CHAPTER IV

DISCUSSION AND CONCLUSIONS

In pharmaceutical industries, product development is one of the most important function of research and development section. It is generally recognizing that the design of product formulation may be considered as the key role of research and development pharmacist. For instance, in the case of formulating a new tablet, the researcher must give his thought on the way how to produce a readily dissolvable tablet. This is a lead to a topic of our following discussions.

The prime objective of this preliminary study aims to provide partial information concerning the concept of product development of paracetamol tablet by way of studying the influence of various additives on the dissolution behaviors of the product. And because of this reason, so we designed our experiments in such a way that only the effect of single individual additive on dissolution rate of paracetamol would be studied at a time.

The dissolution studies were carried out by rotating disk method because it was desirable to eliminate tablet disintegration as an experimental variable. Compression die assembly is superior to the other techniques of rotating disk method because it utilizes less time and easier to prepare the disks. The use

of the die hole prevent the disk from falling out even when the disk had a poor cohesive structure such that layer flaking occured without any support wall.

Slight difference of the intrinsic dissolution rates of paracetamol tablet were obtained when the tablet were compressed at different compressional forces. The results may be explained on the basis of effect of applied pressure. Since paracetamol powder subjected to some elastic deformation on compression and recovery had taken place when the force was removed. This recovery might rupture any bonds those had been formed and partial separation of some particles occured, so the disks compressed at higher pressure gave more rapid dissolution

A similar effect occured when the disk of paracetamol-lactose mixtures were compressed at 4,000 lb. Lactose had no significant dissolution retarding effect because of its rapid solubility and the increase in the amount of lactose did not lower the rate of dissolution. However, if the total dissolution method was employed, it had been found that the greater the quantity of lactose as diluent in tablet dosage form, a more rapid dissolution rate was obtained[7]. Because disintegration of tablet provided high availability of drug surface. It is impossible to incorporate the high amount of lactose into the formula, since the size of tablet and unit costs should be considered as well.

The dissolution inhibitory effect of microcrystalline cellulose indicated that the surface of solid drug was covered by the insoluble microcrystalline cellulose. So the solute was difficult to diffuse into dissolution medium.

Microcrystalline cellulose is a directly compressible vehicle and strong bond would be formed on compression. The binding forces between the particles will increase with increasing of the compressional forces, stronger and denser of disks were produced. The permeation of dissolution medium into the disk and splitting of microcrystalline cellulose were slow. Hence it was seen that dissolution rate of paracetamol from the disk containing 20 and 30 % of microcrystalline cellulose decreased with increasing of compressional force.

It is obvious that when microcrystalline cellulose was employed as a diluent in tablet formulation, A high quantity of this material may retard dissolution of the active drug. Although it enhance disintegration of tablet but the surface of disintegrated particle would be surrounded by this insoluble diluent. Therefore, both concentration and compressional force should be considered when microcrystalline cellulose is employed in tablet formulation.

The processing problem frequently occured in manufacturing of paracetamol tablet is capping. This problem, however, may be eliminated by incorporating microcrystalline cellulose

into the formula to enhance binding property, but low concentration must be used in order to prevent dissolution inhibitory effect.

Regarding dissolution retarding effect of magnesium stearate, we found that magnesium stearate would be softened and spreaded out under compression to provide impervious surface barrier which would decrease the effective solid-solvent interface. It may be concluded from the results that a little difference between the concentration of magnesium stearate in two tablet formula exhibit a huge difference in dissolution rates. Thus the concentration of magnesium stearate in tablet formulation should be employed as little as possible to prevent a marked decrease in dissolution rate.

Talc showed lesser effect in comparing with magnesium stearate, in retarding the dissolution of paracetamol. Since talc was more rapidly wetted by dissolution medium and the insoluble particles could be splitted from the surface of the disk.

The most frequently employed binder is the starch paste and usually prepared in the concentration of 10 % w/w. The amount of starch paste used in tablet formulations by different manufacturers are always different. The experiments showed that a little difference of the quantity of starch paste in formula may exhibited a great influence on dissolution rates changed.

The insoluble viscous film is expected to be formed when

the disk containing starch paste exposed to dissolution medium and this would inhibit diffusion of the active drug. The thickness of this film will depend upon the amount of starch paste used. By comparing starch paste and polyvinylpyrrolidone used as the binder, although polyvinylpyrrolidone may be able to form also a film on the surface of the disk but this film can be easily dissolved. When formulating the tablet, if strong adhesive force is required, increasing the amount of polyvinylpyrrolidone will not affect dissolution rate.

It can be seen that there was not different between two methods of adding polyvinylpyrrolidone. But dry mixing of binder before activating with solvent is preferable, because uniform distribution of binder would result.

The main purpose of adding dry corn starch into the commercial tablet is to enhance disintegration. Disintegration of tablet increase contact between dissolving surfaces and solvent. As a consequence, the large amount of dry corn starch ought to be incorporated into a formula, because it was found the dry corn starch has no dissolution inhibitory effect.

Considerable interest has been developed in study the interaction of two lubricants because a combination of talc and magnesium stearate are commonly employed in tablet formulation.

Study of an interaction effect was performed by incorporating all the components concerned into the formulation in

order to embody condition being similar to the commercial
tablet, However, dry corn starch was not incorporated into the
compressed disk so that the error owing to disintegration of the
disk was eliminated and since it was proved that the presence of
dry corn starch had no effect on dissolution rate.

It was found that the dissolution rate of paracetamol
was affected only by an individual lubricants. When combination
of talc and magnesium stearate were used in our formulation an
increase in the amount of one lubricant did not interfere the
effect of the other.

As previously mentioned, dissolution retarding effect of
talc gradually increase with increasing the amount of talc. In
the case of magnesium stearate, dissolution rate drastically
decreased when the amount of magnesium stearate increased. By
these reasons, an excessive quantity of talc can be added into
the formula, if the more lubricant is needed to solve the pro-
blem associated with tablet compression.

According to the experimental results depicted in Fig.10
13, the assumption was made to find the equation of these
curves to show the relations of fraction of additive in binary
mixture to observed dissolution rate of paracetamol. Therefore,
the experimental data were utilized to establish the quadratic
and exponential equations by performing regression analysis(as
shown in Table 9). Where x and y in equation represent the

Table 9. The Regression Equations for Dissolution Rate of Paracetamol

from Paracetamol-Additive Mixtures.

Composition	Compressional Force, lb	Quadratic Equation	Exponential Equation
D*-Microcrystalline Cellulose	2,000	$y = 9.25\ x^2 - 5.65x + 1.63$	$y = 1.55 \times 10^{-1.1066x}$
	3,000	$y = 8.25\ x^2 - 5.87x + 1.63$	$y = 1.59 \times 10^{-1.4323x}$
	4,000	$y = 8.00\ x^2 - 5.96x + 1.64$	$y = 1.61 \times 10^{-1.5379x}$
D-Magnesium Stearate	All	$y = 507.54x^2 - 40.65x + 1.57$	$y = 1.44 \times 10^{-5.9934x}$
D-Talc	All	$y = 100.11x^2 - 13.45x + 1.61$	$y = 1.56 \times 10^{-2.0841x}$
D-Starch Paste** (10 % w/w)	All	$y = 850.00x^2 - 55.90x + 1.60$	$y = 1.43 \times 10^{-8.9250x}$

*D = paracetamol

** The value of x is the amount of dry mass in starch paste (10 % w/w) mixed with

paracetamol.

fraction of additive and dissolution rate respectively.

The graphical representation of both quadratic and exponential equation were also illustrated in Fig. 15-18. It was noted that the quadratic function is better fit of the experimental data than exponential function. But the quadratic equation could not be used to predict dissolution rate at high value of x, since a further increase the fraction value (x) after reaching the minimum point of the curve caused an increase in y value(as demonstrated in the figure). Thereby, the exponential equation is more suitable to predict an extrapolated dissolution rate in comparing with the quadratic equation.

Conclusions

In designing the formulation of certain tablet dosage form it has been shown that there are a limited number of physico -chemical characters to be controlled or optimized tablet properties such as compressibility, physical stability, chemical stability, unit cost, and physiological availability are the significant ones. In this study concentration was placed on an improving of the physiological availability character of tablet and the dissolution of pharmaceutical play an important role in expressing this character. It is hoped that the results of this preliminary study would be useful and is applicable to product development of paracetamol tablet.

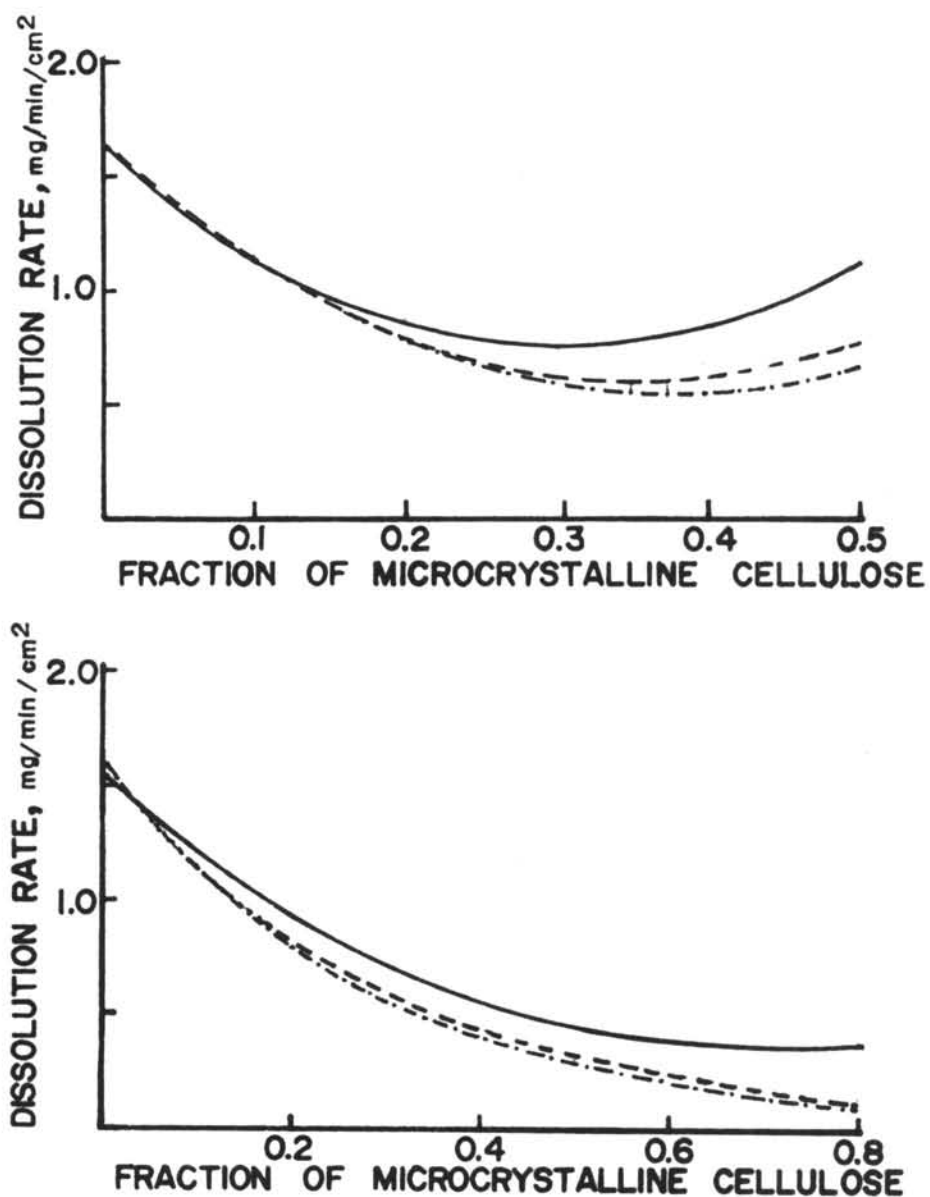As a guideline in fabricating paracetamol tablet formula-

Figure 15. Effect of concentration of microcrystalline cellulose and compressional force on dissolution rate of paracetamol plotted according to equation in Table 9. Top: quadratic equation, Bottom: exponential equation. Key: ——— , 2,000 lb; ---- , 3,000 lb;—·—·— , 4,000 lb.
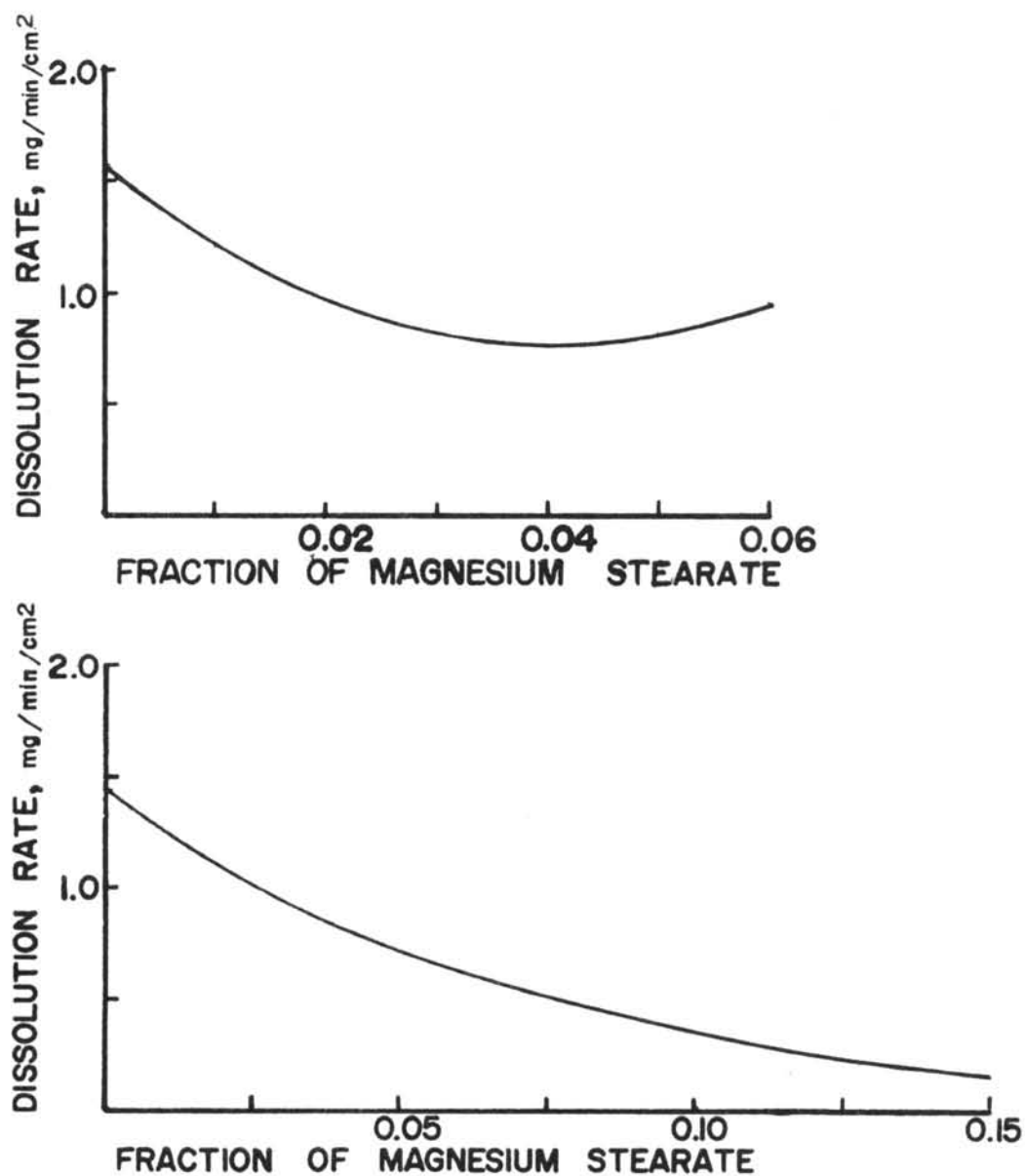
Figure 16. Effect of concentration of magnesium stearate on
dissolution rate of paracetamol at compressional
force of 2,000, 3,000, and 4,000 lb plotted
according to equation in Table 9. Top: quadratic
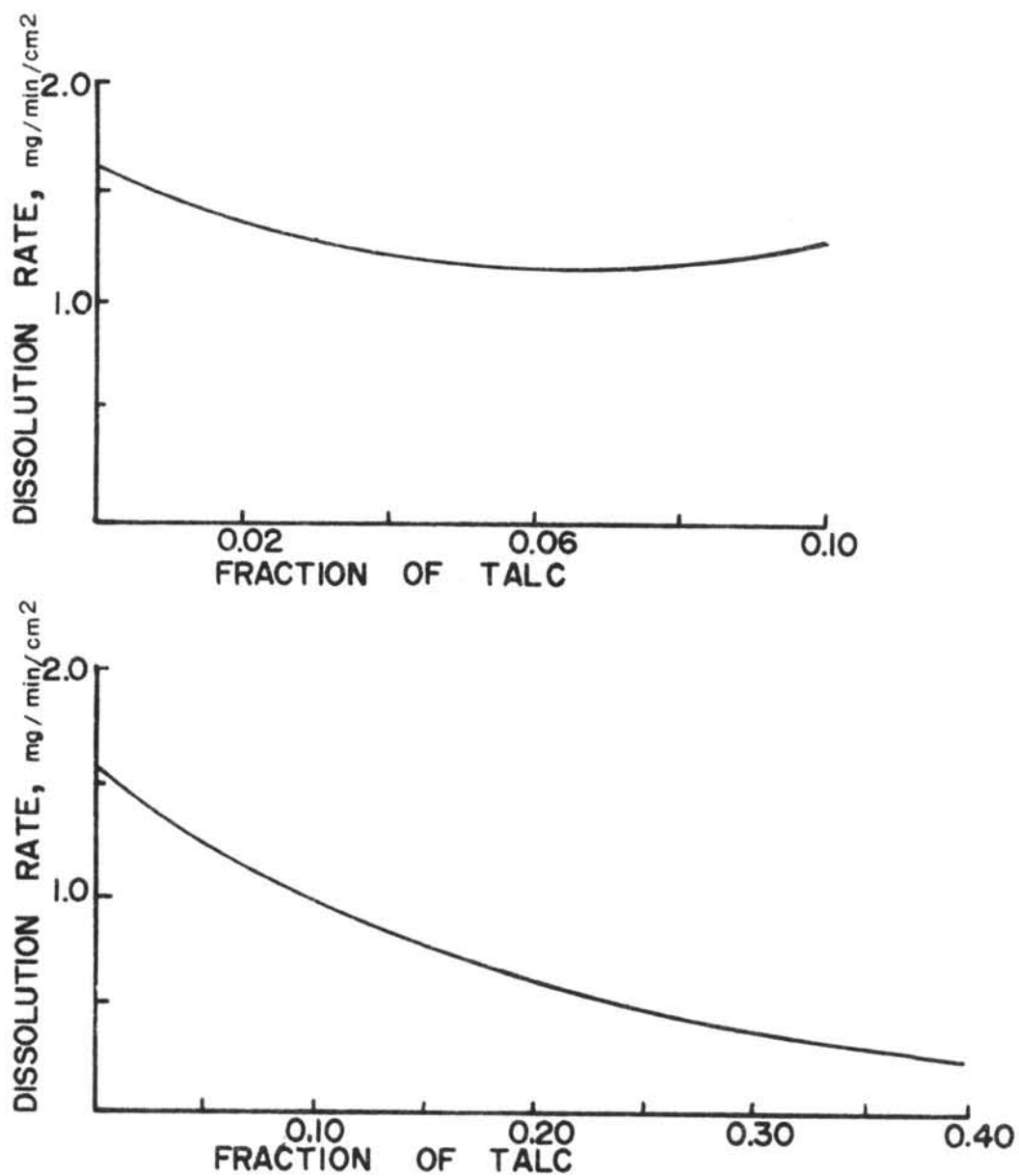equation, Bottom: exponential equation.

Figure 17. Effect of concentration of talc on dissolution
rate of paracetamol at compressional force of
2,000, 3,000, and 4,000 lb plotted according
to equation in Table 9. Top: quadratic equa-
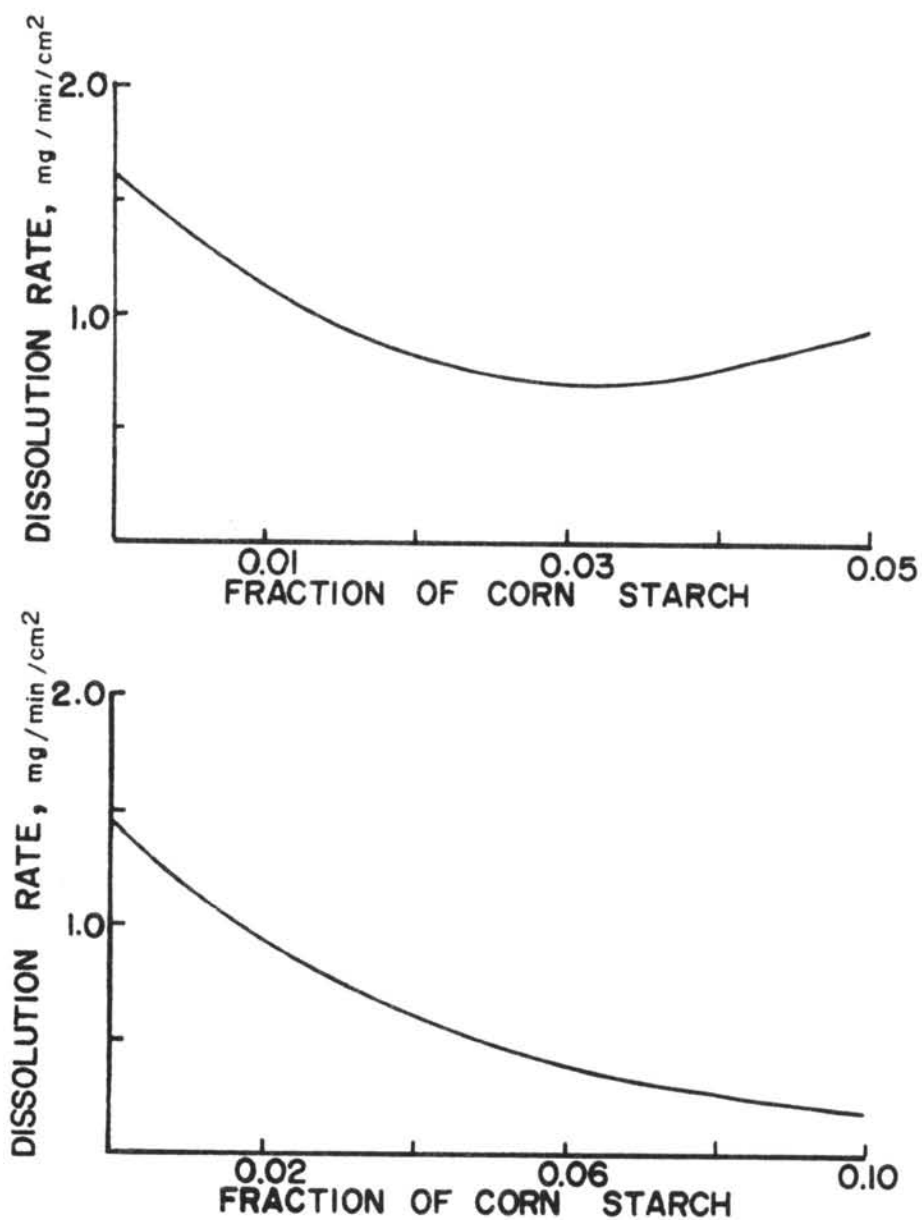tion, Bottom: exponential equation.

Figure 18. Effect of concentration of 10% w/w starch
paste on dissolution rate of paracetamol
at compressional force of 2,000, 3,000,
and 4,000 lb plotted according to equation
in Table 9. Top: quadratic equation, Bottom:
exponential equation.

tion. Lactose ought to be used as diluent. If high degree of hardness is required, microcrystalline cellulose may be used but low concentration must be employed. If wet method is carried out in granulation process, polyvinylpyrrolidone should be used as binder since starch paste is not recommended.

Combination of talc and magnesium stearate may be employed as lubricants. The concentration of magnesium stearate should not exceed 0.5 %. At the same instance, however, talc can be used in excess if any tablet processing problems occur owing to inadequate lubrication. High concentration of dry corn starch must be incorporated into our formulation in order to produce a rapid disintegration and high available surface.