Stability evaluation of oral viscous budesonide formulations to treat Eosinophilic Esophagitis in paediatrics

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1 Introduction

The treatment of Eosinophilic Esophagitis (EoE) consists in the administration of an oral formulation of budesonide (BUD). Due to there is not yet a paediatric formulation commercially available for treating EoE despite recent studies carried out for adolescents and adults (1), the objective of this study was to evaluate two different oral viscous BUD formulations for paediatrics preparing by compounding that ensures the quality of the elaborated preparations, testing the chemical stability of the API and the uniformity of declared doses.

2 Materials and methods

Different excipients accepted for pediatrics at different proportions were used to elaborate the formulations, see table 1. Their composition were selected based on their frequently use in hospital pharmacy services.

TABLE 1: COMPOSITION OF EACH FORMULATIONS

Formulation	F1	F2	F3
BUD (mg)	20	20	20
Tween 80 (mg)	-	2000	-
Glycerin (ml)	2	-	2
Methylcellulose (mg)	1000	3000	1000
Saccharin (mg)	50	50	50
Methylparaben (mg)	50	40	50
Propylparaben (mg)	20	20	20
Sodium citrate (mg)	-	50	50
Citric acid (mg)	-	100	100
Purified water sqf. (ml)	100	100	100

▲ **Table 1:** Composition of the formulations evaluated: formulation 1 (F1), formulation 2 (F2), formulation 3 (F3). sqf: sufficient quantity for.

The test of uniformity of mass of delivered dose from multidose containers, recommended by the European Pharmacopeia (Eu. Ph.) was carried out (2). Chemical stability was evaluated following ICH recommendations (Q1A(R2)) (3), the pH variation was followed along the stability test. To perform this test formulations were storage at 5 ± 0.1ºC (Refrigerator-stove P-selecta. Wedilow type), 25 ± 1.32ºC and at 40 ± 0.1ºC (Climatic chamber ICH110L, Memmert, Spain). The samples were taken by duplicating at times 0, 15, 30 and 60 days evaluating the pH and BUD content. The API was analyzed using a high-performance liquid chromatography (HPLC) method which was properly adapted and validated to ultra-performance liquid chromatography (UPLC) on an Acquity UPLC® H-Class System chromatograph (Waters, Corporation Milford, MA) (4).

3 Results and discussion

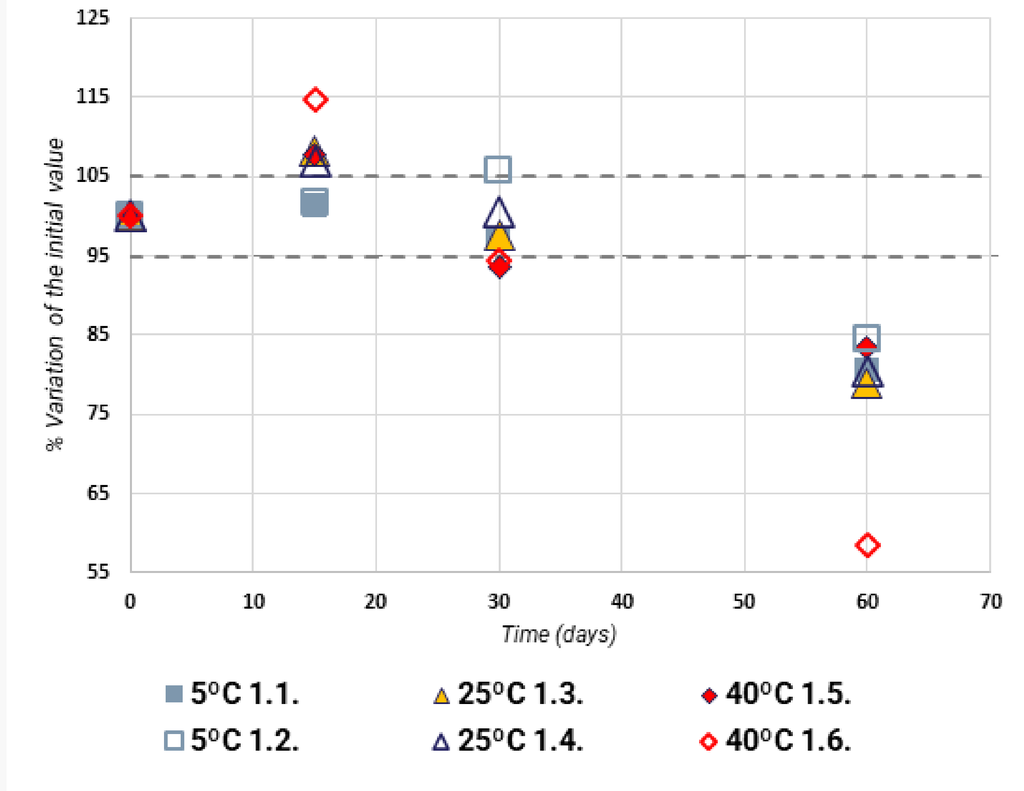
Both formulations met the Eur. Ph. test for mass uniformity of multidose containers. F1 met the desired dose uniformity with an acceptance value (AV) of 10.59, unlike F2, 22.93. See table 2 and figure 2. Therefore, the administration of the prescribed dose and uniformity can only be ensured in F1. There were not significant pH variations for both formulations during the stability test. The stability period established at 25ºC was for F1 was 30 days (99.12 ± 2.12% DV), and for F2 was 15 days at the same temperature (112.24 ± 0.73% DV). F2, in contrast to F1, directly incorporates the citrate proportion to the elaboration, this incorporation allows the formulator to prepare all the batches with the same initial pH (pH: 4.23 ± 0.01, at 25ºC), avoiding pH adjustment errors, see figure 2 and 3.

TABLE 2: DOSE UNIFORMITY EXPRESSED BY PERCENTAGE OF DECLARED VALUE

	F1	F2	F3
% DV ± SD	100.59 ± 4,03	88.85 ± 5.53	97.22 ± 1.45
LI	76.13	73.88	73.88
LS	126.88	123.13	123.13
AV	10.59	22.93	4.76

▲ **Table 2:** dose uniformity test. AV: acceptance value; SD: standard deviation; DV: declared value. F1 and F3 met the desired dose uniformity, unlike F2.

FIGURE 1: CHEMICAL STABILITY FOR FORMULATION 1

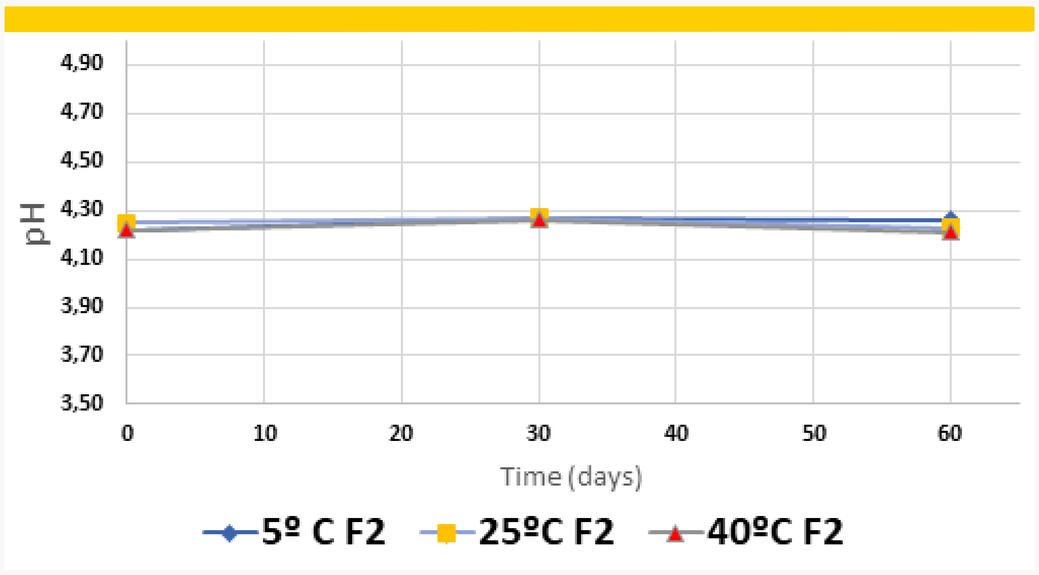


▲ **Figure 1:** Evolution of the average remaining amounts of budesonide in F1 expressed as the % variation of the initial value, as a function of storage time and temperature. F1 lost less than 10% of its initial concentration after 30 days of storage under any of the temperature conditions. However, at 60 days it lost more than 20% of its initial concentration.

4 Conclusion

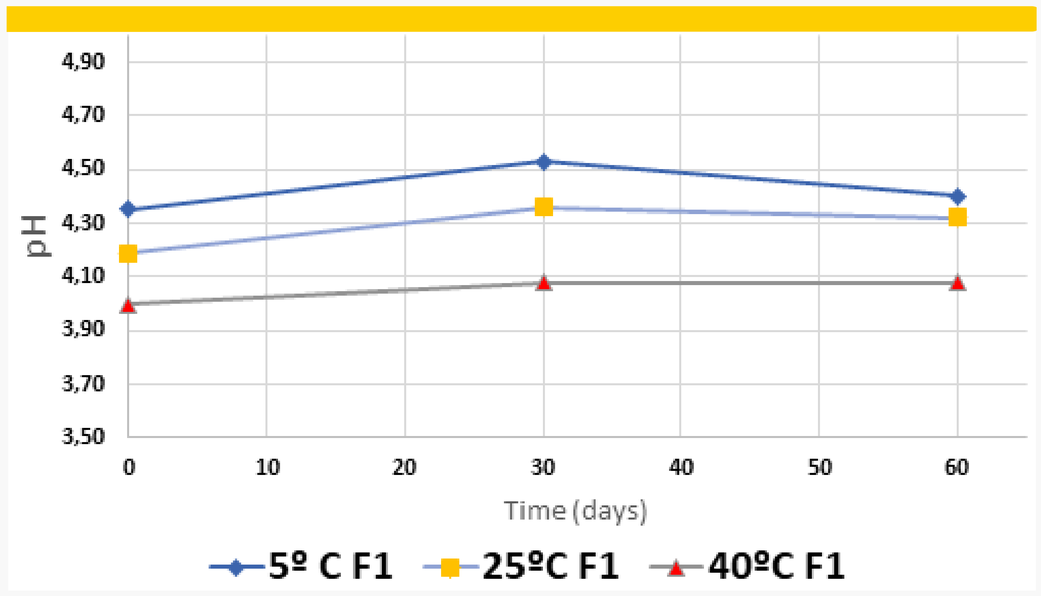
F1 is the formulation that presents the best results in terms of content uniformity and chemical stability. For this reason, it is proposed a third formulation which the same composition of F1 but incorporating the citrate proportion of F2, see the composition of F3 in table 1.

FIGURE 2: PH VARIATION FOR FORMULATION 2



▲ **Figure 2:** pH variation of pH of F2 over time and at different temperatures during the chemical stability test.

FIGURE 3: PH VARIATION FOR FORMULATION 1



▲ **Figure 3:** pH variation of pH of F1 over time and at different temperatures during the chemical stability test.

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