DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(5), 501-517 (1992)

EFFECT OF AMOUNT AND COMPOSITION OF GRANULATION LIQUID ON MIXING , EXTRUSION AND SPHERONIZATION

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ABSTRACT

Avicel RC 581 is regarded as an excellent excipient in formulations for extrusion (1). The CMC-Na in this microcrystalline cellulose improves the binding properties and the plasticity. In this study Avicel RC 581 was mixed in various ratios with theophylline. These mixtures were granulated with either water or water/ethanol (60/40) mixtures in a Collette high shear mixer. The power consumption during mixing was recorded as a function of the amount of granulation liquid. From the mixtures obtained in this way the plasticity / viscosity was determined before extrusion. Measurement of the plasticity / viscosity was carried out in an apparatus similar to the one described by Alleva et al (2). Extrusion was done using a Fuji Paudal extruder (EXD-60); the power consumption during extrusion was recorded.

The influence of the amount and composition of the granulation liquid on the various power consumptions and on plasticity / viscosity will be discussed , as well as the spheronization behaviour of the extruded pellets.

INTRODUCTION

Microcrystalline cellulose is known as an excellent excipient for pellet production by wet granulation, extrusion and spheronization because of its physical properties. After addition of fluids it gives a cohesive plastic mass also in combination with other materials. The amount and composition of granulation liquid plays a critical role in the production process (3).

In the development of pellets, the amount and composition of the granulation liquid is varied in order to obtain a granulate suitable for extrusion and spheronization. We produced pellets and spheres containing various amounts of theophylline (10 and 50 % w/w) by wet granulation and spheronization.

Theophylline was mixed with microcrystalline cellulose (Avicel RC 581) as excipient. The influence of the amount and composition of the granulation liquid was studied.

The amount of granulation liquid was varied from 40-200% w/w {%w/w = % of water or water/ethanol mixtures in relation to the amount of the solid mass}, for 0 % theophylline, 40-160% w/w for 10 % theophylline, 40-110% w/w for 50 % theophylline containing mixtures.

This paper presents a convenient and reliable method for plasticity viscosity measurements, and characterizes the influence of the amount and composition of the granulation liquid.

MATERIALS AND METHODS

Materials.

Theophylline monohydrate, (Knoll AG),Ph. Eur. quality was jet-milled and the sieve fraction < 105 μm was used.

Avicel RC 581 (FMC-corp.) was used as delivered.

Demineralized water as such or mixed with 40 volume parts of ethanol (Ph. Eur. quality) was used as granulation liquid.

Methods

The preparation method of the spheres is outlined in Figure 1.

Wetgranulation.

Each batch used for wet granulation consisted of 800 gram powder mixture of Avicel RC 581 as such or mixed with theophylline. The powder mixtures were prepared by mixing during 30 sec. in a Collette high shear mixer. The speed of the mixer was maintained constant at 150 rpm throughout all experiments. The mixer was connected to an ampere-meter (Duphar) for recording the current (Amperes) and for estimating the energy consumption (Watts).

After the initial mixing the granulation liquid was added to the powder mixture at a constant rate of 100 ml/min., using a Watson 502 S pump. The mixer was allowed to operate for 15 min. The energy consumption during mixing was determined.

Plasticity / Viscosity measurement.

The measurement of plasticity / viscosity was carried out in an apparatus similar to the one described by Alleva et al (2). The slightly modified apparatus is schematically shown in Figure 2.

Plasticity apparatus description.

This apparatus consists of a motor (1) and a driving belt (2) which controls the velocity of the sample tray (3). The sample tray is

PREPARATION METHOD OF SPHERES IS OUTLINED.

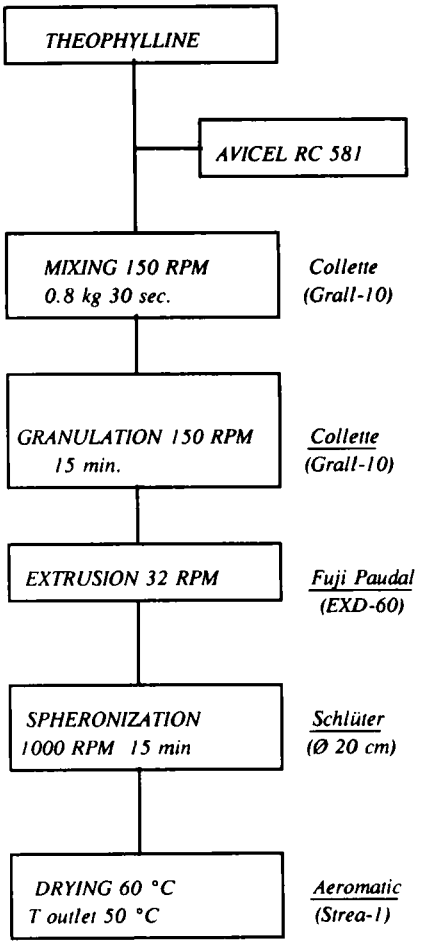

FIGURE 1.

Preparation method of the spheres

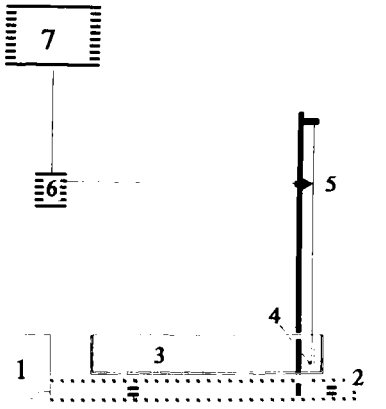

FIGURE 2.

Schematic diagram of the plasticity apparatus

removable. During a run of a sample the tray is moved from left to right. Before each run, the sample tray is filled with 500 grams material. The measuring - fork (4) with 4 tines [the gaps between the tines are 9 mm] was brought down 15 mm into the sample. When the apparatus is started the sample tray moves [with a rate of 3.26 cm/sec.] to the right. If the sample offers some resistance to the fork the shaft will press against the load cell (5) [type 8523 Burster, Germany], attached 22 cm from the fork tines. The signal is amplified (6) [PR 9340 Philips, Holland] and sent to a recorder (7), [Bd 100 Kipp & Zonen , Holland].

Extrusion.

After the plasticity / viscosity measurements the wetted mass was passed through a Fuji Paudal twin screw extruder (EXD- 60), which was operated at 32 rpm and fitted with a 1 mm screen. The power consumption during extrusion was recorded.

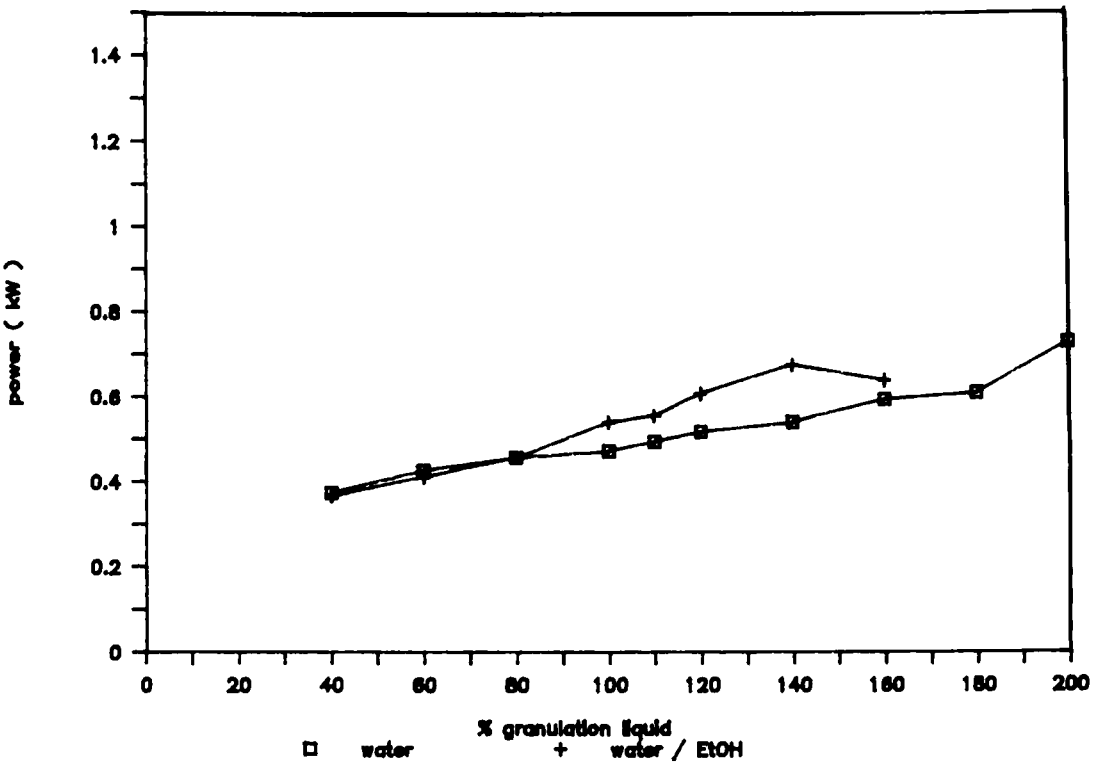

FIGURE 3.

Power consumption mixer

100 % Avicel RC 581

Spheronization.

The obtained pellets were immediately spheronized in portions of 250 gram. The spheronizer (Schlüter, friction plate, diameter of 20 cm) was operated at 1000 rpm.

The spheres were collected after 15 min. residence time, and dried in an Aeromatic Strea-1 fluid bed dryer.

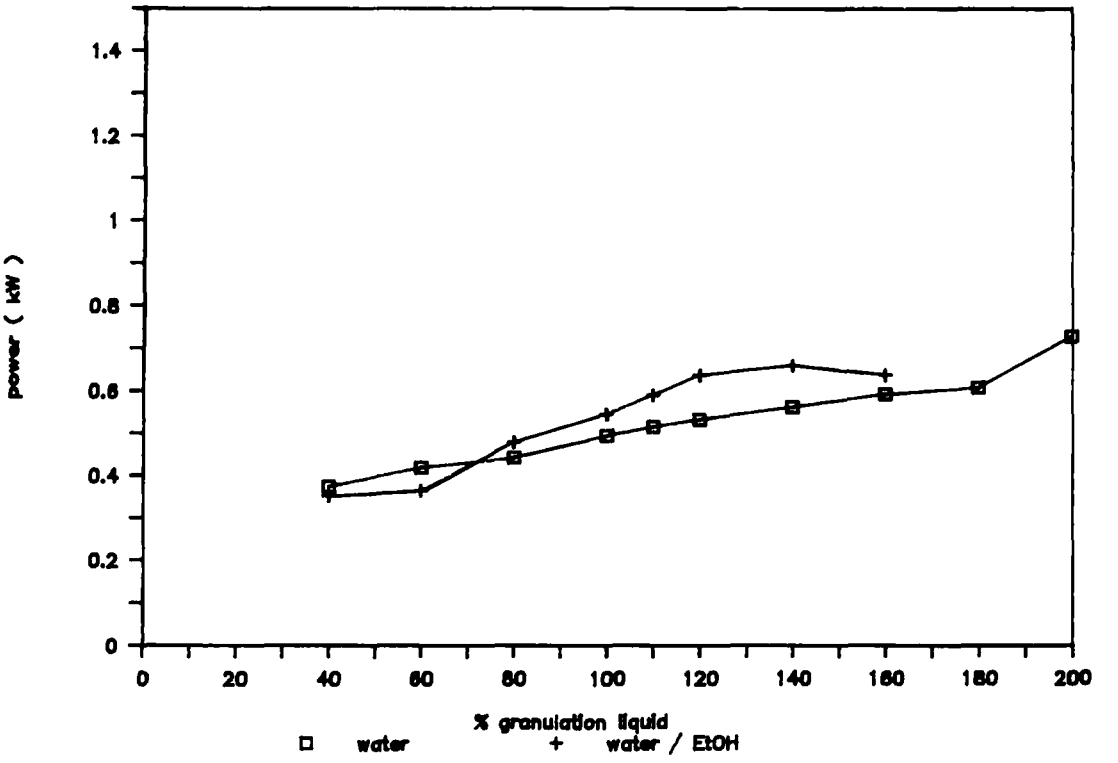

FIGURE 4.

Power consumption mixer

90 % Avicel RC 581 - 10 % theophylline

RESULTS AND DISCUSSION

a. Mixing

The power consumption of the Collette Mixer was measured during mixing of solid with granulation liquid. The solid material was either Avicel RC 581 (A) or Avicel RC 581 with 10% theophylline (B) or 50% theophylline (C). The granulation liquid was water (W) or water/ethanol (60/40, W/E).

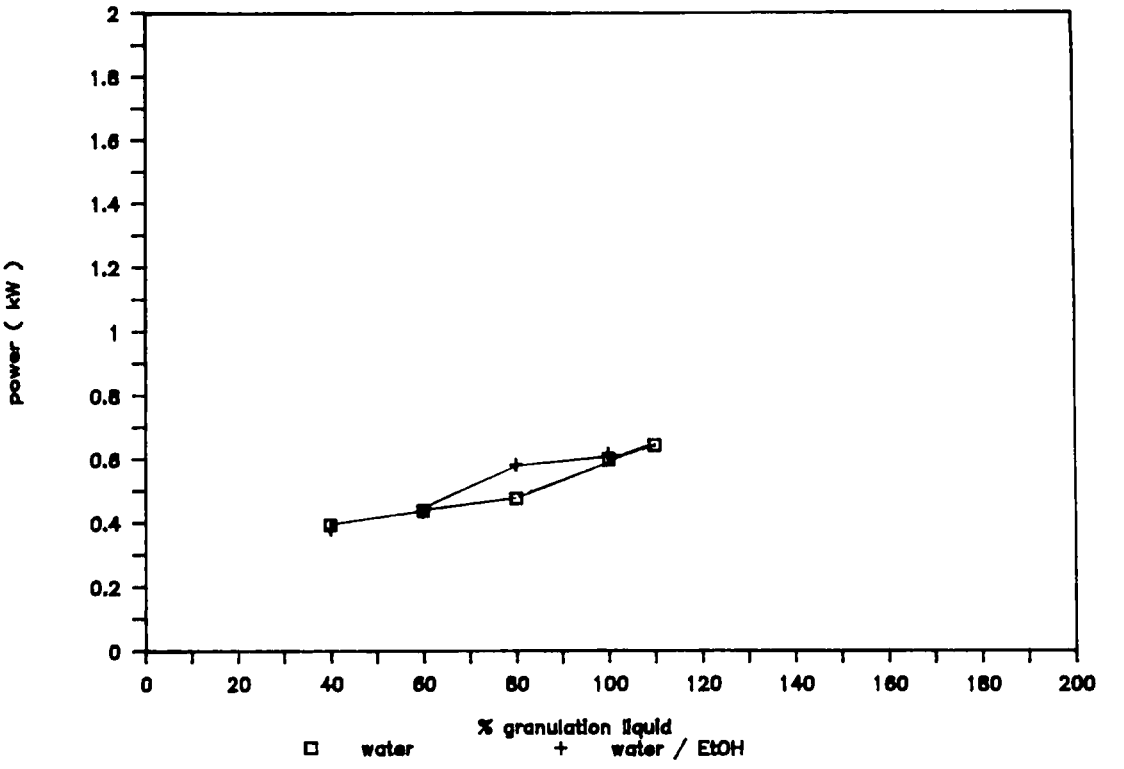

FIGURE 5.

Power consumption mixer

50 % Avicel RC 581 - 50 % theophylline

In fig.3 and fig.4 the power consumption of the mixer for mixtures **A** and **B** is presented as a function of the % w/w (relative to the dry mass) of the granulation liquid. The mixing time, rotational speed and degree of filling of the mixing bowl were always constant.

As can be seen from these figures power consumption increases slightly with increasing amount of granulation liquid. Furthermore, there seems to be a tendency towards a slightly higher power consumption for water / ethanol as granulation liquid compared with water, above the 100% w/w mixture. However, no difference in

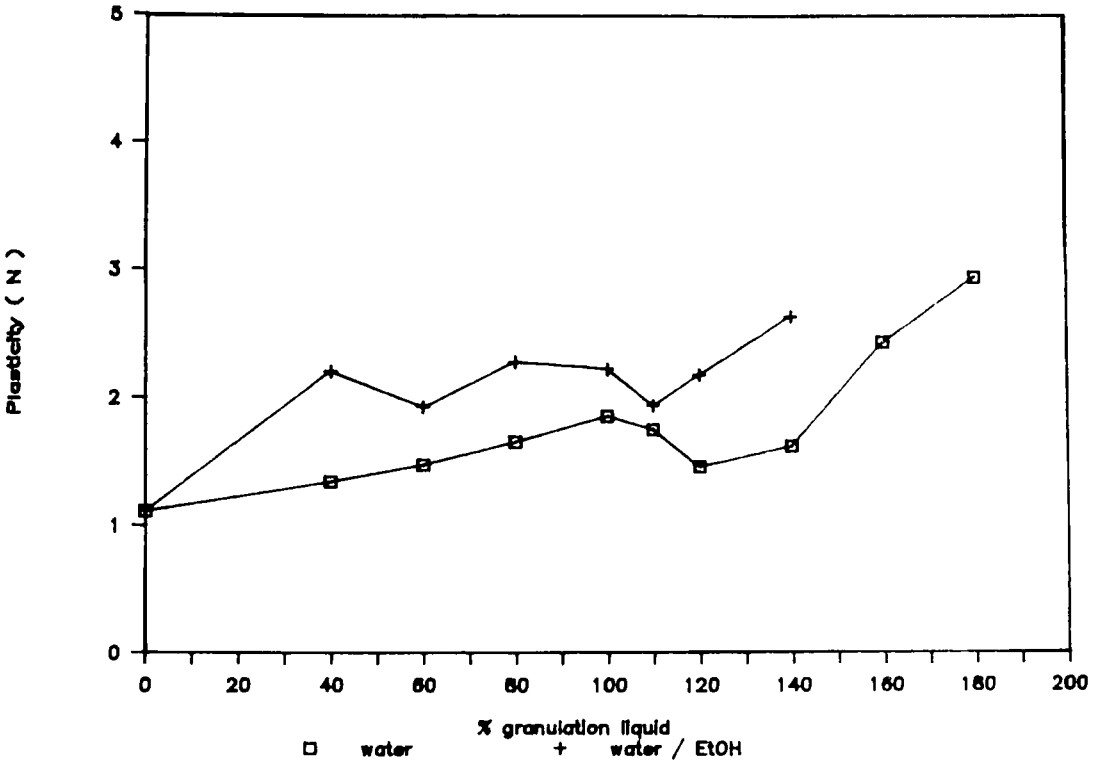

FIGURE 6.

Plasticity curve

100% Avicel RC 581

power consumption exists between the mixtures **A** and **B**. Hence it is concluded from these experiments that the addition of 10% theophylline does not influence the granulation process.

In figure 5 the power consumption of mixture **C** is presented as a function of % w/w granulation liquid. It can be seen that the addition of 50% theophylline results in an increase in power consumption compared with **A** and **B**

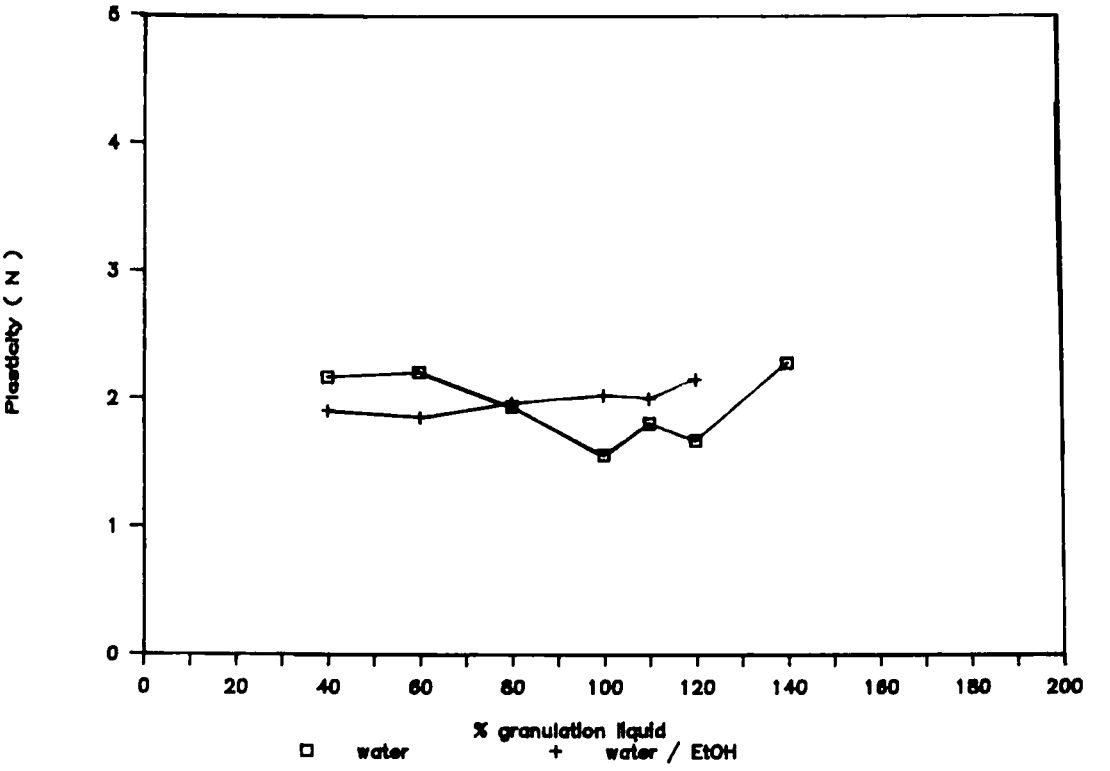

FIGURE 7.

Plasticity curve

90 % Avicel RC 581 - 10 % theophylline

b. **Plasticity measurements**

The plasticity of the mixtures **A**, **B** and **C** with various amounts of both granulation liquids was determined as decribed in the experimental section. The results are presented in figures 6, 7 and 8.

As in the power consumption measurement of the mixing process, no difference is found between the plasticities of the mixtures **A** and **B**. However, mixture **C** shows a strong increase in plasticity with

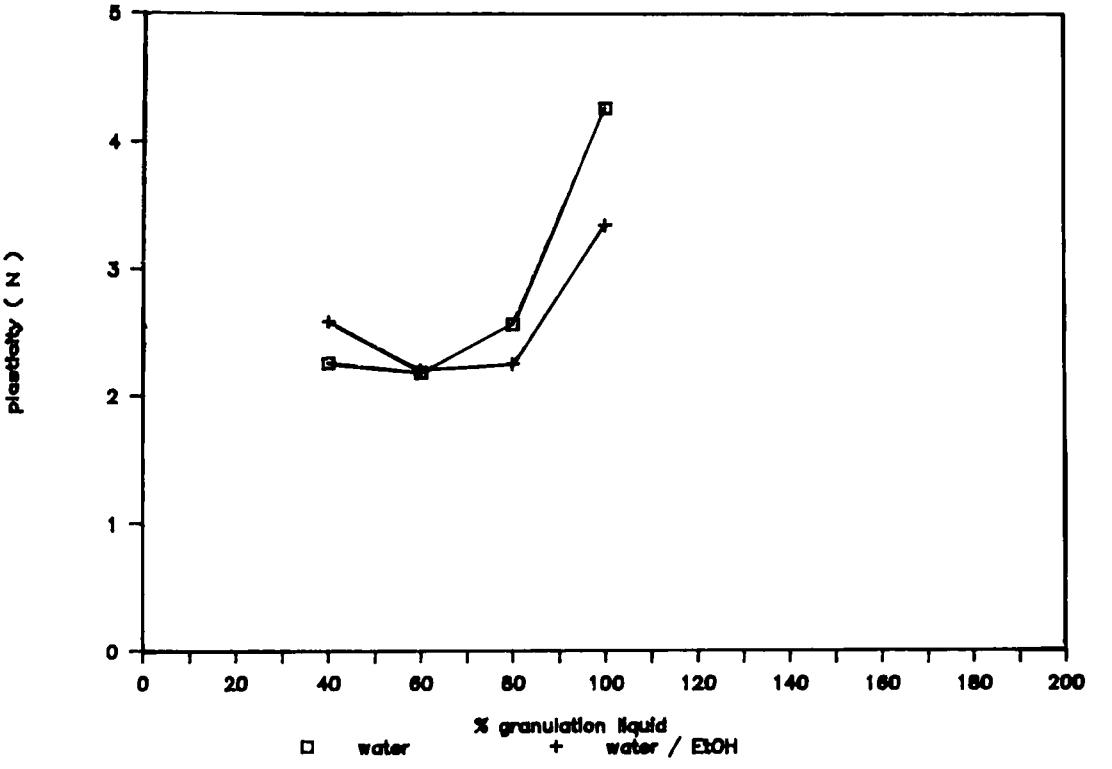

FIGURE 8.

Plasticity curve

50 % Avicel RC 581 - 50 % theophylline

increasing amount of granulation liquid. This is in accordance with the increase found in the power consumption measurements.

c. Extrusion

The power consumption of the Fuji Paudal extruder was measured during the extrusion process of **A**, **B** and **C** mixed with various amounts of the granulation liquids. The results are shown in figures 9, 10 and 11.

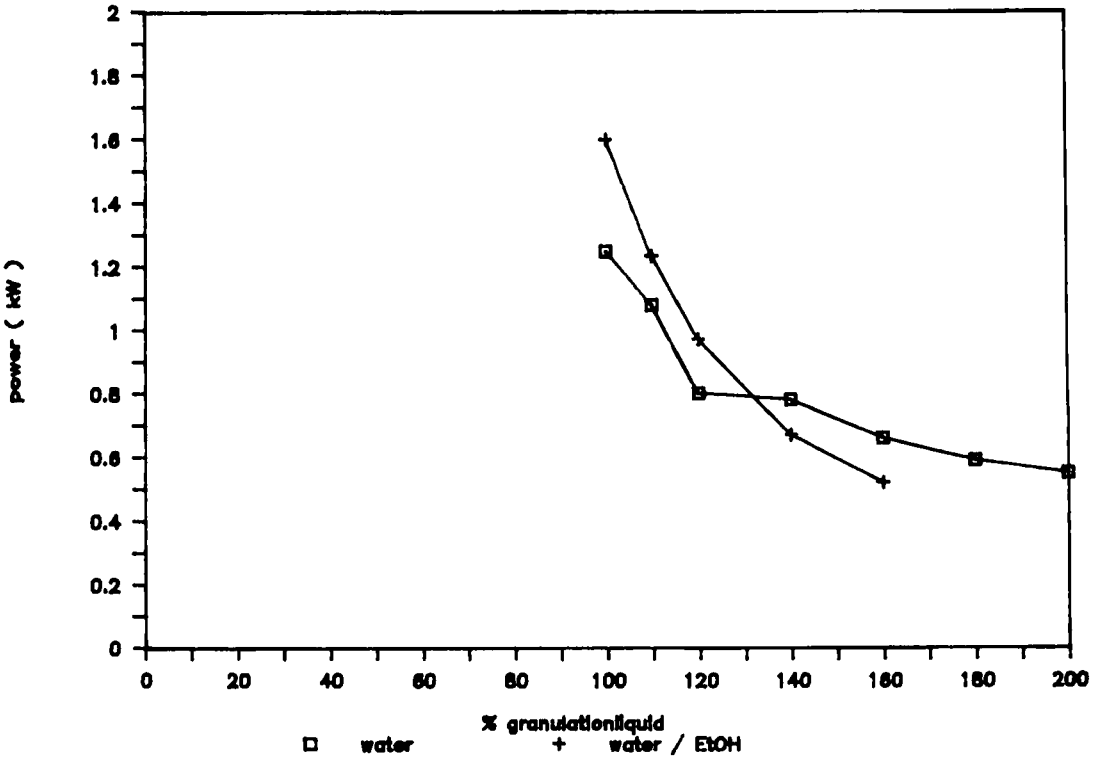

FIGURE 9.

Power consumption extruder

100 % Avicel RC 581

As can be seen from these figures, again there is no difference between the mixtures **A** and **B**. However, the power consumption of **C** differs from that of **A** and **B**. Comparision of the mixtures of **A** and **C** with 100% water e.g. shows a much lower consumption for mixture **C**. This was not expected since the plasticity of **C** was much higher then that of **A**.

The extrudate was spheronized. However, it turned out that spheronization was not possible in all cases. The quality of the

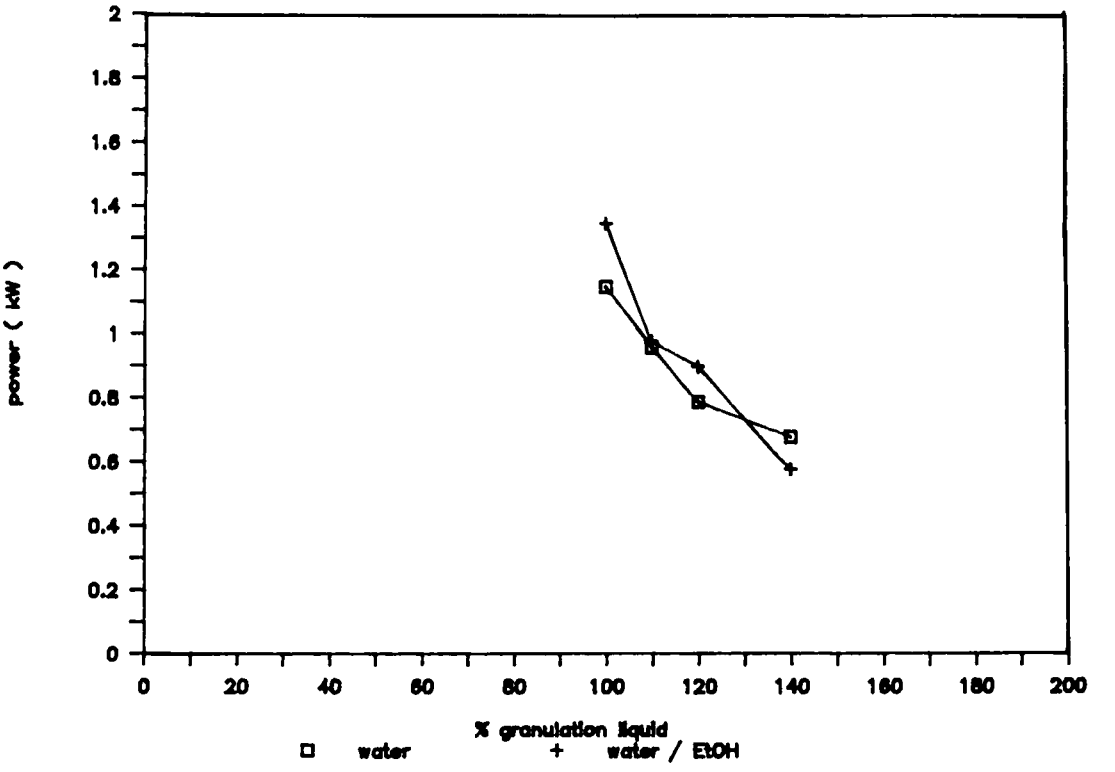

FIGURE 10.

Power consumption extruder

90 % Avicel RC 581 - 10 % theophylline

spheres, if obtained at all, varied from poor to excellent. It was tried to correlate this spheronization behaviour to the parameters measured before. The " **overall - curve** " for **A** and **B**, for plasticity is presented in figure 12.

As can be seen from figure 12 there seems to be a " valley " in the plasticity curve around 120% w/w granulation liquid.

This dip in the plasticity curve occurs when the power consumption of the extruder reaches more or less a minimum value (figure 13). It

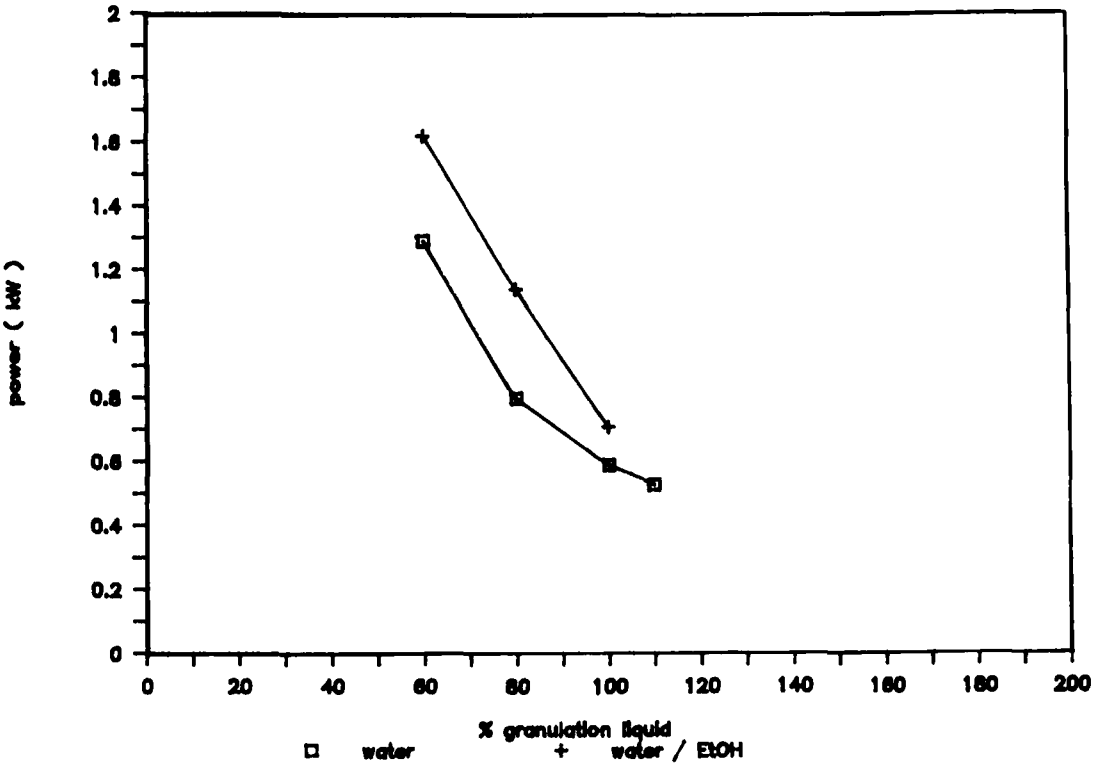

FIGURE 11.

Power consumption extruder

50% Avicel RC 581 - 50 % theophylline

turned out that the best spheres were obtained for those mixtures with a composition in accordance with a mixture-composition represented by the ascending part of the plasticity curve, after the dip. Hence mixtures of **A** or **B** with 140 - 180 % granulation liquid.

For mixture **C** the ascending part of the plasticity curve starts around 60 % granulation liquid (see fig.8). Spheres from mixtures of **C** with 60, 80 and 100 % granulation liquid were perfectly round (With 40 % granulation liquid no spheres could be made).

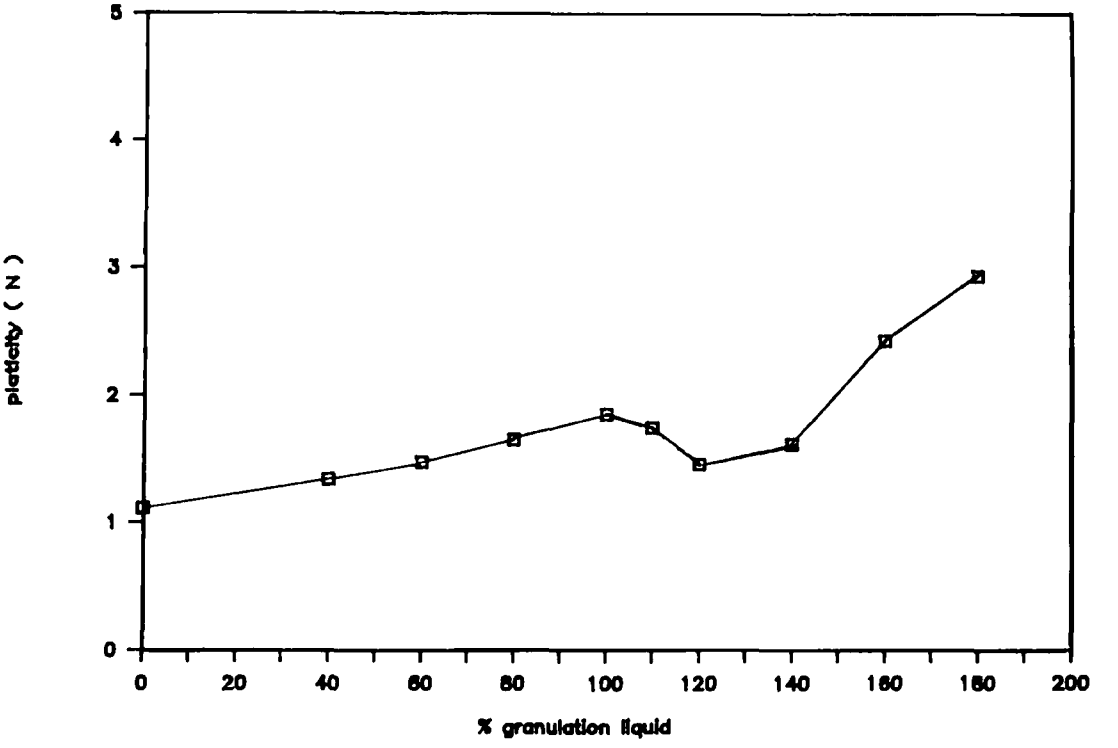

FIGURE 12.

Plasticity curve

CONCLUSION

From these results it can be concluded that the addition of 10 % theophylline to Avicel RC 581 does not influence the mixing, extrusion or spheronization process. Furthermore, the plasticity of the mixtures **A** and **B** show a dip followed by an increase. The best spheres were formed using mixtures with a composition reflected by the ascending part of the plasticity curve directly after this dip.

Addition of 50 % theophylline does influence the physical properties as compared to Avicel RC 581 alone. For the extrusion and

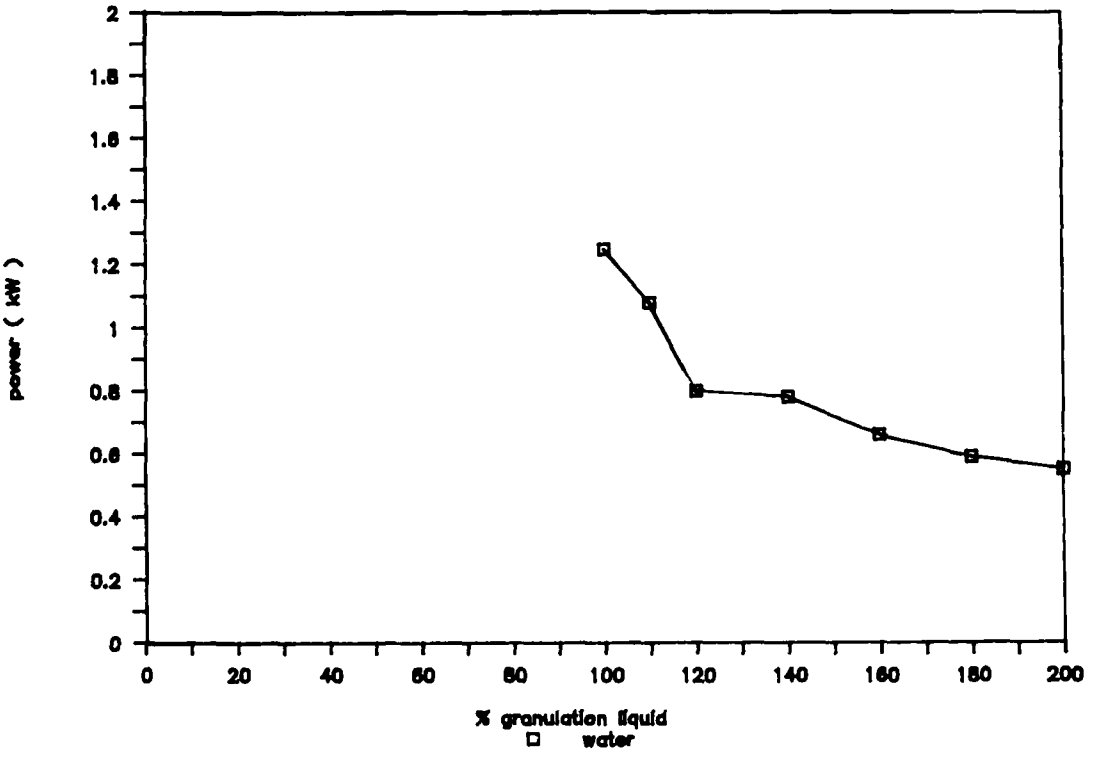

FIGURE 13.

Power consumption extruder

spheronization processes less granulation liquid is needed, so it is concluded that the amount of granulation liquid is related to the amount of Avicel RC 581 in the mixture.

For development work it is expected that optimum conditions for the extrusion / spheronization process can be determined by measuring the plasticity of the drug-excipient mixture as a function of the amount of granulation liquid added.

REFERENCE

1. Avicel spheres, FMC-corp., Company document, 1985.
2. Alleva, D.S. and Schwartz, J.B., Drug Dev. Ind. Pharmacy 12 (1986), 471-487.
3. Staniforth et al, Int. J. Pharm., 41 (1988), 231-236.