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RESEARCH PAPER

Enhance dissolution rate and solubility of solid drugs through pharmaceutical deep eutectic solvents

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A B S T R A C T:

Pharmaceutical active ingredients are usually sold in the markets in the form of solid drugs. These drugs are often associated with some problems like polymorphism, bioavailability and low solubility. In this study, deep eutectic solvents (DESs) are used to change solid drugs into liquids, which may provide a potential solution to these problems. This research describes preparation of pharmaceutical deep eutectic solvents (PDESs) from hydrogen bond donors (HBDs) like urea and glycerol and hydrogen bond acceptors (HBAs) like adiphenine HCl and ranitidine HCl, which are one of the key parts of medicine improvement. Differential scanning calorimetry (DSC) was used to measure glass transition temperatures for the prepared PDESs and fourier transform infrared spectroscopy (FT-IR) was utilized to clarify hydrogen bond formation between HBDs and HBAs. Also, dissolution test apparatus and UV-Vis spectroscopy were used to measure dissolution rate and concentration of the prepared PDESs in this work. The higher dissolution rate was achieved for the tested APIs when in the form of PDESs. This was mainly obvious for ranitidine HCl: glycerol, which was 2.6 times faster than ranitidine HCl.

KEY WORDS: Dissolution rate, Deep eutectic solvents, Adiphenine HCl and Ranitidine HCl.
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1. INTRODUCTION:

Growing attention related to the formation of novel pharmaceutical formulations has been increased significantly in health care in the world. Currently, scientists are strongly looking for new, more active and patient-compliant medicine delivery systems. Using tablets for treatment has been limited due to poor solubility of drugs and thereby bioavailability, systemic toxicity and slight pharmacokinetics (Aroso et al., 2016) . Mixtures with an active pharmaceutical ingredient (API) were used for the first time by Stott and co-workers in 1998, in their study, the authors reported mixtures of different terpenes with an API to increase skin permeation. It is described that the eutectic can enhance the solubility, absorption and permeation of the API (Stott et al., 1998).

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The subject of pharmaceutical ionic liquids has been studied (Malhotra, 2010 and Marrucho et al., 2014). In a similar way, Morrison and co-workers used malonic acid-choline chloride and urea-choline chloride as DESs to solubilize griseofulvin, benzoic acid, danazol and itraconazole. They reported that these molecules have better solubility in DESs rather than in water, in some cases, 5–22,000-fold while compared with their solubility in water (Morrison et al., 2009).

In the current study, the principle of deep eutectic solvents (DESs) is used to make liquid drugs. DESs are mixtures widely produced by combining metal halides like $SnCl_2$, $InCl_3$, $ZnCl_2$ and CuCl or HBDs such as alcohols, carboxylic acids and amides with different quaternary ammonium salts (QASs) such as choline chloride, phenformin HCl, lidocaine HCl, and imipramine HCl. HBDs interact with salts via hydrogen bonding to form DESs (Abbott et al., 2017a and Qu et al., 2021).

Currently, DESs have significantly applied in different industrial applications such as extraction of biomolecules in natural products (Abbott et al.,

2017b), extraction of nonhydrocarbon species from petroleum products and metal extraction (Smith et al., 2014). Moreover, DESs are commonly used in polymer synthesis, metal recycling, metals electrodeposition (Alesary et al., 2020), desulfurization (Qader et al., 2021) and electro polishing (Ismail et al., 2019).The concept of the current investigation was to enhance dissolution rates of drugs.

With respect to the developed Noyes-Whitney equation offers some suggestions to improve the dissolution rate of very poorly soluble drugs in order to increase their oral availability (Liu et al., 2006).The following efforts have been used to improve the dissolution rate of drugs: (a) using water-soluble transporter to form addition complexes; (b) increase the surface area by minimizing the particle size; (c) using drug derivatization and pro-drugs; (d) solubilisation in surfactant process and (e) formation of solid dispersions of drugs by minimizing their crystallinity (Liu et al., 2006). Though, in terms of practice these techniques are not easy (Kapsi and Ayres, 2001). While the dissolution rate is widely increased by decreasing particle size of compounds, there is a limitation in practice to minimize the size of particles. This can be completed by such usually used approaches as controlled grinding and crystallization. Dosage form of drugs in the form of soft powders is also problematic due to poor wettability and handling difficulties (Liu et al., 2006).

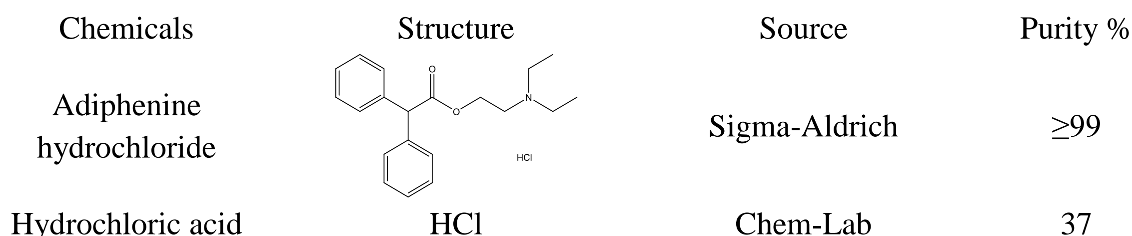
Salt formation as neutral compounds is not possible and the preparation of a proper salt form of compounds, which is weakly acidic or basic may often not be practical (Liu et al., 2006). Solid eutectic mixtures are commonly synthesized by quick cooling of a co-melt of two components to achieve a physical mixture of very soft crystals of the two compounds.

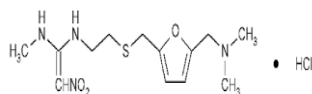
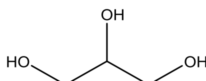
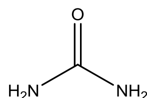
The aim of this work was to expand improving dissolution rate and solubility of two different active pharmaceutical ingredients (APIs), namely ranitidine HCl and adiphenine HCl via PDESs. These drugs were known to display polymorphism in their crystalline state. Adiphenine HCl, is a spasmolytic agent and chemically known as 2-diethylaminoethyl 2,2-diphenylacetate hydrochloride. It is used to reduce convulsion of the gastrointestinal tract, biliary tract, ureter and uterus (Dinç et al., 2014). Ranitidine HCl, is a H2-receptor antagonist with empirical formula $C_{13}H_{22}N_4O_3S$ and its chemical name is N-[2-[[[5-[(*Dimethyl amino*)*methyl]-2-furanyl*] *methyl*] *thio*] *ethyl*]-*N'-methyl-2-nitro-1,1-ethanediamine* hydrochloride. This drug aids relieve the symptoms of stomach-ache and helps the curing of ulcers (Narayana et al., 2010). Urea is used in this work, as it has many brands in the forms of urea topical, which is utilized as an emollient and useful to soften rough and dry skin as a result of eczema, keratosis, psoriasis, etc. (Celleno, 2018). Glycerol is commonly applied in the pharmaceutical industry because it can be combined into a number of pharmaceutical formulations (Abbott et al., 2017a).

2. Materials and methods

All ingredients and chemicals employed in this work were used as received and their sources and purities are listed in **Table 1.** In small test tubes quaternary ammonium salts such as ranitidine HCl and adiphenine HCl were mixed with glycerol and urea separately (molar ratios 2HBD:1QAS) to form eutectic mixtures in a similar method to that described previously (Abbott et al., 2017a).

Table 1: Structure, sources and purity of chemicals used in this study.

Chemicals	Structure	Source	Purity %
Adiphenine hydrochloride		Sigma-Aldrich	≥99
Hydrochloric acid	HCl	Chem-Lab	37

Ranitidine hydrochloride		Sigma-Aldrich	CAS 66357-59-3
Glycerol		Scharlau	99
Urea		Fluka	≥99.5

All mixtures were put in an oven at 50 °C for 24 hours after that, the magnetic stirrer hotplate was used to heat these mixtures at approximately 80 °C and 600 rpm for at least 2 hours until clear homogenous liquids were formed for each.

The produced PDESs are liquids at 25 °C and their glass transition temperatures were measured by a Mettler Toledo Differential Scanning Calorimetry (DSC) from the chemistry department- University of Leicester- United Kingdom.

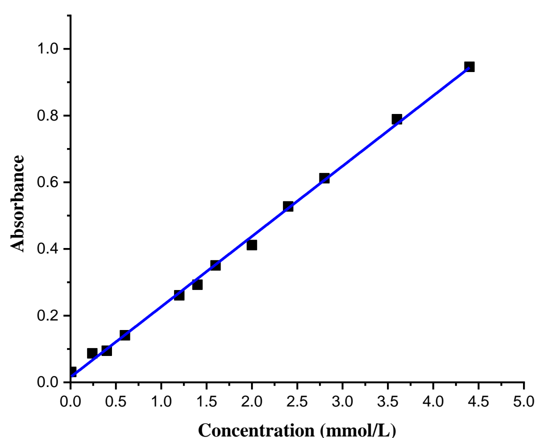
A PerkinElmer, Shelton, CT 06484 USA Lambda 25 UV/VIS Spectrophotometer was used for all UV-Vis absorption amounts. A number of standard solutions were prepared from pure drugs (adiphenine HCl and ranitidine HCl) in 0.1 M HCl separately. The absorbance measured for each solution by UV-Vis spectroscopy. Calibration curves were made in 0.1 M HCl in different concentrations and the results are shown in **Fig. 1** for ranitidine HCl and adiphenine HCl. In this case, the points on the graph made a straight line by using OriginPro 2018 64- bit. The intercept and slope of the produced line form a correlation between concentration and absorbance.

Absorbance = slope * concentration + intercept (1.1)

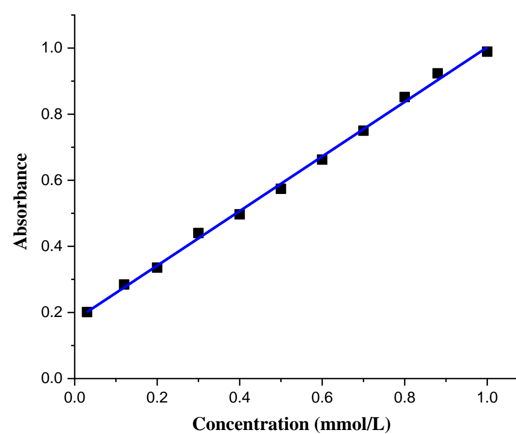
The concentration of adiphenine HCl and ranitidine HCl in their PDESs is measured from the calibration curve. This can be conducted by determine the absorbance of the active ingredients in their PDESs. This absorbance is used with the intercept and slope from the calibration curve to determine the concentration of unknowns' solution.

Concentration = (absorbance – intercept) / slope (1.2)

Two calibration curves for adiphenine HCl and ranitidine HCl were made separately in the range of 0.008 - 4.4 and 0.201 - 0.9891 mmol L^{-1} respectively. The sample concentrations were diluted to be ensure that they were constantly in these ranges.



(a)



(b)

***Figure 1**: Calibration curves using standard known a) adiphenine HCl concentrations in 0.1M HCl which are plotted against absorbance peaks in UV-Vis spectroscopy, b) ranitidine hydrochloride concentrations in 0.1M HCl which are plotted against absorbance peaks.*

PHARMA TEST PT-DT7, dissolution apparatus type Ⅱ with paddle stirrer was used to study the dissolution rate of pure PAIs like adiphenine HCl and ranitidine HCl and the PDESs prepared from these PAIs in 0.1 mol/L HCl (pH=1.0) at 37 ± 0.5 °C (to mimic the behaviour in the stomach).

Furthermore, Fourier-transform infrared spectroscopy (Perkin Elmer Spectrum One FT-IR with ATR)) was applied for the produced PDESs to compare the constituents with their products via hydrogen bonding. Hydrogen bond formations between HBDSs and HBAs were showed using this machine. Thus, hydrogen bond formations can be predictable and investigated via FT-IR. FT-IR is a powerful method to obtain data of hydrogen bonding.

3. Results and discussion

3.1 UV-Vis spectroscopy study

It can be noticed that good linear correlation was carried out for this analytical technique, the R^2 value was more than 0.99 for UV-Vis spectroscopy in all cases. The error bars for most of the results are within the size of the plot symbols displaying that replicate data are accurate. The reproducibility of replicate determinations can again be noticed from the small error bars on the curve. Adiphenine HCl and ranitidine HCl absorbed at around 258 and 314 nm respectively on UV-Vis spectroscopy in 0.1M HCl.

The prepared PDESs are liquid at room temperature as shown in **Fig. 2**. DSC was used to determine glass transition temperatures of adiphenine HCl and ranitidine HCl at their PDESs: (adiphenine HCl + urea), (adiphenine HCl + glycerol), (ranitidine HCl + urea) and (ranitidine HCl + glycerol) were -45, -91, -51 and -87 °C separately. The results show that the solubility and dissolution rate, release profile of these liquids enhanced and may increase the bioavailability.

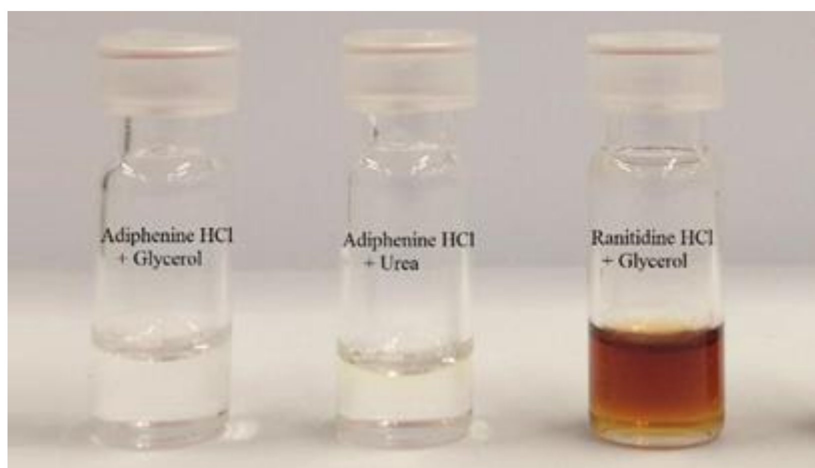


***Figure 2**: Pharmaceutically active ingredients as quaternary ammonium salts formulated into DESs in a 1 QAS: 2 HBD molar ratio.*

Fig. 3 shows that pure active ingredients (adiphenine HCl and ranitidine HCl) and the prepared PDESs from these ingredients were absorbed at the same wave length range without shifting. This indicates that pharmaceutical active ingredients kept their pharmacological effects in their new formulations.

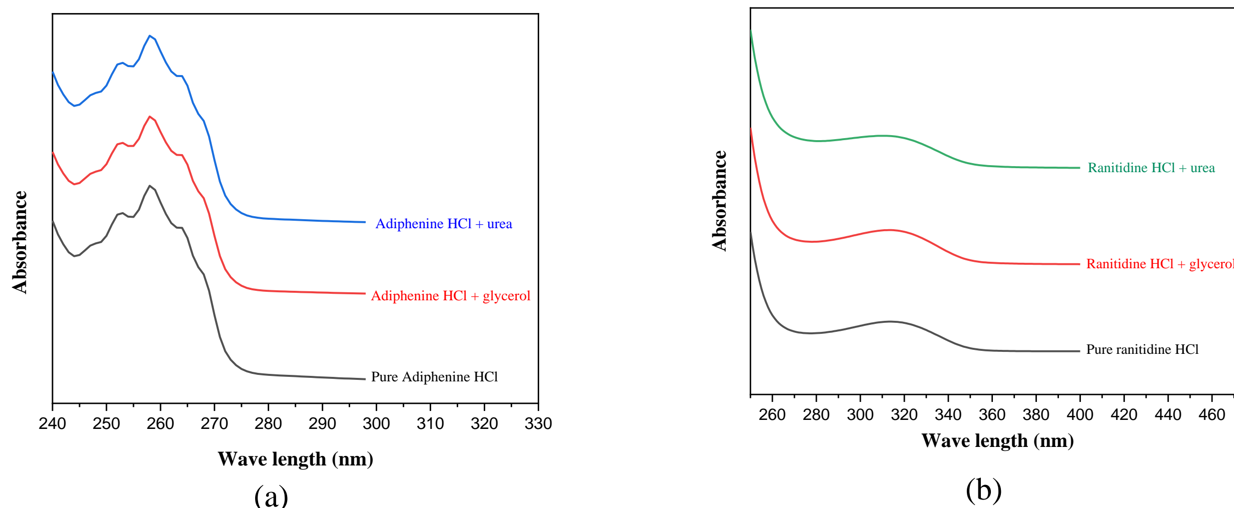


Figure 3*: Absorption spectra of (a) (Adiphenine HCl, Adiphenine HCl + glycerol and Adiphenine HCl + urea) in 0.1mol /L HCl and (b) (Ranitidine HCl, Ranitidine HCl + glycerol and Ranitidine HCl + urea) in 0.1mol /L HCl.*

3.2 Dissolution rate study

In this study, adiphenine HCl and ranitidine HCl were used as hydrogen bond acceptors with urea and glycerol as hydrogen bond donors to form PDESs. The increase in dissolution rate was achieved for the produced PDESs. For example, ranitidine HCl is a polymorphic drug in the form of solid state which its dissolution rate unstable. Thus, PDES from ranitidine HCl: urea and ranitidine HCl: glycerol achieved higher dissolution rates than pure ranitidine HCl as shown in **Fig. 4**.

Aliquots of the HCl solution were used as a function of time and the PDES concentration in solution was measured using UV-Vis spectroscopy using the calibration curves demonstrated above.

PDESs such as (adiphenine HCl + urea), (adiphenine HCl + glycerol), (ranitidine HCl + urea) and (ranitidine HCl + glycerol) performed to be faster dissolution rates than pure adiphenine HCl and ranitidine HCl respectively**. Fig. 4** shows the summaries of their release rate are demonstrated as the percentage of the pure drug as a function of time. It should be mentioned that these experiments were conducted with very slow magnetic stirring which is why the PDESs are not immediately miscible.

It was shown that the dissolution rates of adiphenine HCl and ranitidine HCl at their eutectic preparations: (adiphenine HCl + urea), (adiphenine HCl + glycerol), (ranitidine HCl + urea) and (ranitidine HCl + glycerol) were 2.0, 2.5, 2.3 and 2.6 times faster than their pure drugs respectively.

Touitou *et al*. and Kasting *et al* (Stott et al., 1998) displayed that the solubility of drugs depends on their melting points. They showed that the solubility and transdermal permeation increases by reducing the melting point of a drug molecule. Thus, eutectic formation can be applied as a process to reduce the melting point of PAIs with keeping their pharmaceutical activity (Stott et al., 1998). This section can be concluded that the decrease of melting point causes to increase dissolution rate, solubility and hence increase the bioavailability.

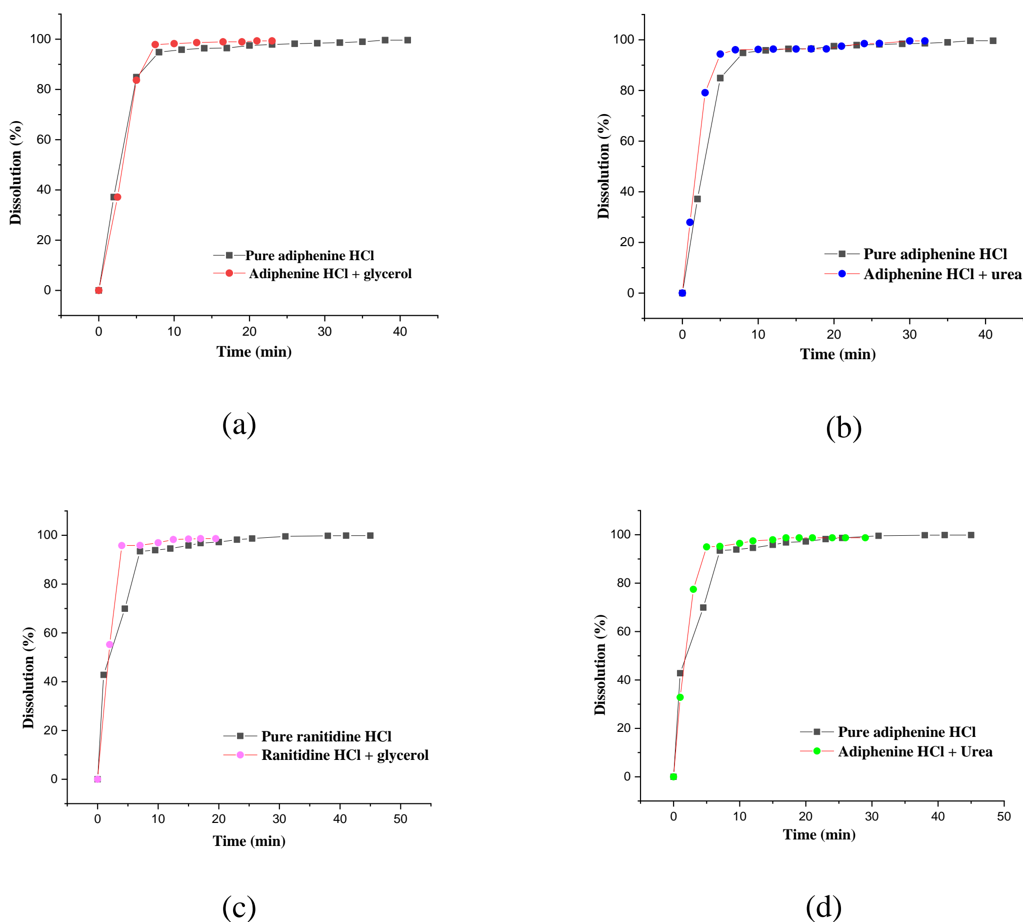


***Figure 4**: a) Adiphenine HCl + glycerol (0.1223 g) in 0.1mol /L HCl at 37 ± 0.5°C, b) Adiphenine HCl + urea (0.1063 g) in 0.1mol /L HCl at 37 ± 0.5°C , C) (ranitidine HCl + glycerol (0.0677g) in 0.1mol/L HCl at 37 ± 0.5°C and d) (ranitidine HCl + urea (0.0596g) in 0.1mol/L HCl at 37 ± 0.5°C.*

3.3 Fourier-transform infrared spectroscopy (FT-IR)

In the present work Fourier-transform infrared was used as a potent method to obtain data of hydrogen bonding. Hydrogen bonding has a significant effect on the OH stretching vibration in HBDs (Hou et al., 2015). **Fig. 5** shows FT-IR spectra of glycerol and PDES formed by glycerol and ranitidine HCl. The OH stretching vibration of pure glycerol was observed at 3299 cm^{-1} which shifted to 3257 cm^{-1} in the PDES produced by glycerol and ranitidine HCl. The FT-IR spectra of the HBDs in the PDESs indicate that the shift in vibrational state happened because a portion of the cloud of electrons of the oxygen atom transfers to the hydrogen bonding, decreasing the force constant (Hou et al., 2015 and Aissaoui et al., 2015).

Hence, the shift of the OH stretching vibration proposes the present of hydrogen bond between glycerol as the HBD and ranitidine HCl as the HBA, when the PDESs were formed. In addition, the FT-IR spectra showed broader peaks for the produced PDESs because of the existence of hydrogen bonding.

Furthermore, FT-IR was also used to further study the interaction between ranitidine HCl and urea, and identify the structure of ranitidine HCl – urea mixtures. The FT-IR spectra of solid urea and the eutectic mixture ranitidine HCl – urea were conducted at room temperature. Compared with individual components, it demonstrated that the absorption band at 3429 cm^{-1} in urea was shifted to 3334 cm^{-1} in ranitidine HCl – urea as shown in **Fig. 6**.

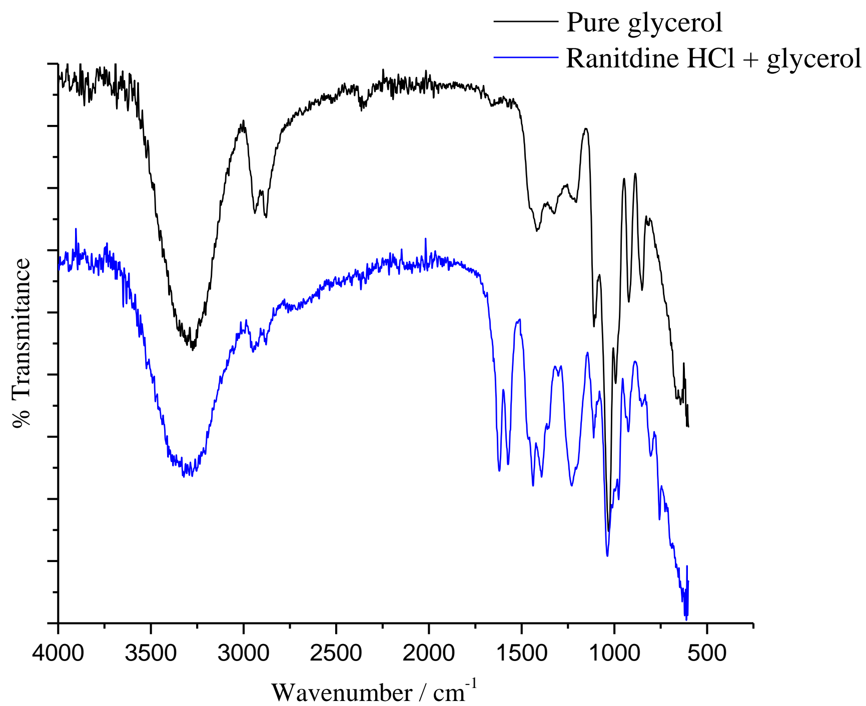


***Figure 5**: FT-IR spectrum of pure glycerol and (ranitidine hydrochloride + glycerol) with molar ratio (1:2).*

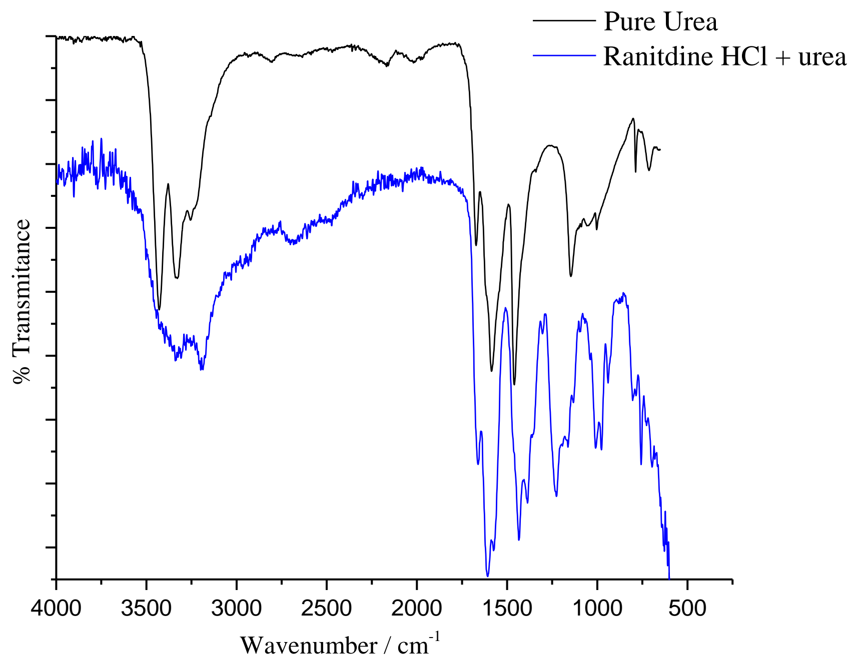


***Figure 6**: FT-IR spectrum of pure urea and (ranitidine hydrochloride + urea) with molar ratio (1:2).*

Hence, the shift of the NH stretching vibration proposes the present of hydrogen bond between urea as the HBD and ranitidine HCl as the HBA, when the PDESs were formed. Moreover, the FT-IR spectra showed broader peaks for the produced PDESs because of the presence of hydrogen bonding.
This in agreement with the study described by Hua Wang *et al* (Zeng et al., 2016) for a formation of DES between urea as the HBD and betaine. In addition, the present study is in agreement with the observation recorded by Aissaoui *et al* (Aissaoui et al., 2015) for DESs prepared by mixing triethylenglycol, diethylenglycol, ethylenglycol and glycerol as HBDs with methyltriphenylphosphonium bromide as a salt. **Table 2** shows the shift of the OH and NH stretching vibrations of (glycerol and urea) and the produced PDESs from these HBDs.

Table 2: The shift of OH and NH stretching vibration of the HBDs.

HBDs	QASs	HBDs: QASs	Wavenumber (cm^{-1}) of pure HBDs	Wavenumber (cm^{-1}) of HBDs + QASs
Glycerol	Ranitidine HCl	2:1	3299	3257
Glycerol	Adiphenine HCl	2:1	3299	3271
Urea	Ranitidine HCl	2:1	3429	3334
Urea	Adiphenine HCl	2:1	3429	3297

4. Conclusion

This research has shown that pharmaceutical active ingredients can be formulated into liquids as PDESs. These active ingredients were known to show polymorphism in the crystalline form. The main point to note is that the PDESs were used as a design strategy to change solid drugs into liquids, which should overcome these issues associated with solid drugs, such as polymorphism, bioavailability and solubility. The compounds selected were adiphenine HCl and ranitidine HCl and the hydrogen bond donors were glycerol and urea. The prepared PDESs have glass transition temperatures which were measured by DSC. In addition, FT-IR was used for the formed PDESs to compare the components with their products via hydrogen bonding. One of the most interesting aspects in this research is the study of the dissolution rate of PDESs. The purpose of this was to improve the dissolution rates and solubilities of adiphenine HCl and ranitidine HCl via PDESs. PDESs based on urea or glycerol mixed with these APIs, were prepared and characterized for dissolution rates and solubilities. The results obtained show higher dissolution rates of the APIs when in the form of PDESs. The increase in dissolution rate was mainly obvious for ranitidine HCl: glycerol. Thus, PDES can be encouraging for increasing dissolution rate and solubility of poorly soluble drugs.

This research has recommended not only that solid drugs can be changed into liquids and increase their dissolution rates, but the capability to formulate the PDES into a gelatin tablet will be studied as well. In addition to that the delivery of drugs from patches by using PDESs can be studied.

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