Ionic Liquids: A novel green approach to the development of anti-inflammatory drugs

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Background

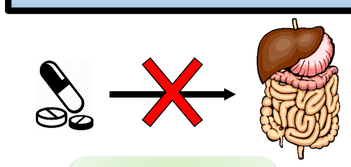
- Pharmaceuticals play a fundamental role in the medical sector, in boosting the quality of life and in increasing life expectancy. The active pharmaceutical ingredients (APIs) of many medicines are commercialized in different dosage forms, however the crystalline form is generally the preferred option [1].

Current Therapeutic Agents

Low water solubility → Poorly dissolved → Compromised absorption into gastrointestinal tract (GIT) [2].

Current Strategies to Increase Solubility

Need large quantities of organic solvents → Health and Environmental concerns



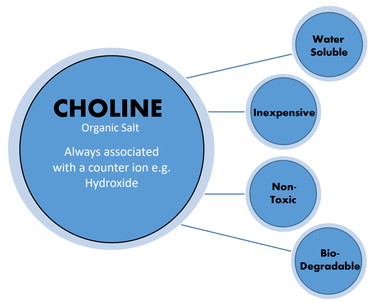
POOR ABSORPTION ↓ INEFFECTIVE THERAPEUTIC EFFICACY

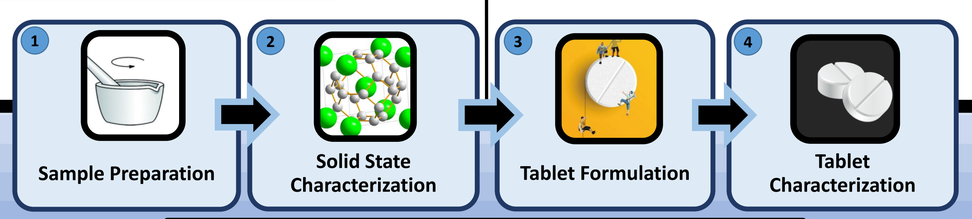
Need for smart medicine approaches to ↑ **bioavailability**
Methods used must be **sustainable and environmentally friendly**

- One novel approach to increase the efficacy of poorly soluble drug molecules is to combine them with another harmless compound (the excipient), in a **solvent-free, environmentally friendly** manner. This forms a sticky liquid known as an **ionic liquid (IL)** [3].
- This process was carried out on the acidic anti-inflammatory molecules **ibuprofen, ketoprofen and naproxen** and a choline compound functioned as the second component**.**

Ionic Liquids

More soluble → Greater absorption → Sustainable approach to **increasing the performance** while simultaneously **reducing their environmental impact** [4].



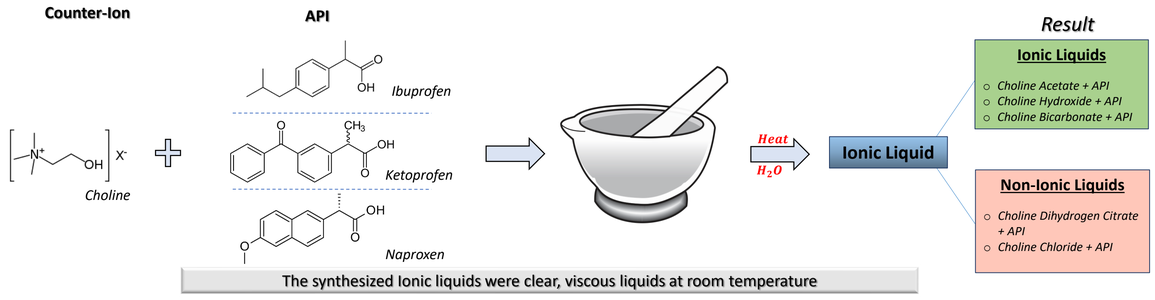


Methodology & Results

1. Sample Preparation

Liquid Assisted Grinding

A sustainable **solvent-free mechanochemical technique** based upon the mechanical grinding of API + a sticky counterion to form a substance.



The synthesized Ionic liquids were clear, viscous liquids at room temperature

2. Solid State Characterisation

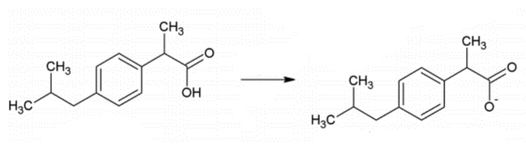
A. Infrared Spectroscopy (IR) – KBr disc

IR spectroscopy provides an in-depth analysis of the **chemical profile** of the samples and allows for identification of ionisation.

- The IR spectrum data of the synthesized compounds were compared to the starting APIs to determine the conversion to ionic liquids.
- The presence of carboxylate anions provided evidence of de-protonation, proving conversion to an IL.
- The disappearance of the absorption band characteristic of C=O stretching of the carboxyl in ibuprofen can be seen in Table 1. and Fig. 1. The spectrum for Ibuprofen + Choline OH contains two new peaks distinctive of **COO^- asymmetric stretching** and **COO- symmetric stretching**.

Compound	Assignment	Wave number (cm^{-1})
Ibuprofen	-COOH	1720
Ibuprofen + Choline Cl	-COOH	1721
Ibuprofen + Choline OH	-COO^- ***asymmetrical*** stretching	1574
Ibuprofen + Choline OH	-COO^- ***symmetrical*** stretching	1388

Table 1. IR absorption bands and characteristic vibrations



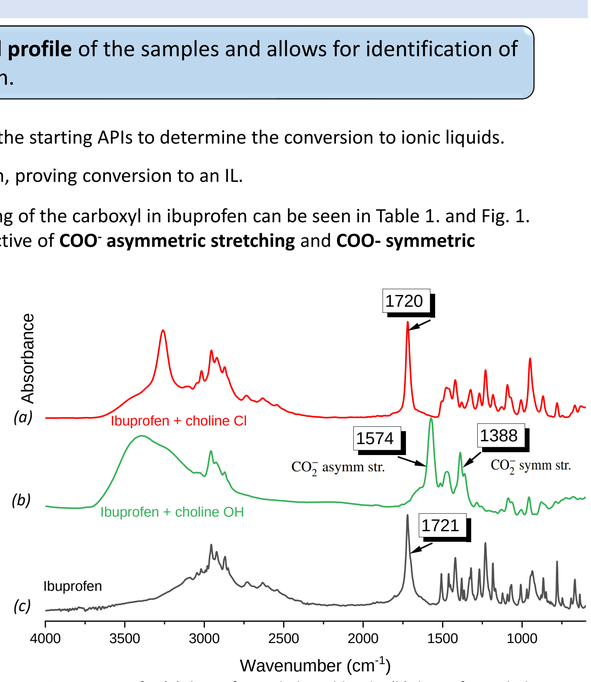
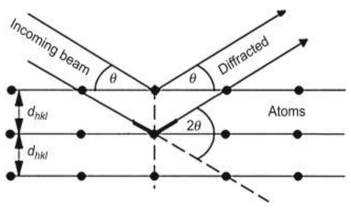


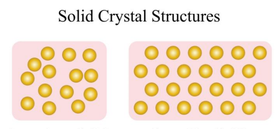
Fig. 1. IR spectra for (a) Ibuprofen + Choline chloride, (b) Ibuprofen + Choline hydroxide and (c) Ibuprofen.

B. Powder X-Ray Diffraction (PXRD)

PXRD is used to assess **the solid state crystallinity** of materials i.e. whether they are crystalline or non-crystalline. It utilizes X-ray scattering to elucidate the crystal structure (Fig. X)

- The **Ketoprofen + Choline Hydroxide** and **Naproxen + Choline Hydroxide** physical mixtures revealed the presence of **crystalline substances** with peaks not corresponding to both Ketoprofen and Naproxen starting materials (Fig. 2).
- Ibuprofen depicted characteristic crystalline sharp diffraction peaks. In comparison the synthesized **Ibuprofen + Choline Hydroxide** IL depicted an irregular broad hump, lacking sharp diffraction.





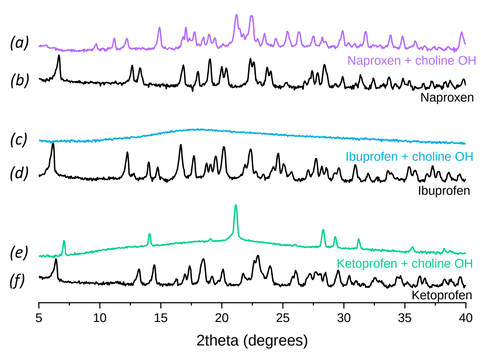
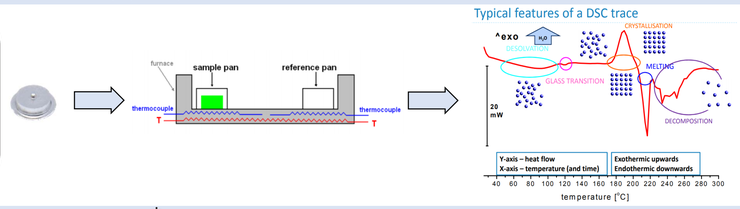


Fig. 2. PXRD patterns of (a) Naproxen + Choline hydroxide, (b) Ibuprofen + Choline hydroxide, (c) Ketoprofen + Choline hydroxide, (d) Naproxen, (e) Ibuprofen and (f) Ketoprofen

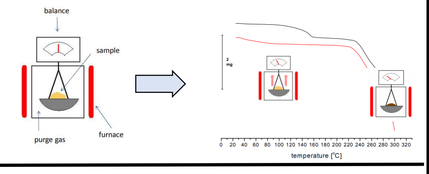
C. Thermal Analysis: Differential Scanning Calorimetry (DSC)

DSC is a fundamental tool in **thermal analysis** which generates information used to understand the crystalline/ amorphous behaviour and polymorphic/ eutectic transitions



D. Thermal Analysis: Thermogravimetric Analysis (TGA)

TGA is a technique used to determine the **moisture content and assess the thermal stability** of a material. It centres on monitoring the weight change of the substance over time whilst the temperature changes.



3. Tablet Formulation

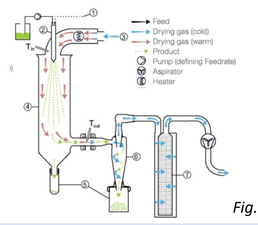
A. Spray Drying (Co-processing technique)

Spray drying is a method of **producing a dry powder from a liquid** through rapidly drying liquid droplets while suspended in a drying gas chamber

- Varying amounts of naproxen and ketoprofen choline acetate IL's mixed with **TRICAFOS** (TRI-CALCIUM phosphate) made up the feeding liquid.

TRICAFOS
- spherical
- good flowability

→ suitable for **direct compression**



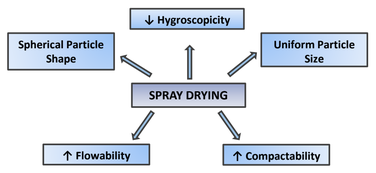
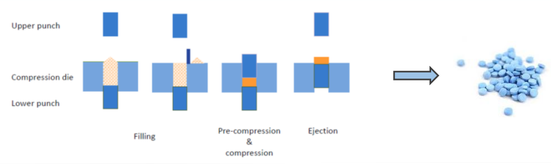


Fig. 3. Spray drying process

B. Hydraulic Tablet Press

- Powders containing a loading of **5% TRICAFOS and 3% ketoprofen** or **naproxen** were compressed into tablets.
- **Pressures used**: 25 MPa, 50 Mpa, 100 Mpa.



4. Tablet Characterisation

A. Hardness Test

- Tablets formed from compression at 25 MPa, 50 MPa and 100 MPa were subjected to the hardness test to determine the **breaking point** and **structural integrity**
- As the compression force increases, the powder is more densely packed. The magnitude of compression force impacts the tablet hardness, depicting a general trend of increased hardness with increased compression pressure.

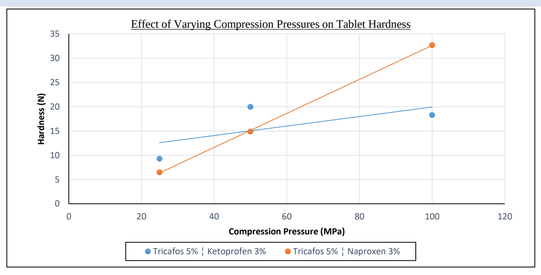


Fig. 4. Relationship between tablet hardness and increasing compression pressure for tablets containing 5% TRICAFOS and 3% ketoprofen or naproxen.

B. Dissolution Studies

Dissolution studies evaluate the ability of the drug to dissolve in specific conditions and **predicts *in vivo* performance.** The dissolution medium used mimicked the acidic environment of the stomach**.**

- Formulations of ketoprofen and naproxen using choline hydroxide showed different release profiles to the commercial products (Keral 25mg, Naprosyn EC 250mg).
- The commercial products disintegrated and released very quickly. In comparison, the ketoprofen choline hydroxide based tablet follows an almost zero-order release profile for approximately 30 minutes. The tablet did not disintegrate, but dissolved and had a slower release as a result. Naproxen is similar to ketoprofen however it lags initially in its release and subsequently is nearly linear from 10-30 minutes.

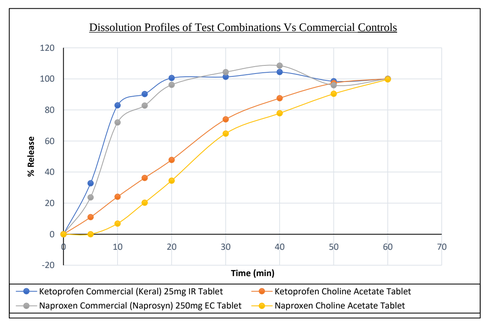


Fig. 5. Dissolution profiles for Choline Acetate Ketoprofen and Naproxen tablets compared to commercial Keral (25mg) and Naprosyn EC (250mg) in 900mL 0.1M HCl at 37°C and 50 rpm for 60 minutes.

Conclusions

- Anti-inflammatory choline-based combinations of ketoprofen or naproxen with choline hydroxide demonstrated a slower release profile than traditional formulations.
- The Naproxen/IL dissolution profile showed a short lag phase of approximately 10 minutes compared to ketoprofen/IL. This is of potential interest in relation to prolonged release formulations.
- The results demonstrate the potential for the use of ionic liquids in the design of drug formulations due to the altered chemical characteristics of APIs.
- Future studies could address how release profiles of the formulated tablets could be altered by the addition of excipients, resulting in profiles which achieve immediate release or controlled release.
- **There exists the potential for positive impact on drug bioavailability and ultimately on drug efficacy whilst simultaneously advancing the principles of Green Chemistry.**

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Acknowledgements

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