DILTIAZEM RELEASE FROM EUDRAGIT NE40 COATED PELLETS AND EFFECTS OF THERMAL TREATMENT

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تم عمل تلبيس رقيق لكريات دواء ديلتيازيم بواسطة معلق من مادة أيودراجيت NE40 المائي. وتم دراسة تأثير المعالجة الحرارية، ووسط الذوبان والقوة الأيونية للوسط على إطلاق الدواء من هذه الكريات. وتم معالجة الكريات الملبسة عند درجات حرارة 37 °م، و40° م، و50° م، و 60° م وذلك لمدة 24 ساعة. وقد أظهرت الكريات الملبسة انخفاضاً قليلاً في معدلات الإطلاق عند درجات حرارة 50° م و 60° م بالمقارنة مع معدلات الإطلاق المبدئية عند درجة 37° م. أما المعالجة الحرارية لطبقة التلبيس عند درجة حرارة ومدة مناسبتين فقد وجدت ضرورية لتحقيق تلاصق حبيبات البوليمر بحيث يكون معدل إطلاق الدواء ثابتاً أثناء التخزين المطول. وكان اطلاق دواء ديلتيازيم مستقلاً نوعاً ما عند درجة الحموضة (الأس الهيدروجيني) والقوة الأيونية لوسط الذوبان ومع ذلك فإن معدلات الإطلاق انخفضت قليلاً بزيادة التراكيز العيارية لكلوريد الصوديوم في الأوساط الراصدة buffer media.

A film coat for diltiazem pellets was applied with aqueous dispersion of Eudragit NE40 using bottom spray Fluidized-bed coater. The effects of thermal treatment, dissolution media and ionic strength of media on drug release from the pellets were evaluated. Coated pellets were treated at 37°C, 40°C, 50°C and 60°C for 24 hours. Thermally treated pellets showed slight reduction in the release rates at 50°C and 60°C compared to initial release profile at 37°C. Curing or thermal treatment of the coat at an appropriate temperature and length of time was found essential to achieve complete coalescence of the polymer particles such that the rate of drug release was stable during prolonged storage. Diltiazem release was fairly independent of pH and the ionic strength of the dissolution media. However, the release rates were slightly decreased with increasing molar concentrations of sodium chloride in the buffer media.

Key words: Controlled release, diltiazem pellets, coating, eudragit NE40D, thermal treatment

Introduction

The recent United States Pharmacopeia (1) only lists three controlled release coatings systems namely cellulose acetate, ethylcellulose and methacrylic acid copolymers that function as a rate controlling membrane. Although other coating exists but these three are widely accepted (2). Commercially available aqueous dispersions of methacrylic acid copolymers used as controlled release coatings are Eudragit RS/RL30D and Eudragit NE30D/40D. Eudragit RS/RL30D are copolymers of ethyl acrylate and methyl methacrylate with trimethyl ammonio-ethyl methacrylate chloride as hydrophilic group in ratios of 1:2:0.1 and 1:2:0.2 respectively. The positively charged quaternary ammonium groups in the chloride salt form of the polymer stabilize the colloidal particles with a polymer content of 30% w/v in water. The release of drug is increased or controlled by mixing Eudragit RL and RS in different ratios. Eudragit NE30D/40D is a copolymer of ethyl acrylate and methyl methacrylate in 2:1

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without functional group and has very low softening temperature as compared to Eudragit RL/RS30D. Eudragit NE30/40D forms flexible and expandable films without any plasticizer while RL/RS30D form hard films under room temperature. Eudragit NE40 has pH independent permeability characteristics and reproducible results (3). Most of the aqueous-based dispersions differ in their minimum film formation temperature (MFT) or the glass transition temperature (Tg) apart from chemical nature. To obtain optimally coalesced film, the substrates are usually subjected to heat treatment at 10°C above the MFT. A number of dispersions including ethyl cellulose latex, silicone elastomer latex, and methacrylate copolymer dispersions (Eudragit RS30D) have higher MFT and require addition of plasticizers for coating at low temperature in order to make soft and flexible films. Plasticizers help to lower the MFT or Tg, thus shorten the time for complete film formation (4). An aqueous coating dispersion system Eudragit NE40 was selected as release rate controlling agent for a highly water-soluble drug, diltiazem HCl that is an orally effective in the treatment of angina pectoris and hypertension (5). Thermal treatment or heating the polymeric membrane above Tg could significantly alter the physico-mechanical properties of the polymer and affect the drug release but the stability of the drug may not be affected. A few polymer containing pharmaceutical dosage forms have been studied with regard to the effects of thermal treatment (6).

In the present study, diltiazem pellets were coated with Eudragit NE40 as the release controlling polymer. The influence of thermal treatment, pH and ionic concentrations of the dissolution media on drug release of coated pellets were investigated.

Materials and Methods

Diltiazem HCl (Reddy Pharma Singapore), Eudragit NE40D (Rohm Pharma, Germany), lactose monohydrate BP (HMS, Holland), microcrystalline cellulose (Avicel PH 101, FMC corporation, USA), polyvinylpyrrollidone PVP (Sigma, USA), talc BP (Merck, Germany) and all other chemicals used were of analytical grade.

Preparation of Inert Pellets:

Inert pellets (1.0-1.18 mm) were first prepared by extrusion-spheronization method using lactose: Avicel: water (1:1:0.9). Lactose and Avicel (1:1) was first blended in a Kenwood planetary mixer for 5 minutes (7). Distilled water (0.9) was then added and mixed for ten minutes. The wet mass was fed between two contrarotating rollers of a rotary extruder or pellet mill (Alexanderwerk, Remscheid, Germany). One of the rollers was perforated or rings die with 1-mm diameter holes on the entire surface while the other for pressing the wet mass through these holes. The extrudates were cut into smaller cylinders by the knife fixed inside the ring die and further processed using a 22.5-cm Spheronizer (G.B.Caleva Ltd, UK) fitted with a cross hatched plate rotated at 1000 rpm for 15 minutes. After spheronization, the pellets were dried in a fluid bed drier (PRL Engineering LTD, UK) at 60°C for 15 minutes. The dried pellets were screened to obtain mesh fraction 1.0-1.18 mm and were used for preparing drug pellets.

Preparation of drug Pellets:

Drug solution was prepared by dissolving 20% w/v diltiazem HCl in an aqueous solution of polyvinylpyrrollidone (2% w/v). Talc (2% w/v) was then added to the drug solution with continuous stirring and was sprayed onto inert pellets (150 g) using bottom-spray fluidized bed coater to produce drug pellets containing 20% diltiazem. The following operating conditions were used: inlet air temperature 55-60 °C, atomizing air pressure 0.6 bar, spray rate 2.0-2.5 ml/min and spray nozzle diameter 0.8 mm.

Coating of drug Pellets:

For aqueous polymer coating, 150g of diltiazem pellets were used. An aqueous dispersion of Eudragit NE40D (NE40) was used. Prior to coating, the polymer was diluted to 10% w/v with distilled water. A small quantity of talc (2% w/v) was added into the coating mixture as an anti-adherent. The mixture was stirred using a magnetic stirrer prior to and throughout the coating process. Coating was performed onto drug pellets under similar operating conditions described above except the inlet air temperature was maintained at 25-30 °C. Fixed coating level of NE40 dispersion was examined and based on theoretical weight gained of 5%.

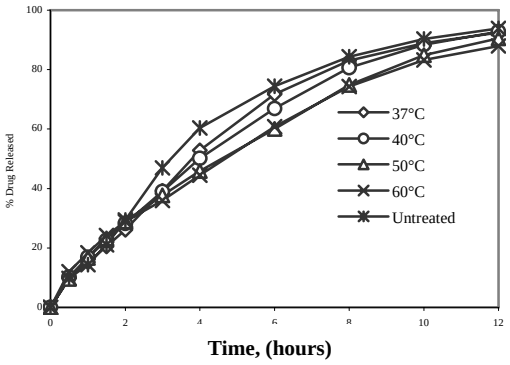

Figure 1. Influence of various curing temperatures on in-vitro diltiazem HCI release from coated pellets using distilled water as dissolution medium.

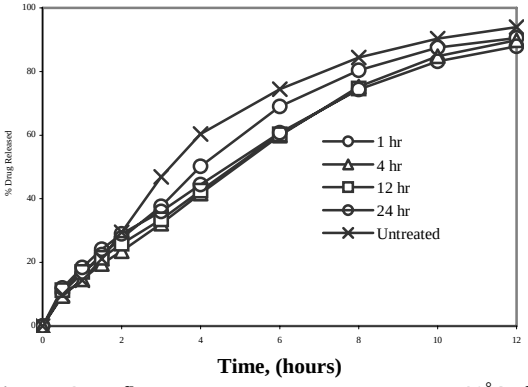

Figure 2. Influence of thermal treatment at 60°C for different durations on in-vitro diltiazem HCI release from coated pellets using water as dissolution medium.

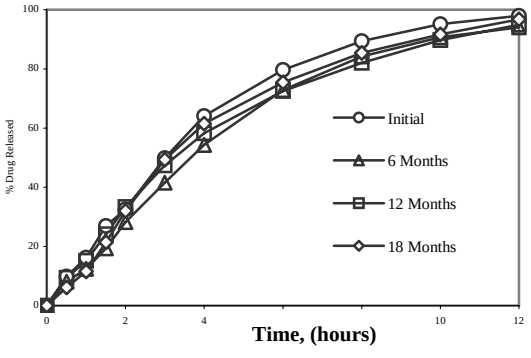

Figure 3. Influence of storage time at 40°C on in-vitro diltiazem HCI release from coated pellets using distilled water as dissolution medium.

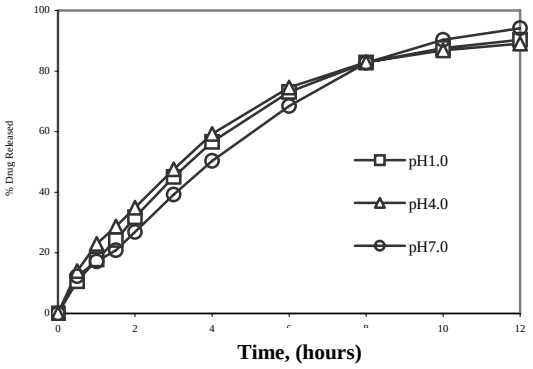

Figure 4. Influence of pH in-vitro diltiazem HCI release from coated pellets in dissolution medium of pH 1, 4 and 7.

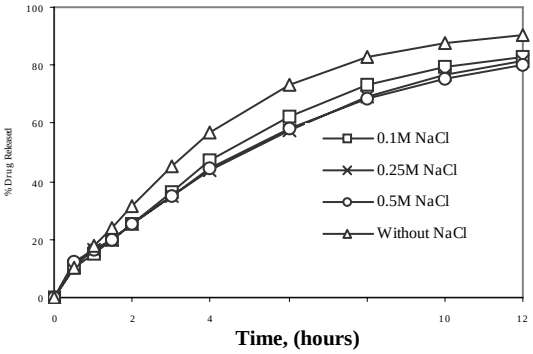

Figure 5. Influence of different molar concentrations of NaCl on in-vitro diltiazem HCl release from coated pellets in dissolution medium of pH1.

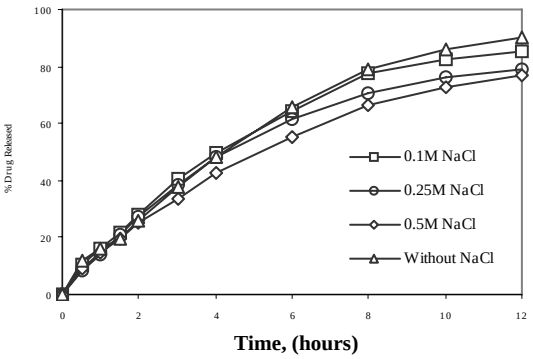

Figure 6. Influence of different molar concentrations of NaCl on in-vitro diltiazem HCI release from coated pellets in dissolution medium of pH 7.

Notes: All figures (1-6) (SD of dissolution data is less than ± 2%).

Thermal Treatment:

The coated pellets were divided into two parts, one part was uncured or untreated while portions of other part were kept in an oven at 37°C, 40°C, 50°C and 60°C for 24 hours. They were also kept at 60°C for different time intervals namely 1, 4, 12 and 24 hours. The treated pellets were then allowed to cool at room temperature in a desiccator and stored in an airtight container before initiating dissolution studies.

Stability Studies:

Stability of the coated pellets with regard to drug release characteristics was conducted following storage under different conditions. The coated pellets were stored in amber glass bottles for 18 months at room temperature (25 ± 2°C), 40 ± 2°C with 80% relative humidity and at low temperature (5 ± 1°C). Samples were removed at the end of 6,12 and 18 months for dissolution testing.

Dissolution studies:

The in-vitro dissolution of all the coated pellets was determined using the USP apparatus II (Sotax AT7, Switzerland). The test was performed in 900 ml distilled water as the dissolution medium with the temperature maintained at 37.0 ± 0.5°C, while the stirring speed was set at 100 rpm. Samples of about 5 ml volume each were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours with an automated fraction collector (SDX, Malaysia). At the end of 12 hours, the pellets were crushed in the dissolution vessels to obtain homogeneous dispersion and the stirring continued for another 15 minutes. Samples were then collected and then analyzed for the drug content. This reading represented the total amount of drug dissolved and was used to determine the percentage of drug release at the different sampling intervals. Diltiazem HCl content sample was analyzed directly or after dilution with the dissolution medium at 237 nm using an UV spectrophotometer (Hitachi U2000, Tokyo, Japan). Triplicate samples of each type of coated pellets were used in the data analysis. The release profiles at pH 1 (0.1 M HCl), 4 and 7 (phosphate buffers) and the effects of molar solutions of sodium chloride namely 0.1, 0.25 and 0.5 on drug release of coated pellets were also evaluated. The buffer solutions were prepared as mentioned in USP, 2000.

Results and Discussions

Influence of thermal treatment on drug release:

Thermal treatment or curing of coated pellets at higher temperature did not affect the stability of diltiazem but may affect its release rate. This was confirmed with spectrophotometric and high performance liquid chromatographic analyses as the additives used in the coating system were inert. All the coated pellets have two layers namely, drug layer around the inert pellets and insoluble polymer coat around the drug pellets. Drug is usually diffused out from the inner drug layer to the outer polymeric membrane when contacted with dissolution medium. Differential scanning calorimetry studies on coated pellets confirmed that there were no drug–polymer interactions or degradation of drug (8).

Fig. 1 and 2 show the release profiles of pellets thermally treated at different temperatures and also those treated at 60°C for different duration respectively. It can be seen from fig. 1 that those pellets treated at 50°C and 60°C showed comparable release profiles, but were both slightly slower than those thermally treated at 37°C and 40°C. In comparison, the untreated pellets showed faster rate of drug release compared to the thermally treated pellets. It appeared that as the treatment temperature was increased, there was a corresponding decrease in the rate of drug release. However, the release rate became stabilized at 50°C and further increasing the treatment temperature to 60°C did not cause further decrease in the rate of drug release. The influence of the curing temperature on the rate of drug release could be attributed to its effect on the film formation. When the polymer particles were deposited on the drug pellet surface during coating, inter-diffusion of the polymer chains among adjacent polymer particles would lead to formation of an integral film around the drug pellets. However, the movements of the polymer chains and hence the film formation process is dependent on temperature, which must be maintained above MFT or Tg. The higher the temperature, the faster would be the film formation process. Also, the higher the temperature, the shorter would be the time taken for complete film formation. From the above results, it appeared that the coat obtained after coating process has not reached complete film formation resulting in a coat that was more porous or permeable. Upon thermal treatment

at various temperatures studied, there was still polymer chain movements and further coalescence of the polymer particles in the coat formed, and at 60°C, complete film formation was achieved after 24 hours (9). Thereafter, further increase in the curing temperature did not cause any further changes in the film structure and provides a stable release profile (10).

The curing time is also crucial for complete film formation and is exemplified by the results shown in fig. 2. It is apparent from the plots that at 60°C, the minimum curing time required was about 4 hours. After 4 hours of curing, the film coat formed appeared to be stabilized. Increasing the curing time to 12 hours and 24 hours did not cause any further decrease in the permeability of the coat. Yuen (11) have shown that curing of the coat was important, not only from the point of its permeability, but also the cured coat was mechanically strong enough to withstand any stress due to swelling of the pellet core during dissolution or due to expansion during storage if the environmental temperature be increased. When the coated pellets were not properly cured, the coat tended to crack during dissolution of the pellets, resulting in rapid release of the drug.

Fig. 3 shows the release profiles of the coated pellets after storing at 40°C (with 80% relative humidity) for 6, 12 and 18 months. There appeared to be a slight decrease in the rate of drug release during storage at 40°C over time but the rate of drug release became stabilized after 6 months of storage. The release profiles after storage for 12 and 18 months were essentially similar to that storing after 6 months. Compared to the thermal treatment at 60°C (Fig. 1) a much longer time was required for the coat to achieve complete film formation or coalescence when the pellets were stored at 40°C. Hence, curing temperature will determine the curing time required for the film to be stabilized. The coated pellets are therefore, properly and adequately cured, otherwise the drug release profiles would change over time upon storage at ambient room temperature. However, the drug release profiles of the samples stored at room temperature or at low temperature were almost similar to their initial release profiles from the coated pellets (results not shown).

Influence of pH and ionic strength :

Fig. 4 shows the drug release from coated pellets in dissolution medium of pH 1, 4 and pH 7. At the two lower pH, the release profiles were essentially similar and superimpossable. At pH 7, there was a slight decrease in the rate of drug release, especially during the initial part of the dissolution study (1 to 6 hours). These results indicate that the release of diltiazem HCl from the coated pellets was slightly affected by the pH of dissolution media. Polymeric coatings with pH-independent permeability may give rise to pH-dependent drug release profile due to differences in solubility of the drug in various pH values. Compared to Eudragit NE40D, drug release from pellets coated with Eudragit NE30D was reported to be highly dependent on the pH of the dissolution media due to pH-dependent solubility of the drug (12).

The influence of the addition of sodium chloride (NaCl) (0.1, 0.25, 0.5 M) in dissolution media having pH 1 (0.1 M HCl) and 7 (phosphate buffer) on the drug release from the coated pellets is shown in Fig. 5 and 6 respectively. Upon addition of NaCl, the slight differences in the drug release appeared and the release rate was slightly decreased with increasing ionic strength or molar concentration of NaCl in the dissolution media. The decrease was more prominent with increase in the electrolyte concentration, especially at pH 7. This could be attributed to the higher osmotic pressure of the dissolution medium and lower solubility of diltiazem HCl in 0.5 M NaCl solution (13). The increase in osmotic pressure of the dissolution medium might reduce the rate of water penetration into the pellets. At the same time the decrease in solubility of diltiazem HCl would cause a decrease in the rate of drug release since the process occurred via passive diffusion, which is concentration dependent. The solubility of diltiazem HCl has been reported to be affected by the electrolyte concentration (14).

Conclusion

Coated pellets of diltiazem HCl were prepared by spraying drug pellets with Eudragit NE40 dispersion using fluidized bed coater. The rate of drug release of thermally treated pellets was slower compared to untreated pellets. Therefore, the pellets must be properly and adequately cured after coating in order to achieve stable drug release profiles. Diltiazem HCl release was found to be fairly independent of pH and increasing the ionic strength of pH 1 and 7 with NaCl caused a decrease in the rate of drug release.

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