FORMULATION AND STABILITY STUDY OF EXTEMPORANEOUS ORAL LIQUID DOSAGE FORMS CONTAINING FLECAINIDE ACETATE 2MG/ML FOR PAEDIATRIC USE

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Flecainide acetate (FlecAc) is an antiarrhythmic drug, effective in children and foetal tachyarrhythmias [1]. FlecAc is commercially available as 50-150 mg oral tablets or intravenous injectable solutions, approved only for use in adults. For paediatric use, an extemporaneous preparation has to be compounded, using the pure active principle or, when this is lacking, the grinded tablet. Few examples of extemporaneous FlecAc preparations are reported in literature, normally at a dose of 20 mg/mL [2]. Nevertheless, in case of neonates and infants, a lower concentration is useful.

AIM OF THE PRESENT WORK

The aim of this work was to compound FlecAc oral liquids (2 mg/mL) using pure powder or grinded commercial tablets and to evaluate the chemical stability of the active principle.

EXPERIMENTAL PROTOCOL - STANDARD OPERATING PROCEDURES

Four types of aqueous solutions were compounded following hospital standard operating procedures.

In three different hospital pharmacies, seven pharmacists compounded a total of 28 preparations.

Preserved simple syrup (PSS) with the addition of a suspending phase

- Pure powder (API) — PSS-API (n=7)
- Grinded commercial tablets (GCT) — PSS-GCT (n=7)

Simple syrup: Weight an exact amount of saccharose to solubilize in half the water, stirring and heating at 50°C. Add glycerol and then citric acid and sodium citrate, previously solubilized in water. Add methyl parahydroxybenzoate, as a preservative. Transfer solution to a 100 mL graduated cylinder, then add water to full volume of 100 mL. Before use, filter the syrup.

Suspending phase: In mortar, carefully mix finely grinded tablets or FlecAc to corn-starch and then to carboxymethyl cellulose to form a thick, smooth paste. Pour approximately half of the syrup in the mortar and mix suspension with pestle. Transfer to a 100 mL graduated cylinder, washing several times mortar with remaining syrup to full volume of 100 mL. Add flavour.

Ready-to-use commercial suspending vehicle, ORA-Plus ORA-Sweet (OPOS)

- Pure powder (API) — OPOS-API (n=7)
- Grinded commercial tablets (GCT) — OPOS-GCT (n=7)

Crush tablets with a mortar and pestle to a fine powder or weight FlecAc. Measure with a graduated cylinder the commercial suspending vehicle (OP). Pour in mortar a small amount of OP and triturate to a thick, smooth paste and then the remaining OP by geometric dilution. The amount of OP should be 50% of the total solution. Transfer all in a graduated cylinder and bring the suspension to a final volume using the commercial flavored syrup vehicle (OS). Transfer in mortar and mix briefly with a pestle until a uniform suspension is formed.

FLecAc was analysed using a HPLC method reported in literature and properly modified [3].

1. DRUG CONTENT

For each compounded preparation, according to Italian Pharmacopoeia, FlecAc content have to be no less than 90% and no more than 110% of the labelled amount per volume.

At time t=0, the mean FlecAc content of all samples was 1.82±0.10 mg/mL, against a labelled content of 2.00mg/mL.

	Conc (mg/ml)	C.V. %	% of labelled value
PSS - API	1.800 ± 0.106	5.89	90.0
PSS - GCT	1.791 ± 0.151*	8.41	89.5
OPOS - API	1.814 ± 0.061	3.38	90.7
OPOS - GCT	1.867 ± 0.071*	3.83	93.3

Note: *significantly different

Duration and method of stirring were further investigated and improved: magnetic stirrer was used for at least 15 min.

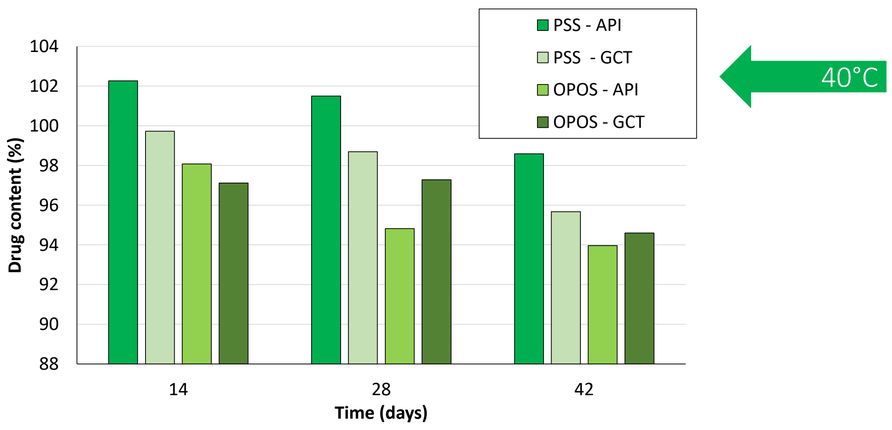
	Conc (mg/ml)	C.V.	% of labelled value
PSS - API (n=8)	1.969 ± 0.038	1.94	98.5
PSS - GCT (n=14)	1.896 ± 0.055	2.90	94.8
OPOS - GCT (n=8)	1.866 ± 0.073	3.92	93.3

The mean FlecAc content of all samples was higher (1.92±0.06 mg/mL) and variability was reduced.

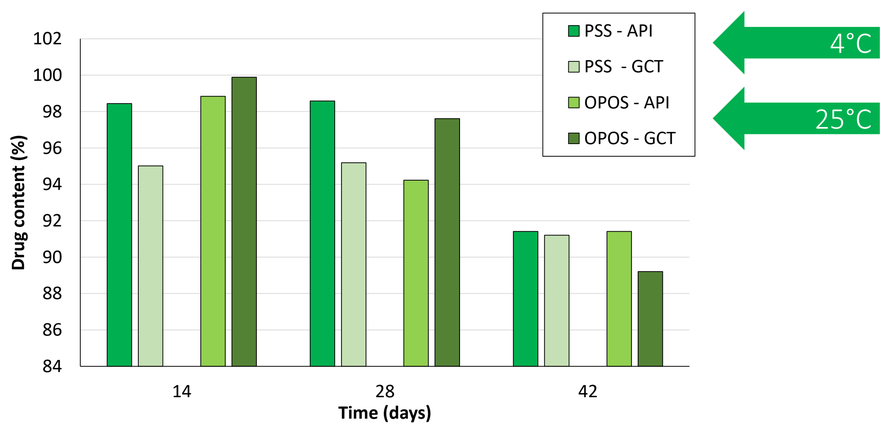
2. STABILITY

FlecAc content was checked for each formulations; they were stored for 42 days at different temperatures and storage conditions (% calculated vs T=0).

Samples of both methods were stored at 40°C.



According to the hospital suggestion some PSS samples were stored at 4°C while OPOS at 25°C.



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CONCLUSIONS

FlecAc is completely solubilized in the proposed vehicles. Therefore, the use of a suspending agent is needed only to mask the excipients of the tablet, if they are not completely solubilized.

Chemical stability was ensured until 42 days. Nevertheless, storage periods longer than 30 days at room or lower temperatures should be carefully considered, because of its influence on FlecAc solubility.

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