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RESEARCH ARTICLE

Retracted: Development and Validation of a USP Apparatus IV Dissolution Method for Dexamethasone in a Povidone-Iodine Ophthalmic Suspension

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Abstract: The exact *in vitro* characterization of complex ophthalmic formulations is an analytical challenge, particularly for suspensions containing active ingredients with divergent physicochemical properties. This study details the development and validation of a robust dissolution testing method using the USP Apparatus IV (flow-through cell) for Dexamethasone (0.1%) within a dual-drug ophthalmic suspension also containing Povidone-Iodine (0.6%). Traditional dissolution techniques often fail to provide physiologically relevant shear forces or adequate hydrodynamic stability for such formulations. Consequently, a method was optimized utilizing a phosphate buffer (pH 7.4) supplemented with 0.1% β -Cyclodextrin. While theoretical sink conditions are achievable in standard buffers, the inclusion of β-Cyclodextrin was critical to enhance wettability, prevent adsorption of the hydrophobic steroid to the apparatus tubing, and ensure method robustness. A 100KD cellulose ester membrane was employed to retain the suspension while facilitating the diffusion of dissolved analytes. Quantification was performed via a specific HPLC method using an ACE Excel 5 C8 column. The method showed superior discriminatory capability across various critical process parameters, including particle size distribution and viscosity modifications. Validation per ICH Q2(R2) guidelines confirmed the method's linearity ($r^2 > 0.999$), precision (%RSD < 2.0%), and accuracy (98.5–101.5%). These results indicate that the developed flow-through cell method is a viable quality control tool for ensuring the consistency and performance of multiphasic ophthalmic dosage forms.

Keywords: USP Apparatus IV; Ophthalmic Suspension; Dexamethasone; Dissolution Method Validation; Flow-Through Cell; ICH Guidelines.

1. Introduction

Ophthalmic suspensions represent a critical class of dosage forms designed to deliver therapeutic agents to the ocular surface, specifically when the active pharmaceutical ingredient (API) possesses limited aqueous solubility. Unlike simple solutions, pharmaceutical suspensions are heterogeneous systems consisting of finely divided solid particles dispersed within a liquid vehicle. These systems require precise engineering to maintain physical stability, prevent caking, and ensure uniform dosing upon instillation [1]. The therapeutic efficacy of such formulations is intrinsically linked to the dissolution rate of the suspended particles within the limited volume of the tear film. This dissolution process dictates the bioavailability of the drug before it is cleared by nasolacrimal drainage mechanisms, which typically turnover the tear volume every few minutes. The formulation under investigation is a fixed-dose combination of Povidone-Iodine (PVP-I) and Dexamethasone. PVP-I is a broad-spectrum iodophore widely utilized for its potent antiseptic properties against bacteria, viruses, and fungi [2, 3]. Dexamethasone, a synthetic fluorinated glucocorticoid, provides essential anti-inflammatory and immunosuppressive effects for managing conditions such as adenoviral conjunctivitis and post-operative inflammation [3, 4].

While PVP-I is freely soluble, Dexamethasone exhibits low water solubility (approximately 0.1 mg/mL). The simultaneous existence of these two agents in a suspension matrix presents unique analytical hurdles. The dissolution profiling of Dexamethasone is particularly challenging due to the need to simulate the low-volume, high-turnover ocular environment while avoiding the artifacts common to static dissolution methods [5].

Dissolution testing is a mandatory quality control parameter that serves as a surrogate for *in vivo* performance. However, conventional methods described in USP General Chapter <711>, such as Apparatus I (Basket) and II (Paddle), often struggle with ophthalmic suspensions [6]. These apparatuses require large volumes of media (500–900 mL) that do not reflect the physiological

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ocular environment. Furthermore, they suffer from hydrodynamic dead zones where suspension particles can settle and form aggregates, leading to erratic and non-reproducible release profiles [5,6].

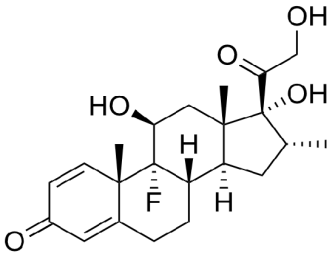

Figure 1. Structure of Dexamethasone

To address these limitations, the USP Apparatus IV (Flow-Through Cell) has emerged as a superior alternative for modified-release, low-solubility, and low-dose dosage forms [7]. As described by Fotaki, the continuous flow of fresh medium through the cell mimics the physiological turnover of biological fluids and minimizes the issues of saturation and "coning" often observed in paddle methods [8-10]. The flow-through cell allows for the use of specialized mounting techniques, such as dialysis adapters, which are particularly advantageous for retaining suspension nanoparticles while allowing the dissolved drug to permeate for analysis. This setup is increasingly favored for establishing *in vitro-in vivo* correlations (IVIVC) for complex parenteral and ophthalmic formulations.

The primary objective of this research was to develop a discriminatory and biorelevant dissolution method for Dexamethasone in this ophthalmic suspension using USP Apparatus IV. This involved the systematic optimization of important parameters, including media composition, flow rate, and filtration techniques, following the principles outlined in USP <1092> [11]. Subsequently, the method was validated in accordance with the International Council for Harmonisation (ICH) Q2(R1) guidelines to confirm its accuracy, precision, specificity, and robustness [7]

2. Materials and Methods

Pharmaceutical grade Povidone-Iodine and Dexamethasone were procured from Synzeal. β -Cyclodextrin, used as a solubility and stability enhancer, was obtained from Merck. High-performance liquid chromatography (HPLC) grade Acetonitrile and Methanol were utilized for all chromatographic analyses to ensure baseline stability and peak purity. All other chemicals, including sodium phosphate salts and acids used for buffer preparation, were of USP grade. To assess the method's differentiation power, formulation variants (control, low/high viscosity, low/high particle size distribution) were manufactured in-house with deliberate changes to critical process parameters (CPPs) [12].

2.1. Instrumentation

Dissolution studies were conducted using a USP Apparatus IV flow-through cell system (Sotax CP7), equipped with a precision piston pump capable of maintaining sinusoidal flow profiles. Chromatographic analysis was performed on a Waters e2695 Separation Module coupled with a Waters 2998 Photodiode Array (PDA) detector. Data acquisition, processing, and reporting were managed using Waters Empower software, ensuring compliance with data integrity standards. Additional equipment included a Metrohm pH meter for precise media preparation and a Sartorius analytical balance for accurate sample weighing.

2.2. Optimized Dissolution Conditions

Following the development and optimization studies, the final dissolution parameters were established. These conditions were selected to maximize reproducibility and discriminatory power.

2.3. Chromatographic Conditions

Quantitative analysis of the dissolution samples was achieved using a validated HPLC method, adapted from principles described by Thamaraikani et al. [13] and Urban et al. [6]. Separation was carried out on an ACE Excel 5 C8 column (250 × 4.6 mm, 5 µm). The mobile phase consisted of a mixture of phosphate buffer containing 0.6% β -Cyclodextrin and Acetonitrile in a 1:1 (v/v) ratio, pumped at a flow rate of 0.8 mL/min. The inclusion of β -Cyclodextrin in the mobile phase was critical for resolving the Dexamethasone peak from the complex iodine matrix and potential degradation products. The detection wavelength was set at 242 nm, near the lambda max of Dexamethasone, with an injection volume of 200 µL to ensure adequate sensitivity for early time-point samples [14]

Table 1. Optimized Chromatographic and USP Apparatus IV Dissolution Conditions

Parameter	Optimized Condition
Apparatus Type	USP Apparatus IV (Flow-Through Cell)
Pump Type	Piston Pump (Sinusoidal flow)
Cell Size	22.6 mm i.d.
Membrane Filter	Cellulose Ester (CE), 100 KD MWCO
Dissolution Medium	Phosphate Buffer pH 7.4 + 0.1% β-Cyclodextrin
Medium Volume	1000 mL (Closed Loop / Fraction Collection)
Flow Rate	8 mL/min
Temperature	37 ± 0.5°C
Sample Size	1.0 g of Suspension
Detection Wavelength	242 nm (HPLC-UV)

2.4. Dissolution Method Development

2.4.1. Selection of Dissolution Medium

The selection of the dissolution medium was driven by solubility and stability studies. Dexamethasone exhibits pH-dependent solubility and degradation. Solubility studies were conducted in various media, including water, 0.1N HCl, acetate buffer (pH 4.5), and phosphate buffers (pH 6.8, 7.4, and 8.0). The solubility of Dexamethasone in standard buffers was insufficient to maintain sink conditions for the formulation dose. To enhance solubility without using aggressive surfactants that might mask formulation differences, β-Cyclodextrin (0.1%) was added to the phosphate buffer (pH 7.4). This medium increased Dexamethasone solubility significantly (7.81 mg/mL) compared to water (1.84 mg/mL) and showed excellent solution stability over 72 hours (Table 2) [15].

2.4.2. Apparatus Setup and Optimization

The USP Apparatus IV was set up using a 22.6 mm flow-through cell. A critical aspect of the development was the containment of the suspension within the cell while allowing dissolved API to pass through. Initial trials with glass beads yielded high variability. Consequently, a dialysis membrane method was adopted. Different membrane molecular weight cut-offs (MWCO) were evaluated, including 8-10 KD, 100 KD, and 1000 KD. The 100 KD Cellulose Ester (CE) tubing was selected as it provided the optimal balance between retention of undissolved particles and diffusion of the dissolved drug, as evidenced by the release profile comparisons (Table 3).

2.4.3. Flow Rate and Sample Volume

Hydrodynamics within the flow-through cell is governed by the flow rate. Rates of 4 mL/min, 8 mL/min, and 12 mL/min were tested. The 8 mL/min flow rate was found to provide a stable laminar flow that minimized turbulence while ensuring adequate media turnover to maintain sink conditions (Table 2). The sample volume was standardized to 1.0 g of suspension to minimize variability observed with smaller sample sizes (0.2 g), which showed higher Relative Standard Deviation (%RSD) values [16]

Table 2. Dissolution volume optimization studies

Time points (Min)	% Drug release	
	1000mL	500mL
15	19	16
30	36	30
60	60	50
120	85	73
180	95	87
240	100	90
360	103	94
480	105	93
720	105	94
960	105	94
1440	104	91

2.5 Method Validation The developed dissolution method was validated according to ICH Q2(R2) guidelines [8].

- **Specificity:** Verified by comparing the chromatograms of the dissolution medium, placebo formulation, and standard drug solution to ensure no interference at the retention time of Dexamethasone.
- **Linearity:** Determined by analyzing standard solutions at concentration levels ranging from 50% to 150% of the target concentration.
- **Accuracy:** Assessed through recovery studies by spiking the dissolution medium with known amounts of API at 80%, 100%, and 120% levels.
- **Precision:** Evaluated through repeatability (intra-day) and intermediate precision (inter-day) by analyzing six replicate samples.
- **Robustness:** Investigated by deliberately varying critical parameters such as flow rate (±4 mL/min), media pH, and temperature to determine the method's reliability under normal usage conditions

3. Results and Discussion

3.1. Method Development and Optimization

The establishment of a robust dissolution method using the USP Apparatus IV requires the precise calibration of hydrodynamic and mechanical parameters. The following subsections detail the optimization of the dissolution medium, apparatus setup, and hydrodynamic conditions.

3.1.1. Selection of Dissolution Medium

The selection of the dissolution medium was predicated on solubility and stability characteristics, as per USP <1092> guidelines [11]. Although theoretical sink conditions (C_s x V > 3 x Dose) were achievable in standard aqueous buffers for the low dose (1 mg) of Dexamethasone—given its solubility is approx 1.6-1.9 mg/mL (Table 3)—the hydrophobic nature of the steroid presented challenges regarding wettability and potential adsorption to the apparatus tubing.

Table 3. Dexamethasone solubility in different media

Sl. No	Dissolution Media	Solubility (mg/mL)
1	Water	1.84
2	0.1N Hydrochloric Acid	1.93
3	Acetate buffer pH 4.5	1.86
4	Phosphate buffer pH 6.8	1.79
5	Phosphate buffer pH 7.4	1.61
6	Phosphate buffer pH 8.0	1.69
7	Phosphate buffer pH 7.4+0.1%β-Cyclodextrin	7.81

Experimental data indicated that while solubility was sufficient in plain buffers, the release rate was inconsistent, likely due to poor wetting of the suspended particles. To ensure robust method performance and prevent adsorption-related recovery losses, β - Cyclodextrin (0.1%) was added to the phosphate buffer (pH 7.4).

Table 4. Dexamethasone solution stability in different media

Sr. No	Media	Parameter	Initial	After 32 hr.at 25°C	After 56 hr.at 25°C	After 71 hr.at 25°C
1	0.1N HCL	Area	1126725	1122945	1119148	1118136
		% Difference	NA	-0.335	-0.672	-0.762
2	Acetate buffer pH 4.5	Area	1085586	1081118	1065324	1072265
		% Difference	NA	-0.412	-1.866	-1.227
3	Phosphate buffer pH 6.8	Area	1045257	1037466	1033033	1027685
		% Difference	NA	-0.745	-1.169	-1.681
4	Phosphate buffer pH 7.4	Area	937775	936930	931870	931308
		% Difference	NA	-0.090	-0.649	-0.690

Sr. No	Media	Parameter	Initial	After 32 hr.at 25°C	After 56 hr.at 25°C	After 71 hr.at 25°C
5	Phosphate buffer pH 8.0	Area	984013	982522	973977	969281
		% Difference	NA	-0.152	-1.020	-1.497
6	Phosphate buffer pH 7.4+0.1% β-Cyclodextrin	Area	4582851	4561956	4539163	4525035
		% Difference	NA	-0.456	-0.953	-1.262

The pH of 7.4 was selected to mimic the pH of tear fluid. The addition of cyclodextrin increased Dexamethasone solubility significantly to 7.81 mg/mL. Moreover, stability studies confirmed that Dexamethasone remained stable in this medium for over 72 hours, which is essential for the extended run times often required in flow-through cell methodologies (Table 4).

3.1.2. Apparatus Setup: Membrane Selection

A critical aspect of the development was the containment of the suspension within the cell. The goal was to retain undissolved particles while allowing the dissolved drug to diffuse freely into the bulk media. Initial trials using a bed of glass beads resulted in high variability, likely due to the migration of fine suspension particles through the bead interstices. Consequently, a dialysis membrane method was adopted [17].

Different membrane molecular weight cut-offs (MWCO) were evaluated. The 100 KD Cellulose Ester (CE) tubing was selected as the optimal barrier. As shown in Table 5, lower MWCO membranes (8-10 KD) restricted diffusion excessively, resulting in artificially low release rates (only 13% at 15 mins). Conversely, larger pores (1000 KD) posed a risk of particle leakage, which would compromise the distinction between dissolved and undissolved drug. The 100 KD membrane provided a diffusion rate that allowed for discrimination based on the drug's dissolution rather than membrane transport limitations.

Table 5. Comparison of Cellulose Membrane

Time points (Min)	% Drug Release		
	8-10 KD	100 KD	1000KD
15	4	13	37
30	9	16	50
60	21	29	66
120	42	53	83
180	58	72	90
240	68	84	94
360	87	95	58
480	94	99	104
720	98	99	104
960	99	100	103
1440	97	101	100

Table 6. Flow rate optimization

Time points (Min)	% Drug Release		
	12 mL Flow	8 mL Flow	4 mL Flow
15	18	9	7
30	23	16	10
60	38	30	17
120	57	55	35
180	68	72	56
240	83	84	62
360	89	92	71
480	91	96	75
720	92	98	80
960	92	98	82
1440	92	97	83

3.1.3. Flow Rate Optimization

Hydrodynamics within the flow-through cell is governed by the flow rate. In USP Apparatus IV, the flow profile (laminar vs. turbulent) significantly affects the diffusion boundary layer thickness around the dosage form [4]. Rates of 4, 8, and 12 mL/min were tested. The 8 mL/min flow rate was found to provide a stable laminar flow that minimized turbulence while ensuring adequate media turnover to maintain sink conditions within the dialysis adapter (Table 6). The 4 mL/min rate appeared insufficient to facilitate timely diffusion across the membrane, while 12 mL/min caused excessive turbulence that could disrupt the membrane integrity.

3.1.4. Sample Volume and Mass Optimization

Sample load optimization studies demonstrated that larger sample masses improved method precision. A sample mass of 1.0 g yielded significantly higher reproducibility (%RSD < 1.0% at later time points) compared to a 0.2 g sample. The smaller sample size suffered from high variability (%RSD > 40% at 15 minutes) due to weighing errors and non-uniform distribution of the suspension within the adapter (Table 7). Additionally, a media volume of 1000 mL was selected over 500 mL to prevent any potential saturation effects in the closed-loop system during the later stages of dissolution (Table 8).

Table 7. Selection of sample preparation

Time points (Min)	% Drug Release			
	0.2g sample volume	% RSD of six Cells	1.0g sample volume	% RSD of six Cells
15	13	40.9	9	25.8
30	16	36.2	16	15.4
60	25	33.6	30	8.6
120	57	28.4	55	2.2
180	79	25.5	72	2.3
240	88	21.3	84	1.6
360	97	19.2	92	0.5
480	99	17.8	96	0.6
720	99	10.4	98	0.6
960	100	8.0	98	0.5
1440	101	8.4	97	0.7

Table 8. % Drug release profile at each time points for batches F-01 to F-09

Time points (Min)	Control (F-01)	Low PSD (F-02)	High PSD (F-03)	Low Viscosity (F-04)	High Viscosity (F-05)	No surfactant (F-06)	High surfactant (F-07)	Low Conc. API (F-08)	High Conc. API (F-09)
15	13	15	9	20	12	9	12	5	20
30	16	25	10	28	14	13	19	9	27
60	29	43	18	45	27	26	35	15	35
120	53	76	45	68	45	49	58	32	61
180	72	88	63	85	55	63	78	47	78
240	84	95	78	95	62	75	88	58	92
360	95	99	86	99	86	83	97	69	100
480	99	100	90	99	91	91	99	72	105
720	99	102	92	100	92	92	100	75	108
960	100	102	92	100	92	93	101	78	111
1440	101	103	93	102	94	92	102	78	116

3.2. Method Validation

The developed dissolution method was validated according to ICH Q2(R1) guidelines [12], evaluating parameters such as linearity, accuracy, precision, and robustness.

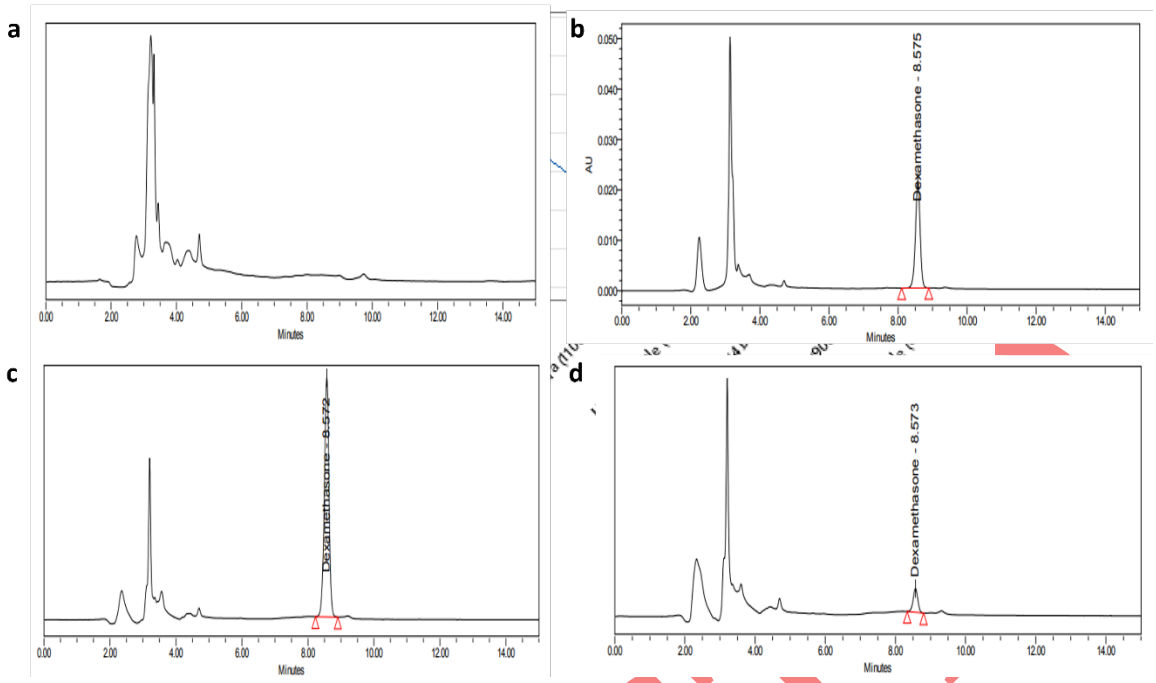

Figure 2. Chromatograms for the a. Blank, b. Standard, c. Sample at Initial Time Point and d. Sample after Complete Drug release

3.2.1. Analytical Performance

The HPLC method demonstrated excellent linearity with a correlation coefficient (r^2) greater than 0.999 across the working concentration range (50% to 150%). Accuracy was assessed via recovery studies, yielding results between 98.5% and 101.5%, which is well within the standard acceptance criteria of 98.0–102.0%. Precision studies (repeatability and intermediate precision) indicated %RSD values well below the 2.0% limit, confirming the reliability of the analytical finish (Table 9).

Table 9. Results of Analytical Method Validation

Validation Parameter	Acceptance Criteria	Result	Conclusion
Linearity	Correlation Coefficient (r^2) ≥ 0.999	r^2 > 0.999	Complies
Range	50% – 150% of target concentration	Linear response observed	Complies
Accuracy	% Recovery: 98.0% – 102.0%	98.5% – 101.5%	Complies
Precision (Repeatability)	% RSD ≤ 2.0%	< 2.0%	Complies
Solution Stability	Change in response ≤ 2.0%	Stable up to 72 hours	Complies
Robustness	No significant change in system suitability	Robust for flow (±10%) and pH	Complies

3.2.2. Robustness

Robustness testing involved deliberate variations in flow rate (±10%), pH, and media composition. The results indicated that the method is robust within small variations of critical parameters, such as a ±10% change in β -Cyclodextrin concentration. However, significant deviations in flow rate marked changes in the release profile, reinforcing the need for precise pump calibration during routine testing.

3.2.3. Distinguishing Power of the Method

A critical attribute of a dissolution method, as emphasized in USP <1092>, is its ability to differentiate between formulations with varied quality attributes (discriminatory power) [11]. To assess this, batches were manufactured with specific modifications in particle size distribution (PSD), viscosity, and surfactant concentration.

Analysis using the difference factor (f1) and similarity factor (f2) was employed to compare profiles. An f2 value between 50 and 100 indicates similarity, while a value below 50 indicates a significant difference. The method revealed that formulations with "Low PSD" and "High Viscosity" were statistically dissimilar to the control batch (f2 < 50), confirming the method's discriminatory capability (Table 10). For instance, the high viscosity batch showed a significantly retarded release profile compared to the control (Table 10), likely due to increased resistance to drug diffusion within the polymer matrix. The method also successfully identified differences in surfactant concentration, highlighting its sensitivity to wetting agents which are crucial for suspension performance.

Table 10. Evaluation of Distinguishing Power Using Difference (f1) and Similarity (f2) Factors

Formulation Variant	f1 Value (Difference)	f2 Value (Similarity)	Inference
Low Particle Size (PSD)	13	49	Dissimilar (f2 < 50)
High Particle Size (PSD)	13	55	Similar
Low Viscosity	12	51	Borderline Similar
High Viscosity	14	49	Dissimilar (f2 < 50)
No Surfactant	12	56	Similar
High Surfactant	5	72	Very Similar
Low Conc. API	34	33	Dissimilar (f2 < 50)

An f2 value between 50 and 100 indicates similarity between the two dissolution profiles.

4. Conclusion

The research successfully established and validated a USP Apparatus IV dissolution method for the evaluation of Dexamethasone in a complex Povidone-Iodine ophthalmic suspension. By optimizing critical parameters such as the membrane molecular weight cut-off (100 KD), flow rate (8 mL/min), and media composition (Phosphate buffer pH 7.4 with β -Cyclodextrin), the method overcame the hydrodynamic and solubility challenges inherent to suspension formulations. The method proved to be highly discriminating, effectively distinguishing between formulations with varying particle sizes and viscosities, which is a key requirement for regulatory approval. Validation data confirmed the method's precision, accuracy, and robustness in accordance with ICH guidelines. This flow-through cell method therefore serves as a valuable tool for the quality control and stability assessment of dual-drug ophthalmic suspensions.

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