Investigation of the Pharmacokinetic Properties of Aspirin Analogues as Potential Anti-cancer Agents

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INTRODUCTION

Colorectal cancer is the second leading cause of cancer-related deaths in the western-world and the third most common cancer in both men and women. There is evidence to suggest that aspirin can prevent colorectal cancer. Deb *et al* (2011) found that aspirin and the aspirin analogue, Benzoyl aspirin (PN514) are toxic to colorectal cancer cells.

If PN514 was to be orally administered there is no guarantee it would survive the acidic conditions in the stomach. As acid can cause accelerated hydrolysis of a drug, it is important to observe how sensitive these molecules are to the acidity of the stomach.

MATERIALS AND METHOD

- Thin layer chromatography (TLC) and infrared spectroscopy (IR) techniques were used to test the purity of the analogues.
- In order to test whether PN514 is suitable for oral administration the hydrolysis reaction was studied in buffers from pH 0-13. (Main buffers included 0.2 M Na_2HPO_4 and 0.1M Citric Acid).
- Rates of the reaction in different buffer systems were recorded using UV spectroscopy techniques.

RESULTS AND DISCUSSION

TLC demonstrated that both salicylic acid and Benzoic acid were formed upon the hydrolysis of PN514. The overall reaction from the ester (Aspirin and PN514) through to hydrolysis products comprises several different modes of catalysis. The pH rate profile determined for PN514 (fig 3) is very similar to that of Aspirin (fig 2). Therefore the same reaction mechanisms are occurring. To begin with specific acid catalysis is the rate determining step as $[H^+]$ increases, the rate increases this may be due to the benzene ring acting as an electron withdrawing group (taking electrons from c=o ester) causing an increase in polarity making PN514 more reactive to acid than aspirin. Closer to the pK_a (4.15) the rate increases, here OH^- ions are beginning to attack the ester directly. The constant rate seen can be due to the mechanism described [2] where PN514 is catalysing its own breakdown. At more alkali pH the rate increases exponentially. Hydroxide ions work as a more effective nucleophile (electron donator) than water due to the dense electron pairs present on the O atom. Therefore the OH^- ions attack the ester faster than water. A Log linear relationship is observed where the $[OH^-]$ is reduced by 10 times the rate falls by one unit (pH 10-13).

CONCLUSION

When analysing the pH rate profile obtained it can be seen that the intramolecular form of catalysis (pH 5-10) is just as effective as the specific acid catalysis reaction (pH 1). This suggests that PN514 is stable at mid-range pH as it hydrolyses its own breakdown at the same rate of that at pH 1.

To conclude the data obtained suggests that PN514 may be able to be taken orally as its reacts more or less identically to aspirin over the whole pH range. This also shows that the rates are both accurate and reliable.

However it is important to state that only when the mechanism of action in the way in which aspirin and aspirin analogues prevent colorectal cancer is fully understood can a suitable dosage form be applied.

Fig 1: (Image on left) TLC plate under UV light, spotted with (from left to right) Benzoylaspirin (PN514), Hydrolysed PN514 (hyrol), Benzoic Acid (Ben Acid) and Salicylic Acid (SA).

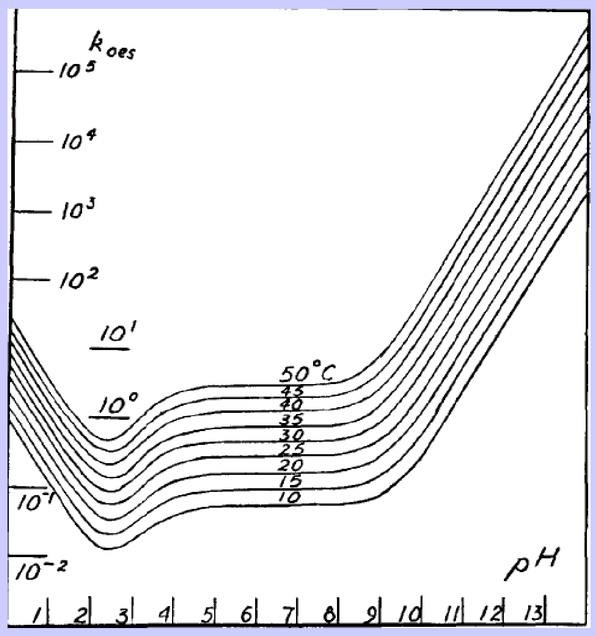

Fig. 2: pH rate profile of Aspirin at 10°C-50°C (Edwards, 1952)

Table 1: Log k_{obs} Rates (s^{-1}) of PN514 and aspirin at 55°c

	Log k_{obs} rates s^{-1}	
pH (rate determining step)	PN514	Aspirin
2.2 (specific acid catalysis)	-4.74	-5.20
6 (intramolecular catalysis)	-3.53	-4.40
12 (specific base catalysis)	-1.39	-1.33

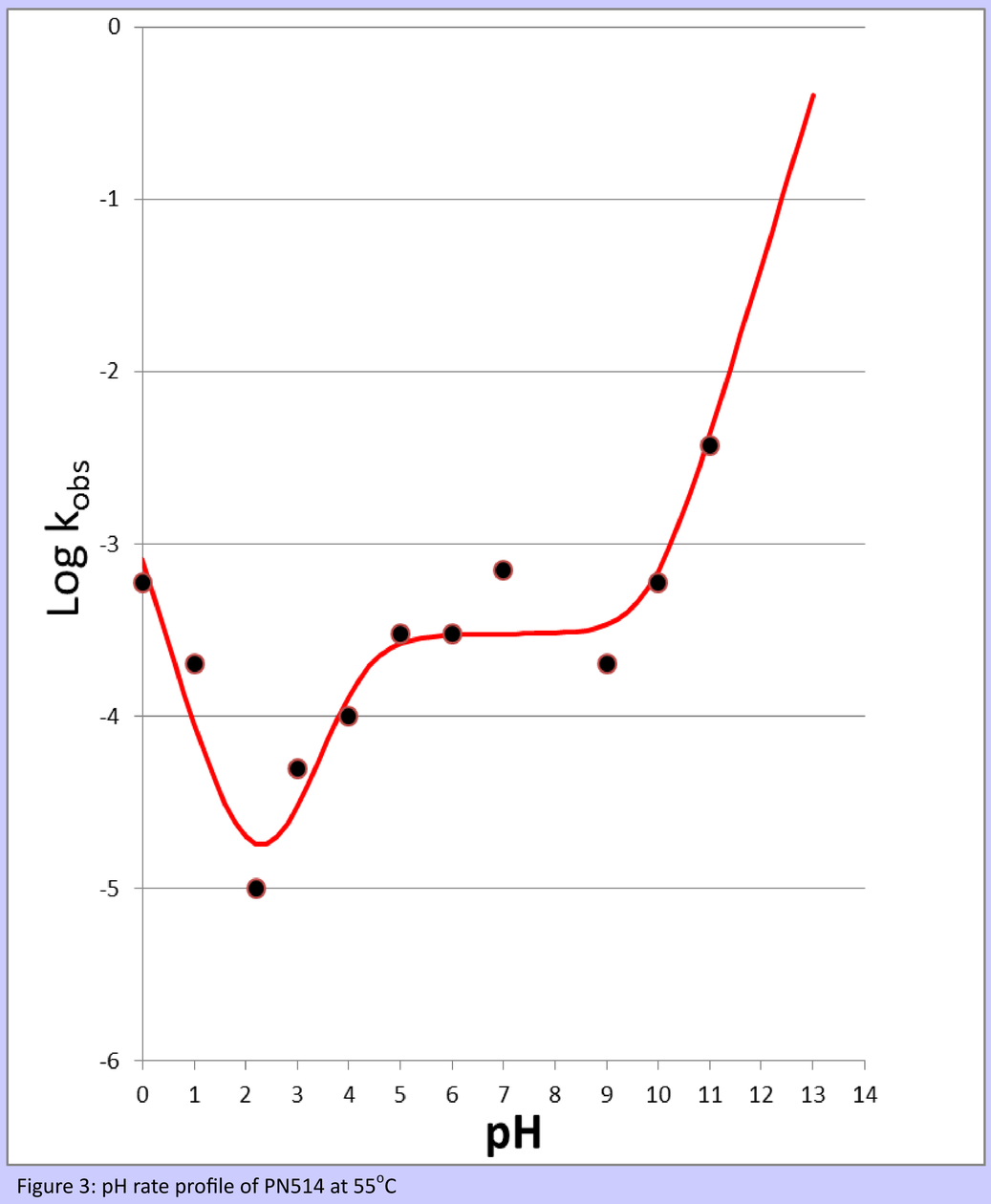

Figure 3: pH rate profile of PN514 at 55°C

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REFERENCES

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Colorectal Cancer Awareness

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