AN INVESTIGATION OF THE PROCESS OF APPLYING PROTECTIVE COATINGS TO TABLETS FROM AQUEOUS SOLUTIONS OF POLYMERS IN A FLUIDIZED-BED APPARATUS

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UDC 615.453.62.014.6

To protect medicinal substances from the action of unfavorable external factors, to decrease their irritant action when taken, and to achieve the directed resorption of the drug in the organism, solid forms of medicinal substances (tablets, granules) are covered with special coatings. For this purpose dragee-making pans are usually used, but, in spite of a whole series of improvements [1, 2], these are extremely imperfect and have a low productivity because of the poor indices of heat and mass exchange and, consequently, of moisture elimination from unit volume of the apparatus. A basically new solution for the intensification of the process of covering solid forms with film-like coatings was introduced by Wurster, who used a fluidized bed for this purpose [3]. Because of the high coefficient of effective thermal conductivity and heat transfer from the fluidizing agent to the solid forms being coated, the duration of the process is shortened 5- to 6-fold as compared with dragee-formation in pans. The fluidized-bed apparatuses also have a number of other advantages in the performance of processes of heat and mass exchange [4-7].

A model of a pilot-plant apparatus for providing tablets with a film-like coating in a fluidized bed has been designed and manufactured in the Special Planning and Design Bureau of the Medicinal Industry

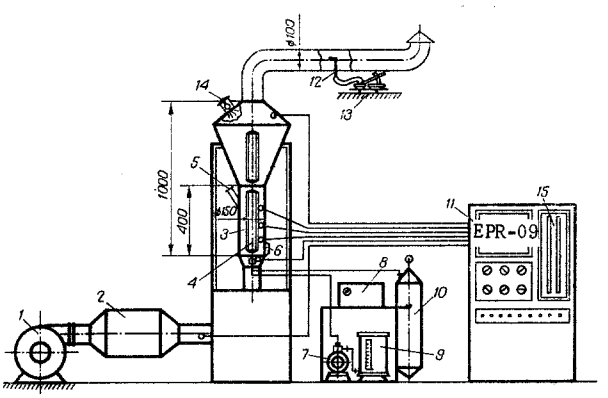

Fig. 1. Sketch of the apparatus for depositing protective coatings on tablets in a fluidized bed. 1) Fan (VVD-5); 2) electric heater (10 kW); 3) apparatus; 4) nozzle; 5) charging aperture; 6) discharge of tablets; 7) metering pump; 8) compressor (UK-40-2); 9) tank with a solution of the polymer; 10) receiver; 11) control console; 12) pneumometric tube; 13) micromanometer (MMN-200); 14) illumination; 15) draught head meter (TDZh).

Leningrad Scientific-Research Institute of Antibiotics. Special Planning and Design Bureau of the Medicinal Industry, Leningrad. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 7, No. 8, pp. 46-49, August, 1973. Original article submitted March 17, 1972.

TABLE 1. Technological Parameters of the Process of Depositing a Filmlike Coating of the Ammonium Salt of Acetylphthalylcellulose on Tablets in a Fluidized-Bed Apparatus

Preparation	Geometrical characteristics of the tablets							Technological parameters of the process												
	average weight (in g)	diameter (in mm)	height (in mm)	height at the edge (in mm)	radius of curvature (in mm)	height of a segment (in mm)	volume (in mm³)	surface (in mm²)	specific surface (in m²/kg)	charge (in kg)	diameter of the apparatus (in m)	height of the stationary bed (in m)	height of the fluidized bed (in m)	porosity of the fluidized bed	throughput of the nozzle (in kg/h)	temperature of the bed (in °C)	velocity of the air (in m/sec)	loading of the grid with moisture (in kg/m²·h)	ratio of the weight of the coating to the weight of the tablet (in %)	degree of uniformity (in ±%)	concentration of the polymer solution (in %)	duration of the process (in h)
Sugar	0,125	5	4,5	2,5	3,6	1,0	90	85	0,678	2	0,15	0,15	0,300	0,7	1,0	52	3,7	56,5	5	0,5	5	2
	0,25	9	5,5	2,5	7,5	1,5	420	211	0,842	1,2	0,15	0,095	0,230	0,75	0,72	50	5,5	40,6	6	3	5	2
Methionine	0,15	7	4,5	2,0	5,5	1,25	194	131	0,871	1,8	0,15	0,13	0,290	0,73	0,9	56	4,7	50,5	7	8	5	2,8
Apressin	0,24	9	6,5	2,0	5,6	2,25	335	215	0,900	0,25	0,082	0,06	0,160	0,72	0,28	52	5,4	530	7	6	5	1,25
Nystatin	0,25	9	6,5	2,5	5,6	2,0	360	223	0,928	1,3	0,15	0,10	0,220	0,64	1,04	50	5,6	58,5	8	5	5	2
Sodium salt of nystatin	0,4	9	6,5	2,5	6,0	2,0	377	228	0,569	1,7	0,15	0,12	0,260	0,72	1,0	60	5,7	56,2	8	8	7	2
Boric acid	0,55	12	7,0	2,0	8,5	2,5	651	340	0,620	1,5	0,15	0,125	0,280	0,96	1,28	60	6,0	72,6	18	3	7	3
Sodium p-aminosalicylate	0,5	10	7,5	3,0	6,7	1,75	378	270	0,540	0,25	0,082	0,06	0,20	0,82	0,2	47	5,8	379	10	4	5	2,5
Streptomycin																						

and it has been set up and trials have been successfully performed in the Leningrad Scientific-Research Institute of Antibiotics. The working chamber of the apparatus was calculated for a load of 2 kg of tablets (see Fig. 1).

In view of the deficiencies of the method of applying polymeric coatings by means of organic solvents, we have attempted to develop the technology of depositing such coatings on tablets from aqueous solutions. The conditions for depositing the polymeric coatings were developed in cylindrical apparatuses with diameters (D_a) of 0.082 and 0.150 m on samples of double-convex tablets with diameters of 5, 7, 9 and 12 mm (tablets of aspirin, methionine, apressin, sodium p-aminosalicylate, nystatin, the sodium salt of nystatin, and streptomycin. The concentrations of the aqueous solutions of polymers used (water-soluble cellulose ethers, shellac) were varied from 2 to 10% according to the molecular weight of the polymer.

As the spraying device we used a penumatic nozzle with internal mixing. The degree of dispersion was controlled by changing the ratio of feeds of solution (by a metering pump) and air passing into the sprayer. In the experiments, the height of the nonfluidized bed of tablets (H), the rate of filtration of the air, the consumption of the polymer solution, and the temperature of the bed were varied. Simultaneously, the influence of various parameters on the kinetics of the process and on the quality of the film coatings was investigated. The process was studied in apparatuses made in two modifications: a) with a cylindrical working chamber (D_a = 0.150 m) and b) with a conical working chamber (diameter of the diffuser 0.075 m, apical angle of the cone 30°). On using the conical working chamber (fountaining conditions) it was found that this variant of the apparatus led to a high percentage of reject material (broken tablets, abrasion). Subsequently, therefore, all the work was performed in the apparatus with a cylindrical working chamber. The hydrodynamic conditions of the process were developed with various gas-distributing grids, which consisted of perforated plates 2 mm thick. To decrease the abrasion of the tablets in the coating process, the whole of the internal part of the working chamber and the grid was lined with fluorinated plastic. The nozzle was arranged vertically in the center of the grid at a height corresponding to (0.3-1.0) H. When the nozzle was arranged at an angle of 30° to the horizontal plane, nonuniform sprinkling of the surface of the tablets and the sticking of the solution of the polymer to the walls of the apparatus took place.

The tests performed showed the optimum height of the nonfluidized bed of tablets [(0.6-0.85) D_a] at which "plug formation" and pulsations in the bed were excluded. A velocity of the fluidizing agent (heat carrier) two to three times greater than the critical velocity of fluidization ("fluidization number") ensured the thorough mixing of the tablets. For brittle and readily-abraded tablets the initial stage of creating the filmlike coatings must be performed at fluidization numbers of 1.1-1.5. The rate of sprinkling the layer was 0.6-1.2 kg/h, which corresponded to a moisture load on the grid of 34-88 kg/m^2·h. The temperature of the air under the grid was 50-75°C and that in the bed was 40-65°C, respectively.

In those cases where the tablets contained readily water-soluble or hygroscopic medicinal substances (salicylates, antibiotics, vitamins), a hydrophobic layer was first created on the tablets before the deposition of the coatings by spraying them with aqueous solutions. For this purpose various waxy-fatty materials (plant waxes, beeswax) preventing the contact of moisture with the preparation were used. The hydrophobic layer also prevented the destruction of the surface of the tablets, decreased the permeability of the water-soluble coatings, and improved the external appearance of the coating. During the investigations, tablets were obtained with decorative coatings of hydroxypropylmethylcellulose, methylcellulose, the sodium salt of carboxymethylcellulose, and also with enteric-soluble coatings from aqueous solutions of the ammonium salt of acetylphthalylcellulose and shellac. The fact that the tablets complied with the requirements of GF X [State Pharmacopoeia of the USSR, Xth Edition] was confirmed on a PRT-2 instrument for determining the disintegrability of tablets, in artificial gastric juice and in artificial intestinal juice. In the case of the enteric-soluble coatings, the tablets did not disintegrate in the synthetic gastric juice for more than 2 h and disintegrated in the synthetic intestinal juice in less than 30 min. Because of some penetration of the polymeric films their thickness was determined from the physicochemical properties of the substance of the tablets and of the polymer used for the coatings (see Table 1).

The good reproducibility of the parameters of the process on passing from the apparatus with D_a = 0.082 m [8, 9] to the model of a pilot plant (D_a = 0.150 m) must be noted. The average time of an operation was 2 h.

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