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RESEARCH PAPER

The Effects of Formulation Factors on the Moist Granulation Technique for Controlled-Release Tablets

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ABSTRACT

Controlled-release tablets were prepared by the moist granulation technique (MGT), a granulating method that uses very limited amounts of liquid and requires microcrystalline cellulose (MCC) to absorb moisture. Acetaminophen (APAP) was the model drug, and the polymer hydroxypropylcellulose (HPC) served as the controlled-release agent. The effects of varying drug, binder (polyvinylpyrrolidone, PVP), polymer, and MCC levels on granule properties and tablet dissolution were studied. Dissolution testing was carried out in distilled water using the USP paddle method. In all cases, the granules flowed and compressed well. The granule properties were evaluated by calculating the mean particle size for all batches from sieve analysis data. The results indicate that MGT can be applied to control drug release, and at a polymer content of 44.6% or more, the process is robust enough to allow slight variations in formulation factors without affecting drug release.

INTRODUCTION

Formulation development for tablets often involves one of the three main processes: (1) direct compression (DC), (2) dry granulation, or (3) wet granulation (WG). Each process has its own advantages and disadvantages. The decision to select any of the above processes is dictated by several considerations, such as the ease of operation, properties and quality of final product, time required, and cost incurred.

There are many references in the literature about the processes described above, but one novel method of granulation called moisture-activated dry

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granulation (MADG) has not received much attention. It was developed by Ullah and coworkers (1). This method is a variation of conventional wet granulation. It uses very little water to activate a binder and initiate agglomeration. It does not require a drying step nor does it require a high-shear granulator. Dry granulation involves the use of a roller compaction or a slugging step followed by milling to obtain granules. Ullah and coworkers did not use either of those steps. Hence, these authors believe that a more appropriate name for this method is moist granulation.

Earlier work in our laboratory demonstrated that the advantages of wet granulation (compared to direct compression), such as increased particle size and improved flow, are achievable with this technique (2). Recently, we showed that this technique is applicable to the development of controlled-release dosage forms (3). The current work was aimed at studying the effect of formulation variables on drug release from controlled-release tablets.

EXPERIMENTAL

Materials

Acetaminophen USP (APAP; Hoechst Celanese, Bishop, TX) was the model drug. The remainder of the ingredients were microcrystalline cellulose (MCC; Avicel® PH-102, FMC Corp., Philadelphia, PA); hydroxypropylcellulose (HPC; Klucel HXF, Aqualon, Wilmington, DE); polyvinylpyrrolidone USP (PVP; Plasdone K 29-32 GAF/ISP, Wayne, NJ); colloidal silicon dioxide (Cab-O-Sil®, Cabot Corp., Boston, MA); and magnesium stearate (Amend, Irvington, NJ). Water was used as the granulating fluid. 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 Drug Level

The initial dose was 80 mg/tablet or 14.8% w/w, which is equivalent to a pediatric dose. To show that an increased drug level could be achieved, the drug level was increased to 19.8% w/w, 24.8% w/w, and 34.8% w/w while decreasing the level of MCC correspondingly.

Effect of Binder Level

The binder used in the general formulation was PVP (3.6% w/w). But, HPC also has binderlike properties, and the possibility of granulating without PVP was considered. When PVP was eliminated from the formula, the tablet weight was reduced to 520.4 mg.

Effect of Polymer Level

The controlled-release polymer in this formulation was HPC. Initially, HPC was present at a level of 44.6% w/w. To explore the possibility of retard-

Table 1

Formulation Table

	Controlled-Release Batch (% w/w)						
Ingredient	12	21[a]	22	23	24	25	26
Acetaminophen	14.8	15.4	24.8	34.8	19.8	14.8	14.8
MCC	35.0	36.3	25.0	15.0	30.0	25.0	30.0
HPC	44.6	46.3	44.6	44.6	44.6	54.6	49.6
PVP	3.6	0.0	3.6	3.6	3.6	3.6	3.6
Cab-O-Sil	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Water	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0

HPC, hydroxypropylcellulose; MCC, microcrystalline cellulose; PVP, polyvinylpyrrolidone.
[a]The tablet weight was reduced to 520.7 mg from 540.1 mg when PVP was removed.

ing the release further, HPC was incorporated at 49.6% w/w and 54.6% w/w. A reduced proportion of MCC accommodated the increased polymer and served to determine that a lower level of MCC could still achieve the objective of MGT.

Moist Granulation

The APAP was passed through a 16-mesh screen and transferred into a Kitchenaid (Hobart, St. Joseph, MI) planetary mixer bowl. PVP and HPC (deagglomerated through a 16-mesh screen) were added and then mixed at the lowest setting on the mixer for 5 min. Moisture was introduced as a fine spray with continued mixing and allowed to distribute. MCC (moisture-absorbing material) was added and mixed for 5 min. The granulation was passed through a 16-mesh screen and then transferred to a 4-quart PK twin-shell blender (Patterson-Kelly, East Stroudsburg, PA). Cab-O-Sil (passed through a 20-mesh screen) was added and blended for 5 min, followed by the addition of magnesium stearate (passed through a 30-mesh screen) and blending for an additional 5 min.

Physical Characterization

The procedure for 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 from a log normal distribution was calculated as previously described (4).

Tableting

Formulations were evaluated for tableting behavior. Each formulation was compressed on a Stokes F press (Warminster, PA) equipped with 7/16-inch, round, flat-faced tooling. The target tablet weight was 540 mg (520.4 mg without PVP), and the tablets were compressed to a hardness of 8–10 kp. We randomly selected 10 tablets for weight variation, thickness, and hardness.

Dissolution

Dissolution (USP paddle, $n = 6$) was carried out in 900 ml of purified water. At predetermined time intervals, 5-ml samples were withdrawn and diluted to 100 ml with the corresponding medium. The absorbance was monitored at 241 nm.

Mathematical Treatment

To elucidate the mechanism of drug release, fractional release was fitted to the power law equation of Ritger and Peppas (5), given by

$$M_t/M_\infty = kt^n \tag{1}$$

where M_t is the amount of drug released at time t, M_∞ is the amount of label claim, k is the release rate constant, and n describes drug release (for $n = 0.5$, release is square root of time, and for $n = 1.0$, release is zero order). This equation is valid for $M_t/M_\infty \leq 0.6$.

Using the diffusion principles developed by Fick, Higuchi (6) found that the kinetics of drug release from a thin slab of homogeneous matrix can be described by the equation

$$Q = [D(2A - C_s)C_s t]^{1/2} \tag{2}$$

This equation is also known as the square-root-of-time relationship, where Q is amount of drug released per surface area, D is the drug diffusion coefficient in the matrix, A is the concentration of drug in the matrix, and C_s is the drug solubility in the matrix.

For a matrix of simple geometry,

$$Q = kt^{1/2} \tag{3}$$

where Q is the amount released per surface area, and k is a constant that incorporates the diffusion coefficient and solubility of the drug in the polymer, as well as the drug loading.

RESULTS AND DISCUSSION

Effect of Drug Level

The level of APAP was increased with a corresponding decrease in MCC levels with a constant polymer level at 44.6% w/w. The dissolution profiles in purified water are shown in Fig. 1. As drug content increased, percentage released remained constant, but the amount of drug released increased with increased drug content. These results do not agree with those of Mitchell et al. (7), who observed that an increase in drug loading was accompanied by an increase in percentage released. It should be noted that Mitchell et al. used propranolol hydrochloride, which is more soluble than acetaminophen. In our formulations, the tablet weight was held constant; however, Mitchell et al. did not do so. Their formulations consisted of 150 mg of Methocel and

20, 40, 60, 80, or 160 mg propranolol hydrochloride per tablet. Thus, the total polymer content was reduced as the drug content increased. Our results indicate that, when the HPC content is at 44.6% w/w, drug and MCC levels have no effect on percentage drug release. They also demonstrate that MGT is successful with as little as 15% w/w MCC.

Effect of Binder Level

The particle size distribution and mean particle size of the batches with and without PVP are shown in Table 2. For the control batch made with 3.6% PVP, 9% of the blend was in the 16/50-mesh cut, and 17% was in the 50/100-mesh cut. For the batch made without PVP, 27% of the blend was in the 16/30-mesh cut, and 25% was in the 50/100-mesh cut. Thus, the absence of binder yielded granules of equivalent or larger size. It is possible that, in the control, PVP and HPC both compete for the water used to granulate. The hydration characteristics of HPC may also be affected by PVP. When PVP is removed from the formulation, HPC can hydrate without any interference, resulting in larger granules. The dissolution profiles in purified water (Fig. 2) are very similar for the two batches, indicating that the

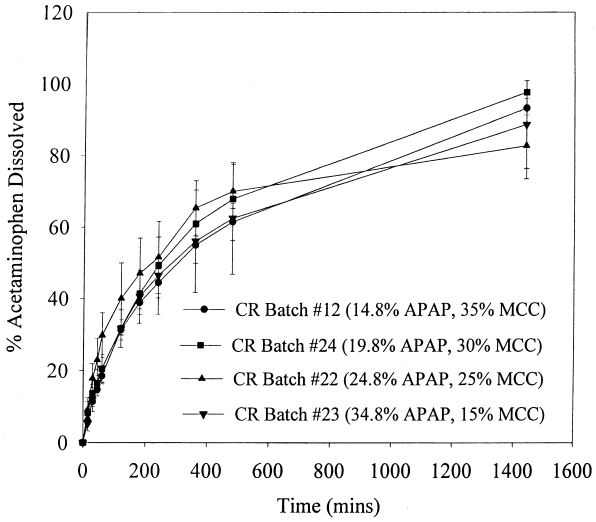

Figure 1. Comparison of aqueous dissolution profiles of 3% MGT batches containing different levels of drug and MCC, but the same level of HPC.

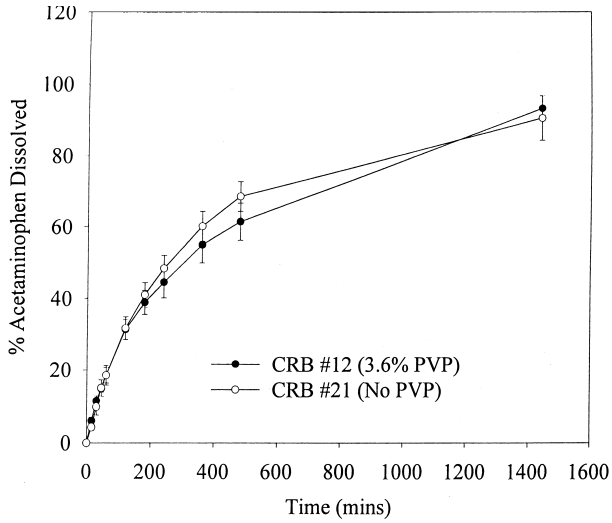

Figure 2. Comparison of aqueous dissolution profiles of 3% MGT batches with and without PVP.

Table 2

Physical Properties of Batches With and Without Polyvinylpyrrolidone (PVP)

Physical Property Sieve Analysis Screen Size	Powder Blend	3.6% PVP	No PVP
16	0.0	0.0	0.0
30	1.0	6.0	18.0
50	1.0	3.0	9.0
100	49.0	17.0	25.0
200	28.0	38.0	27.0
325	19.0	20.0	14.0
Pan	2.0	15.0	7.0
Total	100.0	100.0	100.0
Mean particle size (μ)	190	147	237

presence or absence of binder does not affect drug release, and more importantly, that HPC is the ingredient responsible for controlling drug release.

Effect of Polymer Level

The possibility of increasing the polymer content to retard drug release further was explored. The dissolution profiles are shown in Fig. 3. The profiles are superimposable within experimental error. This indicates that a polymer level of more than 44.6% is not able to retard drug release any further.

Mechanism of Drug Release

During the course of formulation development, it was observed that batches containing 14.8% w/w APAP, 3.6% w/w PVP, 35% w/w MCC, 44.6% w/w HPC, and no diluent showed drug release profiles that were independent of processing (i.e., DC, WG, or MGT). To elucidate the mechanism of drug release from these batches, the fractional amount released (in purified water) was plotted against time (according to Eq. 1), and curve fitting was carried out. Data for the complete dissolution run (i.e., up to 24 h) and for up to 6 h (where $M_t/M_\infty \leq 0.6$) were used. The results (for data up to 6 h) are shown in Fig. 4. The values of k and n are shown in Table 3. The values of n are closer to 0.5 rather than 1.0, which indicates that the mechanism of drug release is Fickian. Indeed, when amount released per surface area was plotted against the square root of time as in Fig. 5, the data were fitted with a straight line, indicating a Higuchi,

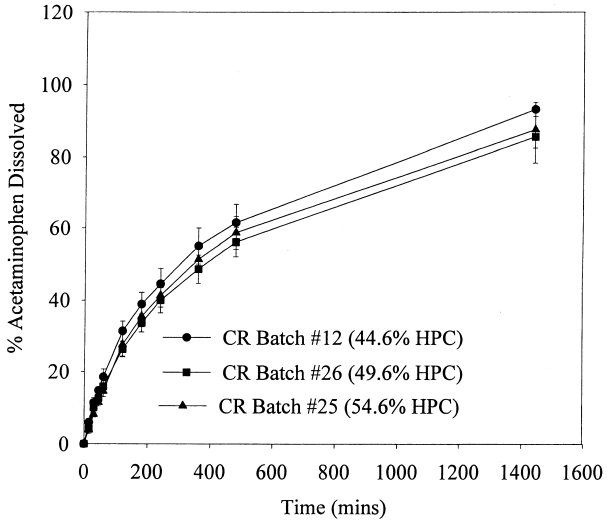

Figure 3. Comparison of drug release profiles of controlled-release batches containing different levels of MCC and HPC, but the same level of drug.

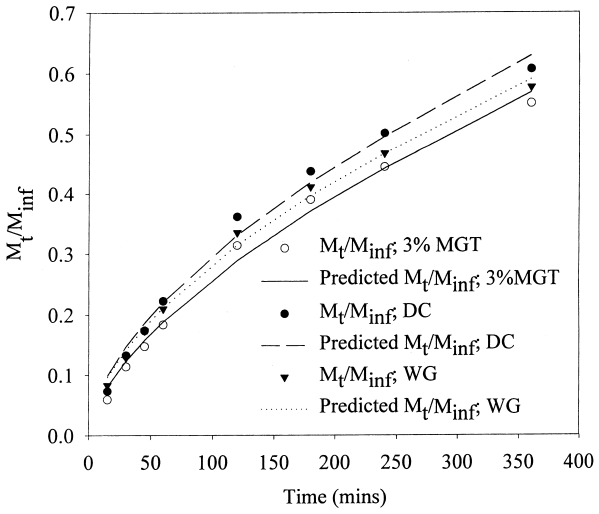

Figure 4. Nonlinear curve fitting for fraction of drug released at steady-state from controlled-release tablets containing 44.6% HPC and no diluent.

Table 3

Values Obtained When Dissolution Data Were Treated Using Equations 1 and 3

	Equation 1		Equation 3
Batch	k (min^{-1})	n	k ($mg/cm^2/min^{1/2}$)
MGT	0.01517	0.61545	0.693
DC	0.02018	0.58419	0.7468
WG	0.02025	0.57278	0.7143

DC, direct compression; MGT, moist granulation technique; WG, wet granulation.

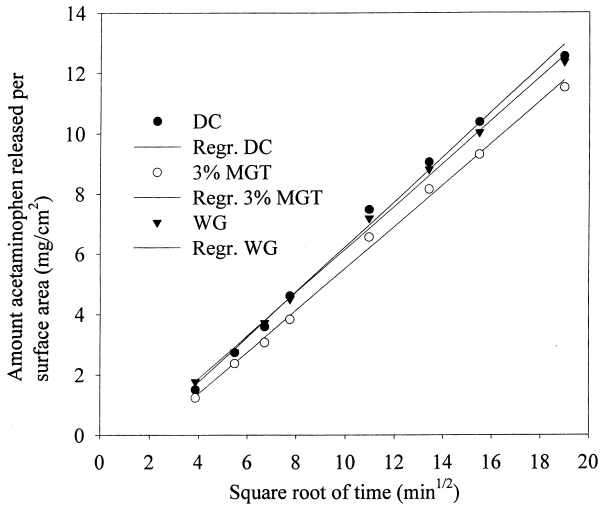

Figure 5. Amount released per surface area versus square root of time for controlled-release batches containing 14.8% APAP, 35% MCC, 44.6% HPC, 3.6% PVP, and no diluent.

diffusion-controlled release mechanism from a swellable matrix.

CONCLUSIONS

From the results discussed above, it can be concluded that MGT can be applied to controlled drug release and at a polymer content of 44.6% w/w or above, and the process is robust enough to allow slight variations in the formulation without affecting drug release. MGT for controlled release can be achieved with MCC levels as low as 15% w/w to allow higher drug levels, and this formulation with a wettable polymer can be processed without the use of additional binder.

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