

Cathy Federici, Alan Brunelle

Summary

Oral controlled release formulations of Ondansetron HCl were developed using a patented monolithic matrix tablet delivery system. Controlled release preparations of 18 and 24 hours duration are described herein.

Introduction

The objective of this work was to develop controlled release tablet formulations of clinically relevant dosages of Ondansetron HCl over two release durations, and to incorporate floating to induce a possible gastroretentive effect in the longer-acting tablet. Ondansetron HCl is used to control or prevent nausea and vomiting, particularly in patients undergoing chemotherapy and radiation treatments. A controlled release preparation could, in theory, control the onset of nausea and prevent later symptoms in patients who currently need repeated dosing.

Experimental Method

Granulations of API, amino acid combinations, flow agents, and polymer were made using a mortar and pestle at the bench scale, or in a V-blender with

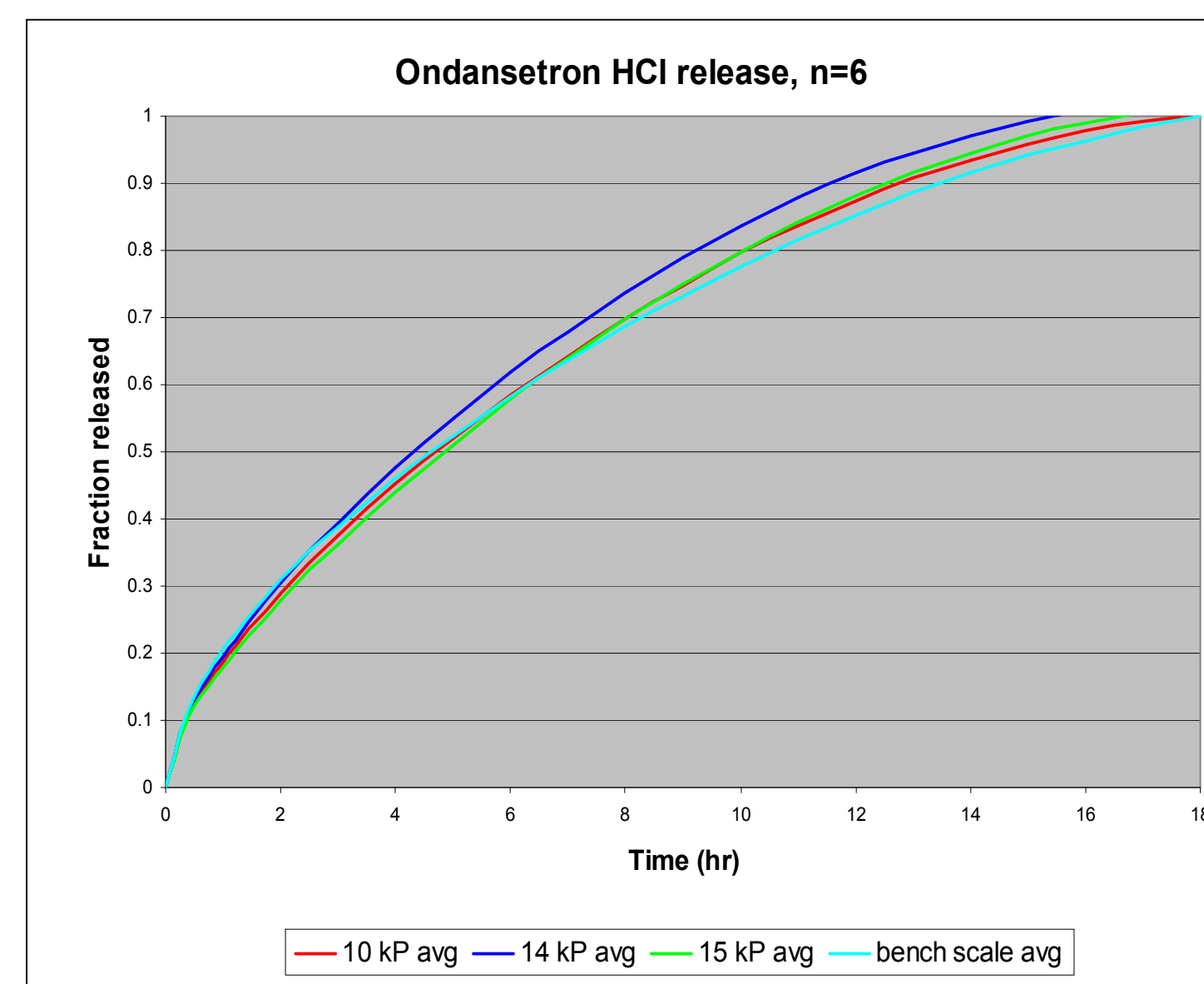
intensifier bar and liquid addition at larger scales. Dried granulation was blended with sodium bicarbonate (in the case of the GR formulation), additional polymer, and lubricants, and compressed on a Carver hydraulic press or Manesty press. Larger-scale production on the Manesty press was performed at a range of compressions to examine release rates of API in tablets of varying hardness. Dissolution was performed without sinkers in a USP Type II apparatus (paddle) at 50 rpm, 37°C. Dissolution medium was USP 0.05M acetate buffer, pH 4.5 or USP 0.1N HCl, pH 1.2. Samples were withdrawn hourly up to 24 hours and analyzed at 308nm using UV spectroscopy.

Results and Discussion

Design of 18-hour release tablet:

This matrix formulation was developed at bench scale before scaling up to approximately 2kg. The 2kg batch was used to determine the effect of compression/tablet hardness on API release. Figure 1 shows the API release from this formulation, at bench scale and 2kg scale. API release does not significantly change within the range of tablet hardness from 10-15kP. Release is complete by 18 hours.

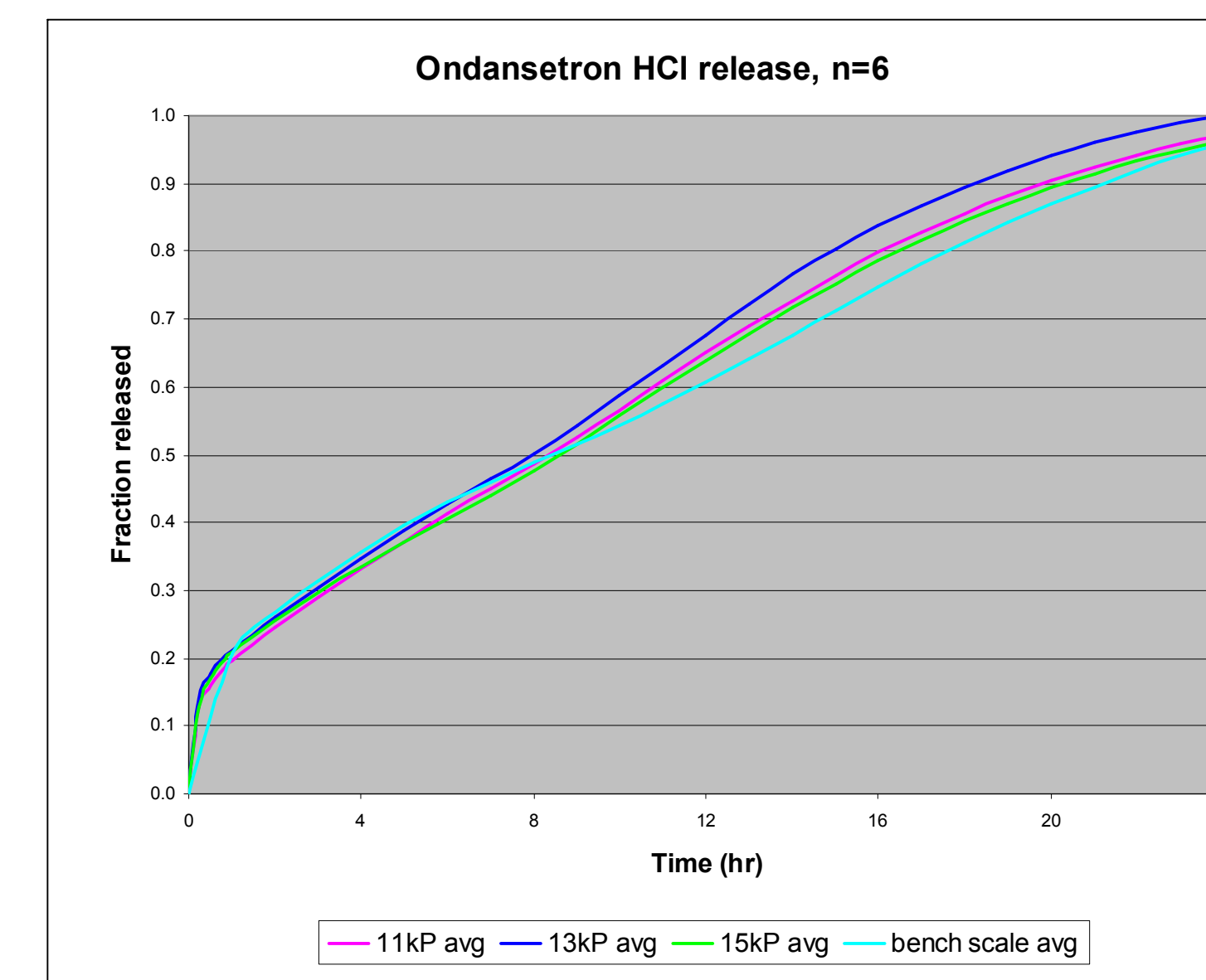
Figure 1. Ondansetron HCl release over 18 hours.



Design of 24-hour release tablet:

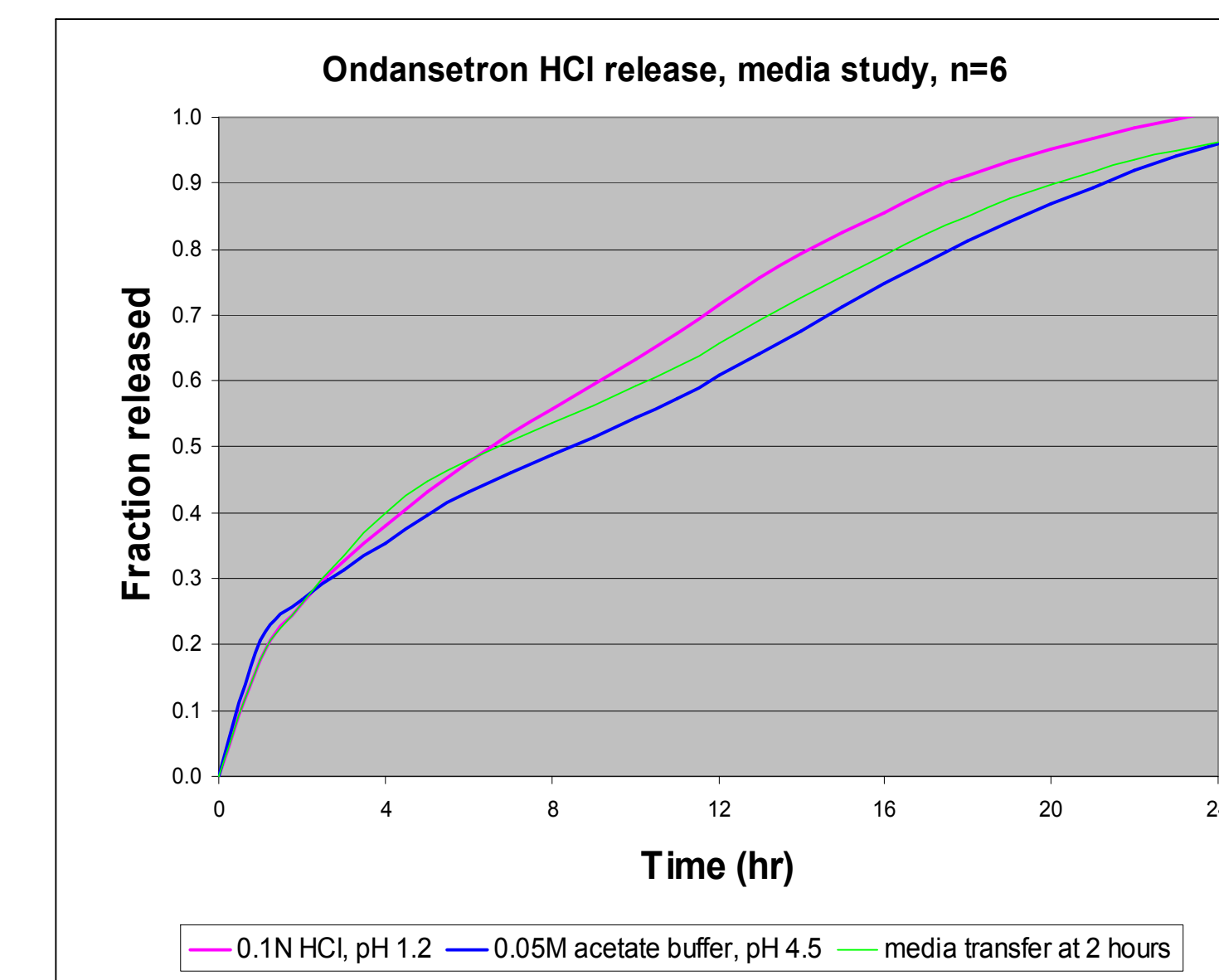
This formulation utilizes a combination of sodium bicarbonate and swelling polymer to generate gas and trap it within the matrix to allow the tablet to float. Dissolution was performed in both 0.1N HCl and 0.05M acetate buffer media, to evaluate floating and release characteristics under both conditions. Figure 2 shows an overlay of bench scale vs. 2kg scale tablets in a hardness range of 11-15kP in acetate buffer medium. All tablets were floating within 15 minutes and remained floating for the duration of dissolution.

Figure 2. Ondansetron HCl release over 24 hours.



Additionally, tablets were tested at 2 hours in 0.1N HCl medium, then transferred to 0.05M acetate buffer medium for the duration of release, to examine the effect of transitioning from pH 1.2 to pH 4.5 on API release and tablet disintegration. Figure 3 illustrates the release of Ondansetron HCl in the different dissolution media, including a transfer from 0.1N HCl to 0.05M acetate buffer after 2 hours.

Figure 3. Ondansetron HCl release from tablet in various dissolution media.



Conclusion

These monolithic tablet formulations effectively controlled *in vitro* release for the desired durations, and the 24 hour formulation was successfully designed to float in low-pH media without compromising release duration.

References

- U.S. Patent 6090411 (Pillay, et al, 2001). *Monolithic tablet for controlled drug release.*
U.S. Patent 6517868 (Fassihi, et al., 2003). *Amino acid modulated extended release dosage form.*

