Development of a Novel Mini-emulsion Based Formulation for the Topical Delivery of Lidocaine

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OBJECTIVE

To develop an emulsion based topical formulation for local anaesthetic delivery, which is stable for at least 1 year and potentially reduces systemic absorption of drugs.

INTRODUCTION

Emulsions containing mixed emulsifier systems (surfactant and co-surfactant) with a droplet size in the range of less than 1µm, typically of a size between 100 and 700 nm are often referred to as miniemulsions.[1] Topically applied lidocaine has been used for analgesia in several clinical settings. Local anaesthetic use on open wounds carries the potential risk of enhanced systemic absorption. Also, there has been a lack of sterile topical formulations containing local anaesthetic for use on open wounds.[2]

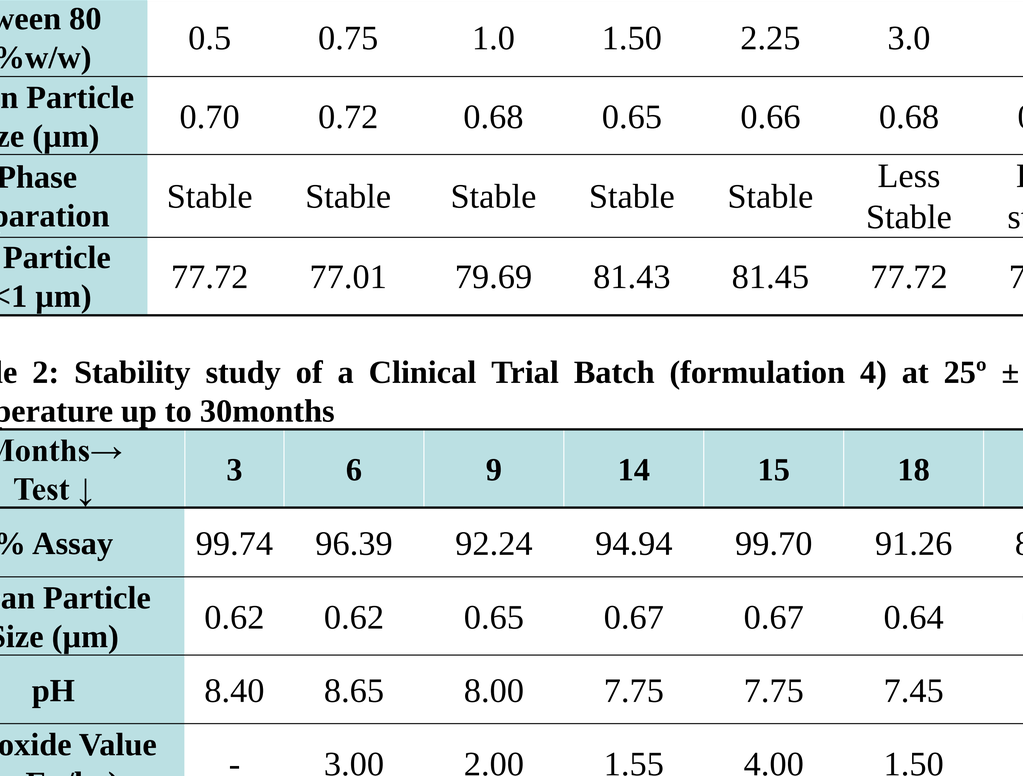
Table 1: Optimisation of mini-emulsion formulations in different ratios of surfactant and co-surfactant

Parameters	Form.1	Form.2	Form.3	Form.4	Form.5	Form.6	Form.7
Lecithin (% w/w)	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Tween 80 (%w/w)	0.5	0.75	1.0	1.50	2.25	3.0	4.5
Mean Particle size (µm)	0.70	0.72	0.68	0.65	0.66	0.68	0.73
Phase separation	Stable	Stable	Stable	Stable	Stable	Less Stable	Less stable
% Particle (<1 µm)	77.72	77.01	79.69	81.43	81.45	77.72	79.41

Table 2: Stability study of a Clinical Trial Batch (formulation 4) at 25º ± 2° C temperature up to 30months

Months→ Test ↓	3	6	9	14	15	18	30
% Assay	99.74	96.39	92.24	94.94	99.70	91.26	89.00
Mean Particle Size (µm)	0.62	0.62	0.65	0.67	0.67	0.64	0.67
pH	8.40	8.65	8.00	7.75	7.75	7.45	7.10
Peroxide Value (mEq/kg)	-	3.00	2.00	1.55	4.00	1.50	1.89

Figure 1: Average distributions of Standardised lidocaine plasma concentration (SLPC) and lidocaine dose (mg) [Emulsion Vs Aqueous]



METHODS

Emulsion formulations were developed using soy oil as an oil phase, polysorbates and lecithin as surfactant and co-surfactant. Different concentration ratios of Tween 80® and lecithin were used. The effect of homogenisation on particle size reduction was determined for the final optimised formulation. Particle size (Mastersizer), pH, phase separation, microscopy, peroxide value and HPLC assay of lidocaine were used as primary parameters for stability evaluation. All the stability samples were stored at ambient temperature of 25 ± 2° C.
A randomised, double-blind, active-controlled, parallel pilot trial was carried out to evaluate safety and efficacy of the optimised product compared to a topical 4% lidocaine hydrochloride aqueous solution. Plasma concentrations of lidocaine were analysed by LC-MS-MS.

RESULTS

The ratio of co-surfactant/surfactant was critical to produce stable mini-emulsions. A ratio of 1:3 or more reduced emulsion stability significantly (Table 1). Homogeniser rotor speed had significant effect on particle size of mini-emulsion. Relationship of rotor speed and reduction in particles size was in agreement with the following relationship. [3]

$$d_{max} = \rho_c^{-0.6} \sigma^{0.6} N^{-1.2} D^{-0.8}$$

The mini-emulsion based formulation was stable for up to 18 months without refrigeration (Table 2). It was a significant breakthrough for a pharmaceutical based emulsion technology.
Both formulations showed a significant analgesia for procedural pain during dressing changes and provided similar outcomes in pain management. The pain scores for mini-emulsion and aqueous were 1.3 ± 0.3 (mean ± SEM) and 1.8 ± 0.4 (p=0.98) respectively. Nearly 90% of patients were very satisfied with their treatment. The mean plasma concentrations of lidocaine for Aqueous and Emulsion were 0.132mg/L and 0.040mg/L respectively (p=0.0694, Figure1).

CONCLUSIONS

Mini-emulsion based formulations produced mean particle size of less than 1µm and significantly increased stability without refrigeration. In a clinical trial set up, the mini-emulsion based topical local anaesthetic provided an improved safety profile.

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