NOTES

Drug Release from Cellulose Acetate Phthalate Gel

The enteric-coating materials such as cellulose acetate phthalate (CAP)[1] or methyl acrylate–methacrylic acid copolymer (MPM)[2] are used to enhance drug release from tablets or granules in intestines. In addition, the soft gelatine capsules are employed for drugs of sustained-release type.[3] However, these materials are not necessarily desirable, because they dissolve in the body and are absorbed. Therefore, a new pharmaceutical form which will swell without dissolving and has properties of both enteric and sustained-release is required. The results from our preliminary studies on a new form of CAP gel are reported herein.

The CAP gel was prepared as follows. CAP aqueous solution containing sodium salicylate (Sal) and a slight amount of triethanolamine (TEA) was poured upon a mixture of glycidyl methacrylate (GM) and carbon tetrachloride and warmed up to 80–85°C. The CAP solution gelated after 1 hr. This gel was finely crushed in acidic water with a homogenizer and dried. The density of the gel was 1.6 g/cm^3. The unreacted CAP was about 16%, and the residual amount of GM, 1 ppm. The dried gel could not be dissolved in alkaline water when warmed to 90°C; however, it swelled considerably, which might be explained by a crosslinked structure between CAP and GM. Kerr et al.[4] reported that amylose molecules could react with epoxides, such as ethylene oxide or propylene oxide, in the presence of a basic catalyst.

To elucidate the mechanism of CAP gelation, some water-soluble polymers were allowed to react with some epoxides in a procedure similarly to that of the CAP gelation. This result (Table I) indicated the following interpretations: (a) The hydroxy or carboxy groups, which are located somewhat apart from the main chain, must react with the epoxides. In this respect, the gelation mechanism is distinct from Kerr's concept. The aldehyde groups of dialdehyde starch (OS) take no part in the gelation. (b) The ester exchange reaction will not occur under these conditions. (c) The epoxides must have a reactive group besides an epoxide group in order to gelate the polymers, e.g., vinyl groups in GM and chloromethyl group in epichlorohydrin (EPC).

From these considerations, the mechanism of CAP gelation was considered as shown in Figure 1. When CAP was gelated, the mobility of each molecule became so restricted that continued gelation became sluggish and stopped. Through this reaction, CAP was crosslinked by the bridge of GM and a number of carboxy groups. The solubility in the higher pH regions was decreased, and the gel consequently became insoluble even in alkaline water.

The release of Sal from the gel was carried out at 37°C at various pH values and the aspect of the release is shown in Figure 2. The concentration of Sal released was determined colorimetrically by the use of a ferric chloride aqueous solution at 520 mμ.[5] The amount of Sal released gradually increased with time, and higher release was observed at higher pH values.

To determine the release rate quantitatively, it was first assumed that the release was caused by a concentration gradient between the gel and the medium. This was similar to the relation for first-order rate processes, and the relation has already been applied quantitatively to the release from microcapsules.[6] This theory was directly extended to the case of the gel and described by eq. (1):

$$-dC_g/dt = k(C_g - C_m)$$

and

$$C_m V_m = (C_0 - C_g)V_g \tag{1}$$

where C_0 is the initial concentration of Sal in the gel of volume V_g, C_m is the concentration of Sal at time t in the medium of volume V_m and C_g in the concentration in the gel, and k is defined as the apparent release factor and comprises various factors that affect the release rate.

TABLE I
Reaction of Water-Soluble Polymers with Epoxides[a]

Polymer	Epoxide			
	GM	EPC	SO	BGE
CAP (10%)	○	○	×	×
MPM (10%)	○	○	×	×
CMC (2.5%)	○	×	×	×
HEC (2.5%)	○	×	×	×
AR (2.5%)	△	×	×	×
PEC (5%)	△	×	×	×
OS (10%)	△	×	×	×
none	△	×	×	×

[a] CAP = Cellulose acetate phthalate; MPM = methyl acrylate–methacrylic acid copolymer; CMC = carboxymethyl cellulose; HEC = hydroxyethyl cellulose; AR = alginic acid; PEC = pectin; OS = dialdehyde starch; GM = glycidyl methacrylate; EPC = epichlorohydrin; SO = styrene oxide; BGE = *n*-butyl glycidyl ether. (○) Gel, (△) some gel, (×) no gel produced.

The solution of eq. (1) is proven by eq. (2):

$$C_m = \frac{V_g C_0}{V_m + V_g}\left\{1 - \exp\left(-\frac{V_m + V_g}{V_m} kt\right)\right\} \tag{2}$$

As V_g was much smaller than V_m, $(V_m + V_g)$ was regarded to be equal to V_m. The concentration of Sal in the medium after infinite time (C_∞) was equal to $V_g C_0/(V_m + V_g)$. And finally, eq. (2) was reduced to eq. (3):

$$\ln (1 - C_m/C_\infty) = -kt \tag{3}$$

When the experimental data of Figure 2 were plotted, with log $(1 - C_m/C_\infty)$ as ordinate and t as abscissa, Figure 3 was obtained. This plot was found to be linear from about 0.7 hr to 3 hr, and in this period the release behavior was in accordance with eq. (3).

Higuchi[7] proposed two models for spherical pellets and showed that the release mechanism did not follow first-order relationships. Wiegand and Taylor[8] and Wagner[9] showed that the per cent release-time data reported in the literature for many sustained-release preparations give linear pseudo- (or apparent) first-order rates over the terminal portions of the data from 0.5 hr to the time

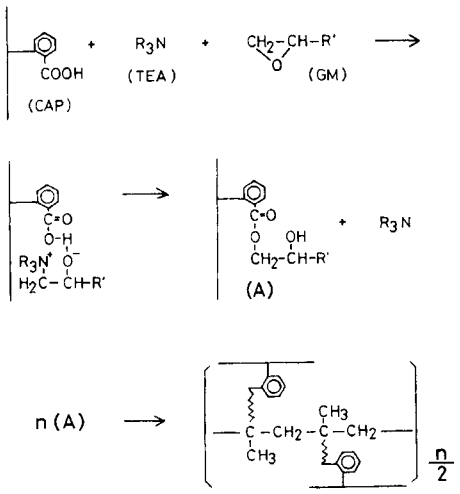

Fig. 1. Mechanism of CAP gelation.

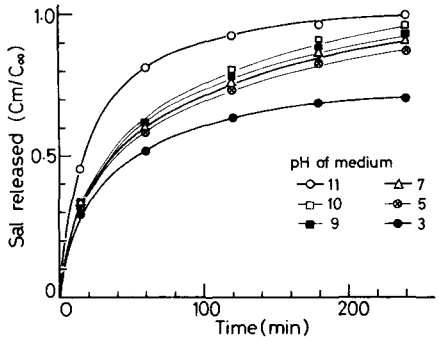

Fig. 2. Release aspects of Sal from CAP gel.

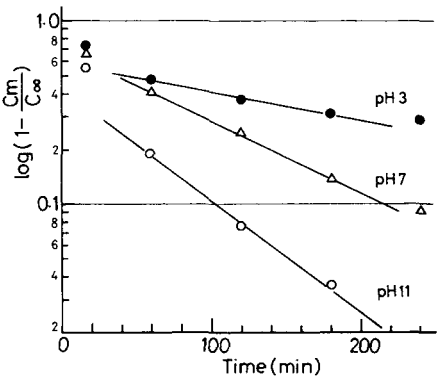

Fig. 3. Relation between log $(1 - C_m/C_\infty)$ and t.

the test was completed. From this viewpoint, the steady state of the release of Sal from the gel could be considered to be governed by first-order law. Consequently, k, which would be a measure for comparing the release rate, was determined from the slope of the linear portion in Figure 3, and the result is shown in Table II.

The difference in release with pH could be assumed to be due mainly to the degree of swelling (Sw) of the gel. The swelling was determined from the apparent increment in volume of the gel when immersed in the medium at pH 3, 7, and 11 (Table II). Kuhn et al.[10] had investigated the reversible change in swelling of poly(vinyl alcohol) membrane containing poly(acrylic acid) with pH change and reported that the membrane was swollen in alkaline regions by electrostatic repulsion due to the negative charge of ionic species such as carboxy groups in the membrane. Also, in the case of CAP gel, the carboxy groups of the CAP molecules may contribute to the swelling.

Here again, to elucidate the role of k obtained from the release data, k was plotted against Sw in a log–log graph and correlated by a straight line with a slope of 2.02, which is shown in Figure 4. This

TABLE II
Apparent Release Factor (k) and Degree of Swelling (Sw) of CAP Gel[a]

pH of medium	k, $\times 10^{-4}$ sec^{-1}	Sw, %
3	2.2	92.5
7	15	223
11	27	294

[a] $Sw = \dfrac{\text{apparent increment in volume}}{\text{initial volume of gel}} \times 100(\%)$.

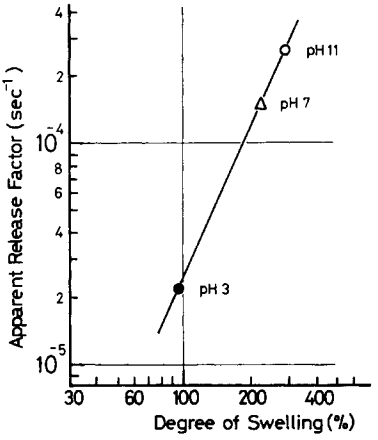

Fig. 4. Relation between k and Sw.

means that k is directly proportional to the square of Sw, namely, $k \propto Sw^2$. If Sal is released through the swollen gel, the diffusivity of Sal (D) in the gel must be related to the rate of release as well as the swelling of the gel. Furthermore, the diffusivity itself may be influenced by the swelling. That is, eq. (4) was presumed:

$$k \propto D \times Sw \text{ and } D \propto \text{Sw} \tag{4}$$

Therefore, this assumption was in agreement with the experimental data shown in Figure 4.

It is necessary to know explicitly the partition coefficient of Sal in the gel and in the medium, or the surface area of the gel, to interpret the experimental data.

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