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COMPATIBILITY STUDY PERFORMANCE OF OPHTHALMIC NANOEMULSION FOR REDUCING OCULAR HYPERTENSION

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ABSTRACT

The objective of present study was to develop a stable ophthalmic nanoemulsion for reducing ocular hypertension using Brinzolamide (BRZ) 10 mg/mL which is therapeutically equivalent to marketed reference drug product. Pre-formulation study was performed to evaluate the compatibility of product with materials which come in contact with the product during manufacturing. Compatibility study was carried out with metal, silicon tubes, filters and plastic containers. Thermal cycling and Photostability study were also performed to ensure the stability of the product. Brinzolamide ophthalmic nanoemulsion was formulated by dissolving the API in Kollisolv MCT 70 in a S.S vessel under continuous stirring. Stability studies at different conditions were also performed. Compatibility study results indicate that drug product was compatible with the product contact materials. Thermal cycling and photostabilty data indicates that there was no significant degradation in the formulation. As a part of aseptic filtration by sterilizing grade filter validation study was performed to challenge *Brevundimonas diminuta* at level of $\geq 1 \times 10^7$ CFU/cm^2. A stable ophthalmic nanoemulsion of Brinzolamide was developed and evaluated for compatibility and stability studies at different conditions were performed and it can be concluded that the product is compatible with product contact materials, thermal and photostable.

KEYWORDS: Brinzolamide, Compatibility Study, Thermal Cycling, Freeze thaw, Stability Study.

INTRODUCTION

The field of ocular delivery is one of the most interesting and challenging endeavour facing the pharmaceutical scientist. The challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. This significantly improved over past few 10-20 years. As an isolated organ the eye is very difficult to study from a drug point of view. It is very difficult to obtain eye tissue containing drugs from humans so one is compelled to use animal tissue. Topical application of drugs to the eye is the most popular and well-accepted route of administration for the treatment of various eye disorders. The bioavailability of ophthalmic drugs is, however, very poor due to efficient protective mechanisms of the eye. Blinking, baseline and reflex lachrymation, and drainage remove rapidly foreign substances, including drugs, from the surface of the eye. Moreover, the anatomy, physiology and barrier function of the cornea compromise the rapid absorption of drugs.[1]

Numerous strategies were developed to increase the bioavailability of ophthalmic drugs by prolonging the contact time between the preparation, and therefore the drug, and the corneal/conjunctival epithelium. The use of a water-soluble polymer to enhance the contact time and possibly also the penetration of the drug was first proposed by Swan.[2] There is no reliable correlation between the performance of ophthalmic vehicles in rabbits and in humans, mainly due to differences in blinking frequency.

Glaucoma is an accumulative optic neuropathy resulted from increasing intraocular pressure. Often, glaucoma has no symptoms and can suddenly result in vision loss. Without proper treatment, glaucoma can lead to blindness. The good news is that with regular eye exams, early detection and treatment, you can preserve your sight. In most types of glaucoma, the eye's drainage system becomes clogged so the intraocular fluid cannot drain. As the fluid builds up, it causes pressure to build inside the eye. High pressure damages the sensitive optic nerve and results in vision loss.[3] There are two major forms of glaucoma in patients: open-angle glaucoma and angle-closure glaucoma. For patients with open-angle glaucoma (defined as having optic nerve damage), lowering IOP is effective and always recommended.[4] In clinical practice, eye drops are the first line treatments for most glaucoma patients including prostaglandin analogue, β-adrenergic antagonists and carbonic anhydrase inhibitors (CAIs). CAIs, such as acetazolamide, methazolamide, dorzolamide and brinzolamide, could decrease the production of the fluid

(aqueous humor) and therefore lower the intraocular pressure.[5]

Brinzolamide (BRZ) is a kind of carbonic anhydrase inhibitors for glaucoma treatment. Brinzolamide (BRZ), a CAI, is a well-known therapeutic agent for glaucoma and intraocular high-pressure, particularly for the primary open-angle glaucoma (POAG).[6] The aqueous solubility of BRZ is very low at pH 7.4 (25°C). Therefore, the commercial available formulation of BRZ (AZOPT®) is a sterile aqueous suspension of 1% BRZ with a physiologic pH of approximately 7.5.[7-9] The granular sensation may cause uncomfortable after instillation and arouse undesirable tear wash to wipe the drug off rapidly. Therefore the solution formulation is necessary to be developed to improve the compliance of patients.

The above findings undoubtedly prove that nanoemulsion is an effective carrier for ophthalmic drug delivery and it may be worthwhile to explore this attribute of nanoemulsion in the ophthalmic applications. In this research paper, an attempt was made to use nanoemulsion carrier approach for ophthalmic drug delivery of Brinzolamide. The nanoemulsion formulation is a complex mixture of oil, surfactant, cosurfactant, water, and drug and the majority of its properties are dependent upon the droplet size of internal phase.[10,11] Maintenance of stability is a next major problem while formulating nanoemulsion.[12] The main objective of the present study was to formulate a stable formulation of Brinzolamide. All related studies such as compatibility study stability study were performed to make the formulation stable.

MATERIALS AND METHOD

Brinzolamide gift sample was received from Indoco Remedies Ltd. Mumbai. Kollisolv MCT 70, Kolliphor ELP, Kollisolv PG samples received from signet chemicals, Mumbai. Other excipients, chemicals and reagents were of Pharmaceutical and or HPLC grade purchased from Merck. Millipore Milli-Q Water Purification System was used to generate purified water for the study.

Nanoemulsion preparation

Primary components (oil, Surfactants, Cosurfactants and water) were evaluated by ternary phase diagram to find out nanoemulsion region. Drug loaded nanoemulsion was formulated by spontaneous phase inversion method. Brinzolamide (API) first dissolved in Kollisolv MCT 70, stir continue till to clear solution obtained. Than Smix of Kolliphor ELP, Kollisolv PG and Glycerin added in drug solution further purified water slowly added to make up to the 90% volume of batch size. Check and adjusted the pH with solution of Phosphate buffer, finally make the volume 100% of batch size with purified water. Aseptically filter the bulk of nanoemulsion through 0.45 micron + 0.2 micron sterilizing grade polyether sulfone membrane absolute filters. Fill the filtered nanoemulsion in 5 ml three piece LDPE bottles for ophthalmic by Rexam. Composition detail and manufacturing process steps described in Table 1.

Table 1: Manufacturing Formula and Manufacturing Steps.

Sr. No.	Ingredients	Qty. (mg/mL)
1	Brinzolamide USP	10 mg
2	Medium Chain Triglyceride USPNF (Kollisolv MCT 70)	50 mg
3	Polyoxyl 30 castor Oil USPNF (Kolliphor ELP)	50 mg
4	Propylene Glycol USPNF (Kollisolv PG)	80 mg
5	Glycerin USP	20 mg
6	Dibasic Sodium Phosphate dehydrate USPNF	q.s. to adjust pH
7	Purified water	q.s to mL
Manufacturing steps		**Material/Equipment used**
Preparation of bulk nanoemulsion		SS316L vessel fitted with mechanical stirrer
Filtration		Sartopore 2 capsule filter (0.45 µm + 0.22 µm PES filter) (Cat. No.: 5445307H9-SS-A)
Filling and sealing		Sterile 5 mL white LDPE three piece bottles with nozzles and pilfer proof screw caps for ophthalmic by Rexam (BPREX)

Filtration

Bulk of nanoemulsion was filtered through Sterilizing grade Sartopore 2 PES 0.45micron + 0.2 micron capsule filter.

Preformulation Study

Preformulation is defined as that phase of research and development process, where physical, chemical and mechanical properties of drug substance are characterized alone and when combined with excipients in order to develop safe, effective and stable formulation. As a part of pre-formulation studies, the following studies were performed:

- SS316L metal and USP type-I glass container compatibility study
- Platinum cured silicone tubing compatibility study
- Filter compatibility study and Filter validation study

- Containers-closures compatibility
- Thermal cycling (Freeze thaw & Cool thaw cycle)
- Photostabilty study

Compounding vessels compatibility study of Brinzolamide Ophthalmic Nanoemulsion with metal (SS 316L) and glass vessels

SS 316L and USP type-I glass containers were used during compounding as manufacturing and holding vessel or tank for preparation of nanoemulsion and as such must not interact with the drug product. The effect of SS 316L vessel on formulation was tested. About 150 mL of the unfiltered bulk solution was stored into SS 316L sterile holding tank and was kept at room temperature for 72 hrs. Samples were periodically collected from the container at 24, 48 and 72 hours and given for analysis of the bulk solution for description, pH, droplet size, assay and related substances (RS). The analytical results are given in the Table 2.

Table 2: Compounding vessels compatibility study results at room temperature (20-30°C).

Test	Specification	Initial	SS316L metal container			USP type-I glass container		
			24 hr	48 hr	72 hr	24 hr	48 hr	72 hr
Description	Clear slight translucent, bluish tinge color liquid.	Complies	Complies	Complies	Complies	Complies	Complies	Complies
pH	Between 5.5 and 7.5	6.57	6.57	6.60	6.71	6.57	6.61	6.67
Droplet Size (nm)	Not more than 150 nm	107.8	118.7	118.4	115.4	112.3	108.6	109.4
Assay (by HPLC) Brinzolamide (%)	Not less than 90.0% and not more than 110.0% of labeled amount.	98.8%	98.4%	99.0%	98.2%	99.0%	99.6%	99.4%
Related Substances (by HPLC)								
Any individual impurity	Not more than 1.0 %	0.05%	0.09%	0.08%	0.09%	0.07%	0.08%	0.07%
Total impurities	Not more than 2.0 %	0.09%	0.18%	0.21%	0.24%	0.16%	0.19%	0.22%

Platinum cured silicone tube compatibility study with filtered bulk solution

In pharmaceutical manufacturing, silicone tubing is used for transfer and filling of nanoemulsion and as such must not interact with the drug product. About 100 mL of the filtered bulk nanoemulsion was stored into glass containers. Clean (soaked with purified water) and dried Platinum cured silicone tubing of approx.10 cm length was immersed into the glass container and kept at room temperature for 48 hrs. Samples were periodically collected from the container at 24 & 48 hours and given for analysis of the bulk nanoemulsion for description, pH, droplet size, assay and related substances. The analytical results are given in the Table 3.

Compatibility study of Brinzolamide Ophthalmic Nanoemulsion with PES membrane filters (0.45µm + 0.22 µm filter)

The compatibility study of filter is the most important test for sterility of final formulation. About 100 mL of the filtered bulk was stored into glass container. Clean and dried 0.45µm + 0.22µm PES membrane filter was immersed into the glass container and the container was kept at room temperature for 48 hrs. Samples were periodically collected from the container at 24, 48 hours and given for analysis of the bulk nanoemulsion for description, pH, droplet size, assay and related substances. The analytical results are given in the Table 3.

Table 3: Platinum cured silicon tube and filters membrane compatibility study results at room temperature (20-30°C).

Test	Specification	Initial	Platinum cured silicone tube		Filters (PES membrane)	
			24 hr	48 hr	24 hr	48 hr
Description	Clear slight translucent, bluish tinge color liquid.	Complies	Complies	Complies	Complies	Complies
pH	Between 5.5 and 7.5	6.51	6.55	6.57	6.57	6.60
Droplet Size (nm)	Not more than 150 nm	107.8	108.9	112.3	104.3	103.5
Assay (by HPLC) Brinzolamide (%)	Not less than 90.0% and not more than 110.0% of labeled amount.	98.8%	98.6%	98.8%	98.4%	99.0%
Related Substances (by HPLC)						
Any individual impurity	Not more than 1.0 %	0.05%	0.07%	0.08%	0.08%	0.09%
Total impurities	Not more than 2.0 %	0.09%	0.18%	0.21%	0.19%	0.22%

Compatibility of Brinzolamide Nanoemulsion with three piece LDPE bottles for ophthalmic

The container-closure system is an essential part of the final presentation of a pharmaceutical product. It defines the protection, and functionality of a container while it ensures the safety and quality of the drug product over the product shelf life. To establish the compatibility of Brinzolamide Ophthalmic Nanoemulsion with LDPE bottles, prepared bulk nanoemulsion of Brinzolamide was filtered through 0.45micron + 0.22micron PES membrane filters. Filtered nanoemulsion was filled in 5 mL white LDPE three piece bottles, closed with dropper plug and sealed with pilfer proof screw caps. Sealed bottles were subjected at different Stability conditions. The analytical results of container compatibility study are given in the Table 4.

Table 4: Analytical Results of Container compatibility study.

Tests	Specification	Initial	40°C ± 2°C/ NMT 25% RH			30°C ± 2°C/ NMT 35% RH	25°C ± 2°C/ NMT 40% RH
			1 Month	2 Months	3 Months	3 Months	3 Months
Description	Clear slight translucent, bluish tinge color liquid.	Complies	Complies	Complies	Complies	Complies	Complies
pH	Between 5.5 and 7.5	6.20	6.22	6.21	6.23	6.25	6.26
Droplet Size (nm)	Not more than 150 nm	99.67	103.41	101.33	104.46	103.43	105.43
Assay (by HPLC) Brinzolamide (%)	Not less than 90.0% and not more than 110.0% of labeled amount.	98.34 %	98.60 %	99.04 %	99.50%	99.61%	98.60%
Related Substances (by HPLC)							
Any individual impurity	Not more than 1.0 %	0.07%	0.07%	0.07%	0.09%	0.09%	0.07%
Total impurities	Not more than 2.0 %	0.14%	0.15%	0.23%	0.30%	0.29%	0.18%

Thermal Cycling (Freeze thaw & Cool thaw cycle) study

The Freeze thaw & Cool thaw cycle study ensures that the product attributes at the extreme conditions of temperature are not altered. This study was designed to simulate the conditions that the product may experience during shipping.

Cool thaw cycle study

Cycle-I: Charge the samples in upright orientation in the refrigerator maintained at temperature between 2 to 8ºC for 1 days. On 2nd day remove all bottles from the refrigerator. Place the above samples in the 40±2°C/NMT 25% RH chamber for 1 day.

Cycle-II: On 3rd day remove all the bottles from the 40±2°C/NMT 25% RH stability chamber. Store them in refrigerator maintained at temperature between 2 to 8ºC for 1 day. On 4th day remove all bottles from the refrigerator. Place them in the 40± 2°C/NMT 25% RH chamber for 1 day.

Cycle-III: On 5th day remove all the bottles from the 40± 2°C/NMT 25% RH stability chamber. Store them in refrigerator maintained at temperature between 2 to 8ºC for 1 day. On 6th day remove all bottles from the refrigerator. Place them in the 40± 2°C/NMT 25% RH chamber for 1 day. Upon completion of Cycle-III, remove all samples from the 40 ± 2°C/NMT 25% RH chambers. Analyze the samples for description, pH, droplet size, assay and related substances.

Samples (Quantity)	(2 to 8°C) Cold storage	40±2°C/NMT 25%RH Accelerated condition	(2 to 8°C) Cold storage	40±2°C/NMT 25%RH Accelerated condition	(2 to 8°C) Cold storage	40±2°C/NMT 25%RH Accelerated condition
10 bottles	1st day	2nd day	3rd Day	4th day	5th Day	6th day
	← Cycle I →		← Cycle II →		← Cycle III →	

Cool thaw cycle study (Study-I)

Thermal cycle (Freeze thaw & Cool thaw cycle) study

Cycle-I: Charge the samples in upright orientation in the deep freezer maintained at temperature -20°C for 1 day. On 2nd day remove all bottles from the deep freezer. Place the above samples in the 50 ± 2°C chamber s for 1 day.

Cycle-II: On 3rd day remove all the bottles from the 50 ± 2°C stability chamber. Store them in deep freezer maintained at temperature -20°C for 1 day. On 4th day remove all bottles from the deep freezer. Place them in the 50 ± 2°C chamber for 1 day.

Cycle-III: On 5th day remove all the bottles from the 50 ± 2°C chamber. Store them in deep freezer maintained at temperature -20°C for 1 day. On 6th day remove all bottles from the deep freezer. Place them in the 50 ± 2°C chamber for 1 day. Upon completion of Cycle-III, remove all samples from the 50 ± 2°C chamber. Analyze the samples for description, pH, droplet size, assay and related substances.

Thermal cycle (Freeze thaw & Cool thaw cycle) study (Study-II)

Samples (Quantity)	Temperature condition(s)					
	(-20°C) Freezer	50 ± 2°C (Short term excursion)	(-20°C) Freezer	50 ± 2°C (Short term excursion)	(-20°C) Freezer	50 ± 2°C (Short term excursion)
10 bottles	1st day	2nd day	3rd day	4th day	5th day	6th day
	← Cycle I →		← Cycle II →		← Cycle III →	

The analytical results are given in the Table 5.

Table 5: Analytical results of Freeze thaw & Cool thaw cycle study:

Test	Specification	Initial	Study I	Study II
Description	Clear slight translucent, bluish tinge color liquid.	Complies	Complies	Complies
pH	Between 5.5 and 7.5	6.51	6.51	6.53
Droplet Size (nm)	Not more than 150 nm	78.0	85.0	74.5
Assay (by HPLC) Brinzolamide (%)	Not less than 90.0% and not more than 110.0% of labeled amount.	99.5%	97.9%	100.23%
Related Substances (by HPLC)				
Any individual impurity	Not more than 1.0 %	0.05%	0.07%	0.07%
Total impurities	Not more than 2.0 %	0.09%	0.20%	0.18%

Photostability study

The study was carried out in Photostability chamber with samples as follows:

Test Sample: Product filled in white LDPE three piece bottles.

Control Sample: Product filled in white LDPE three piece bottles wrapped by aluminum foil.

Carton Pack: Product filled in white LDPE three piece bottles and packed in a carton.

The bottles were exposed to light for an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter. The analytical results of various tests performed in the Photostability studies are presented in the Table 6.

Table 6: Analytical results of Photostability study.

Test	Specification	Initial	Test sample	Control sample	Carton pack
Description	Clear slight translucent, bluish tinge color liquid.	Complies	Complies	Complies	Complies
pH	Between 5.5 and 7.5	6.75	6.73	6.72	6.78
Droplet Size (nm)	Not more than 150 nm	85.4	93.2	84.6	88.9
Assay (by HPLC) Brinzolamide (%)	Not less than 90.0% and not more than 110.0% of labeled amount.	99.20%	98.89%	99.56%	98.92%
Related Substances (by HPLC)					
Any individual impurity	Not more than 1.0 %	0.02%	0.02%	0.03%	0.03%
Total impurities	Not more than 2.0 %	0.11%	0.17%	0.09%	0.15%

Filter validation study

Bubble point test

A bubble point test is a test designed to determine the pressure at which a continuous stream of bubbles is initially seen downstream of a wetted filter under nitrogen gas pressure. The point at which the first stream of bubbles emerges is the largest pore. Therefore, the bubble point value can be used to obtain a relative measure of the size of the single largest pore in a filter element. The purpose of this study was to determine the minimum product bubble point value for the sterilizing grade Sartopore 2 PES 0.45 + 0.2micron midicap filter (Cat. No.: 5445307H9-SS-A) wetted with Brinzolamide Ophthalmic Nanoemulsion. The bubble point of the filter was observed 3860 mbar and the limit of the filter was not less than 3180 mbar.

Bacterial Retention study

Bacterial retention study was performed to check the sterility and integrity of filter. Performance of sterilizing grade filter has been demonstrated to be acceptable as the membrane retained the *Brevundimonas diminuta* challenge concentration equal to or greater than $1*10^7$ CFU/cm^2 of effective filtration area. So it was concluded that the challenge test was passed.

Leachable and Extractable test

Leachables are compounds that migrate into a drug product from the sample container closure (SCC) system

under normal storage conditions. Both the primary SCC in direct contact with the drug product and the secondary SCC, which does not contact the drug product, can be sources of leachables. Extractables are the compounds that can be extracted from the SCC that might become leachables. The conditions of an extraction study are selected based upon the drug product and are designed to mimic a worst-case-scenario for then intended drug product. In the present study no leachable and extractable were found after analyzing the sample by HPLC.

Stability study on development batch

To assess the stability of Brinzolamide Ophthalmic Nanoemulsion; development batches, were kept at accelerated (40°C ± 2°C / NMT 25% RH), intermediate (30°C ± 2°C / NMT 35% RH) & long term (25°C ± 2°C / NMT 40% RH) condition. The analytical results are presented in Table 7.

RESULTS AND DISCUSSION

Brinzolamide is a carbonic anhydrase inhibitor for treatment of ocular hypertension or glaucoma. The main objective of the present study was to formulate a stable formulation of Brinzolamide Ophthalmic Nanoemulsion. Pre-formulation study was performed to evaluate the compatibility of drug product with different optimized excipients. Compatibility study of Brinzolamide Ophthalmic nanoemulsion with platinum cured silicon tubes, vessels or container (SS316L Metal and USP type-I glass), filters (Polyether sulfone membrane) and primary packaging bottles were performed. Compatibility study results indicates that there was no significant degradation in Brinzolamide ophthalmic nanoemulsion in contact with platinum cured silicon tubes, vessels (SS316 L metal and USP type-I glass), and PES membrane filters at room temperature (20-30^{o}C) over a period of 24 hours, 48 hours and 72 hours respectively (Table 2 and 3). Compatibility study of drug product with three piece LDPE bottles was studied at different time periods and results were found well within the specified limits (Table 4). Thermal cycling and Photostability study was conducted on the drug product. Results obtained from Freeze thaw and Cool thaw studies indicate that the product was stable at the extreme of temperature conditions. It can withstand thermal excursions in the range of -20°C to 50°C ± 2°C (Table 5). In Photostability study no significant degradation was observed on Brinzolamide ophthalmic nanoemulsion bottles upon exposure to light so the product was photostable when stored in white LDPE three piece bottles for eye drops (Table 6). Primary packaging material selected with reference to 'AZOPT' conventional formulation Brinzolamide ophthalmic suspension available in market, developed nanoemulsion formulation were packed in similar packaging container. The excipients used in the drug product development analyzed for its physicochemical characteristics and found compatible with the API. All excipients used in the formulation were of pharmacopoeia grade and used within the recommended amount approved for ophthalmic according to FDA in inactive ingredients database. Accelerated stability study was also performed on Brinzolamide ophthalmic nanoemulsion as they are packed in white three piece LDPE bottles for eye drops, closed with dropper plug nozzle and sealed with pilfer proof screw caps. These batches are kept at accelerated (40°C ± 2°C / NMT 25% RH), for 1, 2, and 3 months, intermediate (30°C ± 2°C / NMT 35% RH) & long term (25°C ± 2°C / NMT 40% RH) for 3 months. All results obtained from stability studies were found to be well within the specified limits and results presented in Table 7.

Table 7: Brinzolamide ophthalmic nanoemulsion 10 mg/mL (1% w/v) stability study results at different storage conditions.

Tests	Specification	Initial	40°C ± 2°C/ NMT 25% RH			30°C ± 2°C/ NMT 35% RH	25°C ± 2°C/ NMT 40% RH
			1 Month	2 Months	3 Months	3 Months	3 Months
Description	Clear slight translucent, bluish tinge color liquid.	Complies	Complies	Complies	Complies	Complies	Complies
pH	Between 5.5 and 7.5	6.52	6.51	6.45	6.57	6.61	6.47
Droplet Size (nm)	Not more than 150 nm	104.71	102.86	99.53	107.34	107.34	108.53
Assay (by HPLC) Brinzolamide (%)	Not less than 90.0% and not more than 110.0% of labeled amount.	98.44%	99.45%	99.76%	99.30%	99.70%	99.01%
Related Substances (by HPLC)							
Any individual impurity	Not more than 1.0 %	0.06%	0.08%	0.08%	0.08%	0.07%	0.07%
Total impurities	Not more than 2.0 %	0.09%	0.17%	0.21%	0.22%	0.21%	0.16%

CONCLUSION

In the present investigation formulation of Brinzolamide ophthalmic nanoemulsion 10 mg/mL (1% w/v) was done. Compatibility study of drug product with product contact material was performed. Based on the results obtained it was concluded that Brinzolamide ophthalmic nanoemulsion 10 mg/mL (1% w/v) was found compatible with platinum cured silicon tubes, compounding vessels made of SS316 L metals or USP type-I glass, PES membrane filters and primary

packaging materials three piece LDPE bottles for eye drops. Results obtained from Thermal cycling and Photostability study also conclude that the dug product is stable at the extreme temperature and photostable. Accelerated stability studies at different conditions were performed and results were well within limits.

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