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The Study of Chloramphenicol for Ophthalmic Formulation

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ABSTRACT

Chloramphenicol is still 'gold standard' for conjunctivitis in every age. However, chloramphenicol eye caps and eye drops have no satisfactory results. The objective of the study was to screen oil, evaluate solubility of chloramphenicol in them for ophthalmic formulation. Spectrum and calibration curve of chloramphenicol was prepared. Oils were subjected to scan between 200–400 nm. Those oils had no absorbance considered for equilibrium solubility study. The solubility of chloramphenicol was evaluated in different short listed oils by equilibrium solubility study. One-way ANOVA following Tukey-Kramer multiple comparisons test was used for statistical analysis. Absorbance maximum of chloramphenicol was found to be 274 nm in methanol. Chloramphenicol was exhibited linearity in the range of 10–30 µG/mL of methanol. Neem oil, heavy liquid paraffin, light liquid paraffin, olive oil, isopropyl myristate, peppermint oil, oleic acid, Jasminum sambac oil, mentha oil, isopropyl palmitate, and triacetin were selected for equilibrium solubility studies. Oils had significantly less solubility of chloramphenicol than water.Use of oil and water both phases i.e. emulsion or emulgel of chloramphenicol could be anappropriate formulation for the ophthalmic administration.

KEYWORDS: Chloramphenicol; Conjunctivitis; Solubility; Oil phase; Ophthalmic formulation.

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INTRODUCTION

Multi-microbial infection is observed in conjunctivitis and is susceptible to streptomycin, ampicillin, and chloramphenicol[1]. *Staphylococcus epidermidis* is causing pathogen for conjunctivitis[2]. Chloramphenicol is effective against *Streptomyces venezuelae* and the other anaerobes bacteria's, gram-negative, gram positive bacteria. Chloramphenicol is still 'gold standard' for conjunctivitis in every age[3].Chloramphenicol ophthalmic formulations available in Indian subcontinent pharmaceutical markets are eye caps (Chloromycetin eye caps), eye ointment (Chloromycetin eye ointment), and eye drops (Chloromycetin eye drops). My observations regarding both these formulations have two questions that do patients satisfy with eye drops (regarding recovery in conjunctivitis)? Does ophthalmologist satisfy with drug action of eye caps or ointment? The answersare no. As chloramphenicol is hydrophobic in nature, when eye drops entered into theeyethere is less contact time of chloramphenicol with theconjunctiva[4], less lubrication[5], thedrug can be drained into thethroat by aqueous humor that is secreted by *Canal of Schlemm* and drug action is divided into eye and throat[6]. Patients can feel the bitter taste of chloramphenicol too[7]. Moreover, in eye caps or ointment, soft paraffin or petroleum jelly is not sufficient tobase for therelease of chloramphenicol and contact time of chloramphenicol to theconjunctiva is not high enough. Ointment provides blurred vision and is uncomfortable[7, 8].

The objective of thestudy was to screen out oils, evaluatesolubility of chloramphenicol in them for ophthalmic formulation.

EXPERIMENTAL

Material

Neemoil was purchased from Parker Biotech Pvt. Ltd. Chennai, India. Olive, heavy liquid paraffin, light liquid paraffin, triacetin, mentha oil, oleic acid, and peppermint oil were purchased from Astron Chemicals Ltd, Ahmedabad, India. Isopropyl palmitate and isopropyl myristate, mogra (Jasminum sambac) oil were purchased from Chem dyes corporation Rajkot, India. Chloramphenicol eye caps were purchased from Jyoti capsules, Kanpur, India. Chloramphenicol was purchased from Oxford Laboratory Thane, India.

Calibration curve

A stock solution of chloramphenicol was made with methanol. UV-scan of these solutions were performed between 200–400 nm by Double-Beam UV-visible Spectrophotometer (LT-2900, Labtronics (I) Pvt. Ltd, Ambala, India). A wavelength at which chloramphenicol showed maximum

absorbance was considered as absorbance wavelength(λ_{max})for research work. From the stock solution (100 µG/mL), appropriate solutions (5–30 µG/mL) were prepared in 10 mL volumetric flasks with methanol. The absorbance of these solutions was measured at λ_{max}[9].

Short listing of oils

Oils were subjected to scan between 200–400 nm and were shortlisted. Those solutions had no absorbance was considered for equilibrium solubility study[10].

Equilibrium solubility study of chloramphenicol in different oils

Anexcess amount of chloramphenicol was added into 5 mL of shortlisted oil, stirredcontinuously for 1 h at 50 rpmand 25 ^{0}C (Orbital shaking incubator, 1HB-164, Remi Equipments Ltd., Vasai, India). The oils were allowed to stand for 24 h with occasional shaking. After 24 h, the oils were shaken for 15 minat 50 rpm and 25 ^{0}C. The oil was filtered through filter paper (11 µ pore size, Angle trading, Rajkot, India). The filtrate was diluted with methanol as per requirement. The absorbance of the solution was made at $\lambda_{max}$by UV-visible spectrometerusing methanol as blank[11, 12].

Statistical analysis

All data were represented as mean of five independent experiments. One-way ANOVA (analysis of variance) following Tukey-Kramer multiple comparisons test (considering critical value q >3.773 as significant) was performed between solubility of oil and that of distilled water at 95% of confidence level[13]. In Stat (Graph Pad Software, Inc., La Jolla, CA, USA) was used for statistical analysis.

RESULTS

The spectrum of chloramphenicol in methanol is shown in Fig. 1. $\lambda_{max}$of chloramphenicol was found to be 274 nm in methanol. Calibration curve of chloramphenicol in methanol is represented in Fig. 2.

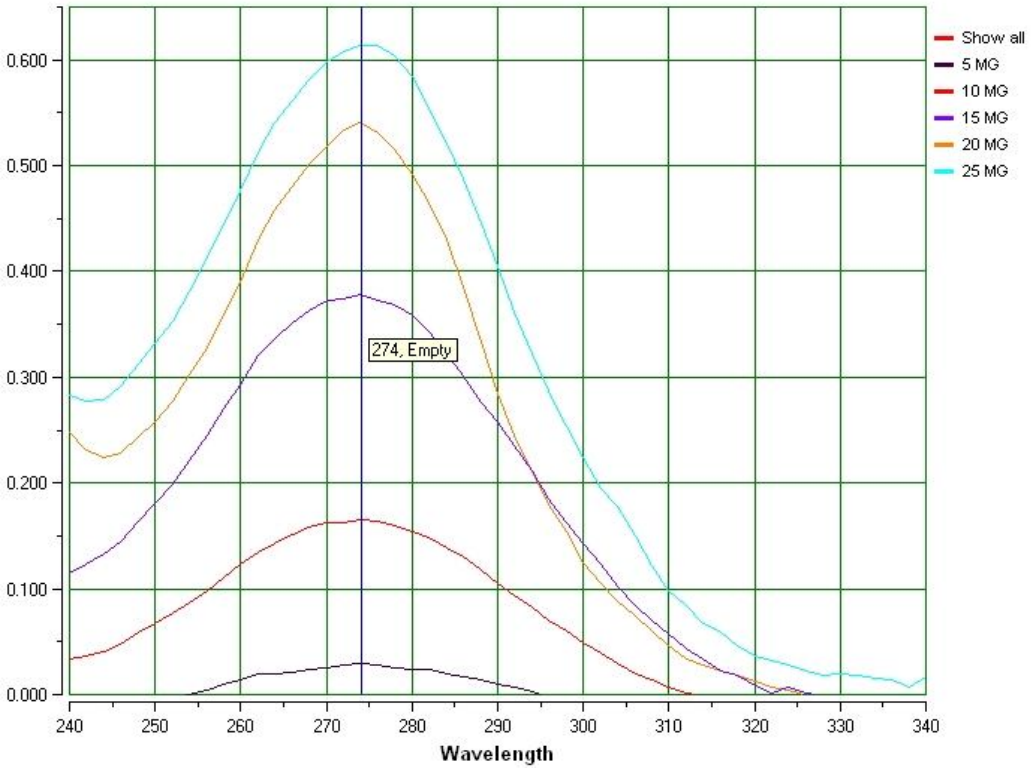

Figure 1: Scanning of chloramphenicol in methanol. Y-axis represented absorbance of chloramphenicol in methanol.

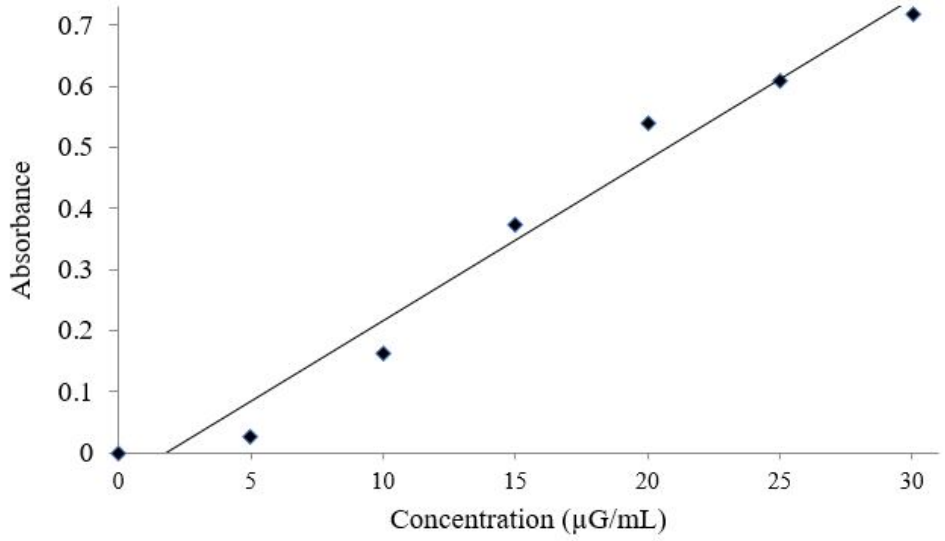

Figure 2: Calibration curve of chloramphenicol in methanol. $y = 0.0243x - 0.031$, $R^2 = 0.9464$.

Table 1: Screening oils for chloramphenicol

Name Oil	Reason for Selection	Selected or Not Why?
Neem oil	No absorbance between 200–400 nm and strong antibacterial	Yes
Clove oil	No absorbance between 250–300 nm and penetration enhancer	No; eye irritant
Heavy liquid paraffin oil	No absorbance between 200–400 nm and pharmaceutically inert	Yes
Light liquid paraffin oil	No absorbance between 200–400 nm and pharmaceutically inert	Yes
Turpentine oil	No absorbance between 200–400 nm, antibacterial, and penetration enhancer	No; eye irritant
Eucalyptus oil	No absorbance between 200–400 nm, antibacterial, and penetration enhancer	No; eye irritant
Olive oil	No absorbance between 250–300 nm and penetration enhancer	Yes
Isopropyl myristate	No absorbance between 200–400 nm and penetration enhancer	Yes
Peppermint oil	No absorbance at 250–300 nm, antibacterial, and penetration enhancer	Yes
Oleic acid	No absorbance at 250–300 nm and penetration enhancer	Yes
Jasminumsambac oil	No absorbance at 250–300 nm, antibacterial, fragrance and penetration enhancer	Yes
Mentha oil	No absorbance at 250–300 nm, antibacterial, and fragrance	Yes
Isopropyl Palmitate	No absorbance between 250–300 nm and penetration enhancer	Yes
Triacetin	No absorbance between 250–300 nm and penetration enhancer	Yes

Screening of various oils for short listing of equilibrium solubility study is reported in Table 1. Oils had significantly less solubility of chloramphenicol than water (Table 2). The solubility of chloramphenicol in various oils is represented in Fig. 3.

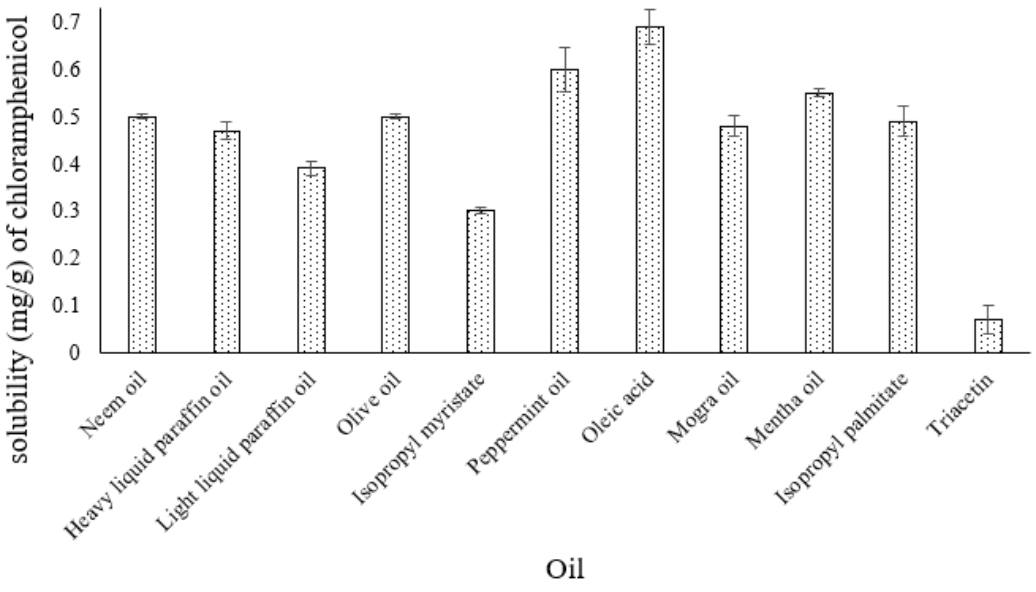

Figure 3: Solubility of Chloramphenicol in various oils. Data were represented as mean ± SD; n = 5.

Table2: Statistical analysis for solubility of different oils with respect to that of distilled water

Oil	p-value	q-value
Neem oil	< 0.0001	5.164
Heavy liquid paraffin oil	< 0.0001	5.421
Light liquid paraffin oil	< 0.0001	5.448
Olive oil	< 0.0001	5.164
Isopropyl myristate	< 0.0001	5.68
Peppermint oil	< 0.0001	4.903
Oleic acid	< 0.0001	4.62
Jasminumsambac oil	< 0.0001	5.251
Mentha oil	< 0.0001	5.035
Isopropyl palmitate	< 0.0001	5.189
Triacetin	< 0.0001	6.273

One-way ANOVA following Tukey-Kramer Multiple Comparisons Test was used for statistical analysis.
A $p < 0.05$ and > 3.773 were considered as significant

DISCUSSION

Chloramphenicol had high solubility in methanol. Chloramphenicol was exhibited linearity in the range of 10–30 µG/mL in methanol[14].With respect to calibration curve data of the study, it was possible to perform astudy using methanol as solvent.

From the results of oils of absorption between 200–400 nm values and unique properties of oil, neem oil, heavy liquid paraffin, light liquid paraffin, olive oil, isopropyl myristate, peppermint oil[15], oleic acid, Jasminumsambac oil, mentha oil, isopropyl palmitate, and triacetin were selected for equilibrium solubility studies.

All oils had less chloramphenicol solubility than water. Therefore, it was not possible to used only oil as abase than water. With respect to solubility studies of chloramphenicol, it was revealed that chloramphenicol eye caps had chloramphenicol in atriturated form, not in solubilized form, which had less penetration and less drug action.

Chloramphenicol has high solubility in water (2.5 mg/mL)[16]. This can easily diffuse chloramphenicol from eye drops into aqueous humor in inflamed eye condition[17]. With respect to thesolubility of chloramphenicol in water, chloramphenicol eye drops cannot provide good drug action in *culde sac* of theeye.

Chloramphenicol eye drops have thehigh comfort of treatment for patients. Chloramphenicol eye ointment or caps have asignificant effect on corneal epithelial problems due to high friction ability between eyelids and corneal epithelium. However, both formulation has asimilar effect on

conjunctiva during eye problems[7, 8]. In respect to disadvantages of both formulations, both formulations are not provided enough drug action in conjunctivitis.

Inlimitations of the study, acalibration curve of chloramphenicol was performed in methanol only. It was not performed in oils. The dose oscillation study of chloramphenicol was not performed.

CONCLUSION

The study of anophthalmic formulation for chloramphenicol had been recommended use of oil and water both phases i.e. emulsion or emulgel for the ophthalmic formulation of chloramphenicol. This dual phase can provide good solubility and penetration for chloramphenicol.

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Conflict of interest

Authors have no conflict regarding criticisms of well-established brands of thecompany. Authors have no any competing interest regarding results and/or discussion reported in the research work.

Authors' contributions

Kalpesh Ashara had performed an investigation, methodology, and drafted, review, and edited the manuscript for intellectual content. Ketan V. Shah had performed project administration, conceptualization, and formal analysis.

Authors Disclosures

The study was part of aPh.D.project of Kalpesh Ashara. The study was presented as anoral presentation at National Conference on Recent Innovations in Science, School of Science, RK University, Rajkot, India on 20 January 2018.

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