FORMULATION DEVELOPMENT OF POORLY STABLE AND POORLY PERMEABLE DRUGS

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ABSTRACT SUMMARY
Formulation development of pharmaceutical drugs which degrade with prolonged contact with gastro-intestinal fluids has always been a challenge. If such drugs work as a p-glycoprotein (ppg) substrate then the formulation development becomes even more complicated since poor permeability makes it more difficult to maintain the required blood plasma level of the drug. In order to overcome this issue, other techniques of drug delivery such as the drug transport through paracellular or active transport could be engineered. However, such drug delivery systems can prove to be very expensive [1]. In this research, a method of multiparticulate system with combination of pulsatile release is discussed. The final dosage form consisted of five bead populations in a specified ratio so that five release bursts of API would occur at five different locations in the gastro-intestinal tract. This approach helps to ensure that the concentrations of API in intestinal tract result in the desired concentration versus time profile of API in blood plasma with reduced C\text{max} and increased T\text{max}, relative to a single immediate-release dose [2, 3].

INTRODUCTION
Pharmaceutical research is increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. In recent pharmaceutical applications involving pulsatile delivery, multiparticulate dosage forms are gaining much favor over monolithic forms because of their potential benefits like predictable gastric emptying, least risk of dose dumping, flexible release patterns and increased bioavailability with minimum inter- and intra-subject variability. Such multiparticulate system could be used effectively to overcome p-glycoprotein expression by dose dumping [4].

In this study, extrusion spheronization was used to produce drug loaded beads approximately 0.8mm in diameter. The beads were coated to produce pH dependant pulsatile releases. The API was BCS class III (poorly permeable) with poor stability in gastro-intestinal fluids. In order to maintain the plasma level of drug in the blood for 24 hours, five types of coated bead populations were mixed to form the final dosage form. The in vitro dissolution results showed that the core beads displayed a pulsatile release of drug in 15 minutes as soon as it reached simulated gastric fluids. The remaining four bead populations were designed to have a pulsatile release in the duodenum, jejunum, ileum and colon respectively. Hence, the API would be delivered to the gastro-intestinal tract from the gastric up to the colon. By combining five populations of beads, it was possible to develop a single-dose product to achieve desired drug plasma concentration for 24 hours, as inferred from the in vitro data.

EXPERIMENTAL METHODS
1. Formulation development: The formulation development was done by choosing and optimizing materials composition to give the pH dependant pulsatile releases and optimizing processes at lab scale. For wet granulation, water was used as a granulating agent. To obtain spherical beads, both formulation and equipment parameters for extrusion and spheronization were optimized. The beads were spherical in shape and had close size distribution around 0.8mm. The beads after spheronization were dried using fluid bed dryer to achieve desired level of moisture in the beads. The dried beads were sieved to remove the agglomerates and fines and then split into smaller sub-lots for coating studies.

Sub-lots of core beads were coated with specific polymers in order to create five bead populations with unique pH dependent pulsatile release. The first pulsatile release was obtained from core beads which release the entire dose in gastric fluids. Eudragit L100-55 coating was applied to obtain the API release in the duodenum, Cellulose Acetate Phthlate (CAP) coating was used to obtain the API release in the jejunum. For the third population of beads hydroxypropyl methylcellulose acetate phthalate (HPMCAS-HF) coating was applied so that the pulsatile release of API could be obtained in the ileum. For the fourth bead population, core beads were coated with Eudragit FS30D to obtain a pulsatile release in the colon. Once the five beads populations were manufactured, the proportion of each bead population was mixed using v-blender and then filled in size 0E capsules to produce final
dosage form. The portions of each bead populations were optimized empirically by conducting several in vitro dissolution tests.

2. Dissolution method development: Various dissolution test methods were used as a part of analytical and formulation development in order to achieve a discriminating dissolution method. The two step sequential dissolution (2 hours in pH 1.2 followed by 4 hours in pH 6.8) did not show enough discrimination in API release from the five bead populations. It was concluded that the sequential dissolution using USP APP I with 100 rpm (2 hours in pH 1.2, 2 hours in pH 5.5, two hours in pH 6.0, 6 hours in pH 7.4) was a satisfactory method to produce the discrimination in dissolution profiles and was used to assess the formulations for the comparative pharmacokinetic study.

RESULTS AND DISCUSSION
In order to eliminate the necessity of implementing the similarity factor (F2) for core beads, the desired dissolution profile of cores was established as at least 85% API release in less than 15 minutes. Figure 1 shows the dissolution profile of core beads using USP APP I at 100 rpm in 0.1N HCl.

The optimized dissolution profiles for the four bead populations are shown in Figure 2. The formulation for the fifth bead population is being optimized and will be presented at a later time. The dissolution profiles show enough discrimination based on pH/time to theoretically obtain four distinct pulsatile releases in-vivo.

CONCLUSION
A formulation consisting of five bead populations with five distinct pulsatile releases was successfully developed. USP APP I (basket) dissolution method with sequential dissolution at 100rpm was found to be a discriminating method to develop the product. The friability of core beads was found to be (< 1.0 %) satisfactory.

REFERENCES

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