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The production and properties of gel precipitated aluminium hydroxide spheres containing imipramine

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The production of aluminium hydroxide spheres containing imipramine by gel precipitation of liquid feed solutions has been described. Washing and heating procedures applied to the precipitated spheres markedly affected the rate of drug release from the spheres into 0·1M hydrochloric acid. Increasing the imipramine content of the spheres also altered the drug release rate. The effects described have been explained with reference to model theories of the precipitation and ageing of aluminium hydroxide gels in the presence and absence of 'foreign' anions.

Spherical particles have potential pharmaceutical uses because of their excellent flow properties, the ease with which they can be subjected to processes such as coating and their ability to pack uniformly and reproducibly. Traditionally, pills were manufactured by manual rolling of wet masses into balls and later, spherical products were made to grow in a rotating drum (Barlow 1968). Today, pan coating, spray drying and spray congealing techniques are used to produce spherical products (Bakan & Anderson 1976) with pan coating also being extensively used to apply various coating materials to drug-supporting nuclei (Robinson 1976).

Spheroidal drug carriers have been described for both enteral and parenteral use. Kala et al (1976) evaluated the drug incorporation and release properties of polyacrylamide spheres while recently the use of magnetic microspheres to target drugs to specific areas of the body has been described (Widder et al 1978, 1979). Controlled release spheres made from synthetic or natural organic polymers have also been reported (Wahlig et al 1978; Yoshida et al 1979; Nakano et al 1979). These are designed to deliver drugs to their sites of action in a predictable and controllable fashion and to ensure maximum therapeutic benefit and convenience for the patient.

Inorganic gels

The formation of a gel from a solution of ions requires formation of colloidal particles and their separation from solution into a continuous framework. Formation of the colloid particles from the solution is usually brought about by inducing supersaturation, whereas separation of the colloid particles may be achieved by temperature change, evaporation, the addition of another substance (e.g. a non-solvent) or by chemical reaction (Hermans 1949).

Metal hydroxide gels are typically precipitated by the chemical reaction between a metal salt solution and an alkaline solution. This can be accomplished either by the addition of the alkali to the metal salt solution or by the addition of the metal salt solution to the alkali. The former has been used extensively for many years to study the formation and ageing of hydrous metal oxide gels (e.g. Weiser 1935), whereas the latter can be used to produce gel particles of controlled shape and size. However, such control is only obtained for a limited number of metal salts and particle sizes.

The process can be made much more generally applicable by adding a gelling agent which is a water-soluble polymer such as a starch. Gel-precipitation processes of this type have been developed for the production of spheres of actinide oxide for use as fuel in nuclear reactors (Marples et al 1981). A jet of metal salt solution containing gelling agent is formed into spherical droplets by the action of a vibrating nozzle. The droplets then fall into a strongly alkaline solution where precipitation occurs. The spherical form of the droplet is maintained throughout precipitation, washing, drying and calcination operations.

This paper describes both the production and properties of gel-precipitated spheres of aluminium hydroxide containing imipramine. An initial short report of this work has been published (Ramsey et al 1979).

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MATERIALS AND METHODS

Materials

All products manufactured and tested in this series of experiments were produced by varying the concentration of imipramine hydrochloride (Courtin and Warner Ltd) dissolved in a standard aqueous feed solution. An aluminium chlorohydrate solution (Albright and Wilson Ltd) equivalent to 0·31 g ml^{-1} Al_2O_3 and a gelling agent, Wisprofloc P, were the other constituents of the solution. Wisprofloc P is a water soluble, non-toxic starch of undisclosed composition and was purchased from Allied Colloids Ltd. Glass distilled, deionized water was used to manufacture all solutions and Strong Ammonia Solution BPC was the precipitating solution.

Methods

Production

Aluminium hydroxide spheres containing imipramine were produced by dropping the feed solution from a dropping funnel, through a nozzle, into the ammonia solution. An air jet blowing across the surface of the precipitating solution container ensured that the solution was not prematurely gelled in the nozzle by ammonia gas. A simple constant head device maintained the distance between nozzle and liquid surface. Precipitated spheres were allowed to stand for approximately 1 h before being filtered from the ammonia solution and subjected to various washing procedures. Following this, the spheres were allowed to dry to constant weight in air at ambient temperatures. The dried spheres were subjected to various heating procedures before analysis. Details of the formulation, washing and heating procedures applied to the gel spheres will be found in the appropriate experimental section.

The size range which can be produced by this process is related to the mechanics of drop formation. For the present work, a simple gravity feed system was employed to provide spheres whose final diameters were in the range of 1 to 2 mm in diameter.

Analytical procedures

The imipramine content and purity in the treated spheres was determined by scanning ultraviolet spectrophotometry in 0·1 M hydrochloric acid. Comparison of the spectrum produced with those of pure imipramine solutions allowed detection of gross chemical change. The absorbance value at 250 nm allowed calculation of drug content by reference to a standard curve.

Ultraviolet absorbance at 250 nm was also used to analyse drug release from the gel spheres in two types of rotating bottle dissolution apparatus. The first consisted of a wheel mounted vertically on a frame within a constant temperature incubator. Sample and dissolution medium were contained in 60 ml screw capped polythene bottles, eight of which could be mounted radially around the wheel. With the wheel turning, a tumbling action was achieved causing the particles to fall repeatedly through the solution. Bottles containing drug spheres in 60 ml dissolution medium were removed from the wheel at various times and their contents filtered and analysed by measurement of absorbance at 250 nm.

A continuous flow rotating bottle apparatus was developed for later investigations and has been described previously (Ramsey et al 1980).

Experimental procedures

A batch of aluminium hydroxide spheres was produced to a standard formula containing 1·6 g imipramine hydrochloride, Wisprofloc P 10 g/150 ml water, aluminium chlorohydrate solution 80 ml. They were then divided and subjected to various washing procedures (unwashed, washed with 1 litre, washed with 6 × 1 litre) before being air dried and subjected to various heating regimens (unheated, 105 °C/4 h, 60 °C/4 h, 80 °C/4 h, 90 °C/4 h, 90 °C/1 h, 90 °C/2 h). All samples were then assayed for imipramine content and drug release properties. A further set of spheres, produced under the same conditions as the previous batch was retained unwashed or washed two, four, six or eight times before being dried in air. Again drug content and release were investigated as before.

Aluminium hydroxide spheres containing different concentrations of imipramine were produced from the standard feed solution containing different concentrations of imipramine hydrochloride (1·6, 2·4, 4·0, 8·0, 24 g). The spheres produced were subjected to heat treatment (90 °C/4 h) after washing (5 × 1 litre) and drying. Drug content and release rate were investigated as described above. 'Open mode' analysis was used in the continuous flow rotating bottle apparatus because of the high drug concentrations involved.

Batches of spheres were produced from a feed solution containing 1·6 g imipramine hydrochloride through two different size nozzles. After precipitation the spheres were allowed to stand in the ammonia solution for 1 h before removal by filtration and washing in 5 × 1 litre of water. Ammonia

and water samples were retained and neutralized by removal of ammonia gas followed by addition of glacial acetic acid. Samples of each solution were analysed for chloride content by the Mohr method (Vogel 1962) and further samples then brought to pH 1 by the addition of hydrochloric acid and analysed for imipramine by ultraviolet spectroscopy.

RESULTS

Effect of washing and heating the spheres on drug release (determined by the rotating bottle system)

Dissolution data showing the effects of washing and heating on drug release are shown in Fig. 1. Plot 1a shows the effect of washing only, 1b the effect of washing and heating, 1c the influence of heating

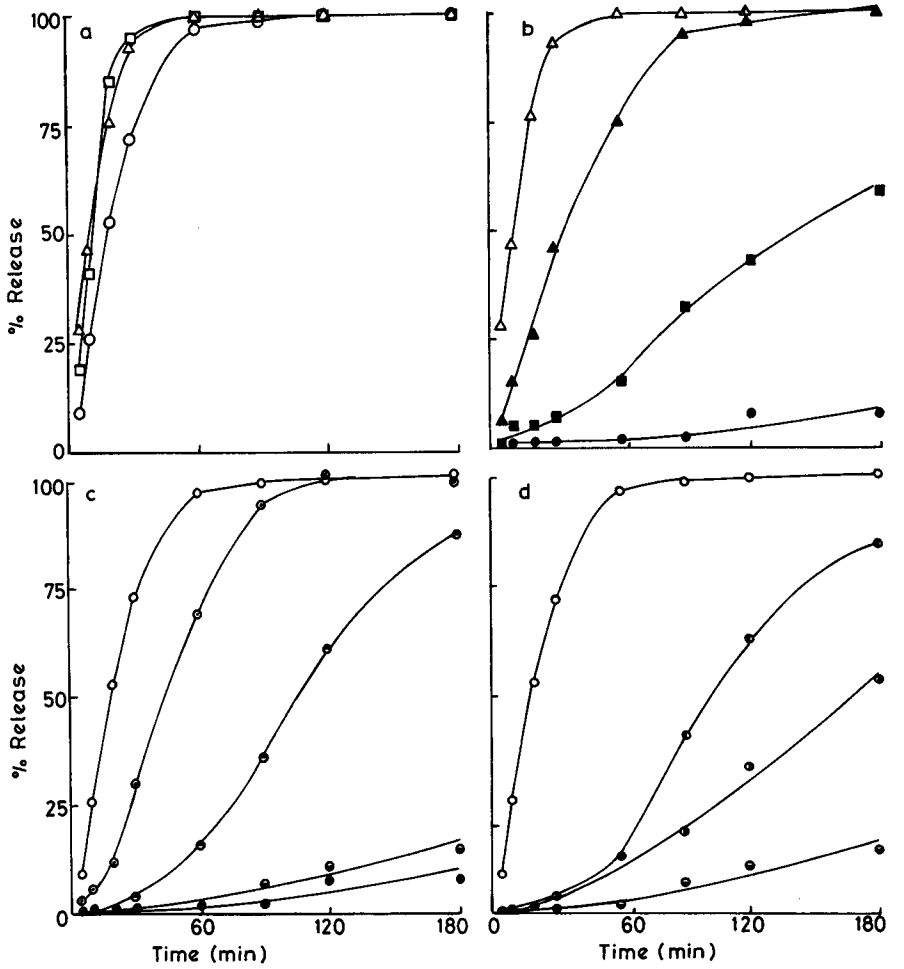

FIG. 1(a) The effect of washing on the release of imipramine from gel spheres. △ Unwashed, unheated spheres (sample 1). □ 1 litre washed, unheated spheres (sample 2). ○ 6 × 1 litre washed, unheated spheres (sample 3).
(b) The effect of washing and heating on the release of imipramine from gel spheres. △ Unwashed, unheated spheres (sample 1). ▲ Unwashed, 105 °C/4 h spheres (samples 4). ■ 1 litre washed, 105 °C/4 h spheres (sample 5). ● 6 × 1 litre washed, 105 °C/4 h spheres (sample 6).
(c) The effect of heating at different temperatures on the release of imipramine from washed gel spheres. ○ 6 × 1 litre washed, unheated spheres (sample 3). ⊙ 6 × 1 litre washed, 60 °C/4 h spheres (sample 7). ◓ 6 × 1 litre washed, 80 °C/4 h spheres (sample 8). ◒ 6 × 1litre washed, 90 °C/4 h spheres (sample 9). ● 6 × 1 litre washed, 105 °C/4 h spheres (sample 6).
(d) The effect of heating for different times on the release of imipramine from washed gel spheres. ○ 6× 1 litre washed, unheated spheres (sample 3). ◐ 6 × 1 litre washed, 90 °C/1 h spheres (sample 10). ◑ 6 × 1 litre washed, 90 °C/2 h spheres (sample 11). ◒ 6 × 1 litre washed, 90 °C/4 h spheres (sample 9).

temperature and 1d the effect of heating duration.

It may be seen from the results that washing and drying of the spheres had little effect on the release rate of imipramine. Heating of unwashed spheres had only a moderate effect whereas heating of washed spheres produced a greatly reduced release rate. Fig. 1c and d show that the time and temperature to which the spheres were subjected also influenced the ultimate drug release rate. Dissolution tests conducted over longer periods (up to 16 h) indicated that all of the drug contained within the spheres was eventually released.

Data for drug release (continuous flow rotating bottle apparatus) from the washed series of spheres is shown in Table 1. The retardation of release due to washing only appeared to reach a plateau after two washes whereas that due to washing and heating required at least four washes.

Visual monitoring of the dissolution of the spheres suggested that drug release was related to physical dissolution of the spheres and showed that heated spheres tended to break into small pieces during dissolution whereas unheated spheres remained whole.

Table 1. Times taken to achieve 25% (T_{25}) and 50% (T_{50}) release of imipramine in a series of washed gels.

Number of washes	Before heating		After heating	
	T_{25} min	T_{50} min	T_{25} min	T_{50} min
0	6	11	7	15
2	17	24	77	118
4	17	24	92	148
6	16	23	92	142
8	18	24	102	162

Effect of drug concentration on the release from gel spheres

The incorporation of imipramine in unwashed and washed spheres produced by precipitation of feed solutions containing varying concentrations of the drug is shown in Fig. 2. There is a clear relationship between the two parameters which shows a deviation from linearity at higher drug concentrations. Drug release data (continuous flow rotating bottle apparatus) for the same spheres is shown in Fig. 3. It may be seen that increasing the concentration of imipramine in the gel spheres reduced the retarding effect of heating on drug release rate. At concentrations of 18% and above there was no retardation after heating. This was substantiated by the observation that the gel spheres containing 29·7% imipramine hydrochloride showed no change in drug release rate after being heated at 100 °C for 8 h. Effects of drug concentration on release rate may also be seen by comparison of the drug release times of the unheated gel spheres. An increase in drug concentration led to a faster release of drug.

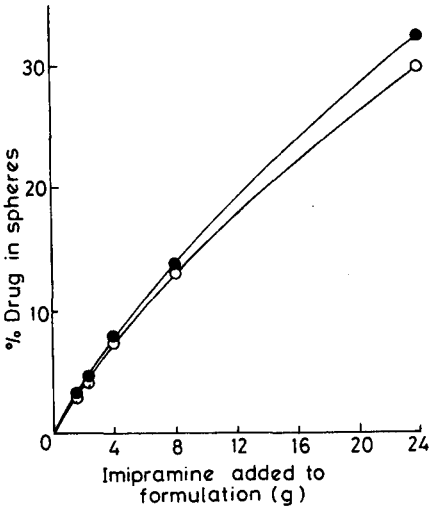

FIG. 2. The incorporation of imipramine into washed, dried spheres as a function of the drug concentration in the feed solution. ○ Unheated spheres. ● Spheres heated 90 °C/4 h.

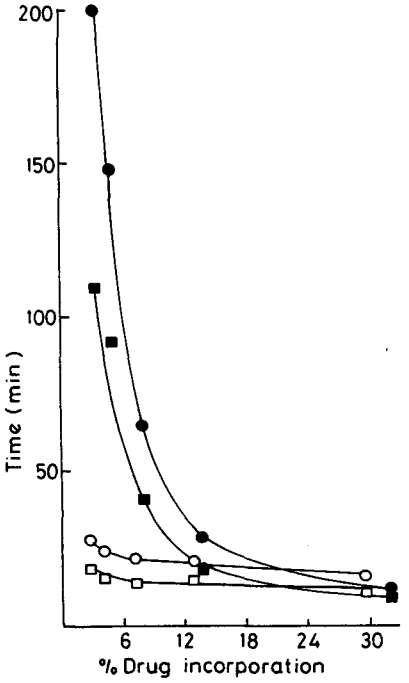

FIG. 3. The effect of imipramine concentration within the washed spheres on the drug release rate. □ 25% drug release from unheated spheres. ○ 50% drug release from unheated spheres. ■ 25% drug release from spheres heated 90 °C/4 h. ● 50% drug release from spheres heated 90 °C/4 h

Visual observation suggested that drug release was a direct consequence of gel sphere dissolution for many of the formulations. However, the heated gel spheres containing high concentrations of imipramine dissolved in a slightly different manner. The opaque, white portion of the sphere dissolved from the outer surface to the centre leaving behind a clear jelly which dissolved within a short time. Unfortunately, because of the high drug concentrations and rapid dissolution times it was difficult to relate drug release to the dissolution of each portion.

Materials removed from the spheres during washing

The results of the washings analyses are shown in Fig. 4. It can be seen that both chloride ion and imipramine were removed from the spheres by the ammonia precipitating solution and by the washing water. Most of the chloride ion was removed by the ammonia and the first three washings, whilst imipramine removal fell to a steady state after two washings.

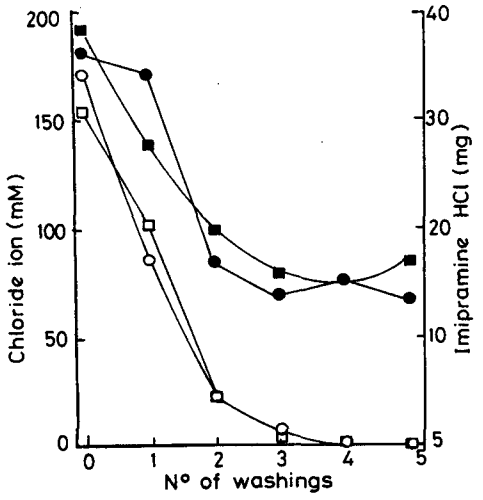

FIG. 4. The removal of chloride and imipramine from precipitated hydrogel spheres, into solution, by washing. □ Chloride from 1 mm spheres. ○ Chloride from 2 mm spheres. ■ Imipramine from 1 mm spheres. ● Imipramine from 2 mm spheres.

DISCUSSION

A combination of washing the undried spheres followed by drying in air and heating had a profound effect on the rate at which they released imipramine. Each process used independently had little effect on drug release rate. Increasing the imipramine content of the gel spheres, however, reduced this effect. During the washing process both chloride ion and imipramine were removed from the gel spheres. The release rate of imipramine from the heated spheres into 0·1 M HCl appeared to depend upon the chloride remaining within the gel. The reduction in release rate achieved by heating depended upon the time and temperature conditions to which the spheres are subjected.

These effects of washing, heating and alteration of impramine concentration upon the subsequent rate of drug release into 0·1 M hydrochloric acid solution will be discussed with reference to current theories of the formation of and development of order within aluminium hydroxide gels.

The formation of aluminium hydroxide gel and its subsequent ageing into more ordered structures takes place by a deprotonation-dehydration mechanism which forms double hydroxide bridges between aluminium atoms. Further hydroxide bridging may take place leading to the formation of highly ordered, acid resistant crystalline forms of aluminium hydroxide (Hsu & Bates 1964; Hem & Roberson 1967). Several studies have shown that the presence of ionic salts or polyhydroxy compounds in solution inhibits the formation of these ordered structures (Sato 1960; Davison & Schaeffer 1961; Hsu 1967; Kerkhof et al 1975). The relationship between the concentration of chloride ion in the gels and their physical properties has been investigated. This anion has been shown to increase gel electrophoretic mobility, decrease gel viscosity (Green & Hem 1974) and to inhibit gel ageing and its related decrease in acid consuming capacity by reducing the rate of hydroxide bridge formation (Nail et al 1976a, b, c).

During the precipitation of aluminium hydroxide spheres, the aqueous environment in which the gel forms becomes rich in chloride ions from both the aluminium chlorohydrate and the imipramine hydrochloride. These chloride ions may be incorporated into the gel structure inhibiting hydroxide bridging and the formation of acid-resistant gels. The washing of the spheres removes the chloride ions (Fig. 4) and hence leads to a structure which will dissolve more slowly in acid media (Fig. 1). Heating the spheres assists the removal of water molecules, further consolidating the gel structure. Spheres subjected to heating after washing released drug more slowly (Fig. 1) despite their tendency to break up in the dissolution medium. This disintegration of the heated spheres was considered to be due to the presence of stress cracks, formed during sphere shrinkage, and attacked by by the dissolution medium.

As the concentration of imipramine within the gel

spheres increases, the liberation rate of the drug also increases (Fig. 3). This phenomenon, exhibited to a slight extent in the unheated gels but more obviously by heated spheres, may be evidence for the weakening action of imipramine on the gel structure. The presence of imipramine inhibits the ordering of the gel structure and hence increasing the drug concentration within the gel spheres produces a more disorganised structure which is thus more acid-reactive. At very high drug concentrations the gel structure, unable to stabilize during heating, exhibits a similar drug release rate before and after heating. Further evidence for this effect may be seen in Table 1 where there is a difference in drug release rates between the spheres washed six and eight times and then heated. Analyses of these gels and their washings showed that although none contained any chloride that could be removed by washing, the gel washed eight times, which released drug more slowly, contained less imipramine.

These hypotheses fail to account for the jelly-like substance seen during dissolution of the spheres containing high concentrations of imipramine. It is possible that the jelly is a complex formed between the imipramine and the Wisprofloc P gelling agent. This complex may not be evident at low drug concentrations either because it dissolves at the same rate as the gels or because it is not formed. Any role of the gelling agent in moderating the release of imipramine from these systems remains to be elucidated.

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