P2.105 EFFECT OF BILE SALTS ON DRUG RELEASE FROM HPMC MATRICES

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Drug release from hydroxypropylmethylcelluose (HPMC) matrices is affected by a variety of factors such as: polymer characteristics, drug type, temperature and ionic strength of the dissolution medium. It has been reported that the anionic surfactant, sodium lauryl sulphate (SLS), decreased the release rate of chlorpheniramine maleate from HPMC tablets (1). The present study concerns the effect of bile salts on drug release from HPMC matrices.

7mm tablets (120mg) were prepared using a formulation containing HPMC (Methocel K4M) and 30mg diclofenac Na (<90μm) by direct compression (hardness of 12 Kp) using an instrumented F3 tablet press. Drug release was monitored in a USP apparatus I (100 rev min^{-1}) in 900ml of distilled water or medium containing 2, 10 or 20mM sodium cholate (SC) at 37°C. HPMC solutions with or without sodium cholate were prepared and after 24 hours their viscosity (at 25°C) and their cloud point temperatures (temperature at which light transmission was reduced by 50%) (2) were measured.

Diclofenac Na release from HPMC K4M tablets decreased progressively as the concentration of sodium cholate in the dissolution medium was increased. The time taken for 50% drug release ($T_{50\%}$) was; 160min in water compared to 182min in 2mM, 218min in 10mM and 255min in 20mM sodium cholate solutions. This enhanced sustained action may be due to an interaction between SC and HPMC polymer. Similar effect reported previously with SLS in HPMC matrices were described to be related to the ability of the anionic surfactant to bind to non-ionic polymers increasing their viscosity (1). Here, it was found that 20mM sodium cholate caused only a slight increase in the viscosity but there was a dramatic increase in the cloud point temperature of the HPMC K4M solutions. Therefore, bile salts may have a major effect on drug release from HPMC matrices.

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P2.106 ASSESSMENT OF TOXICITY OF A NOVEL DEVICE FOR SUSTAINED DELIVERY OF LEVONORGESTREL TO THE UTERUS

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There are several clinical conditions, for example endometrial hyperplasia and post-menopausal hormone replacement therapy, for which sustained, local delivery of progestogens to the uterus may be advantageous due to the reduction of systemic effects. We have previously reported the development of a drug-releasing nylon hollow fibre small enough for easy passage through the cervix and capable of sustained drug release for up to 75 days (Ostad et al., 1994). Using tissue culture techniques, however, we have shown that the released drugs had a deleterious effect on an endometrial cell line (Ostad & Gard, 1995). We now wish to report the effects of these drug delivery devices on uterine histology in a mammalian model.
Hollow nylon fibres containing levonorgestrel (LNG) were inserted into one horn of the guinea-pig uterus following laparotomy. Both horns of the uterus were removed 5 days later and the tissues underwent extensive histological examination to assess the extent of mitosis and death/damage in epithelial, glandular and stromal cells. The untreated contralateral horn was used as a control.
Control hollow fibres containing vehicle, i.e. 100% ethanol (n=3) or 70% ethanol (n=6) had no significant effects on any of the parameters studied. Similarly, in those animals treated with fibres containing 20μg levonorgestrel (in 20μl 70% ethanol, n=6) or 130μg LNG (in 20μl 100% ethanol, n=6) there was no evidence of significant toxicity.
These results indicate that the previous demonstration of a toxic response to the drug-releasing fibres *in vitro* may have been misleading and that there is reduced toxicity *in vivo*, possibly due to distribution and metabolism of the steroid within the endometrial tissue, but not within the cultured cell monolayer. The hollow fibres may therefore be a useful method for targeted, sustained drug release to the uterus.

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P2.107 SLOW RELEASE PELLETS CONTAINING BETA-BLOCKER

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Metipranolol is beta-blocking agent used in the treatment of hypertension and some other cardio-vascular diseases. It is suitable drug for slow release forms. Multiple dosage form - pellets were chosen for their significant advantages: low fluctuation in plasma levels of the drug, longer effect and simple dosage regimen, low incidence of adverse effects in gastrointestinal tract. The indiferent spherical particles (nonpareil) were prepared as the core material. Metipranolol base and metipranolol fumarate in suspension and fluid bed coating technique were used for pellet formulation. Two types of final coatings were prepared to control the drug release: the first one of ethylcellulose, the other one of polymethacrylate derivate Eudragit E. The basket dissolution method was used to determine the release of the drug in vitro conditions. The results showed that the release of the both drugs is pH dependent. This fact made difficulties in formulation of metipranolol base sustained released pellets and caused the first order release kinetics of metipranolol fumarate from prepared dosage form.

P2.108 PARAMETERS AFFECTING THE FORMULATION OF NSAID'S-CONTAINING GASTRORESISTANT BEADS

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When given orally to patients, NSAID'S, can provoke mild to severe gastric irritation side effects. Reduction of gastrointestinal irritation caused by non-steroid anti-inflammatory drugs (NSAID'S), can be achieved using gastroresistant granules which are preferable to coated tablets or capsules that have longer gastric residence times in stomach.

The present work reports the studies of formulation of a model NSAID using a recently described method (1). Briefly, drug-loaded hydroxypropyl methylcellulose phthalate (HP_{50}) beads were prepared using a technique which is based on the variation of HP_{50} solubility with pH. The change in solubility that occurs when an alkaline suspension of HP_{50} and a drug is added dropwise, to a cold citric acid solution under stirring, is sufficient to precipitate HP_{50}, and create spherical particles, that include the drug.

The influence of different process-variables was evaluated and related to the final characteristics of the formulations. Low viscosity of suspensions, stirring speeds of the citric acid between 200-300 rpm, type of agitation leading to the immediate sinking and precipitation of the suspension drops, as well as fluid-bed drying, were found to be the best conditions for the process. Furthermore, the physicochemical properties of the drug itself can influence bead formation.

The preparations resulted in spherical beads, with a monomodal narrow particle size distribution (around 1,4 mm). Values of 1,3 g/cm^3 for the density, 4,3 kg for the hardness and a drug encapsulation efficiency of 100%, confirmed the applicability of the process.

The dissolution tests were made following the specifications of the USP XXIII and confirmed the gastroresistance of the granules, since only 1,5% of the drug was released within 2h in HCl 0,1N and more than 80% was released after 45 min in phosphate buffer. Finally, the dissolution profile fits the model of Wagner (2), which is applicable to matrixes that have solubility-pH dependent, such as gastroresistant polymers.

References

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