EXCIPIENTS

STARCAP 1500®

CO-PROCESSED STARCH EXCIPIENT

Technical Data

Gabapentin Capsules

High Dose/High Solubility

StarCap 1500® Utilized in a Direct-Fill Capsule Formulation of a High Dose/ High Solubility Active Drug - Gabapentin Capsules 300mg

INTRODUCTION

Gabapentin is an analgesic drug that has been indicated for the management of postherpetic neuralgia in adults. Gabapentin is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients, age 3 – 12 years.[1] The marketed product of gabapentin is available as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin.

Among all the solid dosage forms, capsules are the second most popular dosage form to compressed tablets on the market. However, capsules have frequently been considered as the first dosage form used in early clinical trials of a new drug for several reasons. Because of the pressure to expedite the formulation development and manufacture of clinical trial materials, capsules have been proven the best choice for powder filling and the most suitable dosage form for blinding purposes. Capsules can also be used to mask the taste and odor of the active drug contained within the capsule shells. Although a high compactibility characteristic is not a requirement for a capsule formulation to form a hard compact, the selection of excipients in the formula still remains critical to ensure good flow properties and lubrication of the blend on a tamp-filling machine.[2] If the formula is to be encapsulated on a dosator-type machine, then the blend should also have some binding properties to facilitate plug formation for the transfer to the capsule shells. A capsule formulation should have satisfactory powder fluidity, lubrication and compactibility for a successful manufacturing operation. The design of formulations also requires disintegration properties to promote deaggregation of the powder mass into primary drug particles and speed up the dissolution rate of the drug substance.

The innovator formula includes lactose as the main filler along with corn starch and talc. Lactose is widely used and performs well as filler in tablet and capsule formulations. However, lactose as well as other milk derivatives have presented some medical concerns of Bovine Spongiform Encephalopathy (BSE) or Transmissible Spongiform Encephalopathy (TSE) contamination in the products. Other adverse reactions to lactose are also largely attributed to lactose intolerance, which occurs in persons with a deficiency of the intestinal enzyme lactase.[3]

StarCap 1500® is a unique co-processed mixture of globally accepted excipients, corn starch and pregelatinized starch designed specifically for use in capsules and tablets. StarCap 1500 is an inert free-flowing, low dust excipient with disintegration properties and dissolution behavior that are independent of media pH.

The objective of this study was to evaluate the encapsulation performance of StarCap 1500 in a high-dose, high-solubility drug formulation and the in-vitro dissolution performance of the resulting gabapentin capsules.

MATERIALS AND METHODS

Characterization of Gabapentin Drug Substance

Samples of gabapentin drug substance were analyzed using a Malvern Mastersizer-2000 equipped with a Hydro 2000S sample Dispersion Accessory unit and backscatter detectors.

Approximately 100-150mg from each sample was dispersed in a solution containing 0.2% w/v Span-85 in hexane. Then the samples were magnetically stirred for 30 seconds in order to disperse the particles. The dispersed samples were then transferred dropwise to the Hydro 2000S for measurement.

Scanning Electron Micrographs (SEM) were also taken at 100x, 250x, 1000x and 2500x magnifications, with representative samples of gabapentin drug substance (see Appendix).

Formulations

A simple formula was developed with the ingredients listed in Table 1. Gabapentin is freely soluble in water and both basic and acidic aqueous solutions. StarCap 1500 was used as the main filler/ binder and disintegrant along with a low level of magnesium stearate as a lubricant. Each capsule contained 300 mg of gabapentin in a No. 0 white/white hard gelatin capsule shell.

Table 1 – Formulation of Gabapentin Capsules 300mg

Ingredients [Manufacturer]	Formula	
	Percent	mg / Capsule
Gabapentin [Kemprotec]	75.00%	300.0
StarCap 1500 [Colorcon]	24.75%	99.0
Magnesium Stearate NF [Mallinckrodt]	0.25%	1.0
Total	100.0%	400.0
Hard Gelatin Capsule Shell No. 0, White/White [Capsugel]	qs	qs

Colorcon®

The blend was prepared by adding the StarCap 1500 and gabapentin to a twin shell V-blender and mixed for 10 minutes. Prior to weighing, the magnesium stearate was passed through a 40 mesh screen then added to the blend and mixed for an additional 3 minutes.

The moisture content of the final blend was measured using a Denver Instrument IR-20 moisture balance at a temperature of 105°C. The particle size distribution of the blend was performed with a sample of 10 ± 0.1 grams on an ATM Sonic Sifter set up at 5 minutes of testing time, amplitude 4 and sift-pulse mode. The bulk and tapped density were performed in accordance with USP Method 1. The geometric mean diameter of granules and standard deviation were calculated based on a weight cumulative frequency-particle size distribution plotted on a log-probability scale.

Encapsulation and Physical Testing of Filled Capsules

Encapsulation was conducted on a tamp-filling machine, In-Cap (Dott. & Bonapace C.), set up for hard gelatin shells size #0, with a dosing disc of 19.5mm thickness, and encapsulation speed of 3,000 capsules/hr. The pin settings were set in ascending order of 3.5mm, 6.0mm, 6.0mm, and 7.0mm. A composite sample of capsules collected from the bulk was tested for weight variation on an Erweka Multicheck.

Dissolution Test Method

The dissolution method for gabapentin capsules is not currently posted in the USP 29 Monographs. The dissolution test was performed following the recommendations from the FDA.

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium
Gabapentin	Capsule	II (Paddle)	50	0.06 N HCl

Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
900	5, 10, 20 and 30	01/30/2004

RESULTS AND DISCUSSION

Particle size distribution

Particle size distribution was calculated using the polydisperse model and the following refractive indices and results were obtained:

Particle RI: 1.53 Imaginary RI: 1.0 Dispersant RI : 1.38

D(v, 0.1)	D(v, 0.5)	D(v, 0.9)	D[4,3]
68.709	152.236	355.493	187.245

All sizes are reported in microns, and are expressed as volume % undersize. The value of D[4,3] is the mean particle diameter.

Properties of Final Blend

The blend properties of the gabapentin formula are summarized in Table 2. The compressibility index or Carr's index is commonly used to predict the flowability of powder.[4] The Carr's compressibility index of 23-24% indicated satisfactory flow properties of the final blend that was then verified with a low weight variation of capsule fill weight as shown in Table 3.

Table 2 – Blend Properties

	Formula
Loss-On-Drying	2.51%
Bulk Density	0.46g/cc
Tapped Density	0.60g/cc
Calculated Carr's Index	23.8%
Geometric Mean Diameter	162 microns
Geometric Standard Deviation	1.85

Properties of Capsules

A composite sample of empty hard gelatin capsule shells and filled capsules were tested for weight variation with the results presented in Table 3. The values for the empty shells and filled capsules were used to calculate the variation statistics of the capsule fill weight. The capsule fill weight of individual filled capsule was calculated by subtracting the average weight of empty shells from the actual weight of filled capsules.

A low RSD% value for the capsule fill weight indicates excellent flow properties of the blend. Furthermore, a low spread of less than 5% of the mean provides strong evidence of the uniformity of capsule fill weight throughout the run. According to USP 30, the requirements for weight variation of capsules are met if each of the individual weights is within the limits of 90% and 110% of the average weight. The actual average weight of the run was 410.4 mg. The calculated percent values of 95.7% and 104.2% of the average capsule fill weight are well within the USP specification limits.

The content uniformity of gabapentin capsules was tested with 10 capsules sampled from the bulk. The assay result of individual capsules lies within the USP acceptance criteria range of 85.0% to 115.0% of the label claim, and the RSD is less than or equal to 6.0%.

Table 3 – Properties of Filled Capsules

Statistics	Empty Shells	Filled Capsules	Capsule Fill Weight
Number of units tested	46	70	70
Avg Weight (mg)	94.3mg	504.6mg	410.4mg
Standard Deviation (mg)	2.05mg	6.92mg	6.92mg
RSD%	2.18%	1.37%	1.69%
Min Weight (mg)	89.8mg	487.2mg	392.9mg (98.2% target)
Max Weight (mg)	99.1mg	521.8mg	427.5mg (106.9% of target)
Spread (% of the mean)	± 4.9%	± 3.4%	± 4.2%

Target capsule fill weight: 400mg

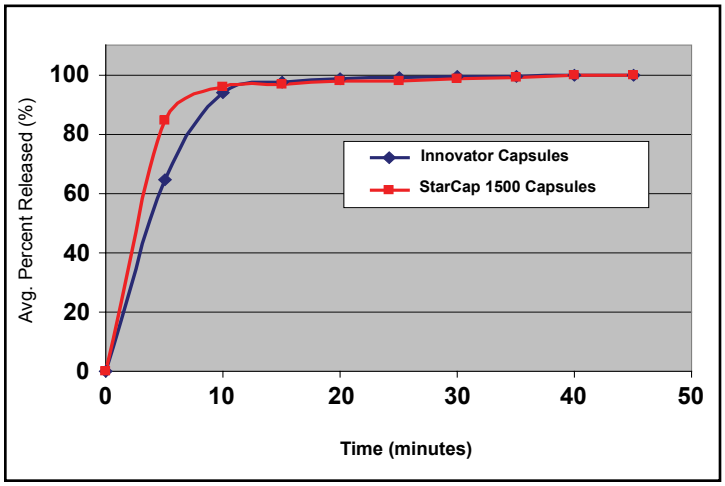
Table 4 – Content Uniformity of Capsules

Statistics	Assay (n = 10)
Average (% LC)	101.2
Min (% LC)	99.2
Max (% LC)	103.3
RSD (% mean)	1.53

Dissolution of Capsules

Dissolution profiles of reformulated gabapentin capsules 300mg were generated to compare with the innovator capsules. A slightly faster release was observed at the 5-minute test point in the profile. However, gabapentin capsules are considered to be rapidly dissolving products with more than 85% of the drug released in 15 minutes or less. A profile comparison is not necessary, and the in-vitro performance of the reformulated gabapentin capsules is similar to innovator.[5]

Figure 1 – Comparative Dissolution Profiles of Gabapentin Capsules and Innovator



CONCLUSIONS

A commercially viable gabapentin capsule formulation using StarCap 1500 was developed. StarCap 1500 was introduced in the formula as filler/binder and disintegrant along with a low level of lubricant to replace lactose, corn starch and talc in the innovator formula. The capsules had low weight variation and good content uniformity. The capsules passed both USP acceptance criteria. The dissolution profile of the reformulated capsules was essentially equivalent to that of the innovator capsules.

References

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Appendix – Scanning Electron Micrographs of Gabapentin Drug Substance