Original Article

Development of Nanocrystal Formulations With Improved Dissolution And Bioavailability for BCS Classs-II Drug- Quitapine

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Abstract

The aim of the present work was to improve the solubility and bioavailability of BCS Class-II Drug Quetiapine using nanocrystal approach.Quitapine nano crystals were prepared by bottom up technology.The resultant nanocrystals were characterised for its physio chemical parameters such as Melting point,solublity,Particle size and drug release From the results it is investigated that prepared nano crystals had improved solubility and particle size compared to pure drug.Among the prepared formulations F6 had shown 97% Drug release in thirty minutes which was 15 times more faster than the pure drug with reduce particle size for optimised formulation of 400nm (F6) using PVP k30 as a stabiliser. Drug Excipient compatibility studies were carried out using FTIR spectroscopic studies and reveals that there is no interaction between the drug and the selected excipients. From DSC studies it reveals that the reduced melting point of prepared nanocrystal of 126^{O}c from 180 ^{O}c of the pure drug clearly distinct the nanosized formation decrease the melting point increase the solubility and dissolution values this may be attributed to the weaker bonds of drug with the stabiliser.Thus nano crystal approach is an effective technology in improving the bioavailability of the pure drug quetiapine.

Keywords: Quitapine, Particle size solubility,bioavailability, Drug excipient compatability ,DSC studies

INTRODUCTION:

Today, nanotechnology permeates every aspect of our daily lives, in the increasing field of bio technology (where new tools to easily interact with proteins in ever smaller sizes are needed [Merkle 1999]) also in the pharmaceutical technology in producing the products in Nanosize range, nanosized agents can provide a whole range of benefits for effective drug therapy. Now a days, literature states that about 60% of all synthesised drugs coming directly from synthesis are poorly soluble[1-4] (Merisko-L iversidge 2002) that suffers with low bioavailability. Use of nanotechnology approaches improves the solubility and bioavailability of these drug molecules.[2,5] Nanocrystals are defined as crystalline nanoparticles between 200 and 500nm in size that have surface stabilizers on them. They increase the saturation solubility, dissolution rate and results in the improved oral bioavailability of drugs exhibiting dissolution rate dependent bioavailability.[3,7] Drug nanocrystals constitute a versatile formulation approach to enhance the pharmaco kinetic and pharmacodynamics properties of poorly soluble drugs. Drug Nano crystals should be separated from polymeric nanoparticles since the latter contain a drug and a polymeric matrix while drug Nano crystals do not. It enhances the oral bioavailability of the medicine leads to rapid onset of action. In the present study, nanocrystal formulations were developed using novel excipients.

Quetiapine is 2-[2-(4-benzo[b] [1,4] benzothiazepine-6-yl piperazin-1-4) ethoxy] ethanol an Antipsychotic agent used for the treatment of Schizophrenia bipolar disorder, psychosis associated with parkinsons disease and as adjunct treatment of major depressive disorder. It is Characterized by Low Solubility and High Permeability belongs to BCS class IIdrug suffers with low bioavailability of 9%.[5-6]

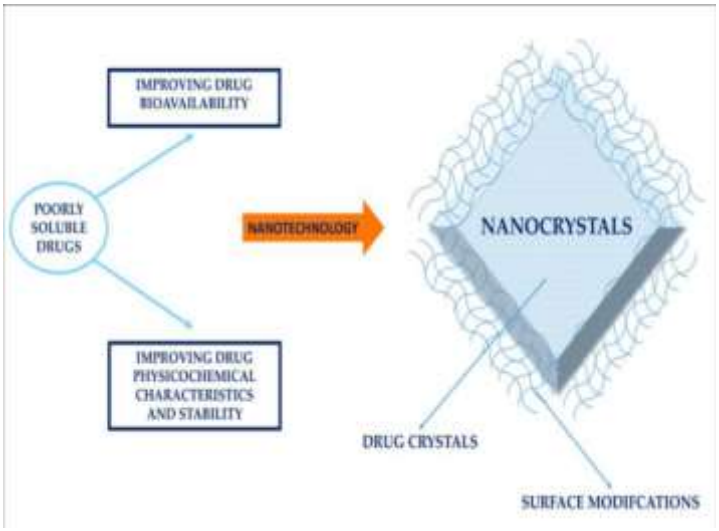

Fig.1: Nanocrystals with surface modifications

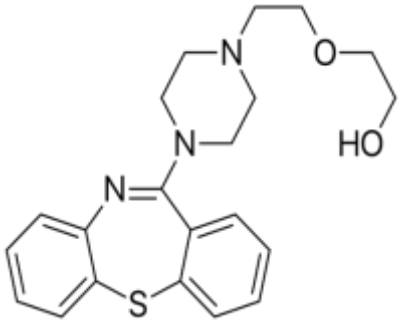

Fig.2: Structure of Quetiapine Fumarate

Materials:

Quitapine fumarate is gifted sample from Aurobindo Pharma Ltd Hyderrabad. HPMC and other chemicals HPMC,PVP,PEG were purchased from S.D.Fine chemicals Mumbai.

Preformualation parameters of Pure Drug Quetiapine fumarate:

S.No.	Parameters	Specifications as per COA	Observation
1.	Physical State	Solid	Solid
2.	Colour	White	White
3.	Odor	Odorless	Odorless
4.	Melting range	174-176°C	173°C
5.	Solubility in water	0.0403mg/ml	0.0421 mg/ml

Table-1: Observed physiochemical parameters of pure drug

Construction of calibration of Quetiapine Fumarate:

Primary Stock Solution:

Dissolve 100mg of drug in little quantity of ethanol until it dissolves completely and make with 6.8 pH Phosphate buffer up to the mark in 10ml of volumetric flask (1000µg/ml).[7]

Secondary Stock Solution:

Withdrawn 10ml of the sample from primary stock solution and dissolve it in 100ml of 6.8 Ph. Phosphate buffer (100µg/ml) which makes the secondary stock solution. Prepare 10, 20, 30, 40,50,60 and 70µg/ml concentration solutions from the secondary stock solution and then absorbance was measured using UV spectrophotometry at 294nm. The linearity graph was drawn by taking concentration on X-axis and Y-axis.[7]

S.NO	CONCENTRATION (µg/ml)	ABSORBANCE
1	4	0.038
2	8	0.089
3	12	0.147
4	16	0.192
5	20	0.226

Table 2: Calibartion studies of Quetiapine Fumarate pure drug in 6.8 pH Phosphate buffer

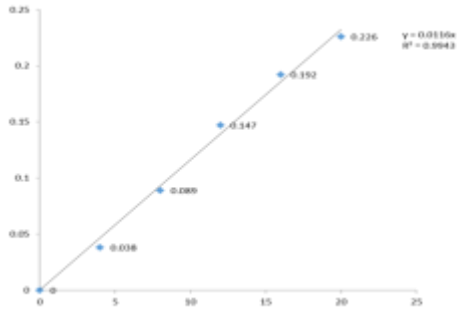

Fig.3: Calibration curve of Quetiapine Fumarate in pH Phosphate Buffer

Fourier transfer Infrared Spectroscopy:

Fourier transfer Infrared Spectroscopy in order to find any possible incompatibilities between drug and excipient. The spectrum was recorded for Quetiapine Fumarate and other excipients used in formulations using infrared spectrophotometer (BREUKER ALPHA). The samples were thoroughly blended with suitable diluting substances by precipitation technique and used for study [8].

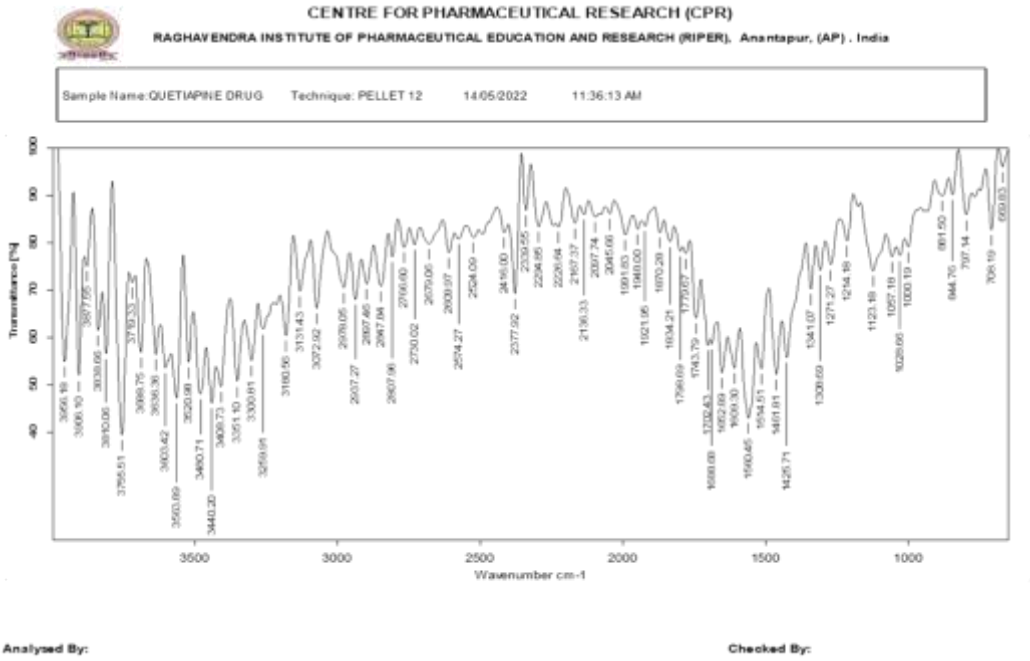

Fig 4: FTIR Spectrum of Quetiapine Fumarate

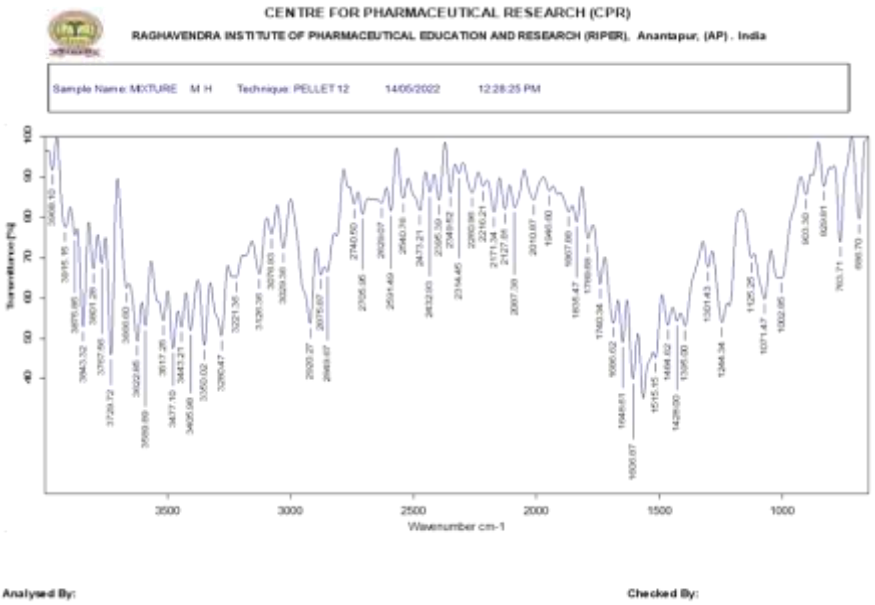

Fig 5: FTIR Spectrum of optimised formulation

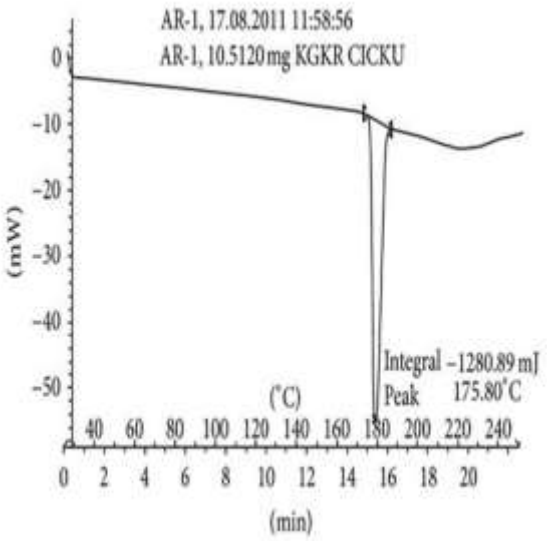

Fig-6: DSC thermogram of Quetiapine Pure drug

Formulation of Quetiapine Fumarate Nano Crystals by Ant solvent-Precipitation Technique:

INGREDIENTS	F1	F2	F3	F4	F5	F6
QUETIAPINE	100	4.5	2.5	6.5	4.5	10
HPMC	1%	1%	-	1%	-	1%
PEG-600	100	200	300	-	1.2	-
PVP-K30				100	200	300
ETHANOL	10	10	10	10	10	10
WATER	30	30	30	30	30	30

Table 3: Formulation table of Quitapine nanocrystals

Precipitation Method of Nanocrystals:

Quetiapine was formulated as Nano suspension using "Bottom-up Precipitation technique". Quetiapine (30 mg/ml) was dissolved in Ethanol on basis of its solubility and was injected to antisolvent (pre-cooled at 40C) containing PVP K30 (1%, W/W), HPMC (1%, W/W),and PEG-600 solution prepared in aqueous medium at 1200 rpm using mechanical stirrer Afterward, ultra sonication of the product suspension was carried for a different length of time (10,15,20, 25, and 30 min) at different ultrasonic inputs (200,300 and 400 W) at a pause of 3s will get nanocrystals through freeze drying process.[10,11,12]

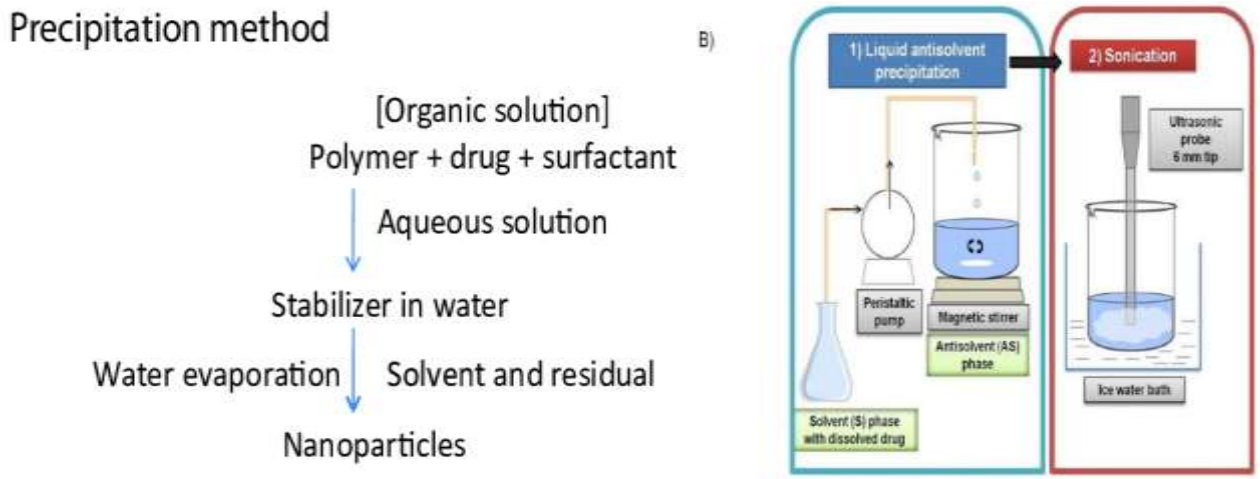

Fig7: Schematic Presentation of Crystal preperations:

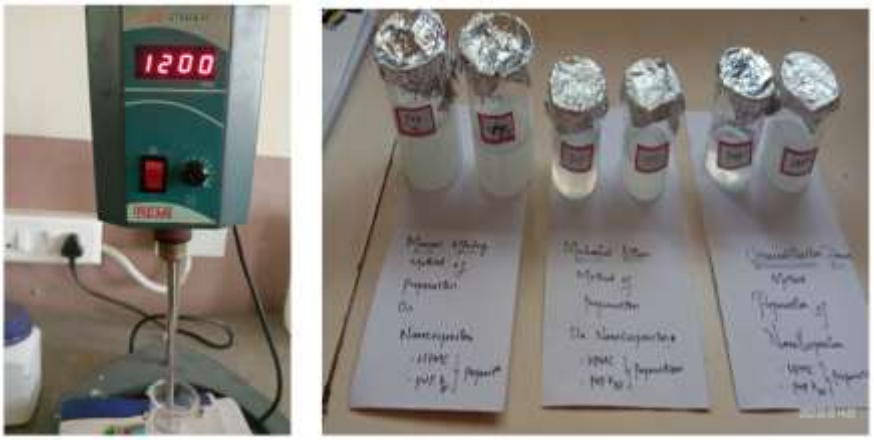

Fig.8: Pictogram of nanocrystals preparation using Anti solvent Precipitation Method

Results and Discussion:

Characterisation of Prepared Nano crystals:

1. Optical Microscopy:

Prepared nano crystals particle size was observed through Binocular Microscope under the magnification 100X resolution, to determine the particle size of prepared nanocrystals.

From the observation it is confirmed the formation of nanocrystals revealed the presence of crystalline structures which were Nano in appearance.[12]

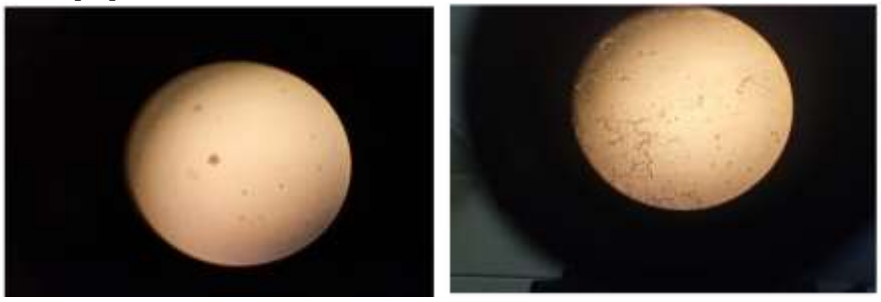

Fig.9: Optical photomicrographs of nanocrystals formulations(F6)

2. Particle Size and Zeta Potential:

Particle size of the optimised formulation was determined using Malvern Zetasizer at 25°C. means of results depicted in fig.10 which indicates the particle size is 700-1000nm range befor sonication,after sonication size reduced to 420nm.

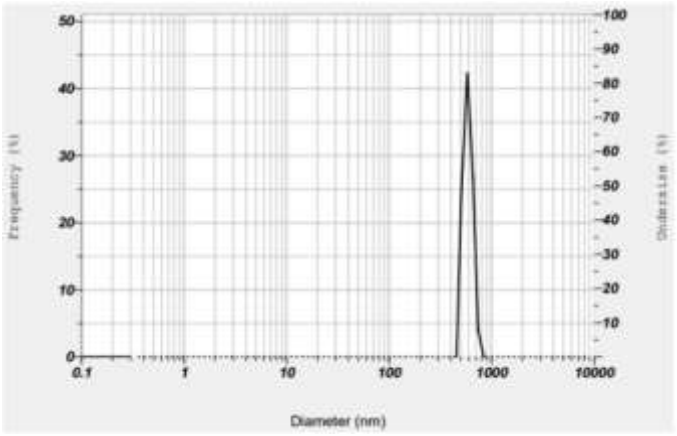

Fig 10: Particle size range of the optimised nanocrystals formulations(F6)

In-Vitro Dissolution Studies:

The in vitro dissolution studies were carried out using USPXXIII Dissolution Test Apparatus by Paddle method. 6.8pH Phosphate buffer used as dissolution medium and temperature maintained at 37±0.5°C with stirring speed of 50rpm value..At regular intervals of 5,10,15,20,25 and 30 minutes, 5ml of sample was withdrawn and replace the same with 6.8 pH Phosphate buffers and samples were filtered and analysed at 294nm using UV Spectrophotometer .(Shidmazu)[13]

Time Interval (in Minutes)	Cumulative Percentage of Drug Release formulations					
	F-1	F-2	F-3	F-4	F-5	F6
0	0	0	0	0	0	0
5	12.53±0.11	14.71±0.16	19.23±0.15	21.71±0.16	39.78±0.24	47.73±0.08
10	25.88±0.02	28.06±0.09	31.13±0.07	34.06±0.09	46.11±0.29	55.01±0.27
15	34.38±0.16	36.77±0.15	41.48±0.14	45.77±0.15	55.82±0.18	67.53±0.16
20	59.46±0.12	52.65±0.17	51.19±0.13	56.65±0.17	70.38±0.17	73.21±0.5
25	66.74±0.4	69.57±0.21	71.68±0.07	77.57±0.21	79.68±0.23	84.53±0.17
30	71.68±0.12	75.08±0.12	77.75±0.08	80.08±0.12	89.39±0.25	97.48±0.09

Table 4: Drug Release characteristics of prepared nano crystal Formulations

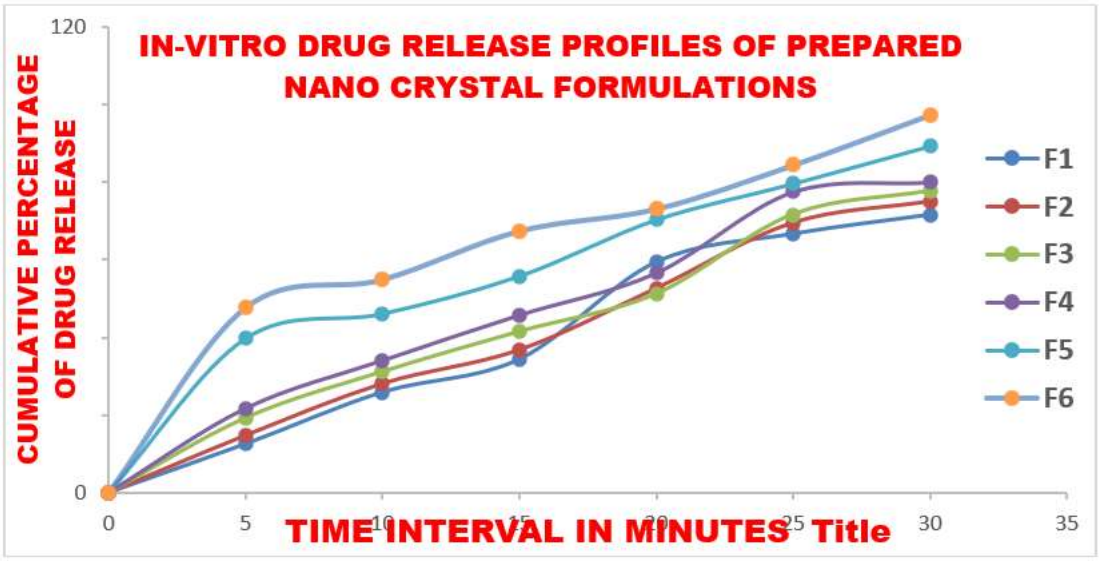

Fig.11: IN-VITRO DRUG RELEASE PROFILES OF PREPARED NANO CRYSTAL FORMULATIONS

Comparison of Drug release studies of pure drug and Optimised (F6) formulation:

Time Interval	Cumulative % of Drug Release	
	Pure Drug	F6
0	0	0
5	3.41±0.22	47.73±0.08
10	5.93±0.18	55.01±0.27
15	9.87±0.35	67.53±0.16
20	17.32±0.41	73.21±0.5
25	23.57±0.35	84.53±0.17
30	32.51±0.25	97.48±0.09

Table 5: Dissolution studies of Pure Drug & Optimised Formulation

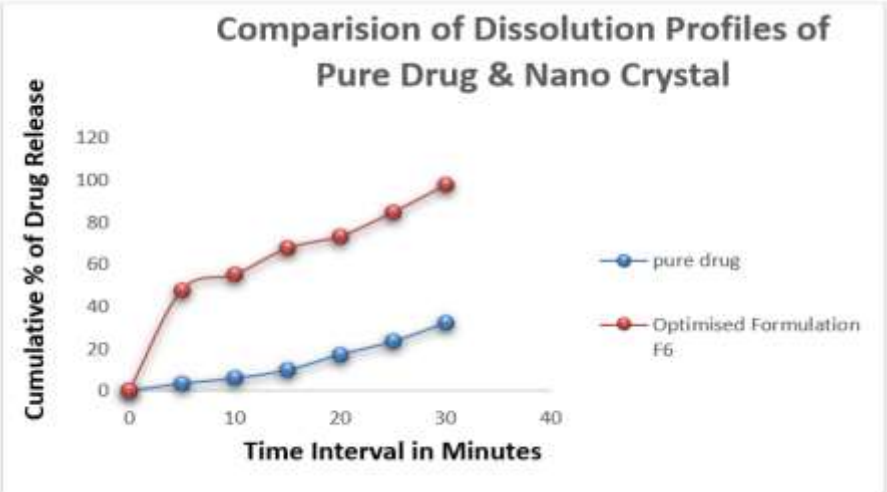

Fig 12: Comparision of Dissolution Profiles of Pure Drug & Nano Crystal

Release Kinetics of Optimised Formulation (F6):

Optimised formulation	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
Code	slope	R^2	slope	R^2	slope	R^2	slope	R^2
F-6	3.650	0.739	0.040	0.830	17.39	0.981	0.815	0.815

Table -6: kinetics Phenomenon of Optimised formulation (F6)

From the Fig 14 it reveals that co crystal formulations prepared with PVPas polymer had enhanced the drug release behaviour compared to PEG this may be attributed to the more hydrophilicity which favour improved solubility and dissolution.The optimised formulation had shown effective cumulative drug release of 97.48% in 30 minutes. The optimised formulation drug release studies compared with pure drug and it was observed that the drug release is drastically increased through nano crystal formulations. The drug release kinetics observed in table no.15 clearly indicates that the optimised formulations follows first order kinetics as value is nearer to linearity.From the Higuchis and Korsemeyer peppas equation values given in table 11 it clearly indicates that the dissolution process depends upon the mass of the drug remained in the dissolution fluids at time rather than surface area as constant.[14]

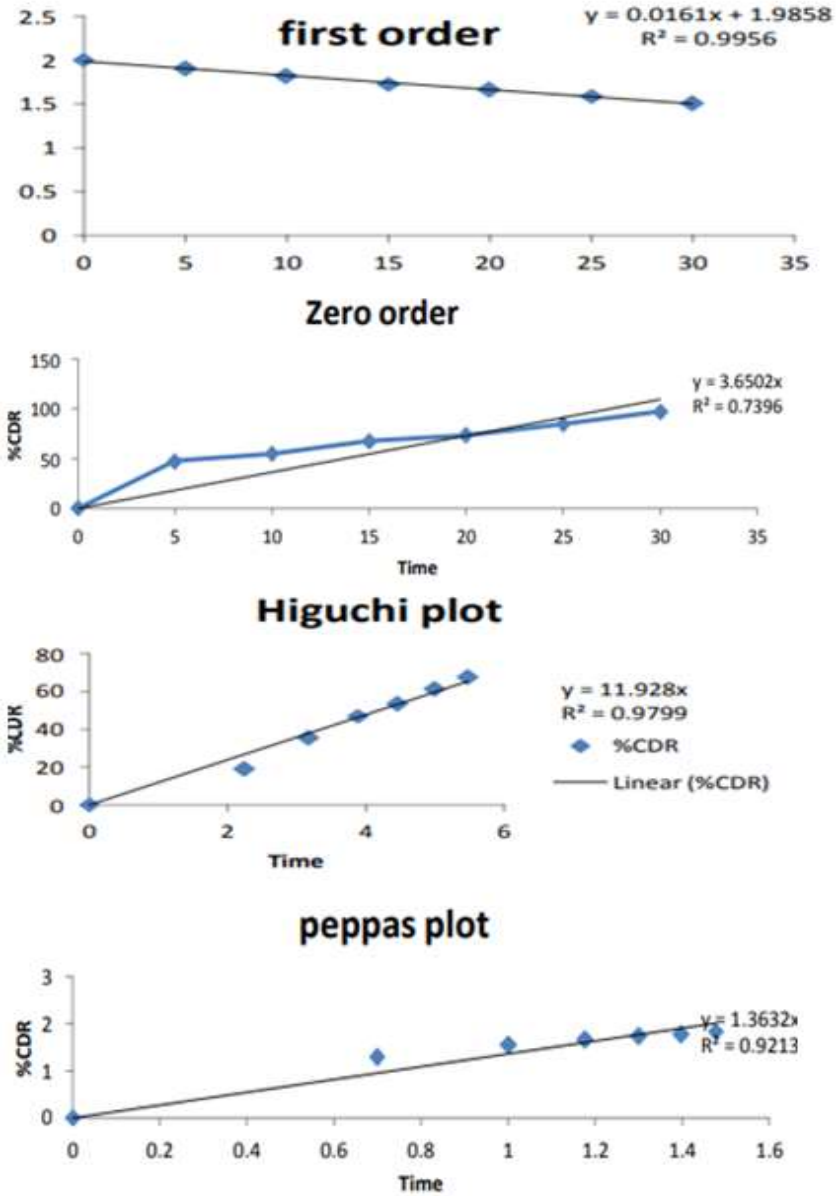

Fig 13: Invitro Release kinetics of Optimised formulation (F6)

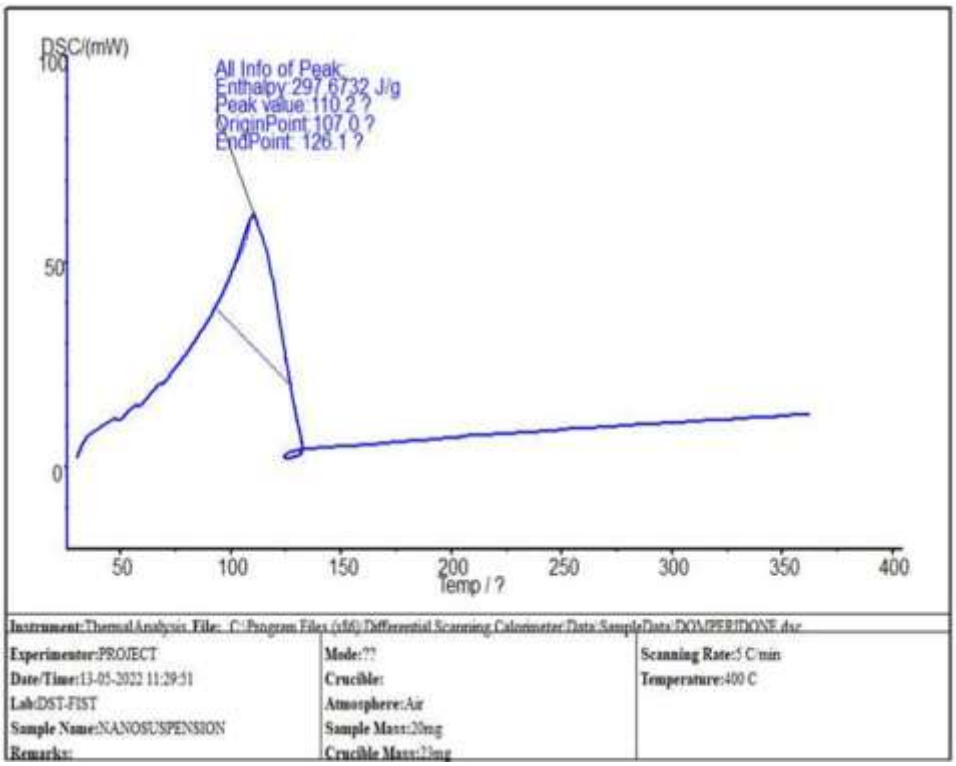

Fig.14. DSC thermogram of optimised formulation F6

From the peak observed in Fig.14 the melting point of optimised formulation was found to be 126^0C and the pure drug shown in Fig.6 was 180 ^{0}C thus results clearly indicates that the prepared nanocrystal had reduce particle size in nanometres which indicates decreased particle size,decrease the melting point and increase the dissolution of the nanocrystals.

CONCLUSION:

From the studies carried out on the pure drug and nanocrystalline formulations,it is observed that nanocrystal formulation is an effective approach in improving the solubility and bioavailability of the poorly soluble drug moiety with effectiveness of decreased particle size 420nm observed in optimised formulation (F6)and increased dissolution rate achieved 97% in 30 minutes for the optimised formulation**.** DSC values indicates the sizereductionof nnaocrystals compared to the pure drug. Increased concentration of stabiliser PVP-K30 increased the formation of coat onto the crystal and favours the stability aspect of nanocrystal with desired size reduction. Thus it is concluded that nanocrystals are the future aspects of manufacturing process in an industry due its inexpensive process with reliability and stability.

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