Study of the Effect of Different Types of Hydrophilic Carriers on Benzthiazide to Understand the Enhancement on the Dissolution Rates

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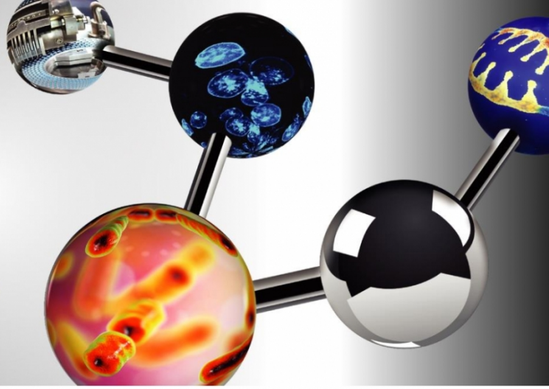
Diego Lucero-Borja[1], Xavier Subirats[1], Elisabet Fuguet[1], Clara Ràfols[1], Andrew Kennedy[2], Samuel Lee[2], Rebeca Ruiz[2]

[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

CONTACT INFORMATION: (Rebeca Ruiz) rruiz@pion-inc.com



PURPOSE

Dissolution testing is a valuable tool throughout the various stages of the drug development process, from the initial selection of phase I drug products, to guiding formulation design in later stages of drug development, and also in assessing post-approval changes to marketed products by providing an alternative to *in vivo* bioequivalence testing. Therefore, there is an ongoing need to develop increasingly discerning dissolution tests which can more effectively characterise the influence of excipient selection in formulations and better predict the *in vivo* performance of drug products.

In this study, a methodology for assessing the effects that different excipients have on the dissolution performance of drugs is presented. Benzthiazide [Bzt], an antihypertensive, was selected as a model compound to compare the effect of hydrophilic water soluble carriers on the dissolution rate. A selection of five commonly used solubility enhancers and inhibitors were included in this research, such as cyclodextrins (Cavasol [CAV], Captisol [CAP]), a copovidone (Plasdone S630 [S630]), a povidone (Kollidon-K17 [KOL]) and a hydroxypropylcellulose (Klucel-EF [KLU]).

METHOD(S)

Pure Bzt and solid solubility enhancers were mixed using a pestle and mortar for 3 minutes, at a weight ratio of 1:1 (w/w). Tablets of 3 mm diameter were prepared using a tablet press, under a force of 100 kgf for 2 minutes. The dissolution rates of the Bzt were studied in two aqueous media (Figure 2), including a mid-assay pH-transition: from pH 2.0 to pH 5.8 and from pH 2.0 to pH 6.5 to mimic the physiological conditions of the gastrointestinal tract; replicating the transition from gastric to fed-state, and gastric to fasted-state intestinal pH conditions, respectively.

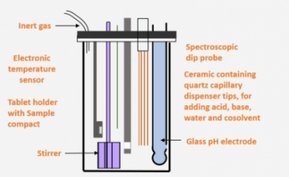


Figure 1: Measurement Cell

Moreover, Biorelevant Dissolution Media (BDM) was also tested by the inclusion of FeSSIF V2 at pH 5.8, and FaSSIF V2 at pH 6.5. A Sirius GLpKa-DPAS system and Pion inForm software (v. 1.5) were used to perform the dissolution rate measurements and calculations.

RESULT(S)

The dissolution profiles obtained for Bzt in the presence of the five studied excipients showed an increase in the dissolution rate (DR) and a notable distinction between the effects of each excipient, as well as an increase of the final concentration of the API in solution.

Aqueous media

It was observed that with the use of CAV (Figure 3A) at pH 2.0 a supersaturated system was created and an immediate drop in concentration is observed when the transition to pH 5.8 takes place. This supersaturation was not present with CAP (the other cyclodextrin) which showed a continued sample release similar to the profile of Bzt without excipient. The remaining excipients displayed jumps to higher concentrations upon pH transition. KLU and S630 showed similar profiles with similar final concentrations. The greatest concentration enhancement was observed with KOL.

Similar behaviour was observed for the transition from pH 2.0 – 6.5 (Figure 3B), however in this case CAV achieved a greater final concentration than KLU and S360. Since Bzt was more ionised at pH 6.5, the final concentration obtained in the profiles at pH 2.0 – 6.5 was slightly higher than those obtained at pH 2.0 – 5.8. The DRs obtained were generally lower in the second sector for all of the excipients with respect to the first sector. However, in the second sectors the differences between the DRs observed for each excipient were less distinct than they were at lower pH. The DRs results also indicated that relative to one another, the effect of the excipient on the dissolution performance of Bzt is vastly greater than the effect of the pH alone, and each excipient also responds to the pH-shift differently.

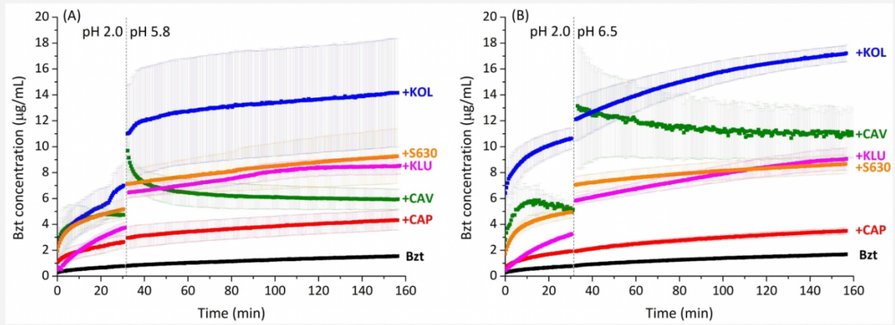


Figure 3 Dissolution profiles of Bzt. (A) pH 2.0 -pH 5.8, and (B) pH 2.0 - pH 6.5.

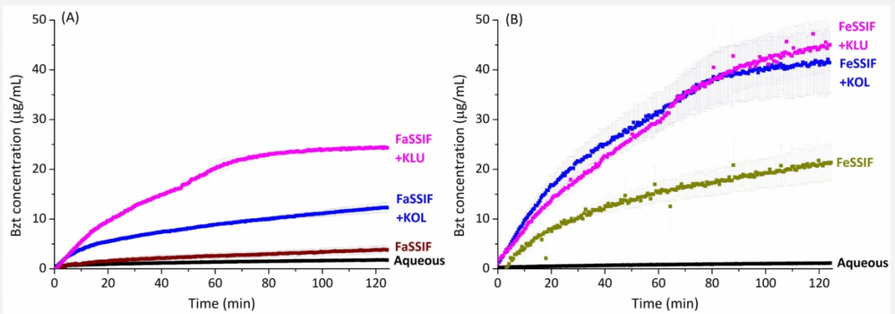


Figure 4: Dissolution profiles of Bzt. (A) pH 6.5 FaSSIF, and (B) pH 5.8 FeSSIF

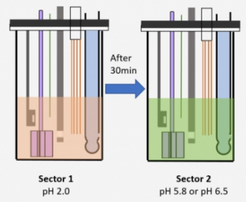


Figure 2: Aqueous media: Media conversion after 30 min from Sector 1 (pH 2.0) to Sector 2 (5.8 or pH 6.5) for further 2 hours.

Biorelevant media

The use of FaSSIF (Figure 4A) slightly increased the dissolution of Bzt with respect to the aqueous profiles, whereas FeSSIF (Figure 4B) drastically enhanced the dissolution. This could be attributed to the increased concentration of lecithin and bile salts present in the FeSSIF media, further promoting the formation of micelles.

The excipients KLU and KOL, yielded enhanced dissolution profiles with comparable final concentrations in FeSSIF medium. Conversely in FaSSIF, where measured concentrations were lower, the dissolution profiles of KLU and KOL were more differentiated. The mixtures of Bzt:KOL and Bzt:KLU in FaSSIF also showed a comparatively greater improvement to the dissolution performance of Bzt when considering the base performance Btz in the absence of excipient. While the endpoint concentrations in FeSSIF are observed to be higher, both KLU and KOL offer only an approximate 2x improvement to the final concentration as opposed to FeSSIF-only conditions; whereas in FaSSIF, the final concentration was improved by 6.4 times for KLU and 3 times for KOL.

The influence of pH

As Bzt is ionised to a greater degree at pH 6.5, the final concentrations observed in the dissolution profiles at pH 2.0 – 6.5 are slightly higher than those obtained at pH 2.0 – 5.8 in the absence of excipient (Table 1). While the use of excipients generally improves the dissolution performance and solubility, the trend of improvement between pH 5.8 and pH 6.5 due to ionisation is not carried for all excipients. CAP particularly shows a marginal drop in both extrapolated DR and final concentration as the second sector pH increases, implying a preference for the neutral form of Bzt.

In the case of KOL and KLU, the only excipients assayed in BDM, the lack of a significant response in the excipient performance relative to the second sector pH under purely aqueous conditions serves to highlight the influence of the BDM on the excipient behaviour, where the comparatively greater micelle concentration in FeSSIF appears to dominate, reducing the overall distinction between the dissolution performance of Btz in the presence of KOL and KLU.

Aqueous Media			
Excipient	pH	Extrapolated DR (µg/mL)	Final Conc (µg/mL)
API	2.0	0.68 ± 0.16	0.78 ± 0.07
	5.8	0.20 ± 0.07	1.54 ± 0.17
	6.5	0.29 ± 0.02	1.68 ± 0.06
CAP	2.0	2.72 ± 0.06	2.03 ± 0.25
	5.8	1.10 ± 0.19	4.34 ± 0.96
	6.5	1.08 ± 0.38	3.50 ± 0.28
CAV	2.0	6.94 ± 1.77	4.05 ± 1.17
	5.8	-	5.94 ± 0.78
	6.5	-	11.11 ± 1.91
KLU	2.0	3.03 ± 0.67	3.50 ± 0.44
	5.8	1.94 ± 0.45	8.47 ± 0.77
	6.5	1.20 ± 0.41	9.05 ± 1.05
KOL	2.0	5.04 ± 0.67	5.62 ± 1.06
	5.8	5.81 ± 4.84	17.00 ± 4.81
	6.5	3.78 ± 0.31	17.19 ± 0.77
S630	2.0	13.94 ± 3.09	5.06 ± 0.72
	5.8	1.07 ± 0.51	9.28 ± 2.59
	6.5	1.39 ± 0.13	8.65 ± 0.88

Table 1 (left): Dissolution Rate and Final Concentration for Bzt. in presence of the studied enhancers.

Table 2 (below): Dissolution Rate and Final Concentration for Bzt. In aqueous and BDM media with KLU or KOL as excipients.

Biorelevant Media			
BDM	pH	Extrapolated DR (µg/mL)	Final Conc (µg/mL)
API- Aqueous	5.8	0.33 ± 0.17	1.26 ± 0.25
FeSSIF		27.33 ± 18.63	21.24 ± 5.16
FeSSIF-KLU		10.70 ± 3.25	45.05 ± 5.82
FeSSIF-KOL		15.70 ± 1.60	41.46 ± 6.23
API- Aqueous	6.5	0.79 ± 0.11	1.73 ± 0.33
FaSSIF		1.53 ± 1.16	3.79 ± 0.78
FaSSIF-KLU		9.74 ± 0.65	24.33 ± 0.11
FaSSIF-KOL		8.24 ± 2.48	12.29 ± 0.95

CONCLUSION(S)

The effects of each excipient upon the dissolution performance appeared to be influenced by the medium selected (aqueous pH or BDM), where either ionisation of Bzt relative to the pH or the presence of micelles would be the dominant factor in determining the response of Bzt to the excipient. The distinction in the observed dissolution performance between KLU and KOL was notably more pronounced between the varied micellular content of FaSSIF and FeSSIF whereas pH alone exhibited less of an influence. Conversely, the pH gave rise to a notable difference in the performance of the CAP, CAV, S630 excipients; though, these were not assessed in BDM.