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Factors governing the formation of THEDESs: A case study with propionic acid NSAIDs and lidocaine

Magdy M. Abdelquader[a,b], Shu Li[a], Gavin P. Andrews[a], David S. Jones[a]*

[a]Pharmaceutical Engineering Group, School of Pharmacy, Queen's University Belfast, 97 Lisburn Road, Belfast BT9 7BL, UK. [b]Pharmaceutical Technology Department, Faculty of Pharmacy, Tanta University, Tanat, Egypt.

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*Corresponding author.
Tel.: +44 (0)28 9097 2011
+44 (0)28 9097 5220
E-mail: D.Jones@qub.ac.uk

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SUMMARY

Deep eutectic solvents (DES) are liquids resulting from melting point depression due to interaction between solid parent compounds. This was exploited to improve drugs' performance by including therapeutically active material (THEDES). DES physicochemical characteristics are affected by those of the parent compounds. To investigate such relation a comparison between THEDES of structural analogues (ibuprofen or ketoprofen) with lidocaine was done. Eutectic composition for both products was similar, indicating the importance of supramolecular complementarity. Glass transition (T_g) of drugs had direct impact on T_g of the formed THEDES. Similarly, the degree of charge involvement was related to drugs' pK_a. Moreover, number of attachment sites affected bonding strength which reflected in in viscosity and thermal stability. Such findings can help in tailoring THEDES formation for specific outcome.

INTRODUCTION

Deep eutectic solvents (DES) are liquids at ambient temperature that result from extensive hydrogen bonding (HB) interactions between solid HB acceptor and HB donor. Charge assisted HB which is a partial proton transfer, chracterized by presence of both COO^- and COOH strecthes in the FTIR spectrum may also be involved. Such extensive network of interactions is responsible for the profound melting point depression (Wang et al., 2014). Exploiting this phenomenon to improve biopharmaceutical behaviour of led to the emergence of the therapeutic DES (THEDES) subcategory, where at least one of the parent compounds is therapeutically active. Currently, THEDES formation is highly depending on trial-and-error despite presence of some valid computerized modelling techniques. However, both approaches are unable to anticipate the physicochemical characters of the product from those of parent materials (Wolbert et al., 2019). To achieve that, we investigated the effect of subtle differences between propionic acid NSAIDs (ibuprofen and ketoprofen) serving as HB donors, when coupled separately with the HB acceptor lidocaine, on the properties of the formed THEDES.

MATERIALS AND METHODS

Lidocaine was purchased from (TCI chemicals, Japan). Ibuprofen and ketoprofen were acquired from (Kemprotec Ltd., UK).

Heating method was adopted. Lidocaine and ibuprofen or ketoprofen were mixed at different molar ratios then heated on a hot plate at 100 °C for 60 minutes. DSC (Netzsch, Germany) was used at a heating rate of 10 °C/min and a cooling rate of 50

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°C/min within the range of -70 to 110 °C, to construct solid-liquid equilibrium (SLE) phase diagrams. In addition to investigations using FTIR (Perkin Elmer, UK) at 4 cm^{-1} resolution and 32 run repetition, TGA (TA, UK) at a heating rate of 20 °C/min, and AR 2000 rheometer (TA, UK) applying 1 - 500 Pa shear stress.

RESULTS AND DISCUSSION

Both ibuprofen and ketoprofen were able to form THEDES with lidocaine between molar ratios of 3:1 to 1:2, as seen from Fig.1, despite their significant difference in MP (~20 °C). Since these drugs are structural analogues, this suggests the important contribution of supramolecular interactions in determination of the eutectic composition, opposed to a single reliance on parent compounds' MPs as proposed by Wolbert et al. (Wolbert et al., 2019). On the other hand, glass transition (T_g) of the formed THEDES was highly dependent on the parent compounds' T_g. Ketoprofen THEDES exhibited higher T_g compared to ibuprofen THEDES because of innate high T_g of ketoprofen. Gordon-Taylor theory can explain such behaviour (Jensen et al., 2016).

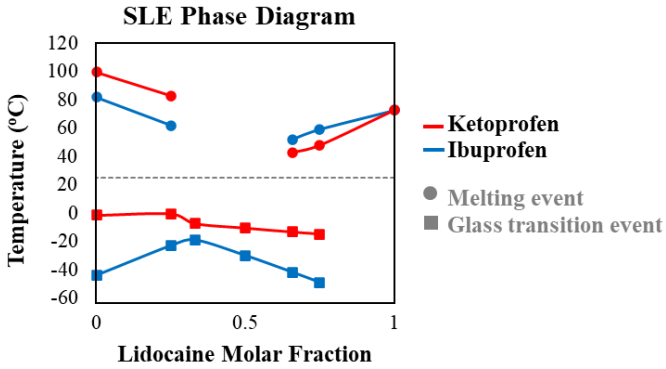

Fig. 1. *SLE phase diagram of formed THEDESs.*

FTIR data showed different patterns of HB and charge assisted interactions within both THEDESs. As shown in Fig.2., COOH/COO^- region revealed higher intensity of charge assisted interactions within ketoprofen THEDES network comapred to ibuprofen network which can be attributed to higher acidity of ketoprofen (Wang et al., 2014).

Moreover, HB network strength was higher in the case of ketoprofen THEDES due to the extra attachment site in ketoprofen structure. This was manifested as higher viscosity and thermal stability in the case of ketoprofen THEDES, as seen from Table 1.

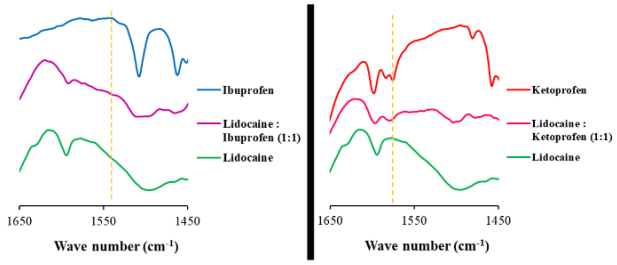

Fig. 2. *FTIR spectra of COOH/COO^- stretch region.*

Thermal stability was expressed as % weight protected at 250 °C, compared to untreated drugs.

Table 1. *Hydrogen bonding related properties*

Material	Viscosity (Pa.S)	% Weight protected[a]
Lido. : Keto. THEDES (1:1)	1.81 (0.08)	62.7
Lido. : Ibup. THEDES (1:1)	0.367 (0.05)	39.4

[a]by subtraction of actual weight loss from expected weight loss. Values between brackets are standard deviation of three replicates.

CONCLUSIONS

Both NSAIDs formed THEDES with lidocaine within the same molar region despite melting point differences. Drugs' T_g, pK_a and attachment sites were affecting the products' physicochemical characters. Such findings can help in establishing structural based approach for THEDES formation.

ACKNOWLEDGEMENTS

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