CHAPTER 2

RATIONALE FOR USING A PHOSPHATE BUFFER FOR S(+) FLURBIPROFEN EYEDROPS
RATIONALE FOR USING A PHOSPHATE BUFFER FOR S(+) FLURBIPROFEN EYEDROPS

Although the eye, eyelids and skin surrounding the eye are sensitive to external stimuli, physiological reactions due to deviations outside the near normal values for osmolality or pH are not always seen.

However, in a state of ill-health or during regular use of ophthalmic preparations, this situation may be more outspoken.

The active principle in the eyedrop can provoke, when not properly dissolved, an irritating or burning sensation leading to lacrimal discharge, occasional haemorrhage or endangering blinking reflexes during surgery. Lacrimal discharge will cause an unwanted dilution and drainage of medicine.

Individual sensitivity may vary and physiological values of tear fluid can fluctuate, which is also dependant on the health condition of the individual eye in general, the nasal corner of the eye being the most sensitive.

Even if the composition of the eyedrop approximates the ideal solution, certain (active) principles may cause discomfort to the eye. Non-irritating eyedrops should comply with: (1) sterility, (2) isotonicity and (3) pH value. Sterility is of paramount importance when an ophthalmic solution is applied to the injured eye.

The character of the active ingredient will to a certain degree determine the above mentioned requirements. The osmotic value of an ophthalmic solution should reflect that of blood, corresponding to a 0,9% sodium chloride solution. Deviations from this value have been noted from 0,6% to as high as 5% sodium chloride without marked discomfort. Yet it is of prime importance to adhere as close as possible to isotonicity, as the optical integrity of the cornea can be influenced significantly by deviations thereof. In this respect the physiological term tonicity seems more appropriate than the physicochemical term osmolality. The cornea functioning as selective permeable biomembrane is better accommodating this term. The osmotic value is commonly expressed in (milli)osmol/liter (osmolality). This can be transformed to osmolality (mosmol/kg) by dividing by the specific gravity of the solution.

Eye irritation must be discerned from an allergy which requires the choice of a different pharmacological agent. Cutaneous hypersensitivity due to a particular stereoisomer has been reported (1).

There are several reasons for buffering an ophthalmic solution:

· To prevent unwanted pH changes caused by hydroxyl ion release from the glass in which the solution is stored.
· In case of a pH-dependent degradation of the active principle, a buffer should be used for stabilization.
In case of a pH-dependent solubility, a buffer can be used to dissolve the required amount of drug.

On the other hand there are also limitations to the use of buffers. First of all, the limited buffer capacity of the lacrimal fluid precludes the use of strong buffers outside the pH range of 6.8 - 7.6.

In addition, adherence to a pH as close to the physiological pH as possible is important for preventing local precipitations of the drug and minimizing deterioration after administration.

For the formulation of S(+) flurbiprofen eyedrops, a published phosphate buffer of pH 7.4, used in an eyedrop, was chosen as a starting point (2). The specialty Ocuflur® containing racemic flurbiprofen sodium (appendix A) is produced in a citrate buffer of pH 6.45. However, the quantitative nature of the citrate buffer used was not disclosed. Analysis by HPLC revealed a citrate concentration of 5.5 gram/l (see appendix B for materials & conditions).

The buffer used by us in preparing S(+) flurbiprofen eyedrops consists of 0.022 M disodium phosphate dihydrate and 0.112 M potassium dihydrogen phosphate, resulting in approximately 0.13 M total salt concentration and an ionic strength of 0.36 M.

It should be realised, that at pH=7.4 practically all dissolved flurbiprofen (pK_a = 4.22) is present in the salt form; the acidic form fraction is determined by

\[
\log \frac{[\text{flurbiprofen acid}]}{[\text{flurbiprofen salt}]} = pK_a - pH; \text{ thus } \% \ [\text{flurbiprofen acid}] = 0.066\%.
\]

The importance of this value is that because only the non-protonized form of an acid (like flurbiprofen) is able to pass the different membranes in the eye, the driving force for permeation is rather low (0.066%). It should be realized, however, that the pH of the ophthalmic solution is not the only parameter determining permeation efficacy.

The choice for a buffer applied to the ophthalmic solution is determined by the best compromise of the following issues:

1. It is convenient for patient and surgeon to stay as close as possible to the natural pH of the tear fluid (7.4).
2. As far as flurbiprofen is concerned, the solubility in aqueous solution is problematic at pH values below 7 (3), as illustrated on the next page:
3. Discomfort for the patient will not be present as long as the pH is between 6.6 - 7.8. Tolerability for the cornea is in the pH range of pH 6.6 - 8.5. Changes in permeability will occur outside the pH range of 4 and 10.

4. The permeation of flurbiprofen increases at lower pH values.

On the basis of the above considerations it follows that the optimal pH is between 7.0 and 7.4. For the present formulation the physiological pH (7.4) was chosen. The often used citrate buffer would have been less favourable, because this buffer composition has hardly any buffering capacity around pH 7.4, in clear contrast to a phosphate buffer.

Interestingly, no difference in pharmacological effect could be demonstrated using ophthalmic solutions of diclofenac, indomethacin or flurbiprofen in a pH range of 5.0 - 7.5 in preventing disruption of the blood-aqueous barrier in a rabbit para-centesis model (4).

In addition, the use of a phosphate buffer provides stable, single stereoisomer formulations of the NSAID ketorelax. This was in contrast to the use of acetate or citrate buffers (5).
REFERENCES


APPENDIX

A
Ocuflur®
Composition according to package insert august 1995 Allergan S.A./N.V.

Flurbiprofen sodium dihydrate 0.03%, Polyvinylacohol, Thiomersal 0,005%, Sodium edetic acid, sodium chloride, sodium citrate dihydrate, sodium chloride, citric acid monohydrate, sodium hydroxide, hydrochloric acid, aqua purificata

B
HPLC method of analysis
Materials & Methods
Column: Chrompack Organic acids 300*6.5mm conventional stainless steel Catalogue No. 28350
Eluent: 0.005 mol/l sulphuric acid
Flow: 0.8 ml/min
Temperature: 35°C
Detector: UV 210 nm
Internal Standard: oxalic acid
Injection volume: 25 µL