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# OPTIMIZATION OF DIRECT COMPRESSION TABLET FORMULATIONS FOR USE IN TROPICAL COUNTRIES.

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## ABSTRACT

With the aid of a combined mixture- and factorial- design, 2 standard tablet formulations were selected suitable for use in tropical countries. The formulations were based on native ingredients or ingredients that are available worldwide. The selection of the standard formulations was based on both the initial tablet properties of the formulations one day after preparation as well as the physical stability after storage under tropical conditions.

The selected formulations were evaluated by adding model drugs (diazepam, 2 mg per tablet or hydrochlorthiazide, 100 mg per tablet) and

measuring tablet properties, not only one day after preparation, but also after storage under tropical conditions. Both selected tablet formulations were suitable standard formulations for tablets prepared by direct compression for use in tropical countries.

## INTRODUCTION

When tablet formulations for use in tropical countries are developed, different aspects should be considered. Attention should be paid to the chemical, the physical and the microbiological stability of the tablets, during storage under extreme conditions. In tropical countries, tablets may be exposed to extreme climatic conditions with high temperatures and high relative humidities, because tablets are frequently dispensed just wrapped in a piece of paper or not packaged at all[1].

Also the price and the availability of the used ingredients should be considered. The use of native excipients is preferred. In a previous study[2], it was shown that native starches, such as rice or tapioca starch, are suitable substitutes for the more commonly used potato or corn starch. The preparation of tablets by direct compression is preferred above the use of the wet granulation technique, because of the lower costs of the first[3].

In the study described in this paper, a mixture design, as described by Huisman et al.[4], and a factorial design were combined to evaluate tablet formulations as a function of mixture- and process-variables. The aim of this study is: to select standard formulations suitable for use in tropical countries and to evaluate the selected formulations by adding model drugs and measuring the properties of the prepared tablets.

In the mixture design the relative amounts of three filler binders are varied. α-Lactose and ß-lactose are selected as filler binders. Both materials are available worldwide and are suitable for use in formulations that are physically stable after storage under tropical conditions[5]. The third selected filler binder is modified rice starch, a granular form of rice starch. In previous studies[2,6], rice starch proved to be an excellent starting material

for the preparation of granulations with good flow properties and sufficient binding capacity after mixing with a lubricant, which can be used as an excipient in tablets prepared by direct compression.

To each formulation a lubricant (magnesium stearate) was added, in order to facilitate ejection out of the die. A disintegrant (sodium starch glycolate) was added to ensure that at each design point the tablets disintegrated and that consequently a model could be calculated for the disintegration time. Oxazepam was added as a model drug, in order to measure the percentage drug dissolved. In this study the influence of two process parameters (compression load and mixing time with magnesium stearate) was investigated. At each mixture design point the process parameters were varied at two levels each, in a $2^2$ factorial design. At each design point the crushing strength, the disintegration time, the friability and the percentage oxazepam dissolved were measured. After storage at 4 different conditions (2 temperatures x 2 relative humidities), for 8 weeks the crushing strength and the disintegration time were measured. The Storage to Initial Ratio of crushing strength (SIR(S)) and of disintegration time (SIR(D)) were used to express the physical stability of the tablets[7]. With aid of multiple linear regression, models were calculated, which express the influence of mixture- and process- variables on each response. Two standard formulations were selected with adequate initial values of crushing strength, disintegration time, percentage drug dissolved and friability and with an acceptable physical stability.

The selected tablet formulations were evaluated by adding two model drugs and subsequently measuring the quality of the tablets, one day after preparation and after storage for 8 weeks, at four different storage conditions.

As model drugs diazepam, a psychotherapeutic, and hydrochlorthiazide, a diuretic, were selected. Both drugs are on the WHO list of Essential Drugs[8]. A preservative (sodium methylhydroxybenzoate) was added to the formulations, in order to ensure adequate microbiological quality after storage under tropical consumers storage conditions[9].

## MATERIALS AND METHODS

### Materials

The filler binders used were α-lactose monohydrate 100 mesh, marketed as Pharmatose[R] 100M (DMV, NL-Veghel), anhydrous ß-lactose, marketed as Pharmatose[R] DCL21 (DMV, NL-Veghel) and modified rice starch, developed as Era-Tab[R] by Erawan Pharmaceutical Research and Laboratory Co. Ltd. (Bangkok, Thailand) and marketed as Primotab[R] ET by Avebe (NL-Veendam). The used disintegrant was sodium starch glycolate, marketed as Primojel[R] (Avebe, NL-Veendam). The tablets were lubricated with magnesium stearate Pharm. Eur. grade (OPG, NL-Utrecht), which was sieved through a 210 μm sieve prior to use. The used drugs were oxazepam Pharm. Eur. grade (Pharmachemie, NL-Haarlem), diazepam BP grade (HPS, NL-Alphen a/d Rijn) and hydrochlorthiazide Pharm. Ned. grade (Bufa-chemie b.v., NL-Castricum). Sodium methylhydroxybenzoate (NaMOB) BP grade (OPG, NL-Utrecht) was added as a preservative. Prior to use, all tabletting materials were stored at 20° ± 1°C and 45% ± 5% relative humidity (RH), for at least one week. The other used materials were of analytical quality.

### Tablet preparation

All ingredients except magnesium stearate were mixed for 15 minutes in a Turbula mixer (model 2P, W.A. Bachofen, CH-Basle) at a rotation speed of 90 rpm. Magnesium stearate was added and the mixing was continued for 2 or 10 minutes. Tablets were prepared on a single punch tabletting machine (HOKO, NL-Rijswijk). The oxazepam tablets (10 mg per tablet, tablet weight 250 mg) and the diazepam tablets (2 mg per tablet, tablet weight 200 mg) were prepared using flat 9 mm punches. The hydrochlorthiazide tablets (100 mg per tablet, tablet weight 500 mg) were prepared using flat 13 mm punches.

Storage of tablets

In order to estimate the physical stability of the tablets, from each batch tablets were stored in open containers at 4 different storage conditions: 2 temperatures x 2 relative humidities. The chosen storage conditions were derived from the climatic zones into which the world is divided for stability testing[5,10]. The tablets were stored in desiccators over saturated salt solutions in a climate chamber (Heraus Vöttsch, D-Balingen). The storage temperatures were: 20° ± 1°C and 31° ± 1°C. The used saturated salt solutions were potassium carbonate (44% ± 5% relative humidity) and sodium chloride solution (75% ± 5% relative humidity). After 8 weeks of storage the crushing strength and the disintegration time of the tablets were measured as described below.

In order to estimate the microbiological stability of the tablets, from each batch tablets were stored in Petri dishes at extreme tropical conditions. The tablets were stored in a climate chamber (31° ± 1°C and 95% ± 5% relative humidity) or in a desiccator over saturated sodium chloride solution in a climate chamber (31° ± 1°C, 75% ± 5% relative humidity; Heraus Vöttsch, D-Balingen). After 4 weeks the microbiological quality was estimated as described below.

Selection of tablet formulations; experimental design

A combination of a mixture design, as described by Huisman et al. (1984), and a factorial design was used to select standard formulations suitable for use in tropical countries. In the mixture design the relative amounts of the three used filler binders (α-lactose, ß-lactose and modified rice starch) were varied. The concentration of the other ingredients (oxazepam, sodium starch glycolate and magnesium stearate) were kept at a constant level. Table 1 shows the general composition of the oxazepam tablets. All possible mixture compositions can be represented in a triangle. The vertices of the triangle were not pure filler binder components, but were so called pseudo-components, that include fixed amounts of drug

TABLE 1
Tablet composition of oxazepam tablets, in the mixture design.

| | | |
|---|---|---|
| Oxazepam | 10 mg | |
| Sodium starch glycolate | 10 mg | |
| Magnesium stearate | 1.25 mg | |
| Modified rice starch | $x_1$ mg | |
| Anhydrous ß-lactose | $x_2$ mg | } 228.75 mg |
| α-Lactose monohydrate 100 mesh | $x_3$ mg | |

(oxazepam), disintegrant (sodium starch glycolate) and lubricant (magnesium stearate). In Figure 1 the mixture design points are shown.

At each mixture design point two process parameters, at two levels each, were used as variables in a $2^2$ factorial design. The process parameters were: the mixing time with magnesium stearate (2 or 10 minutes) and the compression load level (10 or 20 kN).

At each design point several tablet parameters were measured and used as response. With the aid of multiple linear regression, using SAS$^R$ software (SAS Institute Inc., USA-Cary), models were calculated to obain the best prediction for each criterion, as described by Cornell[11] (1981). One day after preparation the crushing strength, the disintegration time, the friability and the percentage oxazepam dissolved were measured as described below.

After storage at 4 different conditions (2 temperatures x 2 relative humidities), for 8 weeks the crushing strength and the disintegration time were measured. The used storage temperatures were 20°C and 31°C and the used storage relative humidities were 44% and 75%.

Physical tablet properties

The initial tablet properties were measured one day after preparation. From each batch the crushing strength of 10 tablets was measured using a

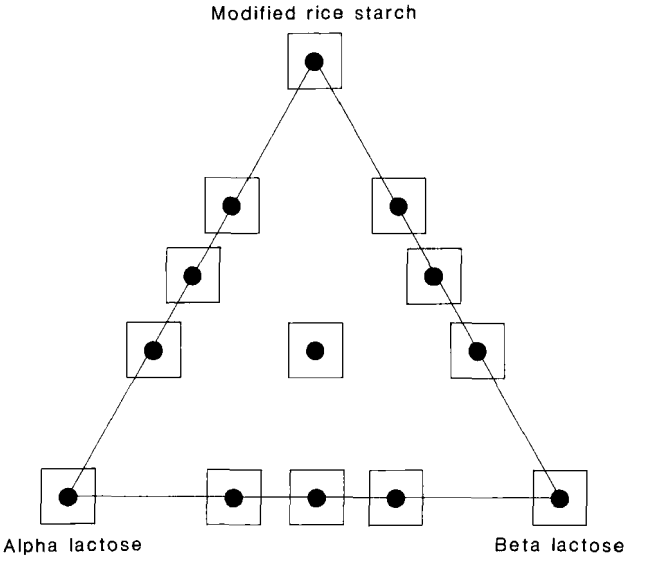


FIGURE 1.
Design points of the combined mixture and factorial design for the composition of oxazepam tablets.

Schleuniger instrument (model 4M, Dr.K. Schleuniger, CH-Zurich).

The disintegration times of 6 tablets from each batch were measured using the Pharm. Eur. apparatus, with water (37° ± 1°C) as a test fluid. The tests were performed without disks. The friability was tested in duplicate in a Roche friabiliator. Ten tablets were weighed and after 5 minutes of rotation and the removal of dust, the percentage of weight loss was calculated. From each batch 20 individual tablets were weighed and the variation coefficient or Relative Standard Deviation (RSD) of the tablet weight was calculated.

Microbiological quality

One day after preparation and after 4 weeks of storage, the total viable count of each batch of tablets was estimated in fivefold. The tablets were suspended in 9.5 ml of universal neutralization liquid (UNL), as

described by Bos et al[9]. Suitable serial dilutions in UNL were made. 1 ml samples of each dilution were plated in duplicate in Trypton Soya Agar (Oxoid, GB-Basingstoke). Plates were incubated at 30°C for 40 hours and the colonies were counted. The results were expressed as colony forming units/tablet (cfu).



Analytical procedures

The dissolution rate measurements of oxazepam from the tablets were performed using the USP XXI paddle method, at 50 rpm. As dissolution medium 1000 ml of deaerated water (37° ± 1°C) was used. The concentration of oxazepam was measured spectrophotometrically at 231 nm (Ultrospec 4052 TDS, L.K.B., NL-Zoetermeer). The measurement was performed automatically, monitored by an Apple computer. Samples were taken every two minutes. Sampling was continued for 20 minutes. From each batch the dissolution rate of 6 tablets was measured.

An HPLC method was used to measure the content uniformity of dosage units and the percentage of diazepam dissolved after 30 minutes. The HPLC system consisted of a Waters, Model 510 Liquid Chromatograph (Millipore, USA-Milford). A Promis autosampler (Spark, NL-Emmen) was used for the injection of the samples, with an injection volume of 100 µl. The analytical column used was a Novapak $C_{18}$ column (150 x 3.9 mm I.D.; Waters, Millipore, USA-Milford). A Reverse Phase guard column (75 x 2.1 mm I.D.; Chromopack, NL-Middelburg) was used before the analytical column. The mobile phase used was acetonitrile : water : acetic acid (1000 : 1000 : 15). The column was maintained at room temperature and the mobile phase flow rate was 1.0 ml/min. Column effluents were monitored at 240nm with a Waters 484 Tunable absorbance detector (Millipore, USA-Milford).

For the content uniformity of dosage units, 10 tablets from each batch were powdered separately and transferred to a 100 ml volumetric flask and diluted with ethanol to volume. After mixing and filtration (0.45 µm), 1.0 ml of this solution was added to 1.0 ml internal standard solution

(30μg/ml prazepam in water) and 8.0 ml of mobile phase. After mixing this solution was used as sample for the HPLC analysis.

A calibration graph was prepared by diluting a solution of a known amount of diazepam in ethanol, with mobile phase and adding a standard amount of prazepam. The peak height ratio of diazepam : prazepam was plotted against the diazepam concentration. The concentration of diazepam in the test samples was calculated using the regression parameters obtained from the calibration graph.

For the percentage diazepam dissolved, the USP XXI paddle method was used, at 100 rpm. The used dissolution medium was 900 ml 0.1 N hydrochloric acid. Six tablets of each batch were tested. After 30 minutes 4.5 ml portions of the filtered dissolution medium were added to 0.5 ml prazepam solution (30μg/ml in water). After mixing this solution was used as a sample for the HPLC analysis. A calibration graph was prepared by diluting a solution of a known amount of diazepam in ethanol, with 0.1 N hydrochloric acid, instead of mobile phase, and adding a standard amount of prazepam.

An HPLC method was used to measure the content uniformity of the tablets and the percentage hydrochlorthiazide dissolved. The HPLC system consisted of a Waters, Model 510 Liquid Chromatograph (Millipore, USA-Milford). A Promis autosampler (Spark, NL-Emmen) was used for the injection of the samples, with an injection volume of 100 μl. The analytical column used was a Novapak $C_{18}$ column (150 x 3.9 mm I.D.; Waters, Millipore, USA-Milford). A Reverse Phase guard column (75 x 2.1 mm I.D.; Chromopack, NL-Middelburg) was used before the analytical column. The mobile phase used was acetonitrile : water : acetic acid (300 : 700 : 7.5). The column was maintained at room temperature and the mobile phase flow rate was 1.0 ml/min. Column effluents were monitored at 270nm with a Waters 484 Tunable absorbance detector (Millipore, USA-Milford).

For the content uniformity of dosage units, 10 tablets from each batch were powdered separately and transferred to a 100 ml volumetric

flask and diluted with ethanol to volume. After mixing and filtration (0.45 μm) and dilution in water (1 : 100), 1.0 ml of the diluted solution was added to 1.0 ml internal standard solution (10μg/ml nitrazepam in water) and 8.0 ml of mobile phase. After mixing this solution was used as sample for the HPLC analysis.

A calibration graph was prepared by diluting a solution of a known amount of hydrochlorthiazide in ethanol, with mobile phase and adding a standard amount of nitrazepam. The peak height ratio of hydrochlorthiazide : nitrazepam was plotted against the hydrochlothiazide concentration. The concentration of hydrochlorthiazide in the test samples was calculated using the regression parameters obtained from the calibration graph.

For the measurement of the percentage hydrochlorthiazide dissolved, the USP XXI paddle method was used at 100 rpm. The used dissolution medium was 900 ml 0.1 N hydrochloric acid. From each batch the percentage hydrochlorthiazide dissolved of 6 tablets was measured. After 30 minutes filtered portions of the dissolution medium were diluted with mobile phase. After addition of a standard amount of nitrazepam and mixing, this solution was used as a sample for the HPLC analysis.

## RESULTS AND DISCUSSION

### Selection of standard tablet formulations

After preparation of the 52 (13 formulations x 2 mixing times with magnesium stearate x 2 compression load levels) batches of oxazepam tablets, tablet properties were measured. One day after preparation the crushing strength, disintegration time, friability and the percentage oxazepam dissolved after 10 minutes were measured. Of each batch tablets were stored for 8 weeks at 4 storage conditions (20°C, 44% relative humidity; 20°C, 75% relative humidity; 31°C, 44% relative humidity and 31°C, 75% relative humidity). After storage the crushing strength and the disintegration time were measured. With aid of multiple linear regression

models were calculated for each response, which expresses the influence of tablet composition, mixing time with magnesium stearate and compression load level on each tablet parameter. For the crushing strength after storage, 4 models were calculated; one for each storage condition. The disintegration time data after storage were treated in the same manner.

The calculated models were used to scan the design space at 10 % intervals and to calculate the tablet properties as a function of tablet composition and process variables. Formulations were selected by setting levels for each parameter above or below which the tablet parameters are sufficient. The levels set for the tablet parameters were respectively: > 60 N for the initial crushing strength, < 240 seconds for the initial disintegration time, < 1% for the friability and > 50% oxazepam dissolved after 10 minutes.

The Storage to Initial Ratio's (SIR) were calculated for the crushing strength (SIR(S)) and the disintegration time (SIR(D)):

$$SIR(Y)_{T,R} = (Y_s/Y_0) \times 100\ \% \qquad (1)$$

in which $Y_s$ and $Y_0$ are: the calculated initial crushing strength or disintegration time, respectively the calculated crushing strength or disintegration time after storage for eight weeks at temperature T and relative humidity R.

The levels for physical stability were set at: > 90% for the $SIR(S)_{31,75}$ and < 110% for the $SIR(D)_{31,75}$. The Storage to Initial Ratio at the most extreme storage condition (31°C, 75% relative humidity) is used as a selection criterion for the selection of physically tablet formulations, because at these conditions the largest influence is expected on the physical stability.

At 32 points all the predicted values for the different criteria met the set requirements for initial tablet properties and physical stability. These 32 points included only 6 different formulations at different levels of compression load and mixing times with magnesium stearate. Figure 2 shows the different mixture compositions that met the set requirements.

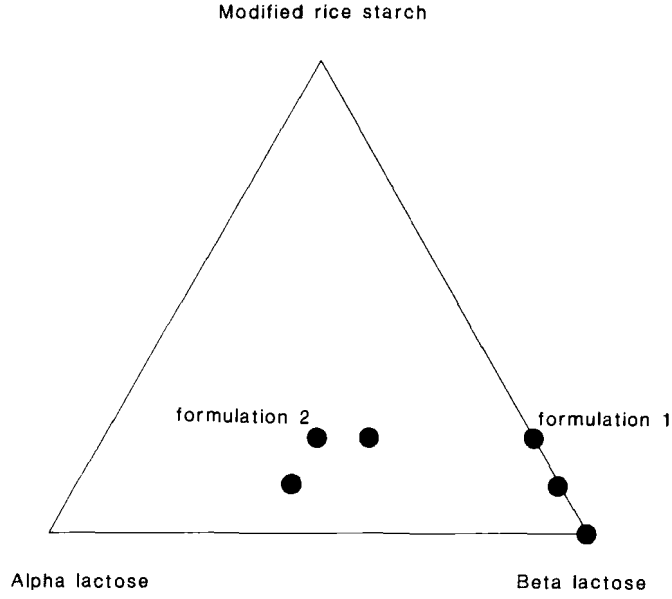


FIGURE 2.
Formulations that meet the set requirements.

From these 6 mixtures, 2 formulations were selected as standard formulations suitable for use in tropical countries. A binary mixture was chosen, consisting of: ß-lactose : modified rice starch (8:2, formulation 1) and a ternary mixture was chosen consisting of the three filler binders: α-lactose : ß-lactose : modified rice starch (4:4:2, formulation 2). The composition of the 2 standard formulations is shown in Table 2. In all the cases the shortest mixing time with lubricant was the most favorable, resulting in tablets with both a higher crushing strength, a higher percentage oxazepam dissolved and with a shorter disintegration time and a lower friability. Tablets with good properties were obtained with compression load levels of 11 kN and larger than 19 kN for formulation 1, respectively formualtion 2.

TABLE 2
Composition of standard tablet formulations for use under tropical conditions.

| Component | Formulation 1 | Formulation 2 |
|---|---|---|
| Sodium starch glycolate | 4.0 % | 4.0 % |
| Magnesium stearate | 1.0 % | 1.0 % |
| Sodium methylhydroxybenzoate | 1.0 % | 1.0 % |
| Modified rice starch | 18.8 % | 18.8 % |
| Anhydrous ß-lactose | 75.2 % | 37.6 % |
| α-Lactose monohydrate 100 mesh | | 37.6 % |

For the evaluation of these standard formulations, model drugs were added, as well as a preservative. In this study sodium methylhydroxybenzoate was used as a preservative, in order to improve the microbiological quality after storage under tropical conditions. Tablet parameters were measured one day after preparation and after storage. The chosen model drugs were diazepam and hydrochlorthiazide. Although hydrochlorthiazide tablets commonly contain 50 mg drug, in this study 100 mg hydrochlorthiazide tablets were prepared with a tablet weight of 500 mg, in order to be able to evaluate the selected standard formulations with respect to the possibility of preparing tablets with high dosage of drug. In order to evaluate the standard formulations with a low dosage drug, 2 mg diazepam tablets with a tablet weight of 200 mg were prepared.

Evaluation of diazepam tablets

Diazepam was added to standard formulation 1 (D1) and to standard formulation 2 (D2). The composition of these two tablet formulations, as well as the results of the measurements of the tablet parameters of the diazepam tablets are shown in Table 3. Because sodium methylhydroxybenzoate, which has a UV-absorbance peak near the

TABLE 3

Diazepam tablets (2 mg)

| Tablet composition | D1 | D2 |
|---|---|---|
| Diazepam | 1.0 % | 1.0 % |
| Modified rice starch | 18.6 % | 18.6 % |
| α-Lactose monohydrate 100 mesh | | 37.2 % |
| Anhydrous ß-lactose | 74.4 % | 37.2 % |
| Sodium starch glycolate | 4.0 % | 4.0 % |
| Sodium methylhydroxybenzoate | 1.0 % | 1.0 % |
| Magnesium stearate | 1.0 % | 1.0 % |
| **Tablet evaluation** | **D1** | **D2** |
| Tablet weight (ϕ 9 mm) | 200 mg | 200 mg |
| Compression load | 15 kN | 23 kN |
| RSD[a] of tablet weight | 1.06 % | 0.83 % |
| Friability | 1.1 ± 0.1 % | 1.9 ± 0.5 % |
| Crushing strength | 51 ± 4 N | 35 ± 5 N |
| Disintegration time | 120 ± 26 s | 63 ± 5 s |
| Percentage dissolved after 30 min. | 89 ± 2 % | 92 ± 1 % |
| Content uniformity | | |
| lowest content | 1.88 mg | 1.94 mg |
| highest content | 2.04 mg | 2.05 mg |
| average content | 1.97 mg | 1.98 mg |
| RSD[a] | 2.8 % | 2.2 % |
| Microbiological quality | | |
| one day after preparation | $1.3 \times 10^1$ cfu/t[b] | $1.1 \times 10^1$ cfu/t[b] |
| after storage 31°C, 75% RH | $< 10^1$ cfu/t | $< 10^1$ cfu/t |
| after storage 31°C, 95% RH | $2.5 \times 10^1$ cfu/t | $2.8 \times 10^1$ cfu/t |
| Physical stability | | |
| SIR(S) 20°C, 44% RH[c] | 100 % | 87 % |
| SIR(S) 20°C, 75% RH | 67 % | 57 % |
| SIR(S) 31°C, 44% RH | 107 % | 103 % |
| SIR(S) 31°C, 75% RH | 79 % | 75 % |
| SIR(D) 20°C, 44% RH[d] | 65 % | 104 % |
| SIR(D) 20°C, 75% RH | 38 % | 80 % |
| SIR(D) 31°C, 44% RH | 66 % | 108 % |
| SIR(D) 31°C, 75% RH | 44 % | 60 % |

[a] RSD = Relative Standard Deviation
[b] cfu/t = colony forming units/tablet
[c] SIR(S) = Storage to Initial Ratio for crushing strength
[d] SIR(S) = Storage to Initial Ratio for disintegration time

TABLE 4.
General requirements for tablet parameters.

| | |
|---|---|
| Crushing strength | |
| tablet diameter 13 mm | > 45 N |
| tablet diameter 9 mm | > 35 N |
| Disintegration time | < 15 min |
| Friability | < 3 % |
| Content Uniformity[a] | |
| lowest content | > 85 % |
| higest content | < 115 % |
| Relative Standard Deviation | < 6 % |
| Relative Standard Deviation of tablet weight[a] | < 6 % |
| Microbiological quality[b] | < $10^4$ cfu/t[c] |

[a] USP XXI
[b] European Pharmacopeia Ed. 1
[c] colony forming units per tablet



absorbance peak of diazepam, was added to the formulations, the USP XXI assay for diazepam had to be adjusted. An HPLC method was developed with which it is possible to measure diazepam concentrations, without interference of sodium methylhydroxybenzoate. This method was used to measure the content uniformity of the tablets and the percentage diazepam dissolved.

In order to prepare tablets with sufficient crushing strength, the compression load level had to be adjusted to higher levels than predicted with the mixture design. Formulation 1 was compressed at a compression load level of 15 kN and formulation 2 at a level of 23 kN, which resulted in batches of tablets with sufficient values for the initial crushing strength and friability. In Table 4 generally applied requirements for physical and microbiological tablet properties are presented. For both batches of diazepam tablets, the variation coefficient or Relative Standard Deviation (RSD) for tablet weight is less than 6.0%, which is the requirement of the USP XXI.

The tablets of both formulations disintegrate within 2 minutes. After 30 minutes, 89% and 92% of the diazepam had dissolved for formulation 1, respectively formulation 2. The USP XXI requirement is, that at least 85% of the dosage should be dissolved in 30 minutes.

The content uniformity of dosage units requirements of USP XXI are met for both batches of diazepam tablets.

The requirements for microbiological quality of the European Pharmacopeia Ed. 1, for preparations for oral use are: total viable count $\leq$ 1,000 - 10,000 colony forming units per gram and total viable count for fungi $\leq$ 100 colony forming units per gram. Both batches of diazepam tablets meet these requirements, even after storage for 4 weeks under extreme tropical conditions (31°C, 75% relative humidity and 31°C, 95% relative humidity).

The diazepam tablets are physically stable; after storage for 8 weeks under either tropical condition (31°C, 44% relative humidity or 31°C, 75% relative humidity) the Storage to Initial Ratio for crushing strength (SIR(S)) is > 79% for formulation 1 and > 75% for formulation 2. The Storage to Initial Ratio for disintegration time (SIR(D)) is < 108% for both formulations after storage at either storage condition.

Evaluation of hydrochlorthiazide tablets

Hydrochlorthiazide was added to standard formulation 1 (H1) and to standard formulation 2 (H2). The composition of these two tablet formulations, as well as the results of the measurements of the tablet parameters of the hydrochlorthiazide tablets, are shown in Table 5.

Because sodium methylhydroxybenzoate has a UV-absorbance peak near the absorbance peak of hydrochlorthiazide, the USP XXI assay for hydrochlorthiazide also had to be adjusted. An HPLC method was developed with which it is possible to measure hydrochlorthiazide, without interference of sodium methylhydroxybenzoate. This method was used to measure the content uniformity of the tablets and the percentage hydrochlorthiazide dissolved.

TABLE 5

Hydrochlorthiazide tablets (100 mg)

| Tablet composition | H1 | H2 |
|---|---|---|
| Hydrochlorthiazide | 20.0 % | 20.0 % |
| Modified rice starch | 14.8 % | 14.8 % |
| α-Lactose monohydrate 100 mesh | | 29.6 % |
| Anhydrous ß-lactose | 59.2 % | 29.6 % |
| Sodium starch glycolate | 4.0 % | 4.0 % |
| Sodium methylhydroxybenzoate | 1.0 % | 1.0 % |
| Magnesium stearate | 1.0 % | 1.0 % |
| **Tablet evaluation** | **H1** | **H2** |
| Tablet weight (ϕ 13 mm) | 500 mg | 500 mg |
| Compression load | 20 kN | 25 kN |
| RSD[a] of tablet weight | 0.58 % | 0.56 % |
| Friability | 1.7 ± 0.1 % | 2.0 ± 0.1 % |
| Crushing strength | 47 ± 3 N | 38 ± 2 N |
| Disintegration time | 121 ± 4 s | 102 ± 4 s |
| Percentage dissolved after 30 min. | 86 ± 2 % | 86 ± 5 % |
| Content uniformity | | |
| lowest content | 98.4 mg | 92.9 mg |
| highest content | 109.5 mg | 101.2 mg |
| average content | 103.9 mg | 99.0 mg |
| RSD[a] | 3.7 % | 2.9 % |
| Microbiological quality | | |
| one day after preparation | $9.1 \times 10^1$ cfu/t[b] | $7.2 \times 10^1$ cfu/t[b] |
| after storage 31°C, 75% RH | $4.2 \times 10^1$ cfu/t | $3.0 \times 10^1$ cfu/t |
| after storage 31°C, 95% RH | $5.0 \times 10^1$ cfu/t | $1.5 \times 10^1$ cfu/t |
| Physical stability | | |
| SIR(S) 20°C, 44% RH[c] | 96 % | 99 % |
| SIR(S) 20°C, 75% RH | 70 % | 67 % |
| SIR(S) 31°C, 44% RH | 104 % | 109 % |
| SIR(S) 31°C, 75% RH | 76 % | 73 % |
| SIR(D) 20°C, 44% RH[d] | 70 % | 73 % |
| SIR(D) 20°C, 75% RH | 98 % | 95 % |
| SIR(D) 31°C, 44% RH | 60 % | 58 % |
| SIR(D) 31°C, 75% RH | 104 % | 82 % |

[a] RSD = Relative Standard Deviation
[b] cfu/t = colony forming units/tablet
[c] SIR(S) = Storage to Initial Ratio for crushing strength
[d] SIR(S) = Storage to Initial Ratio for disintegration time

The compression load level had to be adjusted to 20 and 25 kN for formulation 1, respectively formulation 2, in order to obtain tablets with sufficient values for initial crushing strength and friability. For both batches of hydrochlorthiazide tablets, the variation coefficient or Relative Standard Deviation (RSD) for tablet weight is less than 6.0%, which is the requirement of the USP XXI.

The tablets of both hydrochlorthiazide formulation 1 and formulation 2 disintegrate within 2 minutes. After 30 minutes 86% of the hydrochlorthiazide had dissolved for both formulation 1 and formulation 2. The USP XXI requirement is, that at least 60% of the dosage should be dissolved in 30 minutes.

The content uniformity of dosage units requirements of USP XXI are met for both batches of hydrochlorthiazide tablets.

The requirements for microbiological quality of the European Pharmacopeia Ed. 1, for preparations for oral use are: total viable count $\leq$ 1,000 - 10,000 colony forming units per gram and total viable count for fungi $\leq$ 100 colony forming units per gram. Both batches of hydrochlorthiazide tablets meet these requirements, even after storage for 4 weeks under extreme tropical storage conditions (31°C, 75% relative humidity or 31°C, 95% relative humidity).

The hydrochlorthiazide tablets are physically stable; after storage for 8 weeks under either tropical condition (31°C, 44% relative humidity or 31°C, 75% relative humidity) the Storage to Initial Ratio for crushing strength (SIR(S)) is > 79% for formulation 1 and > 75% for formulation 2. The Storage to Initial Ratio for disintegration time (SIR(D)) is < 110% for both formulations at either storage condition.

## CONCLUSIONS

The use of a mixture design is a suitable method to select a standard direct compression formulation for the preparation of tablets. The addition of either another low dosage drug, such as diazepam or a high dosage

drug, such as hydrochlorthiazide, to either of the selected standard formulations resulted in tablets with suitable properties. However, in order to obtain these results the compression load level had to be adjusted, for both drugs for both formulations. With both drugs the highest compression load level was needed for formulation 2. In this formulation part of the ß-lactose, of formulation 1 is replaced by α-lactose, which has less binding properties than ß-lactose[12]. Therefore formulation 1 (based on anhydrous ß-lactose and modified rice starch), is the best choice for tablets of drugs with poor binding properties.

By using the Storage to Initial Ratio for crushing strength or disintegration time as a selection criterion, standard tablet formulations can be obtained that are suitable for use under tropical storage conditions. For both drugs with both formulations, the crushing strength after storage at 31°C and 75% relative humidity is still acceptable, although the Storage to Initial Ratio is lower than expected from the selection of the standard formulations.

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