International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

Formulation and Evaluation of Cilnidipine Co-Crystals with Different Co-Formers to Enhance Solubility and Dissolution Rate

Ranjana Kumari[1],Praveen Kumar Ashok[2],Gulfsha Parveen[3]
[1]*Student,* [2]*Director,* [3]*Assistant Professor*
[1,2,3]*Gyani Inder Singh Institute of Professional Studies, Dehradun, Uttarakhand*

Submitted: 10-08-2023 Accepted: 20-08-2023

ABSTRACT
The importance of the idea of co-crystallization is shown by the increasing number of reports of co-crystals in published works. Co-crystallization improves a drug's physicochemical qualities by forming intermolecular interactions with a co-former. At least two different molecular components may exist in a co-crystal, but the two must be solid at room temperature and have a well-defined stoichiometric ratio. Pharmaceutical co-crystals are made up of both the active pharmaceutical component and a co-former chosen from the FDA's GRAS list of ingredients. The production of a co-crystal is an experimental process that requires knowledge of a pharmacological target and the careful selection of a co-former. Other useful co-crystallization results include binary eutectics, solid dispersions, amorphous forms, etc. We have briefly discussed some important topics, such as design strategies, co-former selection, and co-crystallization procedures, as well as traditional and freshly synthesized approaches that are more efficient and suited for large-scale applications. The co-crystal preference is illustrated by highlighting the role that multidrug co-crystals play in drug combination strategies for the treatment and management of drug resistance and adverse side effects in the treatment of life-threatening medical conditions that necessitate the administration of high doses, such as tuberculosis, and others.

Keywords: Solubility enhancement, co-crystal, Cilnidipine, drug properties.

I. INTRODUCTION

60-70 percent of recently discovered drugs are associated with It impedes dissolution, solubility, stability, therapeutic efficacy, etc. 2 Present-day requirements call for a variety of approaches to reduce issues with available drugs' solubility and permeability. The development of novel solids, primarily in the pharmaceutical industry, depends on multi-component crystals, such as solvates, hydrates, and salts.[1]

Drugs are altered at the molecular level by crystallization when the drug is modified at the molecular level. Cocrystals are a molecular crystals composed of two or more chemically distinct molecules that form when the molecular changes are carried out in the process of cocrystallization Modification physical properties, particularly its solubility, without changing the drug's pharmacological effect is called a cocrystal. [2,3]

Formulators have always been concerned about the soluble nature of APIs as insufficient aq. Sol. may impede the creation of parenteral products and restrict oral product bioavailability. As pharmaceutical companies expand their drug discovery efforts in an effort to discover novel therapeutic approaches and develop drugs that are better suited to existing therapeutic areas, the issue has become increasingly serious and widespread in recent years. The assays and focus of experimental vary depending on the phase of the procedure for finding and developing drugs, Not a one-time event. Among the five primary physicochemical screens employed solubility leads the list of unfavorable compound qualities. A compound's pharmacokinetics and pharmacodynamics may be affected by its lack of solubility, which can also compromise other property tests, conceal further unwanted qualities, and impair other property assays, and ultimately affect the comp. developability, compounds with insufficient solubility are more likely to fail during discovery and development. Prior to performing any functional evaluations, it would be ideal if solubility liabilities were known. [4]

PROCESSOFSOLUBILISATION:

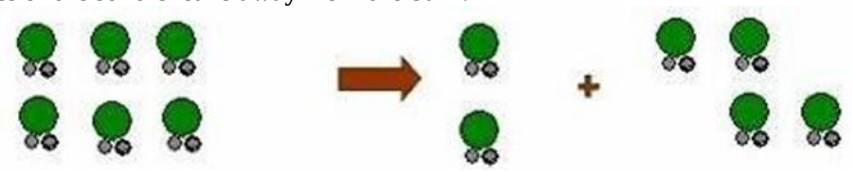
The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent toprovide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

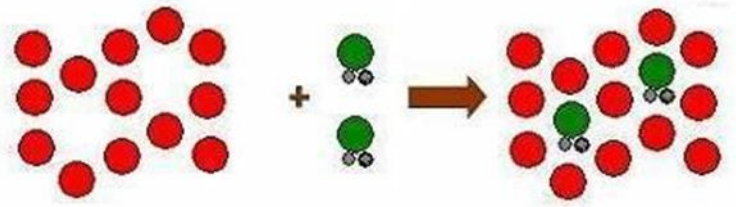
FIGURE1:ProcessofSolubilization

Step 1: Holes opens in the solvent:

Step2: Molecules of the solid breaks away from the bulk:

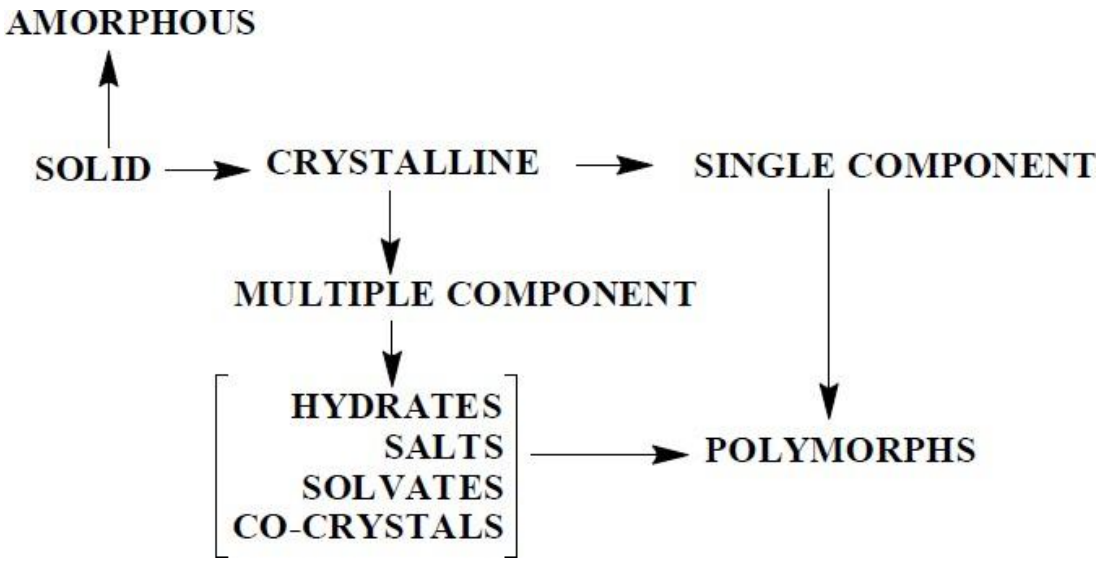


Step 3: The freed solid molecule is intergrated into the hole in the solvent



CRYSTALENGINEERING:

Polymorphism, which is the definite arrangement of molecules within a solid, has been known to influence various physicochemical and biological properties of a crystalline moiety. However, crystal habit has been paid scant attention. Crystallization is commonly employed as the final step for purification of a drug. Use of different solvents and processing conditions may alter the polymorphic state and or habit of the purified drug, leading to variation in raw material characteristics. In addition, crystal habit influences flowability, packing, compaction, syringability, stability and dissolution characteristics of a drug powder.



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

"Crystal engineering is the understanding of intermolecular Interactions in the context of crystal packing and in the utilization of such Understanding in the design of new solids with desired physical and chemical properties."

Crystal engineering allows for the design of new compositions or multicomponent crystalline phase of matter using existing pharmaceuticals, which allows for a much wider range of possible pharmaceutical compositions than present approaches such as salt formation (ion-pairing).

COCRYSTALS:

Pharmaceutical materials science being a fundamental branch that continuously provide important insights, theories, and technologies to formulation sciences. During the development of the pharmaceutical industry, crystallization has been engaged more and more extensively for the purification, separation particle formation and co-crystallization of pharmaceutical materials It is estimated that more than 70% of all solid drugs are produced by crystallization. With regards to this, an understanding of the effect of the crystallization process on the final solid state of a drug is vital for several of the activities of the pharmaceutical industry.

The recent advances in this area have brought the possibility to produce pharmaceutical materials by design. In particular, the formation of co-crystals, i.e. crystalline molecular complexes of two or more neutral molecules, represents a potential route to achieve pharmaceutical materials with improved properties of interest, including dissolution rate and stability under conditions of high relative humidity.

Co-crystals consists of API and a stoichiometric amount of a pharmaceutically acceptable co-crystal former. APIs are among the most valuable crystalline substances and crystal engineering has been successfully utilized in the generation of cocrystals of drugs with improved physicochemical properties such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the API.

Co-crystals-PreparationMethods:

Formation of co-crystal described shows the disreputably difficult situation these systems present with regard to preparation it has been recognized to take 6 months to prepare a single co-crystal of appropriate quality for single X-ray diffraction analysis37. This is partially as such a heteromeric system will only form if the non covalent forces between two or more molecules are stronger than between the molecules in the corresponding homomeric crystals. Cocrystal design strategies are still being researched and the mechanism of formation is far from being understood. Co-crystals can be prepared by solid and solvent based techniques. The solvent-based techniques involve solvent evaporation, slurry conversion, cooling crystallization and precipitation. The solid based techniques involve net grinding, solvent-assisted grinding and sonication (applied to both to dry or wet solid mixtures) 80o to 85°.

Cilnidipine Hydrochloride is the hydrochloride salt form of Cilnidipine, an imidazoline derivate and centrally-acting alpha-adrenergic agonist as well as antagonist with antihypertensive activity. Cilnidipinehydrochloride binds to and stimulates central alpha-2 adrenergic receptors, thereby decreasing sympathetic outflow to the heart, kidneys, and peripheral vasculature. The reduction in sympathetic outflow, leads to decreased peripheral vascular resistance, decreased blood pressure, and decreased heart rate.

AIM & OBJECTIVE

The main aim of present work is to enhance the solubility of co-crystal based solid dosage from.

1. From physical properties perspective, a key advantage of co-crystals as a solid form of an API is the possibility of achieving the high dissolution rate comparable to that of the amorphous form, while maintaining the long-term chemical and physical stability that crystalline forms provide.
2. A major problem in the use of ingredient Cilnidipine as a therapeutic agent is its low solubility and bioavailability. Basic goal in the development of co-crystal is to increase the solubility, stability and dissolution rate of pure drug Cilnidipine.
3. In particular substantial advancement methods of crystal engineering supramolecular technique alter the physicochemical properties of Cilnidipine which can relatively undergoes for formulation.

ANALYTICALMETHODOPTIMIZATION

Number of analytical methods was available for estimation of Cilnidipine such as ultra-violet spectroscopy, reverse phase HPLC with UV detection, gas chromatography, mass spectrometry and spectrofluorimetric method. The

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

following method was used for further studies.

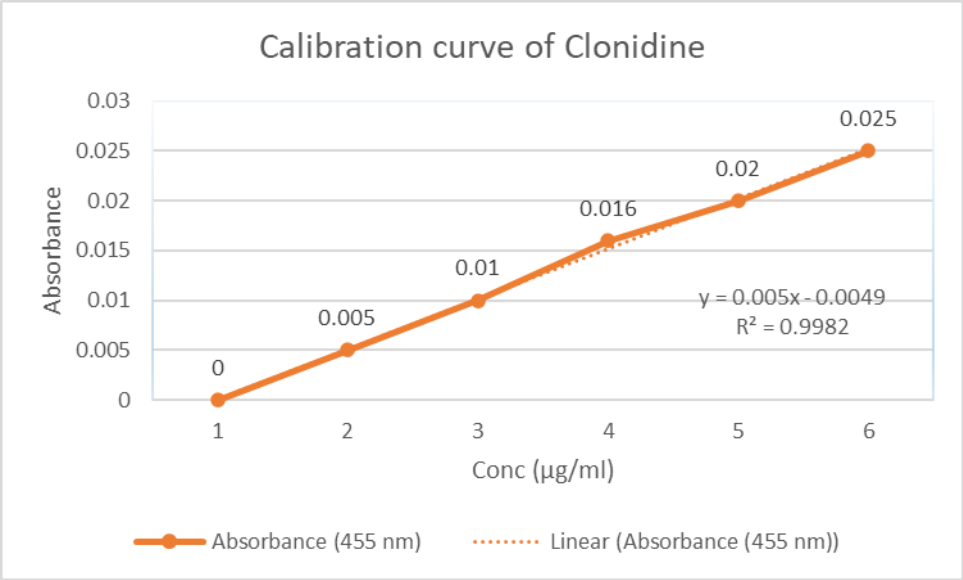
UV-VISIBLESPECTROSCOPY:

Standard Curve of Cilnidipine in pH 1.2 buffer

1mg of Cilnidipinewas dissolved in 100 ml of pH-1.2 buffer by proper ultrasonication for 5-10 mins and further dilutions were made by using pH1.2 buffer to obtain concentrations ranging 2, 4, 6, 8 and 10 µg/ml. The absorbance of solution was measured at 455 nm using UV Visible Spectrophotometer. The readings obtained are tabulated in Table5 and the graph was given in Graph1.

TABLE: Standard Curve of CilnidipineInPh 1.2 Buffer

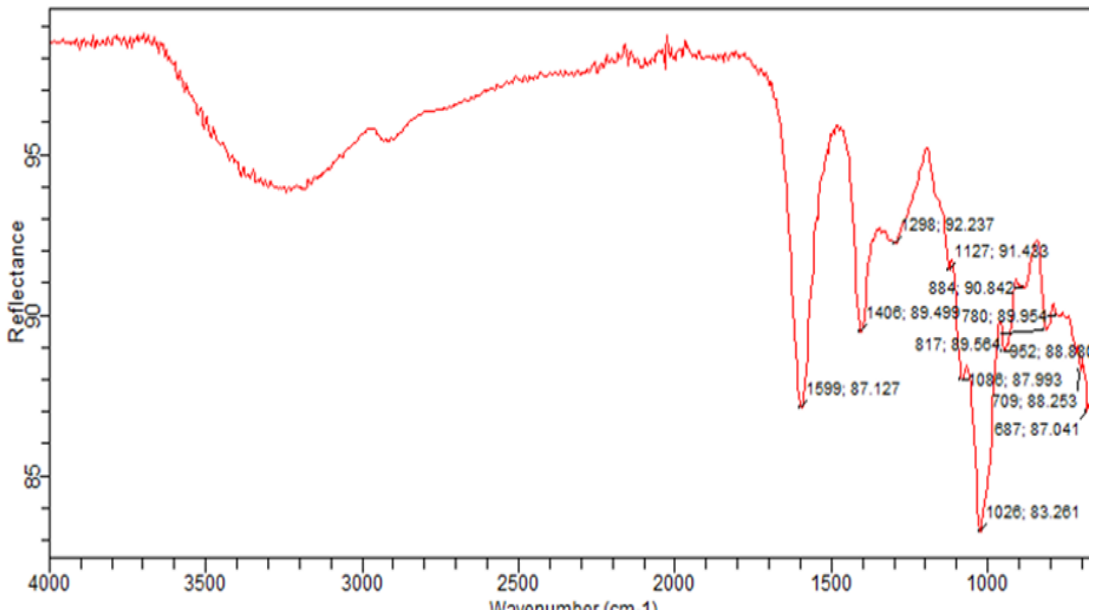
Concentration(µg/ml)	Absorbance (455 nm)
0	0
2	0.005
4	0.01
6	0.016
8	0.02
10	0.025



FTIR (Fourier Transform Infra-red Spectroscopy) Studies of pure Cilnidipine: [18,19]

IR spectroscopy was conducted using a FTIR Spectrophotometer (shimadzu) and Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum of pure CILNIDIPINE, was recorded in the wavelength region of 4000–400 cm−1.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781



Microscopic studies: [19]

Morphology of Cilnidipine was studied by microscopy. Cilnidipine shows small rod like crystals. The microscopic photograph shown in Figure.

FIGURE: Photography of CILNIDIPINE

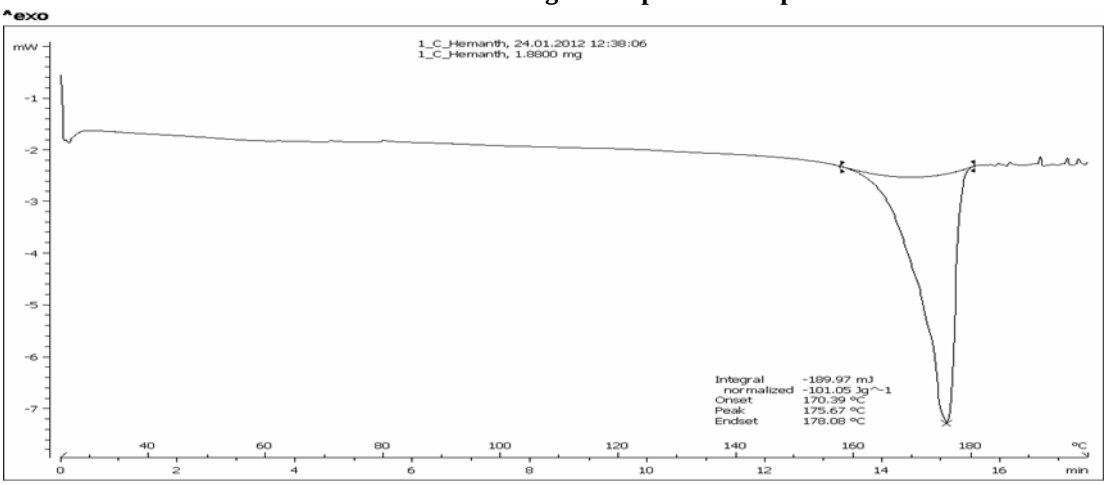
Differential scanning calorimetry (DSC) of pure CILNIDIPINE:

Thermal analysis of pure Cilnidipine, were recorded on a DSC (NETZSCH DSC 204). The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 100 C/min was employed with nitrogen pursing. Powder samples (5- 8mg) was weighed into an aluminum pan and analyzed as sealed with pin holes and an empty aluminium pan was used as reference.

DSC thermo grams of Cilnidipineshows sharp endothermic peak at 175.67 C. This indicates pure crystal form. A DSC thermo gram of Cilnidipine was shown in figure.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

FIGURE: DSC thermo gram of pure Cilnidipine



Powder X-Ray Diffraction (P-XRD):

X-ray powder diffractometry (XRPD) is a powerful technique for the identification of the crystalline solid phases. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification. The study was carried out using X-Ray Diffractometer using Cu kα radiation. The tube operated at 45 kV, 9mA and data was collected over an angular range from 0 to 60 2θ of the diffraction angle in continuous scan mode using a step size of 0.050 2θ and a time of 0.1 s.

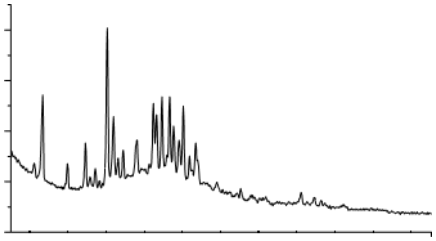


FIGURE:PowderXRDofpureCilnidipine

The X-ray powder diffraction (XRD) spectra of Cilnidipine in figure11 shows characteristic peak of pure Cilnidipine having 100% relative index at 170 of 2θ range indicates pure Cilnidipine.

ScanningElectronMicroscopy (SEM)Studies ofpure Cilnidipine:

The surface characteristics of pure Cilnidipine were studied by SEM (ZEISS Electron Microscope, EVO MA 15). The specimens were scanned with an electron beam of acceleration potential of 20 kV and the images were collected as secondary electron mode. It shows small rod like crystals.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

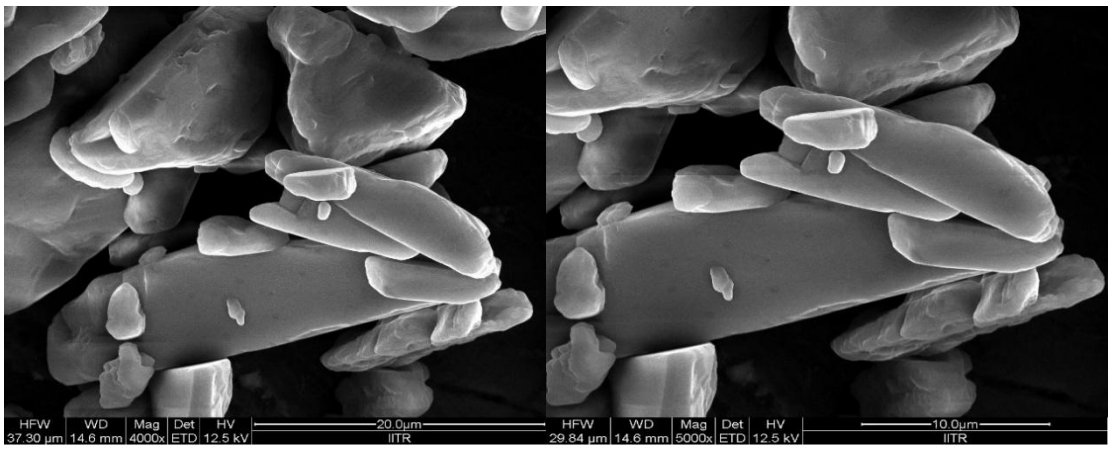


Figure:SEMPhotographofpureCilnidipine

CHARACTERISATION OF COFORMER RESORCINOL:

IR spectroscopy was conducted using a FTIR Spectrophotometer (shimadzu) and Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. The spectrum of pure Cilnidipine, was recorded in the wavelength region of 4000–400 cm−1.

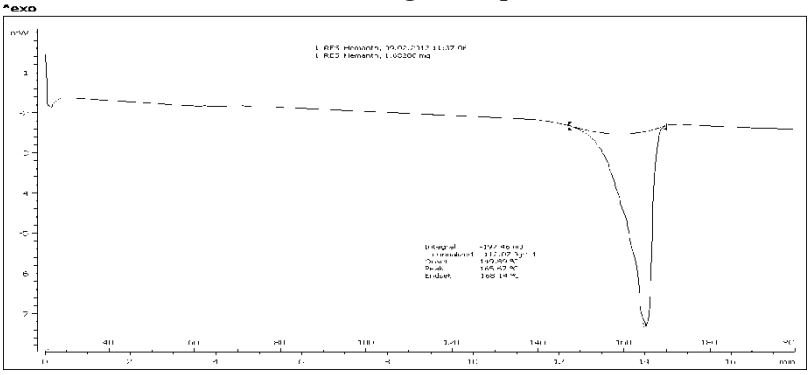
TABLE:FTIR Studies of Resorcinol

GROUP	WAVENUMBER(CM^{-1})
O-H	3255.95
AromaticC=C	1614.47
PhenolC-O	1296.21

DSCSTUDIES:

Thermal analysis of Resorcinol, were recorded on a DSC (NETZSCH DSC 204). The temperature axis and cell constant of DSC were previously calibrated with indium. A heating rate of 100 C/min was employed with nitrogen pursing. Powder samples (5- 8mg) was weighed into an aluminum pan and analyzed as sealed with pin holes and an empty aluminium pan was used as reference.

FIGURE: DSC thermo gram of pure resorcinol



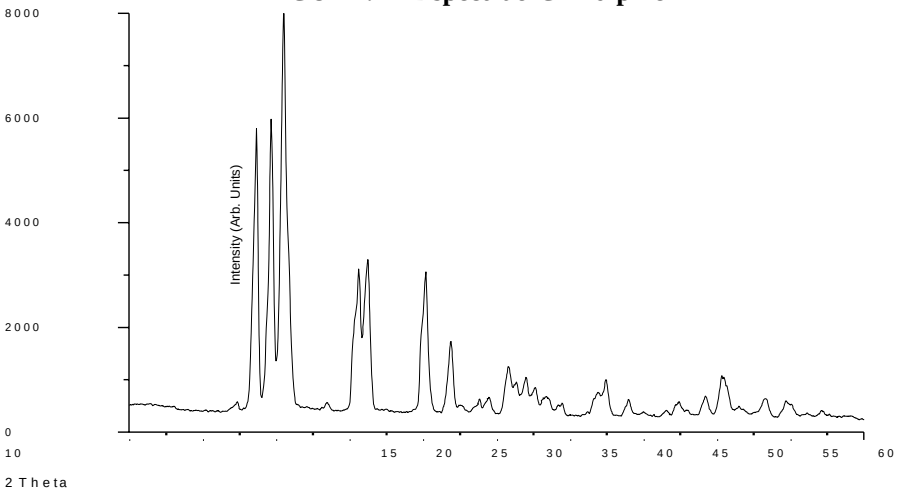
DSC thermo grams of resorcinol shows sharp endothermic peak at 165.370C. This indicates pure crystal form. A DSC thermo gram of resorcinol was shown in figure.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

XRDSTUDIES:

X-ray powder diffractometry (XRPD) is a powerful technique for the identification of the crystalline solid phases. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification. The study was carried out using X-Ray Diffractometer using Cu kα radiation. The tube operated at 45 kV, 9mA and data was collected over an angular range from 0 to 60 2θ of the diffraction angle in continuous scan mode using a step size of 0.050 2θ and a time of 0.1 s.

FIGURE:XRDspectraofCilnidipine



The X-ray powder diffraction (XRD) spectrum of Resorcinol in figure14shows characteristic peak at 20^0 of the 2θ range providing 100% relative intensityand indicates pure resorcinol.

ScanningElectron Microscopy (SEM)Studies of Cilnidipine: [28]

The surface characteristics of pure Resorcinol studied by SEM (ZEISS Electron Microscope,EVO MA 15). The specimens were scanned with an electron beam of acceleration potential of 20 kV and the images were collected as secondary electron mode. It shows spherical crystals

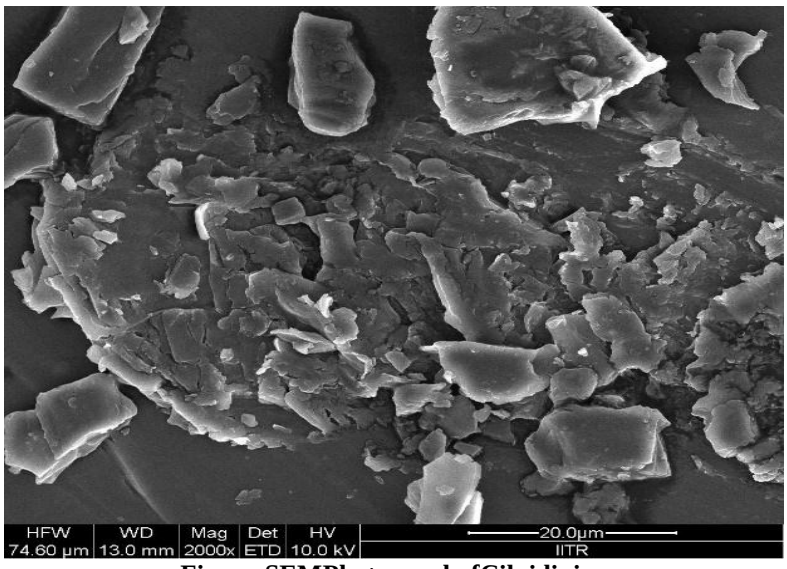


Figure:SEMPhotographofCilnidipine

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

SUPRAMOLECULARSYNTHESIS

PREPARATION OF CRYSTALS:[29,30,31]

LiquidAssisted Grinding (L.A.G.) Method:

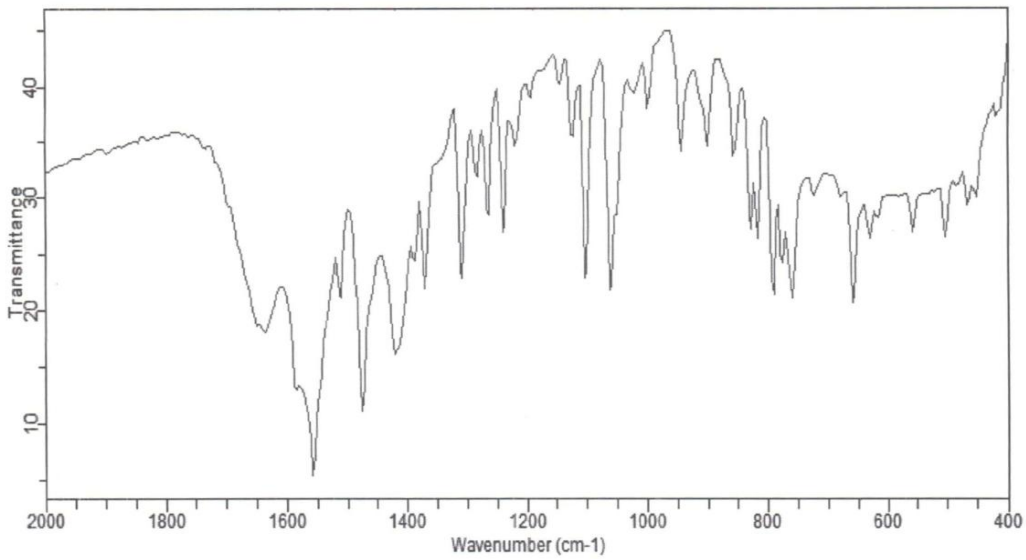
Cilnidipine and resorcinol weighed according to molar ratio (1:1) bases were grinded in a mortar and pestle using small quantity of ethanol (4 to 5 drops) by liquid assisted grinding method. The crystals formed were collected separately and preserved.

In FT-IR analysis, the spectrum showed an intense and well-defined bands characteristic to Cilnidipine at 3433.41 cm-1 (OH-stretching vibration), 1579.75 cm-1 (C=O stretching), 1506.46 cm-1 (Aromatic C=C), 1284.63 cm-1 (Phenol C-O) and 1035.81 cm-1 (Enol C-O). Interpretation of IR spectra of crystals prepared by liquid assisted grinding method has showed in table.

TABLE:FTIRStudiesofpreparedcrystals

GROUP	**WAVENUMBER(CM^{-1})**
O-H	3433.41
C=O	1579.75
AromaticC=C	1506.46
PhenolC-O	1284.63
EnolC-O	1035.81

FIGURE:FTIRspectraofcrystalsbyL.A.G.method

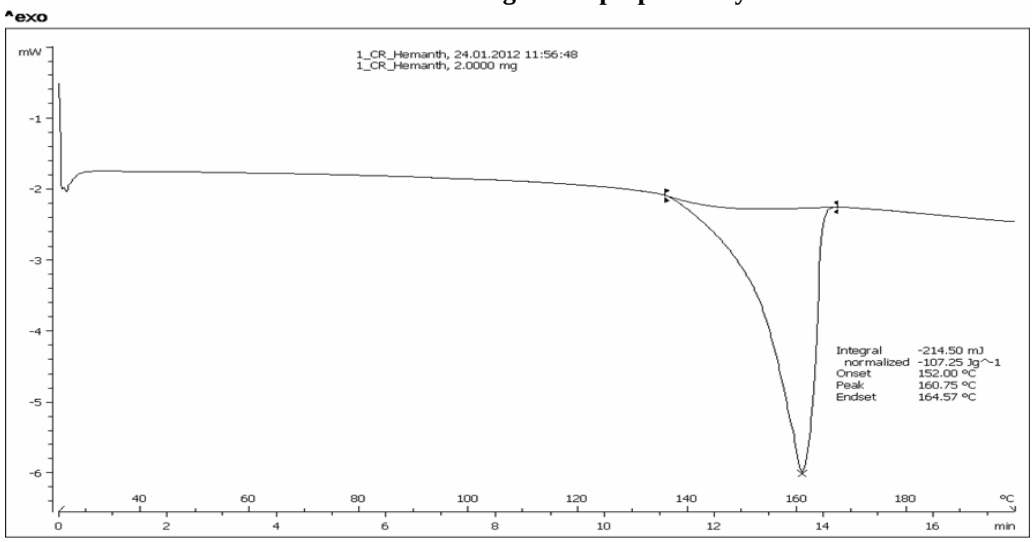


Differentialscanningcalorimetry(DSC)of Cilnidipine-**resrcecinolcrystalsby L.A.G.Method:** [32]

DSC experiments were carried out to study the thermal behaviour of the crystal form in relation to the individual components. DSC thermal data are shown in figure. DSC study of CILNIDIPINE and resorcinol shows endothermic peak at 175.670C and 112.020C C while DSC study of prepared cocrystal shows sharp endothermic value at 165.750C, the sharp endothermic values of crystal form and the individual components agreed with the measured melting range in the melting point determination. The thermal profile of crystal form was distinct, with a different melting transition from that seen with either of the individual components. This indicates the formation of novel crystal phase: crystal form of Cilnidipinewith resorcinol (1:1 molar ratio). This single endothermic transition indicates the absence of any unbound or absorbed solvent or water and also demonstrates the stability of the phase until the melting point.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

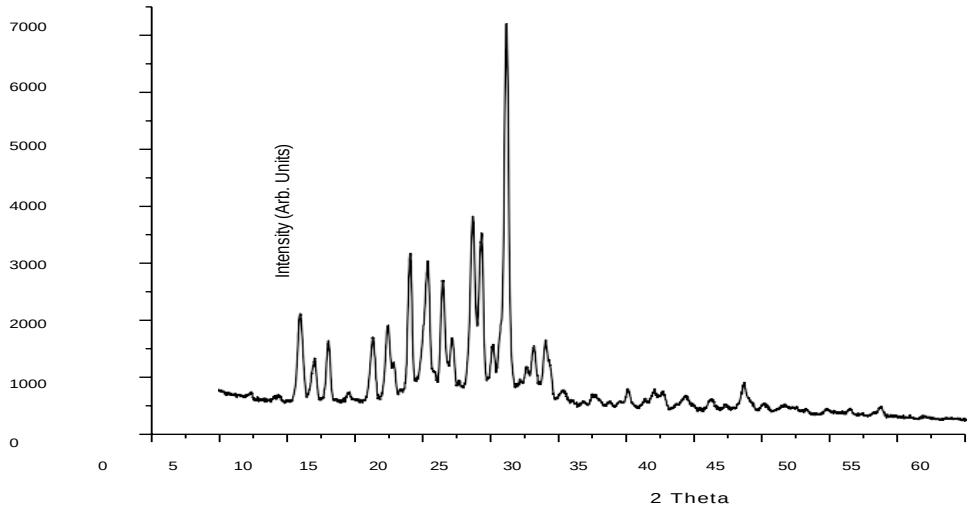
FIGURE: DSC thermo gram of prepared crystals



CrystalPXRD Crystallography:

X-ray powder diffractometry (XRPD) is a powerful technique for the identification of the crystalline solid phases. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification. The study was carried out using X-Ray Diffractometer using Cu kα radiation. The tube operated at 45 kV, 9mA and data was collected over an angular range from 0 to 60 2θ of the diffraction angle in continuous scan mode using a step size of 0.050 2θ and a time of 0.1 s.

FIGURE: PXRD ofprepared crystals



Preparedcrystal

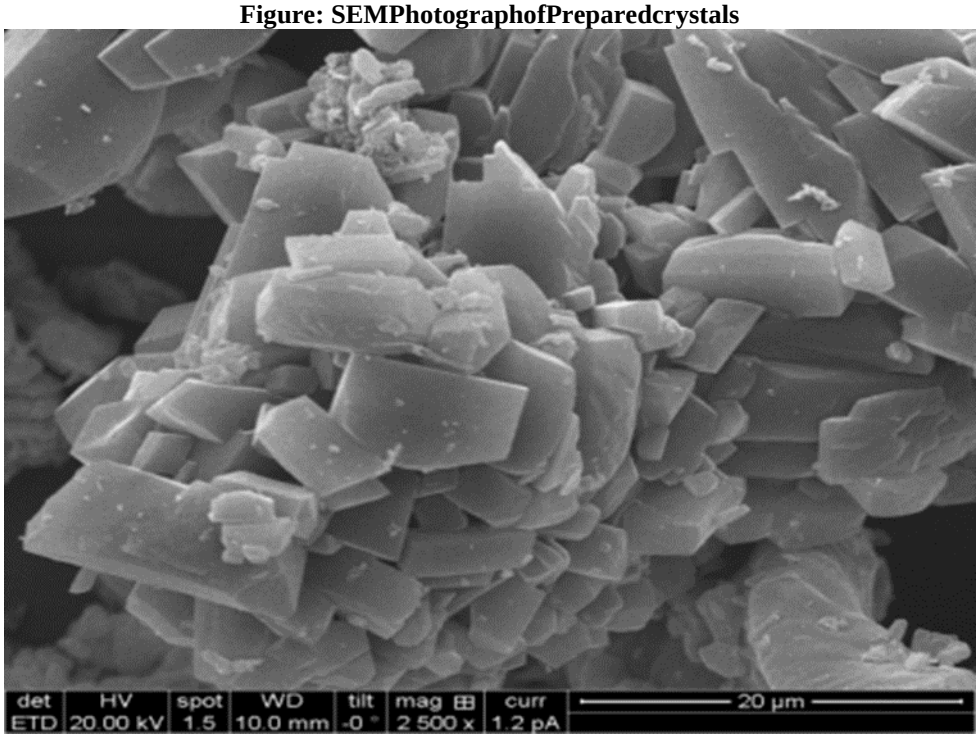
Predicted PXRD pattern of crystal form shown in figure, which was different from its pure drug powder XRD pattern, this indicates the formation of new multi component crystalline phase.

ScanningElectronMicroscopy(SEM)StudiesofPreparedcrystals: [34]

The surface characteristics of pure Resorcinol studied by SEM (ZEISS Electron Microscope,EVO MA 15). The specimens were scanned with an electron beam of acceleration potential of 20 kV and the images were collected as secondary electron mode. It shows spherical crystals.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

Figure: SEMPhotographofPreparedcrystals



SOLUBILITYSTUDIES:

The solubility studies have been performed for the pure drug and prepared crystals. In pH 1.2 buffer the pure drug showed a solubility of 0.071 mg/ml, liquid assisted grinding method showed a solubility of 0.157 mg/ml respectively. The crystals prepared by liquid assisted grinding method have shown the greater solubility than the pure drug.

TABLE:SolubilityDatainP^{H} 1.2 Buffer

SAMPLE		**SOLUBILITY(mg/ml)**
Pure drug in water		0.003±0.01
Crystals	In water	0.017±0.01
	In P^{H}1.2 buffer	0.157±0.01
	In P^{H}7.2 buffer	0.124±0.01

ASSAYOFCRYSTALS:

1mg of CILNIDIPINE crystals prepared by liquid-assisted grinding method were taken and dissolved in 40% EtOH-Water. From that 1ml was taken and diluted to 10 ml. The absorbance of solution was measured at 455 nm using ELICO UV –Visible Spectrophotometer and drug content was calculated.

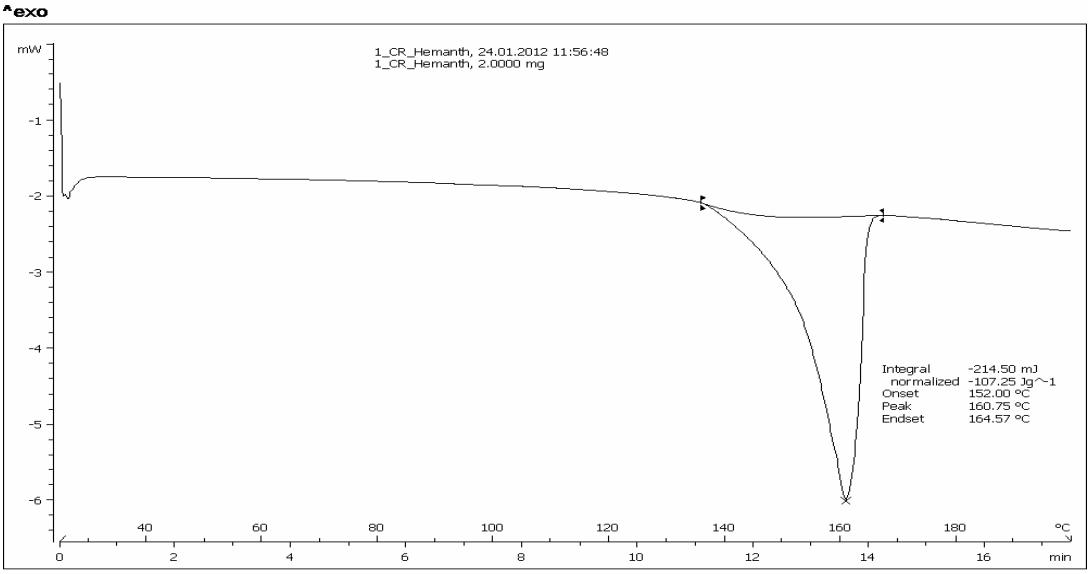
International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

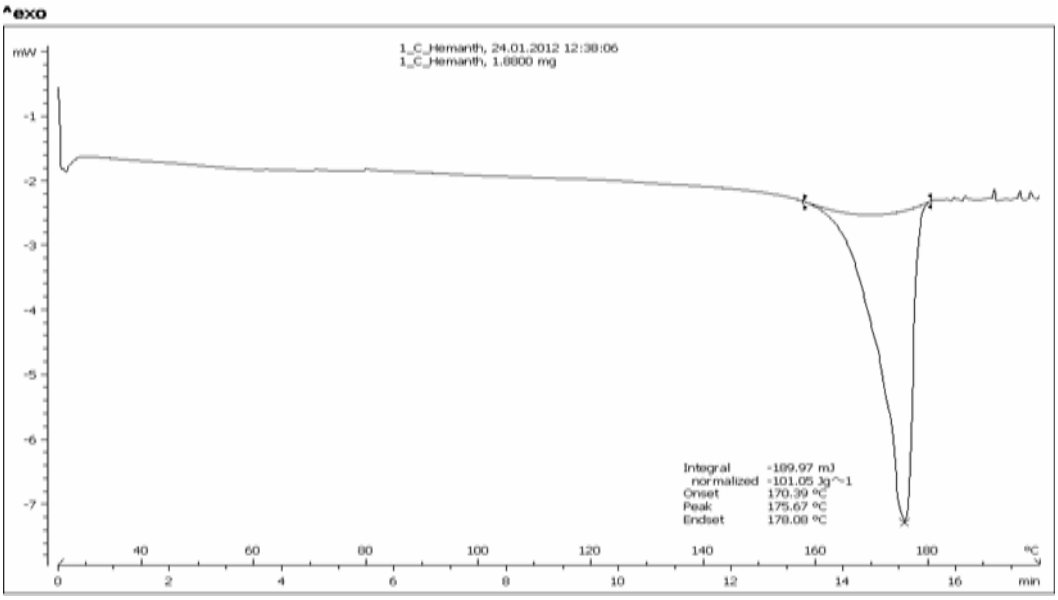
TABLE:Determinationofdrugcontent

SNO	CRYSTALS	DRUGCONTENT
1	CrystalbyL.A.G.method	87.24%

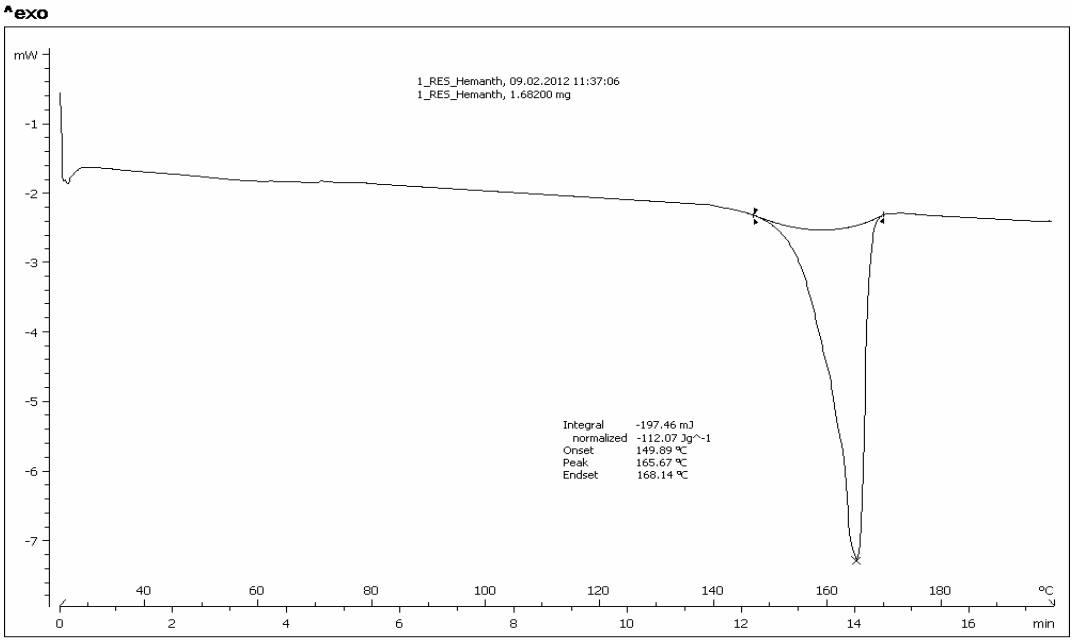
II. RESULT AND DISCUSSION

ComparativeDSCthermogramsofCilnidipine,resorcinolandpreparedcrystals



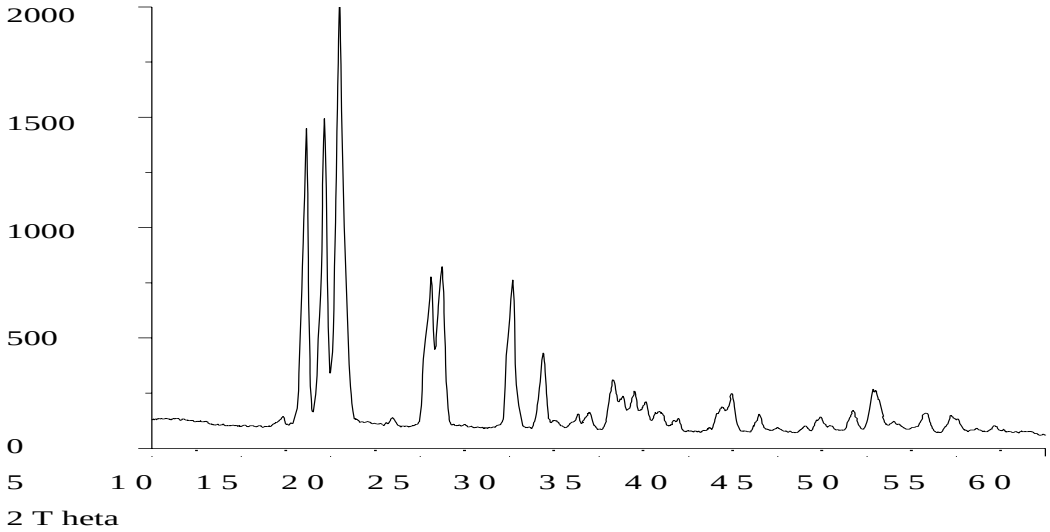


International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781



The above DSC thermo grams showing different thermal peaks at various positions which clearly showing the formation of co-crystal.

ComparativeStudiesofXrdGraphsofPureCilnidipineResorcinolAndPreparedCrystals Crystals



By comparing the above graphs, each graph showing 100% relative intensity at different 2θ ranges, which showing clearly that the formulated crystals having crystal property.

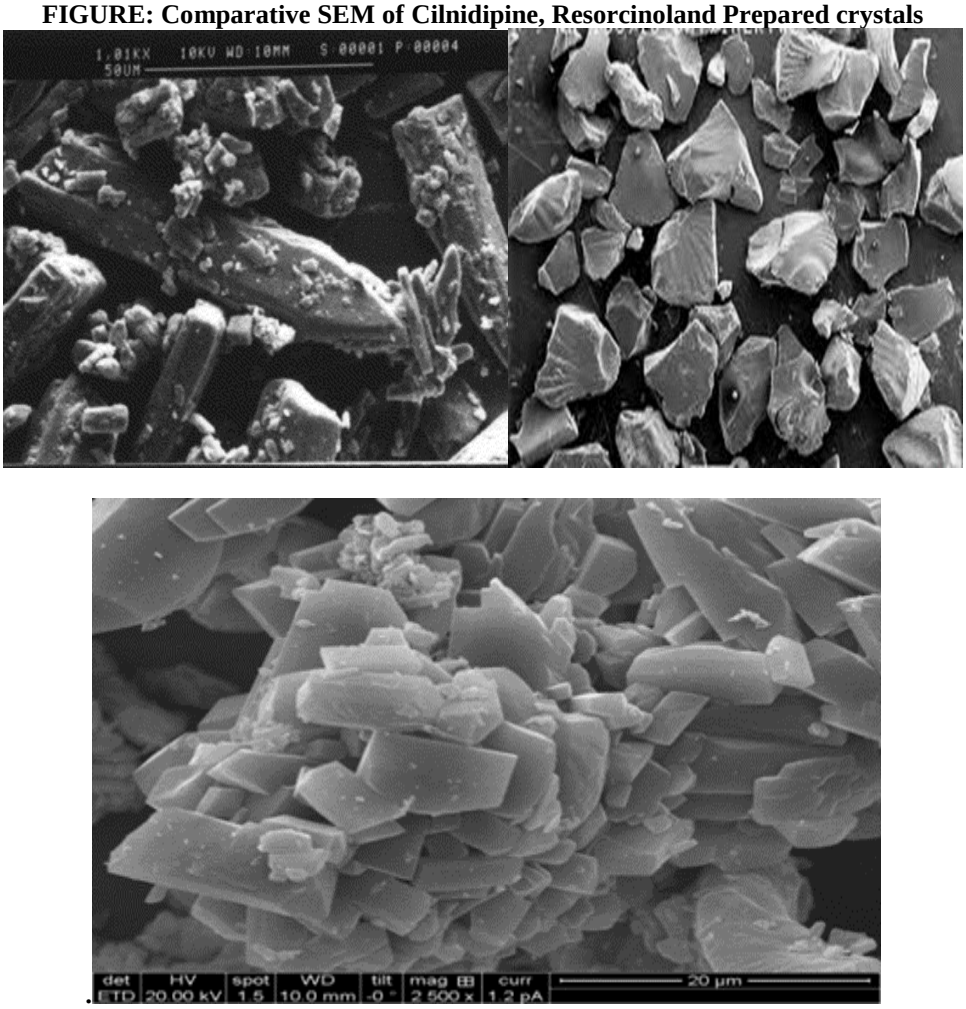
ComparativeScanningelectronmicroscopy(SEM) studies:

SEM photography of prepared cocrystal shows uniform block or rod like crystals while CILNIDIPINE showing different type of crystals and resorcinol showing pellet like crystals when comparing. This indicates the formation of Crystal form. SEM photographs of CILNIDIPINE

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

,Resorcinol and prepared crystals are shown in figure 20.

FIGURE: Comparative SEM of Cilnidipine, Resorcinoland Prepared crystals



CRYSTALSTRUCTUREANALYSIS:

Crystal engineering of organic materials relies on the supramolecular building of crystalline solids based on the interaction of functional groups point of view. For the study of these crystalline materials, it is important to have a knowledge and understanding of intermolecular interactions between various functional groups.

A distinguishing feature of co-crystals, as compared to other crystalline forms of APIs, is that these multi-component systems can be manipulated using crystal engineering. By definition, crystal engineering involves modification of the crystal packing of a solid material by changing the internal arrangement of the molecules that regulate the breaking and forming of non-covalent bonds (e.g., hydrogen bonding, van der Waals forces, π-stacking, electrostatic interactions). In the case of multi-component systems, the co-crystallizing agent brings additional multiplicity into a crystallizing system, thus increasing its diversity in terms of resulting solid-state forms of APIs.

Given that the properties of materials are dependent on their solid-state structure, it is clear that specific characteristics of the APIs can be tailored systematically by varying the co-crystal former. An important initial step in co- crystal design is, therefore, the selection of an appropriate co-crystallizing agent.

The 1:1 co-crystal stoichiometry is sustained by O-H...O hydrogen bonds between the phenolic OH groups of the co-formers to the carbonyl group of CILNIDIPINE .

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

INVITRODISSOLUTIONSTUDIES

TABLE: COMPARITIVE INVITRO DISSOLUTION STUDY OF PUREDRUGANDPREPAREDCRYSTALS

S. No	Time interval	PURE DRUG	CRYSTALS
1	0	0.00	0.00
2	5	0.18±0.03	2.12±0.02
3	15	0.38±0.04	9.54±0.01
4	30	0.69±0.03	14.85±0.02
5	45	1.58±0.03	22.25±0.01
6	60	5.56±0.01	29.15±0.02
7	75	10.24±0.02	33.31±0.01
8	90	13.33±0.01	37.23±0.02
9	105	16.62±0.002	39.45±0.02

Figure:PercentageDrugRelease of PureDrug And Crystals

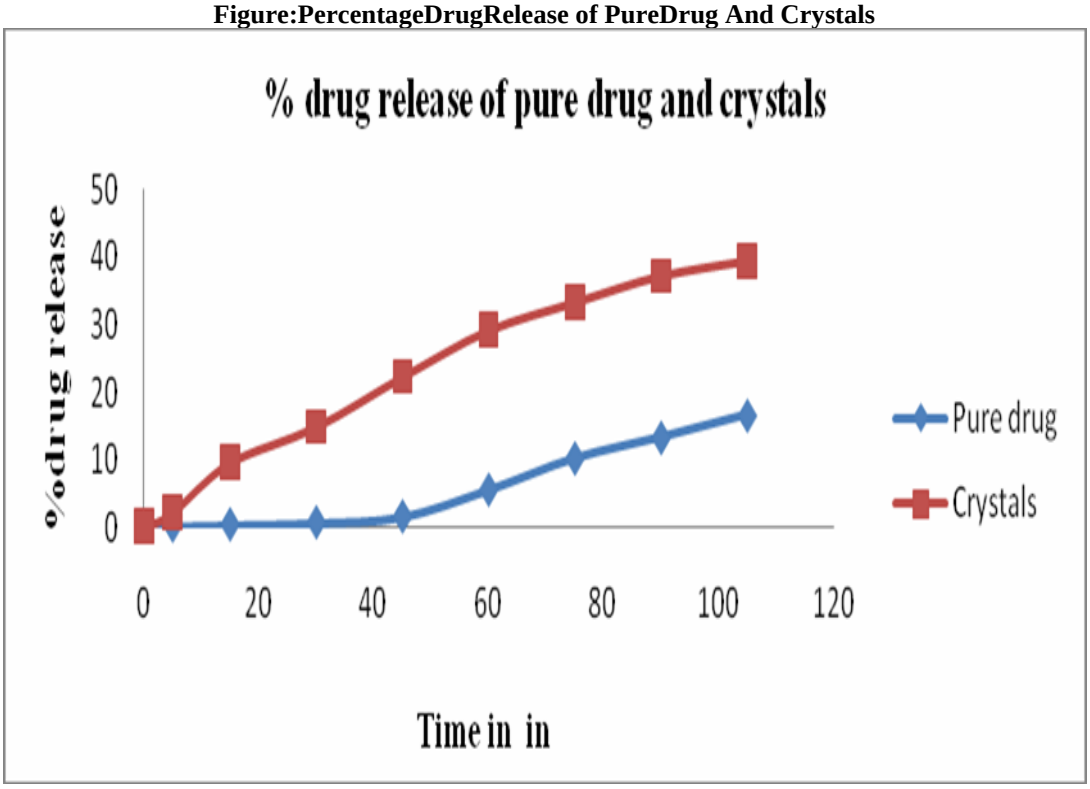


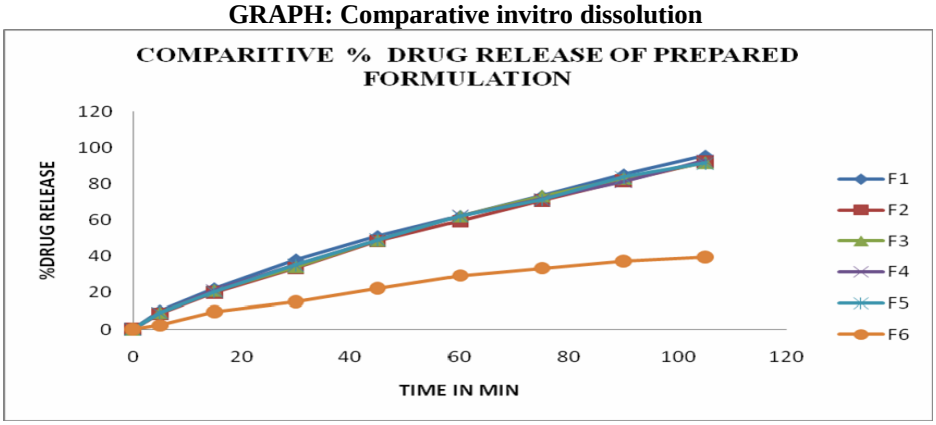
TABLE: COMPARITIVE INVITRO DISSOLUTION STUDY OFPREPAREDFORMULATION(Tablets)

S. No	Time interval	F1	F2	F3	F4	F5	F6

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

1	0	0.00	0.00	0.00	0.00	0.00	0.00
2	5	9.98±0.01	8.55±0.02	9.19±0.03	9.01±0.02	8.99±0.01	2.12±0.01
3	15	22.12±0.02	20.12±0.02	21.11±0.03	21.18±0.02	20.22±0.02	9.54±0.02
4	30	38.12±0.02	33.44±0.01	34.17±0.01	35.15±0.01	35.12±0.03	14.85±0.02
5	45	50.98±0.01	48.44±0.01	48.88±0.02	49.11±0.03	49.12±0.02	22.25±0.02
6	60	62.12±0.01	59.32±0.05	62.22±0.02	62.24±0.02	62.12±0.01	29.15±0.01
7	75	73.14±0.01	70.71±0.01	73.30±0.02	71.41±0.01	71.12±0.02	33.31±0.03
8	90	85.15±0.02	81.81±0.02	83.11±0.01	81.21±0.02	83.75±0.02	37.23±0.02
9	105	95.54±0.02	92.24±0.01	91.84±0.01	92.82±0.03	91.51±0.01	39.45±0.01

GRAPH: Comparative invitro dissolution



III. CONCLUSION

Despite lack of precedence in marketed products and concerns about the safety and toxicity of co-crystal forming agents, there is growing interest and activity in this area, which aims to increase the understanding of co-crystal formation and methods of preparation. Although, some recent developments in crystal and particle engineering have been included nowadays, consideration of established approaches such as the use of high-energy amorphous and metastable crystalline forms is still widespread. In particular substantial advancement methods of crystal engineering, supramolecular technique alters the physicochemical properties of Cilnidipinewhich can relatively undergoes for formulation.

A crystal engineering approach was utilized to prepare 1:1 cocrystals of Cilnidipinewith resorcinol by liquid-assisted grinding. We reasoned that the reactivity of the keto-enol group could be modified through hydrogen bonding with phenolic compounds in co- crystals, which in turn might provide more soluble and stable CILNIDIPINE solid-state forms. A solid form screen of Cilnidipinewith phenolic co-formers afforded novel cocrystals with resorcinol. These CILNIDIPINE cocrystals were characterized by FT- IR, X-ray powder diffraction, and thermal techniques. The present results on more soluble cocrystals of Cilnidipine could provide faster dissolving solid forms of Cilnidipinethat are relatively stable for drug development.

IV. FUTURE PROSPECTIVE

Drug molecules with limited aqueous solubility are becoming increasingly prevalent in the research and development. Molecules of this type can provide a number of challenges in pharmaceutical development and may potentially lead to slow dissolution in biological fluids, insufficient and inconsistent systemic exposure and consequent sub-optimal efficacy in patients, particularly when delivered via the oral route of administration. Advances in the pharmaceutical sciences have led to establishment of a number of

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 4 July-Aug 2023, pp: 1945-1962www.ijprajournal.com ISSN: 2249-7781

approaches for addressing the issues of low aqueous solubility.

Despite its demonstrated efficacy and safety, limited Cilnidipine bioavailability continues to be highlighted as a major concern. As detailed in this work, curtailing Cilnidipine bioavailability and dissolution rate are the main strategies now being explored. Crystal engineering is the attempt to improve the bioavailability and dissolution rate of Cilnidipine in supramolecular technique with Resorcinol as co-former.

However, the limited literature evidence devoted to show improvements in Cilnidipinebioavailability reveals that the Cilnidipinebioavailability enhancement has not gained significant attention. Yet, novel delivery strategies including those of nanoparticles, liposomes, and defined phospholipid complexes offer significant promise and are worthy of further exploration in attempts to enhance the bioavailability, medicinal value, and application of this interesting molecule from Mother Nature.

V. AKNOWLEDGEMENT

The authors report no conflicts of interest. The authors are responsible for the content and writing of the paper. Author highly thankful to Gyani Inder Singh institute of professional studies, Dehradun for providing the all facility for carried out my research work.

CONFLICT OF INTEREST: NIL

REFERENCES

[1]. Wouters, J., et al., Alternative Solid Forms: Co- crystals. Polymorphism in the Pharmaceutical Industry: Solid Form and Drug Development, 2018: p. 61-90.

[2]. Kuminek, Gislaine, et al. Advanced drug delivery reviews, “Cocrystals to facilitate delivery of poorly soluble compounds beyond-rule-of-5.” 2016; 101: 143-166.

[3]. Taylor, D., The pharmaceutical industry and the future of drug development. 2015.

[4]. Almeida e Sousa, L., et al., Supersaturation potential of salt, co-crystal, and amorphous forms of a model weak base. Crystal Growth & Design, 2016. 16(2): p. 737-748.

[5]. Fu, Q., et al., Salt formation of two BCS II drugs (indomethacin and naproxen) with (1R, 2R)-1, 2-diphenylethylenediamine: Crystal structures, solubility and thermodynamics analysis. Journal of Molecular Structure, 2019. 1185: p. 281-289.

[6]. Kalepu, S. and V. Nekkanti, Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharmaceutica Sinica B, 2015. 5(5): 442-453.

[7]. Fong, S.Y.K., A. Ibisogly, and A. Bauer-Brandl, Solubility enhancement of BCS Class II drug by solid phospholipid dispersions: spray drying versus freeze-drying. International journal of pharmaceutics, 2015: 496(2): 382-391.

[8]. Van den Mooter, G., The use of amorphous solid dispersions: A formulation strategy to overcome poor solubility and dissolution rate. Drug Discovery Today: Technologies, 2012; 9(2): e79-e85.

[9]. Dizaj, S.M., et al., Nanosizing of drugs: effect on dissolution rate. Research in pharmaceutical sciences, 2015: 10(2): p. 95.

[10]. Khadka, P., et al., Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian journal of pharmaceutical sciences, 2014; 9(6): 304-316.

[11]. Maragos, S., et al., Effect of cyclodextrin complexation on the aqueous solubility and solubility/dose ratio of praziquantel. AAPS Pharm Sci Tech, 2009; 10(4): 1444-1451.

[12]. Manne, A.S.N., et al., Hot liquid extrusion assisted drug-cyclodextrin complexation: a novel continuous manufacturing method for solubility and bioavailability enhancement of drugs. Drug delivery and translational research, 2021: 11(3):1273-1287.

[13]. Slaìdkovaì, V., et al., Application and comparison of cocrystallization techniques on trospium chloride cocrystals. Crystal growth & design, 2014: 14(6): 2931-2936.

[14]. Guo, M., et al., Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. Acta Pharmaceutica Sinica B, 2021.

[15]. Biscaia, I.F.B., et al., Obtaining Cocrystals by Reaction Crystallization Method: Pharmaceutical Applications. Pharmaceutics, 2021; 13(6): 898.

[16]. Malamatari, M., et al., Experimental

cocrystal screening and solution based scale- up cocrystallization methods. Advanced drug delivery reviews, 2017: 117: 162-177.

[17]. Yu, Z.Q., P.S. Chow, and R.B. Tan, Operating regions in cooling cocrystallization of caffeine and glutaric acid in acetonitrile. Crystal growth & design, 2010: 10(5): 2382-2387.

[18]. Maryam, K., Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications Cryst. Growth Des, 2018; 18: 6370-6387.

[19]. Wang, X., et al., Drug-drug cocrystals: opportunities and challenges. Asian journal of pharmaceutical sciences, 2021: 16(3): 307-317.

[20]. Yamamoto, K., S. Tsutsumi, and Y. Ikeda, Establishment of cocrystal cocktail grinding method for rational screening of pharmaceutical cocrystals. International journal of pharmaceutics, 2012: 437(1-2): 162-171.

[21]. Pando, C., A. Cabanas, and I.A. Cuadra, Preparation of pharmaceutical co-crystals through sustainable processes using supercritical carbon dioxide: a review. RSC advances, 2016; 6(75): 71134-71150.

[22]. Ribas, M.M., et al., Curcumin cocrystals using supercritical fluid technology. The Journal of supercritical fluids, 2019: 152: 104564.

[23]. McNamara, D.P., et al., Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API. Pharmaceutical research, 2006: 23(8): 1888-1897.

[24]. Ahire, E., et al., Parenteral nanosuspensions: a brief review from solubility enhancement to more novel and specific applications. Acta Pharmaceutica Sinica B, 2018: 8(5): 733-755.

[25]. Ahire, E., et al., Nanocrystal based orally disintegrating tablets as a tool to improve dissolution rate of Vortioxetine. Bulletin of Faculty of Pharmacy, Cairo University, 2020: 58(1&2): 11-20.

[26]. K. Amin, R.-M. Dannenfelser, J. Zielinski, B. Wang, Lyophilization of polyethylene glycol mixtures, J. Pharm. Sci. 93 (9) (2004) 2244–2249.

[27]. V.P. Torchillin, Micellar nanocarriers: pharmaceutical perspectives, Pharm. Res. 24 (1) (2007) 1–16.

[28]. R.A. Rajewski, V.J. Stella, Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery, J. Pharm. Sci. 85 (11) (1996) 1142–1169.

[29]. A.J. Humberstone,W.N.Charman,Lipid-based vehicles for the oral delivery of poorly soluble drugs, Adv. Drug Deliv. Rev. 25 (1) (1997) 103–128.

[30]. M. Stuart, K. Box, Chasing equilibrium: measuring the intrinsic solubility of weak acids and bases, Anal. Chem. 77 (2005) 983–990.

[31]. C. Lipinski, Aqueous solubility in discovery, chemistry, and assay changes, Drug Bioavailability 18 (2003) 215–231.

[32]. Dokoumetzidis, P. Macheras, A century of dissolution research: From Noyes and Whitney to sthe Biopharmaceutics Classification System, Int. J. Pharm. 321 (1–2) (2006) 1–11.

[33]. S.L. Morissette, S. Soukasene, D. Levinson, M.J. Cima, O. Almarsson, Elucidation of crystal form diversity of the HIV protease inhibitor ritonavir by high-throughput crystallization, Proc. Natl. Acad. Sci. U. S. A. 100 (5) (2003) 2180–2184.

[34]. Riley, K. McFarland, Dealing with the impact of ritonavir polymorphs on the late stages of bulk drug process development, Org. Process Res. Dev. 4 (5) (2000) 413–417.

[35]. J.M. Miller, B.M. Collman, L.R. Greene, D.J.W. Grant, A.C. Blackburn, Identifying the stable polymorph early in the drug discovery-development process, Pharm. Dev. Technol. 10 (2) (2005) 291–297.

[36]. C.Bergstrom, K. Luthman, P. Artursson, Accuracy of calculated pH dependent aqueous drug solubility, Eur. J. Pharm. Sci. 22 (5) (2004) 387–398.

[37]. Aakeröy CB, Fasulo ME, Desper J. Cocrystal or salt: Does it really matter? Mol Pharma 2007; 4:317–322.