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FLUIDIZED BED COATING TECHNIQUE FOR PRODUCTION OF SUSTAINED RELEASE GRANULES.

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ABSTRACT

A laboratory-scale instrument for fluid-bed spray coating of granules has been constructed. Its major advantage is its suitability for development work on small batches of granules or tablets of between 50 and 300 grams. Commercial equipment available at present requires minimum loadings of 0.5 - 1 Kg. for effective operation.

The instrument has been successfully used for producing sustained-release products by coating granules of model drugs with EC, and data are presented which define important qualities of the products. In particular, the apparatus is capable of giving excellent batch homogeneity and reproducibility.

One of the recent successful developments in pharmaceutical technology is the production of sustained-release dosage forms. The two main approaches utilized in the design of these products are (a) the introduction of a physical barrier preventing contact between

the drug and the fluids of the digestive system, the effect of which is to reduce the rate of diffusion or leaching out of the drug from the dosage form (b) the addition of selected interactants to the formulation, such as ion-exchange resins or complexants, which form weak cnemical bonds with the drug.

The present work is concerned with the first type of product which in practice may be produced using widely different technologies. The main ones are based on (a) coating techniques (b) embedding the drug in a wax or polymer matrix. Prior to 1956, coating was performed by means of the classical rotating pan-method, but in that year Spaulding (1) introduced a controlled spray technique for application of the coating solution to the pan contents, termed the rotating pan-spray technique.

A new and major step in coating technology was the introduction into pharmaceutical manufacturing of the fluidized-bed technique. The term "fluidized-bed" has been defined in a number of ways (2-4); most simply, when a solid is "fluidized" in a process, it shows in its behaviour many of the physical characteristics of a liquid.

In pharmaceutical production, fluidization methods are utilized in stages of drying (5-6), granulation (7) and coating (8-9). As a coating technique, its main advantages over the pan-coating method are as follows:
a) irregular particles may be coated directly, b) loss of material is small, c) the process may be automated and does not require learning the "art" of coating, d) it is very rapid.

The present work is a study of the preparation of sustained-release granules coated by means of the fluid-bed technique. Salicylic acid and caffeine were selected as model drugs, while ethyl cellulose (EC) with polyethylene glycol (PEG) were representative of coating materials.

EXPERIMENTAL

Materials

Ethyl Cellulose, (EC), N-Type, had an ethoxyl content of 47.5-490% (Hercules Incorporated, Delaware, U.S.A.). Caffeine, Salicylic acid and Lactose were from Merck, Darmstadt, Germany and all were B.P. or U.S.P. grade. P.V.P., Arthur N. Thomas Company, Pa. U.S.A. Polyethylene glycol (PEG) 4000 and Calcium Orthophosphate, precipitated, were from B.D.H. Ltd., Poole, U.K.

METHODS

All granules were prepared by the wet-granulation method. The fraction of the drug passing through a 60 mesh sieve was used, together with either lactose or calcium phosphate as fillers and an aqueous PVP solution as binder. The wetted powder mixture was passed through 10 and 20 mesh sieves and the granules were oven-dried at 40^{o}.

Coating Experiments

The general construction of the apparatus is shown in Fig. 1. 100 gram quantities of the granules were introduced on to the wire mesh, the air flow was initiated by means of the pump, fluidizing the granules, and the heating unit was operated. Some five minutes were needed for the temperature in the vicinity of the coating region to reach the required experimental value, after which the coating solution

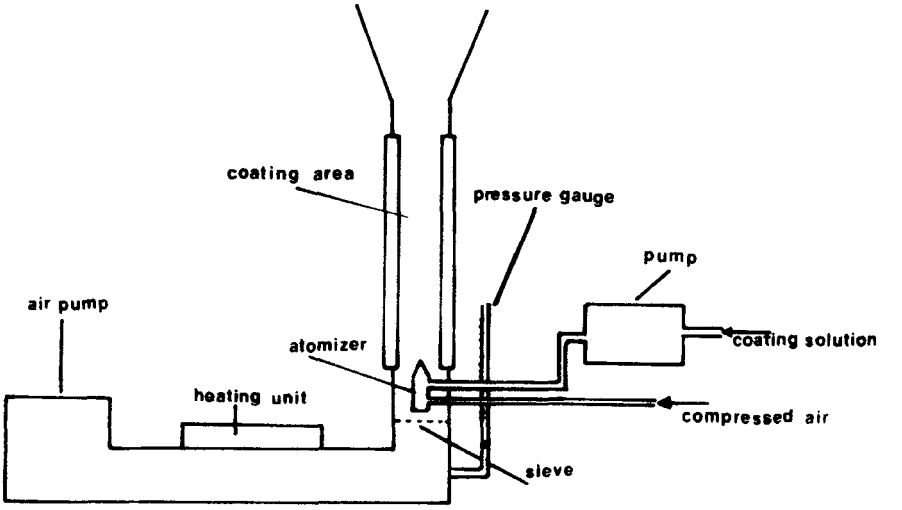

Fig. 1
General construction of the coating apparatus

was fed in and atomized. On completion of coating the granules were fluidized for a further 5 minutes to ensure complete removal of organic solvent. The coating solution used throughout contained PEG and EC in the ratio of 4:6 by weight in chloroform. Details of the coating experiments performed are summarized in Table 1; each experiment was repeated independently four times.

Granule Friability.

Friability was measured by prolonged fluidization of the coated granules in the apparatus. 100 gram samples were tested using the same fluidization conditions as in the coating experiments except for omission of the coating solution. After 30 minutes fluidization, the granules were passed through a 40 mesh sieve and the loss of weight was measured.

TABLE I

Summary of conditions used in coating experiments.

Conditions	Experiment	1	2	3	4	5	6	7	8
Temperature (°C)		30-40	30-40	30-40	50-60	30-40	30-40	30-40	room
Spray pressure (Atm)		1	2	3	3	3	3	3	3
Fluidization pressure[a]		8-11	8-11	8-11	8-11	8-11	8-11	8-11	8-11
Flow rate of coating solution (ml/h)		800	800	800	800	400	800	800	800
Coating solution concentration[b]		1.8	1.8	1.8	1.8	1.8	10	5	1.8

Measurement of release rate of active material from the coated granules.

Initial drug content was determined by extraction into water: 100 mg. quantities of the granules which had been previously crushed,were shaken with 150 ml water in 200 ml measuring flasks for some 5 minutes or sufficient time to ensure complete solution of the drug, after which they were diluted to volume. Samples of the solutions were filtered and their drug content determined spectrophotometrically (Unicam SP1800 U.V. Spectrophotometer-Pye-Unicam Ltd., England) at the maxima 273 nm for caffeine and 296 nm for salicylic acid.

Release rates were measured using banana-shaped extractors designed to enable the granules to be shaken continuously in a reciprocating apparatus at 37^{o}C during drug release and sampling. Volumes of 100 ml extracting fluid (water) were allowed to reach 37^{o}, 3 g quantities, accurately weighed, of intact granules were added, 2 ml samples of the fluid were removed at suitable intervals and diluted as required and the drug content was determined spectrophotometrically.

RESULTS and DISCUSSION

Granule Friability

The fillers tested in this work were lactose and calcium phosphate and the binders investigated were aqueous solutions of gelatin, acacia, starch and PVP. With both types of core, the best results were obtained with PVP, which produced granules disintegrating

rapidly in 2 to 5 minutes in water at room temperature, yet on the other hand responding well to the friability test.

During the fluid-bed coating process, the granules remain in a state of continuous suspension and agitation, in the course of which they undergo a large number of collisions with the container walls and other granules. Inadequate granule binding strength would lead to partial or total attrition. Losses of weight observed in the friability test ranged between 0.5 and 1.5% in the best formulated granules, and rose to 7 to 15% in acacia, gelatin and starch experiments.

Coating Properties

The permeability properties of EC films have been studied previously (10-11). It was shown that they constitute the physical barrier controlling drug release in certain sustained-release film products.

For use of films as a surface barrier, there is need to develop a coating technique for their application capable of yielding strong, stable, reproducible films of controlled thickness. The importance of the technology, as compared with that used in protective film coating, lies in the need for accurate control of the drug penetration rate during the prolonged release time over which the product is yielding active substance from the core reservoir. Since the drug content may amount to the equivalent of two or three doses, variablility of release rate could lead to serious deficiencies or overdosages, which would be particularly serious with drugs of low therapeutic index.

This led to the use of granules rather than tablets as cores in the present work, on the basis that the subdivision of the multidose would reduce the risk of massive release of drug in the event of partial breakdown or damage to the coat, which in the case of a coated tablet would lead to rapid total release.

The coating efficiency of the apparatus was examined on the basis of the following criteria:

a) non-blockage of the spray non-blockage of the spray nozzle

b) non-aggregation of the granules

c) homogeneity of the coating in each batch of granules

d) identity of coatings in repeated batches.

The first two factors are studied during the coating process itself, whereas the last two are most conveniently measured by means of drug release experiments performed on the coated granules. Results of coating experiments performed with variation of apparatus control parameters are summarized in Table II.

The following observations were made:

a) Temperatures of 50 to 60^{o} led to spray nozzle blockage due to rapid evaporation of the solvent during injection (see Expt.4).

b) At room temperature, the granules aggregated (see Expt. 8).

c) Spray pressures of 1 to 2 atm. gave spray-nozzle blockage, 3 atm. being optimal (see Expts. 1 and 2).

TABLE II

Summary of results of coating experiments

(For conditions see TABLE I).

Experiment	1	2	3	4	5	6	7	8
Blockage of Spray nozzle	+	+	-	+	-	-	+	-
	+	+	-	+	-	+	-	-
	+	+	-	+	-	+	+	+
	+	+	-	+	-	+	-	-
Granule aggregation	-	-	-	-	-	+	+	+
	-	-	-	-	-	+	+	+
	-	-	-	-	-	+	+	+
	-	-	-	-	-	+	+	+

d) Coating solution concentrations of 5 to 10% led to granule aggregation and sometimes to spray nozzle blockage as well (see Expts. 6 and 7).

e) The flow rate of the coating solution was not critical provided other parameters were optimized (see Expts. 3 and 5).

These results show that the efficiency of the coating process is controlled by three factors, viz. temperature, concentration of the coating solution and spray pressure.

At a temperature of 30° or higher the rate of evaporation of chloroform, the coating solvent, was excessive during injection, leading to deposition of EC in the nozzle with progressive blockage of the holes. On the other hand, at room temperature the evaporation rate was reduced to a level at which the contact time between colliding granules and the adhesivity of the wet coat were such that fusion of the granules occurred.

With reduction of spray pressure below 3 atm., cold coating solution spread over the nozzle forming a liquid film which, on partial evaporation, caused blockage.

The concentration of the coating solution affects its viscosity directly and at 5 and 10% the viscosity is high, enhancing both spray blockage and adhesion processes.

Flow rate of coating solution is apparently without influence provided that the spray pressure is sufficient to form and project aerosol droplets of the coating solution at a velocity ensuring their rapid movement away from the spray nozzle, assuming the temperature to be such that the rate of solvent evaporation at the nozzle surface is negligible.

It should be borne in mind that the optimal conditions defined for the apparatus described will differ in fluid-bed spray coaters of other dimensions and designs.

Coating Homogeneity and Reproducibility

A typical curve showing caffeine release from coated granules as a function of time is shown in Fig. 2. Ranges indicated by vertical lines show the quantity released each hour and represent four runs, carried out on four samplings of the particular batch. The maximum deviations observed in the tests were ± 4.5% of the mean quantity of drug released, which was low enough for the coatings to be considered uniform and the batches homogeneous.

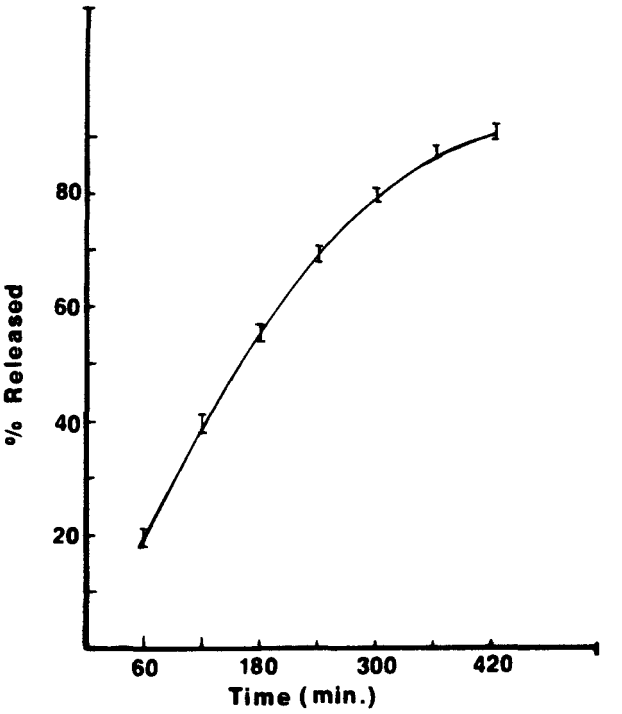

Fig. 2
Typical curve of drug release from coated granules

Coming finally to the major question of batch to batch reproducibility of sustained-release coated products, some results of release rate studies on caffeine and salicylic acid granules are summarized in Table 3. They are presented in the form of first order rate constants which characterize release kinetics from coated granules and are the subject of a separate communication.

The release rate constants represent the means of four coating experiments. Their values and standard deviations indicate that reproducible release rates were obtained from repeated batches.

TABLE III

Release rate constants of caffeine and salicylic acid from coated granules.

Experiment	Release constant	Standard deviation	Coefficient of variation
1[e]	5.5×10^{-3}	0.11	2.48
2[d]	3.1×10^{-3}	0.10	3.18
3[e]	2.5×10^{-3}	0.14	5.64
4[f]	3.3×10^{-2}	0.08	3.00

FOOTNOTES

a) in scale units at the fluidmeter.

Manostat Corp. Tr. Flat US Pat. 2731830.

b) units, %w/v solid in chloroform (PEG: EC ratio 4:6).

c, d, e) 3% caffeine granules coated by 400, 600 and 800 ml coating respectively.

f) 3% salicylic acid coated by 600 ml of coating solution.

g) average of 4 coating experiments.

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