

## EVALUATION OF PRESERVATIVE EFFECTIVENESS IN SOME EYE DROPS IN SYRIAN MARKET BY ANTIMICROBIAL EFFECTIVENESS TEST ACCORDING TO DIFFERENT PHARMACOPEIAS

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*Ophthalmic drops are subject to microbial contamination during use and storage by repeated opening of bottle when administrating individual doses, touching dropper-tip with infected eye/eyelid or contaminated hands, that why preservatives are added to eye drops packaged in multidose containers to prevent preparation spoilage and minimize hazards of ophthalmic infections ,especially in post-operative patients.*

*The aim of this study is to evaluate and compare the effectiveness of preservatives in three commercially marketed ophthalmic drops (timolol maleate solution 0.5%, polyvinyl alcohol solution 1.4%, and prednisolone acetate suspension 1%) in Syrian market by compendial antimicrobial effectiveness test which is not yet subject to international harmonization in different pharmacopeias.*

*The results showed that timolol maleate ophthalmic solution 0.5%, and polyvinyl alcohol ophthalmic solution 1.4% comply with different compendial acceptance criteria in antimicrobial effectiveness test(AET) , while prednisolone acetate ophthalmic suspension 1% didn't comply with any of compendial acceptance criteria.. There are many reasons can lead to preservative failure like adsorption of preservatives on plastic bottles and/or differences in formulation conditions of eye drops (viscosity- increasing agents , surfactants, incompatibility between product's pH range and optimal pH range of preservative used).*

**Keywords:** *ophthalmic/eye drops, sterility, preservative effectiveness, microbial contamination, compendial test.*

### INTRODUCTION

Ophthalmic preparations (eye preparations) are sterile preparations intended for application to the conjunctiva, the conjunctival sac, or the eyelids. Most conventional ophthalmic dosage forms include ointments, solutions, emulsions and suspensions. It is usual that water-soluble drugs are delivered through topical instillation in an aqueous solution and water-insoluble drugs are administered topically as ointments or aqueous suspensions<sup>1&2</sup>.

The importance of eye drops being sterile on use has been increasingly emphasized in recent decades; aseptic preparation, sterilization and addition of preservative are three consequent steps in their manufacture. Demand of sterility of eye drops have been introduced into most pharmacopeias during the past 20 years<sup>3</sup>.

Antimicrobial preservatives are type of excipients added to products to limit microbial contamination during normal use or storage. Preservatives are classified into main classes: antimicrobial preservatives and antioxidants. Antimicrobial preservatives kill or inhibit

microorganisms inadvertently introduced to eye drops during use. Examples of antimicrobial preservatives include: benzoic acid and its salts, phenolic compounds, esters of p-hydroxybenzoic acid (methyl paraben, propyl paraben), quaternary ammonium salts (benzalkonium chloride), mercurials (phenyl mercuric nitrate), and alcohols (chlorobutanol). Antioxidants are used to prevent product deterioration from oxidation like: tocopherols, ascorbic acid, the potassium and sodium salts of sulphurous acid, edetic acid and its salts<sup>4</sup>.

One of the most important compendial microbiological tests for ophthalmic preparations is preservative/antimicrobial effectiveness test (AET) which is important to demonstrate that the preservative agents are effective in the final package, and that they are safe for human use. The AET is used to evaluate the effectiveness of preservatives in multidose dosage forms. AET is a tripartite compendial test performed during development and stability testing of pharmaceutical products intended as a multidose product. The United States Pharmacopeia (USP), Japanese Pharmacopeia (JP), and European Pharmacopeia (Ph.Eur) all describe the assay in a similar fashion, but the acceptance criteria varies amongst the different compendial general chapters. Sampling times and logarithmic ( $\log_{10}$ ) reduction performance criteria of the Ph.Eur are more stringent than those in the USP and JP<sup>5&6</sup>.

The test involves inoculating a measured amount of product with known amounts of microorganisms. Whenever possible, the original containers are utilized for the assay. The containers are protected from light and incubated at ambient temperature for 28 days. The death rate is measured over a 28-day period and compared with the acceptance criteria outlined in the compendial guidance documents<sup>6</sup>.

Samples of commercial eye drops are chosen according to their therapeutic importance (such as topical glucocorticoids prescribed for post-operative patients) and length of treatment period in cases of management of chronic diseases like glaucoma, and dry eye disease (DED).

Timolol maleate belongs to  $\beta$ -blockers, which are topically applied on the eye for glaucoma treatment. It is effective in

diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. The  $\beta$ -blockers are only used for chronic management of glaucoma<sup>7</sup>.

Artificial tears (therapeutic tear substitutes) also known as ocular lubricants are commonly the first-line therapy among eye care providers in managing dry eye disease. Currently, artificial tears are the preferred choice for both patients and practitioners in managing ocular surface disorders due to their simplicity of use, minimal side effects, and affordability. Solutions employed as artificial tears to lubricate the eye contain agents such as carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose and polyvinyl alcohol<sup>8</sup>.

Prednisolone acetate is a SAID (Steroidal Anti-Inflammatory Drug) effective in treating ocular surface and anterior segment inflammation, including pain and post-operative inflammation, seasonal allergic conjunctivitis, blepharo conjunctivitis, and corneo-conjunctival burns. The anti-inflammatory effect is highly used in post-operative inflammation, such as cataract or glaucoma surgery, or in the prevention of corneal graft rejection, as an immunosuppressive agent<sup>2</sup>.

The aim of this present study is to evaluate the preservative effectiveness in some commercial eye drops in Syrian market (timolol maleate ophthalmic solution 0.5%, polyvinyl alcohol ophthalmic solution 1.4%, prednisolone acetate ophthalmic suspension 1%) by antimicrobial effectiveness test and to compare the results with compendial acceptance criteria mentioned in three different pharmacopeias: the United states pharmacopeia USP41, the European pharmacopeia Ph.Eur 9, the Japanese pharmacopeia JP17 which differ in the acceptance criteria.

## MATERIALS AND METHODS

### Culture media and reagents

Culture dehydrated media: Fluid Thioglycolate Medium (FTM), Soybean-Casein Digest Medium (SCDM) for sterility test, Soybean-Casein digest Agar (SCDA/TSA), Sabouraud-Dextrose Agar (SDA), and phosphate buffer (pH= 7.2) for antimicrobial

effectiveness test (AET) were procured from HiMedia, Mumbai, India. Milli-Q water (Millipore) was used to prepare culture media and phosphate buffer (diluent).

### Samples

Commercial samples of three eye drops packaged in plastic bottles, three batches for each eye drop (timolol maleate solution 0.5% symbolized as T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>), (polyvinyl alcohol solution 1.4% symbolized as PVA<sub>1</sub>, PVA<sub>2</sub>, PVA<sub>3</sub>) and (prednisolone acetate suspension 1% symbolized as P<sub>1</sub>, P<sub>2</sub>, P<sub>3</sub>) were collected from local Syrian market, which are the preservatives and excipients in each preparation are non-declared in the labeling.

### Microbiological strains

The microbiological strains used in AET were 5 strains as mentioned in different three pharmacopeias: gram-negative bacteria *Escherichia coli* ATCC 8739 and *Pseudomonas aeruginosa* ATCC 9027; gram-positive bacteria *Staphylococcus aureus* ATCC 6538; yeast *Candida albicans* ATCC 10231 and mould *Aspergillus brasiliensis* ATCC 16404<sup>9-11</sup>.

### Preparation of culture media

Fluid Thioglycolate Medium (FTM), and Soybean-Casein Digest Medium (SCDM) were prepared according to manufacturer's instructions and used in sterility test according to membrane filtration compendial method in USP41<sup>12</sup>.

Soybean-Casein Digest Agar/Tryptic Soy Agar (TSA) was used for culturing bacteria, and Sabouraud-Dextrose Agar (SDA) for culturing yeasts and fungi.

Culture media (TSA and SDA) were prepared, and pH of each medium was adjusted according to manufacturer's instructions written on the dehydrated media bottles. Culture media were sterilized in the autoclave at 121°C and 15 psi for 15 minutes. These media were subjected to growth promotion test to ensure their capability in supporting microbial growth.

### Preparation of microbial suspensions

The ATCC five microbiological strains were subcultured on slants of Soybean-Casein Digest Agar (SCDA) and Sabouraud-Dextrose Agar (SDA) for the growth of bacteria and

fungi respectively to prepare microbial suspensions. Petri dishes containing TSA media were incubated at 22.5 ± 2.5°C for 24 hours for growth of *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC 9027, *Staphylococcus aureus* ATCC 6538, whereas Petri dishes containing SDA media were incubated at 22.5 ± 2.5°C for 52 hours, 6 days for growth of *Candida albicans* ATCC 10231, *Aspergillus brasiliensis* ATCC 16404, respectively.

Cultured bacterial and yeast cells on the surface of media were harvested with sterile sodium chloride 0.9%, while cultured mold cells were harvested with sterile sodium chloride 0.9% and 0.05% of polysorbate 80 and then collected in sterile vessels. The final concentration of each microbial suspension must be between (1×10<sup>7</sup>-1×10<sup>8</sup>) CFU/ml. The viable microbial count was titrated immediately for each suspension before use by pour-plate method to confirm the estimate of microbial suspensions.

### Evaluation of preservative effectiveness by antimicrobial effectiveness test

Since, AET assesses microbiologically the biological activity of preservatives in pharmaceutical preparations; Antimicrobial effectiveness test was performed by following the standard procedure in the United States of America USP41. The results were evaluated according to acceptance criteria in three different pharmacopeias<sup>9-11</sup>.

First, 20 ml of each preparation was inoculated with 1% of microbial suspension and then mixed. Final concentration in inoculated eye drops should be between (1×10<sup>5</sup>-1×10<sup>6</sup>) CFU/mL of product. The viable microbial count (initial count) was calculated immediately for each inoculated product at (0 hour) by pour-plate method.

The inoculated containers were incubated at 22.5 ± 2.5°C in a microbiological incubator (protected from light). 1 mL of each inoculated preparation was tested at defined compendial time intervals. The antimicrobial properties of preservatives were neutralized by dilution the sample with phosphate buffer (pH= 7.2) containing polysorbate 80 1%<sup>13</sup>.

Samples were cultured using TSA media for bacteria, SDA for yeasts and fungi. TSA

media were incubated at  $32.5 \pm 2.5^{\circ}\text{C}$  for 24 hrs, SDA media were incubated at  $22.5 \pm 2.5^{\circ}\text{C}$  for 72 hrs for *Candida albicans*, and for 7 days for *Aspergillus brasiliensis*. Microbial counts were calculated by dilution pour-plate technique.

The rate of microbial contamination in each sample was assessed at five time points (6 hrs, 24 hrs, 7 days, 14 days, 28 days) by reading microbial counts which expressed as (CFU/ml) at these time points.

The  $\log_{10}$  reduction values (death rate) of microbial counts were calculated at (6 hours, 24 hours, 7 days, 14 days, 28 days), compared with the initial microbial count at (0 hour) after inoculation, and assessed according to different pharmacopeial specifications in USP41, Ph.Eur 9, JP17. Table.1, table.2 show acceptance criteria in antimicrobial effectiveness test according to USP41, Ph.Eur 9, JP17.

## RESULTS AND DISCUSSION

### Results

Studied samples of eye drops were subjected to compendial sterility test according to general chapter <71> sterility tests in USP

41. All of tested eye drops passed sterility test after incubation in FTM, SCDM media for 14 days<sup>12</sup>.

### Timolol maleate solution 0.5%

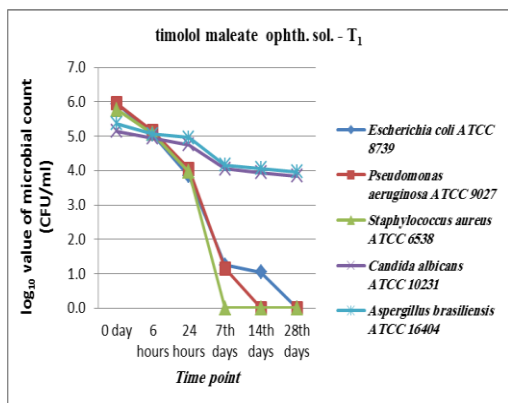
Three batches of timolol maleate solution passed antimicrobial effectiveness test complying with Ph.Eur 9 (EP-B), USP41, JP17 specifications. The  $\log_{10}$  values of microbial counts in all bacterial strains decreased by (2  $\log_{10}$ ) at 24 hrs compared with initial counts. There was little microbial growth in most samples (<10 CFU/ml) at (7 days, 14 days, 28 days) as  $\log_{10}$  values of microbial counts decreased by (5  $\log_{10}$ ) compared with initial counts which means that the specification NR (No recovery) was achieved. The  $\log_{10}$  values of microbial counts in the two fungal strains decreased by (1  $\log_{10}$ ) at 7 days compared with initial count, and it wasn't noted any significant decrease in  $\log_{10}$  values of microbial counts at (14 days, 28 days) compared with the previous time point reading which means that the specification NI (No increase) was achieved. Fig.1 shows results of AET in three batches of timolol maleate ophthalmic solution.

**Table.1:** acceptance criteria for bacterial strains in antimicrobial effectiveness test according to different pharmacopeias.

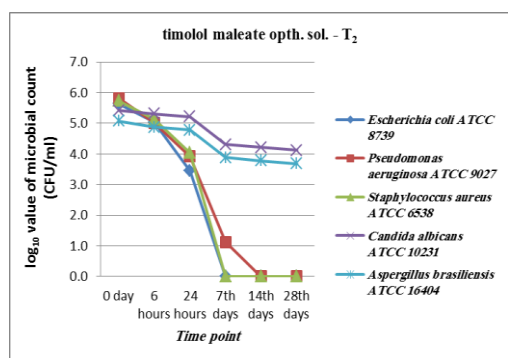
<i>log<sub>10</sub> reduction values of microbial counts for bacteria at sampling time points</i>					
<i>Acceptance criteria according to different pharmacopeias for bacteria</i>	<i>6 hours</i>	<i>24 hours</i>	<i>7th days</i>	<i>14th days</i>	<i>28th days</i>
<i>Acceptance criteria according to Ph.EUR 9 (EP-A criteria)</i>	2	3	-	-	NR (no recovery) from initial count
<i>Acceptance criteria according to Ph.EUR 9 (EP-B criteria)</i>	-	1	3	-	NI (no increase) from previous reading
<i>Acceptance criteria according to USP 41 and JP17</i>	-	-	1	3	NI (no increase) from 14 days' count

**Table.2:** acceptance criteria for fungal strains in antimicrobial effectiveness test according to different pharmacopeias.

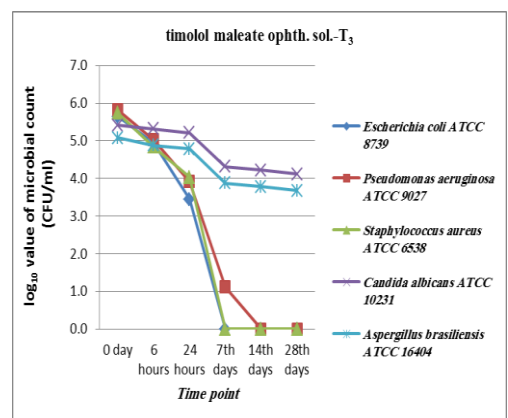
<i>log<sub>10</sub> reduction values of microbial counts for fungi at sampling time points</i>					
<i>Acceptance criteria according to different pharmacopeias</i>	<i>6 hours</i>	<i>24 hours</i>	<i>7th days</i>	<i>14th days</i>	<i>28th days</i>
<i>Acceptance criteria according to Ph.EUR 9 (EP-A criteria)</i>	-	-	2	-	NI (no increase) from previous reading
<i>Acceptance criteria according to Ph.EUR 9 (EP-B criteria)</i>	-	-	-	1	NI (no increase) from previous reading
<i>Acceptance criteria according to USP 41 and JP17</i>	-	-	No Increase from initial calculated count after 7 days, 14 days and 28 days		



**Fig. (1-a)**



**Fig.(1-b)**



**Fig.(1-c)**

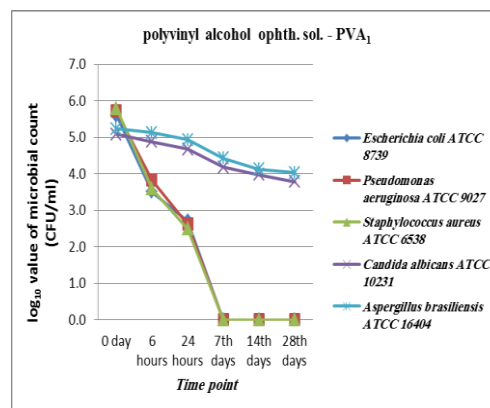
**Fig. (1-a) (1-b) (1-c)** : charts show log<sub>10</sub> reduction values of microbial counts of the five microbiological strains versus time through 28 days in three batches of timolol maleate ophthalmic solution T<sub>1</sub>,T<sub>2</sub>,T<sub>3</sub>, respectively.

**Polyvinyl alcohol solution 1.4%**

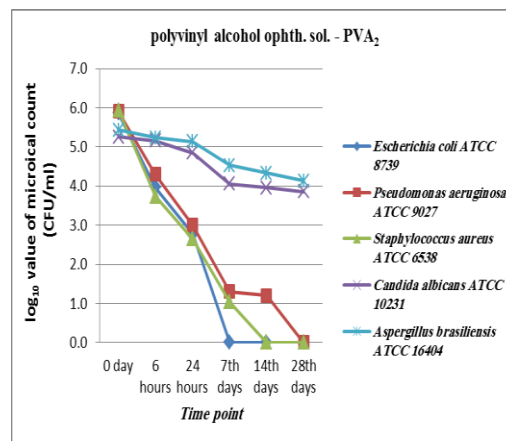
The log<sub>10</sub> values of microbial counts in all bacterial strains decreased by (2 log<sub>10</sub>), (3 log<sub>10</sub>) at 6 hours, 24 hrs respectively compared with initial counts. There was little microbial growth in most samples (<10 CFU/ml) at

(7days,14 days, 28 days) as log<sub>10</sub> values of microbial counts decreased by (5 log<sub>10</sub>) compared with initial counts which means that the specification NR(No recovery) was achieved. The log<sub>10</sub> values of microbial counts in the two fungal strains decreased by (1 log<sub>10</sub>) at 7days compared with initial count, and it wasn't noted any significant decrease in log<sub>10</sub> values of microbial counts at (14 days, 28 days) compared with the previous time point reading which means that the specification NI(No increase) was achieved.

We conclude from the above that all batches of polyvinyl alcohol solution comply with the most stringent criteria Ph.Eur 9 (EP-A) for bacterial strains only, while they comply with Ph.Eur 9 (EP-B) for fungal strains. We can summarize that all batches of polyvinyl alcohol solution comply with Ph.Eur 9 (EP-B), USP41, JP17 specifications for the five microbiological strains. Fig.2 shows results of AET in three batches of polyvinyl alcohol ophthalmic solution.



**Fig. (2-a)**



**Fig. (2-b)**

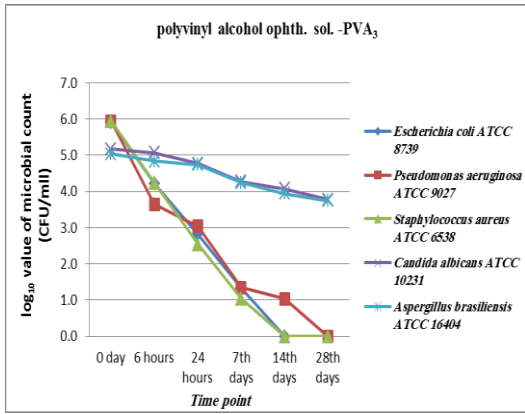


Fig. (2-c)

Fig. (2-a) (2-b) (2-c) : charts show log<sub>10</sub> reduction values of microbial counts of the five microbiological strains versus time through 28 days in three batches of polyvinyl alcohol ophthalmic solution PVA<sub>1</sub>,PVA<sub>2</sub>,PVA<sub>3</sub>, respectively.

**Prednisolone acetate suspension 1%**

All batches of prednisolone acetate suspension failed to comply antimicrobial effectiveness test acceptance criteria according to different pharmacopeias Ph. Eur 9, USP41, JP17. The log<sub>10</sub> values of microbial counts in all bacterial strains didn't decrease until 7 days, which decreased only by (1log<sub>10</sub>) compared with initial counts ,and it wasn't noted any significant decrease in log<sub>10</sub> values of microbial counts at (14 days,28 days) compared with initial count which means that the specification (No increase) was achieved. The log<sub>10</sub> values of microbial counts in the two fungal strains also didn't decrease until 28 days which decreased only by (1 log<sub>10</sub>) compared with initial count. Fig.3 shows results of AET in three batches of prednisolone acetate ophthalmic suspension.

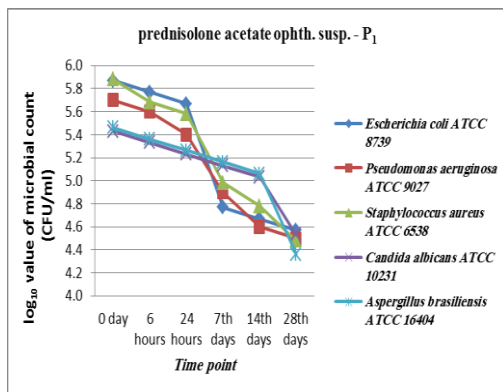


Fig. (3-a)

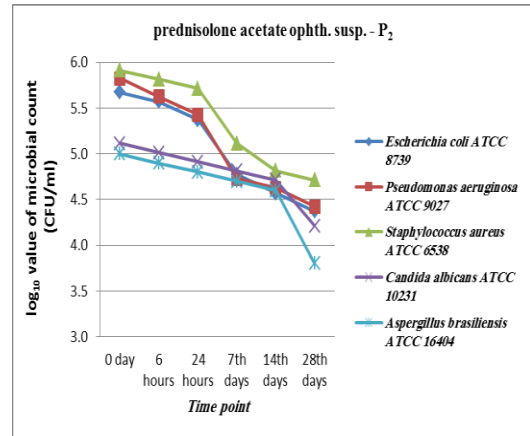


Fig. (3-b)

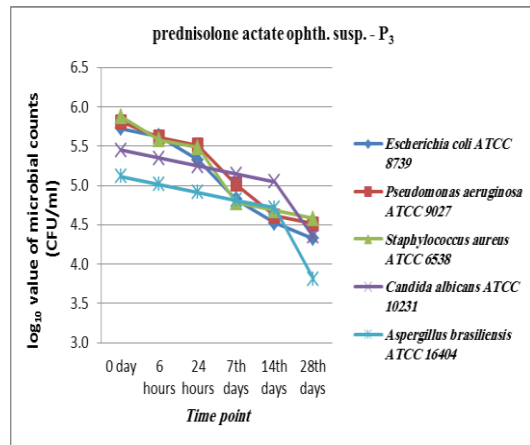


Fig. (3-c)

Fig. (3-a) (3-b) (3-c) : charts show log<sub>10</sub> reduction values of microbial counts of the five microbiological strains versus time through 28 days in three batches of prednisolone acetate ophthalmic suspension P<sub>1</sub>,P<sub>2</sub>,P<sub>3</sub> respectively.

**Discussion**

Microbial contamination of eye drops packaged in multi dose containers caused by accidental entry of microorganisms during use or misuse by patients represents an important factor of negative impact on public health, especially eye health. A preservative will only provide protection from microbial growth for a short time period. For this reason, 28 days is typically stated as the maximum shelf-life after the preservative-containing product is opened<sup>9</sup>.

Preservatives are used to overcome the contamination problem in eye drops. The ideal preservative must be non-toxic, non-irritating to biological tissues, has a broad spectrum encompassing bacteria (Gram-positive and Gram-negative), yeasts, fungi and molds, and

effective throughout the entire shelf life of the product. An effective preservative must reduce a microbial population significantly and prevent subsequent re-growth.

In addition to preservatives, there are several factors help in reducing contamination and preserving dosage forms during storage and use such as proper container design, practicing good personal hygiene habits at home and in hospitals, training patients of proper eye drops administration skills<sup>14&15</sup>.

Polyvinyl alcohol solution had the most effective preservative between tested eye drops followed by timolol maleate solution which both passed different compendial antimicrobial effectiveness test criteria. The preservative activity in polyvinyl alcohol solution was probably enhanced by the viscous nature of formulation which helps in limiting microbiological proliferation.

Prednisolone acetate suspension failed to comply with any of compendial antimicrobial effectiveness test criteria. This may be explained by adsorption of preservative on low density polyethylene plastic bottles, or onto excipients, especially those with large surface areas like suspending agents and viscosity-increasing agents (cellulose-based excipients: hypromellose (HPMC)) leading to minimize preservative concentration below its effective concentration against microorganisms. Moreover, surfactants like polysorbate 80 used in ophthalmic suspensions as suspending and wetting agents have reported to reduce the antimicrobial activity of some preservatives<sup>16-20</sup>.

### Conclusion

The results showed that two eye drops had effective preservatives, whereas one eye drop product failed to have effective preservative. Polyvinyl alcohol solution had the most effective preservative between tested products.

We recommend that more studies and researches should be done in the field of microbiological quality tests to ensure safety and quality of sterile and non-sterile dosage forms. Antimicrobial effectiveness test should be also applied as routine test in quality control labs for all types of dosage forms, and in cases of changes in pharmaceutical formulations or packaging materials. Further future efforts should be done in development and usage of

validated reliable analytical methods (HPLC or spectrophotometric) for quantitative analysis of chemical preservatives within the product to ensure compliance with specifications, and in manufacturing and development of new effective preservatives and packaging materials which are able to protect pharmaceutical products from microbiological contamination for periods longer than 28 days.

### Acknowledgements

The authors are thankful to Faculty of Pharmacy, Al-Baath University for supporting this work.

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## نشرة العلوم الصيدلانية جامعة أسيوط



### تقييم فعالية المادة الحافظة في بعض القطورات العينية المسوقة في السوق السورية باستخدام اختبار فعالية المادة الحافظة وفقاً لدساتير دوائية مختلفة

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تكون القطورات العينية عرضة للتلوث الميكروبيولوجي خلال استخدامها وتخزينها وذلك من خلال الفتح المتكرر للعبوة وإيتاء الجرعات الفردية، ملامسة فوهة القطارة مع العين أو أجزائها المصابة بالخمج (جفني العين) أو مع الأيدي الملوثة. لذلك تُضاف المواد الحافظة إلى القطورات العينية المُعبأة ضمن عبوات متعددة الجرعة لمنع تخرّب المستحضر والتقليل من مخاطر الإلتهابات العينية وخاصة عند مرضى ما بعد العمليات الجراحية

تهدف الدراسة الحالية إلى تقييم فعالية المادة الحافظة والمقارنة بينها في ثلاث قطورات عينية تجارية (المحلول العيني للتيمولول مالبات ٠,٥%، المحلول العيني لعديد فينل الكحول ١,٤%، المعلق العيني للبردنيزولون أسيتات ١%) مسوقة في السوق السورية بالاعتماد على اختبار فعالية المادة الحافظة الدستوري غير الخاضع حتى الآن لعملية الموازنة الدولية وتوحيد المعايير ما بين الدساتير الدوائية المختلفة.

أظهرت النتائج توافق كل من المحلول العيني للتيمولول مالبات ٠,٥%، المحلول العيني لعديد فينل الكحول ١,٤% مع المواصفات الدستورية المختلفة في اختبار فعالية المادة الحافظة، في حين لم يتوافق المعلق العيني للبردنيزولون أسيتات ١% مع أي من المواصفات الدستورية. توجد العديد من المسببات التي قد تؤدي إلى فشل المادة الحافظة في أداء دورها مثل ادمصاص (امتزاز) المادة الحافظة على العبوات البلاستيكية و/أو اختلافات ظروف الصيغ في القطورات العينية (العوامل الرافعة للزوجة، العوامل الفعالة سطحياً، عدم توافق مجال درجة الحموضة المنتج مع مجال درجة الحموضة الأمثل للمادة الحافظة المستخدمة).