Microencapsulation of a Slightly Soluble Drug by Surface Neutralization Method Using an Enteric Polymer[1)]

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Succeeding our previous study on enteric microencapsulation by surface neutralization method for acidic drugs, a new means of application was developed for the encapsulation of non-acidic drugs. Indomethacin was chosen as a model drug in this study because of its low solubility in water and non-acidicity. Carboxymethylethylcellulose (CMEC) was used as enteric polymer as previously.

Indomethacin was not encapsulated as it was, but the encapsulation could be done using its core granules added with an organic acid. Thus, the influences of preparation temperature, species of organic acid and its concentration in the cores as well as the species of binder on the properties of resultant microcapsules (MCs) were examined.

CMEC content in MCs increased as the temperature increased. The CMEC content prepared using maleic acid was higher than that prepared using fumaric acid. These phenomena were correlated with the dissolution rate of organic acid from the cores during the manufacturing process and the phase separation of CMEC determined at various temperatures and pH.

MCs having thick films prepared at high temperatures did not always have high resistance to the dissolution of indomethacin in the 1st fluid. The most effective membrane was obtained when MCs were prepared at around 20 °C.

Binders used in the cores affected the CMEC content in MCs and the dissolution rate of indomethacin. Hydrophobic ethylcellulose (EC) depressed the dissolution more strongly than did hydrophilic polyvinylalcohol (PVA).

Keywords microcapsule; enteric coating; carboxymethylethylcellulose; indomethacin; organic acid; *in vitro* release; neutralization

Some drugs, when administered orally, are decomposed by gastric juice and consequently lead to poor bioavailability[2)] or gastrointestinal side effects by direct contact with gastric mucous membrane.[3)] Pharmaceuticals with an enteric property are beneficial for use with these drugs. They remain in an intact form during passage through the stomach and do not release the drug until they transit to the duodenum.

Enteric coatings are also used for sustained released dosage forms, however, bioavailability of the drug differs with the dosage form because gastric emptying times (GET) of pharmaceuticals vary greatly, especially when drugs are administered after a meal.[4)] It is generally accepted that multiple unit dosage forms vary less in GET than single unit dosage forms[5)]; thus various techniques for preparing multiple unit dosage forms with enteric properties have been developed. Spray coating is the most recent method and it is usually applied to granules ranging in size from 0.8 to 1.5 mm. Microcapsules (MCs) with diameters of less than 0.5 mm are ordinarily difficult to prepare by this method, because of the possible aggregation of cores in the coating process. Reduction in particle size results in an increase of surface attractive forces and generally causes a serious production problem.[6)]

To obtain smaller enteric polymer coated particles, microencapsulation in liquid phase by either chemical or physicochemical means seems to hold many advantages over spray coating.[7)] The phase separation method using a combination of good and poor organic solvents[8)] or the solvent evaporation method[9)] has been employed for this purpose. However, microencapsulation from aqueous solution has the benefits of reducing air pollution,[10)] increasing safty in the workplace and lowering manufacturing cost. Merkle and Speiser[11)] reported a phase separation method involving the use of sodium sulfate in an aqueous solution, but this requires strict control of the preparation conditions.

We have developed a new technique[12)] called the surface neutralization method. When crystals of a sparingly soluble acidic drug are poured into a solution containing an enteric polymer previously dissolved with the aid of an appropriate amount of alkali, the aqueous phase near the crystal surfaces changes from alkaline to acidic. Consequently, the dissolved enteric polymer becomes locally insoluble, adheres to the drug surface and forms a seamless film enveloping the crystals uniformly.

In a previous work,[12)] we applied this method to aspirin which itself shows an acidic property in water. The present step was undertaken to extend the method to non-acidic drugs. Indomethacin was chosen as a model drug because it is non-acidic and slightly soluble in water and has an irritant side effect[13)] on the mucous membrane. To aid the film formation, microencapsulation was attempted by preparing core granules containing indomethacin and an organic acid. The influence of the species of organic acid, binder or preparation condition was examined using carboxymethylethylcellulose (CMEC) as an enteric polymer.

Experimental

Materials Indomethacin was of JP grade and obtained from Yachidai Seiyaku Co., Ltd. Maleic acid and fumaric acid were obtained from Katayama Chemicals Ltd. Polyvinylalcohol (PVA), ethylcellulose (EC), CMEC and polyoxyethylene derivative of hydrogenated castor oil (HCO-60) were obtained from The Nippon Synthetic Chemical Industry Company, Dow Chemical Company, Freund Ind. Co., Ltd. and Nikko Chemicals Co., Ltd., respectively. All other chemicals used were of the highest grade commercially available. All materials were used without further purification.

Preparation of Core Materials The compositions of core materials are shown in Table I. The mixture of powdered indomethacin and organic acid (maleic acid or fumaric acid) was kneaded with a 10% binder solution (EC or PVA was dissolved in 80% alcohol). If necessary, 80% alcohol was added in granulation.

The kneaded mass was extruded through a 0.5 mm screen using of a

TABLE I. Compositions of the Core Materials Used in This Study

Core No.	A	B	C	D	E	F
Indomethacin (g)	97	92	87	77	77	77
Maleic acid (g)		5	10	20		
Fumaric acid (g)					20	20
PVA (g)						3
EC (g)	3	3	3	3	3	

blade-type extruder (basket-type granulator) and the wet strings extruded were cut into pieces of an appropriate length. After drying the resultant granules at 45 °C for 4 h, they were successively sieved through a 28 mesh (590 μm) and 60 mesh (250 μm) screen and used as the core materials. The average diameter determined from microphotographs of the granules was about 450 μm (n=about 100).

Preparation of Microcapsules Three grams of CMEC was dissolved in 100 ml of water by adding 2.25 ml of 10% sodium hydroxide solution. The solution was maintained at a given temperature (from 1 to 60 °C) and core materials (5 g) were poured into the solution. The resultant slurry was agitated for 15 min at a stirring rate of 400 rpm. The MCs produced were recovered by decantation, washed with water and dried at 45 °C overnight. Coagulations occurred primarily during the reaction process and were rarely observed in the drying process. This is an advantageous point in using CMEC as enteric polymer. (Preliminary experiments revealed that coagulation often occurred in this microencapsulation process with other enteric polymers used in place of CMEC).

Assay of Indomethacin and Organic Acid Powdered MCs were dissolved in methanol–phosphate buffer solution (pH 7.0) containing tryptophan as the internal standard. Twenty microliters of this solution was subjected to high-performance liquid chromatography (HPLC). HPLC was carried out using a Shimadzu-5A apparatus equipped with a NUCLEOSIL $5C_{18}$ column (0.46 i.d. × 15 cm) and a Shimadzu SPD-2A UV monitor (254 nm). Methanol–0.01 M phosphate buffer solution containing 5 mM tetrabutylbromide was employed as a mobile phase at a flow rate of 1.0 ml/min.

CMEC Content in MCs If possible, the CMEC content in MCs is better determined by direct assay, however, a proper assay method was difficult to discover, therefore, it was calculated as:

$$\text{The CMEC content in MCs (\%)} = 100 \times (A_{MC} - (A_{OA} + A_{IM} + A_{BI}))/A_{MC}$$

where, A_{MC}, A_{OA}, A_{IM} and A_{BI} mean the amount of whole MC, organic acid, indomethacin and binder, respectively. A_{MC} was determined by weighing whole MCs obtained after the above microencapsulation procedure. A_{OA} and A_{IM} were determined by assaying the organic acid and indomethacin as described above. It was also difficult to estimate A_{BI}, because a proper assay method of PVA or EC could not be found. Therefore, it was calculated assuming that not all the binder used was lost during the microencapsulation process and was recovered in whole MCs. This assumption is reasonable, because neither EC nor PVA is dissolved in water (PVA dissolved only in hot water). In addition, as the amount of the binder used was relatively small compared to indomethacin or organic acid, error attributable to this assumption is small.

Observation of Phase Separation Three hundred milligrams of CMEC was dispersed in distilled water (10 ml) in a 30 ml test tube and was dissolved by the addition of 225 μl of 10% NaOH solution. Then the resultant solution was kept at a constant temperature and was adjusted to a given pH (from 1 to 5) by the use of 10% HCl solution. After standing at constant temperature for 1 h, the physical appearance was noted.

Dissolution Studies Dissolution rate of indomethacin from MCs containing 40 mg of the drug was determined in 900 ml of the 1st and the 2nd disintegration test fluids (JP XI) by the paddle method using an auto-sampler (Toyama Sangyo Co., Ltd.) at 37 °C and the agitation speed of 100 rpm. In the 1st fluid, 1% HCO-60 was added in order to attain a sink condition for indomethacin.

Classification of MC The percentage of single-nuclear MC was estimated from MCs with particle sizes between 250—590 μm and was denoted as $Y_{250-590}$.

Results and Discussion

Effect of Organic Acid and Its Concentration Microencapsulation was attempted using core A in Table I,

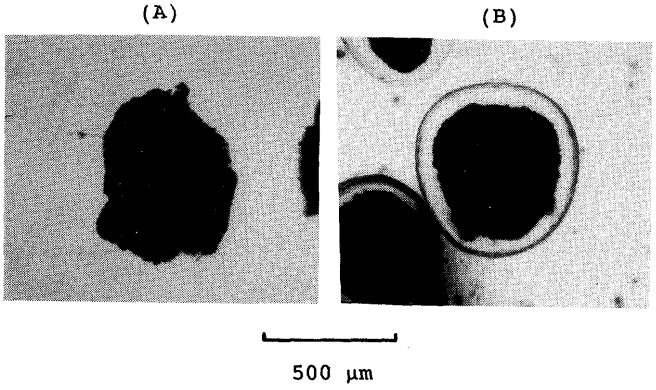

Fig. 1. Photomicrographs of Indomethacin Microencapsules
(A) and (B): Prepared using cores A and B in Table I.

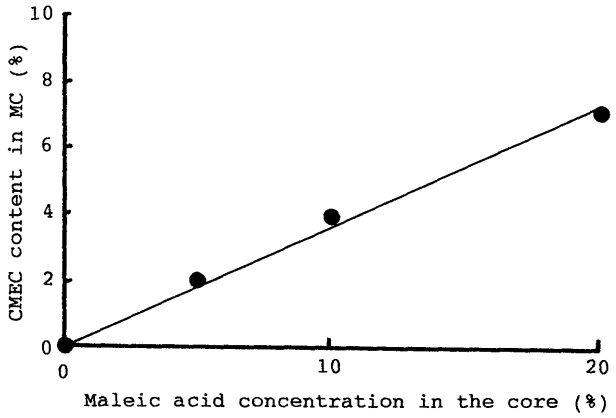

Fig. 2. Influence of the Maleic Acid Concentration in the Core on the CMEC Content in MC
Microencapsulation was performed at 25 °C using 5 g of core (A, B, C or D), 3 g of CMEC, 2.25 ml of 10% sodium hydroxide and 100 ml of water.

since the dissociation constant of indomethacin is 4.6[14] and was expected to be encapsulated as it was. In this case, however, CMEC films were not formed on the surface of the core particles (Fig. 1A).

The pH of the CMEC solution remained almost constant (7.0) after the addition of core A, presumably due to the low solubility (practically insoluble in water)[15] and higher pK_a value of indomethacin than aspirin (solubility in water: 3 mg/ml at 25 °C, pK_a: 3.5).[16] On the other hand, thicker walls were formed when core B was used (Fig. 1B). The mechanism is considered to be as follows. When the core granules are poured into the CMEC solution, the organic acid in the cores dissolves and causes lowering of the pH of the encapsulation medium near the cores. Then, the dissolved enteric polymer becomes locally insoluble, adheres to the core surface and forms a seamless film uniformly enveloping the core material. The pH of the solution decreased to 3 from 7 after microencapsulation had been completed. As CMEC became insoluble at pH 3, the wall prepared was stable in the medium following completion of the reaction. The result suggests that the extended application of this surface neutralization method is possible to a drug, which is not encapsulated as it is, by the addition of organic acid.

Figure 2 shows the influence of the maleic acid concentration on the wall formation using cores B, C and D in Table I at 25 °C.

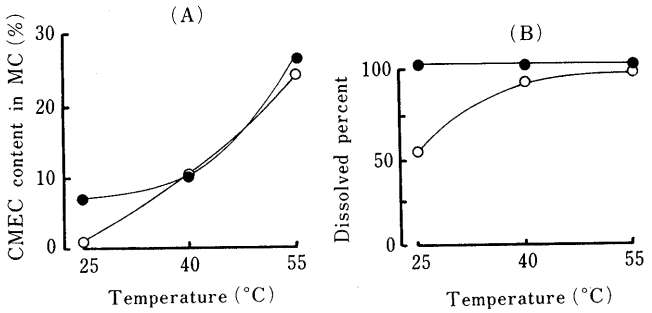

Fig. 3. Influence of Microencapsulation Temperature on CMEC Content in MC (A) and the Dissolved Percent of Organic Acid from Cores during the Microencapsulation Process (B)

●, maleic acid; ○, fumaric acid. The microencapsulation condition was the same as that described in Fig. 2 except that cores D and E were used.

CMEC content in MCs increased linearly as the maleic acid increased and was about 7% when the acid concentration was 20%. This should be interpreted as the increase in the amount of organic acid dissolved from the cores and entering the CMEC solution. The pH near the surface of the cores containing a large quantity of organic acid could be lower than pH of the cores containing less organic acid. The result in Fig. 2 thus suggests that wall thickness can be controlled by the concentration of organic acid in the cores.

Effect of Preparation Temperature Figure 3A shows the CMEC content in MCs when they were prepared at various temperatures using cores D and E containing respectively 20% maleic acid or 20% fumaric acid.

As shown in Fig. 3A, the CMEC content increased with the increase of the preparation temperature. At 25 °C, CMEC content in MCs prepared using maleic acid was higher than in those prepared using fumaric acid. This would be caused by the difference in pH near the cores due to the difference in solubility between maleic acid (about 65% at 25 °C) and fumaric acid (about 1% at 25 °C). CMEC content did not differ between the two MCs above 40 °C.

The dissolution percent of the organic acids from MCs during the microencapsulation process is shown in Fig. 3B. The values were greatly different at 25 °C between the two acids, but were almost equal above 40 °C. This phenomenon was coincident with the result shown in Fig. 3A that CMEC content differed at 25 °C but was almost the same above 40 °C. However, for maleic acid it was typical that CMEC content differed greatly with preparation temperature, although temperature did not affect the dissolution percent.

The reason for this may be that the wall formation is not affected only by the amount of acid released but also by its release rate. That is, the release rate of organic acid at the initial stage of the microencapsulation process could increase with increasing temperature. Then, pH around the core at the initial stage could be lower at higher temperature, and the neutralization reaction could be accelerated. Another possible reason may be that the change in polymer characteristics with temperature affects film formation. Figure 4 shows a phase diagram of CMEC in aqueous medium at various pH and temperatures.

As shown in Fig. 4, all the phase transitions, from region D to C, C to B and B to A, occurred at higher pH as the temperature increased. This suggests that the amount of

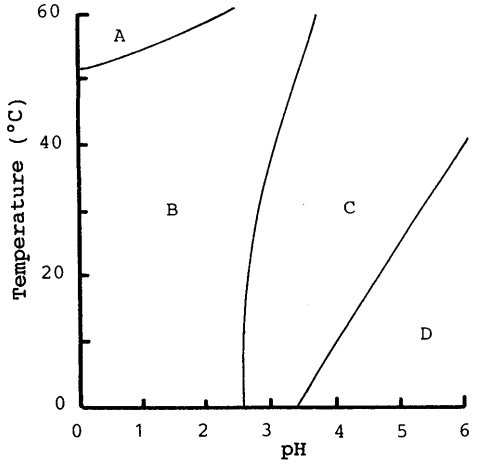

Fig. 4. Phase Diagram of CMEC in Aqueous Medium

Region A: Phase separation occurred. The polymer rich phase was viscous and hard gel state. Aqueous phase was transparent and homogeneous. Region B: Phase separation occurred. Polymer phase was viscous and soft gel state. Aqueous phase was transparent and homogeneous. Region C: Cloudy dispersion. Region D: Transparent aqueous solution.

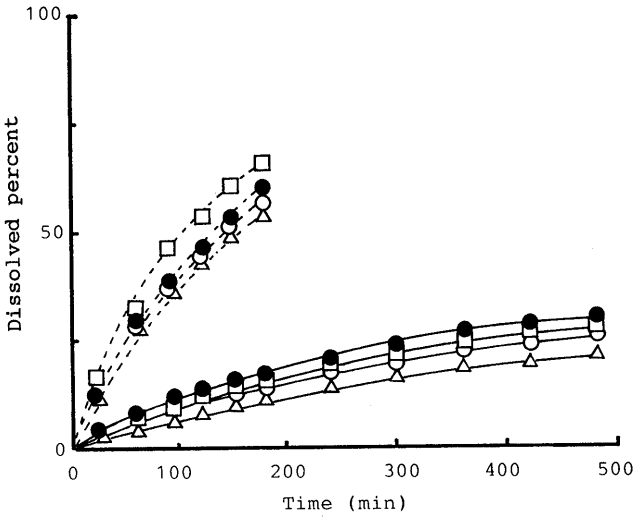

Fig. 5. Dissolution Percent of Indomethacin from the MCs Prepared at Various Temperature

The granules D were used as the core material (solid line, the 1st fluid containing 1% HCO-60; dashed line, the 2nd fluid). ●, core; △, MC prrepared at 25 °C; ○, 40 °C; □, 55 °C.

acid necessary for the phase transition is less at higher temperature. A similar phenomenon known in *o*-methylcellulose; it was apt to precipitate as temperature increased due to the reduced affinity of its hydrophilic group to water.[17] Rising temperature may increase the cohesive force of the polymers to cores, and increase the CMEC content in MCs.

Figure 5 shows the dissolution curves of indomethacin in the 1st fluid containing 1% HCO-60 and the 2nd fluid from MCs prepared at various temperature using core D. In the 1st fluid without HCO-60, indomethacin did not dissolve out at all. HCO-60 penetrated the MCs together with water molecules and dissolved the drug inside the MCs. The resultant concentration difference of indomethacin inside and outside the MCs would be the force driving the release.

In the 1st fluid the dissolution rate the slowest in the MCs prepared at 25 °C, and became faster as the preparation

temperature increased. The dissolution rate from MCs prepared at 55 °C was almost equal to that of the core.

In the 2nd fluid, MCs prepared at 25 and 40 °C showed a little slower dissolution rate than the cores, whereas those prepared at 55 °C showed a little faster dissolution rate than the cores. These results have much similarity with those shown in Fig. 8 and seem to the MC surface state. The reasons will be discussed later.

Effect of Binder Used in Core Materials In the above cases, the dissolution rate of indomethacin from the core itself was slow in the 1st fluid and the efficiency of enteric coating was relatively small. This might be due to the hydrophobic property of EC used as a binder for the preparation of core material. It may restrict the penetration of water molecules into the cores and the subsequent release of indomethacin. Thus the influence of the binder species was compared using cores E and F of which binders were hydrophobic EC and hydrophilic PVA, respectively. The effect of preparation temperature on CMEC content and released percent of fumaric acid is shown in Fig. 6.

CMEC content and dissolution percent of the acid increased as the temperature increased in both cases, but were always greater in the PVA cores than in the EC cores. Penetration rate of water into the cores was faster in the PVA cores because of its hydrophilic properties, consequently, the organic acid from the core could dissolve out easily and increase CMEC content.

Figure 7 shows the dissolution percent of indomethacin in the 1st fluid containing 1% HCO-60 from the MCs prepared at various temperatures using core F. The dissolution rate from each MC was very slow compared with the cores.

In Fig. 8, the times for 50% dissolution (T_{50}) in the 1st and 2nd fluids are plotted against microencapsulation temperature together with CMEC content in MCs.

It is interesting that the dissolution rate in the 1st fluid was not greatly much depressed from the MCs prepared above 40 °C, although their CMEC content was increased. This tendency is also observed in the results shown in Fig. 5 and in the aspirin MC.[12] Microscopic observation revealed that the MC surface was very smooth and uniformly covered when prepared at low temperature, but was rough at higher temperature. Especially at above 55 °C, many large cracks were generated; these cracks might be created by the differences in thermal expansion of the coating film and the core materials as discussed by Rowe.[18]

Another reason may be that the release of organic acid from the cores is too rapid (Fig. 7B) to form a smooth and effective membrane on the core surface due to the increase of temperature. To support this presumption, the percent of MCs with a particle size of from 250 to 590 μm ($Y_{250-590}$) is also shown in Fig. 8 as an index of the yield of single core capsules. $Y_{250-590}$ were high below 20 °C and decreased above 30 °C. This could indicate that the reaction between CMEC and organic acid was too rapid to envelope each MC separately, consequently complex numbers of MCs were coagulated by precipitated CMEC. Thus, a wall produced at low temperature was presumed to be compact, while that produced at high temperature was assumed to be coarse. T_{50} increased at lower temperature following the increase of wall thickness. However, at above 30 °C the wall became so coarse that dissolution rate was not delayed by the increased wall thickness. Due to the above two effects on the dissolution rates, T_{50} would have a maximum around 20 °C as shown in Fig. 8.

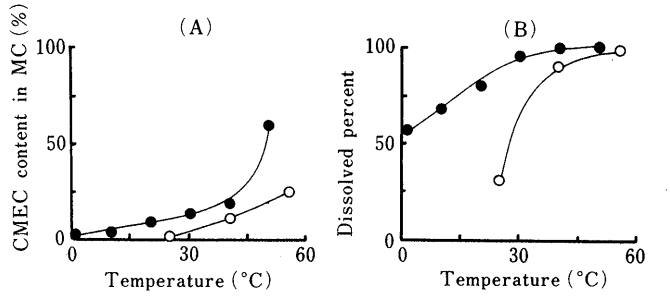

Fig. 6. Influence of the Binder Species on CMEC Content in MC (A) and the Dissolved Percent of Organic Acid from the Cores during Microencapsulation Process (B)

The microencapsulation conditions were the same as those described in Fig. 2 except the core used (E and F). Binder: PVA (●), EC (○).

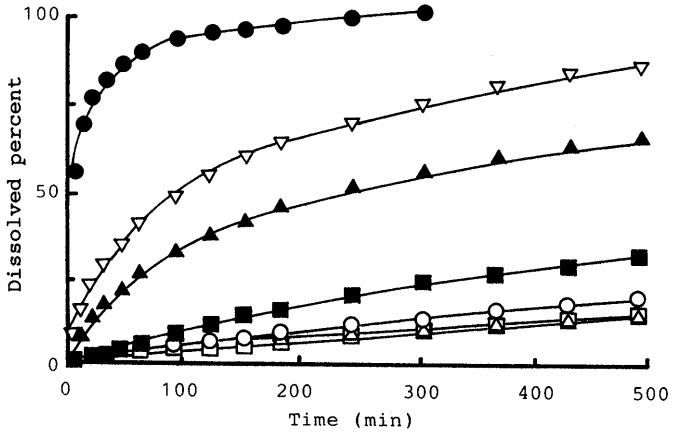

Fig. 7. Dissolution Profiles of Indomethacin from the MCs Prepared at Various Temperatures Using Core F in Table I

The microencapsulation conditions were the same as that described in Fig. 2. ●, core: ■, MC prepared at 1 °C; ○, 10 °C; □, 20 °C; △, 30 °C; ▲, 40 °C; ▽, 50 °C. Test solution: the 1st fluid containing 1% HCO-60.

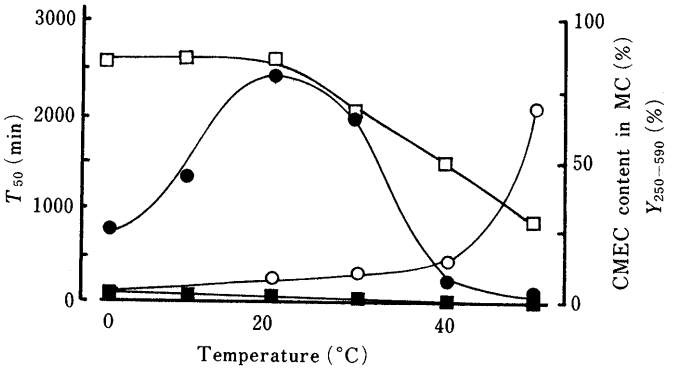

Fig. 8. Influence of Microencapsulation Temperature on the Dissolution Rate and Wall Formation and $Y_{250-590}$

The microencapsulation conditions were the same as those described in Fig. 2. ○, the CMEC content in MC; ●, T_{50} in the 1st fluid containing 1% HCO-60; ■, T_{50} in the 2nd fluid; □, $Y_{250-590}$.

In the 2nd fluid, the dissolution rates were very rapid in all MCs.

Comparing the results in Figs. 5 and 7, the efficiency of enteric coating was more obvious in core F than core E, of which binders were PVA and EC, respectively. In MCs

prepared using EC, the rate determining step of dissolution in the 1st fluid would be the migration of the indomethacin through the core matrix and not through the coating films; while in MCs prepared using PVA, it would be the diffusion process through the membrane on the contrary. This result suggests that the core formulation has great effect on MC properties as well as on drug properties.

Therefore, it can be concluded that the method allows MCs having various dissolution properties to be obtained for non-acidic drugs when a proper binder and organic acid are used.

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