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(54) Title: THE PROCESS FOR MANUFACTURING TOPICAL OPHTHALMIC PREPARATIONS WITHOUT SYSTEMIC EFFECTS

(57) Abstract

For treating eye diseases, various kinds of medications are used. They are used in form of topical preparations or in form of systemic preparations to be taken orally or parenterally. Of topical preparations some are for topical use only e.g. framycetin, neomycin, loteprednol ebanoate, etc. However, large majority of topical ophthalmic drugs are for systemic use also, e.g.. Ciprofloxacin, Gentamicin, Timolol, Clonidine, Dexamethasone, Betamethasone, Carbachol, etc. Some of these drugs when used topically are also found to have systemic effects and if they are of serious nature limits the use of that drug, e.g. cardiopulmonary effects of B–blockers like timolol. Dryness of mouth, flush, fever, tachy cardia, urinary retention, convulsion irritability with atropine. Hypertension with phenylephine. Increased salivation, nausea, vomiting, diarrhea, stomach cramps, bronchial secretions, bronchial constriction, asthma, bradycardia, paresthesia with miotics, Hypotension with clonidine. Dry mouth, fatigue and drowsiness with apraclonidine and brimonidine.

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# THE PROCESS FOR MANUFACTURING TOPICAL OPHTHALMIC PREPARATIONS WITHOUT SYSTEMIC EFFECTS.

The present invention relates to the process for manufacturing topical ophthalmic preparations without systemic effects. Many topical ophthalmic preparations have systemic effects. These systemic effects are responsible for contraindications, side effects, toxicity of some of the topical ophthalmic preparations. Similarly, due to systemic effects certain topical ophthalmic preparations have not been commercialized.

The present invention is directed to manufacturing topical ophthalmic preparations in such a way that systemic effects of that topical ophthalmic preparation do not manifest.

Topical ophthalmic preparations can be divided into two groups. One of the group includes preparations in which active ingredients are for topical use only and have no systemic effects. These group of drugs include antibiotics like Framycetin, Neomycin, Fucidin, steroids like Loteprednol Ebanoate, Triamcinolone, alpha agonist like Apraclonidine, Brimonidine, etc. The other group of topical ophthalmic preparations have active ingredients which are generally used for their effects. These group of preparations include antibiotics like Ciprofloxacin, Norfloxacin, Ofloxacin, Gentamicin, Tobramycin, steroids like Dexamethasone, Betamethasone, β-blockers like Timolol, Betaxolol, etc. Some of these drugs when used topically are also found to have systemic effects. When systemic effects are serious in nature, it results in limiting the use of a drug in the form of contraindication or amount of drug to be used.

Examples of well known systemic effects of topical ophthalmic preparations include cardiopulmonary effects of β-blockers like Timolol, Levobunolol, Metipranolol, Carteolol, etc. Dryness of mouth, flush, fever, tachycardia, urinary retention, convulsion irritability are found with Atropine eye drops. Systemic hypertension is associated with topical mydriatic phenylephrine. Increased salivation, nausea, vomiting, diarrhoea, stomach cramp, bronchial secretions, bronchial constriction, asthma, bradycardia, parasthesia is seen with miotics. Systemic hypotension is main limiting factor for use of clonidine in management of glaucoma. Dry mouth, fatigue and drowsiness seen with Brimonidine and Apraclonidine are some of their systemic effects.

The systemic side effects, manifesting with the use of topical ophthalmic preparations results in discontinuation of therapy or not initiating a therapy or reducing the amount of drug or drug not having wide spread acceptance.

Because of this reason, attempts are made to reduce systemic effects of topically applied drugs.

Systemic effects are due to plasma concentration of a drug. It depends on absorption of the drug from conjunctiva or nasal mucosa into systemic circulation (serum levels of drug).

The mechanisms to reduce plasma concentration of a drug includes reduction in drop size. It reduces the amount of drug available through conjunctiva as well as nasal mucosa.

The blockage of nasolacrimal duct temporarily or permanently also reduces drug reaching to nasal mucosa through nasolacrimal passages and thus reduces the amount of drug available systemically. Increasing the viscosity of a formulation also reduces the plasma concentration of a drug. Slow release of a drug through sustained release mechanism/device are known to reduce plasma concentration of topical ophthalmic preparations. Including vasoconstrictive agents into a topical ophthalmic preparation also reduces the plasma level of topically applied drugs.

The other mechanism used to reduce systemic effects include use of a prodrug as topical ophthalmic preparation which gets converted to active compound only at the site of action, e.g. Dipivetrin for epinephrine and Phenylephrine Oxazoline for Phenylephrine.

The other mechanism known includes formulating a preparation as an ointment. The tear film formed with the use of ointment is thick, with poor light transmission and irregular anterior surface. This results in blurring of vision and so have not been popular. It also causes stickiness of lashes and lid margin. This limits its use to a great extent and whenever used, its use is restricted for bed time application.

None of the above described methods in isolation or in combination with each other have been successful in eliminating systemic effects of topical ophthalmic preparations. Majority of efforts are centered around topical β-blockers to reduce their systemic effect, e.g. reduction in pulse rate. All known methods have been able to decrease the reduction in pulse rate, but none of them have been able to eliminate it completely.

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The objective of present invention is to provide topical ophthalmic preparations without systemic effects without reducing the concentration of active ingredient.

The further objective of present invention is to provide topical ophthalmic preparations which does not cause significant visual disturbances to limit its use during waking hours.

The further objective of present invention is to provide topical ophthalmic preparations which are equally effective after longer period of storage.

The further objective of present invention is to provide topical ophthalmic preparations which do not require special storage conditions.

Accordingly there is provided a process of manufacturing topical ophthalmic preparations without systemic side effects which comprises of the following steps.

1. Liquid formulation of a selected drug is prepared which contains excipients buffers and preservatives in distilled water. The pH of this solution is adjusted to provide stable formulation for topical ophthalmic use.

2. In a separate vessel polymer is dissolved into a solvent preferably water and stirred well till gel is formed.

3. Solution containing selected drug as formulated in step 1 is gradually added to the gel as formed in step 2.

4. Volume is made up by adding distilled water/solvent as required.

5. pH is checked and adjusted as necessary to provide stable formulation for topical instillation into eye.

The drug described above can be any of the existing ophthalmic preparations or any other drug which cannot be used as a topical preparation in a desired concentration for instillation into eye. The drugs which are most frequently used and are known to have systemic effects include β-blockers like Timolol, Levobunolol, Metipranalol, etc.

Similarly, mydriatics like phenylephrine, atropine, cyclopentolate, tropicamide have systemic effects and their use is restricted by it.

Clonidine is an example of a drug which lowers I.O.P. significantly but cannot be used as 0.1% or 0.2% concentration due to its systemic hypotensive effect.
The polymer to be used for preparing topical formulation as per present invention should form a gel when solubilized. For the purpose of present invention it is desirable to select a polymer with mucoadhesive properties. To avoid discomfort and visual disturbances associated with use of viscous solutions, it is desirable that polymer selected demonstrates pseudoplastic behaviour in a formulation.

Polymer to be used for the purpose of present invention having above properties are known and includes polyacrylic acid, polyacrylic esters, polycarbophile, polyvinyl Acetate, Acrypol, Xantham gum, Guar gum, hydroxy ethyl cellulose, polyvinyl alcohol, PVP, carbomers, hydrogels prepared by combination of various polymers etc. Names of above polymer exemplifies the process and are not restricted to for the purpose of invention.

For the purpose of avoiding systemic effects of a formulation prepared as per present invention, it is necessary to have viscosity above 100,000 cps (one hundred thousand cps), preferably above 400,000 (four hundred thousand cps).

The final volume adjustment and amount of polymer to be used has to be designed considering these requirements. The amount of polymer in a final formulation to get desired viscosity is variable but is well known. It varies with polymer to polymer and also with molecular weight of some polymer.

Pharmaceutical preparations so manufactured can be sterilized by known methods of sterilizing, including autoclaving. If sterilization process is likely to result in unstabilization of drug, it can be prepared as a sterile product throughout the process.

## Examples of formulations

I. **Timolol**

A.. Timolol 0.5%

| | |
|---|---|
| Timolol Maleate | 0.72 gm. equivalent to 0.5 gm of Timolol |
| Benzylconium chloride | 0.0107 gm |
| Polyacrylic Acid (Carbopol 940) | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | QS to make 100 ml. |

B. Timolol 0.25%

| | |
|---|---|
| Timolol Maleate | 0.36 gm equivalent to 0.5 gm of Timolol |
| Benzylconium chloride | 0.0107 gm |
| Polyacrylic Acid (Carbopol 940) | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | QS to make 100 ml |

II. **Timolol**

A.. Timolol 0.5%

| | |
|---|---|
| Timolol Maleate | 0.72 gm. equivalent to 0.5 gm of Timolol |
| Benzylconium chloride | 0.0107 gm |
| Carbopol ETD 2001 | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml. |

B. Timolol 0.25%

| | |
|---|---|
| Timolol Maleate | 0.36 gm equivalent to 0.5 gm of Timolol |
| Benzylconium chloride | 0.0107 gm |
| Carbopol ETD 2001 | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml |

III. **Timolol**

A.. Timolol 0.5%

| | |
|---|---|
| Timolol Maleate | 0.72 gm. equivalent to 0.5 gm of Timolol |
| Benzylconium chloride | 0.0107 gm |
| Carbopol 981 | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml. |

B. Timolol 0.25%

| | |
|---|---|
| Timolol Maleate | 0.36 gm equivalent to 0.5 gm of Timolol |
| Benzylconium chloride | 0.0107 gm |
| Carbopol 981 | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml |

IV. **Timolol**

A.. Timolol 0.5%

| | |
|---|---|
| Timolol Maleate | 0.72 gm. equivalent to 0.5 gm of Timolol |
| Benzylconium chloride | 0.0107 gm |
| Polycarbophil | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml. |

B. Timolol 0.25%

| | |
|---|---|
| Timolol Maleate | 0.36 gm equivalent to 0.5 gm of Timolol |
| Benzylconium chloride | 0.0107 gm |
| Polycarbophil | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml |

V. **Clonidine**

A. Clonidine 0.1%

| | |
|---|---|
| Clonidine hydrochloride | 0.1 gm |
| Benzylconium chloride | 0.0107 gm |
| Polyacrylic Acid (Carbopol 940) | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | QS to make 100 ml |

B. Clonidine 0.2%

| | |
|---|---|
| Clonidine hydrochloride | 0.2 gm |
| Benzylconium chloride | 0.0107 gm |
| Polyacrylic Acid (Carbopol 940) | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | QS to make 100 ml |

VI. **Clonidine**

A. Clonidine 0.1%

| | |
|---|---|
| Clonidine hydrochloride | 0.1 gm |
| Benzylconium chloride | 0.0107 gm |
| Carbopol ETD 2001 | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml |

B. Clonidine 0.2%

| | |
|---|---|
| Clonidine hydrochloride | 0.2 gm |
| Benzylconium chloride | 0.0107 gm |
| Carbopol ETD 2001 | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml |

VII. **Clonidine**

A. Clonidine 0.1%

| | |
|---|---|
| Clonidine hydrochloride | 0.1 gm |
| Benzylconium chloride | 0.0107 gm |
| Carbopol 981 | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml |

B. Clonidine 0.2%

| | |
|---|---|
| Clonidine hydrochloride | 0.2 gm |
| Benzylconium chloride | 0.0107 gm |
| Carbopol 981 | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml |

VIII. **Clonidine**

A. Clonidine 0.1%

| | |
|---|---|
| Clonidine hydrochloride | 0.1 gm |
| Benzylconium chloride | 0.0107 gm |
| Polycarbophil | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml |

B. Clonidine 0.2%

| | |
|---|---|
| Clonidine hydrochloride | 0.2 gm |
| Benzylconium chloride | 0.0107 gm |
| Polycarbophil | 1.5 gm to 2.5 gm |
| Sodium hydroxide to adjust pH | 6.5 to 7.5 |
| Water for injection | Q.S. to make 100 ml |

IX. **Betaxolol**

Betaxolol 0.5%

| | |
|---|---|
| Betaxolol hydrochloride | 0.56 gm. equivalent to 0.5 gm of Betaxolol |
| Benzylconium chloride | 0.01 gm |
| Dibasic sodium phosphate | 0.05 gm |
| Sodium phosphate monobasic | 0.025 gm |
| Disodium EDTA | 0.05 gm |
| Sodium chloride | 0.3 gm |
| Propylene glycol | 2.5 gm |
| Carbopol ETD 2001 | 2.0 gm |
| Water for injection | Q.S. to make 100 ml. |

X. **Betaxolol**

| | |
|---|---|
| Betaxolol 0.5% | |
| Betaxolol hydrochloride | 0.56 gm. equivalent to 0.5 gm of Betaxolol |
| Benzylconium chloride | 0.01 gm |
| Dibasic sodium phosphate | 0.05 gm |
| Sodium phosphate monobasic | 0.025 gm |
| Disodium EDTA | 0.05 gm |
| Sodium chloride | 0.3 gm |
| Propylene glycol | 2.5 gm |
| Polyacrylic acid (Carbopol 940) | 2.0 gm |
| Water for injection | Q.S. to make 100 ml |

X.I **Betaxolol**

| | |
|---|---|
| Betaxolol 0.5% | |
| Betaxolol hydrochloride | 0.56 gm. equivalent to 0.5 gm of Betaxolol |
| Benzylconium chloride | 0.01 gm |
| Dibasic sodium phosphate | 0.05 gm |
| Sodium phosphate monobasic | 0.025 gm |
| Disodium EDTA | 0.05 gm |
| Sodium chloride | 0.3 gm |
| Propylene glycol | 2.5 gm |
| Carbopol 981 | 2.0 gm |
| Water for injection | Q.S. to make 100 ml. |

XI.I. **Betaxolol**

| | |
|---|---|
| Betaxolol 0.5% | |
| Betaxolol hydrochloride | 0.56 gm. equivalent to 0.5 gm of Betaxolol |
| Benzylconium chloride | 0.01 gm |
| Dibasic sodium phosphate | 0.05 gm |
| Sodium phosphate monobasic | 0.025 gm |
| Disodium EDTA | 0.05 gm |
| Sodium chloride | 0.3 gm |
| Propylene glycol | 2.5 gm |
| Polycarbophil | 2.0 gm |
| Water for injection | Q.S. to make 100 ml. |

Pharmaceutical composition so manufactured is evaluated for stability and efficacy.

The Pharmaceutical composition so manufactured is evaluated at different test conditions of temperature and humidity (as per ICH guidelines, 40°C/75% RH, 25°C/60% RH) for time interval extending upto 12 months.

The samples of formulations so prepared were used for study.

The topical ophthalmic preparation of Clonidine 0.1% and 0.2% so prepared were evaluated in vivo studies.

Healthy normal volunteers (10) had instillation of drug in their eyes. I.O.P. and B.P. were measured every 2 hours. Control group (10) received placebo.

Drop in I.O.P. was seen only in eyes receiving Clonidine. It was found to be in the range of 30% of initial I.O.P. The effect on I.O.P. was found to last 8 – 10 hours.

Effect on blood pressure in both groups i.e. Clonidine and placebo was identical for systolic as well as diastolic blood pressure and it was insignificant. Peak reduction in systolic B.P. was 4.4 mm of Hg was for placebo, 4.11 mm of Hg for 0.1% Clonidine and 3.93 mm. of Hg for 0.2% Clonidine. Peak reduction in diastolic B.P. was 4.23 mm of Hg for placebo, 4.49 mm of Hg. for Clonidine 0.1% and 2.89 mm of Hg for Clonidine 0.2%.

Clonidine eye drops even when used at 0.05 % to 0.06 % concentration are associated with reduction in systemic B.P.

The topical ophthalmic preparation of Timolol Maleate 0.5% made according to present invention was evaluated for systemic effects and compared with Timolol eye drops and Timoptic XE.

In healthy normal volunteers (10 in each group) various formulations of Timolol and placebo drug were instilled in both eyes. I.O.P. and resting pulse rate were measured every 2 hours. The peak reduction in mean I.O.P. was 25% with Timolol drops, 27% with Timoptic XE and 40% with Timolol made as per present invention. The change in resting pulse rate was identical in placebo and Timolol as per present invention. It was 13.2% with Timolol drops and 13.33% with Timoptic XE.

Thus, both the preparations of Clonidine as well as Timolol made according to present invention were found to have no systemic effect. The efforts were made to find out plasma concentration of drugs but none of the drugs achieved detectable plasma concentrations.

Thus, present invention provides process for manufacturing of topical ophthalmic preparations without systemic effects.

The above examples of formulations are provided as a proof of working of this invention and should not be restricted to this only. Any drug useful after instillation into eye can be formulated according to present invention without systemic effect.

## I claim :

1. The process of manufacturing of formulation of topical ophthalmic preparations without systemic effect comprising the following steps.
   i. Making a gel using polymers with or without physiologically acceptable excipients buffers and preservatives
   ii. Adding liquid formulation of a drug into a prepared gel of step (i) while stirring slowly.
   iii. Adjusting the pH and volume before final packing

2. A process as claimed in claim 1 wherein Polymer can be any polymer having pseudoplastic behaviour.

3. A process as claimed in claim 1 & 2 wherein polymer should have mucoadhesive property.

4. A process as claimed in claim 1 to 3 wherein polymer can be but not restricting to Carbopol 940 (Polyacrylic acid), Carbopol ETD 2001, Carbopol 981, Polycarbophil, Polyvinyl Alcohol, Hydroxyethyl Cellulose, Polyacrylic esters, Acrypol, Xantham gum, Guar gum, polyvinyl ester, Carbomer etc.

5. Polymer as claimed in claim 1 to 4 can be used alone or in combination with other polymers.

6. The process as claimed in claim 1 to 5 wherein viscosity of final formulation is more than 100,000 cps (One hundred thousand cps).

7. The process as claimed in claim 1 to 6 physiologically acceptable buffers excipients and preservatives are used.

8. The process as claimed in claim 1 to 7 wherein liquid formulation of a drug can be in the form of aqueous solution, suspension or emulsion.

9. The process as claimed in claim 1 to 8 wherein volume of formulation is adjusted to get desired concentration of a drug into final formulation.

10. A process as claimed in claim 1 to 9 and substantially described in example in accompanying specification.