DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(9), 1473-1490 (1990)

FORMULATION OF CONTROLLED RELEASE MATRICES BY GRANULATION WITH A POLYMER DISPERSION

George H. Klinger,[1] Evone S. Ghali,[1]
Stuart C. Porter,[2] and Joseph B. Schwartz[1]

[1] Department of Pharmaceutics, School of Pharmacy, Philadelphia College of Pharmacy and Science, 43rd St. and Woodland Ave., Philadelphia, PA, 19104.

[2] Colorcon, West Point, PA, 19486.

ABSTRACT

The objective of this work was to incorporate an ethylcellulose-based controlled-release coating suspension (Surelease, Colorcon) within a tablet matrix to provide a release controlling mechanism. Anhydrous theophylline, chlorpheniramine maleate, and acetaminophen were selected as model drug entities. Surelease dispersion was incorporated as the granulating agent either to the drug entity alone or to a blended mixture of drug and filler. Control batches included simple aqueous granulations and direct compression mixtures. Tablets were prepared on

a single stroke tablet press. Dissolution was performed by the USP Method I (rotating basket) in purified water for the granulations and the resulting tablets. The uncompressed granulations did not exhibit prolonged release. In general, tablets prepared with the polymer suspension as the granulating agent were non-disintegrating, and exhibited slower dissolution than the control tablets. Release profiles were affected by drug concentration and excipient levels. By the dissolution method selected, complete drug release for the various formulations ranged from less than 1 hour to greater than 12 hours. The use of the polymer dispersion appears to enhance the processing characteristics of some materials, and to provide the formulator with control over drug release.

INTRODUCTION

Application of various types of coatings to compressed tablets is a common way of controlling drug release. Several aqueous polymer dispersions are available for this purpose. In this work, an ethylcellulose-based product (Surelease, Colorcon) was utilized in an attempt to control drug release from a tablet matrix by utilizing the dispersion as a granulating agent.

Ethylcellulose has been used in a variety of ways to control drug release from tablets. For example, it has been used to form microcapsules which are compacted.[1,2] It has been used as a granulating agent in alcohol, and to provide organic and aqueous film coatings.[3] The methodology described in this report represents an easy method for incorporating the polymer into a tablet matrix without the use of organic solvents or additional operations.

The objectives of this study were: (1) to determine the feasibility of incorporating this material as a granulating agent, (2) to compress any resulting granulations, (3) to determine the controlled release potential by measuring in-vitro release profiles, and (4) to examine the effects of drug and excipient solubility and processing variables.

MATERIALS AND METHODS

Materials

Anhydrous theophylline, chlorpheniramine maleate, and acetaminophen (Supplied by Colorcon) were utilized as model drug entities.

Hydrous lactose (Foremost), and dicalcium phosphate dihydrate (Stauffer Chemical) were used as

fillers in the wet granulations. Directly compressible unmilled dicalcium phosphate dihydrate (DI-TAB, Stauffer) was used as a filler in the direct compression formulations. Magnesium stearate (Mallinckrodt) was the tablet lubricant.

Surelease (Colorcon) was used as received from the supplier. This product contains ethylcellulose as the film-forming polymer, dibutyl sebacate and oleic acid as plasticizers, and fumed silica as an anti-adherent in a vehicle of ammoniated water. The solids content of the aqueous dispersion is approximately 25%.

Processing

Granulations were prepared by a conventional wet granulation technique in a planetary mixer (Kitchen Aid Model K5SS, Hobart Corp.) with either Surelease or purified water as the granulating agent. The granulations were carried out to a subjective end-point. Wet milling was performed by passing the wet granulation through a #8 mesh screen by hand. The wet granulation was dried in a hot air oven at 40°C. overnight.

The dried granulation was milled using a Fitzpatrick comminutor (Model D-6, Fitzpatrick Co.) equipped with #2 screen (knives forward, medium

speed). The dried, milled granulation was lubricated with magnesium stearate (0.5% of the weight of the dried granulation) and blended for five minutes in a twin shell blender (Patterson-Kelley).

For the direct compression formulations, the drug and filler were blended for 5 minutes in the twin shell blender. Magnesium stearate (0.5%) was added to the mixture, followed by five additional minutes of blending.

Tablets were compressed on an instrumented Manesty F3 single stroke tablet press with 12/32" round, flat-faced tooling. Tablet weight was 450 mg. with a target hardness of 7 - 9 kp (Schleuniger Hardness Tester).

Dissolution testing was performed by the USP/NF Method I in purified water with a basket rotational speed of 50 rpm. Solvents and conditions were varied on selected formulations. Dissolution test samples were assayed by UV spectroscopy.

RESULTS AND DISCUSSION

Theophylline

The evaluation of this material was begun with simple formulations of theophylline in lactose. Since Surelease contains 25% solids by weight, the final

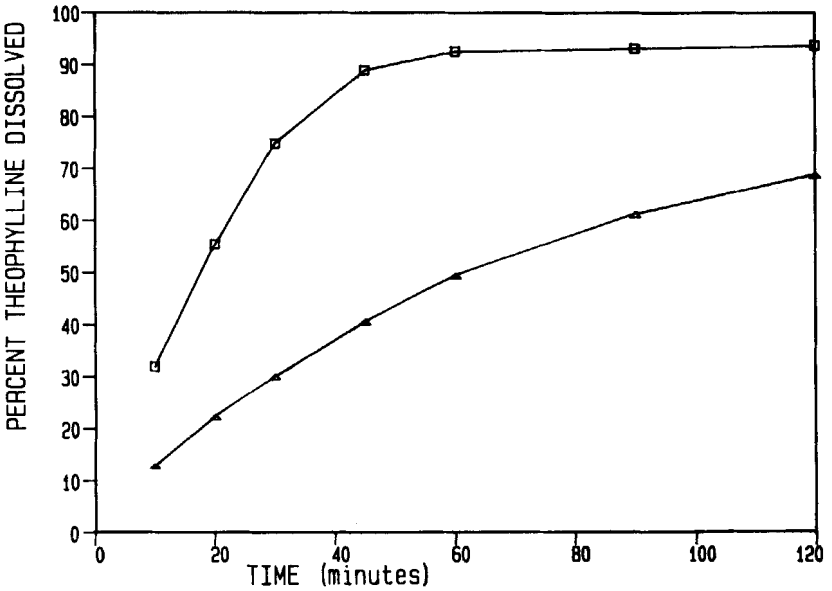

Figure 1 Dissolution profiles for tablets containing 10% theophylline in lactose prepared bt wet granulation with Surelease (Δ) or purified water (□).

concentration of theophylline in the granulation was back-calculated. For example, the formulation containing 10% theophylline in lactose (1000 gm of powders) required 219 gm of dispersion to reach granulation endpoint. This yields 53 gm of Surelease solids remaining after drying. Therefore the final theophylline concentration is 9.5 %. For ease of comparison, all formulations in this report will be classified by the level of drug prior to granulation.

Figure 1 depicts the dissolution profiles of the 10% theophylline formulations granulated with the polymer dispersion, and with purified water. The polymer granulated tablet has a more prolonged dissolution profile than the aqueous granulated control tablet. It is also important to note that the polymer granulated tablet remained intact throughout the dissolution test, while the control tablet had disintegrated. Both of these formulations processed readily. Dissolution testing of the uncompressed Surelease granulation showed that the granulation released all of the drug within 20 minutes. These findings seem to indicate that compaction of the polymer dispersion was aiding in the formation of a non-disintegrating matrix.

In another series of formulations, the theophylline level was increased to 30% and 50%, in lactose. Granulations and tablets were succesfully prepared with the Surelease dispersion and also with purified water as control formulations. For the 10% theophylline formulation, the Surelease solids content of the tablet was 5.2%. For the 30% and 50% formulations, the Surelease solids content of the tablet was 6.9% and 6.5%, respectively. These formulations with increased theophylline yield

TABLE I

Dissolution Data for Tablets Prepared by Wet Granulation

% Theophylline	Percent Dissolved		
	0.5 hr.	1 hr.	2 hr.
A] SURELEASE FORMULAS			
10%	30.1	49.6	69.0
30%	18.1	26.2	35.8
50%	8.8	17.7	29.9
B] AQUEOUS CONTROLS			
10%	74.5	92.6	93.8
30%	24.1	46.6	73.8
50%	16.6	32.0	50.3

dissolution profiles that are slower than the 10% formulation (Table I). However, it was also noted that the dissolution profile for the aqueous granulated controls decreased with an increased theophylline concentration. To further investigate the effect of theophylline concentration, three direct compression formulations containing 10%, 30%, and 50% theophylline in anhydrous lactose were prepared. As shown on Table II, with these formulations also,

TABLE II

Dissolution Data for Tablets Prepared by Direct Compression

% Theophylline	Percent Dissolved		
	0.5 hr.	1 hr.	2 hr.
A] CONTROL FORMULAS			
10%	100.0	--	--
30%	44.1	89.9	92.1
50%	17.2	35.4	62.4

simply increasing the theophylline concentration decreases the dissolution rate.

In all cases, however, the polymer containing tablets have a more prolonged release profile than the corresponding control. In all cases, the polymer granulated tablets remain intact over the dissolution test period, where the aqueous controls have disintegrated or become worn to a very small, soft mass during the course of the test.

Since the effect of the theophylline concentration seemed to be confounding the effect of the polymer dispersion, a more soluble drug was selected for the next phase of evaluation.

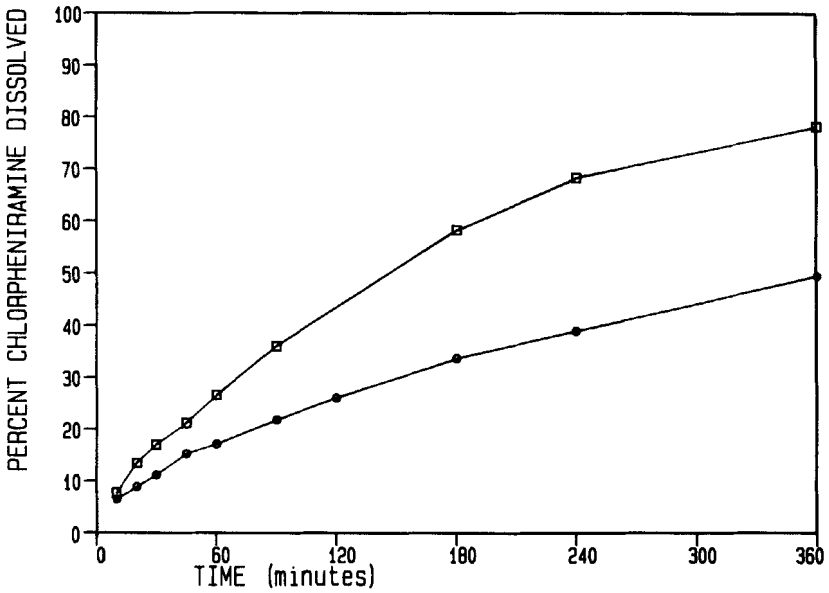

Figure 2 Dissolution profiles for tablets containing 5% chlorpheniramine maleate in dicalcium phosphate prepared by single (□) and double (O) granulation with Surelease.

Chlorpheniramine maleate

Chlorpheniramine maleate (CPM) was selected for this phase of the evaluation. An arbitrary target dissolution result of not more than 50% released after 6 hours was selected.

A formulation containing 5% CPM in dicalcium phosphate dihydrate was prepared with the polymer dispersion. The resulting tablets, containing 8.3% Surelease solids, exhibited a prolonged release profile, but exceeded the arbitrary target. In order

to increase the Surelease content of the dosage form, a double granulation technique was utilized. After granulation, wet screening and drying, the resulting material was granulated again with the polymer dispersion, and the wet granulation was processed as before. The resulting tablets containing 4.2% CPM and 16.6% Surelease solids, met the target profile. Figure 2 depicts the dissolution profile of these two formulations over a six hour period. Both of these formulations were also non-disintegrating.

The aqueous granulated control formulation with 5% CPM in dicalcium phosphate would not run on the tablet press; the granulation caused severe sticking and ejection problems. The Surelease granulations, however, ran well on the press. These formulations demonstrated a positive effect of the dispersion on processing.

The double granulated tablets were tested under a variety of dissolution test conditions to evaluate the effect of these changes. Table III lists the results of these tests. Testing at 50 or 150 rpm by the Basket or paddle method produced essentially the same profile. Testing the formulation in 0.1N HCl, increases the dissolution rate, but the tablet remains intact throughout the test. This increase in release

TABLE III

Dissolution Data for 5% CPM Tablets Prepared by Double Granulation with Surelease

Test Method	Percent Dissolved 1 hr.	3 hr.	6 hr.
A] WATER			
BASKET (50 rpm)	17.2	33.7	49.6
BASKET (150 rpm)	15.0	30.6	47.8
PADDLE (50 rpm)	15.2	30.9	48.4
B] 0.1N HCl			
PADDLE (50 rpm)	28.9	54.2	84.8

rate may be due to the increased solubility of the calcium phosphate excipient in acid.

The dissolution profile of this formulation appears to follow the relationship characteristic of non-disintegrating matrices which was described by Higuchi.[4] This relationship predicts that the amount of drug released will be directly proportional to the square root of time. Figure 3 depicts the dissolution data obtained at 50 rpm in water for the double granulated tablet plotted vs. the square root of time.

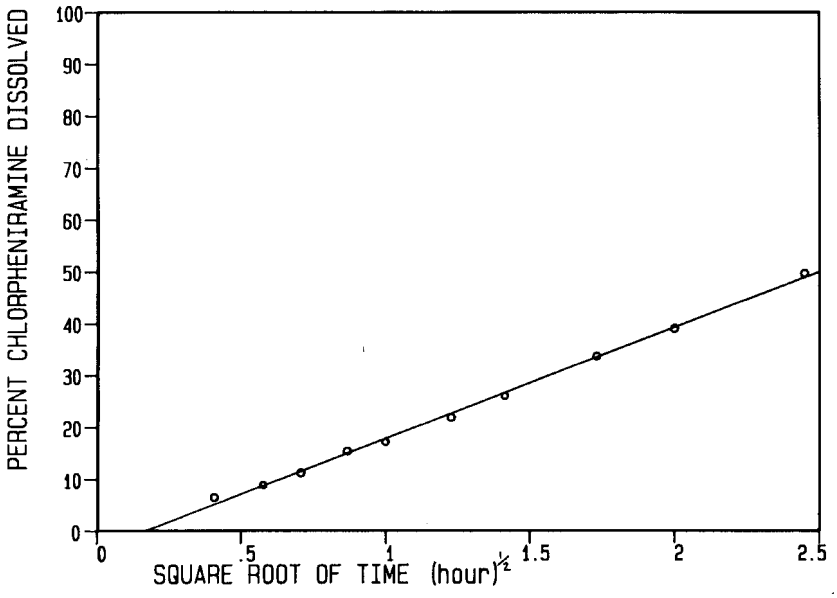

Figure 3 Dissolution data for 5% CPM tablets (double Surelease granulation) versus the square root of time. (Basket method, 50 rpm, purified water).

Preliminary stability data on the double granulated CPM tablet has been obtained. After six months storage at room temperature and at 45°C, there is no change in the dissolution profile by the basket method in water at 50 rpm.

Acetaminophen

The final phase of this evaluation involved granulation of a drug substance with Surelease. The objectives were to compress these granules (without

fillers), and also to combine these granules with a direct compression excipient prior to tabletting.

Acetaminophen (APAP) was selected as a model compound for this evaluation. Single, double, and triple granulations of APAP with the Surelease dispersion were prepared. The APAP powder was granulated with the dispersion, screened, and dried. This process was repeated for the double and triple granulations. The dried granules were milled, lubricated and compressed as before.

APAP, a compound with documented "capping" tendency,[5] could not be compressed on the tablet press alone after the addition of a normal concentration of magnesium stearate as a lubricant. The single granulation with Surelease (7% Surelease solids in the dried granules) could be compressed but only to a hardness of 4 - 5 kp (Schleuniger) without "capping." The double, and triple granulations (13.5% and 19.9% Surelease solids in the dried granules, respectively) compressed easily on the press. These findings again demonstrate the positive effects of the polymer dispersion on processing.

Tablets were compressed from the granulations at a weight to provide 250 mg APAP. All of these

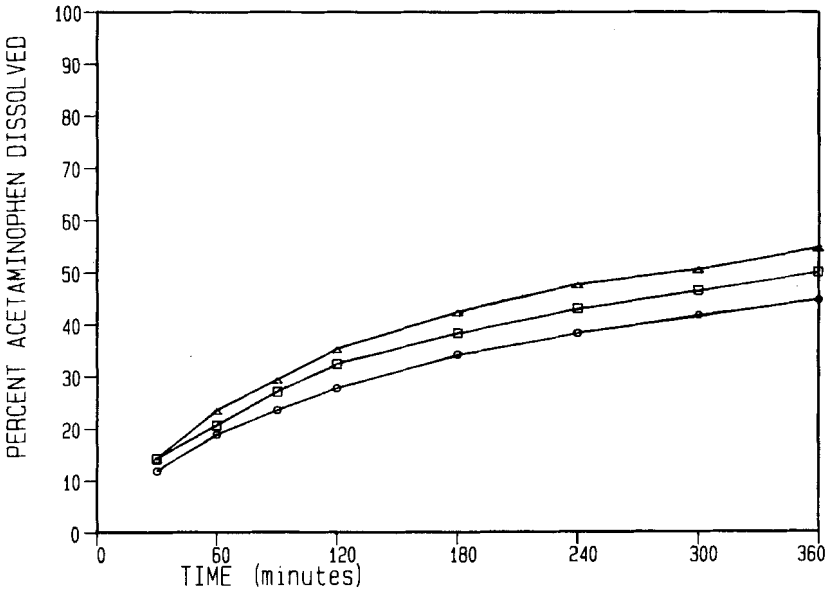

Figure 4 Dissolution profiles for tablets containing 250 mg. acetaminophen prepared by single (Δ), double (□), and triple (○) granulation with Surelease.

formulations yielded non-disintegrating tablets, and a prolonged release profile over the period tested. The percent released after 6 hours ranged from 45 - 55% when tested in purified water at 100 rpm (Figure 4).

Finally, the single and triple granulations were combined with directly compressible unmilled dicalcium phosphate dihydrate (DI-TAB, Stauffer). A control formulation of APAP and DI-TAB was also prepared. These tablets were formulated to provide 250 mg APAP in a 450 mg tablet. As shown on Figure 5, each of

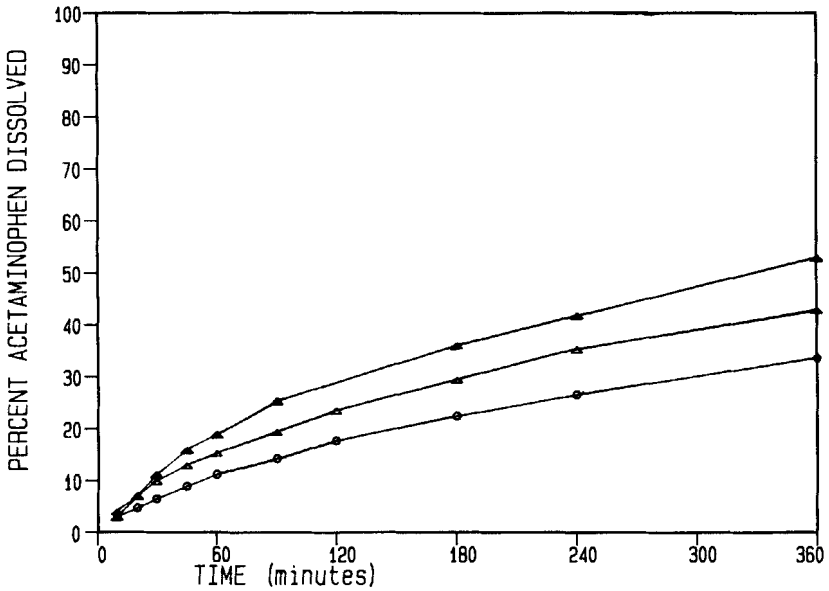

Figure 5 Dissolution profiles for tablets containing 250 mg. acetaminophen in DI-TAB (450 mg. tablet weight). The acetaminophen was either untreated (▲), or a single (Δ), or triple (O) granulation with Surelease.

these formulations provides prolonged dissolution; however, only the triple granulation in DI-TAB was readily processed on the tablet press to the desired hardness; the single granulation/DI-TAB had ejection difficulties, and the control tablets "capped" if compressed to hardness greater than 4 kp.

CONCLUSIONS

It has been demonstrated that incorporation of Surelease dispersion into a tablet formulation by

using it as a granulating agent is feasible. Surelease appears to possess binding properties, producing compressible granulations.

In the systems evaluated, granulation with the polymer dispersion produces non-disintegrating tablets which release the drug more slowly than the corresponding control formulations.

Because of these findings, further study is warranted to determine the release mechanism, and the degree of control available to the formulator.

ACKNOWLEDGMENTS

This research was supported in part by funds from the Ben Franklin Partnership Program, through the Advanced Technology Center of Southeastern Pennsylvania. We wish to thank Dr. Naphthali Lander for his invaluable assistance in this work.

REFERENCES

1. I. Jalsenjak, C.F. Nicolaidou, J.R. Nixon, J. Pharm. Pharmacol., 29, 169 (1977).

2. J.R. Nixon, I. Jalsenjak, C.F. Nicolaidou, M. Harris, Drug Dev. Ind. Pharm., 4, 117 (1978).

3. N.G. Lordi, in "Theory and Practice of Industrial Pharmacy," L. Lachman, H. Lieberman, J. Kanig (Eds.), Lea & Febiger, Philadelphia, 3rd edition, 1986, p. 430.

4. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).

5. S. Leigh, J.E. Carless, B.W. Burt, J. Pharm. Sci., 56, 888 (1967).