powder mixture whereas subsequent sieving and remixing eliminated them completely. Therefore, it was proposed that premixing all the ingredients followed by sieving and remixing would solve the problem and this prediction was fully confirmed in further trials.

In conclusion, based on long experience with hundreds of formulations, it is the firm opinion of this author that the method of "premixing-sieving-remixing" (PSR) tablet powders outperforms the "sieving-mixing" (SM) approach by far. Using suitable production equipment the PSR technique is not much more labour intensive, and, most importantly, it generally furnishes a high degree of confidence in reproducibly manufacturing high quality products with good or excellent content uniformity.

Received January 2, 2001
Accepted February 21, 2001

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Emulsions as oral moisturisers for the treatment of severe xerostomia

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The inability to produce saliva in adequate quantity or quality is a condition known as xerostomia [1]. Current treatment includes oral hygiene measures, diet, gustatory and pharmacological sialogogues (agents which stimulate saliva secretion). In case of severe xerostomia, i.e. if no saliva is produced, saliva substitutes are indicated [2]. Saliva substitutes are aqueous polymer solutions (sodium-carboxymethylcellulose (Na-CMC) and mucin) but they are often unsatisfactory [3], because they require constant dosing to provide adequate mucosal hydration. Therefore formulation of artificial saliva that mimics natural saliva may not be the best strategy to combat xerostomia. The aim of the present work was to perform a pilot study to investigate the potential use of emulsions for the treatment of severe xerostomia.

The emulsions formulated for the study were required to be stable for a period of at least two weeks. They should have a low surfactant concentration and should differ in type, viscosity, and volume fraction of the dispersed phase. The Table shows the composition of the emulsions that were chosen to be used in the pilot study, as well as their type, viscosity and formulation method. Eight patients with severe xerostomia were asked to compare the emulsions to two standard solutions (pure safflower oil and a 1% aqueous Na-CMC solution) and water and to complete a questionnaire to assess the formulations (see Experimental).

There was a significant difference in symptom severity between patients, which could be expected when dealing with a patient group and a condition like xerostomia. However, there was found to be no difference ($p = 0.865$) in symptom severity between weeks.

Emulsions were highly significantly better than water (mean = 2.0, $p < 0.001$). The value 2.0 relates to the answer "better than water" and a value of 3.0 relates to the answer "not different to water". The oil was also clearly found to be "better than water" (mean = 2.2, $p < 0.001$), while the Na-CMC-solution was only slightly better then the use of pure water (mean = 2.6, $p = 0.04$).

Emulsions were used about 3 times a day, while oil and polymer solution were used between 0 and 2 times a day. The emulsions were used significantly more times a day than either the oil or the solution ($p < 0.001$). The emulsions were found to provide significantly longer relief then either the oil or the Na-CMC solution ($p < 0.001$). The mean period of relief provided by the emulsion was 1.6 ± 0.9 h compared to only 0.7 ± 0.7 h relief provided by both the oil and the Na-CMC solution. Patients expressed their dislike of the pure oil feeling in the mouth and felt the polymer solution was often sticky and did not provide adequate lubrication of the oral mucosa. This seems to be the reason for the finding that the patients used the emulsions more frequently than the oil and the polymer solution.

19 out of 29 patient answers (66%) were "no" to continue using the oil and 23 out of 27 patient answers (85%) indicated that the patients did not want to continue using the polymer solution. However, 26 out of 51 patient answers

Table: Emulsion formulations used in pilot study

P	O (%)	W (%)	S (%)	STS (%)	SMS (%)	ESMS (%)	HLB	PHB (%)	MHB (%)	Na-CMC (%)	F	η (mPas)	type
A	19.9	74.7	5	0	3.4	1.6	8	0.08	0.32	0	a	32	O/W
B	19.9	74.6	5	0	3.4	1.6	8	0.08	0.32	0.1	a	290	O/W
C	19.8	74.2	4.9	0	3.3	1.6	8	0.08	0.32	0.7	a	4200	O/W
D	54.7	39.9	5	0	2.5	2.5	9.8	0.08	0.32	0	a	300	O/W
E	54.6	39.8	5	0	2. 5	2.5	9.8	0.08	0.32	0.1	a	680	O/W
F	54.6	39.7	5	0	2.5	2.5	9.8	0.08	0.32	0.3	a	1440	O/W
G	64.7	29.9	5	5	0	0	2.1	0.08	0.32	0	b	400	W/O
Oil	100	0	0	0	0	0	N/A	0	0	0	N/A	44	O
Na-CMC	0	98.9	0	0	0	0	N/A	0.02	0.08	1	N/A	700	W

P: preparation, A-G: emulsion formulations, O: safflower oil, W: water, S: surfactant, HLB: hydrophilic-lipophilic-balance value of the surfactant blend used, STS: sorbitantristearate, SMS: sorbitanmonostearat, ESMS: ethoxy-(20)-sorbitanmonostearate, PHB: propylhydroxybenzoate, MHB: methylhydroxybenzoate, Na-CMC: sodium carboxymethylcellulose, F: formulation method (a and b: see Experimental), η: viscosity (determined as Newtonian viscosity one day after preparation), O/W: oil-in-water, W/O: water-in-oil, N/A: not applicable, all percentages are w/w

(51%) indicated they did want to continue using the emulsion. From these results it can be assumed that the patients are using the emulsions as their primary relief product.

Although the patients did express their preference for emulsions over the oil or polymer solution, there was inconclusive evidence to show which emulsion out of the seven formulations was perceived as best.

Current artificial salivas are formulated as aqueous solutions and evaporation will play a role in the removal of the aqueous lubricating film from the mouth. Oily solutions might provide a better lubrication over time. Pure oil, however, produces an unpleasant oily sensation. Emulsions on the other hand provide the palatability of water and the lubrication properties of oil and will lubricate the mucosa over longer periods of time.

An encouraging feature of this pilot study was that some patients reported that the emulsion was helping them sleep throughout the night and that they were able to speak for longer periods of time.

Results of this pilot study indicate that emulsions are a suitable alternative to currently available artificial salivas in the treatment of xerostomia. In a future study the use of polymer stabilsed o/w emulsions, completely based on food grade excipients in the treatment of severe xerostomia will be investigated.

Experimental

1. Materials

Safflower oil was used as the oil phase for all emulsion formulations. The non-ionic surfactants sorbitan-tristearate, sorbitan-monostearate, and ethoxy-(20)-sorbitan-monostearate used in the formulation of the emulsions were supplied by Croda Surfactants, New Zealand. Methylhydroxybenzoate and propylhydroxybenzoate (Sigma, USA) were used as preservatives. Sodium carboxymethylcellulose (Na-CMC, viscosity of aqueous 1% solution: 700 mPas, Hercules, France) was used as a viscosity inducing agent. Peppermint oil (Colgate Palmolive, New Zealand) was used as flavouring agent.

2. Preparation of emulsions

Method A: Oil and surfactants were heated until the surfactants had dissolved. Preservatives were dissolved in water. Aqueous phase was added and the dispersion was vortexed and homogenised for 4 min (Silverson emulsifier, 10,000 rpm). Peppermint oil (one drop) was added to the emulsion.

Method B: Oil and surfactants were heated until the surfactants had dissolved. Preservatives were dissolved in water. Aqueous phase was added and the dispersion was vortexed. Peppermint oil (one drop) was added to the emulsion. 150 ml of each emulsion per patient was formulated.

3. Characterisation of emulsions

Emulsions were characterised by visual observation, phase contrast microscopy (Nikon Optiphot microscope), conductivity measurements (Riac CM/100 conductivity meter), and rheological measurements (Brookfield DSVIII programmable rheometer (Brookfield Inc, USA) with CP52 and CP 42 spindles.

4. Pilot study

After written informed consent was obtained and the protocol was approved by the Southern Regional Health Authority Ethics Committee (Canterbury, New Zealand) eight patients with primary symptoms of diagnosed severe xerostomia were given two standard solutions (pure safflower oil and a 1% aqueous Na-CMC solution) as well as seven emulsions of varying consistencies. Patients were allowed to use the formulations as required and were asked to compare these with each other and with water. One emulsion per week was randomly assigned to the patients to be tested for a period of 7 days, together with the two standard solutions. After each week the patients were asked to complete a questionnaire. Question 1 asked the patients which product they preferred in relation to using just water: the emulsion, the oil or the 1% Na-CMC solution. Question 2 asked how many times a day on average the patients used the emulsion. Question 3 asked about the duration of relief experienced by the patient after using the three products. Question 4 asked if the patients would like to continue using the emulsion. Statistical analyses (paired and single t-test, chi-square test) were carried out assisted by a bio-statistician using the statistical software package SPSS.

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Received January 2, 2001
Accepted January 31, 2001

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