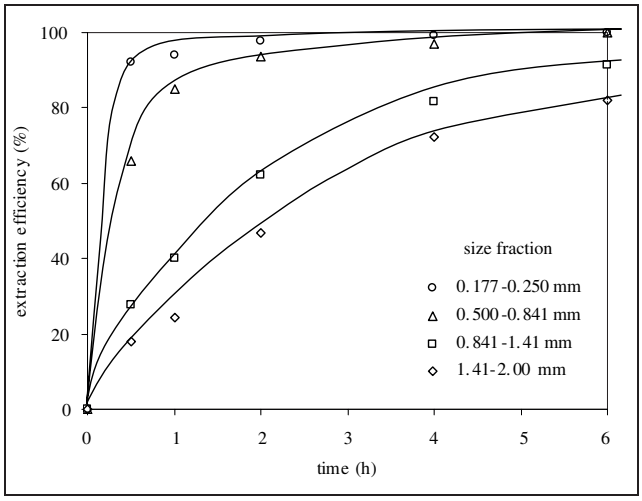

Fig. 2: Effect of the size of herb particles on the amount of extracted matter. Extraction temperature –70 °C, ethanol concentration in the solvent –70% (v/v)

The rate of the extraction process strongly depends on the size of the solid particles. The intensively stirred extraction cell used in the present study suggests that intraparticular diffusion of the solutes is the only rate controlling factor. In the experiments four fractions of ground dry rhizomes of valerian – 0.18–0.25 mm, 0.50–0.84 mm, 0.84–1.41 mm and 1.41–2.00 mm were subjected to the described extraction procedure. In all cases 10 g of each fraction were extracted with 70% (v/v) ethanol at a temperature of 70 °C. The total residue after extract drying was a measure for the extraction kinetics. The results are shown in Fig. 2. In the case of finely ground particles ($d_p < 0.25$ mm), extractable matters are rapidly and almost completely (above 90%) recovered during the first hour of the treatment (taking as 100% efficiency the weight of the extracted mass, obtained after 6 h). In the case of largest (1–2 mm) particles used extraction efficiency was 80–85% after 6 h treatment. It should be kept in mind that the obtained results refer to an intensely stirred dispersion, i.e., in complete absence of diffusion resistance in the continuous liquid phase.

On the basis of the obtained results some useful conclusions about the recovery of valerenic acids, the content of which is the specifying and standardizing characteristic of valerian products (Annon 2002), can be drawn. Ethanol-water mixtures containing 50–96% ethanol extract all three valerenic acids, the higher ethanol concentrations yield a lower amount of dry extract, being enriched in the mentioned acids. Extraction, extract concentration or drying at elevated temperatures up to 70 °C does not lead to a significant degradation of the valerenic acids. The extraction rate of the active components is favored by reducing the size of the solid particles, thus shortening the process duration. However, very fine solid fractions would hamper liquid circulation and extract filtration. A reasonable compromise in this respect should be found.

References

Annon (2002) European Pharmacopoeia 4rd ed. Eropean Dept. for the Quality of Medicines. Council of Europe Strasbourg, p. 2109

Bos R, Woerdenbag HJ et al. (1996) Analytical aspects of phytoterapeutic valerian preparations. Phytochem Anal 7: 143–151.

Bos R (1997) Analytical and phytochemical studies on valerian based preparations. Dr. nat. sci. Thesis Univ. Gronningen.

Gobbato S, Lolla E (1996) A new HPLC method for the analysis of valerenic acids in Valeriana officinalis extracts. Fitoterapia 57: 159.

Houghton PJ (1994) Valerian. Pharm J 253: 95–96.

Thies PW (1969) Zum chromogenen Verhalten der Valepotriate. Arzneim Forsch 19: 319.

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Compatibility of sennoside A and B with pharmaceutical excipients

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This study reports the incompatibility of sennoside A and B with the following commonly used pharmaceutical excipients: stearic acid, sodium carbonate, glucose, lactose, propyl paraben, sodium carbonate, stearic acid, citric acid, PEG, and sorbitol. Drug-excipient compatibility was tested using thermal (DSC) and analytical (HPLC) methods of analysis. Compatibility evaluation showed that dry powder mixtures could be used to formulate sennoside A and B products. However, when mixed with water – propyl paraben, sodium carbonate, stearic acid, citric acid, PEG, and sugar derivatives such as lactose, glucose and sorbitol – should not be used in sennoside containing products.

In order to relieve the symptoms of constipation, laxatives are used to achieve comfortable defecation. Until recently, the laxative most frequently used was the stimulant laxative phenolphthalein. However, phenolphthalein has proven to be a concern, starting in the USA where the National Cancer Institute of America nominated phenolphthalein for study because of its widespread use and lack of adequate testing for carcinogenety (Dunnick and Hailey 1996; Dunnick et al. 1997; FDA 1997; Tice et al. 1998). These studies confirmed the potential carcinogenicity of phenolphthalein prompting the Food and Drug Administration in the USA on 29 January 1999 to issue a final rule on the use of phenolphthalein as an OTC laxative proposing a ban of all phenolphthalein products (Collins et al. 2000). Many other countries quickly followed suit. This ban meant that many laxative products had to be reformulated and it seems the laxatives of choice to replace phenolphthalein are the sennosides. Sennosides fall within the same category of stimulant laxatives as phenolphthalein. This renewed interest in the sennosides prompted this study, which aimed to determine the compatibility of sennoside A and B with commonly used pharmaceutical excipients. Sennosides are anthraquinones and the two stereoisomers sennoside A and sennoside B form the principal constituents of various Senna extracts. Senna extracts come from the leaves and fruits of various species of *Cassia*. In this study thermal (DSC) and analytical (HPLC) methods

were used to evaluate the compatibility of the sennosides and the excipients (Benzler et al. 1999; Araujo et al. 2003).

Excipients for the compatibility study were chosen from each of the major pharmaceutical excipient categories, based on cost, availability, frequency of use, and acceptability (Kibbe 2000). The following excipients were tested: Lactose, dibasic calcium phosphate dihydrate, mannitol, microcrystalline cellulose, pregelatinised starch, polyvinyl pyrrolidone, gelatin, glucose, polyethylene glycol 6000, magnesium stearate, stearic acid, sorbitol, sodium bicarbonate, sodium carbonate, citric acid, and propyl paraben.

In the dry powder mixtures, DSC observed no interactions. In the wet granulated samples, five interactions were discovered because glucose, sodium carbonate, sorbitol, stearic acid, and lactose showed incompatibilities (Fig. 1). These interactions were derived from the disappearance of the dehydration, 72 °C, and melting, 276 °C, peaks of the sennosides, Fig.1(a), in the mixtures. Stearic acid showed one peak at 56 °C, Fig. 1 (b), but an extra peak appeared in the wet granulated sample at 74 °C, Fig. 1 (c). Hot-stage microscopy clearly showed (Fig. 2) that this second peak represents dissolution of the sennosides into the melted stearic acid. Pure sodium carbonate showed one small peak at 87 °C, which shifted to 109 °C in the wet granulated sample, Fig. 1 (e). Lactose showed peaks at 146 °C and at 213 °C, Fig. 1 (f), typical for lactose monohydrate dehydration and melting respectively. The wet granulated lactose samples showed only one small peak at 192 °C, Fig. 1 (g). In the case of glucose in a wet granulated sample, only one peak at 183 °C appeared, the peak for glucose at 156 °C, Fig. 1 (h) and the peaks for the sennosides disappeared at 72 °C and 276 °C, Fig. 1 (a) in the granulated mixture, Fig. 1 (i). Sorbitol melts at 96 °C, this peak disappears, and a new, large endothermic peak appears at 308 °C in the granulated mixture, Fig. 1 (j, k).

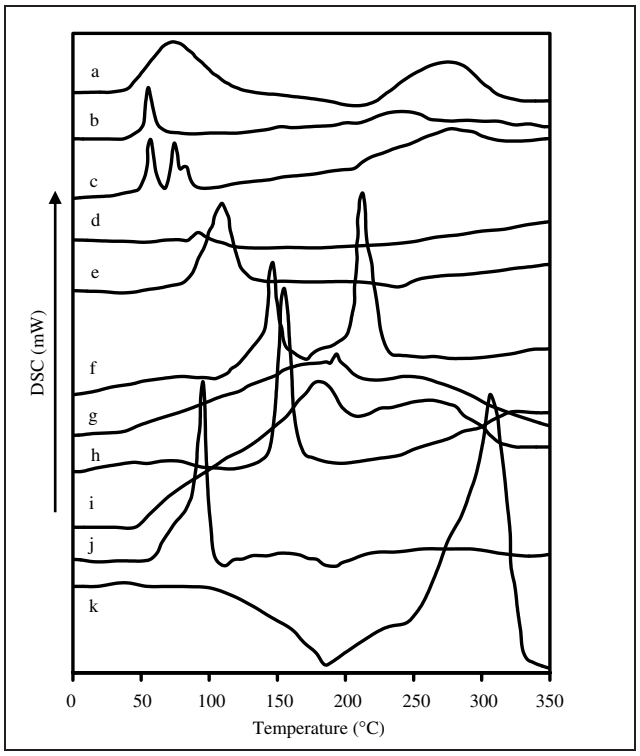

Fig. 1: DSC Thermograms: (a) Sennosides; (b) stearic acid; (c) 1 : 1 stearic acid-sennoside mixture; (d) sodium carbonate; (e) 1 : 1 sodium carbonate-sennoside mixture; (f) lactose; (g) 1 : 1 lactose-sennoside mixture; (h) glucose; (i) 1 : 1 glucose-sennoside mixture; (j) sorbitol; (k) 1 : 1 sorbitol-sennoside mixture. The arrow indicate the direction of endothermic processes

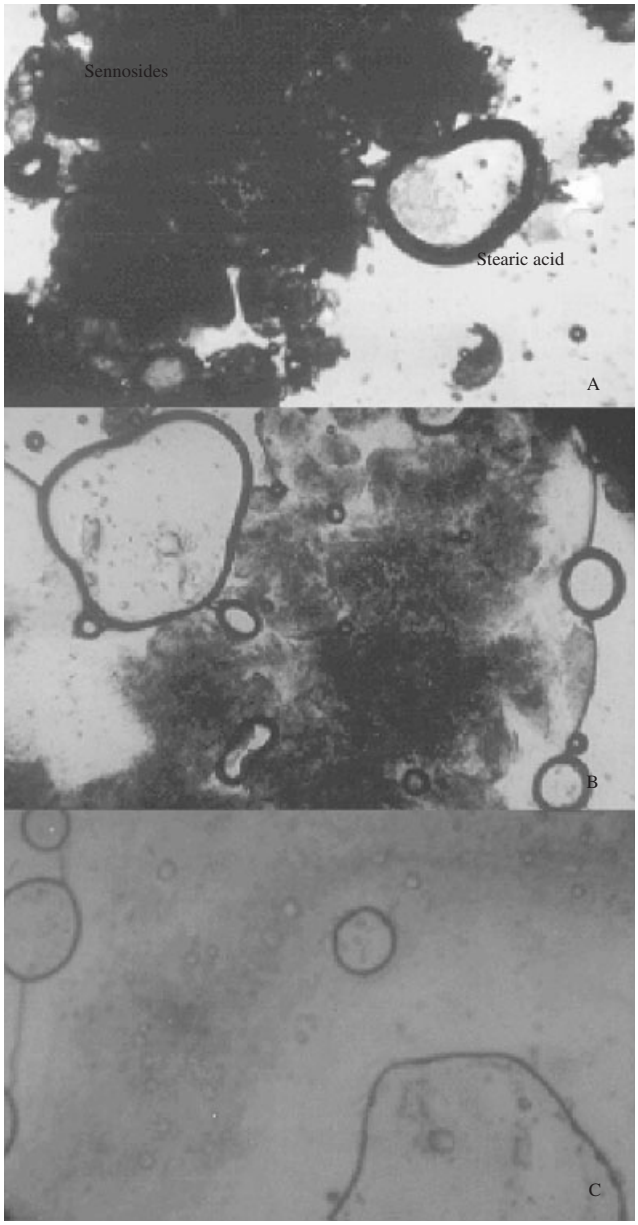

Fig. 2: Hot-stage microscope photos of the mixture of the sennosides (dark crystals) and stearic acid (large transparent particles): (A) before heating at 25 °C; (B) during melting at about 56–75 °C; (C) after melting at about 80 °C

HPLC analysis was used to confirm the incompatibilities obtained by DSC. The chromatogram of the sennosides showed a peak at 9 min (sennoside B) and a peak at 11 min (sennoside A). Interference by individual excipients with the HPLC of the sennosides was tested by injecting samples of the pure excipients. None of the excipients tested had retention times close to that of the sennosides. The HPLC results confirmed that there was no interaction between the sennosides and excipients in the dry state. However, in the granulated samples analysis showed that propyl paraben, sodium carbonate, stearic acid, citric acid, PEG, lactose, glucose and sorbitol was incompatible with the sennosides. Especially, HPLC showed that the recovery for sodium carbonate ($61.7 \pm 0.8\%$), stearic acid ($71.6 \pm 10.3\%$), and citric acid ($34.6 \pm 16.6\%$) was very low in the wet granulated mixtures. Assay values

for the granulated propyl paraben (82.8 ± 4.1%), PEG 6000 (82.0 ± 8.1%), lactose (88.6 ± 2.5%), glucose (88.9 ± 2.1%), and sorbitol (84.2 ± 3.8%) mixtures also did not comply with the USP requirement for sennosides (90–110%) of the labeled amount.

The results of the compatibility study showed that thermal analysis is useful for the determination of reactions between sennosides and excipients, especially when combined with the quantitative analysis of the drug with HPLC. Both DSC and HPLC confirmed no incompatibilities in the dry mixtures. The only inconsistent results between DSC and HPLC were propyl paraben and citric acid that showed an interaction by HPLC and not by DSC. Compatibility evaluation showed that dry powder mixtures could be used to formulate sennosides A and B products. However, when mixed with water – propyl paraben, sodium carbonate, stearic acid, citric acid, PEG, and sugar derivatives such as lactose, glucose and sorbitol – should not be used in sennoside containing products.

Experimental

1. Excipients

The following excipients were used in this study: Lactose (Tablettose®, Meggle Excipients, Germany and Ludipress®, BASF, South Africa), dibasic calcium phosphate dihydrate (Emcompress®, JRS Pharma LP, New York, USA), microcrystalline cellulose (Avicel® pH 101 and PH200, FMC Corporation, Ireland), pregelatinised starch (Starch 1500®, Colorcon, USA), polyvinyl pyrrolidone (Kollidon® 25, BASF), polyethylene glycol 6000 (BASF). Mannitol, gelatin, glucose, magnesium stearate, stearic acid, sorbitol, sodium bicarbonate, sodium carbonate, citric acid, and propyl paraben were obtained from Saarchem (Krugersdorp, South Africa). Sennosides A and B were donated by Novartis (Isando, South Africa).

2. Methods

In this study, 1 : 1 w/w samples of actives and excipients were intimately mixed in a mortar with a pestle, either as dry powders or powders wetted with a small amount of water. The granulated samples were dried in an oven for 1 h at 60 °C. For DSC analysis samples between 2–4 mg were sealed into aluminum pans and then placed in a Shimadzu DSC-50 Differential Scanning Calorimeter (Shimadzu, Japan). The samples were heated at a heating rate of 10 K/min and under a nitrogen purge with a flow rate of 30 ml/min. DSC thermograms of the 1 : 1 w/w mixtures were compared to the thermograms of the individual excipients and sennosides. Incompatibilities were indicated by: elongated or broadened peaks; new peaks; vanished peaks; or shifts in melting endotherms and exotherms. Incompatible mixtures were also evaluated by hot-stage microscopy (Laborlux K, Leitz, Germany). For HPLC analysis of the sennosides, the method described by Muffat et al. (1986) was used. A HP1050 series HPLC and Chemstation data acquisition and analysis software were used (Agilent, California, USA). The column used was a Luna $C_{18}-2$ μm column, 250 × 4.6 mm (Phenomenex, California, USA); mobile phase: methanol: acetonitrile: buffer (240 : 160 : 600 v/v/v); buffer: 0.01 M tetra n-butyl ammonium iodide (3.68 g/l) in water, pH adjusted to 7 using NH_4OH; flow rate: 1.0 ml/min; retention time: ± 9.4 min and 10.9 min for the 2 sennoside peaks; injection volume: 10 μl; detection: UV at 270 nm. The HPLC method complied with USP requirements for method validation. Retention time: sennoside B = 9.4 minutes, sennoside A = 10.9 minutes; number of theoretical plates (N): sennoside B = 7527 plates/column, sennoside A = 6298 plates/column (Tangent method); USP tailing factor (T): sennoside B = 0.95, sennoside A = 1.04; capacity factor (k'): sennoside B = 1.68, sennoside A = 2.09; resolution between peaks: 2.98. A calibration curve of AUC versus drug concentration was linear, $y = 4.59x + 13.9$ ($R^2 = 0.9998$), and was used to determine the concentration of sennoside in unknown solutions.

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References

Araujo AAS, Storpirtis S, Mercuri LP, Carvalho FMS, dos Santos FM, Matos JR (2003) Thermal analysis of the antiretroviral zidovudine (AZT) and evaluation of the compatibility with excipients used in solid dosage forms. Int J Pharm 260: 303–314.

Benzler B, Hoffmann F, Nitschke T (1999) Thermal analysis methods in pharmaceutics. GIT Labor-Fachzeitschrift 43: 1201–1204.

Collins BJ, Grizzle TB, Dunnick JK (2000) Toxicokinetics of phenolphthalein in male and female rats and mice. Toxicol Sci 56: 271–281.

Dunnick JK, Hailey JR (1996) Phenolphthalein exposure causes multiple carcinogenic effects in experimental model systems. Cancer Res 56: 4922–4926.

Dunnick JK, Hardisty JF, Herbert RA, Seely JC, Furedi-Machacek EM, Foley JF, Lacks GD, Stasiewicz S, French JE (1997) Phenolphthalein induces thymic lymphomas accompanied by loss of the p53 wild type allele in heterozygous p53-deficient (±) mice. Toxicol Path 25: 533–540.

Food and Drug Administration (1997) Laxative drug products for over the counter use; proposed amendment to the tentative final monograph. Federal Register 62: 46223–46227. [http://www.access.gpo.gov/su_docs/aces/aces140.html].

Kibbe AH (2000). Handbook of Pharmaceutical Excipients, 3rd ed., Washington, DC, USA: American Pharmaceutical Association, 665p.

Muffat F, Bernard P, Sabot JF (1986) Determination of sennosides A and B in Senna extracts by high-performance liquid chromatography. J Chrom A 396: 261–264.

Tice RR, Furedi-Machacek M, Satterfield DD, Udumudi A, Vasquez M, Dunnick JK (1998) Measurement of micronucleated erythrocytes and DNA damage during chronic ingestion of phenolphthalein in transgenic female mice heterozygous for the p 53 gene. Environ Mol Mutagen 31: 113–124.

USP, United States Pharmacopeia, 24th Ed. (2000). Rockville, MD, USA: United States Pharmacopeial Convention, 2569p.