ABSTRACT SUMMARY
Gastroretentive sustained release matrix captopril (CPT) tablets were manufactured using a direct compression process. A Response Surface Methodology (RSM) approach using a three-factor CCD was used to develop and optimize the tablet formulation. The content of hydroxyl propyl methylcellulose (HPMC), microcrystalline cellulose (MCC) and sodium bicarbonate were selected as key independent variables for the optimization of the formulation. The key responses that were monitored were floating lag time (FLT) and cumulative % CPT released after 0.5, 2, 6 and 12 hours. The results revealed that the HPMC and sodium bicarbonate content were factors that had a significant impact on CPT release and FLT, respectively.

EXPERIMENTAL METHODS
A direct compression process was used to manufacture CPT gastroretentive sustained release tablets and the proposed design for these tablets was a single unit matrix tablet that achieved in vitro buoyancy based on effervescence. The formula for the tablets contained 50 mg CPT, HPMC a hydrophilic matrix former, MCC a filler, sodium bicarbonate an effervescent agent, magnesium stearate a lubricant, talc and colloidal silicon dioxide as glidants. On the basis of a study of the influence of formulation variables on CPT release and the floating properties of the tablets, the composition of HPMC, MCC and sodium bicarbonate content were selected as key variable for the optimization of the tablet formulation using a RSM approach with a CCD. The key responses that were monitored were the cumulative % CPT released after 0.5, 2, 6 and 12 hours of dissolution testing and FLT. Analysis of Variance (ANOVA) was used to quantitatively analyze the significance and relevance of the independent variables. A numerical optimization approach was used to predict a formulation composition that would produce minimal initial CPT release, a short FLT and maximum release after 12 hours. Tablets from each batch that was manufactured were subjected to several quality control tests, in vitro buoyancy and dissolution testing. The short-term stability of the optimized formulation was established by performing stability studies at 25°/60% RH and 40°/75% RH.

RESULTS AND DISCUSSION
The results from the in vitro buoyancy studies revealed that all formulations maintained in vitro buoyancy for up to 12 hours. The achievement and maintenance of in vitro buoyancy is attributed to the presence of the effervescent agent, sodium bicarbonate that was dispersed in the tablet matrix. When the CPT sustained release tablets came into contact with HCl, an effervescence reaction occurred and carbon dioxide bubbles were release into the HPMC gel layer surrounding the tablets.

Visual inspection of the tablets revealed the presence of gas bubbles on the surfaces of the tablets (Figure 1). The ability of the tablets to float for up to 12 hours suggested that Methocel® K100M can form a durable gel layer around the tablets that can effectively entrap gas bubbles and promote in vitro buoyancy for at least 12 hours.
The results for CCD revealed that the linear contribution of HPMC content in the formulation had a statistically significant and antagonistic effect on the % CPT released from the tablets. Therefore an increase in the HPMC content in the formulations resulted in a decrease in the % CPT released. The decrease in CPT release observed when the HPMC content was increased was more than likely the result of an increase in the thickness and viscosity of the HPMC gel layer surrounding the tablets which consequently increased the diffusional path length and slowed CPT release [6]. The sodium bicarbonate content had a significant and antagonistic effect on the FLT and this was likely due to an increase in the amount of carbon dioxide generated during the effervescent reaction which promoted rapid achievement of in vitro buoyancy.

Short-term stability tests for the optimized formulation revealed that there was no significant change in appearance and physicochemical properties of the tablets after 60 days of storage at 25°/60% RH and 40°/75% RH. However long-term stability studies would be required to determine the shelf-life and stability of the tablets over an extended period.

Tablets from each batch that was manufactured were subjected to several quality control tests and the results revealed that the tablets met compendial specifications with regards to weight uniformity, content uniformity, CPT content and friability. Typical CPT release patterns observed for all formulations revealed an initial burst effect during the first 2 hours of dissolution testing which was attributed to the high water solubility of CPT that also possibly induced a high driving force for CPT release [7]. The initial release was followed by a phase that was characterized by a slower release rate of CPT from the tablets until the end of dissolution testing (Figure 2). Further studies to improve this formulation would include approaches to reduce the initial burst effect.

CPT release kinetic studies for the optimized formulation were established by fitting the in vitro release data to several mathematical models. The data were best described using the Korsmeyer-Peppas model ($R^2=0.9971$) and the value of release exponent ($n=0.4787$) suggests that the tablets exhibited an anomalous drug transport mechanism.

CONCLUSION

Gastroretentive sustained release CPT tablets with the potential for further development and improvement were developed in these studies. The optimized formulation released 86% CPT after 12 hours of dissolution testing in 0.1 M HCl and remained buoyant for the duration of the dissolution test. This research has the potential for use as a starting point for the development of gastroretentive sustained release formulations for API that exhibit a high degree of water solubility and/or that may require gastric retention in order to improve in vivo stability.

REFERENCES


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