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Study on Crystallization Techniques for Selected Drugs of Omeprazole Lovastatin and Nateglinide

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Abstract: *Pharmaceutical co-crystals use crystal engineering principles to create crystalline drug forms that have attracted a lot of interest because they have the potential to solve physicochemical issues with drugs, such as poor aqueous solubility, which can impair drug performance. With desirable qualities like solubility, dissolution, bioavailability, stability, hygroscopicity modulation, pH- dependent solubility properties, photosensitivity, thermolability, and micromeritic properties, co- crystallization is an emerging technique for designing novel materials. Several pharmaceutical problems that arose during preformulation and formulation development can also be resolved via cocrystal generation. The pharmaceutical industry continues to face a practical problem with weakly basic, poorly soluble active pharmaceutical ingredients (APIs). The most preferable solutions to this problem are crystal forms such as co-crystals, polymorphs, salts, hydrates, and solvates. According to BCS categorization, the majority of APIs are Class II (low solubility and high permeability) chemicals, hence co-crystals have added to the variety of crystal forms at the disposal of pharmaceutical scientists.*

Omeprazole is a proton-pump inhibitor used in peptic ulcers, gastroesophageal reflux disorder, Zollinger-Ellison syndrome and in H.pylori infections. Omeprazole is unstable at acidic pH, conditions undergoes degradation in stomach, and insoluble in water, having poor bioavailability. To overcome these major drawbacks of omeprazole, co-crystallization was attempted, to produce a stable preparation. Omeprazole co-crystals were prepared by PVP as coformer by antisolvent addition method. Prepared co-crystals were characterized by X-ray diffraction (XRD), fourier transformation infra-red spectroscopy (FTIR), differential scanning colorimetry (DSC), scanning electron microscopy (SEM) to evaluate hydrogen bonding interactions.

Lovastatin is a potent anticholesteremic agent, comes under BCS –II class of drugs, which is almost insoluble in water (0.0004 mg/ml or 1.3 µg/ml) having low bioavailability (<5%). Lovastatin co-crystals were prepared with selected coformer gallic acid by co-grinding method. Prepared co- crystals were characterized by X-ray diffraction (XRD), fourier transformation infra-red spectroscopy (FTIR), differential scanning colorimetry (DSC) and scanning electron microscopy (SEM) to evaluate hydrogen bonding interactions.

Nateglinide was another choice of insoluble (8.8 mg/L) drug, an oral antidiabetic agent used in the management of type II diabetes mellitus. Nateglinide is the drug of interest because it has poor biopharmaceutical properties like half life (t1/2) with 1.5 hrs. Hence co-crystals of nateglinide were prepared by solvent drop grinding method with maleic acid as coformer and 1-propanol as solvent.

Keywords: *Pharmaceutical co-crystals*

I. INTRODUCTION

Omeprazole belongs to class II of BCS classification of drugs, having antisecretory activity that suppress the gastric acid secretions with the aid of specific inhibition of the H+/K+ ATPase enzyme system of the gastric parietal cells. Chemically it belongs to benzimidazole substituent class of antiulcer drugs.

Omeprazole is chemically unstable in acidic conditions, very slightly soluble in water (82.3 mg/L) having 40-50% of oral bioavailability, moreover it is sensitive to heat, humidity and light. Short biological half life, hepatic first pass

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metabolism of omeprazole, thereby attempts were made to improve the bioavailability, solubility by formulating as enteric coated granules were encapsulated in gelatin shell and enteric coated tablets etc.

Omeprazole is chemically unstable in acidic conditions, very slightly soluble in water (82.3 mg/L) having 40-50% of oral bioavailability, more over it is sensitive to heat, humidity and light. Short biological half life, hepatic first pass metabolism of omeprazole, thereby attempts were made to improve the bioavailability, solubility by formulating as enteric coated granules were encapsulated in gelatin shell and enteric coated tablets etc. The efficiency of such dosage forms depends upon the number of parameters such as extent of coating, solubility of coating material and type of dosage form. But omeprazole have a wide individual variation of plasma concentration in humans, to get rid of this problem, alternative dosage forms like rectal suppositories, buccal adhesive tablets were developed, but all the different dosage forms of omeprazole gives only systemic effect. To provide local effect for a long periods of time, enteric coated mucoadhesive sustained release product was developed, which increases the residence time due to attachment with the intestinal mucosa for prolonged time and have local effect in duodenal ulceration, reduction in drug loss and reducing dosage frequency.246

Pharmaceutical co-crystallization is a novel crystal engineering design to produce alterations in the physicochemical properties like solubility, bioavailability, melting point, stability and micromeritic properties of poorly water soluble parent drugs. This technique is most preferred due to its crystalline state with low energy level and thermodynamic stability. Co- crystallization approach was attempted to enhance the solubility, bioavailability and stability of omeprazole.

Lovastatin is a natural product having a potent inhibitory effect on HMGCoA reductase. It was discovered in 1970's later it was developed as a potential anti- lipidemic drug by lowering LDL cholesterol levels. Lovastatin is naturally obtained lactone metabolite isolated or extracted from the fungus Aspergillus terreus cultures. Lovastatin is also produced by natural fungi like Pleurotus ostreatus (oyster mushrooms)

Lovastatin was the first specific inhibitor of HMG coenzyme A reductase had received the approval to treat the hypercholesterolemia. It acts as a potent, specific, competitive inhibitor of HMG CoA reductase which is a rate-limiting major important step in the biosynthetic pathway of cholesterol production. By inhibition of this enzyme, leads to accommodation of HMG CoA a water soluble intermediate which was readily metabolized to simpler molecule. Thus lovastatin stimulates the production of low density lipoproteins receptors in the liver, inaddition to this it also acts as antineoplastic agent, inhibiting tumour cell apoptosis, and tumour cell invasiveness. They arrest the growth of tumour cells in G, phase of cell cycle by inhibiting the protein farnesylation and geranylgeranylataion237.

Lovastatin is a prodrug contains an inactive lactone ring in native form. After administration the gamma–lactone closed ring was hydrolysed by in-vivo to β-hydroxy acid open ring which is active form. Commonly it is used in treatment of dyslipidemia and prevention of cardiovascular diseases. Lovastatin comes under BCS –II class of drugs, which is almost insoluble in water (0.0004 mg/ml or (1.3µg/ml). It undergoes extensive metabolism in the gut, liver and transmembrane efflux via P-glycoprotein, and thus having poor bioavailability (<5%)187. Besides it has oxidative instability therefore it must be stored along with anti-oxidants. To enhance the solubility of lovastatin, crystal engineering technique "Cocrystallization" was attempted in this study to produce lovastatin co-crystals.

Nateglinide belongs to meglitinides class of oral diabetic agents used in type 2 diabetes mellitus, it is structurally unrelated to the oral sulfonylurea insulin secretagogues271. Nateglinide is the drug of interest because it has poor biopharmaceutical properties like half life (t1/2) with 1.5 hrs. Nateglinide is rapidly absorbed with mean peak plasma drug concentrations (Cmax) generally occurred within 1 h (Tmax)210. Nateglinide is assigned as a class II type of drug based on the biopharmaceutical classification system (BCS). It is an anionic compound with pKa value 3.1 and log value 4.2 and freely soluble in ethanol, but it is practically insoluble in water (8.8 mg/L). Several approaches like size reduction, solid dispersion (SD), complexation, prodrug, formation of salts and some techniques like, nanotechnology, co-mixing, co-milling, complexation, and liquisolid have been attempted to enhance solubility of nateglinide211, 212.

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These techniques were fractionally fill their requirements with some limiltations. Co-crystallization is an efficient novel technological and manufacturing approach to enhance the solubility and dissolution rate of highly lipophilic drugs. Pharmaceutical.

II. REVIEW OF LITERATURE

Pharmaceutical crystallization is an important technique used to improve the physicochemical and biopharmaceutical properties of drugs. Most active pharmaceutical ingredients (APIs) are marketed in crystalline form because crystal structure directly affects solubility, dissolution rate, stability, bioavailability, and manufacturing properties. Recent studies have shown that crystal engineering and co- crystallization are effective methods for enhancing the performance of poorly soluble drugs.

Omeprazole is a proton pump inhibitor belonging to BCS Class II drugs and is highly sensitive to acidic conditions, heat, moisture, and light. Due to poor aqueous solubility and instability in gastric pH, researchers attempted co-crystallization using suitable coformers such as PVP through anti-solvent addition methods. Characterization studies such as XRD, FTIR, DSC, and SEM confirmed successful crystal engineering and improvement in stability and dissolution behavior.

Shahid MS et al.172 omeprazole magnesium and cefixime solid dispersions were prepared by slugging method, solvent evaporation, and fusion methods. Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the bioavailability. Omeprazole magnesium and cefixime solid dispersions were prepared with polymer PEG 6000 in the ratio 1:1, 1:2, 1:3 by hot melt method. Solid dispersions were prepared with other carriers like PVP-K30 and urea in the ratio 1:1, 1:2, 1:3 respectively by solvent evaporation method. Solid dispersion with excipients like lactose and sodium chloride with different ratios 1:1, 1:2, 1:3 respectively were by slugging method. Saturation solubility omeprazole solid dispersion with PVP-K30 and urea by solvent evaporation technique gives a better solubility of drug when compared to other techniques.

Soumya M et al.173 formulated omeprazole fast dissolving tablets with super disintegrants such as cross linked alginic acid and calcium silicate. The optimized formulation showed 99.6% drug release at 12min of time. The prepared tablets were carried for all quality control tests, they were lies within the USP limits.

Lovastatin is a cholesterol-lowering drug with very poor aqueous solubility and low oral bioavailability. Studies reported that modification of crystal habit and co- crystal formation using coformers like gallic acid improved dissolution rate and micromeritic properties. Paradkar et al. performed in-situ micronization and crystallization techniques to improve lovastatin performance, while Vuddanda et al. demonstrated enhancement of physicochemical properties through crystal engineering.

Basavaraj N et al.185 prepared lovastatin nanocrystals by simple precipitation method without adding any stabilizer or surfactant. Acetone and methanol was used as a solvent at perticular dilution of water produces nanocrystals of lovastatin with smaller in particle size and slightly changed in crystalinity. Lovastatin nanocrystals had shown enhancement in saturated solubility, dissolution rate and bioavailability when compared to pure lovastatin.

Viswanath V et al.186 formulated lovastatin liquisolid compacts by using microcrystalline cellulose as carrier material, PEG 400 as non-volatile solvent, super disintegrants like sodium starch glycolate, aerosol as coating material, magnesium stearate as glidant and lactose as diluent with other additives. All formulations were evaluated for FTIR studies, results states that there was no chemical interaction were taken place between ingredients. Formulation with high concentration of super disintegrant produced more enhancements in % drug release of drug.

Suparna SB et al.187 they formulated liquid and solid self micro emulsifying drug delivery systems (SMEDDS) of lovastatin using labrafil M 1944, Acrysol EL 135 and lauroglycol as oil, surfactant and co-surfactant respectively. With the help of ternary phase diagram the area of emulsification was determined for the preparation of SMEDDS. Prepared systems were characterized for self emulsification time, robustness to dilution, % transmittance, globule size and thermodynamic stability studies. Dissolution studies shows enhanced release rate of drug when compared to pure and marketed formulation, may be due to lipid excipients or transformation of crystalline drug to amorphous form.

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Nateglinide is an oral antidiabetic drug categorized under BCS Class II with poor solubility and short half-life. Researchers developed co-crystals using solvent drop grinding methods with maleic acid as coformer to improve dissolution and bioavailability. Studies also showed that polymorphic control of nateglinide is essential because different crystal forms exhibit different stability and therapeutic efficiency.

Sarika W et al.203 prepared co-amorphous mixture (COAM) of nateglinide and metformin hydrochloride by co-grinding for about 6 hrs with the help of ball milling technique. They carried characterization studies and revealds that amorphization was taken place between nateglinide and metformin, where as FTIR suggested that hydrogen bonding interactions were presented and solubility studies state a sevenfold rise in solubility of nateglinide from 0.0061 to 0.423 mg/ml.[Sarika W et al.204 they produced nateglinide micro environment pHregulated ternary solid dispersion (MeSD) to achieve the increase in dissolution and bioavailability of nateglinide which is pH dependent solubility drug. MeSD was formulated by nateglinide, poloxamer-188 and sodium carbonate by melt dispersion in 1:2:0.2 w/w ratio. This formulation achieves pH-independent dissolution with reduced Tmax and enhanced bioavailability of nateglinide.

Mohammad Kaleemuddin et al.205 formulated lyophilized oral sustained release polymeric nano particle of nateglinide in order to decrease the frequency of dose, minimize side effects and increase the bioavailability. By emulsion solvent evaporation method with biodegradable and biocompatible polymers like polycaprolactone (PCL) was used for the preparation of nateglinide nanospheres.

Amrta P P et al.206 prepared nateglinide nano suspension by nano precipitation technique. It was evaluated for particle size, in-vitro dissolution study and characterisation studies. Optimized nano suspension was enhanced by 83 % in 50 min relative to micronized suspension of nateglinide (37 % in 50 min).

Different crystallization techniques such as solvent evaporation, cooling crystallization, anti-solvent crystallization, and supercritical fluid crystallization are widely used in pharmaceutical industries. These methods help in obtaining crystals with desired purity, particle size, morphology, and polymorphic form. Seeding techniques and proper solvent selection are also critical for controlling nucleation and crystal growth.

III. PLAN OF WORK

Literature Survey

Collection of information related to crystallization techniques, co-crystals, polymorphism, and pharmaceutical applications of omeprazole, lovastatin, and
nateglinide from journals, books, and research articles.

Selection of Drugs and Solvents

Selection of omeprazole, lovastatin, and nateglinide along with suitable solvents and anti-solvents for crystallization studies.

Procurement of Materials

Collection of drug samples, solvents, anti-solvents, chemicals, and laboratory equipment required for experimental work.

Preparation of Saturated Drug Solutions

Preparation of saturated solutions of selected drugs using appropriate solvents under controlled temperature conditions.

Crystallization Process

Application of different crystallization methods such as:
Solvent evaporation method
Cooling crystallization method
Anti-solvent crystallization method

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Co-grinding or solvent drop grinding method
Collection and Drying of Crystals
Separation of crystals by filtration followed by drying in vacuum desiccator or hot air oven.

Characterization of Crystals
Evaluation of prepared crystals using:
Melting point determination Solubility studies Dissolution studies
FTIR analysis XRD analysis DSC analysis SEM analysis
Evaluation of Physicochemical Properties
Study of crystal size, morphology, flow properties, stability, dissolution rate, and bioavailability enhancement.

Result Interpretation
Comparison of crystalline forms with pure drugs and analysis of improvement in pharmaceutical properties.
Conclusion and Documentation
Preparation of final report including observations, results, conclusion, references, and future scope of study.

IV. OBJECTIVE

Crystallization is a fundamental separation and purification process used in the pharmaceutical industry. More than 90% of all pharmaceutical products contain active pharmaceutical ingredients (APIs) in crystalline form. The crystal structure, size, and shape (morphology) directly influence the drug's stability, solubility, and bioavailability.
This project explores various crystallization technique Specifically solvent evaporation, cooling, anti-solvent, and supercritical fluid methods to optimize the delivery and performance of three specific drugs: Omeprazole, Lovastatin, and Nateglinide.
 Impact of Polymorphism: Many drugs exhibit polymorphism, where the same chemical compound exists in different crystalline forms; these forms can have vastly different therapeutic effects and safety profiles.
 Regulatory Importance: Global health authorities, such as the FDA, require strict control over crystal forms to ensure that every batch of a drug performs identically in the patient's body.
 Economic Factors: Efficient crystallization processes reduce waste and production costs, making life-saving medications like statins and proton pump inhibitors more affordable for the general public.

Omeprazole
Objective of crystallization:
Aims: The main aim of the present investigation was to
1) To prepare and evaluate co-crystals of omeprazole with suitable coformer.
2) To formulate and evaluate dry suspension prepared by using omeprazole co-crystals.

Objectives:
1) To prepare co-crystals of omeprazole using various coformers such as polyvinylpyrrolidone, polyvinylalcohol, magnesium oxide, calcium carbonate, sodium carbonate and magnesium chloride.
2) To select the appropriate coformer and its concentration by preliminary screening methods.
3) To select suitable method of preparation of co-crystals and optimization of various process variables.
4) To characterize the co-crystals by SEM, DSC, FTIR, XRD, melting point, drug solubility and in-vitro drug dissolution studies.
5) To evaluate the micromeritic properties of optimized omeprazole cocrystals.
6) To formulate dry suspension using the optimized omeprazole co-crystals

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7) In-vitro evaluation of the dry suspension by conducting colour change determination, drug content, pH determination and dissolution studies.
8) Comparision of the dissolution profiles of final optimized omeprazole cocrystal formulation with the pure omeprazole formulation and marketed formulation (Omez insta).
9) In-vivo evaluation of the optimized omeprazole co-crystals dry suspension in male albino rats for determination of various pharmacokinetic parameters and antiulcer activity in alcohol induced gastric ulceration model.
10) To conduct stability studies of the omeprazole co-crystal dry suspension as per ICH guidelines.

Lovastatin

Objective of crystallization:

Aims: The main aim of the present investigation was to

1) To prepare and evaluate co-crystals of lovastatin with suitable coformer.
2) To formulate and evaluate conventional tablets prepared by using lovastatin co- crystals.

Objectives:

1) To prepare co-crystals of lovastatin using various co-formers such as maleic acid, gallic acid, citric acid, tartaric acid, mannitol, oxalic acid, glutaric acid, malonic acid, fumeric acid, adipic acid, succinic acid and alanine.
2) To select the appropriate co-former and its concentration by preliminary screening methods.
3) To select suitable method for preparation of co-crystals and optimization of various process variables.
4) To characterize the co-crystals by SEM, DSC, FTIR, XRD, melting point, drug solubility and in-vitro drug dissolution studies.
5) To evaluate the micromeritic properties of optimized lovastatin cocrystals.
6) To formulate a tablets using the optimized lovastatin co-crystals.
7) In-vitro evaluation of the tablets by determining the pre-compressible properties, post-compressible properties and dissolution studies.
8) Comparision of the dissolution profiles of final optimized lovastatin cocrystals formulation with the pure lovastatin formulation and marketed formulation (mevacor).
9) In-vivo evaluation of the optimized lovastatin co-crystals tablets in male albino rats for determination of various pharmacokinetic parameters and antilipidemic activity in diet induced hyperlipidemia in rabbit model.
10) To conduct stability studies of the lovastatin co-crystal tablets as per ICH guidelines.

Nateglinide

Objective of crystallization:

Aim: The main aim of the present investigation was to

1) To prepare and evaluate co-crystals of nateglinide with suitable coformer.
2) To formulate and evaluate conventional tablets prepared by using nateglinide co- crystals.

Objectives

1) To prepare co-crystals of nateglinide using various coformers such as maleic acid, gallic acid, citric acid, tartaric acid, mannitol, oxalic acid, glutaric acid, malonic acid, fumeric acid, adipic acid, succinic acid and alanine.
2) To select the appropriate coformer and its concentration by preliminary screening methods.
3) To select suitable method for preparation of co-crystals and optimization of various process variables.
4) To characterize the co-crystals by SEM, DSC, FTIR, XRD, melting point, drug solubility and in-vitro drug dissolution studies.
5) To evaluate the micromeritic properties of optimized nateglinide cocrystals.
6) To formulate tablets using the optimized nateglinide co-crystals.

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7) In-vitro evaluation of the nateglinide tablets by conducting precompressible properties, post-compressible properties and dissolution studies.
8) Comparision of the dissolution profiles of final optimized nateglinide cocrystals formulation with the pure nateglinide formulation and marketed formulation (Glinate).
9) In-vivo evaluation of the optimized nateglinide co-crystal tablets in male albino rats for determination of various pharmacokinetic parameters and antidiabetic activity in streptozotocin induced type II diabeties in rat model.
10) To conduct stability studies of the nateglinide co-crystal tablets as per ICH guidelines.

VI. CRYSTALLIZATION TECHNIQUES

To achieve the desired crystal habit, different thermodynamic and kinetic approaches are used:
 Solvent Evaporation: The simplest method where a saturated solution is allowed to evaporate. As the solvent volume decreases, the concentration exceeds the solubility limit, leading to crystal formation.
 Cooling Crystallization: Used for solutes whose solubility decreases significantly with temperature. By lowering the temperature of a saturated solution, the system enters the labile zone of supersaturation.
 Anti-solvent Crystallization: A second solvent (in which the drug is poorly soluble) is added to the solution. This reduces the solubility of the API, causing rapid precipitation.
 Supercritical Fluid (SCF) Crystallization: Uses fluids like CO_2 in their supercritical state. This allows for precise control over particle size (often producing nanoparticles) and avoids the use of toxic organic solvents.
 Mechanism of Nucleation: Every crystallization method begins with nucleation, where solute molecules gather into clusters, followed by crystal growth where these clusters reach a stable macroscopic size.
 Seeding Strategies: In cooling and anti-solvent methods, "seeding" (adding a small amount of pure crystals) is often used to bypass the unpredictable spontaneous nucleation phase and ensure a specific polymorph is formed.
 Solvent Selection Criteria: The choice of solvent is critical; it must not only dissolve the drug effectively but also be non-toxic, easily removable, and compatible with the drug's chemical stability.

VII. DRUGS PROFILE

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	Drug	Therapeutic Use	Crystallization Challenges
1)	Omeprazole	Proton pump inhibitor (Acid Reflux)	Highly sensitive to light and moisture; prone to polymorphic conversion
2)	Lovastatin	Cholesterol-lowering agent (Statin)	Poor aqueous solubility; difficult to achieve uniform particle size
3)	Nateglinide	Anti-diabetic (Type 2)	Exists in multiple crystel forms (H form and B form) maintaining the correct polymorph is critical for efficiency

1) Omeprazole
Proprietary name : Losec. Prilosec, Antra, Omeprazon, Omepral
IUPAC name : 6-methoxy-2-[(4-methoxy-3, 5-dimethyl pyridin-2-yl) methylsulfinyl]-IH-benzimidazole.
Molecular weight : 345.42 g/mol
Molecular formula : CHNOS

Structural formula and 3D picture:

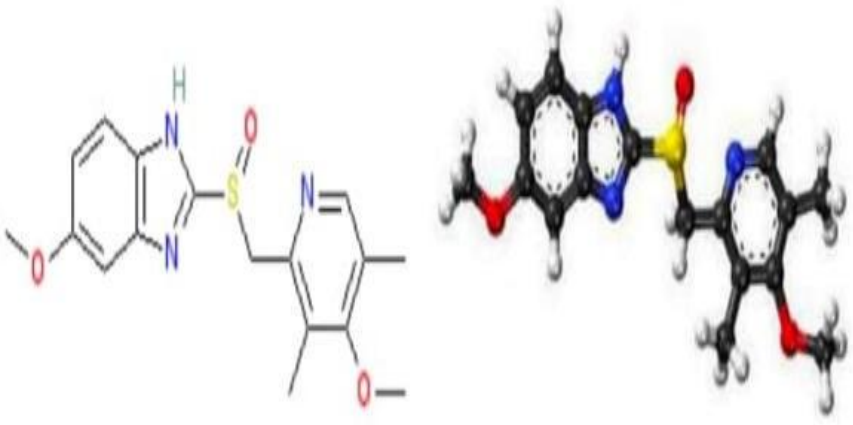

Fig No. 1
Description: It is a white to off-white crystalline powder, having decomposition at 155°C. It is a weak base..

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Solubility : It is freely soluble in DMSO, ethanol and methanol.Slightly
soluble in acetone and iso-propanol, very slightly soluble in water (0.5mg/ml) (or) 82.3 mg/L at 25°C
Melting point range : 155-156°C
Category : Anti ulcer drug
Stability : It is stable under basic pH conditions, rapidly degraded in acidic medium conditions.
Storage temperature : 2-8°C
Caution : It is hygroscopic, photosensitive and thermal sensitive pka Value : 9.29
Octanol /water partition coefficient : 223
Biopharmaceutical classification system (BCS) : It belongs to 11 class
Hydrogen bond donor count : 01 Hydrogen hond acceptor cuant : 06 Rotatable bond count : 05
Functional group : Benzimidazole group
t1/2 : 0.5-1hr
Volume of distribution : Appmamately 0.3 L/kg
Protein hinding : Approximately 95% so human plasma proteins
Clearance : 500-600 ml min
Formulations preparations : capsules, delayed-minase capsules, 10 img prilosec, 20mg prilosec. 40ng. prilosec, omez insta achet, acotref, rapines and santarus.
Maximum absorption in ultraviolet spectrum : 302 m
Toxicological information : Omeprazole rarely been associated with hepatic injury.
Therapeutic Uses : Used in duodenal ulcer, gastric ulcers, NSAID associated gastric and duodenal ulcer, reflas esophagitis, and gastro esophageal reflus. Omeprazole was a proton pump inhibitor widely used in belicobacter pylori eradication in peptic ulcer diseases, Zollinger-Ellison syndrome

2) Lovastatin
Proprietary name : Mevinolin, Mevacor, MK803, Lochol, Rovacor, Lipistat, Lovex, Lovastat, Favolip, Lovameg and Lovalip.
IUPAC name : [(1S,3R,75,8S,8aR)-8-[2-[(2R,4R)-4-hydroxy-6- oxo oxan-2-
y1]ethyl]-3,7-dimethyl -2,3,7,8,8a- hexahydro naphthalen-1-yl] (2S)-2-methyl butanoate.
Molecular formula : C24 H36 O5

Structural formula and 3D picture:

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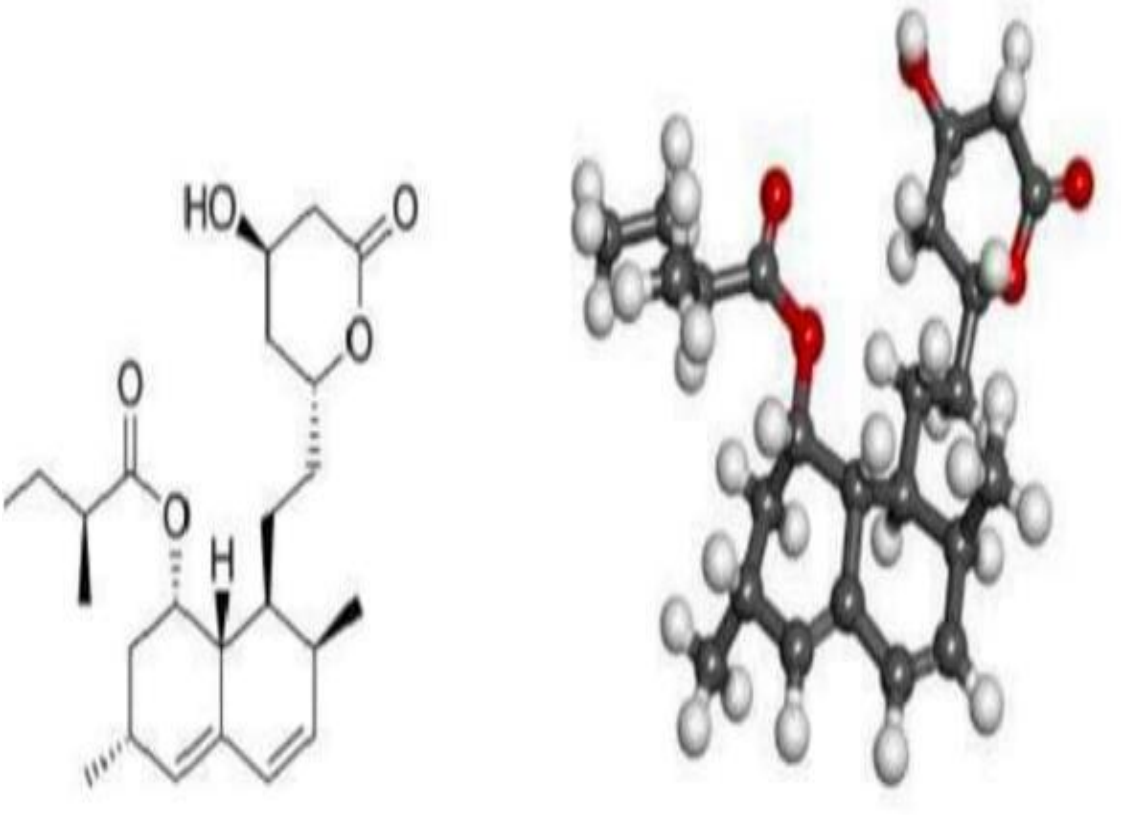

Fig No. 2

Molecular weight : 404.54 g/mol
Melting point range : 174-179°C
Description : white crystalline powder, non-hygroscopic and photosensitive
Solubility : Insoluble in water (0.004mg/ml) at 25°C. It is freely soluble in acetone, acetonitrile, n-propanol, chloroform, iso-propanol, N N-dimethyl formamide, methanol. Slightly soluble in n-butanol, iso-butanol, n- octanol and practically insoluble in hexane.
Category : Anti lipidemic drug
Stability : It has oxidative unstability, needs to add antioxidants
Storage temperature : stored at 5-30°C in light resistant
pKa value : 13.49
Partition coefficient : 4.08 Biopharmaceutical classification system (BCS) : II class
Functional group : Contains two groups, hexahydronaphthalene system and β- hydroxylactone ring
Hydrogen bond donor count : 01 Hydrogen bond acceptor count : 05 Rotatable bond count : 07
t1/2 : 2-5 hr
Protein binding : >98% to human plasma proteins
Volume of distribution : Able to cross blood brain barrier and placenta
Bioavailability : < 5%
λ max in UV : 231 nm and 238 nm
Polarizability : 46.11A03
Topological polar surface area : 72.83 A2

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Formulations /Preparations : Tablets (Mevacor 20 mg, 40mg, 60mg) Extended release tablets 20mg, 40mg, and 60mg (Altoprev). Lovastatin combination with niacin tablets (Advicor)
Toxicological information : Long term over dosage leads to hepatotoxicity in 3 to 5% of patients
Therapeutic uses : Lovastatin belongs to statin medication, used to treat high blood cholesterol and reduce the risk of cardiovascular diseases.

3) Nateglinide
Proprietary name : Starlix, Fastic, starsis
IUPAC name : (2R)-3-phenyl-2-[(4-propan-2-yl cyclohexane carbonyl) amino]propanoic acid.
Molecular formula : C19 H27 NO3
Structural formula and 3D pictuòre:

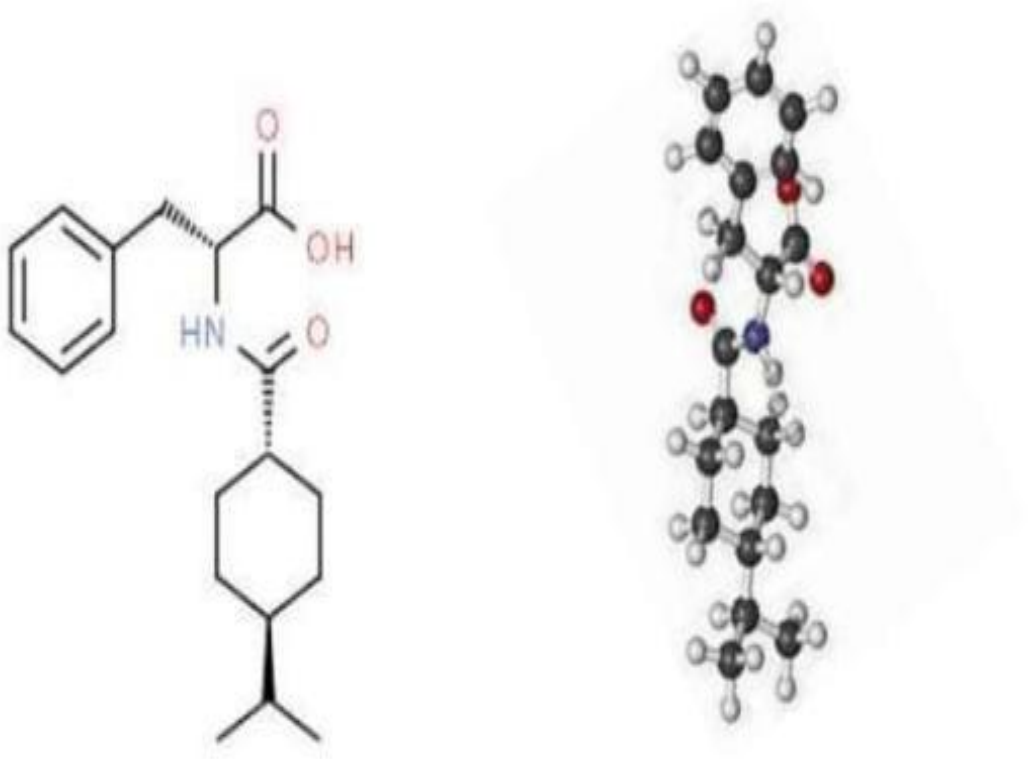

Fig No. 3

Molecular weight : 317.5 gm/mol Melting point range : 129-130°C Description : It is a white powder
Biopharmaceutical classification system (BCS) : II class
Solubility : It is practically insoluble in water (0.0084 mg/ml) predicted. Freely soluble in methanol, ethanol and chloroform. Soluble in ether, sparingly soluble in acetonitrile and octanol.
Category : Anti diabetic drug (Hypoglycemic agent)
Stability : stable under stora 23/34 Storage temperature : 15-30°C pKa value : 3.1
Partition coefficient : 2.4
Functional group : It was a phenylalanine derivative of the meglitinides class of anti- diabetic drugs
Hydrogen bond donor count : 02 Hydrogen bond acceptor count : 03 Rotatable bond count : 06
t1/2 : 1.5 hrs
Protein binding : 98 % bounded to serum proteins

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Volume of distribution : 10 liters in healthy subjects
Bioavailability : Approximately 73%
λ max in UV : 201 nm
Formulations/Preparations : Tablets (starlix -60 and 120 mg) Glinate enteric coated tablets (60mg)
Toxicological information : Rare instances of apparent acute liver injury (hepatotoxicity), if overdose results in hypoglycaemic symptoms
Therapeutic uses : used in diabetes
Directions to use : Take with food or before meals

VIII. EXPERIMENTAL METHODS

Materials: High-purity omeprazole, lovastatin, and nateglinide; solvents (ethanol, methanol, acetone); anti-solvents (distilled water, n-hexane).
Procedure:
1. Preparation: Create a saturated solution of the drug in the chosen solvent.
2. Induction: Apply the specific technique (e.g., slow cooling at 1°c/min or rapid addition of anti-solvent).
3. Filtration & drying: Collect crystals via vacuum filtration and dry them in a desiccator to prevent moisture-induced degradation.
4. Temperature monitoring: Use of high-precision sensors is necessary during cooling crystallization to maintain a steady cooling rate, as fluctuations can lead to uneven crystal sizes.
5. Vacuum filtration parameters: During the filtration step, the vacuum pressure must be carefully managed to avoid "Crushing" Delicate needle-like crystals, which could alter the drug's flow properties.
6. Desiccator conditions: Drying must occur in a controlled environment, often using silica gel or phosphorus pentoxide, to ensure all traces of solvent are removed without introducing humidity.

OMEPRAZOLE

Aim: To prepare pure crystalline omeprazole by crystallization method.
Principle: Omeprazole is dissolved in a suitable solvent at high temperature. On cooling or addition of anti-solvent, the solubility decreases and pure crystals separate out.
Materials Required:
Crude omeprazole, methanol or acetone, distilled water or hexane, beaker, water bath, filter paper, funnel, vacuum desiccator.
Experimental Procedure:
1. Take crude omeprazole in a clean beaker.
2. Add methanol or acetone and heat gently on a water bath until complete dissolution occurs.
3. Filter the hot solution to remove insoluble impurities.
4. Allow the filtrate to cool slowly at room temperature.
5. Add distilled water or hexane slowly as anti-solvent to initiate crystallization.
6. Keep the solution undisturbed for proper crystal growth.
7. After complete crystallization, collect the crystals by filtration.
8. Wash the crystals with a small quantity of cold solvent.
9. Dry the crystals in vacuum desiccator or hot air oven.
Result: Pure crystalline omeprazole crystals are obtained.
Advantages: Improves purity, stability, shelf life, and manufacturing properties.

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S.no	Equipments and instruments	Supplier
1.	Electronic balance	Shimadzu, Japan
2.	Melting point apparatus	Tempo, Mumbai
3.	UV/Visible spectrophotometer	Shimadzu UV-1800, Japan
4.	pH meter	Tempo, Mumbai
5.	Hot air oven	Inco, Ambala
6.	Magnetic stirrer	Remi motors Ltd, Mumbai
7.	Stability chamber	Remi lab world, Mumbai
8.	Dissolution apparatus TDT-08L,	Electro lab, Mumbai

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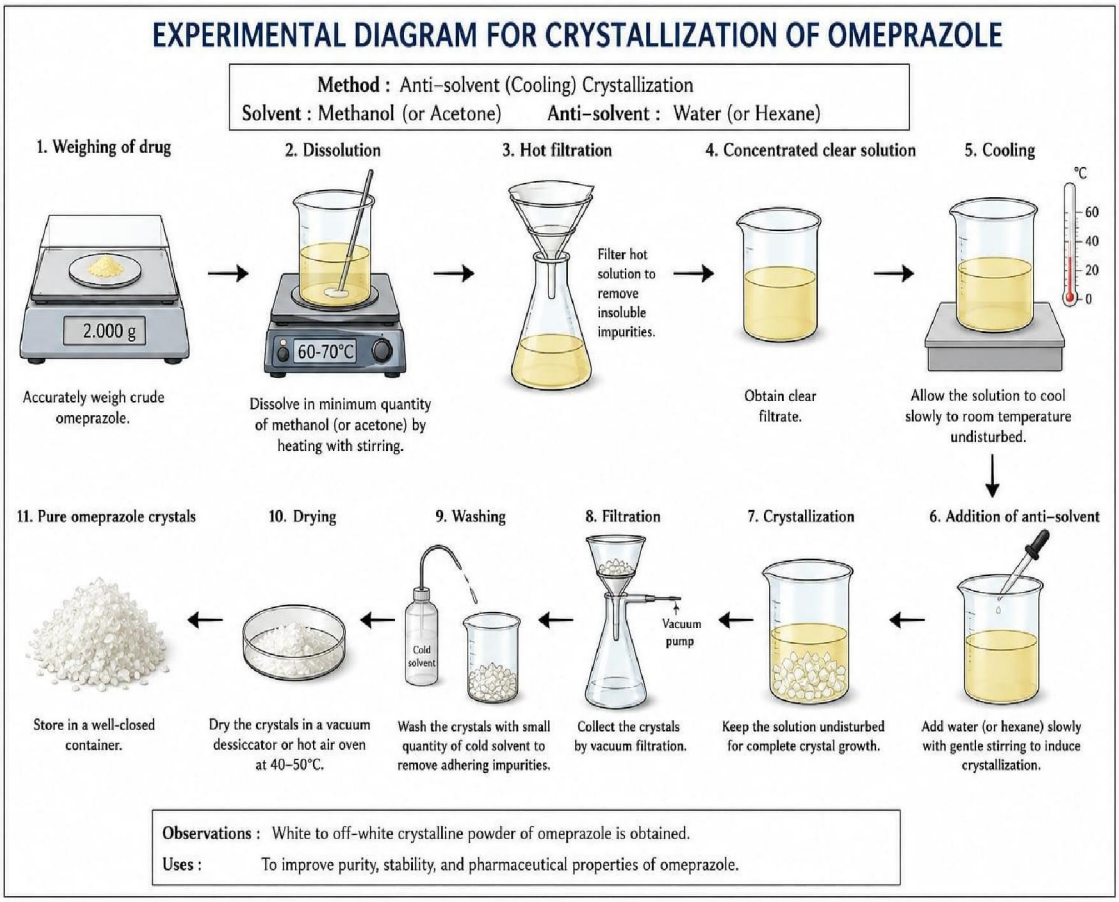

Experimental Diagram For Crystallzation Of Omeprazole
Fig.No.4

LOVASTATIN

Aim: To obtain pure lovastatin crystals by crystallization technique.

Principle: Lovastatin dissolves in hot organic solvent and crystallizes upon cooling due to reduction in solubility.

Materials Required:

Crude lovastatin, ethanol or ethyl acetate, ice bath, beaker, funnel, filter paper, drying oven.

Experimental Procedure:

1. Place crude lovastatin in a beaker.
2. Add ethanol or ethyl acetate as solvent.
3. Heat gently with stirring until a clear solution forms.
4. Perform hot filtration to remove impurities.
5. Allow the solution to cool slowly to room temperature.
6. Further cool the solution in an ice bath to complete crystallization.
7. Collect crystals by vacuum filtration
8. Wash crystals with cold solvent to remove impurities.
9. Dry the crystals at controlled temperature.

Result: Pure lovastatin crystals are obtained.

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Advantages: Produces highly pure drug, improves handling properties, and controls crystal

S.no	Equipment and model	Supplier
1.	Electronic balance	Shimadzu, Japan
2.	Melting point apparatus	Tempo, Mumbai
3.	UV/Visible spectrophotometer	Shimadzu UV-1800, Japan
4.	pH meter MK VI	Tempo, Mumbai
5.	Hot air oven	Inco, Ambala
6.	Magnetic stirrer	Remi motors Ltd, Mumbai
7.	Stability chamber	Remi lab world, Mumbai
8.	Dissolution apparatus (USP) TDT-08L	Electro Lab, Mumbai
9.	Monsanto hardness tester	Vinsyst technologies, Mumbai
10.	Disintegration apparatus	Labtronics Ltd, Mumbai
11.	Roche friabilator PX/FTA-1902	Systonic, Mumbai
12.	Glucometer	Dr. Morepen GlucoOne

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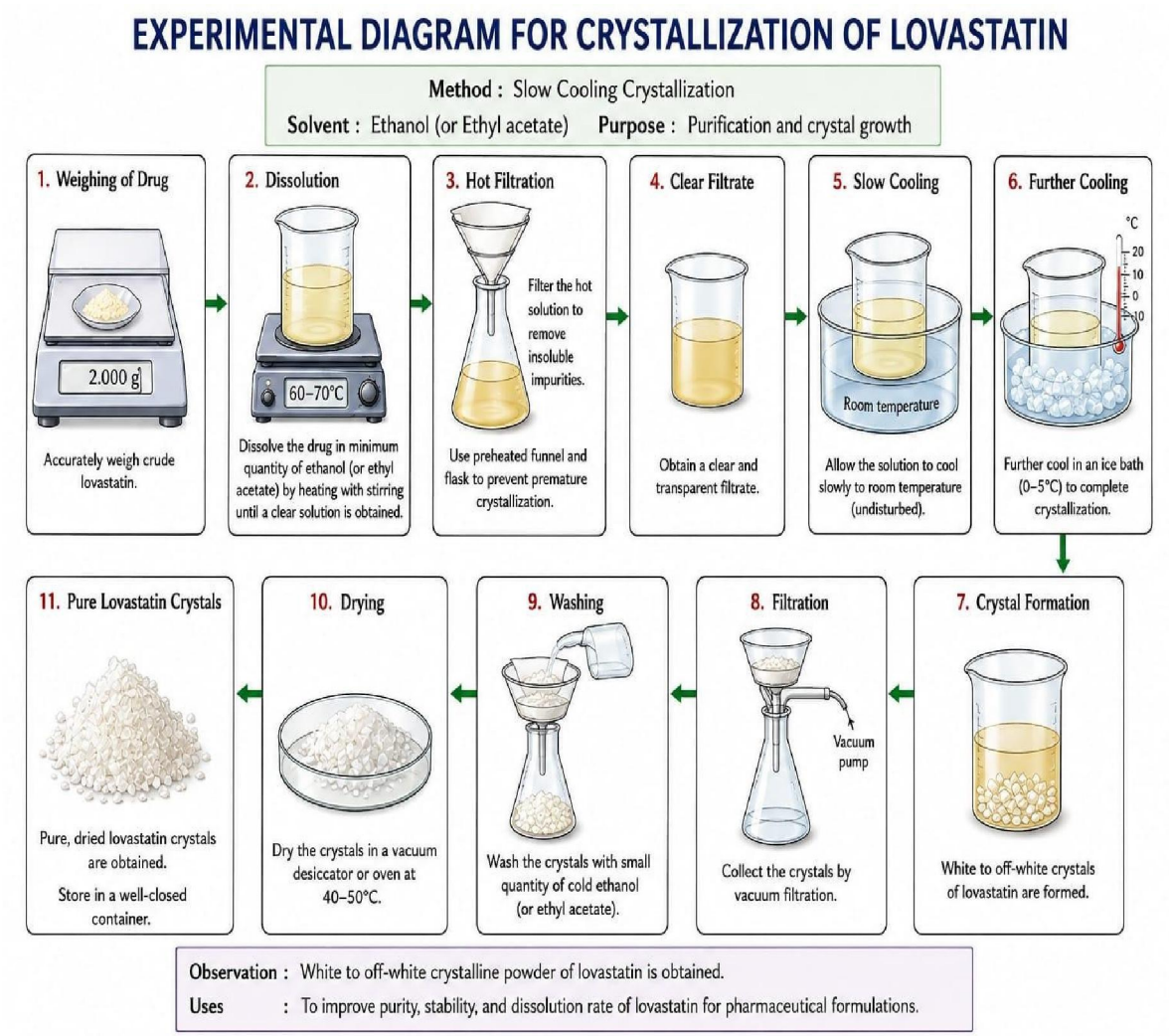

Experimental Diagram For Crystallization Of Lvastatin
Fig No:5

NATEGLINIDE

Aim: To prepare pure crystalline nateglinide by crystallization.

Principle: Nateglinide forms crystals when its saturated solution is cooled or treated with anti-solvent.

Materials Required:

Crude nateglinide, methanol or ethanol, distilled water, beaker, stirrer, filter paper, desiccator.

Experimental Procedure:

1. Dissolve crude nateglinide in methanol or ethanol by gentle heating.
2. Stir continuously to obtain uniform solution.
3. Filter the hot solution to remove insoluble matter.
4. Cool the filtrate slowly at room temperature.
5. Add distilled water slowly as anti-solvent if necessary.
6. Leave the solution undisturbed for crystal formation.

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7. Separate crystals by filtration.
8. Wash crystals with cold solvent.
9. Dry the crystals in vacuum desiccator.

Result: Pure crystalline nateglinide is obtained.

S.no	Equipments and Instruments	Suppliers
1.	Electronic balance	Shimadzu, Japan
2.	Melting point apparatus	Tempo, Mumbai
3.	Dissolution tester (USP) TDT-08L	Electro Lab, Mumbai
4.	UV/Visible spectrophotometer	Shimadzu UV-1800, Japan
5.	Hot air oven	Inco, Ambala
6.	pH meter MK VI	Tempo, Mumbai
7.	Stability chamber	Remi lab world, Mumbai
8.	Monsanto hardness tester	Vinsyst technologies, Mumbai
9.	Glucometer	Dr. Morepen GlucoOne
10.	Disintegration apparatus	Labtronics Ltd, Mumbai
11.	Roche friabilator PX/FTA-1902	Systonic, Mumbai

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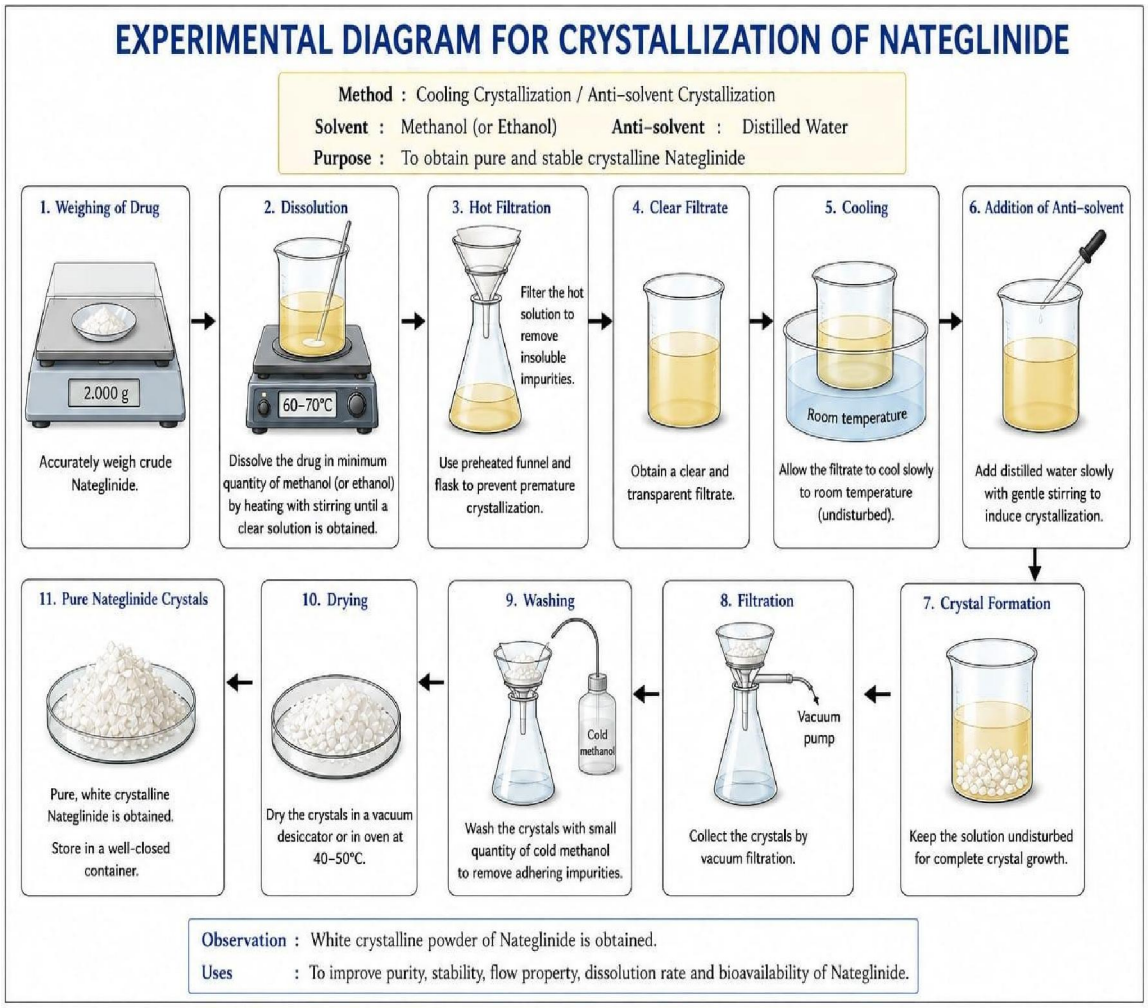

Experimental Diagram For Crystallization Of Nateglinide
Fig No:6

IX. RESULT

1. Omeprazole Result -

Preparation: Omeprazole co-crystals were successfully prepared by the anti-solvent addition method using PVP (Polyvinylpyrrolidone) as coformer. The crystallization process produced a white to off-white crystalline powder.

Drug	Method Used	Coformer	Key Outcome
Omeprazole	Anti-solvent Additi on Method	PVP (Polyvinylpyrrolido ne)	Enhanced solubility, bioavailability & stability; significant antiulcer activity
Lovastatin	Co-grinding Method	Gallic Acid	Improved dissolution, absorption & increased half-life; lipid-lowering effect confirmed
Nateglinide	Solvent Drop Grinding Method	Maleic Acid (1- propanol as solvent)	Better bioavailability; prolonged antidiabetic action 5–6 hrs vs pure drug

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Formulation Evaluation (Dry Suspension):
The dry suspension formulated using optimized omeprazole co-crystals showed acceptable results in all in-vitro evaluation parameters including colour change determination, drug content, pH determination, and dissolution studie.

2. Lovastatin — Results
Preparation:
Lovastatin co-crystals were successfully prepared by the co-grinding method using gallic acid as coformer. Pure white crystalline powder was obtained after drying.
Tablet Formulation Evaluation:
Conventional tablets prepared using optimized lovastatin co-crystals passed all in-vitro evaluation parameters including pre-compressible properties (angle of repose, bulk density, tapped density), post-compressible properties (hardness, friability, weight variation, disintegration time), and dissolution studies.

3. Nateglinide — Results
Preparation:
Nateglinide co-crystals were successfully prepared by the solvent drop grinding method using maleic acid as coformer and 1-propanol as solvent.
Tablet Formulation Evaluation:
Tablets prepared using optimized nateglinide co-crystals demonstrated acceptable results in pre-compressible properties, post- compressible properties, and dissolution studies within pharmacopoeial limit

X. CONCLUSION

Omeprazole :- In the view of resulted findings, it can be concluded that omeprazole cocrystals were successfully prepared by anti-solvent addition method. All the results of characterization studies confirmed that the drug was successfully crystal engineered to omeprazole co-crystals. Omeprazole co-crystal posses enhancement in solubility, dissolution, bioavailability and micromeritic properties. The dry suspension containing omeprazole co-crystals showed acceptable results in-vitro evaluation parameters.
In-vivo pharmacokinetic study proved that the optimized omeprazole cocrystal containing dry suspension showed better enhancement in obsorption and bioavailability than pure drug. Pharmacodynamic study of omeprazole co-crystals formulation showed significant antiulcer activity in ethanol induced ulceration rats when compared to pure drug and disease control group of rats
Finally particle engineering technique "co-crystallization" produced omeprazole co- crystals containing dry suspension, have proven to be a successful formulation for drug delivery and showed a better drug release over marketed product.
Lovastatin :- In the view of resulted findings, it can be concluded that lovastatin cocrystals were successfully prepared by co-grinding method. All the results of characterization studies confirmed that the drug was successfully crystal engineered to lovastatin co-crystals. Lovastatin co-crystal posses enhancement in solubility, dissolution, bioavailability and micromeritic properties. The tablets containing lovastatin co-crystals showed acceptable results in-vitro evaluation parameters.
In-vivo pharmacokinetic study proved that the optimized lovastatin cocrystal tablets showed better enhancement in absorption, bioavailability and increased half life than pure drug tablet. Pharmacodynamic study of lovastatin cocrystals tablets showed significant lipid lowering effects in cholesterol induced rabbits in comparison to standard and disease control group of rabbits.
Finally particle engineering technique "co-crystallization" produced lovastatin co- crystals containing tablets, have proven to be a successful formulation for drug delivery and showed a better drug release over marketed product.
Nateglinide :- In the view of resulted findings, it can be concluded that nateglinide cocrystals were successfully prepared by solvent drop grinding method. All the results of characterization studies confirmed that the drug was

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successfully crystal engineered to nateglinide co-crystals. Nateglinide co-crystal posses enhancement in solubility, dissolution, bioavailability and micromeritic properties. The tablets containing nateglinide co-crystals showed acceptable results in-vitro evaluation parameters.

In-vivo pharmacokinetic study proved that the optimized nateglinide cocrystal tablets showed better enhancement in absorption, bioavailability and increased half life than pure drug tablet and marketed tablet. Pharmacodynamic study of nateglinide co- crystals tablets showed better antidiabetic activity with prolonged time of action for about 5-6 hrs when compared to pure nateglinide tablet.

Finally particle engineering technique "co-crystallization" produced nateglinide co- crystals containing tablets, have proven to be a successful formulation for drug delivery and showed a better drug release over marketed product.

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