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Examination of veterinary boluses containing albendazole and prepared by dry granulation

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The effect of the change of technological process on the physical and the in vitro dissolution properties of boluses was studied. Boluses containing albendazole were prepared leaving the composition unchanged and turning the manufacturing technology from wet to dry granulation using the roll compaction method. Thus, the effect of the preparation method was examined. For comparison purposes, boluses were prepared by direct compression.

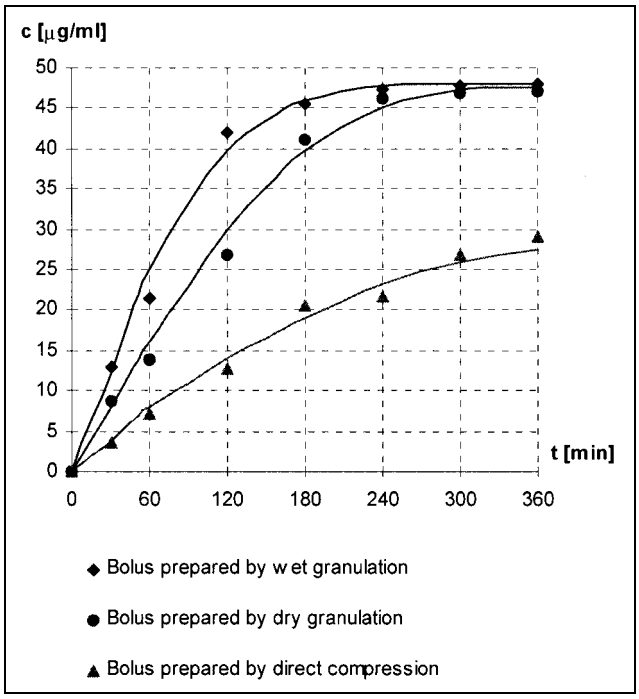
The physical properties of the boluses are compared in the Table. It can be seen that the hardness of boluses prepared by dry granulation is higher than that of boluses prepared by wet granulation. However, the disintegration time of the former is shorter than that of the latter. The relatively high compression strength for bolus preparation by dry granulation promotes the development of closer bonds. Accordingly, the particle size distribution showed that approx. 30% of the particles were larger than 800 μm, compared with approx. 10% in the case of wet granulation. Low hardness of boluses prepared by direct compression can be caused by the laminar structure formed. Here a small particle size ($x < 500$ μm) was dominant (99.3%). The friability of the boluses is low in the first two cases, and increases for a bolus prepared by direct compression, although in the latter case it does not reach the maximum values specified by pharmacopoeias.

In Fig. 1A it can be seen from the dissolution curves that the concentration of the dissolved active ingredient initially increases substantially. After the 260th minute in the case of boluses prepared by wet granulation, or the 330th minute in the case of dry granulation, the dissolution process slows down greatly. Concentrations of the dissolved active ingredient from boluses prepared by dry granulation are lower than those from boluses prepared by wet granulation. In the 120th minute the concentrations of the dissolved active ingredient are 42.0 μg/ml and 26.8 μg/ml, respectively. The bolus prepared by direct compression was found to have the worst dissolution properties (12.7 μg/ml). By comparing the dissolution values of boluses prepared by dry granulation and direct compression with the values of boluses prepared by wet granulation it can be seen that disintegration is a condition but not a guarantee of dissolution. Powdered cellulose (Vitacel F120) and cross-linked polyvinylpyrrolidone (Kollidon CL) used in the outer phase and mixed to the granules form intergranular bonds [1] inside the bolus and help their disintegration to granules via their capillary activity [2]. The dissolution properties are thus determined mainly by the properties of the granule. Higher dissolution from the boluses prepared by wet granulation could be caused by higher porosity of the granules prepared by compaction technology and by the polyvinylpirrolidone (Kollidon 30)

Table: Physical properties of albendazole containing boluses prepared by various technologies

Properties	Boluses prepared by wet granulation	Boluses prepared by dry granulation	Boluses prepared by direct compression
Hardness (N)	215 (± 1.56)	270 (± 2.71)	40 (± 3.69)
Disintegration time (min)	5.50 (± 0.15)	3.50 (± 0.12)	1.25 (± 0.21)
Friability (%)	0.33 (± 0.02)	0.32 (± 0.02)	1.04 (± 0.04)
Particle size ranges (μm)	Quantity in the range indicated (%)	Quantity in the range indicated (%)	Quantity in the range indicated (%)
$1400 < x$	0.00	20.96 (± 0.62)	0.00
$1000 < x < 1400$	0.90 (± 0.13)	6.60 (± 0.85)	0.15 (± 0.07)
$800 < x < 1000$	8.60 (± 0.37)	3.70 (± 0.25)	0.10 (± 0.02)
$500 < x < 800$	22.00 (± 0.53)	7.43 (± 0.48)	0.42 (± 0.04)
$x < 500$	66.60 (± 0.55)	61.31 (± 0.63)	99.33 (± 0.56)

Results are mean values (± SD) for 6 samples



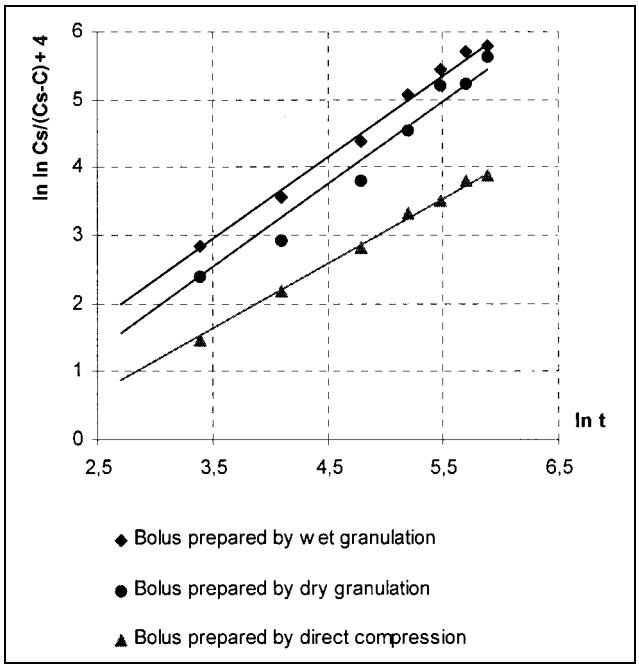


Fig. 1: A: Dissolution of active ingredient of 600 mg albendazole containing boluses prepared by different technological processes; Dissolution medium: artificial rumen fluid (pH: 6.5)
B: Linearized forms of the dissolution curves (Standard deviation of the slope (S_m): 1. (± 0.045); 2. (± 0.091); 3. (± 0.025)

in contact with the active ingredient. Linearized forms of the dissolution curves are compared in Fig. 1B. Values of rate constants for dissolution [3, 4] are (min^{-1}):

$$K_1 = 5.97 \cdot 10^{-3}; \qquad K_2 = 3.15 \cdot 10^{-3};$$
$$K_3 = 2.81 \cdot 10^{-3}.$$

Experimental

1. Preparation of boluses

Aerosil 200 (colloidal silicon dioxide) (Wacker Chemie GmbH), Albendazole USP 23 (Transchem), Potato starch (AVEBE), Kollidon 30 (polyvinylpyrrolidone) (BASF), Kollidon CL (cross-linked polyvinyl pyrrolidone) (BASF), Lactose monohydrate (Pharmatose 200M) (DMV International), Magnesium stearate (Carasco), Vitacel F120 (powdered cellulose) (J. Rettenmaier & Söhne GmbH).

Boluses of identical composition and the same average mass of 2.5 g (2.375–2.625 g; Size: 28.4 × 13.5 × 7.1 mm; oval, round shape) were prepared using three kinds of technology.

Composition of boluses: Inner phase – albendazole (100%) 24.0 w/w %, Pharmatose 200M 40.0 w/w %, Potato starch 12.5 w/w %, Vitacel F120 10.0 w/w %, Kollidon 30 3.5 w/w % (dissolved in water (3.5 g/3.0 ml) when applying wet granulation); Outer phase – Vitacel F120 6.0 w/w %, Kollidon CL 2.0 w/w %, Magnesium stearate 1.0 w/w %.

Equipment: Lödige FM 130 homogenizing device (Lödige), Manesty oscillating sieve (BWI Manesty), Aeromatic fluid bed dryer (Aeromatic – Fielder AG), Frewitt SMG vibrating sieve (Frewitt Apparatebau GmbH).

IR 520 Chilsonator compaction/granulation system (Fritzpatrick): speed of the vertical feed screw (260 rpm), speed of the horizontal feed screw (55 rpm), velocity of the compaction rolls (20 rpm); (the surface texture of the roll was selected depending on the quality of the material), distance between the rolls (1.9 mm), (the gap between the rolls and the resulting thickness of the compacted product were depending on the setting of the above mentioned parameters), pressure applied (air to hydraulic actuator regulates pressure exerted on rolls) (45 bar), rotor speed (300 rpm), screen type (mesh size: 3.18 mm, rough surface, round holes).

Ed. Frogerais excenter tablet press (ed. Frogerais): compression force 15–16 kN.

2. Physical tests

Pharma Test Friabilator PTF, Pharma Test disintegration tester PTZ 1, Pharma Test hardness tester (Pharmatest Apparatebau GmbH).

3. Dissolution experiments

Acetic acid >99.5% (Fluka), ammonium hydroxide 1 M (Fluka), butyric acid >99.5% (Fluka), citric acid (Reanal), propionic acid >99.5% (Fluka), sodium citrate (Reanal), sodium hydroxide (Merck).

Composition of artifical rumen fluid [5]: acetic acid 65 mmol/l, propionic acid 21 mmol/l, butyric acid 14 mmol/l, ammonium hydroxide 5 mmol/l, sodium hydroxide 98 mmol/l.

Equipment: Sotay CE6 dissolution testing apparatus (Sotax AG) with flow through cell. Sample unit of the preparation: 1 bolus (containing 600 mg albendazole); reservoir for the dissolution medium: 12.5 l; temperature (in accordance with temperature of the biological medium): 40.0 ± 0.5 °C. [6]; sample: 5 ml; 13 mm diameter Millex-HV_{13} filters with 0.45 μm pores (Millipore GmbH).

HPLC: Varian 9010 gradient pump, Varian 9065 detector (Polychrom diode array detector), Varian Star chromatographic software, Nucleosil C-18 (octadecyl silica) column, colum length: 250 mm, column inner diameter: 40.0 mm, particle size: 5 μm. Eluent: 85% methanol – 15% distilled water, 25 mM/l dihydrogene phosphate. Flow rate: 1.0 ml/min, detection wavelength: 234 nm, Injection volume: 10 μm.

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The influence of captopril on unsaturated fatty acids in sunflower oil stabilisation

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In our previous paper captopril (1-[(2*S*)-3-mercapto-2-methyl-propionyl]-L-proline) has been shown to have very strong antioxidant properties *in vitro* [1, 2]. Captopril contains a sulphydryl group which was supposed to act as a free radical scavenger. It was established that captopril significantly inhibited the rate of peroxide formation in sunflower oil. The peroxide value is used as one of the basic analytical parameters to monitor autoxidation changes in oils (BP 93, DAB 10, FPV). However, the peroxide value can only generally characterise the changes in oils.

The aim of this work was to find out the mechanism of the captopril induced delay of unfavourable changes in the unsaturated glycerides of fatty acids during autoxidation. A GC method was used to determine the contents of oleinic and linoleic acids in sunflower oil. The antioxidant properties of captopril were compared with those of octyl gallate (as a reference) which is a well known antioxidant, used in the lipid phase. The sunflower oil samples with or without captopril or octyl gallate in concentrations of 0.05%, 0.1% and 0.2% were incubated at 313 K and 333 K.

All samples were analysed in reference to the fresh sunflower oil incubated at 278 K. The fatty acids composition of lipid samples was determined by GC of the corresponding methyl esters [3]. We determined the percentage decrease of oleinic and linoleic acids in sunflower oil in all samples with and without antioxidants. All samples were examined when they had achieved a peroxide value of approximately 10.0 (a limit determining stability of many lipids according to DAB 10).

The results of percentage changes of oleinic and linoleic acids are given in Table. The investigation confirms our

Table: Content of oleinic and linoleic acid in sunflower oil incubated at different temperatures

Temperature	Sample	Oleinic acid (%)	Linoleic acid (%)
278 K	fresh oil	26.6 ± 0.11	63.6 ± 0.15
313 K	oil	21.9 ± 0.20	62.3 ± 0.23
	oil + captopril 0.05%	22.1 ± 0.15	62.4 ± 0.12
	oil + captopril 0.1%	24.1 ± 0.22	63.6 ± 0.21
	oil + captopril 0.2%	24.5 ± 0.10	63.5 ± 0.15
	oil + octyl gallate 0.05%	22.1 ± 0.18	62.0 ± 0.20
	oil + octyl gallate 0.1%	23.9 ± 0.22	63.0 ± 0.14
	oil + octyl gallate 0.2%	24.1 ± 0.18	63.0 ± 0.17
333 K	oil	21.8 ± 0.10	58.5 ± 0.20
	oil + captopril 0.05%	21.6 ± 0.20	57.9 ± 0.20
	oil + captopril 0.1%	23.3 ± 0.12	63.0 ± 0.21
	oil + captopril 0.2%	23.3 ± 0.14	63.4 ± 0.25
	oil + octyl gallate 0.05%	21.9 ± 0.10	58.7 ± 0.15
	oil + octyl gallate 0.1%	22.0 ± 0.18	60.0 ± 0.10
	oil + octyl gallate 0.2%	22.5 ± 0.18	61.8 ± 0.12