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Long-term stability characterization of a controlled release gastrointestinal therapeutic system coated with a cellulose acetate pseudolatex

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The objective of the present study was to study the long term effects of storage of osmotically controlled gastrointestinal therapeutic system (GITS) in exaggerated conditions of temperature and humidity. Bilayered osmotic tablets were obtained with atenolol, Polyox® N80, Carbopol® 934P and magnesium stearate in one layer, and Polyox® 303, Carbopol® 974, sodium chloride and magnesium stearate in the other layer. A customized cellulose acetate (CA) pseudolatex was used to provide semipermeable housing around the tablet and an orifice was drilled into the drug layer to obtain the Atenolol GITS. The GITS were stored at 4 °C (refrigeration), 25 °C, 37 °C, 45 °C, 55 °C, 37 °C/11% RH, 37 °C/51% RH, and 37 °C/91% RH. Quantitative X-ray diffraction and dissolution studies were performed at regular intervals for one year. Aqueous CA polymeric film formation continued in GITS stored at higher temperature by gradual evaporation of moisture and coalescence of polymer. At lower temperatures atenolol crystallinity increased with time, but at higher temperatures the crystallinity was decreased. At higher humidity, a decrease in crystallinity was observed. A decrease in dissolution rate and extent was observed at higher temperature and higher humidity conditions. Exaggerated temperature and humidity conditions affected the dissolution profile by modifying the CA pseudolatex membrane and crystallinity of atenolol.

1. Introduction

Several methods have been adapted for developing oral drug delivery devices to control the amount of drug released in a defined period of time in gastrointestinal tract [1]. Different pH levels in various segments of the gastrointestinal tract tend to interfere with the release mechanism and release profile of the drug from the dosage form. Osmotically controlled devices, however, are actuated by osmotic pressure difference across the semipermeable membrane and therefore, independent of gastrointestinal motility and pH [2]. Core tablets coated with semipermeable polymeric films impermeable to drug but with an orifice for drug release actuated by osmotic pressure difference across the film is generally referred to as gastrointestinal therapeutic systems (GITS) [3–5]. The gastro-intestinal systems can be coated by organic solvent-based as well as aqueous-based systems.

Aqueous coating dispersions are advantageous over organic coating dispersions due to absence of explosion hazard, reduced toxic effects and atmospheric pollution, and its ability to accommodate high solid content. Perhaps, the preparation of a polymeric solution with water soluble polymer is the quickest way to achieve a aqueous polymer coating solution. However, since the polymer is dissolved, the evaporation time and energy needed for evaporating the water during coating could be the limiting factors for aqueous polymer solutions. The technique of dispersion of insoluble polymer in water in finely subdivided fashion is devoid of all these disadvantages and has revolutionized the preparation of aqueous based coating systems [6]. Since then, several aqueous-based coating systems have been developed and are available commercially.

The temperature and humidity at which coated dosage forms are stored may affect physico-chemical properties such as swelling of the coating, change in crystalline/amorphous nature of the drug, interaction between drug and excipients, and the drug release profile. The stability of coated dosage forms is generally influenced by the period of storage time, type of film coating, drug, excipients, storage conditions, and packing materials [7]. Upon storage, coatings obtained from aqueous dispersions such as cellulose acetate pthalate and hydroxypropyl methylcellulose acetate succinate showed changes in enteric performance or release characteristics by hydrolysis of ester linkages in the polymer or plasticizer, evaporation of the plasticizer, and delayed film formation [8]. At high humidity and temperature conditions, conversion of mesylate salt of delavirdine to its free base form and reaction between freed methanesulfonic acid and the carboxyl sites of the croscarmellose sodium were observed [9]. Degradation rate of oxytetracycline hydrochloride from directly compressed and Eudragit® E film coated tablets stored in high temperature and humidity decreased as the thickness of the applied film increased [10]. At elevated temperature, disintegration time of ethylcellulose coated aspirin tablets increased primarily due to coalescence of the polymeric particles [11]. Stability of pseudolatex dispersions in exaggerated temperature [12] and stability of pseudolatex dispersion films with respect to plasticizers [13] have also been reported.

The degree of crystallinity increased over a period of time in indomethacin coprecipitates stored at exaggerated temperature and humidity and reflected on decrease in dissolution rates [14]. Matrix diphylline tablets made up of Carbopol 971P exhibited changes in crystalline and thermal behavior of diphylline from anhydrous to hydrate form with a corresponding decrease in dissolution profile [15]. Changes in dissolution properties of conventional and modified release dosage forms during storage period have been extensively reviewed by Murthy and Ghebre-Sellassie [16].

Earlier studies in our laboratory were focused on development, characterization and optimization of zero order release atenolol and captopril GITS [17–19]. Several process and formulation variables have been extensively investigated. However, long term stability studies on GITS or GITS coated with aqueous pseudolatex dispersion have not been reported adequately. Therefore, the purpose of the present study was to investigate the long term effect of exaggerated temperature and humidity conditions on atenolol GITS coated with cellulose acetate dispersion.

2. Investigations and results

To study the quantitative change in crystallinity, the peak intensity ratio of atenolol (I) at 21.7 2θ to the standard (aluminum, I_0) 44.8 2θ was calculated. The characteristic peak of atenolol at 21.7 2θ was studied as it responded more sensitively to the changes in the crystalline drug concentrations. Further, the peak at 21.7 2θ had no interference from any of the additives used in the formulation. A representative X-Ray diffraction pattern of the atenolol GITS is shown in Fig. 1. A plot of I/I_0 values against the duration of storage at different conditions is shown in Fig. 2. An increase in the ratio indicates a growth in crystallinity of atenolol.

The fit factors f_1 and f_2 are two indices that compare the dissolution profiles of a reference formulation to that of a test formulation. These fit factors allow the systematic comparison of dissolution profiles at different time points. The representative profile of atenolol GITS stored at 45 °C are shown in Fig. 3. Similar profiles were obtained at all other stability conditions and f_1 and f_2 values were computed by the equations given below [20].

$$f_1 = \frac{\sum_{t=1}^{n} Rt - Tt}{\sum_{t=1} Rt} \times 100$$

$$f_2 = 50 \log \left\{ \left[1 + 1/n \sum_{t=1}^{n} Wt(Rt - Tt)^2 \right]^{-0.5} \times 100 \right\}$$

where Rt is the reference drug content at time point t and Tt is the test drug content at time point t, n is the number of sampling points and Wt is an optional weight factor. Since all the dissolution time points were treated equally Wt was taken as 1. The average difference between the reference and test profile is represented linearly by test fit factor, f_1 and exponentially by fit factor, f_2. The fit factor f_1 is zero when the test and reference profiles are identical and increases proportionally with dissimilarity between two profiles. The fit factor f_2 is 100 when the test and reference profiles are identical and decreases proportionally with dissimilarity between two profiles [20]. In the present study, dissolution profile at zero time point represents the reference curve and the dissolution profiles at different time intervals of stability studies represent the test curve. The rate and extent of dissolution of atenolol from GITS stored at different conditions decreased with time. Therefore, an increase in f_1 or decrease in f_2 reflects on decrease in rate and extent of dissolution (Figs. 4 and 5).

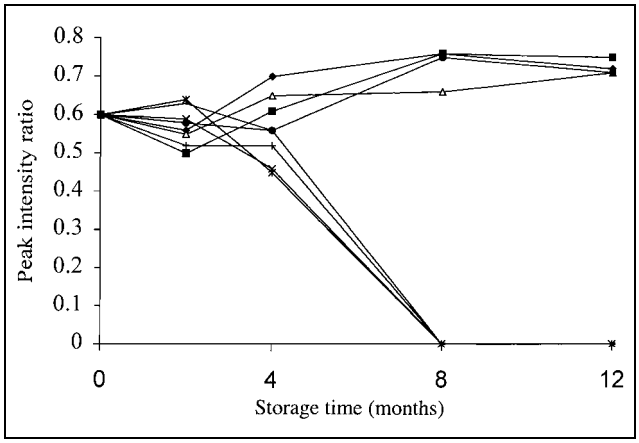

Fig. 2: X-ray peak intensity ratios (I/I_0) of atenolol in GITS with the standard
—◆— 4 °C, —■— 25 °C, —△— 37 °C, —×— 45 °C, —✳— 55 °C, —●— 37 °C 11% RH, —+— 37 °C 55% RH, —▬— 37 °C 91% RH

Atenolol is a crystalline compound with a melting point of 147 °C. Figure 2 shows an increase in crystallinity over a period of time in atenolol GITS stored at 4 °C and 25 °C. However, this change in crystallinity did not influence the extent of the dissolution, since atenolol is soluble in water. The average difference (f_1) at 12th month was 8.5% and 11.9% for GITS stored at 4 °C and 25 °C respectively. This trend in increased crystallinity was also observed in indomethacin coprecipitates with polymer mixtures [21]. However, since the indomethacin is very slightly soluble in water the increased crystallinity decreased the dissolution.

The crystallinity decreased in the GITS stored at 45 °C and 55 °C. At higher temperatures, atenolol quantitatively showed a decrease in crystallinity with time, at 8th month and 12th month no crystalline peak was observed. The GITS consists of Polyox® N80 in the drug component that has a melting point around 60 °C. At high temperature, the partially molten Polyox® N80 might have acted as solvent for atenolol resulting in decreased crystallinity of the drug. The decreased crystallinity may also be due to the anti-nucleating tendency of Polyox® N80.

Contrary to the decreased crystallinity and expected increased dissolution, the rate and extent of dissolution de-

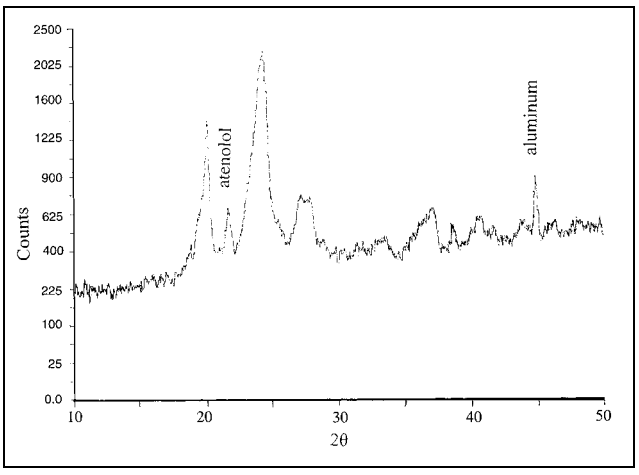

Fig. 1: 12th month x-ray diffraction pattern of atenolol GITS stored at 4 °C

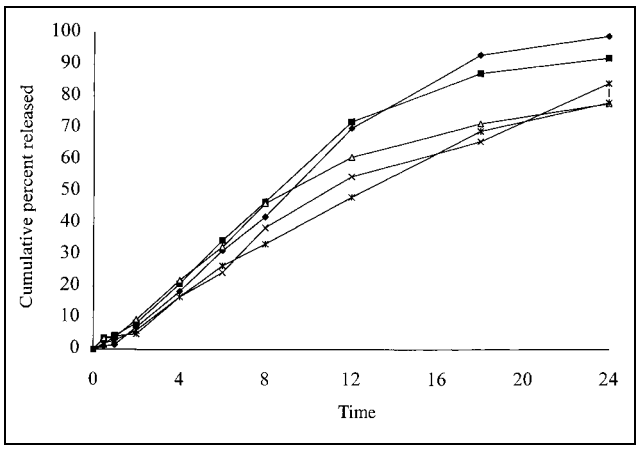

Fig. 3: Dissolution profiles of atenolol from GITS stored at 45 °C
—◆— 0 day, —■— 2 month, —△— 4 month, —×— 8 month, —✳— 12 month,

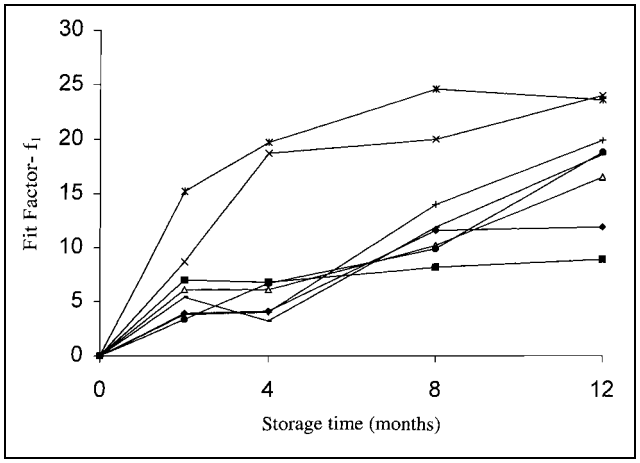

Fig. 4: Fit factor-f_1 of atenolol GITS dissolution profiles
—◆— 4 °C, —■— 25 °C, —△— 37 °C, —×— 45 °C, —✳— 55 °C, —●— 37 °C 11% RH, —+— 37 °C 51% RH, —▬— 37 °C 91% RH

creased due to the influence of the increased temperature on the pseudolatex membrane. At higher temperatures, the reduced dissolution rates (increase in f_1 value and decreased f_2 values) could also be attributed to the physical changes in CA pseudolatex membrane coating. Aqueous-polymeric dispersions form dense films after spray deposition on the solid substrate. The process is further supported by evaporation of water and the coalescence of the polymer particles into a homogenous film. The films become more homogenous upon aging due to further gradual coalescence [22]. The plasticizer might have also escaped from the system at elevated temperature leading to decreased free-volume in the films. In the atenolol GITS stored at 45 °C and 55 °C, the average differences in the dissolution profile were up to 24% and 23.6% respectively at 12th month.

The crystallinity increased in the GITS stored at 37 °C and 37 °C/11%RH. The dissolution profiles of GITS stored at 37 °C and 37 °C/11% RH at 12th month differed by more than 15% (f_1) compared to the initial ones. This might be due to the effect of increased temperature on the pseudolatex membrane. The crystallinity decreased in the GITS stored at 37 °C/55% RH and 37 °C/91% RH. X-RD pattern did not show any presence of crystalline atenolol at 8th month in the GITS stored at 37 °C/91% RH and at 12th month in the GITS stored at 37 °C/55% RH (Fig. 2).

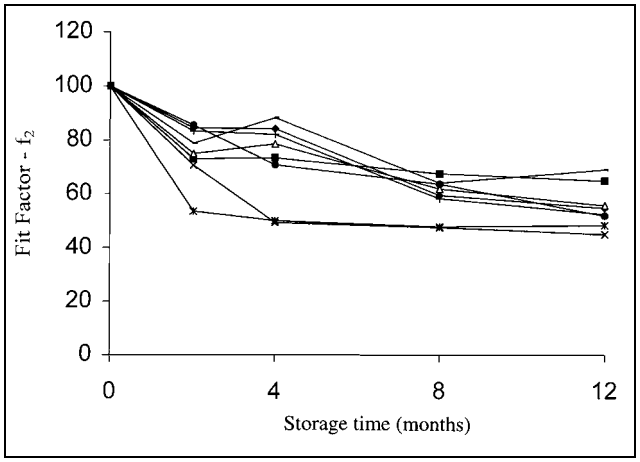

Fig. 5: Fit factor-f_2 of atenolol GITS dissolution profiles
—◆— 4 °C, —■— 25 °C, —△— 37 °C, —×— 45 °C, —✳— 55 °C, —●— 37 °C 11% RH, —+— 37 °C 51% RH, —▬— 37 °C 91% RH

In high humidity, selective permeation of water vapor might have dissolved the atenolol, thus reducing the crystallinity. The decrease in crystallinity with respect to humidity conditions was not adequately reflected on dissolution profile. The f_1 values for GITS stored at 37 °C/55%RH at 8th and 12th month were 14 and 19.9, respectively and for GITS stored at 37 °C/91% RH at 8th and 12th month were 11.9 and 18.6, respectively. Because of modification of membrane, it might have offered low resistance to the water permeability across the membrane. Polyox® N80 and 303 are hydrophilic polymers and in the presence of high relative humidity, atenolol GITS were found to swell. This phenomenon was visually observed in the atenolol GITS at 8th and 12th month. Hydration and swelling of Polyox® N80 and 303 might have contributed to a decrease in the crystallinity of atenolol.

3. Discussion

From the XRD studies it is evident that the lower storage temperatures tend to increase the crystallinity of atenolol in GITS with time. Conversely, higher storage temperature and higher humidity decreased the crystallinity of the atenolol. The pseudolatex membrane had more control on dissolution profiles of GITS than the crystalline behavior of the atenolol. Higher temperature reduced the dissolution rate and extent. In general, the atenolol gastrointestinal therapeutic system was fairly stable at low temperature and humidity as compared to the high temperatures regardless of the crystalline changes.

4. Experimental

4.1. Materials

The following materials were received as gifts: atenolol from Invamed Inc., Dayton, NJ; Polyox® N80 and 303 from Union Carbide Corp., Danbury, CT; Cellulose acetate (39.8% acetylation) from FMC Corp. Philadelphia, PA; Carbopol® 934P and 974P from BF Goodrich Co., Cleveland OH; FD&C red (No. 27HT23) from Colorcon, West Point, PA; Destab™ Placebo tablets from Particle Dynamics, St. Louis, MO. Sodium chloride was purchased from Mallinckrodt Specialty Chemical Co., Paris, KT. Magnesium stearate was purchased from Spectrum Chemical Mfg. Corp., Gardena, CA. All the above mentioned chemicals were used as received. All other chemicals were of reagent grade and used as received. Water used in all experiments was distilled and deionised.

4.2. Preparation of bilayered GITS

Bilayered osmotic tablets were prepared as follows: The drug layer was comprised of 100 mg of atenolol, 100 mg of Polyox® N80, 150 mg of Carbopol® 934P and 0.8 mg of magnesium stearate. The osmotic layer was comprised of 75 mg of Polyox® 303, 100 mg of Carbopol® 974P, 5 mg of sodium chloride, 0.8 mg of magnesium stearate, and 1.4 mg of FD&C red dye. Bilayered, standard convex tablets having 0.5 inch diameters were prepared using a Carver press (Model C) attached to a Carver semiautomatic compression accessory (M2729). The compression pressure was adjusted so that the average hardness of the tablets was 7–8 kg.

4.3. Cellulose acetate pseudolatex coating

The tablets were seal coated initially with a 2% cellulose acetate solution in acetone to prevent the highly water swellable Carbopols and Polyox resins from coming in contact with water. Following this seal coating, experimental pseudolatex coating was provided. CA pseudolatex was prepared as reported elsewhere [23]. Diacetin (160% w/w based on solids content of pseudolatex) was dispersed in water and slowly added to the pseudolatex with mild stirring. Final solids content of plasticized pseudolatex was adjusted to 8.1% w/v by further diluting with water. The seal coated experimental captopril osmotic tablets were mixed with placebo tablets of Destab™ in a laboratory model Uniglatt fluidized-bed coater (Model 2817). The nozzle employed had 1.0 mm diameter. The tablet bed was warmed for 5 min before the pseudolatex was sprayed onto the tablets. During the entire coating process the outlet temperature and the spray rates were maintained at 60 ± 2 °C and 7–10 g/min, respectively. The spray was interrupted whenever the outlet temperature dropped below

58 or exceeded 62 °C. Following coating, the coated tablets were cured in an oven at 45 for 48 h and stored in a closed amber colored container at room temperature. Before the tablets were subjected for the stability studies, an orifice of 0.014 inch diameter was drilled into the drug layer using a Dremel® (model 395 T5) varied speed mechanical drill.

4.4. Stability studies

Atenolol GITS were stored at 4 (refrigeration), 25, 37, 45, 55 °C, 37 °C/ 11% RH, 37 °C/51% RH, and 37 °C/91% RH. Saturated salt solutions were used to maintain 11%, 51%, and 91% relative humidity (RH) in dessicators. An adequate number ($n = 8$) of atenolol GITS were placed in air tight amber colored bottles and stored in the incubators/dessicators maintained at different temperature and humidity conditions as specified above. After obtaining the initial dissolution and X-ray diffraction patterns, atenolol GITS were analyzed for one year at regular intervals.

4.5. X-ray diffraction

Quantitative X-ray diffraction (XRD) studies were performed using a Philips X-ray diffractometer, model 1840. Measurements were carried out at 40 kV and 35 mA current at a continuous scan rate of 0.5 s per step. To study the quantitative change in the degree of crystallinity, the peak intensity ratio of atenolol (I) at 21.7 2θ to the standard (aluminum, I_0) 44.8 2θ was calculated. The samples were bisected horizontally through the drug layer and mounted on an aluminum holder for analysis.

4.6. Dissolution studies

The tablets were subjected to dissolution testing using the USP 23 Paddle Method, employing distilled water as the medium. The tablets were placed in the dissolution vessel and the dissolution was carried out for 24 h. The temperature of the dissolution media was maintained at 37 ± 1 °C. The stirring speed was 100 rpm. Five ml samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 12, 18, and 24 h time points, diluted suitably, and assayed by Hewlett Packard Diode array UV spectrophotometer (model 8451A) at 226 nm. After each sampling, an equivalent volume of distilled water was added to the media to replace sample volume. The dissolution profiles were obtained by plotting the cumulative percent of atenolol dissolved with time. All experiments were performed in triplicate.

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