CRYSTALLIZATION OF PHARMACEUTICAL COMPOUNDS IN DEEP EUTECTIC SOLVENTS.

Surya Kumari Nalli[1,2] P. Shashikala [2] JyothiThati*[2]

[1,2]Department of Chemical Engineering, Jawaharlal Nehru Government Polytechnic, Department of Technical Education ,Hyderabad, Telangana State , 500013, INDIA.

[2]Department of Chemical Engineering, University college of Technology, Osmania University, Hyderabad, Telangana State, 500007, INDIA.

Corresponding Author, Jyothi Thati, E-mail: kattajyothi@gmal.com, MOBILE:+91 99591 67505

Abstract

Application of deep eutectic solvents, DES in diverse fields of science, organic synthesis, electrochemistry, biotechnology, and food, cosmetic, chemical, and pharmaceutical industries is drastically increasing day by day due to the special properties like lower melting point, less volatility, biodegradability, less toxicity, and other advantages compared to organic solvents. DES aids in the improvement of the physico-chemical properties of the solvent in an economically feasible way. API is the main constituent of therapeutic drugs and pharmaceutical compounds. Most pharmaceutical and chemical industries employ the process of crystallization as the final step for the separation and purification of API, and to obtain the drugs in a desired pure state in a cost-effective method. India is the second largest manufacturer of API, next to china. The cost of production depends on the raw materials used for solvent, the method of solvent preparation, the recovery of the final product, etc. The stability and safety of pharmaceutical products are analyzed for quality control checks to adhere to environmental and health safety regulations. Judicial selection of solvent and method of crystallization is critical as it affects the size, structure and polymorphism of final product obtained. Conventional organic solvents form a large proportion of solvents used for the crystallization of pharmaceutical drugs. The toxicity, low bioavailability, poor dissolution rates, and high costs lead to an intense search for alternative green solvents.

Ionic liquids were widely used as an alternative to conventional solvents due to the ease of preparation, low toxicity, tunability and option to design ionic liquids with desired properties from a wide range of compounds available. DES gained significance in recent times owing to their special properties as green solvents. On mixing two components, one of them being a hydrogen bond acceptor, HBA and the other a hydrogen bond donor, HBD in specific optimal ratios, a deep eutectic mixture that exhibits depression in melting point, lower than that of the initial constituents is formed. Natural deep eutectic solvents (NADES) are solvents derived from plant sources. NADES are mostly prepared by combining derivatives of quaternary ammonium salts and functional groups of organic acids, sugar alcohols and amino acids.

Volatile deep eutectic solvents, VODES are sub-class of DES, consisting of one volatile component. A recently published article reported the crystallization of protein lysozyme (hen-egg white) using choline chloride-based DES. Various publications by Jason Potticary and the team reported the crystallization of a few pharmaceutical compounds including paracetamol and benzamides using VODES. Form II polymorph of paracetamol was crystallized using the VODES mixture. A review of the above investigations is reported.

Conclusions
Crystallization of the pharmaceutical compounds with deep eutectic solvents as crystallization media resulted in the enhancement of solubility, stability of the compound and attained better control on polymorphism of crystals by the simple method of changing the molar ratios, HBA: HBD and the solvent constituents.

Keywords: Deep eutectic solvents, crystallization of active pharmaceutical ingredients, polymorphism, volatile deep eutectic solvents.

INTRODUCTION

In the crystallization process, solute present in a liquid solution is separated as solid crystalline material. Crystallization process is used as the final step for the separation and purification of materials in many industries including the fine chemicals, food, agrochemical and pharmaceutical industries. Crystallization of Active pharmaceutical ingredients (API) is commonly used commercially to produce high quality crystals with desired specifications. The crystals obtained are in pure form with long shelf life, ease of storage, and favorable for good packaging and transportation.

Different sizes and shapes of crystals are described by crystal morphology. During the process of crystallization, molecules of APIs arrange in various configurations. The different molecular arrangements of crystals with same chemical formula are called polymorphs. Polymorphs differ from each other and have distinct properties at different temperatures, and also vary in applications. Variety of crystal shapes is due to variation of relative sizes of the faces of a crystal. This variation describes the external shape of a crystal is called a crystal habit. Process conditions of crystallization such as properties of solvent, presence of impurities affect the crystal habit. The crystallization of industrial APIs yields more than one polymorphic form. Identification and isolation of the desired polymorph is an essential step in pharmaceutical industries [2], [7], [8].

The following steps are involved in the industrial crystallization of API

i. Choosing suitable solvent.
ii. Dissolving solute to get a saturated solution by increase in the temperature.

iii. Supersaturation of the solution by any one of the crystallization methods. (Supersaturation by cooling/evaporation/antisolvent addition / chemical reaction).
iv. Generation of crystals from a supersaturated solution by nucleation and growth of crystals (crystallization of the product)
v. Maximum yield of the crystalline product obtained at equilibrium state.
vi. Filtration and drying of the pure product.

The most common methods of crystallization process are batch crystallization method and continuous crystallization method. Batch crystallization process is oldest and predominant method of crystallization used in most pharmaceutical industries. The withdrawal of the product for the batch crystallization process is made only once at the end of the process. Batch crystallization process of API involves mixing of solid APIs and heating with solvents to reach dissolution. This method is preferred for compounds with high viscosity, presence of many impurities and when the concentration of product is less. In continuous crystallization feed is continuously flowed in and the product is continuously withdrawn. Higher process efficiency and uniform product quality are possible in continuous crystallization. Good design of crystallizers through control strategies aid in precise process control, economic process operation and desired product properties. Commercial crystallizers are designed to adapt to the requirements of pharmaceutical industry. The advancements in different control strategies aid in design of crystallizers (batch or continuous) with improved performance [2], [5] and [7].

The qualities of the product obtained are determined by the process parameters and properties of the solvents. Optimization of the process parameters, like rate of agitation, method of attaining supersaturation of solution hold time, cooling rate, temperature cycle and solvent properties (type of solvent, stability, dissolution rate, concentration, impurity profile) effect the physical and chemical characteristics of end product such as crystal habit and polymorphic form [3],[7].

The challenge encountered in industry on scale up is changes in rate of nucleation , rate of crystal growth, reproducibility of the processes, difficulty in scale- up of mass transfer and heat transfer factors which leads change in crystal qualities, product containing large particles and non-uniform particle size distributions [13]. In pharmaceutical industries, crystallization process development of API starts with identification of suitable solvents, evaluation of critical process parameters, understanding of crystallization mechanism, thus enable to develop a scalable manufacturing plant. Screening for selection of the desired polymorph is essential so that the end product obtained is of the desired properties. The strategies adopted to overcome the challenges are selection of a suitable solvent to obtain desired crystal size distribution. The properties of the solvent such as polarity, reactivity with the solute, melting and boiling points, molar ratios of constituents, physical and chemical properties are the important factors to be considered while selecting a solvent [12].

Several other strategies are adopted to enhance the solubility and obtain the crystalline product with the required characteristics. Addition of co-crystals, anti-solvents, seeding, and use of multi-

component solvents, dispersion of solids into solution ,use of cooling rate are few methods employed to enhance solubility [6], [7].

In depth studies on crystallization mechanisms like nucleation, growth etc., control of crystallization systems, process parameters and the properties of the solvent contribute to better understanding and to design crystallization processes that aid to obtain the end product with desired crystal properties. Availability of solvent selection guides and various design software models such as ENNM (ensemble of neural network model) aid in selection of suitable solvent [21]. Advanced analytical technology and computing software aid in optimisation of industrial crystallization process by efficient and accurate monitoring and process control [11, 12].

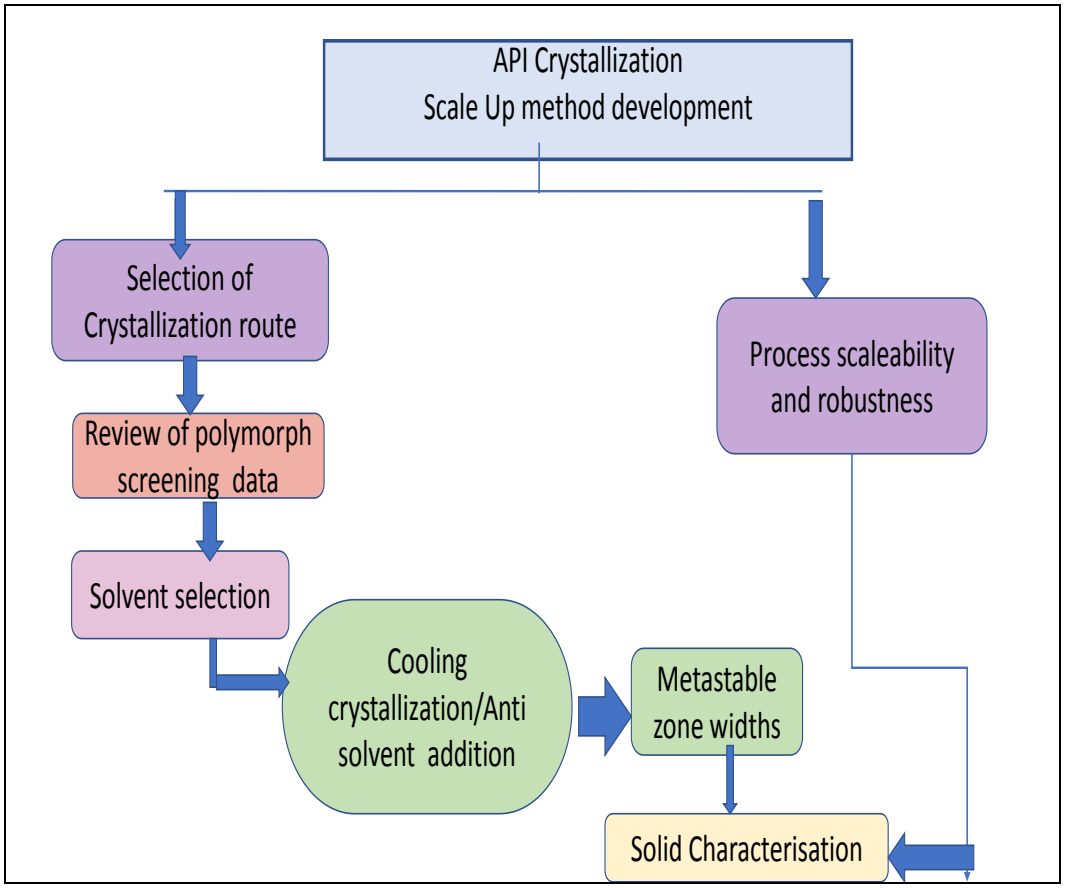

Figure.1: Summary of steps in -scale up method development for industrial crystallization process of API

VARIOUS SOLVENTS USED IN CRYSTALLISATION OF API.

CONVENTIONAL ORGANIC SOLVENTS

Petrochemical-based compounds like benzene, toluene, ethylene, etc. form a large proportion of solvents used in industries. Conventional organic solvents are characterized by properties such as relatively high volatility, flammability, instability, non-biodegradability, and toxicity and are derived from non–renewable energy sources The type of solvent, impurities present, polarity, molar ratios, concentration, and reactivity with the solute impact the growth rate of crystals and its properties [3].

The properties of solvent such as solubility, stability, bioavailability, less toxic nature, reactant concentrations, method of preparation, and low costs, are to be considered for the application of solvents in the crystallization of pharmaceutical compounds [8].

IONIC LIQUIDS, ILs

Ionic liquids, ILs were introduced in the late 1990s and were widely used as solvents for crystallization due to their advantages over conventional organic solvents. Ionic liquids are prepared by the interaction of various anions and cations of compounds and can be designed in many combinations as per the requirement. The ease of preparation, low toxicity, tunability and option to design ionic liquids with desired properties from a wide range of compounds resulted in its application in numerous fields including chemical and pharmaceutical industries, bio-catalysis, electrochemistry, food and agro-industries. Investigations reported that paracetamol can be crystallized by using imidazolium based ionic liquids and cooling crystallization process to obtain polymorph form I. Polymorphism can be controlled by using different ILs ,changing concentration of solution and method of crystal growth [4]. In 2019, Shanmugam and team reported the unseeded batch cooling crystallization of ibuprofen from ethyl lactate, a biodegradable lactate ester and a green solvent [11] [12].

DEEP EUTECTIC SOLVENTS, DES

Deep eutectic solvents, DES classified as green solvents gained significance in the past two decades due to the ease of preparation, the possibility to design solvents with required parameters from a broad range of liquids. DES are preferable due to special properties such as bioavailability, stability at room temperature, and ability to fulfill the norms laid for green solvents. On mixing two constituents ,one of them being a hydrogen bond acceptor, HBA and the other a hydrogen bond donor, HBD in specific optimal ratios, a liquid mixture which melts at a significantly lower temperature compared to the individual constituents is formed.

DESs are made from combination of anionic and cationic species containing large, nonsymmetrical ions mostly Lewis or Bronsted acids and bases that have low lattice energy. The main characteristic of accepting or donating an electron pair by Lewis acids and bases and capability of Bronsted acids and bases to provide and accept protons respectively lead to hydrogen bond network within HBA (a halide salt) and a hydrogen bond donor. The network so formed is the cause of significantly lower melting point of the mixture [5], [6] [10].

For example, DES was prepared with choline chloride (melting point 573.15 K) and urea (melting point 406.15K) both solid substances in a molar ratio of 1:2 and heating below 373.15 K for less than an hour. The mixture forms a liquid at atmospheric pressure and a temperature of 285.15K, melting temperature below that of the individual constituents [1].

Experimental investigations combined with computational studies aid in the knowledge of the structure of DES. Quantum mechanics methods are used to determine the physical parameters of the solvents. The structure, conformation and acidity of HBD impact the interactions with HBA. Macroscopic characteristics of eutectic mixture are determined by the nature of interactions between HBD and HBA [9]. Molecular level dynamic simulations of the hydrogen bond interaction and energies involved that lead to formation of DES was studied for commercially used and most common mixtures constituting choline chloride as one the eutectic constituent and urea, ethylene glycol, and glycerol (reline, ethaline, and glyceline respectively).Studies on pharmaceuticals such as mthylphenidate, nitrofurantion, spironolactone, trimethoprim (less soluble in water),trichloroacetaldehyde mono-hydrate (soluble in water but instable), ranitidine HCL (polymorphic API) were reported [10].

Choline chloride salt is the most commonly used hydrogen bond acceptor, in the preparation of DES. It is rich in B- vitamin and used as an additive in animal feed, especially chicken feed for promoting growth. Glycerol is trihydroxy alcohol and belongs to class of sugar alcohol. It is a hygroscopic syrupy viscous liquid used as a solvent in the pharmaceutical, food, and cosmetic industries [3].

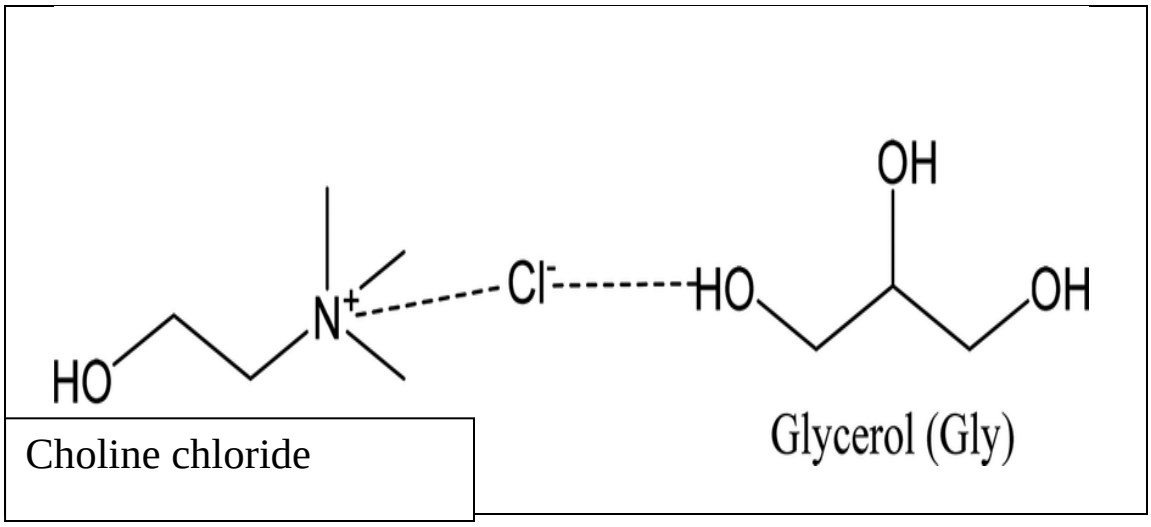

Figure.2: Structure showing hydrogen bond formation between choline chloride and glycerol.

Choline chloride and glycerol mixture at molar ratio of 1:2 forms deep eutectic mixture [1].In the presence of glycerol, when sufficient quantity of glycerol is added to the choline chloride salt, the anion component of the salt i.e. Cl^-, attracts hydrogen atom of the glycerol molecule due to

the charge distribution between the molecules. Consequently hydrogen bond is formed between the chloride anion of the salt and glycerol molecule [1].

Investigations reported that DES was synthesized with sucrose as one of the constituents and the molar ratio of water affected viscosity, polarity and other properties of the DES. Compared to the solubility of Piroxicam in water its solubility increased drastically in 1:1 molar ratio of sucrose and citric acid DES with 30%(w/w) water content at 318.15 K [22].

NADES, THEDES and VODES

The DES is derived from natural origin component sources like plants are known as natural deep eutectic solvents, NADES. Most commonly NADES are combination of derivatives of quaternary ammonium salts and functional groups of carboxylic acids, sugar alcohols or amides [12]. DES that enhance the permeability and solubility of pharmaceutical drugs prepared from API as one of the constituents of the eutectic solvents are termed as THEDES and are so called due to the therapeutic properties. THEDES reported constitute mixtures of choline chloride/menthol, menthol/ibuprofen, lidocaine/ ibuprofen combined with APIs, benzoic acid, acetylsalicylic acid, phenylacetic acid etc. Studies also reported successful preparation of THEDES compromising mixtures of choline chloride based solvents in combination with APIs namely itraconazole, benzoic acid and grisefulvin [9]. In the year 2018, a new class of DES was identified and termed VODES. One of the constituents of the DES evaporated due to its volatile properties leaving behind the other constituent, the mixture is known as the volatile deep eutectic solvent, VODES. VODES was first identified by Jason Potticary and the team at the University of Bristol, UK [16].

SELECTION OF APPROPRIATE SOLVENT

The choice of solvent impacts the crystallization processes of API to obtain suitable polymorphic crystal form and desirable crystal properties for downstream processes including efficient filtration, drying, drug formulation and product manufacture. Use of solubility parameters, similarity principle (like dissolves like) are common methods at early stages in deciding the solvents.Harvesting the desired polymorph form of the compound can be done by predicting hydrogen bonding ability and electron density on solute and solvent molecules.

Control and automated monitoring of variables such as solvent concentrations, temperature, and supersaturation followed by use of analytical techniques (powder X-ray diffraction, SEM etc.) are essential in pharmaceutical industries. Commercial software's such as COMSOL, gCRYSTAL® and Dynochem® are employed for multi variable controlling of crystallization process in industries. Developments in process analytical technology (PAT) result in effective design, control and optimisation of industrial crystallization process [8].

Design of DES will aid in achieving constant product quality, control on polymorphic form , crystal size distribution, efficient and economical process operation. DES chosen affects molecular interactions between solvent and solute Screening can be done for different molecular arrangements during the crystallization and alter the nucleation and growth condition via tunable DES or additives to obtain preferred polymorphic form.

The physical form of solute (amorphous state or crystalline state) impacts its solubility in the solvent as particles with smaller dimensions (higher free energy) are readily soluble resulting in greater solubility. Crystal lattice cell packing energy determines the melting point.

Derivatives of quaternary ammonium salts and functional groups of carboxylic acids, sugar alcohols or amides in different molar ratios can be tailored to form DES and obtain the desired physcico-chemical properties of solvent such as conductivity, density, viscosity, freezing or melting point. The investigations reported that different morphologies can be produced while still maintaining the most stable form [16]. Solubility of the API in DES is considered an important parameter to be chosen as solvent for crystallisation. Lab scale experimental methods are employed to check the solubility by researchers for initial screening of solvents. An organized comprehensive database and solvent guide's aid in screening of solvents. Rank order of solvents and estimation of the solubility of API in selected DES can be predicted using COSMO-RS (Conductor –like screening model for real solvents) [15].

The criteria for choosing the DES are

- Higher solubility advantage of compound in DES compared to organic solvents and water.
- Optimal molar ratios of HBD to HBA.
- Transparent homogenous liquid which is stable at room temperature.
- Thermal stability of the solvent.
- Low volatility.
- Bioavailability
- Low or negligible environmental hazard.
- Negligible health hazard risk.
- Cost effective and easily available
- Simple method of preparation that is scalable.
- Recovery and reutilisation of the solvent.
- Inherent safe properties of the solvents(safe to handle, store and transport)
- Replacement of aromatic hydrocarbons by a non VOC safe solvent.

SUMMARY OF INVESTIGATIONS REPORTED ON THE USE OF DES AS CRYSTALLIZATION MEDIA

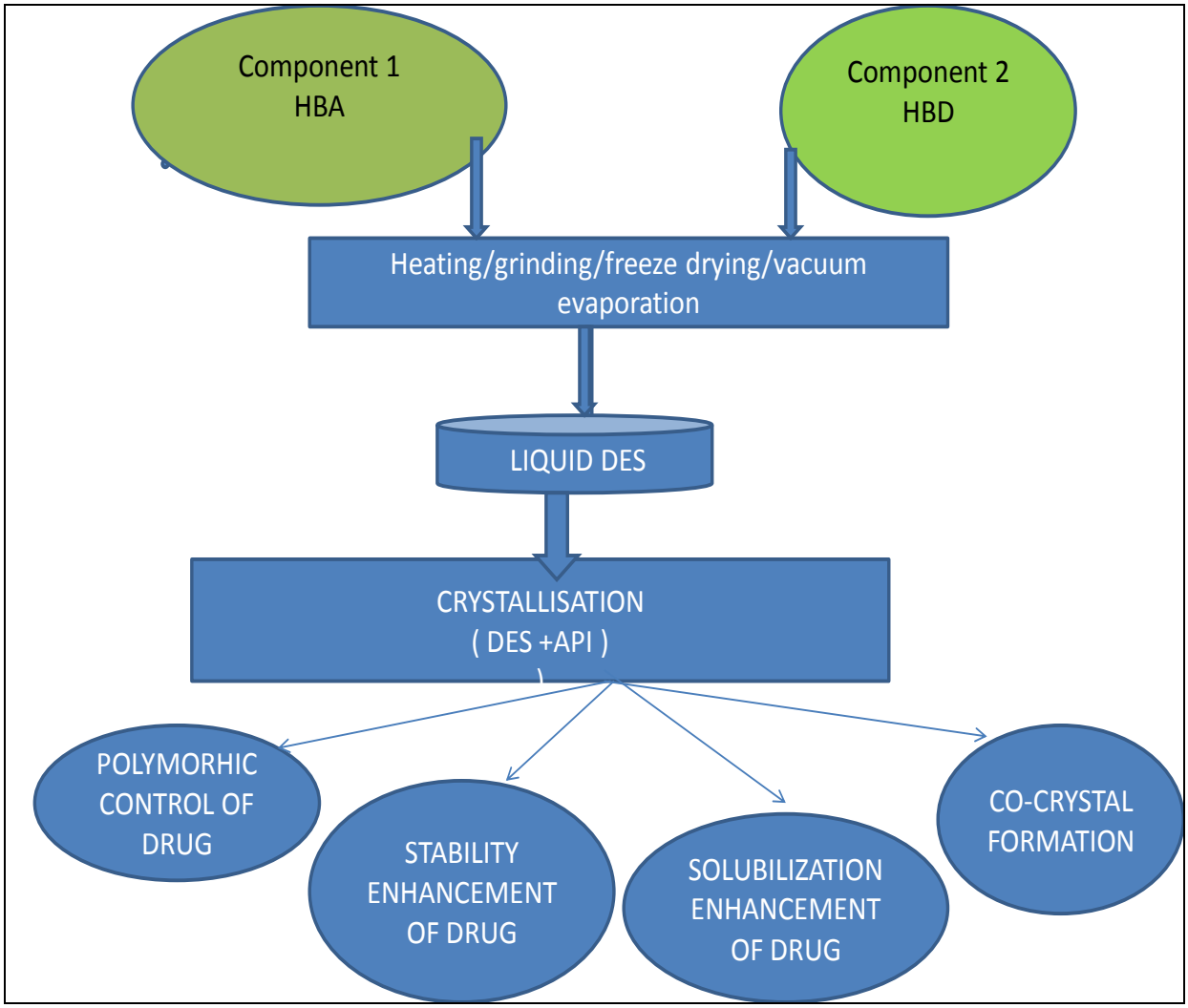

Figure.3: Schematic diagram showing summary of crystallization of API in DES.

1. PROTEIN CRYSTALLIZATION IN DIFFERENT EUTECTIC MIXTURES

A recently published article, reported the crystallization of protein lysozyme (hen-egg white) using choline chloride-based DES. It is noteworthy that this is the first ever experimental investigation reported using DES as crystallization media. The DES mixtures constituted choline chloride, HBA and HBD (glycerol, urea, and glutamic acid respectively) in 1:2 molar ratios respectively. Protein crystallization in various eutectic mixtures with varying levels of hydration was conducted. It was inferred that the crystallization process

was influenced by volumetric ratio of respective solution and DES. The rate of crystallization was tunable by DES hydration. Application of DES in the field of biotechnology at the industrial level is recommended [20].

2. CRYSTALLIZATION OF 1)PARACETAMOL (API) AND 2) BENZAMIDES IN DEEP EUTECTIC SOLVENTS CONSTITUTING PHENOL (VOLATILE COMPONENT).

Paracetamol is the most commonly used effective medicine for fever and other health conditions in children and adults globally with a prescribed therapeutic dosage. It acts as analgesic and produced in bulk as polymorph form I namely acetaminophen(PAP).In PAP, the ring position of the acetamide group is at the Para position. One of the three regioisomers of paracetamol, where the ring position of the acetamide group is at the meta position is named N-acetyl-m-aminophenol, (MAP) and is obtained as form II polymorph. Even though MAP is less harmful and can be easily obtained in tablet form than PAP, it is not produced in bulk quantities due to the economic aspects and difficulties encountered in the separation of selective polymorph in n bulk quantities. Heating to high temperatures, cooling, and additional process conditions makes it an impossible task to produce form II, in bulk. Moreover, PAP and MAP exhibited different physical properties, MAP being a more soluble and effective drug [4].

Jason Potticary and others in the year 2020 reported the successful crystallization of MAP using Volatile Deep Eutectic Solvents, VODES at room temperature. The solvent was prepared by mixing Phenol and paracetamol (API) in different molar ratios .The mixture with molar ratios between 7:1-9:1 resulted in spontaneous crystallization at room temperature and formation of MAP, proving that polymorphism can be controlled by easy method of selecting optimal stochiometric ratios of HBD:HBA.MAP is left behind as a product after the crystallization process during which phenol being the inherent volatile component evaporates completely. The product obtained was thermodynamically stable [16].

The investigations included

a)Crystallization in deep eutectic solvents constituting phenol (volatile component) and paracetamol (API) in the molar ratios 4:1 -6 :1 resulted in obtaining crystals of polymorph form I of paracetamol. The crystals obtained were diamond in shape.

b) Crystallization in deep eutectic solvents constituting phenol (volatile component) and paracetamol (API) in the molar ratios 7:1 -9:1 resulted in obtaining crystals of polymorph form II (MAP). The crystal habit reported was feather-like needles.

c) VODES crystallization of Benzamides constituting phenol as HBD and benzamides as conformer in the molar ratios 3:1 -10:1.

d)Thermal analysis and study of eutectic behavior of the phenol: API mixtures of all compositions in molar ratios in the range of 1:1 to 10:1.The API s selected for the study are form I and II of paracetamol, form I and III benzamides, carbamazepine, verapamil hydrochloride, metaxalone.

e) The experimental results inferred that crystal formation was not observed for the compounds carbarmazepine and verapamil hydrochloride, for any ratios considered.

e) For metaxalone crystallization occurred at higher ratios of phenol and reports confirmed formation of co-crystals.

f) Isolation of co-crystals of 2-ethoxybenzamide and phenol at a 1:2 ratio.

g) Isolation of co-crystals of harmine and phenol at a 1:1 ratio [16].

3. CO-CRYSTALS OF 2-ETHOXYBENZAMIDE AND HARMINE OBTAINED USING VODES

Various other work published by Jason Potticary and his team in the year 2020 reported the crystallization of the following compounds using VODES. Benzamide compounds as model samples were chosen for studies on crystallization using VODES. Co-crystals of 2-ethoxybenzamide and Harmine, the intermediates were obtained by evaporation of respective phenol VODES mixtures. The formation of co-crystals was observed during the phase transition and cooling method of crystallization. HBA components were successfully crystallized from VODES mixtures consisting of Phenol: metacetamol, Phenol:2-ethoxybenzamide, and Phenol: Benzamides of 8:1,8:1 and 9:1 molar ratio respectively [17].

3. RACEMIC CONGLOMERATE FORMATION VIA CRYSTALLIZATION OF METAXALONE.

VODES method of crystallization was also used to crystallize metaxalone. Different molar ratios of the solvent constituents, phenol, and metaxalone were studied to obtain the selective polymorph form of metaxalone. The studies on crystallization using VODES aided in understanding the properties and analyzing the phase behavior of crystals [18].

5. OLANZAPINE COCRYSTALS OBTAINED USING VODES

The mixture of phenol and benzoic acid derivatives was used to crystallize the olanzapine compound and obtain pure olanzapine crystals. The nanocrystalline phase was confirmed by reports from differential scanning calorimetric tests, electron diffraction, and XRD methods. The reports aided in crystal structure analysis [19].

.

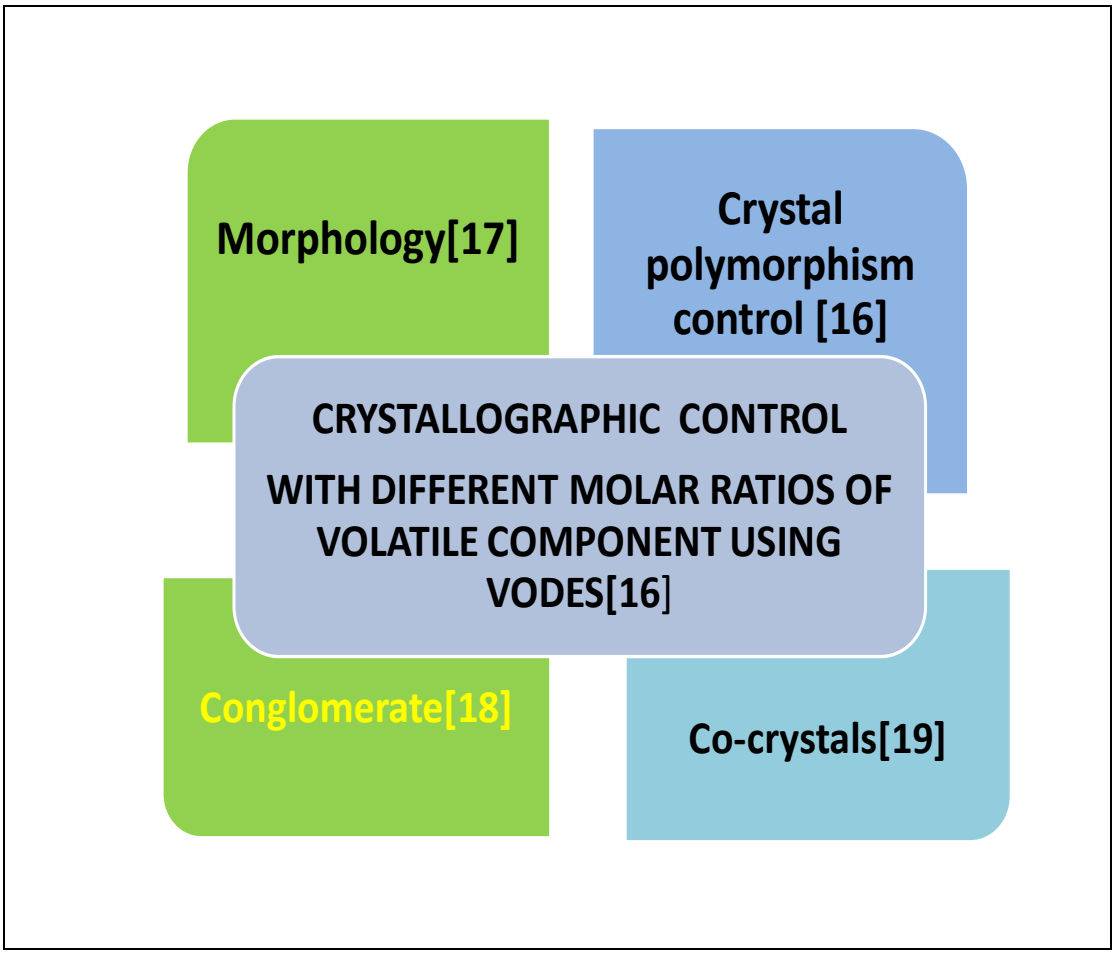

Figure.4: Schematic diagram of reported work on crystallization control using VODES by reference [16]. *Crystal Growth & Design* **2020** *20* (5), 2877-2884 [17]**.** Chem. Commun 2020. 56(73), 10726-10729 [**18]**.Crystal Growth & Design, 2020 20(7), 4731-4739. [**19]** Andrusenko, I., Potticary, J., Hall, S. R. & Gemmi (2020). Acta Cryst. B76, 1036-1044.

CONCLUSIONS

In the present work, a review has been made on various investigations reported on the use of deep eutectic solvents, DES as crystallization media. Studies reported that crystallization of the pharmaceutical compounds in DES resulted in enhancement of solute solubility, stability of the compound and attained better control on polymorphism of crystals by the simple method of varying the composition of HBA:HBD. Isolation co-crystals, selectivity of API polymorph, and control of crystal growth kinetics at room temperature are possible in a scalable way using VODES. Further research is required to gain knowledge of the parameters that control the crystallization process of compounds using DES, to identify the optimal molar ratios of the solvent constituents and understanding the complete landscape of crystal properties and

structure. Despite of the many advantages and applications of DES in diverse fields like organic synthesis of materials, extraction of bio materials, bio catalysis, electrodeposition, preparation of nanomaterials etc. very few investigations are reported on use of DES as crystallization media. Therefore application of DES as crystallization media is worth exploring.

REFERENCES

1. Abbott, A.P.; Capper, G.; Davies, D.L.; Rasheed, R.K.; Tambyrajah, V. Novel solvent properties of choline chloride/urea mixtures. Chem. Commun. 2003, 9, 70–71.
2. Yu, Z.Q., Chew, J.W., Chow, P.S. and Tan, R.B.H., 2007. Recent advances in crystallization control: an industrial perspective. Chem. Eng. Res. and Des. 85(7), 893-90.
3. Abraham, M. H., Smith, R. E., Luchtefeld, R., Boorem, A. J., Luo, R. and Acree, W. E. (2010), Prediction of solubility of drugs and other compounds in organic solvents. J. Pharm. Sci., 99: 1500–1515.
4. Smith, Kenny & Leeke, Gary & Bridson, Rachel. (2014). Crystallization Control of Paracetamol from Ionic Liquids. Cryst Eng Comm. 16. 10.1039/C4CE01796J.
5. Cameron C. Weber, Samir A. Kulkarni, Andreas J. Kunov-Kruse, Robin D. Rogers, Allan S. Myerson. "The Use of Cooling Crystallization in an Ionic Liquid System for the Purification of Pharmaceuticals", Crystal Growth & Design, 2015.
6. Mali, Audumbar & Jadhav, Santosh. (2015). An Overview on Co-crystallisation Inventi Rapid: Pharm Tech. 2015. 1-8.
7. Fergal P. Byrne, Saimeng Jin, Giulia Paggiola, Tabitha H. M. Petchey et al. "Tools and techniques for solvent selection: green solvent selection guides" , Sustainable Chemical Processes, 2016
8. Zhenguo Gao, Sohrab Rohani, Junbo Gong, Jingkang Wang, and Recent Developments in the Crystallization Process: Toward the Pharmaceutical Industry, Engineering, Volume 3, Issue 3, 2017, Pages 343-353, ISSN 2095-8099.
9. Luciana I.N. Tomé, Vanessa Baião, Wanderson da Silva, Christopher M.A. Brett, Deep eutectic solvents for the production and application of new materials, Applied Materials Today, Volume 10,2018,Pages 30-50,ISSN 2352-07.
10. Temirlan Zhekenov, Nursultan Toksanbayev, Zhanna Kazakbayeva, Dhawal Shah, Farouq S. Mjalli,Formation of type III Deep Eutectic Solvents and effect of water on their intermolecular interactions, Fluid Phase Equilibria, Volume 441,2017,Pages 43-48,ISSN 0378-3812.

11. Qingying Zeng, ‡a Arijit Mukherjee, ‡a Peter Muller, ¨ c Robin D. Rogers Myerson, Allan S Exploring the role of ionic liquids to tune the polymorphic outcome of organic compounds Chem. Sci., 2018, 9, 1510 -1520.
12. Solvents and Eutectic Solvents, Encyclopedia of Analytical Science (Third Edition), Academic Press,2019,Pages 184-190, Francisco Pena-Pereira, Inmaculada de la Calle,
13. Rosenbaum, T.; Tan, L.; Engstrom, J. Advantages of Utilizing Population Balance Modeling of Crystallization Processes for Particle Size Distribution Prediction of an Active Pharmaceutical Ingredient. *Processes* **2019**, *7*, 355.
14. Shanmugam, Karthika & Radhakrishnan, T. & Ponnusamy, Kalaichelvi. (2019). Crystallization and Kinetic Studies of an Active Pharmaceutical Compound Using Ethyl Lactate As a Green Solvent. ACS Sustainable Chemistry & Engineering. XXXX. 10.1021/acssuschemeng.9b06031.
15. Palmelund, H., Andersson, M. P., Asgreen, C. J., Boyd, B. J., Rantanen, J., & Löbmann, K. (2019). Tailor-made solvents for pharmaceutical use? Experimental and computational approach for determining solubility in deep eutectic solvents (DES). International Journal of Pharmaceutics: X, 1, [100034].
16. Jason Potticary, Charlie Hall, Victoria Hamilton, James F. McCabe, and Simon R. Hall, *Crystal Growth & Design* **2020** *20* (5), 2877-2884
17. Charlie Hall, Jason Potticary, Victoria Hamilton, Simon Gaisford, Asma Buanz, Simon Hall. "Metastable Crystalline Phase Formation in Deep Eutectic Systems Revealed by Simultaneous Synchrotron XRD and DSC" , Chemical Communications, 2020, 56(73),10726-10729
18. Victoria Hamilton, Iryna Andrusenko, Jason Potticary, Charlie Hall et al. "Racemic Conglomerate Formation via Crystallization of Metaxalone from Volatile Deep Eutectic Solvents", Crystal Growth & Design, 2020 20(7), 4731-4739.
19. Andrusenko, I ., Potticary, J., Hall, S. R. & Gemmi, A new olanzapine co-crystal obtained from volatile deep eutectic solvents and determined by 3D electron diffraction, M. (2020). Acta Cryst. B76, 1036-1044.
20. Introducing Protein Crystallization in Hydrated Deep Eutectic Solvents, Benny Danilo Belviso, Filippo Maria Perna, Benedetta Carrozzini, Massimo Trotta, Vito Capriati, and Rocco Caliandro,*ACS Sustainable Chemistry & Engineering* **2021** *9* (25), 8435-8449
21. Surya Kumari Nalli, Jyothi Thati, P. Shashikala. Recent Developments on Volatile Deep Eutectic Solvents for Application in Crystallization of Pharmaceutical Compounds. International Journal of Chemical Separation Technology. 2022; 8(1): 20–26p, ISSN: 2456-6691.
22. Characterization of some sucrose-based deep eutectic solvents and their effect on the solubility of piroxicam.