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Paediatric formulation: budesonide 0.1 mg/mL viscous oral solution for eosinophilic esophagitis using cyclodextrins

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Abstract

Background: Viscous oral solutions of budesonide (dose range: 1 mg to 2 mg) have long been used to treat eosinophilic oesophagitis in children. The objective of the present study was to provide a convenient paediatric pharmaceutical formulation of a viscous budesonide solution at a dose level of 0.1 mg/mL, using cyclodextrin as a solubilizer.

Methods: Solubility studies were performed with γ -cyclodextrin and hydroxypropyl- β -cyclodextrin, and viscosity was tested with a Brookfield viscometer. The stability of the final formulation was tested in a climatic chamber. Levels of budesonide, budesonide impurities and degradation products were assayed using the HPLC–UV method described for the budesonide-related substance assay in the European Pharmacopoeia monograph.

Results: The solubility of budesonide increased linearly with both cyclodextrins. Gamma cyclodextrin (complexation efficiency: 0.147) was preferred to hydroxypropyl- β -cyclodextrin (complexation efficiency: 0.064) as a solubilizing agent. Hydroxypropylcellulose (1 % m/v) was added to increase viscosity, and sucralose was added to improve palatability. The sterilized, filtered, final formulation was stable for at least 3 months when packed aseptically in sterile 15 mL type 1 amber glass vials.

Conclusions: We have developed a convenient, stable, preservative-free, viscous formulation of a budesonide solution for the hospital- and home-based treatment of paediatric patients.

Keywords: budesonide, cyclodextrins, eosinophilic esophagitis, pediatrics

Introduction

Budesonide (Figure 1) is an anti-inflammatory corticosteroid that is notably used to treat asthma, allergic rhinitis and Crohn's disease. Powders/suspensions for inhalation, nasal sprays, and enteric solid dosage forms are administered locally to act on the lung, nose or digestive tract, respectively. Budesonide has a low systemic bioavailability (< 30 %, due to extensive pre-systemic metabolism) but is generally well tolerated; systemic side effects are rare [1].

Oral viscous budesonide has been used to treat eosinophilic oesophagitis in children at dose levels ranging from 1 to 2 mg [2, 3]. Due to the lack of availability of a dedicated formulation of budesonide in this indication, an extemporaneous formulation is generally prepared by mixing water, five to ten 1 g packets of an artificial sweetener (1.1 % m/m sucralose in maltodextrin/glucose; SLENDA®, Heartland Food Products Group, Indianapolis, IN, USA) and a budesonide suspension for inhalation [4, 5]. Even though these extemporaneous formulations have been successfully tested against a placebo in a small clinical trial and constitute a standard treatment for eosinophilic oesophagitis [2], they are not practical for daily use. Furthermore, there are few published data on the formulations' physicochemical characteristics (e. g. stability). We therefore decided to compound and study a budesonide formulation suitable for oral administration to children in an indication of eosinophilic oesophagitis.

We considered that the above-mentioned extemporaneous formulation could be improved. The intrinsic solubility of budesonide in water is around 20 mg/L which may hamper its efficiency; hence, solubilizing it may improve the drug's topical action [6, 7]. As eosinophilic oesophagitis is an allergic disease, we also wanted to limit the use of preservatives such as parabens or benzoic acid, which are known to cause allergies [8]. Given that the oesophageal transit time ranges from 1.5 to 6 s in children aged between 6 days and 16 years [9], we reasoned that adding a viscous

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Figure 1: The chemical formula of budesonide; * indicates the chiral centre responsible for the two epimeric forms.

mucoadhesive might also improve the formulation's effectiveness [5]. To enhance palatability, we kept sucralose in the formulation at doses compatible with the FDA's acceptable daily intake of 5 mg/kg/day.

The objective of the present study was to provide a convenient, paediatric pharmaceutical formulation of budesonide 0.1 mg/mL for the treatment of eosinophilic oesophagitis, using cyclodextrins as a solubilizer.

Materials and methods

Experiments were performed in a stepwise manner; each step enabled us to validate the choice of an excipient and its quantity.

Materials

All excipients were of pharmaceutical grade. Hydroxypropyl- β -cyclodextrin (CAVASOL W7 HP PHARMA), γ -cyclodextrin (CAVAMAX W8 PHARMA) and hydroxypropylcellulose (KLUCEL GF PHARM) was purchased from Ashland (Alizay, France). Micronized budesonide (manufactured by Farmabios) and Sucralose (manufactured by Vitasweet) were purchased from INRESA (Bartenheim, France). Suitable analytical-grade reagents were used for stability testing.

Solubility testing

Solubility studies were performed in the presence and absence of cyclodextrins in purified water (at 24 °C, and protected from light). Increasing concentrations of cyclodextrin (0.2, 0.4, 0.7, and 2 mM) were added to a large excess of budesonide in a 10 mL volumetric flask. The suspensions were sonicated for 1 h, stirred overnight (for 16 h, protected from light) and then centrifuged twice (5000 rpm for 10 min) before measurements. The supernatants were carefully pipetted and diluted in methanol

(from 1:2 to 1:4). The budesonide concentration was then measured at 240 nm with an UV spectrophotometer (UV2600, Shimadzu) vs. a calibration curve prepared daily. Cyclodextrins were selected on the basis of the phase diagram and the complexation efficiency (CE, as described elsewhere) [10].

Viscosity testing

The viscosity of 1 % hydroxypropylcellulose solutions ($n = 3$) at 22 °C was measured in a 500 mL beaker using a rotational viscometer (VR 3000, Myr); the L1 spindle was used. Glycerol (10 % m/v) was used to facilitate the preparation of solutions. The cyclodextrins' influence on the solution's viscosity was assessed. Viscosity was measured after 2 h without agitation. The formulations' non-Newtonian fluid properties (e. g. shear thinning and thixotropy) were investigated at various rotational speeds (from 10 to 200 rpm) and various experiment durations.

Stability testing

Budesonide, budesonide impurities and degradation products were assayed using the European pharmacopoeia (EurPh) high-performance liquid chromatography method, as described in the budesonide-related substance assay (EurPh 01/2010:1075). Briefly, samples were diluted 1:5 in purified water, and 20 μ L of these solutions were eluted on an octadecyl column (4.6 x 150 mm, 3.5 μ m; Symmetry[®], Waters) at 50 °C, using an ethanol, acetonitrile, phosphate buffer (pH 3.2) gradient (Table 1) and a flow rate of 1 mL/min with an ultra-high-performance liquid chromatograph (Nexera[®], Shimadzu). The method's performance in our hands was checked against the chemical reference substance (budesonide for system suitability, Y0001148, European directorate for the Quality of Medicines and Healthcare). The budesonide level was measured at 240 nm against a three-point calibration curve (80 %, 100 % and 120 % of the nominal concentration) prepared daily.

Table 1: Gradient of mobile phase A (anhydrous ethanol, acetonitrile, phosphate buffer pH 3.2, 2:32:68, v/v/v) and mobile phase B (acetonitrile, phosphate buffer pH 3.2, 50:50, v/v).

Time (min)	Phase A (% v/v)	Phase B (% v/v)
0 – 38 min	100	0
38 – 50 min	100 $\rightarrow$ 0	0 $\rightarrow$ 100
50 – 60 min	0	100

Forced degradation studies were performed on the final formulation in type I transparent glass vials placed in a climatic chamber (KBF, Binder) at 24 °C/60 % relative humidity with 1.1 W/m² UV/visible exposure, according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q1B guidelines to ease the detection of degradation products on final stability testing. Final stability testing was performed on the formulation in type I amber glass vials placed in climatic chamber (KBF, Binder) at 24 °C/60 % relative humidity for 3 months.

Results

Solubility

The intrinsic solubility of budesonide increased 5-fold with a 1:5 molar ratio of γ -cyclodextrin and a 1:12 molar ratio of hydroxypropyl- β -cyclodextrin (Figure 2). The CE was 0.147 for γ -cyclodextrin and 0.064 for hydroxypropyl- β -cyclodextrin. According to the binary phase diagram, around 1.7 mg/mL of γ -cyclodextrin and around 4.5 mg/mL of hydroxypropyl- β -cyclodextrin are needed to solubilize 1 mg/mL of budesonide.

Viscosity testing

The mean $\pm$ SD viscosity of a 1 % (m/v) hydroxypropyl-cellulose and 10 % (m/v) glycerol solution in purified water with and without 0.2 % (m/v) of γ -cyclodextrin was 47 $\pm$ 2 mPa·s and 48 $\pm$ 2 mPa·s, respectively, using the L1 spindle at 100 rpm. No major changes in viscosity were observed at the various speeds used (10, 20, 50, 100, and 200 rpm).

Stability testing

The final formulation

To improve palatability (as judged by the investigators), sucralose was added to the viscous budesonide solution within the manufacturer's recommended range of concentrations (i. e. 0.03–0.24 % (m/v)). The final formulation (Table 2) was sterilized by filtration through a 0.2 μ m polyethersulphone membrane (STERICUP, Millipore), and then 10 mL were dispensed under aseptic conditions into sterile 15 mL type I amber glass vials (unidose).

Figure 2: Solubility of budesonide (mean $\pm$ SD) as a function of the amount of hydroxypropyl- β -cyclodextrin (blue squares) or γ -cyclodextrin (red diamonds). The target budesonide concentration is indicated by a red, dashed line.

Table 2: Final formulation of the budesonide 0.1 mg/mL viscous oral solution.

Ingredients	Quantity (mg)
Budesonide	10
γ -cyclodextrin	200
Hydroxypropylcellulose	1000
Glycerol	10,000
Sucralose	400
Purified water	QS 100 mL

Shelf-life

The budesonide content remained stable for at least 3 months (Figure 3), no significant degradation was detected on the HPLC chromatogram (Figure 4, Table 3) and there was no change regarding the solution's colour, clarity or pH (around 4.7). Conversely the chromatogram corresponding to forced degradation shows many degradation products (Figure 4).

Discussion

Cyclodextrin complexation is one of the most widely used techniques for improving the solubility [11], palatability [12] and topical delivery [13] of lipophilic compounds. Hydroxypropyl- β -cyclodextrin [14, 15] and γ -cyclodextrin [16] have already been successfully used to enhance the dissolution rate and solubilization of budesonide. Indeed,

hydroxypropyl- β -cyclodextrin reportedly forms an inclusion complex with budesonide [15]. In the present study, budesonide's solubility increased linearly with both cyclodextrins in the tested range [0.2 – 2 mM]. The calculated CE was greater for γ -cyclodextrin (0.147) than for hydroxypropyl- β -cyclodextrin (0.064), confirming that γ -cyclodextrin was a better water solubilizer for budesonide than hydroxypropyl- β -cyclodextrin at the concentrations tested here. Even though we did not obtain a formal proof that budesonide and γ -cyclodextrin had formed an inclusion complex, we hypothesize that γ -cyclodextrin's wider cavity reduces steric hindrance and thus increases the complexation efficiency. When used with Biopharmaceutics Classification System class II compounds like budesonide, cyclodextrins may improve bioavailability [17, 18] and so dose adjustment may be needed. It has previously been reported that the oral bioavailability of budesonide is primarily restricted by pre-systemic metabolism after complete absorption of the drug [1]. Thus, cyclodextrin is not expected to improve oral bioavailability. Conversely, we considered that sequestration and thus limitation of budesonide's topical action were unlikely because (i) γ -cyclodextrin is rapidly hydrolysed by salivary amylase [19], and (ii) cyclodextrin complexes of budesonide [15] and compounds with similar structures (e. g. dexamethasone [20]) have already been used successfully for topical administration. Further studies need to be done to confirm it. Although all the investigators considered that the palatability of the solution was good, this parameter was not rigorously tested. The addition of sucralose improved palatability enough to avoid the need for further adjunction of aromas.

Figure 3: Budesonide content of formulations (n = 3 at each time point) when stored in type 1 amber glass vials at 24 °C/60 % relative humidity.

Figure 4: Typical HPLC–UV chromatograms of budesonide raw material freshly dissolved in methanol (top), the final formulation stored in type 1 amber glass vials for 3 months at 24 °C/60 % relative humidity (middle), and the final formulation stored in type 1 transparent glass vials under forced photodegradation conditions (bottom).

Table 3: Typical table of compounds of the chromatogram obtained with the final formulation stored 3 months at 24 °C/60 % relative humidity; *: retention time of minor degradation products present in less than 0.1% on other chromatogram, AU: arbitrary units, epi: epimer, % budesonide: percentage of total budesonide area (area/sum of the two budesonide epimers' areas).

Retention time (min)	Area (AU)	Area (% budesonide)	Identification
3,543	85	0,02	
4,351	383	0,11	
4,901	102	0,03	
5,375	324	0,09	
6,006	111	0,03	
9,089*	0	0,00	
12,637	750	0,21	Imp. D epi
14,057	256	0,07	Imp. D epi
16,539*	0	0,00	
18,339*	0	0,00	
20,969	189,762	52,40	Budesonide epi B
22,415	172,357	47,60	Budesonide epi A
27,049	261	0,07	

We also chose to add a cellulose hydrocolloid to the solution, since it provides a good compromise between viscosity enhancement and mucoadhesion, and was compatible with the use of cyclodextrins [21]. Furthermore, it has been shown that drug/cyclodextrin/cellulosic hydrocolloid complexes may enhance the topical action of drugs [22]. We kept the viscosity under 150 mPa·s (i. e. the viscosity of a simple syrup) because higher values impeded the filtration step. When tested separately, the adjunction of 0.2% (m/v) γ -cyclodextrin neither increased the viscosity nor modified the non-Newtonian properties of a 1% hydroxypropylcellulose solution. The hydroxypropylcellulose KLUCEL GF PHARM has a nominal viscosity of 150 – 400 mPa·s as a 2% (m/w) aqueous solution (data from the manufacturer), and halving its concentration reduced its nominal viscosity by more than half in our experiments.

Lastly, no significant loss of content was observed during a 3-month stability study, and no significant degradation (i. e. >0.5% of the total budesonide) was

observed. Rapid photodegradation was observed when the final formulation was stored in transparent glass vials in the light – confirming previous reports and emphasizing the need for photoprotection [23].

Conclusion

We provided a convenient, stable formulation of budesonide for treating our paediatric patients in hospital and then at home, if required. The formulation was as simple as possible, and special efforts were made to limit the number and quantity of excipients in the final formulation because eosinophilic esophagitis mainly has an allergic aetiology. Consequently, the patients' exposure to potential allergens was limited by our exclusion of aroma or preservatives. Further studies of the efficacy and safety of our new formulation may now be warranted. Given that budesonide's bioavailability is mainly limited by pre-systemic metabolism, complexation with cyclodextrins is unlikely to remove this obstacle. Hence, the previously tested budesonide doses could be used for further studies.

Conflict of interest statement: Authors state no conflict of interest. All authors have read the journal's Publication ethics and publication malpractice statement available at the journal's website and hereby confirm that they comply with all its parts applicable to the present scientific work.

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Bionotes

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