CHAPTER VII

EVALUATION OF MODIFIED TAPIOCA STARCH AS TABLET DISINTEGRANT IN PARACETAMOL TABLETS

The full potential value of a compressed tablet is assured only when the tablet dissolves rapidly so that the active ingredient can affect the desired therapeutic action, the primary action in dissolution process is disintegration of tablet. Of all the commonly used disintegrating agents ordinary starch is by far the most widely used materials (Gadalla, El.Hameed and Ismail,1989). At first, starch have been applied directly in the native forms. Since 1965 the first successful attempted to improve the disintegrant efficiency of native starch by chemical modification of potato starch. The carboxymethylated of potato starch was hydrophilic but insoluble and strongly increased its swelling properties.

Mendell (1974) studied the three most commonly used tablet disintegrants corn starch, algenic and and microcrystalline cellulose (Avicel^{R}) by comparing with carboxymethyl starch for disintegration time. In direct compression, carboxymethyl starch was shown to be better disintegrant than the others for both water soluble and poorly soluble drugs.

For the last many years, a number of new disintegrants has been studied. A new tablet disintegrating agents: crosslinked polyvinylpyrrolidone have been studied by Kornblum and Stoopak (1973). They suggested that crosslinked polyvinylpyrrolidone demonstrated superiority over starch USP and alginic acid in most of the experimental tablet formulations made by either dry or wet granulation. And also Rudnic, et al. (1980) have studied the different particle size grades of crosslinked polyvinylpyrrolidone in direct compressed tablets. They found that increased in mean particle size enhanced powder flow,

disintegration and dissolution. They concluded that polyvinylpyrrolidone exhibited powerful disintegrant at low concentrations.

Bhatia, Desai and sheth (1978) have studied the disintegration of tablets using CLD® (crosslinked carboxymethyl cellulose) and other excipients. They found that CLD®, Explotab® and Sta-R_X 1500 improved disintegration of lactose formulations but Sta-R_X formulations capped at high pressure. With dicalcium phosphate formulations, very low levels of CLD® and Explotab® (as low as 0.5 percent) were highly effective disintegrants.

An evaluation of crosscarmellose as tablet disintegrant has been studied by Gorman, Rhodes and Rudnic (1982). The data clearly showed that both forms of croscamellose(Ac-Di-Sol® and CLD®) were markedly superior to corn starch and were active at quite low concentrations.

Rubinstein(1980) studied the effect of disintegrants: Explotab®, polyplasdone® XL, Amberlite® IRP 88, maize starch and Elcema® P 100 on bioavailability of furosemide 40 mg tablets. With maize starch and Elcema® P 100, the drug was significant less bioavailable than with the others. The tablets containing Explotab® gave the highest bioavailability.

Schwatz and Zelinskie (1978) studied the binding and disintegrant properties of the corn starch fractions: amylose and amylopectin. They suggested that amylose fraction of starch seemed to be an extremely effective disintegrant.

The effectiveness of cyclodextrin polymer as a disintegrating agent for directly compressed tablets containing furosemide have been investigated. It was found that cyclodextrin improved the disintegration time and the dissolution rate. Allthough increased hardness of the tablets, it provided a good stability of dissolution profile (Fenyvesi, 1984).

Paronen, Juslin and Kasnanen (1985) studied the disintegrant properties of xylan a polymerization of the pentose sugar xylose. They concluded that the disintegrating properties of xylan were weaker than those of Primojel^R, but almost as good as those of Sta-R_X 1500 and clearly better than those of Avicel^R PH 101 and Elcema^R G 250. They suggested that an essential disintegrant mechanism of xylan was swelling of primany particles.

Trivedi, et al.(1986) improved a disintegrating property of gum acacia bycrosslinking with epichlorohydrin and evaluated the gum as disintegrant. Crosslinked gum acacia brought about rapid disintegration as compared to corn starch. They found that an increase in percent of disintegrant from 2.5% to 7.0% reduced the disintegration time in all case.

Roe and Chang (1986) studied Key-Jo Clay as a new tablet disintegrant. They suggested that Key-Jo Clay was the most suitable tablet disintegrant when added until it was 25 percent of the tablet weight.

Visavarungroj and Remon (1990) evaluated the different types of crosslinked starches and pregelatinized crosslinked starches as disintegrating agent in comparison to potato starch and a number of super disintegrants. The tablets formulated with pregelatinized starch, with or without crosslinking, showed variable and long disintegration times in comparison to the super-disintegrant: Ac-Di-Sol^R, Explotab^R and polyplasdone^R XL.

Akande, Deshpande and Bangudu (1991) evaluated the starch obtained from pearl Millet as a binder and disintegrant for compressed tablets. The results showed that Millet starch compared favorably with maize starch with regarded to most of the parameters used to evaluate the tablets. Millet starch was suitable for the use as a binder and disintegrant in tablet formulation.

Visavarungroj and Remon (1991) have evaluated the hydroxypropyl starch as disintegrant and binder in tablet formulations. They suggested that

pregelatinized hydroxypropyl starch showed some good disintegrant properties and could be used as a binder in wet granulation.

Bhargava et al. (1991) have evaluated the smecta as a tablet disintegrant. Smecta, a non fibrous attapulgite, performed well as a disintegrant in tablets made by water soluble and water insoluble systems. It was superior to veegum and starch 1500, but inferior to Ac-Di-Sol^{R} and Polyplasdone^{R} XL. In the hydrochlorothiazide tablets containing smecta as disintegrant exhibited dissolution profile superior to those containing Ac-Di-Sol^{R}.

Besides searching new powerful disintegrant, improving the conventional disintegrant has been developed such as the study of surfactant treated tapioca starch on disintegration time and dissolution of sulphadiazine tablets which investigated by Nasipuri and Omotosho (1984). They found that the disintegration and dissolution rates were faster with starch in which surfactant was incorporated in dry state than with starch treated with solution of surfactant.

In addition, increasing the efficiency of carboxymethyl starch as tablet disintegrant have been studied by Bolhius, Kamp and Lerk (1984). They suggested that purification of the sodium starch glycolates enhanced their disintegrating efficiency.

Due to disintegrating efficiency were affected by a number of factors such as compression forces and the method of disintegrant incorporation into the formulation. Hence, these factors which affected to disintegrating efficiency should be studied.

Khan and Rooke (1976) have studied the effect of disintegrant to dissolution and compression pressure relationship. It was apparent that disintegrant type have significantly affected the compression force and dissolution efficiency relationship.

Hill (1976) have studied the effect of compression force and corn starch on tablet disintegration time. He found that the varying disintegration time of tablets compressed at the same compression forces was related to the pressure or absence of disintegrant starch in tablet as well as to the ratio of disintegrant starch to paste starch. He concluded that the tablet without disintegrant starch would disintegrate by a different mechanism and showed a different disintegration time-compression profile.

Miller, et al. (1980) have evaluated the effect of disintegrant and compression force on breaking strength, disintegration and dissolution properties of acetaminophen tablets. They found that sodium carboxymethyl starch, and the two crosslinked sodium carboxymethylcellulose derivatives tested provided the greatest enhancement of disintegration as well as showing the least sensitivity to compression force effects.

Kitamori and Makino (1982) improved the pressure-dependent dissolution of trepibutone tablets by using intragranular disintegrants. It was found that the incorporation of disintegrant in the granular formulation prevented the decrease in dissolution rate of the drug from tablet by compression. They concluded that addition of disintegrant in granular formulation resulted in little prevention of the particle aggregation during compression. The swelling of disintegrant grain in water was considered to play an important part in the deaggregation of drug particle.

Vades, et al, (1984) have studied the effect of compression force on tablets containing cellulosic disintegrant. They found that two internally cross-linked sodium carboxymethylcellulose disintegrants were the most efficient and their efficiency increased with increasing compression force.

Rubinstein and Bodey (1976) have studied disaggregation of compressed tablet by varying the percentage and method of incorporation of disintegrant. The tablets were compressed in a different compression forces. They found that an increase in compacting presssure, increased the disintegration

time. Increasing the ratio of extragranular starch above 5% (w/w) produce a decreased in dissintegration time.

In addition, there was a report to study the effect of amount and composition of granulating solution on physical characteristics of tablets. (Shira kura, et al., 1992). They suggested that physical characteristics of tablets such as hardness and disintegration of tablet were strongly affected by the amount and composition of granulating solution in preparation of tablet granules by wet granulation.

Purpose of the study.

The scope of the study in this part is to study the disintegrating efficiency of modified tapioca starch on disintegration times of paracetamol tablets. The disintegration time will be investigated and compared to the tablets containing Explotab^R, Primojel^R, Polyplasdone^R XL and Ac-Di-Sol^R as disintegrating agents. The tablets containing 4% MTS as tablet disintegrant were compressed in different compression forces to investigate the effect of compression forces on disintegration time. Also, to elucidate the relationship of the methods of disintegrant incorporation and disintegration time, the tablets will be prepared by three different disintegrant incorporation methods: intragranular, extragranular and 50% intragranular plus 50% extragranular.

Materials and Methods

Materials:

Paracetamol (Monsanto, USA)

Explotab^R (Mendell, NY, USA, Lot. No. E4222)

Primojel^R (AVEBE, Holland)

Ac-Di-Sol^R (FMC Corporation, USA, Lot. No. T934)

Polyplasdone^R XL (GAF, USA)

Methods:

1. Preparation of paracetamol tablets

The experimental formulation of paracetamol tablet was.

R_X

Paracetamol	500 mg
PVP 30 K(10% in alcohol)	20 mg
Disintegrant	20 mg
Stearic acid	5 mg
Magnesium stearate	0.1 mg

The drug and binder employed in each formulation were passed through a 80 mesh screen. The accurate amount of drug and the binder used in formulation were weighed and mixed thoroughly by Kenwood mixer for 10 minutes. The mixture was kneaded into damp mass with ethanol for 5 minutes. The granules were tray dried in oven for 6 hours at 50^0 C. The dried granules were passed through a 20 mesh screen and then lubricants were incorporated into dried granules and mixed thoroughly in mortar for 5 minutes. The tablets were compressed on single punch tablet machine with strain gauge using flat face, 20/32 inches punch. The pressure were kept about 1680, 2240 and 2800 pounds to investigate the effect of compression pressure on disintegration time of tablet.

2. Preparation of tablets containing different disintegrants.

The tablets were prepared by the same procedures as in 1. The amount of binder and lubricant were constantly maintained in the formulation for each batch. The various disintegrants were Explotab^R, Primojel^R, Ac-Di-Sol^R, Polyplasdone^R XL and MTS. The compression pressure was kept about 2800 pounds.

3. Preparation of tablets by different disintegrant incorporation methods.

The tablet were prepared by the same procedures as in 1. The MTS disintegrant was incorporated by three different methods: intragranular, extragranular, and 50% intragranular plus 50% extragranular. The compression pressure was kept about 2800 pounds.

4. Preparation of tablets using different granulating fluids.

The tablet were prepared by the same procedure as in 1. The MTS disintegrant was used as tablet disintegrant. The granulating fluid used were water and ethanol and the compression pressure of tabletting was kept about 2800 pounds.

5. Evaluation of Tablets

5.1 Hardness

Ten tablets were randomly selected and subjected to a hardness tester (Schleuniger-2E model 2E/205). The mean and standard deviation were calculated.

5.2 Disintegration times of tablets

The disintegration times of tablets were determined in deionized water using Hanson Research Tablet Disintegration Tester (model 64-700-156, series No.1529-17, USA). The mean of six determinations and standard deviation were calculated.

5.3 Dissolution study

The dissolution study were conducted using USP dissolution type II method (Hanson Research SR2, California, USA). A 900 ml of phosphate

buffer, pH 5.8, was used as dissolution medium, which maintained at 37° C. The paddle were rotated at the speed of 50 rpm. Five milliliters samples were withdrawn by syringe at various time intervals. The absorbances of sample were determined using ultraviolet spectrophotometer (Hitachi spectrophotometer, model 150-20 serial No. 5914-30) at maximum wavelength, 243.2 nm and the contents were calculated from the absorbance-concentration relationship. To maintain constant volume of dissolution medium, a five milliliters of fresh medium was replaced after removal of each sample.

Results and Discussion

Disintegration times and dissolution study of paracetamol tablets containing various disintegrants.

Figure 67 showed disintegration times (DT) of paracetamol (APAP) tablets containing MTS, Explotab^R, Primojel^R, Polyplasdone^{R}XL and Ac-Di-Sol^R as tablet disintegrants (see Appendix 18 for data). The tablets containing MTS, Explotab^R, Polyplasdone^{R}XL and Ac-Di-Sol^R as tablet disintegrant exhibited short disintegration times (about 1 minute) and more closely resembled.

The tablet containing Polyplasdone^R XL as tablet disintegrant showed longer disintegration time. It was due to Polyplasdone^R XL dissolved in ethanol which used as granulating fluid then played a role as a binder. It caused the tablets disintegrated slowly.

The dissolution study of paracetamol tablets containing various disintegrant was shown in Figure 68. The dissolution rates of paracetamol tablets containing MTS, Explotab^R, Primojel^R and Ac-Di-Sol^R as tablet disintegrant were better than tablets containing Polyplasdone^R XL as tablet disintegrant. This result was corresponding to the disintegration times study.

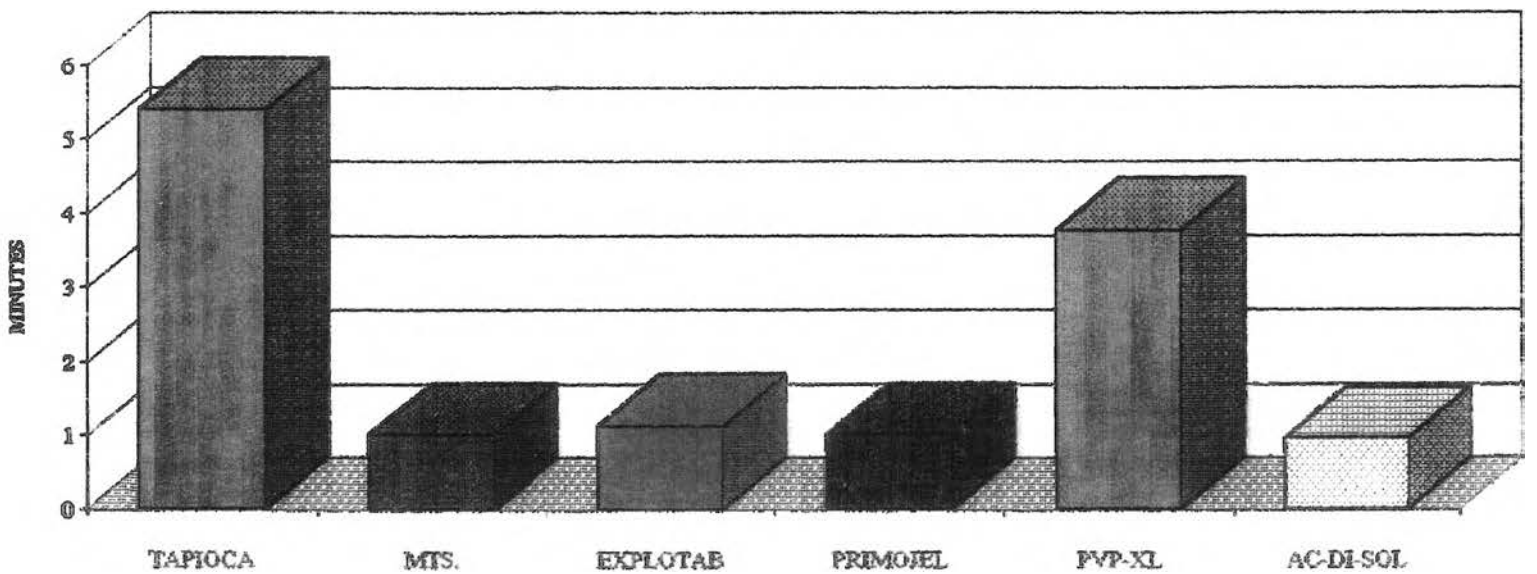
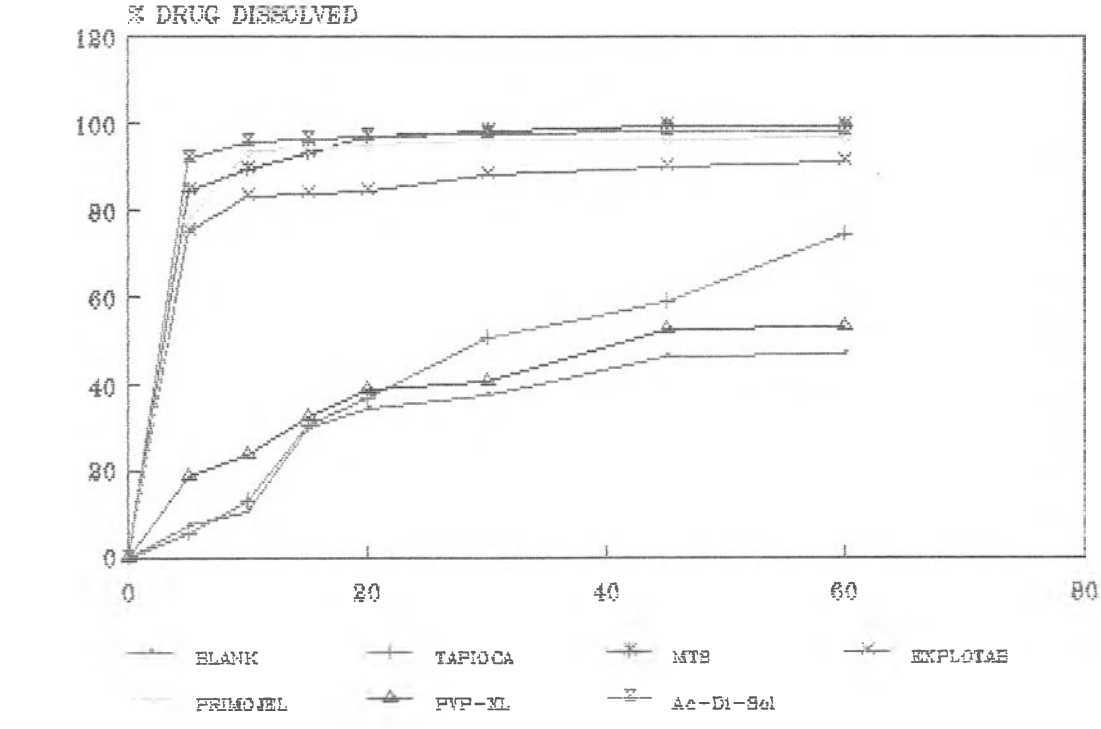


Figure 67 Disintegration Time of Paracetamol Tablets Containing Various Disintegrants.



PVP-XL = POLYPLASDONE XL

Figure 68 Dissolution Profiles of Paracetamol Tablets Containing 4 % Various Disintegrants.

This can be attributed to the Polyplasplasdone^{R} XL dissolved in ethanol which used as granulating fluid and then acted as a binder. In addition, the adhesion of magnesium stearate flakes to the drug-Polyplasdone^{R}XL agglomerate resulted in a decrease in drug dissolution (Chowhan and Li Hua Chi, 1986).

Effect of compression forces on disintegration time of paracetamol tablets containing MTS as tablet disintegrant.

Figure 69 showed the effect of compression forces on hardness of paracetamol tablets. It was found that hardness of tablets containing MTS as disintegrant increased when the compression force increased. In fact, the compression force increased from 1680 pounds to 2240 pounds resulted decreased in disintegration time and the disintegration time of tablets increased when the compression force increased from 2240 pounds to 2800 pounds. It might be explained that the tablets made with low pressure have high porosity and, hence, too much space. When MTS swells, no pressure was exerted so disintegration was slow. Medium pressure allowed just enough space so that when the MTS swelled, it exerted pressure on the granules to cause disintegration. High pressure, producing low porosity, decreased the ability of fluid to enter, so disintegration was again slow as shown in Figure 70.

Effects of incorporating methods of MTS and type of granulating fluids on the disintegration times of paracetamol tablets.

The effect of three different methods of disintegrant incorporation into formulation: intragranular, extragranular and 50% intragranular plus 50% extragranular on disintegration time have been studied. The disintegration time of paracetamol tablets prepared by different methods of incorporation of MTS disintegrant were shown in Figure 71. The disintegration times of tablets prepared using water as granulating fluid were significantly different

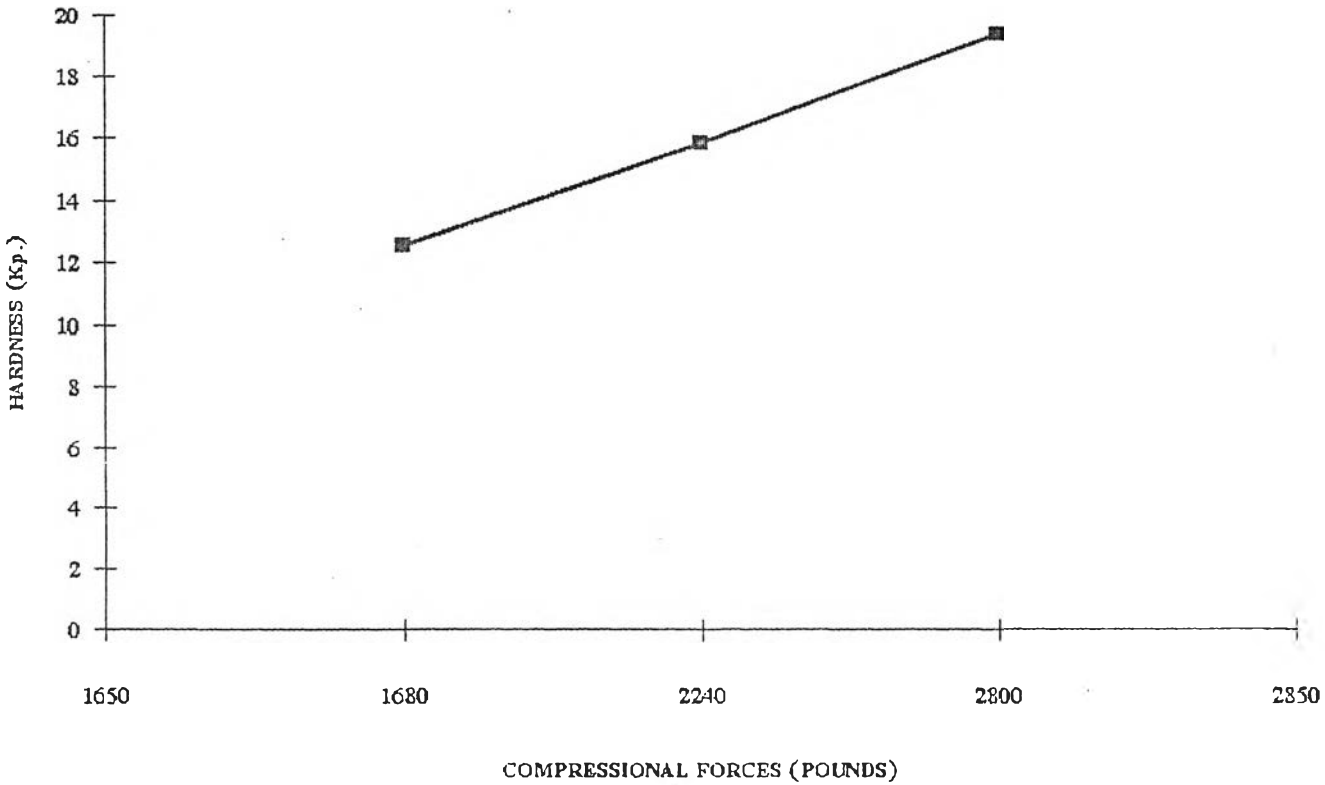


Figure 69 Effect of Compressional Forces on Hardness of Paracetamol Tablets.

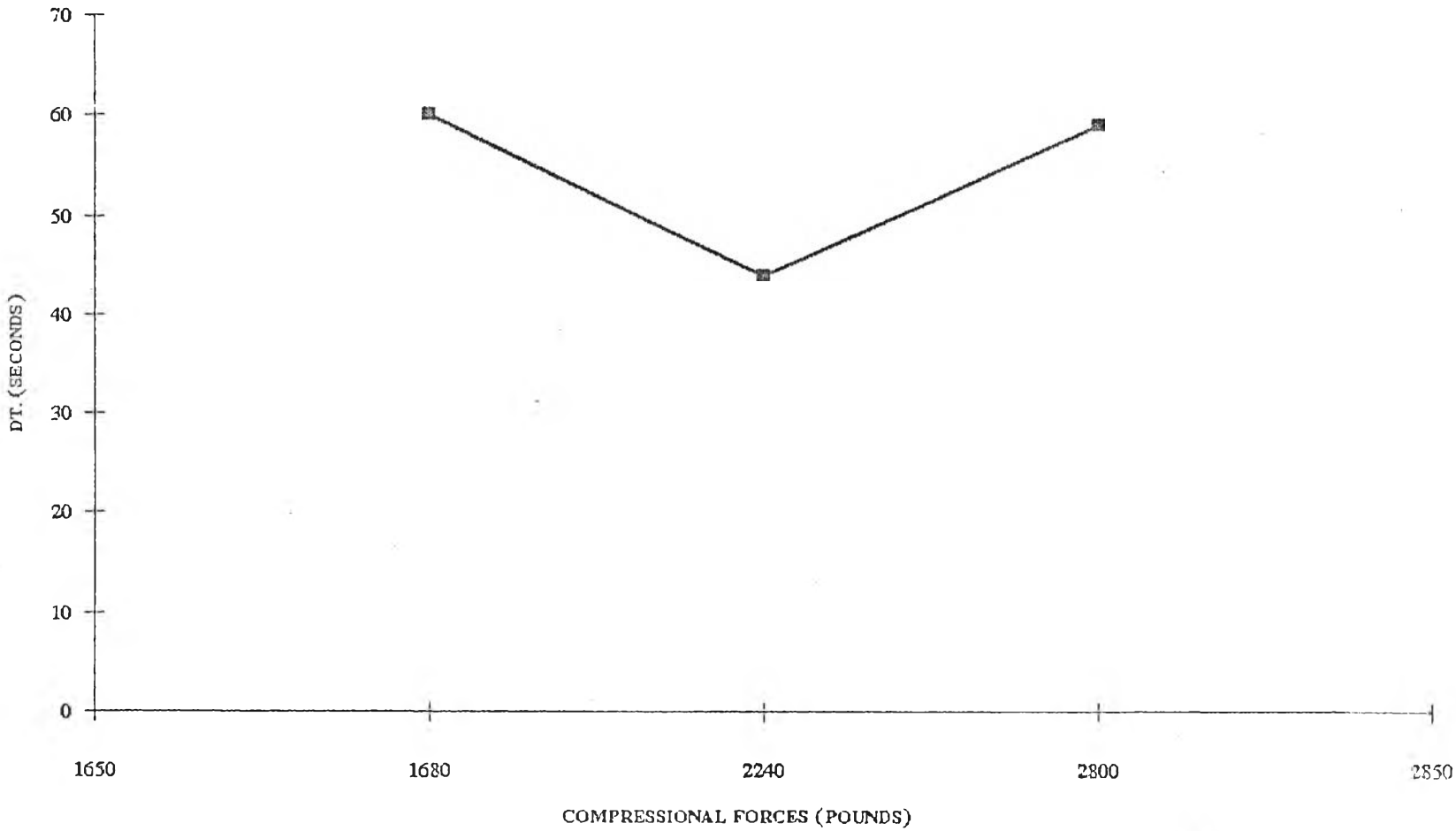


Figure 70 Effect of Compressional Force on DT of Paracetamol Tablets.

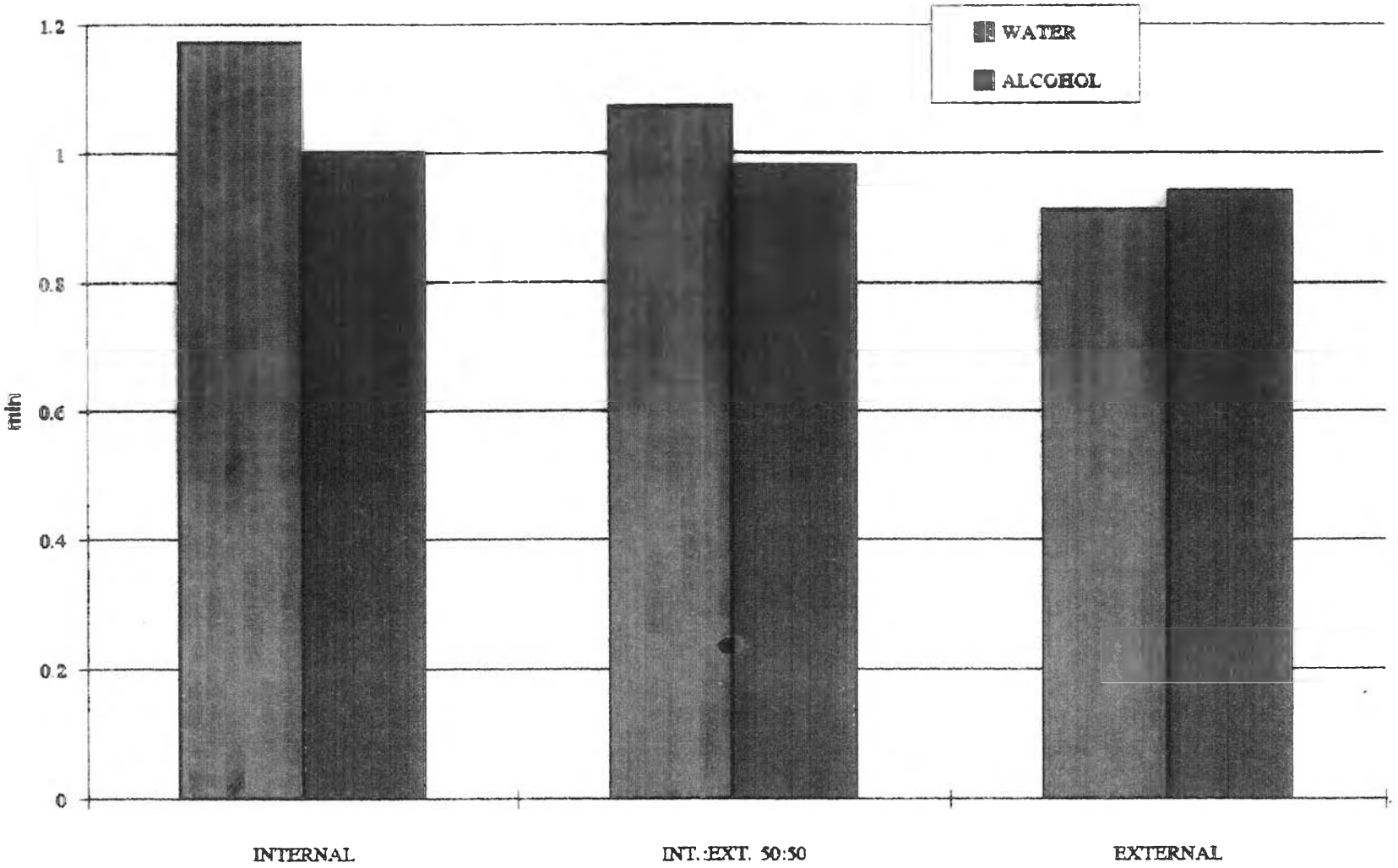


Figure 71 Effect of Incorporating Methods of MTS on DT OF Paracetamol Tablet.

($F_{2,15,0.05}$ = 3.68, F_{ratio} = 30.73). The disintegration times (min) were ranked as the following: internal (1.17 ± 0.04)> 50% internal plus 50% external (1.07 ± 0.0657)> external (0.91 ± 0.06). This could be explain that internal incorporation of MTS as disintegrant may be affected by water which used as granulating fluid. The MTS swelled when contact with water and partially dissolved, during wet granulation, caused partially loss of disintegrating efficiency. Contrastly, the external incorporation of MTS caused hydrophilic region at the surface of tablet and around granules to facilitate the disintegration medium penetrated into tablet matrix resulted rapid disintegration.

Although the different incorporation methods (internal, 50% internal plus 50% external and external) of MTS into granules of paracetamol tablets which prepared using ethanol as granulating fluid. The disintegration of tablet were not significantly different ($F_{2,15,0.05}$ = 3.68, F_{ratio} = 1.09). This can be described that MTS less dissolved and less swelled in ethanol, hence, granulating fluid (ethanol) did not affect to disintegration of tablets.

Conclusions

The comparative study of disintegration times of paracetamol tablets containing various disintegrants was investigated. It was found that the MTS disintegrant exhibited the disintegrating efficiency equivalent to the other super disintegrants such as Explotab^R, Primojel^R and Ac-Di-Sol^R at the same level of concentration. The disintegrating capacity of MTS was affected by the granulating fluid such as water, therefore in the wet granulation process the type of granulating fluid should be considered. Furthermore, the compression force affected the disintegration time of paracetamol tablets, hence, the optimum compression force during tabletting should be considered.