A NOVEL GRANULATION TECHNIQUE TO OBTAIN ZERO ORDER RELEASE FROM SOLID DOSAGE FORMS

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ABSTRACT SUMMARY
Developing formulation to obtain a zero order release profile for a water soluble drug molecule is always challenging. Release controlling polymers such as hydroxypropyl methyl cellulose (HPMC) gels in water and allows the drug release through permeation. If such polymers are used in the matrix type formulation, the drug release profile is always first order. Traditionally, zero order release is obtained either by using polymers such as Carbopol which produces more viscous gel or by film coating tablets using release controlling polymer such as methacrylate polymers.

In this research, a novel approach for is discussed to obtain a zero order release by retarding initial burst. HPMC (K100LV) grade was chosen as a release controlling polymer for proof of concept since this polymer provides first order release with a substantial initial burst when traditional granulation approaches are used. A small portion of HPMC (K100LV) was added in the granulation. Rest of the portion of HPMC (K100LV) was added as an extra-granular material. During granulation, the drug particles agglomerated with HPMC which helped in retarding initial burst during dissolution. The dissolution results from tablets manufactured using granulation techniques such as moisture activated dry granulation, high shear granulation, fluid bed granulation, roller compaction were compared to investigate the effects of granulation techniques on the drug release kinetics.

INTRODUCTION
There are several techniques available for formulation scientists to achieve the zero order release kinetics. However, most of these techniques are quite complicated, expensive, time consuming, and difficult to manufacture. There are many formulations developed so far and are available in the literature but few formulation techniques that have resulted in a successful zero order release mechanism [1-3].

We wanted to develop a simple formulation technique based on a matrix type system that would retard the initial burst in drug release and provide zero order release for 12 hours for water soluble drugs. Since, only a small portion of release controlling polymer was added in the granulation, the overall dissolution profile of drug did not slow down as compared to when the formulations are prepared using traditional high shear granulation technique. Our approach helped only to retard the initial burst and thus a zero order release was obtained.

EXPERIMENTAL METHODS
The tablets were manufactured by granulating the drug and excipients along with portion of HPMC (K100LV). The granules were then dried to desired moisture level. The dried granules were subjected to milling and then extra-granular materials such as remaining portion of the release controlling polymer (HPMC) and lubricant were added. Compression was carried out using the round standard concave tablet tools. The tablets were subjected to multiple dissolution media, such as pH 1.2, pH 4.5, and pH 6.8 buffers.

For high shear wet granulation and moisture activated dry granulation trials, Key KG-5 with 5 L bowl was used. For fluid bed granulation trials, GPCG-3 was used. For all the blending and milling trials, 1-cu ft V blender and Fitzmill respectively were used.

RESULTS AND DISCUSSION
The tablets prepared were robust with respect to the manufacturing process and release profiles. Tablets were subjected to dissolution study in various media for up to 12 hours. The dissolution data was subjected to different mathematical models such as Higuchi, Hixon Crowell, Korsemeyer - Peppas and Sahlin – Peppas to evaluate the mechanism of drug release for individual granulation technique.

Results from initial trials show that the release burst can be minimized by adding some of the release controlling polymer into wet granulation. The release data from three formulations is
compared in Figure 1. All three formulations contain HPMC K100LV 20% w/w. The materials composition of all three batches is exactly the same. In batch 1, a high shear granulation technique was used with all the HPMC added as extra-granular material. In second and third batch, moisture activated dry granulation and high shear granulation was used respectively with 5% w/w HPMC as intra-granular material and 15% HPMC as extra-granular material.

In batch 3 (high shear granulation) the initial burst was reduced significantly due to effective binding of HPMC and the drug. The overall release was still controlled by gelling of HPMC. For batch 2 (moisture activated dry granulation), there was no significant reduction in the initial burst since in this type of granulation, the binding is very weak.

The tablet release kinetics was found to be following pseudo zero order release profile for the batch 2 where 5% w/w HPMC was added in the high shear granulation. In this case, the drug diffusion followed complex two step diffusion process which in turn retarded the initial burst. Further experimentation using four different granulation techniques is underway to validate the theory.

CONCLUSION

Extended zero-order drug releases from tablets were confirmed by fitting the dissolution data to the mathematical models. The dissolution results, mathematical model calculations, and the resultant $R^2$ values indicated that the release mechanism of the tablet formulations exhibited zero order release kinetics for tablets prepared using this approach for various granulation techniques. The dissolution profiles from the formulations prepared using various granulation techniques were compared to evaluate the mechanism of drug releases for these techniques. This approach of retarding initial burst can be employed as a platform technology but, more work needs to be done to check the process scalability and design space for critical manufacturing processes.

REFERENCES


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