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Note

Compressibility of floating pellets with verapamil hydrochloride coated with dispersion Kollicoat SR 30 D

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Abstract

The purpose of this study was to work out a method of compression of floating pellets with verapamil hydrochloride (VH) in a dose of 40 mg. It was assumed that this form should reside in the stomach floating for several hours and gradually release the drug in a controlled way. Compression of pellets into tablets, being a modern technological process, is much more perfect than enclosing them in a hard gelatin capsule. Kollicoat® SR 30 D was selected for coating. In experiments three plasticizers were examined—propylene glycol, triethyl citrate and dibuthyl sebecate (all at concentration of 10%). It was found that VH release from pellets coated by the films of the same thickness (70 μm), however, containing plasticizers is considerably different. Pellets were prepared by wet granulation of powder mixture, spheronization of the granulated mass and coating of the cores with a sustained release film. Two kinds of cellulose, microcrystalline and powdered, and sodium hydrocarbonate were the main components of pellet core. Proper pellet coating film thickness, ensuring obtaining desirable VH release profile and flotation effect, was defined. X compositions of tablets with pellets were examined in order to obtain formulation, from which VH release would mostly approximate pellets before compressing. The best formulation was evaluated taking into account the effect of compression force an tablet hardness and friability, and pellet agglomeration and flotation. Tablet cross-section photographs were taken confirming necessary coating film thickness preventing their deformation caused by compressing into tablets.

Keywords: Verapamil hydrochloride; Floating pellets; Coating compressibility; Plasticizers; Controlled release

1. Introduction

Pellets are spherical granules for oral application used mostly commonly in a form of a hard gelatin capsule. It is an example of a multiparticulate drug, in which dose is divided into several reservoirs [1].

Compression of pellets into tablets is a modern technological process. However, it is much more ideal than enclosing them in a hard gelatin capsule [2]. A larger drug dose can be contained in the tablet. The method of dosing is also easier because of the possibility of dividing the tablet in any way. The method of preparing is simpler, cheaper, more efficient, and it does not require complex control of the process of capsules filling with pellets. Compressibility of pellets ensures also lower risk of copying the technology process of the drug form by a competing producer.

Coating of the pellets with a film possessing proper flexibility and thickness along with selecting of reasonably flexible core of pellets is a key issue as regards to pellets compressibility. Proper proportion of pellets and pharmaceutical filler (binding excipients in the tablet mass) should be maintained.

The purpose of this study was to work out a method of compression of floating pellets containing verapamil hydrochloride (VH) in a dose of 40 mg. According to the assumption that the tablet should disintegrate in the stomach into undeformed pellets floating in this environment for 5–6 h, releasing the drug would be in a controlled way.

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The better solubility of VH in acidic environment of the stomach may result in a larger amount of the drug absorbed and its higher concentration in plasma.

In the present study, obtaining of VH release rate from compressed pellets resembling ones before compressing was assumed. Modification of VH release rate from compressed pellets was achieved by means of proper composition of Kollicoat® SR 30 D coating mixture, film thickness and the choice of other excipients in the tablet.

2. Materials and methods

2.1. Materials

Verapamil hydrochloride (Recordati, Milano, Italy), sodium hydrocarbonate (Merck, Darmstadt, Germany), microcrystalline cellulose (Avicel® PH 101, mean particle size 50 μm, FMC, Brussels, Belgium), (Avicel® PH 102, mean particle size 100 μm, FMC, Brussels, Belgium), powdered cellulose (Arbocel® P 290, particle size 70 μm, IRS, Rosenberg, Germany), lactose (Ubichem, Eastleight, United Kingdom), Povidone K-30 (Flukachemie, Steinheim, Germany), Kollicoat® SR 30 D (BASF, Ludwigshafen, Germany), propylene glycol (Merck, Darmstadt, Germany), triethyl citrate (Lancaster, Morecambe, United Kingdom), dibutyl sebacate (Flukachemie, Steinheim, Germany), Kollidon® VA 64 (BASF, Ludwigshafen, Germany), sorbitol (POCh, Gliwice, Poland) mannitol (POCh, Gliwice, Poland), Kollidon® Cl (BASF, Ludwigshafen, Germany), Ludipress® (BASF, Ludwigshafen, Germany), Vivapur® 12 (IRS, Rosenberg, Germany), magnesium stearate (Riedel-de Hean, Seelze, Germany), talc (Ph. Eur.).

Statistical analysis of the results was performed with Microsoft Excel (Microsoft, Washington, USA).

2.2. Preparation of floating pellets cores with VH

Pellets were prepared by wet granulation of powder mixture, spheronization of the granulated mass and coating of the cores with a sustained release film. On the basis of the initial experiments the composition of cores was determined: VH-20.0%; sodium hydrocarbonate—20.0%, Avicel® PH 101—10.0%, Arbocel® P 290—33.4%, lactose—12.3%, Povidone K-30—4.3%. The four first substances were carefully mixed in a mortar and moistened with portions of 5% water solution of Povidone K-30 (up to 85 g/100 g of the powder mixture). The moist mass was rubbed through a metal sieve (Retsch, Hann, Germany) having 1.25 mm mesh diameter. Then, the obtained granulate underwent spheronization process.

Spheronization process was performed in Caleva Model 120 apparatus (Caleva, Dorset, UK). Spheronizer shield rotation speed measured by means of tachometer Caleva was 1200–1300 rpm, spheronization time of a 20-g portion of granule was 4 min. Wet cores were dried in a blow-dryer at 40 °C for 12 h and then separated into fractions of 0.8–1.25, 1.25–1.6 and 1.6–2.0 mm by means of a sieve set. Pellets of 1.25–1.6 mm in diameter comprised the largest fraction (about 60%) in the given conditions of spheronization.

2.3. Coating of the pellets cores

Films A–E possessing different thickness and kind of comprised components were prepared on the basis of Kollicoat® SR 30 D. The composition of the coating mixtures is collected in Table 1. The preparation procedure of coating mixtures was performed as follows. The appropriate amount of Kollicoat® SR 30 D was introduced to a beaker with a magnetic stirrer. Next, portions of water were added during stirring process. At the same time Povidone K-30 was dissolved parallel in the water earlier. Then, proper plasticizers, propylene glycol (PPG), triethyl citrate (TEC) and dibutyl sebacate (DBS) were added and was stirred for 2 h. 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; incoming air pressure of 6 bar, air pressure in spray nozzle of 2 bar and peristaltic pump feeding rate of 3 ml/min. Pellets were dried in a blow-dryer at 40 °C for 30 h precisely.

Pellet coating film thickness was designated after cross-sectioning with a scalpel, 10 randomly selected pellets from each formulation. The received hemispheres were placed under a microscope (Motic, Wetzlar, Germany) coupled with a digital camera (Panasonic, Osaka, Japan) and coating film thickness was measured. Average value was calculated on the basis of the received results.

2.4. Compressibility of floating pellets containing VH

Pellets 1.25–1.6 mm in diameter with film A (20 and 35 μm) and film B (50 μm) were selected to study the optimal compression conditions. Compression was carried

Table 1
Composition (%) of coating mixtures A–E

Substance	Coating mixtures				
	A	B	C	D	E
Kollicoat SR 30 D	50.8 (72.0[a])	50.8 (60.0[a])	48.2 (45.0[a])	48.2 (45.0[a])	48.2 (45.0[a])
Propylene glycol	2.5 (12.0[a])	2.5 (10.0[a])	3.2 (10.0[a])	–	–
Triethyl citrate	–	–	–	3.2 (10.0[a])	–
Dibutyl sebacate	–	–	–	–	3.2 (10.0[a])
Povidone K-30	–	4.0 (16.0[a])	11.3 (35.0[a])	11.3 (35.0[a])	11.3 (35.0[a])
Talc	3.5 (16.0[a])	3.5 (14.0[a])	3.4 (10.0[a])	3.4 (10.0[a])	3.4 (10.0[a])
Water	43.2	39.2	33.9	33.9	33.9

[a] Calculated on dry mass.

Table 2
Composition (%) of tablets' masses with floating pellets coated film A (I–V) and B (VI–X)

Substance	Formulations									
	I	II	III	IV	V	VI	VII	VIII	IX	X
Pellets VH (40 mg)	38.2	38.2	38.2	38.2	38.2	38.2	38.2	38.2	38.2	38.2
Avicel PH 101	13.5	–	51.3	51.3	–	–	–	–	–	–
Avicel PH 102	–	13.5	–	–	13.5	13.5	–	–	–	–
Kollidon VA 64	–	–	–	3.0	–	–	–	–	51.3	–
Sorbitol	–	–	–	–	37.8	–	–	–	–	51.3
Mannitol	37.8	37.8	–	–	–	37.8	–	–	–	–
Ludipress	–	–	–	–	–	–	51.3	–	–	–
Vivapur 12	–	–	–	–	–	–	–	51.3	–	–
Kollidon Cl	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

out with the use of laboratory Korsch tableting machine (Korsch EK0, Berlin, Germany). The device was 'home-med' modernized to enable the measurement of the pressure force. Tablets weighing 0.55 g were compressed by means of spherical punches (12.0 mm in diameter) with the use of pressure of 12 kN. It was assumed that in a single tablet pellets contain 40 mg of VH. Composition of tablet masses of 250 g is presented in Table 2.

2.5. In vitro drug release test

The measurement of release rate of VH from pellets and tablets formulations was performed using the Ph Eur paddle apparatus, Pharma Test Model PTWS-3 (Pharma Test, Hainburg, Germany). Vessels were filled with 750 ml of hydrochloric acid (0.1 mol/l) at temperature of 37 ± 0.5 °C. The concentration of VH in the samples was determined spectrophotometrically at 278 nm. Spectrophotometer JASCO V-530 (Jasco Corporation, Tokyo, Japan) was used for investigation. For a given pellet formulation, in vitro drug release test was repeated five times.

2.5.1. Pellet flotation starting time measurement

After filling five beakers of the apparatus (p. 2.5) with hydrochloric acid (0.1 mol/l) and setting temperature, certain formulation pellets were added to each beaker. Pellets should be found in the lowest point of the beaker bottom curve, under the rotation axis of the stirring apparatus. Consequently, by means of stop-watch, the time was measured after which most pellets will start flotation. The average from five notations was accepted as final result.

2.6. Physical properties of tablets

2.6.1. Determination of uniformity of single tablet mass

Determination of uniformity of single tablet mass was performed according to USP 27.

2.6.2. Determination of uniformity of VH content in tablets

Uniformity of VH content was determined in 10, selected at random tablets of one series. The contents of VH in each tablet should be comprised between 85 and 115% of average contents.

2.6.3. Determination of tablets resistance to crushing (hardness of tablets)

Determination of tablets resistance to crushing was tested with the use of automatic hardness tester type TBH 20 (Erweka, Hensenstamm, Germany). Resistance to crushing was determined for 10 tablets randomly selected. Hardness of tablets was determined calculating hardness factor described by the following equation

$$T = \frac{P_{\max}}{2rh}$$

where

$P_{\max}$ force needed to crash a tablet (kG)
r tablet's radius (mm)
h tablet's thickness (mm)

2.6.4. Tablets friability

Friability of uncoated tablets was performed according to USP 27.

3. Results and discussion

The idea of floating pellets was realized taking advantage of change in physical properties of the drug from after its passing to the acidic environment of hydrochloric acid in vitro or to the acidic stomach environment in vivo. Thus sodium hydrocarbonate was added as a component of the core of the pellets. This substance after reacting with hydrochloric acid, creates carbon dioxide whose bubbles adsorb on the surface of the spherical core of the pellets and cause their floating in the fluid in vitro or in vivo [3]. Increased bioavailability of floating pellets containing VH, enclosed in a gelatin capsule in comparison to a conventional tablet was confirmed in our previous study [4].

It is most essential in preparing pellets for compression to avoid film damage and deformation during that process. The film is an element modifying VH release from the core.

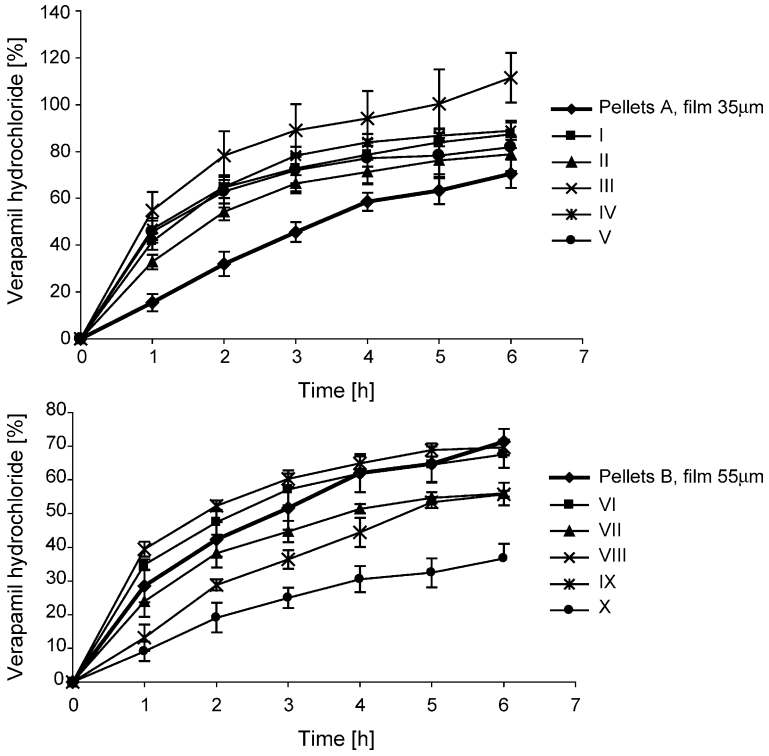

Fig. 1. In vitro verapamil hydrochloride release from pellets with film A (35 μm) with comparison tablets I–V and from pellets with film B (50 μm) and tablets VI–X.

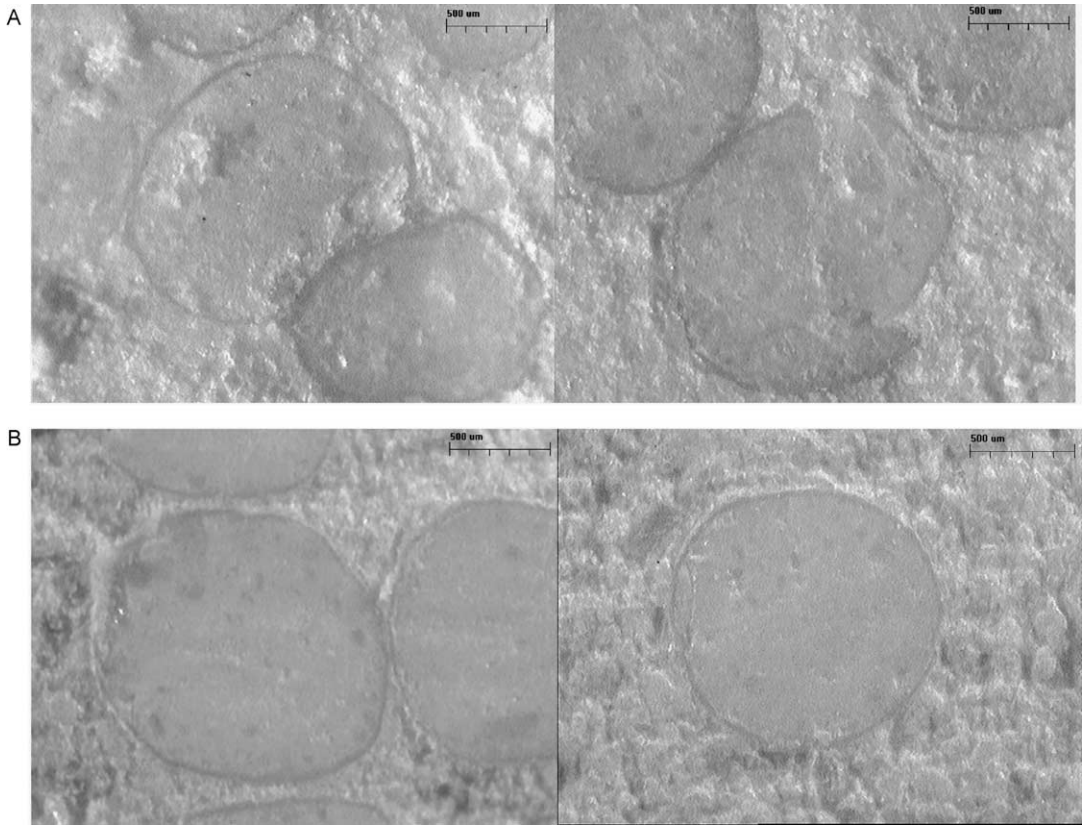

Fig. 2. Cross-sections of tablet of formulation III, IV (A) and VI (B).

Film damage during compressibility could change drug release rate. Therefore, in selecting polymer for coating, not only its diffusion properties but also physical properties, namely resistance to compressing, were taken into account [5].

On the basis of data from literature [6], Kollicoat® SR 30 D—polyvinyl acetate dispersion (27%) stabilized with Povidone (25%) and sodium laureth phosphate (0.3%) were selected for coating. Those data indicated that this kind of dispersion can ensure creating of possessing film having proper resistance properties [7]. Composition of coating mixtures is presented in Table 1. PPG, TEC and DBS play the role of plasticizers and Povidone is a porophore.

Pellets having 35 or 50 μm thick film settled on the bottom of the beaker and then, as a result of hydration and film swelling, carbon dioxide vesicles got out raising pellets to the surface of the liquid. Those experiments three plasticizers were examined, PPG, TEC and DBS. It was found that VH release from pellets coated with films of the same thickness (70 μm) but containing different plasticizers is considerably different. With a such film thickness the amount of released VH for the whole formulation appeared to be too small. DBS and TEC slow down diffusion in the highest degree. DBS and TEC, which in contrast to PPG have low solubility in water, slow down diffusion to the greatest degree. DBS and TEC solubility in water in 20 °C amounts to 0.01 and 5.5–6.3% (mV), respectively [8].

Therefore, VH pellets with film A (35 μm) and B (50 μm) with PPG as plasticizers were selected for compression process.

Data from literature [9], indicating that apart from pellets, more than 20% of components should be included. Content of tablet masses with floating pellets comprising VH is presented in Table 2. Substance possessing strong swelling properties—Kollidon® CL in flotation drug form is indispensable because the tablet has to disintegrate quickly into undeformed pellets, which next flow up and release VH in a controlled way.

Compressibility of all tablet mass formulations proceeded properly. Sticking of tablets to punches or their opercularization was not observed. Obtained tablets had a smooth surface, on which quite regularly distributed darker points showing pellets location were visible.

In the case of formulations I–V, tablets (Fig. 1), pellets A with film of (35 μm) thickness appeared to be too small and most probably deformed as a result of compressing. This is also confirmed by the microscopic inspection of the tablets III and IV cross-section (Fig. 2A). Therefore, VH release from tablets is considerably faster than from non-compressed pellets. Film damage may also have occurred as a result of core deformation caused by pressure force. Increasing pellets B film (50 μm) in a greater degree prevents its damage caused by compressibility (formulation VI–X, Fig. 1). Formulation VI with Avicel® PH 102, mannitol and Kollidon® CL used as swelling agent appeared to be the most appropriate tablet mass for floating pellets. The profile of VH release from those tablets was identical to non-pressed pellets. It proves that most probably neither core and film nor pellets were considerably damaged as a result of compression. This is also confirmed by the picture microscopic inspection of the tablet VI cross-section (Fig. 2B). Kollidon® VA 64 and sorbitol in formulations IX and X proved to be the strongest binders. Those tablets do not disintegrate into single pellets but into their agglomerates consisting of 8–10 units. Therefore, the amount of released VH was considerably smaller than from non-compressed pellets.

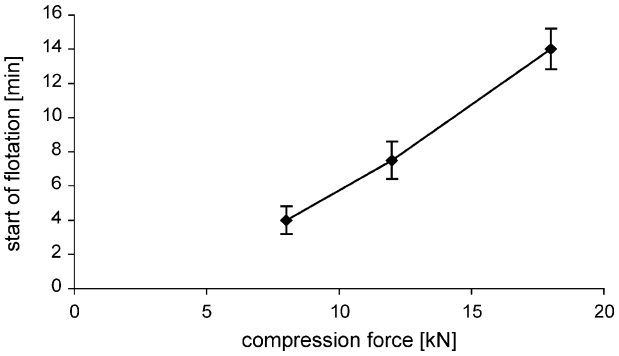

Fig. 3. Start of flotation of pellets with verapamil hydrochloride from tablets VI as a function of compression force.

'The tablets VI have low friability (0.1%) and a high hardness factor (0.116 kg/mm^2). Proper uniformity of VH contents in tablet proves that matrix was uniformly buried. Distinct tablet mass stratification in pouring tunnel was not observed.

Tablets VI were evaluated as regards to effect of upper punch compression force on mechanical strength, friability and pellets flotation starting time in the process of compression too. Es expected it was proved that increasing compression force from 8 to 18 kN contributed to greater hardness and lower tablet friability. Higher pressure resulted also, after tablet disintegration, in longer start of flotation pellets: when the pressing force was 8 and 18 kN the start of flotation time was 4 and 14 min, respectively (Fig. 3). The results in Fig. 3 were statistically compared using one-way ANOVA test. The obtained results of analysis, calculated Snedecor F values were bigger than theoretical value, indicating significant difference.

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