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MICONAZOLE CHEWING GUM AS A DRUG DELIVERY SYSTEM TEST OF RELEASE PROMOTING ADDITIVES

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ABSTRACT

The release of the antifungal drug miconazole from chewing gum formulations was evaluated in vitro and in vivo. It was proven that the addition of the anionic surfactant Panodan® 165 and polyethyleneglycol 6000 increased the release of miconazole. The anionic surfactant made the chewing gum tacky. The addition of polyethyleneglycol 6000 reduced the tacky properties of the chewing gum. 4 healthy volunteers obtained therapeutically active concentrations of miconazole in saliva when they chewed gum. The salivary concentrations of miconazole were estimated, both by a reverse phase HPLC method and a plate microbioassay.

INTRODUCTION

Chewing gum could be an attractive delivery system for the antifungal drug miconazole intended to act

locally on oral mycoses. Miconazole has low water solubility (1). This means that the drug is released very slowly from chewing gum if it is incorporated by a conventional method (2).

Several efforts have been made to increase the release from chewing gum of drugs with low water/saliva solubilities, e.g.(2,3,4,5,6). When an increased release of drug was obtained it was often due to a booster effect during the very first minutes of chewing.

The aim of this study was to formulate a special chewing gum which is able to release considerable amounts of miconazole continuosly during the 30 to 60 min. of chewing. Lipophilic anionic surfactants were applied to obtain this. The release effect of the surfactants was evaluated both in vitro and in vivo.

MATERIALS AND METHODS

Miconazole was a present from Janssenpharma A/S (Denmark). Panodan® AB 90, Panodan® AM, Panodan® 165, diacetyl tartaric acid esters of mono- diglycerides made from refined vegetable fats, and Acidan® CA-L, a citric acid ester of monoglyceride based on refined sunflower oil, were given by Grindsted Products A/S (Denmark). Polyethyleneglycol (PEG) 6000 was purchased from Mecobenzon A/S (Denmark). All other chemicals and reagents were of analytical grade except for the bacto yeast morphology agar from Difco (USA). A strain of Candida albicans PF 1607 88 was isolated from a patient and subcultivated at the Statens Seruminstitut (Denmark) before it was delivered to this laboratory.

Manufacturing of Chewing Gum

The chewing gum was manufactured at Fertin Laboratories A/S (Denmark) from common gum ingredients and with the use of a conventional mixer. Each piece of

chewing gum was planned to weigh 880 mg and to contain 55 mg (6.25%) miconazole base. Chewing gum formulations containing 6.25% miconazole and 5% of one of the surfactants, Panodan® AB 90, Panodan® AM, Panodan® 165, or Acidan® CA-L, were manufactured. The tacky properties of the formulations were evaluated by volunteers who chewed the gum. The formulation containing Panodan® 165 was found to be the least tacky gum. A detaching agent, talcum, lecithin, titanium dioxide or PEG 6000, in amounts corresponding to 5% was added to the chewing gum together with 6.25% miconazole and 5% Panodan® 165.The most effective of the detaching agents was PEG 6000 evaluated by chewing the gums.

Two formulations each containing 6.25% miconazole, 5% Panodan® 165 and 5% PEG 6000 were prepared. One was prepared by pounding the three ingredients in a mortar and subsequently adding the mixture to the chewing gum, while the other was prepared by melting the three ingredients, miconazole, PEG 6000 and Panodan® 165, and by adding the molten mixture to the chewing gum. A chewing gum formulation containing 6.25% miconazole and neither surfactants nor detaching agents was manufactured too.

The release from the three formulations was evaluated in vitro and in vivo.

Content of Miconazole in Chewing Gum

The content of miconazole in chewing gum and in the chewing gum remains after mastication was determined as described previously (2,5).

Release of Miconazole from Chewing Gum

The gums were stored for a couple of weeks before the release was measured. The in vitro release experiments were performed on a mastication device (7) as described previously (5).

Informed consent was obtained from 4 healthy persons, aged 26 - 49. None of the persons wore dentures. The local comittee of ethics had approved the study.

The volunteers fasted for 2½ hours, i.e. half an hour prior to and 2 hours after taking the chewing gum. Each volunteer chewed one piece of the three formulations for 30 min. each. In addition, 2 volunteers chewed one piece of one of the formulations for 120 min. There was an interval of at least 48 hours between the chewings. Saliva samples of about 0.5 ml were collected by expectoration just before the chewing gum was taken and again 2,10,30,60,120,300 and 480 min. after. Saliva samples were in addition taken after 180,240,360 and 600 min. from 2 volunteers who chewed a piece for 120 min.The reverse phase HPLC method used to estimate the concentration of miconazole in the saliva samples has been reported (5).

Microbiological Estimation of Miconazole in Saliva

The miconazole concentrations in some of the saliva samples were measured by a plate microbioassay in addition to the HPLC assay. An indicator strain of Candida albicans PF 1607 88 was grown for 48 hours at 32°C on a dish of agar, composed like the agar used in the microbioassay. The strain was seeded to a concentration of 10^5 yeasts per ml in agar at 48-50°C. The composition of the agar was as described previously (5). The seeded agar was poured in lots of 35 ml into 14 cm Petri dishes. 9 wells were cut, each 6 mm in diameter. 25 µl samples of saliva and standard solutions of miconazole of 0.00, 0.10, 1.00, 10.0 and 100.0 µg/ml prepared in saliva from stock solutions in dimethyl sulphoxide were placed in the wells according to a randomisation scheme deviced in advance. The dishes of agar were incubated at 32°C for 18 hours and miconazole

TABLE 1

In vitro release of miconazole from chewing gum in 0.05 M phosphate buffer pH 7.4. Concentration of miconazole (µg/ml) in dissolution medium as a function of mastication time. Analysis method: HPLC. n = 3.

Time	Chewing gum formulations containing:		
	Pure miconazole	Miconazole, Panodan® 165, PEG Pounded mixture	Miconazole, Panodan® 165, PEG Molten mixture
Min	Mean miconazole conc. ± standard deviation (µg/ml)		
2	3.4 ± 1.0	100.3 ± 43.0	182.9 ± 116.8
4	2.0 ± 0.1	105.9 ± 17.5	199.1 ± 66.1
6	1.2 ± 0.2	75.5 ± 5.6	131.5 ± 13.7
10	1.0 ± 0.2	61.2 ± 5.7	57.4 ± 3.7
14	0.9 ± 0.3	48.5 ± 11.5	25.7 ± 12.0
18	0.7 ± 0.3	28.8 ± 8.5	25.4 ± 16.4
24	0.7 ± 0.2	23.6 ± 6.3	14.4 ± 5.5
30	0.6 ± 0.1	17.3 ± 8.3	9.1 ± 5.3

concentrations determined from diameters of inhibition zones by reference to standard curves of log. miconazole concentration against zone diameter.

RESULTS AND DISCUSSION

The results of the in vitro release experiment are depicted in table 1.

The results showed that an addition of the anionic surfactant Panodan® 165 and of PEG 6000 had a prolonged promoting effect on the in vitro release of miconazole from chewing gum. The formulation containing a molten mixture of miconazole, Panodan® 165 and PEG 6000 seemed to release more miconazole during the first 6 min. of mastication than the formulation containing the mortar pounded compounds. During the rest of the mastication period the two formulations released equal amounts of miconazole.

TABLE 2

Miconazole concentrations (μg/ml) in saliva from 4 healthy subjects after chewing different formulations for 30 min. Analysis method:HPLC.

	Chewing gum formulations containing:					
Time	Pure miconazole		Miconazole, Panodan® 165,PEG Pounded mixture		Miconazole, Panodan® 165,PEG Molten mixture	
Min	Miconazole conc. (μg/ml) in saliva					
	Mean	Range	Mean	Range	Mean	Range
0	0.0	-	0.0	-	0.0	-
2	3.7	9.5-1.4	50.2.	87.1-32.0	28.9	41.7-19.6
10	1.8	3.7-0.5	44.9	96.3-23.1	34.4	51.4-12.8
30	1.9	3.1-0.8	72.4	204.6-21.0	73.8	127.1-19.1
60	0.5	0.8-0.0	6.4	20.9- 0.7	3.8	7.5- 1.2
120	0.3	0.7-0.0	2.9	8.4- 0.6	1.2	2.1- 0.6
300	0.0	-	0.8	2.2- 0.0	0.7	1.3- 0.0
480	-	-	0.3	1.5- 0.0	0.5	1.1- 0.0

The results of the in vivo comparison of the formulations when using HPLC to measure the saliva concentrations of miconazole are presented in table 2.

It is obvious that Panodan® 165 and PEG 6000 had a miconazole release promoting effect in vivo. The average miconazole concentrations in the saliva when formulations containing Panodan® 165 and PEG 6000 were chewed were several times higher than the concentrations obtained during the chewing of the formulation which only contained miconazole. The persistence of miconazole in the saliva after the subjects removed the chewing gum from their mouths was also increased by the formulations containing Panodan® 165 and PEG 6000.

Salivary miconazole concentrations estimated by the plate microbioassay and by the HPLC assay are presented in table 3.

TABLE 3

Miconazole concentrations (μg/ml) in saliva from 2 healthy subjects after chewing 2 different formulations for 30 min. Analysis: HPLC method and plate microbioassay.

	Chewing gum formulations containing miconazole, Panodan® 165 and PEG							
	Pounded mixture Subject No.				Molten mixture Subject No.			
	1		2		1		2	
Time								
Min	HPLC	Microbio	HPLC	Microbio	HPLC	Microbio	HPLC	Microbio
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	32.0	14.1	87.1	13.5	41.7	44	30.6	14.0
10	23.1	25	96.3	12.3	51.4	30	50.5	23
30	35.1	32	204.6	21	120.7	53	127.1	35
60	2.7	2.3	20.9	8.4	4.6	3.7	7.5	6.6
120	1.7	1.4	8.4	2.5	1.2	1.1	2.1	1.9
300	2.2	1.5	0.4	0.1	1.3	0.8	0.8	0.4
480	1.5	0.8	0.8	0.2	0.9	0.5	1.1	0.8

The standard curve for the plate microbioassay was non linear in the range 0.1-100 μg/ml. Std.% = 22 (25 μg/ml, n=5). The detection limit was below 0.1 μg/ml. A comparison of the HPLC assay and the plate microbioassay showed that the concentrations estimated by the bioassay tended to be lower than the concentrations estimated by the HPLC assay. The reason might be that miconazole was extracted from small chewing gum particles when acetonitrile was added to saliva before the HPLC analysis. A similar phenomenon concerning sulphathiazole chewing gum has been reported (8).

It is remarkable that miconazole was detectable in saliva by both methods even 450 min. after the subjects removed the chewing gum.

2 subjects chewed one of the formulations for 120 min., table 4. According to the results in table 4 the chewing gum was able to release miconazole for 120 min.

TABLE 4

Concentration of miconazole (μg/ml) in saliva from 2 healthy subjects after chewing a formulation containing a molten mixture of miconazole, Panodan 165 and PEG for 120 min. Analysis method: HPLC.

Time min.	Miconazole in saliva (μg/ml) Subject No. 1	2
0	0.0	0.0
2	17.7	35.7
10	30.7	34.2
30	51.5	38.5
60	36.4	34.6
120	8.9	9.3
180	3.9	4.7
240	1.2	1.2
300	0.7	1.7
360	0.4	0.9
480	0.5	0.5
600	<0.3	0.5

although the miconazole concentration in saliva seemed to fall during the last 60 min. of mastication.

During 30 min. of mastication the average release of miconazole from the chewing gum containing a molten mixture of miconazole, Panodan® 165 and PEG 6000 was 3.6 mg corresponding to 6.7% of the dose while on average 3.9 mg corresponding to 6.9% were released from the formulation containing the mortar pounded ingredients. The amount released ranged from 2.6 mg to 5.0 mg.

The difference observed in vitro between the release of drug from the two formulations was not significant in the in vivo experiments.

The release of miconazole from the molten mixture chewing gum which was chewed for 120 min. by two subjects was 8.6 mg (15.8%) and 7.8 mg (14.3%) respectively.

The shown miconazole release promoting effect of Panodan® 165 and PEG 6000 may be due to the surface-

active properties of the two substances. The surface-activity of the substances may facilitate the release of miconazole by increasing the amount of saliva absorbed in the chewing gum during the mastication. The solubilising property of Panodan® 165 on miconazole may also contribute to the effect;data not shown. Furthermore, the acidity of Panodan® 165 may be a partial explanation of the increased miconazole release because the solubility of miconazole increases with decreasing pH.

As for the salivary concentrations of miconazole obtained by chewing gum it is remarkable that the concentrations can compete with the salivary concentrations obtained when 5 ml or 10 ml 2% miconazole oral gel (Daktarin®, Janssen) were ingested by healthy subjects (9,10). 5 ml 2% oral gel correspond to 100 mg miconazole while the average release of miconazole during 30 min. of mastication was 3.8 mg.

A clinical trial of miconazole chewing gum is still in progress.

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