APM-ACN*

Fig. 5[a-b]: SEM photographs of pure APM & APM-CAN

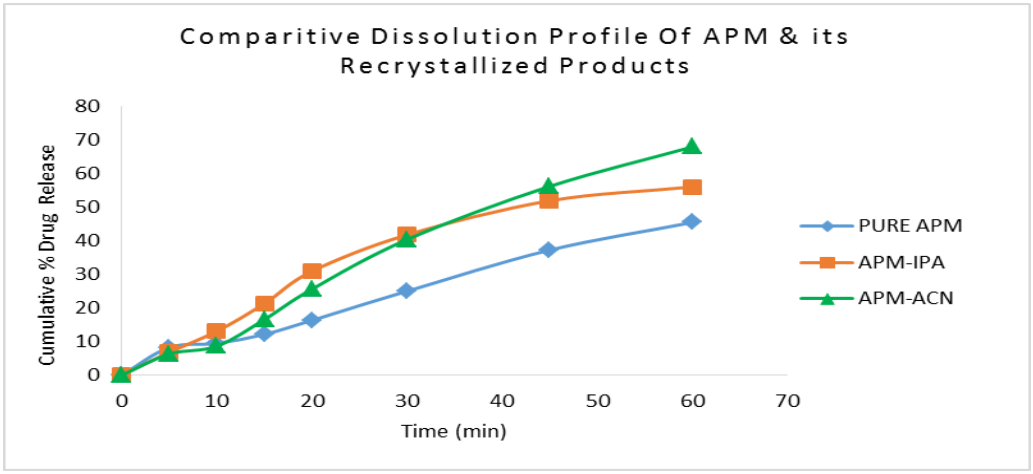


Fig. 6: Comparative Dissolution profile of APM & its optimized recrystallized products

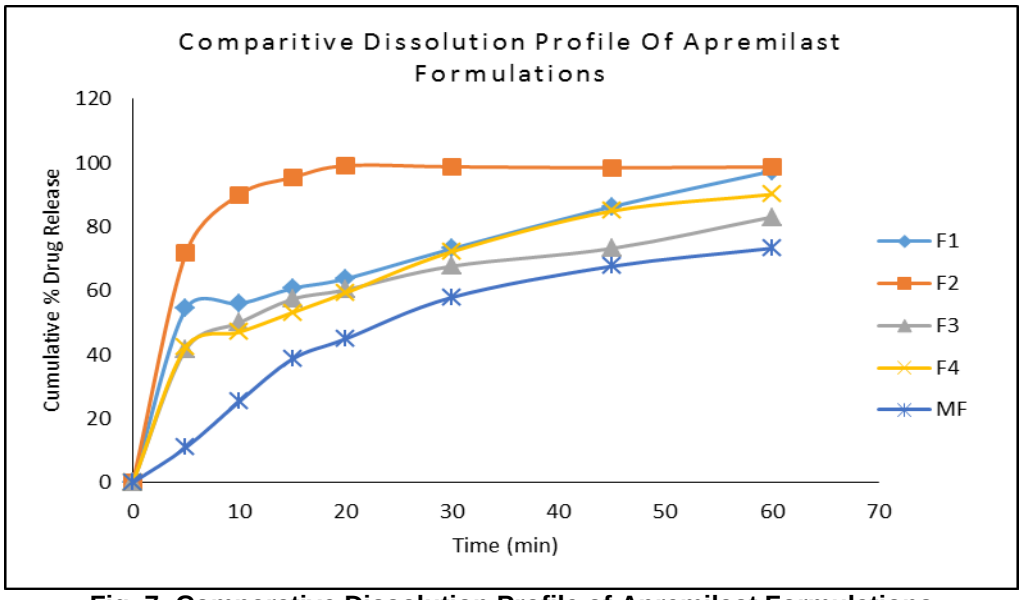


Fig. 7: Comparative Dissolution Profile of Apremilast Formulations

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