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SHORT COMMUNICATION

TABLETING OF FLOATING PELLETS WITH VERAPAMIL HYDROCHLORIDE: INFLUENCE OF TYPE OF TABLET PRESS

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Compression of powders and granules into cohesive mass is a complex and irreversible dynamic process. Mechanically, the compaction process consists of progressive strain on the powder mixture confiding it to a final volume and porosity. Compression of pellets into the tablet form is more complex. It should be taken into consideration not only pellets properties (their compressibility, shape, porosity, mechanism of compression, brittle or plastic characteristic) and polymer film properties but also powder mass – matrix of tablet (their mechanism of compression, compressibility) (1-3).

The aim of this paper was to evaluate the influence of type of tablet press on the tableting of floating pellets with verapamil hydrochloride and releasing rate of active substance. Presented evaluation is the continuation of studies concerns tableting of the floating pellets (4-6).

EXPERIMENTAL

Materials

Crospovidon (Kollidon CL, BASF, Ludwigshafen, Germany), lactose (Ubichem, Eastleight, UK), microcrystalline cellulose (MCC) (Avicel® PH 101, mean particle size 50 μm and Avicel® PH 102, mean particle size 100 μm, FMC, Brussels, Belgium), magnesium stearate (Riedel-de Haen, Seelze, Germany), polyacrylate aqueous dispersion (Eudragit NE 40D, Evonik, Degussa, Darmstadt, Germany), polyethylene glycol (Macrogol 6000S, Fluka Chemie, Buchs, Switzerland), povidone K-30 (PVP K-30) (Kollidon K-30 BASF, Ludwigshafen, Germany), sodium hydrocarbonate (Merck, Darmstadt, Germany), talc (Ph. Eur.), verapamil hydrochloride (VH) (Recordati, Milano, Italy).

Statistical analysis of the results was performed with Microsoft Excel (Microsoft, Washington, USA) and Statistica v 7.1 (StatSoft, Inc., Tulsa, USA).

Preparation of floating pellets with verapamil hydrochloride

Pellets' cores were prepared by extrusion and spheronization method. On the basis of the initial experiments the composition of cores was determined: VH – 20.0%; sodium hydrocarbonate – 20.0%, MCC (Avicel® PH 101) – 43.4%, lactose – 12.3%, PVP K-30 – 4.3%. The wet mass was extruded in Caleva Extruder 25 (Caleva, Dorset, UK). Then, the obtained extrudate underwent spheronization process in Caleva Model 120 apparatus (Caleva, Dorset, UK), spheronization time 4 min, and rotation speed 1500–1600 rpm. Wet cores were dried in a blow-dryer at 40°C for 12 h and then separated into fractions.

The composition of the coating mixtures was as follows: Eudragit NE 30D – 43.1%, talc – 7.0%, macrogol 6000 – 1.3%, distilled water – 48.6%. Core coating (200 g) was prepared in Uni-Glatt apparatus (Glatt, Systemtechnik, Dresden, Germany): incoming air temperature of 40°C, outgoing air temperature of 30°C; air pressure in spray nozzle of 2 bar and peristaltic pump feeding rate of

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3 mL/min. Pellets were dried in a blow-dryer at 40°C for 24 h precisely.

Preparation of tablets, tableting of floating pellets

On the basis on initial studies the optimal tablet formulation was selected. The consistent of tablet formulation was as follows: floating pellets with VH – 43 %; Avicel PH 102 – 12.7 %; macrogol 6000 – 34.3 %; Kollidon CL – 9.5 %; magnesium stearate – 0.5 %. The pellets and powder were blended in bin tumbler (Zanchetta type: Canguro, Lucca, Italy) 10 min with 12 rpm, after magnesium stearate addition 5 min additionally.

Compression was carried out with the use of single stroke tablet press (Korsch EK0, Korsch, Berlin, Germany), rotary tablet press (Erweka RTP-D8, Erweka, Hensenstamm, Germany) and industrial rotary tablet press (Korsch XL 200, Korsch, Berlin). The single stroke tablet press was equipped to permit measurement of the pressure force. Tablets weighing 0.55 g were compressed by means of round punches (∅ = 12.0 mm, R = 20 mm). In single stroke press forces 6, 12 and 18 kN were used, in the case of rotary presses 6 or 8, 12, 18 kN and additionally, in industrial press 35 and 45 kN compression force were used.

***In vitro* drug release test**

The determination of release rate of VH from pellets and tablets formulations was performed using the Ph. Eur. paddle apparatus, Erweka DT-800 (Erweka, Hensenstamm, Germany), 75 rpm, medium – hydrochloric acid (0.1 mol/L) 750 mL, at temperature of 37 ± 0.5°C, The concentration of VH in the samples was determined spectrophotometrically at 278 nm, after dilution. Spectrophotometer JASCO V-530 (Jasco Corporation, Tokyo, Japan) was used for investigation.

RESULTS AND DISCUSSION

Pellet cores were obtained by means of extrusion-spheronization. Microcrystalline cellulose (MCC) constitutes almost 50% of their content. MCC is flexible enough to form spherical cores, undergoes deformation easily and constitutes a good binder (7). The cores obtained at the presence of MCC have suitable properties, which are a factor controlling the degree of pellet deformation (8). As a polymer, used to achieve the prolonged release of the model drug – verapamil hydrochloride (VH), Eudragit NE was selected. This polymer is characterized by elasticity and resistance to deformability (9).

The main ingredient of tablet formulation, beside pellets coated with VH (43%) and MCC (12.7%), was PEG 6000 (34.3%), moreover, 9.5% of Kollidon CL and 0,5% of magnesium stearate were added. MCC and PEG 6000 are characterized by good plasticity and susceptibility to deformation during compression (2, 10, 11).

It was found the increase of releasing rate of VH from pellets tableted by eccentric press with 6 kN (S 6 kN) compression force (Fig. 1). It was connected with deformation, fracture and the final

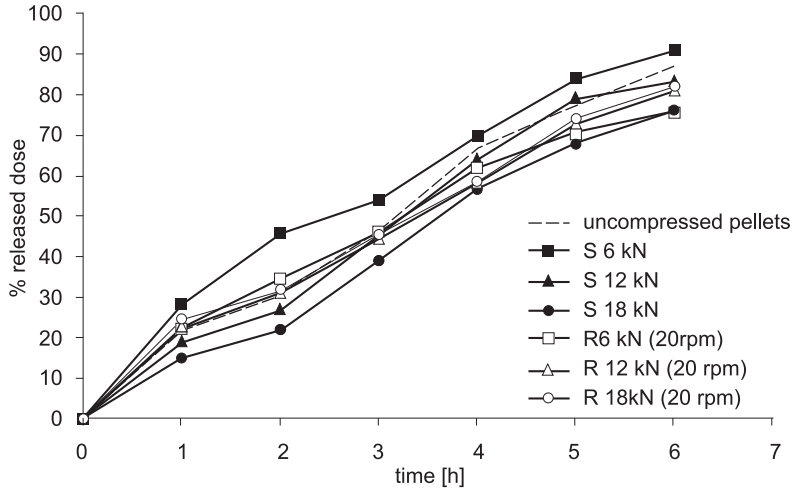

Figure 1. *In vitro* verapamil hydrochloride release from uncompressed pellets with comparison to tablets, compressed by a single stroke tablet press (S) and a laboratory rotary tablet press (R) with different compression force

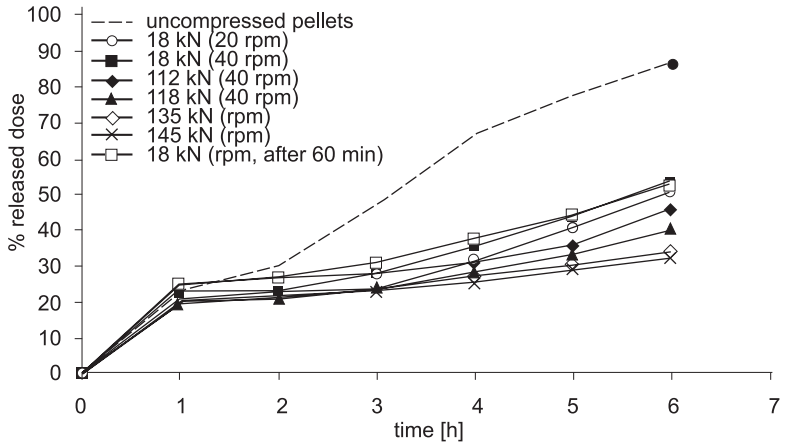

Figure 2. *In vitro* verapamil hydrochloride release from uncompressed pellets with comparison to tablets compressed by the industrial rotary tablet press (I), with different compression force, and rotation speed of turret

increase of permeability of Eudragit NE film, caused by unsymmetrical force impact. The increase of compression force to 12 and 18 kN (S 12 kN and S 18 kN, respectively) caused a slight decrease of releasing rate (Fig. 1).

The release of VH from pellets compacted by laboratory rotary tablet (R) was characterized by lower rate, especially after 3rd hour of releasing test. In this case, it was no statistically significant differences between releasing from pellets compressed with 6, 12 or 18 kN compression force ($p = 8.7 \cdot 10^{-4}$, one way ANOWA test).

The mechanism of drug release from insoluble in water polymer, Eudragit NE, coated drug delivery is believed to be a diffusion controlled process defined by Fick's law. Diffusivity is depended on porosity factor and tortuosity factor of diffusion membrane (12). These factors can be changed by mechanical influence, e.g., compression.

During the compression process in industrial tablet press the "extra pressing" of polymer membrane to pellets' cores have taken place. As the result, the diffusivity of the polymer film was changed. It was shown during releasing test, where much slower release rate is visible, in contrast to uncompressed pellets and compressed by other type tablet presses (Fig. 2). Taking into consideration different parameters of compressing (compression force 8 – 45 kN, rotation of turret 20 – 40 rpm) it should be assumed, that the release rate decreases with the increasing of compression force and rotation speed of the turret. The increase of rotation speed of turret causes a decrease of compaction time. The rearrangement phase of compression is reduced. In this case much more significant influence of tablets matrix on pellets is observed.

It was found, that the release rate wasn't changed during one hour's duration of tableting process series I – 8 kN with speed 20 rpm (Fig. 2). Ravis and Chen suggested that incorporation of a large amount of PEGs may cause capping following compression (13). In our case, any tendencies to lamination, capping or picking were not observed.

Single station eccentric press is still used to preformulation studies and to acquire the stress/strain data. In this type of machine only the upper punch penetrates the die to compress the material, whilst the position of the lower punch does not change (except ejection) during the tablet formation. For this reason, the unsymmetrical influence of compression force is observed. Anyway, an eccentric press cannot reproduce the compression conditions occurring on a rotary multistation press (especially industrial type), where both of punches penetrate the die.

All these differences between the two types of machines depend on the duration of the dwell time.

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