INFLUENCE OF ACRYLIC ESTERS AND METHACRYLIC ESTERS ON FLOTATION OF PELLETS AND RELEASE RATE OF VERAPAMIL HYDROCHLORIDE

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Abstract: Eudragit® RL (ERL) and Eudragit® RS (ERS) are biocompatible cationic copolymers, pH-independent and insoluble in aqueous environment. In this study drug delivery system consisting of a capsule filled with floating pellets with verapamil hydrochloride (VH) is proposed. The release of VH in the stomach results in better solubility in an acid gastric environment in vivo and may result in greater amount of the VH absorbed and its higher concentration in plasma. The scope of this study was to investigate the influence of ERL and ERS ratio on VH release in 0,1 M HCl from floating coating pellets. The stability of this film was also investigated. The ERL film is much more permeable than ERS, and an increase of ERL film thickness did not retard the release rate. The combination of ERL and ERS are forms of the sustained release film. It was a necessary to add the uncoated pellets, which constituted the initial dose. The start of flotation depends on permeability of polymeric film, and decreases with addition of ERS. There is no change in the start flotation time after 12 months under room condition (25°C/60% RH). The drug delivery from uncoated pellets and pellets coated with ERL/ERS is stable after 12 months under room condition (25°C/60% RH).

Keywords: acrylic esters, methacrylic esters, floating pellets, controlled release, start of flotation

Eudragit® RL (ERL) and Eudragit® RS (ERS) are acrylic and methacrylic acid esters. These polymers are widely used in solid oral dosage forms (1,2). Controlled release of active substance is obtained from oral dosage forms with Eudragits® in many ways. Enclosing the drug in a controlled-permeable membrane is an important basic principle of controlled time release (3).

ERL and ERS are biocompatible cationic copolymers. The quaternary ammonium groups are responsible for the hydration of the polymer. They are pH-independent and insoluble in aqueous environment. The only difference in the structure of ERL and ERS is an existence of the quaternary ammonium substitution. ERL has higher amount (50 mEq./100 g polymers) of such groups than ERS (25 mEq./100 g polymers) (4). This is the reason, why water can penetrate ERL more freely than ERS film.

Nowadays aqueous based polymeric dispersion is used for film coating as an alternative to organic solution. Latex dispersion has many advantages compared to organic solvent, including fewer health, safety and environmental concerns. It has lower viscosity and higher concentration too.

Targeted release in the stomach has many advantages, e.g. better bioavailability of several active substances and increased probability of therapeutic effect. Also, drug forms are made to reside in the stomach for a long time assuring slow delivery of the drug from its absorption site providing more reproducible bioavailability (5-7). Approaches aiming to increase gastrointestinal residence time include: bioadhesive drug delivery systems; size-controlled delivery systems with an increase in the stomach environment to retard the passage through the pylorus; and density-controlled delivery systems, which float or sink in gastric fluids. Floating has been achieved by low-density solid systems, i.e. systems with decreased density upon contact with gastric fluid (swelling agents or CO₂ generation). Floating pellets can be used in a form of hard gelatin capsules or compressed into the tablets (8).

In this study drug delivery system consisting of a capsule filled with floating pellets with verapamil hydrochloride (VH) is proposed. It is assumed that better solubility of VH in an acid gastric environment in vivo may result in greater amount of the VH absorbed and its higher concentration in plasma (9).
The purpose of this study was to investigate the influence of ERL and ERS ratio on VH release in 0.1 M HCl from floating coating pellets. The stability of this film was also investigated.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride (Recordati, Milano, Italy), sodium hydrogen carbonate (Merck, Darmstadt, Germany), microcrystalline cellulose (Avicel PH 101\textsuperscript{®}, mean particle size of 50 µm, FMC, Brussels, Belgium), lactose (Ubichem, Eastleigh, United Kingdom), Povidone K-30 (Fluka Chemie, Steinheim, Germany), Eudragit\textsuperscript{®} RL 30D and Eudragit\textsuperscript{®} RS 30D (Röhm GmbH, Darmstadt, Germany), triethyl citrate (Lancaster, Morecambe, United Kingdom), Aerosil (Degussa, Frankfurt/M., Germany), talc (Ph. Eur.) Statistical analysis of the results was performed with Statistica v 6.1 (StatSoft Inc., Tulsa, USA) and Microsoft Excel 2000 (Microsoft, Washington, USA).

Preparation of floating pellets cores with VH

Verapamil hydrochloride (20%), sodium hydrogen carbonate (20%), Avicel PH 101 (45.2%) and lactose (12.3%) were mixed in a mixer (Philips H 7720/06, Budapest, Hungary) for 5 min and then wet granulated with Povidone K-30 (5%) as a 50% w/w aqueous solution. The moistened mass was extruded using Caleva Extruder 25 (Caleva, Dorset, United Kingdom) through a 1.2 mm extrusion screen. The extrudates were spheronized in Caleva Model 120 apparatus (Caleva, Dorset, United Kingdom). Spheronizer shield rotation speed measured by means of tachometer Caleva was 1500 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 24 h and then separated into fractions of 0.8–1.0, 1.0–1.25, 1.25–1.5 mm by means of a sieve set. Pellets of 1.0–1.2 mm in diameter comprised the largest fraction (about 85%) under the given conditions of spheronization and were selected for further study.

Preparation of coating dispersions

The composition of the coating mixtures is presented in Table 1. The preparation procedure of coating mixtures was performed as follows. The appropriate amount of ERL (A) or ERS (B) was introduced to a beaker with a magnetic stirrer and in formulation C-D Eudragit\textsuperscript{®} RS 30 D was added as a thin stream. Next, portions of water were added during the stirring process. After 30 min the appropriate amount of talc (passed through 80 µm mesh sieve) was added. The dispersion was stirred for 2 h.

Coating of pellets cores

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 1.8 bar and peristaltic pump feeding rate of 5 mL/min. Pellets were dried in a blow-dryer at 40°C for 24 h precisely. After the coating process the pellets were stored with 2% of Aerosil 200 in HDPE container.

Morphology of pellets cores

The morphology of the pellets was studied by scanning electron microscope (SEM). The samples were sputter-coated with gold for SEM analysis. The pellet structure was examined in a JEM-1200 EX II electron microscope (Jeol, Tokyo, Japan) equipped with an EM-ASID 11 Scanning Image Observation Device using secondary electron imaging.

Measurement of film thickness

Pellet coating film thickness was determined after cross sectioning, with a scalpel, of 30 randomly selected pellets from each formulation and placing them under a microscope (Motic, Wetzlar, Germany) with a digital camera (Panasonic, Osaka, Japan).

Table 1. Composition [%] of coating mixtures A ñ D.

<table>
<thead>
<tr>
<th>Substance</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eudragit\textsuperscript{®} RL 30 D</td>
<td>46.7</td>
<td>-</td>
<td>25.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Eudragit\textsuperscript{®} RS 30 D</td>
<td>-</td>
<td>46.2</td>
<td>25.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Talc</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Water</td>
<td>46.3</td>
<td>46.3</td>
<td>43.0</td>
<td>43.0</td>
</tr>
</tbody>
</table>
Drug release test

The in vitro release test was performed using the Ph Eur paddle apparatus, Pharma Test Model PTWS-3 (Pharma Test, Hainburg, Germany). The beads were evaluated by dissolution test in 750 mL 0.1 M HCl solution at 37°C, at a paddle speed of 75 rpm. Accurately weighed samples (n=6) containing 120 mg VH were introduced in dissolution medium. The concentration of VH in the samples was determined spectrophotometrically at 278 nm, using spectrophotometer JASCO V-530 (Jasco Corporation, Tokyo, Japan).

Pellet flotation starting time measurement

After filling 6 beakers of the apparatus (p. 2.6.) with hydrochloric acid (0.1 mol/L) and setting temperature, certain formulation pellets were added to each beaker. Pellets were in the lowest point of the beaker bottom curve under the rotation axis of the stirring apparatus. Consequently, by means of stopwatch, the time was measured after which most pellets will start flotation. The average from 6 measurements was accepted as final result.

RESULTS AND DISCUSSION

The concept of floating pellets is based on the change in physical properties of drug delivery after passing to the acidic environment of hydrochloric acid in vitro or to the acid stomach environment in vivo. As a component of the pellets core sodium hydrogen carbonate was added, which after reacting with hydrochloric acid generates carbon dioxide, whose bubbles are adsorbed on the surface of the spherical core of the pellets. The change of total density causes their floating in the fluid in vitro or in vivo (10).

The releasing of VH in the stomach causes the increase of bioavailability, which was proved in previous study (9).

The cores of pellets were prepared by extrusion and spheronization method. The shape of cores was spherical (Figure 1) and there was no agglomeration.

The difference in the mechanical properties of dry films could be explained with the different plasticizing efficiencies of the plasticizers on the polymer. The data from literature report about the necessity of using the plasticizer, as a component of coating mixture, generally triethyl citrate (11). The plasticizer should protect the film from damage during e.g. fluidized bed coating. The results of microscopic examination and in vitro release tests show lack of film damages, which remains without splinters and without rapid release (Figure 2).

During the in vitro investigation, pellets settled on the bottom of the beaker and then, as a result of hydration and film swelling, carbon dioxide vesicles got out from raising pellets to the surface of the liquid. The different property of film, e.g. permeability, resulted in different start of flotation (Figure 3).

The results of the start of flotation measurement were statistically compared using t-test. It is obvious that pellets coated with film B had the most delayed start of flotation. There was no statistically significant difference between pellets coated with film A of different thickness. Also, there were no statistically significant differences between film A (70 µm) and C. Comparing the results of the start of flotation for pellet D initially and after 12 months indicated a statistically significant difference (p=0.03). The RSD in this case amounted to 7.4% and 4.9%, respectively.

Figure 1. The scanning electron micrographs the pellet’s core with verapamil hydrochloride prepared by extrusion and spheronization method.

Figure 2. The cross-section of the pellet coated with film D.
The uncoated pellets were released immediately, up to 4 min. The formation of carbon dioxide, in the reaction of sodium hydrogen carbonate and hydrochloric acid, entailed a rapid disintegration of uncoated pellet (pellet’s core) – effervescent effect (Figure 4).

The ERL film was much more permeable than ERS film. It was impossible to obtain a sustained release (5-6 h), using only ERL. Increasing film thickness from 35 µm to 70 µm caused only a little slowdown of the release rate (Figure 4).

ERS is less permeable for water. Using this polymer without porophore causes that the film is practically impenetrable. The amount of VH released during 4 h was less than 3%, in 0.1 M HCl environment. It corresponded with the delayed start of flotation. In film C the ratio of ERL and ERS was 1:1. Addition of 50% ERS did not entail the change of release rate (Figure 1). The results of VH in vitro release from pellets with film A (70 µm) and C (35µm) were statistically compared using t-test. The obtained results of analysis calculating p values was bigger than α – 0.05, indicating the lack of statistically significant difference.

In case of formulation with film D, using 80% of ERS and 20% of ERL caused a slowdown in release rate in 5 h period of time (Figure 2). Release rate of VH in the first hour was too low. Using the blend of uncoated (20%) and coated (80%) pellets gave the expected result (Figure 5).

The ERS and ERL film swells in aqueous environment, which is the reason of lag time (Figure 6).

It was a necessary to add the uncoated pellets, which constituted the initial dose. After 1 h of release test the characteristic of film was changed and the film became hydrated. This is the reason of the rapid increase of the release rate (Figure 6) After 4 h the difference of concentrations on both sides of the film decreased. Therefore, there was a decreased release rate of VH from floating pellets in the final hours of a release test.

The data from literature (12,13) indicate the possibility of instability of methacrylate-acrylate films. The mechanism of drug release from Eudragit® RL or RS coated drug delivery is believed to be a diffusion controlled process (DCP). DCP is defined by Fick’s law. D value from Fick’s law can be characterized as (12):

\[ D_a = D_r \epsilon^2 \tau \]

where: \( D_a \) – diffusion coefficient in the medium, \( \epsilon \) – porosity factor, \( \tau \) – tortuosity factor.

The instability of methacrylate-acrylate films could be a result of chemical reactions or physical changes. More often the changes in drug release rate are a result of changing film porosity or tortuosity. This could alter the diffusion coefficient.
In the present study, the pellets with VH coated film D were stored at 25∞C/60% RH in HDPE container and protected from light for 12 months. After the coating process the pellets were dried for 24 h in 40∞C in blow-dryer and stored with 2% of Areosil 200.

The influence of storage time on VH release from pellets coated with ERL/ERS 1:4 is illustrated in Figure 7.

The results in Figure 7 were statistically compared using t-test. The obtained results of the analysis indicate a lack of statistically significant difference.

CONCLUSION

The ERL film is much more permeable than ERS, and the increase of ERL film thickness did not prolong the releasing time of verapamil hydrochloride. The mixture of ERL and ERS are forms of the sustained release film.

It is impossible to obtain a sustained release (5-6 h) without lag time, from floating pellets with VH without addition of uncoated pellets, which constitute the initial dose.

There were no differences in release from ERL and ERS pellets coated with VH after 12 months under room conditions.

REFERENCES


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