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Eutectic Mixtures: A promising Solvent in Drug Delivery System

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REVIEW

Eutectic Mixtures: A Promising Solvent in Drug Delivery System

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Abstract

Eutectic systems, including eutectic salts, deep eutectic solvents, and eutectic molecular mixtures, have recently been shown to have enormous potential in a number of technological and scientific endeavors. Eutectic mixtures, along with other binary systems including solid dispersion, cocrystals, and inclusion complexes, could be used simultaneously to improve a number of drugs, including stability, permeability, and dissolution. Over the past few years, their usefulness in the pharmaceutical field has expanded. On a laboratory scale and an industrial scale, eutectics could be produced quite readily (and occasionally spontaneously). In order to fully utilize eutectics in the pharmaceutical industry, it is essential to understand their preparation process, characteristics, and evaluation criteria as well as how they affect drug dissolution.

Keywords: Carrier, Eutectic mixtures, Phase diagrams, Crystal lattice

1. Introduction

The majority of solid active pharmaceutical ingredients (APIs) have issues with polymorphism, inadequate bioavailability, insufficient dissolution, and, ultimately, treatment effectiveness. Many methods based on deep eutectic solvents (DES) and eutectic mixtures were calculated to get around such restrictions [1]. Eutectic salts, eutectic metals, and deep eutectic solvents are the three common categories of eutectics. They are all eutectic systems, and they share the same eutectic principle. Problematic organic solvents are employed in the formulation of many drugs, and researchers are working to develop more benign alternatives. DESs are frequently mistakenly classed as a subclass of ionic liquids (ILs) because of the physical similarities between the two substances [2]. Yet, DESs are combinations of natural molecules as opposed to ILs, which are made up of a pair of an inorganic or organic anion and large asymmetric organiccations. High viscosity, low vapor pressure, non-flammability, low cost, biodegradability, and low toxicity, a wide liquid range, the capability of dissolving a variety of solutes, as well as thermal and chemical stability, are shared by the two distinct types of solvents [3]. In spite of having many of the same features as ILs, DESs have certain advantages over them, such as a lack of water reactivity, no or low toxicity, ease of synthesis, biodegradability, and affordable and easily accessible ingredients, which suggests DEM as flexible substitutes [4].

The majority of problems that arose in the administration of many (APIs) with limited solubility, insufficient bioavailability, poor stability, and polymorphism, as well as formulation issues, were exacerbated by EM. Additionally, EM enhanced the skin permeation regarding topical formulations of poorly soluble drugs, which can be beneficial for the local treatment of a number of infections and more beneficial through offering fewer side effects, quick drug delivery to target site, and higher drug amounts in the tissues [5]. These problems highlight the urgent necessity for the creation of a eutectic mixture (EM) dosage form for pharmaceuticals. A

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mixture of at least two substances that, in most cases, do not combine to produce new chemical compounds but, at specific ratios, prevent one another from crystallizing, leading to a system with a lower melting point compared to any components, is referred to as a EM. Eutectic temperature is the temperature at which the system is in the liquid phase. Above this temperature, the components exist as a liquid, and below this temperature, they are solids or combined into a multi-component compound made up of at least two crystalline solids which show immiscibility in the solid state and don't combine in order to create a new chemical complex. However, at a specific ratio, the eutectic composition will show a melting or solidification point considerably lower than its constituents [6,7].

At the eutectic composition, the two components exhibit a reduction in particle size and are evenly disseminated, which helps to increase the drug's bioavailability and dissolution rate [8]. By boosting entropy and elucidating the melting point depression, it is clear and simple to comprehend [9]. EM could form between excipients, between excipients and APIs, or between APIs. This allows for a wide range of applications in pharmaceutical formulations [10]. The word is a combination of the Greek words "eu," meaning "easy," "well," "good," and "tecsis," meaning "melting." A highly effective and encouraging method for monitoring the polymorphism and aqueous solubility of solid drugs is the use of the eutectic mixture. APIs that involve EM should have better biopharmaceutical and physicochemical properties than solid or crystalline APIs [11]. A superlattice mixture known as a eutectic mixture is one that either melts or solidifies at lower degree of the temperature compared to melting point of any one of the constituent compounds. It is a solid homogeneous mixture made of a minimum of two solid components that produces change of phase to liquid at some specific temperature. It is frequently indicated as an alloy mixture (Fig. 1) [12].

2. Characteristics are typically responsible for EM formation

(1) components should be immiscible in the solid state and generally miscible in a liquid state
(2) The contact-induced melting point depression requires close contact between the eutectic forming materials.
(3) Physical bonds, for example, intermolecular hydrogen bonding, resulted from interaction among two-chemical groups
(4) molecules that are in accordance with the modified VantHoff equation has the ability of forming the eutectic mixes [13].

Concerning eutectic temperature; that remains the lowest melting temperature unrelatedly of the compositional ratios. When a superlattice reaches this temperature, all of the components will start to evaporate, and the mixture will be melted. As opposed to a eutectic mixture, in a non-eutectic mixture, each portion solidifies into a lattice at its temperature before the whole mix solidifies [8]. Eutectic compositions are formed using the geometric dilution method and are made up of at least two elements of the same melting and freezing properties. The mixture is created by the crystallization process, allowing the product to behave as a unit. The materials can form a dense crystal network and melt together simultaneously, with no distinction. EM has many advantages like (a) low cost (b) chemically inert with water (c) easy to prepare due to the fact that they're obtained from the simple mixing of 2 components, as a consequence bypassing all waste disposal and purification problems that encountered with ILs and (d) they are biodegradable, bio-compatible and non-toxic, highlighting the greenness of these media [14].

3. Methods of preparation

The main approaches for the preparation of the deep eutectic solvents are heating approach, solvent evaporation and the Grinding approach [15].

3.1. Melting (heating) approach

Obi and Sekiguchi, who prepared a physical mixture of sulfathiazole and urea, were the first to use this technique. In order to produce supersaturation of the mixture, the technique entailed heating the components until they melted. The molten mixture then settled quickly with constant stirring at a low temperature while employing an ice bath. These conditions cause substance molecules to become "trapped" in the matrix of a system that is quickly solidifying. To standardize the size of the grains obtained, the solid mass generated is pulverized then sieved. This method improves the crystals' dispersion within the EM [16]. This technique has so far been utilized to create EMs of urea with chloramphenicol and acetaminophen [17]. This method has recently been used to create EMs of benznidazole and Posaconazole, which typically call for an additional step like grinding and sieving to minimize particle size. It is well known that

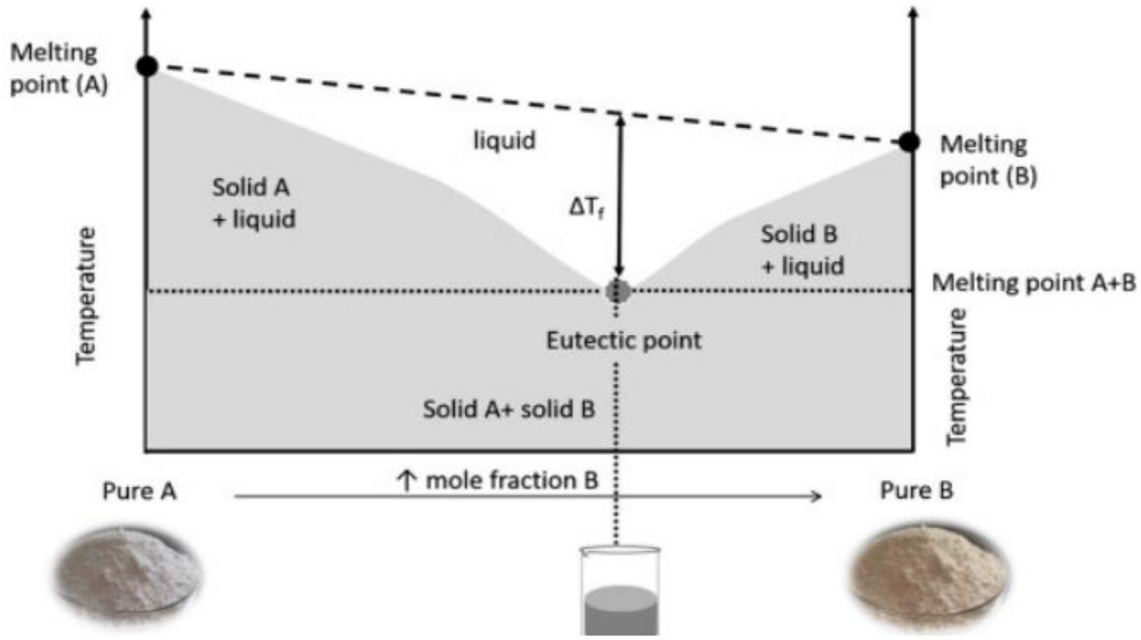

Fig. 1. Diagram representing the phases of two components' scheme [12].

throughout the heating process, molecule mobility and reorganization lead to weak intermolecular interactions in a eutectic [18]. Despite being widely used the fusion approach has certain drawbacks. Only when the drug substance and the carrier combine homogeneously after heating could it be used, according to E. Zaini et al. 2015 for ketoprofen. The fact that both the drug substance and the carrier degrade at high temperatures is a significant restriction of this approach. A volatile drug or a carrier might evaporate as a result of heating. Heating or melting the mixture in a vacuum is one method for resolving this issue. Additionally, the procedure might be carried out in an environment where inert gases—like nitrogen—prevent the drug or carrier from degrading due to oxygen. Phase separation results from a change in the components' mutual miscibility during cooling, which is another undesirable aspect of this approach. The mixture slowly cooled, and it was then possible to see the drug crystallizing. However, quick cooling encourages the development of amorphous solid dispersions [6].

3.2. Grinding method (Mechanical methods)

On a laboratory scale, this approach is utilized for the preparation of the eutectic mixes. The function of grinding can be performed by using a mortar pestle, while in large-scale, vibratory mills [19], mechanical grinders are used. This method has some drawbacks, so this is not used conventionally [20]. By Mechanical grinding of the binary components, breaking bonds resulted on account of the shearing and stress, which exposes reactant surfaces' area and reorganization via the transformation of the bulk phase into the micro-structures. Accommodating counter molecules could result in arbitrarily ordered arrangement with the weak non-covalent forces. Those weaker attractive forces need less amount of the activating energy to melt at lower degree of the temperature (i.e. eutectic melt) and it conveys sufficient thermo-dynamic stability of the eutectic mixes [21]. The pressure of grinding through breaking and making hydrogen bonds frequently encourages the cocrystal formation, but in the case where there is incompatibility or lack of the secondary interactions to produce stable lattice structure, the product will result in simple eutectic composition [18].

3.3. Solvent evaporation method

In this method, an in situ eutectic mixture was formed using three or more substances with lower alkyl esters of p-hydroxybenzoic acid. It was first used by Tachbani and Nakamura by preparing solid dispersion of lipophilic β-carotene in PVP as a hydrophilic carrier, by dissolving both drug and a carrier in a volatile solvent, such as chloroform or dichloromethane. Then by complete evaporation of solvent at 23–65 °C, and the resulting film was dried

and pulverized [18]. The solvent type and the rate of removal are essential factors in determining the dissolution rate of drug substances in solid dispersion obtained. They affect the crystallographic structure of the resulting system. The advantage of this method is preventing the degradation of the drug substance by maintaining the low temperature needed for solvent evaporation. The disadvantages include high cost of production, difficulties with the selection of volatile solvent to be completely removed, chemical stability of the substance, besides the problem with the reconstruction of the crystalline form [18,22].

4. Dissolution rate enhancement mechanism by eutectic mixtures

Throughout solubility improvement, the Dissolution rate enhancement will result from the use of a eutectic mixture when coming in contact with the gastrointestinal fluids due to the immediately dissolving of the insoluble drug which is left in a very fine subdivision state.

1 E. Zaini and colleagues 2015, tested the dissolution properties of pure ketoprofen and eutectic mix (0.6:0.4 M fraction) in phosphate buffer (pH 7.4). An EM of ketoprofen and nicotinamide (0.6:0.4 M fraction) revealed a better profile of the dissolution rate than intact ketoprofen. At 30 min, the amount of pure ketoprofen that had been dissolved was 77.94 ± 0.91%, while the amount of ketoprofen that had been dissolved from the eutectic mixture reached 100.65 0.89. Sekiguchi and coworkers in 1961 reported the same thing [16]. The preparation with EM has a longer shelf life because it keeps the formulation from hydrolyzing. The EM has higher stability than other solid formulations due to its crystalline structure [7,15].

2 Park CW et al. 2012, examined the phase behaviors of the itraconazole–phenol mixes and evaluated feasibility of the topical formulations of the itraconazole utilizing the eutectic mix systems. Despite the high log partition coefficient and the high molecular weight of the Itraconazole, the results indicate a potential of the itraconazole for topical delivery utilizing itraconazole–phenol eutectic system for the enhancement of the permeation of the skin· [5].

3 Figueirêdo CB et al. 2017, Report formation of eutectic mix in addition to amorphous solid solution of PCZ and BNZ (at a characteristic ratio of 80:20wt%) that had provided improved solubility and dissolution rate for the two APIs. Utilizing 3 approaches of the preparation of those binary pharmaceutical BNZ and PCZ compositions:

1 Evaporative crystallization method.
2 Alternative approach for the generation of the crystalline eutectic mix.
3 Hot melt and cooling approach.

Different PCZ to BNZ ratios (96:04, 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 30:70, 20:80, and 10:90w/w %, respectively) have been combined and dissolved in 100% ethyl alcohol to produce PCZ/BNZ mixtures. A white or off-white crystalline powder was produced by solvent being evaporated at 50 _C for around 1 h. The obtained eutectic crystalline PCZ/BNZ mixes were further ground to decrease the particle size, and resulting powder with particle sizes between (75 mm–150mm) was collected with the use of a mini sieve for further characterization. The results showed that the eutectic mixture had higher rate of the dissolution than the API alone [23].

4 Bazzo GC and coworkers 2019, pointed out that There has been an increase in solubility of Efavirenz (EFZ) in water in presence of a hydrophilic drug, tenofovir disoproxil fumarate (TDF), on solubility and dissolution rates of poorly water-soluble drug EFZ, that may be utilized in a simultaneous manner in treating human immuno-deficiency virus type-1 infection. It has been evident that TDF solubility strongly impacts EFZ solubility in various media, being EFZ solubility favored in acidic medium and reduced in the phosphate buffer pH 6.8. However, the TDF solubility has not been affected by EFZ. Additionally, both drugs form eutectic mixt, especially in molar ratio of EFZ/TDF (65/35) that resulted in improving the solubility and dissolution rate of EFZ in an acidic medium through a simple technique of mixing, in defined proportions, without the need for other technological approaches [24].

5 Additionally, Park H. et al. 2020, formulation of glimepiride and L-arginine (GA) as binary mixtures in 2020, using a variety of molar ratios to keep the medicinal material in a crystalline state, has the specific advantage of being thermodynamically stable. Raised wettability and the development of a microenvironment where glimepiride's solubility was increased due to a high local concentration of the hydrophilic reagent in the surrounding solution can both be used to explain why eutectic mixtures have improved dissolution capabilities. The dissolution profiles

regarding samples of a powdered GA mixture performed in a phosphate buffer at pH 6.8 [25].

6 Using differential scanning calorimetry, Maasoi C. et al. 2021, developed and examined the role of the formulation of bromazepam and citric acid as binary mixtures and drug dissolution in oral absorption. Increased bromazepam dissolution rate and improved therapeutic efficacy of the active pharmaceutical ingredient are advocated by the mixture's eutectic [26].

7 Hyun SM et al. 2019, studied the formulation of eutectic mixtures, as binary pharmaceutical compositions of the Celecoxib (CEL) with saccharin (SAC) and adipic acid (ADI), which have been identified via phase diagram that has been intended for the improvement of wettability and dissolution rates of the poorly water-soluble Celecoxib. This study has shown that contact angles at 0's in liquid–solid interface have been almost θs (theta) 79.70 ± 0.50° and 86.65 ± 0.45° for the CEL-ADI and CEL-SAC, respectively, which have been considerably lower compared to value that has been obtained for the CEL (92.05 ± 0.75°θ) which revealed that the rate of the dissolution gas been increased with the decrease of the contact angle [27].

8 Additionally, Kim D. et al. 2021, has a specific goal to create a naproxen (NPX) eutectic mixture with an API greater than 20 wt%. The maximum NPX content was only approximately 15% wt%, rendering eutectic compositions impractical through restricting the NPX dose to <150 m, assuming the upper limit of the mixture is considered to be 1000 mg. Cases of naproxen eutectic formation were infrequently documented (particularly with small molecules) [28].

9 A number of EMs of fatty acids were created by Parveen F. 2022 and colleagues as natural supplies with exceptional, alluring physicochemical characteristics, such as stability, security, availability, affordability, and compatibility with healthy human cells. The reversible solid–liquid phase transition is in charge of holding the drug in place or causing it to be actively released. To create a tunable thermoresponsive platform, liquid lipid (oleic acid) and eutectic mixes of fatty acids (myristic acid and stearic acid) have been combined. With the help of a combination of the hot melt encapsulation (HME) and sonication methods, doxorubicin-loaded lipid nanocarriers have been efficiently created, and they were then characterized for achieving improved permeability and retention (EPR) effect-based solid tumor targeting in response to exogenous temperature stimulus. The resulting Doxorubicin-loaded lipid nanocarriers show exceptional colloidal stability, a spherical shape, a limited size distribution (94.59 nm–219.3 nm), and a PDI (0.16–0.479). The developed Z.P value ranges from 22.7 to 32. The tunable thermoresponsive properties of lipid nanocarriers make them promising bio-compatible drug delivery systems for more effective targeted delivery of chemotherapeutic agents [29].

10 Through the use of salicylic acid as a conformer during the eutectic formation, Narwal S. 2021 and his team enhanced the medication curcumin's poor water solubility. When compared to pure curcumin, in-vitro dissolution studies for the eutectic mixture (69.38%) showed enhanced dissolution behavior (40.53%) [30].

11 In the case when the mixture was characterized, it was discovered that PEG and fenofibrate form a simple eutectic mixture with 20–25% (w/w) fenofibrate at the eutectic point. Law D. and coworkers 2003 studied the enhancement regarding the dissolution rate of a poorly soluble compound through the formation of PEG-drug eutectics using fenofibrate. Fenofibrate crystals were discovered to be < 10 microns in size as a result of eutectic crystallization, which produced an uneven microstructure. The phase diagram and the fenofibrate dissolution rate improvement were both related, and the amount of fenofibrate released from the eutectic mixture containing fenofibrate was at least ten times greater than that of untreated fenofibrate [31].

5. Characterization of the eutectic mixtures

Predicting the formation of eutectics is considered a challenging process since the depression in melting point by thermal methods is the only indicator of eutectic formation. In addition, the phase diagram will show the extent of solid–solid solubility, and the eutectic composition. Spectroscopy and powder x-ray diffraction is commonly used for the prediction of multicomponent solids like salts and cocrystals. Eutectic mixtures do not show any change in spectroscopic and x-ray diffraction patterns when compared to their individual components. Eutectic mixtures show minor changes in spectral peaks and x-ray

diffraction. Therefore, thermal analysis is the best method for the prediction of eutectics. SEM analysis is done for the particle size determinations [7].

5.1. Differential scanning calorimetry (DSC)

DSC technique is used to investigate the phase change temperature (T_{fus}) and enthalpy of fusion ($\Delta_{fus}H$) indicating the eutectic phases. The thermogram of the eutectic mixture indicates the melting point which lies between the melting point of the drug and Coformer and as a result of higher entropy and weaker interactions of non-random products, the melting point of the eutectics will be lowered. In this technique, the physical mixture is heated in a DSC pan at a rate of heating 50 C/min, then upon grinding, the formation of the eutectic phase occurred, by increasing the temperature the breaking and reorganization of bonds occurred leading to the formation of eutectic phases. By DSC we can indicate that eutectic formation is enhanced by grinding. DSC thermograms show a classical "v" shape in which the molar ratio is denoted at the minimum point of "v" and this minimum point also represents eutectic point [7,30–32].

5.2. Thermogravimetric analysis (TGA)

It is a thermal analysis technique that measured the change in mass either loss or gain with respect to temperature or time in a controlled atmosphere. Mostly it is combined with other methods. The composition of the material and thermal stability is predicted by using TGA. It is an effective tool for the determination of oxidative stability of drugs, lifetime of drug product, product decomposition analyses, the composition of a material, etc. [33].

5.3. Types of TGA

1 Isothermal or static thermogravimetry: Temperature is constant.
2 Dynamic thermogravimetry: Temperature is changed in a linear manner.
3 Quasi Static thermogravimetry: A series of increasing temperatures and the weight of the sample is kept constant during the heating series [30,33].

5.4. Powder x ray diffraction

The powder x-ray diffraction technique is used as one of the confirmatory tools for the characterization and identification of crystalline material and detection of the formation of EM. On the basis of wavelength of incident rays and angle (ɵ) where constructive interferences occurred, the tested material can be identified. Basically, spacing between crystal lattice atoms can produce constructive interferences which can be determined by using Bragg's equation. In crystal structures there are many planes of atoms, then the reflection from all planes is used to determine the crystal structure [6,7,33].

PXRD results for EMs exhibit a pattern that is comparable to that of the pure component. The addition of a minor component that occurs as a substitution in the major component only slightly alters the XRD lines, and as a result, the molecular arrangement in the crystal lattice (domain structure) is mostly intact when put to comparison with the individual components. In order to ensure that no new peaks are seen and that the ground mixtures contain all of the diffraction peaks of the initial components [34,35] Atomic pair distribution function (PDF) analysis is another method that may be used to examine the local structure of both amorphous and crystalline (nanocrystalline) solids. It is based on real space fitting for a pair of atoms separated by a distance 'r' [32,35].

It has the potential to be used to research the eutectic microstructure. The Fourier Transform of the PDF method incorporates the diffuse scattering intensity along with the traditional Bragg reflections, making it sensitive to local structure ordering. When compared to the typical crystallographic structure, PDF estimates the instantaneous atomic arrangements and displays the local structure (low r region) [36,37].

5.5. FTIR spectroscopy

FTIR spectroscopy is used for the prediction of intermolecular interactions and studying the compatibility between the drug and the conformer. A few milligrams of the sample are required for analysis for solid. It is a fast technique and gives IR spectra that resemble NMR correlation spectroscopy. In the eutectic systems principle, a single phase formation is commonly described as a basic association between entities containing electron donor and electron acceptor groups [33]. These groups bind together via hydrogen bond formation mainly between the hydroxyl group — OH of one compound with the carbonyl group CO- of the other Which is identified by the application of Fourier-transform infrared (FTIR) spectroscopy analysis of the pure components and their eutectic liquid [38]. In this regard, IR

spectroscopy gives a response with respect to changes in vibrational modes of covalent bonds due to changes in intermolecular either stretching or bending has been allocated to hydrogen bonding. The information of molecular structure and dynamics is given by 2D IR spectra. Eutectics can be differentiated from salts. In case of eutectics, there is a slight change in the pattern of a spectral line in comparison to the individual compounds [39,40].

5.6. Hot-stage microscopy (HSM)

HSM, which combines the thermal analysis and microscopic approach, is utilized in the pharmaceutical industry to examine how the chemical and physical properties of a material change with time and temperature [18]. It is utilized to support DSC and TGA observations as well as to identify small changes in the sample that TGA and DSC could have missed during a thermal experiment. In general, HSM could be utilized to investigate the crystallization process, polymorphism, desolvation, melting and boiling points, phase transitions, incompatibility, and glass transitions between different medicinal compounds [39,41]. In this method, observations are made while a small number of substances are heated and cooled on a microscopic slide. In either a closed or open environment, the sample is heated in a sapphire crucible or glass slide. It may also be fitted with a liquid nitrogen unit for quick cooling, high pressure pumps, or purge gas. A modern computer-controlled hot stage has a temperature range of 200 °C−600 °C [41].

5.7. Raman spectroscopy

Most of APIs are more polarisable and they tend to produce strong Raman bands as compared to the excipients. The IR spectrum generally covers a low-frequency range of about 4000 cm^{-1}. Raman used to determine any change in the chemical structure, formation of new molecules, and/or formation of chemical or physical interaction in the eutectic solution. Raman bands which are produced by amorphous substances are broad and below 400cm-^{1} and show a tendency to disappear [42]. In pharmaceuticals, raman spectroscopy is appropriate for investigation of single crystals, powders or lump of substances. Transmission raman spectioscopy is reliable to analyse polymorphic content in bulk samples. Two types of instruments are used for raman measurements one is dispersive spectrometer and another is fourier transform spectrometer. The dispersive spectrometer involves a visible region, gratings and detectors (silicon charged coupled devices). The FT R is operated with NIR laser, an interferometer and a semi conductor detector. Strong signals are given by the dispersive spectrometer and minor component can be detected by this device while FT R gives weaker signals, and these are only applicable to quantitative analysis. In case of eutectics there is slightly change in the pattern of spectral line in comparison to the individual compounds [18,43].

5.8. Scanning electron microscopy (SEM)

The morphological characteristics of EMs, like particle shape, morphology, and size, which may be linked with flow parameters, were identified and compared using SEM [18]. Emami et al. 2018, investigated SEM to assess morphological variances regarding succinic acid and glicazide EM which were synthesized with the use of various methods. SEM images demonstrated that the method used to get EM had a substantial impact on the shape and size of the glicazide particles. With the use of liquid assistance in the grinding process, polydisperse particles ranging in size from a few hundred nanometers to micrometers are produced. In contrast, the electrospray deposition process created a homogenous dispersion of submicron-sized particles that aggregated to form foam-like clusters with micrometer sizes [44].

6. Applications of eutectic Mixtures in the pharmaceutical industry

The eutectic system was used in the pharmaceutical field as the best alternative choice to boost the solubility regarding poorly water-soluble drugs, absorption and permeation, or applying as an oil phase in an emulsion system [45]. Since it is affordable, biodegradable, nonflammable, and nontoxic, the system of liquid eutectic made of quaternary ammonium salts and organic component was utilized as deep eutectic solvent (DES) [38,46]. There are a variety of pharmaceutical actions that use compounds that are used as eutectic components, including pain relief, local anesthetic, antiflatulent, antipuritic, and antimicrobials. Menthol works similarly as a permeation enhancer. By mixing menthol and camphor for forming a liquid eutectic that could be used as an analgesic and an anti-inflammatory at room temperature [47–49].

Excipient selection during the pre-formulation role is critically influenced by studies on the compatibility of excipients and drugs, which could assist anticipate potential physical incompatibilities between drug and excipient molecules [50]. EM is

used to extract and purify a small number of compounds, including natural products and metabolites. Extraction media are DES. A two-step extraction approach is as follows: (i) the capability of DES to better solubilize the target compound than source tissues or a chemically complex matrix, which is considered a pro for DES as extraction media [51]. EMs are frequently employed in the development and distribution of pharmaceuticals for a variety of administration routes, including transdermal drug delivery. EM is used in the production of pharmaceutical dosage forms to help prevent manufacturing problems. For instance, during tablet compaction, the heat generated in the punch and die cavities might cause the tablet powder compacts to fuse or melting, resulting in manufacturing defects [52]. EM could be used to detect substances like ergotamine and allobarbital that have identical melting points but a differing eutectic point [7]. EMs have a significant role in enhancing the skin penetration of topical formulations for poorly soluble drugs, leading to reduced treatment effects, quicker drug delivery to the target location, and higher tissue drug levels [5]. The capability of the drug to maintain its form in a specific environment, such as under biological conditions, was improved by the application of EMs [53]. Many structural or external elements, such as temperature, light, oxidation, pH, or enzymes, have an impact on stability. For instance, after a prolonged period of storage in water, many ester-containing APIs, such as aspirin, might undergo hydrolysis [54]. Compared with the stability of APIs in aqueous media, EM has been demonstrated to be vital solvent to increase the chemical stability of these solvents [55,56].

7. Conclusion

In time to improve the solubility of weakly water-soluble drugs used in oral therapy, EMs have long been recognized. However, there has been a significant number in publications over the past few years. These straightforward EMs have also demonstrated promise as strategies for enhancing drug solubility. Solid dispersion and EM are contrasted. It is thought that the crystalline form of EM components has advantages over the amorphous form of solid dispersion. The amorphous form has a tendency to recrystallize, especially under high humidity conditions during manufacture, storage, or dissolution, which is viewed as a concern even if it significantly enhances the pace of dissolution in comparison with the crystalline complement. Since EM already exists in crystalline form, researchers primarily created crystalline EM to address this disadvantage. Simple, inexpensive techniques that are simple to scale up could be used to prepare additional EMs.

Additionally, EMs allow the blending of therapeutically suitable active pharmacological ingredients (drug–drug EMs) for creating fixed-dose combined systems. As a result, EMs offer a promising way to enhance the properties, therapeutic effect, and delivery of drugs. The drawbacks of Ems are associated with the characterization challenges that deter researchers from this straightforward system because it is still complicated to employ technologies that can get a better knowledge of eutectic mixtures, which calls for more research. Lately, several researchers have become interested in the creation of solid dosage forms containing EMs. To expand the EMs on a commercial level, significant attempts are required. The pharmaceutical field will have a wide range of prospects thanks to EMs, and the previously reported positive studies will keep motivating researchers to expand their use in other claims.

Conflicts of interest

The authors declare no conflict of interest.

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