M1130-07-050

Do all solid hydrophilic carriers enhance dissolution rates? An investigation into the relationship between solid hydrophilic carriers and their effect on dissolution rates

Diego Lucero-Borja[1], Xavier Subirats[1], Elisabet Fuguet[1], Clara Ràfols[1], Andrew Kennedy[2], Samuel Lee[2], Breeze Outhwaite[2], Konstantin Tsinman[2], Rebeca Ruiz[2]

[1]Institute of Biomedicine (IBUB) and Department of Chemical Engineering and Analytical Chemistry, University of Barcelona, Martí i Franquès 1-11, 08028 Barcelona, Spain. [2]Pion Inc., Forest Row, East Sussex, UK

aaps PharmSci 360
ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

Solubility is a key consideration when developing a formulation of an API, as poor solubility will limit the quantity of drug in solution available to partition across the GI tract membrane, resulting in decreased bioavailability. Solubility enhancing excipients are a key tool when developing low solubility (BCS class II and IV) drug discovery compounds into clinically effective formulations.

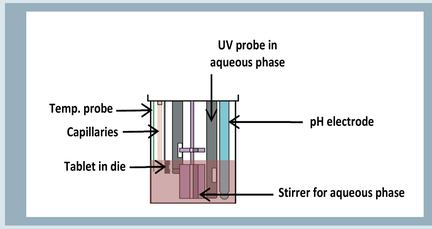
This study investigated the effect of hydrophilic water soluble carriers on the dissolution rates of physical mixtures of active pharmaceutical ingredients (APIs). Commonly used cyclodextrin (Cavasol) and povidone (Kollidon K17) solubility enhancers were included in this research. Anti-inflammatory (isoxicam, piroxicam) and antihypertensive (bendroflumethiazide) acidic drugs were selected as model compounds.

METHOD

Pure API and solid solubility enhancers were mixed using a pestle and mortar for 3 minutes. A variety of API-excipient mixtures containing 0%, 25%, 50% and 75% excipient by weight were prepared into 3mm and 8mm tablets using a tablet press at a pressure of 100kg for 3 minutes. Only one tablet face is exposed to the dissolution medium.

The dissolution behaviour was studied using a Pion inForm and a Sirius GLpKa equipped with in situ UV fibre-optic spectroscopy probes to quantitate the amount of API dissolved, using a previously determined pH dependent molar extinction coefficient for each API.

Dissolution was performed at two consecutive pH sectors, pH 2.0 and 5.8 or pH 2.0 and 6.5, to observe the dissolution behaviour under gastric pH, fed-state intestinal pH and fasted-state intestinal pH conditions.



Dissolution vial and probe set on Pion inForm instrument.

RESULTS

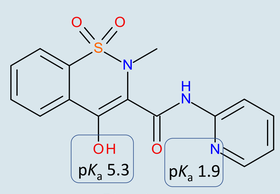
The dissolution behaviour of an 8 mm Isoxicam tablet was measured at 37 °C and compared with 8mm tablets containing 50 wt.% mixtures of Isoxicam-Cavasol and Isoxicam-Kollidon (Figure 1). Both excipients were observed to increase the dissolution rate of Isoxicam overall. The molecule is ionised at pH 5.8 which increases the rate of dissolution. The solubilising effect of the excipients is also exaggerated at pH 5.8.

In the case of Bendroflumethiazide (Figure 2) (8 mm tablet, 37 °C) dissolution is also enhanced in 50 wt.% mixtures with Cavasol and Kollidon K17. The molecule is neutral in both pH sectors and no pH dependence is observed.

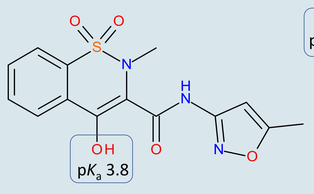
8 mm tablets of Piroxicam (Figure 3), 50 wt.% Cavasol and 50 wt.% Kollidon K17 were measured under pH 2.0 and 5.8. The Kollidon containing tablet exhibited a greater dissolution rate than Piroxicam alone and Piroxicam-Cavasol. The extent of dissolution of Piroxicam-Kollidon is exaggerated by tablet breakages occurring during the dissolution experiment, illustrated by the red circles on the profile. At the end of the experiment Piroxicam-Cavasol total mass released was lower than Piroxicam alone. The reduction in dissolution rate of Piroxicam with 50 wt.% of Cavasol in relation to pure API (Figure 3) might be attributed to a reduction in exposed surface area of Piroxicam. The higher the Cavasol content in the formulation, the lower amount of Piroxicam exposed to the dissolution media at the tablet surface.

The behaviour of Piroxicam-Cavasol at pH 5.8 (Figure 3) shows a different trend to the observation at pH 6.5 (Figure 4, 3 mm tablets of Piroxicam consisting of 100% API, then 25 wt.% and 50 wt.% enhancer), where Cavasol improves the dissolution of API. This could be attributed to differences in pH (as the pK_a of Piroxicam is 5.3, a greater portion of the API molecules present are ionised at pH 6.5) and the effect of temperature (25 or 37 °C) in the rate of dissolution.

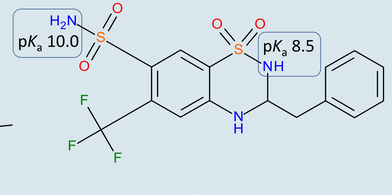
Isoxicam was prepared into 3 mm tablets with different wt.% of Kollidon K17 and dissolution rates were studied at pH 2.0 and 5.8 (Figure 5) or 6.5 (Figure 6). As the API is ionised at pH 5.8 and 6.5, little difference is observed in the enhanced solubilizing effect of 25 wt.% Kollidon. Disintegration of the tablet disc is again seen to have a large effect on the overall dissolution profile for the tablet of 75% excipient content, especially at pH 6.5.



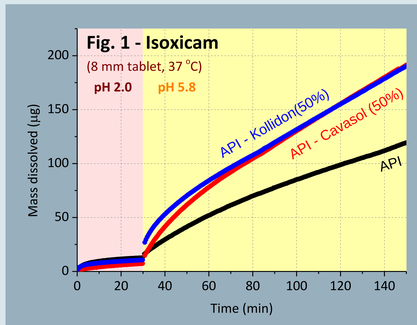
Piroxicam

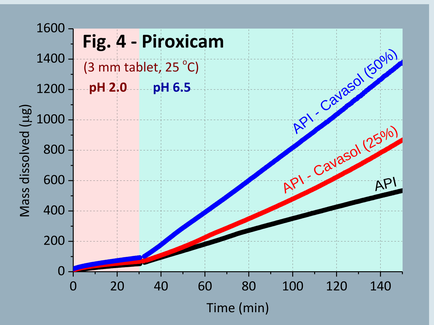


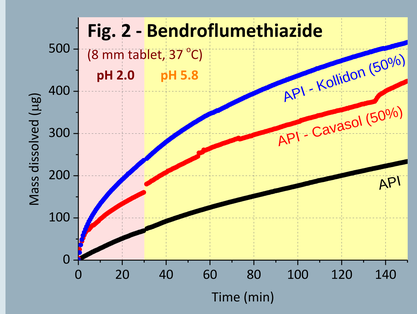
Isoxicam

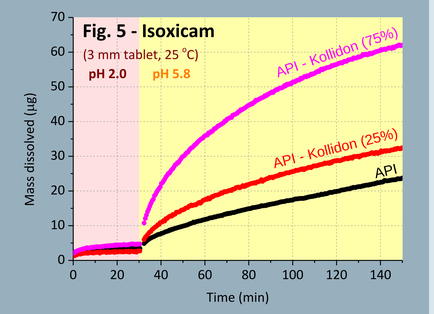


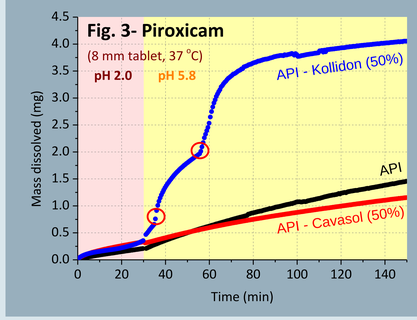
Bendroflumethiazide

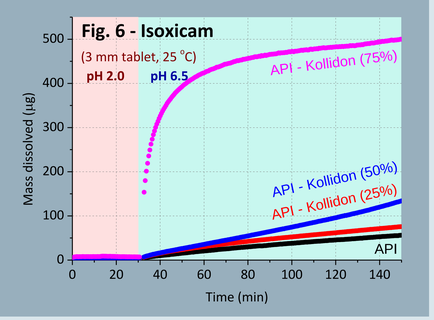












CONCLUSION

Significant effects on the extent and rate of dissolution are seen for all the tested APIs. The ionisation of Piroxicam and Isoxicam gives rise to a distinct improvement in the effectiveness of Cavasol and Kollidon as solubilizing excipients. This can be attributed to the increase in hydrophilicity associated with ionisation. The lack of a response to the pH change in the case of Bendroflumethiazide dissolution in hydrophilic excipients is a result of its weakly acidic nature. It is noted that the inclusion of excipient into pressed tablets of a controlled surface area may reduce the apparent dissolution rate of an API, given that increasing the wt.% of excipient reduces the amount of API exposed to the dissolution medium at the tablet surface. However, in most cases the improvement in dissolution rate with respect to increasing excipient mass appears to dominate.

REFERENCES

Gravestock, T. B., K. Comer, J. Frake, E. Judge, S. Ruiz, R. , *The "GI dissolution" method: a low volume, in vitro apparatus for assessing the dissolution/ precipitation behaviour of an active pharmaceutical ingredient under biorelevant conditions*. Anal. Methods 2011, 3, 560-567

Pion

UNIVERSITAT DE BARCELONA