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Original Article

Rationale for Manufacturing of Cut-Pressed Granules from Herbal Raw Material Rich in Essential Oil: An Example of Chamomile Flowers and Sweet Flag Rhizome

Olga Trifonova[1,2], Olga Evdokimova[3], Vera Prokofieva[4], Alexey Matyushin[5,*]

ABSTRACT

Background: Currently, there are at least 43 different dosage forms present on the Russian Federation pharmaceutical market. A novel, unique dosage form – cut-pressed granules (CPG) – was developed in order to improve manufacturing characteristics and, therefore, quality of herbal drug products released in tea bags. However, treatment conditions may result in decreased levels of active substances in some of the plants, especially those containing essential oil, which is prone to degradation. The aim of this study was to assess feasibility of CPG manufacturing from herbal raw material rich in essential oil. **Materials and Methods:** Different morphological groups of raw material from two commonly used medicinal plants, chamomile (*Matricaria recutita* L.) flowers and sweet flag (*Acorus calamus* L.) rhizome, were chosen as the objects of the study. Qualitative composition of lipophilic constituents in herbal raw materials and CPG was assessed using thin-layer chromatography. Essential oil content was determined by steam distillation. **Results:** The results confirmed equivalence of chromatographic profiles for the analyzed raw materials and CPG; thus, granulation didn't affect qualitative composition of lipophilic components in chamomile flowers and sweet flag rhizome. The study also showed that the granulation process, in fact, promoted stability of the dosage form: during long-term storage the content of essential oil in all of the assessed cut-pressed granules was equivalent or higher than in corresponding herbal raw material. **Conclusions:** It can be concluded that *Matricaria recutita* L. flowers and *Acorus calamus* L. rhizome can be used as herbal raw material for CPG manufacturing.

Key words: Chamomile, Cut-pressed granules, Dosage form, Essential oil, Herbal drugs, Sweet flag.

Olga Trifonova[1,2], Olga Evdokimova[3], Vera Prokofieva[4], Alexey Matyushin[5,*]

[1]Department of Pharmacy, Sechenov First Moscow State Medical University, Moscow, RUSSIAN FEDERATION.
[2]JSC "Krasnogorskleksredstva", Krasnogorsk, RUSSIAN FEDERATION.
[3]Federal State Budgetary Institution Scientific Centre for Expert Evaluation of Medicinal Products of the Ministry of Health of the Russian Federation, Moscow, RUSSIAN FEDERATION.
[4]A.P. Arzamastsev Department of Pharmaceutical and Toxicological Chemistry, Sechenov First Moscow State Medical University, Moscow, RUSSIAN FEDERATION.
[5]Department of Analytical and Forensic Toxicology, Sechenov First Moscow State Medical University, Moscow, RUSSIAN FEDERATION.

Correspondence

Alexey Matyushin

Sechenov First Moscow State Medical University, 8, Trubetskaya st., Moscow, 119991, RUSSIAN FEDERATION.

Phone no: +7 906-705-75-52;

E-mail: matyushin@sechenov.ru

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INTRODUCTION

Providing access to the novel safe and effective high-quality medicinal products is the ultimate aim of the pharmaceutical industry. Although synthetic drug products and biologics remain in leading positions in key markets, products of herbal origin begin to draw more and more attention of the researchers and manufacturers. New herbal medicines can reach consumers in two ways: either by comprehensive study of various medicinal plants or by development of novel dosage forms. Currently, there are at least 43 different dosage forms present at the Russian pharmaceutical market; only some of them are actually utilized for herbal drugs.[1] This justifies the necessity for interdisciplinary development of prospective dosage forms for medicinal herbal products.

Among various herbal preparations, infusions and decoctions are traditionally in well-earned favor. Optimal extraction of biologically active substances into aqueous media is influenced by several conditions, the degree of fineness being the most crucial one. Excessively large particles of herbal raw material fail to release enough active constituents, whereas exceedingly small powder contaminates extract with plant tissue particles and inert substances. Besides, herbal powders often demonstrate poor flow properties, which often hinder exact dosing on high-performance manufacturing lines. This negative factor affects most of the cut and powdered dosage forms, including herbal drugs released in tea bags; it is usually mitigated by special treatment of herbal raw material.[2-4]

These aspects have led to the development of a novel, unique dosage form for herbal medicinal products – cut-pressed granules (CPG). This dosage form provides better dosing accuracy and, therefore, improved consistency of aqueous infusions. Besides, it enhances mixing uniformity if the herbal raw material consists of different morphological groups (i.e., flowers, leaves, etc.).[5-8]

Despite obvious advantages, CPG should be manufactured only using raw material that does not degrade during processing.[9] Feasibility of granulation should determined on case-by-case basis, confirming that the qualitative and quantitative composition of the material does not significantly change during processing.

Essential oils are widely used by pharmaceutical and cosmetic industry due to their pharmacological and aesthetic properties. Comprised of various lipophilic components, they are prone to degradation

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during storage.[10] This is also true for the herbal material containing essential oils. For example, essential oil content in chamomile significantly changes during long-term storage, decreasing by 46% during 31-month storage at 16 °C and 60 percent relative humidity.[11] Therefore, the aim of current study was to assess possibility of CPG manufacturing from two commonly used herbal raw material rich in essential oil – flowers of chamomile (*Matricaria recutita* L.) and rhizome of sweet flag (*Acorus calamus* L.), and to assess possible loss of essential oil during processing.

MATERIALS AND METHODS

Commercial batches of powdered chamomile flowers (*Matricaria recutita* L., flos; corresponds to the requirements of the State Pharmacopoeia[9]) and powdered sweet flag rhizome (*Acorus calamus* L., rhizome; corresponds to the requirements of the State Pharmacopoeia[12]) were used in the study. All chemicals used in the study were of reagent grade. Reference standards were obtained from PhytoLab (Germany).

Both types of herbal raw material were reduced to particles passing through mesh 10 sieves. After that the material was treated with saturated steam for 3-4 minutes under constant stirring. Next, moistened material was transferred into extruder and was forced though 5-7 mm aperture yielding 10-30 mm cylinders, which were transferred to the air dryer. After cooling, obtained cylinders were ground to granules passing through mesh 10 sieve.

Qualitative analysis of lipophilic compounds in powdered raw material and obtained CPG was performed using thin-layer chromatography (TLC) on TLC Silica gel 60 F254 plates (Merck, Germany). Samples were further grounded to particles passing through mesh 18 sieve. About 1,0 g of the powdered material or granules were places into a 100 ml ground glass Erlenmeyer flask, 10 ml of 95% ethyl alcohol were added, and the flask was heated on a boiling water bath under backflow condenser for 20 minutes. After cooling to a room temperature, the content was filtered through a paper filter, obtaining *Test Solutions.*

About 0.005 g of Sudan III reference standard (reagent grade, Ph.Eur.) were dissolved in 10 ml of 95% ethyl alcohol, obtaining *Sudan III Reference Solution.*

About 0.0025 g of Sudan Red G reference standard (reagent grade, Ph.Eur.) were dissolved in 10 ml of 95% ethyl alcohol, obtaining *Sudan Red G Reference Solution.*

About 0.01 g of menthol (reagent grade, Ph.Eur.) were dissolved in 10 ml of 95% ethyl alcohol, obtaining *Menthol Reference Solution*

During TLC analysis of *M. recutita* flowers, 20 µl (0.02 ml) of *Test solution* and 10 µl (0.01 ml) of *Sudan III Reference Solution* were applied to a 100×100 mm TLC plates as 10 mm bands.

In case of *A. calamus* rhizome, 10 µl (0.01 ml) of *Test solution* and 5 µl (0.005 ml) of both *Sudan Red G Reference Solution* and *Menthol Reference Solution* (one over another) were applied to a 100×100 mm TLC plates as 10 mm bands.

Following application, the plated were dried for 15 min at room temperature and placed in pre-saturated for 30 min TLC chambers (Camag, Switzerland) lined with filter paper. *Test solutions* of *M. recutita* powdered flowers and CPG were eluted using chloroform, whereas *A. calamus* rhizome *Test solutions* were eluted utilizing mixture of toluene-ethyl acetate (95:5).

Obtained chromatograms were sprayed with *Anisaldehyde Solution*, which was obtained by mixing together 0,5 ml of anisaldehyde, 10 ml of glacial acetic acid, 85 ml of 95% ethyl alcohol, and 5 ml of concentrated sulfuric acid. Photographs were obtained using Reprostat 3 system (Camag, Switzerland) and processed using Adobe Photoshop 7.0 software (Adobe, USA).

The effect of granulation process on the essential oil content during long-term storage in cool, dry place away from light was assessed using conventional hydrodistillation technique.[9]

RESULTS AND DISCUSSION

After solvent front has passed about 80-90% of the path, the plates were removed from TLC chambers and air-dried until complete evaporation of solvent residues. Chromatograms were sprayed with *Anisaldehyde Solution*, heated at 105 °C in a temperature chamber for 2-3 minutes, and examined under daylight.

Chromatographic profiles of *M. recutita* flowers powder and pilot batches of CPG are presented in Figure 1.

From the Figure 1 it can be observed that chromatographic profiles of both powdered chamomile flowers and corresponding CPG are almost identical. Thus, granulation process didn't affect qualitative composition of lipophilic compounds of *M. recutita*, suggesting that no degradation occurs during CPG manufacturing.

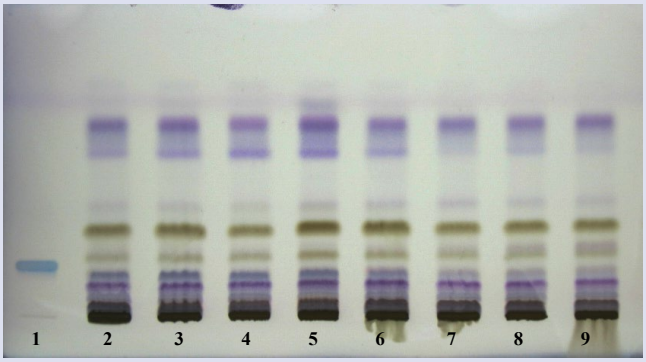

Figure 1: Chromatogram of *M. recutita* lipophilic compounds from powdered material and CPG (daylight): 1 – *Sudan III Reference Solution* (10 µl); 2 – *Test solution* of CPG batch No. 250418 (20 µl); 3 – *Test solution* of CPG batch No. 280418 (20 µl); 4 – *Test solution* of CPG batch No. 490518 (20 µl); 5 – *Test solution* of CPG batch No. 480518 (20 µl); 6 – *Test solution* of CPG batch No. 991217 (20 µl); 7 – *Test solution* of CPG batch No. 670817 (20 µl); 8 – *Test solution* of CPG batch No. 730916 (20 µl); 9 – *Test solution* of CPG batch No. 250418 (20 µl).

Chromatographic profiles of *A. calamus* rhizome powder and corresponding CPG are presented in Figure 2.

Similarly, no changes in qualitative composition of lipophilic compounds were observed during manufacturing of CPG from *A. calamus* rhizome.

Assessment of several pilot batches of cut-pressed granules from chamomile flowers and sweet flag rhizome showed that the essential oil content in them remained within pharmacopoeial limits (Table 1): not less than 0.3% for *M. recutita* flowers[9] and not less than 2.0% for *A. calamus* rhizome.[12]

Essential oil content dynamics was assessed in order to provide insight into stability of manufactured CPG. The results (Tables 2 and 3) show that the granulation process, in fact, enhanced stability, as the essential oil content in CPG is equal or higher than in corresponding herbal raw material.

CONCLUSION

It was found that chromatographic profiles for the herbal raw material and corresponding cut-pressed granules were equivalent, suggesting that the granulation process does not affect qualitative composition of lipophilic constituents of *M. recutita* flowers and *A. calamus* rhizome.

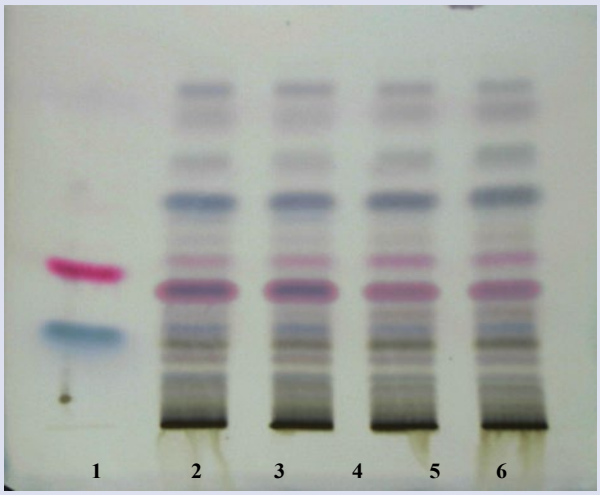

Figure 2: Chromatogram of *A. calamus* lipophilic compounds from powdered material and CPG (daylight): 1 – *Sudan Red G* and *Menthol Reference Solutions* (5 µl each); 2 – *Test solution* of CPG batch No.10117 (10 µl); 3 – *Test solution* of CPG batch No. 20117 (10 µl); 4 – *Test solution* of CPG batch No. 30117 (10 µl); 5 – *Test solution* of CPG batch No. 30117 (10 µl).

Table 1: Essential oil content in powdered *M. recutita* flowers and *A. calamus* rhizome, and corresponding CPG (mean of three measurements).

M. recutita flowers		M. recutita CPG	
Batch No.	**Essential oil content, %**	**Sample**	**Essential oil content, %**
250416	0.37	CPG from batch 250416	0.36
280416	0.42	CPG from batch 280416	0.40
490516	0.43	CPG from batch 490516	0.42
480516	0.44	CPG from batch 480516	0.43
991216	0.42	CPG from batch 991216	0.41
670816	0.36	CPG from batch 670816	0.36
730915	0.38	CPG from batch 730915	0.37
A. calamus rhizome		**A. calamus CPG**	
Batch No.	**Essential oil content, %**	**Sample**	**Essential oil content, %**
10117	2.4	CPG from batch 10117	2.4
20117	2.9	CPG from batch 20117	2.8
30117	2.6	CPG from batch 30117	2.5

Table 2: Essential oil content in *M. recutita* flowers and corresponding CPG following long-term storage (mean of three measurements).

	Batch/sample	Essential oil content, %						
		M00	**M06**	**M12**	**M18**	**M24**	**M30**	**M36**
M. recutita flowers	250416	0.37	0.37	0.36	0.35	0.35	0.35	0.33
M. recutita CPG	CPG from batch 250416	0.36	0.36	0.36	0.36	0.36	0.36	0.35
M. recutita flowers	280416	0.42	0.42	0.38	0.36	0.36	0.36	0.36
M. recutita CPG	CPG from batch 280416	0.40	0.40	0.38	0.38	0.38	0.37	0.38
M. recutita flowers	490516	0.43	0.43	0.36	0.36	0.35	0.35	0.36
M. recutita CPG	CPG from batch 490516	0.42	0.42	0.40	0.38	0.38	0.36	0.36
M. recutita flowers	480516	0.44	0.44	0.36	0.36	0.37	0.36	0.36
M. recutita CPG	CPG from batch 480516	0.43	0.43	0.40	0.40	0.38	0.38	0.36
M. recutita flowers	991216	0.42	0.42	0.36	0.36	0.35	0.36	0.36
M. recutita CPG	CPG from batch 991216	0.41	0.41	0.39	0.38	0.38	0.36	0.36
M. recutita flowers	670816	0.36	0.36	0.35	0.35	0.35	0.35	0.33
M. recutita CPG	CPG from batch 670816	0.36	0.36	0.36	0.36	0.36	0.36	0.36
M. recutita flowers	730915	0.38	0.38	0.35	0.36	0.35	0.35	0.35
M. recutita CPG	CPG from batch 730915	0.37	0.37	0.36	0.36	0.36	0.36	0.36

Note: M – months.

Table 3: Essential oil content in *A. calamus* rhizome and corresponding CPG following long-term storage (mean of three measurements).

	Batch/sample	Essential oil content, %			
		M00	M06	M12	M18
A. calamus rhizome	10117	2.4	2.2	2.2	2.2
A. calamus CPG	CPG from batch 10117	2.4	2.3	2.2	2.3
A. calamus rhizome	20117	2.9	2.3	2.3	2.3
A. calamus CPG	CPG from batch 20117	2.8	2.5	2.4	2.4
A. calamus rhizome	30117	2.6	2.4	2.3	2.2
A. calamus CPG	CPG from batch 30117	2.5	2.3	2.3	2.3

Note: M – months.

Moreover, it was found that the granulation process had no negative impact on the essential oil content of the studied herbal material. In fact, cut-pressed granules were found to be more stable in terms of essential oil content during long-term storage.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ABBREVIATIONS

CPG: Cut-pressed granules; **TLC**: Thin-layer chromatography.

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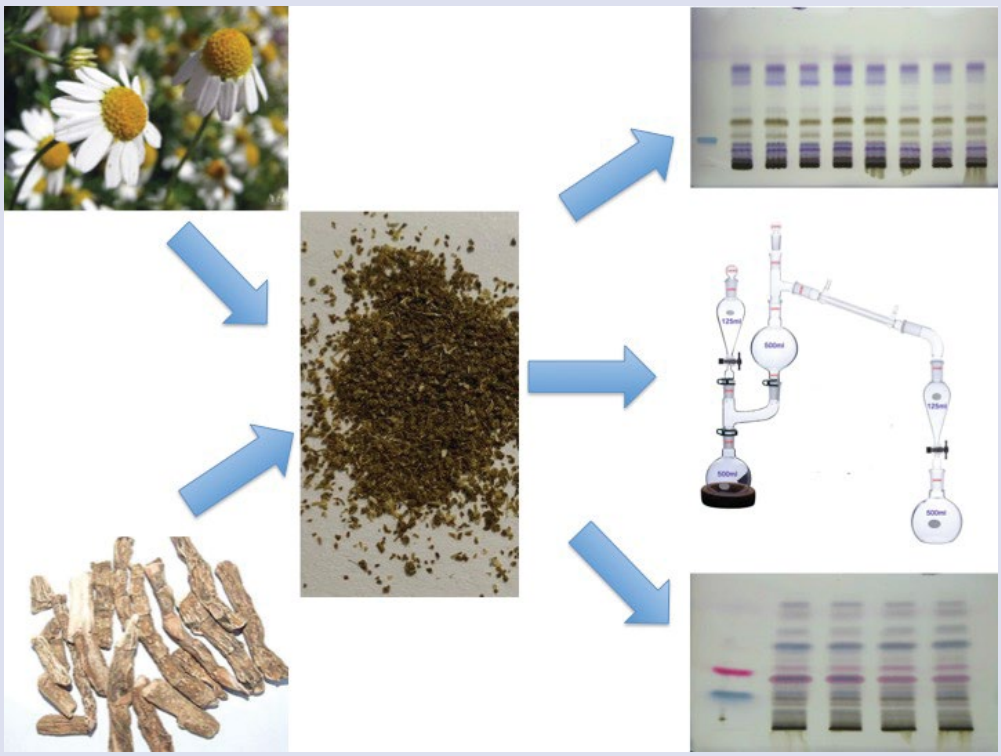
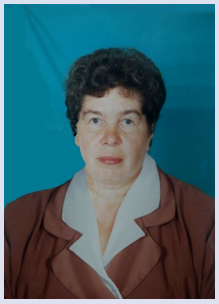
GRAPHICAL ABSTRACT



ABOUT AUTHORS

Olga B. Trifonova, a member of the Council for State Pharmacopoeia, graduated from Pharmaceutical Faculty of the Sechenov First Moscow State Medical Institute in 1998 and finished her PhD research in 2018. Since 1999 she is working at the "Krasnogorskleksredsta" – an oldest manufacturer of herbal medicinal products in the Russian Federation. Currently she holds the position of the Director for Quality and Development. Her scientific interests are focused on pharmaceutical analysis and resource-saving technologies in herbal drugs manufacturing.

Olga V. Evdokimova, a member of the Council for State Pharmacopoeia, graduated from Pharmaceutical Faculty of the Sechenov First Moscow State Medical Institute in 1989, earned her PhD degree in 1996, and her D.Sc.Pharm degree – in 2012. Since 2018 she works as the Chief Analyst of the Center of Pharmacopoeia and International Collaboration of the FSBI "Scientific Center for Expert Evaluation of Medicinal Products". Her scientific interests are focused on development and standardization of herbal raw material, herbal drugs, and herbal food supplements.



Vera I. Prokofieva, a member of the Council for State Pharmacopoeia, graduated from Pharmaceutical Faculty of the Sechenov First Moscow State Medical Institute in 1966, obtained her PhD degree in 1969, and her D.Sc.Pharm. degree – in 1989. Since 1990 she works as the professor of the A.P. Arzamastsev Deparment of Pharmaceutical and Toxicological Chemistry. Her scientific interests are focused on pharmaceutical analysis of drug substances by spectral and chromatographic methods.

Alexey A. Matyushin graduated from Pharmaceutical Faculty of the Sechenov First Moscow State Medical Academy in 2008, earned his PhD degree in 2011, and MA degree – in 2018. Currently he's working as the Associate Professor of the Department of Analytical and Forensic Toxicology. His main scientific interests are focused on identification and standardization of novel herbal drugs and herbal raw materials, separation and purification of biologically active substances from natural sources, and herbal drugs development.

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