CHAPTER IV

DISCUSSION AND CONCLUSIONS

4.1 The Physical Properties of the Yeast Extract Powder

As shown in Figure 3-1 the yeast extract particle possessed quite a spherical shape because it was a product of spray drying process. The histogram of particle size distribution of the yeast extract powder is not normal (Figure 3-2). Its particle size is mostly smaller than 100 μm. so it is fine powder.

The DTA thermogram of the yeast extract powder in Figure 3-3 showed two broaden endothermic peaks at 50 °C and at 200 °C. At 50 °C, the peak may occur because of fusion of lipid. When the temperature reached 200 °C, the decomposition of the organic composition probably occurred (Lóránt, 1972).

The moisture adsorption isotherm curve of the yeast extract powder is typical sigmoid curve (Figure 3-4). Equilibrium moisture slowly increased with an increase in relative humidity of the environment up to 45 percent relative humidity, beyond which there is a steep rise in moisture. Normally, the ambient relative humidity is more than 50 percent. Moisture content of the yeast extract powder was 7.59 percent (Table 3-1). At ambient it certainly absorbs moisture, thus, it can conclude that the yeast extract powder is hygroscopic.

In this study, the flowability of the yeast extract powder was measured in flow rate. It was seen that the powder did not flow through the orifice of the funnel. In general, fine particles with very high surface to mass ratios are more cohesive than coarser particles which are influenced more by gravitational forces. The particle size falls below 100 μm., powder become more cohesive and flow problems are likely to occur (Lantz and Schwartz, 1990 ; Staniforth, 1988). Besides, the hygroscopic nature of the yeast extract powder is probably another important factor that can cause poor flow. In addition, the compressibility value of the yeast extract powder, which was calculated from the bulk density and the tapped density, is 22.00 % which is in the range of poor flowing.

Inadequate flowability may cause inadequate filling of the die during tablet compression so that a consistant weight of tablets does not exist. In general, powder flow can be improved by incorporating a glidant into a formula or by making particles as spherical as possible. The popular method of increasing the flow property of powder is by granulation. So the first trial which was chosen in this study is to add a glidant.

4.2 Preliminary Studies

Although the particle of the yeast extract powder had spherical-like shape, it had hygroscopic property which may cause the caking of the powder and it was fine powder which was another

problem for free flowing. Poorly flowing powder could present many difficulties to the yeast extract tablet making.

The selected glidant, Cab-O-Sil®, in concentration of 1% was primarily incorporated to the yeast extract powder. Then magnesium stearate was added as lubricant. The tablet could be formed, thus, it is shown that the powder probably had self binding property. However, the tablet was sticking to the upper punch and there was a powder flow problem during the compression due to the hygroscopic property of the yeast extract powder.

By trial and error through the direct compression method, Emcompress®, Starch 1500®, and Avicel PH101® individually incorporated in formulation as diluent. Each yeast extract tablet contained diluent not more than 60% of the yeast extract content. One percent of Cab-O-Sil® was added as glidant and one percent of magnesium stearate was added as lubricant. The sticky problem of the tablets on the upper punch and the flow problem still occurred. Thus, it is indicated that the yeast extract tablet can not be made by using the direct compression method since the amount of adsorbent, Cab-O-Sil®, and the diluents were limited to not more than 1% and 60% of the yeast extract powder, respectively.

The wet granulation method is reasonably needed to enlarge the particle size of the yeast extract powder and is carried out to confer flowability and to decrease the surface area of the particle. Each tablet weight was assigned to be approximately 350 mg. containing

200 mg. of the yeast extract powder. The tablet diameter was 3/8 inches. Diluents were used in concentration not more than 50% of the yeast extract powder in each formulation. The commonly used and inexpensive excipients were selected in the formulation.

As shown in Table 3-2, firstly, the investigation was concerned with diluents. Lactose and corn starch were chosen as diluents while corn starch paste was a binding agent. The appearance of the compressed tablet was not acceptable. The browning color on the tablet probably occurred because of the Maillard reaction. The yeast extract powder was consisted of many amino acids (Chernchit, 1985) whereas the lactose was a reducing sugar. In addition, the difficulty in passing through the screen of the sticky wet mass and the long drying period during granulation process were not suitable in industrial practice. Both yeast extract powder and lactose were water soluble matter. So the addition of the water base binding agent might cause physical and chemical changes at the surface of the particles. There might be the physical softening of the surface which became moulded together (Pilpel, 1971).

The sticky property of the moistened yeast extract was also the cause of screening difficulty. Usually, stickiness of materials can be decreased by using high excipient ratios, by using abrasive inorganic excipients, by wet massing and/or by adding magnesium stearate up to 2% (Wells and Aulton, 1988). Therefore, calcium hydrogen phosphate which is water insoluble was chosen as a diluent instead of lactose and corn starch. The resulting tablet showed

mottling by plastic deformation of calcium hydrogen phosphate (Wells and Aulton, 1988). The sticky problem and the long drying period still remained. Even though calcium hydrogen phosphate and corn starch were used together. the starch reduced tablet mottling of granule fracture on compression. The starch grains were thought to reduce granule fragmentation by accommodating compressive force by elastic deformation (Armstrong and March, 1976).

The next formulation, an adsorbent, magnesium carbonate light, was chosen to incorporate with the yeast extract powder due to its high adsorptive capacity in apparently dry state and its water insoluble property (American Pharmaceutical Association, 1986). The wet mass was easily passed through the screen and the shorter drying time was developed. Nevertheless, the use of magnesium carbonate was limited by its laxative property. The usual dose as an antacid is 250-600 mg. and as a laxative is 2-5 g. (American Pharmaceutical Association, 1986). Therefore, the lower amount of magnesium carbonate should be used for evading the laxative result. Corn starch was firstly chosen to be a co-diluent to lower the amount of magnesium carbonate. It is seen that the drying period was satisfactory but the appearance of the tablet was unacceptable. Thus, the corn starch was alternately changed by using calcium hydrogen phosphate which likely caused the wet mass stickier and the appearance of the tablet was not satisfied.

The next trial, corn starch and calcium hydrogen phosphate were used together in the equal amount with magnesium carbonate. In

general, calcium hydrogen phosphate caused tablets to be harder than corn starch. Corn starch was more compressible than calcium hydrogen phosphate. It was seen that the surface and the edge of the tablet had better appearance. The white spots which were seen on the tablet surface might be affected by talcum. Thus, Cab-O-Sil® was chosen to be glidant instead of talcum. This might be due to its more flow promoter property than talcum when they are used in the same amount and it could absorb large quantity of water without liquifying (American Pharmaceutical Association, 1986).

During the investigation of appropriate diluents, The least possible amount of binder for good granulation and good tabletting appearance would be used in the formulations.

At last, the disintegrating agent was considered. Dried corn starch was used in the formulation since the beginning of this preliminary wet granulation. Actually, its ability to swell is slower and less than sodium starch glycolate (Explotab®), a modified starch, when they are used in the same quantity (Rubinstein, 1975). It could be observed during the studies that the disintegration time was not different between the use of dried corn starch and the use of Explotab® for the yeast extract tablet.

The tablet weight was assigned in the range of 325-350 mg.. The amount of ingredients in each formulation was shown in Table 2-1.

4.3 The Physical Properties of the Yeast Extract Granule

It is seen in Figure 3-6 that the surface and texture of the yeast extract granule is irregular which can cause poor flow. But the 16 formulation granules showed larger particle size (Table 3-3), compared to the yeast extract powder. The flow rate of the yeast extract was improved. The percent compressibilty of the yeast extract granules were apparently decreased, comparing to the yeast extract powder whereas the density values were within the same ranges.

There was no significant effect of magnesium carbonate and/or corn starch paste on every properties that were studied at 95% confidential level (Appendix B). This probably due to the narrow ranges of concentration levels.

4.4 The Physical Properties of the Yeast Extract Tablet

4.4.1 Weight Variation

The statistical result of the factorially designed experiment and the result of normal probability plot (Appendix C-1) showed nonsignificant effect of all the factors on the percent of coefficient of weight variation. This may be due to the statistically nonsignificant results which showed that there was no difference in the yeast extract granule properties. So the result can not indicate any effect of those factors on these properties of the yeast extract tablet. However, the weight variation of the formula No.1 was outside the limit specified in the USP XXII standard.

4.4.2 Hardness

Only the effect produced by factor C, the high amount of dried corn starch, was found to be statistically significant for the hardness of the yeast extract tablet (Appendix C-2). This probably due to the dried corn starch mixed with the granules in the higher amount than the Cab-O-Sil® and the magnesium stearate before the compression of the tablets. it can be observed from the data in Table 3-4 that almost all the formulae which contained the high amount of dried corn starch showed the decrease in the hardness values, comparing with the formulae consisted of the same ingredients and absence of the factor C. The formula No.9 and No.13 were the exception. These conform to the knowledge that a loss of bonding and cohesion in tablets often happen when high amount of starch is extragranularly mixed before tablet compression.

4.4.3 Friability

It is seen in Table 3-4 that the tablets of the formula No.4, 10, and 14-16 possessed nagative values of friability. This directly indicated that the yeast extract tablet absorbed moisture during the friability determination. Thus, the effect of the considering excipients may be hindered by the tablet moisture absorption. After scrutinizing the friability data, it can not be clearly concluded that which of these interesting factors influence on the yeast extract tablet moisture absorption. As shown in Appendix C-3 the statistical results showed nonsignificant effect of all the factors on the percent friability of yeast extract tablet, however.

4.4.4 Thickness

As the statistical results (Appendix C-4), the factor BC, high-level corn starch paste together with high-level dried corn starch, was the only significant effect. It can be noticed from the data of the percent coefficient of variation of the thickness that the formulae, using the factor BC, almost showed the lower values whereas the formulae, using the factor B, high-level corn starch paste, or the factor C, dried corn starch, showed the higher values of thickness. This may indicate that the factor B and the factor C have antagonistic interaction. However, the formula No.6, 7, and 16 were the exception probably due to the smallest effect of the factor BC seen from the estimated effect values in Appendix C-4.

4.4.5 Disintegration Time

The statistical results showed that the high amount of magnesium stearate and the high amount of dried corn starch together with the high amount of magnesium stearate significantly affected the disintegration time of the yeast extract tablets. According to the estimated effect values (Appendix C-5), the factor C, high-level dried corn starch, and the factor D, high-level magnesium stearate, show positive values but the interactive effect CD shows negative value which is the smallest effect so this indicates that factor C and factor D have antagonistic interaction. And factor D shows more influence on the disintegration time than the factor CD. It means that the high amount of magnesium stearate lengthened the disintagration time more than the high amount of dried corn starch together with the high amount of magnesium stearate. These results relate to

disintegration time values in Table 3-4. When the formula No.1, 2, and 4 are compared to the formula No.13, 14, and 16, respectively, it can be seen that the high amount of dried corn starch together with the high amount of magnesium stearate causes the longer disintegration time. The formula No.3 and 15 were the exception. Next, the pair comparison of the disintegration time of the formula No. 5, 6, 7, and 8 to the formula No. 13, 14, 15, and 16, respectively, showed that the high amount of magnesium stearate causes increase in disintegration time. When the formula No. 2, 3, and 4 are compared to the formula No. 6, 7, and 8, respectively, it is seen that high-level magnesium stearate lenghtened disintegration time more than the combination of high-level dried corn starch and high-level magnesium stearate. Magnesium stearate usually retards disintegration time due to its hydrophobic property whereas dried corn starch, disintegrant, usually promote disintegration but dried corn starch is less effective on enhancing the tablet to disintegrate explodedly (Rubinstein, 1988) and during the test it was seen that the tablet was disintegrated *via* erosional dissolution. However, it was notable that the tablet was sticked on the bottom of the plastic disc of the disintegration apparatus and the disintegrating medium was clouded due to the color of the yeast extract and the insoluble excipients, so the end point of testing probably varied.

4.5 Salmonella Test

The test for *Salmonella* in the yeast extract powder and the yeast extract tablets were negative. These results meet the standard of yeast tablet (American Pharmaceutical Association, 1986).

4.6 Aging Studies

Yeast extract is previously known to be hygroscopic powder. The physical properties of the yeast extract tablets, thus, were investigated to develop the comprehensive data of the storage under humid conditions.

4.6.1 In Closed Containers

Most of the tablet formulation showed no change in weight, thickness, and hardness. Although the disintegration times showed fluctuation, their values were found to comply with the requirement of the yeast tablet (NF XIII). The formula No.12 showed distinct weight increase during storage and its weight variation at every aging period did not pass the USP requirement. Consider the largest deviation of the thickness value of this formula at the initial condition (Table 3-4), it might be said that the nonuniformity flowing due to the heterogeniety of particle size mixture (granules and excipients) was the main reason for its great weight variation. The aging results of the 16 yeast extract tablets stored in closed containers under humid conditions did not show any consistent correlation among the 4 physical properties possibly due to the difference in formulations.

It could be concluded that most of the produced yeast extract tablet had no change or slightly change in physical stability over the three-month storage in closed container even kept under the high relative humidity environment.

4.6.2 In Opened Containers

Significant increases of all formulation tablet weight and thickness and the decrease of hardness were observed at the three storage conditions over the periods of 30 days. The disintegration time fluctuated, however, in the 30-day period. The tablets tended to pick up moisture which made them softer, heavier, thicker and taking more time to disintegrate. The great change in hardness of the tablets which were kept under 70 percent ambient relative humidity were clearly observed even during the first week. This might be due to saturation of moisture adsorption of the tablets.

The change in tablet hardness during storage may not relate to the change in disintegration time. According to the results of weight, hardness, and thickness changes, it could be concluded that the tablets were softened with aging whereas increased in weight and thickness. It is noticed that some formulations which were kept at 30 percent relative humidity condition had no change in some tablet properties within 30 days.

4.7 Conclusions

a) The yeast extract powder had no flowability due to its fine paricle size and hygroscopic property.

b) From the preliminary studies, yeast extract granules were produced for tablet preparation using wet granulation method with the incorporation of magnesium carbonate light as adsorbent, corn

starch and calcium hydrogen phosphate as diluents, corn starch paste as binder, dried corn starch as disintegrant, Cab-O-Sil® as glidant, and magnesium stearate as lubricant.

c) According to 2^2 factorial experiment the adsorbent and the binder did not significantly affect the physical properties of the yeast extract granules (α=0.05).

d) The 2^4 factorially designed experiment which was carried out to investigate the influence of magnesium carbonate, corn starch paste, dried corn starch, and magnesium stearate on the physical properties of the yeast extract tablets showed nonsignificant effect on weight variation and friability of tablets. The tablet hardness decreased by the high-level dried corn starch. The thickness variation decreased by the combination of the high amount of starch paste and high amount of dried corn starch. High content of magnesium stearate lengthened the tablet disintegration time more than the interactive effect of high-level dried corn starch and high-level magnesium stearate.

e) Almost all yeast extract tablet formulations retained their physical properties conforming to the standard after aging in closed containers for 3 months. In opened containers, all formulation tablets kept under high humid condition became softer, heavier, and thicker. But the disintegration time results could not be concluded.

f) Most of the yeast extract tablet formulations in this study were satisfactory except for formula No.1 and No.12 which did not pass the USP XXII weight variation standard. And the thickness variation of formula No.12 did not conform to the requirement of pharmaceutical industry.

4.8 Suggestion

For successfully industrial production of yeast extract tablet, it needs more investigation foe solving its hygroscopic property which is a major problem in making into the tablets. Probable means to improve may be as follows :

a) Strickly control relative humidity of manufacturing area
b) Reduce quantity of yeast extract per tablet
c) Try to prepare spray dried yeast extract with less hygroscopic property by co-spray drying with nonhygroscopic material so it can be produced into tablet by direct compression method
d) Produce yeast extract in granular form by vacuum drying which may be less hygroscopic
e) Analysis of nutrient composition in each yeast extract tablet have to be done in order to know whether it has quantity alteration during processing or not. Moreover, nutrient stability test of some nutrients such as vitamin have to be investigated.