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Deep eutectic solvents formed by pharmaceutical ingredients and their potential influences on solid preparations

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Abstract: Some active pharmaceutical ingredients (APIs) and excipients can form deep eutectic solvents (DESs), which will lead to severe defects in solid preparations. This work first prepared related typical DESs by mixing APIs and excipients from marketable drugs. Then two different types of the binary eutectic mixtures were investigated, which were composed of menthol (HBD) and citric acid (HBA), ME/CA, as well as phenyl salicylate (HBA) and benzoic acid (HBD), Salol/BA. These binary mixtures were applied to investigate their possible effects on capsules and tablets, which could be liquefaction or the stickiness of the solid formulations. The comprehensive characterizations and studies on phase behaviours of the binary mixtures were carried out, and the spectral analysis confirmed the formation of the eutectic liquids from individual components. Furthermore, the binary mixtures have increased the tablet strength when increasing the compression force, leading to the stickiness of powders during pressing. Moreover, the capsules were softened by the existence of DESs. After morphological observation and quantitative analysis, the corresponding suggestions and countermeasures were provided in the conclusions.

Keywords: excipients; marketable drugs; binary mixtures; phase behaviours.

INTRODUCTION

Deep eutectic refers to the phenomenon of wetting or liquefaction after mixing two or more substances. Sometimes it can be used, but occasionally it adversely affects the products.[1] The resulting deep eutectic solvents (DES) or deep eutectic liquids (DEL) have attracted considerable attention recently, which correspond to a broad class of low melting temperature liquids that are composed of at least two substances with H-bonds, mainly a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD).[2] These eutectic liquids are generally featured

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by strong solubility, biodegradability, a wide range of polarity, high thermochemical stability, water compatibility and a negligible toxicity profile.[3] Moreover, H-bonds play an essential role in their properties (*e.g.*, melting point, density, viscosity, *etc*.), which can be revealed by infrared and nuclear magnetic resonance spectroscopy.[4] Besides that, some possible reactions occurring between two kinds of solids also attract attention from researchers and some key mechanisms are being continuously explored.[5,6]

The breakthroughs achieved in green solvents promote the emergence of therapeutic deep eutectic solvents (THEDES) or active pharmaceutical ingredient–deep eutectic solvents (API–DESs), and many APIs are HBD for containing amines, carboxylic acids or hydroxyl groups. The most commonly used is menthol, which can be combined with coenzyme Q10, borneol, paeonol, ibuprofen, aspirin and other APIs to form DESs.[7–9] Moreover, three kinds of arginine-based THEDES were designed as drug solubilization vehicles for lidocaine;[10] Shekaari *et al*.[11] have successfully prepared a stable ion-gel system containing an anti-cancer drug, 5-fluorouracil, and a choline chloride-ascorbic acid DES. A recent study[12] showed that DESs could play the multiple roles of the solvent, reactant and shape control agent simultaneously. With the increasing application of DES in the pharmaceutical field, many problems that have not been paid attention to before need to be studied; one of them is the effect of DES formation on various solid preparations.

Despite all the promising features of DESs in the pharmaceutical field, there are some potential problems that are related to the formation of eutectic mixtures between APIs or between APIs and excipients upon the manufacturing processes, resulting in incompatibilities and instability of the final pharmaceutical products. For the solid preparations, the granules can be liquefied, the tablets can be adhered, or the capsules can become soft or leak resulting from deep eutectic phenomena. Sticking on the formed punch is a severe issue in the tablets production process; when it occurs, the tablet machine must be repaired, which is a costly process.[13] In fact, it is known that applying the compression forces causes damage and changes in terms of the drug properties. Moreover, the contact between the APIs and the excipients upon compression facilitates the formation of the eutectic mixtures. Ibuprofen is one of the APIs that is commonly used in tablet preparation. However, when mixed with other drugs or excipients, this component forms a eutectic mixture. Setyawan *et al*.[14] studied the sticking phenomena of ibuprofen–stearic acid due to the formation of the eutectic liquid by the compression forces. This eutectic formation was further confirmed by FTIR, X-ray powder diffraction, scanning electron microscopy and hot-stage microscopy studies. To the best of our knowledge, there are no studies focused on the effect of deep eutectic solvents on solid pharmaceutical preparations. After searching and summarizing for marketable medicines, it has been found that the

mixtures of some ingredients show deep eutectic behaviours and can affect related solid preparations (see Fig. S-1 of the Supplementary material to this paper); however, a part of the DELs was unstable (*e.g.*, the acetaminophen, ibuprofen and salicylic acid series). Racemic menthol, citric acid, phenyl salicylate and benzoic acid are four common components in these medicines (the former two as ingredients in Orofar capsules, Pharma Express, France; the latter two as ingredients in Hyophen tablets, BioComp Pharma, Inc., USA), and there is a chance of using them together. Meanwhile their mixtures can become stable DESs.

EXPERIMENTAL

Chemical reagents and materials

Menthol (99.0 %), citric acid (98.5 %), phenyl salicylate (98 %) and Sudan red were from Aladdin Company (Shanghai, China). Benzoic acid (95.5 %) was obtained from the Fangzheng reagent factory (Tianjin, China). Ethanol (99.5 %), glycerin (99 %), methanol (99 %), choline chloride (99.0 %) and urea (99.5 %) were bought from Kelong Chemicals Inc. (Chengdu, China). Acetone (99.5 %) was purchased from Changlian Chemicals Inc. (Chengdu, China). Deionized water was obtained by a UPH-1-10T water purification system (Chengdu, China). Empty gelatin capsules, glutinous rice capsules, and enteric capsules were obtained from a local drug store.

Formation of DESs

According to the DESs in Fig. S-1, menthol was mixed with citric acid at 150 °C under constant stirring for 2 to 4 h until a homogeneous liquid formed. The mole ratios of the eutectic compositions were found to be 3:1, 4:1, 5: and 6:1 (marked as DES 1–4) for menthol and citric acid. The prepared mixtures were dried under vacuum at 50 °C for 24 h before characterization.

The second kind of DES was prepared by mixing phenyl salicylate and benzoic acid in different molar ratios at 80 °C for 3 h until transparent liquids were obtained. The unsuccessful preparations were also eliminated for further characterization; only the products with mole ratios of 12:1 and 9:1 were liquids at room temperature.

Characterization of DESs

Attenuated total reflection-Fourier transformed infrared spectroscopy (ATR-FTIR) analysis. ATR-FTIR analysis of DESs and their individual components was performed by using a Spectrum Two FTIR spectrometer equipped with ATR (PerkinElmer, Waltham, USA) for liquid samples. For each sample, 32 scans were taken from 4000 to 400 cm^{-1}. Spectra were analyzed using Excel Ms. The results are shown in Fig. S-2 of the Supplementary material. It can be found that the FTIR spectrum of menthol exhibits a series of typical IR absorbance peaks, as illustrated in Fig. S-2A, which includes the stretching modes of the OH at 3255 cm^{-1}, and the C–H at 2959 and 2868 cm^{-1}. The FTIR spectrum of citric acid showed absorption bands at around 3491 cm^{-1} for the free hydroxyl group (–OH) in the molecule, C=O stretching at 1728.30 cm^{-1}, a peak at approximately 1133 cm^{-1} corresponding to the C–OH band, and 786 cm^{-1} attributed to CH_2 stretching. The menthol–citric acid binary mixtures spectrum displays O–H, C–H, C=O, and C–O stretching modes, appearing at around 3600–3230 cm^{-1}, 2958–2846 cm^{-1} and 1711 and 1019 cm^{-1}, respectively. Both representative groups of components were identified, and the O-H stretching band was shifted in the spectra of the prepared binary mixture, which confirms the formation of the eutectic liquid.

Similarly, Fig. S-2B shows the FTIR spectra of the pure components and their binary mixtures of different mole ratios (12:1 and 9:1), the spectrum of benzoic acid exhibits strong broad band around 3300–2500 cm^{-1}, which can be assigned to O–H stretching; the featured band at 1670 cm^{-1} corresponds to carbonyl (C=O) stretching vibration, and the C–O stretching of benzoic acid exists at 1287 cm^{-1}. Salol exhibited O–H bonding at 3400–2900 cm^{-1} and a C=O carbonyl stretching vibration peak at 1687 cm^{-1}. There are also several peaks due to C–O stretching vibrations around 1335–1127 cm^{-1}. The FTIR results of the DESs prepared by salol-benzoic acid further confirm the formation of eutectic solvents. The vibration bands at nearly 3300 to 3000 cm^{-1} refer to the hydroxyl group. The peaks at 1679 cm^{-1} refer to the presence of the C=O carbonyl stretching vibration peak. The peaks at 1330–1125 cm^{-1} are due to C–O stretching vibrations. The FTIR spectra of binary mixtures displayed the main vibration frequencies corresponding to pure components with slight shifts, which supports the formation of a eutectic system. Furthermore, FTIR validated the formation of H bonds between choline chloride and various HBDs by shape changes and shifts in the characteristic absorbance of the specified chemical compounds.

Proton nuclear magnetic resonance analysis. Proton NMR spectra were recorded with an AV II-400 MHz spectrometer (Bruker, Billerica, MA, USA), and the chemical shift data were processed using MestReNova software. The ^{1}H-NMR spectra of menthol, citric acid and the DESs are shown in Fig. S-3A–F of the Supplementary material. All the normal peaks of both pure components appeared in the spectra of the prepared DES with a slight shift, this suggests the formation of the hydrogen bonds between the menthol and citric acid again. The proton NMR analysis of the phenyl salicylate–benzoic acid and its pure components are shown in Fig. S-4A–D of the Supplementary material. The ^{1}H-NMR spectra of the mixtures are almost identical to those of the pure components. Moreover, the chemical shift of the –OH group of phenyl salicylate was slightly shifted from 10.52 to 10.54 ppm; this slight shift of hydrogens of the neat components toward the downfield of the spectra is the evidence of hydrogen bonds forming between phenyl salicylate and benzoic acid.

Phase diagrams. The melting points of the DESs were measured using the generally acknowledged thermometer method. A small amount of each mixture was put in a sample tube attaching to a WRS-1A thermometer (Jiahangbochang Sci. & Tel. Inc., Beijing, China) placed in a heating bath (±0.1 °C), and the temperatures at which the mixtures started to melt and the temperatures at which the mixtures melted completely were recorded. All the experiments were performed in triplicate.

Viscosity. The viscosity of DESs was determined using the NDJ-5S/8S type digital rotary viscosity rotational viscometer (Meiyu Instrumental Inc., Shanghai, China) equipped with a water circulator (±0.1 °C). The heating profile was set at a temperature range from 5 to 35 °C for the menthol–citric acid DESs and 35 to 55 °C for the phenyl salicylate–benzoic acid DESs. All the experiments were performed in triplicate. The viscosity–temperature dependence of the tested DESs can be described in this work using the VTF equation:

$$\eta = A\mathrm{e}^{(B/(T-T_0)} \quad (1)$$

where η is the dynamic viscosity, mPa s; T is the temperature in K; A, B and T_0 are VTF fitting parameters. The fitting parameters of A (mPa s), B (K) and T_0 (K) are tabulated in Table S-I of the Supplementary material along with the fitting coefficient R^2 values. The predicted viscosity values are depicted in Fig. S-5 of the Supplementary material.

Density. The density of the newly synthesized DESs was determined using the pycnometer method. Firstly, the dry flask and stopper were weighed on the analytical balance; sec-

ondly, the pycnometer filled with UP water was also measured using the analytical balance; finally, the pycnometers filled with the prepared eutectic mixtures were measured on the precise analytical balance (±0.0001 g). After determining the weight of each sample, the density was calculated using the following formula:

$$\rho_M = \rho_w \frac{m_M - m_p}{m_w - m_p} \quad (2)$$

where ρ_M is the density of the DESs, g/cm^3; ρ_w is the density of water, g/cm^3; m_M is the mass of the dry pycnometer full of DESs, g; m_p the mass of the dry pycnometer, g; m_w is the mass of the dry pycnometer full of water, g. Each measurement was repeated in triplicate, and the average value was adopted. All the measurements were carried out in a temperature range of 5 to 35 °C for menthol–citric acid DESs and 35 to 55°C for the phenyl salicylate–benzoic acid DESs.

The excess molar volume was determined using the following equation:

$$V_E = V - x_1V_1 - x_2V_2 \quad (3)$$

where V represents the molar volume of the mixture, cm^3/mol; x_1 and x_2 are the mole fraction of component 1 and 2, respectively, and V_1 and V_2 are the molar volume of component 1 and component 2 of the system, respectively, cm^3/mol.

Determination of DESs solubility in different solvents

The saturated solubility of DESs in various solvents, including water, glycerin, ethanol, methanol and acetone, was determined at room temperature according to the appendix of China Pharmacopoeia (2020 edition). The results are provided in Table S-IV of the Supplementary material.

Study of eutectic liquids formed by APIs on capsules

Dissolving test. Three different types of capsules were chosen for the study of the eutectic phenomenon in capsules, including enteric, glutinous rice and gelatin capsules; each type of capsule shell was cut into small pieces, then placed in sample vials that contained 5 ml of the prepared eutectic mixtures based on menthol and citric acid (DES 1–4). Each vial was placed into a temperature-controlled bath at different temperatures (±0.1 °C) with constant stirring (300 rpm). The dissolving process was observed during different periods, namely after 12 and 24 h.

Corrosion test. The eutectic liquids in different molar ratios were mixed with the pigment of Sudan red, which was used to make the corrosion in the capsules easier to notice. Then, each capsule type was loaded with the mixture of the tested eutectic liquid and this red pigment. The filling was in the body part of every capsule, which was closed by putting the top half of the capsule over the bottom and pressing down. Then, the loaded capsules were placed on filter papers in a vertical position in the incubator at 25, 30 and 40 °C for observing the change.

Soften test. Each type of capsule was cut into strips of several mm in length and placed in vials containing DESs of different molar ratios. The capsule shell fragments were kept in the DESs for one day. The tension measurements were carried out by using a ZP-5 type digital force gauge test machine (<0.5 kg, ±0.001 kg, Fuma Electrical Instrument Inc., Dongguan, China). Soften coefficient of the different types of capsules incubated in DESs of different mole ratios, which was calculated using the following equation:

$$\text{Soften coefficient} = 100\frac{\text{Soften data after soften by DES}}{\text{Soften data after soften by DES}} \quad (4)$$

Study of eutectic liquids formed by APIs on tablets

Tablet pressing. For clear observation, the tablets were made of pure components of phenyl salicylate and benzoic acid without any pharmaceutical excipients, as well as the binary mixtures of phenyl salicylate–benzoic acid in the previously known ratios, forming DES mainly in the 12:1 and 9:1 ratios. The powders were mixed in a mortar to homogenize the mixture and then compressed using the HY-12 type tablet pressing machine (Tianguang Optical Instrument Co., Ltd., Tianjin, China) in various compression forces (5, 10, 15, 20 and 25 MPa) and held for 3 min.

Tablet tensile strength. The previously prepared tablets were compressed with different forces and used to measure the tablet tensile strength. Each tablet was measured in thickness and diameter using a digital caliper (±0.01 cm). The hardness of the tablets was measured using the YPD-300d tablet hardness tester (Huanghai Drug Testing Instruments Co., Ltd., Shanghai, China). Tensile strength was determined using the following equation:

$$\sigma = 2F/\pi Dt \quad (5)$$

where σ is tensile strength, N/cm^2; F is tablet hardness, N; D is tablet diameter, cm; T is thickness of the tablet, cm.

Fourier-transform infrared spectroscopy

The powders were mixed with KBr and compressed at 15 MPa using a hydraulic press until a transparent disc was formed. The FTIR spectra were obtained using the spectrophotometer (PerkinElmer, Fermont, USA) in the range of 450–4000 cm^{-1}.

Scanning electron microscopy

The morphology of compressed pure components and binary mixture tablets was observed using JSM-7500F scanning electron microscopy (SEM, 25–800,000×, JEOL, Tokyo, Japan).

RESULTS AND DISCUSSION

In the following study, two different types of deep eutectic systems were investigated, including the binary mixtures of menthol (HBD) and citric acid (HBA), ME/CA, as well as phenyl salicylate (HBA) and benzoic acid (HBD), Salol/BA. Firstly, the formed DESs were identified according to the spectral analysis shown in Figs. S-2–S-4 of the Supplementary material. As we know, to determine the system composition and melting temperature at the eutectic point as well as melting temperature of the system at any specific composition, phase diagram of the eutectic systems, should be known. Thus, a binary phase diagram obtained by measuring the melting points of individual component, *i.e.*, menthol (ME) and citric acid (CA) as well as their binary mixtures, is shown in Fig. 1A. As depicted, the melting temperatures of the system at any examined composition of ME/CA mixture are lower than those of the individual components, forming a single eutectic point at mixture composition of 80 mol % ME and 20 mol % CA. This system is a simple eutectic, with a eutectic temperature of 37.0 °C. In the case of Salol/BA (Fig. 1B) a depression of the melting temperature, similar

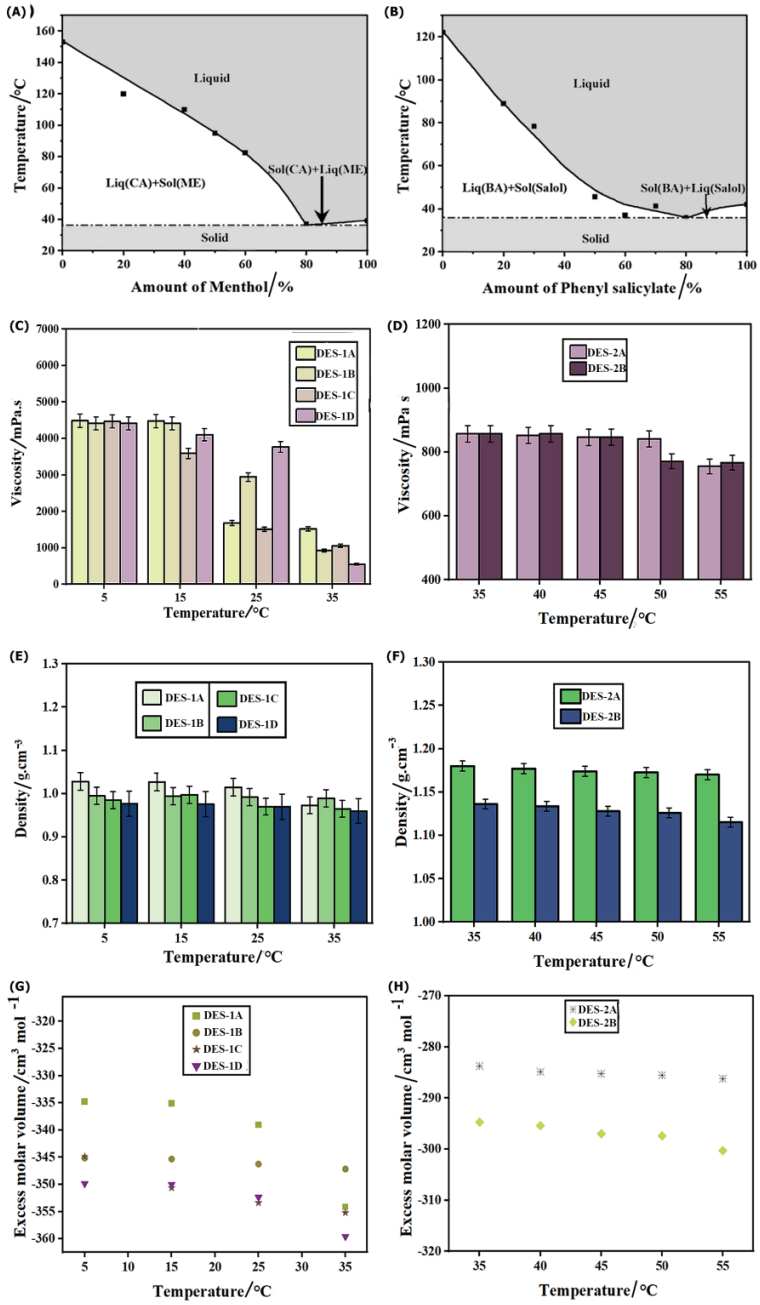

Fig. 1. Phase diagrams of binary mixture: A) menthol/citric acid (ME/CA) and B) phenyl salicylate/benzoic acid (Salol/BA); temperature dependence of: viscosity of: C) DES-1 and D) DES-2, density of: E) DES-1 and F) DES-2, and excess of molar volume of: G) DES-1 and H) DES-2; DES-1 and DES-2 denotes eutectic systems ME/CA and Salol/BA, respectively.

to the first examined system (ME/CA), occurs for 80 mol % Salol and 20 mol % BA (eutectic composition), and melting temperature/point of mixture at eutectic composition is 36.5 °C. This result was consistent with prior investigations[15] that found DESs to have a lower melting temperature than their individual components. The results indicate that they can remain liquid under normal drug production, storage and transportation temperatures (0.0–50.0 °C) once the DESs are formed, thus having a significant impact on the appearance and quality of solid preparations.

Generally, DESs have a higher viscosity than organic solvents, which will make the solid preparations sticky. The viscosity of the DES-1 with different composition of single compounds, *i.e.*, ME/CA mole ratio: 3:1 (DES-1A), 4:1 (DES-1B), 5:1 (DES-1C) and 6:1 (DES-1D) when temperature varied in the range 5.0–35.0 °C, was examined. For the second examined system (DES-2), viscosity was determined for two different composition of single compounds, *i.e.*, Salol/BA mole ratio 12:1 (DES-2A) as well as 9:1 (DES-2B) when temperature varied in the range 35.0–55.0 °C. As shown in Fig. 1C and D, the temperature significantly affects the viscosity of both chemical types of DESs (DES-1 and DES-2) at all DESs eutectic compositions (DES-1A-D and DES-2A-B).The order of decreasing the DESs viscosity was DES-1A > DES-1C > DES-1B > DES-1D. Furthermore, the viscosity of the mixture increases (at a given temperature) as the CA proportion in examined mixtures increases. This was confirmed by Shafie *et al*., who noticed that increasing the concentration of citric acid in the mixtures led to a high viscosity value.[16]

Density is widely used to evaluate the fluidity and compressibility of particles, which has a significant impact on all aspects of pharmaceutical production. It also helps researchers to understand the liquid behaviours. Likewise, the temperature and liquid composition effects on density. At room temperature, most of the previously studied DESs have densities in the range of 1.0–1.35 g cm^{-3},[17] and are generally higher than those of water.[18] With the temperature increased from 5.0 to 35.0 °C, the density values decreased for DES-1A from 1.028 to 0.9730 g cm^{-3}, DES-1B from 0.9950 to 0.9894 g cm^{-3}, DES-1C from 0.9850 to 0.9651 g cm^{-3}, and for DES-1D from 0.9767 to 0.9600 g cm^{-3} (see Fig. 1E). As is expected, the increase in the citric acid molar ratio in the mixture results in a high density of DESs, which explains why DES-1A has a higher density than the other binary mixtures. This finding is in accordance with Shafie's study, which found that increasing the concentration of citric acid leads to a higher density.[16] As shown in Fig. 1F, the densities of phenyl salicylate–benzoic acid mixtures decreased as the temperature increased from 35.0 to 55.0 °C; it can be clearly noticed that the density of the mixtures increased when the molar ratio of phenyl salicylate to benzoic acid increased from 9:1 to 12:1. Therefore, the temperatures as well as composition of examined DESs are affect its measured density. Fur-

thermore, it was found that as the amount of Salol increases in the mole ratio, the density of DES-Bs decreases. At 25.0 °C, choline chloride–urea DES (as control) has been reported to have densities ranging from 1.0921 to 1.4851 g cm^{-3}, which is higher than the densities of the menthol–citric acid DESs studied here. This is due to the larger molecular size and the polar nature of the choline chloride-based DESs compared to the formed DESs in this study.[18] Overall, at 35.0 °C, the highest density was obtained for molar ratio of Salol to BA of 12:1 (DES-2A), while the lowest density was observed for molar ratio of ME to CA of 6:1 (DES-1D). Commonly, the thermal motion of ions and the increase in free volume increase the coefficient of isobaric expansion as the temperature increases, meanwhile the density becomes lower. Here isobaric thermal expansion coefficients at 35.0 °C for Salol to BA of 12:1 and ME to CA of 6:1 were also investigated and compared here. As the result, 4.91±0.05 K^{-1} (for the former) and 2.78 ± 0.07 K^{-1} (for the latter) were obtained, respectively. It indicates the thermal motion within molecules in DES-1D system was more sensitive to temperature change than in DES-2A.

The excess molar volumes (V_E) of DESs for different molar ratios of single component at different temperatures can be used to understand more about the behaviour of eutectic mixtures; moreover, it can provide information on a solution's non-idealities and the intermolecular interactions. According to the results in Tables S-2 and S3 and Fig. 1G–H, the V_E values were negative for all the DESs-1A–1D. The negative V_E of menthol and citric acid DESs are attributed to their strong interactions, unlike molecular interactions through hydrogen bonding.[19] Therefore, a more efficient packing interaction occurred when the two components were mixed. Furthermore, the V_E values decreased when the concentration of menthol in the mixture increased, which indicates that the mole ratios have an effect on the excess molar volume and that the concentration of menthol in the mixtures has a more significant effect on the volume of the mixture compared to the concentration of citric acid in the mixtures. Moreover, the higher the temperature, the lower is V_E. This result indicate that the mixture exhibits a lower volume than the sum of the pure menthol and pure citric acid volumes in DES--1A–1D and pure phenyl salicylate–benzoic acid in the DES 12:1 and 9:1 It is a characteristic of eutectic mixtures and reflects the strong intermolecular interactions and the formation of a single solid phase at the eutectic point. Other studies on binary mixtures also have negative values of V_E.[19,20] Finally, according to the results in Table S-IV, all the tested DESs are obviously hydrophobic.

In the following investigation, three kinds of most popular capsules were firstly chosen, including gelatine, glutinous and enteric capsules (containing cellulose acetate phthalate), which are all mainly based on hydrophilic materials. It can be found that the tested DESs will not dissolve their small pieces under general storage temperature within 24 h (see Fig.S-6 of the Supplementary material); however, they will make them softer. The soften coefficients of the different

types of capsules incubated in DES- different molar ratios of ME:CA, are shown in Fig. 2A.

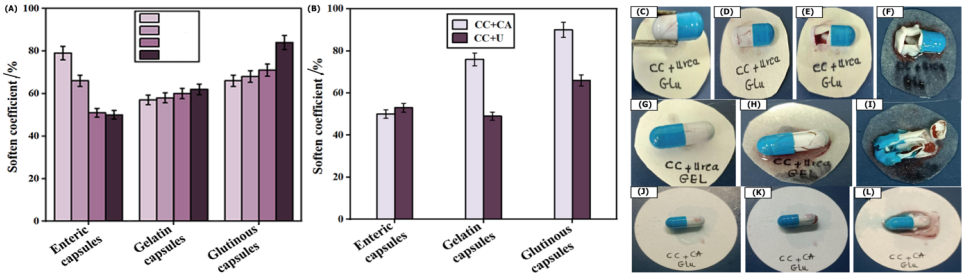

Fig. 2. Soften coefficient of enteric, gelatin and glutinous capsules incubated in: A) DES-1A–1D and B) choline chloride–citric acid (CC+CA) as well as choline chloride–urea (CC+U) DESs; photographs of different kind of capsules (glutinous and gelatinous) filled with CC and U based DESs after different time: 10 (C), 20 (D), 30 min (E) and 1 day (F) (glutinous capsules) and 10 (G), 15 min (H) and 1 day (I) (gelatinous capsules), as well as photographs of glutinous capsules filled with CC and CA based DESs after different time: 10 (J), 15 min (K) and 1 h (L). All measurements were performed at room temperature.

The enteric capsules exhibit a high soften coefficient (79 %) at the DES (menthol–citric acid) with mole ratio of 3:1, while the lowest soften coefficient was observed at the mole ratio of 6:1. The second type of capsules (gelatin capsules) show similar results, with the soften coefficient varying from 57 to 62 %. As for glutinous capsule, it had the highest soften coefficient among all the other types of capsules in menthol–citric acid with mole ratio of 6:1, whereas the soften coefficient lowered to 66 % for the ratio of 3:1. Clearly, the results above suggest that the DESs have a mollification effect on the tested capsules, making them more brittle. This change cannot be detected visually or by other methods; only the tests in this section can perform quantitative analysis for it. These findings suggest that the molar ratio of the eutectic solvent components can play a significant role when the degree of softening of the capsules shell is involved. In order to explore the possible difference, two choline chloride-based DESs were compared with DES-1A–1D for it is the most widely used HBA (Fig. 2B). As the result, for all DESs, the highest soften extent occurred in the DES formed by choline chloride–citric acid (1:1) and glutinous capsules (nearly 90 %); the second soften extent occurred in the DES formed by menthol–citric acid (6:1) and the corresponding capsules. Predominately, the enteric capsules exhibited the strongest resistance to DESs. The overall trend reflects not only the influence of different HBD and HBA types, but also the impact of the varied molar ratio of the two components. Finally, the results of the soften extent corrosion test further prove the DESs with the HBA of choline chloride have obvious effect on all the three kinds of capsules (Fig. 2C). As the fastest case, the leakage and crack were

noticeable from the fifth minute onward for the glutinous capsule filled with choline chloride–urea. Secondly, the gelatinous capsules started to break 10 min after loaded with the same DES. The glutinous capsules filled with the choline chloride–citric acid started to break after 1 h. Differently, the hydrophobic DES--1A–1D did not corrode all the capsules under the same conditions within 24 h (Fig. S-7 of the Supplementary material). Therefore, special attention should be paid to the choline chloride-involved mixture.

As for the tablet pressing, the tablets based on the binary mixture of the ratio 12:1 at 25 N broke when it was tried to remove from the mould (Fig. 3A). The eutectic liquid was formed during the compression up to 15 N for all the binary mixtures. Fig. 3B shows a graphical presentation for the tablet tensile strength versus the compression forces of the tablet made of phenyl salicylate, benzoic acid and their eutectic formation ratios 12:1 and 9:1. These two ratios demonstrated the tensile strength of 265.2 and 172 N cm^{-2} at 15 N, respectively. The tensile strength of both ratios increased with the compression forces. However, the ratio of 12:1 showed higher tensile strength values over the ratio 9:1. Moreover, both ratios showed higher tensile strength from 10 to 25 N. Similar trend was observed in the previous studies on binary mixture of ibuprofen–stearic acid[14] and acetaminophen–caffeine anhydrous and acetaminophen–prophylphenazone at certain pressure.[21] One possible explanation for this increase of tensile strength values is the formation of eutectic solvents when mixing the two components at certain ratio and applying certain pressure. The eutectic formation between the components may have influenced the crystal structure and the alignment of the material, leading to weaker intermolecular forces and lower tensile strength values. By examining the obtained tensile strength values, it was determined that the most appropriate sample was the binary mixture with a ratio of 12:1 and its compressed tablet under a force of 15 N. Finally, the changing trend of the tablet weight and tensile strength in stability test is shown in Fig. S-8 of the Supplementary material. It can be found the influence of DES on the tensile strength is more significant than that on the tablet weight in one week. Moreover, the rate of strength decline is accelerating, and the formation of DES is obviously disadvantageous for the tablet stability during its storage.

FTIR spectra (KBr) of phenyl salicylate, benzoic acid and their binary mixture ratio 12:1 compressed at 15 N is shown in Fig. 3C, the FTIR spectrum of phenyl salicylate shows a typical absorbance band O–H at wavenumber ranges of 3982–2835 cm^{-1} and 3733–3596 cm^{-1}, the peaks in 2421–2227 cm^{-1}, 2226––2014 cm^{-1} and 2017–1857 cm^{-1} are due to the asymmetric and symmetric stretching vibrations of the C=O group. The spectrum of benzoic acid compressed in 15 N shows peaks at 3770–3609 cm^{-1} is due to the stretching vibration of the –OH group. The peaks at 651 and 510 cm^{-1} refer to out-of-plane bending vibration of the C–H bond in the aromatic ring. The changes including the

changes in position of peaks, the changes in the intensity of peaks noticed in FTIR spectrum of the binary mixture ratio 12:1 are indicative of the formation of eutectic mixtures. Moreover, the FTIR spectrum of a binary mixture of ibuprofen and stearic acid[14] was studied after being compressed at a pressure of 19.9 kN. The study revealed changes in the spectrum of the binary mixture, suggesting some form of interaction between the compounds.

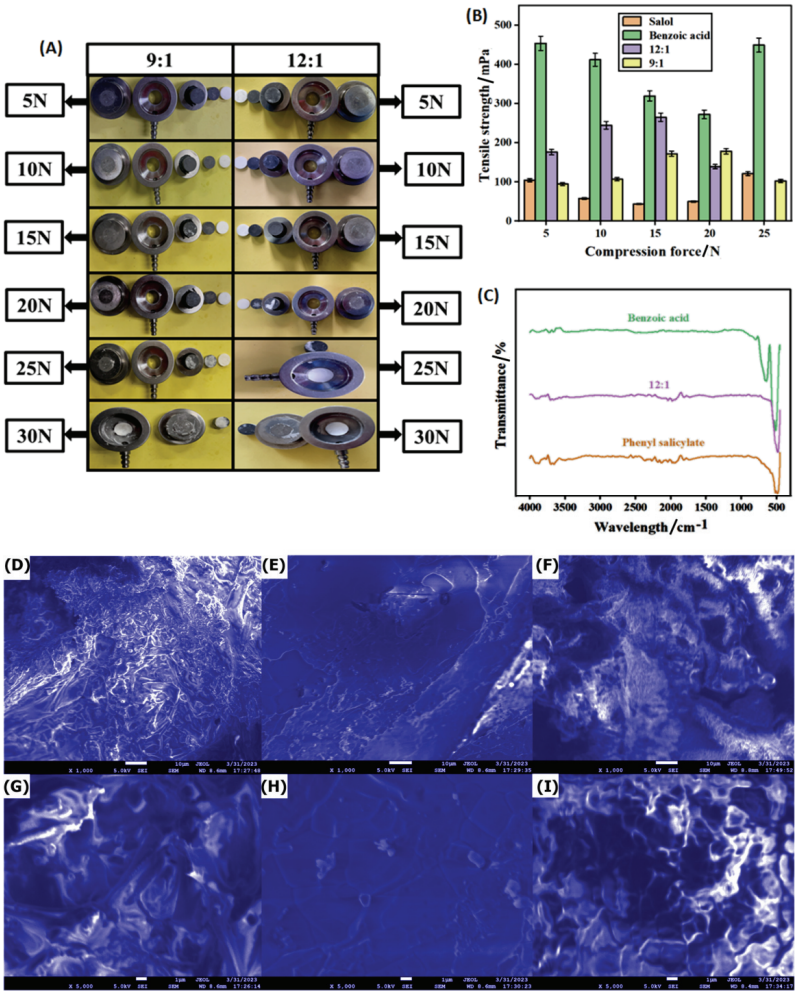

Fig. 3. A) Adhesion phenomena of phenyl salicylate-benzoic acid at different ratios (9:1, 12:1) and compression forces (5–30 N); B) tensile strength of pure components and its binary mixtures at different compression force (5–25 N); C) FTIR spectra of phenyl salicylate, benzoic acid and their binary mixture ratio 12:1 compressed at 15 N; SEM images: D) compressed phenyl salicylate at 15 N, 1000×; E) compressed benzoic acid at 15 N, 1000×; F) compressed binary mixture of phenyl salicylate–benzoic acid at 15 N, 1000×;

G) compressed phenyl salicylate at 15 N, 5000×; H) compressed benzoic acid at 15 N, 5000×; I) compressed binary mixture of phenyl salicylate–benzoic acid at 15 N, 5000×.

In order to study the morphology, SEM analysis was performed for phenyl salicylate, benzoic acid and its binary mixture 12:1 compressed on 15 N. The obtained photographs are shown in Fig. 3D. The loss of boundaries was observed in the three kinds of tablet resulting in a smooth surface. This phenomenon observed in the tablets is called sintering of the tablets. The same phenomenon occurred in the stearic acid and the ibuprofen-stearic acid the compressed tablets prepared by Setyawan *et al.*[14] The sintering phenomenon occurs when the temperature rises upon compression which forms the eutectic liquid, the presence of which affects the morphology and the structure of the pure components, allowing the particles to be rearranged and the filling of voids between the particles.[14]

CONCLUSION

In summary, the resulting DESs have lower melting points than their pure components and form simple eutectic point systems. The nature of the DESs has a different impact on capsules; menthol–citric acid DESs exhibit hydrophobic characteristics that result in a comparatively weaker effect on capsules than choline chloride-based DESs, which possess hydrophilic characteristics. DESs that have hydrophilic nature alter more the capsules in a short time. The tablets contain a mixture of phenyl salicylate and benzoic acid, confirming that the applications of the pressure to the APIs results in the formation of eutectic liquids; the applied force directly correlates with the degree of stickiness observed. Considering the deep eutectic is a common problem in the pharmaceutical field, and it can be prevented by several approaches. During the compression of the powders, the temperature tends to rise, leading to the formation of deep eutectic solvents. Thus, changing the temperature and the compaction forces can be an effective approach to avoid or reduce this phenomenon. The on-line monitoring of temperature can be of help to avoid reaching the eutectic point and maintain the APIs in a solid state. One another effective approach is to use the encapsulation technology. For instance, using the lyophilization method can transform the liquid form of nanoparticles into dry powders; this process ensures the stabilization and prevents the degradation of the product to be used in the creation of solid preparations. In addition, the solid dispersion is a useful way to prevent the formation of DESs during the manufacturing process and maintain the stability during the storage and the transportation by the dispersion of drugs in a stable matrix resistant to high temperatures. At last, the prevention of direct contact between the DES-forming APIs can be realized by changing the order of mixing the components, allowing the dissolution of each component separately. Alternatively, the multilayered tablets or capsules can also divide the ingredients into different layers, allowing APIs with low melting points to be positioned in the centre layer

and surrounded by stable excipients at high temperatures. Finally, nano-coating the APIs with a thin layer of polymers or surfactants is ideal to prevent the deep eutectic by creating a physical barrier between the APIs and excipients.[22,23]

SUPPLEMENTARY MATERIAL

Additional data and information are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/12564, or from the corresponding author on request.

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ИЗВОД

ЕУТЕКТИЧКИ РАСТВАРАЧИ ДОБИЈЕНИ ОД ФАРМАЦЕУТСКИХ САСТОЈАКА И ЊИХОВИ ПОНТЕЦИЈАЛНИ УТИЦАЈИ НА ПРИПРЕМУ ЧВРСТИХ ФОРМУЛАЦИЈА

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Одређени активни фармацеутски састојци (APIs) и ексципијенси могу формирати еутектичке растваче (DESs), који доводе до стварања дефеката у припреми чврстих формулација. У овом раду су припремљени типични DESs мешањем APIs и ексципијенаса присутних у регистрованим лековима. Затим су испитивана два различита типа бинарних еутектичких смеша, које су се састојале од ментола и лимунске киселине као и фенил салицилата и бензојеве киселине. Испитиван је потенцијални утицај ових бинарних смеша на капсуле и таблете, који може довсети до ликвефације или лепљивости чврстих формулација. Извршена је детаљна карактеризација и испитивање фазног понашања бинарних смеша, и спектрална анализа је потврдила формирање еутектичких течности из индивидуалних компоненти. Такође, бинарне смеше су повећале чврстину таблете при повећању силе компресије, што резултује лепљивошћу прашкова при примени притиска. Додатно, капсуле су омекшале у присуству DESs. Након морфолошких испитивања и квантитативне анализе, одговарајуће сугестије и првентивне мере су дате у закључцима.

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