CHAPTER 4

DISCUSSION

The experiment was designed in such a way that only the effect of single individual polymer on release pattern of indomethacin was studied, therefore two major components presented in each formulation were drug and a cellulose derivative. Wet granulation process was used because of two main reasons :

1. Cellulose derivative itself could act as a binder, it can be used in both dry form granulated with water or organic solvent, and solution.

2. Poor granule flowability and hence tablet uniformity could occurred if the process of direct compression was used because both indomethacin and Methocel exhibited poor flow property. The presence of large amount of flow aids or direct compressible diluent to improve flowability, if direct compression was selected, would affect tablet disintegration time and also indomethacin release pattern.

In wet granulation, water sprayed onto the mixture of drug and hydrophilic cellulose caused partial hydration of polymer with binding property and the matrix between drug and polymer was obtained.

Hydration occurred when molecules of water attached to the hydroxyl (-OH) groups along the cellulose chain. So hydration capacity was depended on the amount of -OH groups on each molecule of cellulose. As shown in Figures 2,3 and Tables 5,6, the amount of -OH groups substituted in the molecule of Methocel as well as hydration capacity could be ranked from maximum to minimum as Methocel K, E and A. Because the cellulose turned viscous and

exhibited binding property while hydrating, thus wet mass or matrix prepared from polymer with high hydration capacity might be stick and difficult to be sieved. This was correlated to the results that wet mass prepared from Methocel K was sticky and more difficult to be sieved than Methocel A and E, respectively. It can be concluded that hydration capacity of Methocel should be taken into account of criteria in selection of the type and amount of hydrophilic cellulose derivatives to produce matrix via wet granulation process.

For hydrophilic cellulose derivatives, the increase in the amount of polymer (Methocel A, E and K) in formulation increased the amount as well as the rate of drug release. This depended upon various factors. Indomethacin is a sparingly water soluble drug, the present of water soluble or hydrated substances should increase the amount of water attached to the drug in the matrix, thus increased the wettability. The increase in the amount of hydrophilic cellulose derivatives in formulations should increase the amount of drug dissolved. As a result, more drug release was observed.

Basic structure of cellulose molecule or its derivatives allied on long chain of 1,4-β-D-linked polyanhydroglucopyranose with or without substituted groups on the three hydroxyl (-OH) groups of each glucopyranose ring. This long chain was called elementary fibril. When two or more chains came close enough together latterally to lock in any way, the crystallite was formed. A crystallite consisted of a cluster of associated long chain molecules. The disordered part of elementary fibrils which were not close together but random placed or tied over each other was called the less-ordered or amorphous region (51,52). Typical fine structure of these two regions is illustrated in Figures 22-23. The accessibility of cellulose was generally conceived as the reactivity towards a giving reagent (53,54). Two main accessibility were

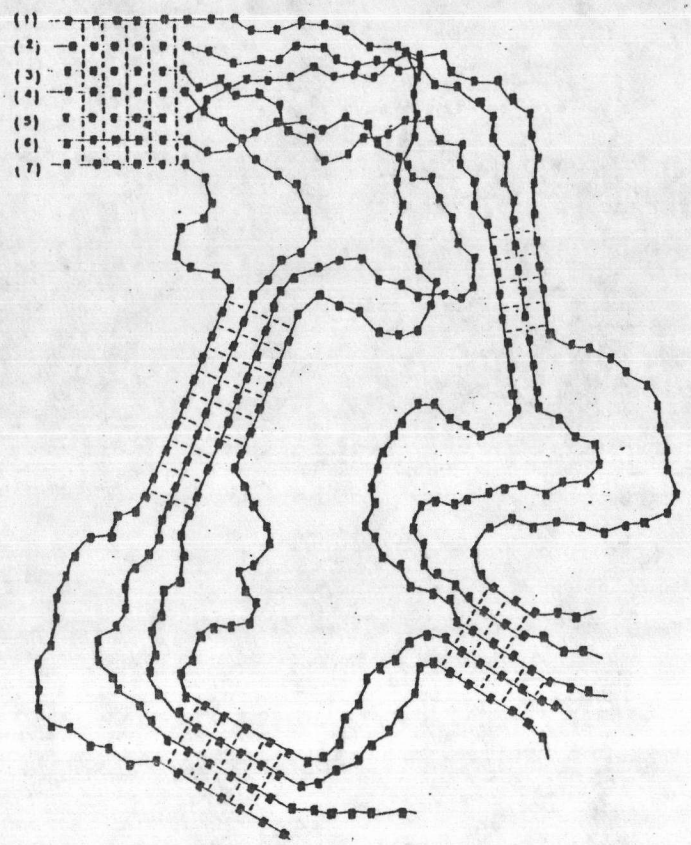

Figure : 22 Diagram Showing Cellulose Molecules banded together to form Ordered Nuclei (Crystallites).

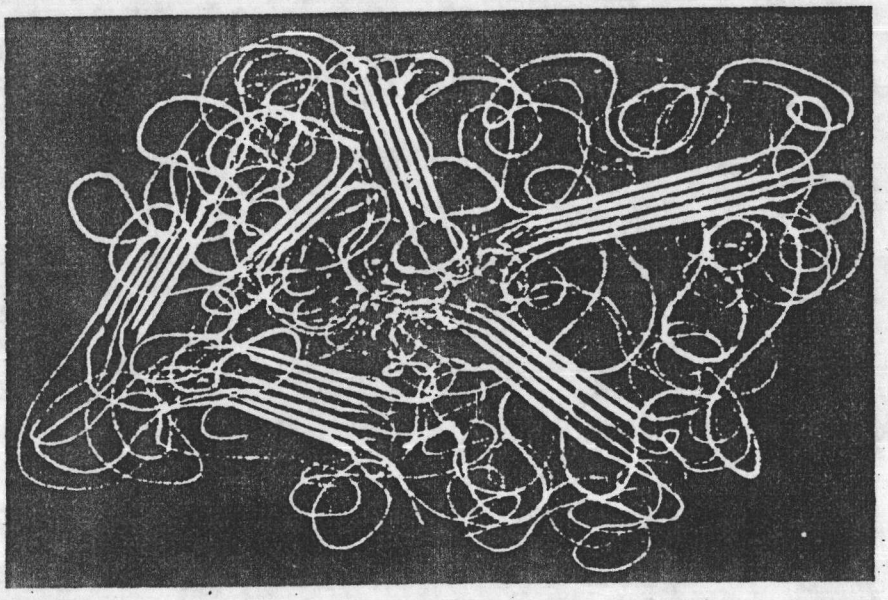

Figure : 23 Sketch showing Crystalline Areas embedded in a Matrix of Disorganized Chains of Cellulose.

usually found, first was the amorphous regions (included connecting chains and the disordered parts of the elementary fibrils), the second was the surface of the crystallites (54). All interaction in adsorption, exchange or substituted process occurring in fibers state started on the surface of the elementary fibrils or crystallites and from the accessible interlinking regions (52). In the present of water, the molecules of water caused first swelling and stretching of cellulose fibers by latching on the available -OH groups along the elementary fibers in amorphous regions (55), and also bounded with the other molecules of water surrounded fiber cause the increase in diameter of fiber. Cleavage of H-bond may occure and the intra and inter-molecular forces may decrease. The hydrated polymer chain would be relaxed or unfolded when bounded with molecules of water as illustrated in Figure 24(56). As a result of chains cleavage (relax or unfold), molecules of indomethacin which in the former existed close to polymer chain or probably connected to them by Van de Wal force or H-bonding were pushed or forced to located in the looser state and eroded or released from matrix. The same phenomenon also occurred at the elementary fibrils on the surface of crystallites and slowly occurred inwards.

In summary, more water penetrating through matrix, an increase in the wettability of drug, and an increase in the amount of the relax or cleavaged cellulose chains resulted in the increase of indomethacin released from tablet as the amount of hydrophilic celluloses increased.

The release profiles of tablets containing Methocel E 5 and E 15LV in Figures 11 and 12 showed that there was an optimal concentration of polymer which caused the fastest drug release. When the amount of polymer was more than this concentration the same maximum release rate was observed. The optimal concentration of Methocel E 5 was 15% while of Methocel E 15LV was 10%. This optamal

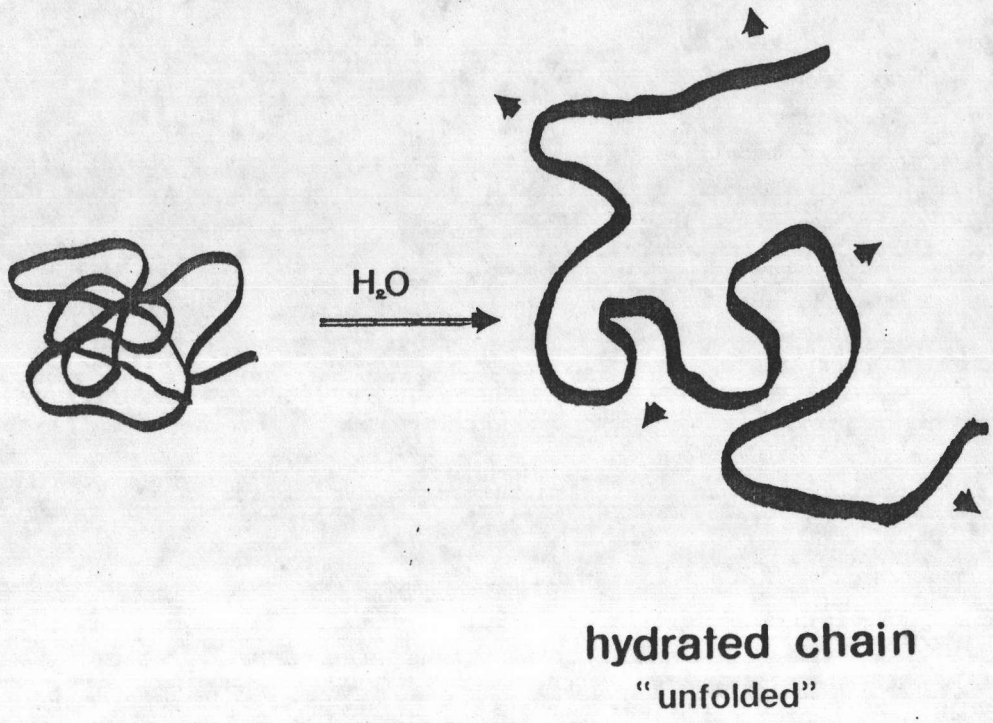

Figure : 24 Hydration Behavior of Cellulose Chain.

concentration was constant for one tablet system and may depend on various factors such as : type of hydrophilic cellulose as well as its hydration capacity, or properties and amount of drug or diluents used, or size of tablet.

The effect of molecular weight on release pattern was clearly observed when Methocel E (HPMC) was used. The higher molecular weight (Methocel E 15LV) caused more drug release than the lower one (Methocel E 5). This was because the chain of higher molecular weight polymer was longer thus its hydration capacity was more than the lower molecular weight polymer.

The H-bondings presented between long chains in crystallites also play an important role on the release of drug. They were much more and stronger than those in amorphous region due to its close pack of elemetary fibrils as mentioned before. The amount of H-bonding and its strength depended on the degree or molar substitution (DS) and the bulk or size of substituted groups. For DS, the more -OH groups were substituted the less amount of -OH groups could form H-bonding between cellulose chains. In addition, the larger the size of substituted groups were, the further the chains were separated, as shown in Figure 25 and the less H-bonding will occur (57). It could be assumed that the crystallites region in higher DS cellulose derivatives were looser than that in lower DS if both cellulose derivatives had the same molecular weight. So the molecules of water could intercalate between the packed chains in crystallites part of lower DS cellulose derivatives slower than they could in the higher DS cellulose. From structures of Methocel in Figures 2 and 3 together with degree or molar substitution in Table 6, DS of Methocel E (HPMC) was higher than Methocel A (methylcellulose), and Methocel E consisted of two substituted groups while Methocel A consisted of one. When considered the crystallites of Methocel E 15LV and Methocel A 15LV (which have the equal

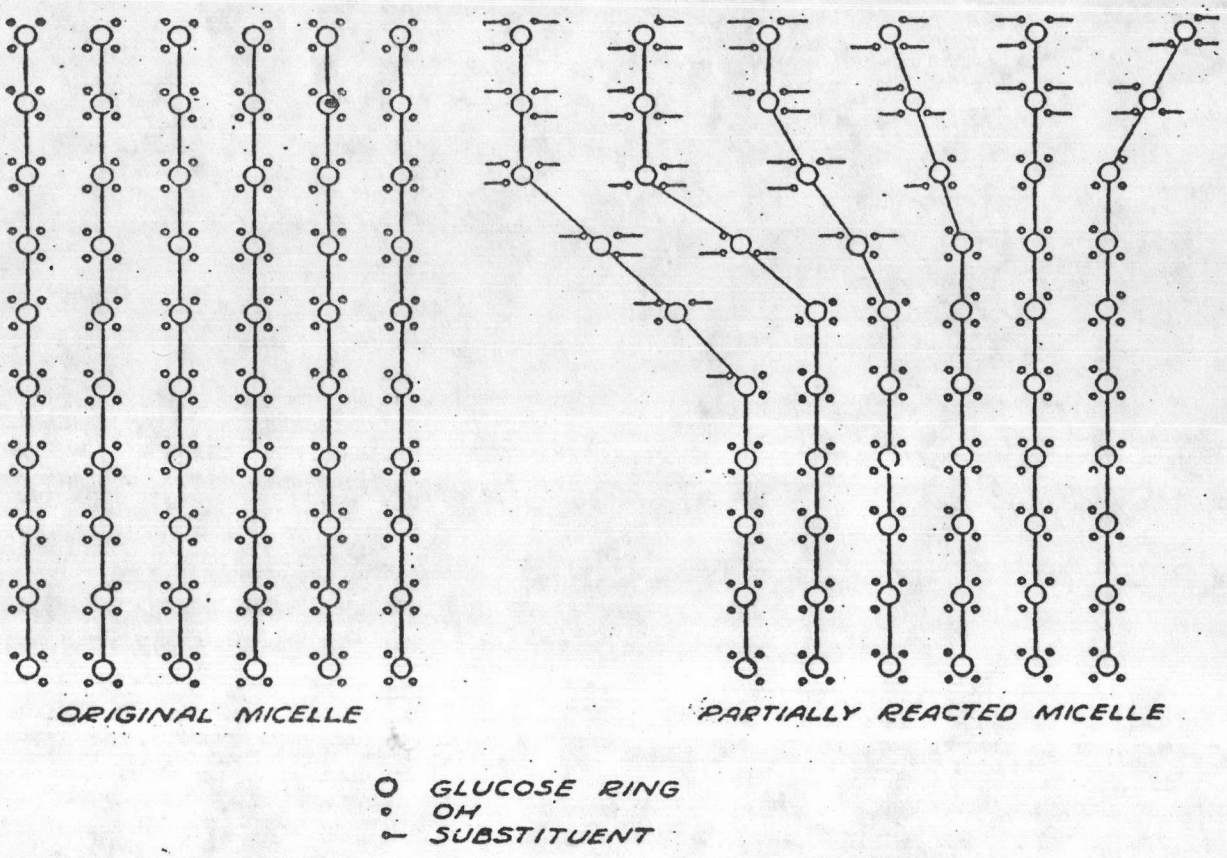

Figure : 25 Schematic Picture of the Initial Opening up of a Crystallite of Cellulose with the formation of a Cellulose Derivatives.

molecular weight) the crystallites of the former might be looser and hydrated faster than the latter. This explained the release profile shown in Figures 8 and 11 of which drug released faster from tablet containing Methocel E 15LV than from tablet containing Methocel A 15LV at every concentration. The same reason happened to the faster drug release from tablet containing 3% of Methocel K 100M than from 5% and 10% Methocel A 4M which were shown in Figures 10 and 13, respectively.

The release mechanism of formulations containing hydrophilic polymer seemed to be both diffusion and first order kinetics because the maximum r values were observed from both relationships between % drug released v.s. square root time and log % drug remained v.s. time as shown in table 21.

Ethylcellulose was water insoluble substance, the rate and maximum amount of indomethacin released from tablets containing this polymer was less than from tablets produced without polymer as shown in Figures 15 and 17. The increase in amount of ethylcellulose did not affect both release rate and maximum amount of drug release. To explain the reason for this phemomemon the release of drug from the blank tablet was discussed. Surface area of the blank tablet which exposed to dissolution medium consisted of only molecules of drug. While exposing to the medium the molecules of drug at the surface dissolved, the new molecules or inner surface would replaced and continued to expose to the same dissolution medium. The cumulative percent of drug released was 28%. When considered the tablet containing ethylcellulose, its surface area consisted of molecules or portion of drug mixed with chains or portion of ethylcellulose. In this case surface area of drug exposed to medium was less than the former (the blank tablet), thus the amount of drug release was reduced. Maximum amount of drug release from tablets containing ethylcellulose (5,10,15 and 20%) was 20%. Data from Table 18 showed

that the ratio between the amount of ethylcellulose increased and thickness increased was constant in both compressional pressures, it can be assumed that the ratio of indomethacin and ethylcellulose molecules which exposed to dissolution medium at surface area of tablet was also constant though the amount of ethylcellulose increased. Thus the amount of drug release as well as the rate was the same when increasing polymer concentrations. In this case dissolution might be the mechanism of drug release from tablet, by this mechanism dissolution rate was depended on the solubility of indomethacin. Slow release rate was observed because of poor solubility of drug.

For HPMCP, though it was reported to be insoluble in water, however it can dissolve in aqueous buffer solution at a particular pH. The HPMCP HP-50 used in this experiment was soluble in aqueous buffer solution at pH $\geq$ 5.0. The pH of medium used in this study was about 7 and the volume used was 900 ml which can be assumed to be a sinked condition thus HPMCP HP-50 can be dissolved in this medium.

Drug which existed close to the dissolved part of HPMCP HP-50 could be released thus the more amount of HPMCP used might increase the amount of drug release from tablet. However, the effect of the concentration of HPMCP on the amount of drug release was less when compared to that of hydrophilic celluloses because the solubility of HPMCP depended on the pH of medium. Correlation coefficients presented in Table 21 indicated that mechanism of drug release from HPMCP matrix might be first order kinetics that the release rate was proportional to the amount of drug left in matrix which related to the amount of dissolved HPMCP.

Compressional pressures did not affect the release of indomethacin in this study. The reason is that the hydration of celluloses play an important role on the release of drug from the matrix.

From the above discussion, the hydrophilic cellulose derivatives alone could not produce prolonged and constant indomethacin release rate due to its hydration and erosion effect. Hydrophobic part may be possible to form more rigid matrix with hydrophilic polymer which retarded the hydration and cleavation (erosion) of hydrophilic part. HPMCP 1% was the optimum concentration which could form a rigid or partial stabilized the matrix with Methocel E 5 10% (in combination 1), it can retard the release of drug for 12 hours. Correlation coefficient of combination 1 in Table 22 indicated that indomethacin release from tablet by diffusion and the release rate was constant according to Higuchi's equation. Different in the amount of drug release from combination 1 and 1 * at any time interval was statistically non-significant at $P \geq 0.01$.

However, HPMCP 1% could not retard the erosion effect from 7.5% Methocel E 15LV in combination 3. The r value from Table 22 indicated that indomethacin release from this system by first order kinetics. On the otherhand, ethylcellulose 5% formed more rigid matrix with Methocel E 5 10% in combinaiton 2 until the erosion of hydrophilic part was too slow. The drug released from tablet by first order kinetics.

Conclusion

Indomethacin sustained release tablets could be formulated by using combination between hydrophilic and hydrophobic cellulose derivatives which was Methocel E 5 10% and HPMCP HP-50 1%. This combination produced tablets which gave a complete drug release as well as linear profiles for 12 hours, the mechanism of drug release from tablet was found to be diffusion. Dissolution studies revealed that using only one type of cellulose derivatives could not achieve the sustained release system. The effect of concentration and types of polymers on release pattern occurred when using hydrophilic type. In selection of type and concentration of cellulose used in combined formulation, the effect of concentration of single polymer on drug release pattern should be taken into account. Compressional pressure did not affect drug release patterns of all formulations in this study.