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PROSPECTS FOR USE OF CONDENSED GASES AND SUPERCRITICAL FLUIDS IN PHYTOCHEMICAL PRODUCTION

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Indroduction

Nowadays one of the major factors hindering development of commercial scale phytochemistry is obsolescence of power- and time-consuming extraction technologies.

Improvement of manufacturing processes in phytochemical production requires, first of all, intensification of extraction of crude drugs which is the most power-consuming and long-lasting stage, and introduction of so-called „green technologies". The latter involves replacement of the most of traditional organic solvents (methanol, acetone, chloroform, ethylacetate, etc.) which are toxic and flammable with alternative extractants. As it's known, in high-developed countries the specified trends are carried out in two main ways – by use of supercritical fluids (SCF) and condensed gases including fluorinated hydrocarbons (freons) [1–7]. These trends are the most universal for intensification of extraction and/or purification processes acceptable for commercial scale. Other alternative methods of extraction (ultrasonic, microwave, electrohydraulic ones) are applied rarely.

Now sufficient scientific base concerning application of SCFs in chemical, pharmaceutical and food industries is available only for supercritical CO_2 (SC-CO_2). However, despite obvious advantages of SC-CO_2-extraction in comparison with traditional technologies, this method meets rather serious difficulties if transferred to commercial scale. Firstly, most of extraction processes are run under working pressures in the range of 200-700 bar that imposes significant limitations on reactor volumes and requires large capital and working costs on the equipment, its operating and maintenance. From here it's obvious that introduction of SCF extraction has sense only for production of expensive enough and highly active substances (alkaloids, cardiac glycosides, taxols, etc.) or for purification of primary extracts obtained by other technologies [4, 5, 8–10].

Secondly, owing to zero electrical dipole moment of SC-CO_2 the range of biologically active substances (BAS) taken with SC-CO_2 is limited mainly to hydrophobic compounds, but polar or high-molecular substances are almost insoluble in it [6, 7, 11–13]. In some cases the problem of low dissolving power of SC-CO_2 is solved by its replacement with other SCFs. So, for example, supercritical ethane at temperature 70°C and pressure 250 atm can extract oil and xanthine alkaloids from cocoa beans much better than CO_2, and SC-ethane : crude drug ratios 1:5-1:10 appeared sufficient for completeness of the BAS extraction, at the same time quantity of SC-CO_2 needed is 100 times more [14].

Thirdly, SCF-extraction doesn't always surpass other methods in its efficiency. Authors [15] have found high performance extraction of lipophilic substances from hawthorn fruits, chamomile and calendula flowers with SC-CO_2 under pressure of 300 bar and above, however the yield of polyphenolic and glycoside compounds was low even under pressure near 700 atm and adding 20% of ethanol as modifier. Terpenic lactones and flavonoids from ginkgo leaves started to be taken under pressure of 310 bar and temperature 60°C only if at least 10% of ethanol, freon-134a or N_2O were present in SC-CO_2, but even under such conditions yield of the BAS was much lower than after alcoholic extraction in Soxhlet apparatus [16]. In the method of obtaining of bioactive extract from *Macleaya microcarpa* [17] in which the main BAS are alkaloids, the raw crude drug was extracted with supercritical CO_2 under temperature 40-70°C and pressure 250-300 bar. However, under these conditions SC-CO_2 at absence of cosolvent extracted mainly hydrophobic substances. As within plant cells where weak acid environment prevails alkaloids are in the salt form soluble in polar extractants, yield of these BAS is low.

Similarly SC-extraction of boldine related to aporphine alkaloid group from leaves and bark of *Peumus boldus* even under temperature 60°C and pressure 600 atm was found ineffective: the yield of this BAS was 0,003% though after routine maceration with 70% alcohol or 1 M acetic acid it reached 3% recalculated to dry weight of the crude drug [18].

Thus, the supercritical technology cannot be considered versatile for phytochemical production. For each certain species of a plant and BAS containing therein it's necessary to provide experimental researches with purpose to prove expediency of introduction of one or another intensification method including SCF-extraction [12].

Considering lacks of SCF-extraction described above, during last decades scientists and manufacturers showed increasing interest to extractants alternative to carbon dioxide [1–3, 7, 13, 19–21].

Condensed gas extraction of herbal drugs (HD) seems to be one of the prospective alternatives to supercritical technology; however, range of scientific researches in this field, unfortunately, is few enough for today. There are only some foreign patents concerning equipments and methods of plant extraction with fluorohydrocarbons (freons) [22, 23], however for the present time these technologies still have not got commercial scale.

In Ukraine since 80-es experimental research concerning use of freons as extractants for HDs were carried out, however, most of them engaged only difluorodichloromethane (freon R12) and difluorochloromethane (freon R22) which were used to obtain complexes of mainly lipophilic compounds [24, 25]. Extraction processes with alternative condensed gases and SCFs until this time were not studied enough, though some of them or their mixes are capable to withdraw some middle polar and even hydrophilic BAS from herbal drugs under certain conditions.

Hence, substantiation of extraction technologies using various condensed gases, research of herbal drug preparations obtained from vegetative HDs are still actual problems of modern phytochemistry.

The objective of the article

Considering the above-stated the purpose of presented article is to carry out critical review of the literature and

patent data concerning use of condensed gases under subcritical conditions as extractants for intensification of extraction processes.

Comparative analysis of CO_2 and other condensed gases as extractants

The major advantages of condensed gases as extractants are: their low viscosity and interfacial tension which promote fast penetration of an extractant into plant cells and considerably accelerate internal diffusion; easy pressure regulation, low boiling point of these solvents that allows to completely remove them out from an extract even at ambient temperatures saving thermolabile and aromatic substances; high selectivity of some condensed gases and, accordingly, purity of extracts; extraction process can be carried out within closed circuit without air access that practically eliminates extractant losses and oxidation of BAS, and also chemical inertness and fire safety (except for liquid ammonia, propane and isobutane). And the major technical advantage of the most of condensed gases is relatively low working pressure of saturated vapors (5-15 atm) which is 1-2 orders less than in supercritical equipment [26, 27].

Abovementioned physico-chemical properties of condensed gases allow to consider them as the most prospective extractants for herbal BAS. However, until nowadays only some of them were applied in commercial scale for obtaining of lipophilic compounds: liquid (subcritical) CO_2, difluorodichloromethane R12 and difluorochloromethane R22 [28].

For the first time condensed gases have started to be used as extracting solvents in the beginning of 30es in the former USSR, and in commercial scale from 60es – in food industry (Krasnodar). The most studied extractant used was liquefied CO_2, applications of propane and butane were much more rare. The substances taken were mainly of hydrophobic nature: fats, essential oils, carotenes, sterols, tocopherols and terpenoids [27, 29]. Now liquefied CO_2 remains the most popular extractant in Russia and abroad. So, for example, sesquiterpene artemisinin was obtained from wormwood with liquefied CO_2 yielding 1,4 times more than after ethanol and even ultrasonic extraction [30]. Now in Krasnodar many CO_2-extracts are manufactured commercially from various plant species: mints, chamomile, yarrow, fennel, carrots, parsley, carnation, elecampane, thyme, St. John's wort, eucalyptus and etc. [31].

Prospective alternatives for CO_2 in phytochemical production are other condensed gases with wider range of physico-chemical properties: fluorinated derivatives of hydrocarbons (freons), liquid ammonia, dimethyl ether (DME), sulfur hexafluoride (insulating gas) etc. Their major characteristics include lower vapor pressure if compared with CO_2, antimicrobic activity allowing to solve one the main problem in phytochemical production – microbial contamination of extracts (and other herbal drug preparations), possibility to extract not only lipophilic, but also more polar substances depending on choice of solvents or their mixes [32–36].

Authors [37] extracted essential oil (EO) from *Lippia sidoides* leaves with liquid CO_2 selectively enough under near-critical conditions (67 atm and 15-25°C), and found that solubility of the BAS in CO_2 is very sensitive to temperature changes in near-critical field: if it grows from 15 to 20°C the EO solubility increased by 14 %, but at 25°C – decreased by 42 %. Yielded EO contained 74 % of monoterpenoids and 21 % of sesquiterpenoids.

After research of extraction process of ginger, black and red peppers with condensed propane, dimethylether and SC-CO_2 under temperatures +40-50°C the authors [2] found that DME gives maximum yield of the extract even at the minimum ratio of its quantity to weight of the crude drugs (1:1–1:2), at the same time to reach comparable efficiency of extraction it was necessary to take 15-20 times more of SC-CO_2 by weight. Similar results have been received at research of extraction of coriander seeds with condensed propane and SC-CO_2 [38], and even at crude drug : extragent ratio 1:2 the solvent completely took BAS during 50 minutes but in case of SC-CO_2 in pressure range of 100-300 atm at temperature 35°C 6 hours were needed for this purpose.

In the paper [21] it has been also found that liquid propane and DME with parameters approaching to critical point dissolved lipophilic compounds much better than SC-CO_2 did, and DME was especially applicable for extraction of polar lipids. It was pointed that in Australia and New Zealand these solvents are officially allowed for use in food industry.

According to the patent [39] dimethyl ether can be used for extraction of triglycerides, fat-soluble vitamins, alkaloids and some water-soluble substances. DME is also capable to remove residual moisture and natural pigments (chlorophyll, polyphenols, etc.) from raw materials. In this method it is provided to extract herbal drugs under temperature from –25°C to +80°C and pressure 1-10 atm, more preferable at 25°C and 5 atm for 30 minutes. Besides, it is underlined that DME renders sterilizing effect that is very important for phytochemical production.

By the data [40] under 40°C liquid propane was capable to extract fat oil from fruits of milk thistle *Silybum marianum* with yield of 23 % recalculated to weight of the crude drug, pressure and temperature changes almost did not influence it. At the same time to reach comparable yield (20 %) 10-fold quantity of CO_2 was needed under pressure 200-300 atm and temperature 25°C, and increase of the latter at 200 atm sharply worsened extraction efficiency. On the other hand, propane extracts contained much less of tocopherol than CO_2-extracts that points on lower solubility of vitamin E in propane.

The paper [41] revealed extremely high dissolving power of condensed propane for fat oil of rose hips and its main BAS – carotenoids, tocopherols and unsaturated fatty acids. So, under temperature 25°C, pressure 50-80 atm and the solvent to raw material ratio just 1:1 it took the oil completely (100%); at the same time for this purpose 10 times more of SC-CO_2 under pressure 250 atm was needed. Besides, "propane" oil contained 1,5-2 times more vitamins than oil obtained with CO_2. Total yield of the oil together with BAS was 3,0-3,5 % of the whole fruit weight.

Among condensed gases used today freons have all advantages inherent to SC-CO_2: high penetrability, inertness, absence of toxicity and combustibility, selectivity to certain groups of BAS depending on freon type, low power inputs for evaporation and condensation, possibility to extract thermolabile substances due to low boiling points [24]. Besides, the main advantage of freons is their much higher dissolving power in comparison with SC-CO_2 [8].

In the 20th century in the former USSR and abroad mainly chlorine-containing freons R11, R12, R113, R114, R22 were applied. In Ukraine P. P. Vetrov studied extraction processes of some plant species with the solvents specified [24, 27, 42]. It has been found that some kinds of freons (for example, R22) due to their higher polarity were able to take wider spectrum of BAS than liquid CO_2: essential and fat oils, fat-soluble vitamins, coumarins, carotenoids, phenolic alcohols, valrates, iridoids, some alkaloids and flavonoids. Besides, certain freons (for example, C318) have very high selectivity allowing to extract essential oils without accompanying fats [27].

In nineties research on use of freons have considerably reduced because of unreasonable relation to them as the main factor in ozone layer deplete. However, many scientists denied this theory.

But now, when according to the Montreal report the majority of chlorine-containing freons (except for R22) have been withdrawn from manufacture in all developed countries, Ukrainian and foreign markets are being filled with wide assortment of fluorine-containing freons safe for environment: R23, R32, R125, R134a, R143a, R152a, R227ea, etc. They considerably differ from each other by their polarity, dissolving power and selectivity concerning certain groups of BAS, and many of them are almost ideal extragents [26]. Therefore now freons find again the great prospect for their use in phytochemical branch. As authors [6, 21] mark, the specified freons and also DME can dissolve polar substances much better than SC-CO_2 that is explained by higher values of their electrical dipole moments and dielectric constants.

Authors [43–45] showed the possibility to obtain lipophilic complexes from valerian roots, milk thistle seeds and dog rose hips of better quality than by traditional methods, moreover, duration of technological process took 2–3 hours and recovery of BAS reached 98 %. Besides, extraction with freons in certain modifications allowed to take even middle polar substances [43].

The comparative analysis of various extraction methods for rose hips (traditional in Soxhlet apparatus, ultrasonic, microwave, sub- and supercritical ones) has shown that subcritical extraction with condensed gases resulted in the highest yield of oil with the highest concentration of target BAS – carotenes and polyunsaturated fatty acids [10].

The author [20] developed the technology of rose hips lipophilic complex (oil) using freon R22. In this study it has been found that the oil yield considerably depended from comminution degree of the crude drug and its moisture content. So, at optimum moisture of 7 % from fine fraction of rose hips the oil has been received yielding 6,2 %, 8,4 % and 8,9 % at crude drug : extragent ratio 1:3, 1:7 and 1:10 respectively. Apparently, the given results are much better than those described in the paper [41].

In the work [46] lipophilic complexes from beer pollen pellet have been received with yield of 6,3-6,6 % by extraction with freons R12 and R22 at crude drug : extragent ratio 1:5 and processing time 3 hours. It has been found that both extracts had almost the same physico-chemical parameters. Similarly, fat oils of similar composition from milk thistle fruits were obtained with condensed freons R12 and R22 yielding about 30 % that is significantly more than by traditional methods [47].

The article [48] underlined the possibility for obtaining of the hypocholesteremic extract from medicinal herbal tea with freon R22 in 1 hour, thus yield of 22,65 % from herb weight was reached.

In the patent [3] method of obtaining of plant extracts containing carotenoids, anthocyanins, fatty acids, terpenoids and alkaloids with ratios corresponding to initial plans is described. The method provides application of both traditional solvents and condensed gases under sub- and supercritical conditions, in particular, fluorohydrocarbons R134a, R23, R32 and other modern freons capable to extract middle polar compounds.

In the research [13] ability of freons R134a, R23, R32 to dissolve polar biodegrading polymer polylactide at pressure 10 times less than with SC-CO_2 has been revealed.

The authors [7] have shown that aminophenol and benzoic acid derivatives have good solubility in supercritical difluoromethane (freon R32) even in the absence of any modifier. So, for example, salicylic acid was soluble two times more in SC-freon-32 than in SC-CO_2 at the same temperature and pressure regimes.

Now abroad the most often usable extragent is 1,1,1,2-tetrafluoroethane (freon R134a) as an alternative to SC-CO_2. So, for example, in the patent [49] method for extraction of aromatic substances from variety of plant and microbiological raw materials is claimed, and the inventor specifies that at temperature lower than +20°C this freon has high selectivity to the most volatile components of essential oils and does not extract accompanying waxes and fat oils. The author [50] also points on the similar properties of tetrafluoroethane and in his invention provides to extract fat and mineral oils with the specified solvent under heating above 40°C and, besides, to use its mixes with various cosolvents if needed including fluorohydrocarbons, DME and liquid ammonia. In the paper [51] it's also underlined the possibility of fractionation of free fatty acids, squalene and triglycerides in liquid freon R134a: under 60 atm increase in temperature from 30 to 80°C caused enhancing solubility of these substances by 2,5-3 times, besides, they considerably differed between themselves by this index. Pressure changes within 60-200 atm also considerably influenced solubility of the specified BAS.

In studies of extraction process of cumin essential oil, taxols and some alkaloids with freon-134a and its mixes with cosolvents [23, 34] it has been shown that addition of 10 % of liquid butane or dimethyl ether to the freon increased yield of cumin BAS by 2 and 2,6 times respectively. Efficiency of taxol extraction increased depending on composition of mixes by 2-5 times compared with pure freon R134a. Substances monensine and citohalasine-D were quantitatively taken by the specified extragent from aqueous solutions even at absence of cosolvents. In the claimed patents possibility for use of other methane-, ethane- and propane-derivative freons is also provided.

The method of solvent extraction of compositions containing such BAS as penicillin, alkaloids, paclitaxel, monensine or citohalasine [52] is also known. According to this method the composition is extracted with fluorohydrocarbons (freons) from range C_1–C_4. Besides, addition of cosolvents in the form of C_2–C_6– alkanes or dialkylether or their

mixes to the specified extragents is provided. However, extragents specified in the patent [52] are incapable to take salt forms of alkaloids from raw materials where acidic environment usually prevails.

In the method of fractional extraction of BAS from plant raw materials [53] condensed freons, mainly R134a, and also fluorohydrocarbons of propane range were used thus providing high selectivity to certain groups of aromatic compounds at various temperatures and/or at presence of cosolvents. So, for example, freon-134a at extraction temperatures 0°, 5°, 16°, 26°, 35° and 45°C took 6 fractions from *Piper methysticum* roots which considerably differed in their organoleptic and physico-chemical properties. The similar situation was observed after extraction of St. John's wort herb by freon-134a with addition of 0-20 % of methanol as cosolvent.

In the paper [54] it was pointed on possibility of fractional extraction of lipophilic compounds with liquid freon R134a varying process temperature, i.e. this solvent can be as selective as SCF though the latter needs for considerably higher pressure. So, at temperature up to 40°C R134a is almost unable to dissolve fat oils and other substances with high molecular weight, but at 60-70°C it extracts such compounds as well. As a rule, by its dissolving power subcritical R134a at elevated temperatures prevails over SC-CO_2. However, solubility of carotene in liquid freon-134a is comparable to that in SC-CO_2, but rise in temperature from 40 to 70°C increases the solubility almost by order of magnitude. Pressure rise from 64 to 343 atm influences solubility of carotene less considerably, increasing it only by 1,5-1,7 times.

The authors [55] have found that in the extract obtained from *Tilia tomentosa* inflorescences with freon-134a at temperature +15°C the main groups of BAS extracted were aromatic oxygen-containing compounds (36,8 %) among which phenylethyl alcohol (about 25 %), oxygen-containing monoterpenes (9,25 %) and also alkanes (33,6 %) were dominants.

After chemical analysis of the extracts obtained from the same herbal drug with carbon dioxide CO_2 under conditions approached to critical (pressure 70±2 atm, temperature 30±2°C) it was revealed that most of the withdrawn substances referred to the aldehyde group, both aromatic and aliphatic ones, and benzaldehyde (14,2 %) was dominating one, phenethyl alcohol was also present in noticeable amounts (about 10 %), the total content of carboxylic acids and their ethers was 9,5% [56]. Thus in studies [55, 56] it was noticed that any of the extracts did not have antimicrobial action against test strains, but in the research [57] antibacterial activity of linden essential oil obtained by hydrodistilling has been revealed.

The author [58] has patented equipment and method of obtaining of highly-purified herbal drug substances, in particular *Catharanthus roseus* alkaloids. The technology was based on application of solvents including freon-22 in sub- and supercritical states and varying of their composition.

The research [59] pointed on perspectivity for use of condensed dichlorodifluoromethane (freon-12) for extraction of alkaloids in a circulating system.

Consecutive and/or alternate application of extragents in condensed and supercritical states allows to obtain maximally purified sums of BAS and by combining with chromatographic methods of purification – even individual substances. So, for example, in the method of extraction of vincristine and vinblastine alkaloids from *Catharantus roseus* [60] use of CO_2, N_2O, propane, ethane and freon-22 in subcritical, near-critical and supercritical conditions (SC/NC/SC–fluids) as extragents and mobile phases at their chromatographic purification is provided for obtaining of crude extracts. Besides, according to the claimed method at stages of BAS extraction from the raw material and their subsequent purification organic solvents are applied as cosolvents: aliphatic alcohols C_1-C_4, preferably methanol, acetone, hexane, methylene chloride either as mixes with each other or with SC/NC/SC-fluids. According to the claimed method at the first stage of technological process removal of unwanted lipophilic substances by means of non-polar SC/NC/SC-fluids is carried out. Further target BAS together with accompanying substances are extracted with mixes of SC/NC/SC-fluids with polar cosolvent(s) from the marc obtained on the previous stage.

Similarly, in the method of extraction separation [61] it has been shown that extraction of BAS is better to provide with liquid CO_2 in subcritical state and separation of components – under temperatures and pressure slightly exceeding critical values (by 5-20°C and 20-30 atm respectively). The claimed technology is based on that under such conditions on phase diagrams additional areas of gas-liquid equilibrium appear as a result of presence of other components, in particular extractives, in SCF-solution, and better selectivity of the process is thus reached. According to the patent [62] hellebore alkaloids were also separated under conditions approaching to the critical point: temperature 40°C, pressure in the first and second separators – 80 and 60 atm respectively.

In the study [20] the technology for obtaining barberry alkaloids using freon-22 modified with 10% of liquid ammonia has been developed that allowed to reach 99% of recovery under certain conditions.

Condensed gases also can be used for extraction of lipophilic BAS from herbal raw materials for the purpose of its subsequent comprehensive processing. So, for example, in the method of obtaining of belladonna extract [63] for the raw material extraction use of liquid CO_2 in subcritical state is provided at first to remove lipophilic substances, and then – extraction with aqueous-alcoholic mixes from degreased marc to obtain sum of alkaloids is used.

The authors [64] have found that in production of St. John's wort tincture extraction efficiency of flavonoids increased by 33 % if the raw material is preliminarily treated with condensed gas in order to withdraw lipophilic compounds.

In the papers [65–67] it has been shown that during consecutive processing after extraction of lipophilic complex from lime flowers with freon-22 at the first stage the yield of phenolic substances at the following stage increases by 22-25 %.

Condensed gases can be used as well for obtaining of hydrophilic BAS. Thus such solvents should be polar enough or can be mixed with less polar modifiers. From this point of view within existing range of condensed gases great attention is attracted by DME and liquid ammonia. The latter, despite its potential danger, finds wide applications in many fields [68–

70]. So, for example, in the paper [70] it was shown that condensed ammonia is perspective fuel for automobile engines and is much cheaper than usual hydrocarbons. In the field of biotechnology liquid ammonia is applied for pretreatment of fodder vegetative biomass to destruct cellulose matrix in cellular walls and, as a consequence, to intensify extraction of proteins [71].

The authors [68, 72, 73] patented methods for obtaining of natural saponins by extraction of Manchurian aralia roots, medicinal fuller herb, licorice and eleutherococcus with condensed ammonia under periodically changing pressure to make cavitation effect. In the patent [73] method for obtaining of food emulsifying agent from eleutherococcus roots which provides raw material extraction with condensed ammonia under periodic pressure change in pulsing regime was claimed.

The method for preparing of gelling carbohydrate concentrate by multiphase extraction of sugar beet and micromycete biomass using SC-CO_2 and liquid ammonia at different stages is also known [74]. This offered method allows to considerably increase yield of pectines during complex processing of raw materials.

The authors [75] offered the method for production of dry licorice extract using liquid ammonia as an extragent under pulsing pressure mode; it was underlined that duration of extraction process can be reduced by 10-15 times in comparison with existing prototype. In the paper [35] possibility for use of ammonia in supercritical state for extraction of saponins from licorice roots is also shown.

Condensed ammonia can be used for production of quercetin dye by extraction of mix of onions peels with comminuted bark of coniferous trees [A7] that point on ability of this extragent to dissolve flavonoids.

In the papers [69, 77] it has been shown that after extraction of ginseng roots with liquid ammonia yield of panaxosides was almost twice more than after use of water or 60% aqueous methanol, and specified BAS did not decompose and could be obtained in native state even from damp fresh raw material. According to the invention [69] mixes of condensed ammonia with hydrocarbons C_2-C_6 are effective extragents for aforementioned group of BAS, it was also found that SC-CO_2 was unable to extract panaxosides from ginseng roots at all.

The authors [33] presented experimental data concerning extraction of purine alkaloids. It has been shown that solubility of theobromine and caffeine in liquid ammonia was several times more than those in boiling water, chloroform and alcohol.

In all research described above it is not underlined that liquid ammonia potentially can interreact with vegetative BAS forming products of semisynthesis. However, studies [19, 78] resulted in that alkaloids berberin and coptisine partially reacted with liquid ammonia, forming 8-amino-derivatives though the latter are very unstable and in acidic medium and even on air transform back into initial alkaloids.

Hence, condensed ammonia seems to be perspective extragent for extraction of hydrophilic BAS. Advantages of this solvent are easy leakage detection and simplicity of its deactivation in case of emergency. However, it has essential lacks: high toxicity, explosiveness in high concentrations. Therefore it's more safe for pharmaceutical production to use mixes of ammonia with more inert gases, for example, with freons.

Condensed gases can be used as well for extraction in liquid-liquid system which is usually carried out in separating funnels or in columns working in countercurrent regime. However, as the authors [29, 79] specify, lacks of such devices is instability of hydrodynamic regime, formation of stable emulsions which are hard to separate and also low mass transfer intensity that requires large-sized equipment in its height and it is especially undesirable for extraction under pressure. The specified lacks are eliminated in devices working by principle of membranous separation. According to the patent [79] for embodiment of this process condensed gases from the range of CO_2, N_2O, hydrocarbons C_1–C_4, freons, ammonia, sulfur hexafluoride or methyl chloride are chosen.

Thus, condensed gases have wide prospects for application in phytochemical production being not inferior to supercritical fluids and in some cases even surpassing them.

Conclusions

Among existing methods for intensification of stage of plant extraction the most applicable for commercial scale is use of condensed gases and supercritical fluids as extragents. It is found that for today in the world the most widespread SCF is carbon dioxide.

The main lacks of CO_2 as an extragent are high working pressure and narrow spectrum of extractable BAS which is limited only to lipophilic substances. This induces the search for alternative condensed gases and SCF among which fluorohydrocarbons (freons) are of the greatest interest.

Also perspective methods of extraction intensification are applications of ultrasound, microwave field and some other methods of raw material processing, but meanwhile they have not got industrial value because of insufficient scientific base.

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PROSPECTS FOR USE OF CONDENSED GASES AND SUPERCRITICAL FLUIDS IN PHYTOCHEMICAL PRODUCTION

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In the given review article analysis of the literature and patent sources concerning main methods for intensification of extraction processes of medicinal vegetative raw materials – use of condensed gases and supercritical fluids (SCF) on more acceptable extractants has been carried out for last 20 years. Urgency of the specified technologies consists in need for replacement of traditional extraction methods on power- and time-saving ones, and also in use of nontoxic, fire-proof and low-boiling solvents because the most of routine organic solvents (ethanol, methanol, acetone, chloroform, ethylacetate, etc.) are toxic and/or flammable or expansive and rather hard to evaporate out from extracts obtained. The abovementioned trends are the most universal for intensification of extraction processes and sometimes purification of final or intermediate products acceptable for commercial scale of manufacture. The main advantages and disadvantages of the given methods are compared for different plant species and groups of biologically active substances (BAS). It has been shown that in most cases supercritical CO_2 (SC-CO_2) are inferior in its dissolving ability to number of condensed gases and, besides, such technology is much more expensive. The range of BAS taken with SC-CO_2 is limited to mainly lipophilic compounds because of zero electrical dipole moment of SC-CO_2 and its low polarity. As extractants alternative to SC-CO_2 with higher dissolving ability SC - ethane, nitrogen monoxide, freons - R134a, R23, R32, R408 and number of others can be used. Also to enlarge range of extractable BAS it is possible to add different cosolvents, mainly ethanol or methanol in quantity up to 20%. At the same time in phytochemical production prospective alternatives to liquid or supercritical CO_2 are certain condensed gases with wider range of physicochemical properties: fluorinated derivatives of hydrocarbons (freons), liquid ammonia, dimethyl ether (DME), sulfur hexafluoride (insulating gas) or their mixtures, etc. Their major characteristics include lower vapor pressure if compared with liquid CO_2, antimicrobic activity allowing to solve one the main problem in phytochemical production – microbial contamination of extracts (and other herbal drug preparations), possibility to extract not only lipophilic, but also more polar substances depending on choice of solvents or their mixes and their higher extraction rate.It has been found that some kinds of freons (for example, R22) due to their higher polarity are able to take wider spectrum of BAS than liquid CO_2: essential and fat oils, fat-soluble vitamins, coumarins, carotenoids, phenolic alcohols, valrates, iridoids, some alkaloids and flavonoids. Besides, certain freons (for example, C318) have very high selectivity allowing to extract essential oils without accompanying fats. Some condensed gases, such as liquid ammonia, dimethyl ether and difluoromethane (freon R32) can be used as well for obtaining of hydrophilic BAS (saponins, alkaloids, flavonoids). Thus such solvents should be polar enough or can be mixed with polar modifiers. Supercritical fluids and some subcritical condensed gases are suitable for fractionating of primary (crude) extracts because their selectivity considerably depends on temperature, pressure and composition (in case of mixtures with each other or with cosolvents). Also high selectivity of condensed gas and SCFs is shown in near-critical areas. Very important property of most of condensed gases and SCFs is their ability to considerably reduce microbial contamination of extracts in comparison with initial plant raw materials.
Conclusions. Among existing methods for intensification of stage of plant extraction the most applicable for commercial scale is use of condensed gases and supercritical fluids as extractants. It is found that for today in the world the most widespread SCF is carbon dioxide. The main lacks of CO_2 as an extractant are high working pressure and narrow spectrum of extractable BAS which is limited only to lipophilic substances. This induces the search for alternative condensed gases and SCF among which fluorohydrocarbons (freons) are of the greatest interest. Also perspective methods of extraction intensification are applications of ultrasound, microwave field and some other methods of raw material processing, but meanwhile they have not got industrial value because of insufficient scientific base.
Keywords: condensed gases, supercritical fluids, plant raw materials, extraction, freons, carbon dioxide.