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FAST DISINTEGRATING TABLETS CONTAINING *RHODIOLA ROSEA* L. EXTRACT

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Abstract: Tablets with 250 mg of *Rhodiola rosea L.* extract disintegrating in less than 10 min were developed. The influence of the extract content and type of fillers and disintegrants on disintegration time and tablet hardness was evaluated. Type of the filler and the extract/filler ratio but not the type of disintegrant determined fast disintegration of the tablets. It was demonstrated that the extract:filler ratio lower than 1:1.5 enables preparation of tablets with the required disintegration time. The tablets containing microcrystalline cellulose as a filler, povidone as a binder and crospovidone as a disintegrant were stable during 6 months storage at 25°C/60% RH, however, due to the decrease of hardness they did not pass the stability test at 40°C/75% RH.

Keywords: *Rhodiola rosea*, herbal extract, tablets, disintegration, stability.

In Eastern Europe and Asia *Rhodiola rosea* L. (roseroot) is a popular plant in traditional medicine with many pharmacological properties, used mainly as an adaptogen for regulation of the nervous system. The *Rhodiola rosea* L. roots contain a range of biologically active substances including phenylpropanoids like rosavin, rosarin, rosin, salidroside and tyrosol, regarded as responsible for the pharmacological activity (1-3).

Rhodiola rosea L. extracts are standardized for rosavin content which is 1-3.6% and the recommended daily therapeutic dose of the extract, depending on rosavin content, is from 100-170 mg to 600 mg (2, 3).

The aim of this work was to develop tablets which contain up to 500 mg of roseroot extract. Although bioavailability study of the active substances from herbal preparations is still not a common requirement but tablets or capsules should be developed considering biopharmaceutical properties like dissolution rate and disintegration time. Disintegration is a process preceding the liberation of the active substance from drug formulation and its absorption *in vivo*. Slow or incomplete disintegration leads to a low bioavailability of the active substance (4, 5). Herbal dry extracts, mainly due to their hygroscopic nature (6-9), usually increase tablet hardness and prolong disintegration time and this is why production of tablets containing high doses of extracts is often impossible (6, 9-11). Moreover, tablets with herbal extracts are more sensitive to the environment conditions (6) and higher humidity during storage affects their physicochemical characteristics what is easily demonstrated by disintegration time determination (6, 12).

The pharmacopoeial disintegration test can be a good tool to confirm appropriate composition and stability of herbal tablets in respect to their ability to provide large surface area for the following dissolution process (5). Generally, for uncoated tablets disintegration time (DT) longer than 15 min is unacceptable (13).

Among the excipients used for the herbal tablets the choice of disintegrants and fillers is a critical step for development of products which possess short DT and are stable during storage. In the present work the effect of the content of extract and type of the fillers and disintegrants on DT and hardness of the tablets with *Rhodiola rosea* L. extract was studied.

The aim of the study was to develop herbal extract containing tablets with the disintegration time less than 15 min.

EXPERIMENTAL

Materials

Dry extract of *Rhodiola rosea* L. roots was obtained from Tianjin Jianfeng Natural Product

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(P.R. China). The extract was standardized to contain 1.0% salidroside and 3.0% rosavin. The extract was mixed with microcrystalline cellulose in the ratio 10:1 to reduce its hygroscopic properties while handling.

The following tablet excipients were used: lactose monohydrate (Bufa, Uitgeest, The Netherlands), microcrystalline cellulose (Avicel PH 101; FMC, Brussels, Belgium), povidone (Kollidon K-30; Fluka Chemie, Steinhein, Germany), crospovidone (Kollidon CL; BASF, Ludwigshafen, Germany), Copovidone K 28 (Kollidon VA 64; BASF, Ludwigshafen, Germany) – used for direct compression, cross-linked sodium carmellose (Ac-Di-Sol, Brussels, Belgium), sodium starch glycolate type A (Primojel, Generichem, Little Falls, USA), potato starch (Brenntag, Mulheim, Germany), sorbitol (Neosorb; Roquette, France), hypromellose (USP; Shin-Etsu Chemical, Tokyo, Japan) – used once as a binder, colloidal silicon dioxide (Aerosil; Cabot Corporation, USA), macrogol (PEG 4000; Merck, Darmstadt, Germany), calcium phosphate, dibasic anhydrous (JRS Pharma, Rosenberg, Germany), talc (Merck, Darmstadt, Germany), and magnesium stearate (Faci, Carasco, Italy).

Preparation of tablets

Tablets were prepared by wet granulation of the powder mixture. Three types of tablets containing 500 mg of the *Rhodiola rosea* L. extract were prepared as indicated in Table 1: with 400 mg of a filler either with or without disintegrants (60 mg) and without fillers but with 400 mg of a disintegrant. Fillers were mixed with *Rhodiola rosea* L. extract and appropriate amount of 5% w/w aqueous povidone solution was added as a binder (0.6-4.0% of tablet mass, depending on the formulation). The moist mass was passed through a 0.8 mm sieve and the resulting granules were dried at 40°C to a final moisture content 3-6%. The agglomerates were eliminated by forcing the dried granules through 0.8 mm sieve. The resulting granules were mixed with crospovidone as a disintegrant. Magnesium stearate (0.5%) and talc (2%) were also added as a lubricant and glidant, respectively. In the case of formulations containing no fillers, disintegrants were added before granules with the binder were formed.

The granules were compressed by means of spherical punches (13 mm in diameter) using laboratory single-punch (Korsch type FE 236 hFC, Berlin, Germany) or rotary tablet press (Erweka RTP-D8, Hausenstamm, Germany).

For comparison, tablets containing neither fillers nor disintegrants were prepared by direct compression of the *Rhodiola rosea* L. extract and magnesium stearate powder mixture.

In order to evaluate the effect of the *Rhodiola rosea* L. extract on disintegration time, tablets with various content of the extract and different extract/microcrystalline cellulose ratio were prepared using the granulation methods described above and tabletted with 11 mm or 13 mm punches

Table 1. Disintegration time of tablets containing 500 mg of the *Rhodiola rosea* L. extract and different fillers and disintegrants (povidone was used as a binder).

Disintegrant	Content [mg]	Filler (400 mg)	Disintegration time [min]
—	—	—	20-22 *
		Lactose	31-32
		Lactose : Sorbitol 1:1	19-21
Crospovidone	60	Lactose	29-32
		Sorbitol	10-16
		Calcium phosphate	33-39
		Colloidal silicon dioxide	26-40
		Macrogol	> 60
		Microcrystalline cellulose	33-40
Crospovidone	400	—	22-24
Potato starch	400	—	> 60
Sodium starch glycolate	400	—	45-50
Cross-linked sodium carmellose	400	—	25-29

* – tablets produced by direct compression

Table 2. The effect of the *Rhodiola rosea* L. extract content and extract/filler ratio on the disintegration time and hardness of tablets containing microcrystalline cellulose (MC) as a filler and crospovidone (6.4% w/w) as a disintegrant.

Extract content [mg]	Extract : MC ratio	Tablets mass (diameter)	Hardness [N]	Disintegration time [min]
100	1 : 8	1031 mg (13 mm)	60.4	< 1
	1 : 4	573 mg (11 mm)	72.9	< 1
200	1 : 3.5	1014 mg (13 mm)	68.2	< 1
	1 : 2	669 mg (12 mm)	114.7	2-15
	1 : 1.5	555 mg (11 mm)	129.0	14-20
	1 : 1	444 mg (10 mm)	112.0	27-44
250	1 : 2.6	1009 mg (13 mm)	120.7	< 1
	1 : 2	837 mg (13 mm)	124.5	2-8
	1 : 1.2	611 mg (11 mm)	66.0	9-19
	1 : 0.8	500 mg (11 mm)	127.8	39-47
300	1 : 2	1003 mg (13 mm)	84.0	1
	1 : 1.5	832 mg (13 mm)	154.6	14-26
400	1 : 1.25	1000 mg (13 mm)	139.5	15-21
500	1 : 0.8	1000 mg (13 mm)	95.2	33-40

Table 3. Stability of tablets containing *Rhodiola rosea* L. extract: A – 500 mg and sorbitol as a filler; B – 250 mg and microcrystalline cellulose as a filler (batches B1 and B2 prepared with single punch and rotary press machine, respectively).

	Time of storage	Formulation A	Formulation B1	Formulation B2
25°C/60% RH				
Disintegration time [min]	t = 0	14-15	1-3	3-7
	1 month	20-23	1	2-7
	3 months	> 30	1-2	5-9
	6 months	n.s.	2	5-8
Hardness [N]	t = 0	70.7 ± 6.9	124.5 ± 7.6	117.8 ± 8.2
	1 month	85.5 ± 5.2	116.0 ± 1.4	118.3 ± 16.4
	3 months	97.5 ± 22.2	111.6 ± 17.4	121.5 ± 7.7
	6 months	n.s.	n.s.	115.8 ± 6.2
40°C/75% RH				
Disintegration time [min]	1 month	19-20	1	1-3
	3 months	> 30	1	1
	6 months	n.s.	< 1	< 1
Hardness [N]	1 month	160.1 ± 5.8	106.1 ± 5.2	98.8 ± 4.2
	3 months	290.8 ± 182.1	71.5 ± 14.6	72.9 ± 8.9
	6 months	n.s.	46.3 ± 2.4	33.6 ± 1.8

ns. – not studied

(Table 2). Crospovidone (6.4% w/w) was used as a disintegrant in these formulations.

Analysis of tablets

Disintegration time

The disintegration time (DT) of tablets was determined according to Ph. Eur. 5 using a disintegration tester (Pharma Test, Hainburg, Germany). Six tablets randomly selected from each batch were used for the test. The disintegration medium was distilled water maintained at 37±0.5°C.

Tablet hardness

Twenty tablets randomly selected from each batch were used for the test. Erweka automatic hardness tester type TBH 20 (Erweka, Heusenstamm, Germany) was employed.

Stability

For the stability testing two formulations exhibiting the shortest disintegration times were selected. Formulation A contained 500 mg of the *Rhodiola rosea* L. extract and sorbitol (400 mg) as a filler, while formulation B was prepared with 250 mg of the extract and microcrystalline cellulose (500 mg) (Table 3). The amounts of povidone, talc and magnesium stearate were the same as for all other formulations. Two batches of formulation B were prepared using a single punch (B1) and rotary (B2) tabletting machine, both equipped with 13 mm punches.

The tablets were placed in closed plastic jars in climatic chambers at 25°C/60% RH and at 40°C/75% RH. The analysis of hardness, disintegration time and tablet mass was performed after 1, 3 and 6 months.

RESULTS AND DISCUSSION

Rhodiola rosea L. dry extract is a compressible substance which can be tabletted practically without other excipients. Tablets containing 500 mg of the extract and magnesium stearate (0.5 %) were easily produced, however, they were hard, with disintegration time about 20 min (Table 1). When direct compression was performed, disintegrants like potato starch, crospovidone and cross-linked sodium carmellose (8%) did not reduce DT sufficiently (data not presented).

A good compressibility of the extract is most probably caused by its water content which was 3.9% w/w. Since the physical properties of the extract batches usually are not reproducible, what can affect flowability of the powder during tabletting and cause serious problems in uniformity of the final product, the most common method of herbal tablet production is through a granulation step. Thus all other investigated formulations were prepared using this method.

Different fillers and disintegrants were used in the process while the binder solution was 5% w/w povidone. Table 1 presents DT of tablets containing 500 mg of the *Rhodiola rosea* L. extract and most common fillers and disintegrants used in tabletting technology.

The only filler which enabled preparation of tablets with DT below 16 min was sorbitol. These tablets disintegrated by surface dissolution. Interestingly, sorbitol allowed for shorter DT than lactose, although the former is usually used for prolonging disintegration time, for example in compressed lozenges. The same effect was observed for tablets with no disintegrant – replacing part of lactose by sorbitol resulted in reduction of DT from 30 min to 20 min.

Different types of crospovidone as well as cross-linked sodium carmellose were introduced to the sorbitol containing tablets but no further reduction of DT was achieved (data not presented). This allowed to conclude that disintegration time can not be reduced in tablets which disintegrate by surface dissolution. It can be also noticed that crospovidone did not reduce the DT of tablets with lactose either (Table 1).

When fillers were removed from the composition and replaced with disintegrants, no improvement in DT was observed, but even opposite effect occurred, since DT values were in the range of 22-60 min and above.

The results of this part of the study indicated that neither fillers which can theoretically largely reduce hygroscopic and compacting properties of the extract, nor disintegrants allow for preparation of fast disintegrating tablets with *Rhodiola rosea* L. extract used in a dose 500 mg per tablet. The failure to develop tablets in this stage of the study was most probably related to the high dose of the extract which acts as a strong binder.

In the next step of the investigation the relationship between extract/filler ratio and DT was studied. Table 2 presents the results for tablets containing microcrystalline cellulose (MC) as a filler and povidone as a binder. It is evident that low extract/MC ratio allows for preparation of tablets disintegrating immediately, within less than 1 min, while their hardness is also reduced. Sufficiently low extract/MC ratio can not be used, however, for tablets with the extract content higher than 300 mg since the size and mass of the tablet is a limiting factor. Tablets with the mass not exceeding 1000 mg are of the acceptable size and the results indicate that up to 300 mg of the extract may be incorporated while DT is still below 1 min. For the extract/MC ratio 1:1.5 or higher DT exceeded 15 min.

Tablets containing 250 mg of *Rhodiola rosea* L. extract and extract/MC ratio 1:2.0 were studied for stability. Two batches were prepared using either a single-punch or rotary tabletting press. Despite of the similar hardness the tablets prepared on a rotary press disintegrated within 2-9 min, while for tablets prepared on a single punch machine DT was 1-3 min (Table 3). Stability studies proved that the formulations retained their ability to disintegrate fast for 3 months of observation. After 6 months of storage at room temperature no change in the studied parameters was observed. However, the hardness of tablets

stored at 40°C/75% RH was largely reduced what resulted in an immediate disintegration. The tablets were stored in standard capped plastic jars and the conclusion is that better protection against moisture should be provided for the tablets to achieve required stability.

For comparison, the best formulation among those prepared with 500 mg extract i.e. containing sorbitol as a filler was also subjected to the stability studies (Table 3, formulation A). In this case after 3 months of storage significant increase in tablet hardness and DT was observed that was related to the high extract/filler ratio and the resulting hygroscopic properties of tablets. In the presence of moisture sorbitol, unlike microcrystalline cellulose, forms hard tablet cores.

It may be concluded that for short DT of tablets containing dry extracts the most relevant is sufficient content of a filler expressed by a low extract/filler ratio, while the choice of disintegrants is less important. It was observed that disintegrants are not effective in formulations which exhibit long DT due to binding properties of the herbal extract not being reduced by a filler. Surprisingly, in tablets containing 500 mg of the *Rhodiola rosea* L. extract sorbitol allowed for shorter DT in comparison with other filler, however, stability of such tablets was very poor. Stable, fast disintegrating formulation was produced with lower dose of the extract (250 mg) using MC as a filler.

REFERENCES

1. Brown R.P., Gerbarg P.L., Ramazanov Z.: HerbalGram, 56, 40 (2002).
2. [Anonymus]: Altern. Med. Rev. 7, 421 (2002).
3. Kelly G.S.: Altern. Med. Rev. 6, 293 (2001).
4. Kristensen J., Schaefer T., Kleinebudde P.: Drug Dev. Ind. Pharm. 28, 1201 (2002).
5. von Eggelkraut-Gottanka S.G., Abed S.A., Müller W., Schmidt P.C.: Pharm. Develop. Technol. 7, 433 (2002).
6. Soares L.A.L., Ortega G.G., Petrovick P.R., Schmidt P.C.: AAPS PharmSciTech. E 359 (2005).
7. Soares L.A.L., Ortega G.G., Petrovick P.R., Schmidt P.C.: AAPS PharmSciTech. E 367 (2005)
8. Eder M., Mehnert W.: Pharmazie, 53, 285 (1998)
9. Schiller M., von der Heydt H., März F., Schmidt P.C.: S.T.P. Pharma Sci. 13, 111 (2003).
10. Onunkwo G.C., Egeonu H.C., Adikwu M.U., Ojile J.E., Olowosulu A.K.: Chem. Pharm. Bull. 52, 649 (2004).
11. Rocksloh K., Rapp F.R., Abu Abed S., Muller W., Reher M., Gauglitz G., Schmidt P.C.: Drug Dev. Ind. Pharm. 25, 1012 (1999).
12. Alebiowu G., Femi-Oyewo M.N.: Phytother. Res. 12, 123 (1998).
13. Polish Pharmacopoeia, 6th edition, PTFarm, Warsaw (2002).

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