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Simultaneous determination of lactose and sodium cromoglycate in a dry powder inhalation formulation

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A method is described for the simultaneous determination of lactose (excipient) and sodium cromoglycate (SCG). SCG, disodium cromoglycate or cromolyn sodium is the sodium salt of the cromoglycic acid and is given by inhalation for prophylaxis of asthma [1]. Lactose is one of the most commonly used excipients in pharmaceutical technology and in dry powder inhalation formulations it is used as a carrier and/or diluent [2].

Several analytical methods have been reported for the determination of SCG based on different techniques: radioimmunoassay [3], spectroscopy, fluorimetry, polarography [4], HPLC [4, 5]; also several have been reviewed for lactose: colourimetric and spectrometric, titrimetric, enzymatic, chromatographic, etc. [6]; the determination of lactose by FIA (Flow Injection Analysis) [7] or by HPLC with refractive index [8] has also been described. The aim of this work was to develop a method for the determination of both substances applicable to Twin Impinger (TI) experiments, where small amounts have to be quantified. The method chosen, for the SCG determination consists of UV spectroscopy at 238 nm [9] and, for the lactose HPLC with refractive index (RI) detection was used enabling the quantification of both lactose and SCG and proved to be useful for solid dosage forms, particularly for dry powder inhalers.

Although HPLC with RI detections is less sensitive and less reproducible than with the UV detector, the results obtained were of sufficient precision for the intended purpose. As RI measurement is highly sensitive to temperature fluctuations [10], the column temperature was controlled using a thermostatted oven. The acetonitrile/water ratio was adjusted in order to obtain the lactose peak at about 5 min. It was demonstrated that SCG was not affected by the evaporation procedure required to quantify it in the lactose mixture and that lactose did not interfere with the SCG quantification.

Calibration data for both substances are presented in Table 1, indicating sufficient linearity and precision. Table 2 summarizes the results obtained from the TI experiments with 3 capsules containing 20 mg of SCG and 20 mg of lactose. Approximately 25% of the SCG was found in the lower compartment while about 4% of lactose settled in that part of the TI. The total recovery was around 95% (SCG) and 93% (lactose), indicating that the method is valid for the *in vitro* testing of dry powder inhalations.

Experimental

1. Materials and equipment

SCG (Industria Chimica Prodotti Francis, S.p.A.), Lt. 570-U-09-02. Granulac 220 (Meggle, D-Wasserburg), batch 958. Phosphate buffer pH = 7.4 (prepared adding 13.63 g KH_2PO_4 and 3.2 g NaOH in a 5000 ml volumetric flask and completing the volume with distilled H_2O and the pH was adjusted if necessary (pH meter, Metrohm, 638). Solvents were of HPLC grade. Water HPLC grade was obtained by distillation from demineralised H_2O and after passing through a 0.45 μm membrane filter. Other reagents were of analytical grade.

The UV/VIS spectrometer used (Perkin-Elmer 550) was set at 238 nm. The HPLC system (Shimadzu) consisted of a dual piston reciprocating pump (model LC-6A), a refractive index detector (model RID 10A), integrator (model C-R6A Chromatopack) and a Rheodyne injector equipped with a 20 μl loop. The column used was a ET 250-4 Nucleosil Carbohydrate column (length × i.d. of 250 × 4 mm, 10 μm particle size) commercialised by Macherey-Nagel. The mobile phase used was CH_3CN/H_2O 72:28 (w/w). The flow rate was set to 2.0 ml/min and the pressure was about 51 ± 1 bar; the run was 7 min and the column was kept at 35 °C in a (heating chamber/oven) column thermostat (Company: Knaur, model BFO-04). The integrator was set as follows: paper speed at 5 mm/min, attenuation = 5, width = 5, slope = 70, minimum area = 10000, stop time = 7 min. The detector was set as follows: auxiliary range = 2, cell temperature = 35 °*C*, balance = 0, RI = 0, range = 10, mode = A.

2. Methods

Standard solutions of SCG and lactose were prepared, from stock solutions of 100 mg/100 ml in phosphate buffer (pH = 7.4), and 1 g/50 ml in H_2O, respectively. In each case the response linearity was determined using seven solutions from the stock standard solution repeating 4 times. The precision (quantified as % CV) was studied with four solutions (at different concentrations for lactose and SCG) measured 6 times each (i.e. the repeatability).

This method was developed as a need for the quantification of the SCG and/or the excipient (lactose) after deposition of a dry powder inhaler in the TI. Thus, the compartments of the TI were rinsed with CH_3OH (using the least volume possible) and transferred to evaporating flasks in order to

Table 1: Calibration data for UV analysis of SCG and HPLC analysis of Lactose

Parameter	SCG	Lactose
Concentration range	0.1–1.6 mg/100 ml	0.3–20 mg/ml
Number of points	28	28
r^2 (relative reduction of Sum of squares)	0.9985	0.9975
Slope	0.5460	111.4E+03
Intercept	0.0035	5.75E + 03
Residual sum of squares	3.53E − 03	4.27E + 10
Coef. variation of the slope	1.36E − 04	1.64E + 09
Regression equation	f(x) = 0.5460x + 0.0035	f(x) = 111.4E + 03x + 5.75E + 03
Precision (coef. variat.; n = 6)	1.7%	3.3%

Table 2: Mean values in mg (SD) for 3 capsules containing a mixture of Granulac 220 (lactose)/SCG (20:20 mg), resulting from the Twin Impinger chemical analysis

Compound	Capsule plus device	Twin Impinger chambers				
		Upper	Medium	Lower	Total (mg)	Total (%)
Lactose	3.69 (0.22)	7.35 (0.41)	6.60 (0.50)	0.87 (0.02)	18.60 (0.21)	93.02 (1.05)
SCG	5.28 (0.19)	4.37 (0.70)	4.40 (0.31)	4.92 (0.51)	18.97 (0.11)	94.86 (0.56)

SD = Standard deviation

evaporate the CH_3OH until dryness using a rotavapour, at a pressure of 0.9 bar. After dryness, 1 ml of HPLC-H_2O was added to the evaporating flasks and shaken until all lactose or lactose and SCG was dissolved (aqueous solution A). All samples (solutions and standard) were filtered through a 0.45 μm membrane filter prior to injection on the HPLC system. The average of 3 replicates of each sample was taken in order to obtain the SCG and/or lactose concentration. If a mixture of both SCG and lactose was studied, the latter was analysed as before and the SCG as follows: 50 μl of the aqueous solution A is placed into a 25 ml volumetric flask and the volume completed with phosphate buffer pH = 7.4. This solution is analysed by UV spectrophotometry according to Braun et al. [9]. If absorption readings were outside the calibration range, the assay was repeated using only 25 μl aliquot diluted to 25 ml.

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Controlled drug release from coherent systems Part 1: Liberation from hydrocarbon gels

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One of the basic tasks of modern pharmaceutical technology is to control drug release. The drug release from coherent systems for external use (ointments, gels, etc.) is influenced by a great number of factors such as vehicle composition, the state of drug distribution, or the structure of the drug/vehicle boundary surface [1–6].

The aim of our experimental work was to perform a detailed study on the relationships between the properties of the drug and drug release. We intended to determine which properties accelerate drug release and which make it slow and prolonged. The following drug properties were studied: (i) the suspended or dissolved state of the drug, (ii) the solubilization of the drug, (iii) the microencapsulation of the drug and (iv) entering the drug into a molecular capsule – into an inclusion complex. Salicyclic acid (SA) was found to be suitable for the examinations. In each experimental series the base was constant so that the relationship between the drug and liberation could be studied. This paper will present the results of liberation obtained with hydrocarbon base.

The Fig. shows the time course of this process. Based on the liberated drug vs. diffusion time functions the process can be described with a power function in which the exponent is about 0.5:

$$Q = Q_0 t^{ma},$$

where Q is the quantity of the liberated drug, Q_0 is liberation at time 0 ($Q_0 \approx 0$), m is the rate constant of the process, a ≈ 0.5.

The correlation coefficient (r) and the values of factors a and m are summarized in the Table. Calculations were made to determine two other constants from the equation; the time required for the liberation of 1000 μg SA and the quantity of SA liberated in 12 h.

The power function gives an exact description of the kinetics of the process, r is invariably between 0.9–1, while the value of a is around 0.5.

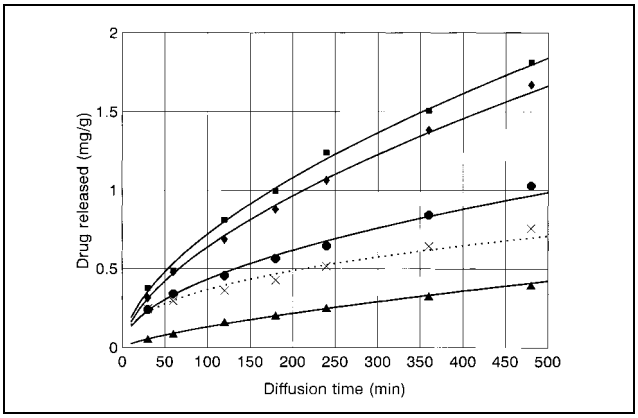

Fig.: Release of salicylic acid from white petrolatum
× SA in suspended state,
◆ SA in dissolved state,
▲ SA in inclusion complex (α-cyclodextrin, physical mixture),
■ SA in solubilized state (surfactant: Cremophor A 25),
● SA in microencapsulated form (covering agent: carboxy-methylcellulose sodium)