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CHEWING GUM AS A DRUG DELIVERY SYSTEM FOR NYSTATIN INFLUENCE OF SOLUBILISING AGENTS UPON THE RELEASE OF WATER INSOLUBLE DRUGS

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ABSTRACT

Nystatin is an antifungal drug with a poor solubility in water and saliva. Consequently, only a small amount of the drug was released from nystatin chewing gum during testing on a mastication device. The addition of solubilising agents to chewing gum increased the release of nystatin by a factor of 50-70, whereas the agents only increased the solubility of nystatin by a factor of 3-7. The solubilising agents were Cremophor® RH 40, Tween® 60 (non-ionic surfactants) and Panodan® AB 90 (an-ionic surfactant). There was no linear relationship between the amount of nystatin in chewing gum and the release. A method to estimate the content of nystatin in chewing gum was developed.

INTRODUCTION

Chewing gum could be a valuable delivery system for drugs intended to act locally in the oral cavity.

The antifungal drug nystatin is widely used against oral and gastro-intestinal mycoses. Nystatin is not absorbed. It acts locally and a long duration of action may be obtained by incorporating the drug in chewing gum.

Nystatin has a low solubility in water and saliva (1). This means that the quantity of released drug will probably be small if the drug is incorporated in chewing gum by a conventional method (2).

It is known that the solubility of water-insoluble drugs can be increased by solubilisation. A higher solubility of a drug has been shown earlier to increase the release of drug from chewing gum (3). The release of nystatin from chewing gum might therefore be enhanced by the addition of solubilising agents.

The solubilising agents used in the present study were chosen through the consideration of their use in pharmaceuticals and/or nutrients.

An investigation of the relationship between the nystatin content of chewing gum and the amount of drug released in vitro was also carried out.

MATERIALS

Nystatin BP 80 5480 IE/mg was purchased from Mecobenzon Ltd., Denmark. Methanol and n-heptan both of analytical grade were purchased from Merck, Germany, and Ferak Ltd., Germany. The solubilisers were generous gifts: Cremophor® RH 40, polyoxyethyleneglycol trihydroxy stearate 40, DAC (non-ionic), BASF Ltd., Denmark, Tween® 60, polyoxyethylene (20) sorbitan monostearate (non-ionic), ICI, Atlas Chemie Ltd., Denmark and Panodan® AB 90, monoglyceride diacetyl tartrate (anionic), Grindsted Products Ltd., Denmark. All other chemicals and reagents were of analytical grade.

METHODS

Analytical method

The amount of nystatin was determined UV-spectrophotometrically, using the amplitude of the first derivative measured between the maximum at 316 nm and the minimum at 323 nm. A Shimadzu UV-visible Recording Spectrophotometer UV-160 was used for the determination. Compared with common absorbance measurements, the amplitude of the first derivative of the nystatin UV-spectrum shows a better correlation with the results of microbiological assays (4).

Solubility of nystatin

The equilibrium solubility of nystatin was determined in a 0.05 M potassium dihydrogenphosphate / di-sodium hydrogenphosphate / HCl buffer, pH 7.4.

500 mg nystatin was suspended in 10 ml solvent, equilibrated for 18 hours on a rotation device at room temperature 22 ± 1°C and filtered through a Sartorius® cellulose acetate filter (0.2 µm). It was ensured that equilibrium solubility was obtained within 18 hours. Before the spectrophotometrical measurement, an appropriate dilution was made in such a way that the methanol/phosphate buffer ratio was 3:1.

A stock solution was prepared by dissolving 50.0 mg nystatin in 100.0 ml methanol. Standard solutions for the spectrophotometrical determinations were made through an appropriate dilution with methanol:phosphate buffer (3:1).

Solubility of nystatin in the presence of solubilising agents

The equilibrium solubility of nystatin in the phosphate buffer containing different concentrations of

solubilising agents was determined by the method described above. Panodan® AB 90 was not soluble in methanol, so the diluent was changed to a mixture of N,N-dimethyl formamide:1 M acetic acid (17:2). To ensure that no interference occurs, solutions of solubilising agents were measured spectrophotometrically in the same way.

Chewing gum manufacturing

The chewing gum was manufactured by Fertin Laboratories Ltd., Denmark, by using common gum ingredients and a conventional mixer.

Chewing gum containing different doses of nystatin was manufactured.

Chewing gum formulations containing nystatin and a solubilising agent were manufactured by incorporating a mixture of nystatin and the solubilising agent (1:1) to obtain a good contact between the drug and the solubiliser. Furthermore, chewing gum which only contained a solubilising agent was manufactured to control the influence of these on the measurements.

Determination of nystatin in chewing gum

A piece of chewing gum was cut into small pieces and suspended in 25 ml n-heptan and stirred on a magnetic stirrer for at least 30 minutes. 125 ml methanol was added and the mixture was stirred for another 30 minutes to dissolve the drug. The solution was paper filtered into a 150 ml volumetric flask and adjusted with methanol. The nystatin content was determined spectrophotometrically after appropriate dilution with methanol.

To determine the percentage of extraction, known quantities of nystatin (45-60 mg) were simply incorporated in pieces of chewing gum after heating the

placebo chewing gum to 60°C. The pieces were analyzed by the method mentioned above. A standard curve was prepared by suspending placebo chewing gum and known amounts of nystatin in 25 ml n-heptan, using the procedure described above.

In vitro-release of nystatin from chewing gum

The in vitro-release experiments were carried out using a mastication device (5). The mastication rate was set at 60 chewing cycles/minute, and the temperature was fixed at 37 ± 1°C. The release tests were carried out in 0.05 M phosphate buffer, pH 7.4. 10 ml of dissolution medium was added to the mastication device at t = 0 minutes. The dissolution medium was replaced by another 10 ml every 2 minutes during 30 minutes of mastication.

Samples were collected after 2, 4, 6, 10, 14, 18, 24 and 30 minutes of mastication and diluted with methanol to dissolve particles of nystatin. After standing for 15 minutes the samples were filtered through a Sartorius® cellulose acetate filter (0.2 µm) and after appropriate dilution with methanol the nystatin content was measured spectrophotometrically.

RESULTS AND DISCUSSION

Solubility of nystatin

The solubility of nystatin was found to be 40 µg/ml at 22 ± 1°C.

Other authors have found the solubility gravimetrically to be 4.0 mg/ml at 28 ± 4°C (6) and spectrophotometrically (absorbance) to be 0.36 mg/ml at 24 ± 1°C (7).

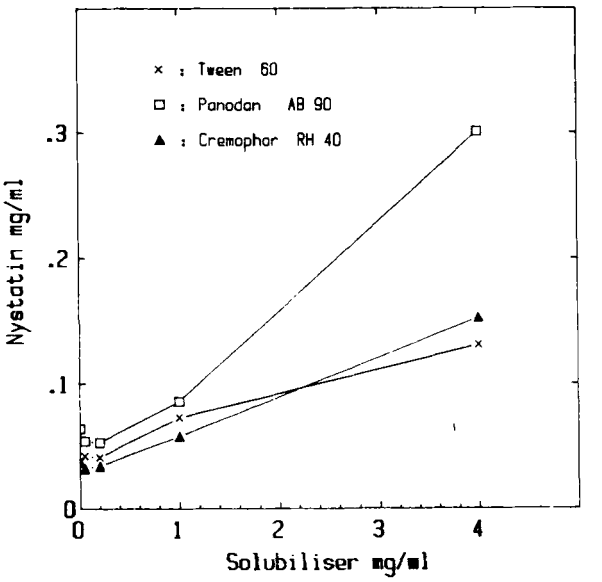

FIGURE 1
Solubility of nystatin in phosphate buffer pH 7.4 as a function of the concentration of solubiliser.

The relatively low solubility of nystatin found in the present study might be a consequence of the first order spectrum method, which is probably more selective (8) than the gravimetrical and the spectrophotometrical methods used in (6, 7).

The solubility of nystatin is increased by the addition of increasing amounts of solubilising agents. As shown in figure 1 the solubility of nystatin is increased maximally by a factor of 7.

Determination of nystatin in chewing gum

A linear standard curve was obtained between the measured amplitude and the concentration of nystatin.

TABLE 1

Formulation	Content of nystatin mean (mg) ± RSD%	Amount released dose x 100% ± SD
Pure nystatin	29.7 ± 1.4	1.4 ± 0.2
- -	61.5 ± 1.1	1.6 ± 0.1
- -	87.7 ± 0.8	1.2 ± 0.1
- -	111.6 ± 2.0	1.0 ± 0.1
nystatin + Cremophor® RH 40	58.2 ± 1.0	71.5 ± 1.9
nystatin + Tween® 60	58.7 ± 0.3	70.4 ± 2.4
nystatin + Panodan® AB 90	58.8 ± 1.9	95.0 ± 2.1

The measurements were carried out after dilution to a concentration range of 12-16 µg/ml, correlation coefficient (r) 0.9947, intercept close to zero.

It was possible to extract 99.1% (RSD = 1.8%), n = 6, of the incorporated amount of nystatin.

The test shows that it is possible to extract practically all of the incorporated amount of nystatin, and the method can be used as a quantitative assay.

The contents of nystatin in the chewing gum formulations are shown in table 1. 3 pieces of chewing gum of each formulation were analysed.

In vitro release of nystatin from chewing gum

The release of nystatin from the formulations containing varying amounts of nystatin (table 1) showed no linear relationship as can be seen in figure 2, linear regression analysis, $P < 0.01$.

The amounts released from chewing gum containing 50-100 mg nystatin did not differ much. It is not possible to explain this by the experiments performed.

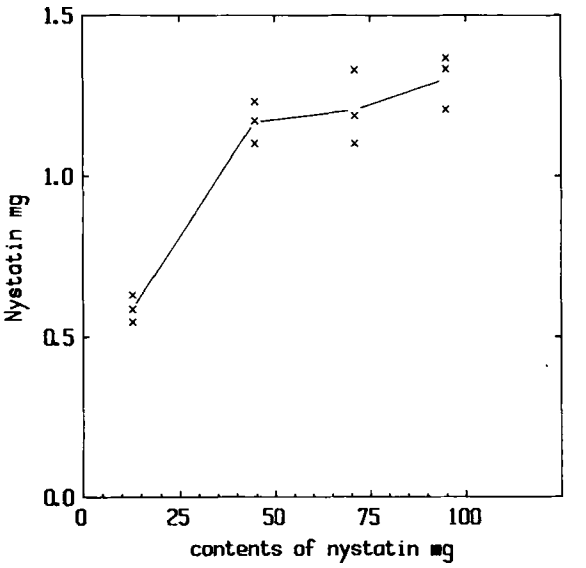

FIGURE 2
Release of nystatin in phosphate buffer pH 7.4 from chewing gum as a function of the content of drug in chewing gum.Mastication time 30 min.

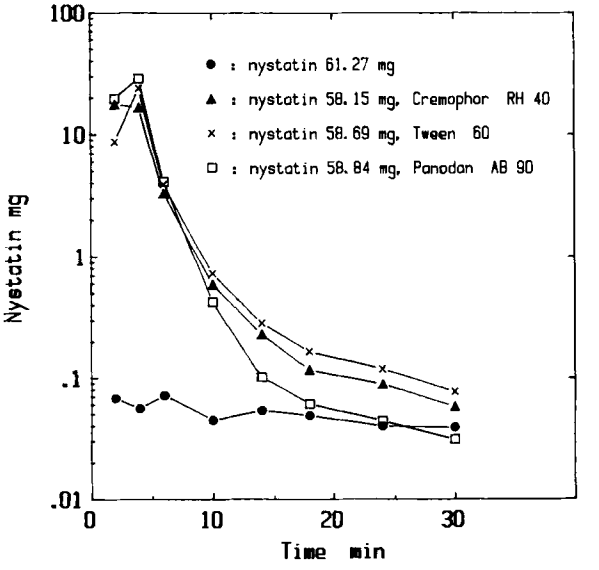

FIGURE 3
Release of nystatin from different chewing gum formulations in phosphate buffer pH 7.4.Semilogarithmic plot.

The release of nystatin from the formulations containing nystatin and a solubilising agent are shown in figure 3.

Adding a solubilising agent to chewing gum containing nystatin causes a surprisingly drastic increase in the release of nystatin. Cremophor® RH 40 and Tween® 60 show a 50 times increase and Panodan® AB 90 causes a 70 times increase. The release promoting effect of the solubilisers is especially pronounced during the first 10 minutes. 98-99% of the totally released amount of nystatin is released during this period.

The shown effect of the solubilising agents cannot only be explained by their ability to increase the solubility of nystatin, but may also be seen as a result of the manufacturing process. Nystatin and the solubilising agent are mixed before incorporation into the chewing gum and may be assumed to be in contact during the manufacturing process and during the mastication. It is anticipated that the release promoting effect is at least partially due to the hydrophilic properties of the solubilisers. Simple observations made it clear that the samples collected during mastication contained great amounts of nystatin particles.

Addition of the solubilising agents is presumed to be a valuable method to increase the release of water insoluble drugs from chewing gum.

Further improvements of nystatin chewing gum will be made in the very near future in an endeavour to optimize the release in relation to the desired therapeutic effect. In vivo experiments will be included.

ACKNOWLEDGEMENT

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