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Extraction of medicinal compounds from botanicals using bulk liquid membrane in rotating film contactor: Recovery of vinblastine from catharanthus roseus.

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Abstract

The interest of application of liquid membrane (pertraction) processes for recovery of medicinal compounds from dilute ammoniacal leach solutions is demonstrated. Selectivity of the liquid membrane ensures a preferential transport of the desired solute from the native extract into the strip solution, vinblastine was successfully extracted from basic media (pH 9.2) and stripped by acidic media of sulfuric acid (pH= 1.3) applying continuous pertraction in a rotating discs contactor and using n-decane as liquid membrane. Transport of vinblastine in three-liquid-phase system was studied and performed by means of a kinetic model involving two consecutive irreversible first-order reactions. The kinetic parameters (apparent rate constants of the vinblastine extraction and re-extraction reactions (K1, K2), the maximum fraction of the vinblastine in the liquid membrane (XS.Max) and the time when this maximum is reached (TMax)) were calculated. Solute transfer into the LM is mainly diffusion-controlled.

Keywords**:** Liquid membrane, Pertraction, Extraction, vinblastine, catharanthus roseus

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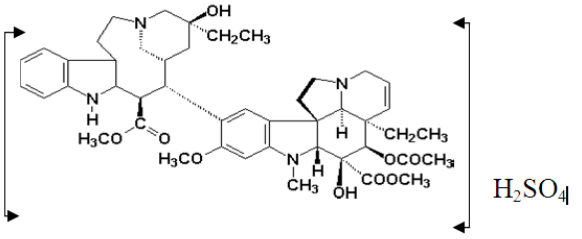
Introduction

The established idea of a membrane is a thin, semi-permeable and solid barrier. A liquid membrane (LM) is nothing like this. It is a liquid phase, usually organic, interposed between two miscible aqueous solutions. At one side of the membrane (feed solution) the material to be transported is extracted, while at the other side (stripping solution) re-extraction occurs. Since in each of the aqueous solutions some specific, and different for each of them, thermodynamic conditions exist, the extraction and re-extraction occur simultaneously. Such process is called pertraction i.e., extraction in one side and stripping of the extract at the other side simultaneously. The liquid membrane extraction was introduced as an alternative separation technique to the liquid-liquid extraction and to the separation by means of solid polymeric membranes [1]. This property of membranes makes them useful in the textile and food industries, in hydrometallurgy, medicine, biotechno-logy environmental protection, in the separation of hydrocarbons and gases, and in the concentration and separation of amino acids, metal ions and other mixtures and suspensions [2].

Vinca or Periwinkle (Catharanthus roseus (Linn.) G.Don.) is an erect handsome herbaceous perennial plant which is a chief source of patented cancer and hypotensive drugs. It is one of the very few medicinal plants which has a long history of uses as diuretic, antidysenteric, haemorrhagic and antiseptic. The dimeric indole alkaloids from Catharanthus roseus L, vinblastine (Fig. 1) present in the leaves, it is mainly useful for treating Hodgkin's disease, lymphocytic lymphoma, histiocytic lymphoma, advanced testicular cancer, advanced breast cancer, Kaposi's sarcoma, and Letterer-Siwe disease. These drugs because of extremely low yields are among the most expensive in the pharmaceutical market. Attempts to improve their yields through cell and tissue culture have so far met with limited success. Growth and differential stage-dependent biosynthesis of these alkaloids are still poorly understood [3].

A new bulk liquid membrane (BLM) process for recovery of medicinal compounds from dilute ammoniacal leach solutions has been studied in this work. vinblastine alkaloids was extracted by means of a rotating film pertractor using various organic liquid membranes as carrier, A simple kinetic model of the mass transfer of solute in BLM is advanced by considering two consecutive reactions (extraction–re-extraction of the solute) with three diffusion steps in the feed, organic and stripping solutions.



Free base: $C_{46}H_{59}N_4O_9$; M.W. 811

Sulphate: $C_{46}H_{59}N_4O_9$; M.W. 909

Fig.1 Chemical Structure of VBL and VBL sulphate.

Experimental Work

Materials (solvents and aqueous solutions)

Organic solvents used in this work as liquid membrane, n-decane and n-nonane; BDH, n-heptane; RIEDEL_DEHAËN and methylcyclohexane; HOPKIN & WILLIAMS. Ammonia and sulfuric acid were used as donor and accepter solution respectively. The acidity of the aqueous solutions was measured using a pH-meter (OAKTON pH 2100 series manufactured by EUTECH instruments Singapore).

Procedure of pertraction

Among the large variety of liquid membrane techniques [1, 4-12] the pertraction in rotating film contactor (RFC) was selected because of its stability. Kinetics of vinblastine transport in three-liquid-phase system was studied in laboratory RFC, presented schematically in Fig. 2. The lower part of the contactor is divided into two compartments: One for the feed and the other for the stripping solution. The liquid organic membrane covers both aqueous solutions and occupies the common upper part of the contactor. The hydrophilic disc (1mm thick, 18cm in diameter) rotates in each compartment. The distance between Two discs are 15mm. The discs rotation provides a formation and continuous renewal of aqueous films of solutions F and R on discs surfaces as well as the agitation of all three phases. To homogenize the aqueous solutions and to eliminate the dead zones or become little both liquids were re-circulated by means of two peristaltic pumps.

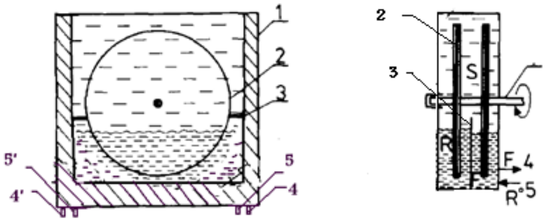


Fig.2, Diagram showing the RF contactor used. 1: apparatus body; 2: rotating discs; 3: separating half-walls; 4, 4': feed inlet and outlet; 5, 5': strip solution inlet and outlet; 6: rotating shaft.

The velocity of discs rotation was fixed at 10 rpm.

Experimental procedure

5.0 grams of fresh leaves were cut into small pieces and extracted using buffer solution of (NH3-(NH4)2SO4) at pH 9.2. The volumetric flask was shaking for half hour using a shaker, filtered and poured into the RFC using glass funnel. The acceptor solution was adjusted to pH 1.3 of sulfuric acid and placed into the second compartment, the reminder volume filled with the liquid membrane.

Procedure of equilibrium studies

The study of vinblastine transport across a liquid membrane, and its equilibrium distribution between organic and aqueous phases was established using laboratory rotating film contactor. 10 mg of vinblastine dissolved in 250 ml of buffer solution of (NH3-(NH4)2SO4) and adjusted to appropriate pH and placed in the first compartment. A volume of 250 ml of sulfuric acid solution (pH= 1.3) placed into the second compartment. 500 ml of n- nonane covers both aqueous solutions.

Samples were taken from each feed, stripper and the organic layer at a certain intervals.

Analysis of vinblastine

Vinblastine samples from aqueous solutions and organic solvent during the experimental period were analyzed by Ultra-Violet /Visible spectrometer (shimadzu 160) (λ= 276).

Results and Discussion

1.Choice of solvents: extraction of vinblastine by organic solvents

To apply liquid membrane process for vinblastine recovery from aqueous media it is necessary to find conditions suitable for its extraction by an organic liquid, but also conditions favorable for its back extraction into the aqueous solution. Preliminary test were carried out to find the optimum pH of feed (Donor) solution (best diffusion to the liquid membrane), and best pH of stripping solution. The results of the extractability experiment shown in Fig. 3. As shown there at law pH vinblastine protonated (sulphate salt), while for pH above 9 the results show decrease in the extractability of vinblastine. This decrease might be due to that ammonia starts to be extracted above pH 9 [13]. The loss of ammonia to the organic layer will decrease the basicity of feed solution.

It is to be concluded that the best pH for the feed solution (good extraction around 9, and the best accepter (stripper) would be around pH of 1.3. Such results are in agreement with that obtained by K.Dimitrov et al [14] and S. K. Volkov et al [15].

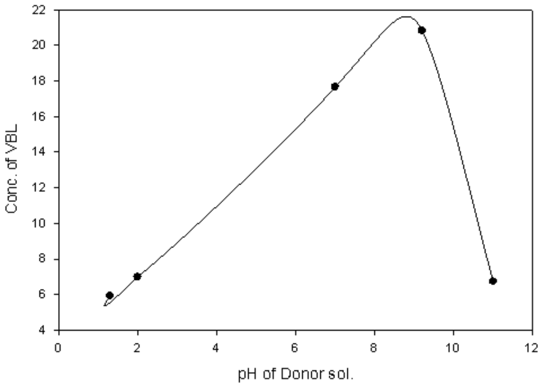


Fig. 3, Diffusion of VBL through the liquid membrane (n-decane)

2. Solvent extraction of vinblastine by n-decane and other organic solvents

Many organic non-polar solvent are used as liquid membrane (viz. n-decane, n-nonane, n-heptane, methylcyclohexane). Low molecular weight of the organic solvent failed to give reasonable extraction efficiency while n-decane (the highest molecular weight 142.29) gave a good extracting ability as shown in Fig. 4. The lowest extracting ability is that of methylcyclohexane (Cyclo derivative hydrocarbons) [16]. The studied alkanes are suitable for liquid membrane permeation of vinblastine, providing conditions favorable for vinblastine extraction into the organic solvent This results are agreement with the results which obtained by Krasimir D. et al [8]

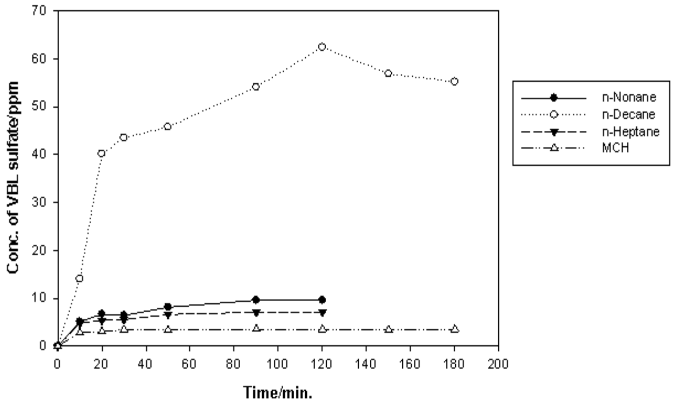


Fig. 4, Effect of type of membrane on the concentration of VBL sulphate (pHa= 1.3, pHb =9.2).

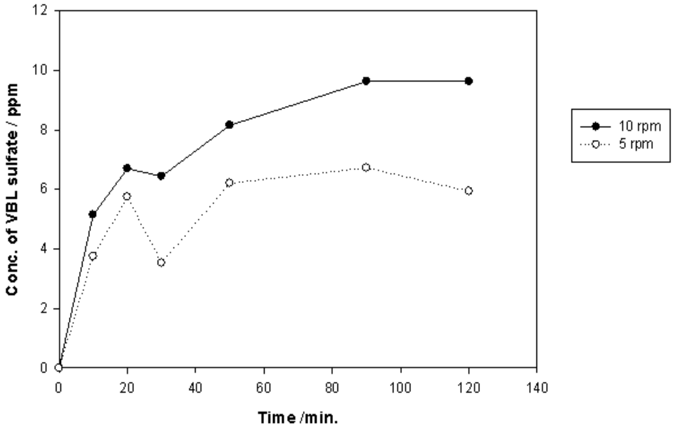


Fig. 5, Pertraction study of the discs speed using n-nonane as LM, pHa =1.3 and pHb =9.2

3. Various studies in pertraction

a) Discs rotation speed

Pertraction efficiency grows with the increase of discs rotation velocity as shown in Fig. 5, due to the better agitation of all three phases and the faster renewal of the aqueous films .The variation of pertraction efficiency with the agitation indicates a diffusion control of the process. These results agree with the results obtained by K. Dimitrov et al [14] and K. Dimitrov et al [15].

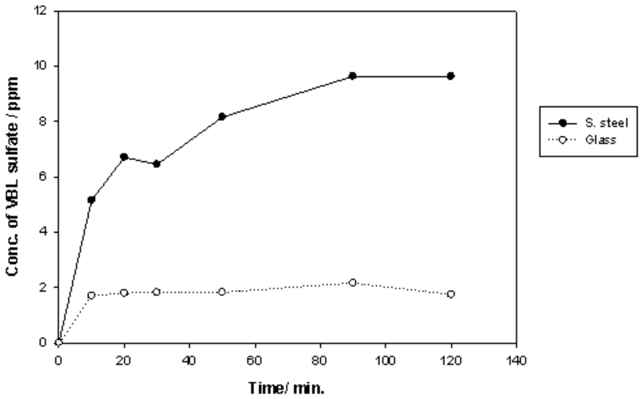


Fig. 6, Pertraction study of the discs material using n-nonane as LM, pHa =1.3 and pHb =9.2

b) Discs material

In order to choose the proper hydrophilic disc material, two types of disc material was prepare; Glass and Stainless steel. The results of the pertraction of vinblastine using these two types are shown diagrammatically in Fig. 6. Stainless steel gives better to manipulate than glass which easily damaged [16].

4. Pertraction of vinblastine

A simple kinetic model of the mass transfer of solute in BLM can be advanced by considering two consecutive reactions (extraction–re-extraction of the vinblastine) with three diffusion steps in the feed, organic and stripping solutions.

A comparative study of vinblastine was performed by applying this model. To do this, the following kinetic parameters were evaluated: the apparent rate constants of the solute extraction and re-extraction reactions (k1, k2), the maximum reduced concentration of vinblastine in the liquid membrane (XSmax), the time of the maximum value of XS (Tmax).

These results suggest that the solute transport conforms to two consecutive irreversible first-order reactions according to the kinetic scheme:

$$F \xrightarrow{K_2} S \xrightarrow{K_2} R \qquad 1$$

Where,   F: Solute concentration in feed solution.

S: solute concentration in extracting solution.

R: solute concentration in stripping solution.

K1 & K2 the extraction and stripping transfer rate coefficient respectively.

For practical reasons, dimensionless reduced concentrations of vinblastine in feed solution XF, liquid membrane XS, and the stripping solution XR were used:

$$XF = \frac{F}{F_{\square}} \quad ; XS = \frac{S}{F_{\square}} \quad ; XR = \frac{R}{F_{\square}}$$

The kinetic scheme for consecutive irreversible reactions (Eq. 1) can be described by the following rate equations:

$$\frac{dX_F}{dt} = -K1XF \qquad (2)$$

$$\frac{dX_S}{dt} = K1XF - K2XS \qquad (3)$$

$$\frac{dX_R}{dt} = K2XS \qquad (4)$$

Integrating Eqs. 2–4 is easily carried out and R-values are obtained when k1≠k2, giving:

$$XF = e^{-K\square.t} \qquad (5)$$

$$XS = \frac{K\square}{K\square - K\square}\left(e^{-K\square.t} - e^{-K\square.t}\right) \qquad (6)$$

$$XR = \frac{1}{K\square - K\square}\left(K1\, e^{-K\square.t} - K2\, e^{-K\square.t}\right) + 1 \qquad (7)$$

At the maximum value of XS, when dXS/dt=0, this reduced concentration and TMax can be calculated as follows:

$$Tmax = \frac{\ln\frac{K\square}{K\square}}{(K\square - K\square)} = \frac{1}{K_{lm}} \qquad (8)$$

$$Xs\ max = \left(\frac{K\square}{K\square}\right)^{\frac{K\square}{(K\square - K\square)}} \qquad (9)$$

From figure 7, Tmax= 109 min, XS.Max= 0.52.

By substituting these results into Eqns. (8 and 9) and using MATLAB program gives:

K2= 0.006 min-1

K1 = 0.01331 min-1

Figure 7 shows the evolution of vinblastine repartition between the three liquid phases during a continuous pertraction process at constant acidity of the feed solution pHb 9.2. The interaction between solute molecules of the feed solution and n-nonane occurred at the first interface F/S where vinblastine was partially extracted to organic phase. The process beginning is characterized by a sharp decrease of vinblastine amount in the feed solution and its instantaneous accumulation in the organic liquid membrane. Due to the concentration gradient created vinblastine molecules extracted in the organic membrane phase were transferred to the second interface S/R, where the pH of the receiving solution (pHa) was 1.3, therefore, vinblastine transferred and accumulated into this solution.

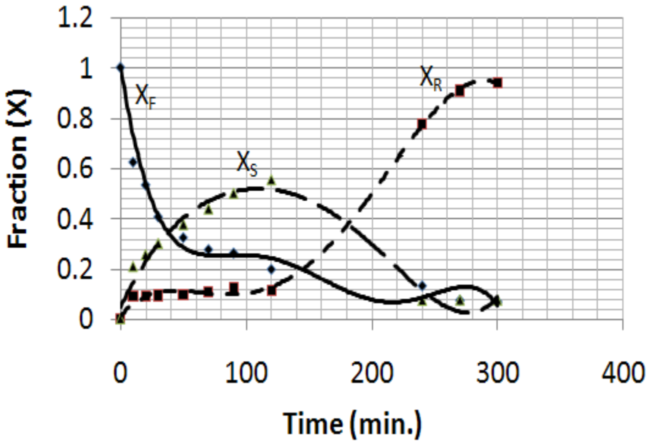


Fig. 7, Time dependencies of XF, XR and XS in the transport of VBL sulphate (Liquid Membrane: n-nonane.)

At the end of experimental run, almost of vinblastine was accumulated in the receiving solution.

Conclusions

When the behavior of vinblastine extraction from aqueous media by various organic solvents at equilibrium was studied, the Non-polar n-decane was found to be the most suitable for vinblastine recovery by pertraction process. Best diffusion to the organic layer of feed (Donor) solution was achieved by using buffer solution of (NH3-(NH4)2SO4) at pH 9.2, and the best stripper (accepter) solution by using H2SO4 with pH 1.3. Increasing the leaves weight lead to increasing of amount of vinblastine in feed solution, at the same time in the membrane as well as in the stripping phase. Increasing discs rotation velocity, to a certain degree, gives a better agitation of all three phases and the faster renewal of the aqueous films.

The hydrophilic discs constructed of stainless steel gave a good material for manufacturing the discs with advantages of being very hygienic and easy to clean.

The rate of diffusion constants was performed by means of a kinetic model involving two consecutive irreversible first-order reactions. K1 and K2 were found to be 0.01331 and 0.006 min-1.

Nomenclature

Notation	**Description**
Conc.	Concentration.
F/S	Interface between the Donor
	Solution and Organic Membrane.
K_1	Rate Constant of Solute Extraction.
K_2	Rate Constant of Solute re-
pHa	Extraction.
pHb	pH of accepter solution.
RFC	pH of donor solution.
rpm	Rotating Film Contactor.
S/R	Revolution per Minute.
	Interface between the Organic
t_{Max}	Membrane and Stripping Solution.
	Time of Maximum Concentration of
VBL	Solute in Organic Layer.
X_{SMax}	Vinblastine.
	Dimensionless of Maximum Conc.
	of Solute at Organic Membrane
	Feed Interface.

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