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Implications of Industrial Technologies in the Preparation of Vegetal Derivatives (**)

Medicinal plants, which provided for centuries the main source of medicines, still account with their derivatives for about 20% of prescriptions in industrialized countries and for about 80% of prescriptions in developing countries.

Among the active principles of natural origin, pure substances and purified standardized extracts are acquiring increasing importance because they can be characterized better than traditional products and therefore they can satisfy the quality, efficacy and safety requirements typical of a modern drug. In fact, according to international health regulations, every preparation used in human therapy, like any drug, must meet certain basic criteria of consistency, stability, sterility and absence of potentially toxic contaminants such as residual solvents, pesticides, etc. These requirements must be met also in the industrial preparation of natural products though this often involves considerable difficulties, which are generally greater for simple products such as extracts than for pure active principles, even when the latter are present in the original raw material at very low concentrations.

The most critical steps in the preparation process are generally represented by the choice of the raw vegetal material and by the identification of a suitable extraction solvent, which should be as selective as possible for the desired active principle. In the preparation of a pure principle, the quality of the vegetal material is a purely economic problem in the sense that by using a material giving a greater yield it is possible to reduce the cost of the final product. In the preparation of a normal or standardized extract, however, the quality of the raw material is more critical because it is this quality that determines the characteristics of the final product.

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In fact, for the preparation of a standardized product it is necessary to take into account:

— the variability in the concentrations of the active principles in the raw material;

— the variability in relative ratios between different active principles within the same botanical species;

— the occasional presence in the same botanical species of different secondary metabolites.

Currently, the approach normally used to overcome these problems is to analyse carefully different lots of the material and to select those which are more suitable or, preferably, to mix different proportions of the analysed lots in order to obtain a final mixture containing constant ratios of the individual components. This procedure allows the widest application, since it can be applied to all medicinal plants, including herbs and trees. From the industrial point of view, however, the preparation of the mixture, technically simple despite the considerable analytical work involved, contributes importantly to raise the cost of the final product because it requires the maintenance of large stocks of raw material. A different solution, more modern and effective, which will provide the basis in the future for the preparation of standardized products, consists in the cultivation of genetically homogeneous plants or, at a technologically more advanced stage, in the production of genetically homogeneous tissue cultures in a fermentator.

At present, the most practicable of these new procedures, already usefully applied in some cases, is the cultivation of genetically select plants by micropropagation on tissue cultures. Basically, the method consists in analyzing several hundreds of plants individually and in obtaining suitable tissue aliquots from those showing the most desirable composition. The selected tissue is then cultured in order to induce sprouting of genetically identical plants, which are then explanted and grown in the open field. This technique allows the production of homogeneous composition in active principles. Obviously, the procedure is feasible only for medicinal plants having a short life cycle (annual or biennial) and it cannot be applied, for example, when the raw material is represented by roots of forest trees, etc. Of course, the plants must be grown and collected under strictly standardized conditions. In these cases, the preparation of the vegetal material represents by itself a technological advance which is often superior to the technological aspects involved in the sophisticated but already established processing operations.

After a suitable raw material for producing the vegetal derivative has been selected, the preparation procedure will require several steps, which I will now discuss by highlighting the main problems involved and the most appropriate equipment which can be used. These steps consist in:

— Grinding the raw material.
— Extracting the active principles.
— Concentrating the extract.
— Counterextracting/partitioning the active principles.
— Drying the extract of the active principles.

The grinding step represents the first operation of the whole procedure and is essential for a successful result of the subsequent extraction, in terms of both total yield and solvent flow rate, and therefore speed of exhaustion. The most important goal to be achieved in the grinding procedure is the homogenicity of the particles, the size of which must be carefully studied in each case in relation to the type of extraction equipment and to the type of solvent subsequently used. It is advisable to avoid the formation of too fine particles (less than 0,5 mm in diameter) because these, while theoretically increasing the solute/solvent exchange, hinder the efficiency of the filtration process and make impractible any automation. If the extraction is carried out by using large installations operating continuously, such fine particles should not account for more than 10% of the ground mass. Technologically, the problem can be solved by choosing carefully suitable equipment. The most common types of grinding machinery used for these purposes include cutting or grinding systems equipped with grids of appropriate mesh. The following schemes show some examples of the most commonly used systems (Fig. 1). These mills are used to pulverize dry materials; completely different problems arise when the extraction is carried out by using fresh materials or materials containing large amounts of water.

In the latter cases, it is necessary to perform a cryogrinding procedure at temperatures around —20°C, in order to prevent or to minimize enzymatic reactions leading to degradation of the active principles. If grinding is carried out at room temperature, these enzymatic reactions take place within a few minutes and may not always be prevented by addition of specific inhibitors. For these reasons, the grinding of fresh materials at room temperature is carried out only when the enzymatic reactions can be usefully exploited as part of the preparation procedure. A situation of this kind arises, for example, in the isolation of certain secondary glucosides derived from primary glucosides by enzymatic removal of a saccharidic chain, which otherwise would need to be cleaved by careful selective hydrolysis. These cases, however, are rather exceptional because the use of fresh materials is steadily declining, due to the cost limitations and problems of storage.

The step following grinding is the extraction. The main purpose of the extraction process is to separate in a more or less purified form the active ingredients from the other components present in the ground material. The extraction of the active principles is normally obtained by diffusion and/or washing. The removal of the principles from intact vegetal cells is obtained by slow diffusion of the solvent into the cell with subsequent transfer of the drug until an equilibrium is reached between solute and solvent. The washing process, on the other hand, consists in the solubilization of the active principles present in the cell fragments produced by the grinding and drying procedure or by the extraction procedure itself. Normally, the two processes occur simultaneously: frequently, it is preferable to enhance washing by adding hypotonic solutions or deionized water, which cause swelling and lysis of the vegetal cells. From a theoretical point of view, the extraction processes in general can be classified, according to a chemical-physical concept, into two main categories:

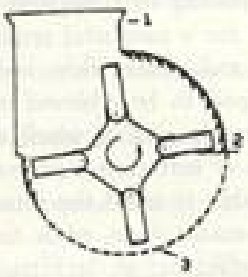


Diagram of hammer mill: 1 - Drug feed; 2 - Hammers; 3 - Grid.

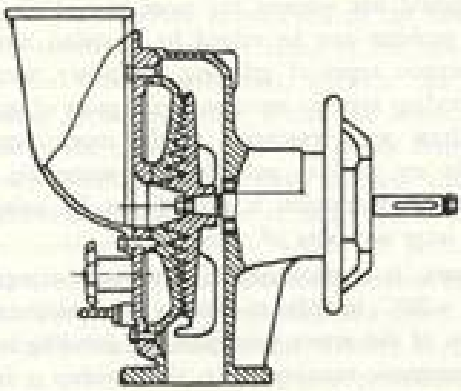
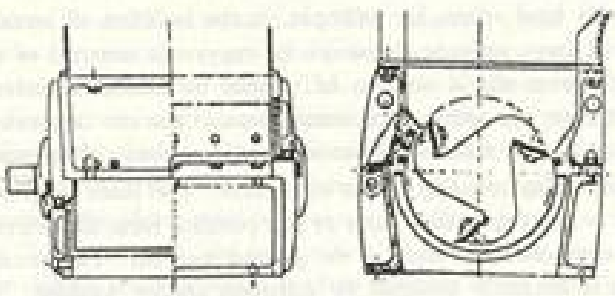


Diagram of teeth mill.



Different types of knife mills.

Fig. 1

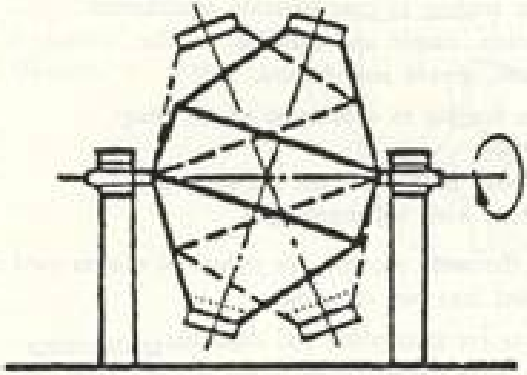
— Procedures leading to concentration equilibrium:
  a) Maceration, simple and dynamic;
  b) Digestion, simple and dynamic.
— Procedures leading to exhaustion of the drug:
  c) Percolation;
  d) Continuous counter-current extraction;
  e) Extraction with hypercritic gas.

According to the same concept, the industrial system used for the extraction can also be classified into two categories:

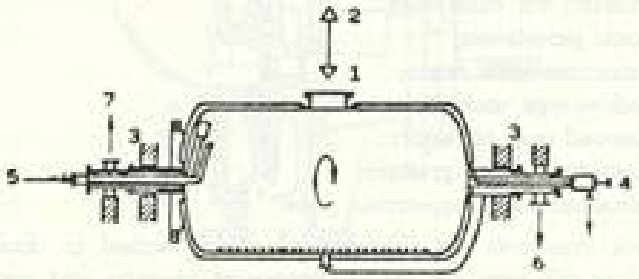
— Instruments for maceration and digestion:
  a) with stirring action related to the intrinsic structure of the instrument;
  b) with mixer;
  c) mixers with cochlea.
— Instruments for exhaustion:
  d) Static percolators;
  e) Extractors with mixer;
  f) Cochlea-type continuous extractors;
  g) Carousel-type extractors;
  h) Extractors under pressure;
  i) Extractors using hypercritic gases.

Maceration represents the simplest and oldest method to obtain a vegetal derivative and is still used for the production of tinctures and macerates. The procedure consists in immersing the vegetal material in a suitable solvent for a certain period, followed by separation of the drug under pressure or by filtration. To speed up the extraction process, macerations are normally carried out under agitation and at different temperatures by using 5 to 10 parts of solvent. Industrially, the use of these procedures is declining because they do not allow exhaustion of the drug. The extracts obtained in this way are normally used without undergoing concentration or further processing and, due to their low content in active principles, they tend to be unsuitable for pharmaceutical formulations, especially solid formulations. The equipment used for this kind of extraction is represented by mixers with different capacity; the most common models are reported in Fig. 2. Of course, many of these instruments can be used to carry out multiple extractions which lead to exhaustion of the drug and therefore they can practically serve as percolators and achieve the same results by using more sophisticated equipment.

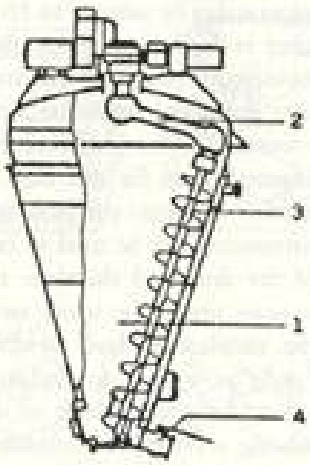
Percolation provides the simplest method to obtain exhaustion of the drug and can be used for small scale as well as for industrial applications. The most commonly used percolators may be either static or dynamic; in the former the drug keeps still and the moving solvent is continuously recycled by appropriate pumps, whereas in the latter the drug is agitated continuously by the blades of a rotating shaft. The following schemes give an idea of available instruments, which can be quite versatile and suitable for both small and large scale productions (Fig. 3).



Schemes of dynamic extractor suited for maceration.

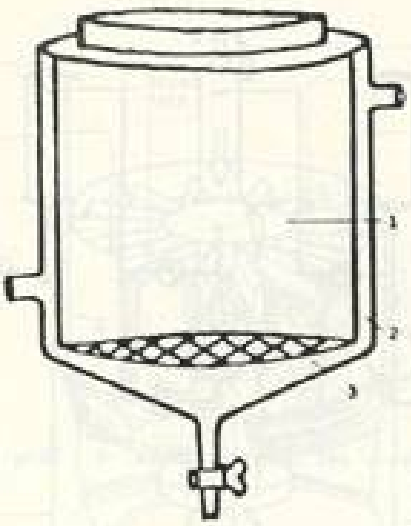


Horizontal extractor rotating on its shaft: 1 - Solids feed; 2 - Solid discharge; 3 - Bearing; 4 - Heating; 5 - Fresh solvent; 6 - Extract; 7 - Vapours.

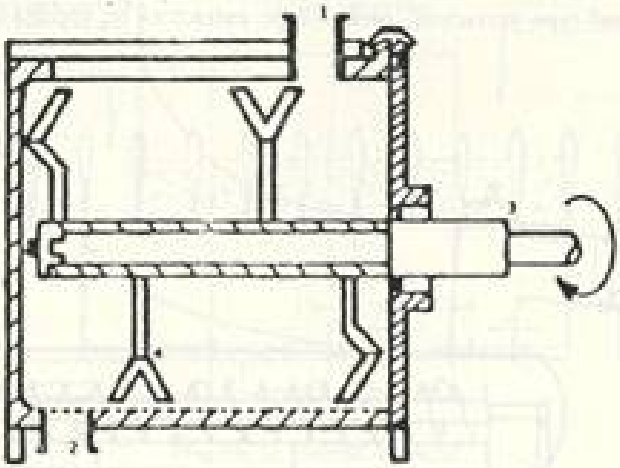


Nauta extractor: 1 - Extractor; 2 - Swinging arm; 3 - Mixing screw; 4 - Solids discharge.

Fig. 2



Scheme of traditional percolator: 1 - Percolator; 2 - Jacket; 3 - Grid.



Scheme of extractor with agitator: 1 - Drug feed; 2 - Solids discharge; 3 - Shaft; 4 - Arm.

Fig. 3

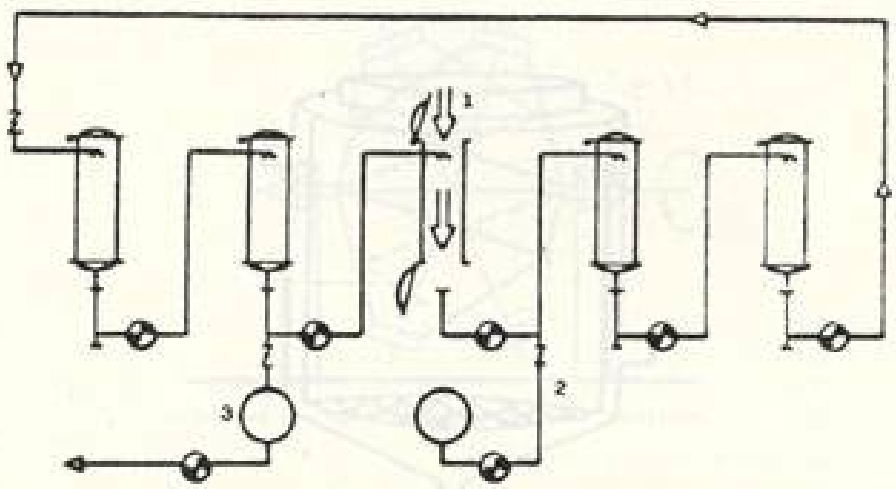
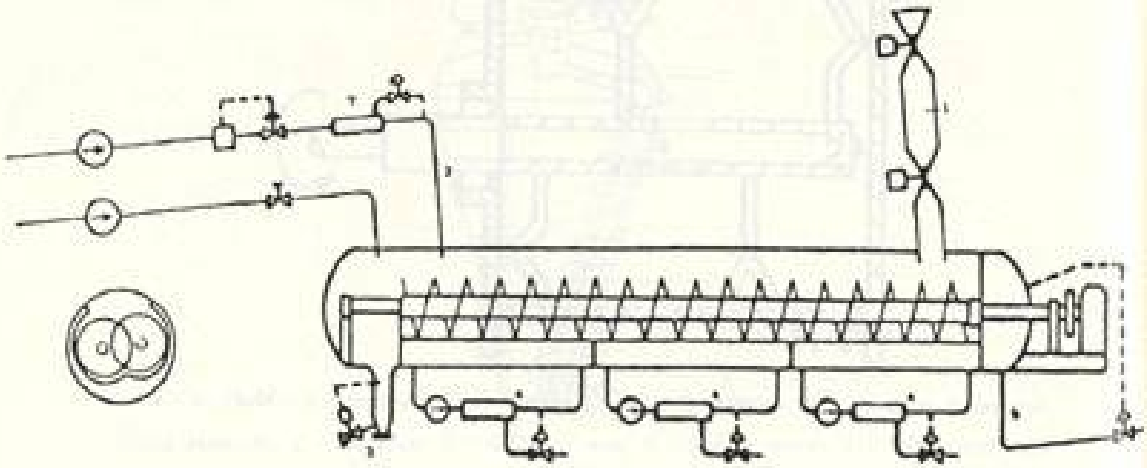


Fig. 4 - Battery of percolators and operation scheme: 1 - Drug feed; 2 - Fresh solvent; 3 - Extract.

One of the advantages of these kinds of instruments is the possibility of using them separately or in series (Fig. 4). In this way, it is possible to obtain, with obvious saving of solvents, extracts already concentrated which exhibit reproducible contents in active principles and retain unaltered the organolectic properties of the final product. For large scale production, the best systems are those operating in continuous counter-current, or in counter-current in continuous: these include basically carousel-type extractors, cochlea-type extractors or cochlea-like extractors (Fig. 5).



Countercurrent horizontal extractor: 1 - Solids feed; 2 - Solvent inlet; 3 - Solids discharge; 4 - Heat exchanger; 5 - Extract; 6 - Spent-solvent outlet; 7 - Heater.

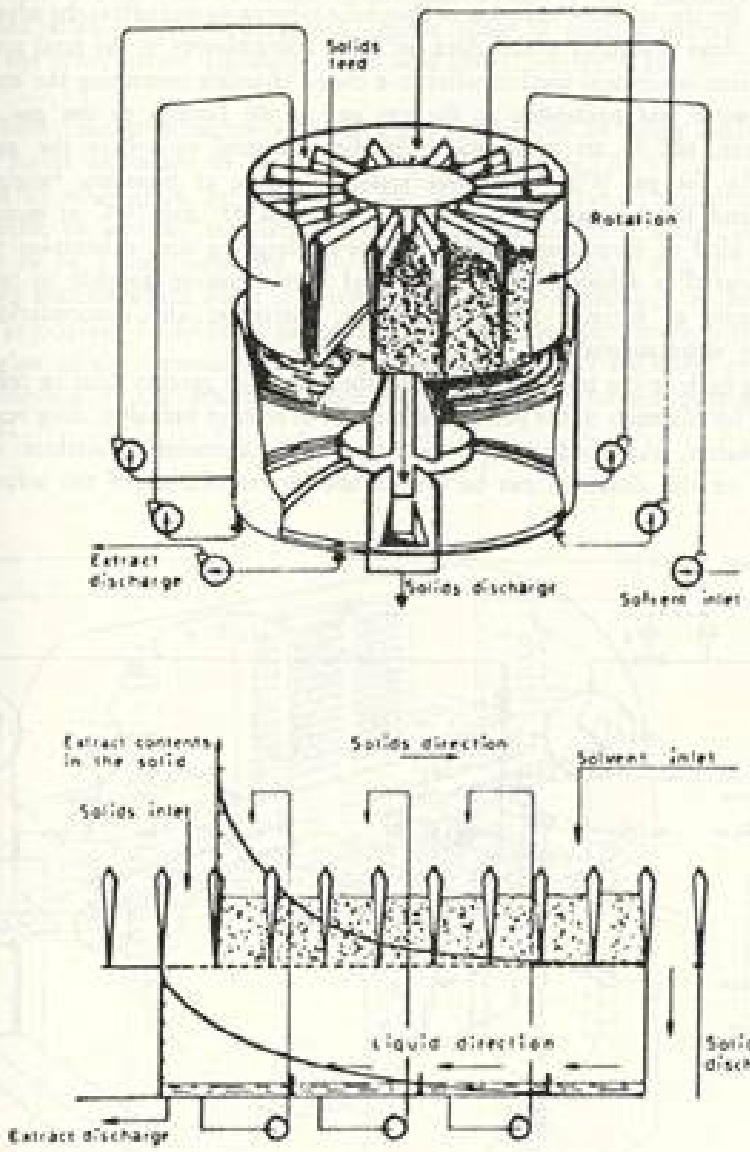


Diagram of carousel extractor.

Fig. 5

A new extraction method which is also beginning to be applied in the preparation of active principles in the pharmaceutical field is represented by the use, as a solvent, of gas under hypercritic conditions. Of course, this extraction system is convenient for the selective isolation of lipophilic substances and offers the advantage of being a clean procedure which does not leave contaminants in the final product. The extraction equipment used consists in a closed chamber containing the material to be extracted and permeable at the top and at the bottom to the gas acting as a solvent, and in an evaporation chamber designed to collect the product extracted by the gas (Fig. 6). These systems operate at pressures ranging between 70 and 400 bars and at temperatures between 35° and 70°C or more. By using this kind of instruments, which are never large in size, exhaustion of the vegetal material is achieved very rapidly and it is therefore possible to produce large amounts of extract. In these systems, extraction and concentration are carried out simultaneously.

Going back to the traditional systems, the extraction process must be followed necessarily by filtration of the percolates in order to remove turbidity, drug residues, etc. Thereafter, the product must undergo a concentration procedure which, depending on the situation, can be carried out by evaporation of the solvent or

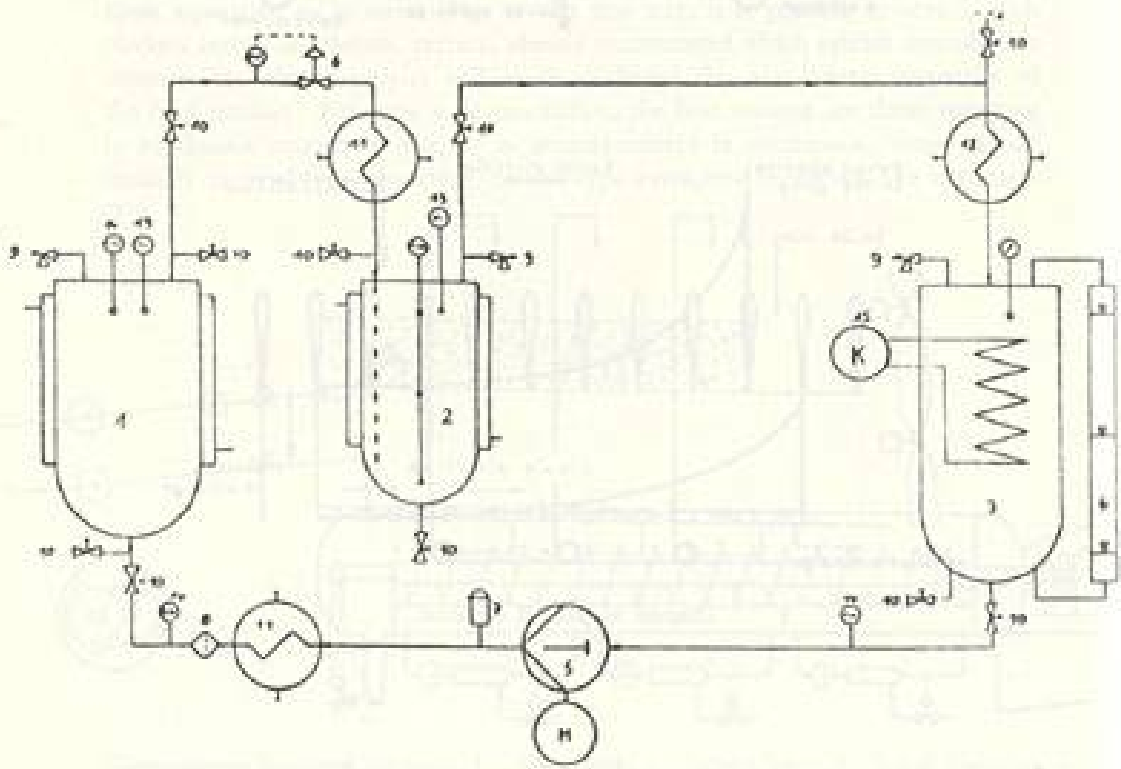
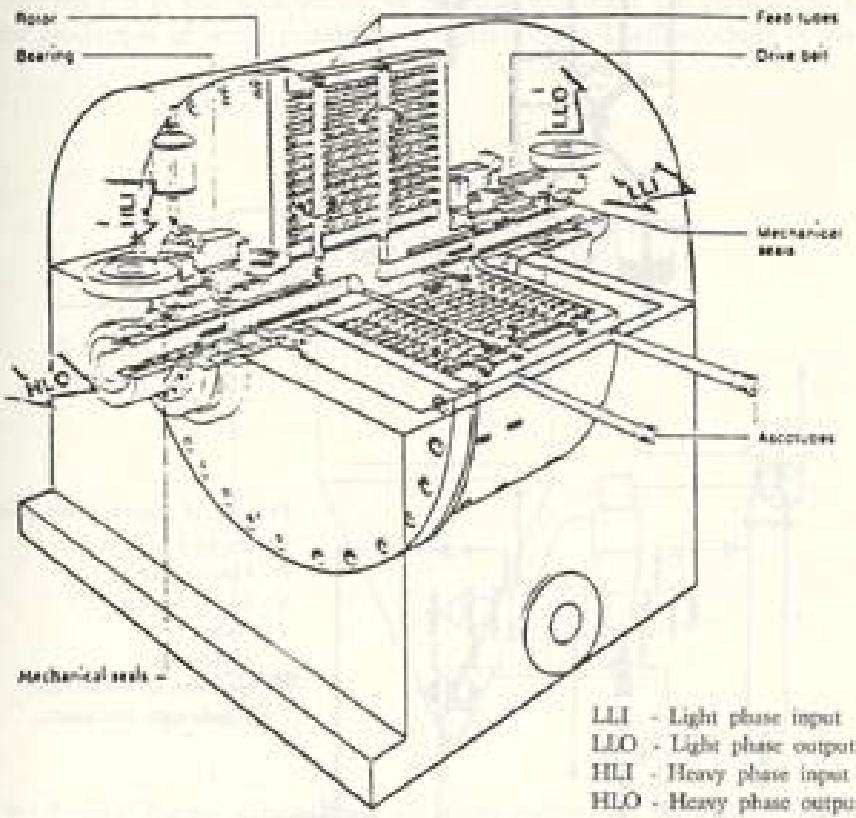


Fig. 6 - 1 - CO_2 container; 2 - Extractor; 3 - Condenser.

by counter-extraction with solvents not mixable with the percolate. Classical examples are provided by the extraction of alkaloids with aromatic or aliphatic hydrocarbons followed by direct counter-extraction of the extract with concentrated acids. After washing, the organic phase is used to extract new drug while the concentrated alkaloids in the acid phase are ready for the purification step.

These counter-extraction operations are carried out by using counter-current liquid/liquid separators or liquid/liquid centrifuges (Fig. 7).

In all other cases, the extraction liquids must undergo a concentration step, irrispective of whether the final product is represented by a liquid, soft or dry extract or by a pure substance. Normally, this concentration step is carried out by using systems which allow to minimize the thermal degradation of the extracted active principles. In addition to the classical long-tube evaporators with or without cyclon, of the chemical industry, which can be used for the initial evaporation, it is common to use descending film distillators or submersed plate distillators (Fig. 8).

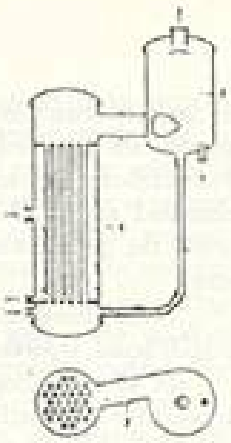


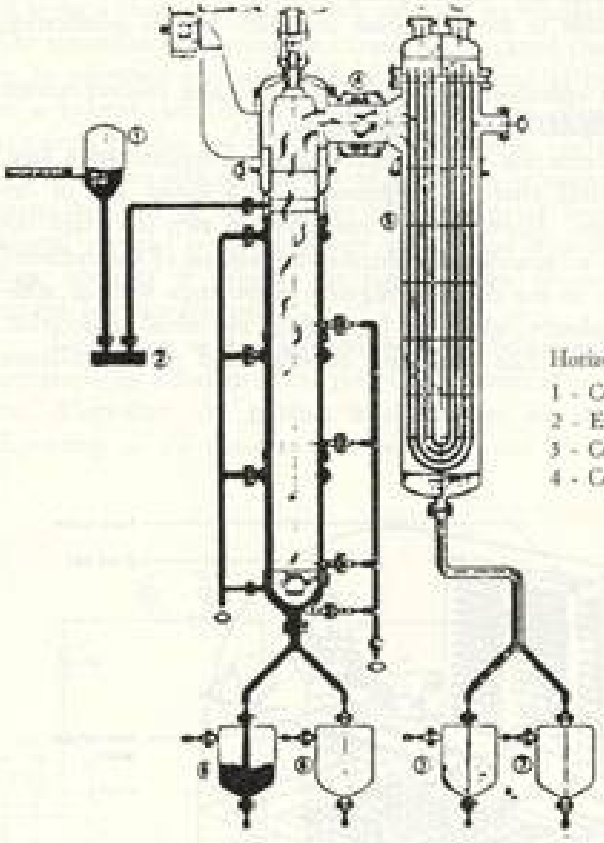
LLI - Light phase input
LLO - Light phase output
HLI - Heavy phase input
HLO - Heavy phase output

Fig. 7

Traditional Robert type concentrator:

1 - Concentrator;
2 - Vapours chamber separation;
3 - Concentrator section.





Horizontal thin layer concentrator

1 - Concentrator;
2 - Extract feed;
3 - Condenser;
4 - Concentrate.

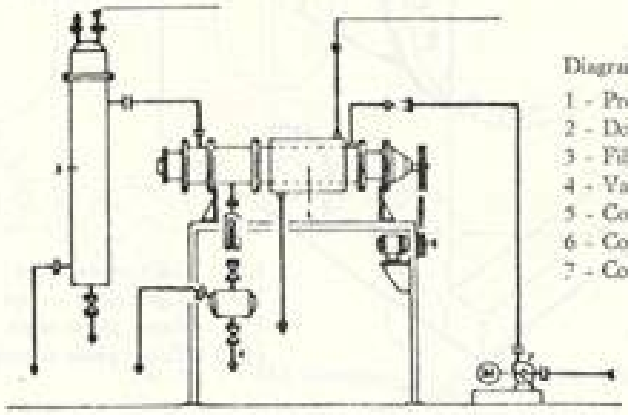


Diagram of concentration plant:

1 - Product feed tank;
2 - Dosing pump;
3 - Film evaporator;
4 - Valve;
5 - Condenser;
6 - Concentrate containers;
7 - Condensate containers.

Fig. 8

By using these systems, it is possible to obtain evaporation of the water at temperatures near room temperature, to reduce foam formation and to avoid important degradations due to overheating and incrustations.

In the preparation of extracts, the concentration step is normally followed by clarification, which can be carried out with supercentrifuges or decanters or filters under pressure. Finally, whenever possible, the product undergoes a drying step. Extracts in dry form are generally preferred because they are usually stable, they can be handled more conveniently and they are less vulnerable to bacterial contamination.

The drying procedure is a delicate and very crucial step which has important implications for the quality of the final product. Obviously, the drying of an extract is often a difficult operation due to the heterogeneity of its ingredients, which include essential oils, fats, mucilages and many other hygroscopic products. Many of the problems have been overcome by using atomizers (Fig. 9) and by adding, when necessary, appropriate excipients. By using atomizers equipped with appropriate accessories, it is possible today to obtain products virtually free of bacterial contamination, homogeneous in granulometry, scarcely coloured due to lack of degradation, etc.

At the end of this rapid review of the main equipment and installations used in the production of active principles of vegetal origin, I will conclude by giving

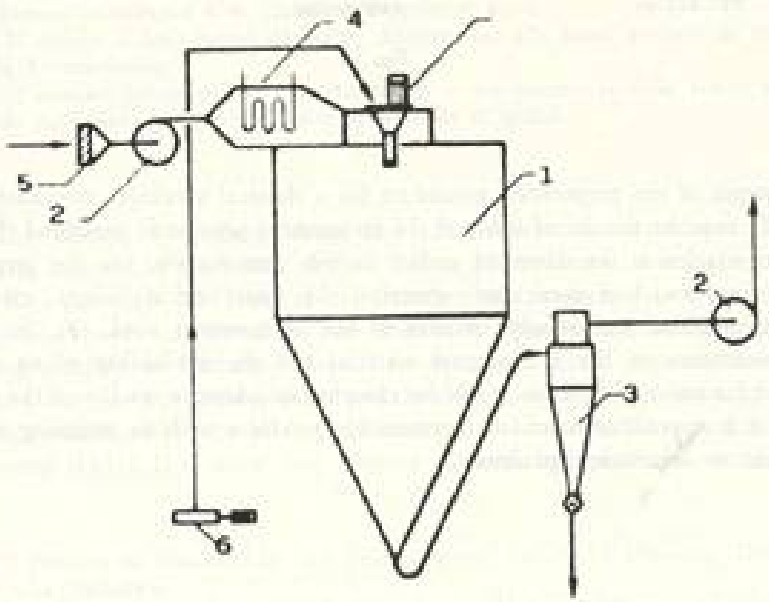


Fig. 9 - Principle diagram of spray dryer: 1 - Drying chamber; 2 - Ventilator; 3 - Cyclone; 4 - Air heater; 5 - Filter; 6 - Pump.

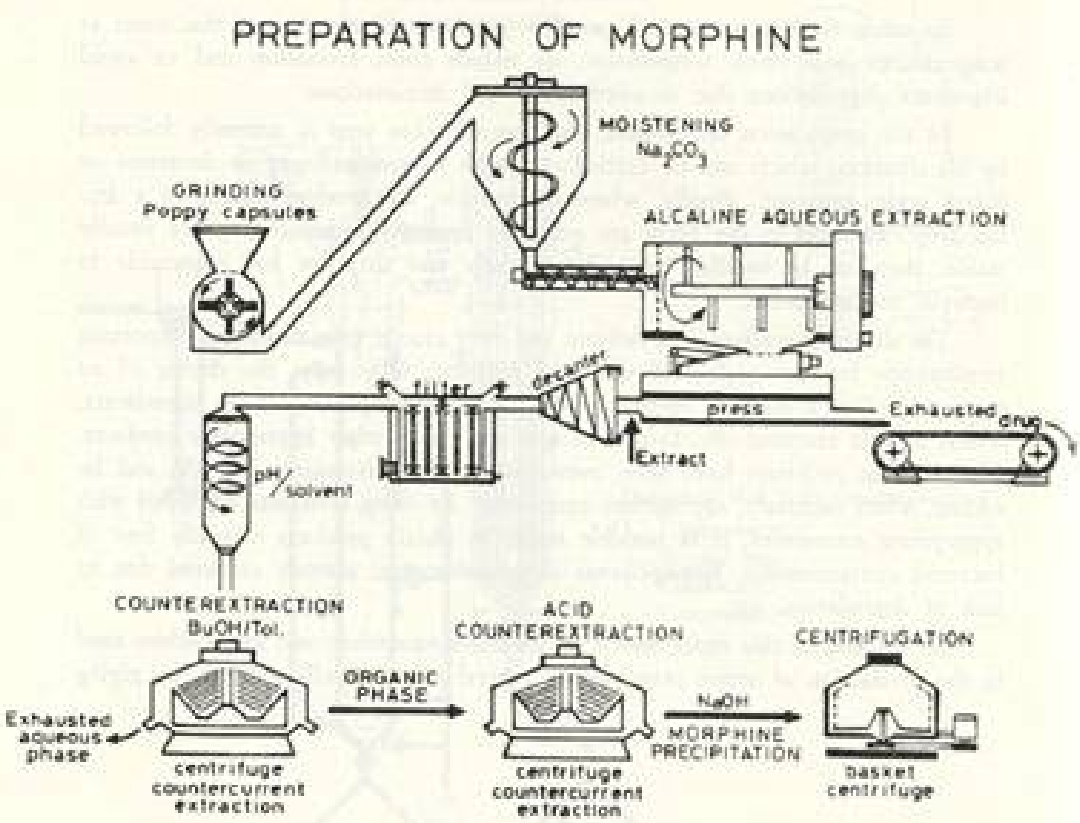


Fig. 10

an example of the preparation procedure for a classical alkaloid: morphine, which typically requires the use of many of the instruments previously described (Fig. 10).

In conclusion, as discussed earlier in this presentation, for the preparation of all products, and particularly extracts, the most critical factors, more than the sophisticated technologies related to the instruments used, are the quality and consistency of the raw vegetal material and the availability of an accurate method for monitoring them. Only by ensuring an adequate quality of the original material is it possible to obtain reproducible products without resorting to artful dilutions or enrichment processes.