Pure Appl. Chem., Vol. 76, No. 4, pp. 697–705, 2004.

Voltammetry of drugs at the interface between two immiscible electrolyte solutions*

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Abstract: In this review, the results of the electrochemical investigations made on the transfer of ionizable drugs at the interface between two immiscible electrolyte solutions (ITIES) in the last decade have been presented. In many of the studies, cyclic voltammetry has been used to investigate the transfer characteristics of the charged species and deduce their partition coefficients, which are very important parameters to infer the lipophilicity of drugs in biological systems. The electrochemical technique allows the precise determination of the distribution of ionic species between two phases in a wider pH range. Such studies point out the complexity of the distribution of ionizable compounds and offer a new approach to relate the structure of such compounds to their passive transport across biological membranes.

INTRODUCTION

The interface between two immiscible electrolyte solutions (ITIES) has been studied extensively, especially with the help of electrochemical techniques [1–3]. Electrochemical experiments at polarizable ITIES enable one to measure precisely the Galvani potential difference. This potential difference in turn determines the partition of ionic species between the two electrolyte solutions. The transfer of charged species across the interface is illustrated as a current response under potentiostatic conditions. As a result, the Gibbs energy of ion transfer, which is directly related to the partition coefficient, can be obtained from voltammetry measurements.

One of the interests in these studies among others is the transfer of ionizable drugs across liquid/liquid interfaces and the determination of their partition coefficients. Measurement of the partition coefficient of an ion yields its lipophilicity (hydrophobicity). Lipophilicity represents the affinity of a compound for a lipidic environment. It is a very significant molecular parameter used in different areas of chemistry, medicine, and pharmacology for predicting the transport through membranes, interactions with biological receptors and enzymes, toxicity, and biological effects in general [4–6]. Lipophilicity is the most widely used parameter to design drugs, relate the structures and physicochemical properties of drugs to their biological activities, and assess their performances, mainly through the establishment of quantitative structure–activity relationships (QSARs) [7–9]. QSARs are mathematical relationships linking chemical structure and pharmacological activity in a quantitative manner for a series of compounds [10].

In a biphasic system, lipophilicity of a solute is commonly measured by its partition coefficient, P. The partition coefficient of an ion, $\ln P_i$, depends on the Galvani potential difference across the interface as shown by the following equations [11].

*Plenary lecture presented at the Southern and Eastern Africa Network of Analytical Chemists (SEANAC), Gaborone, Botswana, 7–10 July 2003. Other presentations are published in this issue, pp. 697–888.

$$\ln P_i = (z_i F/\mathrm{RT})\Delta_o{}^{w}\phi - (\Delta G^{o}{}_{tr,i}{}^{w \rightarrow o}/\mathrm{RT}) \quad (1)$$

$$= \ln P_i^{o} + (z_i F/\mathrm{RT})\Delta_o{}^{w}\phi \quad (2)$$

where $\Delta_o{}^{w}\phi$ is the Galvani potential difference, $\Delta G^{o}{}_{tr,i}{}^{w \rightarrow o}$ is the standard Gibbs energy of transfer of i, and $\ln P_i^{o}$ is the standard partition coefficient of i when the interface is not polarized. $\mathrm{Ln}P_i^{o}$ is directly related to the half-wave transfer potential of the ion $\Delta_o{}^{w}\phi_{1/2}$, and it can be directly deduced from voltammetric experiments [12]. Voltammetry at ITIES is particularly well suited for the experimental determination of $\ln P_i^{o}$, because it allows for the control of the interfacial potential and hence of the ionic distribution between the two adjacent phases, and affords a direct measure of $\ln P_i^{o}$.

For a long time, the understanding of the lipophilicity of ionizable drugs was limited by a lack of reliable methods to determine the partition coefficients of ions. It has been traditionally accepted that ionizable compounds cross membranes only in their neutral form or as ion pairs. Recent studies, however, have shown a significant passive partition of ionic organic compounds into the organic phase [13–15]. Therefore, studies on the lipophilicity of ionizable drugs give better understanding of drug activity and distribution and help to develop new drugs.

Numerous other techniques have been used to obtain lipophilicity parameters. These include the shake-flask method [16,17], chromatographic methods [18–20], filter probe method [21], flow-injection extraction [22], microscale partitioning method [23], the generator column method [24], potentiometric method [25], and theoretical computation based on the molecular structure of a drug [26]. However, all of these methods have their disadvantages. For example, if the partition coefficient of a drug is very low or very high, it is difficult to measure the equilibrium concentrations accurately, and changes in the partial molar volumes of the solutions must often be taken into account. Furthermore, carrying out partition experiments with care is slow and tedious. The problem associated with theoretical computing is that it is difficult to evaluate all the factors that affect solvent–solute interactions [27].

Electrochemistry provides a convenient, fast, and accurate method for studying the equilibrium and transport properties of ionic solutes [28]. In recent years, cyclic voltammetry (CV) has been introduced in medicinal chemistry for the determination of the lipophilicity of ionic drugs and study of their mechanism of transfer at ITIES. This method requires the use of a polarizable interface. The system usually used is 1,2-dichlorethane/water. The main advantage of CV at ITIES is that, in contrast to all other techniques that do not control the Galvani potential difference, the potentials are here monitored. This provides standard log P independent of experimental conditions. It is believed that the voltammetric lipophilicity determination of drugs at ITIES could become an important competitor to the potentiometric titration, which is the most popular technique to date [9].

The purpose of this paper is to give brief accounts of the drugs that have been studied at ITIES to determine their partition coefficients using voltammetric methods for nitrobenzene/water, *o*-nitrophenyl octyl ether/water, and 1,2-dichlorethane/water systems.

LOCAL ANESTHETICS

The pharmacological activity of local anesthetic agents in biological systems is proportional to the lipophilicity [29]. Thus, lipophilicity has generally been used to evaluate pharmacological activity. Different investigators have studied the electrochemical transfer behavior of local anesthetics at ITIES. Arai et al. [30] studied the electrochemical transfer of several drug ions, including local anesthetics, such as lidocaine, tetracaine, benzocaine, procaine, and dibucaine across the water/nitrobenzene interface using polarography with a dropping electrolyte electrode. A linear relationship between the half-wave transfer potentials of the anesthetic agents and the pharmacological activity was established with good correlation. The half-wave potential becomes more negative with higher pharmacological activity. Since these drugs transfer across the nitrobenzene/water interface as protonated cations, the half-wave potentials become more negative with higher drug hydrophobicity. This indicated that an increase in

hydrophobicity causes increased pharmacological activity. It is known that an increase in the hydrophobicity of local anesthetic agent causes increased anesthetic activity or toxicity [29]. Very recently, the voltammetric behavior of eight local anesthetics: three ester-linked local anesthetics (procaine, tetracaine, and oxybuprocaine) and five amide-linked, local anesthetics (prilocaine, mepivacaine, lidocaine, and dibucaine and bupivacaine) was investigated using CV with a stationary nitrobenzene/water interface in a wider pH range [31]. The partition coefficients of both neutral and ionic forms of local anaesthetic between the organic and aqueous phases were determined from the reversible half-wave potentials vs. pH curves. A high correlation coefficient between the pharmacological activity and the partition coefficient of the ionic form of the amide-linked local anaesthetics has been shown. In another investigation, Samec et al. [32] studied the voltammetric and AC-impedance behavior of the protonated ion of several local anaesthetics at the *o*-nitrophenyl octyl ether/water interface, and determined the apparent rate constants of transfer of the ions at the interface. It was observed that the pharmacological activity of local anesthetic increases with a decrease in their ion-transfer standard potential, which is consistent with the data obtained at the nitrobenzene/water interface [30,31]. These authors suggested that the activity could be related to the ion partition between the body fluid and the membrane, or to the rate of membrane ion transfer at a constant potential difference. The Galvani potential differences of the local anesthetics at the nitrobenzene/water (NB/W) and *o*-nitrophenyl octyl ether/water (*o*-NPOE/W) interfaces are shown in Table 1. The $\Delta\phi^{o}_{BH^+}$ values in Table 1 represent the hydrophobicity or lipophilicity of the drugs in their ionic form and are related to the partition coefficient of the drugs in their ionic form.

Table 1 Galvani potential differences of local anesthetics at the nitrobenzene/water and *o*-nitrophenyl octyl ether/water interfaces.

Drug	$\Delta^{w}_{o}\phi^{o}_{BH^+}$/ V (NB/W)[a]	$\Delta^{w}_{o}\phi_{1/2\ BH^+}$/V (NB/W)[b]	$\Delta^{w}_{o}\phi^{o}_{BH^+}$/ V (*o*-NPOE/W)[c]
Procaine	–0.068	–0.025	0.053
Tetracaine	–0.165	–0.057	–0.032
Oxybuprocaine	–0.187		
Prilocaine	0.002		0.102
Mepivacaine	–0.050		
Lidocaine	–0.057	–0.005	0.063
Bupivacaine	–0.123		–0.022
Dibucaine	–0.169	–0.065	–0.093
Benzocaine		–0.30	
Cocaine			–0.047

[a]From ref. [31].
[b]From ref. [30].
[c]From ref. [32].

β-BLOCKERS

β-blockers are widely used in the treatment of various cardiovascular diseases such as hypertension, angina pectoris, and cardiac arrhythmias [33,34]. The electrochemical transfer behaviors of β-blocking drugs were studied at the nitrobenzene/water [30] and 1,2-dichloroethane/water interfaces [27,35]. Arai et al. investigated four β-blocking agents at the nitrobenzene/water interface and obtained a linear relationship between the pharmacological activity and the half-wave potential with a negative slope [30]. The half-wave potential becomes negative with higher pharmacological activity, showing that an increase in hydrophobicity may cause a decrease in pharmacological activity. The study indicated that hydrophobicity could be used to determine the activities of these drugs. CV was used to study the transfer of seven β-blocking agents (Table 2) along with other drugs at the 1,2-dichloroethane/water interface [27]. The study was made with the objective of showing that electrochemical methods can be used

in a straightforward manner to determine the partition coefficients of drugs that can exist as ions in aqueous solutions. In another study, the lipophilicity parameters of a number of β-blockers were measured using different methods and different solvent systems in order to validate new experimental techniques used to measure the log *P* of protonated drugs [35]. CV was applied for the transfer of β-blockers at the 1,2-dichloroethane/water interface. Table 2 compares the partition coefficients of cations and neutral molecules of β-blockers obtained by CV and centrifugal partition chromatograph (CPC) for 1,2-dichloroethane/water system. The results demonstrated that CV is an informative technique to measure partition coefficients of ionized compounds.

Table 2 Partition coefficients of β-blockers for the 1,2-dichloroethane/water system.

Drug	log P^c (CV)[a] (DCE/W)	log P^c (CPC)[a] (DCE/W)	log P^N (CV)[b] (DCE/W)
Acebutolol	–2.22		
Alprenolol	–1.84		
Atenolol	–5.45		
Bisoprolol	–2.38	–2.40	
Carazolol	–2.03	–2.09	
Carteolol			1.52
Carvedilol	–0.47	–0.99	
Clonidine			2.78
Metipranolol	–1.87	–1.87	
Metoprolol	–2.20	–2.54	2.23
Oxprenolol	–1.30	–2.51	
Papaverine			4.10
Penbutolol	–0.65	0.12	
Pindolol	–3.26	<–3.0	
Propranolol	–2.08	–1.93	2.70
Sotalol			1.05
Timolol	–2.89		

[a]Partition coefficients of cations from ref. [35].
[b]Partition coefficients of neutral molecules from ref. [27].

QUATERNARY AMMONIUM DRUGS

Quaternary ammonium drugs are generally applied as antiseptics, disinfectants, preservatives, and sanitizers and for environmental purposes and for water treatment [33]. The transfer of four cholinergic agents (acetylcholine, acetyl-β-methylcholine, carbamylcholine, and carbamyl-β-methylcholine) and five anticholinergic agents (tetramethylammonium, tetraethylammonium, hexamethonium, succinylcholine, and tubocurarine) was studied at the nitrobenzene/water interface [30]. The half-wave potentials of the drugs in each group were found to be similar, indicating that the hydrophobicity of the drug ions within a group is the same. A linear relationship between the transfer half-wave potential and the pharmacological activity was obtained for each agent. This study exhibited that ion-transfer voltammetry is a promising method in assessing the hydrophobicity of quaternary ammonium drugs. Recently, Testa et al. made a comprehensive study on the lipophilicity of 18 quaternary ammonium drugs and model compounds using CV at the 1,2-dichloroethane/water interface [36]. Table 3 summarizes the standard transfer potentials and the standard partition coefficients for the cations and neutral molecules of the quaternary ammonium drugs investigated. The results of this study evidenced that the partition of such ions is not influenced by the formation of ion pairs. The increase in lipophilicity of quaternary ammonium ions observed when a lipophilic anion is added in excess is only governed by the Galvani

potential difference and does not depend on any ion pair formation. These investigators proved that CV yields a standard value of the partition coefficient, which does not depend on experimental conditions (unlike, e.g., the shake-flask method) and must be considered as an intrinsic value that can be used as reference.

Table 3 Standard transfer potential of cation c, standard partition coefficient of cation c, and estimated partition coefficient of the corresponding neutral form of the quaternary ammonium cation at the 1,2-dichloroethane/water interface. (Reprinted with permission from ref. [36] © 2001 Plenum Publishing.)

Drug	$\Delta^{w}_{o}\phi^{o}_{c}$ (V)	log $P^{o,}_{c}$	log P^{N} (est.)
Acetylcholine	0.210	–2.0	1.88
S-Butyrylthiocholine	0.025	–0.4	3.31
Carbamoylcholine	0.210	–3.5	0.90
1-Ethylquinoline	0.005	–0.1	4.58
Homidium	–0.192	3.2	7.11
N-Methylderamciclane	–0.225	3.8	7.76
Methylhomatropine	0.042	–0.7	3.18
Methylquinidine	–0.115	1.9	4.89
14-Methylrutecarpine	–0.012	0.2	4.47
Neostigmine	0.036	–0.6	3.50
Propantheline	–0.218	3.7	7.50
Pyridostigmine	0.055	–0.9	2.01
Tetra-*N*-butylammonium	–0.225	3.8	9.01
Tetra-*N*-ethylammonium	0.019	–0.3	3.87
Tetra-*N*-methylammonium	0.160	–2.7	1.57
Tetra-*N*-penthylammonium	–0.361	6.1	11.58
Tetra-*N*-propylammonium	–0.091	1.5	6.44
Trantheline	–0.163	2.8	5.97

ANIONIC DRUGS

The lipophilicity of 28 acidic compounds with various functional groups was studied very recently by CV and potentiometry in the 1,2-dichlorethane/water system and by potentiometry in the *n*-octanol/water system. The study was made in order to understand the lipophilicity of neutral and ionized acids and to clarify the solvation mechanisms responsible for their partition [37]. The results were used to calculate the compounds' $\Delta\log P^{N}_{\text{oct-dce}}$ parameter that is the difference between log *P* of *n*-octanol/water and log *P* of 1,2-dichlorethane/water systems for neutral molecules (see Table 4). This parameter is of interest in pharmacokinetics (which is defined as the collection of effects exerted by a biological system upon a drug) since it describes the H-bond donor capacity of drugs and is negatively correlated to membrane permeability [38,39]. The study of these compounds containing different acidic groups has shown the variable lipophilic behavior of anions. The parameter *diff*($\log P_{\text{dec}}^{\text{N-A}}$) (i.e., log *P* of the neutral acid minus standard log *P* of the conjugated anion in 1,2-dichloroethane/water) was shown to depend not only on intermolecular interactions and conformational effects in the neutral and anionic forms, but also on the delocalization of the negative charge on the anion. The value of this parameter decreases when the delocalization of negative charge increases, due to the increased stabilization of the anion in the organic phase. The lipophilicity of a series of nitrophenols was studied in the 1,2-dichloroethane/water system using CV at ITIES [40]. The effects of charge and intramolecular structure on the lipophilicity of the phenolic compounds were investigated. The study illustrated the influence of intramolecular interactions on the partition of ionizable compounds. Moreover, it showed

that the 1,2-dichlorethane/water system is a promising means to identify intermolecular H-bonds acting on the lipophilicity of neutral species and the charge delocalization diminishing the polarity of ions.

Table 4 Physicochemical parameters of acidic compounds. (Reprinted with permission from ref. [37] © 2001 Wiley-VCH Verlag GmbH.)

Drug	pK_a[a]	$\Delta\log P^{N}_{oct\text{-}dce}$[b]	$\log P^{o,N}_{dce}$[c]	*diff*$(\log P_{dce}^{N\text{-}A})$[d]
Phenol	9.99	0.85	–2.3	2.9
2-Nitrophenol	6.92	–1.04	–2.0	4.8
3-Nitrophenol	8.10	1.08	–2.4	3.3
4-Nitrophenol	6.90	1.24	–2.5	3.3
2,4-Dinitrophenol	3.96	–0.79	–1.7	4.2
2,5-Dinitrophenol	4.97	–0.74	–2.3	4.8
7-Isoxicam	3.93	–1.06	–1.0	4.9
4-Bromobenzoic acid	4.15	1.82	–5.0	6.0
4-Chlorobenzoic acid	3.93	1.60	–4.8	5.9
3-Chlorobenzoic acid	3.82	1.74	–5.0	6.0
4-Iodobenzoic acid	3.87	1.54	–4.7	6.3
1-Naphtoic acid	3.64	1.26	–4.9	6.7
Ketoprofen	4.25	0.39	–4.0	6.4
Suprofen	4.05	0.47	–4.3	6.7
Naproxen	4.18	0.49	–4.2	6.8
Piroprofen	4.01	0.80	–4.2	7.0
Flurbiprofen	4.21	0.90	–3.2	6.1
Ibuprofen	4.31	1.00	–3.7	6.6
Carprofen	4.45	1.46	–3.6	6.2
Indomethacin	4.42	1.40	–2.8	5.7
Sulindac sulfide	4.88	0.50	–2.2	6.5
Sulindac	4.03	0.47	–4.8	7.6
Sulindac sulfone	4.16	–0.35	–4.4	8.0
Phenylbutazone	4.61	–1.62	–1.6	6.3
Sulfinpyrazone Sulfide	2.55	–2.39	0.9	6.8
Sulfinepyrazone	2.37	–1.13	–1.6	6.3
Sulfinepyrazone Sulfone	2.09	–2.02	–0.1	6.1

[a]Measured by potentiometry.
[b]$\Delta\log P^{N}_{oct\text{-}dce} = \log P^{N}_{oct} - \log P^{N}_{dce}$.
[c]Measured by cyclic voltammetry.
[d]*diff*$(\log P_{dce}^{N\text{-}A})$[d] standard partition coefficient of cation c, and estimated partition coefficient of the corresponding neutral form of the quaternary ammonium cation at the 1,2-dichloroethane/water interface.

ZWITTERIONIC, MONOBASIC, AND DIBASIC DRUGS

Zwitterions have a positive and a negative charge at neutral pH by virtue of the strength of their ionizable groups [41]. Zwitterions in drug research occur in various therapeutic classes, such as nonsteroidal anti-inflammatory drugs, antihistaminic drugs, and antibacterial agents, and they may also be produced as metabolites [42]. The lipophilicity of various zwitterionic drugs was examined by CV and potentiometry at the 1,2-dichloroethane/water interface [43–45]. The drugs whose partition coefficients were measured by CV consist of cetirzine and hydroxyzine (antihistaminic agent), labetalol (antihypertensive agent), azapropazone, piroxicam, tenoxicam and isoxicam (anti-inflammatory agents), and raclopride and eticlopride (neuroleptic agents). Their physicochemical parameters are shown in Table 5.

These studies revealed the very informative nature of CV to examine the lipophilicity of cationic and anionic forms of zwitterions and enabled us to understand the intermolecular interactions responsible for the lipophilic behavior of the drugs. In theses studies, theoretical and experimental ionic partition diagrams have been used to explore the pH-absorption profiles of the drugs. Ionic partition diagrams are potential-pH diagrams illustrating the predominance area of neutral and ionic species according to their acid/base character [9,40,46–48]. The ionic partition diagrams have proved to be useful representation of thermodynamic equilibria involving ionizable species in biphasic liquid systems. The transfer mechanisms of monobasic drugs and (amfepramone, *N*-methylephedrine, 3,5,*N*,*N*-tetramethylaniline, and *N*,*N*-diethyaniline) dibasic drugs (quinine and trimetazidine) were studied by CV at the water/1,2-dichlorethane interface [49]. The partition coefficients of the various ions were deduced from the voltammograms (see Table 5), which were monitored as a function of aqueous pH. The results obtained were displayed in the form of ionic partition diagrams, which define the predominance domains of each species in both phases. In a similar study the transfer of a series of weak acids, bases and ampholytes [lauric acid, *N*-(*p*-methylbenzyl)hexylamine, diclofenac, pyridine, nicotine, hydralazine, and phenylalanine] has been studied by CV at the water/1,2-dichlorethane interface in order to determine their lipophilicity [50]. Physicochemical parameters of these compounds for the neutral and ionized forms were measured as a function of aqueous pH and some of the data are presented in Table 5. The results obtained were presented in the form of ionic partition diagrams. This presentation affords both a precise description of the mechanisms governing the transfer from one phase to the other, and a re-

Table 5 Physicochemical parameters of zwitterionic monobasic and dibasic compounds at the 1,2-dichloroethane/water interface.

Drug	$\Delta^{w}_{o}\phi^{o}$ (mV)	logP^{N}	log$P^{o,C}$	log$P^{o,A}$	*diff*(log$P_{dce}^{N\text{-}C}$)	*diff*(log$P_{dce}^{N\text{-}A}$)
Azapropazone[b]		0.2	–3.0			3.2
Cetirizine[b,c]		0.7	0.7	–3.1	0.0	–3.8
Labetalol[b]		1.7	–2.6	–4.8	4.3	6.5
Tenoxicam[b]		4.0		–1.3		5.3
Isoxicam[b]		4.0		–1.0		5.0
Raclopride[b]			1.0	–3.9		
Eticlopride[b]		4.7	2.4		2.3	
Piroxicam[a]			–0.3			
Hydroxyzine[c]		3.6	1.3		2.3	
Amferpramone[d]	36	3.7	–0.6		4.3	
N-methylephedrine[d]	163	1.6	–2.8		4.4	
3,5,*N*,*N*-tetra-methyl aniline[d]	170	4.0	–2.9		6.9	
N,*N*-diethylaniline[d]	135	4.2	–2.3		6.5	
Trimetazidine[d]	163	1.0	–2.8		3.8	
Quinine[d]	85	2.4	–1.4		3.8	
N-(*p*-methylbenzyl)hexylamine[e]	29	4.2	–0.5		4.7	
Lauric acid[e]	–179	3.6	–3.0		6.6	
Pyridine[e]	266	0.7	–3.8		4.5	
Diclofenac[e]	–124	3.2	–2.1		5.3	
Nicotine[e]	261	0.7	–4.4		5.1	
Hydrazine[e]	160	–0.0	–2.7		2.7	
Phenylalanine[e]	474	–2.5				

[a]From ref. [43].
[b]From ref. [44].
[c]From ref. [45].
[d]From ref. [49].
[e]From ref. [50].

liable assessment of pH lipophilicity profiles. This study also demonstrated that both charged and neutral species can penetrate into the organic phase and showed the importance of the passive transfer of organic ions for drug disposition and pharmacokinetics. Recently, sildenafil (Viagra) was examined for its ionization and lipophilicity by electrochemistry at ITIES and two-phase titration in the 1,2-dichloroethane/water system [51]. The dissociation constants (basic pK_a = 6.78, acidic pK_a = 9.12) and physicochemical parameters of the various species (for the cation $\Delta^{w}_{o}\phi^{o}_{i}$ = –5.5; log P^{o}_{i} = 0.1; *diff*(log P^{N-I}) = 3.65 and for the anion $\Delta^{w}_{o}\phi^{o}_{i}$ = –115.7; log P^{o}_{i} = –2.7; *diff*(log P^{N-I}) = 6.45), together with the effects of electrical potential, were used to construct an ionic partition diagram. This allowed interpreting the transfer mechanism of sildenafil at liquid/liquid interfaces, suggesting in particular that an intramolecular H-bond influences the lipophilicity of the neutral and cationic species. In a very recent work, a novel method to readily determine the lipophilicity of electrogenerated charged species has been reported [52]. This is achieved by local electrolysis at a Pt-coated micropipette and subsequently driving the electrogenerated species to transfer across the liquid–liquid interface under potential control. The method proposed is facile and enables of potentially unstable charged products of electron-transfer reactions.

In conclusion, the present review shows the extent of the usefulness of ion-transfer voltammetry in assessing the distribution of drug ions in biphasic systems. The employment of the method to gain information about lipophilicity parameters is progressing rapidly and may facilitate the development of screening methods for producing new drugs. Thus, it is likely that this method becomes widely used by the pharmaceutical companies.

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