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RESEARCH ARTICLE

SOLUBILITY ENHANCEMENT OF LERCANIDIPINE HYDROCHLORIDE BY COCRYSTALLISATION.

***Asija Rajesh[1], Mangukia Dhruv[2], Asija Sangeeta[2], Patel Jaimin[2], Patel Chirag J[2], Patel Pinkesh[2]**

[1]Professor & Principal, Maharishi Arvind Institute of Pharmacy, Mansarover, Jaipur, Rajasthan, India-302020.

[2]Department of Pharmaceutics, Maharishi Arvind Institute of Pharmacy, Mansarovar, Jaipur, Rajasthan, India-302020

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ABSTRACT

In this study, the significant effect of malonic acid on enhancement of solubility of lercanidipine hydrochloride by simple solvent change process has been demonstrated. Malonic acid and lercanidipine hydrochloride were simultaneously crystallised using water as anti-solvent. The pure drug and different concentrations of malonic acid were characterized in terms of solubility, percentage yield, melting point, crystallinity, thermal behaviour, compatibility studies and surface morphology. The optimised cocrystal formulation exhibited enhancement in aqueous solubility.

KEY WORDS: Lercanidipine Hydrochloride, Cocrystals, Solvent Change Approach, Solubility Enhancement.

INTRODUCTION:

Solubility is an intrinsic material property describing solubilisation phenomena [1]. For any drug to be absorbed into systemic circulation, it has to be present in solution form at the site of absorption. In many cases, solubility of drug is not sufficient enough for it to solubilise completely in the fluids at the site of absorption. For such drugs, solubility is the limiting factor to drug absorption and when administered as solid dosage form, dissolution is the rate limiting step to drug absorption. Thus solubility enhancement of such drugs also improves the bioavailability [2].

There are several ways by which drug solubility or the dissolution rate can be enhanced. Cocrystallisation is one such technique. There are several methods to prepare cocrystals. These are: solution method, grinding method, supercritical fluid technology, ultrasound assisted solution crystallisation and cocrystallisation by solvent change approach [3].

In solvent change approach, API is dissolved in an organic volatile solvent in which API has maximum solubility and an aqueous solution of cocrystal former/stabilizer is prepared. The two solutions are mixed under stirring conditions and are allowed to dry either in stirring or undisturbed condition. Cocrystals produced by solvent change/anti-solvent/solvent precipitation method are of narrow size distribution and of high polymorphic purity. Solvent change approach is advantageous against traditional techniques like jet milling, milling in a pearl or ball mill or high pressure homogenisation since later techniques frequently produces agglomerates due to high energetic surfaces creating materials with poor wettability properties [4, 5, 6, 7].

Physicochemical properties of cocrystals are a combination of individual properties of both drug and cocrystal former. For most of the properties of cocrystals, when quantified, has a value that lies between conformer and pure drug. The previous statement is supported by the data of melting point analysis of cocrystals which usually, is found to be in between pure drug and cocrystal former. From stability point, Cocrystals are stable with respect to moisture under normal processing and storage conditions. Thermal stress and chemical stability are relatively less studied areas about crystal properties. Pharmaceutical cocrystallisation has emerged as a novel technique to improve the solubility of poorly water soluble drugs. Solubility of cocrystal product is usually more than that of pure drug but less than that of conformer. However, this is not always the case since there has been evidence of reduced solubility of cocrystal product in comparison to API. If solubility of cocrystal product is increased in comparison to API, intrinsic dissolution is also improved for cocrystals in comparison to pure drug and vice versa. Bioavailability is greatly improved for cocrystals in comparison to pure drug [6, 8].

Practical yield, drug content, crystal size and solubility study are preliminary studies that are required to be performed for a cocrystal product. Practical yield gives an idea whether the process can be applied for commercial production or not. Percentage drug content gives the value

*Corresponding author: Dr. Asija Rajesh | Email: asijar@gmail.com

of drug recovered in final product form while solubility study confirms whether process was successful or not. Crystal size at preliminary level may be evaluated by optical microscope using stage micrometer and eye-piece micrometer. Cocrystals are also evaluated for *in vitro* dissolution studies, stability studies and bioavailability studies [9, 10, 11, 12].

IR is a very common spectroscopic technique in determining the chemical conformation of compounds. DSC is the preferred technique for obtaining comprehensive melting point data and additional thermal data, such as the enthalpy of melting, can also be obtained simultaneously. SEM is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals which provide information about the sample's surface topography. It is applied to determine the cocrystal micrograph and particle size [13].

Single X-ray diffraction (SXRD) is a basic characterisation technique for determination of the solid-state structure of cocrystals at an atomic level. However, the problem is that a single pharmaceutical cocrystal which is qualified for SXRD testing cannot always be produced. Therefore, powder X-ray diffraction (PXRD) are utilised more frequently to verify the formation of cocrystals [14, 15].

Lercanidipine is a calcium channel blocker of dihydropyridine class acting as antihypertensive drug. Lercanidipine exhibits very slight solubility in water. Hence, it was selected for solubility enhancement by crystallization.

MATERIALS AND METHOD:

MATERIALS:

Lercanidipine hydrochloride and chitosan were obtained as a gift sample from torrent research center, Ahmedabad, Gujarat. Malonic acid, caffeine, nicotinamide, saccharin sodium, HPMC (5 cps), citric acid monohydrate, PEG 4000, urea, p- amino benzoic acid (PABA), methanol and ethanol were purchased from Central drug house, New delhi, India. All the chemicals used were of analytical grade.

METHODS:

PREPARATION OF COCRYSTALS:

A solution of Lercanidipine hydrochloride in ethanol and a solution of cocrystal former in distilled water was prepared. The two solutions were mixed, stirred for 5 minutes to ensure uniform mixing and was left for drying under undisturbed conditions. Based on results of pilot study, optimisation study was performed.

EVALUATIONS:

PERCENTAGE YIELD:

Percentage yield was calculated for all the batches that were selected for optimisation study. Percentage yield for optimised batch (the one with maximum solubility) was repeated for another 5 trials and average yield for 6 batches was calculated.

DETERMINATION OF MELTING POINT:

Melting point was determined using Thiele's tube filled with liquid paraffin. Melting point was determined for all the batches with positive result.

SOLUBILITY ANALYSIS:

The solubility of the prepared product was analysed by agitation method. Saturated solution of prepared product was prepared in water and stirred for 24 hours. The solution was then centrifuged for 15 min over 10,000 rpm and filtered through whatmann filter paper (#44). The concentration of lercanidipine was determined using UV-visible spectrophotometer (UV-1800, Shimadzu corporation) against water as blank.

COMPATIBILITY STUDIES (IR SPECTROSCOPY):

IR spectroscopy was performed to check the compatibility of drug with coformer. IR spectroscopy was conducted using a Shimadzu IR 8300 Spectrophotometer. The procedure consisted of dispersing a sample in KBr and compressing into discs by applying a pressure of 5t for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded.

SCANNING ELECTRON MICROSCOPY (SEM):

The surface characteristics of optimised batch of cocrystals were studied by SEM (JSM-5610, Tokyo, Japan). The samples were mounted on double sided adhesive tape and coated with platinum sputter coater and then analysed. The accelerating voltage was 15kV.

POWDER X-RAY DIFFRACTION (P-XRD):

The powder X-ray diffractogram (D/max-r A, Rigaku Denki, Japan) was scanned with the diffraction angle increasing from 5° to 50°, 2θ angle, with a steep angle of 0.04° and a count time of 1 second.

DIFFERENTIAL SCANNING CALORIMETRY:

The samples were sealed in the aluminum crimp cell and heated at the speed of 10°C/min from 0 to 500°C in

nitrogen atmosphere (60 ml/min). The peak transition onset temperature of drug, phospholipid, drug–phospholipid complex and physical mixture of drug and phospholipid were determined and compared with the help of a Mettler DSC 30 S (Mettler Toledo, UK).

RESULTS AND DISCUSSION:

The percentage yield of cocrystals of lercanidipine ranged from 33.33% to 68.96%. Results are mentioned in table 4 and table 5. Solubility analysis of pilot batches revealed maximum solubility in cocrystals prepared using malonic acid and saccharin sodium as conformer. Melting point data was further confirmed by DSC analysis.

No new peaks were observed in the IR spectra of physical mixture and cocrystals. These observations suggest that some weak physical interactions between drug and coformer take place during the formation of phytosomes.

The XRD data of prepared cocrystals exhibited an increase in number and intensity of peaks compared to pure lercanidipine indicating crystallinity or partial amorphization.

Table 1: Table indicating formulation for solvent change approach (Pilot study)

Batch code	Solution A		Solution B		Polymer concent-ration	aqueous tri sodium citrate solution (5 ml)	Ratio of solution A : solution B
	Drug	Ethanol	Coformer	Solvent			
B101	50 mg	1 ml	Chitosan	GLA (1% v/v)	0.1 %w/v	-	1:4
B102	100 mg	1 ml	Caffeine	DW	0.1 %w/v	-	1:4
B103	50 mg	1 ml	Malonic acid	DW	0.1 %w/v	-	1:4
B104	50 mg	1 ml	Nicotinamide	DW	0.1 %w/v	-	1:4
B105	50 mg	1 ml	Saccharin sodium	DW	0.1 %w/v	-	1:4
B106	50 mg	1 ml	Chitosan	GLA (1% v/v)	0.1 %w/v	0.2 %w/v	1:4
B107	50 mg	1 ml	HPMC (5 cps)	DW	0.05 %w/v	-	1:4
B108	50 mg	1 ml	PEG 6000	DW	0.1 %w/v	-	1:4
B109	50 mg	1 ml	Citric acid monohydrate	DW	0.1 %w/v	-	1:4
B110	50 mg	1 ml	PEG 4000	DW	0.1 %w/v	-	1:4
B111	50 mg	1 ml	Urea	DW	0.1 %w/v	-	1:4
B112	50 mg	1 ml	Chitosan	GLA (1% v/v)	0.1 %w/v	2 %w/v	
B113	50 mg	1 ml	PABA	DW	0.1 %w/v	-	1:4

Table 2: Table indicating formulation for solvent change approach (optimisation study)

Batch code	Solution A		Solution B		Polymer concentration	Ratio (solution A:solution B)
	Drug	Solvent (Ethanol)	Conformer	Solvent		
F1	50 mg	1 ml	Saccharin sodium	Distilled water	0.1 %w/v	1:4
F2						1:3
F3						1:2
F4						1:1
F5	50 mg	1 ml	Saccharin sodium	Distilled water	0.05 %w/v	1:4
F6						1:3
F7						1:2
F8						1:1
F9	50 mg	1 ml	Malonic acid	Distilled water	0.1 %w/v	1:4
F10						1:3
F11						1:2
F12						1:1
F13	50 mg	1 ml	Malonic acid	Distilled water	0.05 %w/v	1:4
F14						1:3
F15						1:2
F16						1:1

Table 3: Observation table for solvent change approach (Pilot study)

Batch code	Observation	Result	Conclusion
B101	Huge variation in crystal size and shape.	Positive	This method was successfully employed for the preparation of cocrystals of Lercanidipine hydrochloride
B102	Huge variation in crystal size and shape.	Positive	
B103	Highest degree of uniformity in crystal size and shape.	Positive	
B104	Huge variation in crystal size and shape.	Positive	
B105	Highest degree of uniformity in crystal size and shape.	Positive	
B106	Huge variation in crystal size and shape.	Positive	
B107	Huge variation in crystal size and shape.	Positive	
B108	Huge variation in crystal size and shape.	Positive	
B109	Huge variation in crystal size and shape.	Positive	
B110	Huge variation in crystal size and shape.	Positive	
B111	Huge variation in crystal size and shape.	Positive	
B112	Huge variation in crystal size and shape.	Positive	
B113	Huge variation in crystal size and shape.	Positive	

Table 4: Percentage yield (optimisation study)

Batch code	Weight of reactants (mg)	Weight of product (mg)	Percentage yield
F1	54	31	57.41%
F2	53	24	45.28%
F3	52	23	44.23%
F4	51	17	33.33%
F5	52	31	59.62%
F6	51.5	23	44.66%
F7	51	22	43.14%
F8	50.5	24	47.52%
F9	58	37	63.79%
F10	53	30	56.60%
F11	52	26	50.00%
F12	51	21	41.18%
F13	52	19	36.54%
F14	51.5	20	38.83%
F15	51	23	45.098%
F16	50.5	20	39.60%

Table 5: Percentage yield (optimised batch)

Batch code	Weight of reactants (mg)	Weight of product (mg)	Percentage yield
F9	58	37	63.79%
OS101	58	40	68.96%
OS102	58	36	62.07%
OS103	58	39	67.24%
OS104	58	40	68.96%
OS105	58	37	63.79%
Average	394.81/6		65.803%

Table 6: Melting point data (pilot study batches)

Batch code	Melting point (˚C)	Batch code	Melting point (˚C)
B101	110.0	B108	104.0
B102	94.2	B109	104.2
B103	130.0	B110	88.6
B104	116.0	B111	128.2

B105	154.4	B112	92.0
B106	92.4	B113	94.0
B107	136.2	-	-

Table 7: Melting point data (optimised batch)

Batch code	Melting point (˚C)	Batch code	Melting point (˚C)
F1	154.2	F9	131.8
F2	154.0	F10	132.2
F3	154.0	F11	132.2
F4	154.2	F12	132.0
F5	154.2	F13	132.0
F6	154.2	F14	132.0
F7	153.8	F15	132.2
F8	154.0	F16	132.0

Table 8: Solubility analysis (pilot study)

Batch code	Concentration (mg/ml)	Batch code	Concentration (mg/ml)
B101	0.4286	B108	0.2698
B102	0.3333	B109	0.2063
B103	0.1429	B110	0.3016
B104	0.1905	B111	0.3174
B105	0.4286	B112	0.4127
B106	0.3968	B113	0.2222
B107	0.1587	-	-

Table 9: Solubility analysis (optimisation study)

Batch code	Concentration (mg/ml)	Batch code	Concentration (mg/ml)
F1	0.4286	F9	0.1429
F2	0.3016	F10	0.9365
F3	0.2381	F11	0.6190
F4	0.111	F12	0.4920
F5	0.1746	F13	0.5714
F6	0.0952	F14	0.4286
F7	0.0317	F15	0.3175
F8	0.0159	F16	0.2381

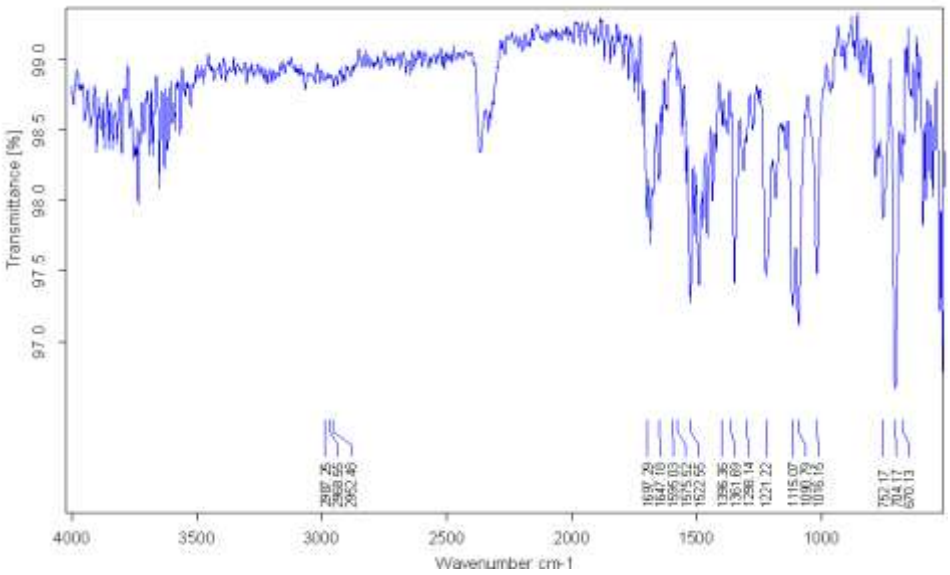

Figure 1: IR spectra of pure drug

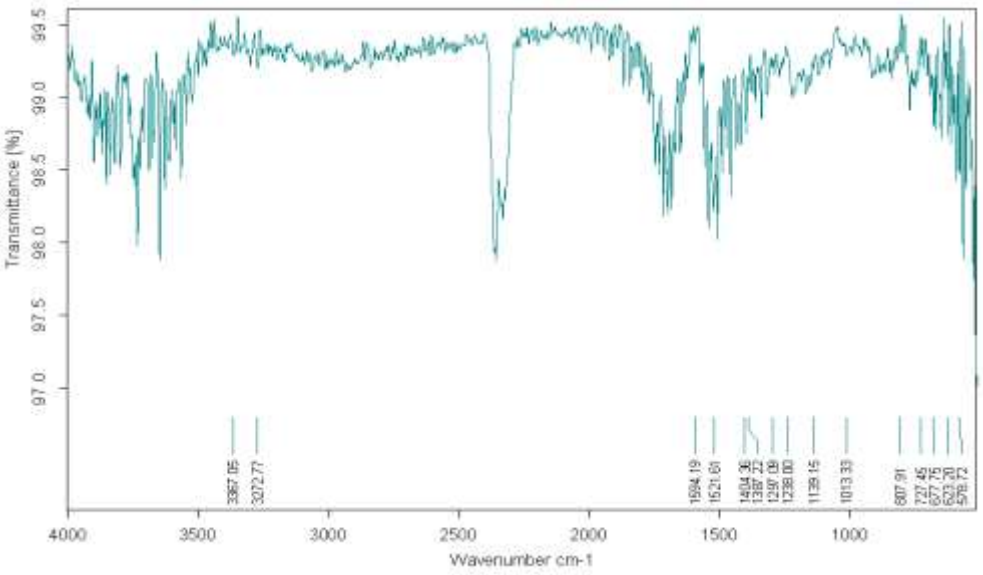

Figure 2: IR spectra of Malonic acid

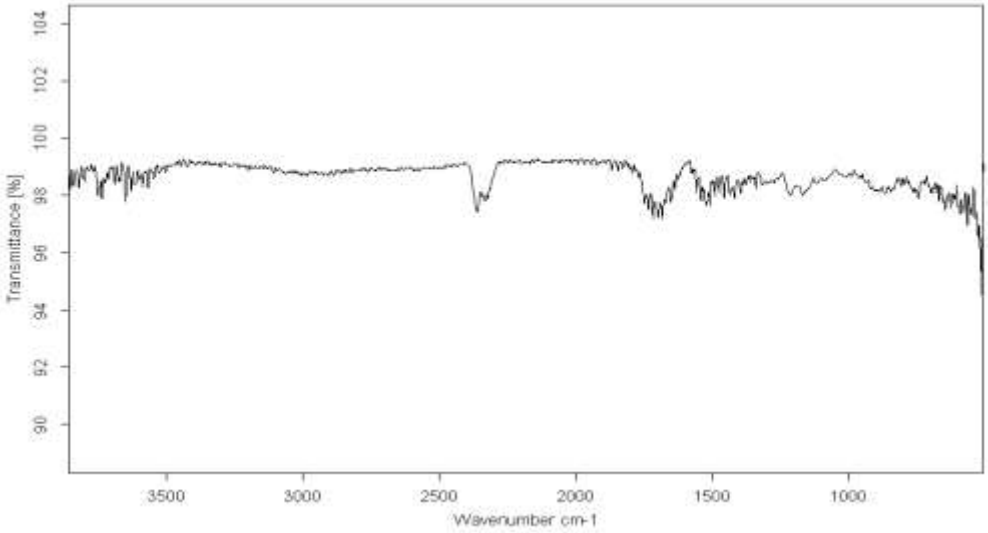

Figure 3: IR spectra of Lercanidipine with Malonic acid (Physical Mixture)

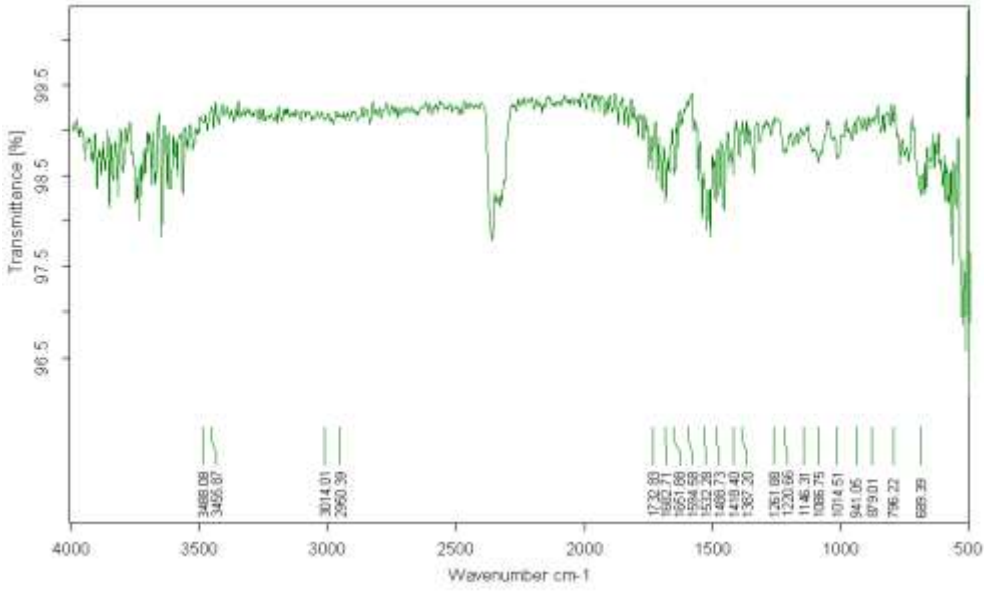

Figure 4: IR spectra of product

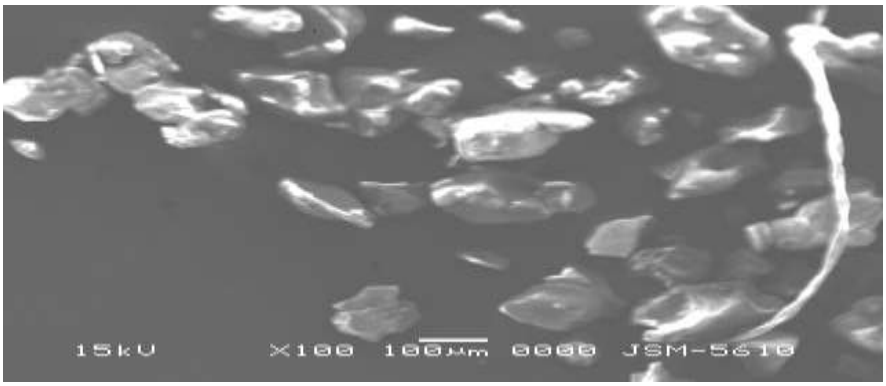

Figure 5: Scanning electron microscope of cocrystals of Lercanidipine

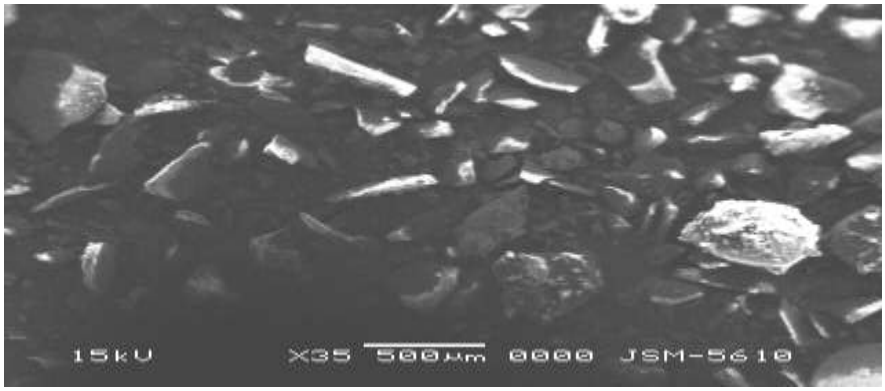

Figure 6: Scanning electron microscope of cocrystals of lercanidipine

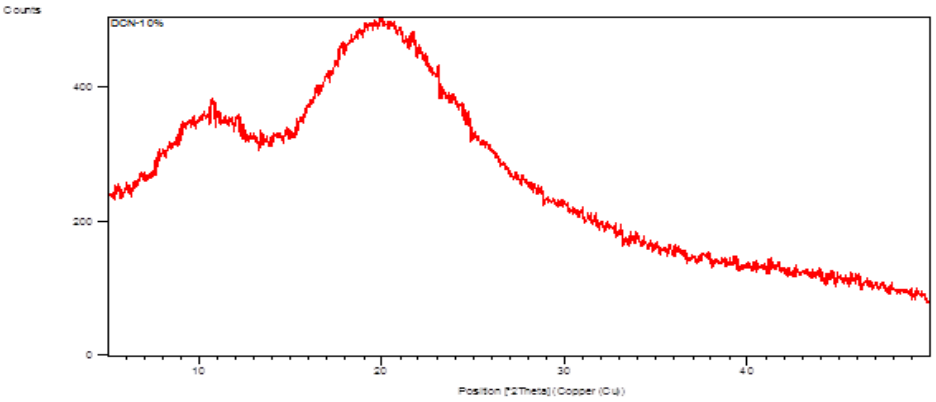

Figure 7: X-ray diffraction of drug

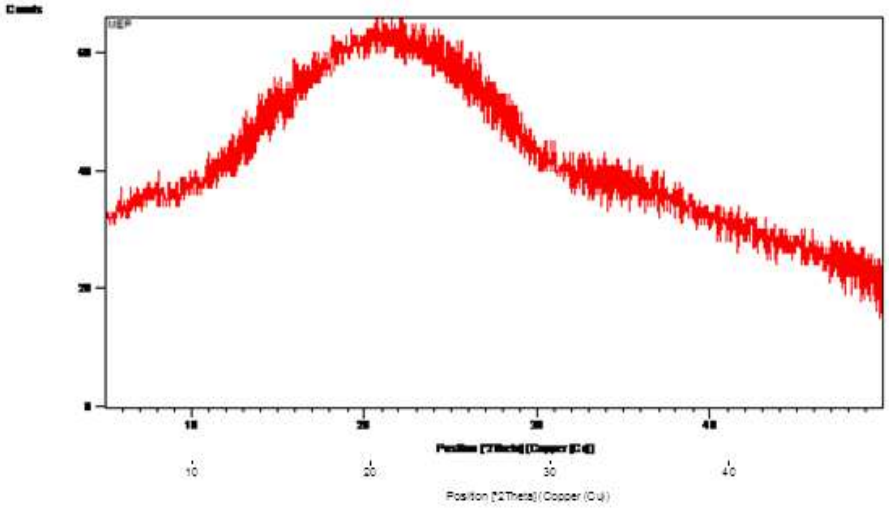

Figure 8: X-ray diffraction of product

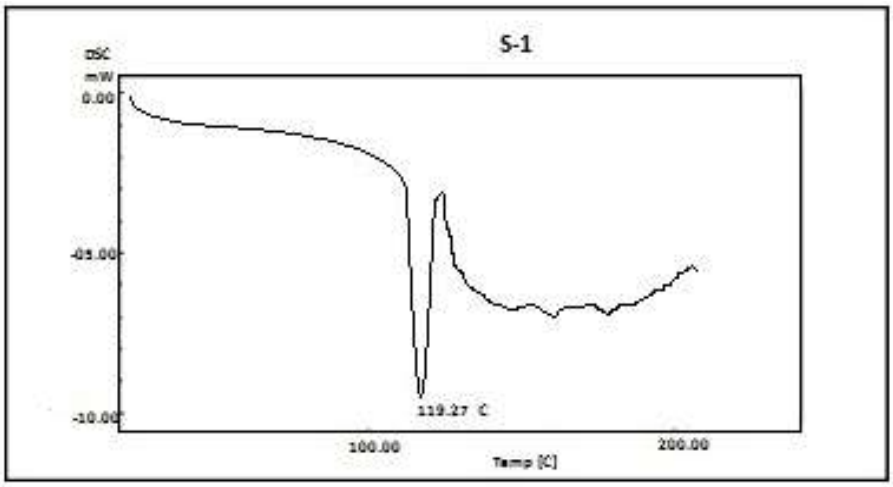

Figure 9: DSC of Lercanidipine

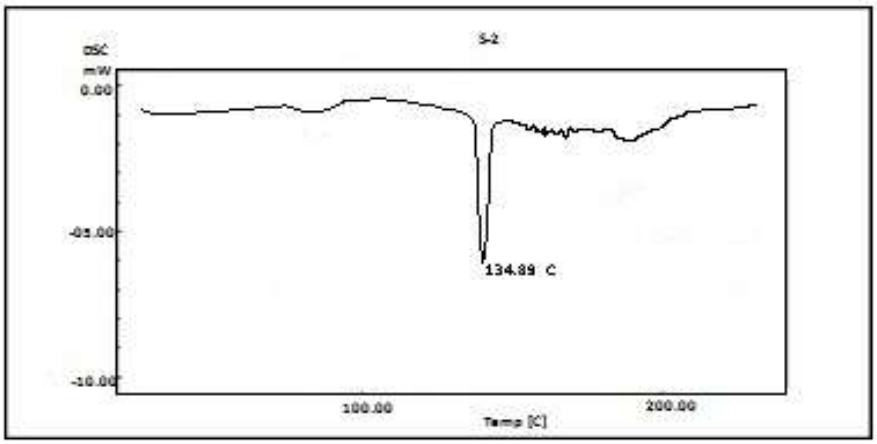

Figure 10: DSC of Malonic acid

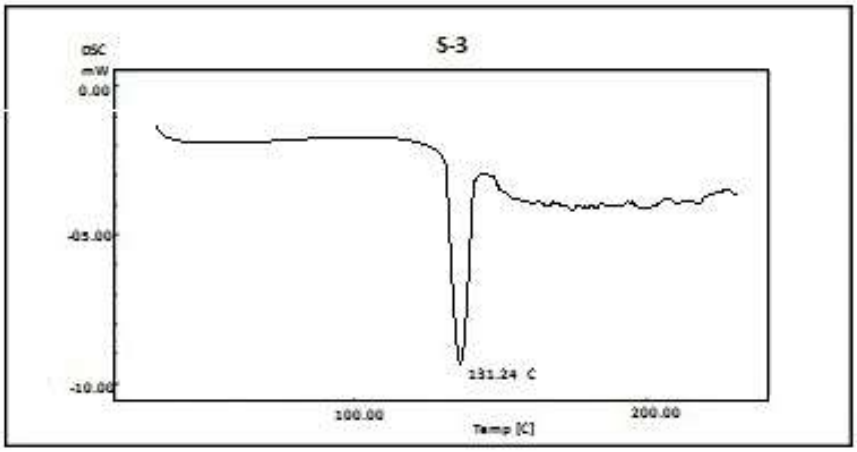

Figure 11: DSC of cocrystals

CONCLUSION:

The present study demonstrated a simple and successful method to prepare cocrystals of lercanidipine for solubility enhancement. No processing variables that could potentially affect the outcome were detected. If this process can be scaled up to manufacturing level, this technique has the potential to develop into invaluable technology in future.

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REFERENCES:

1. Sinko PJ, Singh Y. Martin's physical pharmacy and pharmaceutical sciences. Wolters Kluwer – Lippincot Williams & Wilkins. 2006; 6th ed: 182 – 196.
2. Brittain HG. Drugs and the pharmaceutical sciences: Physical characterisation of pharmaceutical solids. Marcel Dekker Inc. 1995; Volume 70: 321-386.
3. Brahmankar DM, Jaiswal SB. Introduction to biopharmaceutics. Vallabh prakashan. 2002; 2nd Ed: 24-27.
4. Gagniere E, Mangin D, Puel F, Rivoire A, Monnier O, Garcia E, Klein JP. Formation of cocrystal: kinetic and thermodynamic aspects. Journal of Crystal Growth. 2009; 311: 2689–2695.
5. Aakeroy CB, Salmon DJ. Building co-crystals with molecular sense and supramolecular sensibility. CrystEngComm. 2005; 7: 439–448.
6. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt A. Pharmaceutical cocrystals: An overview. Int. J. Pharm. 2011; 419: 1-11.
7. Chieng N, Hubert M, Saville D, Rades T, Aaltonen J. Formation kinetics and stability of carbamazepine–nicotinamide cocrystals prepared by mechanical activation. Cryst. Growth Des. 2009; 9: 2377–2386.
8. Bak A, Gore A, Yanez E, Stanton M, Tufekcic S, Syed R, Akrami A, Rose M, Surapaneni S, Bostick T, King A, Neervannan S, Ostovic D, Koparkar A. The co-crystal approach to improve the exposure of a water-insoluble compound: AMG 517 sorbic acid co-crystal characterization and pharmacokinetics. J. Pharm. Sci. 2008; 97: 3942–3956.
9. Aakeroy CB, Salmon DJ, Smith MM and Desper J. Cyanophenyloximes: reliable and versatile tools for hydrogen-bond directed supramolecular synthesis of cocrystals. Cryst. Growth Des. 2006; 6: 1033–1042.
10. Lu E, Rodriguez-Hornedo N, Suryanarayanan R. A rapid thermal method for cocrystal screening. Cryst Eng Comm. 2008; 10: 665–668.
11. Mohammad MA, Alhalaweh A, Velaga SP. Hansen solubility parameter asa tool to predict cocrystal formation. Int. J. Pharm. 2011; 407: 63–71.
12. Miroshnyk I, Mirza S, Sandler N. Pharmaceutical co-crystals - an opportunity for drug product enhancement. Expert Opin. Drug Deliv. 2009; 6: 333–341.
13. He GW, Jacob C, Guo LF, Chow PS, Tan RBH. Screening for cocrystallization tendency: the role of intermolecular interactions. J. Phys. Chem. B. 2008; 112: 9890–9895.
14. Li ZJ, Abramov Y, Bordner J, Leonard J, Medek A, Trask AV. Solid-state acid–base interactions in complexes of heterocyclic bases with dicarboxylic acids: crystallography, hydrogen bond analysis, and 15N NMR spectroscopy. J.Am. Chem. Soc. 2006b; 128: 8199–8210.
15. Zimmerman A, Millquist-Fuerby A, Elema MR, Hansen T, Mullertz A, Hovgaard L. Adsorption of pharmaceutical excipients onto microcrystals of Siramesine hydrochloride: effect on physicochemical properties. Eur. J. Pharm. Biopharm. 2009; 71: 109-116.

