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# OPTIMIZATION OF TABLET FORMULATIONS BASED ON STARCH/LACTOSE GRANULATIONS FOR USE IN TROPICAL COUNTRIES.

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## ABSTRACT

Several granulations consisting of α-lactose monohydrate 200 mesh and native starch (corn, potato, rice or tapioca) were prepared. The influence of starch concentration, storage temperature and relative humidity on the physical properties of the tablets prepared from these granulations was estimated. Two granulations, which resulted in tablets with adequate initial values of crushing strength and disintegration time and with an acceptable physical stability were selected as standard granulations. The selected standard granulations were evaluated by incorporating a drug (diazepam, 2 mg or mebendazole, 100 mg). The tablet properties were determined one day after preparation. The crushing strength, the disintegration time and the microbiological quality were also measured after storage under tropical conditions. Both selected

formulations proved to be adequate for the preparation of tablets by wet granulation, suitable for use in tropical countries.

## INTRODUCTION

When tablet formulations for use in tropical countries are developed, next to the physical, microbiological and chemical stability also special attention should be given to the cost and the availability of the used excipients. The use of native and/or cheap, worldwide available excipients is preferred. In a previous study[1] native starches proved to be suitable excipients for use in tablet formulations.

For some formulations it may be necessary to prepare tablets by means of a wet granulation technique, because, for example:

- to render the material free flowing;
- to densify the material;
- to improve the compression characteristics of the drug; or
- to reduce dust problems[2].

This publication is devoted to the selection of standard lactose/starch granulations for use in tropical countries and subsequent evaluation of these granulations on their tabletting properties, by incorporating model drugs into these granulations.

Two drugs from the WHO Essential Drugs List[3] were selected as model drugs for the evaluation of the selected standard granulation formulations; the anthelmintic mebendazole and the psychotherapeutic diazepam. Mebendazole is a high dosage drug, which can not be used in direct compression formulations, due to its poor flow and compression characteristics. Diazepam is selected as a model low dosage drug. In several publications concerning the priority of drugs in a system of standardized drug supply it was shown that both mebendazole and diazepam are drugs of high priority[4,5,6].

In a previous study[7] it has been proven that the addition of a preservative, such as sodium methylhydroxybenzoate, can prolong the microbiological shelf life of tablets, prepared by wet granulation. The addition of a preservative prevents the spoilage of tablets due to the growth of natural contaminants, during storage under tropical conditions, with high temperatures and relative humidity. In this study sodium methylhydroxybenzoate was added to the mebendazole and the diazepam tablets and the microbiological quality of the tablets was estimated after storage under tropical conditions.

## MATERIALS AND METHODS

### Materials

α-Lactose monohydrate 200 mesh, marketed as Pharmatose$^{R}$ (D.M.V., NL-Veghel) was used as tablet filler binder. The used tablet disintegrants were corn starch Pharm. Eur. grade, rice starch Pharm. Eur. grade (both from Brocacef, NL Maarssen), tapioca starch (product of Thailand) and potato starch Pharm. Eur. grade (Avebe, NL-Veendam). Pregelatinized starch, marketed as Prejel$^{R}$ (Avebe, NL-Veendam) was used as a binder. Sodium methylhydroxybenzoate (NaMOB) BP grade (OPG, NL-Utrecht) was added as a preservative. The selected model drugs were mebendazole USP grade (100 mg/tablet, Janssen Pharmaceutica, B-Beerse) and diazepam BP grade (2 mg/tablet, HPS, NL-Alphen a/d Rijn). Magnesium stearate (Centrachemie, NL-Etten-Leur) was used as lubricant and sieved through a 150 μm sieve, prior to use. Before 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.

### Granule preparation

The materials (lactose, disintegrant, pregelatinized starch (1 % w/w) and, if required, drug and sodium methylhydroxybenzoate (1 % w/w) were

mixed in a planetary mixer (model KM 250, Kenwood Ltd., GB-Hants) for 5 minutes. Water was added dropwise and mixing was continued for another 10 minutes. The wet mass was forced through a Frewitt 1000 μm screen (Erweka GmbH, D-Main). After drying at 40°C in a ventilated traydrier, the granules were passed again through a Frewitt 1000 μm screen.

Tablet preparation

Prior to tabletting the granulations were mixed with 0.5% w/w magnesium stearate as a lubricant, for 2 minutes in a Turbula mixer (model 2P, W.A. Bachofen, CH-Basle) at a rotation speed of 90 rpm. Tablets were prepared on a single punch tabletting machine (HOKO, NL-Rijswijk). The placebo lactose/starch tablets (250 mg) and the diazepam tablets (200 mg) were prepared using flat 9 mm punches. The mebendazole tablets (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[8,9]. 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 two 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 granule formulations; experimental design and calculations

Granulations were prepared, containing α-lactose monohydrate as a filler binder, starch (corn, potato, rice or tapioca) as a disintegrant and pregelatinized starch (1% w/w) as a binder. The starch concentration was 10 or 20 % w/w. For each combination of lactose and starch, a $2^3$ factorial design was used to study the effect of 3 adjustable variables (disintegrant concentration, storage temperature and storage relative humidity, at two levels each), on the physical stability of the tablets, as described by Bos et al.[9]. The general form of the model which describes the effect of the variables is given by the following formula:

$$SIR(Y) = B_0 + B_1.c_n + B_2.t_n + B_3.r_n + B_4.c_n.t_n + B_5.c_n.r_n + B_6.t_n.r_n + B_7.c_n.t_n.r_n, \quad (1)$$

in which $c_n$, $t_n$ and $r_n$ are respectively the normalized disintegrant concentration, the normalized storage temperature and the normalized relative humidity. The adjustable variables are normalized as by Bos et al.[10]. With aid of multiple linear regression (Statgraphics$^R$, Statistical Graphics Corporation, USA) the values of the model coefficients ($B_i$) were calculated. The response SIR(Y) is either the Storage to Initial Ratio of the crushing strength (SIR(S)) or of the disintegration time (SIR(D)) after 8 weeks of storage. The Storage to Initial Ratio (SIR(Y)) was calculated as:

$$SIR(Y) = (Y_8 / Y_0) \times 100\ \%, \quad (2)$$

in which $Y_8$ is the response after 8 weeks of storage and $Y_0$ the average of the response measurements one day after preparation[10].

Physical tablet properties

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

tablets was measured using a Schleuniger instrument (model 2E, Dr K. Schleuniger, CH-Zurich). The disintegration time of 6 tablets from each batch was measured using a 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.[7]. 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/t).

Analytical procedures

The content uniformity of dosage units of the mebendazole tablets was measured according to the method described in the USP XXI.

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.

## RESULTS AND DISCUSSION

### Selection of standard granulations

The batches of placebo lactose/starch tablets were compressed at compression load levels of 30 kN. The results of the measurements of initial crushing strength and disintegration time are shown in Table 1.

TABLE 1.
Initial values of crushing strength ($S_0$) and disintegration time ($D_0$) of tablets prepared from lactose/starch granulations (compression load level 30 kN).

| Composition | Starch concentration (% w/w) | $S_0$ (N) | $D_0$ (s) |
|---|---|---|---|
| α-Lactose monohydrate/ Corn starch | 10 | 134 (4)[a] | 139 (9)[b] |
| | 20 | 124 (7) | 89 (4) |
| α-Lactose monohydrate/ Potato starch | 10 | 105 (5) | 223 (22) |
| | 20 | 91 (4) | 113 (22) |
| α-Lactose monohydrate/ Rice starch | 10 | 148 (6) | 334 (35) |
| | 20 | 149 (6) | 241 (9) |
| α-Lactose monohydrate/ Tapioca starch | 10 | 116 (4) | 236 (23) |
| | 20 | 99 (4) | 96 (5) |

[a] mean (standard deviation), n = 10
[b] mean (standard deviation), n = 6

Although the crushing strength of the tablets was high, the tablets disintegrated within 5 minutes, with the exception of the granulation with 10% w/w rice starch.

After storage under four different conditions the crushing strengths were measured again and the Storage to Initial Ratio of crushing strength (SIR(S)) was calculated, according to equation 2. With aid of multiple linear regression, the influence of normalized starch concentration, storage relative humidity and temperature was calculated and expressed as in equation 1. In Table 2 the coefficients of the equations for the different combinations are given. Each combination experiences a negative effect of the concentration ($B_{1,SIR(S)} < 0$). For the combination with rice starch however, the concentration influence is very small. Also a negative effect of the storage relative humidity ($B_{3,SIR(S)} < 0$) is seen for all the

TABLE 2.

Coefficients for the equation of the Storage to Initial Ratio of crushing strength (SIR(S)) for tablets prepared from granulations based on lactose and starch.

| Coefficient | Variable | LA-CS | LA-PS | LA-RS | LA-TS |
|---|---|---|---|---|---|
| $B_{0,SIR(S)}$ | intercept | 76.9 | 89.6 | 82.0 | 87.1 |
| $B_{1,SIR(S)}$ | $c_n$ | -4.8 | -7.1 | -1.9 | -9.1 |
| $B_{2,SIR(S)}$ | $t_n$ | * | 4.1 | 2.1 | * |
| $B_{3,SIR(S)}$ | $r_n$ | -12.1 | -14.9 | -12.1 | -15.2 |
| $B_{4,SIR(S)}$ | $c_n.t_n$ | * | * | 1.4 | * |
| $B_{5,SIR(S)}$ | $c_n.r_n$ | -1.7 | -3.5 | * | -2.3 |
| $B_{6,SIR(S)}$ | $t_n.r_n$ | * | 2.4 | * | 2.8 |
| $R^2$ adj. | | 88.4 | 87.6 | 89.3 | 90.7 |

LA = α-lactose monohydrate RS = rice starch
CS = corn starch TS = tapioca starch
PS = potato starch * = not significant (1%)

combinations. This effect is smallest for the rice and the corn starch combinations. For the combination with corn starch the relative humidity/starch concentration interaction is small and for the rice starch combination the interaction is absent. Only 2 of the combinations (with potato and rice starch) are influenced by the temperature.

For the disintegration time the same calculations were performed as for the crushing strength. The coefficients of the equations for the different combinations are listed in Table 3. From these results it can be concluded that none of the investigated variables has a strong increasing effect on the disintegration time of the tablets. The equations calculated for the SIR(D) of the combinations with potato respectively tapioca starch showed a poor fit ($R^2$adj. is small), when compared with the other combinations. This indicates that either the variation in the measurements is large, resulting in loss of the effect of the adjustable variables in the 'noise' or, that the SIR(D) is not influenced by the adjustable variables.

TABLE 3.
Coefficients for the equation of the Storage to Initial Ratio of disintegration time (SIR(D)) for tablets prepared from granulations based on lactose and starch.

| Coefficient | Variable | LA-CS | LA-PS | LA-RS | LA-TS |
|---|---|---|---|---|---|
| $B_{0,SIR(D)}$ | intercept | 92.5 | 103.2 | 120.1 | 84.6 |
| $B_{1,SIR(D)}$ | $c_n$ | -20.3 | 5.0 | -29.0 | * |
| $B_{2,SIR(D)}$ | $t_n$ | 7.5 | 4.9 | * | * |
| $B_{3,SIR(D)}$ | $r_n$ | * | * | 5.9 | * |
| $B_{4,SIR(D)}$ | $c_n.t_n$ | * | * | * | * |
| $B_{5,SIR(D)}$ | $c_n.r_n$ | -5.8 | * | -16.7 | * |
| $B_{6,SIR(D)}$ | $t_n.r_n$ | * | * | 3.3 | * |
| $R^2$ adj. | | 89.8 | 26.2 | 95.3 | 27.7 |

LA = α-lactose monohydrate RS = rice starch
CS = corn starch TS = tapioca starch
PS = potato starch * = not significant (1%)

From these results, it is concluded that concerning the physical stability neither combination is preferred above the other combinations. Therefore the selection of standard granulations is determined by the initial values of crushing strength and disintegration time and the availability of the excipients.

The combinations with corn and with rice starch are selected as standard granulations, because they give the highest values for crushing strength. When preparing tablets with a drug, the compression load can be adjusted to obtain tablets with adequate values for crushing strength. For the combination with corn starch the granulation with a low starch concentration (10% w/w) is chosen (granulation 1). Since the initial disintegration time of the lactose/10% w/w rice starch tablets was more than 5 minutes and the rice starch concentration influence small, the highest starch concentration (20% w/w) was chosen for the granulation with rice starch (granulation 2).

For the evaluation of these standard granulations, the selected model drugs were incorporated, as well as a preservative. In order to improve the microbiological quality after storage 1% w/w of either potassium sorbate or sodium methylhydroxybenzoate can be added[7]. In this study methylhydroxybenzoate was used as a preservative. Tablet parameters were measured one day after preparation and after storage. The chosen model drugs were diazepam and mebendazole. Mebendazole is a high dosage drug. The normal dosage of mebendazole is 100 mg in a chewable tablet. Mebendazole is a material with poor flow and compression properties. Therefore mebendazole is unsuitable for processing in direct compression formulations. In this study 100 mg mebendazole tablets were prepared with a tablet weight of 500 mg. Diazepam is a low dosage drug. In this study 2 mg diazepam tablets were prepared with a tablet weight of 200 mg.

Evaluation of mebendazole tablets

Mebendazole was incorporated into standard granulation 1 (M1) and into standard granulation 2 (M2).

The composition of these two tablet formulations, as well as the results of the measurements of the tablet parameters of the mebendazole tablets are shown in Table 4.

The initial crushing strength and friability of both batches of tablets are sufficient.

Generally applied requirements for the different tablet parameters are shown in Table 5. Mebendazole tablets are usually chewable tablets, therefore no demands concerning the disintegration time or the percentage dissolved are made for mebendazole tablets. For both batches of 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 added sodium methylhydroxybenzoate did not interfere with the USP XXI method for the estimation of mebendazole.

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

TABLE 4.
Mebendazole chewable tablets (100 mg)

| Tablet composition | M1 | M2 |
|---|---|---|
| Mebendazole | 20.0 % | 20.0 % |
| Corn starch | 10.0 % | |
| Rice starch | | 20.0 % |
| α-Lactose monohydrate 200 mesh | 67.5 % | 57.5 % |
| Pregelatinized starch | 1.0 % | 1.0 % |
| Sodium methylparahydroxybenzoate | 1.0 % | 1.0 % |
| Water | q.s. | q.s. |
| Magnesium stearate | 0.5 % | 0.5 % |
| **Tablet evaluation** | **M1** | **M2** |
| Tablet weight (ϕ 13 mm) | 500 mg | 500 mg |
| Compression load | 15 kN | 10 kN |
| RSD[a] of tablet weight | 1.47 % | 2.58 % |
| Friability | 2.8 ± 0.1 % | 2.8 ± 0.8 % |
| Crushing strength | 50 ± 5 N | 60 ± 9 N |
| Disintegration time | > 30 min | > 30 min |
| *Content uniformity* | | |
| lowest content | 95.5 mg | 97.2 mg |
| highest content | 102.7 mg | 112.9 mg |
| average content | 98.7 mg | 106.8 mg |
| RSD[a] | 2.3 % | 4.2 % |
| Microbiological quality | | |
| one day after preparation | $< 10^1$ cfu/t[b] | $1.5 \times 10^1$ cfu/t[b] |
| after storage 31°C, 75% RH | $< 10^1$ cfu/t | $2.2 \times 10^1$ cfu/t |
| after storage 31°C, 95% RH | $< 10^1$ cfu/t | $2.2 \times 10^1$ cfu/t |
| Physical stability | | |
| SIR(S) 20°C, 44% RH[c] | 91% | 102% |
| SIR(S) 20°C, 75% RH | 104% | 80% |
| SIR(S) 31°C, 44% RH | 107% | 103% |
| SIR(S) 31°C, 75% RH | 84% | 88% |

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

TABLE 5.
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



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 mebendazole 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 mebendazole 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 > 80 % for both formulations.

Evaluation of diazepam tablets

Diazepam was incorporated into standard granulation 1 (D1) and into standard granulation 2 (D2). The composition of these two tablet

TABLE 6.

Diazepam tablets (2 mg)

| Tablet composition | D1 | D2 |
|---|---|---|
| Diazepam | 1.0 % | 1.0 % |
| Corn starch | 10.0 % | |
| Rice starch | | 20.0 % |
| α-Lactose monohydrate 200 mesh | 86.5 % | 76.5 % |
| Pregelatinized starch | 1.0 % | 1.0 % |
| Sodium methylhydroxybenzoate | 1.0 % | 1.0 % |
| Water | q.s. | q.s. |
| Magnesium stearate | 0.5 % | 0.5 % |
| **Tablet evaluation** | **D1** | **D2** |
| Tablet weight (ϕ 9 mm) | 200 mg | 200 mg |
| Compression load | 13 kN | 10 kN |
| RSD[a] of tablet weight | 1.94 % | 1.89 % |
| Friability | 1.6 % | 1.3 % |
| Crushing strength | 39 ± 8 N | 41 ± 7 N |
| Disintegration time | 276 ± 51 s | 902 ± 103 s |
| Percentage dissolved after 30 minutes | 99 ± 2 % | 98 ± 2 % |
| Content uniformity | | |
| lowest content | 2.02 mg | 2.03 mg |
| highest content | 2.13 mg | 2.14 mg |
| average content | 2.08 mg | 2.09 mg |
| RSD[a] | 1.8 % | 1.7 % |
| Microbiological quality | | |
| one day after preparation | $< 10^1$ cfu/t[b] | $< 10^1$ cfu/t[b] |
| after storage 31°C, 75% RH | $< 10^1$ cfu/t | $< 10^1$ cfu/t |
| after storage 31°C, 95% RH | $< 10^1$ cfu/t | $< 10^1$ cfu/t |
| Physical stability | | |
| SIR(S) 20°C, 44% RH | 102% | 104% |
| SIR(S) 20°C, 75% RH | 75% | 88% |
| SIR(S) 31°C, 44% RH | 108% | 118% |
| SIR(S) 31°C, 75% RH | 74% | 84% |
| SIR(D) 20°C, 44% RH[d] | 126% | 110% |
| SIR(D) 20°C 75% RH | 119% | 123% |
| SIR(D) 31°C, 44% RH | 128% | 97% |
| SIR(D) 31°C, 75% RH | 108% | 125% |

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

formulations, as well as the results of the measurements of the tablet parameters of the diazepam tablets are shown in Table 6.

Because sodium methylhydroxybenzoate, which has a UV-absorbance peak near the 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, without interference of sodium methylhydroxybenzoate. This method was used to measure the content uniformity of the tablets and the percentage dissolved.

The initial crushing strength and friability of both batches of tablets are sufficient. 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 formulation 1 (D1) disintegrate within 5 minutes, the tablets of formulation 2 (D2) disintegrate in 15 minutes. After 30 minutes 99% and 98% of the diazepam had dissolved for formulation 1 (D1) respectively formulation 2 (D2). 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 or 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 > 70 % for formulation 1 (D1) and > 80% for formulation 2

(D2). The Storage to Initial Ratio for disintegration time (SIR(D)) is < 130 % for both formulations.

## CONCLUSIONS

Both granulation 1 (lactose/10% w/w corn starch) and granulation 2 (lactose/ 20% w/w rice starch) were found to be suitable standard formulations for the preparation of tablets by wet granulation, suitable for use in tropical countries.

Both with a low dosage drug, such as diazepam, and a high dosage drug, with poor compression properties, such as mebendazole, it is possible to achieve good tablets with the two suggested standard granulations. The tablet properties meet the different tablet requirements one day after preparation. Also both the physical and the microbiological quality are sufficient, even after storage under conditions, such as may occur in tropical countries.

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