PREFORMULATION APPROACH FOR THE DEVELOPMENT OF PRESERVATIVE FREE STEROID-BASED FORMULATION

Karla Dubaić, Nina Popović, Ivan Sušanj, Sofija Ivković, Anja Kovač, Zdravka Knežević, Maša Safundžić Kučuk, Leo Štefan

JGL d.d Jadran Galenski Laboratorij, Svilno 20, 51000 Rijeka, Croatia

INTRODUCTION

Preservative free ophthalmic preparations are more preferred due to the deteriorating effect of preservative on ocular surface [1]. The aim of this study is to develop stable preservative free suspension containing steroid based active pharmaceutical ingredient (API) with comparable characteristics as reference listed drug (RLD). For stability of this suspension critical influence have suspending agent 1-ethenyl-2-pyrrolidone homopolymer (**Kollidon®**) and surfactant 4-(1,1,3,3-Tetramethylbutyl) phenol polymer with formaldehyde and oxirane (**Tyloxapol®**).

Preformulation phase of development begins with characterization of RLD and defining Quality Target Product Profile (QTPP) with critical parameters that influence products stability, safety and quality (Table 1).

1. DEFINITION OF QTPP

Table 1. Characterization of RLD and defining QTPP.

QTPP	RLD characterization and requirements
pH	4.0-5.5
Osmolality	250-310 mOsmol/kg
Viscosity	1.90-1.95 mPas
Particle size distribution (PSD) using optical microscopy	$d_{100} < 15$ µm
Rheology	Shear thinning viscosity
Assay of API	95.00-105.0%

2. DETERMINATION OF QUALITATIVE (Q1) AND QUANTITATIVE (Q2) COMPOSITION

Two approaches:

1. Q1 and Q2 acquired through publicly available information about RLD:
   - Kollidon grade (25/30/90) is unknown.

   Several formulation prototypes with different Kollidon grades were analyzed.
   Kollidon 30 is the most probable candidate.

2. Deformulation study.

   Kollidon 30 and different Q2 for Kollidon and Tyloxapol .

   TO BE TESTED

Figure 1. PSD microscopy for test formulation at T0.

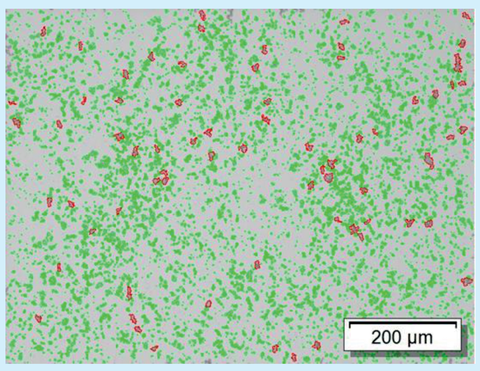
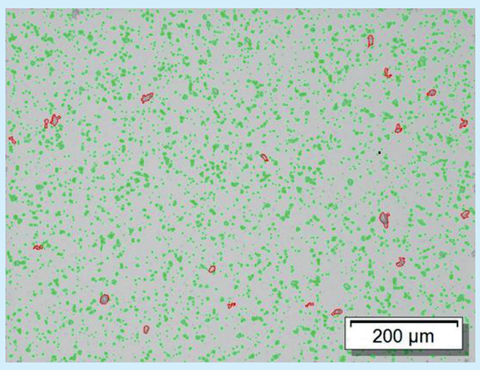


Figure 2. PSD microscopy for RLD at T0.



3. PREFORMULATION STRESS STUDY

Table 2. Results of preformulation stress study for 28 days at normal and stress conditions.

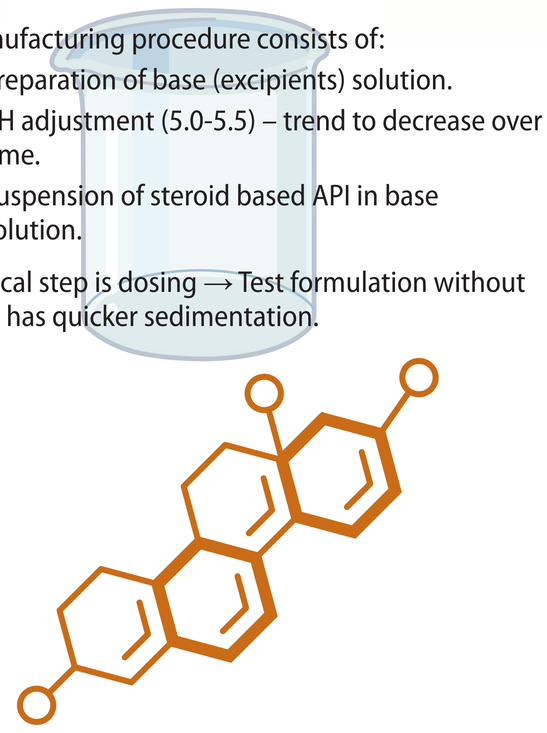
		Test formulation without BAC with Kollidon 30		Reference listed drug	
Parameter		25°C/60%RH	50°C/75%RH	25°C/60%RH	50°C/75%RH
pH	T0	5.28		4.20	
	T28	4.96	4.06	4.27	3.98
Viscosity (mPas)	T0	1.96		1.95	
	T28	1.93	1.95	1.93	1.93
Osmolality (mOsmol/kg)	T0	0.284		0.286	
	T28	0.285	0.286	0.283	0.284
Zeta potential (mV)	T0	-19.1		41.8	
	T28	-19.3	-20.5	41.6	42.1
PSD microscope	T0	98.17		99.78	
	T28	83.96	92.98	99.69	99.57
Assay of API%	T0	102.5		100.5	
	T28	100.1	98.3	100.7	99.6

MANUFACTURING PROCEDURE

Manufacturing procedure consists of:

- Preparation of base (excipients) solution.
- pH adjustment (5.0-5.5) – trend to decrease over time.
- Suspension of steroid based API in base solution.

Critical step is dosing → Test formulation without BAC has quicker sedimentation.



4. RESULTS OF PREFORMULATION STRESS STUDY

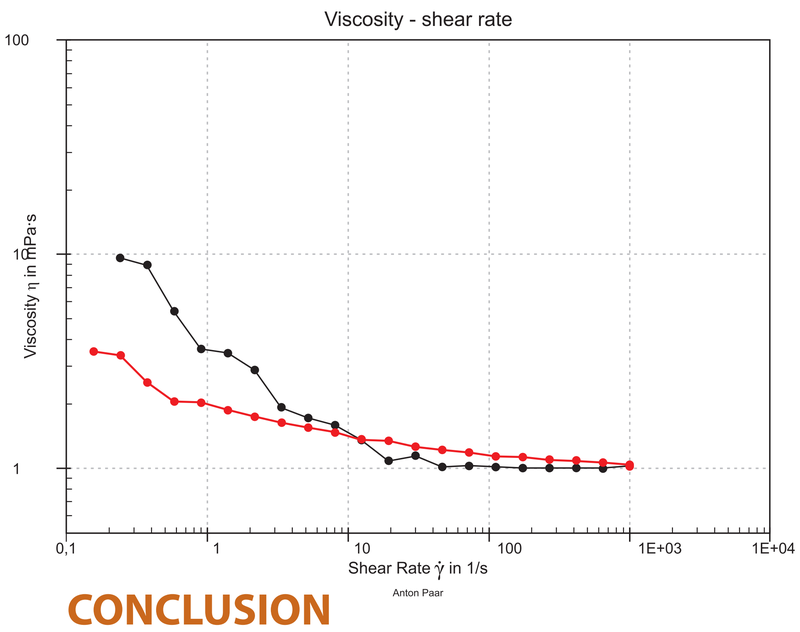
Preliminary stability study at normal (25°C/60%RH) and stress (50°C/75%RH) conditions was conducted to confirm Kollidon grade (Table 2.) Viscosity, pH, osmolality, and assay of API are aligned with RLD.

Zeta potential was measured to get insight into suspension stability. Shift in zeta potential between test formulation and RLD is due to removal of the preservative - BAC (cationic surfactant) [3]. Particle size of test formulation differs in T28 from RLD, confirming that BAC influences suspension stability.

Based on results, test formulation with Kollidon 30 has similar physio-chemical properties as RLD but different stability.

After stress study, further research was conducted on test formulation with **Kollidon 30**

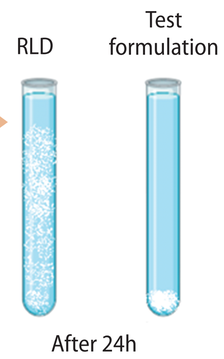
Figure 3. Rheological characterization: Test formulation (red) and RLD (black).



It is desirable for eye drops to have shear thinning behaviour (decrease in viscosity after blinking).

Shear rate sweep test was performed on Test formulation without BAC and RLD. Test formulation has lower initial viscosity compared to RLD but obtains comparable shear thinning behaviour (Figure 3).

Figure 4. Redispersibility test of RLD and Test formulation.



Test formulation without BAC has quicker sedimentation

But faster and easier redispersibility (shaking 3X)

Sample	Assay of steroid API
RLD batch no .1	84.10%
RLD batch no .2	48.10%
Test formulation	100.96%

Redispersibility test was conducted on Test formulation and RLD using 3x shaking as equal procedure. Test formulation has better redispersibility compared to RLD (Figure 4).

CONCLUSION

Preformulation approach for development of preservative free eye drops consists of defining QTPP, deformulation studies in order to obtain Q1 and Q2 and stability studies. Test formulation with Kollidon 30 provided similar physio-chemical parameters as RLD and has potential benefits with easier redispersibility than RLD. However, several critical steps need to be elucidated: final Q1/Q2, dosing procedure, and in use test .

REFERENCES

[1] Vitoux M-Adrien, Kessal K, *Toxicol Lett*. 2020, 319, 74-84.

[2] Kulshreshtha, Singh, Wall, *Pharmaceutical Suspensions, 2010th Ed., Springer, New York, 2009.*

[3] Fadeel B., Pietroiusti A., Shvedova A., *Adverse effects of engineered nanomaterials, 2nd Ed., Academic Press, London,* 2017.

[4] Watrobska–Swietlikowska D, *AAPS PharmSciTech* 2020, 21, 1-10.