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Rheology of pharmaceutical granulations

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The rheological transformations that take place when granulating fluid is added to pharmaceutical powders have been monitored by means of a laboratory scale (approx. 50 g amounts) torque rheometer. The three formulations studied, based on lactose, sulfadiazine, and benoxaprofen, had common characteristics in that each passed through a granulation peak of maximum torque. In the zone immediately before the peak the granules were growing, while after it the material had properties of a cohesive, viscoelastic mass. Therefore, the rheological state of the material under process is not specified by a single torque reading, but by the rheological history of the granulation.

In the wet granulation process it is normally desired to stop the conversion at some intermediate, non-equilibrium condition in which the granules are forming and growing. Several investigators have recently proposed methods for detecting conversions during the pharmaceutical granulation process. Kay & Record (1978) monitored changes in particle momentum. Leuenberger et al (1979) continuously recorded the power consumption.

Transient and non-steady state phenomena can be investigated with rotational viscometers since the reaction of material to the imposed shear field may be directly recorded. I have used a Plasti-Corder rotational torque rheometer (C. W. Brabender Instruments, Inc.) to monitor rheological changes during the granulation process. Advantages included the need for only limited quantities of materials for each experiment (approx. 50 g), a very sensitive detection system (Pony brake principle), and a chart recording of the conversion process.

MATERIALS AND METHODS

The three formulations examined (Table 1) contained placebo lactose, the antibacterial sulfadiazine, or the anti-inflammatory drug benoxaprofen. They had components in common in that two contained water-insoluble drugs, two, starch as the disintegrant, and two, polyvinylpyrrolidone as the binder. Materials were of USP grade except benoxaprofen (Eli Lilly and Company). The grade of polyvinylpyrrolidone corresponded to a molecular weight of about 40 000.

The rheometer (Fig. 1) had a granulating chamber of 50 cc capacity, jacketed to control the wall temperature, with two rotors that rotated in opposite directions. Material to be granulated, and medium, were loaded through the top V-chute. On the drive side of the rotors there was a dynamometer (not shown) mounted in precision bearings. The resistance to rotation experienced by the rotors was transmitted to the dynamometer, causing a rotational displacement in the opposite direction. This rotation was recorded on a strip chart recorder as the reaction torque (as a function of time). Usually the

Table 1. Description of formulations.

	Formulations			
	Benoxa-profen-I	Benoxa-profen-II	Sulfa-diazine	Lactose
Dry powder mixture				
Drug*	100	100	100	100
Disintegrant	MC/A 12	MC/A 12	S17	S12
Binder	0	PVP 5	0	PVP 7
Granulating fluid				
Binder	PVP 5	0	PS 14	0
Water	26	26	20	7

* Data are normalized to 100 g of active component.
MC/A = Microcrystalline cellulose/Amberlite.
PVP = Polyvinylpyrrolidone.
PS = Pregelatinized starch.
S = Starch.

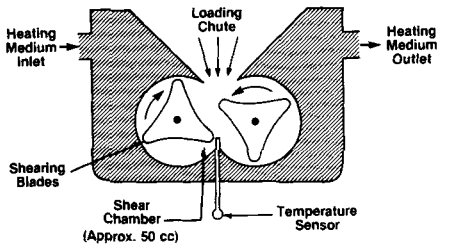

FIG. 1. Diagram of equipment.

premixed powders were added to the rheometer chamber, followed by granulating fluid in one addition. The granulating water level was determined as the quantity that would convert the powders to a viscoelastic mass within 4–10 min based on the following criteria: shearing blades—roller, type 6; chamber temperature—25 °C; shearing rate—40 rev min^{-1}; total solid per experiment—50 g (basis). The viscoelastic conversions are described below with the formulations discussed in order of increasing complexity.

RESULTS AND DISCUSSION

The torque versus time plots for the replicates of the benoxaprofen-I formulation (Fig. 2A) closely coincide whilst those for the benoxaproven-II formulation (Fig. 2B) show more variation but level off

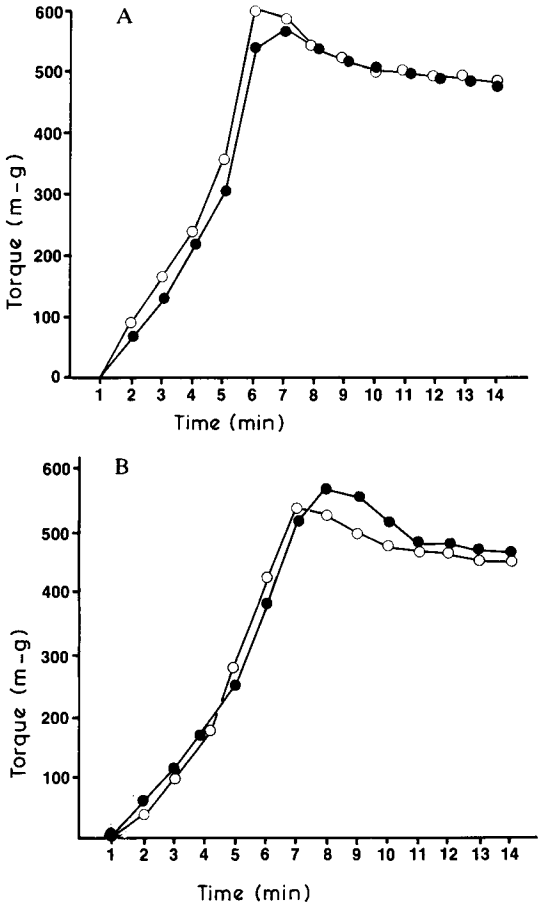

FIG. 2. Rheological transformations of benoxaprofen-I formulation (A) and of benoxaprofen-II formulation (B). Open and solid symbols represent replicate results.

together. At first sight there would appear to be much variation in the sulfadiazine torque versus time plot (Fig. 3) with the torque varying from 475 to 730 m-g at 3·5 min. However, when viewed on a time basis, the results show that torque reproduces within about

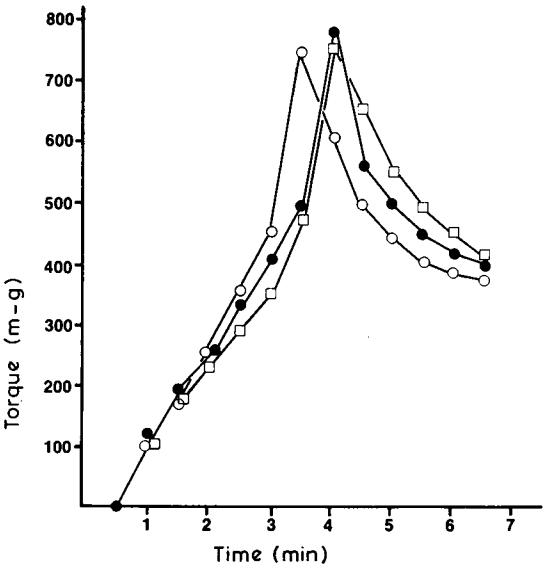

FIG. 3. Rheological transformations of sulfadiazine formulation. Symbols represent replicate results.

±0·5 min. With the lactose formulation (Fig. 4), for which three different chamber temperatures were maintained, the three sets of data were essentially the same up to about 9 min. But after 10 min the curves differed as might be expected with molten materials, i.e. the resistance to flow decreased as temperature increased.

The least complex of the formulations was that for benoxaprofen. The experiments with the benoxaprofen-I formulation (binder dissolved in water, Fig. 2A) revealed that in the zone before the granulation peak (i.e. before 7 min) the main processes taking place were those of granule development and microdispersion. At the granulation peak a cohesive mass was formed and the solid particles (i.e. drug and disintegrant) were microdispersed. The zone after the granulation peak therefore represents the viscosity stabilization of this viscoelastic mass. When it is desired to produce granules for subsequent compression to tablets, the rheological transformation process would be terminated before the granulation peak. But for extrusion

of the material for alternate dosage forms, such as spherical pellets (e.g. Conine & Hadley 1970), processing would continue to the zone of viscosity stabilization.

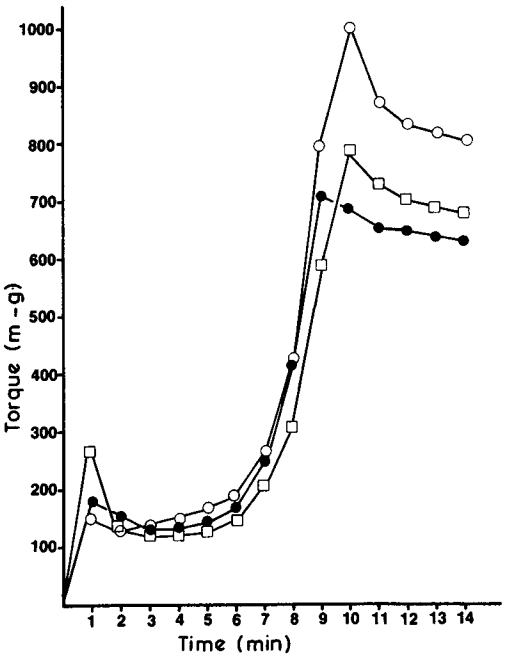

FIG. 4. Rheological transformations of lactose formulations. Chamber temperatures. ○ 25 °C, □ 35 °C, ● 40 °C.

The benoxaprofen-II formulation (incorporation of polymeric binder in dry powder mixture) behaved as shown in Fig. 2B. The primary difference between the formulations I and II was that the benoxaprofen-II results were slightly lower, particularly in the granule development/microdispersion zone. The similarities are not surprising if the interaction of each of the components of the formulation with water are considered, since benoxaprofen is virtually insoluble in water (Ridolfo et al 1979), disintegrants imbibe water rapidly (see e.g. Martin 1965), and polyvinylpyrrolidone possesses properties of both good surface wetability and low viscosity solutions. It is apparent that the process of in-situ dissolution of polyvinylpyrrolidone in the formulations occurs rapidly and at a similar rate as that of granule development-microdispersion.

In the sulfadiazine formulation the water was combined with the polymeric binder to form a 'jelly' as the granulating medium. Although there was more variation than with the combined benoxaprofen data, the rheological states were readily discernible (Fig. 2B) and the time to terminate the rheological conversion process (depending on end use intended) would be as discussed for benoxaprofen. However, if the end use of formulation is to be based on rheological conversion beyond the granulation peak, the rapid viscosity decay with time must be taken into account. Among the factors that could contribute to this viscosity erosion are thixotropy and degradation of the starch (by hydrolysis or other means). The relative magnitude of each of these potential contributions is not known.

The lactose formulation was the most complex of the formulations studied. Three experiments were conducted, at chamber temperatures of 25–40 °C (Fig. 4). Compared with the other two formulations the lactose formulation had an intermediate plateau between minor and major granulation peaks. To help understand what was happening on this plateau, discs of individual components of the formulation were compressed at 2500 psi and the contact angles for water placed on these discs measured (Mack 1935). The contact angle was 47° for polyvinylpyrrolidone but could not be determined for lactose or starch as the water droplet was absorbed too rapidly. Thus, an explanation for the intermediate plateau is that the water added to the granulation initially associates with the lactose and starch to form a weak 'pseudo' granulation (2–6 min into the process). By about 6 min, sufficient water has been taken up by the polyvinylpyrrolidone particles to cause an appreciable amount of the polymer to dissolve, with granule size and granule strength increasing as the rest of the binder dissolves (6–9 min into the process). After about 10 min the viscoelastic mass is formed, the viscosity of which is inversely related to temperature. The two major zones for terminating the rheological conversions thus become apparent: for conventional granules this would be between the plateau and the major granulation peak, while for extrusion processes it would be after the major granulation peak.

The torque rheometer therefore appears to be a useful instrument for (reproducibly) monitoring conversion of pharmaceutical granulations. As only some 50 g of solids is required each time, the rheometer should prove useful in formulation research, granulation process optimization, and production problem solving. The feature common to the three formulations studied was that each passed through a granulation peak. In the zone immediately before this peak the granules are growing and may be further processed by conventional wet-sieving equipment. In the zone after the granulation peak (i.e.

after the viscoelastic mass is formed) granule sizing must take place by power intensive equipment, such as extruders. Thus, the rheological state cannot be specified by a single torque reading, but the rheological history of the sample is required.

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REFERENCES

Conine, J. W., Hadley, H. R. (1970) Drug Cosmetic Ind. 106(4): 38–41

Kay, D., Record, P. C. (1978) Manuf. Chem. Aerosol News, 49(9): 45–46

Leuenberger, H., Bier, H. P., Sucker, H. B. (1979) Pharm. Technol. 3(6): 61–68

Mack, G. L. (1935) J. Phys. Chem. 40(2): 159–167

Martin, E. W. (1965) Remington's Pharmaceutical Sciences 13th Edition, pp 565–566

Ridolfo, A. S., Thompkins, L., Bechtol, L. D., Carmichael, R. H. (1979) J. Pharm. Sci. 68(7), 850–852