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IMPROVEMENT IN PRESSURE-DEPENDENT DISSOLUTION OF TREPIBUTONE TABLETS BY USING INTRAGRANULAR DISINTEGRANTS

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ABSTRACT

In developing compressed tablets trepibutone 40mg, dissolution studies indicated that the compression pressure applied exerted strong influence on drug dissolution from the tablets. It was found that the incorporation of disintegrants in the granular formulation prevented the decrease in dissolution rate of drug from tablets by compression. Instead of the intragranular disintegrants, incorporation of a rubber powder, which does not swell at all in water and has some elastic recoveries after compression, did not improve the drug dissolution from tablets. It was concluded that the addi-

tion of disintegrants in the granular formulation resulted in little prevention of the particle aggregation during compression. The swelling of disintegrant grains in water is considered to play an important part in the deaggregation of drug particles.

INTRODUCTION

Trepibutone [3-(2'4'5'-triethoxybenzol) propionic acid] is a new potent antispasmodic for biliary smooth muscle.[1,2]

In developing compressed tablets trepibutone 40mg, it was found that the dissolution of the drug from the tablets was strongly affected by the compression pressure applied. The pressure-dependent dissolution certainly depended upon the drug content in the tablet.[3] Therefore, the effect of the compression pressure on the dissolution can be eliminated when the drug content is lower than 10%. The drug content, however, should be kept above 30% so that the tablet size will not be too large for easy oral intake.

The incorporation of disintegrants in the granular formulation prevented the drug dissolution of tablets from decreasing by compression. The mechanism of the improvement in the pressure-dependent dissolution was also investigated.

EXPERIMENTAL

Materials: The crystal form of trepibutone (manufactured by Takeda Chemical Industries, Ltd., Lot 014) is fibrous and its appearance is like a cotton-wool. The drug is a hydrophobic weak acid and poorly soluble in water or an acidic solution. The pk_a value is 5.45 and solubility in McIlvain buffer (pH 5.0) is 1.5×10^{-4} g/ml at 37°.

Lactose J.P. (D.M.V., Holland) was used as an adjuvant. Cornstarch J.P. (Nihon Cornstarch Ltd.) and carboxymethyl cellulose calcium J.P. (ECG-505, Gotoku Pharmaceutical Enterprise Inc.) were used as disintegrants. A rubber powder* was chosen as a model of a disintegrant. Hydroxypropyl cellulose J.P. (HPC-L, Nihon Soda Co.) was used as a binder.

Preparation of granules and tablets: The drug was mixed with lactose and disintegrant, and moistened with aqueous hydroxypropyl cellulose solution in a mortar. The moistened powder was massed with a pestle and passed through a 32-mesh sieve. The granules were then dried in a vacuum dryer (55°) and repassed through a 32-mesh sieve. The granules were prepared at varying levels of

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* This is kindly prepared by Naniwa Rubber Co. for our studies.

drug and disintegrant content, where lactose was used to adjust the drug and disintegrant contents.

The granules were compressed into tablets each 400mg on a physical testing instrument (Autograph IS-5000, Shimadzu Seisakusho Ltd.) using a 10mm flat-faced punch and die system.

Dissolution rate measurements: Recently Kitamori and Makino found it possible to elucidate the change in the particle state during compression from the pressure-dependent dissolution behavior of tablets by comparing the dissolution rates for suspensions or granules containing the same amounts of drug.[4)]

The dissolution profiles for disintegrated tablets as well as for granules were measured by a modification of the U.S.P. method. A schematic diagram of the dissolution apparatus used are shown in Fig.1. A magnetic stirrer was used to agitate the dissolution medium without rotating the basket. The agitation speed was regulated to 300rpm by a tachometer generator (Toyo Seisakusho Co.). Suspensions or disintegrated tablets were thrown into the beaker directly. The solution was pumped continuously at a flow rate of approximately 2.9 ml/min from the reservoir through the flowcell by a proportioning pump (Auto Analyzer, Technicon, U.S.A.) and returned to the reservoir. The absorbance at 271nm was

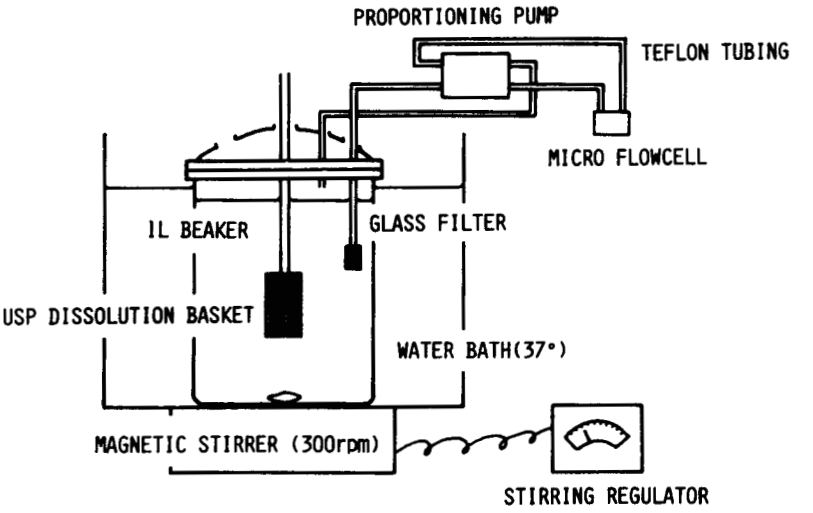


FIGURE 1

A Schematic Diagram of the Dissolution Apparatus

continuously measured using a spectrophotometer (124, Hitachi Ltd.) and recorded (by Hitachi Recorder 056). One liter of a McIlvain buffer (pH 5.0) maintained at 37° was used as the dissolution medium. For each dissolution study the samples of disintegrated tablets were used in amounts that were corresponding to 20mg of trepibutone so that apparent sink conditions were maintained throughout the dissolution test since the quantity of drug was less than one tenth of its solubility. The time necessary for 50 or 80% dissolution was employed to represent the dissolution rates for disintegrated tablets or granules.

RESULTS AND DISCUSSION

The granules containing 10, 32 and 50% drug without any disintegrant were compressed at different pressure levels. Therefore, the dissolution rates for disintegrated tablets were measured in order to eliminate the effect of disintegration time on the dissolution rate. The results were shown in Fig.2, where the dis-

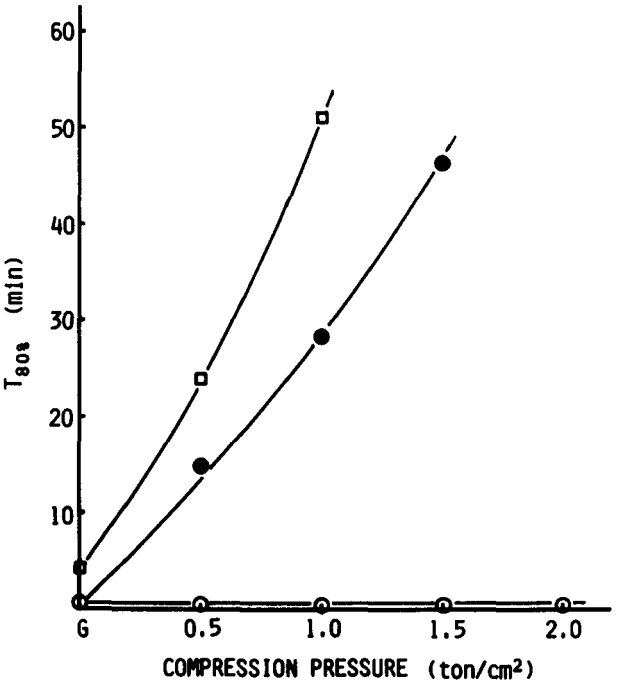


FIGURE 2

Effect of Compression Pressure on Dissolution Rate of Trepibutone from Disintegrated Tablets.

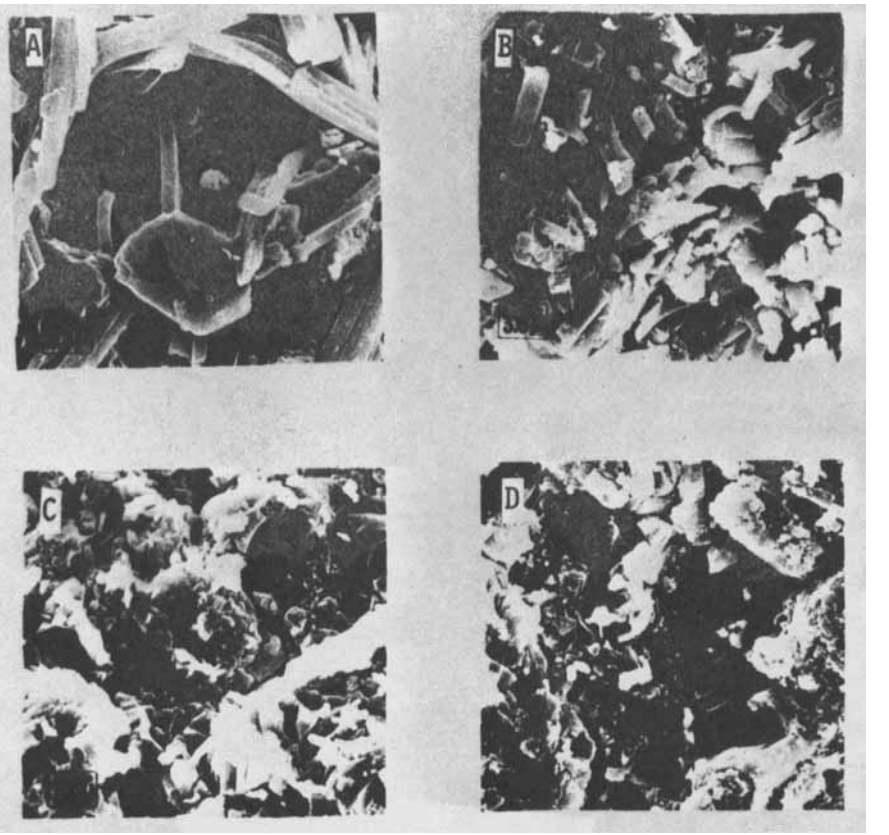
Key: Drug Content is (○) 10%, (●) 32% and (□) 50%.

solution rates for granules before compression were plotted at zero compression pressure on the abscissa.

It is clear that dissolution behavior for disintegrated tablets of higher drug content than 10% is pressure-dependent. It should be noted that the dissolution rate for granules containing 50% drug differs from those for other granules even though no compression pressure has been applied.

Fig.3 shows the scanning electron microphotographs which are the cross-sectional views of granules containing 32% drug and their tablets compressed at 0.5, 1.0 and 2.0 ton/cm^2 respectively. Nevertheless the drug content in the granules is not so high, drug particles are especially striking on these photos. The density of the drug is 1.26 g/ml and is not so small than those of lactose or other materials. Therefore, the content of the drug by volume is nearly equal to that by weight. It can also be seen that fibrous crystals are aggregated each other in the granules. The compression pressure breaks up the crystals and tighter aggregates of drug are formed. Aggregation of drug particles may provide the decrease in apparent specific surface areas.[5] It must be the reason that the compression lowers the dissolution rate of drug from tablets.

In order to improve the pressure-dependent dissolution of the trepibutone tablets, the use of some surfac-



Cross-Sectional Views of Granules Containing 32% Drug and Their Tablets

Key: (A) Granules (B) Tablet Compressed at 0.5 ton/cm^2, (C) 1.0 ton/cm^2 and (D) 2.0 ton/cm^2.

tants and disintegrants in the granular formulation was attempted. Cooper[6] and Agiar[7] reported that incorporation of surfactants into tablet formulations was effective in reducing disintegration time. The effect of surfactants on dissolution of trepibutone, however, was not observed in this case. A possible explanation for this result may be as follows. The main binder used in their tablet was acasia having a poor surface activity, which is thought to have resulted in an insufficient improvement in the wettability of hydrophobic drugs. On the contrary, hydroxypropyl cellulose used in our formulation enhanced wettability of drugs without any help of surfactants.

It is suggested from the examination of the scanning electron micrographs and from the results of incorporation of surfactants that separation of drug particles from their aggregates has to be positively done by the explosive power of disintegrants.[8,9] From this point of view, extragranular disintegrants in the tablet formulation was not effective in enhancing the dissolution rate except in reducing disintegration time of the tablet as shown in Fig.4. The similar results have been also obtained in other formulations, where the aggregation of drug particles during tableting depended only upon the drug content in granules and did not depend upon the apparent drug content in the tablet.

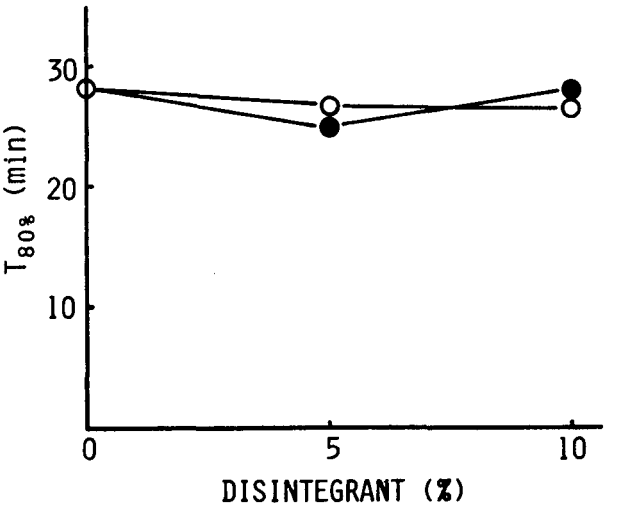


FIGURE 4

Effect of Extragranular Disintegrants on Dissolution Rate of Trepibutone from Disintegrated Tablets. Tablets Containing 32% Drug were Compressed at 1.0 ton/cm^2.
Key: (○) Cornstarch (●) ECG-505.

Incorporation of disintegrants in the granular formulation drastically improved the pressure-dependent dissolution behavior. Fig.5 shows the improvement in the dissolution rate for disintegrated tablets of trepibutone compressed at 1.0 ton/cm^2 when cornstarch or ECG-505 has been used as an intragranular disintegrant. The dissolution rate increased or, in other words, $T_{80\%}$ decreased as the content of disintegrants in the granules increased. The dissolution rates for these disintegrated tablets,

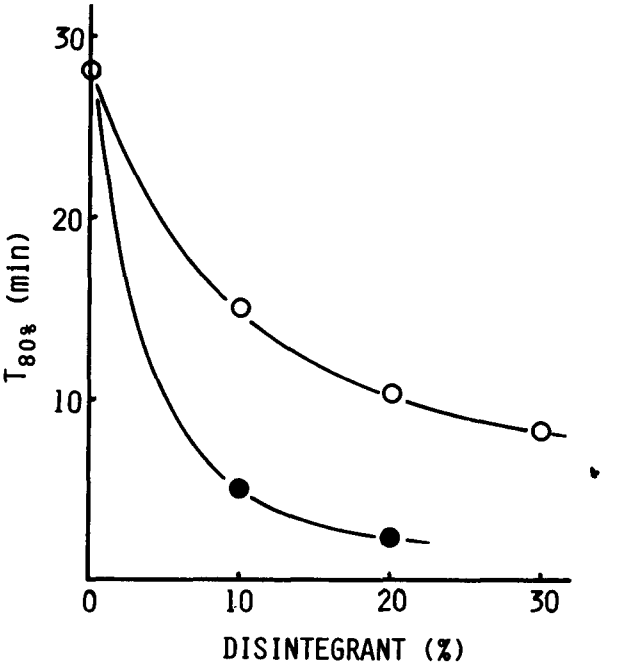


FIGURE 5

Improvement in Dissolution Rate of Trepibutone from Disintegrated Tablets. Tablets Containing 32% Drug were Compressed at 1.0 ton/cm^2.

Key: (○) Cornstarch (●) ECG-505.

however, did not reach that for granules before compression within the concentration range of disintegrants used. The dependency of the compression pressure on the dissolution rate did not vanish completely. The dissolution rate ($T_{80\%}$) versus the compression pressure is shown in Fig.6. It seemed that the improvement in the dissolution rate by using disintegrants

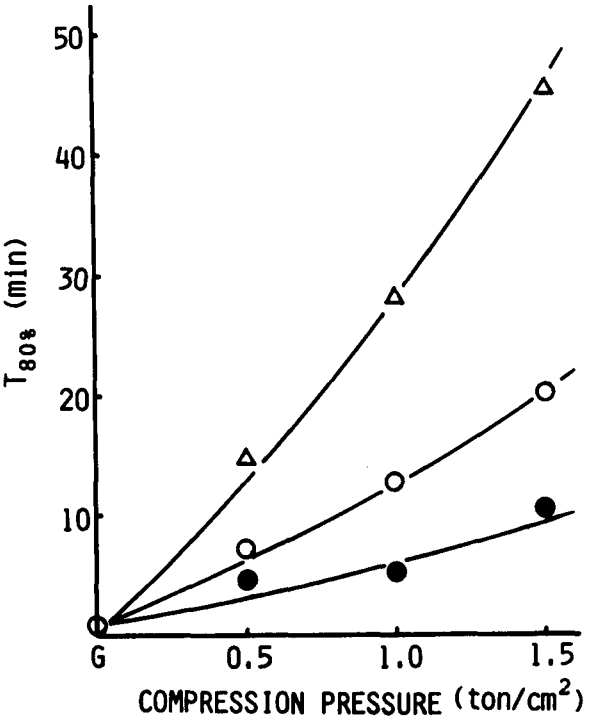


FIGURE 6

Effect of Intragranular Disintegrants on Relationship between Compression Pressure and Dissolution Rate of Trepibutone from Disintegrated Tablets.
Key: (△) without Intragranular Disintegrants, (○) Cornstarch, (●) ECG-505.

corresponded to the swelling of disintegrant particles in water.[10]

As mentioned above, the improvement in dissolution rate by disintegrants must result from dispersion of drug particles from their aggregates. Studies were

carried out to determine whether preventing the drug particles from aggregating each other during compression by the elastic properties of disintegrants or dispersing the particles from their aggregates during disintegration by the swelling properties of disintegrants was more effective. For this purpose, a rubber powder, which does not swell at all in water and has some elastic recoveries after compression, was chosen as a model of disintegrant. Fig.7 shows the dissolution profiles for disintegrated tablets containing 32% drug with 10% rubber powder and without disintegrants. The dissolution profile for granules before compression is also shown in Fig.7. It is clear from the figure that the dissolution profile for disintegrated tablets containing a rubber powder is almost the same as that for disintegrated tablets without disintegrants, nevertheless only low hardness could be obtained in the granules with a rubber powder. Therefore, it was concluded that the addition of disintegrants in the granular formulation resulted in little prevention of the particle aggregation during compression.

Lowenthal[11] stated that the water absorbed by the disintegrant particles in the tablets might be a factor in tablet disintegration. The tablet containing 32% drug with 30% starch as a disintegrant and having a porosity of 10% was compressed. The tablet expanded to their porosity of 13% during the storage at 25° and 75%

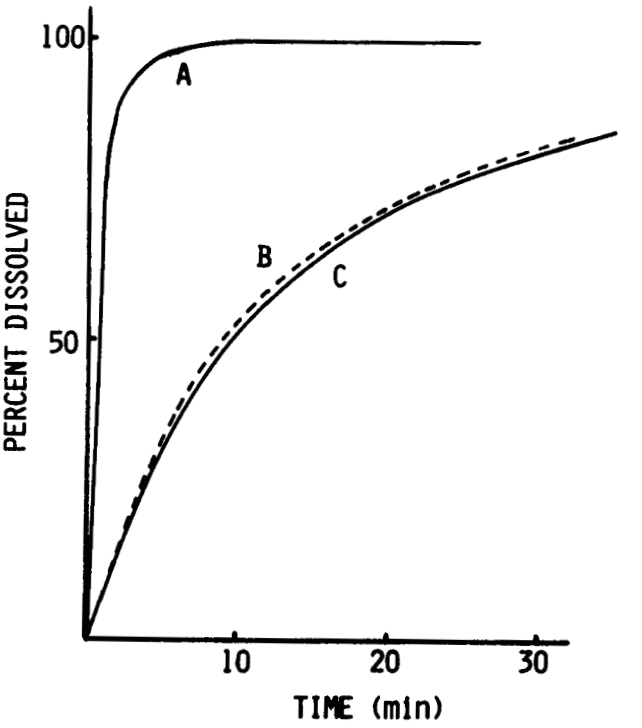


FIGURE 7

Dissolution Profiles for Disintegrated Tablets containing 32% Drug with 10% Rubber Powder and without Disintegrants. Key: (A) Granules (B) with 10% Rubber Powder (C) without Disintegrants.

relative humidity for one day. The dissolution rate ($T_{50\%}$) for the disintegrated tablets was prolonged from 6 to 7 minutes by the moisture absorption, whereas the dissolution rate for disintegranted tablets originally compressed to the porosity of 13% was 4 minutes. It was suggested that the sudden swelling of disintegrant

grains in water may play an important part in the deaggregation of drug particles.

REFERENCES

1) T.Murata, H.Satoh, A.Nohara, K.Ukawa, H.Sugihara and Y.Sanno, Eur.J.Med.Chem., 12, 17(1977).

2) Y.Sawa, S.Imai and T.Murata, J.Takeda Res.Lab., 36, 200(1977).

3) N.Kitamori and T.Makino, J.Pharm.Pharmacol., 31, 505 (1979).

4) N.Kitamori and T.Makino, J.Pharm.Pharmacol., 31, 501 (1979).

5) T.Higuchi, L.N.Elowe and L.W.Busse, J.Am.Pharm.Assoc. Sci.Ed., 43, 685(1954).

6) B.F.Cooper and E.A.Brecht, J.Am.Pharm.Assoc.Sic.Ed., 46, 520(1957)

7) A.J.Aguiar, J.E.Zelmer and A.W.Kinkel, J.Pharm.Sci., 56, 1243(1967).

8) E.Shotton and G.S.Leonard, J.PharmPharmacol., 24, 798(1972).

9) E.Shotton and G.S.Leonard, J.Pharm.Sci., 65, 1170 (1976).

10) Y.Nakai, H.Fukuoka, T.Ogasawara and T.Fujikura, The 93th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1973.

11) W.Lowenthal, J.Pharm.Sci., 61, 1695(1972).