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Kinetic and Thermodynamic Behavior of Extraction of Oleoresin Containing Curcuminoids from Turmeric (*Curcuma longa* L.) in Acetone and Their Bioavailability

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Authors' contributions

This work was carried out in collaboration among all authors. Author ABK designed and supervised the study, wrote the protocol and wrote the draft of the manuscript. Author HMK is the experimentalists of the results of this paper. Authors JCK and MBK managed the proof reading and correction of manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: Why this miraculous and amphiphilic compound, the curcumin, which has a very extraordinary therapeutic potential (because can react with many targets in the organism), has a weak bioavailability in the organism and is metabolized in compounds having very weak activity or

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inactive compounds?. How to improve substantially its bioavailability and therefore its absorption in the organism in order to allow its incorporation in making of pharmaceuticals regardless of its nanoparticles of which obtention is furthermore hardworking?
Aim: It seems indicated to search the response in the kinetic and thermodynamic behavior of this compound or in its co-administration with the other compounds in vitro in order to understand how to increase its absorption in vivo because bioavailability entails hydrosolubility (hydrophile) of curcuminoids of which the molecules are naturally hydrophobes.
Objective: So our objective is to make better our understanding of the absorption of natural curcuminoids in the organism without resorting to chemical transformation in nanoparticles that is additionally hardworking.
Methodology: In this paper, kinetic and thermodynamic study of extraction of oleoresin containing curcuminoids from Turmeric (*Curcuma Longa L.*), using KUNYIMA's first law, has been performed in acetone that can be reduced in propan-2-ol which is water-like solvent by catalytic hydrogenating (H_2,Ni) or by chemical reduction ($LiAlH_4$).
Results: The weak global kinetic constant of extraction of oleoresin containing curcuminoids has been determined at 250 rpm (round per minute) and found the same at 500 rpm (k= 0.1520 ± 0.0005) min^{-1} for temperature of 27,5°C and constant pressure in acetone in closed system.
Conclusion: Kunyima's first law has made possible the kinetic and thermodynamic study of extraction of oleoresin containing curcuminoids from Turmeric. Kinetic constant is a measure of solubility of oleoresin containing curcuminoids and therefore a measure of solubility of curcuminoids in a given solvent, ethanol and acetone being concerned in this paper as solvents. Results show that kinetic constant is inversely proportional to solubility of solvent and it can be a parameter abling the determination of the endothermic or exothermic behavior of extraction of curcuminoids. The endothermic behavior of curcuminoids hereby determined in ethanol and acetone in vitro, increased by magnetic stirring, suggests their weak bioavailability and therefore the weak bioavailability of curcumin. The challenge of this actual research is to improve our understanding of kinetics and thermodynamics of extraction of oleoresin containing curcuminoids from Turmeric in vitro in order to presage their bioavailability still weak for an efficient validated action. The increase of bioavailability will be done whether through improved formulations of curcumin or through new pathways of administration. The conception of curcumin analogous is also a way to promote its effects. More the phenomenon is exothermic in water-like solvents, more the involved chemical compound is bioavailable.
The study revealed the predominance of keto form of curcumin in acetone and the lack of bioavailability of curcumin (curcuminoids) through the endothermic behavior of extraction of oleoresin containing curcuminoids and through the weak global kinetic constant.
The variation of entropy in acetone has shown without surprise the disturbance of the system after extraction.
The values of kinetic constants in acetone and ethanol as water-like solvents have been compared and showed the great solubility of curcuminoids in acetone evidenced by the weak kinetic constant compared to that in ethanol.
Curcumin predicts anyway hopeful future.

Keywords: Bioavailability; curcuminoids; endothermic; kinetic constant; Kunyima's first law.

1. INTRODUCTION

Curcumin administered without any modification or coupling is very quickly degraded. Indeed, when it is absorbed alone orally, it is found at nearly 75% in the stools. When administered intravenously, nearly 50% of the dose is excreted in the bile within 5 hours. On the other hand, urinary secretion remains very low in both cases (less than 0.1% of the dose) [1]. Many studies have been conducted to improve the bioavailability of curcumin (curcuminoids) in the human body.

By co-administering piperine and curcumin to healthy volunteers in 1998, SHOBA et al. [2] evaluated the pharmaceutical parameters of curcumin. They showed that at a dose of 2g of curcumin administered orally with 20mg of piperine, the bioavailability of curcumin was increased by 2000% compared to the same dose of curcumin administered alone. It appears that this co-administration increases cerebral tissue distribution by up to 48% more in the brain than in the rest of the body. This is what Ryu et al. [3] published in the American Journal of Medicinal Chemistry in 2006. This association of natural

compounds and their influence on metabolism is intriguing.

Due to its strong structural similarity, piperine has common properties with curcumin such as antioxidant activity, antitumor activity and antipyretic activity.

Piperine also inhibits the breakdown of drugs and natural products such as curcumin in a large number of metabolic pathways via enzymes such as arylhydrocarbon hydroxylase (AHH), uridine diphosphate-(UDP-) glucuronyl transferase, ethylmorphine -N-demethylase, 7-ethoxycoumarin-O-deethylase, 3-hydroxy-benzo(a)pyrene glucuronidase, UDP-glucose dehydrogenase (UDP-GDH), 5-lipoxygenase, cyclooxygenase-1 and cytochrome P450.

Inhition of these enzymes by piperine increases the concentration of active curcumin. The concomitant administration of piperine and curcumin increases the bioavailability of the latter by 20 times. In addition, piperine increases intestinal permeability through its pro-inflammatory activity on the intestinal mucosa. This allows better absorption of curcumin, but also of endotoxins, pollutants, undigested proteins (gluten) and other toxic substances [1]. This is the door open to food intolerances and autoimmune diseases.

Since the discovery of the effect of piperine on the bioavailability of curcumin, other natural derivatives have been co-administered.

Cruz-Correa et al. [4] co-administered curcumin (480 mg) and quercetin (20 mg) orally three times a day for 6 months to 5 patients with familial adenopathy polyposis. The size of the polyps was reduced by 50.9% and their number by 60%. Unfortunately, they did not compare the effects of a possible administration of each of the active ingredients alone.

Curcumin has been also the subject of a study in co-administration with epigallocatechin-3-gallate (EGCG) in 2013 [5]. This natural compound is extracted from green tea. This combination led to significantly reduce in vitro proliferation of uterine leiomyosarcoma cells through restoration of apoptotic pathways, inhibition of protein kinase β (PKβ), mammalian target of rapamycin (mTOR) and kinase-mediated phosphorylation 6S. The lipophilicity of the essential oil of curcumin increases its bioavailability by 7 times [1]. However, high doses of curcumin (at least 300 mg) are required to be effective. Numerous formulations have been made possible to answer this requirement.

The Biocurcumax® formulation based on essential oil is safe for the body. Since curcumin is fat-soluble, its association with phospholipids improves its absorption by the body. Its bioavailability is multiplied by 19 [1]. These phospholipids are generally potentially allergenic soy or rapeseed lecithins. The Meriva® formulation in capsules contains 20% curcuminoids for 40% lecithins and 40% microcrystalline cellulose.

Cyclodextrin is a hydrophilic agent that encapsulates curcumin and acts as a protective shell, giving it good compatibility in aqueous media. It is obtained from potato or corn starch. Its Cavacurmin® formulation is one that allows absorption 40 times greater than conventional curcumin [1]. Fenugreek fibers, soluble in water, counterbalance the hydrophobic inclination of curcumin. The CurQfen® formulation has two advantages, namely a prolonged release of curcuminoids thanks to the formation of a gel in the colon and a bioavailability of curcumin increased by 16 times.

Yin-Meng Tsai et al. [1] have shown that the absorption of curcumin is greater in the form of nanoparticles. In this form, curcumin is less excreted in the stools than curcumin powder. On the other hand, it is excreted very weakly in the urine whatever its form. According to a study conducted on 23 people with curcumin coupled with polysorbate 80, a synthetic emulsifier (E 433), the absorption of NPCS (nanoparticles loaded with curcumin) is multiplied by 185 times compared to the classic form. Polysorbate is controversial because it is suspected of toxicity to the intestines from a certain dose.

The NovaSol® formulation, capsules with a low dose of curcumin (25 mg for 500 mg in total) i.e. nearly 94% polysorbate, is not recommended for long periods in inflammatory bowel diseases (IBD).

The Theracurcumin® formulation is curcumin mixed with glycerin and vegetable gum. Its bioavailability is only increased by 27 times for total health safety. Some laboratories add silicon dioxide (E 551) for its nanoparticle anti-caking effect, which leads to the production of free radicals that can alter DNA and cause tissue damage. Other curcumin formulations exist on the market with different bioavailabilities [2,6-9].

An in-depth theoretical study of the curcumin molecule was carried out using the DFT (Density Functional Theory) method [10-13] with the aim of determining the structural and electronic characteristics (geometric properties, i.e. bond length and angle, frontier molecular orbitals i.e. HOMO-LUMO, reactivity indices). This study was carried out using Gaussian 09 software [14].
According to the DFT theory, enol form of curcumin is significantly more stable than its keto form and the dissociation enthalpy of O-H bond from phenol is significantly lower than that of central O-H bond suggesting that the extraction of hydrogen atoms takes place in phenolic group [15-17].

Despite this abundant literature, there may still be a lot to know about curcuminoids. Very recently on July 2022 Kunyima et al. have published an article on the kinetics and thermodynamics of the extraction of oleoresin containing curcuminoids from turmeric (*Curcuma Longa* L.) [18]. Two months after they published on Antimyocardial infarctus, efficient Antipoison and Antiprostate mighty spicy miscellany [19]. This miscellany contains curcurma, honey and other spicies.

2. MATERIALS AND METHODS

2.1 Materials

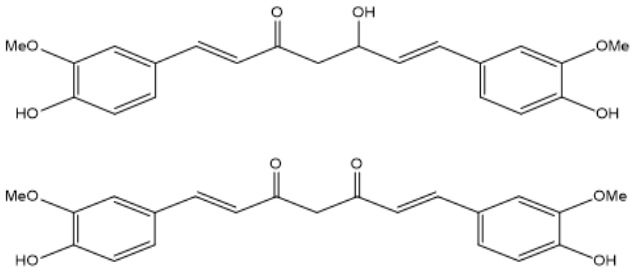


Fig. 1. Chemical structures of curcumin (enol and keto forms)

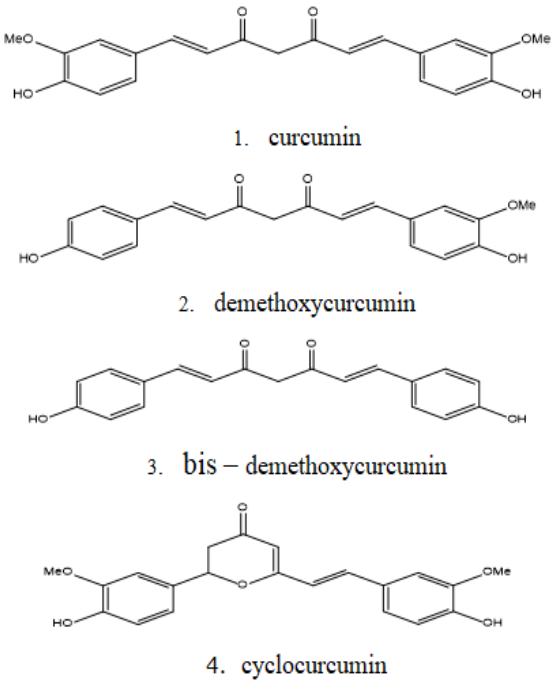
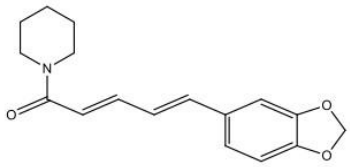
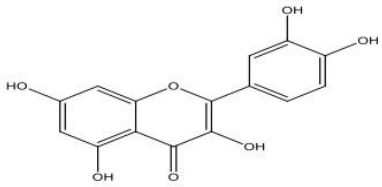


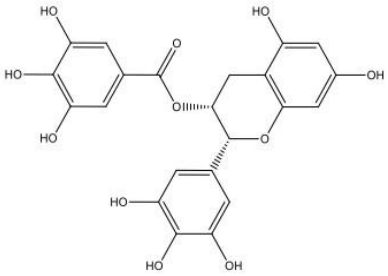
Fig. 2. Structure of curcuminoïds



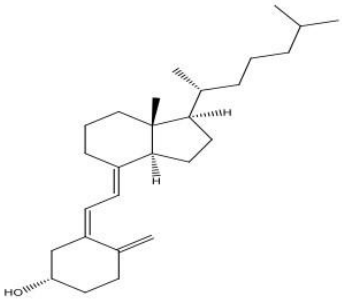
a. piperine



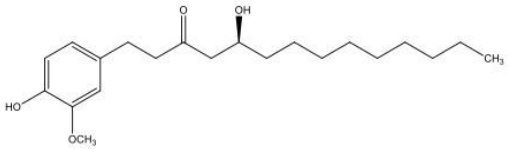
b. quercetin



c. epigallocatechin -3-gallate

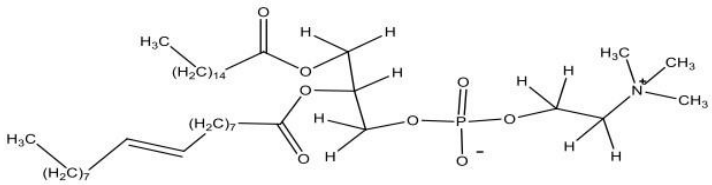


d. vitamin D_3 (cholecalciferol)



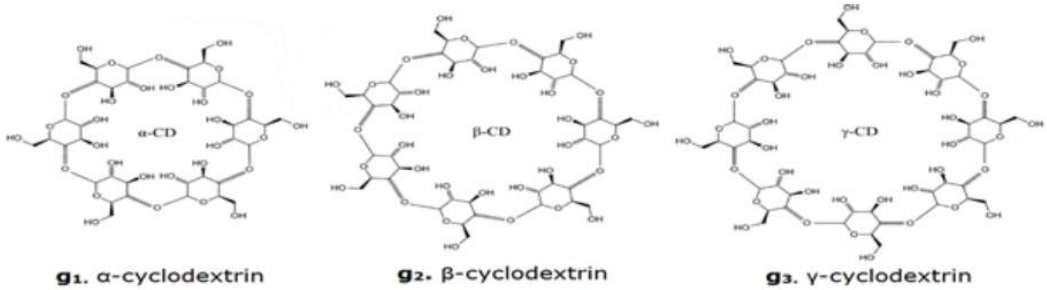
e. gingerol

(s)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone



f. Lecithin

(1-palmitoyl-2-oleoyl-phosphatidylcholine)



g1. α-cyclodextrin **g2.** β-cyclodextrin **g3.** γ-cyclodextrin

Fig. 3. Structure of some important chemical compounds in co-administration with curcumin (a, b, c, d, e, f, g_1, g_2, g_3)

2.2 Methods

Kunyima's first law has made possible this investigation [20-23]

$$\log\left(\frac{m_0}{m_0 - m_e}\right) = \frac{k}{2.3}t$$

Kunyima's first law can take the following form:

$$x = m_e = m_0\left(1 - e^{-kt}\right)$$

$$x = m_e = m_0 - m_0 e^{-kt}$$

m_0 is constant

$$m_0 - m_e = m_0 e^{-kt}$$

$$\Rightarrow e^{-kt} = \frac{m_0 - m_e}{m_0}$$

$$v = \frac{dx}{dt} = km_0 e^{-kt} = \frac{km_0\left(m_0 - m_e\right)}{m_e}$$

$$v = \frac{dx}{dt} = k\left(m_0 - m_e\right)$$

Where v is the extraction velocity or massic velocity (massic debit) in $\frac{g}{s}$, $\frac{g}{\min}$, $\frac{g}{h}$ depending on expression of time used in experiment.

In the case in study extraction velocity will be expressed in $\frac{g}{\min}$ because the stirring time is expressed in minute.

Calculations of extraction enthalpy (ΔH) and extraction entropy (ΔS) in closed system have been made using the relation:

$\Delta H = -RT\ln k$ from Arrhenius law $k = A'e^{-E/RT}$ [23]

where k is kinetic constant, T the constant temperature of work at constant pressure

$$\Delta S = \frac{\Delta H}{T}$$

2.3 Experimental Section (Extraction protocol)

Natural turmeric rhizomes have been bought on Kinshasa market, dried at 50°C and afterwards ground. One gram of turmeric powder has been placed in cartridge. This cartridge has been placed in flat bottom balloon flask containing a magnetic stirrer and 100 ml of acetone as solvent. The thermometer has been placed in balloon flask orifice to control temperature that must be constant during all the experiment (27.5°C) in the lee of light. The balloon flask endowed of magnetic stirrer with its content has been placed on heating agitator to be stirred at 250 rpm during a certain time. At each stirring time the solvent (acetone) has been removed from mixture by means of spin evaporator (mark Hei –VAP 1.0) programmed at 59°C for acetone during 10 minutes at 80 rpm (round per minute). Afterwards the balloon flask has been placed in drying oven at 80°C during 5 minutes and cooled in desiccator before to be weighed in order to determine the extracted mass of oleoresin containing curcuminoids. At each stirring time the experiment has been repeated in exactly the same condition. The experiment has been also performed at 500 rpm.

3. RESULTS AND DISCUSSION

Intravenous (i.v.) administration of a drug is reserved for situations where a rapid effect is desired or for drugs that cannot be administered extravascularly because they are poor or poorly absorbed. The absorption step exists for all extravascular routes of administration (oral, cutaneous, intramuscular, pulmonary, etc.). It may be accompanied by a loss of drug, corresponding to an unabsorbed fraction which will not reach the general circulation. The absorption phase can be limiting and the study of this process is essential and mandatory for each route of administration considered.

After administration of a single dose via the extravascular route, the concentration does not increase instantaneously as in the case of intravenous (i.v.) administration because the drug must cross biological barriers before reaching the general circulation (see Fig. 4).

The evolution of the concentrations over time is the result of the entry of the drug into the body and its elimination. Unlike single intravenous (i.v.) administration, absorption and elimination processes coexist and the appearance of the curve will vary with the respective durations of each of these phases:

- Concentration increase phase: concentrations increase as long as absorption is greater than elimination.

- Concentration peak: at a given concentration level, the rate of elimination is equal to the rate of absorption and the concentration reaches a maximum value ($C_{\max}$)
- Phase of decreasing concentrations: the processes of absorption and elimination still coexist but the rate of elimination is greater than the rate of absorption

The evolution of the concentrations over time responds to the equation:

$$C = -Ae^{-kat} + Be^{-ket}$$

The absorption constant ka includes all variations due to the pharmaceutical form and the transmembrane passage; ke is the elimination constant.

Thus, the absorption of a drug depends on:

- The route of administration; the same drug will be absorbed differently orally, rectally, cutaneously, etc.
- The galenic form (tablet, capsule, liquid), which will modify the kinetics of release of the active ingredient and therefore its availability for absorption.
- Bioavailability is defined by the amount of drug that reaches the bloodstream after extravascular administration and the rate of this, which depends on the rate of absorption from the site of administration.
- The bioavailable fraction is expressed by the factor F (it is a percentage that can vary from 0 to 100%)
- The speed factor is assessed by the maximum concentration ($C_{\max}$) reached and the time ($T_{\max}$) for obtaining this maximum concentration.

In short, the plasmatic concentration of drug, which is a measure of its bioavailability, increase with the absorption degree; the maximal plasmatic concentration is reached when the elimination velocity of drug is equal to its absorption velocity. There are many causes contributing to the weakness of bioavailability [25]. The orally administered drugs must cross the intestinal wall and reach the liver through the portal circulation ; both of them are the frequent sites of first hepatic passage (metabolism occurring before a drug reach the systemic circulation). So many drugs can be metabolized before reaching the optimal plasmatic concentrations. A weak bioavailability is often met with oral forms of few soluble drugs in water and slowly absorbed. A long insufficiently presence in the alimentary canal is a frequent cause of weak bioavailability. If the drug is not rapidly dissolved or if it cannot penetrate the epithelial membrane (i.e. when it is very ionized and polar), the time at the adsorption site can be insuffiscient. In such circumstances, the bioavailability undergoes considerable variations. Age, sex, physical activity, genetic factors, stress, pathologies (i.e. achlorhydria, malabsorption syndrome), as well as possible previous surgical intervention on the digestive tract (i.e. bariatric surgery), can also modify the bioavailability of drugs. The chemical reactions that reduce the absorption can also reduce the bioavailability. They include the complex formation (i.e. between a tetracyclin and multivalence metallic ions), the hydrolysis by gastric juices or by digestive enzymes (i.g. penicillin hydrolysis and chloramphenicol palmitate hydrolysis), the conjugation in intestinal wall (i.e. the sulfoconjugation of isoproterenol), the adsorption to other drugs (i.e. from digoxin to the cholestyramine) and the metabolism by gut flora.

Our lecturers are advised to consult specialized books for calculation of bioavailability.

Such a phenomenon depending on velocity justifies the kinetic and thermodynamic study hereby performed as follows in the Table 1.

Table 1 gives the extracted mass (m_e) of oleoresin containing curcuminoids at each stirring time (250 rpm, T= 27.5 °C).

Observing this Table 1 it can be seen that the extracted mass (m_e) of oleoresin containing curcuminoids increases with increasing stirring time expressed in minutes until it becomes almost constant at 70 minutes, point after which the extractable mass (m_0) of oleoresin containing curcuminoids has been assessed (m_0 = 0.8696 ± 0.0004 g) as it is indicated in Fig. 5.

According to the results in this Table 1 Kunyima's first law has been applied to find the value of global kinetic constant by means of origin program 9.2 as below mentioned in Fig. 6 where $\log\left(\frac{m_0}{m_0 - m_e}\right)$ is plotted versus stirring time.

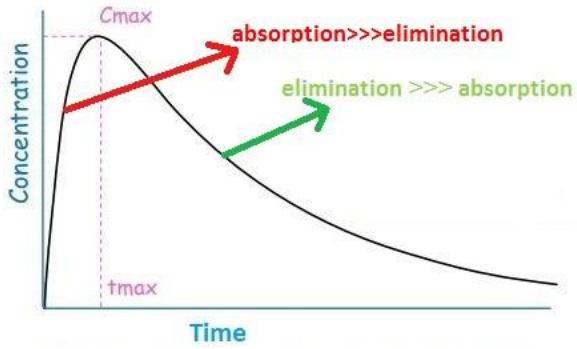


Fig. 4. Evolution of blood concentrations of the drug after extravascular administration [24]

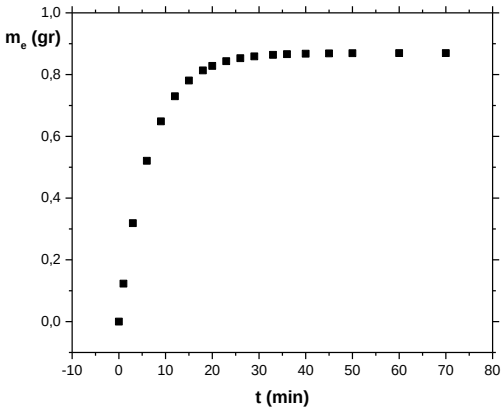


Fig. 5. Extracted mass (m_e) of oleoresin containing curcuminoids versus stirring time at 250 rpm

Table 1. Extracted mass of oleoresin containing curcuminoids as a function of stirring time at 27.5°C (250 rpm)

Temps (min)	m_e *(gr)*	$m_o(gr)$	$m_o - m_e$ *(gr)*	$\frac{m_o}{m_o - m_e}$	$log\frac{m_o}{m_o - m_e}$
0	0	0.8696±0.0004	0.8696±0.0004	1	0
1	0.1228±0.0004	0.8696±0.0004	0.7468±0.0004	1.1644	0.0661
3	0.3188±0.0003	0.8696±0.0004	0.5508±0.0003	1.5788	0.1983
6	0.5207±0.0005	0.8696±0.0004	0.3489±0.0005	2.4924	0.3966
9	0.6486±0.0003	0.8696±0.0004	0.2210±0.0003	3.9348	0.5949
12	0.7296±0.0004	0.8696±0.0004	0.1400±0.0004	6.2114	0.7932
15	0.7809±0.0002	0.8696±0.0004	0.0787±0.0002	11.0496	1.0433
18	0.8134±0.0003	0.8696±0.0004	0.0562±0.0003	15.4733	1.1896
20	0.8282±0.0005	0.8696±0.0004	0.0414±0.0005	21.0048	1.3223
23	0.8434±0.0004	0.8696±0.0004	0.0262±0.0004	33.1908	1.5210
26	0.8530±0.0003	0.8696±0.0004	0.0166±0.0003	52.3855	1.7192
29	0.8591±0.0004	0.8696±0.0004	0.0105±0.0004	82.8190	1.9181
33	0.8639±0.0005	0.8696±0.0004	0.0057±0.0005	152.5614	2.1834
36	0.8660±0.0003	0.8696±0.0004	0.0036±0.0003	241.5556	2.3830
40	0.8676±0.0004	0.8696±0.0004	0.0020±0.0004	434.8000	2.6383
45	0.8687±0.0003	0.8696±0.0004	0.0009±0.0003	966.2222	2.9851
50	0.8692±0.0003	0.8696±0.0004	0.0004±0.0003	2174	3.3372
60	0.8695±0.0005	0.8696±0.0004	0.0001±0.0005	8696	3.9393
70	0.8696±0.0004	0.8696±0.0004	-	-	-

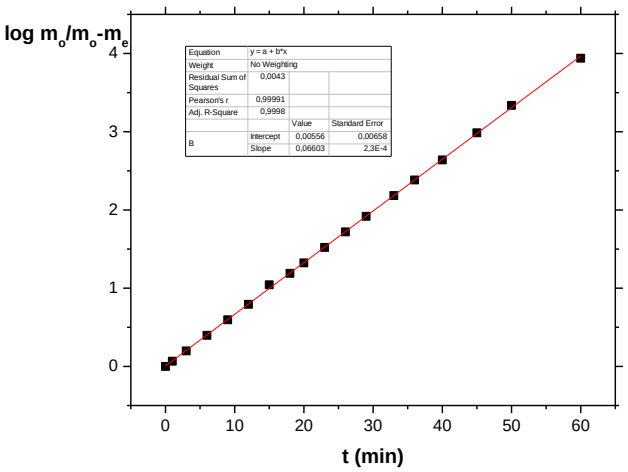


Fig. 6. $\log\left(\frac{m_0}{m_0 - m_e}\right)$ **versus stirring time at 250 rpm**

The value of global kinetic constant has been found (k= 0.1520 ± 0.0005) min^{-1}.

The tenet of like dissolves like leads to the predominance of the keto form of curcumin in presence of its tautomeric enol form see Table 2.

Table 2 gives the extracted mass (m_e) of oleoresin containing curcuminoids at each stirring time (500 rpm, T = 27.5 °C).

Likewise it can be remarked in this Table 2 the increasing of extracted mass (m_e) of oleoresin containing curcuminoids as a function of stirring time expressed in minutes until reaching a constant value (m_0 = 0.8942 ± 0.0003 g) at almost 70 minutes, point at which the extractable mass of oleoresin containing curcuminoids has been evaluated as it is shown in Fig. 7.

Table 2. Extracted mass of oleoresin containing curcuminoids as a function of stirring time at 27.5°C (500 rpm)

Temps (min)	m_e ***(gr)***	$m_o(gr)$	$m_o - m_e$	$\frac{m_o}{m_o - m_e}$	$log\frac{m_o}{m_o - m_e}$
0	0	0.8942±0.0003	0.8942±0.0003	1	0
1	0.1260±0.0004	0.8942±0.0003	0.7682±0.0004	1.1640	0.0660
3	0.3272±0.0005	0.8942±0.0003	0.5669±0.0005	1.5774	0.1979
6	0.5348±0.0003	0.8942±0.0003	0.3594±0.0003	2.4880	0.3958
9	0.6663±0.0006	0.8942±0.0003	0.2279±0.0006	4.9236	0.5937
12	0.7495±0.0003	0.8942±0.0003	0.1447±0.0003	6.1797	0.7910
15	0.8026±0.0004	0.8942±0.0003	0.0916±0.0004	9.7620	0.9895
18	0.8361±0.0004	0.8942±0.0003	0.0581±0.0004	15.3907	1.1872
20	0.8513±0.0006	0.8942±0.0003	0.0429±0.0006	20.8438	1.3196
23	0.8670±0.0005	0.8942±0.0003	0.0272±0.0005	32.8750	1.5169
26	0.8770±0.0004	0.8942±0.0003	0.0172±0.0004	51.9884	1.7159
29	0.8833±0.0005	0.8942±0.0003	0.0109±0.0005	82.0367	1.9140
33	0.8882±0.0006	0.8942±0.0003	0.0060±0.0006	144.0333	2.1733
36	0.8904±0.0003	0.8942±0.0003	0.0038±0.0003	235.3158	2.3716
40	0.8921±0.0005	0.8942±0.0003	0.0021±0.0005	425.8095	2.6292
45	0.8932±0.0004	0.8942±0.0003	0.0010±0.0004	894.2000	2.9514
50	0.8938±0.0006	0.8942±0.0003	0.0004±0.0006	2235.5000	3.3494
60	0.8941±0.0003	0.8942±0.0003	0.0001	8942.0000	3.9514
70	0.8942±0.0003	0.8942±0.0003	0	-	-

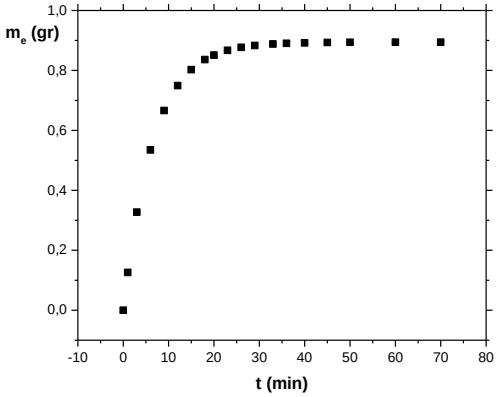


Fig. 7. Extracted mass (m_e) of oleoresin containing curcuminoids versus stirring time at 500 rpm

Also Kunyima's first law has been applied in such conditions using origin program 9.2 by plotting $\log\left(\frac{m_0}{m_0 - m_e}\right)$ versus stirring time (see Fig. 8).

Kinetic constant has been found the same (k = 0.1520 ± 0.0005) min^{-1}.

Table 3 gives the evolution of massic velocity (v) as a function of stirring time and extracted mass (m_e) of oleoresin containing curcuminoids at 250 rpm (T=27.5 °C).

Linear decreasing evolution between massic velocity as a function of extracted mass (m_e) of oleoresin containing curcuminoids at each stirring time has been pointed out as shown in Fig. 9 signifying the saturation of solution.

Table 4 shows the evolution of massic velocity (v) as a function of stirring time and extracted mass (m_e) of oleoresin containing curcuminoids at 500 rpm (T=27.5 °C).

Similarly linear decreasing of massic velocity(v) as a function of extracted mass (m_e) of oleoresin containing curcuminoids at each stirring time has been observed (see Fig. 10).

Mean values of extraction enthalpy and extraction entropy have been calculated with mean error as precision on extraction enthalpy according to the value of kinetic constant obtained by origin program 9.2 (k = 0,1520 ± 0,0005) min^{-1} showing three values of kinetic constant (k_1 = 0,1520 min^{-1}, k_2 = 0,1515 min^{-1}, k_3 = 0,1525 min^{-1}).

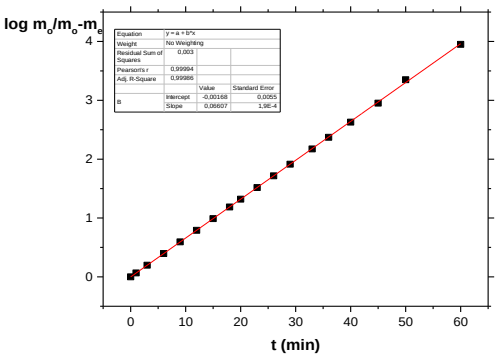


Fig. 8. $\log\left(\frac{m_0}{m_0 - m_e}\right)$ versus stirring time at 500 rpm

Table 3. Massic velocity (v) as a function of extracted mass of oleoresin containing curcuminoids (m_e) at 250 rpm (T = 27.5 °C)

Temps (min)	m_e *(gr)*	$m_o(gr)$	$m_o - m_e$ *(gr)*	$k(min^{-1})$	$v\ (gr.min^{-1})$
0	0	0.8696±0.0004	0.8696±0.0004	0.1520±0,0005	0.13218±0,0000
1	0.1228±0.0004	0.8696±0.0004	0.7468±0.0004	0.1520±0,0005	0.11351±0,0001
3	0.3188±0.0003	0.8696±0.0004	0.5508±0.0003	0.1520±0,0005	0.08372±0,00005
6	0.5207±0.0005	0.8696±0.0004	0.3489±0.0005	0.1520±0,0005	0.05303±0,00008
9	0.6486±0.0003	0.8696±0.0004	0.2210±0.0003	0.1520±0,0005	0.03360±0,00005
12	0.7296±0.0004	0.8696±0.0004	0.1400±0.0004	0.1520±0,0005	0.02128±0,00010
15	0.7809±0.0002	0.8696±0.0004	0.0787±0.0002	0.1520±0,0005	0.01196±0,00003
18	0.8134±0.0003	0.8696±0.0004	0.0562±0.0003	0.1520±0,0005	0.00854±0,00005
20	0.8282±0.0005	0.8696±0.0004	0.0414±0.0005	0.1520±0,0005	0.00629±0,00008
23	0.8434±0.0004	0.8696±0.0004	0.0262±0.0004	0.1520±0,0005	0.00398±0,00001
26	0.8530±0.0003	0.8696±0.0004	0.0166±0.0003	0.1520±0,0005	0.00252±0,00005
29	0.8591±0.0004	0.8696±0.0004	0.0105±0.0004	0.1520±0,0005	0.00160±0,0001
33	0.8639±0.0005	0.8696±0.0004	0.0057±0.0005	0.1520±0,0005	0.00087±0,00008
36	0.8660±0.0003	0.8696±0.0004	0.0036±0.0003	0.1520±0,0005	0.00055±0,00005
40	0.8676±0.0004	0.8696±0.0004	0.0020±0.0004	0.1520±0,0005	0.00030±0,00010
45	0.8687±0.0003	0.8696±0.0004	0.0009±0.0003	0.1520±0,0005	0.00014±0,00005
50	0.8692±0.0003	0.8696±0.0004	0.0004±0.0003	0.1520±0,0005	0.00006±0,00005
60	0.8695±0.0005	0.8696±0.0004	0.0001±0.0005	0.1520±0,0005	0.00002±0,00008
70	0.8696±0.0004	0.8696±0.0004	0	0.1520±0,0005	0

Table 4. Massic velocity (v) as a function of extracted mass of oleoresin containing curcuminoids (m_e) at 500 rpm

Temps (min)	m_e *(gr)*	$m_o(gr)$	$m_o - m_e$	$k(min^{-1})$	$v\ (gr.min^{-1})$
0	0	0.8942±0.0003	0.8942±0.0003	0.1520±0,0005	0.13592±0,00000
1	0.1260±0.0005	0.8942±0.0003	0.7682±0.0005	0.1520±0,0005	0.11677±0,00008
3	0.3272±0.0003	0.8942±0.0003	0.5669±0.0003	0.1520±0,0005	0.08617±0,00005
6	0.5348±0.0002	0.8942±0.0003	0.3594±0.0002	0.1520±0,0005	0.05463±0,00003
9	0.6663±0.0004	0.8942±0.0003	0.2279±0.0004	0.1520±0,0005	0.03464±0,00006
12	0.7495±0.0006	0.8942±0.0003	0.1447±0.0006	0.1520±0,0005	0.02199±0,00009
15	0.8026±0.0003	0.8942±0.0003	0.0916±0.0003	0.1520±0,0005	0.01392±0,00005
18	0.8361±0.0005	0.8942±0.0003	0.0581±0.0005	0.1520±0,0005	0.00883±0,00008
20	0.8513±0.0002	0.8942±0.0003	0.0429±0.0002	0.1520±0,0005	0.00652±0,00003
23	0.8670±0.0006	0.8942±0.0003	0.0272±0.0006	0.1520±0,0005	0.00413±0,00009
26	0.8770±0.0004	0.8942±0.0003	0.0172±0.0004	0.1520±0,0005	0.00261±0,00006
29	0.8833±0.0005	0.8942±0.0003	0.0109±0.0005	0.1520±0,0005	0.00166±0,00008
33	0.8882±0.0003	0.8942±0.0003	0.0060±0.0003	0.1520±0,0005	0.000912±0,00005
36	0.8904±0.0004	0.8942±0.0003	0.0038±0.0004	0.1520±0,0005	0.00058±0,00006
40	0.8921±0.0003	0.8942±0.0003	0.0021±0.0003	0.1520±0,0005	0.00032±0,000005
45	0.8932±0.0004	0.8942±0.0003	0.0010±0.0004	0.1520±0,0005	0.00015±0,00006
50	0.8938±0.0002	0.8942±0.0003	0.0004±0.0002	0.1520±0,0005	0.00006±0,00003
60	0.8941±0.0003	0.8942±0.0003	0.0001±0.0003	0.1520±0,0005	0.00002±0,00005
70	0.8942±0.0003	0.8942±0.0003	0	0.1520±0,0005	0

$$\Delta H = -RT\ln k_1 = -8.314J/molK \times 300.5K\left(\frac{\ln 0.1520}{60\text{sec}}\right) = +78.44W/mol$$

$$\Delta H = -RT\ln k_2 = -8.314J/molK \times 300.5K\left(\frac{\ln 0.1515}{60\text{sec}}\right) = +78.58W/mol$$

$$\Delta H = -RT \ln k_3 = -8.314 J/molK \times 300.5K \left(\frac{\ln 0.1525}{60\text{sec}} \right) = 78.31 W/mol$$

$$\overline{\Delta H} = +78.44 \pm 0.14 W/mol$$

$$\overline{\Delta H} = T\Delta S$$

$$\Delta S = \frac{\Delta H}{T} = \frac{78.44}{300.5} = 0.2610 W/molK$$

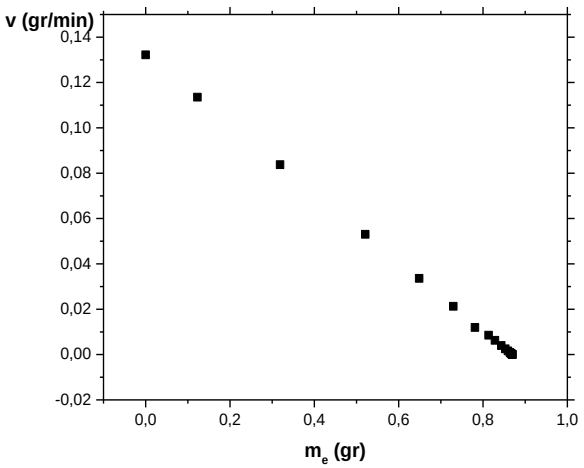


Fig. 9. Massic velocity (v) versus extracted mass of oleoresin with its content (m_e) at 250 rpm

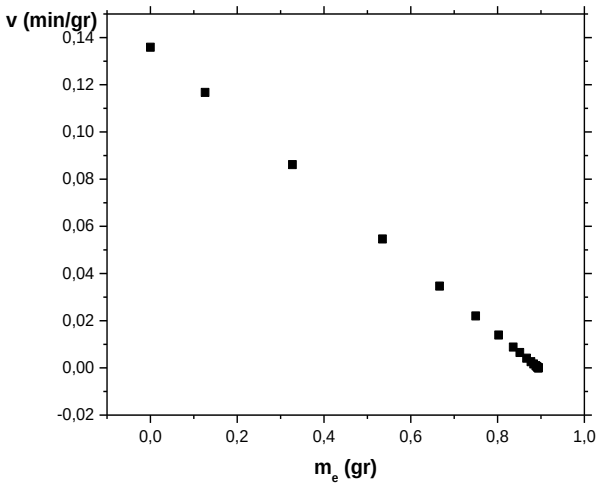


Fig. 10. Massic velocity (v) versus extracted mass of oleoresin with its content (m_e) at 500 rpm

The error on ΔS has been calculated by logarithmic method.

For us there is no errors on the lecture of temperature

$$y = Tx$$

$$x = \frac{y}{T}$$

$$\ln x = \ln y - \ln T$$

$$\Delta x = \frac{\Delta y}{y} x$$

$$\Delta S = \frac{0.14}{78.44} \times 0.261 = 0.00046 \approx 0.0005$$

$$\Delta S = (0.2610 \pm 0.0005) W / molK$$

Scrutinizing the units of extraction enthalpy and extraction entropy it can be pointed out the power per mole while the extraction concerned the mass of oleoresin containing curcuminoids expressed in gramme. This can be considered as an equivalent power per mole of material of a well known chemical structure.

The value of ΔS in acetone suggests without surprise the disturbance occurring in the system after extraction.

With respect to the value of extraction enthalpy it suggests endothermic behavior of oleoresin containing curcuminoids and therefore the endothermic behavior of curcuminoids in vitro.

Acetone indeed is a solvent that can easily accept a proton and becomes a like solvent of water which constitutes more than 60% of human body. These chemicals compounds (curcuminoids) which exhibit endothermic behavior in vitro in like solvent of water constituant of more than 60% of human body are known weakly bioavailable. This behavior has been also observed in ethanol in previous work [18].

So there is certainly an extraordinary link between bioavailability of such compounds and their endothermic behavior in like solvents of water in vitro.

It can be then deduced that more the exothermic behavior will be high, the bioavailability will be greater.

The kinetic constant which play a capital role in endothermic or exothermic behavior of curcuminoids must be outnumbered at least greater than 1 to impose exothermic behavior.

Comparison has been made between kinetic-thermodynamic parameters and ethanol- acetone properties as it is shown in Table 5.

The values of extraction enthalpy and extraction entropy in ethanol have been recalculated with error like in the case of acetone.

The comment of this Table 5 will concern specially dipole moments, kinetic constants and extraction enthalpies.

Indeed the curcuminoids are more soluble in acetone than in ethanol because acetone has a great dipole moment, this can be observed in Table 1 and Table 2 at each stirring time and the values of extractable masses in ethanol and in acetone (m_0). Whereas the kinetic constant in acetone is more weak than in ethanol.

This suggests that when the solubility is greater in solvent , that means easy, the kinetic constant which is measure of solubility is small.

With respect to the values of extraction enthalpies, the value of ΔH in acetone is a little bit high than the value in ethanol while the experiments have been performed in the same conditions of temperature, pressure and stirring. This suggests that to the energy of stirring is added the energy of dipole moment of acetone which is high.

Table 5. Comparison between kinetic-thermodynamic parameters and ethanol-acetone dipole moments in Debye (D)

Solvent	Dipole moment μ (D)	k (min^{-1})	ΔH ($W\ mol^{-1}$)	ΔS ($W\ mol^{-1}\ K^{-1}$)
Ethanol	1,66	0,1597 ± 0,0012	75,71 ± 1,7	0,2519 ± 0,006
Water	1,85	-	-	-
Acetone	2,88	0,1520 ± 0,0005	78,44 ± 0,14	0,2610 ± 0,0005

Concerning the values of entropy variation the system is a little bit more disturbed in the case of acetone.

It should nevertheless be emphasized that there is already, Active Nutripure, on the market as we have pointed out, a water-soluble and therefore bioavailable active curcumin under the Cavacurmin formulation, without chemical adjuvant, without GMOs (Genetically Modified Organisms) or nanoparticles in the form of capsules, 39 times or 40 times assimilated than a turmeric extract standardized to 95% curcuminoids. Its assimilation is fast, and it does not contain harmful excipients [i].

Indeed, the extracts of Curcuma Longa L. 95% contain curcuminoids which are naturally poorly assimilated by the body because these molecules are not soluble in water. They pass the intestinal barrier with difficulty, then are eliminated in the stools with a weak passage in the blood stream. The effect for the organism is weak.

Curcumin, Active Nutripure, is surrounded by complex sugars derived from plants (corn for example or potato starch) called cyclodextrin, a hydrophilic molecule which encapsulates curcuminoids and acts as a protective and transport shell in the aqueous medium. Being dissolved in water, it will easily pass the intestinal barrier to the bloodstream, unlike 95% turmeric extracts.

The complex sugars are then broken down by a pancreatic enzyme (hydrolysis), releasing curcuminoid molecules including curcumin, demethoxycurcumin and bisdemethoxycurcumin. This hydrolysis will release maltose, maltodextrin and a little glucose (<1g per day), harmless to the body. The liver then exerts several metabolic cascades on the curcuminoids generating active metabolites.

Also it should be noted that the significant presence of acetone in the human body should be discouraged because, absorbed by inhalation, through the skin or orally, it is neurotoxic in the same way as methanol, mercury, arsenic, lead, benzene, carbon tetrachloride, chloroform, chloromethane, etc… and attacks the central nervous system (brain, brainstem, spinal cord) as well as the peripheral nervous system (ganglia, sensory nerves, motor nerves) acutely or chronic[ii].

Central nervous system effects include:

- General effects such as headaches, loss of appetite, drowsiness, etc.
- Mood and personality disorders such as sleep disturbances, increased irritability, depression, anxiety, etc.
- Cognitive impairments such as learning disabilities, concentration, memory, speech, etc.

Peripheral nervous system effects include:

- Motor impairments such as weakness, tremors, incoordination, convulsion, etc.
- Sensory damage such as reduced hearing, color vision, tinnitus, loss of balance, etc.

However, along with acetylacetic acid and beta-hydroxybutyric acid, acetone is one of the ketone bodies found in blood and urine, in very small amounts.

An acetone crisis refers to an abnormality in the concentration of elements produced by fats in the blood. It is often linked to diabetes, but also occurs during other medical conditions such as hypoglycemia or during fasting.

Thus, the use of acetone in this work has only a purely scientific purpose to better understand the kinetic and thermodynamic behavior of curcuminoids in vitro in order to predict their use in co-administration in vivo.

Our Laboratory has set itself the objective of finding a curcumin that is 80 times assimilable by the body whithout nano-particles transformation.

4. CONCLUSION

Kunyima's first law has made possible the kinetic and thermodynamic study of extraction of oleoresin containing curcuminoids from Turmeric. Kinetic constant is a measure of solubility of oleoresin containing curcuminoids and therefore a measure of solubility of curcuminoids in a given solvent, ethanol and acetone being concerned in this paper as solvents. Results show that kinetic constant is inversely proportional to solubility of solvent and it determines the endothermic or exothermic behavior of extraction of curcuminoids.

The endothermic behavior of curcuminoids hereby determined in ethanol and acetone in

vitro suggests their weak bioavailability and therefore the weak availability of curcumin. The challenge of this actual research is to improve our understanding of kinetic and thermodynamic of extraction of oleoresin containing curcuminoids from Turmeric in vitro in order to presage their bioavailability still weak for an efficient validated action. The increase of bioavailability will be done whether through improved formulations of curcumin or through new pathways of administration. The conception of curcumin analogous is also a way to promote its effects.

More the phenomenon is exothermic in water-like solvents, more the involved chemical compound is bioavailable. Curcumin predicts anyway hopeful future.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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