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Development and scale up of a new film coated tablet containing dry herba extract

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The paper reports the development and scale up of new film-coated tablets containing dry herba extract, from the Senna plant, containing sennoside A and B. Film coated tablets containing 10 and 20 mg active ingredient were developed. They had the same disintegration, dissolution and stability behaviours as a reference sugar coated dragee.

1. Introduction

During development of a dosage form containing a dry herba extract one has to take into consideration that these kinds of active ingredients usually are hygroscopic and very sensitive to humidity. This was similar in case of our active ingredient, the dry extract of Senna leaves (*Cassia angustifolia* or *acutifolia* [1]). This extract contains Sennoside A and B, hydroxyanthrachinone type glacoside [2] having a laxative effect [3]. In the large intestine (colon) the Senna preparations are hydrolysed by bacteria to release the active free anthrachinones [4, 5].

For protection of an active material against humidity in a solid dosage form sugar or film coating can be used [6–8]. The present paper reports the comparison of different coating compositions on a tablet core containing Senna dry extract.

In addition to 10 mg active ingredient containing tablets, 20 mg film coated tablets were also developed. The scale up was carried out in cases of both tablets to compare the quality and stability of the tablets coated with the best film produced in the laboratory (3 kg) and in 150 kg batch sizes.

2. Investigations, results and discussion

2.1. Choice of the suitable film forming agent

The tablet cores were coated with the film forming agents (see 3.1.) in the Driacoater 500 coating pan (batch size 3 kg). Coating conditions: spray rate: 8–10 g/min, inlet air temperature: 30–50 °C, drum-speed 10–12 RPM, number of the nozzles: 1, Nozzle diameter: 0.8 mm.

The stability data of the coated tablets, tested in varying environments, are presented in Table 1. The results were the same in both tablet strengths. The data show, that the most stable films are numbers 5 and 6 (see 3.1.) and in these cases the active ingredient contents are the highest after 30 d. It could be explained by the high hydrophobicity of the water insoluble components of these films (ethylcellulose and polymethacrylic acid). On the other hand, Hydroxypropyl-methyl cellulose (HPMC) increases sticking of the coatings on the cores containing microcrystalline cellulose.

To prepare the coating suspension 6 one needs to be very cautious because HPMC and Eudragit® can coagulate in the suspension. Taking into consideration the facts above we have chosen the most stable, easiest to use and most humidity resistant film formulation (5) on our core.

To guarantee the same therapeutic effect, the dissolution profile of the film tablet must be the same as the reference sugar coated dragee. The Figure shows the dissolution curves of both dosage forms and the requirements. Taking into consideration the pharmacokinetic properties of the active ingredient, the two different dosage forms containing 10 mg active ingredient are *in vitro* equivalent. The dissolution curve of the 20 mg active ingredient containing film tablet is the same as it can be measured from two 10 mg film tablets dissoluting at the same time.

Table 1: Stability data of the film tablets containing 10 mg Senna dry extract in different humidity areas

Film forming agent	Rel. humidity (%)	After 3 d		After 14 d		After 30 d	
		Weight gain (%)	Sennoside A + B content (%)	Weight gain (%)	Sennoside A + B content (%)	Weight gain (%)	Sennoside A + B content (%)
1	70	2.10	99.20	3.10	98.95	cracked	97.62
	90	cracked	90.40	–	–	–	–
2	70	3.00	97.50	cracked	96.50	–	–
	90	cracked	89.60	–	–	–	–
3	70	1.20	99.80	2.80	99.70	2.85	97.65
	90	9.65	97.21	cracked	98.63	–	–
4	70	1.05	97.63	2.50	96.52	3.00	95.44
	90	cracked	95.57	–	–	–	–
5	70	1.10	99.85	1.64	99.82	1.75	99.79
	90	5.50	99.80	8.00	99.79	8.50	99.70
6	70	2.20	99.91	3.00	98.87	3.50	99.80
	90	5.22	99.79	8.50	99.77	cracked	99.69
Sugar coated dragee	70	3.60	99.65	cracked	99.59	–	–
	90	cracked	98.92	–	–	–	–

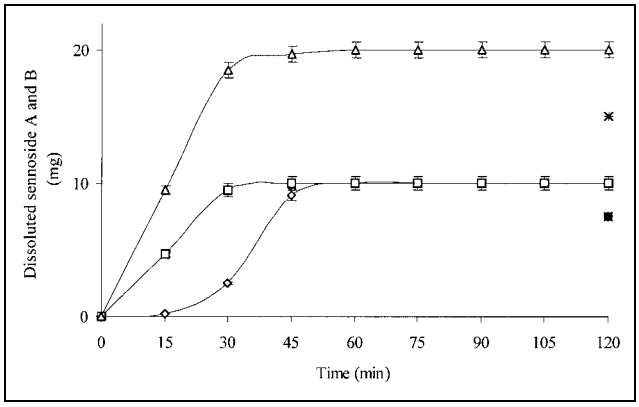

Fig.: Dissolution rate of coated tablets containing 10 and 20 mg Senna dry extract (6 tablets in water, at 37.5 ± 0.0 °C)

—◇— sugar coated dragee
—□— 10 mg film tablet
—△— 20 mg film tablet
—×— USP 23. requirement for 10 mg sennoside content tablets
—✱— USP 23. requirement for 20 mg sennoside content tablets

2.2. Scale-up

The choosen film tablet formulations were produced in the production plant with a batch size of 150 kg (Coating conditions: spray rate: 0.5 kg/min, inlet air temperature: 60 °C, core temperature: 48–50 °C, drum-speed 3–6 RPM, number of nozzles: 5, nozzle diameter: 1.2 mm). The production of the tablet cores and the coating was not problematical. The quality of the cores and the film tablets was the same as the quality of those prepared in the 3 kg lab batch size (Table 2).

2.3. Stability data

To evaluate the stability of the coated tablets produced in the laboratory as well as in large batch size, stability tests were carried out according to the ICH Guidelines. The tablets were packed into blister packs, the storage conditions were: 25 ± 2 °C; 30 °C/60% RH and 40 °C/70% RH. The active ingredient content, dissolution profile and physical parameters of the film tablets are comparable to the starting data after 6 months (Table 3).

3. Experimental

3.1. Materials

On the tablet cores the following coating formulations were tested:
Eudragit L 12.5% solution in propan-2-ol [9] (Röhm Pharma, Darmstadt, Germany): film forming agent 1.
Sepifilm 003 [10] (Seppic, Paris, France) 12% solution in water contains HPMC and 1% of titanium dioxide: film forming agent 2.
Opadry-OY-AM (colorcon ltd., Orpington, UK) 12.5% solution in water (contains maltodextrin, titanium dioxide, polyethylene glycole 400 and 4000, sodium alginate and colloidal anhydrous silica). film forming agent 3.
Opadry-OY-D (Colorcon Ltd., Orpington, UK) 12.5% solution in water (contains HPMC 3cP, titanium dioxide, polyethylene glycole 400, sodium laurylsulphate and talc): film forming agent 4.
Ethylcellulose water dispersion, Aquacoat E30D [11] (FMC Corporation, Philadelphia, USA) mixed with 35% HPMC (pharmacoat 606, USP, FMC Corporation, Philadelphia, USA) contains talc, iron(III)-oxide pigment colourant, titanium dioxide, polyethylene glycole 6000, in a water solution with 12% solid content: film forming agent 5.
Polymethacrylic acid water dispersion (Eudragit L30D, Röhm Pharma, Darmstadt, Germany) mixed with HPMC (Pharmacoat 606, FMC Corporation, Philadelphia, USA) in 1 : 5 ratio, in a water solution with 12.5% solid content: film forming agent 6.

Table 2: Quality parameters of the cores and the coated tablets produced in 3 kg and 150 kg batch size

Parameter	Cores		Coated tablets	
	Lab scale (3 kg)	Large scale (150 kg)	Lab scale (3 kg)	Large scale (150 kg)
Tablet weight (mg)	200.8	200.7	237.0	235.0
Weight-uniformity (%)	−1.0; +0.8	−1.0; +1.0	−2.0; +2.0	−2.0; +1.0
Disintegration time (min)	20	20	25	20
Friability (%)	0.1	0	–	–
Tablet hardness (N)	128–152	120–160	230–315	249–320
Sennoside A + B content (%/tablet weight)	98.5–101.2	98.7–100.5	98.23–100.2	98.5–100.1
Dissolution rate (%)				
after 15 min	–	42–49	–	41–49
after 30 min		95–102	–	95–101

Table 3: Quality parameters of the cores and the coated tablets produced in 3 kg and 150 kg batch size after 6 month storage in different areas (packaged in PVC/Alu blisters)

Parameter	Lab scale (3 kg)				Large scale (150 kg)			
	Initial	25 ± 2 °C	30 °C/60% RH	40 °C/70% RH	Initial	25 ± 2 °C	30 °C/60% RH	40 °C/70% RH
Tablet weight (mg)	232.4	232.9	233.1	233.8	232.6	232.8	233.1	233.5
Disintegration time (min) (Water, 37.5 °C)	24	25	30	30	25	29	30	30
Loss on drying (%) (60 °C, constant weight)	3.0	4.1	4.3	4.9	3.1	4.2	4.4	4.9
Tablet hardness (N)	249–320	290–321	227–268	134–172	290–315	280–311	217–249	129–172
Sennoside A + B content (%)	98.2–100.2	98.8–100.0	99.2–99.9	97.7–98.9	98.5–100.1	98.4–100.0	98.7–99.9	97.9–98.9
Dissolution rate (%)								
after 15 min	42.0–49.0	40.5–45.5	39.0–44.5	35.0–40.2	41.0–49.9	40.1–44.9	39.1–44.3	34.9–40.1
after 30 min	95.0–102.0	90.2–100.0	90.2–99.9	82.0–85.4	95.0–101.0	90.2–99.9	89.9–98.9	81.0–86.4

Gummi arabicum (Riedel de Haen AG, Hannover, Germany) mixed with HPMC (Pharmacoat 606, FMC Corporation, Philadelphia, USA) in 1 : 1 ratio, in a water solution with 12.5% solid content: Agent 7.

3.2. Tablet cores

The tablet cores contain active ingredient, microcrystalline cellulose, Avicel pH 200 [12] as filling agent, and magnesium stearate as glidant.

3.2. Equipment

The tablet cores were compressed by direct pressing by Ronchi 8M (Officine Meccanice F.illi Ronchi, Milano, Italy) and Manesty express (Manesty Machines Ltd., Liverpool, UK) rotary tableting machines with rotating paddle feeder. The tableting force in both cases was 30 kN, speed of machines: 15 000 tablets/h.
Coating of the tablet cores in the laboratory scale (3 kg) was performed using a Driacoater 500 (Driam Metallproduct GmbH & Co. KG., Friedrichshafen, Germany), and in the production plant (batch size 150 kg) in a Driacoater 1600 (Driam Metallproduct GmbH & Co. KG., Friedrichshafen, Germany) coating pan.

3.4. Analytical methods

3.4.1. Physical tests

The tablet core hardness and friability were measured by an Erweka TB-24 (Erweka GmbH, Heusenstamm, Germany) tester. The disintegration time was measured by a Pharmatest PTZ-1 (Pharmatest Apparatebau GmbH, Hainburg, Germany) apparatus [13] in purified water at 37.5 ± 0.5 °C.

3.4.2. Dissolution testing

The USP 23 Paddle method was employed at a rotational speed of 100 RPM. 1000 ml of 0.1 N HCl were used as dissolution medium at 37.5 ± 0.5 °C. Six coated tablets of each were tested. Samples were removed at 15, 30, 45, 60, 80, 100 and 120 min, filtered and assayed spectrophotometrically at 346 nm by a UV-308 Spectrophotometer (Labor MIM, Budapest, Hungary).

3.4.3. Stability tests

To compare the stability of the tablets coated with different film forming agents with that of the sugar coated dragees, the weight gain of the bulk coated tablets and the active ingredient content were measured at ambient temperature in 70% and 90% relative humidity (RH) areas. Accelerated stability test of the best coated tablets was carried out according to ICH Guidelines with tablets packed bottles as well as PVC/Al blisters, in 30 °C/60% RH and 40 °C/70% RH areas. The measurement of the active ingredient content were carried out by a HP 8452-A diode-array UV-Visible spectrophotometer (Hewlett-Packard Co., Toulose, France) om 346 nm wavelength. The results were the same as with the HPLC method described by Momma [14].

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