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Study of triethyl citrate migration from coating polymers to tablet cores

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Migration of plasticizers from film coating polymers towards the core and to the storage medium could result in serious changes in the mechanical properties and permeability of coatings thus greatly influencing rate and extent of drug release. The purpose of the present study was to follow the migration of water soluble triethyl citrate applied as a plasticizer in Acryl-Eze coating by Gas Chromatography/Mass Spectrometry (GC/MS). 20%w/w Acryl-Eze dispersions containing triethyl citrate of different concentrations were prepared. Placebo tablets were compressed and coated with the prepared dispersions. The coated tablets were stored under different relative humidity conditions for different time intervals. Considerable migration of triethyl citrate towards the tablet cores was found. The extent of the triethyl citrate migration was influenced by the relative humidity of the storage medium.

The volatility of a plasticizer depends on its effective vapour pressure and its diffusion rate in the polymer film (Lippold and Pagés 2001). Partial loss of the plasticizer occurs by migration into the core, to the film surface and/or into the packaging material. Loss through volatility (loss at the surface during contact with air) or through migration into the core (during contact with a solid) can occur when material containing non-polymer plasticizers are stored, as well as by hydrolytic cleavage reactions. Due to the loss of plasticizers mechanical stability can be decreased during production or storage and the release rate of the corresponding formulation can be changed. The plasticizer glyceryl triacetate is subject to very rapid cleavage, while triethyl citrate is chemically more stable (Guo 1994; Frohoff-Hulsmann et al. 1999; Thoma and Bechtold 1999). The aim of the present study was to follow triethyl citrate migration into the core of tablets coated with Acryl-Eze under different relative humidity conditions. The Fig. shows the chromatogram of triethyl citrate and that of the dimethylphtalate applied as an internal standard. Triethyl citrate showed considerably migration towards the cores of coated tablets depending on the initial plasticizer concentration of the coating polymer and on the relative humidity of the storage medium. With increasing humidity, triethyl citrate migration into the tablet core was remarkably increased due to the increased water adsorption and the consequent increase of the movement of the water front into the tablet. Although the water solubility of the triethyl citrate is moderate (5.5 g/100 ml at 25 °C), the increase of the triethyl citrate concentration in the polymer film increases the dissolved triethyl citrate content in the adsorbed water which is able to migrate into the tablet core along with the water front. The Table summarizes the migrated triethyl citrate contents of cores of coated tablets stored under different relative humidity conditions for 14 days. Since considerable migration was found within a relatively short storage period, it is essential to evaluate the extent of plasticizer migration to the tablet core for stability tests during the formulation phase of coated dosage forms.

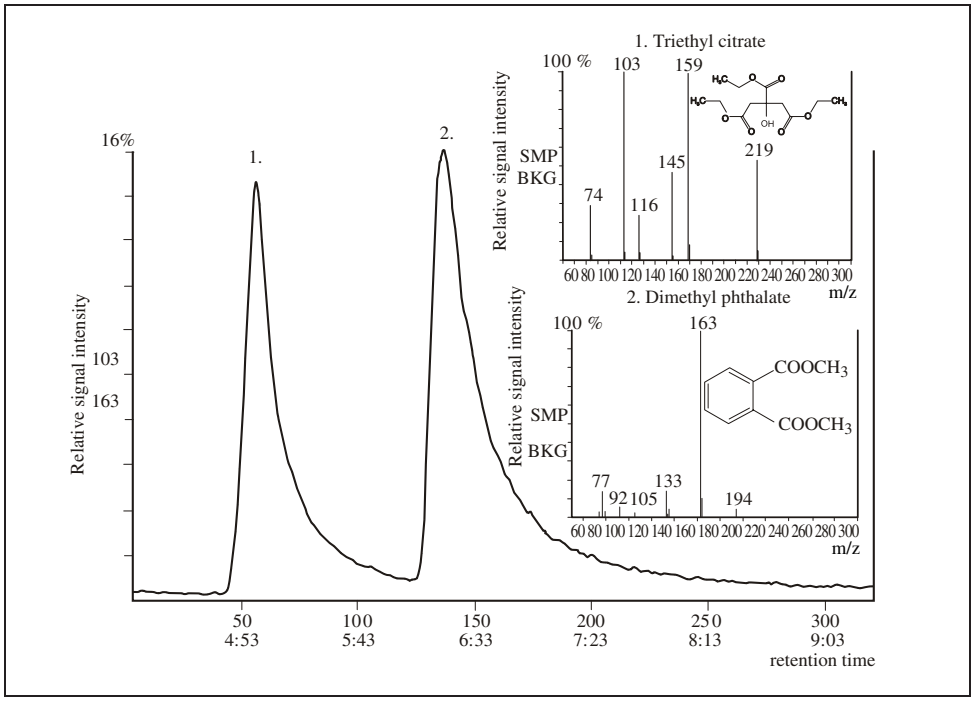

Fig.:
Selective ion monitoring of m/z 103 for triethyl citrate and m/z 163 for dimethylphtalate

Table: Migrated triethyl citrate contents (% w/w) of cores as a function of different relative humidity conditions of the storage medium after 14 days of storage

Relative humidity	Initial triethyl citrate concentration of the coating		
	10% w/w	5% w/w	1% w/w
75%	1.13 ± 0.11	0.56 ± 0.05	0.14 ± 0.01
65%	1.09 ± 0.10	0.47 ± 0.05	0.14 ± 0.01
35%	1.00 ± 0.09	0.44 ± 0.03	0.08 ± 0.01

Experimental

Direct compression was applied to obtain placebo tablets based on Ludipress of 6 mm diameter. The average weight of the tablets was 0.10 ± 0.01 g and the breaking force was 90 N (Erweka). The inner phase of the tablets contained Ludipress and the applied lubricant was 2%w/w Macrogol 4000. 20%w/w Acryl-EZE (Aqueous Acrylic Enteric System, Colorcon, UK) dispersion containing triethyl citrate (Ph.Eur.4) of 1, 5 and 10%w/w concentrations were used for the coating procedure. After the determination of the surface of one tablet, the amount of coating dispersions containing triethyl citrate of different concentrations was calculated to obtain 5.5 g/1000 cm^2 polymer on the core surface of each tablet charge. Fluidized bed coating was achieved with a Aeromatic Strea-1 (Aeromatic AG, Switzerland) laboratory-scale fluidization equipment. The process parameters were the following: Quantity of each charge: 250 g tablets; amount of Acryl-Eze dispersions: 69.2 g; inlet air temperature: 35 °C; drying temperature: 35 °C; atomizing pressure: 2 bar. The coated tablets were transferred into separated desiccators kept at 35%, 65% and 75% RH and room temperature. For storage periods 3, 6, 9 and 14 days were chosen at each RH value. After clearing the coating from the tablet core away with a microtome, the triethyl citrate contents of the tablet cores were quantified by GC/MS. Each sample was dissolved in methanol. A model GCQ mass spectrometer system (Finnigan Corp., Austin, TX) was used with manual split injection (split: 1/50) and 30QC2/BPX5 (SGE) bonded and cross-linked (5% phenyl) methylpolysiloxane capillary column (30 m × 0.25 mm). The temperature of the injection port was 220 °C; the initial temperature of the column was 100 °C and the heating rate was 9 °C/min and the final temperature of the column was 200 °C. The transfer line temperature was constant (200 °C) and the source temperature was 180 °C. Detection was started 4 min after injection. The selective ion method was applied to determine the diagnostic fragments of triethyl citrate (103 m/z) and that of the internal standard (163 m/z). Dimethylphtalate was employed as internal standard and triethyl citrate as external standard. Calibration curves were constructed by plotting the area ratio of triethyl citrate (103 m/z) and internal dimethylphtalate standard (163 m/z) against the amount injected.

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Alkaloids from the bulbs of *Crinum bulbispermum*

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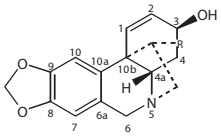
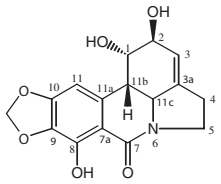
Two new alkaloids, namely 8-hydroxylycorin-7-one and 2-deoxylycorine were isolated from *Crinum bulbispermum* along with the known compounds vittatine, 11-hydroxyvittatine and hippamine.

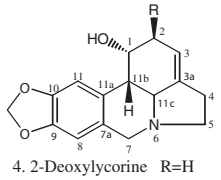
The genus *Crinum* (Amaryllidaceae) is a rich source of alkaloids that are derived mainly from three fundamental types; norbelladine, lycorine and vittatine/crinine-type (Gosal et al. 1985). Many *Crinum* species have been widely used in traditional and modern medicine (Fennell and Van Stader 2001). Recent studies showed that some species of the genus have anti-allergic (Ckpo and Adeyemi 2002a), antianaphylactic (Ckpo and Adeyemi 2002b), analgesic (Ckpo et al. 2001) and anti-inflammatory activities (Samud et al. 1999). Earlier investigations of *C. bulbispermum* grown in Egypt led to the isolation of crinamine, hippadine, powelline and lycorine (El-Moghazi and Ali 1976), crinine and the new alkaloid bulbispermine (Ali et al. 1984). The present study deals with the isolation and structure elucidation of two new alkaloids namely 8-hydroxylycorin-7-one and 2-deoxylycorine, in addition to the known alkaloids vittatine, 11-hydroxyvittatine and hippamine. Structural elucidation of the isolated alkaloids could be achieved using EIMS, 1D- and 2D-NMR spectra.



1. Vittatine R=H
2. Hydroxyvittatine R=OH



3. 8-Hydroxylycorin-7-one



4. 2-Deoxylycorine R=H
5. Hippamine R=OCH_3