Impact of Manufacturing Processes on Critical Quality Attributes of Brinzolamide Ophthalmic Suspensions

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PURPOSE

Brinzolamide (BRZ) ophthalmic suspension 1% (Azopt®), a drug product used for the treatment of elevated intraocular pressure, was approved by the FDA in 1998. Currently there are no approved generic drugs on the market. This study aimed to characterize the dosage form and evaluate the relationship between manufacturing variation and product characteristics. Such in-depth understanding can facilitate both product development and assessment of attributes that can affect bioequivalence.

OBJECTIVES

- To characterize the commercial product in term of particle size distribution, polymorphism, rheology, dissolution, surface tension, pH, and osmolality.
- To evaluate impact of manufacturing process on drug product quality attributes as well as in vitro performance (e.g., dissolution).

METHODS

Suspension formulations were prepared using a top-down approach, where sterilized BRZ slurry and polymer dispersion were prepared separately before combining at the last step (Fig. 1). The milling of the BRZ particles were achieved using a Thinky NP-100 planetary centrifugal miller.

The particle size distribution (PSD) was determined using laser diffraction (LD) (Malvern MasterSizer 3000), where a placebo dispersion was used to perform background subtraction to eliminate the polymer interference.

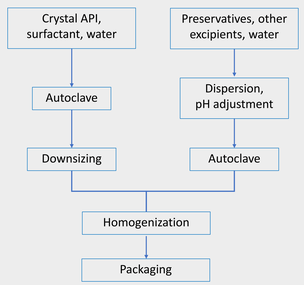

Fig1. Flow chart of the suspension preparation process.

Polymorphism of the drug particles was determined using x-ray powder diffraction (XRPD, Bruker D8 Advance). Suspension samples were centrifuged at 15,000 rpm for 15 min, after which the sediments were vacuum dried (40°C, 49 mmHg for 5 hours). Rheological properties of suspension samples were evaluated using a stress-controlled hybrid rheometer (DHR-3, TA Instruments), equipped with a 40 mm parallel sandblasted geometry with a 200 µm gap height. Surface tension and surface rheology of the suspension formulations were determined using a drop shape analyzer (DSA 100A, Kruss GmbH). Dissolution test was conducted using a µDISS Profiler (Pion Inc.), where the BRZ concentrations were monitored in-situ using UV fiber optical probes. The test was performed at 34°C, with a stirring speed of 150 rpm. The sample volume was 0.9 mL, and the dissolution medium 15 mL of pH 7.4 simulated tear fluid.

RESULTS

Characterization of the Commercial Drug Product (Azopt®)

Table 1: Physicochemical properties of the commercial drug product (mean±sd, n=3).

Sample	Surface tension [mN/m]	pH	Osmolality (mOs/kg)	Assay (%)	Drop weight (mg)	D [4,3] (µm)	SPAN
Lot 1	34.45 ± 0.14	7.57 ± 0.01	284 ± 3	N/A	28.2 ± 1.3	2.61 ± 0.01	1.00 ± 0.00
Lot 2	35.04 ± 0.08	7.56 ± 0.02	284 ± 1	N/A	29.5 ± 1.1	2.97 ± 0.01	1.08 ± 0.01
Lot 3	34.89 ± 0.02	7.53 ± 0.01	295 ± 2	101.9	29.3 ± 1.2	2.69 ± 0.03	1.00 ± 0.01

- The commercial product exhibited minimal lot-to-lot variations in all of the measured properties (Table 1), except for rheology
- Noticeable variations were found in rheology (i.e., yield stress and viscosity)

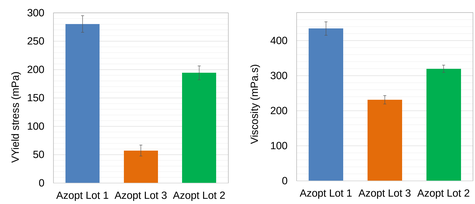

Fig 2. Yield stress and viscosity (at 10 s^{-1}) of the commercial products (mean±sd, n=3).

Particle size distribution of the BRZ suspensions

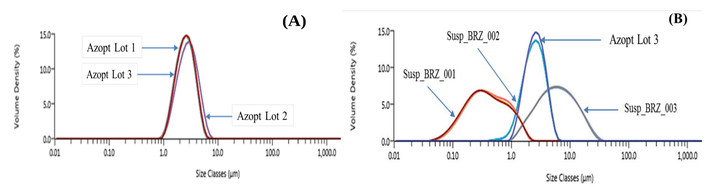

Fig 3. PSD Histograms of (A) 3 lots of AZOPT®, and (B) representative in-house formulations.

- Scanning Electron Microscopy / Energy Dispersive X-Ray Spectroscopy (SEM/EDS) images confirmed the LD particle size analysis results of both commercial and in-house formulations.
- Milling parameters greatly influenced the PSD of the suspensions (from submicron to coarse suspensions).

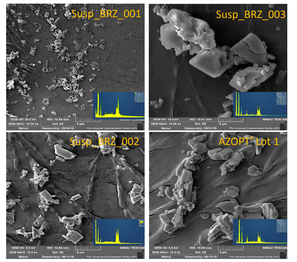

Fig 4. Representative SEM/EDS images of the AZOPT® and in house formulations.

Rheological properties of the inhouse BRZ suspensions

Table 2. Yield stress and viscosity (at 10 s^{-1}) of the in-house BRZ suspensions (mean±sd, n=3).

Sample	Yield stress (mPa)	Tan (delta)	Viscosity (mPa·s)		
			1 s^{-1}	10 s^{-1}	100 s^{-1}
Susp_BRZ_001	753 ± 30	0.08 ± 0.00	5708 ± 42	765 ± 10	116 ± 16
Susp_BRZ_002	47 ± 4	0.31 ± 0.01	822 ± 62	191 ± 10	59 ± 2
Susp_BRZ_003	40 ± 6	0.34 ± 0.03	708 ± 40	174 ± 3	55 ± 0
Susp_BRZ_004	4 ± 1	1.39 ± 0.32	114 ± 8	40 ± 1	19 ± 0
Susp_BRZ_005	504 ± 66	0.11 ± 0.00	3325 ± 212	602 ± 34	138 ± 14
Susp_BRZ_006	420 ± 14	0.10 ± 0.00	2156 ± 390	323 ± 24	55 ± 2

- Rheological properties of the suspensions were governed by:
  1) Polymer concentration, and
  2) PSD of the suspension particles

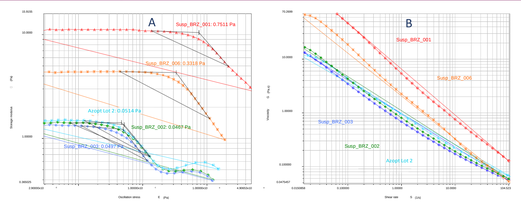

Fig 5. Representative rheological profiles BRZ suspensions. A) Storage modulus *vs.* shear stress, B) viscosity *vs.* shear rate.

In Vitro Dissolution of the BRZ suspensions

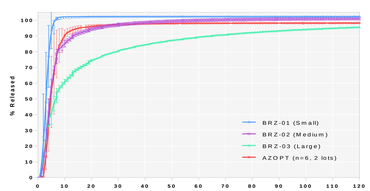

Fig 6. Representative dissolution profiles of BRZ suspensions (mean±sd, n=3).

- An novel low-volume, rapid detection, non-sink dissolution method was developed, which was capable of detect differences in critical product quality attributes (e.g., PSD) resulted from manufacturing process changes.
- Entire dissolution process completed within minutes, similar to the ocular residence time.
- There was good correlation between particle size and dissolution of the suspension.
- Differences in formulation rheology had minimal impact on BRZ dissolution.

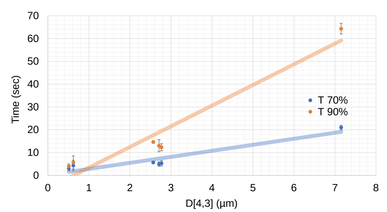

Fig 7. Dissolution time ($t_{70\%}$ and $t_{90\%}$) vs. particle size (D[4,3])

Polymorphism of the BRZ suspensions

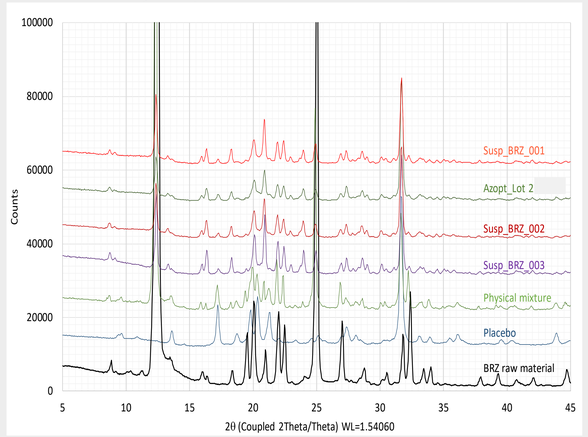

Fig 8. X ray diffractogram of dried suspension samples.

- BRZ in the suspension was in crystalline form.
- There was no difference in term of polymorphism between the commercial product and in-house formulations.

CONCLUSION

Samples from three lots of the commercial product (Azopt®) and various in-house prepared BRZ suspensions were characterized. Such in-depth characterization enabled us to determine the impacts of manufacturing processes on the critical quality attributes. In particular, the milling process was found to have a significant impact on the PSD, rheological properties, as well as in vitro dissolution of the BRZ suspensions.

ACKNOWLEDGEMENTS

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DISCLAIMER

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