

Evaluation of STARCAP 1500® in a Propranolol Hydrochloride Capsule Formulation

Franklin J. Gulian, Budhi H. Simon, Kurt A. Fegely, Gus B. LaBella, and Thomas P. Farrell; Colorcon, West Point, PA, USA

OBJECTIVES

To compare the flow properties of STARCAP 1500® to other excipients commonly used in capsule filling and to evaluate the performance of STARCAP 1500 in a propranolol hydrochloride hard gelatin capsule formulation.

INTRODUCTION

Powders for use in capsule filling must be free flowing, non-adhesive, and cohesive enough to form plugs at low compression forces.¹ Carr's compressibility index is commonly used as a parameter to indicate flowability and has been correlated to the variation of capsule fill weight.^{2,3} Intermediate values of Carr's index may be required in some cases to avoid filling problems associated with low flowability (high Carr's index) or excessive flowability (low Carr's index).^{2,4} Higher flowability often corresponds to lower cohesiveness which may be detrimental to formation of plugs or their quantitative transfer.^{2,4}

Encapsulation properties of STARCAP 1500 were previously demonstrated on an IMA Imatic 200 high speed continuous movement dosator machine operating at 100,000 capsules per hour with a fill weight of 380mg into size 1 capsules and a relative standard deviation of 1.2%.

STARCAP 1500 is a unique co-processed mixture of corn starch and pregelatinized starch developed to provide rapid disintegration properties across the pH range present in the human digestive track. STARCAP 1500 was evaluated in a capsule application using propranolol hydrochloride to demonstrate stability, disintegration and dissolution properties. STARCAP 1500 was also compared to lactose.

METHODOLOGY

Carr's index was calculated using the following equation with bulk and tapped density values measured according to USP <616> (method 1 in both cases).

$$\text{Carr's Index} = \left(1 - \frac{\text{Bulk Density}}{\text{Tapped Density}} \right) \times 100$$

Size 1 gelatin capsules were filled using powder blends of propranolol hydrochloride (Medilon BP2000/EP) and STARCAP 1500 (Colorcon) by Pharmaceutical Research Company, Exton, PA. Gelatin capsules were provided by Capsugel® and filled with 240 mg powder (80% excipient / 20% drug).

Capsules were stored at 30°C / 65% RH and 40°C / 75% RH conditions in heat sealed HDPE bottles with desiccant and cotton. At predetermined time points, disintegration time was determined on 6 capsules in 0.1 N HCL, deionized (DI) water, and 6.8 phosphate buffer. Dissolution profiles of propranolol hydrochloride were determined according to the USP monograph for *Propranolol Hydrochloride Tablets*. Dissolution profiles were also obtained using DI water and 6.8 phosphate buffer. Assays were determined using the USP *Propranolol Hydrochloride Tablet* monograph modified for capsules (10 capsules emptied into 400 ml methanol & shaken).

Another set of capsules was prepared using powder blends of either propranolol hydrochloride and STARCAP 1500 or propranolol hydrochloride and spray dried lactose monohydrate in a 75% excipient to 25% drug ratio. Spray dried lactose was obtained from Foremost (Fast-Flo Lactose #316). Capsugel gelatin capsules, size 0, were filled using a MiniCap 50 capsule filling machine for a drug content of 50 mg. Initial dissolution profiles (USP, *Propranolol Hydrochloride Tablets*) were compared to profiles obtained after 1, 3, & 6 months storage in heat sealed HDPE bottles at 40°C/75% RH conditions. Capsules were also stored for one month in an open dish at 40°C / 75% RH conditions.

Viscosity was measured on moisture corrected 10% solids' slurries using a Rapid Visco Analyzer manufactured by Newport Scientific.

RESULTS

Carr's Index

Results show that the Carr's index of STARCAP 1500 is comparable to commonly used excipients for capsule filling.

Table 1. Carr's Index for Capsule Filling Excipients

STARCAP 1500	20.3
Microcrystalline Cellulose, 90 M	24.7
Spray Dried Lactose (monohydrate)	20.5

Disintegration Time

The following figures present disintegration time results in 0.1 N HCL, DI water, and 6.8 phosphate buffer with STARCAP 1500/propranolol hydrochloride capsules (Figures 1-3). The bars represent the 95% confidence intervals. A small variation in average disintegration time was observed in the different media: 81, 110, & 87 seconds, respectively, in 0.1 N HCL, DI water, & 6.8 phosphate buffer. Although these differences are statistically significant, the maximum difference was only 90 seconds for all time zero and aged samples.

Figure 1. Capsule Disintegration Time in 0.1 N HCL 80% STARCAP 1500, 20% Drug, 240 mg fill

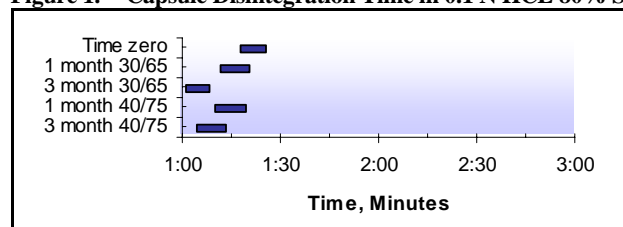


Figure 2. Capsule Disintegration Time in DI Water 80% STARCAP 1500, 20% Drug, 240 mg fill

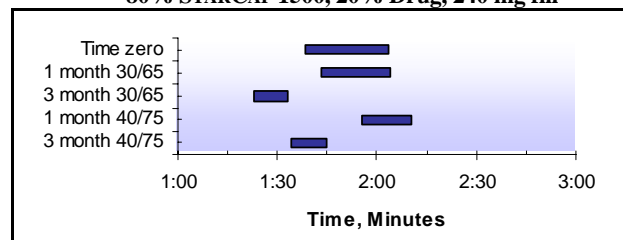
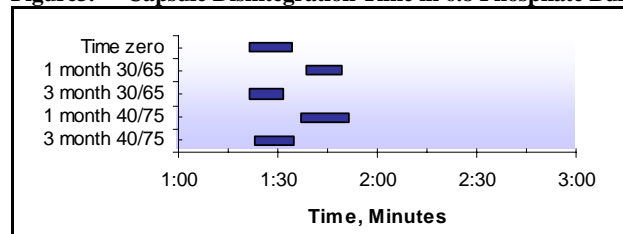


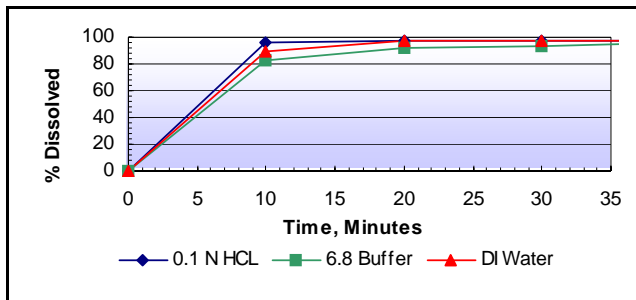
Figure 3. Capsule Disintegration Time in 6.8 Phosphate Buffer - 80% StarCap 1500, 20% Drug, 240 mg fill



Dissolution Time

Dissolution results demonstrate that the release rate is rapid and independent of pH. (The apparent difference at 10 minutes is within the limit of uncertainty at 95% confidence.) Chemical stability and compatibility with the drug are indicated by the assay data obtained after 3 months' stressed storage at 40°C / 75% RH conditions in HDPE bottles, as shown below in Figure 4.

Figure 4. Dissolution of Propranolol HCL with STARCAP 1500



Propranolol HCL Assay

	(%)
Time zero	101
1 month 40°C/75% RH	100
3 month 40°C/75% RH	98

STARCAP 1500 Compared to Lactose

The stability of STARCAP 1500 relative to lactose is shown below. The lactose system develops a lag in the dissolution profile with storage at 40°C / 75% RH conditions in HDPE bottles with desiccant and cotton. (The difference in the six-month profile at the 10-minute point is greater than the 95% confidence limit illustrated in Figure 5.) The STARCAP 1500 system does not show any changes in dissolution profile (Figure 6). The same result was obtained from the one-month open dish samples.

Figure 5. Dissolution of Propranolol HCL with Lactose 0.1 N HCL, HDPE Bottles

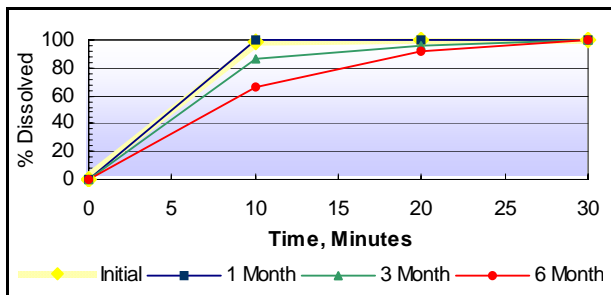
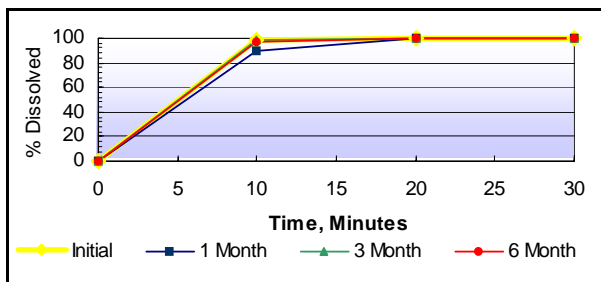


Figure 6. Dissolution of Propranolol HCL with STARCAP 1500 0.1 N HCL, HDPE Bottles

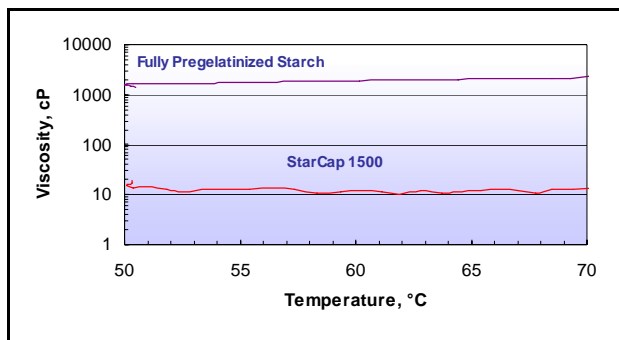


StarCap 1500

STARCAP 1500 has a low degree of gelatinization and cannot be gelatinized by exposure to pH environments present in the human digestive system. Therefore, STARCAP 1500 cannot produce high viscosity gels which could reduce dissolution rates or lengthen disintegration time. The viscosity of a STARCAP 1500 10% solids slurry (dry basis) is 2 orders of magnitude lower than that of a fully pregelatinized starch (Figure 7).

STARCAP 1500 also benefits from reduced enzymatic activity for non-gelatinized starches.⁵ This improves microbiological stability and reduces the release rate of glucose in the GI tract.

Figure 7. Starch Viscosity - 10% Solids, Rapid Visco Analyzer



CONCLUSIONS

STARCAP 1500 is a stable co-processed starch based excipient with flow properties developed for capsule filling. The Carr index is comparable to spray dried lactose and microcrystalline cellulose, and a previous study has shown that STARCAP 1500 has excellent encapsulation properties on high speed production scale equipment.

STARCAP 1500 has dissolution properties which are independent of media pH. The release rate and disintegration time are stable at 40°C / 75% RH storage conditions.

The degree of gelatinization of STARCAP 1500 is low. STARCAP 1500 is more resistant to enzymatic degradation than gelatinized starches and does not form high viscosity gels which could delay drug release or increase disintegration time.

ACKNOWLEDGMENTS

The authors wish to thank David Ferrizzi, Alfred Skele, Buffy Young, and Jennifer Payne for performing all laboratory work for this evaluation.

References

1. Dekker, Marcel (2002) Encyclopedia of Pharmaceutical Technology.
2. Heda, P. et. al., (2002) AAPS PharmSci., 4 (3), 17.
3. Tan, S. et. al., (1990) International Journal of Pharmacy, 61 (145-155).
4. Podczeck, F., et. al., (1999) International Journal of Pharmacy, 185 (237-254).
5. Belitz, H., & Grosch, W., Springer-Verlag, Food Chemistry, 1987

AAPS Annual Meeting and Exposition, Nashville, November, 2005

World Headquarters

Colorcon

415 Moyer Blvd., P.O. Box 24, West Point, PA 19486-0024

Tel: 215-699-7733 Fax: 215-661-2605 Website: www.colorcon.com/pharma

e-mail: info@colorcon.com

Locations	Telephone	Facsimile	Locations	Telephone	Facsimile
<i>United States</i>			<i>Asia/Pacific</i>		
Santa Ana, California	714-549-0631	714-549-4921	Singapore	65-6438-0318	65-6438-0178
Indianapolis Indiana	317-545-6211	317-545-6218	Fuji-gun, Shizuoka, Japan	81-5-4465-2711	81-5-4465-2730
Humacao, Puerto Rico	787-852-3815	787-852-0030	Shanghai, China	86-21-5442-2222	86-21-5442-2229
			Goa, India	91-832-288-3434	91-832-288-3440
			Seoul, Korea	82-2-2057-2713	82-2-2057-2179
<i>Europe</i>			<i>Latin America</i>		
Dartford, Kent, England	44-1322-293000	44-1322-627200	Buenos Aires, Argentina	54-11-4552-1565	54-11-45523997
Bougival, France	33-1-3082-1582	33-1-3082-7879	Cotia, Brasil	55-11-4612-4262	55-11-4612-3307
Idstein, Germany	49-6126-9961-0	49-6126-9961-11	Bogota, Colombia	571-418-1202	571-418-1257
Gallarate, Italy	39-0331-776932	39-0331-776831	Caracas, Venezuela	58-212-442-4819	58-212-442-8724
Budapest, Hungary	36-1-200-8000	36-1-200-8010	Santa Fe, Mexico	52-55-3000-5700	52-55-3000-5701&02
Istanbul, Turkey	90-216-465-0360	90-216-465-0361			
Barcelona, Spain	34-9-3589-3756	34-9-3589-3792			

The information contained herein, to the best of our knowledge is true and accurate. Any recommendations or suggestions are made without warranty or guarantee, since the conditions of use are beyond our control. Any information contained herein is intended as a recommendation for use of our products so as not to infringe on any patent.

© 2005 Colorcon. The information contained in this document is proprietary to Colorcon and may not be used or disseminated inappropriately.

STARCAP and the Colorcon ellipse are trademarks of BPSI Holdings, LLC

ex_poster_starcap_prophcl_ver1_1105_updated102006