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# Rheological and functional characterization of new antiinflammatory delivery systems designed for buccal administration

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**Abstract**

The aim of the present paper was to investigate the influence of different formulation parameters on the rheological and functional properties of emulgels (gelified emulsions), intended for the buccal administration of the antiinflammatory drug flurbiprofen. The influence of formulation parameters, such as (a) the amount of gelling polymeric emulsifier (Pemulen® 1621 TR-1) used, (b) the oil to water ratio present in the O/W emulgel and finally (c) the pH of the formulation, was studied by a experimental design (DoE) approach. Formulations were analyzed in term of size and morphology of the internal semi-solid oil droplets as well as in term of rheological properties in the presence or in the absence of flurbiprofen by "shear stress *vs*. shear rate tests" and "frequency sweep tests". Emulgels were also characterized *in vitro* both by bioadhesion tests and release studies. In particular release studies demonstrated that flurbiprofen is released by the emulgels in a controlled manner, the drug release efficacy within the first 100 min was comprised between 50 and 80% of the total amount of the drug. Finally, *in vivo* tests on healthy volunteers have demonstrated that emulgels were able to remain on buccal mucosa for an average period of 1 h, moreover emulgels did not have bad taste and volunteers referred that were agreeable and pleasant.


*Keywords:* Buccal delivery; Mucoadhesion; Emulgels; Flurbiprofen; Rheology

## 1. Introduction

In recent years, there has been an increasing interest on the study and treatment of oral cavity diseases. The inflammatory status of oral tissue is in fact not only involved in a number of local pathologies, including gingivitis, periodontitis, oral ulcers and apthous stomatitis (Montagna et al., 2000), but represents also a risk factor for a number of systemic diseases such as: metabolic disorders (*e.g.*, diabetes), blood dyscrasias (*e.g.*, leukemia) and autoimmune disease (*e.g.*, pemphigus). Pregnancy, vitamin shortage and drug side effects are often the causes of a great part of oral mucosa inflammations, that are often treated with non-steroidal antiinflammatory drugs (NSAID) (Palazzo et al., 1996; Heasman et al., 1993). The NSAID therapy of oral diseases was mainly based on two different approaches: extensive local treatment with topical formulations and systemic administration. The topical formulations commonly employed (mouthwash, sprays, gels, lozenge) are often characterized by a limited drug retention time in oral cavity, due to its self-clearing mechanism and various mechanical movements. Therefore numerous and repeated administrations are required in order to obtain effective drug levels.

Mucoadhesive semi-solid formulations could overcome the problem of scarce bioavailability by allowing the application of the drug at the pathological site, thereby increasing the contact time between formulation and mucosa (Bonacucina et al., 2006).

In a recent review on the effects of selective and non-selective NSAIDs on the treatment of periodontal diseases (Salvi and Lang, 2005), the authors have stated that the development of topical NSAIDs formulations with a daily application seems to be of particular interest. This may help to further reduce adverse systemic effects of non-selective NSAIDs in the long-term host modulation of periodontitis-susceptible patients.

In this respect, semi-solid formulations can possess a high biocompatibility and bioadhesivity, allowing adhesion to the mucosa in the dental pocket; finally, they can be rapidly elimi-

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Table 1
Effect of emulgel composition on the size and size distribution of internal oil droplets

| Formulation | Polymer (%, w/v) | O/W ratio (w/w) | pH | Mean diameter ± S.D. (μm) |
|---|---|---|---|---|
| #1 | 0.3 | 0.5 | 5.5 | 33.8 ± 14.5 |
| #2 | 0.3 | 0.5 | 6.5 | 8.6 ± 2.6 |
| #3 | 0.3 | 1.0 | 6.0 | 23.3 ± 9.0 |
| #4 | 0.3 | 1.5 | 5.5 | 22.5 ± 18.3 |
| #5 | 0.3 | 1.5 | 6.5 | 33.4 ± 20.3 |
| #6 | 0.4 | 0.5 | 6.0 | 32.6 ± 14.1 |
| #7 | 0.4 | 1.0 | 5.5 | 26.1 ± 10.4 |
| #8 | 0.4 | 1.0 | 6.0 | 19.5 ± 6.3 |
| #9 | 0.4 | 1.0 | 6.5 | 29.9 ± 8.6 |
| #10 | 0.4 | 1.5 | 6.0 | 33.7 ± 21.4 |
| #11 | 0.5 | 0.5 | 5.5 | 16.6 ± 6.6 |
| #12 | 0.5 | 0.5 | 6.5 | 13.7 ± 6.3 |
| #13 | 0.5 | 1.0 | 6.0 | 37.5 ± 17.4 |
| #14 | 0.5 | 1.5 | 5.5 | 21.3 ± 9.0 |
| #15 | 0.5 | 1.5 | 6.5 | 15.2 ± 9.7 |

nated through normal catabolic pathways, decreasing the risk of irritative or allergic host reactions at the application site.

The aim of this study was to prepare and characterize new mucoadhesive semi-solid formulations (O/W emulsions, emulgels) designed for flurbiprofen (FLUR) administration. This drug is a member of the phenylalkanoic acid derivative family of NSAIDs.

The topical formulations, here described, are based on the polymeric emulsifier Pemulen® 1621 TR-1 (Acrylates/C10-30 alkyl acrylate crosspolymer).

Pemulen® polymeric emulsifiers are high molecular weight, cross-linked copolymers of acrylic acid and a hydrophobic comonomer. This chemical structure allows these compounds to function as primary emulsifiers in oil-in-water emulsions. In fact the lipophilic portions of the polymer adsorb at the oil–water interface, while the hydrophilic portions swell in water forming a gel network around oil droplets to provide exceptional emulsion stability to a broad range of oils.

For the production of the emulgels, as internal phase of the O/W emulsions, was employed the solid, neutral lipid glycerol behenate (Compritol®888ATO) that is widely used as an excipient in many pharmaceutical dosage forms including sustained release tablets and capsules.

In particular, this paper describes: (a) the formulation study of the flurbiprofen-containing semi-solid emulgel formulations, (b) the rheological characterization of emulgels, (c) the *in vitro* release kinetics of flurbiprofen from emulgels and finally (d) the evaluation of their *in vivo* performances in the treatment of oral inflammations.

## 2. Materials and methods

### 2.1. Materials

Pemulen® 1621 (TR-1), was a gift from BF Goodrich Company (Ohio, U.S.A.); Compritol®888 ATO was a gift from Gattefossè (Milano, Italy), ultrafiltered water was prepared by QI system (Billerica, U.S.A.); flurbiprofen was provided by Angelini (Ancona, Italia). All other materials were of reagent grade. Froben®, Benactiv®Gola, Alovex®gel, Gengigel®, Daktarin®gel, Corsodyl®dental gel, Dentosan® parodontal gel, present in italian market, were purchased from a pharmacy.

### 2.2. Preparation and experimental design analysis of emulgels

Emulgel formulations were prepared by a three step method: (i) polymer dispersion in water, (ii) neutralization of the polymeric aqueous dispersion, and (iii) emulsification of the oil phase. With respect to the first step, three different TR-1 percentages, namely 0.3, 0.4 and 0.5%, w/v, were used. The polymer was suspended in deionized water under stirring at 900 rpm, for 20 min, at room temperature using a mechanical stirrer equipped with a three blade helical impellers (DLS VELP® Scientifica). The resulting slurry was neutralized by a NaOH solution (18%, w/v) to a final pH value of 5.5, 6.0 and 6.5. The neutralization process caused the distension of polymer chains resulting in a clear stable gel. In order to obtain a complete polymer hydration, the gels were stored at 4 °C for 24 h before the addition of the oil phase. Successively different amounts of oil phase (O), constituted by Compritol®888ato, were slowly added to the gels (W, water phase), at three O/W ratios (w/w): 0.5, 1.0 and 1.5, respectively. The addition was performed under stirring at 800 rpm at 80 °C. After cooling at room temperature, the pH value was measured (Table 1).

The effect of the main experimental parameters (concentration of polymer, O/W ratio and pH) on the dimensional characteristics of the internal phase of the emulgels, was studied by DoE approach, based on a randomized central composite face-centered design (CCF), consisting of 17 runs. The parameters were varied as reported in the experimental matrix (see Table 1). The experimental design and the evaluation of the experiments were performed by a PC software (MODDE 8.0, Umetrics AB, Sweden), followed by multiple linear regression (MLR) algorithms.