Development and assessment of captopril loaded matrix-type pellets

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ABSTRACT SUMMARY
Captopril (CPT) loaded matrix-type pellets were manufactured using extrusion-spheronization. The purpose of the study was to investigate the effects of formulation variables such as polymer type and concentration on the physicochemical properties of the pellets and their formation. The pellets were characterized in terms of their shape, surface morphology, flow properties and in vitro release. The results revealed that inclusion of as little as 5% w/w hydroxypropyl methylcellulose (HPMC) in the formulations resulted in poor spheronization and the formation of dumbbell-shaped pellets due to the plasticity of HPMC. CPT pellets with acceptable morphological and physicochemical characteristics were successfully manufactured using MCC, HPC and distilled water. In vitro drug release studies revealed that CPT was rapidly released from all formulations.

EXPERIMENTAL METHODS
CPT loaded matrix-type pellets were manufactured using Caleva® extrusion-spheronization equipment (Sturminster Newton, United Kingdom). All pellet formulations consisted of microcrystalline cellulose (MCC), hydroxypropyl cellulose (HPC) and distilled water. The dry excipients were blended using a Kenwood® FP693 planetary blender for 20 minutes. A sufficient amount of distilled water was added to the powder blend and the wet mass was immediately transferred to a Caleva® Extruder 20 (screen aperture diameter size = 1 mm) operated at 35 rmp. The extrudate was collected and spheronized for 2 minutes at 800 rpm in a Caleva® Spheronizer MBS (250 bowl). The final product was tray dried at 35°C until a constant mass was achieved. The dried pellets were screened through 2000, 1250, 800 and 315 µm screens and stored at room temperature prior to analysis.

RESULTS AND DISCUSSION
CPT loaded matrix-type pellets with acceptable morphological and physicochemical characteristics were successfully manufactured using MCC, HPC and distilled water. The effects of the addition of different water soluble and water insoluble excipients such as ethyl cellulose (EC) on pellet formation were investigated. The influence of high and low CPT loading and the feasibility of incorporating a hydrophilic swellable polymer such as HPMC into the formulation were investigated. The flow properties, yield, CPT content and size distribution of the pellets were determined using appropriate methodologies. The surface morphology of the pellets was assessed using a Vega® Scanning electron Microscope (Tescan, Vega LMU, Czechoslovakia Republic). In vitro release studies were performed using USP Apparatus 2 dissolution tester (Model No 73-100-104, Hanson Research, Chatsworth, CA, USA) coupled to an auto sampler.

INTRODUCTION
The process of developing products for new chemical entities can be challenging, time consuming and expensive [1,2]. With this in mind an increasing emphasis has been placed on developing and improving drug delivery systems for well-known currently available therapeutic compounds [1,2]. This approach is cost effective and requires shorter developmental times [1,2]. The use of multi-particulate drug delivery systems (MDDS) has been extensively studied in an effort to enhance the clinical benefits of well-established therapeutic compounds [3-7]. The advantages of MDDS over conventional single-unit dosage forms include free dispersion in the gastrointestinal tract and decreased variation in gastric emptying and overall transit time [4,8,9]. MDDS are less susceptible to dose dumping and are flexible for further modification such as the application of polymeric films or compaction into tablets [4,8]. Extrusion-spheronization is an established approach for the manufacture of MDDS. The quality and physicochemical characteristics of pellets manufactured by extrusion-spheronization are influenced by several factors including excipients and process parameters [9,10]. In the present study matrix-type pellets were manufactured using the freely water soluble angiotensin converting enzyme inhibitor, CPT. The aim of the study was to manufacture CPT loaded matrix-type pellets using extrusion-spheronization and to determine the effects of formulation variables on the physicochemical properties of pellets and their formation.
Formulations containing up to 20% w/w EC produced pellets with acceptable physicochemical characteristics. Drug content studies showed that the CPT content of the pellets typically ranged from approximately 88-101%. In vitro drug release studies revealed that CPT was rapidly released from all the matrix-type pellet formulations and the drug was released virtually in totality within 2 hours. A typical dissolution profile for CPT release from pellets manufactured using 40% w/w CPT, 59% w/w MCC and 1% w/w HPC is shown in Figure 2.

CONCLUSION

The type and quantity of the polymers used for extrusion-spheronization influence the formation and quality of pellets. Careful selection of excipients for the extrusion-spheronization process is essential for the formulation and manufacture of pellets with acceptable physicochemical characteristics for MDDS. The high water solubility exhibited by CPT and the large surface area of the pellets contributed to the rapid release of the drug from the pellets. The application of a polymeric film to the pellets may be an approach for modulating drug release from these systems.

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REFERENCES