IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

CO-AMORPHOS MIXTURE: SOLUBILITY ENHANCEMENT TECHNIQUE

[1]Miss. Pranali Hatwar, [2]Mr.Avinash Manke, [3]Mr.Akash Ghuge,[4] Mr. Jayraj Mhaske, [5]Dr. Gajanan Sanap

[1]Assistant Professor, [2]Student, [3]Student, [4]Student, [5]Principal

[1]Pharmaceutics,

[1]Late Bhagirathi Yashwantrao Pathrikar College of Pharmacy (D & B pharmacy) Pathri, Aurangabad, Maharashtra, India.

Abstract: Co-amorphous drug delivery systems (CAMS) are characterized by the combination of a crystalline material with low molecular weight co-former that forms a homogeneous single-phase amorphous system. Over past decades it is a most promising approach for enhancement of solubility as well as bioavailability of poor water soluble drugs (BCS class II and IV). In this review provides updated overview on the CAMS using various quantitative approaches i.e., co-formability, dissolution performance and physical stability, Glass Transition Temperatures. Along with review also covers specifically, co-formability, molar ratio of drug and co-former, preparation methods for CAMS, physical stability as well as in vitro and in vivo performance with the various positive outcomes in which low soluble drug solubility markedly increased several folds by using CAMS.

KEYWORDS:-Solubility enhancement, bioavailability, Co- amorphous, Co- former.

INTRODUCTION

Solubility is one of the predominant trouble associated with the most of the chemical that can be kindly addressed via way of means of the drug amorphization. Solubility is described as the spontaneous interaction of or more substances to form a homogeneous molecular dispersion. Solubility is likewise described as the concentration of the solute in a saturated solution at a certain temperature in quantitative time period. [1]

NEED OF SOLUBILITY INHANCEMENT

Approximately 40% of recent drug applicants below development are poorly soluble in Water that are associated with various formulation-associated overall performance issues [2,3,4]. Improving the bioavailability of those drugs with the aid of using solubility/dissolution enhancement has become important for pharmaceutical corporations in search of to bring efficacious drugs to sufferers in affordable dosing regimens [3, 5]. Drug absorption from the GI tract may be limited with the aid of using a several of things maximum significant Contribute being poor aqueous solubility and poor membrane permeability of the drug. When administered an active agent orally it have to first dissolve in gastric and/ or intestinal fluids earlier than it can transfuse the membranes of the GIT to reach systemic circulation. Hence, regions of pharmaceutical studies that concentrate on upgrading the oral bioavailability of active dealers include; improving of solubility and dissolution rate of poorly water soluble drugs [6].

WHAT IS CO-AMORPHOUS MIXTURES:-

In amorphous systems use small molecules like urea, citric acid, tartaric acid as an amorphous stabilizers had reported in several study [7, 8] .Co-amorphous technology was currently added to stabilize drugs with inside the amorphous state for drug improvement. The term co-amorphous was discovered by Chieng etal [9]. This term was develops to distinguish amorphous mixture containing small molecules from the term PASD. Co-amorphous system is defined as a multi-component single phase amorphous solid system which lacks periodicity in the lattice and is associated with the aid of using weak and discrete intermolecular interactions among the components [10].

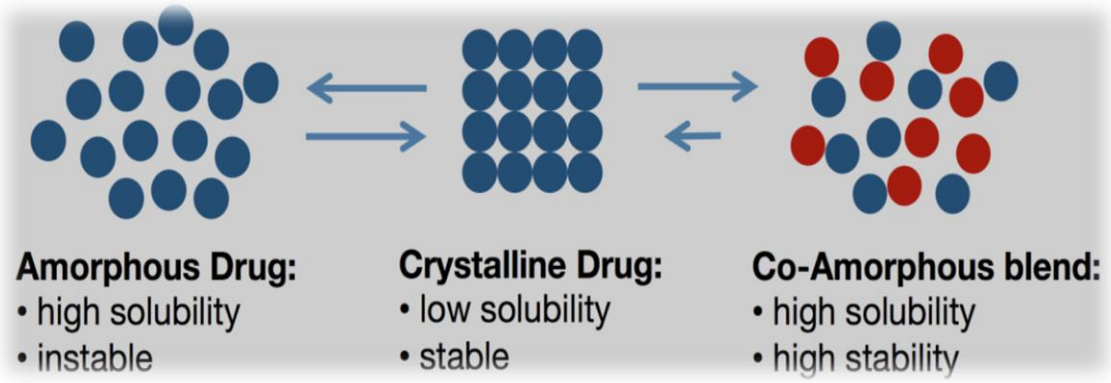

Fig no.01.co-amorphous system [14]

Chieng et al. introduced systems wherein drugs had been able to stabilize each other with inside the amorphous form, introducing the term co-amorphous. Co-amorphous here refers to an amorphous mixture consisting simplest of low molecular weight components in contrast to glass solutions, which include the drug together with a polymer [9]. These co-amorphous formulations exhibited the progressed physical stability of the amorphous form, in addition to the advanced dissolution rate of the drugs, as compared to the amorphous drugs alone [09–14].

CO-FORMER:-

Co crystals are multicomponent system wherein one aspect is Active Pharmaceutical Ingredient (API) and some other is called co-former. Different coformer are utilized in formations of co amorphous mixture such as

ADVANTAGES OF CO-AMORPHOUS MIXTURE

1. Higher intermolecular interactions.

2. Prevent recrystallization.

3. Higher miscibility and prevent phase separation.

4. Improves aqueous solubility and physical stability.

5. It has potential to improve therapeutic efficacy. [7]

CLASSIFICATION OF CO-AMORPHOUS SYSTEM

A. Drug-drug co-amorphous system: Drug-drug co-amorphous system is a binary system. There are several drug-drugs CO-AMORPHOUS was reported like as co-amorphous system of sulfamerazine, mefenamic acid and carbamazepine [15], Naproxen-cimetidine [11]. It shows several advantages like as solubility, stabilization, and dissolution, as well as useful in combinational therapy of the drug.

B. Drug-excipient co-amorphous system: This system are prepare by mechanisms such as like as charge assisted interactions and hydrogen bonding, drug-excipient co-amorphous system enhance solubility and stability. Sugars, urea Carboxylic acids, and amino acid used as a co former for the stabilization of drug in various co-amorphous preparations. Amino acids are extensively used in various co-amorphous system preparation.[12,13]

METHOD OF PREPARATION OF CO-AMORPHOUS MIXTURE:-

Co amorphous formulations prepared with the aid of using special methods should exhibit significant variations in their physical stability and dissolution overall performance. Based at the mechanism involved, strategies for co-amorphous mixture preparation may be divided into types, namely, thermodynamic techniques and kinetic disordering techniques. During thermodynamic process, drugs are in melt or solution states [17].

The co-amorphous drug formulation approach remains in its early level of development, as a result majority of studies targeted at the primary understanding of those systems the use of laboratory-scale preparative techniques including quenching [31,32] . Solvent evaporation [33] and ball milling. [34,35]. All of those techniques are attractive as they represent rapid and easy ways of co-amorphization, and are perfect for screening purposes as only small sample sizes are required. In addition, quenching gives the opportunity to fast assess.

METHOD OF PREPARATION:-

1. Kinetic Method

A. Ball Milling

B. Cryogenic milling

2. Thermodynamic methods

A. Solvent evaporation

B. Melt Quenching

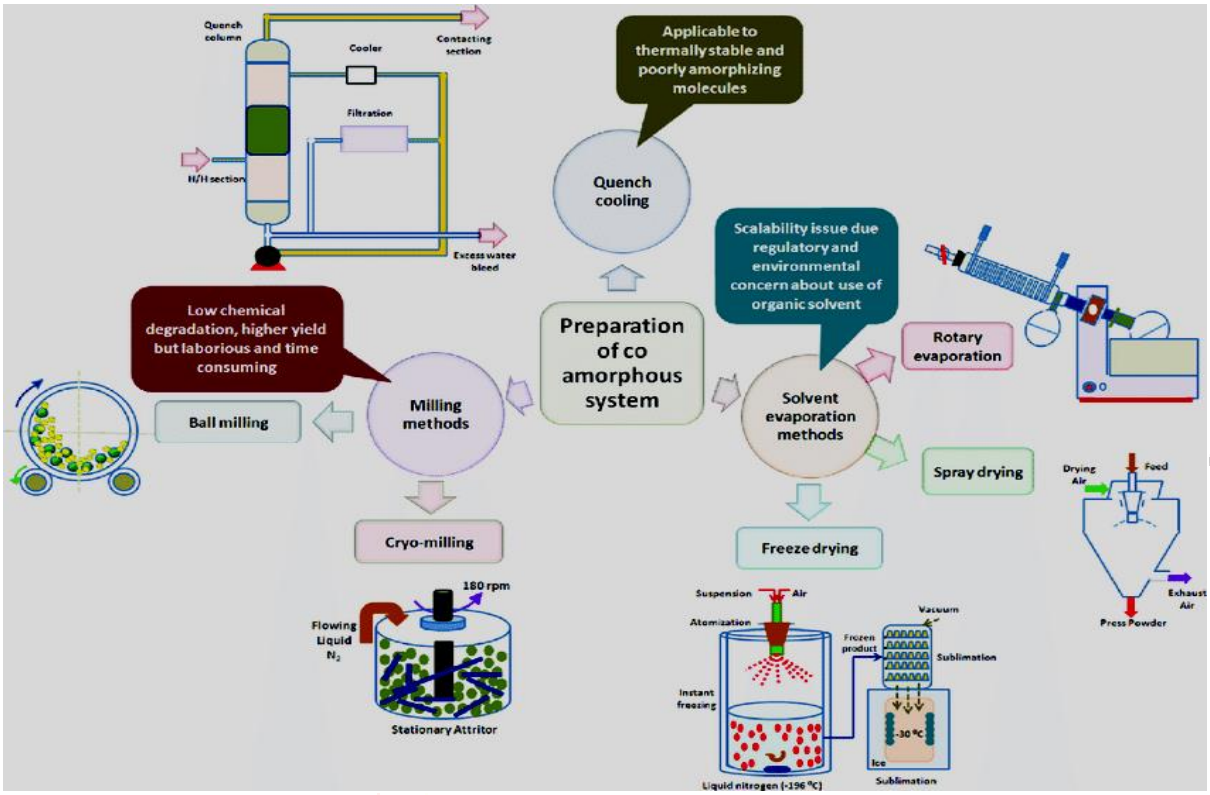

Fig no.02.Preparation methods of co-amorphous mixture

Table.01.Preparation methods of CAMs

Preparation methods	Advantages	Disadvantages	Application
Ball milling	Free of organic solvents, excessive yield, green, excessive strength	Time-consuming, warmness generation at some point of milling process,	Suitable for drugs of thermal stability
Cryomilling	Temperature, keeping off speedy re-crystallization, no thermal decomposition	Time-consuming and laborious	Especially for thermal instable drugs, and drugs with low TgS
Solvent evaporation	Fast preparation	Difficult to choose a appropriate solvent to dissolve each drug and co-former	Suitable for a few drugs which can be soluble with inside the solvent with low boiling point
Spray drying	Drying Rapid amorphization, appropriate for large-scale manufacturing	High energy intake, excessive cost, difficult to choose a appropriate solvent to dissolve each drug and co-former	Suitable for drugs with thermal stability
Freeze drying	Good appearance and shape, proper stability	High cost, time-consuming, excessive energy intake and limited solvent choice	Especially for drugs with thermal instability
Quench cooling	Simple operation, less time, higher amorphous purity through fast quench.	Causing structural damage and degradation to the drug itself through heating	Only suitable for drugs of thermal stability

1. MILLING METHOD:-

Milling is a famous method to provide the disordered pharmaceutical material attributable to the mechanical activation. From the molecular packing perspective, crystalline materials should lose their long-variety crystallographic periodicity with the aid of using introducing mechanical stress this is sufficient to create crystal defects [18,19] . The kinetics of transition from crystalline to amorphous state strongly depends at the milling situations. During the milling method, there's a kinetic competition between mechanically brought about amorphization and thermodynamically driven re-crystallization. Sometimes traditional ball milling isn't always efficient enough to provide amorphous materials because of an increase temperature throughout the milling method, which may also potentially increase re-crystallization. Given the significance of milling temperature, undertaking milling at low temperatures promotes the formation of amorphous materials even as keeping off rapid re-crystallization.

A.BALL MILLING:-

Mechanical milling is an efficient kinetic technique to produce the disordered product with the aid of using the mechanical activation, which includes ball milling, cryomilling, liquid assisted grinding [20]. The induced mechanical activation generates crystal lattice defects and reasons transformation from crystalline to amorphous state. Since neither organic solvents nor excessive temperature are concerned, ball milling will become a “green” and excessive yield method for preparation of co-amorphous mixture [21, 22] . The duration of ball milling performs vital function for the formation of co-amorphous mixture. Ball milling is a mechanical method this is widely used to grind powders into fine particles. The reactants are commonly broken aside the use of solvent molecules with inside the conventional technique; however in ball milling, reactants are damaged with the aid of using the use of mechanical forces. The term mechanochemistry has been introduced very recently.

Advantages:

1. It is an easy technique.

2. Also its capability to acquire very high yields.

3. It performed in low cost, and environment friendliness,

Conventional ball milling is on occasion insufficient to convert crystals into amorphous solids because of heat manufacturing while milling, which may also potentially induce recrystallization. Given the increase of temperature, cryomilling is usually carried out to compromise the generated heat throughout milling method [23, 24] . For cryomilling, the samples have been placed and sealed in milling jars, after which immersed in liquid nitrogen, followed by milling. Due to the cryogenic temperature far under Tg of most amorphous drugs, the solids are quite brittle and easily mechanically milled into disordered state. For example, because of low Tg of atenolol, Moinuddin et al. decided on cryogenic milling to to produce hydrochlorothiazide-atenolol CAM [23]

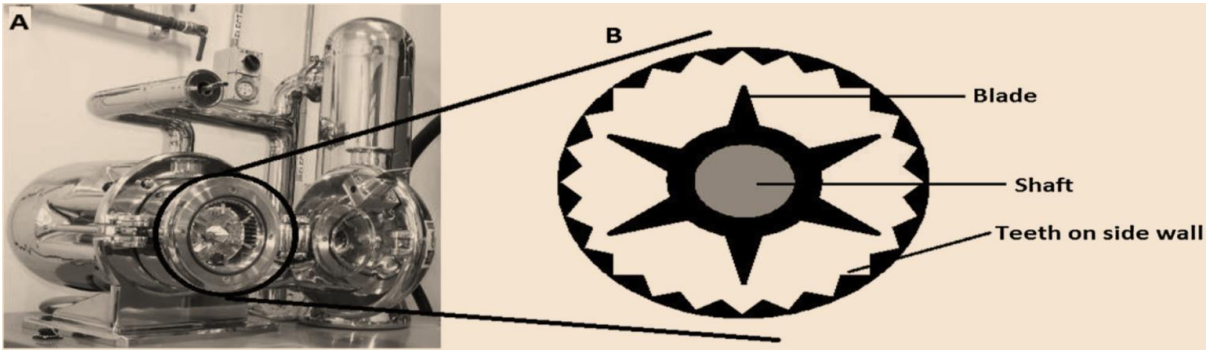

Fig.no.03 A) Cryogenic mill, B) Schematic diagram displaying a cross-phase of the cryogenic milling chamber.

Cryogenic ecosystem is supplied with inside the chamber The physical mixture of hydrochlorothiazide and atenolol became placed in an hermetic tube and eventually have become a entire CAM as much as 48 min with the aid of using milling at 10 Hz. Ojarinta et al. Developed indomethacin-amino acids CAMs prepared with the aid of using cryomilling [25] . To keep away from overheating causing degradation or solid-state transition, the milling cans have been eliminated every 10 min and cooled in liquid nitrogen for 2 min. Cryomilling is tremendous in that it minimizes the degradation of thermo labile drug substances and loss of volatile drug compounds. It additionally reduces the chance of explosion, oxidation of formulation constituents and particle aggregation throughout the milling.

2. SOLVENT EVAPORATION:-

Solvent evaporation is an extensively used method for to produce CAM [26, 27, 28]. Rapid evaporation connecting vacuum is the most regularly used, since the organic Solvents can be eliminated quickly in a brief duration and drugs precipitate from the solution state without sufficient time for rearrangement, nucleation and crystal growth [29]. The issue for solvent evaporation technique is to choose an appropriate solvent for dissolving both drugs and co-formers [30]. For.eg.Carboxylic acid is used as a conformer in solvent evaporation.

3. MELT QUENCHING:-

Apart from milling and solvent evaporation techniques, the melt-quenching method is one of the usually used techniques for transforming crystalline physical mixtures to coamorphous solids [36,37]. In this technique, APIs and/or excipients are first heated to a molten liquid country wherein the additives go through extensive mixing. The ensuing liquid is then rapidly cooled to properly under the melting temperatures of the compounds to keep away from crystallization. The fast cooling rate prevents the nucleation and crystal growth, thus facilitating the formation of amorphous solids. Hot melt extrusion (HME), initially adopted from the plastic industry, is a single continuous technique that melts or softens materials at increased temperatures accompanied with the aid of using downstream cooling to provide solidified phase[38,39] . Consisting of a temperature-managed barrel and rotating screws to combine and feed materials via a die, a hot melt extruder is specially beneficial for developing amorphous solid dispersions from the laboratory scale to destiny scale-up or commercialization. Compared to the massive scale spray drying method, there's no solvent concerned with inside the method of HME, resulting in a low stage of residual solvent with inside the amorphous extradites and coffee threat of solvent-brought on recrystallization. For the primary time, Lenz et al. to produce the indomethacin-arginine coamorphous solids with the aid of using the use of a twin-screw extruder [40]. They determined that the coamorphous formulations containing indomethacin in mixture with arginine and copovidone confirmed more advantageous dissolution behaviour over the formulations with only copovidone or arginine [40] .It is vital to notice that the physical attributes and pharmaceutical overall performance of extruded solids may be greatly affected by the HME method situations which includes feeding, melting, plasticizing, conveying, mixing, stripping and cooling [38]. Attentions have to be paid throughout the HME method because of the risk of thermal degradation of compounds at excessive operating temperatures that are frequently required to melt drugs and decrease the viscosity of liquid for extrusion.

4. SPRAY DRYING:-

Spray drying was first used with inside the pharmaceutical field to provide herbal API. Since then, it is been used ever more and more in several specialized formulations which consist of nanoparticles, microcapsules, liposomes and ASDs [41]. Spray drying also can be applied to provide co-amorphous mixture and easy to scale up [42,43]. Two steps which consist of nebulization and drying are involved in spray drying method [44].The nebulization step sprays a solution of the additives as mist droplets right into a heated chamber [41,42, 44] . For the drying step, the droplets preserve an outward motion and solvent removal, resulting in particles of perfect size and morphology [45]. Lu et al. developed budesonide-arginine co-amorphous mixtures for inhalation administration with the useful resource of the use of spray drying. Budesonide and arginine had been dissolved in ethanol/water binary co-solvent and pumped to a spray dryer with the subsequent conditions (i.e. inlet temperature: 100 ^{0}C, drying air flow rate: 35 m3/h, feed rate: 4

mL/min, and atomization air flow rate: 742 L/h) [46]. The obtained budesonide-arginine co-amorphous mixture with round morphology and preferred size (a good deal much less than 5 µm in diameter) became suitable for inhalation administration. Beyer et al. attempted to provide naproxen-indomethacin CAM with the aid of the use of spray drying [47]. They determined that the recrystallization trend and crystallinity of the spray dried sample have been mainly tormented by pump feed rate and inlet temperature. In general, higher inlet temperature and decrease pump feed rate may also need to accelerate the evaporation of solvent, resulting in lower solvent residue with lower recrystallization rate. Remarkably, outlet temperature have to be below the Tg of the sample to preserve away from crystallization and sticking at the wall of the drying.

CONCLUSION:-

The co-amorphous technology has set up itself as a promising method to improve dissolution/solubility of poorly water-soluble drugs and probably to enhance bioavailability. Although it has capacity to grow to be a platform technology to deal with those drugs, it's far still a new technology and the concept desires to be in addition established.

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