

MICONAZOLE AND MICONAZOLENITRATE CHEWING GUM AS DRUG DELIVERY SYSTEMS - A PRACTICAL APPLICATION OF SOLID DISPERSION TECHNIQUE

Morten Pedersen and Margrethe R. Rassing
Department of Pharmaceutics
Royal Danish School of Pharmacy
2 Universitetsparken
DK 2100 Copenhagen Ø
Denmark

Abstract

Miconazole and miconazolenitrate are antifungal drugs with poor solubilities in water and saliva. The low solubilities meant that only small amounts of the drugs - incorporated by a conventional method in chewing gum - were released during mastication. The experiments were performed on a mastication device.

In this study it was shown that application of a 20% miconazole - 80% polyethyleneglycol 6000 solid dispersion drastically improved the in vitro release of miconazole from chewing gum, when a medium similar to saliva was used. In addition to polyethyleneglycol 6000, polyvinylpyrrolidone 40000, xylitol and urea were tested as carriers. It was also shown that the release rate of miconazole from chewing gum was much greater than the release rate of miconazolenitrate.

No certain correlation could be shown between the dissolution rates of the solid dispersions measured by a stirring paddle method and the release rates of miconazole from solid dispersions in chewing gum.

The solid dispersion systems were characterized by differential scanning calorimetry. The systems containing

polyethyleneglycol 6000 and xylitol were eutectic. Polyvinylpyrrolidone 40000 prevented crystallisation of miconazole when the percentage of drug in the solid dispersion was less than 50%.

Introduction

Chewing gum could be a valuable delivery system for drugs intended to act in the oral cavity or to be absorbed through the oral mucosa. Such drugs often have low water/saliva solubility, and unfortunately they are released slowly from chewing gum during mastication (1).

In this study miconazole (1-(2,4-dichloro-8-((2,4-dichlorobenzyl)oxy) phenetyl)-imidazole) and miconazole-nitrate have been used. Miconazole and the nitrate salt are antifungal drugs which are widely used against oral and gastrointestinal mycoses. The drugs have low water solubility (2). This means that the drug release from chewing gum will probably be small if the drug is incorporated in the chewing gum by a conventional method.

It has been shown for numerous drugs that the dissolution rate can be increased by application of solid dispersion techniques, e.g. (3), (4) and (5).

It was therefore predicted that the release of miconazole-nitrate from chewing gum could be improved by application of solid dispersion techniques.

When solid dispersion systems are prepared by a melt procedure, it is favourable if the drug has a low m.p. That is why miconazolenitrate m.p. 181-183°C corrected was converted to miconazole m.p. 79.5-80.5°C corrected. In addition miconazole probably has preferable solubilities in the carriers compared to miconazolenitrate as regards the possibilities of making solid dispersions where the drug is present in a molecular or colloidal form.

Materials and methods

Miconazolenitrate purchased from Sigma Chemicals, U.S.A. was used without further purification. Miconazole (free base) was obtained by slowly adding water to a basic ethanolic solution of the nitrate. Crystals of the free base were formed immediately. The crystals were isolated,

washed and dried, m.p. 79.5-80.5°C corrected, which is in agreement with (6). Late in the study miconazole was supplied by Janssenpharma A/S, D.K. It is noted in the article when miconazole from Janssenpharma A/S was used. Polyethyleneglycol (PEG) 6000, PEG 400, polyvinylpyrrolidone (PVP) 40000 and urea purchased from Mecobenzon, D.K. were of pharmaceutical grade. Xylitol supplied by Fertin Laboratories A/S, D.K. was of pharmaceutical grade. The rest of the chemicals and reagents were of analytical grade.

Solid dispersion preparation

In this study solid dispersions of miconazole and water soluble carriers were obtained by melt, solvent and combined melt/solvent procedures.

PEG 6000, xylitol, PVP 40000 and urea were tried as carriers for miconazole.

- Solid dispersions of PEG 6000 and miconazole were prepared by a melt procedure and by a combined melt/solvent procedure. A physical mixture of PEG 6000 and miconazolenitrate was also prepared.

- Solid dispersions of xylitol and miconazole were prepared by a melt procedure and by a melt/solvent procedure.

- Solid dispersions of PVP 40000 and miconazole were prepared by a solvent procedure.

A preparation of urea and miconazole solid dispersions by a melt procedure was tried but the melted compounds were immiscible.

None of the solid dispersions were discoloured during preparation.

Melt procedure

Miconazole and carrier were mixed in a mortar and the mixture was sieved through a 300 µm mesh sieve. The mixture was placed in a beaker and allowed to melt in an oil bath placed on a heating plate. The temperature of the oil bath was 100°C. The mixture was stirred with a glass spatula. A homogenous liquid was obtained and it was kept in the oil bath for 10 min. Then it was poured on to an icecooled aluminium plate and kept on the plate for 2 hours. The product was placed in an excicator for 48 hours. The solid mass was crushed in a mortar and put through a 300 µm mesh sieve. The solid dispersions were stored in excicators.

Solvent procedure

A physical mixture of miconazole and carrier was made as described above and dissolved in a minute quantity of absolute ethanol. Evaporation of the ethanol was carried out on a rotary evaporator at 50°C. The obtained sticky mass was kept in an oven at 50°C for 24 hours. The solid mass was crushed, sieved and stored as mentioned above.

Melt/solvent procedure

Miconazolenitrate was suspended in 1 N aqueous sodium hydroxide. Five percent excess of sodium hydroxide compared to miconazolenitrate was added. A minute quantity of absolute ethanol was added to dissolve the nitrate salt. In the basic solution miconazole was present as free base, $pK_a = 6.67$ (7). The carrier was added together with additional absolute ethanol. The solution was transferred to a beaker, which was placed in an oil bath at 60°C. The temperature was increased from 60°C to 110°C in the course of 20 min. The temperature was kept at 110°C for 10 min. after which the melt was poured on to an icecooled aluminium plate. The solid mass was handled as described under the melt procedure.

Solubility

The equilibrium solubilities of miconazolenitrate and miconazole were determined in a 0.05 M sodium citrate/HCl buffer pH 3.0 and in 0.05 M potassium dihydrogenphosphate/ di-sodium hydrogenphosphate/ NaOH pH 7.9. The buffers were prepared of freshly boiled distilled water. The equilibrium solubility of miconazole in the citrate buffer containing different concentrations of PEG 6000 was also determined. 20 mg drug was suspended in 10 ml solvent, stirred for 24 hours at $37 \pm 1^\circ\text{C}$ and filtered through a Sartorius celluloseacetate filter pore size 0.2 μm . It was ensured that equilibrium solubility was obtained in the course of 24 hours. The solubility was determined once in each medium. The concentration was measured by a HPLC method. It was ensured that interfering peaks from PEG 6000 were not present. A stock solution of miconazolenitrate was prepared by dissolving 200.0 mg of the drug in 200.0 ml methanol. Standard solutions were made by appropriate dilutions with citrate buffer.

Dissolution rate

A stirring paddle method (8) was used to measure the dissolution rates of the solid dispersions, the pure miconazolenitrate and the pure miconazole Janssen. The dissolution studies were run in 500 ml 0.05 M citrate

buffer pH 3.0 prepared as above. The paddle was operated at 50 r.p.m. A recycling and automatic recording system was used for all dissolution rate studies. The fluid was circulated by a peristaltic pump, Ismatec mp-ge, through a 10 mm path length quartz flowcell at a flow rate of 25 ml/min. The outlet tube was equipped with a Frisenette paper filter, which kept back particles down to 6 μm . The absorbance of miconazole at 270,5 nm was measured on a Perkin Elmer model 124 double beam spectrophotometer and was recorded on a Servogar S RE 541.

The solid dispersions were stored for a couple of weeks before the dissolution rate measurements. The solid dispersions were passed through a 300 μm mesh sieve before the test. Miconazolenitrate and miconazole Janssen were put through a 125 μm mesh sieve before the test.

Thermal analysis

In order to establish phase diagrams for systems with miconazole and the carriers : xylitol, PVP 40000 and PEG 6000, a number of solid dispersions were prepared by the above mentioned procedures. PEG 6000 and xylitol solid dispersions prepared by the melt procedure and PVP 40000 solid dispersions prepared by the solvent procedure were used. The solid dispersions contained 0, 2, 5, 10, 20, 50, 80 and 100 % miconazole.

A Perkin Elmer differential scanning calorimeter, type D.S.C.-1 B was used. The D.S.C. curves were recorded with a range setting of 8 mcal/sec. and a scan speed of 4°C/min. on a Perkin Elmer Recorder model 56. Dry nitrogen at a flow rate of 25 ml/min. was used as a carrier gas. The 6 mg samples placed in aluminium pans were run in the temperature interval 37°C to 140°C.

The D.S.C. experiment was performed after storage of the solid dispersions for a couple of weeks.

Chewing gum manufacturing

The chewing gum was manufactured at Fertin Laboratories A/S, D.K. with the use of common gum ingredients and a conventional mixer.

The manufactured chewing gum formulations contained : pure miconazolenitrate, pure miconazole Janssen, 20% solid dispersion melt/solvent procedure miconazole/PEG 6000, 20% solid dispersion melt/solvent procedure miconazole/xylitol, 20% solid dispersion solvent procedure miconazole/PVP 40000, 20% physical mixture miconazole-

nitrate/PEG 6000 and 20% miconazole in PEG 400 - a viscous solution, which was added to sorbitol before the chewing gum was mixed.

Determination of miconazole in chewing gum

A colorimetric method developed to determine miconazole in powder and cream (9) was simplified and used to analyse the content of miconazole in chewing gum. A piece of chewing gum was cut up and suspended in 25 ml n-heptane on a magnetic stirrer for at least 30 min. 70 ml methanol was added and the mixture was stirred for at least 30 min. to dissolve the drug. The solution was paperfiltered into a 100 ml volumetric flask which was adjusted with methanol. 300 μ l of the resulting solution was transferred to a 50 ml separator containing 9.00 ml chloroform. 15.0 ml 0.1 mM bromocresolgreen aqueous solution and 5.0 ml citrate buffer were added to the separator. The yellow complex of bromocresolgreen and miconazole was extracted to the chloroform layer by vigorous shaking for 1 min. After 5 min. the chloroform layer was transferred to a tube and centrifuged at 2000 r.p.m. for 15 min. The absorbance of the solution was measured against a similarly prepared reagent blank at 419 nm. A Shimadzu double beam spectrophotometer model 190 with 10 mm quartz cells was used.

A standard curve was prepared by suspending placebo chewing gum and known amounts of miconazolenitrate in 25 ml n-heptane. The procedure as described for miconazole chewing gum was followed.

In vitro release of miconazole from chewing gum

The in vitro release experiments were performed with the use of the mastication device described in (10). The mastication rate was set at 60 cycles/min. The release tests were carried out in both 0.05 M citrate buffer pH 3.0 and 0.05 M phosphate buffer pH 7.9. The buffers were prepared as mentioned above. A volume of 10 ml dissolution medium was added to the mastication device at 0 min. The mastication lasted 30 min. and the 10 ml dissolution medium was replaced every 2 min. The samples after 2, 4, 6, 10, 14, 18, 24 and 30 min. of mastication were collected.

The samples with pH 3.0 were filtered through a Sartorius celluloseacetate filter pore size 0.2 μ m. The concentration of miconazole in the filtered samples was measured by a HPLC method.

To the collected samples with pH 7.9 an equivalent volume of methanol was added. Miconazole is fairly soluble in 50% methanol. The mixtures were stored for 15 min., filtered through a Sartorius filter and chromatographed as mentioned above. To ensure that interfering peaks were not present, placebo chewing gum was chewed on the mastication device and the dissolution samples were chromatographed.

A stock solution of miconazolenitrate was prepared by dissolving 20.0 mg in 50.0 ml citrate buffer. Standard solutions were made by appropriate dilutions using the same solvent. The chewing gum was stored for a couple of weeks before the release measurements.

Reversed high-pressure liquid chromatographic method

A Merck/Hitachi HPLC model 655 A-11 equipped with a Rheodyne model 1725 injection valve fitted with a 20 μ l sample loop was used. A Merck/Hitachi variable wavelength UV-monitor model 655 A-22 connected with a Merck chromatointegrator D 2000 was used as detector and recorder. The chromatography was performed on a reversed phase lichrosorb RP 18, 7 μ m column, 250 mm x 4 mm i.d. (Merck). A guard column lichrosorb RP 18, 1.0 mm x 4 mm i.d. (Merck) was used. The detection wavelength and the mobile phase were as reported (11). The column flow rate was set at 1.5 ml/min. The retention time was 7.20 min.

For quantitative determination a linear calibration curve was found in the range 0.5 - 900 μ g/ml, correlation coefficient, $r = 0.9982$ with the intercept close to zero. The detection limit was 0.5 μ g/ml. The reproducibility of the chromatogenic procedure was indicated by 6 replicate injections of a 10 μ g/ml standard solution, which gave a relative standard deviation of 0.8%

Results and discussion

Dissolution rate

A stirring paddle method was chosen because it is considered to be the most convenient method to compare dissolution rates of solid dispersions and pure drug (12), and it is widely used.

It was checked that the Beer-Lambert Law is valid in the concentration range studied. Since PVP 40000 interferes

with the assay at 270.5 nm, blank PVP 40000 assays were used to correct the dissolution curves of solid dispersions containing PVP. The Beer-Lambert Law is valid for PVP interference.

All samples were run in duplicate at least. 6 determinations of the 75% dissolution time of a solid dispersion containing 50% miconazole and 50% xylitol prepared by the melt procedure showed a relative standard deviation of 2,9%. Four batches of solid dispersion containing 20% miconazole and 80% PEG 6000 prepared by the melt/solvent procedure and four batches of the 50% miconazole and 50% xylitol solid dispersion, just mentioned above, showed a relative standard deviation of T 75% of 18% and 9% respectively.

The equilibrium solubility of miconazole and miconazole-nitrate in citrate buffer was determined to be 754 µg/ml and 451 µg/ml respectively. The solid dispersion systems subjected to dissolution studies in 500 ml citrate buffer contained 9.6 mg of miconazole. This means that the dissolution test was run under sink conditions.

The dissolution rate curves for the solid dispersions containing PEG 6000 and xylitol prepared by the melt procedure are presented in fig. 1 and fig. 2. Comparison of the systems dissolution rate was done by means of the 75% dissolution times table 1. Table 1 shows that it is possible by solid dispersion technique to create systems which have a dissolution rate which is 13 times faster than the dissolution rate for the pure drug miconazole Janssen. It is noted that 95% of the particles are smaller than 100 µm and 50% smaller than 45 µm, personal information from Janssenpharma A/S, Denmark.

The T 75% dissolution times for miconazole Janssen and pure miconazolenitrate are 2.60 min. and 3.80 min. respectively. By microscopy of miconazolenitrate it was seen that the particles were rod shaped and only a few of the particles were longer than 25 µm.

It is noteworthy that the T 75% values of pure miconazole which has been melted, averaged 6.17 min. while a precipitate from absolute ethanol had a T 75% value of 1.36 min.

It is seen by comparison of T 75% values that the solid dispersion systems prepared by PEG 6000 melt procedure and PVP 40000 solvent procedure show an optimum at the system containing 10% miconazole. The optimum could be explained as the result of two factors: 1) An increased

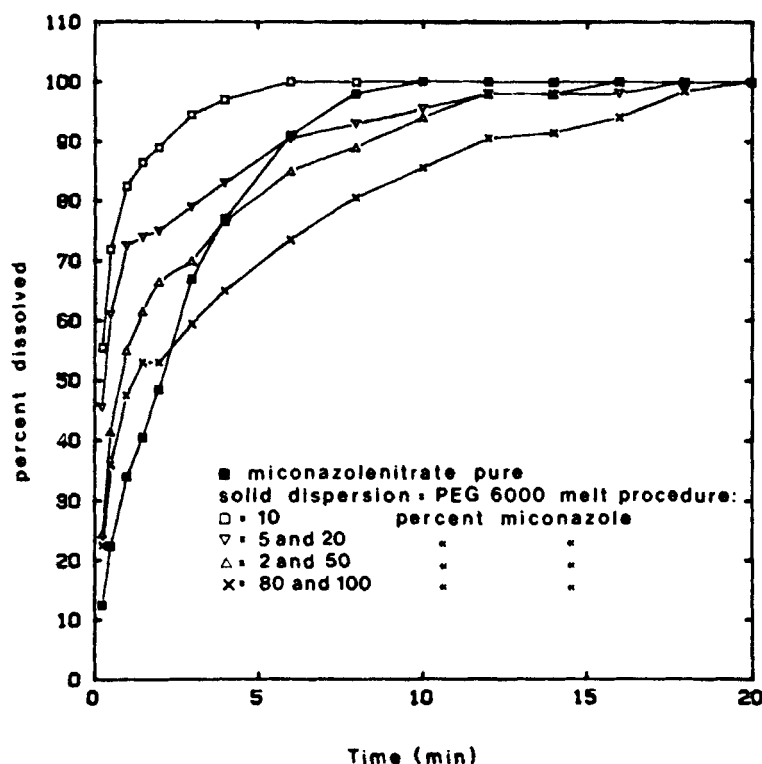


Figure 1. Percent miconazole dissolved in citrate buffer pH 3.0 as a function of time. Stirring paddle method.

weight ratio of miconazole in the solid dispersion leads to the presence of miconazole crystals or larger miconazole crystals and thus to a decrease in the dissolution rate. 2) The dissolution rates of the carriers are rate limiting for systems containing a small percentage of miconazole. In fact it was observed that the solid dispersions containing PVP 40000 and PEG 6000 settled down at the bottom of the beaker where it formed a gel which slowly dissolved. Contrary to this a visual inspection of the xylitol systems showed that the xylitol was dissolved in about 1 minute, but for the systems containing a high percentage of the drug a remainder was left. The remainder was thought to be pure miconazole. The fast dissolution rate of xylitol might explain the big difference between the T 75% values for the 20% and the 50% solid dispersion systems containing xylitol and

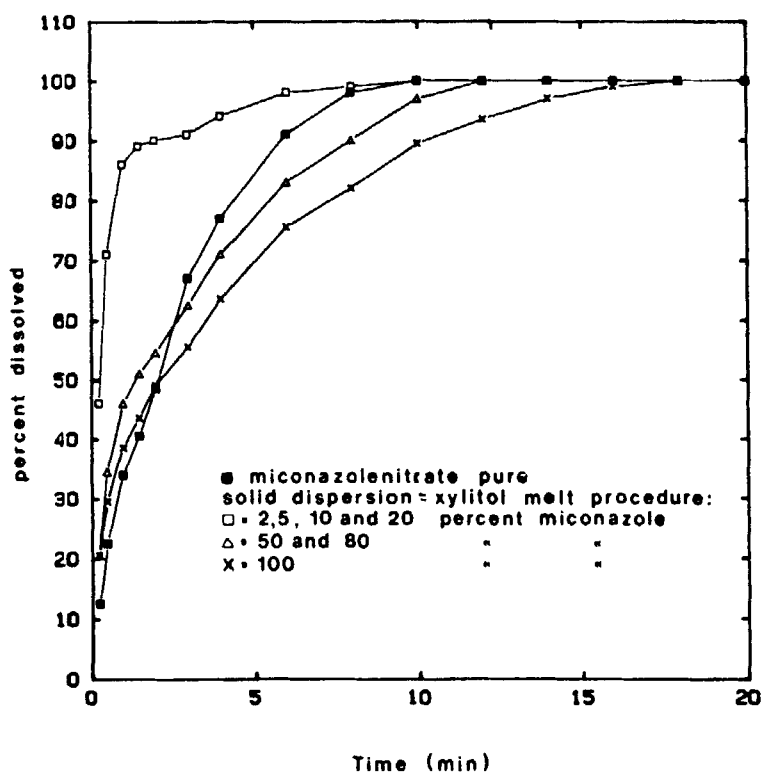


Figure 2. Percent miconazole dissolved in citrate buffer pH 3.0 as a function of time. Stirring paddle metode.

prepared by the melt method, see table 1. The xylitol melt procedure gives a faster dissolution rate than the one obtained by the xylitol melt/solvent procedure for a system containing 20% miconazole. The reason is perhaps that a part of the miconazole fractionated as a liquid during cooling of the last mentioned solid dispersion. The miconazole liquid solidified during storage on the icecooled aluminium plates.

The melt/solvent procedure seems to give a better dispersion of 20% miconazole in PEG 6000 than the melt procedure, according to table 1.

The three 10% solid dispersions, see table 1, had very fast dissolution rates, but the amount of carrier in these systems was so big that it was considered incon-

Table 1

per cent miconazole system	2	5	10	20	50	80	100
Miconazole nitrate	-	-	-	-	-	-	3.80
PEG 6000 melt procedure	3.80	1.87	0.55	1.87	3.80	6.47	6.47
PEG 6000 melt/solvent	-	-	-	1.00	-	-	-
xylitol melt procedure	0.55	0.55	0.55	0.55	4.67	4.67	5.87
xylitol melt/solvent	-	-	-	4.27	-	-	-
PVP 40000 solvent procedure	7.73	1.36	0.20	1.36	1.36	3.48	1.36
miconazole Janssen	-	-	-	-	-	-	2.60

T 75% dissolution times (min.)

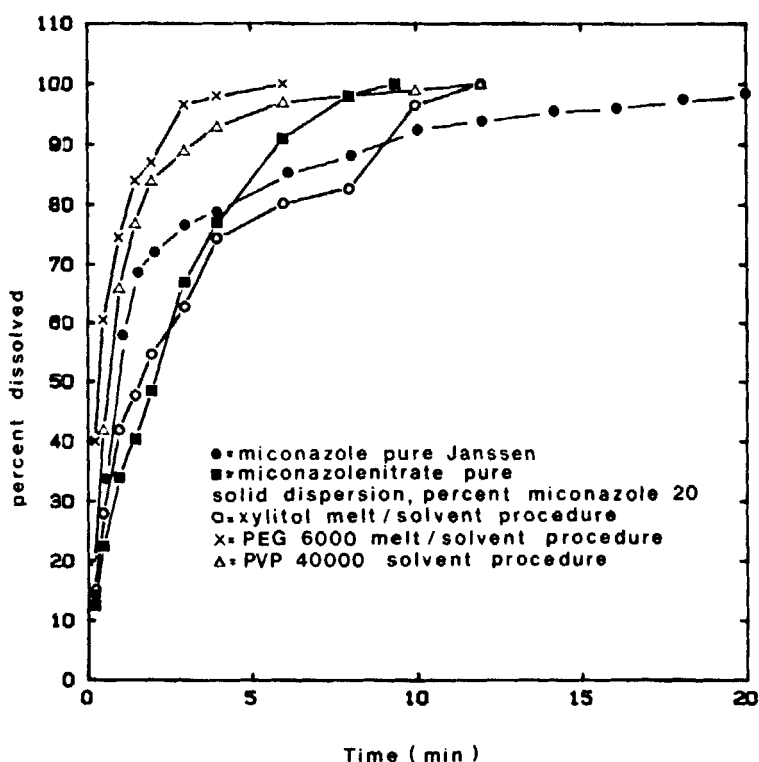


Figure 3. Percent miconazole dissolved in citrate buffer pH 3.0 as a function of time. Stirring paddle metode.

venient to use them in chewing gum. That was why the 20% solid dispersions were selected for application in chewing gum.

All the dissolution curves of the solid dispersions which were tested in chewing gum are presented in fig. 3.

Thermal analysis

The D.S.C. thermograms were run in duplicate and they were highly reproducible.

The only PVP 40000 system which gave a peak for the melting of miconazole was the solid dispersion containing 80% miconazole. The lack of a miconazole melting peak for the systems containing 50% or less of the drug indicates that PVP 40000 prevents crystallisation of

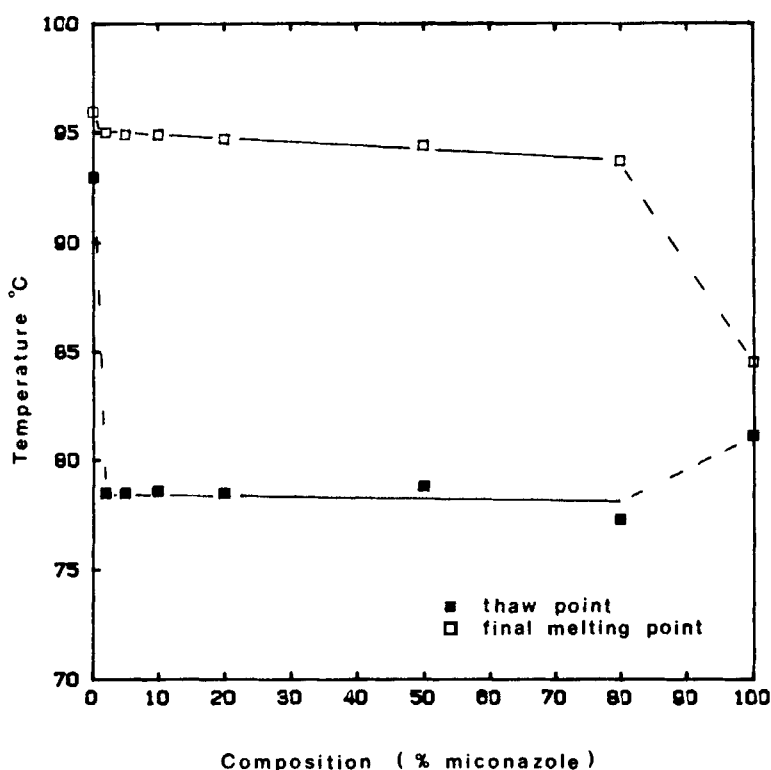


Figure 4. Phase diagram of miconazole:Xylitol

miconazole. Visual inspection of the solid dispersions showed that they were indeed glassy.

The D.S.C. curves of the miconazole xylitol systems were used to construct a phase diagram, presented in fig. 4. The phase diagram shows that the system is eutectic but it does not reveal the eutectic composition. The solid solubility of miconazole in xylitol is less than 2% according to (13).

The solid dispersions containing PEG 6000 and prepared by the melt procedure were also investigated by D.S.C. The system seems to be simple eutectic, but nothing conclusive can be said. X-ray diffraction measurements and additional D.S.C. studies are needed.

Table 2

Amount added (mg)	Amount found (mg)	Per cent recovery of amount added
51.5	52.3	101.6
51.1	51.3	100.4
52.1	52.1	100.0
50.7	51.1	100.8
50.0	49.6	99.2

Recovery and precision data
for determination of miconazole in chewing gum

Mean = 100.4%

RSD% = 0.9%

Determination of miconazole in chewing gum

Under the proposed experimental conditions and at 419 nm a linear relationship was obtained between absorbance and concentration of miconazole in the final test solution over the 11-20 µg/ml range, correlation coefficient, $r = 0.9978$ with the intercept close to zero. The reproducibility of the colorimetric method was tested by analysing six replicate samples of miconazole and placebo chewing gum each containing 17.0 µg/ml miconazole in the final test solution. The relative standard deviation was 1.7%.

Pieces of chewing gum were manufactured according to (14) with known amounts of miconazole. The results are presented in table 2.

The recovery and precision data indicate that the method can be satisfactorily applied to the estimation of miconazole in chewing gum. The content of miconazole in the chewing gum formulations is presented in table 3. Five pieces of each formulation were analysed.

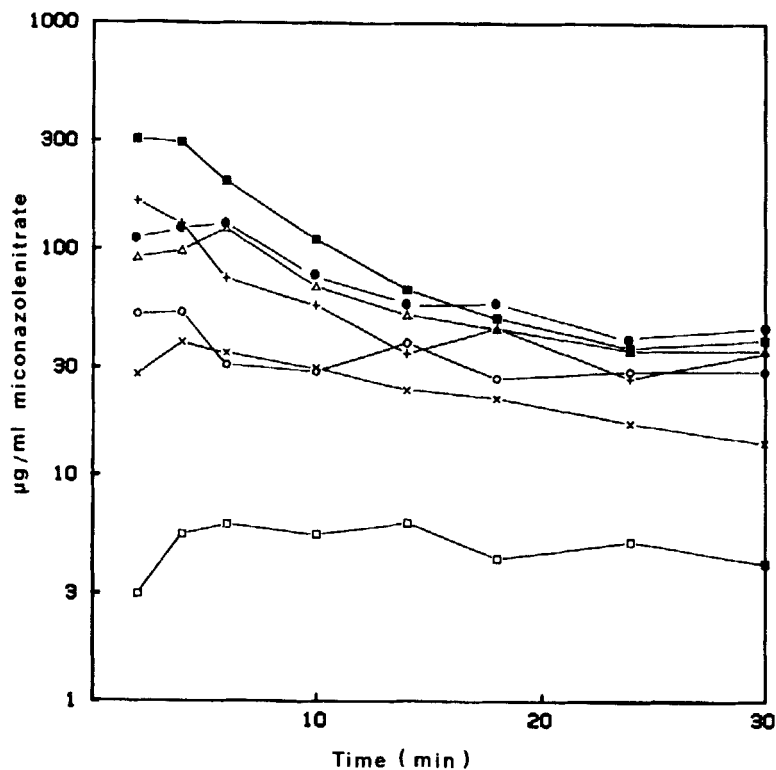
According to table 3 the contents of miconazole in all formulations are similar except for the chewing gum containing PVP 40000. A probable explanation for the large contents in PVP chewing gum is that the water contents of PVP have been reduced during the drying of the solid dispersion.

Table 3

Formulation	Contents of miconazole Mean (mg) $\pm$ RSD%	amount released $\times$ 100% $\pm$ SD dose
miconazolenitrate	50.8 $\pm$ 3.0	1.5 $\pm$ 0.1
20% sd PEG 6000 melt/solv.	51.0 $\pm$ 2.7	30.8 $\pm$ 3.5
20% sd xylitol melt/solv.	49.0 $\pm$ 27.1	10.2 $\pm$ 4.1
20% sd PVP 40000 solvent	62.2 $\pm$ 3.8	14.6 $\pm$ 3.1
20% miconazole, 80% PEG 400 and sorbitol	50.7 $\pm$ 2.9	17.0 $\pm$ 1.5
physical mixture, 20% miconitr., 80% PEG 6000	53.6 $\pm$ 1.3	6.7 $\pm$ 0.6
miconazole Janssen	51.1 $\pm$ 2.9	22.8 $\pm$ 1.8

Cont. of miconazole (free base)
in chewing gum (n = 5).

Release in citrate buffer
pH 3.0 after 30 min. (n = 3)



Keys to fig. 5 and 6.

- ■ miconazole pure Janssen
- = miconazolenitrate pure
- + = PEG 400:Miconazole: 80:20
- × = physical mixture PEG 6000:Miconazolenitrate-80:20
- Solid dispersion
- = PEG 6000 20% miconazole melt/solvent procedure
- = xylitol 20% " " " "
- △ = PVP 40000 20% " " solvent procedure

Figure 5. Release of miconazole - calculated as nitrate salt - from chewing gum in citrate buffer pH 3.0. Semilogarithmic plot.

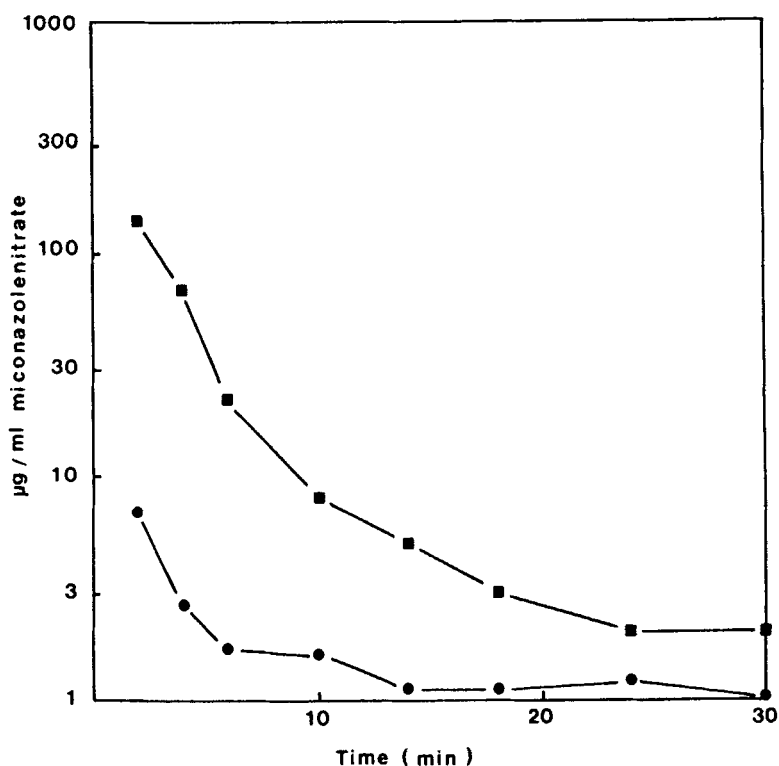


Figure 6. Release of miconazole crystals – calculated as nitrate salt – from chewing gum in phosphate buffer pH 7.9. Semilogarithmic plot.

The relative standard deviations of the contents of miconazole are almost equal and acceptable apart from the formulation containing xylitol solid dispersion. The reason is perhaps the fractionation of miconazole liquid during the cooling of xylitol solid dispersion as mentioned earlier.

In vitro release of miconazole from chewing gum

The release data at pH 3.0 and pH 7.9 are presented in fig. 5 and 6 respectively. The amounts released from chewing gum at pH 3.0 are presented in table 3. The data presented in fig. 5, fig. 6 and table 3 are the average values of 3 mastications.

Table 4

Drugs	Solubility in citrate buffer $\mu\text{g/ml}$		
	pure	5mg/ml PEG 6000	10 mg/ml PEG 6000
Miconazolenitrate	451	-	-
Miconazole	754	775	804
Miconazole Janssen	794	-	-

Solubility of miconazole and miconazolenitrate in citrate buffer pH 3.0.

The chewing gum release results in the citrate buffer can be compared directly with the results of the dissolution rate studies of solid dispersion.

Although miconazole has greater solubility and a higher dissolution rate in citrate buffer than miconazolenitrate, it is surprising that the release of miconazole from chewing gum is so much bigger than the release of miconazolenitrate, see table 3 and 4. A physical mixture of PEG 6000 and miconazolenitrate has some improving effect on the release of the drug.

A comparison of fig. 5 and fig. 3 shows that there is no certain correlation between the results of the two types of experiments. According to fig. 3 it is expected that chewing gum containing a 20% solid dispersion prepared by the solvent procedure and containing PVP 40000 should have a faster release rate than chewing gum containing pure miconazole Janssen, but this turns out not to be so. The explanation is perhaps that PVP 40000 forms a gel which prevents the release of miconazole from the chewing gum.

The only solid dispersion system which seems to be superior to the chewing gum containing pure miconazole Janssen is the PEG 6000 system, see table 3 and fig. 5. A possible explanation for the effect of PEG 6000 on the release of miconazole from chewing gum could be that PEG 6000 increases the solubility of miconazole in the dissolution medium.

According to table 4, it can explain the effect of PEG 6000.

The chewing gum release experiments in phosphate buffer pH 7.9 were performed because it is expected that the solubility of miconazole in the phosphate buffer will be similar to the solubility of the drug in saliva. The solubilities of miconazole and miconazolenitrate in the phosphate were below 0.5 µg/ml which was the detection limit for the HPLC method.

According to fig. 6, the PEG 6000 solid dispersion system drastically increases the release of miconazole particles from chewing gum compared with the release of miconazole particles from chewing gum containing pure miconazole Janssen. It is noted that chewing gum containing PVP 40000 or xylitol solid dispersion of miconazole did not improve the miconazole particle release from chewing gum, data not presented.

The shown effect of PEG 6000 solid dispersion technique is presumed to be due to the fact that the drug is kept in a hydrophilic environment when the solid dispersion and the chewing gum ingredients are mixed. When the pure drug is added to chewing gum in a conventional way, the drug is intimately mixed with the lipophilic ingredients which prevent the release of the drug.

It is presumed that application of the PEG 6000 miconazole solid dispersion in chewing gum can be valuable in vivo.

It is possible that solid dispersion technique can be applied by formulation of other drugs in chewing gum.

Further improvements of miconazole chewing gum are currently under investigation. In vivo release experiments are planned in the near future.

Acknowledgements

The authors thank Fertin Laboratories A/S, Denmark for manufacturing the chewing gum and for financial support.

Janssenpharma A/S, Denmark is acknowledged for supplying miconazole.

The authors thank Ms Ruth Hansen and Ms Vibeke G. Christensen for their excellent laboratory work.

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