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# The moisture content of NIPRISAN® a polyherbal formulation for the management of sickle cell anaemia affects the direct compression tableting properties of silicified microcrystalline cellulose

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*The aim of this study is to investigate the effect of the moisture content of NIPRISAN®, a herbal extract on the direct compression tableting properties of SMCC 50 and SMCC 90. NIPRISAN® extract was exposed to a saturated solution of potassium nitrate in a glass dessicator for one week. Granules were compressed at varying compression pressures and subjected to various tests. Results obtained show that, the SMCC 50-NIPRISAN® combinations had higher moisture content than SMCC 90-NIPRISAN® combination. At 18 – 25 KN compression pressure, tablet hardness decreased with addition of the herbal extract. There was no discernible difference in the effect of moisture on tablet hardness irrespective of whether SMCC 50 or 90 was used as the direct compression agent. Initial addition of the extract to SMCC had the most pronounced effect on tablet strength. At moisture level greater than 18.4 %, no suitable tablets could be produced. With tablets compressed at 26.25 KN, the initial addition of the extract did not have any appreciable effect on the hardness of the tablet, with both grades of SMCC used. Increasing the moisture content to 26 % with SMCC 50 resulted in tablets of unsuitable hardness. Deformation characteristics of SMCC 50 were more affected by moisture than SMCC 90. Generally, there was increased tablet hardness with increase in the compression pressure irrespective of the grade of SMCC used. Friability results show that as the moisture content of the tablets increased, the tablets become more friable. Results of tablet disintegration show that, the presence of the extract in the formulation increased the disintegration time irrespective of the SMCC used and this was most pronounced at the higher compression pressures of 25 and 26.25 KN. Disintegration times with SMCC 50 was longer than those of SMCC 90. Pressure variation and moisture content also affected disintegration times. At lower pressures and increased moisture contents, there was a decreased disintegration time irrespective of SMCC grade. SMCC 50 and 90 are suitable direct compression excipients and disintegrants in herbal solid dosage formulations, the optimal moisture level was found to be 28.7 %.*

## Introduction

Microcrystalline cellulose (MCC) is used as a filler and binder for wet granulation, direct compression tabletting and as a filler for hard gelatin capsules. In addition to this, it has low chemical reactivity combined with excellent compatibility at low pressures. However, there are a number of limitations to the use of MCC including low bulk density, high lubricant sensitivity and poor flow characteristics [1]. A number of modifications have been attempted to improve MCC in order to overcome these problems. SMCC, which is obtained by the silicification of MCC, is one of the most successful modifications. SMCC has been reported to possess a number of pharmaceutical advantages in terms of flow [2], tablet strength [3], lubricant sensitivity and wet granulation [4] compared to MCC. These make it an obvious choice as a direct compression agent in which role it has been found to perform well [5]. Tobyn et al [6] found that, there were no differences in the physical characteristics of SMCC and MCC.

The standardization of herbal medicines has become a point of interest to researchers in the recent past especially in the developing countries where over 80 % of the people depend on herbal medicines for their medical needs. Since one of the major problems with herbal medicines in such countries is their poor and sometimes unhealthy presentation, a major aspect of this standardization process is the development of suitable dosage forms for the herbal medicines. Because of the convenience associated with it, the tablet is the most preferred dosage form. However, a major drawback in its use is the several steps involved in its formulation. For example, the wet granulation process involves several steps such as drying, mixing, addition of liquid binder and drying. Since in most cases the chemical natures of the active component of these plant parts or extracts are unknown, some of these processes may affect their activity. Direct compression is therefore considered one of the most suitable options in formulation of herbals. NIPRISAN® is a herbal remedy that is used in the management of sickle cell anaemia disease [7]. It is obtained from the freeze-dried water extract of a combination of different parts of a number of plants.

The aim of this study is to investigate the effect of the moisture content of NIPRISAN® on the direct compression tableting properties of two grades of SMCC (SMCC 50 and 90) at different compression pressures. The effect of increasing the moisture content of the extract on the tablet properties were also is evaluated.

## Materials and Methods

### Materials

Silicified microcrystalline cellulose [Prosolv (SMCC) 50 and 90] was obtained from Penwest Pharmaceuticals, Patterson, NY; NIPRISAN® powder was prepared as earlier described by Gamaniel et al [7].

### Methods

### Preparation of Extract/SMCC mixtures

NIPRISAN® extract was exposed to a saturated solution of potassium nitrate in a glass dessicator for various lengths of time as shown in Table 1 to obtain different moisture contents. Moisture content of the extract was determined on a moisture balance (Ohaus Corporation, USA). The extract and either SMCC 50 or 90 were then mixed in a ratio of 1:1 in a multimix MX32 blender (Braun, Germany) for 5 minutes at a speed setting of 3.

### Compression of granules

A single punch power-driven tablet press (Shanghai Tianziang and Chentai Pharmaceutical Machinery Co. Ltd., China) fitted with 12 mm concave punch and die set was used. Tablets were produced at four compression pressures; 18.75, 22.5, 25.0, and 26.25KN. The lowest compression pressure of 18.75KN had earlier been determined to be the lowest at which tablets could be obtained. The machine speed was 12 tablets per minute with a tablet weight of 500 mg.

### Evaluation of tablet properties

### Hardness

A Mosanto hardness tester which measures in kg, the force required to crush a tablet was used. The mean of six determinations is reported.

### Friability

Tablets were subjected to friabilation in an Erweka double drum friability tester (Copley Tar) at 25 rpm for 4 minutes. The weight of 10 tablets before and after the test was taken. The percent loss of weight was calculated to obtain the friability. The mean of triplicate determinations is reported.

**Disintegration time**

Six tablets were assessed in a BP [8] disintegration test apparatus with distilled water at a temperature of 37 $^{o}$C as medium. The mean of triplicate determinations was calculated.

**Results and Discussion**

Table 1 shows that while SMCC 50 and 90 had a moisture content of 4.6 and 4.9 % respectively, the unexposed extract (NIPRISAN®) had relatively high moisture content of 18.4 %. This is much higher than that for synthetic drugs, which would not usually exceed 5.0 %. It was also observed that SMCC 50-NIPRISAN® combination had higher (18.0 %) moisture content than SMCC 90- NIPRISAN® (16.2 %) on day 6. This may be attributed to the higher surface area of SMCC 50 which allowed the mixture to absorb more moisture.

Table 1. Moisture content of NIPRISAN and SMCC/NIPRISAN mixtures

| Time (days) | Moisture content (%) | | |
|---|---|---|---|
| | NIPRISAN | SMCC 50/NIPRISAN | SMCC 50/NIPRISAN |
| 0 | 18.4 ± 1.45 | 4.6 ± 0.45 | 4.9 ± 1.45 |
| 3 | 26.0 ± 1.05 | 15.3 ± 2.45 | 12.4 ± 1.01 |
| 6 | 28.7 ± 2.25 | 18.0 ± 1.55 | 16.2 ± 1.31 |

***n = 3; Values ± Standard deviation***

At the lowest compression pressure of 18.75KN, tablet hardness decreased on addition of NIPRISAN® to SMCC i.e. increasing the moisture content (Table 2). This trend continued with increase in moisture content. Some workers have observed that, the presence of moisture increases tablet strength. Teng et al [9] have suggested that adsorbed surface water may act as a binder during compression. The nature and strength of such forces would depend on the nature of the material and the amount of water present in the formulation. Nystrom and Glazer [10] for example attributed the better binding effect of PVP during direct compression to its hygroscopic nature leading to increased number of liquid bridges in the compacts. Bangudu and Pilpel [11] also found that tablets made of mixtures with 2 – 4 % water were stronger than those made of mixtures without additional moisture. The effect of water in the formulation would however depend on the amount present. At the pendular stage, the solid particles are held together by lens-shaped rings of air spaces between them, a force is thus developed which binds the particles. Increasing the amount of water results in the furnicular stage where the air voids are displaced by the liquid with more bridges being formed, further increase will result in the complete elimination of the air voids with the particles still being held together by the liquid by means of capillary forces. If there is any further increase beyond this point, the particle might be totally surrounded by water which could result in over wetting and the subsequent dissolution of the bonds and a generally weakening of other forces involved in bond formation. Since tablet hardness is a measure of the strength and number of solid bridges and bonds formed in the tablet, the observed decrease in hardness would therefore seem to indicate that, the intrinsic moisture content of the freeze-dried herbal extract (18.0 %) was high enough to weaken the tablet rather than enhance bonding. SMCC would be expected to form tablets mainly by plastic deformation [12] even though some fragmentation of the particles

under compression might also be involved [13]. This could be enhanced either by hydrogen bonding with neighbouring cellulose chains [14] or interlocking of the particles [15]. The presence of so much moisture could also have increased interparticulate space such as to weaken the other forces involved in bond formation such as interlocking due to change in surface characteristics and any hydrogen bonding. No difference was observed in the effect of moisture on tablet hardness irrespective of whether SMCC 50 or 90 was used as direct compression agent.

The decrease in hardness was most pronounced (75 %) on addition of the extract to SMCC compared to the effect of subsequent increases in the moisture contents of the extract. At moisture levels greater than 18.4 %, no suitable tablets were obtained at 18.75KN and the hardness was practically zero. This could be an indication that, the increase in interparticulate spaces was most pronounced with increase in moisture to 18.4 %, which was the highest increase in moisture level. It could also be that, most of the bridges had been destroyed, thus reducing the effect of further increases in moisture content. No difference was observed in the effect of moisture on hardness between SMCC 50 and 90 possibly because the moisture content was so high as to completely mask the expected role of surface area in the formation of interparticulate bonds.

Increasing the compression pressure to 22.5KN did not change the trend observed (Table 2). The extent of decrease in hardness was however dependent on the grade of SMCC used. While it was highest between 18.4 and 26.0 % moisture content for SMCC 50, it was highest with increase in moisture content to 18.4 % for SMCC 90. This could have resulted from the relatively larger surface area of the SMCC 50 particles absorbing some of the moisture from the extract, thus reducing its bond weakening effect. Further increase in moisture content seemed to have reduced its ability to do this thus resulting in tablets of unsuitable physical strength, as was similarly observed with SMCC. At 25KN compression pressure, the trend obtained was similar to that at 22.5KN (Table 2). It was however observed that increasing moisture content from 18.4 to 26.0 % had no effect on the hardness of those tablets containing SMCC 50. With tablets compressed at 26.25KN, the initial addition of the extract did not have any significant effect on the hardness of the tablets with both grades of SMCC

Table 2. Effect of moisture content and compression pressure of NIPRISAN on the tablet hardness and friability

| Compression pressure (KN) | Moisture content (%) | Hardness (kgf) | | Friability (%) | |
|---|---|---|---|---|---|
| | | a | b | a | b |
| 18.75 | SMCC | 1.20 ± 0.75 | 2.33 ± 0.11 | 2.54 ± 0.11 | 1.36 ± 0.02 |
| | 18.4 ± 1.45 | 0.27 ± 0.15 | 0.62 ± 0.11 | 14.93 ± 1.05 | 8.13 ± 0.05 |
| | 26.0 ± 1.05 | 0.20 ± 0.15 | 0.00 ± 0.00 | 5.90 ± 0.10 | 100.00 ± 0.10 |
| | 28.7 ± 2.25 | 0.00 ± 0.05 | 0.01 ± 0.00 | 100.00 ± 0.10 | 100.00 ± 0.10 |
| 22.50 | SMCC | 6.00 ± 0.15 | 7.93 ± 0.13 | 0.31± 0.10 | 0.64 ± 0.10 |
| | 18.4 ± 1.45 | 3.87 ± 0.15 | 1.77 ± 0.06 | 0.69 ± 0.10 | 1.09 ± 0.15 |
| | 26.0 ± 1.05 | 0.20 ± 0.15 | 1.70 ± 0.06 | 11.40 ± 1.7 | 0.83 ± 0.15 |
| | 28.7 ± 2.25 | 0.50 ± 0.15 | 0.73 ± 0.06 | 2.63 ± 0.10 | 1.38 ± 0.43 |
| 25.00 | SMCC | 17.40 ± 0.06 | 21.73 ± 0.18 | 0.37 ± 0.10 | 0.24 ± 0.15 |
| | 18.4 ± 1.45 | 11.10 ± 0.37 | 6.47 ± 0.16 | 0.50 ± 0.12 | 0.06 ± 0.05 |
| | 26.0 ± 1.05 | 0.80 ± 0.15 | 6.60 ± 0.15 | 2.00 ± 0.20 | 0.11 ± 0.15 |
| | 28.7 ± 2.25 | 2.50 ± 0.55 | 2.70 ± 0.15 | 0.96 ± 0.34 | 0.41 ± 0.15 |
| 26.25 | SMCC | 24.33 ± 0.11 | 25.47 ± 0.11 | 0.79 ± 0.23 | 0.24 ± 0.15 |

| | | | | | |
|---|---|---|---|---|---|
| | 18.4 ± 1.45 | 22.33 ± 0.11 | 24.60 ± 0.13 | 0.06 ± 0.01 | 0.06 ± 0.01 |
| | 26.0 ± 1.05 | 2.00 ± 0.08 | 10.20 ± 0.12 | 0.40 ± 0.10 | 0.11 ± 0.15 |
| | 28.7 ± 2.25 | 4.40 ± 0.10 | 3.40 ± 0.15 | 0.99 ± 0.10 | 0.41 ± 0.15 |

***n = 3; values ± Standard deviation; a and b are tablets with SMCC 50 and SMCC 90 as direct compression agents respectively.***

used (Table 2). However, an increase in moisture did. Although, the tablets with SMCC 90 at 26.0 % were of suitable hardness, there was also very sharp drop in the values. For every formulation and formulation conditions, there is a critical amount of moisture beyond which tablets get significantly softer, it would seem that, this was at 18.0 and 26.0 % for SMCC 50 and SMCC 90 respectively. Considering its higher surface area, it would have been expected that, the value be higher for SMCC 50. The result obtained could be an indication that, due to its higher surface moisture, its deformation characteristics was more affected by moisture than SMCC 90.

Generally, there was increased tablet hardness with increase in the compression pressure, irrespective of the grade of SMCC used. This is as expected since increased compression pressure would result in the formation of more solid particle-particle bridges as well as increase the effect of the other forces involved in bond formation. The extent of the effect however depended on the moisture level (Table 2).

With SMCC 90 at 25 KN, the largest decrease in hardness was noted on addition of the extract (NIPRISAN®) to SMCC i.e. increasing the moisture content from about 4.5 to 18.0 % (Table 2). This is understandable since this was the largest single increase in moisture content. It would seem that, the comparatively higher compression pressure of 26.25KN which resulted in the formation of more and stronger bonds masked or even eliminated the effect of this factor. On the other hand, with SMCC 50, the reduction of hardness was least on addition of NIPRISAN® at compression pressure of 22.5, 25.0, and 26.25KN. Since the only difference between the 2 grades of SMCC is particle size and consequently surface area, this result could have been due to the higher surface area of SMCC 50 resulting in adsorption of the moisture. This could have improved the ability of the SMCC to resist the effect of the relatively high moisture increase from 4.5 to 18.4 %. At the lower compression pressure of 18.75KN, no difference was observed between the 2 grades of SMCC. As would be expected from the hardness results, there was a general increase in friability of the tablets with increased moisture content (Table 2). In some cases, there was decreased friability with increased moisture content. This was due to the wetness of the tablets leading to a reduction in the breaking tendency of the tablet. The hardness values of such tablets were all below 2.0kgf (Table 2). At moisture content higher than 26.0 %, tablets were so soft that friability values were erratic and largely meaningless. In general, except for a few exceptions, with both grades of SMCC, there was reduced tablet friability with increased compression pressure irrespective of the moisture content (Table 2). This is due to the formation of more and stronger bonds with increased pressure, the driving out of excess moisture from the tablet pores due to increased densification and thus a reduction of the wetting effect of the moisture within the tablet. While at the lower pressure (18.5 and 22.5KN) the addition of NIPRISAN® to SMCC i.e. increasing the moisture content from 4.5 to 18.4 % resulted in increased friability, it had no significant effect at the higher pressures (25.0 and 26.25KN). This again shows that, at the higher pressures, the effect of moisture on tablet strength is minimal, with plastic deformation of SMCC being predominant.

The disintegration time of the tablets was also determined. The results in Table 3 indicate that, the effect of moisture depended on the specific amount and the compression pressure. The addition of the extract

(NIPRISAN®) to both grades of SMCC resulted in increased tablet disintegration time. SMCC is a well known disintegrant which acts by swelling as well as by capillary action [16]. Wang and Heng [17] have proposed that, the mechanism by which MCC (which is physicochemically the same as SMCC) acts as an efficient tablet disintegrant is through the process of wicking and dissociation of hydrogen bonds on wetting. The reduced disintegration rate obtained with the addition of NIPRISAN® could be due to the effect of NIPRISAN® on channel formation and continuity, thus reducing water uptake and consequently disintegrant efficiency. The results (Table 3) indicate that, the increase in disintegration time with addition of NIPRISAN® was most pronounced at the higher compression pressures of 25.0 and 26.25KN. This is an indication that compression force and hence porosity are important factors that affect the disintegration action of SMCC.

In virtually all cases, the disintegration times of formulations containing SMCC 50 were longer than those of SMCC 90. This followed the same general trend with tablet hardness (Table 2). A low particle size such as for SMCC 50 results in increased surface area, which would increase the surface available for the formation of many stable bonds between particles resulting in increased disintegration time.

At a compression pressure of 18.75KN, increasing the moisture content from 18.0 to 26.7 % resulted in increased disintegration time with tablets containing SMCC 50 while the opposite effect was obtained with SMCC 90. Further increase in moisture content to 28.7 % resulted in decreased disintegration time in both cases. At the other compression pressures, there was decreased disintegration time with increased moisture content from 20.0 to 28.7 % with both grades of SMCC (Table 3). This is probably because, at the moisture level of 28.7 %, the granules rather than break up into individual particles agglomerated into a mass, which was too large to pass through the mesh, thus prolonging the disintegration time.

Table 3. Effect of moisture content and compression pressure of NIPRISAN on the tablet disintegration time

| Compression pressure (KN) | Moisture content (%) | Disintegration time (min) | |
|---|---|---|---|
| | | a | b |
| 18.75 | SMCC | 0.04 ± 0.00 | 0.04 ± 0.00 |
| | 18.4 ± 1.45 | 1.83 ± 0.02 | 1.38 ± 0.00 |
| | 26.0 ± 1.05 | 4.50 ± 0.01 | 0.27 ± 0.00 |
| | 28.7 ± 2.25 | 0.18 ± 0.00 | 0.04 ± 0.00 |
| 22.50 | SMCC | 0.05 ± 0.00 | 0.25 ± 0.00 |
| | 18.4 ± 1.45 | 4.98 ± 0.00 | 3.75 ± 0.05 |
| | 26.0 ± 1.05 | 0.13 ± 0.00 | 0.32 ± 0.00 |
| | 28.7 ± 2.25 | 0.23 ± 0.00 | 0.00 ± 0.00 |
| 25.00 | SMCC | 3.67 ± 0.01 | 2.70 ± 0.03 |
| | 18.4 ± 1.45 | 10.00 ± 0.02 | 8.88 ± 0.02 |
| | 26.0 ± 1.05 | 8.00 ± 0.00 | 0.40 ± 0.01 |
| | 28.7 ± 2.25 | 8.68 ± 0.03 | 24.53 ± 0.07 |
| 26.25 | SMCC | 11.87 ± 0.04 | 9.92 ± 0.01 |
| | 18.4 ± 1.45 | 18.37 ± 0.01 | 9.53 ± 0.00 |

| | | | |
|---|---|---|---|
| | 26.0 ± 1.05<br>28.7 ± 2.25 | 12.12 ± 0.01<br>21.47 ± 0.20 | 7.33 ± 0.03<br>23.13 ± 0.20 |

*n = 3; values ± Standard deviation; a and b are tablets with SMCC 50 and SMCC 90 as direct compression agents respectively.*

At the highest compression pressure of 26.25KN however, further increase in moisture to 28.7 % from 26.0 % resulted in a dramatic increase in disintegration time probably because, the SMCC channels had been completely disrupted by the excess moisture and the almost complete elimination of pores.

## Conclusions

Tablets of NIPRISAN®, a herbal extract were produced by direct compression. It was found that, both SMCC 50 and SMCC 90 were suitable direct compression and disintegration agents in the production of the tablets in spite of the very high moisture content of the extract (18.4 %) relative to synthetic drugs. While the addition of the extract and increased moisture increased the physical strength and disintegration rate of SMCC, tablets with suitable properties were obtained. The effect of moisture was reduced at the higher compression pressures of 25.0 and 26.25KN. In conclusion, SMCC 50 and SMCC 90 can be used to obtain suitable tablets of NIPRISAN® at moisture contents up to 28.7 % with the specific tolerable moisture level depending on the compression pressure used.

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