EXCIPIENTS

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Cyclobenzaprine Formulation
Target Capsule Fill Wt. 150.0 mg.

Development of a Common Cyclobenzaprine Formulation for Both Encapsulation and Tabletting Using StarCap 1500®

N. Do, Ph.D. and T. Farrell, Ph.D. (Colorcon, Inc.)

OBJECTIVE

To demonstrate the feasibility of using a common formula that can be encapsulated into hard gelatin capsules for clinical trials and subsequently compressed into tablets for commercialization.

INTRODUCTION

The ability of hard gelatin capsules to blind the contents has made them uniquely suitable for blinding a new drug and its positive comparators in early clinical trials. The trials are usually designed to compare one medication with another to evaluate the relative safety and/or efficacy of the new drug. In those tests, it is a common practice to blind the medications in order to prevent any prejudice from investigators and/or patients.

As compared with other oral dosage forms including hard gelatin capsules, compressed tablets still remain the manufacturers' dosage form of choice for commercialization because of their overall low cost of manufacturing. Furthermore, many coating techniques have been developed to enhance the aesthetic appearance and stability, and mask the taste and odor of the products. In order to eliminate extra steps required for the conversion of clinical capsule formulations to commercial tablet formulations, there is a need of developing a common formula for both capsules and tablets in the early clinical phases.

A low-dose and high-water solubility drug, cyclobenzaprine hydrochloride, was selected for the formulation/process development. A direct blend and encapsulation process was used for the capsules. The tablets were manufactured by direct compression & film-coated with Opadry® II 85F white. Dissolution profiles were generated to compare the *in-vitro* performance of the capsules and film-coated tablets.

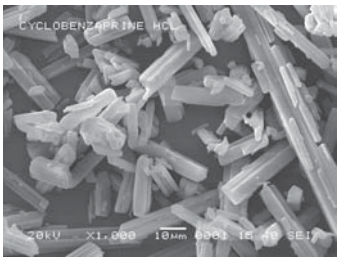
MATERIALS & METHODS

Capsule/Tablet Formulation & Process

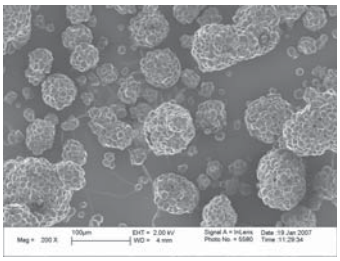
Ingredient	Percent
Cyclobenzaprine HCl [Vasudha Pharma Chem Ltd]	6.67%
StarCap 1500 [Colorcon]	58.91%
Microcel® 102 [Blanver]	33.67%
Cab-O-Sil® M5-P [Cabot]	0.25%
Magnesium Stearate NF [Mallinckrodt]	0.25%
Opadry II 85F18422 white [Colorcon]	qs

Target capsule fill weight/tablet weight: 150.0mg

With the disintegration properties of StarCap 1500, no additional disintegrants or superdisintegrants were required in the formula.



SEM of Cyclobenzaprine HCl



SEM of StarCap 1500

Direct Encapsulation:

Bonapace In-Cap capsule filling machine @ 1500 caps./hr.
Hard gelatin capsule shells No. 3, white/white

Direct compression:

10-station instrumented Piccola tablet press @ 30rpm
9/32" Std. round concave

Film-Coating:

20% solid w/w suspension & 3% weight gain
15" Thomas Accela Cota coating pan

Inlet Air Temperature:	65ºC
Exhaust Air Temperature:	45-50ºC
Tablet Bed Temperature:	45ºC
Air Flow:	255m^3/hr (150ft^3/min)
Spray Rate:	8g/min
Number of Guns:	1
Atomization Air:	1.7 bar (25psi)
Pattern Air:	1.7 bar (25psi)
Pan Speed:	15rpm

Physical Tests

Common Final Blend:

Loss-On-Drying	(Denver Instrument IR-20 Moisture Balance at 105ºC)
Bulk/Tapped Density	(VanKel Tap Density Tester – USP Method I)
Dynamic Flow Properties	(Sotax FT 300 Flowability Tester)

Colorcon®

Tablets:

Wgt Variation
(Erweka Multicheck Tablet Tester)
Crushing Strength
(Erweka Multicheck Tablet Tester)
Friability
(Vanderkamp Friability Tester)
Disintegration Time
(Erweka ZT DT 44 Apparatus)

Capsules:

Wgt Variation

Dissolution Test Method for Capsules & Tablets

Drug Name/ Dosage Form	USP Apparatus	Speed (RPM)	Medium	Vol. (ml)
Cyclobenzaprine HCl Tablet	I (Basket)	50	0.1N HCl	900

RESULTS & DISCUSSION

Properties of Final Blend

Test ID	Test Results
Loss-On-Drying	7.95%
Bulk Density	0.48g/cc
Tapped Density	0.65g/cc
Calculated Compressibility Carr's Index	25.4%
Dynamic Flow Properties by Sotax	4.75g/sec
Geometric Mean Diameter	83 microns

Properties of Uncoated Tablets

Test ID/Statistics	Test Results
Avg Weight (N=55)	149.8mg
RSD%	0.61
Min. Weight	148.0mg
Max. Weight	152.2mg
Spread (% of the mean)	± 1.40
Avg Crushing Strength (N=10)	10.7kp
Friability (N=20)	0.0%
Disintegration Time (N=6)	3min. 24sec. – 3min. 59sec.
Ejection Force	87N
Avg Compression Force	18kN

With a poorly compactible drug substance such as cyclobenzaprine hydrochloride, the selection of StarCap 1500/MCC combination is suitable to provide not only high tablet hardness & low friability required for film-coating but also a fast disintegration and dissolution rate to the formula.

The disintegration time of 3-4 minutes required for the dispersion of tablet granules into the dissolution media corresponds to the dissolution time of approximately 3-4 minutes of the hard gelatin capsule shells.

The satisfactory flow properties of the blend were confirmed with the low RSD% in the weight variation test of the capsules and tablets.

Weight Variation of Capsules

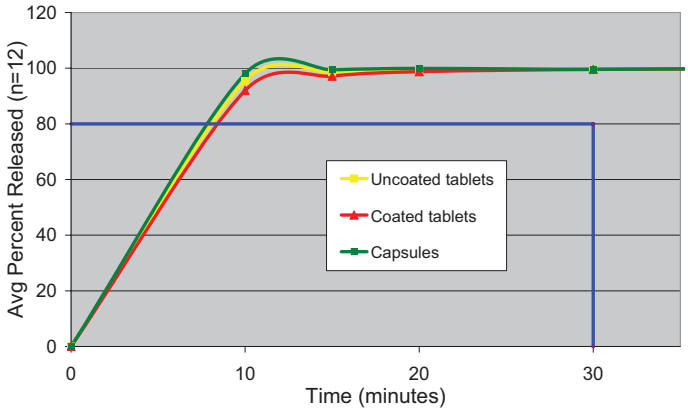
Statistics	Filled Caps.	Caps. Fill Wgt
Avg Weight (N=96)	200.9mg	153.2mg
RSD%	2.15	2.82
Min. Weight	192.7mg	145.0mg
Max. Weight	210.1mg	162.4mg
Spread (% of the mean)	± 4.33	± 5.68

Content Uniformity of Capsules & Tablets

Statistics	Capsules	Coated Tab.
Avg Potency Assay (N=10)	95.1%	94.7%
Min. Potency Assay	90.8%	93.3%
Max. Potency Assay	100.3%	95.5%
RSD%	2.94	0.74

The variability in content uniformity of the capsules and tablets is consistent with the variability in capsule fill weight and tablet weight. The observation indicates a uniform distribution of the active in the final blend, and the homogeneity was maintained during the encapsulation and compression operation.

Comparative Dissolution of Cyclobenzaprine HCl Capsules & Tablets 10mg



USP 30 – NF 25 Tolerances for cyclobenzaprine HCl tablets — Not less than 75% (Q) of the labeled amount of drug is dissolved in 30 minutes

The cyclobenzaprine hydrochloride tablets and capsules in this study fall into the category of rapidly dissolving products with more than 85% released in 15 minutes or less, and a profile comparison is not necessary.[1]

The dissolution of the Opadry II 85F white coating was fast and did not significantly affect the dissolution rate of the coated tablets.

The dissolution performance of uncoated and coated tablets is similar to that of capsules.

CONCLUSIONS

The common formula has all the key properties required for the manufacture of hard gelatin capsules and film-coated tablets by a direct blend/encapsulation and direct compression process.

The combination of StarCap 1500/MCC is suitable to provide good compactibility characteristic to the formula and fast disintegration/dissolution to the film-coated tablets.

The satisfactory content uniformity of the capsules and tablets was achieved as a result of the excellent flow properties of the final blend and minimum potential segregation of the active during process.

The *in-vitro* performance of capsules and film-coated tablets has been proven similar with a complete release in the first 15 minutes of the dissolution profiles.

There is a possibility to eliminate the extra steps required to reformulate clinical formulas of hard gelatin capsules into film-coated tablets for commercialization.

ACKNOWLEDGMENTS

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Reference:

[1] Vinod P. Shah, Yi Tsong, Pradeep Sathe and Roger L. Williams. Dissolution Profile Comparison Using Similarity Factor, f2. *Office of Pharmaceutical Science, Center for Drug Evaluation and Research - Food and Drug Administration, Rockville, MD*

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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
United States		
Santa Ana, California	714-549-0631	714-549-4921
Indianapolis, Indiana	317-545-6211	317-545-6218
Humacao, Puerto Rico	787-852-3815	787-852-0030
Stoughton, Wisconsin	608-887-8970	608-887-8984
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Istanbul, Turkey	90-216-465-0360	90-216-465-0361
Barcelona, Spain	34-9-3589-3756	34-9-3589-3792

Locations	Telephone	Facsimile
Asia/Pacific		
Singapore	65-6438-0318	65-6438-0178
Fuji-gun, Shizuoka, Japan	81-5-4465-2711	81-5-4465-2730
Shanghai, China	86-21-5442-2222	86-21-5442-2229
Goa, India	91-832-288-3434	91-832-288-3440
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Cotia, Brasil	55-11-4612-4262	55-11-4612-3307
Bogota, Colombia	571-418-1202	571-418-1257
Caracas, Venezuela	58-212-237-9842	58-212-238-2259
Santa Fe, México	52-55-3000-5700	52-55-3000-5701 /02

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