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Supercritical CO_2: a 'green' route for the encapsulation of drugs

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INTRODUCTION

Supercritical Carbon-dioxide (CO_2) is fast becoming an important commercial and industrial solvent of choice, largely due to its solvating efficiency and low environmental impact. In many instances, supercritical CO_2 can replace the use of hazardous solvents as well as limit the use of precious water resources. Due to its "green" characteristics, much research has focused on using supercritical CO_2 as solvent for the preparation of pharmaceutical and food products. At the Council for Scientific and Industrial Research (CSIR), we have already developed and patented an encapsulation method using supercritical CO_2 and we are currently investigating the development of a novel transdermal drug delivery system using this technology to further strengthen our expertise in this field.

SUPERCRITICAL CO_2 – AN OVERVIEW

When CO_2 is raised above its critical pressure of 73.8 bar and critical temperature of 31.1 °C, it becomes supercritical (**Figure 1**). In the supercritical phase, CO_2 possesses a unique combination of properties: it has the density of a liquid, giving it solvating characteristics similar to liquid solvents, yet it has a gas-like viscosity, imparting on it favourable mass transfer properties. The density of supercritical CO_2 can also be easily "tuned" by small changes in pressure which means that its solvent power can be altered without changing its molecular structure1.

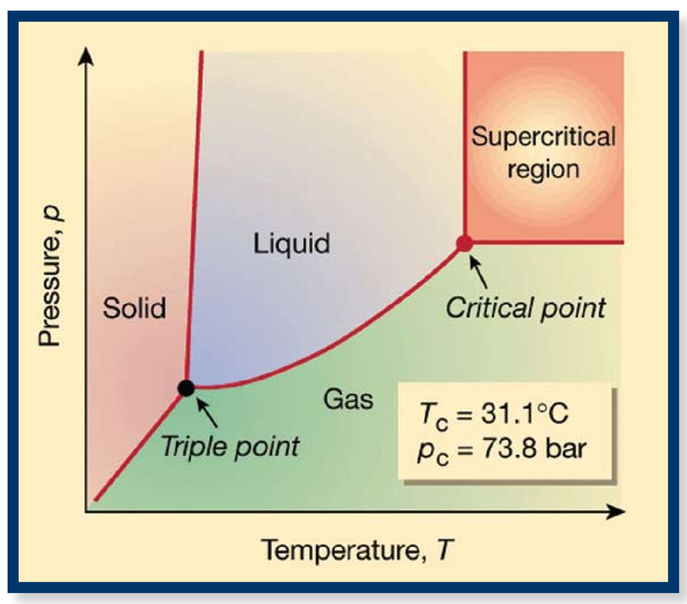


Figure 1: Phase diagram of carbon dioxide

Supercritical CO_2 possesses a low degree of polarity which allows low molecular weight non-polar and some polar substances to be dissolved in supercritical CO_2, while higher molecular weight substances such as polymers can be plasticised and processed at temperatures well below their melting points. Specific interest in CO_2 as replacement for conventional solvents is increased by its perceived "green" properties: it is non-flammable, non-toxic, recyclable and relatively inert. In addition, the difficulties posed with residual solvent are eliminated since CO_2 is gaseous at ambient conditions and can thus be removed from the product completely[2].

These favourable characteristics have led to a number of applications in which supercritical CO_2 is used as processing medium. For instance, small molecules such as caffeine, essential oils, antioxidants, omega-3 fats and spices can be extracted[3]. Solubility of CO_2 in various polymers allows for impregnation with small molecules, such as dyes and antioxidants, as well as preparing polymer foams at temperatures well below the melting temperature of the polymer[4]. The pharmaceutical industry benefits the most from supercritical CO_2 technology as non-toxicity, low temperatures and the absence of residual solvents are important requirements. As a result, supercritical CO_2 is used successfully in many pharmaceutical processes such as: drug micronisation and microencapsulation, as well as for the preparation of tissue-engineering scaffolds[5].

Supercritical CO_2 is a unique class of solvent and offers many advantages over conventional solvents, which is supported by extensive research and increasing incorporation in many industrial processes.

SUPERCRITICAL CO_2 TECHNOLOGY AT THE CSIR

Early in 2003, the CSIR embarked on a project to encapsulate probiotics as a means of enhancing its shelf-life and improving its survival rates during consumption. Due to the sensitivity of probiotics to heat and conventional solvents, the use of supercritical CO_2 as process medium was explored for the first time. By applying a CSIR-patented encapsulation technology inside a supercritical CO_2 reactor (**Figure 2**), it was possible to encapsulate probiotics without loss of activity. In addition, encapsulation successfully enhanced both shelf-life and gastric transit survival rates of the probiotics to commercially acceptable levels[6].

Figure 2: Supercritical CO_2 reactor

The CSIR is currently exploring using supercritical CO_2 technology for the preparation of a transdermal drug delivery system. In transdermal delivery, a drug is delivered through the skin into the systemic circulation and to the target organs via a drug-loaded adhesive patch. A unique transdermal delivery system is formed when two polymers – polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) – interact through hydrogen bonding. This interaction results in a high free-volume polymer network structure (**Figure 3**), which has properties unlike the individual polymers, such as elasticity and high tackiness. However, such a structure is traditionally prepared in aqueous or organic media, which limits the use of certain drugs and requires energy intensive drying processes or prolonged periods for removal of toxic solvent.

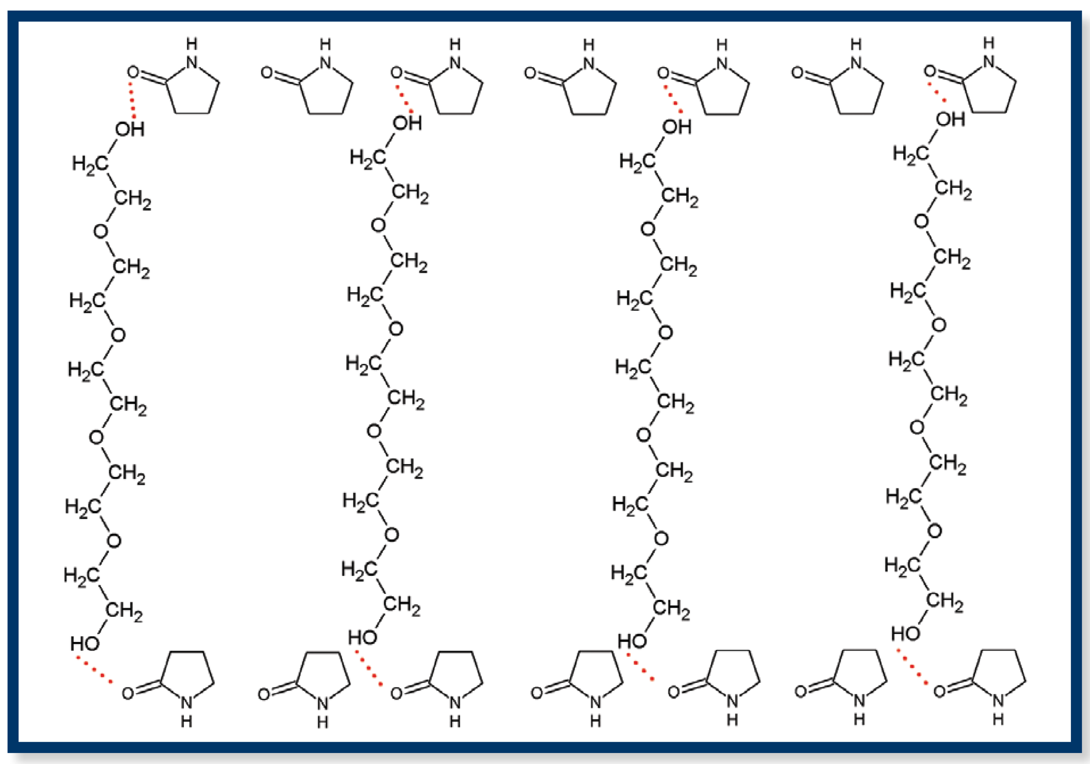


Figure 3: Structure of the interpolymer complex between polyethylene glycol and polyvinylpyrrolidone

In our work, we initially did a comparative study on the degree of homogeneity and hydrogen-bond interaction in blends of PEG and PVP prepared in supercritical CO_2, ethanol and as physical mixtures. We showed that, due to CO_2 providing improved mass transport properties (induced through viscosity reduction and swelling), interdiffusion of PEG and PVP was enhanced in supercritical CO_2, which resulted in homogenous blends. Upon CO_2 venting, PEG-PVP hydrogen-bond interactions were initiated. Thus, with supercritical CO_2 technology, it was possible to form PEG-PVP polymer networks in rapid time without the use of high temperatures or toxic solvents.

Following up on the above work, mixtures of PEG-PVP loaded with ibuprofen (a non-steroidal anti-inflammatory drug often used in transdermal delivery for treatment of rheumatoid arthritis and osteoarthritis) were prepared. One of the requirements for effective transdermal delivery is that the drug is molecularly dispersed within the polymer matrix, as a crystalline drug in the polymer matrix would lead to poor transdermal diffusion.

Supercritical CO_2 is able to dissolve ibuprofen due to its small size and favourable interaction between CO_2 molecules and the carbonyl groups of ibuprofen (**Figure 4**). This results in the break-up of ibuprofen-ibuprofen interactions. The enhanced transport properties provided by supercritical CO_2, allow the ibuprofen molecules to be dispersed within the polymer blend and eventually bind to the polymer chains via hydrogen bond interactions with the polar sites of the polymers (**Figure 5**). By reducing CO_2 pressure to atmospheric values, a PEG-PVP transdermal delivery system containing molecularly dispersed ibuprofen, is formed.

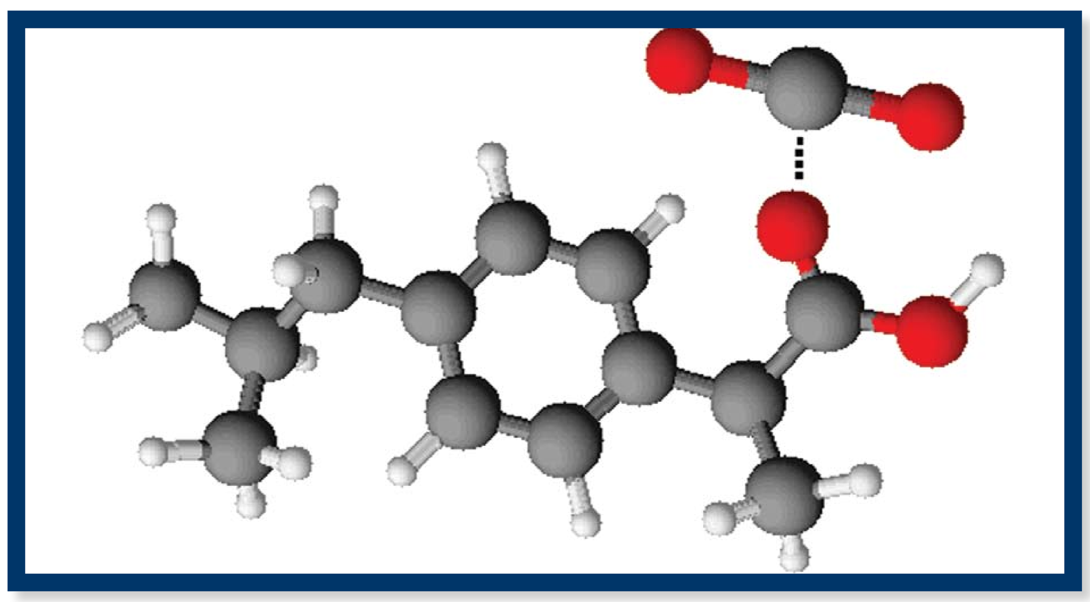


Figure 4: Interaction between a CO_2 molecule and ibuprofen

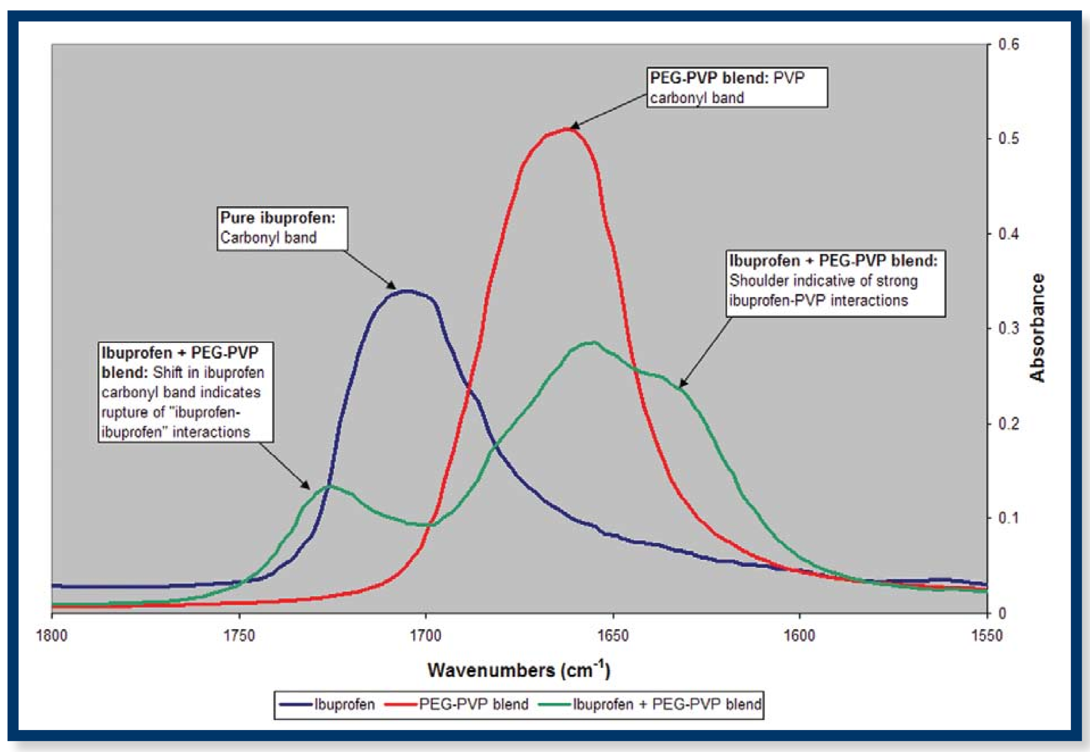
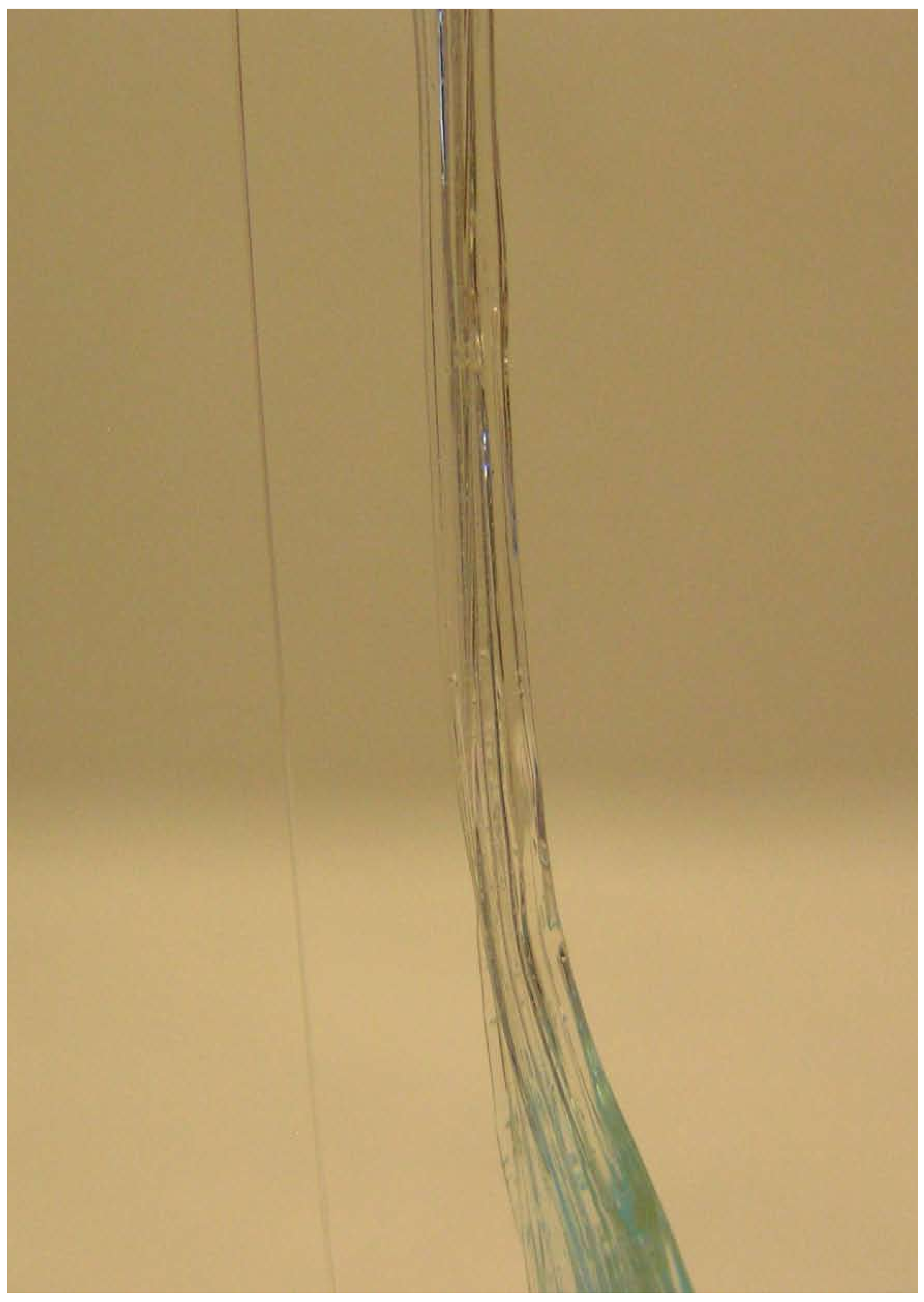


Figure 5: Infra-red spectra showing ibuprofen interaction with the carbonyl group of polyvinylpyrrolidone

The CSIR is developing drug delivery systems using supercritical CO_2 as solvent – a non-polluting, non-toxic and non-flammable alternative to conventional solvents.



CONCLUSIONS

- The use of supercritical CO_2 as "green" solvent is showing rapid growth internationally;
- Supercritical CO_2 technology is particularly useful in the food and pharmaceutical industries;
- The CSIR has already successfully encapsulated sensitive actives using supercritical CO_2 as process medium; and
- With supercritical CO_2 as solvent, transdermal drug delivery systems can be prepared in rapid time without the use of toxic solvents or elevated drying temperatures.

ACKNOWLEDGEMENT

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