CHAPTER IV

DISCUSSION AND CONCLUSIONS

In this study, diclofenac sodium was prepared in three preparations: capsules filling spray dried powder, matrix tablets containing spray dried powder and capsules filling matrix pellets. The physicochemical properties and drug released characteristics based on amounts and types of drug and excipient including diluents, polymers and plasticizers, method of preparations and dosage forms of these three preparations were compared.

Formulations Modifications

The smallest and fewest amounts and types of excipients were used in order to decrease the undesired effects from those components. The reason was to be able to show effectively the properties of the polymer on the dissolution profiles of the products. Colloidal silicon dioxide (Aerosil® 200) was used as anti-adherent in spray drying process and as lubricant in tabletting process. The tackiness of the polymer was improved when colloidal silica was used as additive. Moreover, the agglomeration of coated drug crystals was decreased since the drug crystals wetted with the polymer solution was dried up in the drying chamber without contacting each other (Kawashima Y.et al.,1983; Takeuchi H.et al.,1987 & 1989). This study found that the proper amount of Aerosil® 200 was 5% of total dry weight of drug and polymer.

From the preliminary study, the highest amount of chitosan used as suspension feed could not be more than 15% w/w, because the suspension was too sticky and viscous to be sprayed and the obstruction in the spraying head nozzle was found. Although 5%w/w of Aerosil® 200 was added, large amount of the spray dried powder was still adhered to the chamber and the cyclone walls, which would reflect the low percentage yield of the spray dried powder.

A suitable feed type had to be used to optimize the production of the microcapsules and the efficiency of the spray drying process (Wan L.S.C.et al.,1992). Because of undissolved properties of diclofenac sodium and Aerosil®200 in acidic Seacure® solution, the suspension feed type was used. The encapsulated products from a suspension feed occurred by the deposition of the polymer enclosing these encapsulated particles, whereas spray drying with solution feed caused precipitation of both drug and polymer. These former spray dried products showed better flow properties and slower drug dissolution than that of solution feed (Bodmeier and Chang,1988).

Recently, chitosan was widely proved to be a suitable polymer for controlled release preparations (Karlsen J.,1991; Wan et al.,1994; Miyazaki et al.,1981; Sawayanagi et al.,1982; etc.). Thus, it might delay the release characteristics of spray dried products in this study. But in the study of Pearnchob N. (1996), the spray dried formulations of diclofenac sodium using chitosan as polymer showed no capability to control the drug released as sustained release products, because the spray dried microparticles had porous, irregular sponge-like structure. In addition, their irregularity of the microparticles increased when the proportion of chitosan was increased. To solve this problem, plasticizer was added in order to reduce the minimum film-forming temperature (MFT) of the polymer. The MFT of the film was lower compared with the glass transition temperature (Tg) of the dry polymer. So, the continuous film was formed easily under distinct drying conditions and elasticity of the polymer film was improved after mixing the polymer with suitable plasticizers (Lehmann K.O.R.,1989; Lin S.et al.,1991; Bodmeier and Paeratakul, 1992).

The most effective plasticizers generally resemble most closely the structure of the polymer they plasticized (Radebaugh G.W.,1992). Thus, hydrophilic plasticizers such as triacetin, propylene glycol (PG), polyethylene glycol (PEG) and glycerin, were suitable for hydrophilic chitosan solution, even a potential disadvantage of water-soluble plasticizers, the leaching property, would be occurred (Bodmeier and Paeratakul, 1992). The other unfavorable result of using of plasticizer was the possibility

to maximize the adhesion of the spray dried products onto the spray drying chamber and affect the percent yield of product. The use of additives such as colloidal silica, which could reduce these unpleasant phenomena, should be voluntarily avoided because they affected the characteristics of the spray dried particles and so, evaluating the effect of the other parameters became more difficult (Palmieri G.F.,1994).

Propylene glycol and glycerin were chosen as plasticizers for chitosan solution because their highly hydrophilic property and molecular structure were easily compatible with the property of the chitosan, while triacetin and PEG400 were incompatible with chitosan because of their molecular structure. Triacetin is ester which could be compatible with amine and hydroxyl groups of chitosan. Whereas PEG400 contained several ethylene oxide groups and its size was too large to accommodate into crystal lattice structure of chitosan film. The results exhibited increasing degree of bleeding and translucent free film (Paechamad T.,1994).

Most spray dried powders showed uncontrollable release rates that were not good enough to be formulated into sustained release preparations. Compression of spray dried products was an useful idea to prolong the release rate and achieve the preferred release characteristic. The compaction characteristics of microspheres had been mentioned earlier that compression force and filler composition exhibited great effect on the drug released characteristics (Kornblum S.S.,1969; Bodmeier and Chen,1989; Lin and Kao, 1991; Dangprasirt and Rhitthidej, 1997; Kulvanich P.et al.,1997). McGinity, Cameron and Cuff (1983) reported their interesting results that compaction force as well as hardness should play minimal role on release rate within the ordinary range of 6.8 - 15.0 kg hardness. This implied that as the compaction force was increased up to the certain limit, the compact mass would elastically deform so that the tablet porosity fell to minimum value and remained constant thereafter. For better results, the hardness value in this study was narrowed to the range of 11.0 - 18.0 kp or about 5.0 - 8.0 kg.

Tablets produced from spray dried powder of drug alone faced many problems during tabletting process. The spray dried products including colloidal silica were tableted easily due to their better flowabilities. Compressibility of spray dried products was improved with increasing amount of the additives as clearly appeared with tablets containing colloidal silica (Takenaka H.et al.,1980). In tabletting process, additionally 1% of Aerosil®200 was mixed to the spray dried products before tabletting.

The number of excipients available for successful pelletization by extrusion-spheronization technique were limited (Chien Y.W. 1990; Tapia C.et al.,1993; Hileman G.A.et al.,1993; Goskonda S.R.et al.,1993 & 1994). The formulations using both lactose and microcrystalline cellulose (Avicel® PH101) at various drug to excipients ratios could produce the pellets. Whereas, pellets could be produced by using Avicel® PH101 alone but not by lactose at any ratio. In effect, Avicel® PH101 modified the rheological properties of the formulations and imparted plasticity to the pellets (Bhalla and Jathar, 1994). While on the contrary, the lower capillary forces of lactose could lead to an excess of water at the surface of the pellets during spheronization and had a trend to stick together and form large agglomerate (Fielden et al.,1993).

Chitosan solution, acted as a binder, was prepared as in the spray drying process but the highest concentration of chitosan was preferred to reduce the quantity of water in the formulations because water, itself, could be used as a binder too. This method could increase the percent of dry chitosan used as much as possible to present the better sustained-release dissolution profiles. The study showed that suitable mass load should not be lower than 300 g for completely mixed and suitable moistened mass. Too small batch made difficult thoroughly mix and too big batch overloaded the machine. There was no significant difference in size ,shape and dissolution profiles, when different spheronization speed was used. So the lower speed was chosen for saving the energy and preventing overload of the machine. The shortest spheronization time which smooth-surfaced, sphere and rigid pellets were made was 15 minutes. Conversely, the longest spheronization time of 30 minutes made the pellets too dry and showed no different physical properties from the standard time.

Physicochemical Properties of Preparations

Spray Drying Preparations

The preferred microcapsules characteristics in this experiment were round, smooth surfaces with a hollow inside the spherical shape. These characters showed the good flowability of spray dried powders that gave a lot of benefits in tabletting process.

The spray dried particles were generally not of the matrix type. They were usually hollow spheres (Wan et al.,1990 & 1991). This microparticle had been named "microballoon" due to characteristic internal hollow structure. It was explained that in the initial drying of droplet the moisture contents fell to a critical value with the formation of a solid crust at the droplet surface. As the inlet air temperature was above the boiling point of the droplet solution, vapor was formed within the droplet, setting up pressure internally. Depending on the crust formed, the droplet might be punctured a "balloon" might form. Such particle could not withstand mechanical handling and fragmented easily. Spherical particles with a smooth surface or some surface shrinkage and folds were observed. The shrinkage of the surface wall was due to the entrapped air bubbles expanding considerably at higher drying temperature, a process that was offset partially by the loss of water. Deep indentations on the microballoon were also found occasionally, which was probably the result of water loss from the drying drop during the early stage of processing (Lin and Kao,1991).

In scanning electron photomicrographic process, some microcapusules were exploded because the high energy, electron beam used for photomicrography directly attacked on the surfaces of the microcapsules. Especially at the higher magnifications, the air inside those hollowed microcapsules were heated causing the breakage of microcapsules into two-capped characters. This result found only in microcapsules produced from the glycerin-plasticized formulations that had smooth surfaces.

The shape and surface topography of the spray dried microcapsules were found to be affected by the drug to polymer ratio in the formulation (Takeuchi H.et al.,1989; Palmieri G.F.et al.,1994). In this study, the porous, irregular sponge-like structure and the irregularity of the particles increased when the proportion of chitosan increased. At polymer to drug ratio of 1:5 using both grade of Seacure®, the formation of fibres were occurred instead of microcapsules. It must be concluded that suspension feed of 1:5 ratio was to viscous to spray even atomizing air pressure of 4 bar was used. This pressure was insufficient to brake up the liquid filaments into droplets. The studies showed that the successful dispersion on the filaments into polymer droplets depended strongly on the type of polymer used and to a lesser degree on the viscosity of the spray solution (Bodmeier and Chang,1988). It was important that the liquid feed should first form into thin sheets to assist liquid instability for effective air-liquid contact and breakdown of liquid into ligaments or individual droplets. Unless 'feed prefilming' took place, ineffective atomization results, even at high air velocities.

The improved property of the polymer film was improved by the aid of suitable plasticizers. The formulations with plasticizers, propylene glycol and glycerin, provided smaller size of microcapsules compared to those of unplasticized formulations at the same polymer to drug ratio. Addition of these plasticizers also disappeared the fibre-like particles that found in the formulation using polymer to drug ratio of 1:5.

Percent of plasticizers used in the formulation also affected the smoothness of the surface of microcapsules. Nevertheless, the shrunken microcapsules and more agglomerated products were produced, when the higher amount of plasticizers was used. Smaller particles produced during spray drying were more cohesive which tended to form aggregates hence larger agglomerates were obtained. Agglomerated particles yielded the higher geometric mean diameter (Patomchaiviwat V.,1993). The stickiness of propylene glycol and glycerin increased the agglomeration of the microcapsules in this study. The result was clearly seen, when amount of plasticier was increased.

Suitable amount of plasticizer is an important factor affecting the surface topography of the microcapsules. The optimum amount of plasicizer depended on the amount of the polymer. Microcapsules from the formulations using polymer to drug ratio of 1:5 from both grades of polymer with plasticizers were still incomplete, even though 33% of plasticizers were added. This finding showed that plasticizing property of propylene glycol and glycerin were inadequate for that amount of polymer. In addition, the formulations using the highest amount of propylene glycol (40%) presented the microparticles looked like microspheres or irregular shaped particles rather than microcapsules.

Both types of plasticizers presented the same results on size and shape of the microcapsules except the surface characteristics. The needle-like microcrystals were detectable at any level of propylene glycol used in spray drying products. It was proved that the microcrystals presented on the surface of the microcapsules must be composed of propylene glycol, because increasing in amount of propylene glycol in the formulation, the amount and size of the microcrystals were increased. The same phenomena was presented by Palmieri G.F.et al. (1994). Fish scale-like surfaces with some pores were presented instead of needle-like microcrystals in the formulation using glycerin as plasticizer.

In summary, it was found that the shape and surface topography of the spray dried particles depended on the polymer to drug ratio and the amounts and types of plasticizers. On the other hand, different grades of Seacure® showed no effect on microcapsule characteristics. The polymer concentration in the solution to be sprayed might play an important role in microparticle formation; hence it would mainly affect the shape of microparticles (Conte et al.,1994). The opposite consequence was revealed from those of Kawashima (1992) and Takeuchi et al. (1989) that the surface became smoother when the concentration of the polymer increased. Whereas Lin and Kao (1991) informed no significant difference in surface topographs, although Eudragit® L30D was used in different amount.

The interaction of drug and diluents in spray dried products were confirmed by IR spectra. The reduced intensities of the IR spectra were found in the mixtures compare to that of pure drug. The spray dried products exhibited the combination of the characteristic bands of the original diclofenac sodium with the most characteristic N-H bending peak of chitosan. This peak was shifted from 1653 cm^{-1} to 1694 cm^{-1} in all formulations, whereas the other characteristic peaks were shifted lower than 5 cm^{-1}. From the results, it could be concluded that the interaction between drug and polymer was hardly seen and grade of polymer had no effect on the IR spectra.

The crystallinity of the spray dried products were investigated by X-ray diffraction analysis. These diffractograms were similar to those of the drug indicating the presence of diclofenac sodium as crystalline form in the spray dried products. The peaks in the X-ray diffraction patterns of the spray dried products were less intense than those of original crystals. This finding indicated that some diclofenac sodium crystals were converted to a disordered form due to rapid crystallization during spray drying (Takenaka H.et al.,1980; Kawashima Y.et al,1983). The change in the patterns of the diffractograms from spray dried formulations were observed by an absence in some peaks of diclofenac sodium that indicated the presence of drug in polymorphic form. Whereas, raising in the baseline exhibited the presence of the drug in amorphous form. (Takenaka H.et al,1980 & 1981; Takeuchi H.et al,1987; Otsuka M.et al,1992 & 1993; Corrigan O.I.et al.,1983). The X-ray diffractograms of the spray dried products observed in this study might consist of both amorphous and polymorphic diffraction patterns.

The significant difference in X-ray diffraction patterns were found from the spray dried formulations with glycerin that evaluated from the two models of X-ray powder diffractometer, Joel JDX-3530 and Rigaku Denki (Miniflex). The former evaluated characteristics peaks at the same positions compared to those of diclofenac sodium at any amount of glycerin used, though the higher baseline was detected from the formulations using 33%glycerin. On the other hand, the latter presented the significant different diffractograms with shifting of the characteristic peak positions from the glycerin-plasticized formulations compared to those of pure drug. This finding might be

the effect of aging. The evaluations by Joel JDX-3530 was done in about 4 - 6 months after spray drying process, while those of Rigaku Denki was done in 1 month. The effect of aging and storage condition on the crystallinity of solid dispersion were reported by Chiou W.L. (1977) and Save and Venkitachalam (1992). It was concluded that drug melt with PEG 6000 might change their crystallinity to the most stable form after keeping for long period or in unpleasant environments. Moreover, amount of glycerin in the formulations also affected the change in X-ray diffractograms. The higher amount of glycerin used, the irregularity of diffractograms was easier detected. It might be concluded that the presence of glycerin resulted in deformation of the drug molecules to be the most stable form.

The major use of the thermal analysis in evaluation spray dried product was to identify the change in the polymorphic or crystalline form of the drug that caused by spray drying process. The principle change in thermal energy as a function of temperature of the substances showed in the term of endothermic and exothermic peaks between diclofenac sodium and spray dried products. The sharp peaks of diclofenac sodium thermogram was observed at about 290°C indicating the drug melting point followed by decomposition. The DSC thermograms of all spray dried products was lower than that of pure diclofenac sodium. The lower in melting point indicated the presence of amorphous or polymorphic forms of spray dried products. Corrigan O.I.et al.(1983) reported that spray drying, either in the presence and absence of excipients, can result in the formation of high energy drug polymorphs or amorphous phases not normally obtained by conventional precipitation procedures.

Water evaporation was found from the DSC thermograms of both Seacure® 243 and 343 at about 108°C. The area of the broad peaks could be calculated to the energy of consumption used for evaporating the water contained in the chitosan powder. Thus it is easy to find the water content of the substances from this evaluation. The spray dried products from the formulations containing glycerin also exhibited broad peaks at about 100°C in the thermograms that were the results of water

evaporation from the spray dried powders. This finding was directly confirmed by the hygroscopic property of glycerin (Wade and Weller, 1994).

The spray drying formulations containing plasticizers exhibited the irregular patterns in DTA thermograms compared to those of diclofenac sodium and unplasticized formulation. The amount and type of plasticizers in spray drying formulations did not obviously affect the change in thermograms. The DTA thermograms confirmed that the compatible plasticizers for chitosan in the spray drying formulation were propylene glycol and glycerin. The reducing in glass transition temperature indicated that these two plasticizers had the ability to plasticize the polymer (Banker G.S., 1966). The change in the temperatures of propylene glycol happened when heat of the reaction was increased. The DTA thermograms of propylene glycol revealed two endothermic peaks at 106.5°C and 129.7°C. From the result, it might be concluded that propylene glycol was degraded in the spray drying process because the inlet temperature used (160°C) was higher than the degradation temperature of propylene glycol. Whereas glycerin did not show any sign of degradation until the end of the evaluation.

In general, the products containing greater amounts of fine particles often have higher bulk densities because those smaller particles could easily fill the void between the larger particles. Tapped density is necessary when the loosely agglomerates are formed, especially the spray dried product. The tapping force reduces the particles size through breakdown of these agglomerates (Amidon and Houghton, 1985). In this study, the percent compressibility was affected by the amount of polymer and plasticizer in spray drying formulation, whereas grade or type of polymer and plasticizer presented no significant difference in this value. All spray dried materials had poor flow characteristics, as a result of the low value of bulk and tapped density and high value of compressibility index (Lin and Kao, 1991). This result was represented in the term of "angle of repose" which lower values indicated better flow characteristics (Aiache and Beyssac, 1994). The angle of repose spray dried products from this study generally ranged from 28 - 32° that was in the acceptable range (25 - 45°) recommended by

Wodke, Serajuddin and Jacobson (1989). The spray dried products that represented the angle of repose lower than 25° might have good flowability. These powders contained single larger and more spherical particles so higher flowability was obtained. Conversely, the products that showed the angle repose more than 35° would lead to a reduction in free flowability because more irregular shaped particles with agglomerates was observed.

The data of percent yield also supported the effect of formulation modifications that included the amount and type of polymer and plasticizer. Spray drying process allowed only few formulations to achieve good yield of production. The percent yield of the spray dried products obtained from unplasticized formulations were higher than those plasticized about 20 - 30%. When amount of the plasticizer was increased, the percent yield of the product was obviously decreased. These formulations tended to adhere to the chamber wall and resulted in the lower yield. The experimental region where yields are greater corresponds to the region where residual activity levels are lowest. Clearly a prerequisite for the use of this process would be that drying could be accomplished without any activity losses. Nevertheless, low yields are persistent problems with the laboratory scale spray dryer (Broadhead J.et al,1994).

The loss on drying value of the spray dried products was typically controlled between 2 - 5% (Broadhead J.et al.1994). The incomplete drying of spray dried particles with large and irregular shape before leaving the drying chamber was caused by very coarse droplets being formed in the spray and ineffective atomization. This resulted in the deposition of these large particles on the cyclone collector that explained the much lower yields (Master K.,1979; Wan et al.,1991). The formulations containing glycerin at any level and 40% propylene glycol had the loss on drying values higher than 5%. The highly hygroscopic property of glycerin were obviously presented. Even the higher temperature can reduce the moisture in the products, the outlet temperature not exceed 120°C must be regulated in order to avoid damage of the plant (Mobile Minor, Niro Spray Dryer Handbook).

The loss on drying values were correlated with drug contents values in this study. The components in spray dried formulations played important roles on both loss on drying and drug content values. Percent differences between theoretical and experimental drug content were in wide range ((-8.60) - 20.29). The unplasticized formulations revealed the parallel values of moisture content and percent difference. Whereas the plasticized formulations presented the opposite results. This result showed that amount and type of plasticizers had strong influence on the percent differences and also the loss on drying values of the spray dried powders, while the amount and grade of polymer presented slightly effects on these values. Percent differences of the propylene glycol-plasticized formulations were higher than 10%, while those of the glycerin-plasticized formulations were lower than 5%.

Matrix Tablets Preparations

In tablets evaluations, scanning electron photomicrographs of matrix tablets containing spray dried powders were detected both before and after dissolution test at different sides of tablets. The spherical particles of spray dried products distributed and embedded into the excipient mixture were shown from the topographies of matrix tablets. The wall material of the spray dried particles acted as a dry binder to combine the excipients to form exceptionally hard tablets. Voltaren® SR tablet, a commercial product of diclofenac sodium manufactured by Ciba-Geigy, is a hydrophobic matrix consisting of cetyl alcohol. Thus its morphological characteristics after dissolution was obviously different from those of spray dried matrix tablets.

The photomicrographs could predict the release mechanism of chitosan matrix tablets. The presence of some small pores on the flat surface of the matrix tablets was shown before dissolution testing. After the test, however, the tablet surface had become very even in nature and covered with numerous pores. It was appeared that the dissolution media entered the pore present on the tablet surface and progressively dissolved accessible soluble drug and excipients which then moved out of the tablet by diffusion in the resultant enlarged pores. The same results were seen from the wax

matrix and hydrogel sustained release diclofenac sodium tablets produced by Bain J.C.et al.(1991). Thus it was summarized that the release mechanism of Voltaren® SR was assumed as swelling followed by diffusion, whereas chitosan in the unplasticized formulations caused the swelling tablets and released by erosion that was clearly interpreted from the large, deep hollows with rougher surface. Nigalaye A.G.et al.(1990) were also found that various concentration of chitosan produced different release mechanism of matrix tablet. An insoluble non-erosion type matrix was formed by chitosan more than 50% of tablet weight. While erosion type matrix was formulated using 10% of chitosan with the aids of carbomer-934 and citric acid.

The difference in polymer to drug ratio and polymer grades played a role on matrix tablets topographies. The stronger results were detected from amount and type of plasticizers used in the spray dried formulations. Before dissolution test, the needle-like microparticles attached on the tablets containing propylene glycol-plasticized formulations were pre-approved as propylene glycol microcystals. These microcrystals were no longer found, when glycerin was used instead of propylene glycol. After 24 hours dissolution test was passed, swelling of the polymer was clearly seen from the lowest magnifications of photomicrographs. Evidence showing the increasing in size and number of hollows were detected especially at the sides of the tablets by using both types of plasticizers. It was concluded that the leaching of water-soluble plasticizers from chitosan matrix tablets showed very strong effect in this phenomena. As seen, mechanism of release from matrix tablets was mainly erosion more than swelling, while the erosion of matrix tablets form the formulation using propylene glycol was faster than that using glycerin.

Density and compressibility of spray dried powders are directly related to thickness and hardness of matrix tablets. Use of hydraulic press was one of the simple ways to produce the matrix tablets (Wadke et al.,1989). Powders that form hard compacts under applied pressure without exhibiting any tendency to cap or chip can considered as readily compact. Hardness is defined as the resistance of a solid to deformation and is primarily related to its plasticity. Even thickness of the tablets is

corresponded with the hardness, it is really controlled by weight per tablets that directly related to amount of components in the formulations. The hardness values of the plasticized formulations tended to be higher than those of unplasticized formulations except at the polymer to drug ratio of 1:5 was used. The dissatisfied hardness values over 18.0 Kp were presented from most of spray dried powders composing highest amount of chitosan and propylene glycol.

Matrix Pellet Preparations

Morphology of pellets from different formulations was studied by SEM using different magnifications. Pellets produced by two excipients showed the rougher surface compared to those containing Avicel® PH101 alone. The roughness of the pellets was directly affected the surface area that showed the great influence on drug release. Microcrystalline cellulose was needed in order to produce satisfactory beads in the terms of size, shape and surface characteristics. These properties were mentioned as ones of the most critical factors to obtaine and maintain the desired drug release profiles of the microspheres (Celik and Maganti, 1994). The increase in amount of Avicel® improved the smoothness of the pellets. Using highest magnifications, the white microparticles adhered around the surfaces were clearly seen and had a trend to increase when the amount of Avicel® was increased. It might be concluded that those microparticles were Avicel® that caused the surface to be smoother. These white particles also found in the work of Bataille B.et al.(1993).

The higher spheronization speed yielded smoother, smaller and rounder pellets. The main disadvantage from higher speed observed was the over-dried surface of the pellets that presented the lack of water in the pellet mass. The variables in spheronization time did not have significant effects on any of the response studied, except slightly smaller in size. It was summarized that these two factors controlled the pellet shape and density (Hileman G.A.et al.,1993). Conversely, the surface drying was found to be the effect of prolonged spheronization times. Moreover, pellet shape

appeared to be dependent on the moisture modulating capability of each formulation as well as the spheronization conditions.

The initial characterization process involved the determinations of the particle-size distribution of the pellets. Both polymer grades and concentration used significantly affected the size distributions, while different amount of excipients showed weak effect on pellet size. The higher viscosity grade of chitosan (Seacure® 343) produced the bigger pellets than those used the lower viscosity grade (Seacure® 243). Moreover, the distribution in size was higher in the formulations using Seacure® 243 compared to that of Seacure® 343. The same effect on type and concentration of the polymer used in pellet formation was performed by Goskonda S.R. (1994). Further, these factors affected the capsule fill weight which is the calculated mg of pure drug in a capsule probably due to their effects on shape and density of the pellets.

The spheronization speed and times also exhibited great influence on the size distributions of the pellets. The decrease in size distributions, smoother surface and larger in size were detected, when the spheronization speed was higher (Batallie B.et al.,1993). The compaction of the mass is denser by increasing the spheronization speed that leaded to an increase in hardness of the pellet. In fact, in the spheronization process because the centrifugal force that linked to the speed gives greater inter-particular impacts, thus a decrease in empty space. Consequently, pellets having a more compact structure will be harder, less porous and will have a smoother surface. An increase of the yield of the smaller fractions was seen, probably due to a greater degree of fragmentation during the initial stage of the spheronization process. In contrast, a decreasing amount of fines and increasing spheronization speed correlating with an increased mean diameter were also observed (Vervaet C.et al.,1995).

The variation in spheronization time did not play any effect on size distributions in this study. A wide variety of effects was witnessed when assessing the importance of this parameter on pellet formulations (Vervaet C.et al.,1995). It could not be summarized to the accurate effects of this parameters.

Dissolution of Diclofenac Sodium Preparations

The sustained-release preparations for oral route as tablets or capsules were supposed to pass the entire upper gastrointestinal tract, so they would be assumed that the release of drug was constant over a wide range of pH values (from 1 to about 7). Therefore an in vitro test for controlled-release tablets should at least covered this pH range. Wilder Ph.V.et al. (1991) researched for the appropriate in vitro dissolution system for two oral controlled release preparations of diclofenac sodium. The summary mentioned that the drug release is strongly medium dependent. Faster release dissolution was obtained in the media without acidic stage or with higher pH values. The delay might be explained by a lower micro pH environment in the formulations due to the acidic soaking stage.

NSAIDs presented a dominant hydrophobicity, that have weak acidity, low solubility and dissolution rate in water, but high partition coefficient in their acidic form. The sodium salts were more soluble in water than the corresponding acid form (Fini A.et al.,1995). The aqueous solubility of diclofenac sodium is depended strongly on pH of the medium. Because of the pKa values (pKa in water = 4), it dissolves poorly at low pH values but the solubility increases rapidly when pH of the medium rise above pKa. The solubility of diclofenac sodium in acidic media (pH 1.2 to 3) was below 0.4 mg% that could not be measurable as indicated (Herzfeldt and Kummel,1983; Adeyiyi and Li,1990). This fact might lead to erroneous conclusions, and this low release in acidic conditions could be interpreted as the results of the favorable characteristics of the gastric resistance of the polymer or those of the microcapsules that prevent the release of the active substance, instead of being interpreted as the result of the very low solubility of this substance at those pHs (Palomo M.E.et al.,1997)

From the previous study (Tangsumranjit A.,1997), the results showed that in pH-change system, diclofenac sodium spray dried preparations could be sustained throughout 24 hours compared to commercial products. Whereas diclofenac sodium from the same formulations in phosphate buffer pH 6.8 systems was released

immediately because the polymer could not have capability to control the drug release throughout 24 hours. In order to simulate the in vivo environment, pH-change systems was chosen to evaluate the released pattern of all diclofenac sodium preparations (Lin and Kao,1991; Sheu M.et al.,1992; Lin C.et al.,1995; Gohel and Amin, 1998).

Effect of dissolution apparatus and stirring rate of the apparatus were observed by Sheu M.et al. (1992) and Palomo M.E.et al.(1997). It was noted that floating of microcapsules at the media interface caused by their low density could be minimized by using baskets. Although microcapsules were floating inside the baskets, some of them were leaving the baskets due to size decreased as the coat dissolved that resulted in lower dissolution efficiency. The doubling in stirring rate from 50 to 100 rpm had only a slight effect on rate of drug release and were not significant bioavailability sequels especially when matrix tablets formulations were tested. In this study, the baskets (USP apparatus I) with the rate of 100 rpm was used for all formulations as previous study.

The decrease in dissolution rate might be due to the decreased solubility of diclofenac sodium in the medium with higher salts concentration and a salting-out effect of sodium chloride on the dissolution of diclofenac sodium (Kawashima Y.et al.,1985). When the rate of accumulation of diclofenac sodium was measured using dissolution media containing either sodium chloride or potassium chloride, the rate of solution was found to be inversely proportional to the salt content with NaCl having greater effect (Sheu M.et al.,1992). Thus further suppression on the solubility of diclofenac sodium by a common ion effect due to Na^+ from tri-sodium phosphate using in basic medium would be operative, resulting in a slower dissolution rate compared to that of di-potassium hydrogen phosphate. The percent released of only 78% from Voltaren® SR after 24 hours was affected from this phenomenon.

The release profiles of diclofenac sodium from spray dried powders and matrix tablets formulations depended on many factors such as: drug properties especially its solubility, polymer properties and its concentration, compressional force, etc. When these matrix preparations were brought in contact with medium, a series of mass transport phenomena occurred. First, the pores near the surface of the products were filled by medium and initial drug diffusion was controlled by the dissolution of drug in the medium-filled pores and by its continuous diffusion in medium (Gurny et al.,1982). Thus the porosity of spray dried powders and matrix tablets seen in the SEM might play a major path for drug dissolution. In addition, particle size, particle morphology and surface area from SEM evaluation can produce important and significant effects on the dissolution rate of drug (Holgado M.A.et al.,1995).

In all preparations, the lag phase was observed in the first 2 hours that 0.1N HCl was used as medium. It was proved that even at a rate of neutralization occurring over 2 hours period (the shortest simulated residence time in the stomach) almost no drug is in solution (Sheu M.et al.,1992). Due to the solubility of chitosan at the low pH there was gel formation around the spray dried particles or on the tablet surface in acidic medium, this property could delay the release of drug from those preparations. However, diclofenac sodium preparations did not gain from this phenomenon because of the limited solubility of the drug. After the medium was adjusted, chitosan solubility decreased causing diminished gel formation. This was reflected in the dissolution results which showed immediately the burst of diclofenac sodium effected from the rapid dissolution in basic medium (Kristmundsdottir T.et al.,1995). This phenomenon was shown from all capsules filling spray dried powders and matrix tablets containing spray dried powders, except the spray dried powders prepared from Seacure®243 at the polymer to drug ratio of 1:5 and the matrix tablets containing both grade of Seacure® at the ratio of 1:5. The complete ineffectiveness in controlling drug release was probably due to the rich in release surface area and high porosity of the powders that could be confirmed as the weakness of spray drying process. On the other hand, the effect of the compaction was slower the drug released rate of the matrix tablets when compared to those of spray dried powders (Palmieri F.G.et al.,1994).

The increase in percent drug released caused by increasing in chitosan concentration was found conversely from Kawashima Y.et al.(1985) and Sawayanagi Y.et al. (1982). It might be assumed that the concentration of chitosan used (<20%w/w) was not enough to yield the successful gel-forming barrier. The release rate of diclofenac sodium was mainly controlled by the polymer viscosity. Specifically, the drug release rate was inversely proportional to the quantity of the higher viscosity polymer when the formulations using the same polymer concentration was compared (Liu C.et al.,1995). The opposite result from the matrix tablets containing Seacure® at the ratio of 1:5 was summarized from SEM that because of the higher polymer concentration, the erosion was found instead of swelling. The large diminution in tablet size was detected after the dissolution test.

The drug release rate of the matrix tablets corresponded reasonably well to those of the spray dried powders, although the drug release rate of the matrix tablets were significantly delayed. The tablets containing spray dried chitosan did not disintegrate during the dissolution test, which might account for the significantly decreased release rate of the tablets. This results suggested that the rate determining step was the dissolution of diclofenac sodium dispersed on the tablet surface as well as in the chitosan matrix, rather than the dissolution of the chitosan matrix of the tablet.

Plasticizer played a role in dissolution rate based on its types and concentration used but its influence was weaker than that of polymer. The leaching of water-soluble plasticizers from the polymeric film after contact with dissolution fluids was seen from the SEM in present study. The larger and deeper pores on the surface and side of the tablets of the plasticized formulations compared to those of unplasticized formulations were the results of leaching effect. The release kinetic would vary because of this change in matrix composition, the system was therefore difficult to be controlled accurately (Bodmeier and Paeratakul, 1992). Both propylene glycol and glycerin decreased the percent released of the tablets using Seacure® 243 at the ratio of 1:5 about 25% and 50%, respectively. SEM was used to refer that the property of reducing the erosion of the matrix tablets of glycerin was stronger than that of propylene glycol.

On the contrary, the percent released of the matrix tablets using the lower amount of Seacure® was increased, when plasticizers were added. In general, both propylene glycol and glycerin could easily dissolve from the matrix that caused the medium to penetrate through those pores immediately after pore-forming. After chitosan dissolved the drug could easily diffuse and dissolve resulted in the higher drug released rate.

Effect of plasticizers concentration could not be clearly concluded but corresponded to the type of plasticizers used. Because of the degradation of propylene glycol in the spray dried process, weak effect was presented from this plasticizers. The result showed that 40% of propylene glycol was over needed, since it decreased the total percent release about 20% from the formulations containing 33% propylene glycol. No significant difference in drug released was detected from the other concentration of propylene glycol. In the case of glycerin, the conclusion was not achieved except a trend of decreasing in drug released as the glycerin concentration was increased.

The diclofenac sodium pellets preparations containing chitosan were not capable to reduce the rate of drug release in all formulations. The same experimental scheme was done by Tapia C.et al. (1993) and the nearly same results was produced except the effect of different pellet size that did not have any influence in this study. Like the pellets produced by Goskonda and Upadrashta (1993), pellets appeared to swell but not disintegrate in acidic medium. The production of the gel structure was not enough to prevent the burst of the drug after changing the medium. The reason was the concentration of chitosan used in the formulation was very low (2.1-3.3 %w/w) and limited by amount of water in chitosan solution. The higher viscosity grade chitosan showed the slightly better property in decreasing the drug released rate than lower viscosity grade chitosan. Because the viscosity of Seacure®343 solution was higher, the amount of the binder used was lower than Seacure® 243 when the same formulation was produced. However, the release rate of the formulation using Seacure®343 was still slower. An increase in chitosan concentration caused an increase in hardness, disintegration time and dissolution rate of the products. It was postulated that at higher chitosan concentration, porosity and capillary pores were reduced (Upadreshta S.M.et al.,1992).

The amount of Avicel® PH101 in the formulations was the other parameter that showed the important effect on the increase in percent diclofenac sodium release, when the same pelletization condition and pellet size were regulated. To reduce the release rate, the smallest amount of Avicel® might be used. The other advantage was the lower capsule fill weight was achieved due the lower drug to diluent ratio was used. When lactose was added as secondary diluent, the release profile was not different from the formulation using Avicel® alone. As this result, effect of pellet size, spheronization condition, both speed and residence time, showed no different in drug released profiles.

Conclusions

Diclofenac sodium controlled release system was prepared in three preparations: spay dried powders, matrix tablets containing spray dried powders and matrix pellets. Two viscosity grades of chitosan were used as a polymer in the study. Their properties were not good enough to control the drug release from spray dried preparation even the good characteristics of microcapsules were produced. After compression into matrix tablets, the very effective controlled release system was observed. Propylene glycol and glycerin were used to improve the properties of the microcapsules and also increase the dissolution profiles from those of unplasticized formulations. About 60% drug released was achieved from the best matrix tablet formulation. The influence of the plasticizers on the release characteristics were weaker than that of chitosan. The efficiency in delaying drug released from spray dried powders, matrix tablets and matrix pellets could not be compared, because of their significant difference in release profiles.

The drug solubility, the operation conditions, the polymer to drug ratio and the presence of plasticizer are the main parameters to take into account in the realization of the optimal formulation.