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RESEARCH PAPER

# Use of a Moist Granulation Technique (MGT) to Develop Controlled-Release Dosage Forms of Acetaminophen

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## ABSTRACT

*The moist granulation technique (MGT), which involves agglomeration and moisture absorption, has only been applied to immediate-release dosage forms. Our results indicate that MGT appears to be applicable in developing a controlled-release formulation. A small amount of granulating fluid (water) was added to a powder blend to activate a dry binder (such as polyvinylpyrrolidone [PVP] at 2% and 3.6%) and to facilitate agglomeration. Then, a moisture-absorbing material (microcrystalline cellulose [MCC]) was added to absorb any excess moisture. By adding MCC in this way, a drying step was not necessary. Acetaminophen (APAP) was the model drug, with diluents lactose FastFlo® and dicalcium phosphate. Hydroxypropylcellulose (HPC) was used as the controlled-release agent. The MGT was compared to conventional wet granulation (WG) and direct compression (DC) processing methods. The results indicate that MGT appears to be applicable in developing a controlled-release formulation. Particle size distribution of MGT and WG batches containing 3.6% PVP is similar.*

**KEY WORDS:** *Agglomeration; Controlled release; Moist granulation technique.*

## INTRODUCTION

Flow of powdered materials is improved by dry or wet granulation. Wet granulation is by far the most utilized granulation method. A novel granulation method was described by Ullah et al. (1). The method, moisture-activated dry granulation (MADG), involves agglomeration and moisture distribution. This method utilizes very little granulating fluid, does not require a high-shear granulator, and eliminates a costly drying step. Initially, a third

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of the final formula is blended with a binder (added as a dry powder). Agglomeration takes place when granulating fluid (water) activates the binder. The remaining ingredients are then added with continued mixing, with the most moisture-absorbing material added last. True dry granulation is granulation obtained using either slugging or roller compaction to achieve densification. Since slugging or roller compaction was not used in the method described in the literature, a more appropriate name for this process is *moist granulation*. Earlier work in our laboratory for an immediate-release dosage form showed that advantages of wet granulation such as increased particle size and better flow were achieved using MGT. The feasibility of applying MGT to develop controlled-release dosage forms for acetaminophen (APAP) was investigated. Acetaminophen does not have good flowability and is also well characterized. Hence, it was chosen as a model drug.

## EXPERIMENTAL

### Materials

The ingredients were acetaminophen USP (Hoechst Celanese, Bishop, TX), microcrystalline cellulose (MCC; Avicel® PH-102, FMC Corp., Philadelphia, PA), hydroxypropylcellulose (HPC; Klucel HXF, Aqualon, Wilmington, DE), lactose FastFlo® (Foremost, Baraboo, WI), unmilled dicalcium phosphate dihydrate (Ditab®, Rhone-Poulenc, Shelton, CT), polyvinylpyrrolidone USP (PVP; Plasdone K 29-32 GAF/ISP, Wayne, NJ), fumed silica (Cab-O-Sil®, Cabot Corp., Boston, MA), magnesium stearate (Amend, Irvington, NJ). Water was used as the granulating fluid. For wet granulation, 85 ml (approximately 16% of the dry ingredient weight) water were used. For moist granulation trials, the level of water added was 3% of the dry ingredient weight.

### Methods

#### Formulation Development

The batch size for the experiments was 540 g. The formula used for these trials is shown in Table 1.

#### Effect of Binder Level

The binder used in the formulation was PVP. The effect of PVP was studied at 2% w/w and 3.6% w/w for formulations containing lactose as the diluent. A reduced proportion of lactose accommodated increased binder.

***Table 1***

*Formulation Table*

| Ingredient | % (w/w) | mg/Tablet |
|---|---|---|
| Acetaminophen | 14.8 | 80.0 |
| Microcrystalline cellulose | 35.0 | 189.6 |
| Hydroxypropylcellulose | Varied | Varied |
| Diluent[a] | Varied | Varied |
| Polyvinylpyrrolidone | Varied | Varied |
| Cab-O-Sil | 1.0 | 5.4 |
| Magnesium stearate | 1.0 | 5.4 |
| Water | 3.0 | 16.2 |
| Total | 100.0 | 540.6 |

[a] Either lactose or dicalcium phosphate was used.

#### Effect of Diluent Type and Level

Initially, a water-soluble diluent (i.e., lactose) was utilized. Later, a water-insoluble diluent (i.e., dicalcium phosphate) was included. The proportion of diluent (either lactose or dicalcium phosphate) was changed to accommodate HPC levels. To study the effect of diluent only, immediate-release formulations containing 44.6% w/w of either diluent were also made.

#### Effect of Polymer Level

The controlled-release polymer in the formulation was HPC. Initially, HPC was present at a level of 30% w/w. If necessary, HPC could be incorporated at higher levels.

### Moist Granulation

APAP was passed through no. 16 mesh screen and transferred into a Kitchenaid (Hobart, St. Joseph, MI) planetary mixer bowl. PVP and HPC (delumped through no. 16 mesh screen) were added and then mixed at the lowest setting on the mixer for 5 min. Moisture was introduced manually with a squeeze bottle with continued mixing and was allowed to distribute. Lactose or dicalcium phosphate were added, followed by MCC (moisture-absorbing material), and mixing continued for 5 min. The granulation was passed through a no. 16 mesh screen and then transferred to a 4-quart PK twin-shell blender (Patterson-Kelly, East Stroudsburg, PA). Cab-O-Sil (passed through no. 20 mesh screen) was added and blended for 5 min, followed by the addition of magnesium stearate (passed through a no. 30 mesh screen); blending was continued for an additional 5 min.

### Direct Compression

All ingredients except MCC and magnesium stearate were put in a Kitchenaid mixer bowl and mixed for 5 min. Then, MCC was added, followed by mixing for 5 min. The blend was passed through no. 16 mesh screen and transferred to a 4-quart PK twin-shell blender. Cab-O-Sil (passed through no. 20 mesh screen) was added, and blending continued for 5 min, followed by the addition of magnesium stearate (passed through a no. 30 mesh screen); blending was continued for an additional 5 min.

### Wet Granulation

All ingredients except MCC and magnesium stearate were put in a Kitchenaid mixer bowl and mixed for 5 min. Then, MCC was added, followed by mixing for 5 min. Water was slowly added using a graduate cylinder and was allowed to distribute. Mixing was carried out for an additional 5 min after water addition. The granulation was wet milled and dried overnight in an oven at 45°C. Dried granulation was passed through no. 16 mesh screen and transferred to a 4-quart PK twin-shell blender. Cab-O-Sil (passed through no. 20 mesh screen) was added and blended for 5 min, followed by the addition of magnesium stearate (passed through a no. 30 mesh screen); blending was continued for an additional 5 min.

### Physical Characterization

Determination of particle size distribution for all batches was carried out on a C. E. Tyler portable sieve shaker (Mentor, OH) using 16, 30, 50, 100, 200, and 325 mesh screens after shaking for 5 min. The mean particle size was calculated as described in Ref. 2.

Bulk and tapped density were determined on a VanKel tap density tester (Chatham, NJ) for batches made by all procedures. The compressibility factor (%C) was calculated from the bulk and tapped density results using the following formula (3):

$$\%C = [(\rho_t - \rho_b) \div \rho_t] \times 100$$

where $\rho_t$ is the tapped density, and $\rho_b$ is the bulk density. The loss on drying was determined on a CSC Cenco moisture balance (Fairfax, VA) at 90°C for information only. This value was of interest because there is no drying step for MGT.

### Tableting

Formulations were tested for tableting behavior. Each formulation was compressed on a Stokes F press (Warminster, PA) equipped with 7/16-inch round flat-face tooling. The target tablet weight was 540 mg, and the tablets were compressed to a hardness of 8–10 kp. There were 10 tablets randomly selected for weight variation (540 ± 4 mg), thickness, and hardness.

### Dissolution

Dissolution (USP paddle; $n = 6$) was carried out in purified water, as well as 0.1 N HCl. Samples of 5 ml were withdrawn at predetermined times and diluted to 100 ml with the corresponding medium. A standard curve was constructed in both media in the concentration range 0.1 μg/ml to 8 μg/ml at an absorbance maximum of 241 nm.

## RESULTS AND DISCUSSION

### Effect of Binder Level

The physical properties of 3% MGT batches containing 2% w/w and 3.6% PVP are shown in Table 2. Increase in binder resulted in a corresponding increase in particle size distribution and mean particle size. Improvement in the compressibility factor was also seen (Table 2). The particle size distribution of MGT batches was better than DC and closer to WG when PVP was increased from 2% w/w to 3.6% w/w. A significant increase in particle size and improvement in compressibility factor was found for WG batches. The level of PVP was 3.6% w/w for all the batches discussed below.

### Effect of Diluent Type and Level

Dissolution profiles in water and 0.1 N HCl were very similar. Hence, only the aqueous profiles are discussed. Aqueous dissolution profiles for tablets containing 15.6% lactose and 30% HPC made by DC, 3% MGT, and wet granulation (WG) are shown in Fig. 1. Tablets containing lactose released 79.9% (DC), 63% (MGT), and 68.5% (WG) drug at the end of 30 min. It appears that DC tablets released drug faster than MGT or WG tablets; thus, processing may affect drug release. Figure 2 shows the aqueous dissolution profiles of batches containing 14.6% dicalcium phosphate and 30% HPC. Tablets containing dicalcium phosphate released 52.4% (DC), 23.3% (MGT), and 26.4% (WG) drug at the end of 30 min. Again, DC tablets seem to have faster drug release than MGT or WG tablets (processing effect). This is consistent with the results of Inghelbrecht and Remon (4),

***Table 2***

*Physical Properties of Batches Containing 2% w/w or 3.6% w/w Polyvinylpyrrolidone (PVP)*

| | Batch Type, % Retained | | | | | |
|---|---|---|---|---|---|---|
| | 3% MGT | | DC | | WG | |
| Property | 2% PVP | 3.6% PVP | 2% PVP | 3.6% PVP | 2% PVP | 3.6% PVP |
| Sieve analysis screen size | | | | | | |
| 16 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 30 | 4.0 | 11.0 | 1.0 | 1.0 | 13.0 | 20.0 |
| 50 | 2.0 | 18.0 | 1.0 | 1.0 | 13.0 | 34.0 |
| 100 | 40.0 | 31.0 | 37.0 | 49.0 | 54.0 | 29.0 |
| 200 | 34.0 | 19.0 | 43.0 | 28.0 | 14.0 | 12.0 |
| 325 | 17.0 | 12.0 | 17.0 | 19.0 | 5.0 | 3.0 |
| Pan | 3.0 | 4.0 | 1.0 | 2.0 | 1.0 | 2.0 |
| Total | 100.0 | 99.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Mean size (μ) | 189 | 284 | 181 | 190 | 329 | 731 |
| Density (g/ml) | | | | | | |
| Bulk | 0.37 | 0.41 | 0.41 | 0.40 | 0.39 | 0.36 |
| Tapped | 0.45 | 0.49 | 0.56 | 0.54 | 0.49 | 0.43 |
| %C | 18.0 | 16.0 | 27.0 | 26.0 | 20.0 | 16.3 |

%C, compressibility factor; DC, direct compression; MGT, moist granulation technique; WG, wet granulation.

who observed that addition of water increased granule strength and decreased dissolution rate.

Tablets containing dicalcium phosphate seemed to show slower drug release than those containing lactose, indicating that the type of diluent affects drug release. To study the effect of diluent, two direct compression batches without any polymer were made. These control batches contained 44.6% w/w diluent. Aqueous dissolution profiles ($n = 3$) of these batches are shown in Fig. 3.

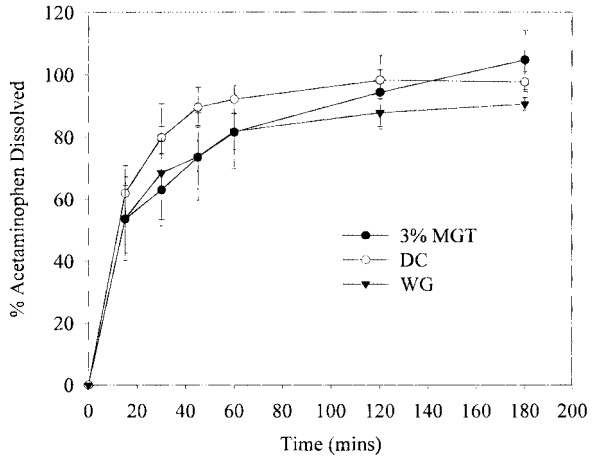


**Figure 1.** Aqueous dissolution profiles of controlled-release batches containing 15.6% lactose and 30% HPC.

In the first 30 min, drug release from tablets containing lactose was faster than the drug release from tablets containing dicalcium phosphate.

## Effect of Polymer Level

It was desirable to have a formulation in which the release rate was less influenced by the diluent. Hence,

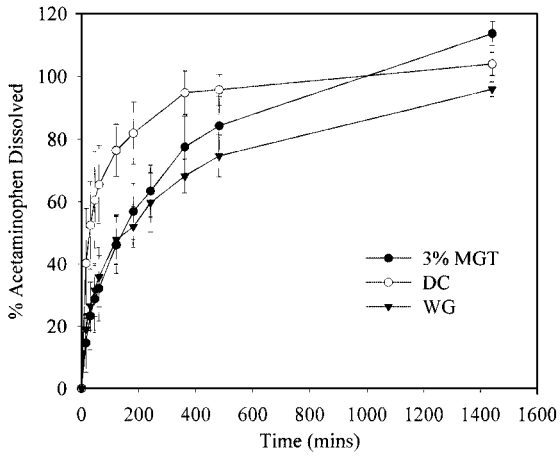


**Figure 2.** Comparison of aqueous dissolution profiles of controlled-release batches containing 14.6% dicalcium phosphate and 30% HPC.

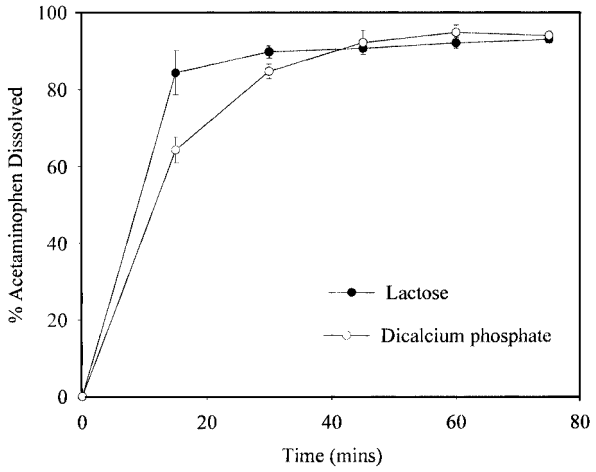


**Figure 3.** Effect of diluent on aqueous dissolution profiles of batches made without HPC.

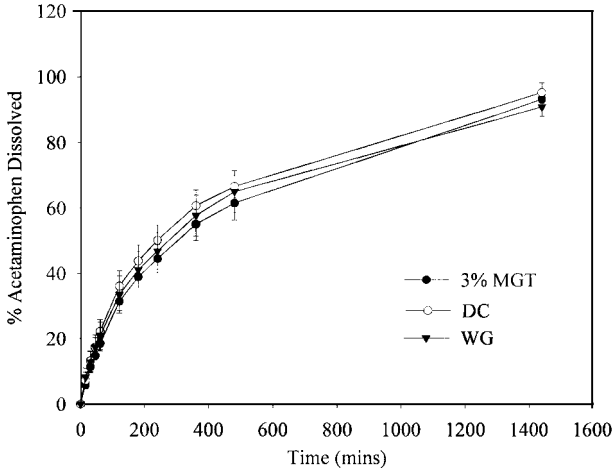


**Figure 5.** Comparison of aqueous dissolution profiles of controlled-release batches containing 44.6% HPC and no diluent.

controlled-release batches were made with 37.6% w/w HPC and 7% w/w diluent. The aqueous dissolution profiles of these batches are shown in Fig. 4. It is evident that processing had an effect on drug release; the type of diluent had no effect on drug release as far as DC tablets were concerned. In the case of 3% MGT and WG, tablets made with dicalcium phosphate showed slightly slower drug release than those made with lactose. To investigate the level of polymer at which processing had no effect, diluent was eliminated from the formula, and the polymer content was increased to 44.6% w/w. The results are shown in Fig. 5. The dissolution profiles are superimposable within experimental error; hence, one can conclude that processing effects can be eliminated when the polymer level is at 44.6% w/w. Batches from the same process were compared on the basis of differences in polymer and diluent level.

Figures 6, 7, and 8 show the aqueous dissolution profiles of DC, MGT, and WG tablets, respectively, containing varying levels of HPC and lactose. For the DC batches, release rates were as expected, that is, 30% HPC $>$ 37.6% HPC $>$ 44.6% HPC. In the case of 3% MGT and WG, the release rates were 30% HPC $>$ 44.6% HPC $>$ 37.6% HPC, that is, rank order was not followed.

Figures 9, 10, and 11 show the aqueous dissolution

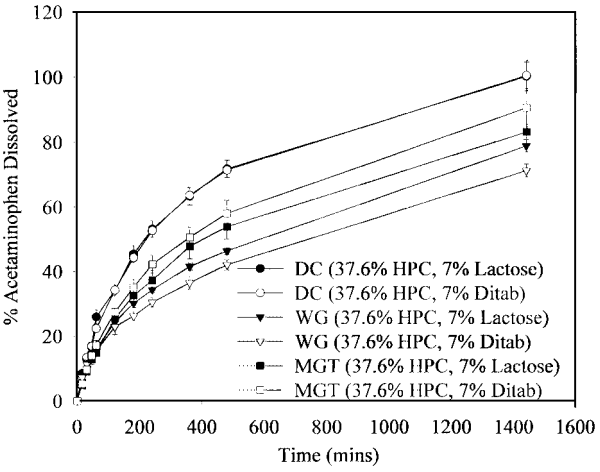


**Figure 4**. Comparison of aqueous dissolution profiles of controlled-release batches containing 37.6% HPC and 7% diluent.

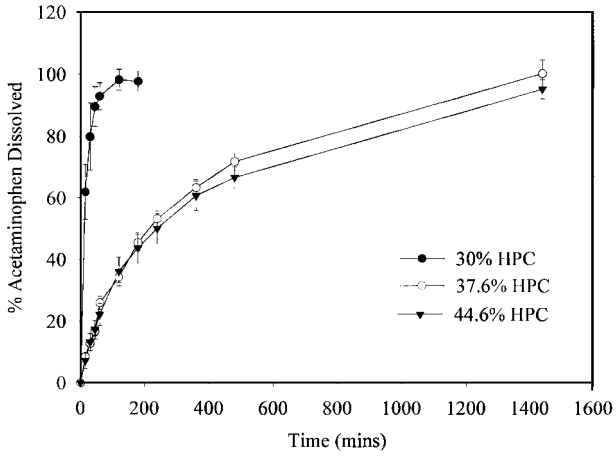


**Figure 6.** Comparison of aqueous dissolution profiles of controlled-release batches (DC) containing varying levels of HPC and lactose.

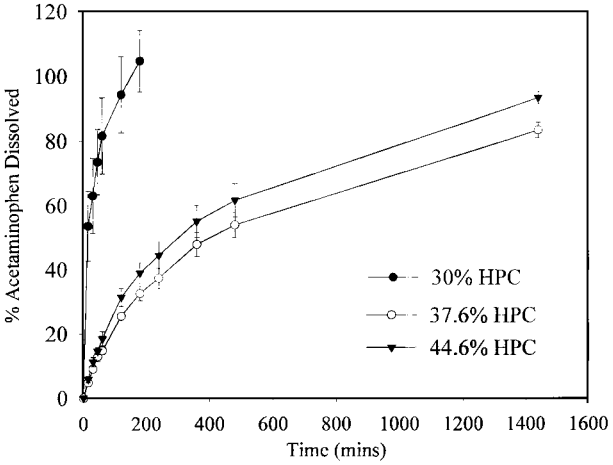


**Figure 7.** Comparison of aqueous dissolution profiles of controlled-release batches (3% MGT) containing varying levels of HPC and lactose.

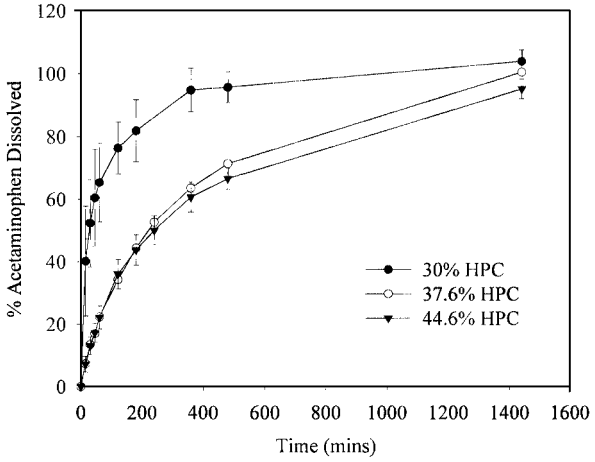


**Figure 9.** Comparison of aqueous dissolution profiles of controlled-release batches (DC) containing varying levels of HPC and dicalcium phosphate.

profiles of DC, MGT, and WG tablets, respectively, containing varying levels of HPC and dicalcium phosphate. The trend is similar to that observed with tablets containing varying levels of HPC and lactose. It appears that the presence of 7% diluent in the formulations containing 37.6% HPC strengthens the gel structure of the MGT and WG tablets.

Indeed, these findings are in agreement with those of Rizk et al. (5). These authors prepared tablets containing varying levels of scleroglucan, which served as the gelling agent, and lactose or Emcopress® (dicalcium phosphate). The authors monitored water uptake and swelling, as well as dissolution profiles. Their explanation was that the presence of diluent resulted in the formation of a resistant gel layer, which reduced the speed of water penetration. Since dicalcium phosphate is insoluble in water, the resulting gel layer affected the drug diffusion rate by blocking the surface pores of the tablet and slowing the uptake of the dissolution medium. It also appears that the use of moisture during the processing of WG and MGT

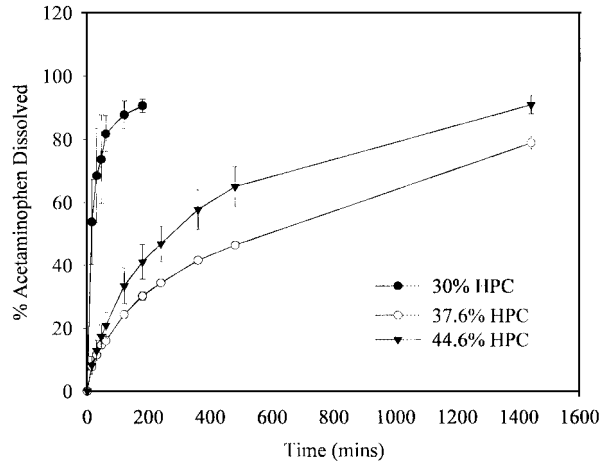


**Figure 8.** Comparison of aqueous dissolution profiles of controlled-release batches (WG) containing varying levels of HPC and lactose.

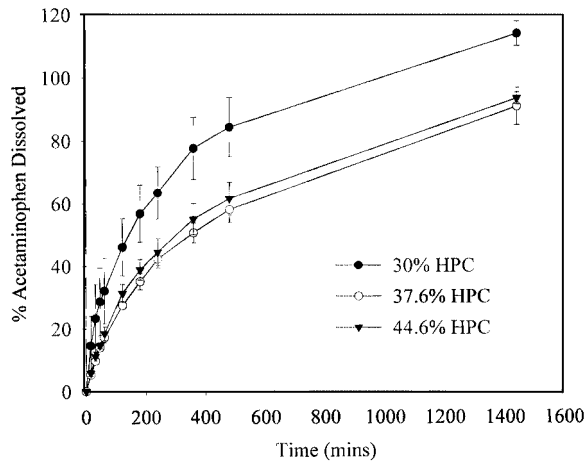


**Figure 10.** Comparison of aqueous dissolution profiles of controlled-release batches (3% MGT) containing varying levels of HPC and dicalcium phosphate.

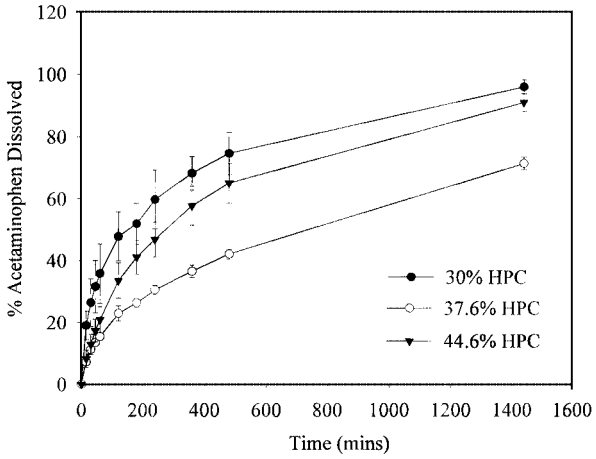


**Figure 11.** Comparison of aqueous dissolution profiles of controlled-release batches (WG) containing varying levels of HPC and dicalcium phosphate.

batches produced granules since the polymer (HPC) was acting as a binder in addition to its controlled-release properties.

## CONCLUSIONS

Results comparable to conventional wet granulation were obtained from blends and tablets made using the moist granulation technique. It is possible to apply the MGT to the development of controlled-release dosage forms. At low polymer levels, diluent type affects drug release. Processing also has an effect at low polymer levels. By eliminating the diluent completely, processing differences can be eliminated. At a level of 37.6% HPC, the presence of diluent may contribute to the gel strength of the tablets.

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