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An oral drug delivery system based on interpolymer complex formation between poly(acrylic acid) and poly(vinyl pyrrolidone-co-vinyl acetate)

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Introduction

- A number of the most successful drugs are going off patent in the next 5 years
- Generic prescription drugs are continuously making up a larger proportion of the total drug market
- A generic prescription drug is required to achieve the same bioequivalence as the corresponding reference-listed drug
- Therefore, the drug delivery systems used to deliver the generic drugs needs to be adjustable

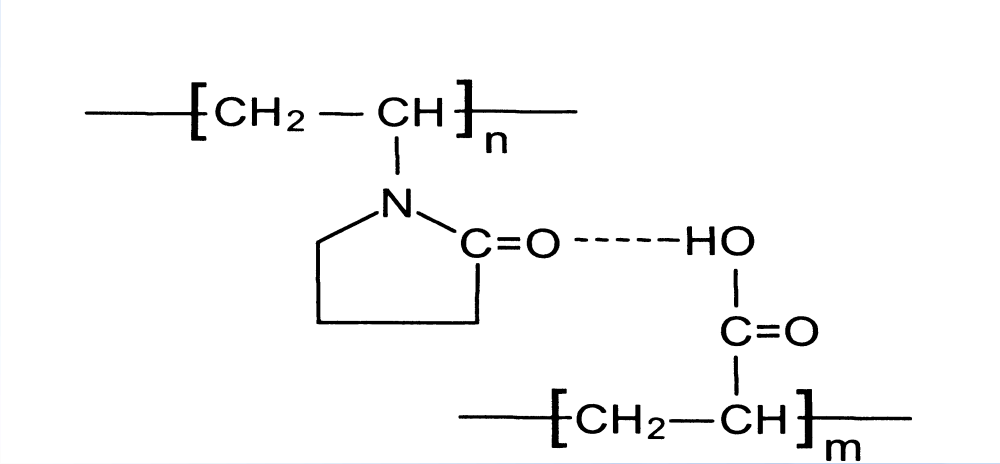
Oral drug delivery

- The most preferred route for drug delivery
- Oral drug delivery systems are required to protect the drug as it passes through the acidic medium of the stomach (pH 1-2)
- The drug is released upon entering the basic medium of the lower intestines (pH 6.2-7.4)
- The delivery system should thus be pH-sensitive
- A system based on inter-polymer complexation is ideal for this application

Polymer complexation

- The interpolymer complex is formed through H bonding between functional groups on the polymer backbones
- The interpenetrating network (IPN) is formed, trapping the drug molecules in the polymer matrix
- The IPN is pH sensitive:
  - at low pH the equilibrium is shifted towards complexation, retarding the trapped drug release
  - at high pH the H bonds are destroyed, increasing the release rate

Polymer complexation



Polymer complexation

- FDA approved polymers
- Polyacids
  - crosslinked poly(acrylic acid) (PAA)
  - poly(methacrylic acid) (PMAA)
  - poly(vinyl acetate phthalate) (PVAP)
  - cellulose acetate phthalate (CAP)

- Polybases
  - poly(vinyl pyrrolidone-co-vinyl acetate) (PVP/VAc)
  - hydroxypropyl methylcellulose (HPMC)

Aims

The aims of this study are:

- To develop a generic oral delivery system based on the complexation of PAA with various other polymers
- To study the *in vitro* release of model drugs: verapamil, diclofenac sodium and clarithromycin
- To study the *in vivo* release of diclofenac sodium from the polymeric drug delivery system to achieve bioequivalence

Tablet preparation

Tablets were prepared as follows:

- Various ratios of PAA, PMAA and PVP/VAc solutions were added and stirred, all with a total polymer mass of 5 g
- Ethanol was added to inhibit complexation before spray drying
- After spray drying, the dry polymer formulations were mixed with an equivalent mass of drug
- The polymer/drug mixtures were pressed into tablets using a single punch press

Dissolution studies

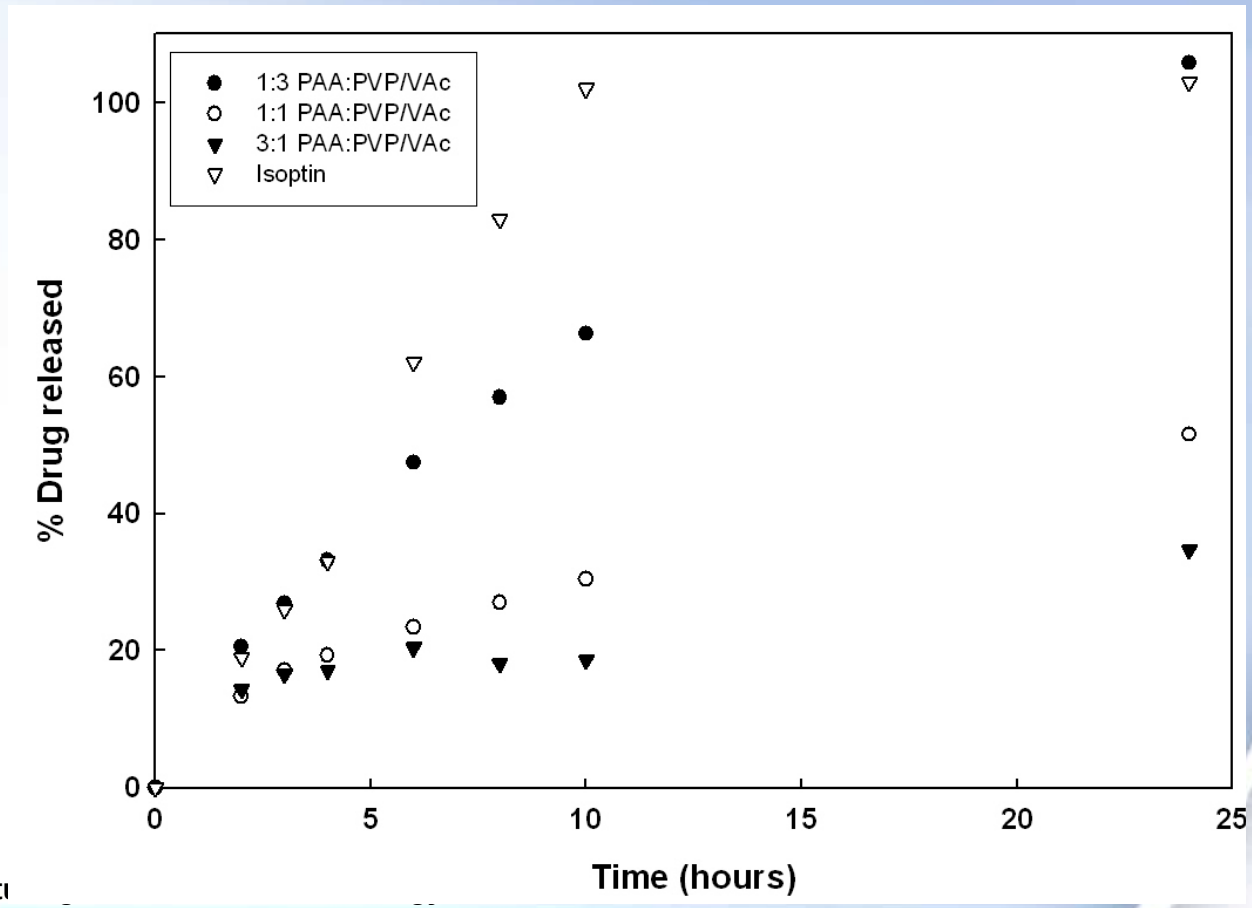
The *in vitro* studies were all carried out according to US Pharmacopoeia (USP) standards:

- Drug release was determined using an SRII 8-flask rotating paddle dissolution bath
- Gastric and intestinal pH conditions were simulated using a standard 1.2 pH, 0.1 N HCl acid buffer, and 6.8 pH phosphate buffer, respectively
- Dissolution in acid buffer for 2 h, thereafter in basic buffer for 24 h
- Analysis using HPLC

In vitro verapamil release studies

Results

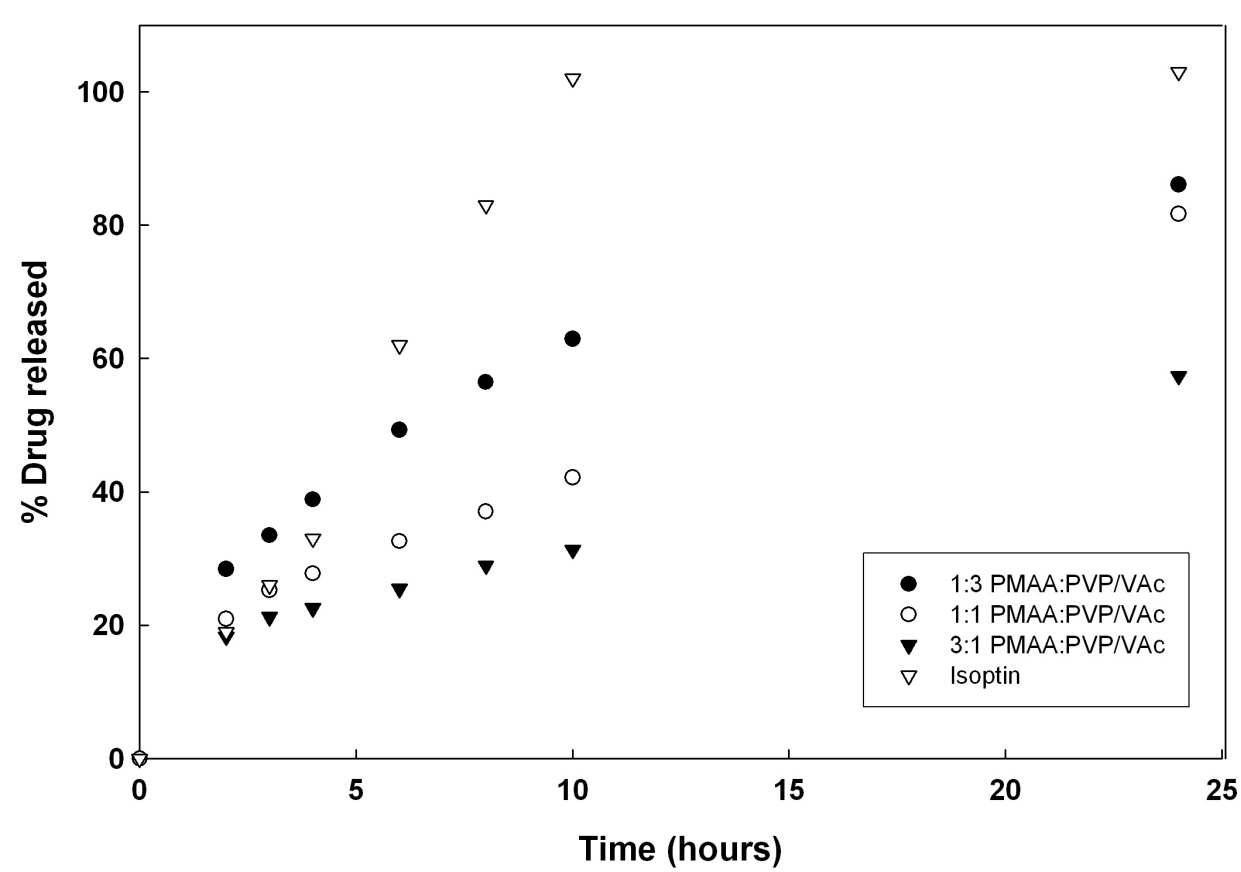
Release profiles of verapamil from different ratios of PAA and PVP/VAc systems



In vitro verapamil release studies

Results

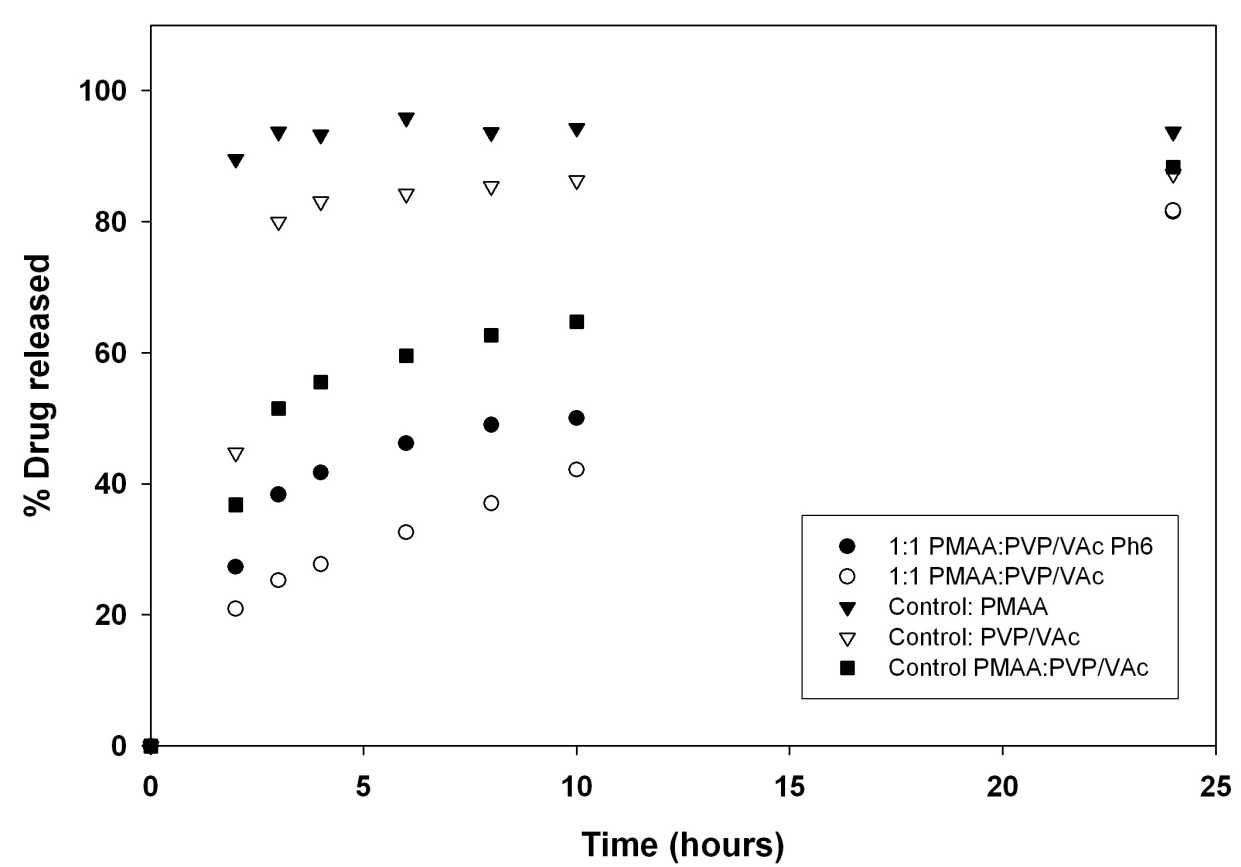
Release profiles of verapamil from different ratios of PMAA and PVP/VAc systems



In vitro verapamil release studies

Results

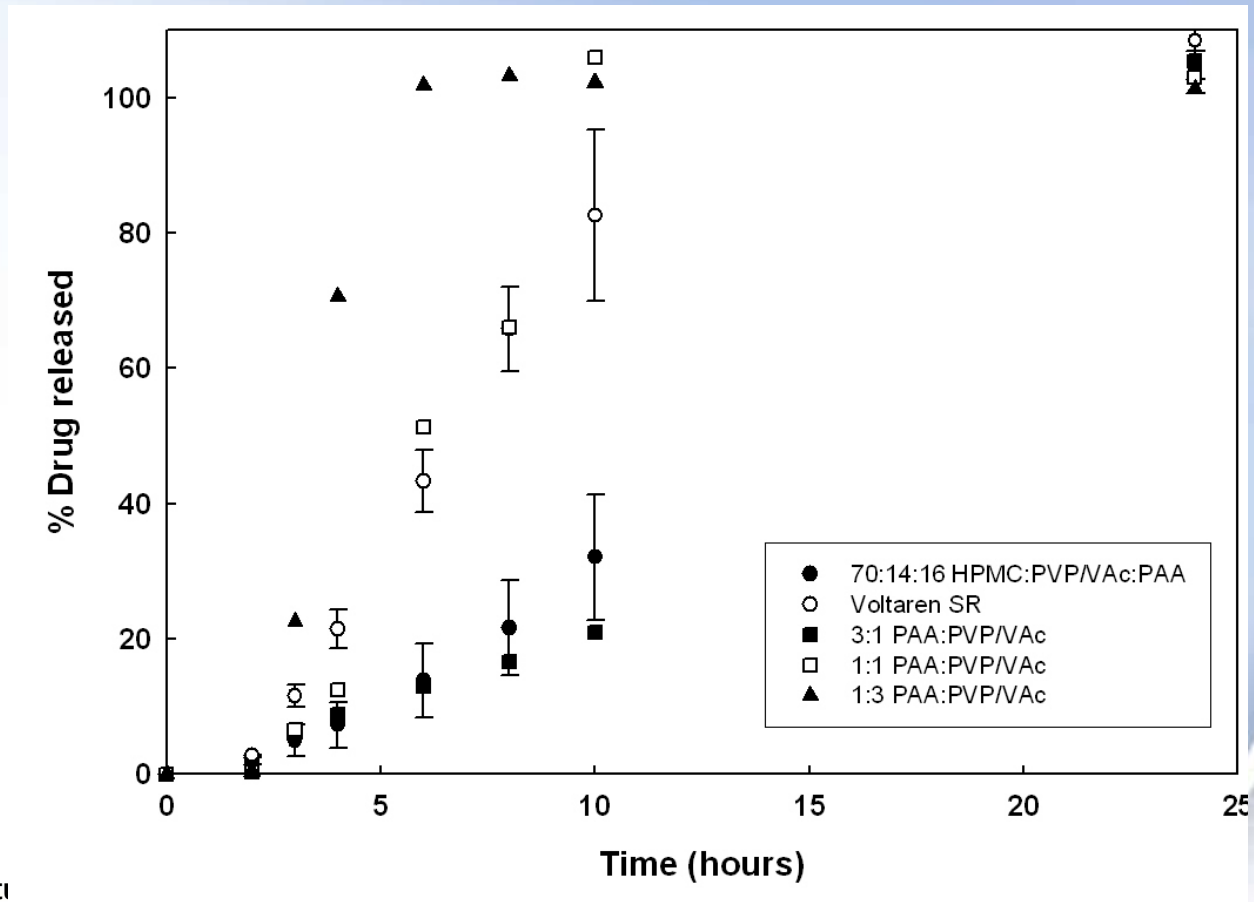
Release profiles of verapamil from PMAA and PVP/VAc systems and controls



In vitro diclofenac sodium release studies

Results

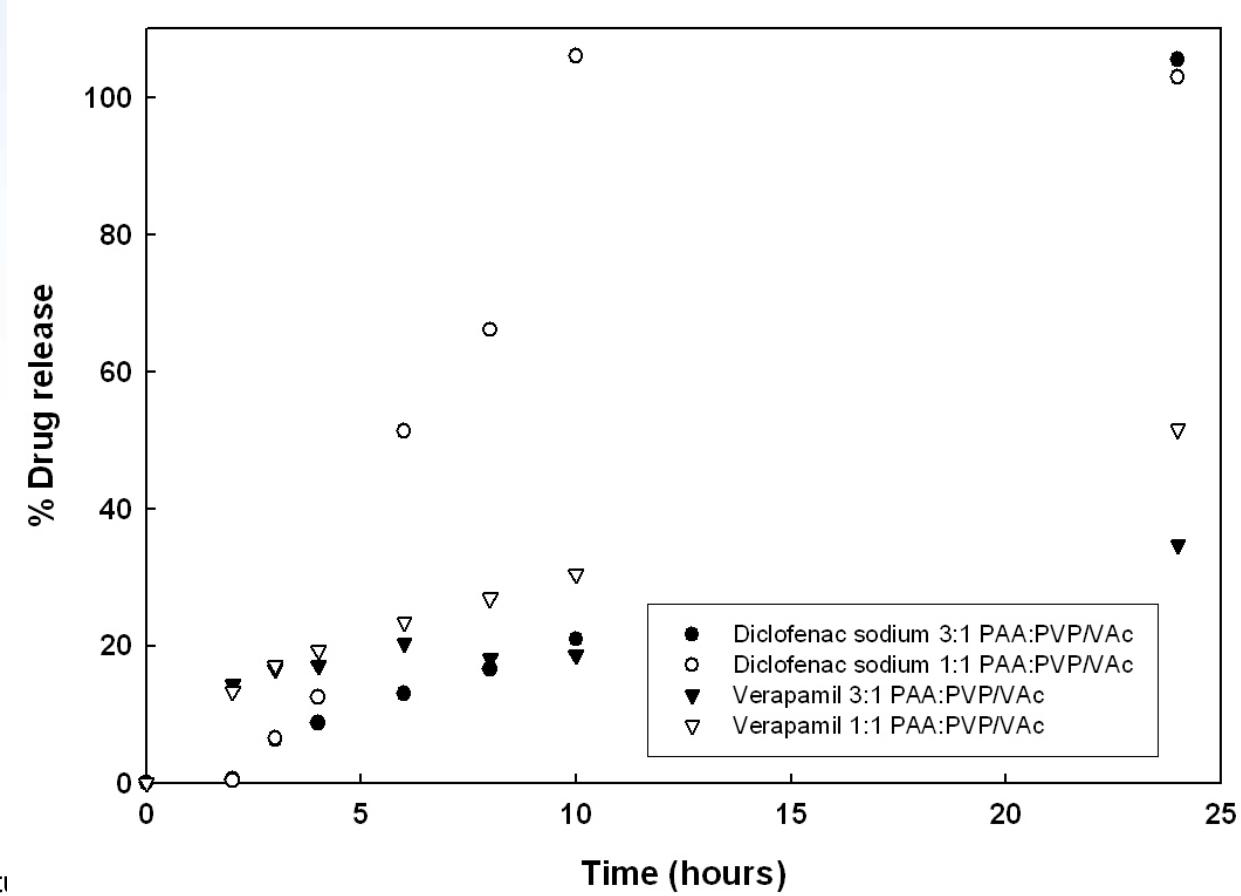
Release profiles of diclofenac sodium from different ratios of PAA and PVP/VAc systems



In vitro diclofenac sodium release studies

Results

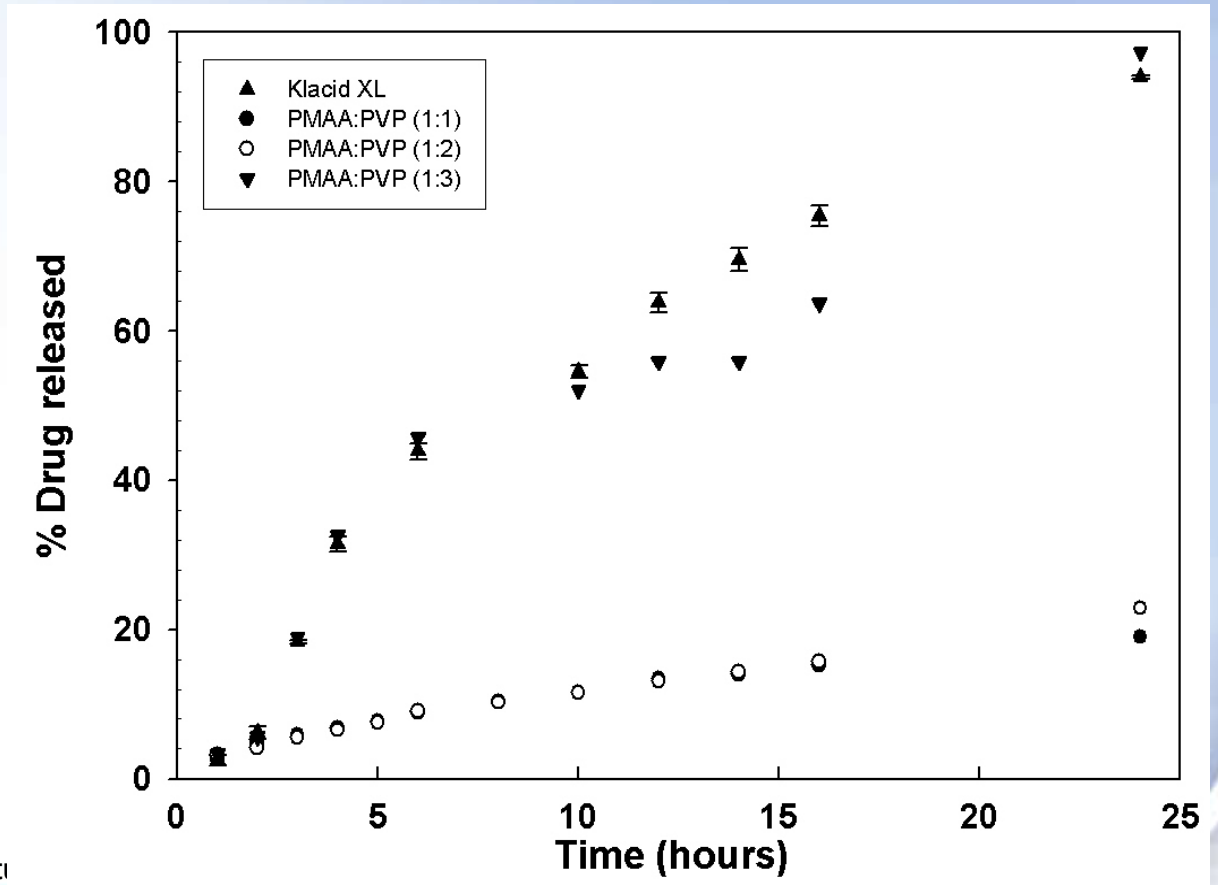
Release profiles of diclofenac sodium and verapamil from different ratios of PAA and PVP/VAc systems



In vitro clarithromycin release studies

Results

Release profiles of clarithromycin from different ratios of PAA and PVP/VAc systems



In vivo diclofenac sodium release studies

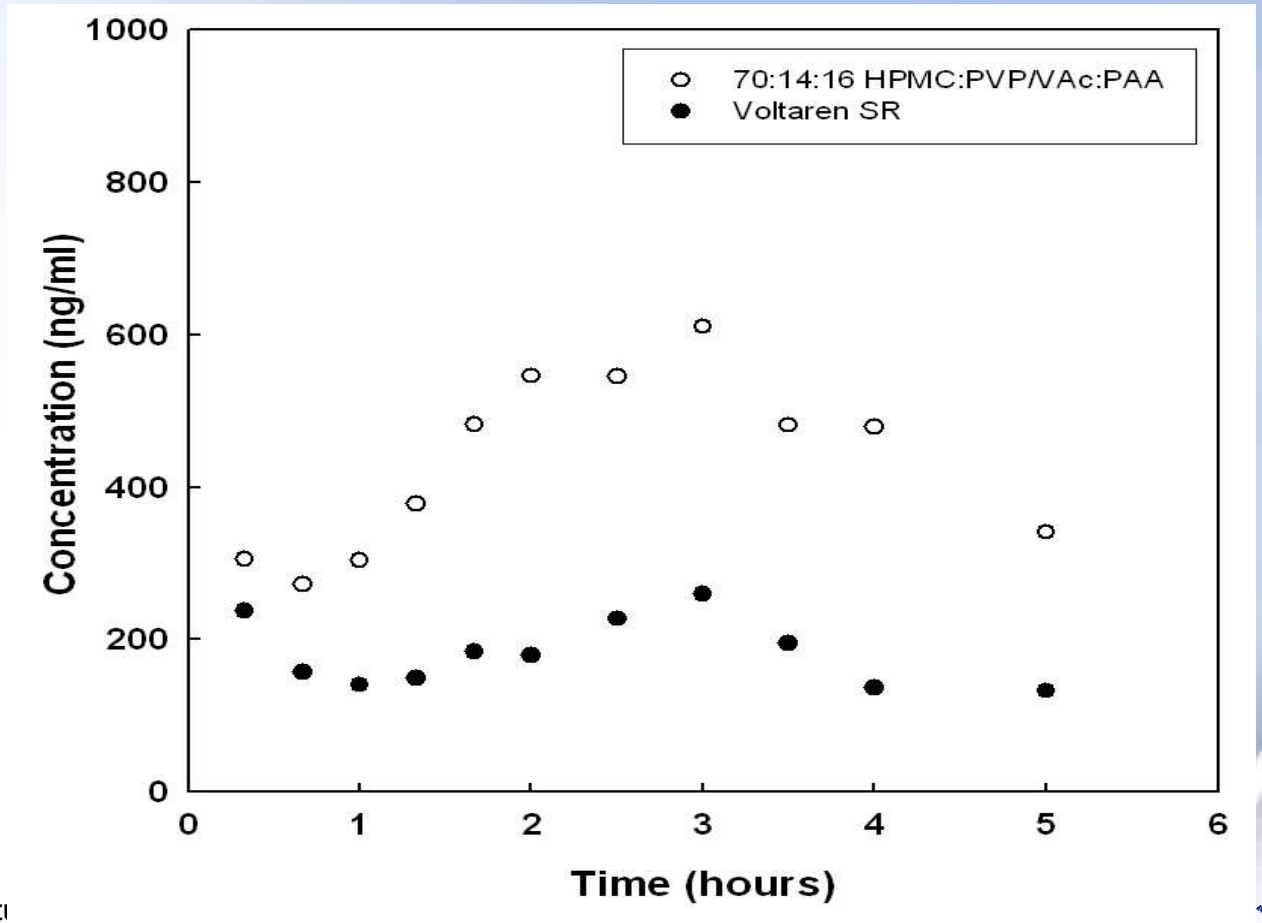
Results

- The *in vivo* release of diclofenac sodium were studied on six healthy male volunteers, aged between 18 and 30 years
- The study was based on a single dose, randomised, balanced, two-way crossover
- Plasma samples collected pre-dosing on clinic days and post-dosing for 5 hr
- Washout period of at least 7 days between each dosing period

In vivo diclofenac sodium release studies

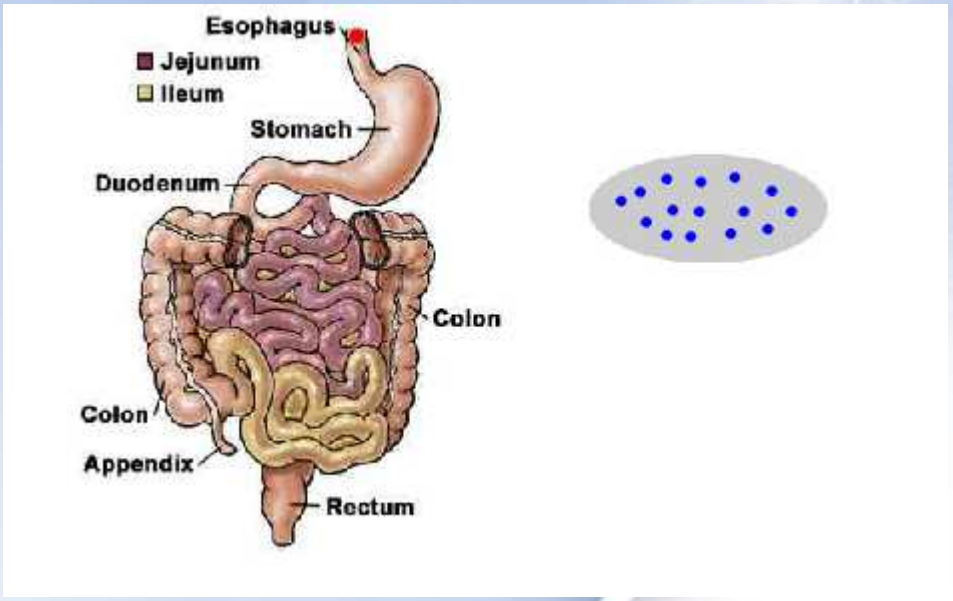
Results

In Vivo release profiles of diclofenac sodium from formulation containing PAA, HPMC and PVP/VAc



Conclusions

- Process based on polymer complexation
- Constant release achieved via:
  - Swelling of the hydrogel
  - Dissolution
  - Solubility of drug
- Release rate can be tailor-made by manipulating:
  - Polymer ratios
  - Complexation strength
- Can be used on acidic & basic drugs



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