Faculty of Pharmacy[1], University of Ljubljana; Krka d.d.[2], Novo mesto, Slovenia

Design of a drug delivery system with bimodal pH dependent release of a poorly soluble drug

B. Kovačič[1,2], F. Vrečer[1,2], O. Planinšek[1]

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Prof. Odon Planinšek, Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, Ljubljana, Slovenia
odon.planinsek@ffa.uni-li.si

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A delivery system which provides bimodal pH dependent release of poorly water soluble carvedilol in gastric and intestinal environment was designed. Preparation of solid dispersion with porous silica ensured a significantly higher dissolution rate of carvedilol in acidic and alkaline media in comparison to pure drug, while granulation of that solid dispersion with enteric polymer dispersion resulted in diminished immediate release in acidic media and fast release of the remaining drug in alkaline media. The ratio in quantities of first vs. second release was controlled with amount of enteric polymer dispersion used for granulation process. Desired 25 mg release of carvedilol at pH values 1.2 and 6.8 was achieved when 1.80 g of polymer per 1.0 g of solid dispersion (drug to silica ratio = 0.25 g : 2.0 g) was used.

A great number of newly developed active pharmaceutical ingredients (API) exhibit low oral bioavailability due to their poor aqueous solubility and pre-systemic metabolism (Amidon et al. 1995). Carvedilol is a drug molecule that has a low solubility in gastrointestinal fluids and is extensively metabolized in the liver, which results in an absolute bioavailability of less than 30% after oral intake (Morgan 1994). Dosage forms which ensure increased dissolution of carvedilol can improve its bioavailabilty up to fourfold (Wei et al. 2005).

Dissolution rate of poorly soluble API can be improved by various methods, such as micronization of the drug particles, formation of solid dispersions with soluble hydrophilic carriers, transformation of drug molecule into a better soluble salt, polymorph or amorphous form. The dissolution rate of carvedilol was increased through formation of the cyclodextrin inclusion complex or through the preparation of self-emulsifying drug delivery systems (SEDDS) or self-microemulsifying drug delivery systems (SMEDDS) (Wei et al. 2005). Adsorption and deposition onto high-surface-area carriers such as porous silica is also a known method of drug dissolution rate improvement (Rupprecht et al. 1974; Vrečer 1992; Speybroeck et al. 2008).

Bimodal pulsatile drug delivery generally refers to release of a portion of the total drug quantity in a dosage form in a burst, followed by periods of little or no release in a defined temporal pattern, and then a second phase of rapid drug release of the remaining drug quantity. Bimodal release formulations can provide therapeutic blood levels similar to those produced by oral application of two smaller doses taken separately over an extended period of time (Streubel et al. 2000). Dual pulsatile dosage forms of diclofenac sodium, which were fabricated by a nonconventional method (three dimensional printing^{TM} process) using multiple enteric polymers in a single tablet, have been described and showed immediate release in gastric fluid followed by a lag time of 7 h before the second pulse was released. The lag time of the second release was controlled by the erosion of the enteric polymer Eudragit L (Rowe et al. 1999).

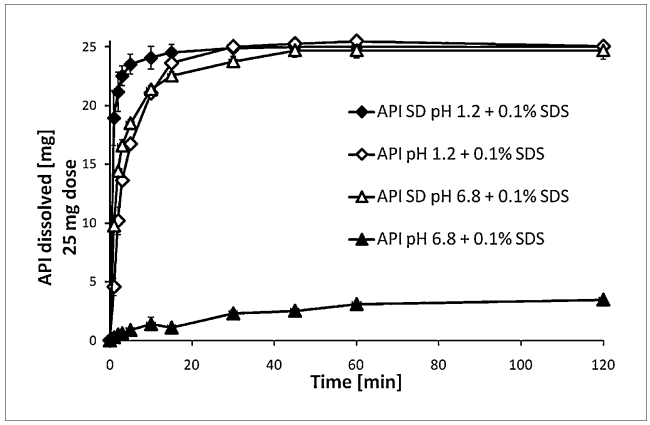

Fig. 1: Dissolution of pure crystalline carvedilol and solid dispersions of carvedilol in porous silica in aqueous HCl at pH 1.2 + 0.1% SDS and Phosphate buffer solution at pH 6.8 + 0.1% SDS dissolution media determined by USP 2 paddle method.

A commercial product (Coreg CR) exhibits a biphasic release of carvedilol. It is available for once-a-day administration as controlled-release oral capsules filled with carvedilol phosphate immediate-release and controlled-release microparticles that are drug-layered and then coated with methacrylic acid copolymers (RxList 2010). The daily dose of two 25 mg immediate-release carvedilol (free base) tablets can be switched to 80 mg carvedilol phosphate (equivalent to 60 mg of carvedilol free base) once a day capsules. Slow release and absorption from controlled-release microparticles increases drug metabolism which results in 15% lower bioavailability when compared to immediate release carvedilol tablets.

The aim of present study was to prove a new concept in a development of a delivery system which would increase the dissolution rate of the poorly water soluble model drug carvedilol and at the same time exhibit a bimodal pH dependent drug release. Such delivery system provides rapid dissolution of the first part of the dose in gastric media followed by a second burst dissolution of the remaining drug in the intestinal fluids.

Solid dispersions of carvedilol in porous silica (Sylysia 350) were prepared by solvent evaporation in a vacuum evaporator which ensures efficient pore filling procedure. Due to high specific surface area of the carrier, most of the drug is entrapped within mezopores. Such delivery systems ensure deposition of a drug within pores in a form of thin layer or nanoparticles. In addition improved wettability of drug results in faster dissolution rate of carvedilol with similar release kinetics in aqueous dissolution media of pH 1,2 (0,1 M HCl) and 6.8 (Phosphate buffer solution), as shown in Fig. 1.

Solid dispersion particles were then further granulated with an aqueous dispersion of methacrylic acid copolymers (Eudragit L 30D). As can be seen in Fig. 2, the portion of the drug released in acidic media can be effectively controlled with the amount of gastro-resistant polymer used for granulation. However, dissolution studies were performed for 2 h in pH 1.2 and then 2 h in pH 6.8. In the case of oral intake of granules it is unrealistic to expect that granules would stay in the stomach for

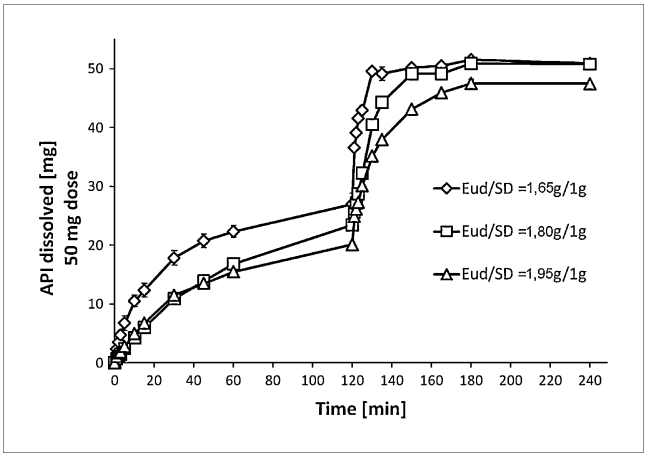

Fig. 2: Dissolution of carvedilol from granulated solid dispersions in aqueous HCl at pH 1.2 (0-120 min) and pH 6.8 dissolution media (121–240 min). Solid dispersions were granulated with 1.65 g, 1.80 g and 1.95 g of Eudragit L per 1 g of solid dispersion.

2 h, yet such experiments confirm that by granulation of solid dispersions with gastroresistant Eudragit dispersion it is possible to control that the drug releases in as a first pulse partially in the stomach. Lowest quantity of enteric polymer used (1.65 g of Eudragit L per 1 g of solid dispersion) results in a higher level of released drug in acidic medium followed by a faster release in pH 6.8 compared to dissolution study of samples with greater amount of gastro-resistant polymer. Future studies will try to optimize the composition of the drug delivery system to ensure an appropriate lag time between first and second pulse dissolution of carvedilol. Depending on the amount and type of polymer the second part of the dose can be released in a pulsatile manner lower down in the gastrointestinal tract (e.g. colon using Eudragit FS). The introduced concept could enable the formulation of a single dose bimodal pulsatile drug delivery system.

Experimental

1. Preparation of solid dispersion and granulate

Solid dispersion (SD) particles of carvedilol (CAR) with porous silica particles were prepared using the solvent evaporation method. 0.25 g (0.6 mmol) of CAR was dissolved in 20 ml of tetrahydrofurane. In the prepared drug solution, 2.0 g of porous silica (Sylysia) was suspended for a few minutes and the suspension was evaporated by a rotary evaporator (IKA RV 05, Staufen, Germany) at a temperature of 50 °C with pressure values ranging from 70 to 130 mbar. The prepared samples were additionally dried in a vacuum chamber (Heraeus, Germany) at room temperature for 1 h to remove the remaining THF. 1 g of prepared solid dispersion was manually granulated with 5.5 g, 6.0 g and 6.5 g of Eudragit L 30D dispersion (corresponds to 1.65 g, 1.80 g and 1.95 g of Eudragit L, respectively) using a sieve with 1.0 mm aperture size. Granules were then dried at 70 °C, which is above the glass transition temperature of Eudragit L film coating.

2. In-vitro dissolution test

The dissolution studies were performed using a USP type II apparatus (VK 7000, VanKel, Cary, NC, US), equipped with standard glass vessels and paddles. Samples equivalent to 50 mg of CAR (double maximum single dose) were placed in a dissolution vessel containing 750 ml of aqueous HCl solution (pH 1.2) with 0.1% SDS and maintained at 37 ± 0.5 °C and stirred at 50 rpm. After 2 h 250 ml of 0.2 M solution of trisodium phosphate dodecahydrate with 0.1% SDS and equilibrated to 37 °C was added into aqueous HCl solution and the dissolution medium was quickly adjusted to pH 6.8 with a solution of hydrochloric acid or sodium hydroxide. All the dissolution experiments were carried out in triplicate. Samples were collected periodically, filtered through a 0.45 μm pore filter (Minisart RC 25, Sartorius, Göttingen, Germany) and replaced with a fresh dissolution medium. The concentration of CAR was determined spectrophotometrically at 243 nm using UV-spectrophotometer.

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References

Amidon GL, Lennernäs H, Shah VP, Crison JR (1995) A theoretical basis for a biopharmaceutic drug classification: The correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. Pharm Res 12: 413–420.

Morgan T (1994) Clinical pharmacokinetics and pharmacodynamics of carvedilol. Clin Pharmacokinet 26: 335–346.

Wei L, Sun P, Nie S, Pan W (2005) Preparation and evaluation of SEDDS and SMEDDS containing carvedilol. Drug Dev Ind Pharm 31: 785–794.

Rowe CW, Katstra WE, Palazzolo RD, Giritlioglu B et al. (2000) Multimechanism oral dosage forms fabricated by three dimensional printing ™. J Control Release 66: 11–17.

Rupprecht H, Biersack MJ, Kindl G (1974) Freigabe schwer löslicher Substanzen von den Oberflächen partiell belegter Kieselsäuren. Colloid Polym Sci 252: 415–416.

RxList (2010) The internet drug index, Coreg CR, Dosage and administration. Available : http://www.rxlist.com/coreg-cr-drug.htm.

Speybroeck MV, Barillaro V, Do Thi T et al. (2008) Ordered mesoporous silica materials SBA-15: A broad spectrum formulation platform for poorly soluble drugs. J Pharm Sci 98: 2648–2658.

Streubel A, Siepmann J, Peppas NA, Bodmeier R (2000) Bimodal drug release achieved with multi-layer matrix tablets: transport mechanisms and device design. J Control Release 69: 455–468.

Vrečer F (1992). Ph.D. Thesis, University of Ljubljana.