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Preparation and Evaluation of Ethylcellulose Microcapsules of Indomethacin*

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Abstract□Indomethacin was microencapsulated with ethylcellulose using a modified spherical agglomeration process, aiming at a sustained release preparation without side effects on the stomach. The surface morphology of the microcapsules was examined using scanning electron microscopy. The microcapsules were porous and spherical, and their porosity increased with increasing the viscosity of ethylcellulose. *In vitro* dissolution process followed Higuchi's diffusion model for first 3 hr. Release rate of the drug from microcapsules decreased as the viscosity of ethylcellulose or the weight ratio of indomethacin to ethylcellulose was decreased. The release rate also decreased with increasing the microcapsule size. The microcapsules induced less gastric ulcer in rats than raw drug.
Keywords□Indomethacin, Microcapsule, Ethylcellulose, Diffusion model, Ulcer index.

Indomethacin is a typical nonsteroidal antiinflammatory agent available for the treatment of inflammatory diseases such as rheumatoid arthritis and goat.[1-2] Although indomethacin is only very slightly soluble in water, it is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration.[3] Indomethacin is very potent to the extent that the concentration in plasma required for an antiinflammatory effect is less than 1μg/ml, but it causes severe side reactions, including peptic ulceration, anorexia and headache like other analgesic and antiinflammatory agents.[4] These side effects are dose-related and are due to a stimulant effect on the stomach upon oral ingestion and to a indirect effect caused by the prevention of prostaglandin synthesis.[5]

Conventional pharmaceutical dosage forms of indomethacin such as tablets and capsules should be administered 3-4 times per day, and had a difficulty in maintaining a continuous antiinflammatory blood concentration level.

Therefore, many studies on new dosage forms of indomethacin have been carried out to provide a more constant drug level, hopefully avoiding side effects and patient inconvenience. For example, the sustained release preparations of suppository,[6-8] ointment,[9] plaster,[10-11] microcapsule[12-15] and lipid microsphere form,[16] and the osmotically controlled delivery preparations[17-18] have been reported.

A complex coacervation method using a gelatin-acacia system has been attempted to microencapsulate indomethacin, but this method requires an inconvenient process of improving the wettability of indomethacin in addition to the complexity of the method itself.[12]

In present study, we prepared ethylcellulose microcapsules containing indomethacin by means

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of a modified spherical agglomeration process, which has been recently reported as a simple and economical method,[19] aiming at a sustained release preparation of indomethacin with less side effects on the stomach. We also evaluated the microcapsules by checking their release behavior and the severity of stomach ulcer induced by them in rats.

EXPERIMENTAL METHODS

Materials

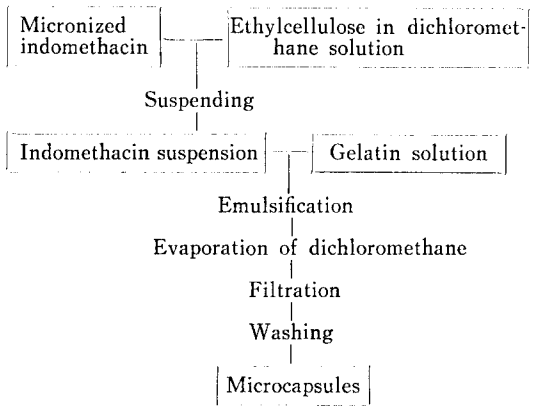
Indomethacin (micronized, Sumitomo Chem.), Ethylcellulose standard 20 cp, 50 cp and 100 cp (Ethocel,® Dow Chem.), Gelatin (Shinyo Pure Chem.), Dichloromethane (Junsei Chem.), Chloroform (Tedia Company, Inc.) were used. All materials were of reagent grade. Female Sprague Dawley rats (180~220g) were obtained from the Experimental Animal Farm of Seoul National University.

Preparation of Microcapsules

Ethylcellulose microcapsules of indomethacin were prepared using a modified method of Kawashima's spherical agglomeration process.[21] Procedure for the preparation of microcapsules is shown in Scheme I.

Indomethacin was suspended in previously prepared ethylcellulose dichloromethane solution using a magnetic stirrer, then the resultant suspension was added to the gelatin solution being stirred by means of a mechanical stirrer with teflon-wrapped baffles in a cylindrical vessel. Continuous and intense agitation evaporated dichloromethane from the suspension and resulted in discrete and hardened microcapsules. The microcapsules were separated by filtration and rinsed with water to remove any gelatin adsorbed on the microcapsule surface. They were oven-dried at 40° for 24 hr, yielding free-flowing microcapsules.

Various kinds of microcapsules were prepared by changing the rate of agitation, the concentration of gelatin solution, the viscosity of ethylcellulose, and the weight ratio of indomethacin to ethylcellulose. All batches were triplicated.



Scheme I: Preparation of ethylcellulose microcapsules.

Particle Size Separation of Microcapsules

A nest of sieves mounted on a moving sieve shaker was employed for the separation of microcapsules in various size range. Particles passing through one sieve and retained on the next finer sieve were assigned the arithmetic mean size of the two screens. Sieves of 200, 100, 45, 20 and 10 mesh were used.

Total Drug Contents of Microcapsules

The microcapsules were dissolved in chloroform and assayed spectrophotometrically (Pye-Unicam SP 1750) at 322 nm, using a calibration curve based on standard solutions in chloroform. Ethylcellulose in chloroform did not absorb at this wavelength.

Scanning Electron Microscopy

Dried samples of microcapsules were mounted on a sample stub with double-sided adhesive tape and were vacuum coated with gold film approximately 60nm thick. The surface topog-

raphy of the microcapsules were investigated by a JSM-35 Scanning Electron Microscope (Jeol).

Dissolution Procedure

Release of indomethacin from ethylcellulose microcapsules was measured using a rotating basket dissolution apparatus (Hansen Research Corp. model no. 72-400-109).

20 mg of indomethacin powder or the corresponding amount of microcapsules was put in a basket which was then immersed in a beaker containing 900ml of pH 7.2 phosphate buffer at 37±0.5°, immediately rotated at 100 r.p.m. by means of a constant rate adjustable stirrer.

Drug release was determined spectrophotometrically (Beckman Du-8 Spectrophotometer) at 320nm using a flowcell with a periostaltic pump and automatic recorder. Dissolution experiments were triplicated and were closely reproducible.

Ulceration Procedure[20]

16 rats were divided into 3 groups (4 to 6 rats in each group), microcapsule group, raw drug group and control group. The rats were fasted in screen-bottom cages for 24 hr prior to drug administration, then 20 mg/kg of the raw drug or the corresponding amount of microcapsules suspended in 1% gelatin solution was administered by gastric intubation. The animals were allowed access to drink water at all times. 6 hr later, each group of rats was sacrificed. At autopsy, after both the pylorus and esophagus were securely tied, 10ml of chloroform (1 v/v %) was injected into the gastric cavity to prevent excessive wrinkling of tissues. Then, the stomach was removed, opened along the line of greater curvature, and observed for the presenence of bleeding and the degree of ulceration. The results were described by means of the following ulcer index (U.I.).

$$U.I. = \frac{A-S}{S}$$

where A and S are the area of ulcer in test group and control group, respectively.

RESULTS AND DISCUSSION

Kawashima *et al*[21] has reported that the spherical agglomeration process had a problem of solid sticking to the interior of the mixing vessel, but the problem could be elminated by replacing the glass vessel with a polyethylene vessel and wrapping the metal baffles in teflon tape. In this study, this problem was reduced to some extent using a cylindrical vessel in place of a conventional beaker and metal baffles wrapped in teflon tape.

As large microcapsules were obtained at low agitation rate, 800 r.p.m. was adopted as an agitation rate considering the size of microcapsules produced.

Gelatin solution used as a surface-active agent led to severe aggregation at concentrations lower than 1%. Filtering and washing were difficult at concentrations higher than 4%. Therefore, 2% gelatin solution was employed.

Scanning electron micrographs of ethylcellulose microcapsules are shown in Figure 1. The microcapsules were spherical and had porous surface (Figure 1. A). No drug particles were seen on the surface of the microcapsules. These particles are essentially polynuclear microcapsules containing indomethacin. The porosity of the microcapsules increased with increasing the viscosity of ethylcellulose (Fig. 1. B,C and D). The pores can act as the entrance of solvent, therefore the porosity may affect release rate. According to Kawashima *et al*[21], the initial porosity is independent of particle size and mainly dependent on the initial bridging liquid

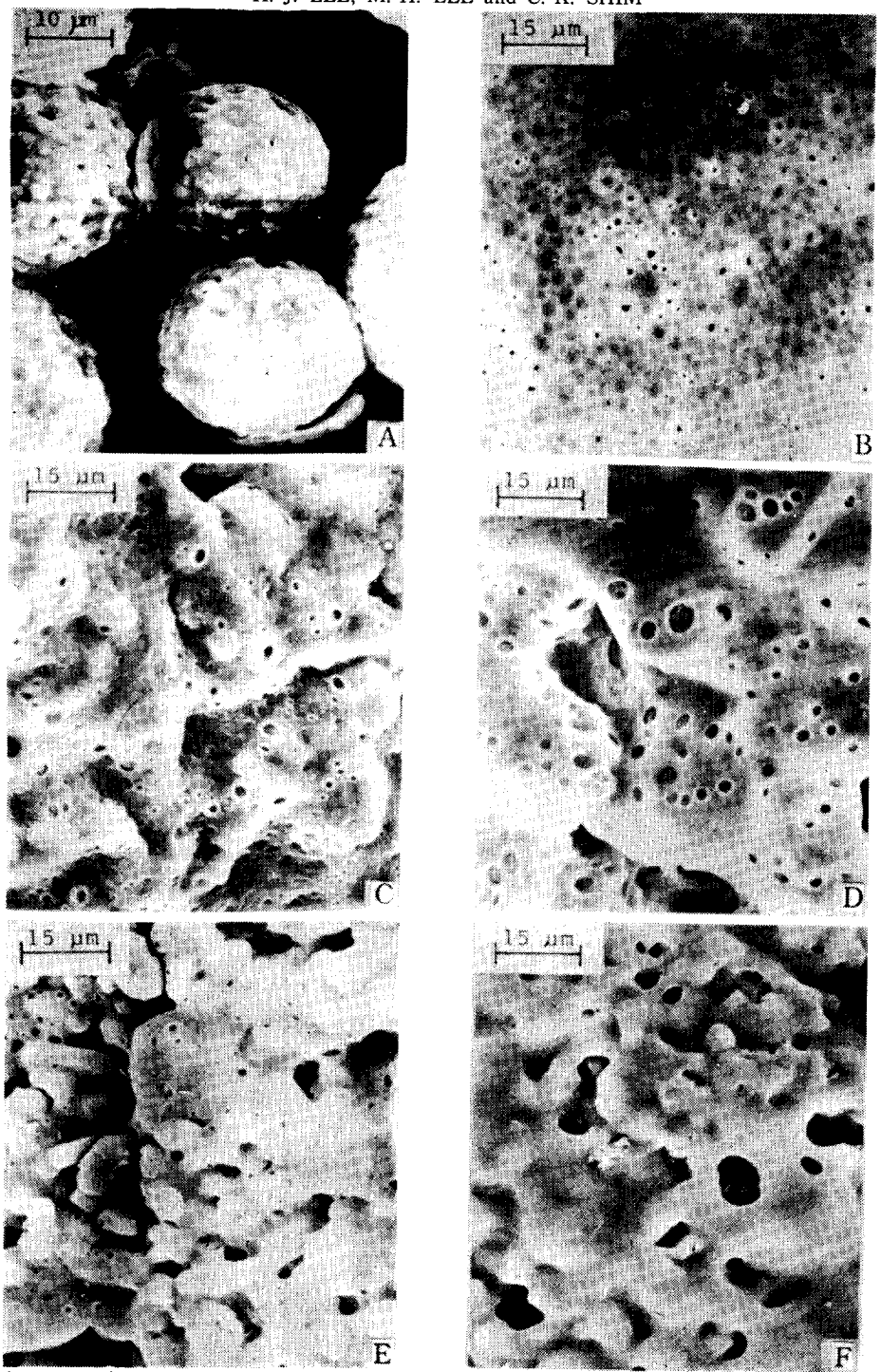


Fig. 1: Scanning electron micrographs of ethylcellulose (EC) microcapsules containing indomethacin (IMC). A~B) EC 20 cp, IMC: EC=2 : 1. C) EC 50 cp, IMC : EC=2 : 1. D of D) EC 100cp, IMC : EC=2 : 1. E) EC 20 cp, IMC : EC=4 : 1. F) After 3 hours of dissolution.

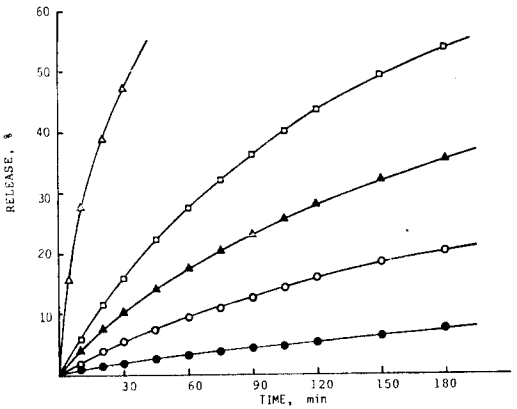


Fig. 2: Release(%) of indomethacin from microcapsules of various mean size. ●: 398.5μm, ○: 223μm, ▲: 111.5μm, □: 55.5μm, △: raw drug

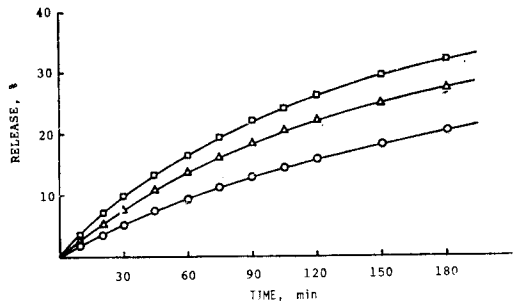


Fig. 3: Release(%) of indomethacin from microcrocapsules (mean size; 223μm) prepared with ethylcellulose 20 cp (○), 50 cp (△) and 100 cp (□).

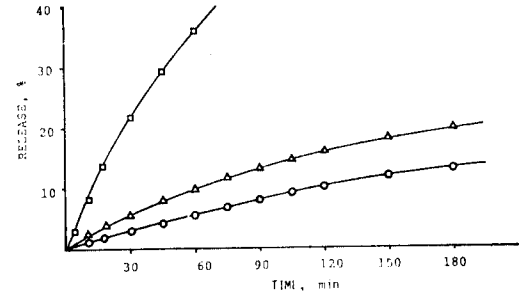


Fig. 4: Release(%) of indomethacin from microcapsules (mean size; 223μm) preparedat various indomethacin to ethylcellulose ratios. ○: 1:1, △: 2:1, □: 4:1

level. Thus, it seems that the porosity and consequently release rate of microcapsules can be controlled by adjustment of the viscosity or concentration of ethylcellulose. The high weight ratio of indomethacin to ethylcellulose led to roughness of the surface and friability of microcapsules (Figure 1. B and E). This resulted from that microcapsules couldn't be encapsulated sufficiently at high ratios of indomethacin owing to lack of the polymer. Figure 1. F shows that the surface of microcapsules after 3 hr of dissolution test was eroded with a slightly enlarged pore, in contrast to Figure 1. D.

Figure 2 shows the effect of microcapsule size on the release rate of indomethacin. Release of all the microcapsules was delayed, compared with that of the raw drug. As the diameter of microcapsules was increased, release rate decreased probably because of a decrease in the effective surface area.

Release rate increased as the viscosity of ethylcellulose was increased (Figure 3). Deasy et al[22] has reported that the release rate from microcapsules coated with ethylcellulose 10 cp was greater than that from microcapsules coated with 20 cp or 100 cp, probably because of the greater fragmentation and porosity associated with increased swelling of the polymer. Contrary to the report, the release rate of indomethacin from our microcapsules increased as the viscosity of the polymer was increased. This result seems to aggre with the scanning electron microscopic observation that the porosity of microcapsules increased with increasing the viscosity of the polymer, causing an increase in penetration rate of the dissolution solvent.

Figure 4 shows that the release rate increased as the weight ratio of indomethacin to ethylcellulose was increased. This may be due to the

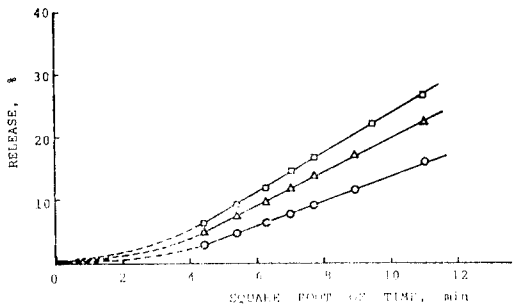


Fig. 5: Square root of time plot of Fig. 3. ○: 20 cp, △: 50 cp, □: 100 cp

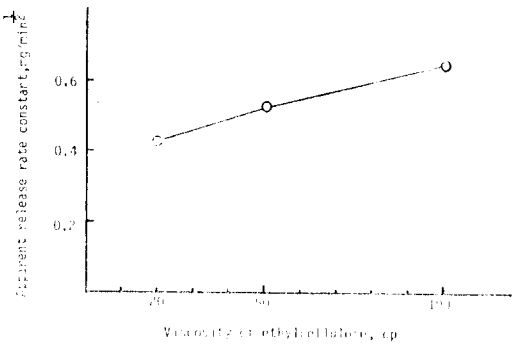


Fig. 6: Apparent release rate constant (K) obtained from Fig. 5 as a function of the viscosity of ethylcellulose.

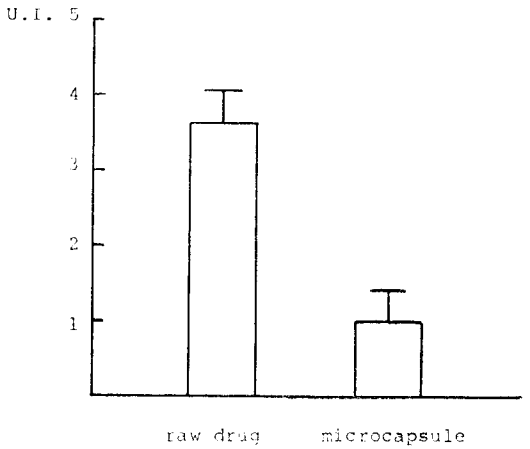


Fig. 7: Comparison of ulcerogenic effect of indomethacin (20mg/kg) administered orally. Ulcer index (U.I.) was determined 6 hours after the drug administration. ($n=4$, $p<0.01$)

enlargement of the surface area associated with the increased roughness of surface of the microcapsules as the ratio of indomethacin increased. (See also Figure 1)

The drug release from insoluble polymer matrix-type drug delivery system in which the drug is homogeneously dispersed as discrete crystals or solid particles occurs by a diffusion-controlled process after a finite period of drug elution, and can be described by the following Higuchi's equation:

$$Q=[D(2A-Cs)Cs\cdot t]^{1/2} \quad (1)$$

where Q is the cumulative amount of drug released from a unit surface area; D is diffusivity; A is initial concentration; Cs is solubility of the drug in the matrix; and t is time. In the homogeneous case, drug release is directly proportional to the square root of time. Equation 1 then reduces to

$$Q=K\cdot t^{1/2} \quad (2)$$

where K is the release rate constant given by

$$K=[D(2A-Cs)Cs]^{1/2} \quad (3)$$

Plotting of the data from Figure 2 according to the above equation is shown in Figure 5. Linear relationship existed between the quantity released and the square root of time after 30 min of dissolution test. The first 30 min is thought to be the lag time, the time required for a penetrant to establish a uniform concentration gradient. Therefore, the release process of indomethacin from the microcapsules seems to be diffusion-controlled. Relationship between apparent release rate constants (K') obtained from the slope of the graph in Figure 5 and the viscosity of ethylcellulose was linear (Figure 6). Therefore, release rate of ethylcellulose microcapsules may be controlled by adjusting the viscosity of ethylcellulose.

Microcapsules were evaluated by means of ulcer index which indicated the degree of gastric

ulcer induced in rats. The ulcer index is shown in Figure 6. As expected, microcapsules induced less gastric ulcer in rats than raw drug. This may be largely due to the reduction of a stimulant effect of indomethacin on the stomach in the case of microcapsules.

CONCLUSION

Indomethacin microcapsule was prepared using ethylcellulose as a wall material. The surface of microcapsules appears to be porous and rough, and the porosity increased with increasing the viscosity of ethylcellulose. *In vitro* dissolution process followed Higuchi's diffusion model for first 3hr. The release rate of indomethacin from ethylcellulose microcapsules was less than that from the raw drug. Release of indomethacin from microcapsules was delayed greatly as the viscosity of ethylcellulose or the weight ratio of indomethacin to ethylcellulose was decreased, and as themicrocapsule size was increased. Ethylcellulose microcapsule of indomethacin induced significantly less gastric ulcer than the raw drug in rats.

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