

# FORMULATION AND *IN VITRO* EVALUATION OF CHLORAL HYDRATE RECTAL SUPPOSITORIES FOR PAEDIATRIC USE

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## Introduction

Chloral hydrate (CH) is a short-term sedative and hypnotic normally given to children as a syrup to assist with sleep and alleviate anxiety prior to painful dental or medical procedures which entail the patient to be still (*e.g.* scans and EEGs) [1, 2].

However, when given orally, it exhibits a bitter taste and the most common adverse reaction shown is gastric irritation. Moreover, the onset of reaction occurs about 30 minutes after oral dosing, delaying the observation of the sedative and hypnotic effect [1].

Since observation of the therapeutic effect is known to be faster by the rectal route of administration and this route would also overcome taste and gastric irritation problems, rectal suppositories, especially useful for treating young patients, were deemed as appropriate alternative dosage forms.

The aim of this study was the formulation and *in vitro* evaluation of a rectal suppository dosage form of CH intended for paediatric use in a local hospital. A strategy for prolonged drug release of selected formulations was also assessed.

## Materials and Methods

Suppocire (SP) bases with different melting points (m.p.) and hydrophilicity (Table I) were a kind gift from Gattefossé (France). CH and quinaldine ethyl iodide were from Sigma-Aldrich (Germany) and Carbopol 934 (CP) from Noveon (USA). Polyethylene glycol (PEG) 6000 and 1500, supplied by Clariant (Germany), were used at a 60:40 ratio (m.p. 41-45°C). Other reagents were of analytical grade.

**Preparation of CH suppositories:** Moulds were calibrated and the dosage replacement factors of CH for both water-miscible and fatty bases determined experimentally. Suppositories (~1g) containing 200 mg of CH were prepared by the fusion method [3]. In short, the base was molten at the lowest temperature possible to avoid degradation, followed by addition of the active drug (and CP when appropriate) and thorough

**Table I.** Physical properties of the different SP bases

Suppocire	Melting Point (°C)	Hydroxyl Value
BM	36-37.5	< 10
NB	36.5-38.5	20-30
BP	35-37	30-50
CM	38-40	< 10
C	38-40	20-30
NC	38.5-40.5	20-30
CP	38.5-40.5	30-50
D	42-45	20-30

mixing. The mass obtained was then poured into metallic moulds at a temperature near to the solidification point. CH was previously ground until particles were impalpable and sieved to guarantee that they were below 150 µm.

### *Evaluation of CH suppositories:*

**Disintegration time,** *i.e.* the time required for the entire suppository to melt when immersed in a water bath at a constant temperature of 37°C, was determined in four suppositories, randomly chosen from each batch.

**Uniformity of weight:** Ten samples from each batch were weighed individually using an electronic balance.

**Uniformity of content:** Four suppositories from each batch were melted or dissolved in 50ml of water at 37°C. The mixture was allowed to cool for the base to re-solidify and then filtered through a 0.5 µm syringe filter to remove the base. The solution was assayed spectrophotometrically (Unicam, UK) at 605nm for CH by the AOAC official method [4]. Unmedicated suppositories were used as blanks.

**Mechanical strength:** The force, in kg, required to fracture four individual suppositories (kept in the fridge) from each batch was determined using a hardness tester (CT5, Engineering Systems, UK).

**In vitro drug release studies:** The release of CH from four individual suppositories chosen at random from each batch was carried out using the USP flow through cell dissolution method [5] (Sotax AG CH-4008, Switzerland). The flux of the dissolution media (deionised water at 37°C)

was set to 5 ml per minute and samples collected at 5, 10, 15, 20, 30, 40, 60, 80 and 110 minutes, were assayed for CH against blanks as before [4].

## Results and Discussion

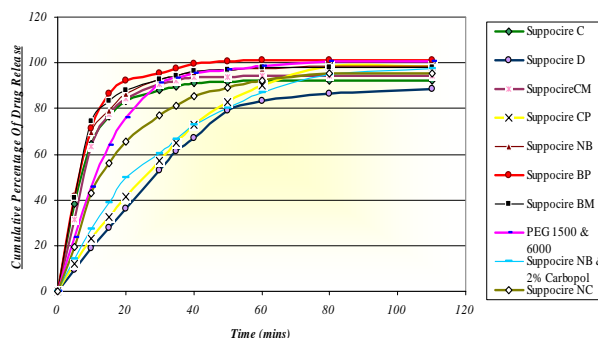
The physical characteristics and *in vitro* drug release of CH rectal suppositories formulated using a variety of emulsifying fatty bases (SP) and water-miscible bases (PEG) were assessed as responses. A release modifying agent (CP) was incorporated into selected formulations to attain prolonged release of CH. Results indicate that all formulations show acceptable physical characteristics regarding uniformity of weight (data not shown), drug content, and disintegration time (except SP D; Table II). It is well established that CH lowers the m.p. of bases and, therefore, many of the formulations seemed to deform rather than break under the application of pressure. Mechanical strength was highly dependent on the m.p. of the base, varying from 0.3 (SP B range; lower m.p.) to 3.13 kg (PEGs).

**Table II.** Characteristics of the CH suppositories batches. Results are mean  $\pm$  s.d.; n=4.

Batch	Disintegration Time (min)	Drug Content (%)
SP BP	4.23 $\pm$ 0.05	100.98 $\pm$ 2.62
SP NB	5.05 $\pm$ 0.25	100.43 $\pm$ 3.59
SP BM	4.56 $\pm$ 0.03	99.13 $\pm$ 1.28
SP C	5.44 $\pm$ 0.06	97.37 $\pm$ 7.39
SP CM	5.35 $\pm$ 0.03	102.03 $\pm$ 7.14
SP CP	16.35 $\pm$ 0.35	99.80 $\pm$ 3.43
SP NC	6.56 $\pm$ 0.26	96.22 $\pm$ 1.93
SP D	*	97.43 $\pm$ 5.76
PEG 6000:1500 (60:40)	31.17 $\pm$ 0.13	101.69 $\pm$ 2.09
SP NB+2% CP	7.21 $\pm$ 0.02	100.85 $\pm$ 1.79
SP NB+10% CP	82.14 $\pm$ 0.59	102.10 $\pm$ 0.68
PEG 6000:1500 (60:40)+2% CP	37.84 $\pm$ 0.31	99.66 $\pm$ 2.35

\*exceeded the disintegration time allowed by USP [5].

The release of the drug from the suppositories was evaluated by dissolution testing (Fig.1). Results correlate with disintegration times and m.p. of bases, with SP B range of suppositories showing the fastest CH release (71% within 10 min.). However, these suppositories melted on handling and hydroxyl value ( $I_{OH}$ ) did not seem to affect drug release. Generally, within the C range (higher m.p.), as the  $I_{OH}$  of the base increased (CM>C> NC>CP), the slower the drug release was.



**Fig. 1** CH release profiles from the different SP and PEG suppositories. Results are mean of 4 estimates.

CH release from the PEG base was slower (65% after 20 min.) than the SP B range and SP C and CM, since it was dependent upon the rate of dissolution of the base rather than melting. In fact, a water soluble drug such as CH, is expected to show better release from fatty bases. Prolonged release CH suppositories were formulated using up to 10% CP and SP NB. These suppositories released drug for up to four hours. Sustained release was not attained with a PEG base.

## Conclusions

Accuracy and precision are of the utmost importance when compounding for children, especially in the case of CH, since wrong dosage can cause serious problems, even death. Rectal suppositories meeting USP requirements could be prepared for hospital use, utilizing both water-miscible and fatty bases. Fatty bases of the SP C range gave the best suppositories with respect to *in vitro* release and handling. Prolonged drug release was achieved by incorporating CP into the fatty base formulation, which is especially important for procedures that require longer time than CH duration of action (1-2h) [2].

CH suppositories should be kept in the fridge to avoid volatilisation and facilitate application. Further investigations on stability are warranted.

## References

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