

4. Pharmaceutical properties of fluticasone propionate nasal drops: a new formulation

Authors' affiliations:

S. Denyer, Professor, Head of Department of Pharmacy, School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton, UK

A variety of corticosteroid delivery systems have been considered for the treatment of nasal polyposis. Safety considerations favour local delivery of the drug to the nasal cavity. No topical delivery system is entirely without problems, however, and formulations must address issues of microbiological quality, drug stability, reproducible drug delivery and adequate drug distribution at site, while also offering environmental and patient acceptability. Fluticasone propionate has been formulated in a new nasal drop preparation. As a highly water-insoluble compound, the active fluticasone propionate requires micronization to an optimal particle size and subsequent dispersion with a surface-active wetting agent. The product is presented in a unit dose low-density polyethylene container, manufactured by a blow-fill-seal process and stored in an aluminium foil overwrap. Micronized active has been used to promote optimal local drug delivery, and excipients have been selected for low irritancy potential and high formulation stability. There is no microbiological risk with fluticasone propionate unit dose nasal drops 400 µg and therefore no need to include a preservative in the preparation. They provide a convenient and effective treatment option for patients with nasal polyposis.

Introduction

All new pharmaceutical formulations have to meet a series of challenges, which are determined both by the characteristics of the active ingredient and by the failings of existing drug-delivery systems. The starting point, therefore, for the development of any drug-delivery system is to try to identify what the ideal treatment system should offer. For the

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Table 1. Challenges of nasal drug delivery

Method	Preservative present	CFC propellant	Accuracy of dosing	Deposition in nozzle	Drug distribution
Nasal drops	+	–	–	N/A	+++
Aqueous nasal drops	+	–	+	–	++
Aerosol spray	±	+	+	+	++
Dry powder	–	–	+	–	+
Tablets	±	–	+	N/A	+

treatment of nasal polyposis with corticosteroids, the following characteristics need to be considered:

- ease of use for the patient
- accuracy and consistency of dosing
- effective delivery to the site of action
- potent topical activity
- low systemic absorption to minimize possible systemic adverse effects
- a method of delivery which is accessible to long-term treatment.

Through recognition of these ideal characteristics, the failings of existing treatment modalities can be determined and rectified. The strengths and weaknesses of existing corticosteroid delivery systems are summarized in Table 1. The major weakness of aerosol sprays is the use of CFC propellants, which are currently being phased out throughout the world because of their deleterious effects on the ozone layer (1).

Preservatives in drug-delivery systems

Aqueous systems are frequently required to be protected from potential microbiological contamination; this is particularly critical in multidose formulations. There is considerable controversy in the literature as to whether antimicrobial preservative agents exhibit sufficient selective toxicity. Over the years, the range of available preservatives has reduced from around 25 to the 12–15 commonly used today (2). This change results from increasing concerns over toxicity, among those withdrawn from use.

Conventionally, benzalkonium chloride is used in aqueous nasal delivery systems. More recently, sorbic acid has been used, and there are other experimental preservative systems under investigation. Benzalkonium chloride confers good antimicrobial protection (3), but there have been a number of reports of *in vitro* studies and studies in animals

indicating local cytotoxicity (4, 5). This, therefore, constitutes a possible weakness in aqueous formulations where protection is required against the occasional risk of bacterial contamination, although there are no reports of *in vivo* cytotoxicity due to preservatives in patients.

Accuracy of dosing

Accuracy of dosing is critical in all treatment regimens. Single-dose systems provide far greater accuracy than multidose delivery systems. Studies have indicated that the dose from multidose nasal and ophthalmic drop delivery systems can vary between 40% and 340% of the labelled dose (6, 7).

Deposition and retention of the drug in the nozzle also affects the dose delivery of aerosol spray systems, and this can lead to a decline in dose consistency with time.

Drug distribution

Drug distribution to the site of action is critically important, particularly with topical application. In nasal polyposis, the target area is the sinus mucosa. With aqueous delivery, nasal drops produce extensive distribution within the nasal cavity, whereas with pump-activated and propelled spray systems, most deposition occurs at the anterior area of the cavity (8). In cases where systemic therapy may be appropriate, the drug is not specifically directed toward the target area.

Fluticasone propionate (FP) nasal drops

The weaknesses in current delivery systems have been overcome with the introduction of a new formulation of fluticasone propionate (FP), which has been specifically developed for the treatment of nasal polyposis.

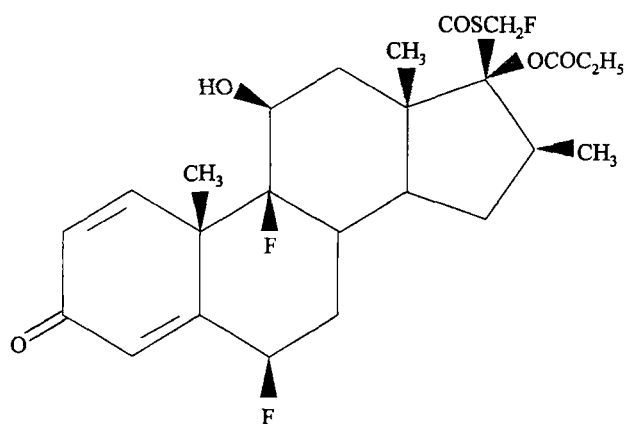


Figure 1. Chemical structure of fluticasone propionate.

Formulation composition

FP (Fig. 1) is a highly water-insoluble molecule. For this reason, a formulation system was developed to deliver undissolved FP to the site of action. This was achieved by micronization of the drug to produce very small particles (1.5 μm in diameter) of a relatively constant size. These particles are then maintained in aqueous suspension by using a combination of two wetting agents, polysorbate 20 and sorbitan laurate. These agents bind to the surface of the particles and produce an outer layer of hydrophilic groups, which keep the particles in suspension and prevent aggregation. Chemical stability is maintained by the addition of sodium phosphate buffer with an isotonic regulator, sodium chloride, incorporated for the patient's convenience and comfort; the vehicle is water.

Microbiological quality

The bulk formulation of FP is sterilized by autoclaving and distributed aseptically into containers to provide a product which is very low in microbiological burden. In fact, there are no microorganisms present, although for regulatory reasons the formulation is not claimed to be sterile. As the containers are sealed and will only be used once as a single dose, there is no microbiological risk and therefore no need to add a preservative.

Stability

Stability studies have shown that there is no change in FP particle size for periods of up to 18 months in storage. This is particularly important, as any agglomeration would tend to

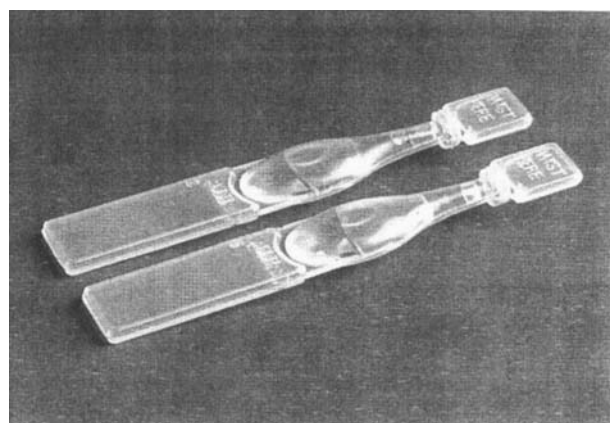


Figure 2. Photograph of unit dose droppers.

bring the particles out of suspension. The suspending and wetting agents used in the formulation are effective in maintaining the long-term stability of the system.

The container system used for the single doses is made of low-density polyethylene (Fig. 2). The advantage of this system is that it is malleable and therefore can be used as the delivery device. A potential problem with this system, however, is that it is permeable to water. If left unprotected, the formulation would lose approximately 2% of its water content per month, which is unacceptable in terms of long-term stability.

Light also has an effect on the contents of the unprotected container. The principal effect is conversion of the drug to the 17- β -aldehyde. Stability studies on unprotected ampoules of FP under conditions mimicking the normal light cycle during storage have shown that there is little change in FP content, but the 17- β -aldehyde content increases by about 100% per month, accumulating to a substantial level over a period of months. The problems of moisture loss and photodegradation have been overcome by packaging the single-dose ampoules in light- and moisture-occluding aluminium foil.

The polyethylene ampoules have also the potential to adsorb some of the active drug, and 3% is lost in this way by irreversible binding. This loss is nullified by the addition of an appropriate overage in the unit dose. A further slight volume excess is added to account for the fact that the ampoule can never be emptied completely.

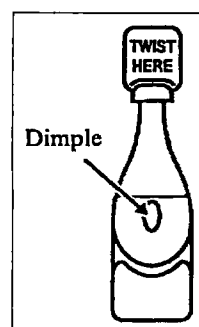
Quality controls

The dose unit of FP (400 μg) is contained in a single ampoule with a nominal volume of 400 μl , plus the additional excess, to account for adsorption onto the

ampoule and the portion retained after use (Fig. 3). This provides an accurate and reproducible dose to within 3 % of the nominal.

Production of the drug-delivery system requires special technology. The delivery unit is produced by a blow-fill-seal process, in which extruded polythene is forced onto the sides of a split mould by pressurized sterile air. The sterile drug solution is then introduced into the container, and the top is closed to produce a sealed sterile ampoule. Quality control checks on volume, wall thickness and overall pack seal integrity are performed throughout each batch run.

FP Nasal Drops: Design Issues



- One dose (400 µg) contained in one unit
- Unit volume (400 µl nominal; 60 µl average)
- Accurate dosing (103 ± 3%)
- Tolerance to nozzle size
- Success of break

Figure 3. Diagram – FP nasal drops: design issues.

Acceptability to patients

For patients with nasal polyposis, single-dose ampoules provide a convenient, effective and safe method for administration of FP. The risk of microbiological contamination is eliminated through use of the single-dose unit. There is extended stability of the formulation during storage before use.

Once-daily dosing and ease of use are both important factors in ensuring patient compliance. About 30–50% of medicines prescribed for chronic illnesses are not taken as directed (9); patient noncompliance thus represents a significant cost to national health-care systems.

Conclusions

FP nasal spray has been used successfully in the treatment of nasal polyposis for a number of years, but it has the disadvantage of all nasal spray systems in that most of the dose is deposited in the lower nose. Single-dose ampoules of FP nasal drops have been specially formulated to overcome this problem. They provide a simple and efficient method of delivering an accurate and reproducible dose of FP, which provides maximum exposure to the paranasal sinus mucosa. The single-dose unit ensures that there is little or no risk of microbiological contamination, and dispenses with the need for preservatives. FP nasal drops also have the advantage of once-daily dosing, which is the most conducive to patient compliance.

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