PHARMACEUTICAL COATINGS BULLETIN
102-4

INFLUENCE OF TRIETHYL CITRATE ON THE PROPERTIES OF TABLETS CONTAINING COATED PELLETS

The popularity of controlled-release multiple unit dosage forms has increased when compared to single unit dosage forms. Although similar drug release profiles can be obtained with both types of dosage forms, multiparticulates offer several advantages. The coated pellets spread uniformly throughout the gastrointestinal tract and high local drug concentrations can be avoided, along with the risk of a localized toxic reaction due to a restricted tablet in the gastrointestinal tract. Premature drug release from enterically coated dosage forms in the stomach may result in drug degradation or irritation of the gastric mucosa. These problems can be reduced with coated pellets due to the rapid transit time when compared to enterically coated tablets. The better distribution of multiparticulates throughout the GI-tract has, in several instances, improved the drug bioavailability which potentially could result in a reduction in the side effects and the drug dosage requirements. Inter- and intra-individual variations in bioavailability that may be caused by food effects, are often reduced with multiparticulates.

For coated single dose delivery systems, the coating must remain intact during the drug release phase and any damage to the coating would result in a loss of the sustained-release properties, as well as dose dumping. Multiparticulates can either be filled into hard gelatin capsules or be compressed into tablets. The compression of multiparticulates into tablets is becoming more popular since, unlike the hard gelatin capsule, the tablet is a tamper-proof dosage form. Tablets containing film coated pellets can be prepared at a lower cost when compared to the pellet-filled capsules, because of the higher production rate of the tablet press and the cost of the hard gelatin capsules. In addition, tablets containing multiparticulates could be scored without losing the controlled-release properties. Scored tablets allow a more flexible dosage regimen.

In previous bulletins', the influence of citrate esters on the physical and mechanical properties, and dissolution properties of acrylic and cellulosic films were presented. These plasticizers were demonstrated to effectively lower the glass transition temperatures of acrylic and ethylcellulose films. The citrate esters promote coalescence of the latex and pseudolatex particles and cause a homogeneous and continuous polymeric film to form.

Triethyl citrate from Morflex is one of the most widely used plasticizers in aqueous and organic film coatings. This plasticizer has an official monograph in the current U.S.P./NF [4]. The basic and applied properties of this plasticizer have been extensively discussed in the previous bulletins(3) and references therein. In the current bulletin, the properties of tablets containing film coated pellets are reported. Due to the widespread acceptance of triethyl citrate as being a premier plasticizer in aqueous film coatings, the polymeric dispersions used to coat theophylline pellets, were plasticized with triethyl citrate.

From a technology standpoint, there are many important formulation and process parameters that must be controlled in order to obtain pellet-containing tablets which ideally have the same drug release properties as the individual coated pellets. The compaction of coated multiparticulates into tablets could result in the fusion of the multiparticulates to form a matrix tablet. Ideally, the compacted pellets should disintegrate rapidly into the individual pellets in the gastrointestinal fluids. The pellets should not fuse into a non-disintegrating matrix during compaction. The polymeric coating must contain sufficient plasticizer to be able to withstand the compression force. The polymeric film will deform during compression, but not fracture or rupture. The concentration of plasticizer in the film must be sufficient such that the polymeric film is sufficiently elastic to maintain its integrity during the compaction process. Ideally, the drug containing cores should have some degree of plasticity which can accommodate changes in shape and deformation during compaction.

Theophylline-loaded (60%) pellets were prepared by an extrusion-spheronization technique. The pellets were coated with either Aquacoat or Eudragit RS/RL 30D (9:1) in a fluidized bed coater. The Aquacoat-coated pellets and the Eudragit RS/RL 30D-coated pellets were cured at 60°C for two hours or 40°C for 24 hours, respectively. One of the advantages of using the combination of Eudragit RS 30D and Eudragit RL 30D as a coating dispersion for tablets or pellets is that the drug release rate can be widely modulated through the addition of the more permeable RL polymer. The mechanical properties of the mixed polymer system do not significantly change with the ratio of the two components. The desired mechanical properties can be achieved by the incorporation of a citrate ester, such as triethyl citrate. The theophylline beads were coated with a 10% weight gain of Eudragit RS/RL 30D (9:1), which was plasticized with 20% triethyl citrate. The tablets contained 50% coated pellets, 49.5% Avicel PH101 and 0.5% magnesium stearate. The influence of the compressional force on the drug release characteristics from tablets containing coated beads (20/30 mesh) is shown in Figure 1. At 100kg and 200kg the release profiles of theophylline from the tablets containing the coated pellets, were very similar to the coated beads. The drug release increased significantly at the higher compaction forces of 500-1,000kg,

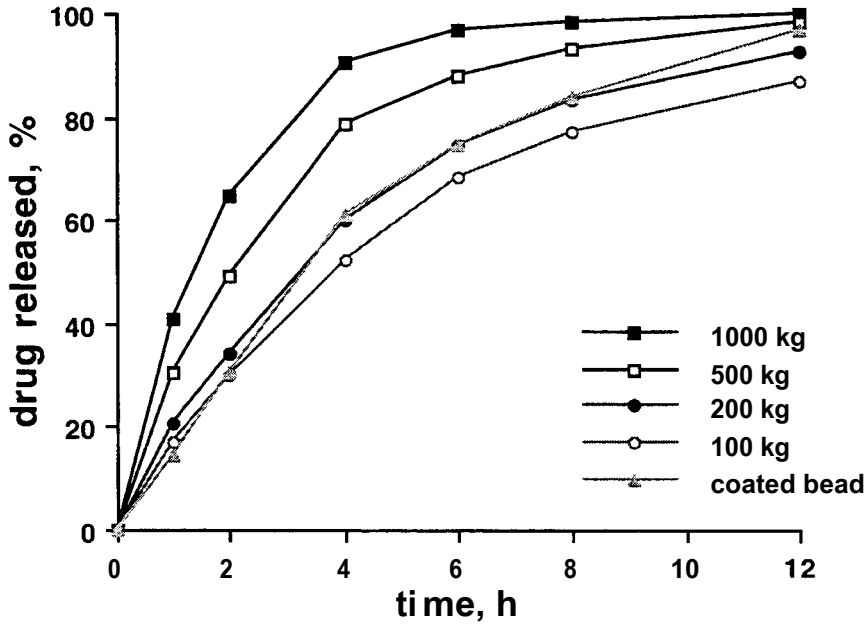

Figure 1 Effect of compression force on theophylline release from tablets containing pellets coated with 10% Eudragit RS/RL 30D (9:1) and plasticized with 20% triethyl citrate.

indicating that the film coating fractured during the compaction process. The scanning electron micrographs in Figure 2 show the surface morphology of coated beads, A; tablets containing coated beads (B-D) and the cross section of tablets containing coated beads (E-F). The selection of the filler excipient in these cushioned-matrix tablets is extremely important. Lehmann [5] reported in 1984 that when lower amounts of excipients are included in the tablet formulation, the coatings on the pellets will adhere to each other to form stable, nondisintegrating and sometimes slowly eroding matrix tablets. The inclusion of microcrystalline cellulose in these tablet formulations was found to prevent the rupturing process during tableting. The author recommended that at least 30% filler excipients was necessary to prevent disintegration problems and to insure that the dissolution of drug from the coated pellets in the tablets was similar to the individual coated pellets.

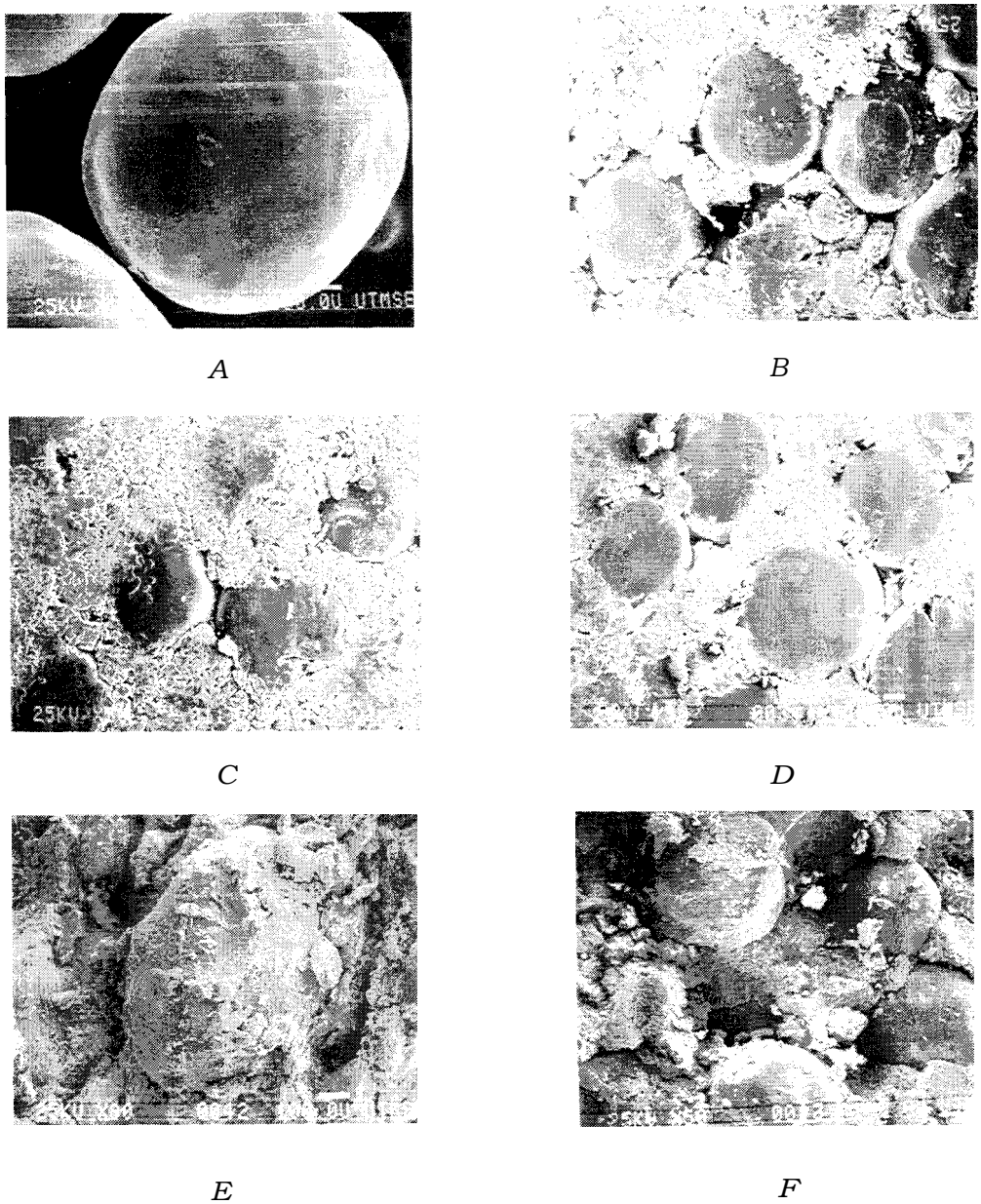

Figure 2. Scanning electron micrographs of 10% Eudragit RS/RL 30D (9:1, 20% triethyl citrate)-coated pellets, and tablets containing coated pellets. A: pellet surface; B: tablet surface, 200 kg; C: tablet surface, 500 kg; D: tablet surface, 1000 kg; E.. cross-section of tablet, 200 kg; F.. cross-section of tablet, 1000 kg.

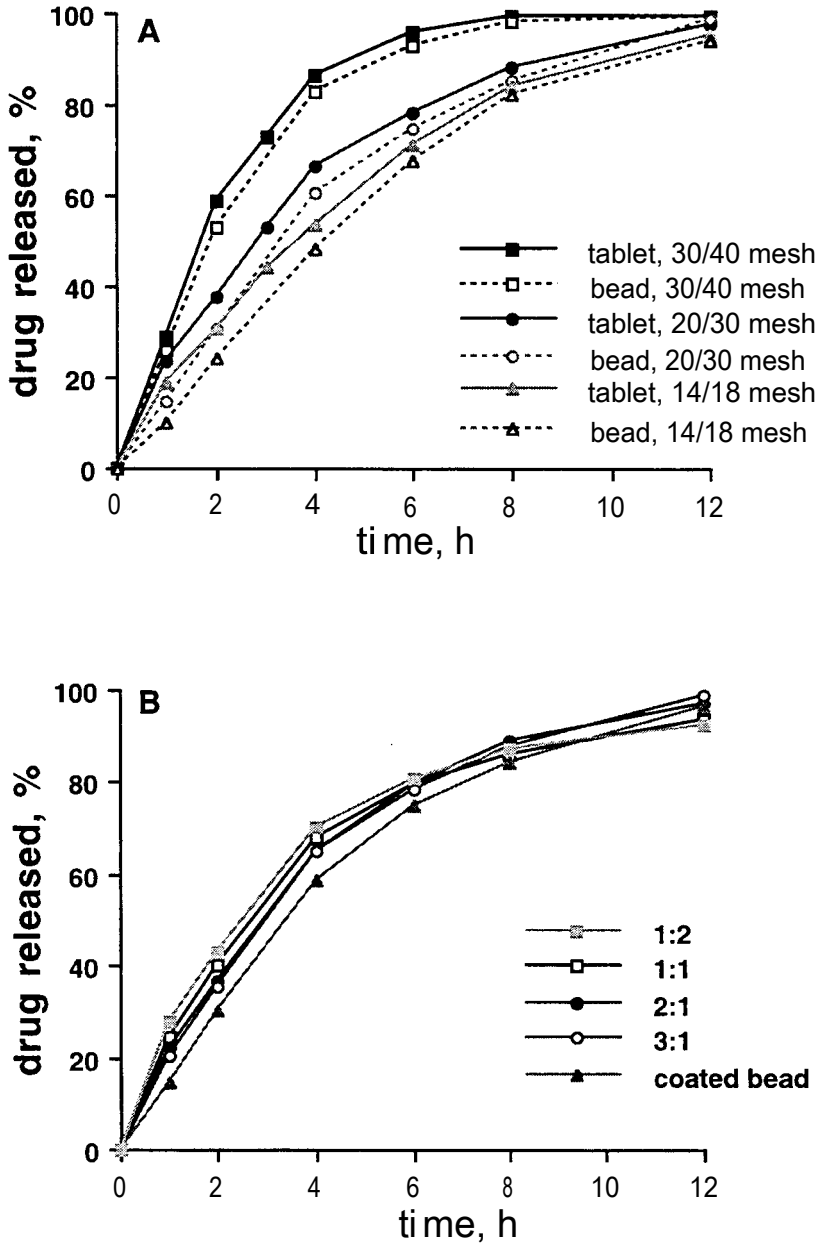

Figure 3. A. Effect of bead size on theophylline release from tablets containing 10% Eudragit RS/RL 30D (9:1, 20% triethyl citrate)-coated pellets. B: Effect of ratio of Avicel PH 200 and 10% Eudragit RS/RL 30D (9:1, 20 triethyl citrate)-coated pellets on theophylline release from tablets.

When the plasticizer level in the polymeric coating for the pellets was reduced from 20% triethyl citrate to 10% triethyl citrate, faster drug release rates were found from the tablets at all compression pressures studied due to the fractures in the film coating. When the plasticizer levels were increased above 20%, the acrylic polymers became very flexible. To avoid sticking problems in the coating chamber, high levels of antiadherent are needed to prevent adhesion during the coating process and to avoid similar problems during the curing or heat treatment of the coated pellets. The photographs in Figure 2 (C, D) clearly show the formation of cracks on the surface of the coated beads in tablets compressed at higher pressures. Crack formation increased with increasing compaction force.

The results in Figure 3A show the effect of bead size on the drug release from tablets containing coated beads. Although no significant difference in drug release rates was found with coated beads and tablets containing coated beads, a faster initial drug release rate was seen with the smaller beads. The ratio of Avicel PH 200 to coated beads had a minimal influence on the drug release rate from tablets containing beads when ratios of Avicel:coated beads from 1:2 to 3:1 were investigated. Triethyl citrate at the 20% level was used as the plasticizer for the RS/RL 30D dispersion. The results in Figure 4 demonstrate that the particle size of the microcrystalline cellulose, Avicel PH 101 (50 microns), PH 102 (100 microns) and PH 200 (180 microns), was found to have no significant effect on drug release rate from tablets containing film coated pellets. A comparison of the effect of the anti-sticking agents on the dissolution properties of theophylline from tablets, is seen in Figure 5. Since a high level of the triethyl citrate (20%) was incorporated into the acrylic dispersion to insure a flexible film over the pellet, the antiadherent was incorporated into the dispersion to prevent the pellets from sticking to each other during the coating and curing processes. The level of antiadherent was based on the dry solids content of polymer in the aqueous dispersion. The tablet formulations showed a slight increase in the release rate versus the bead formulations, when compressed at 200 kg.

The influence of the filler excipient on the release properties of tablets containing the coated beads is seen in Figure 6. The results in Figure 6 demonstrate that filler excipients exert a significant impact on the dissolution properties of the film coated pellets. Microcrystalline cellulose deforms by plastic deformations, however, most excipients undergo brittle fracture and deform by fragmentation. The tablets containing the calcium phosphate dihydrate (DI-TAB) formed weak tablets at a compaction force of 200kg. This could also account for the rapid dissolution rate of the theophylline from these tablets. Due to the brittle nature of the powder, the formation of fractures in the coatings will result in a more rapid drug release profile. When starch 1500 was used as a filler, the tablets disintegrated rapidly but the coated pellets were not completely separated into individual beads.

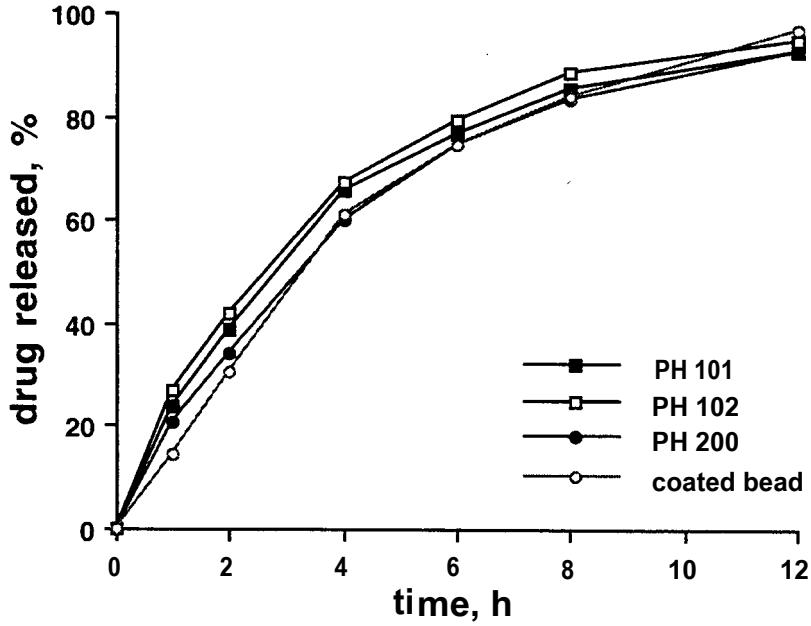

Figure 4. Effect of Avicel grades on theophylline release from tablets containing 10% Eudragit RS/RL 30D (9:1, 20% triethyl citrate)-coated pellets.

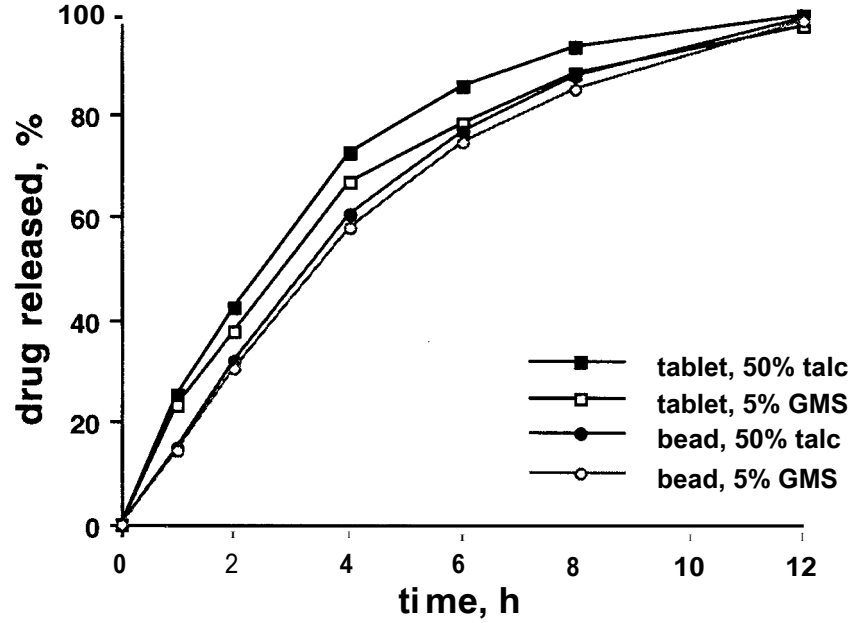

Figure 5. Effect of antisticking agents on theophylline release from tablets containing 10% Eudragit RS/RL 30D (9:1, 20% triethyl citrate)-coated pellets.

Most tablet formulations had an unacceptable hardness at 200kg and poor bonding of granules and beads was seen with these compacts.

In a more recent report, Lehmann and co-workers coated crystals, granules and pellets with various acrylic polymeric dispersions (Eudragit NE 30D, RS/RL 30D, and L30D-55) and compressed these coated units into fast-disintegrating tablets [6]. Coatings with elongation values in excess of 75% showed little or no

change in the drug release properties since the elasticity of the polymer was sufficient to prevent the rupture of the coating during compression. Enteric coatings based on Eudragit L30D-55 were brittle and the compression of the pellets resulted in film damage. New, more flexible, enteric polymers have been developed by Rohm GmbH for the compression of coated pellets'. The more flexible acrylic polymer has a glass transition temperature in the range of 45-60 °C, which is much lower when compared to the U.S.P./N.F. methacrylate acid co-polymers used for enteric coating. The addition of 5-10% triethyl citrate will result in an elongation value up to 300%.

Most studies on the compaction of pellets coated with ethylcellulose reveal that the coating was damaged causing a resultant loss in the sustained-release properties. The brittle nature of ethylcellulose films may be explained by the interchain hydrogen bonding and the bulkiness of the glucose sub-units. These results are not surprising due to the weak mechanical properties of the cellulosic polymer. The drug release profiles from compressed niacin/microcrystalline cellulose Pellets coated with the aqueous colloidal ethylcellulose dispersion, Surelease (7% **w/w), demonstrated** much faster release rates when compared to *the dissolution rate of niacin from the uncompressed pellets [8]. At higher* compression pressures, the pellets were fractured and simultaneously underwent fusion. This resulted in a slight decrease in drug release when compared to the release from compacts compressed at lower compression pressures. Similar faster drug release profiles were found with the compaction of diltiazem hydrochloride *pellets coated with ethylcellulose [8]. To overcome the brittle character of* ethylcellulose, Altaf and co-workers prepared multilayered beads consisting of approximately ten alternating layers of ethylcellulose (Aquacoat®), drug and *mannitol [10]. Drug release profiles indicated, however, that all polymeric layers were* ruptured during compression even though sustained release properties were obtained from the non-disintegrating compressed matrices.

In conclusion, dissolution profiles of theophylline from pellets coated with Eudragit RS/RL 30D and plasticized with 20% triethyl citrate, were comparable from both the uncompressed beads and bead containing compacts, when the latter were compressed at 100kg and 200kg. At higher compression forces, the release

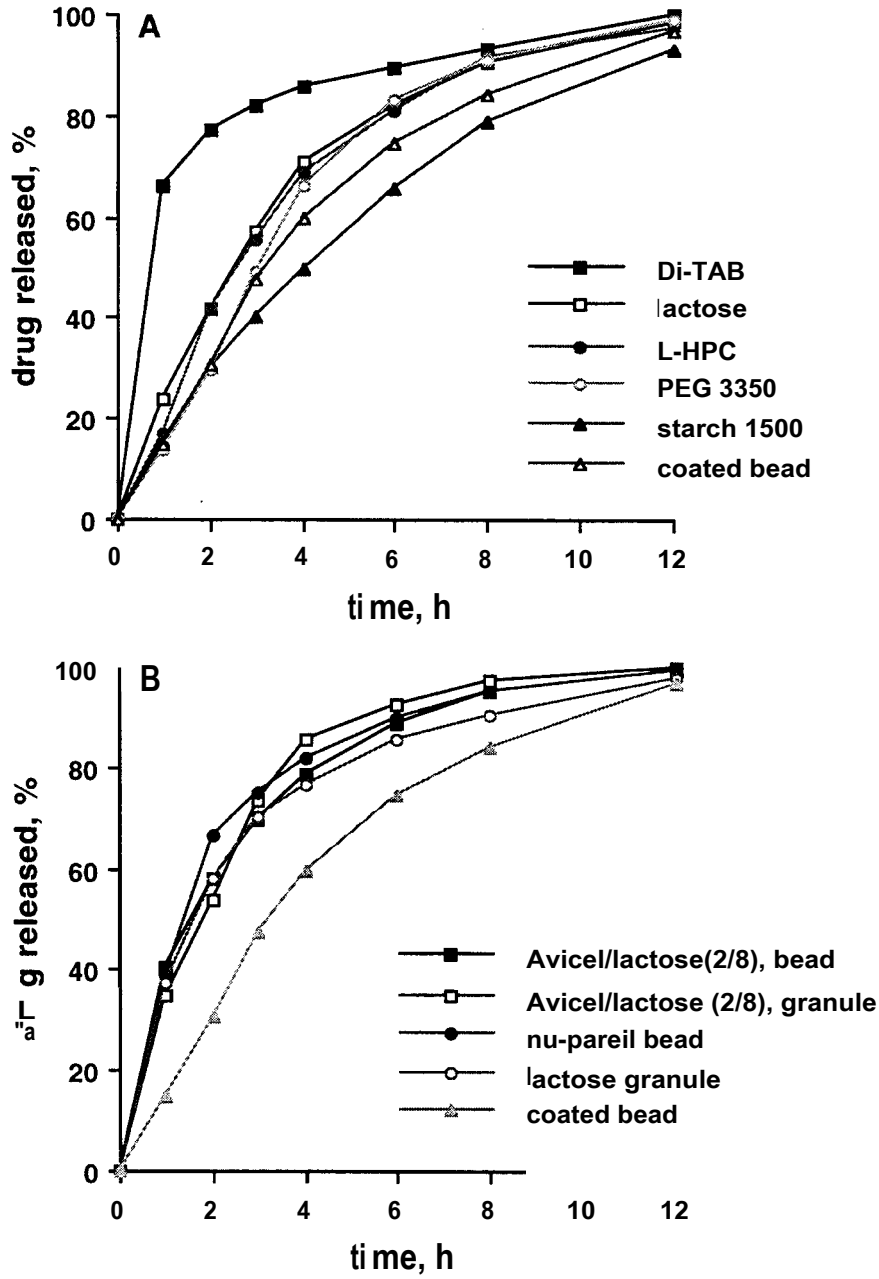

Figure 6. Effect of filler excipients and granules on theophylline release from tablets containing 10% Eudragit RS/RL 30D (9:1, 20% triethyl citrate)-coated pellets: A filler excipients B. granules and beads

profiles were faster since the coatings fractured under the higher loads. These findings were in agreement with previously published work. Studies will continue with the pseudolatex dispersions of ethylcellulose to select and optimize a suitable plasticizer and processing conditions to prevent fracture of the ethyl cellulose during the compaction process.

References

1. Influence of Citrate Ester Plasticizers on the Properties of Acrylic Resin Polymers", *Pharmaceutical Coatings Bulletin 102-1,* Morflex, Inc., (1993).

2. "Physical and Mechanical Properties of Acrylic and Cellulosic Polymers Plasticized With Citrate Esters" *Pharmaceutical Coatings Bulletin 102-2,* Morflex, Inc., (1994).

3. "Influence of Plasticizers on the Dissolution and Physical Properties of Ethyl Cellulose Films and Coated Beads", *Pharmaceutical Coatings Bulletin 102-3,* Morflex, Inc., (1995).

4. U.S.P. 23/NF 18, "Triethyl Citrate-Official Monograph", p. 2316, (1995).

5. Lehmann, K., "Formulation of controlled release tablets with acrylic resins", *Acta. Pharm. Fenn.,* 93, 55-74 (1984).

6. Lehmann, K., Petereit, H.-U., and Dreher, D. "Fast disintegrating controlled-release tablets from coated particles." *Drugs Made in Germany,* 37, 53-60 (1994).

7. Lehman, K. and Sufke, T., "New methacrylic acid copolymers for improved coating triethylcellulosehnology." *Pharm. Res.,* 12(9), 5-137 (1995).

8. Bansal, P., Vasireddy, S., Plakogiannis, F. and Parikh, D., "Effect of compression on the release properties of polymer coated niacin granules." J. *Control. Rel.,* 27,157-163 (1993).

9. Sarisuta, N. and Punpreuk, K., "In vitro properties of film-coated diltiazem hydrochloride pellets compressed into tablets." J. *Control. Rel.,* 31, 215-222 **(1994).**

10. Altaf, S.A., Hoag, S.W. and Ayers, J.W., "Bead compacts I: Effect of multi-layered beads (MLB) on the maintenance of polymer coat integrity." *Proceed Intern. Symp. Control. Rel. Bioact. Mater.,* 22, 290-291 (1995).

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