Intrinsic dissolution of lithium carbonate in aqueous solutions

B. P. Wall, J. E. Parkin, V. B. Sunderland*, School of Pharmacy, Western Australian Institute of Technology, Kent Street, Bentley, Western Australia

Intrinsic dissolution rate studies were carried out on lithium carbonate discs that were prepared with the disc in a component on the final support. This overcame the problem of further handling of the fragile discs. Dissolution media employed were similar to those used for the routine evaluation of lithium carbonate dosage forms. Linear dissolution rate profiles were found in simulated gastric fluid (SGF), Tris buffer and water. Data in SGF and water showed positive intercepts with the Levich model. The dissolution process of lithium carbonate was considered to be complex. Dissolution profiles in simulated intestinal fluid (SIF) containing phosphate showed a marked initial curvature and a subsequent reduced dissolution rate. This was due to the precipitation of trilithium phosphate onto the disc. Dissolution rate studies on lithium carbonate dosage forms could be invalidated where a phosphate buffer system has been used.

The dissolution of pure solids into aqueous media is considered to be rate-limited by either surface reaction or transport of dissolved molecules from the surface to the bulk liquid. Most data have been found to comply with the latter (Grijseels et al 1981). Kaplan (1972) has suggested that substances with intrinsic dissolution rates less than 60 mg $cm^{-2} s^{-1}$ are likely to exhibit bioavailability difficulties, and that an assessment of intrinsic dissolution rates for new drugs would provide a means of estimating whether bioavailability needs to be considered in the formulation of a dosage form.

Early reports of bioavailability problems with lithium carbonate both as conventional or sustained release tablets prompted a study of its intrinsic dissolution behaviour in media relevant to dissolution studies of its dosage forms.

Materials and methods

Discs were prepared from lithium carbonate (A.R. grade). Trilithium phosphate (Li_3PO_4) was prepared by addition of excess aqueous lithium chloride solution to a solution of trisodium phosphate. The resulting precipitate was washed repeatedly with distilled water and dried in a vacuum desiccator. SGF was simulated gastric fluid USP (1980a) without addition of pepsin and SIF was simulated intestinal fluid USP (1980a) without addition of pancreatin. All other chemicals were of analytical reagent grade. Discs were made in a die (Beckman RIIC 28 mm) modified by the use of a sleeve and smaller punch so that the disc was compressed within a steel rim giving a 21·7 mm diameter disc (Fig. 1). These rims were then fitted flush into a stainless steel

* Correspondence.

holder and connected by a 6 mm shaft to a dissolution test apparatus (Hanson Research Corp., USA). A pressure of $6·63 \times 10^5$ kPa was applied for 3 h under vacuum, and the pressure released over 15 min. Dissolution experiments were performed in triplicate at the rotational velocities of 0·83, 1·67 and 2·5 rev s^{-1} in 900 ml of medium. The rotational velocities correspond to Reynolds numbers (Re) of 890; 1760 and 2640 as defined by Re $= r^2 w/v$ where w = rotational velocity and v = kinematic viscosity which are well below that quoted by Levich (1962) for transition from laminar to turbulent flow at the disc surface. Samples of 10 ml were withdrawn at pre-determined intervals with replacement and assayed as previously described (Wall et al 1982) against matched standards. No evidence of dissolution from the edge of the disc was visible, the join between the disc and the steel rim suffered no erosion over the course of the experiment.

Infrared spectra were obtained of lithium carbonate and lithium phosphate by dilution with potassium bromide.

The solubility of trilithium phosphate was determined by shaking excess substance in carbon dioxide-free distilled water for several days at 37 °C. A sample after filtering through a 450 nm filter was assayed as above. A subsequent sample was also assayed to ensure that equilibrium had been achieved.
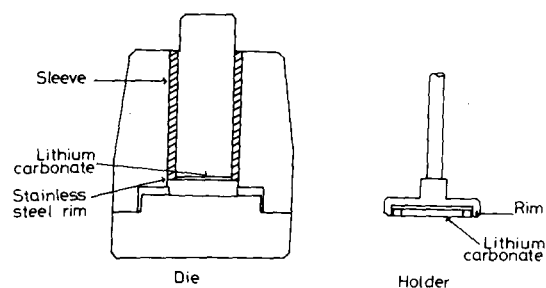

Fig. 1. Apparatus used to prepare lithium carbonate discs within a stainless steel rim and the holder employed for the dissolution tests.

Results and discussion

The apparatus used (Fig. 1) was similar to that of Levy & Sahli (1962) but had the advantage of the disc being prepared inside a component of the final support. This design overcame the need for handling of the fragile lithium carbonate discs. The experimen-

tal difficulties experienced by Prankongpan et al (1976) were also minimized since immersion of the whole die assembly in the dissolution medium was unnecessary.

Dissolution rates obtained from lithium carbonate discs at each rotational velocity are recorded in Table 1. With the exception of those obtained into SIF, the dissolution profiles exhibited linear relations and the intrinsic dissolution rates were calculated from least-squares fits of the slopes of the relation ($r \geq 0.998$). An example at 1.67 rev s^{-1}, which is typical of all data is found in Fig. 2.
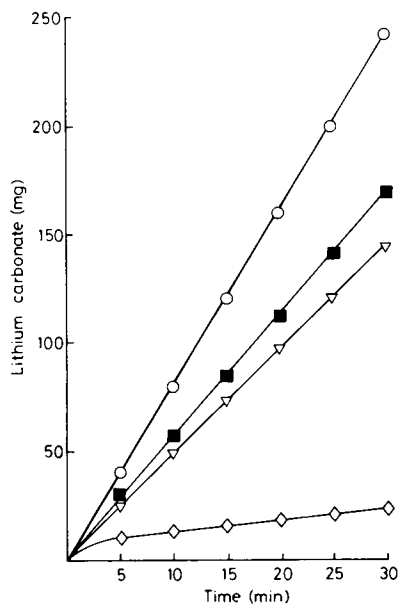

FIG. 2. The intrinsic dissolution profiles of lithium carbonate from discs at 1.67 rev s^{-1} in SGF ○; water ■; Tris buffer ▽ and SIF ◇.

Dissolution profiles in SIF showed a marked initial curvature. Intrinsic dissolution rates obtained from the latter linear portion of the plot were typically 10% of those found in Tris buffer of identical pH and ionic strength.

Examination of these discs showed a thin, distinct new layer of material on the surface. Such a phenomenon has been previously reported by Levy & Procknal (1962) for aluminium acetylsalicylic acid in an acidic medium and Higuchi et al (1965) for sodium tolazamide in phosphate buffers.

Table 1. Dissolution rates of lithium carbonate from discs ($mg\ cm^{-2}\ s^{-1} \times 10^2$)

Medium	Rotational velocity (rev s^{-1})		
	0.83	1.67	2.50
SGF	2.78	3.60	4.18
Water	1.60	2.17	2.51
Tris buffer	1.78	2.51	3.10

This new layer was carefully scraped from the disc, boiled in carbon dioxide-free distilled water, filtered off and dried overnight in a vacuum desiccator. Infra-red spectrophotometry indicated a spectrum that matched that of trilithium phosphate in all respects. The product of the lithium ion concentration in a saturated solution of lithium carbonate (pH 10.7) and the phosphate anion (PO_4^{3-}) cubed at $5 \times 10^{-2}\ mol\ dm^{-3}$ is 3.94×10^{-4}. This exceeds the estimated solubility product of lithium phosphate (5×10^{-9}) by a factor of 10^5. This assumes that the liquid boundary layer at the surface of the disc, had a pH of a saturated solution of lithium carbonate. These data indicate a theoretical basis for the precipitation of trilithium phosphate under these conditions.

In some cases lines appeared on the surface of the discs similar to those described by Levich (1962). Where such lines were visible the results were discarded although the data were indistinguishable from those obtained from discs not exhibiting such lines. The lines were particularly noted when the dissolution rate was from 2.5×10^{-2} to $3.1 \times 10^{-2}\ mg\ cm^{-2}$ s^{-1}, and not at higher or lower rates. Their occurrence was not simply a function of rotational velocity since they were evident at the lowest value in SGF and the highest in both water and Tris buffer.

The dissolution process involves contact of the solid interface with solvent; a physical reaction which is followed by transport of the solute away from the interface into the bulk solution. When surface equilibrium is rapid the rate of dissolution (J) is determined by bulk transport only, according to the following equation:

$$J = \frac{AD(C_s - C)}{h} \tag{1}$$

where A = surface area of solid exposed to the solvent: D = diffusion coefficient of solute in the solvent; C_s = the saturated concentration of solute: C = concentration of solute in the bulk and h = Nernst effective diffusion layer thickness. According to Nernst diffusion layer theory, the total resistance for solute transfer from the solution immediately adjacent to the solid surface into the bulk is given by h/D, a purely diffusional term. Bircumshaw & Riddiford (1952) have expressed the effect of stirring rate in terms of this model:

$$J = a(w)^b \tag{2}$$

where w is the angular velocity of rotation. For a diffusion controlled reaction the exponent (b) is equal to or less than one. Excellent linear relations were obtained for this model with exponents of 0.5 for Tris buffer and slightly lower in water and SGF.

In most dissolution situations both convection and diffusion are expected to be important. For the rotating disc methodology the mass flux under these two processes is given by Levich (1962) as:

$$J = 0.62\ AD^{2/3}\ v^{-1/6}\ w^{1/2}\ (C_s - C) \tag{3}$$

where v is the kinematic viscosity. It is only in Tris buffer that adherence to the Levich model occurred (Fig. 3). Positive intercept values found in SGF and water implies that dissolution occurred when the disc is static. Such a result is not unexpected in the experimental conditions employed. An analysis indicates lithium carbonate dissolution to be complex. Lithium carbonate undergoes dissolution to give Li^+ and $CO_3{}^{2-}$; as the $CO_3{}^{2-}$ species diffuses towards a bulk 'solution of lower pH, $HCO_3{}^-$ will be formed and some buffering effect may occur. Proton diffusion to the disc interface will produce CO_2 gas that will be given off and formation of OH^- which will diffuse out of the diffusion layer. With so many species involved with different transport properties the assumption of a constant-thickness boundary layer may not be correct. There is also possible evidence (Fig. 3) of both surface and transport reactions controlling the rate of dissolution. Each of these rate limiting processes may change in the process of the experiment. Furthermore, the diffusion coefficients of charged species are subject to significant change with changes in ionic strength, an additional complication (Erdey-Gruz 1974).
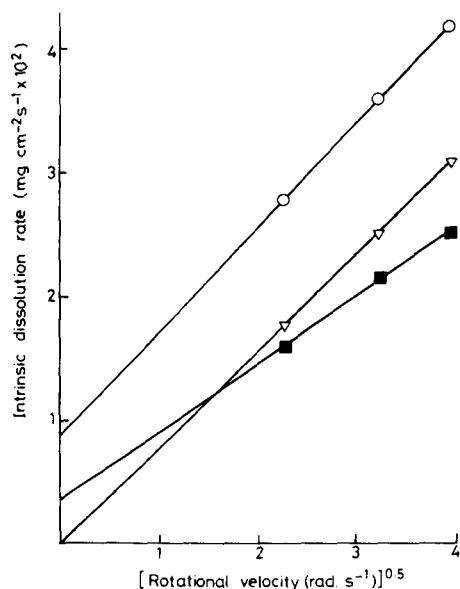

FIG. 3. Plot of the intrinsic dissolution rates of lithium carbonate against the square root of the rotational velocity in SGF ○; water ■ and Tris buffer ▽.

The media initially selected for study were those either prescribed by the BP (1980) or USP (1980b) for dissolution studies of lithium carbonate. Tris buffer was also used to provide pH control in a similar manner to phosphate buffer without the complication of further salt formation. A possible explanation for Tris buffer conforming with the Levich relationship is the concentration of hydrogen ion is much lower than in SGF where the surface reaction may be significant. Hence in Tris buffer a diffusion layer is formed which is maintained constant owing to buffering of the bulk solution. Mooney et al (1981), however, have shown that, where several species are involved, the total flux equation can collapse to where the diffusivity of one species becomes the dominant term.

The results for the dissolution in water are further complicated by the unbuffered bulk solution. The pH of the bulk solution increased up to a maximum of 3 pH units during the course of the experiments, the bulk solution pH being dependent upon the amount of lithium carbonate in solution. Since carbonic acid has two pK_a values (6·35 and 10·25) the species present and buffering in any diffusion layer would change during this pH rise. Hence the dissolution rate not obeying the Levich model is again possibly explained in terms of the complexity of the system investigated.

It is therefore concluded that dissolution rate studies on lithium carbonate dosage forms could be invalidated if a phosphate buffer system has been used. The BP (1980) currently prescribes phosphate buffers for the dissolution testing of slow lithium carbonate tablets. The selection of dissolution media for official tests should therefore require an intrinsic dissolution test to be carried out. This would assist in the detection of interacting media.

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