determination of ISMN in human plasma was developed and validated. The method was found to be suitable for the analysis of plasma samples obtained from 20 volunteers in the conduct of bioequivalence study of two sublingual 5-mg tablet formulations of ISDN [9].

Experimental

1. Chemicals and reagents

ISMN was purchased from European Pharmacopoeia (Strasbourg, France). Isomannide dinitrate, used as internal standard, was supplied from Elpen (Athens, Greece). Acetonitrile and ethyl acetate, both of HPLC grade, were purchased from J. T. Baker (Deventer, Netherlands). Isooctane for chromatography was obtained from Merck (Darmstadt, Germany). All other chemicals and solvents used were of analytical grade and water was milli-Q grade.

2. Chromatographic conditions

The GC system consisted of a Varian 3400 gas chromatograph coupled to a Varian electron-capture detector, a Varian 8035 autosampler (Walnut Creek, CA, USA), and a Hewlett-Packard HP3394A integrator (Avondale, PA, USA). Separation was performed on a 15 m × 0.53 mm DB-5 capillary column with a film thickness of 1.5 μm (J & W Scientific, Folsom, CA, USA). The injector temperature was 200 °C and the electron-capture detector was set at 220 °C with argon/methane (95 : 5) at a flow rate of 20 ml/min. The initial column temperature was 130 °C and the temperature was raised up to 145 °C at a rate of 5 °C/min, hold for 3 min.

3. Calibration curves and sample extraction

Working standard solutions of ISMN containing 25, 50, 100, 200, 350, and 500 ng/ml and of internal standard containing 4 μg/ml were prepared daily in acetonitrile/water (50 : 50, v/v). 50 μl of these working ISMN solutions and 50 μl of the working internal standard solution were added to 0.5 ml drug-free plasma to prepare the calibration standard samples containing 2.5, 5, 10, 20, 35, and 50 ng/ml of ISMN. Following addition of 1.5 ml of ethyl acetate, the samples were vortexed for 1 min and then centrifuged at 2000 × g for 10 min. The organic phase was transferred into another tube and evaporated to dryness at 20 °C with the aid of a gentle stream of air. The residue was dissolved in 0.5 ml of acetonitrile, 1 ml of isooctane was added and after vortexing for 1 min the isooctane was evaporated and 0.5 ml acetonitrile was added and mixed. This solution was transferred to autosampler vials and 2 μl were injected into the column.

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Mixing of pharmaceutical powders in tablet manufacture

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Suitable mixing of solid, particulate ingredients (powders) in tablet manufacture is of paramount importance in order to ensure a high quality product having appropriate content uniformity, not only of the active drug substance but of all components in the formulation.

Mixing of tablet ingredients is almost always accompanied with sieving, the main purpose of the latter being elimination or reduction of aggregates and agglomerates in the raw materials since most ordinary mixing equipment is unable to decompose them during mixing. Most pharmaceutically active agents are fine or very fine powders that are more or less prone to aggregation/agglomeration. Several excipients possess this property as well, even direct compression materials.

It appears to be common practice to start a mixing operation by sieving the raw materials separately followed by mixing in a suitable mixer. This approach, however, must be considered to be highly questionable since materials that tend to aggregate/agglomerate will rapidly re-aggregate/agglomerate after sieving. By contrast, premixing of the ingredients followed by sieving and remixing will in most cases effectively prevent the presence of aggregates/agglomerates in the finished blend due to the simultaneous intermixing of all ingredients effected by this method.

The above considerations generally apply to "ordinary" materials, i.e. those consisting of very fine or fine particles (approx. 20–100(200) μm). Some substances, e.g. micronized (particle size less than approx. 20 μm), highly cohesive or coarse materials may demand special sieving/mixing/milling methods. Elaborate procedures may also be necessary with formulations containing ingredients in very small amounts (less than approx. 1%).

The following example is given to illustrate the importance of the positioning of the sieving step in mixing operations. In this case the goodness of mixing could simply be estimated visually thus eliminating uncertainties possibly arising from demixing in sampling or handling of samples and/or chemical analytical errors.

3,750 g pregelatinized starch, 250 g colloidal silicon dioxide and 400 g red iron oxide were sieved separately through a 0.5 mm screen (Comil) and mixed for 5 min in a 25 l intensive mixer (Gral). This is called the "separate mix".

2,125 g Hydroxypropyl methylcellulose, 3,750 g pregelatinized starch, 46,500 g lactose, 250 g colloidal silicon dioxide and 15,500 g microcrystalline cellulose were sieved separately through a 1.0 mm screen (Comil) and mixed with the previously mentioned separate mix in a 300 l tumbling mixer (GEI IBC) at 12 rpm for 17 min.

Visual inspection of the resulting blend revealed the presence of numerous white aggregates/agglomerates in the powder bed. Consequently, the blend was sieved through a 1.0 mm screen (Comil) followed by mixing at 12 rpm for 5 min in the tumbling mixer. No aggregates/agglomerates could be detected visually in the resulting mixture.

These findings unambiguously demonstrate that sieving the ingredients separately prior to mixing did not prevent the presence of aggregates/agglomerates in the resulting

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.

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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