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TECHNOLOGY DEVELOPMENT OF HARD CAPSULES CONTAINING LADY'S BEDSTRAW HERB LIPOPHILIC COMPLEX

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Summary: technological parameters manufacturing of capsules containing Lady's Bedstraw's herbs lipophilic complex (Galium verum L.) have been substantiated, namely, conditions, mixing sequence, temperature mode and so on. The water absorption kinetics of different composition powder mixtures has been studied. The expediency of using lactose as a diluent has been confirmed experimentally, that allowed us to obtain practically non-absorbent capsule mass containing Lady's Bedstraw's herbs lipophilic complex. On the basis of these studies, the manufacturing technology of capsules codenamed "Galiver" has been developed.

Key words: Lady's Bedstraw (Galium verum L.), capsules, lipophilic complex, technology, manufacturing flowchart.

Introduction. The herbs are an inexhaustible source for searching the bioactive substances (BAS), which are widely used in therapy of various diseases. Herbal medicinal products (HMP) [4, 20] remain actual even in the times of scientific and technological advance due to variety of advantages. In the view of pharmaceutical technology, the production of medicinal preparations based on HMP has certain difficulties that is connected with a duration of multistage processes, and strict demands as for their quality [16, 23, 24]. However, it is an uncontestable fact that, in case of following such demands, HMP can be successfully used for the treatment of diseases, for which the usage of synthetic ones is ineffective and unjustified from a pharmacoeconomic point of view [11].

Currently, in Ukraine, the data on HMP domestic market share is quite arguable and ambiguous, however, the gradual growth of their quantity is observed. The detailed researches as for the overall dynamics of HMP market were not carried out, although data on some pharmacotherapeutic groups is known [1, 3, 8, 9, 11, 17, 19]. When taking the above-mentioned into account, it is possible to conclude that the usage of HMP is quite actual, and their research requires the efforts of different specialists.

The successful HMP competition in the market of Ukraine depends on a great number of factors, the one of which is their appropriate pharmaceutical development. The confirmation of the evidence-based approach to herbal medicinal products development is multistage and many-sided study of maximal number of factors, which together form their quality [10, 15]. The modern conception of new HMP creation requires following the strict conditions of the appropriate practices system [16]. Thus, the usage of modern scientific and technical achievements in the herbal medicinal products technology is actual and well grounded.

The achievements of a great number of researches from different countries, and the experience of the usage of the mentioned herb in folk medicine were the premise of the development of new HMP on basis of Lady's Bedstraw (Galium verum L.) [5, 14, 18, 21]. Nevertheless, at the time of submitting the article in press, we did not find any reference to oral dosage form creation in the form of hard capsules.

Thus, the goal of the given work is the development of the technology of encapsulated HMP, which contains the Lady's Bedstraw herb lipophilic complex (LBLC), received by means of extraction of mentioned raw material by liquefied difluorochloromethane [13].

The methods of research. The original substance was LBLC, which further was mixed with excipients with the aim of receiving free-flowing powder mixture. Based on the previous researches [22], we received the powder mixtures, the fillers of which were potato starch, lactose with particles size of 180 microns (80 mesh) and their combination in a ratio of 50/50. In order to provide the necessary flowability of model mixtures, the addition of aerosil took place. For carrying out the researches, 10 samples, which possessed satisfactory flow properties, were selected.

The LBLC was added in the form of a solution in methylene chloride (1:6 wt.) at the rate of 6,06 mg of standardized LBLC per capsule that corresponds to the average effective dose, established during previous researches.

The capsular fillers were prepared in a laboratory mixer with the stirrer rotational speed of 45-60 rpm. The part of a filler, riddled through the sieve № 355

according to SFU, was placed in a laboratory mixer and then the calculated number of aerosil was added. Thereafter, we added the solution of LBLC, and continued mixing until a homogenous, uniformly colored mass was obtained, then we added the remnants of a filler and continued mixing again during 10-15 minutes. The obtained mass was dried in a vacuum oven at a temperature of 40±2°C.

During carrying out the researches of pharmaco-technological indicators of capsular fillers, the pharmacopoeial methods were used.

The absorbability of capsular fillers was determined by the sample mass growth in percent in relation to the initial mass of a weigh, which was placed in desiccator with purified water, where 100% humidity was maintained. The received data was used for construction of a moisture absorption kinetics graphically.

The results and their discussion.

The moisture absorption kinetics is represented in Fig. 1, A and 1, B. On the 10th day, a mould appeared on the researched samples (Fig. 1, B). That is why the further researches on absorbability determination were not carried out any more, and there the experiment was discontinued.

As it can be seen from data in Fig. 1, A and 1, B, the greatest influence on absorbability is caused by the nature of diluent and aerosil content. The moisture absorption of samples increases in the series of diluents: lactose – lactose and starch potato mixture (50/50) – potato starch. During the dilution of LBLC with diluent, the decrease of absorbability is observed.

The capsular fillers on lactose basis with addition of 4% aerosil possess absorbability, which is almost 28 times less than one of analogous fillers on basis of lactose and potato starch mixture, and almost 33 times less than one of a mixture on potato starch basis. The low moisture absorption of LBLC mixtures with lactose and aerosil makes it possible to conclude that such mixtures will be more stable during the capsules production process and their further storage.

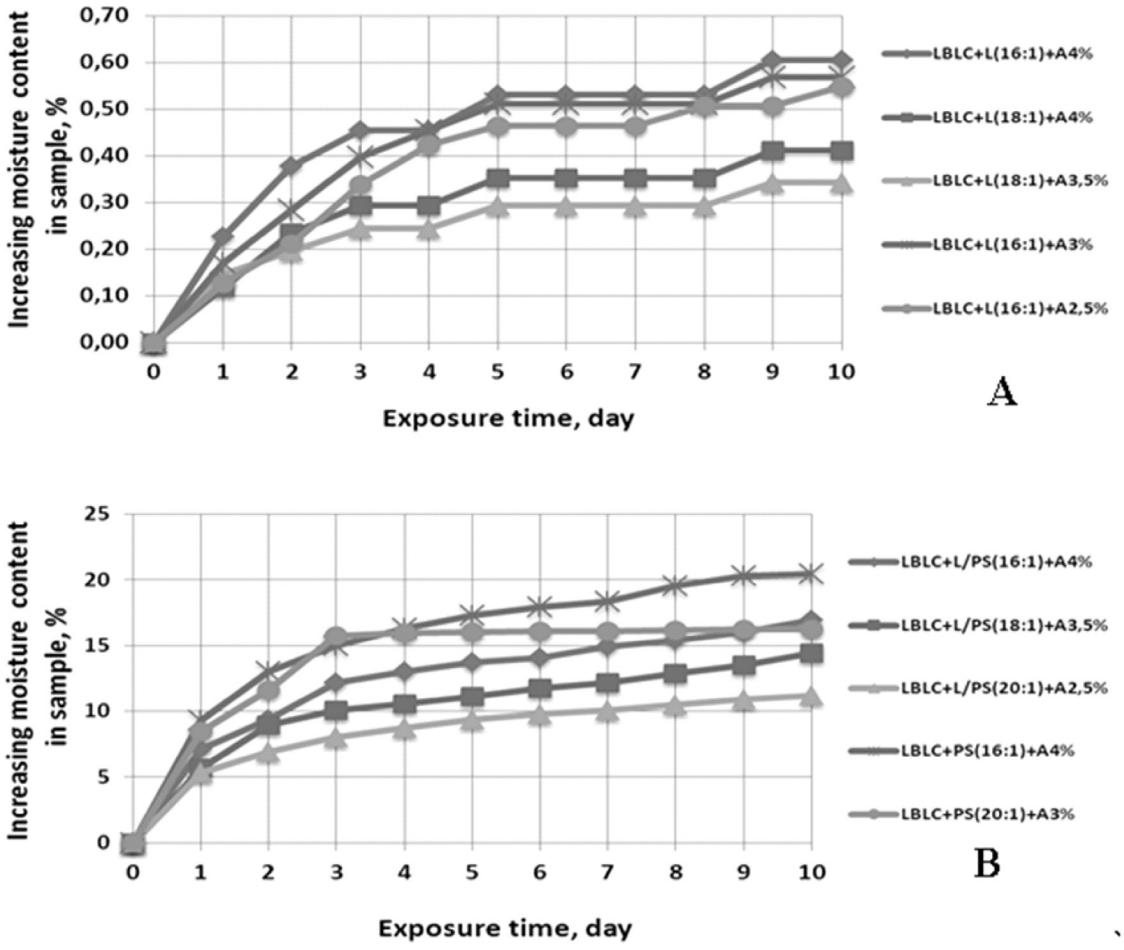

Fig. 1. **The absorbability of capsular fillers from *LBLC*** (A – samples, which contain LBLC, lactose (L) and aerosil (A) in various ratios; B – samples, which contain LBLC, the mixture of lactose and potato starch (50/50) (L/PS) or potato starch (PS) and aerosil (A) in various ratios).

At the same time, the increase of aerosil content in researched samples led to the increase of humidity growth. The similar regularity also took place in works [2, 6, 7]. Thus, the composition of capsular filler, which contain lactose 80 and LBLC in the ratio of 18:1 and 3,5 % of aerosil, was selected.

The technological process of obtaining capsules from LBLC consists of the stage of auxiliary works; the main technological process stage; the stage of packing, marking and shipment of finished products to a warehouse. The research results were used during the development of technological instruction of the capsules production from LBLC and were included to pharmaceutical drug development.

The production of the developed capsules under the conventional name «Galiver» consists of four stages of main technological process and three stages of packing, which are briefly described below. The critical parameters and critical stages, indicators, which are directly controlled and which concern the production control, are shown in Fig. 2.

The stage 1. The raw material preparation

The raw material for preparation is subject to incoming control. After passing the incoming control, the raw material is delivered to the area with a help of a transport trolleys.

In the vessel, the calculated amount of lactose is weighed, and then it is aseptically transferred to a vibrating sieve with sieve mesh size of 0,355 mm. The sifting is gathered in a sterile polythene bag and then it is transferred to the stage 3.

The calculated amount of aerosil is weighed in a dry vessel and quantitatively transferred to a separate clean sealed vessel. Thereafter, aerosil is transferred to the stage 3.

The stage 2. LBLC dissolution

With the aim of the obtained LBLC standardization, it is necessary to carry out its dilution with a calculated amount of methylene chloride on basis of the results of the analysis of the quantitative content of BAS.

After receiving the positive conclusion from Quality Control Department (QCD) laboratories as for the LBLC indicators, its weighed amount is placed into reactor, where the calculated quantity of methylene chloride is flowed by gravity from a dosimeter. The solution of LBLC is mixed by compressed air flow for 5 minutes, and then it is poured out by gravity into a vessel and weighed on the scales. The obtained solution is hermetically sealed and transferred to the stage 3.

The stage 3. The obtaining mass for capsulation

The mixing of ingredients is carried out in mixing-type dryer of SYH-100 type, which consists of frame, electric drive, vessel with a cover and planetary stirrer.

The part of sifted lactose and aerosil from the first stage are loaded into the mixer. The calculated amount of a solution of LBLC in methylene chloride (1:6 wt.) is picked out from a vessel into a glassware and is poured into a mixer, and then a cover is hermetically closed and a stirrer is switched on. In 5 minutes after starting the mixing, the warm water, having temperature of 40-42?C, is supplied to a mixer envelope, and the cold water – to heat exchangers pipes. The methylene chloride, which has condensed in heat exchanger, is poured out to a dosimeter by gravity.

The mixing is carried out during 15 minutes. Thereafter, the mixer is switched off and the remnants of lactose are loaded. The mixer is switched on and a mass is mixed for another 15 minutes, and then the mixer is switched off, the valves of heat exchanger are blocked, the vacuum is supplied to the mixer and the remnants of a solvent are distilled from a powder mixture.

In 15 minutes of vacuumization, the sample of a powder is taken and transferred to QCD laboratory for researching the technological parameters and for analysis of residual content of a solvent. In case if the content of methylene chloride in a powder exceeds 0,05 %, the additional distillation should take place.

The prepared powder mixture is unloaded from the mixer into the vessel and then it is transferred to the stage 4.

The stage 4. The capsules filling

The hard gelatin capsules № 4 are filled with a powder mixture from the third stage on a machine of the type LZ/64 Zanazi (Italy).

The process of capsules filling on a machine includes 8 operations: capsules supply to matrix socket, opening of empty capsules, placing the capsules according to the target level, volumetric dosing, rejection, closing the capsules with a cover, extrusion of filled capsules and their dedusting.

After carrying out the capsules filling with a mass for capsulation, the necessary amount of capsules for conducting the ongoing check of their quality is selected. After a positive conclusion from QCD laboratory, the filled conditioned capsules are transferred in a vessel to the stage 5.

The stage 5. The packing into blisters

The capsules «Galiver» are loaded from a vessel to a bin of automatic blistering machine of the type KDB-120, which is equipped with electronic counting device, and 10-capsules packing in blister packs is realized. After carrying out the random visual check, the blisters with capsules are transferred to the stage 6.

The stage 6. The blisters packing into cartons

At this stage, 2-blister packing with capsules and instruction for medical use into cartons takes place. The packed production is subject to full analysis according to methodics, described in QCM. When

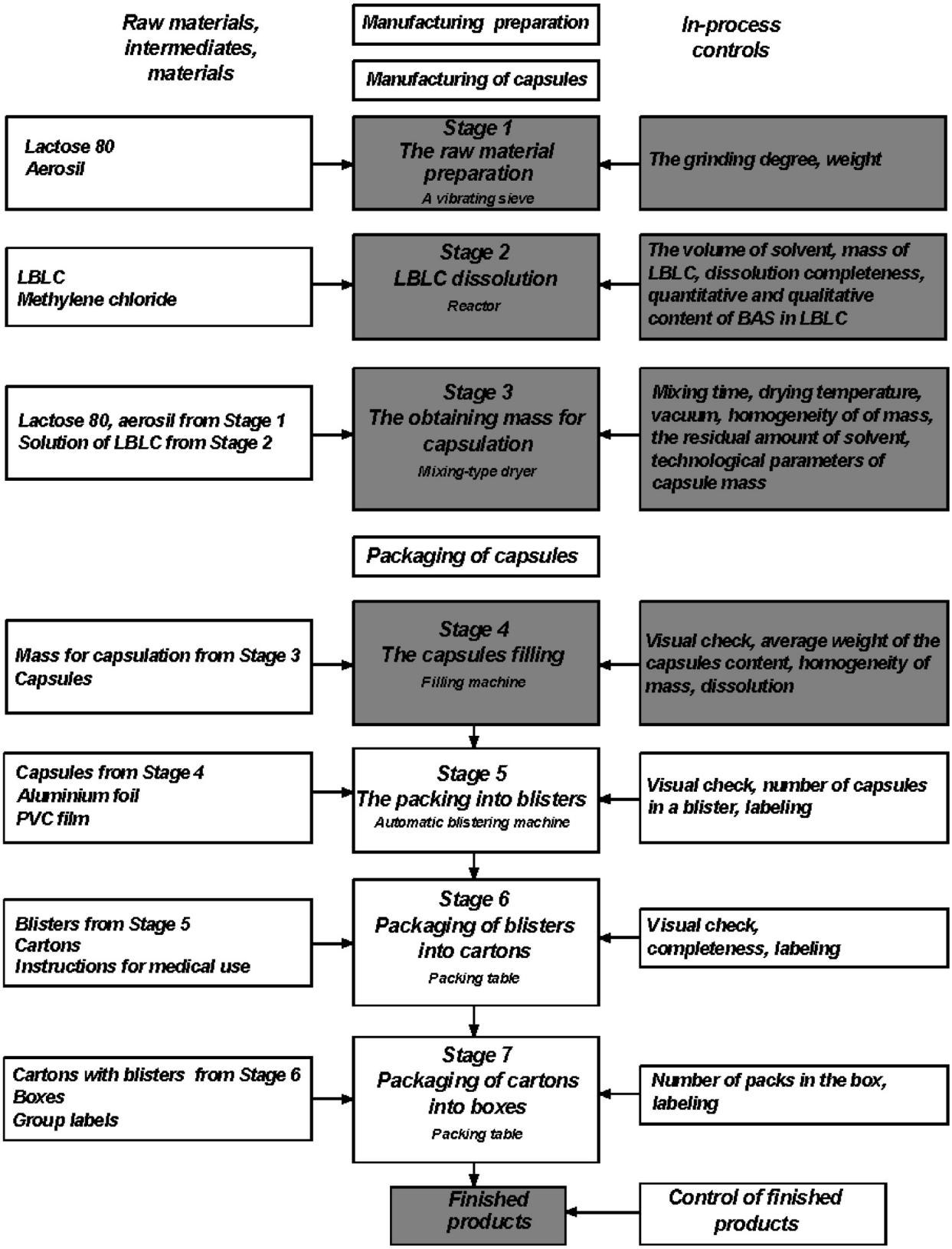

Fig. 2. **The technological scheme of «Galiver» capsules production.**

receiving the positive results of the analysis, the cartons with blisters are transferred to the stage 7.

The stage 7. The cartons packing into boxes

For hand packing, the cartons packing into boxes from corrugated cardboard is carried out on the table, the packing list is put in, a group label is attached and then the boxes are sealed up with a sealing tape and transferred to the quarantine store, and then to the finished products warehouse. The series of finished products is formed in view of one load of the mixer.

Conclusions.

The research of technological properties of capsular fillers containing freon extract of Lady's Bedstraw herb was conducted.

During the study of absorbability, it was determined that compositions with lactose of 80 mesh and aerosil content till 4% absorb no more than 0,7 % of water even during storage under the conditions of 100% humidity, so they are not absorbent.

The formula and optimal technology of the preparation «Galiver» in capsules, which contain Lady's Bedstraw herb lipophilic complex and excipients, were developed. On basis of the conducted researches, the technological scheme of obtaining the preparation «Galiver», taken as a basis of the technological instruction on its production, was developed.

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РОЗРОБКА ТЕХНОЛОГІЇ ТВЕРДИХ КАПСУЛ ІЗ ЛІПОФІЛЬНИМ КОМПЛЕКСОМ ТРАВИ ПІДМАРЕННИКА СПРАВЖНЬОГО

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Резюме: обґрунтовано технологічні параметри виробництва капсул із ліпофільним комплексом трави підмаренника справжнього (Galium verum L.), а саме: умови, послідовність змішування, температурний режим тощо. Досліджено кінетику вологопоглинання порошкових сумішей різного складу. Експериментально підтверджену доцільність використання лактози як дилюенту, що дозволило отримати практично негігроскопічну капсульну масу із ліпофільним комплексом трави підмаренника справжнього. На підставі проведених досліджень розроблено технологію виробництва капсул під умовною назвою «Галівер».

Ключові слова: підмаренник справжній (Galium verum L.), капсули, ліпофільний комплекс, технологія, технологічна схема виробництва.

РАЗРАБОТКА ТЕХНОЛОГИИ ТВЕРДЫХ КАПСУЛ С ЛИПОФИЛЬНЫМ КОМПЛЕКСОМ ТРАВЫ ПОДМАРЕННИКА НАСТОЯЩЕГО

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Резюме: обоснованы технологические параметры производства капсул с липофильным комплексом травы подмаренника настоящего (Galium verum L.), а именно: условия, последовательность смешивания, температурный режим и т. д. Исследована кинетика влагопоглощения порошковых смесей различного состава. Экспериментально подтверждена целесообразность использования лактозы в качестве дилюента, что позволило получить практически негигроскопичную капсульную массу, содержащую липофильный комплекс травы подмаренника настоящего. На основании проведенных исследований была разработана технология производства капсул под условным названием «Галивер».

Ключевые слова: подмаренник настоящий (Galium verum L.), капсулы, липофильный комплекс, технология, технологическая схема производства.

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