Drug Development and Industrial Pharmacy, 23(12), 1201-1205 (1997)

RESEARCH PAPER

A Novel Wet Granulation Method for Carbopol® Resin. I. Extragranular Addition

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INTRODUCTION

This study describes a novel wet granulation method (by extragranular addition) for hydrophilic polymers and its effect on the controlled-release properties of theophylline tablets. Hydrophilic polymers of the carbomer family including Carbopol® 934P resin, Carbopol 971P resin, and cellulosic polymers including Klucel® EF and HF, are used as controlled-release agents. Carbopol 934P resin is a synthetic, high molecular weight polymer of acrylic acid, crosslinked with a polyalkenyl polyether. Klucel EF and HF are hydroxypropylcelluloses of low and high viscosity, respectively. The Klucel EF and HF polymers are non-ionic cellulose ethers. Carbopol 934P resin is an anionic polymer. Carbopol 934P resin, on hydration, swells quickly and therefore forms agglomerates during the wet massing process. Such agglomeration can be avoided by the method suggested in this report. The Klucel polymers are water-soluble resins, which are frequently used as controlled-release agents in solid dosage forms. We also discuss the effects of this wet granulation process on the controlled-release properties of polymeric tablets, as evidenced by the theophylline dissolution curves, specifically in relation to the drug release mechanism.

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MATERIALS AND METHODS

Mortar and pestle, Mettler balance, and 16 oz. bottles and caps were used. Hobart Mixer with flat blade, atomizer for water, nos. 6,8, 12, and 16 stainless steel mesh screens, Teflon®-coated aluminum foil, air oven set at 60°C, and an air line for the atomizer were used.

Model Formulation

This formulation has been structured according to the drug requirement, using a 100-g batch for tablets made on a Stokes single-station laboratory press employing manual powder feed (Table 1). One hundred tablets (wt ≈ 300 mg) were made from each formulation. The hardness of the tablets did not exceed 30 kilopounds. The tablets made were analyzed for hardness, friability, disintegration time, and theophylline dissolution (see Scheme 1).

The following procedure has been found to be successful using 20% water in the wet massing stage.

Compounding the Formulation (Dry Stage)

The drug and the dry ingredients are added geometrically, while being ground together using the mortar and

Table 1

Theophylline Tablet Formulation

Number	Ingredient	Percent
1	Theophylline (Sigma)	32.9
2	Hydrated lactose (Sigma)	56.0
3	Carbopol 934P resin (BFGoodrich)	10.0
4	Cab-O-Sil® (Cabat)	0.4
5	Magnesium stearate (SynPro)	0.7

pestle. The polymer and magnesium stearate are not added at this time. After thorough grinding, the powder is placed in a V-mixer, blended for 25 min, and then stored in a bottle to await wet massing.

Addition of Water (Wet Massing Stage)

After the compound from the dry stage procedure is poured into the Hobart mixer, it is mixed at a moderate speed. Using the atomizer, demineralized (DM) water is sprayed over the compound until the required percent of water is obtained. If too much water is added, the compound tends to become sticky. At this stage, the compound packs well and breaks apart easily.

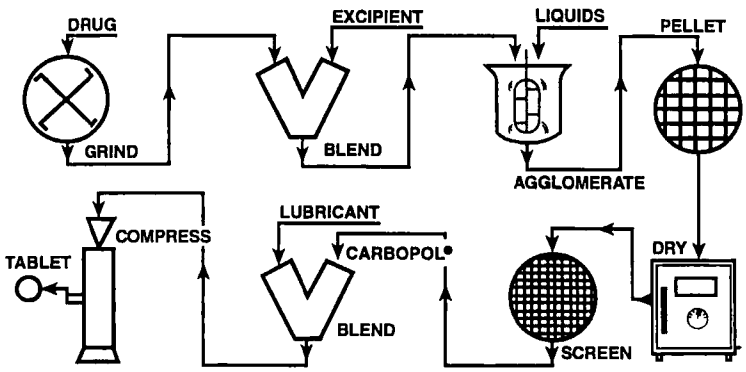
After the compound is mixed, the wet compound is screened through #6 and #8 stainless steel mesh screens and placed on the Teflon-coated foil. It is then dried in an air oven for 4 hr at 60°C. The dried compound is then screened through #12 and #16 stainless steel mesh screens. The granules are transferred to a V-mixer and mixed for 15 min. The polymer is then added as required by the formulation (5, 10, or 15%) and mixed for another 15 min. This process is illustrated in Scheme 1.

Tableting is done according to the procedure described earlier. Dissolution testing was carried out with the USP Apparatus II, paddle method (dissolution test station, Sitco-Pharma), with a Perkin-Elmer Lambda 3 UV/Vis Spectrophotometer interfaced with a Perkin-Elmer 3700 Data Station. All tests were done at 37°C and 50 rpm paddle speed, in 900 ml of either 0.2 M hydrochloric acid (pH 1.2) or 0.2 M potassium phosphate monobasic buffer adjusted to pH 6.8 to simulate gastric or intestinal fluid, respectively. Six tablets of each drug were simultaneously tested in the dissolution cells (n = 6). Drug dissolution profiles were obtained by plotting the fraction of drug released versus time. The T_{90} (time for 90% of the dose to dissolve) values were determined using the SAS® non-linear regression analysis program (NLIN).

RESULTS AND DISCUSSION

The physical characteristics of the tablets generated by this novel wet granulation method are described in Table 2. Comparatively harder tablets were made with Carbopol 934P resin than with either of the Klucel varieties. Crosslinked polyacrylic acid polymers are known for their adhesive properties, which may account for the strength of the tablets at such low polymer concentration (1). This factor may account for the longer disintegration times, lower friability, and prolonged uniform dissolution profiles of these tablets (Figs. 1 and 2).

Figs. 1 and 2 show the release profiles for all three matrix tablets containing theophylline at various percentages of different polymers. The results of the drug release study are described in Table 3. These data indicate that the tablets generated by the novel wet granulation method gave a prolonged theophylline re-



Scheme 1. Wet granulation by extragranular addition of carbopol resin.

Table 2

Physical Properties of Theophylline Tablets After Wet Granulation

Polymer	Concentration (%)	Hardness (kp)	Disintegration Time (min)	Friability (%)
Carbopol 934P	5	14.4	60	0.15
Carbopol 934P	10	15.9	78	0.09
Carbopol 934P	15	18.5	91	0.09
Klucel EF	5	12.1	31	0.11
Klucel EF	10	12.1	32	0.09
Klucel EF	15	12.9	37	0.08
Klucel HF	5	10.4	5	0.14
Klucel HF	10	9.4	6	0.11
Klucel HF	15	9.1	5	0.12

lease T_{90} of over 10 hr in simulated gastric fluid (SGF), at all concentrations of Carbopol 934P NF resin. In simulated intestinal fluid (SIF), there was a polymer concentration-dependent increase in theophylline dissolution T_{90}. In the latter case, as the percentage of the polymer increased in the tablets, so did the dissolution T_{90}. Carbopol 934P NF resin tablets showed a slight concentration effect on dissolution in the acidic environment of gastric fluid.

At low pH, Carbopol 934P NF resin is essentially in an un-ionized state and the swelling of the polymer is mainly due to the hydration process. The swelling of this polymer (pKa = 6.0) is greater at the higher pH of simulated intestinal fluid due to the ionization and mu-

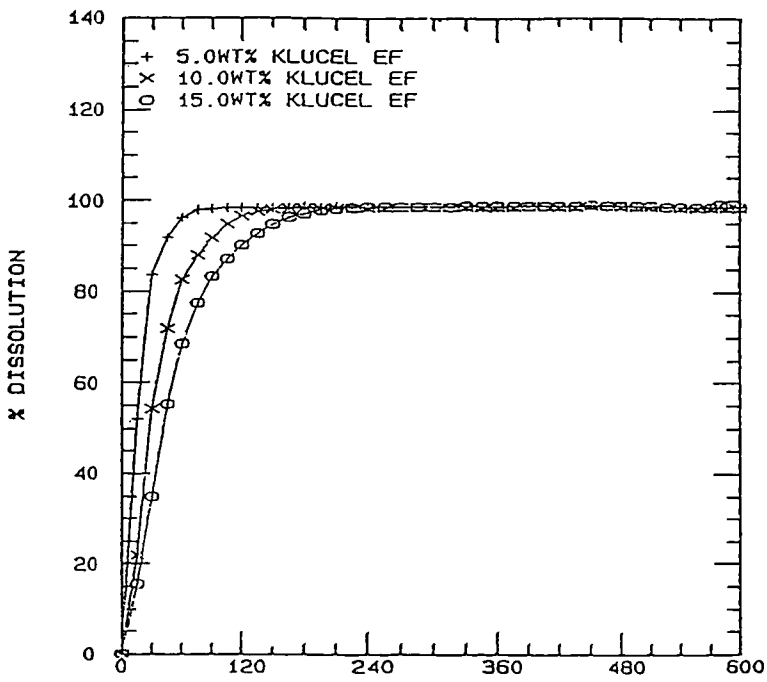


Figure 1. Theophylline dissolution from Klucel EF tablets in simulated intestinal fluid.

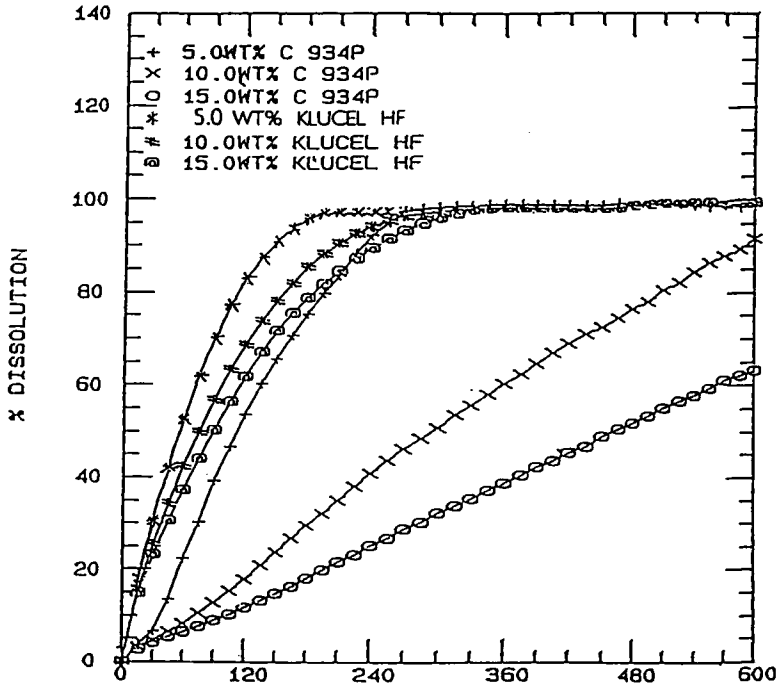


Figure 2. Theophylline dissolution from carbopol 934P and Klucel HF tablets in simulated intestinal fluid.

tual repulsion between the negatively charged carboxylic groups of acrylic acid residues. Therefore, a concentration-dependent sustained release of theophylline is observed. Similar results were obtained by Hincal et al. (2), who studied the influence of insoluble carbomer matrices on the release of potassium chloride from tablets. They visualized the diffusion of potassium chloride from carbomer matrices as being dependent on the hydration and swelling of the tablet. They found that a decrease in the amount of carbomer causes a decrease in the embedding capacity of matrix tablets. However, for cellulosic polymers, drug release can be attributed

Table 3

Theophylline Tablet Dissolution T_{90} (min) at 5, 10, and 15% Polymer Concentration

Dissolution Fluid	Polymer Concentration (%)	Carbopol 934P Resin	Klucel EF	Klucel HF
		Dissolution T_{90} (min)		
SGF	5	656.8 ±9.0	67.1 ±15.3	235.0 ±52.4
SGF	10	660.8 ±17.2	101.9 ±10.6	280.8 ±58.1
SGF	15	676.0 ±40.6	112.0 ±1.2	220.4 ±55.8
SIF	5	232.3 ±10.4	42.0 ±1.7	145.8 ±5.3
SIF	10	587.8 ±19.2	83.1 ±5.9	205.4 ±20.8
SIF	15	903.5 ±4.2	117.1 ±21.7	245.3 ±13.5

to the formation of a hydration layer, which may not resist attrition, but may remain intact. Hence, attrition dependence is more important than diffusion, and the hydrated layer erodes away very quickly. This results in faster theophylline release from tablets containing Klucel EF and HF.

CONCLUSION

The wet granulation method described in this article is more suitable for tableting with hydrophilic polymers like Carbopol 934P NF resin. These tablets can form a stable gel barrier on the tablet surface (at low polymer concentrations), due to swelling of their crosslinked structure and insolubility in the aqueous environment. Thus, these tablets resist attrition and erosion processes at much lower concentrations, as compared to water-soluble polymers like Klucel EF and HF.

The polymer is not exposed to the granulation fluid. Therefore, agglomeration of the polymer is eliminated. Polymer swelling occurs only during the drug dissolution process. Thus, by a simple and manageable process, the controlled-release properties of the polymer are unaffected.

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