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Some factors affecting the release of imipramine from gel-precipitated aluminium hydroxide spheres

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Changing the pH of the dissolution medium has been found to affect the release of imipramine from gel-precipitated aluminium hydroxide spheres. Release from unwashed, unheated spheres into solutions of pH 1·2 was controlled by dissolution of the gel matrix, whereas that into solutions of pH 3 and pH 5 appeared to be under diffusion control. The liberation of drug from unwashed, heated spheres into the media of higher pH exhibited more complex kinetics. Washed spheres failed to release significant amounts of imipramine into the solutions of pH 3 and 5. Changing the ionic strength of the media had little effect on drug release. These phenomena have been explained with reference to model theories of the precipitation and ageing of aluminum hydroxide gels and their pH-solubility profiles.

Gel precipitation of metal hydroxides from metal salt solutions occurs when colloidal particles separate from that solution and form a continuous framework. In the presence of a gelling agent, gel precipitation can be controlled in a manner which produces spherical particles containing drug substances, and offers a potential controlled release oral drug delivery system. The subsequent processing of the spheres has been shown to determine the rate at which the spheres release the drug into 0·1 M hydrochloric acid solution (Ramsey et al 1984).

This paper describes the effects of the pH and ionic strength of the dissolution medium on the release of imipramine from aluminium hydroxide spheres and discusses potential mechanisms for the solution phenomena observed.

MATERIALS AND METHODS

Materials

The imipramine hydrochloride (Courtin and Warner Ltd) was BP quality and the aluminium chlorohydrate solution (Albright and Wilson Ltd) was reagent grade, equivalent to 0·31 g mL^{-1} Al_2O_3. Wisprofloc P is a water-soluble, non-toxic starch of undisclosed composition purchased from Allied Colloids Ltd. Strong ammonia solution was of BPC quality. Glass-distilled deionized water was used for all solutions.

Methods

The spheres were produced according to a previously described method (Ramsey et al 1984).

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Aluminium hydroxide spheres containing imipramine were produced to a standard formula containing 1·6 g imipramine hydrochloride, Wisprofloc P (10 g in 150 mL water) and 80 mL aluminium chlorohydrate solution. The precipitated spheres were divided and subjected to various washing procedures (unwashed or washed with 5 × 1 L of water) before being dried in air and subjected to various heating procedures (unheated or 90 °C/4 h).

The release of imipramine from weighed samples of the gel spheres was assessed in a continuous flow rotating bottle dissolution apparatus (Ramsey et al 1980) in the 'open mode' for a number of dissolution media at 37 °C. The media were 0·1 M hydrochloric acid (pH 1·2), 0·1 M citrate buffer (pH 3·0), 0·1 M citrate buffer (pH 5·0), 0·1 M sodium chloride solution (pH 3·0), 0·5 M sodium chloride solution (pH 3·0). All dissolution tests were carried out in duplicate.

A rapidly releasing unheated sphere formulation containing 2·63% imipramine hydrochloride and its slowly releasing, heated counterpart were subjected to dissolution testing in 'open mode' in 0·1 M hydrochloric acid solution. The solution was continuously analysed for imipramine concentration and subsequently collected in fractions at 5 min intervals, each fraction being analysed for aluminium concentration.

Analytical procedures

The imipramine content and purity in the treated spheres and imipramine content of dissolution solutions were determined by ultraviolet spectro-

photometry. All results are expressed as imipramine hydrochloride content.

Some dissolution solutions were analysed for aluminium concentration by atomic absorption spectrophotometry (Model 603, Perkin-Elmer) using an acetylene/nitrous oxide flame and measuring at 396·2 nm.

RESULTS

Drug release into 0·1 M hydrochloric acid solution

The relationship between the concentration of aluminium and imipramine in solution during 'open mode' release into 0·1 M hydrochloric acid solution is shown in Fig. 1. It may be seen that there is a good correlation between imipramine and aluminium concentration in solution for each set of spheres. There was a lag in initial imipramine release from the unheated spheres which is not seen in the dissolution of the aluminium hydroxide matrix. This phenomenon was not seen in the heated spheres. Observation of the spheres during dissolution revealed that the unheated spheres remained intact whereas the heated spheres broke into smaller fragments.

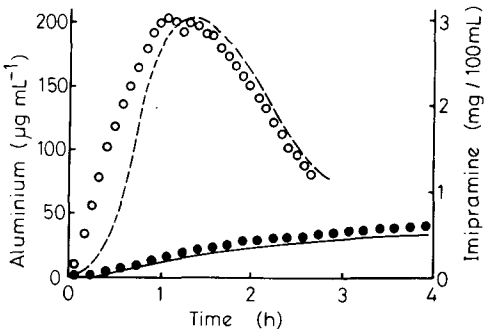

FIG. 1. The relationship between the concentration of aluminium and imipramine in solution during 'open mode' dissolution testing from unheated and heated spheres into 0·1 M hydrochloric acid. ○ Unheated spheres aluminium; — — — Unheated spheres imipramine; ● Heated spheres aluminium; ——— Heated spheres imipramine.

The effect of dissolution medium pH and ionic strength on the release of imipramine from aluminium hydroxide spheres

The release of imipramine from unwashed, unheated spheres into various media is shown in Fig. 2 and Fig. 3 where the same data are expressed as a function of the square root of time. It may be seen that the release curves fall into three distinct groups depending upon the pH of the dissolution medium with ionic strength having comparatively little effect.

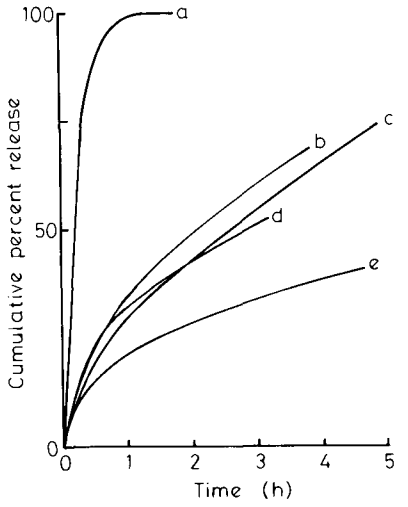

FIG. 2. Derived cumulative dissolution curves to illustrate the effect of dissolution medium pH and ionic strength on the release of imipramine from unwashed, unheated spheres as a function of elapsed time. a. 0·1 M hydrochloric acid; b. 0·1 M sodium chloride/pH 3; c. 0·1 M citrate buffer/pH 3; d. 0·5 M sodium chloride/pH 3; e. 0·1 M citrate buffer/pH 5.

Dissolution rate decreased with increasing solution pH.

In solutions of pH 3 and pH 5 the drug release data showed a linear relationship with the square root of time for periods of up to 4 h and up to 70% release.

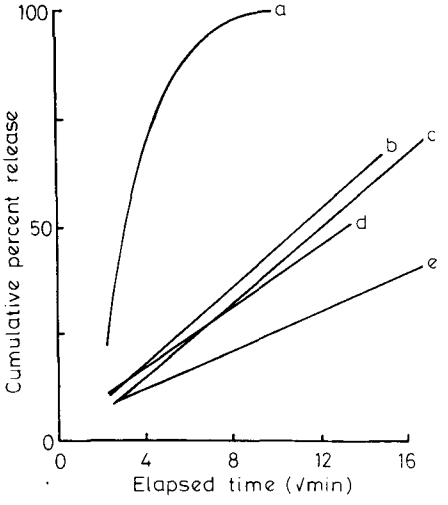

FIG. 3. Derived cumulative dissolution curves as a function of the square root of elapsed time, illustrating the effect of dissolution medium pH and ionic strength on the release of imipramine from unwashed unheated spheres. a. 0·1 M hydrochloric acid; b. 0·1 M sodium chloride/pH 3; c. 0·1 M citrate buffer/pH 3; d. 0·5 M sodium chloride/pH 3; e. 0·1 M citrate buffer/pH 5.

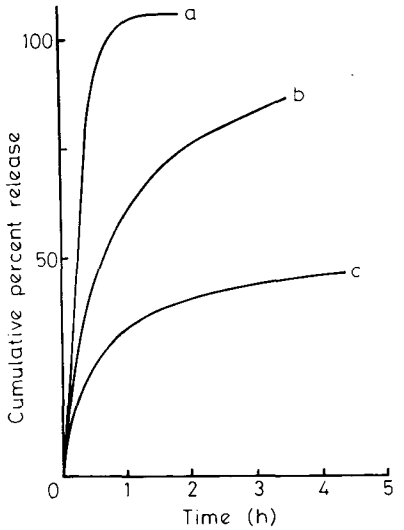

FIG. 4. Derived cumulative dissolution curves illustrating the effect of dissolution medium pH on the release of imipramine from unwashed spheres heated at 90 °C for 4 h as a function of elapsed time. a. 0·1 M hydrochloric acid; b. 0·1 M sodium chloride/pH 3; c. 0·1 M citrate buffer/pH 5.

Imipramine release from unwashed spheres heated for 4 h at 90 °C is shown in Fig. 4 and as a function of the square root of elapsed time in Fig. 5. Again, an increase in pH resulted in a reduction in drug release rate. At pH 3 and pH 5 the drug was released more rapidly than from the spheres' unheated counterparts and there was no direct relationship between drug release and the square root of time. The curves were, however, biphasic.

No significant drug release was detected from washed spheres into solutions of pH 3 and pH 5.

Visual monitoring of the spheres during dissolution suggested that little or no gel dissolution took place at pH 3 or pH 5. The heated gel spheres did, however, break into small pieces whereas their unheated counterparts remained intact.

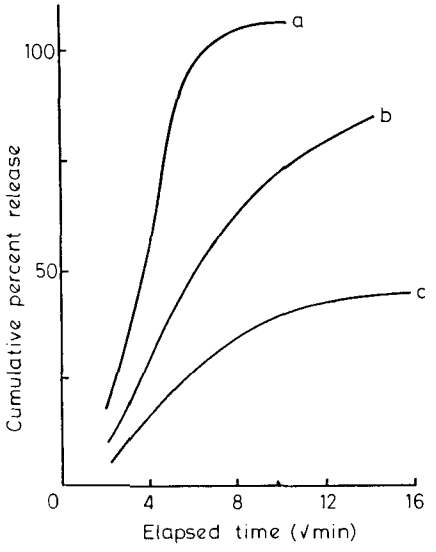

FIG. 5. Derived cumulative dissolution curves as a function of the square root of elapsed time illustrating the effect of dissolution medium pH on the release of imipramine from unwashed spheres heated at 90 °C for 4 h. a. 0·1 M hydrochloric acid; b. 0·1 M sodium chloride/pH 3; c. 0·1 M citrate buffer/pH 5.

DISCUSSION

Ramsey et al (1984) reported previously that the release of imipramine from gel-precipitated aluminium hydroxide spheres into 0·1 M hydrochloric acid solution could be controlled by a combination of heating and washing operations. The results shown in Fig. 1 indicate that this release is controlled by the dissolution of the aluminium hydroxide matrix. In the case of unheated spheres, the initial lag phase in drug release is not exhibited by dissolution of the matrix. This suggests the possibility of a 'skin' of aluminium hydroxide around the spheres which contains a lower concentration of drug. The heated gel breaks up in the medium, thus presenting the interior of the spheres for dissolution without initial removal of the 'skin'. Hence, there is no disparity between aluminium and imipramine concentrations in solution. The results in Figs 2–5 show that the release of drug is also a function of the pH of the dissolution medium. Increases in the pH of the solution reduced the release of drug from the unwashed spheres. Washed spheres released little or no drug at pH 3 and pH 5.

The effects seen with the unwashed spheres can be attributed to changes in the solubility of aluminium hydroxide in solutions of different pH. Aluminium hydroxide is amphoteric, dissolving readily in solutions of extreme pH but being almost insoluble at intermediate values (Millot 1970; Wefers & Bell 1972). If drug release is, in fact, controlled by dissolution of the gel matrix then the rate will be much reduced in solutions of higher pH. Of potentially greater significance, however, is the observation that the release of imipramine from unwashed, unheated spheres in solutions of pH 4 and pH 5 was linearly related to the square root of elapsed time over the whole period of study. This is an indication that dissolution of the gel is not occurring and that the drug is being released from the matrix by a diffusion controlled mechanism (Higuchi 1963).

Heating of the unwashed spheres caused them to exhibit more rapid drug release when compared with their unheated counterparts in the same dissolution media. This enhanced release may be related to the partial disruption of the spheres into smaller pieces which then remained intact for the remainder of the test. The biphasic nature of drug release from these spheres is a possible indication of two separate drug release mechanisms. The first, rapid release phase may be a result of the disruption of the gel resulting from solvent infiltration of stress cracks formed during heating. The latter phase may represent drug diffusion from the irregular small particles of gel which form.

The finding that unwashed gel spheres released imipramine into media of higher pH whereas their washed counterparts failed to do so is of significance. It indicates facilitated infiltration of dissolution medium into the unwashed gel. This is probably due to the presence of chloride within the unwashed product which reduces the overall order of the gel by inhibiting hydroxide bridge formation (Ramsey et al 1984). Aqueous solutions are thus able to penetrate the gels because of their greater hydrophilicity and less organized nature. As the liquid penetrates the gel matrix, drug will be taken into solution and then diffuse into the bulk of the dissolution medium. Washed spheres, which form more ordered crystal structures will be virtually insoluble at pH 3 and pH 5 and offer no sites for aqueous penetration. The more rapid release from unwashed spheres into media of pH 3 when compared with media of pH 5 may reflect the slight solubility of aluminium hydroxide in the former. Changes in the ionic strength of the dissolution media would not significantly affect dissolution by the proposed mechanism.

The findings have implication for the use of drug-containing gel-precipitated spheres for oral administration in view of the variations in pH and ionic control of the gastrointestinal tract.

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