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Letter to the Editor

It is necessary to comment on aspects of a paper recently published in Int. J. Pharm., which deals with the stability of rifampicin (Shishoo et al., 1999). Firstly, it is claimed (without supporting references or evidence) that HPLC mobile phases for rifampicin must be 'selected very carefully' to avoid co-elution of this compound with its principal degradation product, 3-formylrifamycin SV. In a paper published some 7 years previously (Prankerd et al., 1992), HPLC mobile phase conditions were reported which gave baseline separation for these two species with peak retention volumes of 6.0 ± 0.1 and 10.0 ± 0.1 ml, respectively. This hardly qualifies as a difficult separation, which used a standard column (C8), mobile phase components (acetonitrile, water and Tris buffer) and equipment.

Secondly, the paper claims that rifampicin degrades by first order kinetics, based on very sparse data. This was clearly demonstrated to be otherwise in earlier detailed mechanistic studies (Prankerd et al., 1992), which were conducted under conditions that avoided the possible complications of oxidation products. As expected, these showed that hydrolysis to 3-formylrifamycin SV and 1-amino-4-methylpiperazine (Fig. 1) was in fact reversible and followed complex kinetics. The hydrolysis was controlled by a fast pseudo-first order forward reaction and a slower pseudo-second order reverse reaction. When hydrolysis data was analysed by a kinetic scheme that accounted for both the forward and reverse reactions, the differences between the rigorously defined forward rate constant (k_f) and the rate constant obtained on the assumption of pseudo-first order degradation (k_{init}) were significant.

A reversible reaction such as that given in Fig. 1 must necessarily follow a non-first order kinetic scheme, due to the presence of a second order reverse reaction involving equal concentrations of the two reactants. A very early study (Seydell, 1970) made this clear for rifampicin, by showing that $t_{50\%}$ was concentration-dependent in the range 2–100 mg/100 ml. As a consequence, pseudo-first order reaction kinetics was ruled out. Other examples of this reaction type have also been reported (Han et al., 1977; Prankerd and Stella, 1989), although on one other occasion with the inappropriate use of a first order kinetic scheme (Inotsume and Nakano, 1981) to account for the concentration-time profile.

The reason for the apparent assumption of (pseudo-) first order kinetics in the paper under discussion is that the degradation reaction simply was not followed for an adequate duration. While the paper may well have had a major focus on the extent of degradation that would occur during a time frame (1 h) that is roughly comparable with gastric transit time, it is not appropriate to use the resulting limited data to assess physicochemical (i.e. rate) constants, which require significantly more time to do so with any degree of precision. The paper suggests a half-life for hydrolysis of 330 min at 37°C and in 0.1 N HCl, based on data collected for $< 20\%$ of that time. It is a dictum that rate constants (and reaction orders) must be assessed from a meaningful time span, usually regarded as two half-lives (Taylor and Shivji, 1987). Although the data were reported to be the mean of three determinations, no assessed errors were reported, so it is difficult to gauge the reproducibility of the rate constants. The reported rate constants, for comparable conditions and even

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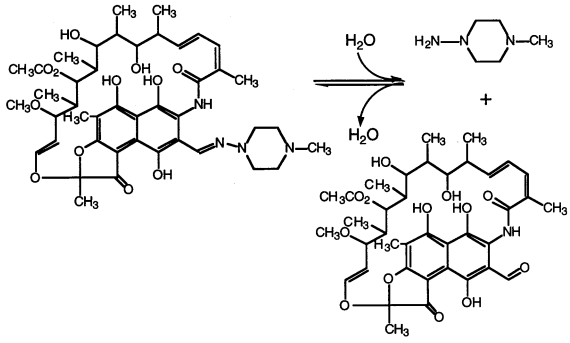

Fig. 1. Reversible hydrolysis reaction for rifampicin under acid conditions.

assuming that the pseudo-first order kinetic scheme is valid, are at variance with those reported in the earlier paper by a factor of > 2.

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