SHORT COMMUNICATIONS

Low Frequency Physical Failure Affecting *in Vitro* Release of Theophylline from Sustained Release Tablets.

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The dissolution test can be used to provide the formulator with valuable information for the design of dosage forms.[1] Two marketed sustained release tablets, Product A and Product B, were evaluated for *in vitro* release using USP XX Type 2 dissolution apparatus at 37±0.5° for a period of 12 hrs. Dissolution studies were carried out separately in three different buffers having pH values 1.2, 4.5 and 7.2, at three different paddle speeds, namely, 50, 100 and 150 rpm at each pH.

THE **in vitro** pH and agitational conditions were varied over a wide range because they are recognised as major **in vivo** factors/ conditions contributing to inter-subject and intra-subject variability; and it has been stated that if dissolution rate differences exist as a function of pH or agitation then there could be a subgroup of population for which therapeutic effectiveness could be different from the average or normal group.[2] The potential for dose-dumping from sustained release tablets made them good candidates for the study and theophylline was chosen as it has a narrow therapeutic window. Four batches of each of the two products were studied.

In all, we tested 108 tablets of each product in order to detect low frequency defects which would have a lower probability of being detected in a bioequivalence trial. Such low frequency defects (1 in 108) in sustained release tablets of drugs such as theophylline which have a narrow therapeutic window need attention because marketed tablets are consumed by a large population.

We found that 1 out of 108 tablets of product A and 4 out of 108 tablets tested of product B showed separation of the crown or layer of tablet after a few to several hours of dissolution. This failure was different from capping or layering in that it occurred after penetration of dissolution medium and thus was different in its mechanism. **Figure 1** gives the release profiles of those dissolution tests for which tablet failure was observed. Other results and data are given elsewhere.[3] For the few incidences of tablet failure that occurred there was a large increase in the percent drug released immediately after tablet failure. Thus if the tablet failure also occurred under **in vivo** conditions it would result in dose-dumping. In this context, a close scrutiny of the results reveals that 50 rpm for product A there was one incidence of tablet failure at 100 rpm. For product B, there was one tablet failure at 100 rpm each two and three at 150 rpm. Tablet failure thus appears to be related to agitational intensity occuring more readily at higher agitational intensity. This factor raises important issues. Would it be correct to argue that tablet failure would not occur at a possibly lower agitational intensity in the g.i.t. or would tablet failure due to intense agitation of tablets be a possibility, for example, during the fed state when stomach contents are forced towards the simultaneously constricting pyloric sphincter? The issue is of correlation of observed **in vitro** defect with **in vivo** defect. It would be too difficult to experimentally verify such

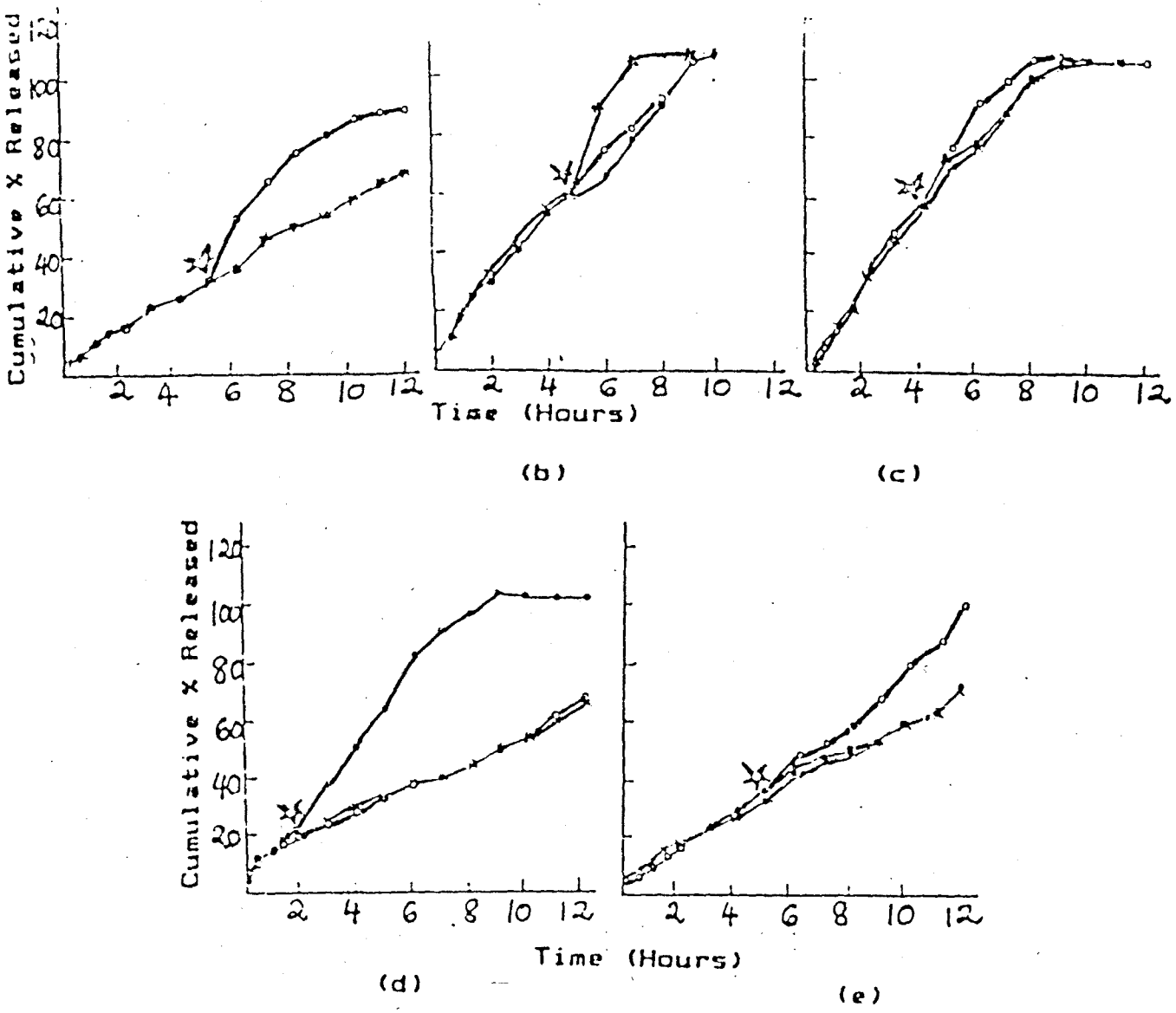

Fig. 1: The effect of tablet failure upon release of theophylline : (a) Product A, pH 7.2, 100 rpm; (b) Product B, pH 4.5, 150 rpm; (c) Product B, pH 4.5, 150 rpm; (d) Product B, pH 7.2, 100 rpm; (e) Product B, pH 7.2, 50 rpm. Asterisk represents the time at which the tablet failure occured. The uppermost profile in each of the graph is that of the capped tablet whereas the lower two represent the individual profiles from two uncapped tablets from the same batch.

a correlation, however, in order to properly address the issue of low frequency physical failure of sustained release tablets it is necessary to quantify the agitational intensity and characterise the g.i.t. hydrodynamics in and around tablets. Media composition may also influence such tablet failure. In our view, development of **in vitro** agitational tests based on this knowledge appeares to be a proper scientific approach to address this problem. For the present situation, the fact that **in vivo** agitational intensity shows large inter and intra-subject variability[2] should be considered and sustained release tablets formulated so that they do not exhibit tablet failure even under the more rigorous agitational conditions such

as 150 rpm for six hours in the USP type II apparatus. Our findings also confirm the advantage of pills or pellets[4] over tablets as sustained release dosage forms.

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Synthesis and Evaluation of Polyacrylate Pressure Sensitive Adhesives

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In the fabrication of transdermal patches the cost of the pressure sensitive adhesive (PSA), including its application, release and prime coating, often surpasses the price of the backing many times.[1] Lalla et al.[2] have earlier reported the synthesis and evaluation of polyacrylate pressure sensitive adhesive. the solubility of the drug in the adhesive and the fraction of drug unionized can be important factors affecting the skin permeation rates of drugs from adhesive matrix types transdermal systems. Therefore, we have synthesized a neutral PSA (PSA I) and an acidic PSA (PSA II) by the method of solution polymerization.The formula are given in Table I.

THE monomers methyl methacrylate, methacrylic acid and 2- ethylhexy acrylate were obtained from Merck-Schuchardt. Methyl acrylate was procured from Fluka Chemie, while acrylic acid was obtained from Aldrich Chemical Co. Inc., USA. All solvents and other reagents used were of A.R. grade.

PSA I was synthesized in two different batches in order to test the reproducibility of the characteristics of the PSA prepared in two different batches. The stabilizers (hydroquinone and hydroquinone monomethyl ether) present in the commercially available monomers were removed by six washings with equal volume of 5% w/v sodium hydroxide solution; and their removal confirmed by a zero absorbance reading at 313.7 nm. The monomers were passed through anhydrous sodium sulphate bed to remove moisture.

The synthesis was carried out by solution polymerization at 70 ± 0.5° in a 3-necked round bottom flask while agitating the contents by an overhead teflon-blade stirrer, initially at 150 rpm but later at higher speeds as viscosity of the contents increased. At the end of 4 hrs for PSA I and 2 hrs for PSA II, the polymer precipitated. The excess methanol was decanted off and the copolymer dissolved in ethyl acetate.

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