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Kinetic studies of the release profiles of antiepileptic drug released from a nanostructured TiO_2 matrix.

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ABSTRACT

In this paper is reported the “in vitro”release kinetic studies of antiepileptic drugs released from an inorganic, titanium oxide (TiO_2)porous matrix. In order to determine the drug release mechanism, the experimental values were fitted to different mathematical models: zero-order, firs-order, Higuchi, Hixson-Crowel and Peppas. TiO_2 was prepared by the sol-gel method adding valproic acid (VPA) or phenytoine (DHP) during the titanium n-butoxide hydrolysis step. The drug-TiO_2 systems were observed by scanning electron microscopy. The “in vitro” release experiments were performed at laboratory scale following theUnited States Pharmacopeia (USP)standards.The obtained materials have a morphology of nanoparticle agglomerates. The particles have different sizes with some roughness and spherical shape. Peppas model suggests for both systems, that the release mechanism is controlled by two parallel processes. The firstone is by diffusion of the drug through the matrix and the second is related to a gradient of constant diffusion byingress of the solvent in the matrix.

Indexing terms/Keywords

Antiepileptic drugs, Titania matrix, release mechanism, drug release

Academic Discipline And Sub-Disciplines

Chemistry

SUBJECT CLASSIFICATION

Physical - Chemistry

TYPE (METHOD/APPROACH)

Chemical kinetics

1.INTRODUCTION

Currently, the interest on the designing and preparation of drug delivery systemshas significantly increaseddue to their potential advantages that those may offer in comparison to conventional drug therapies[1-6]. At present, there are a large number of research papers devoted on the preparation of drug release system using nanotechnology [7-11].The highdemand is thanks to the possibility to reach efficient and safe levels required for the introduction of drugs; it is possible to including poorly soluble drugs and biomacromolecular drugs. The benefits ranging from the retention of the therapeutic activity of the drug, protection of the drug from chemicaland enzymatic degradation, control of drug release rate, to increasing the bioavailability, and reduction of toxicity, immunicity, and other biological side-effects. In different nanometric-forms (nanotubes, nanoparticles, nanospheres, etc.) polymeric and/or inorganic materials have been used for drug delivery applications[12-17]. Among the various inorganic materials, titanium dioxide, or titania (TiO_2) has shown to be biocompatible [18, 19] and environment friendly. In addition, titania has a stable structure, is non-immunogenicity, is easy to prepare and has unique photoresponsive properties. Some biomedical applications of TiO_2including phothosensitizer carrieron TPD, for DNA delivery,diagnostic imaging, and biosensors have been reported in literature[20–22]. Mesoporous TiO_2networks havealso been synthesized for encapsulation and release of antiepileptic drugmolecules [23], anticancer drug [24, 25] promoter of bone formation [26], antibiotics [27],

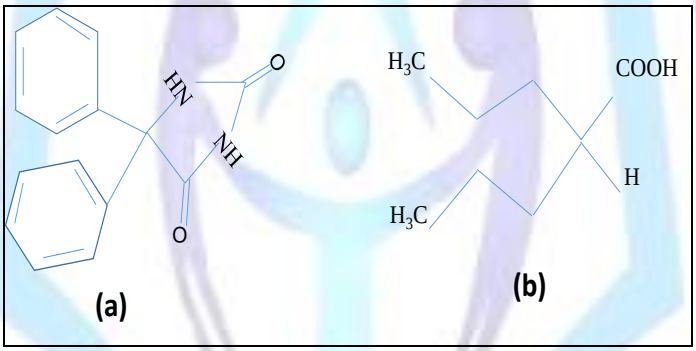
anti-inflammatory [28], among others.

"In vitro" release studies allow us to know the rate drug through the matrix, then to determine the parameters that influence in the drug release mechanism allowing optimizing the studied formulation. It also is possible to adapting the release mechanism of a studied drug with respect to the commercial drug. Finally, it providesus similarinformation about release behaviorthat may take place in "*in vivo*" applications.

The "in vitro" experimental values can be fitted to both simple and sophisticated mathematical models in order to make a theoretically study of the drug release mechanism. Most of the models that have been developed are based on solutions of the Fickian diffusion equation. The phenomenon of diffusion is intimately connected to the structure of the materialthrough which the diffusion takes place.Themechanisms of drug release offer a convenient way to categorizecontrolled release systems into: (i) diffusion-controlled; (ii) swelling controlled; and (iii) chemically controlled [29].There are severalmodels which describe the different drug release mechanism: 1) Zero-order modeldescribes the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems [30, 31]. 2) First order modelis used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices [32].3) Higuchi modeldepicts the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs [33]. 4) Hixson Crowell modelisapplied to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes that are parallel to thedrug surface if the tablet dimensions diminish proportionally,in such a manner that the initial geometricalform keeps constant all the time[34]. 5) In the Korsmeyer-Peppas model**,** the value of "n" characterizes the release mechanism of drug as follow: if $n \leq 0.45$, the release mechanism follows Fickian diffusion; if $0.45 < n < 0.89$, the release occurs by non-Fickian diffusion; and if $n = 1$, it is a zero order process [35].

In the present work, valproic acid and phenytoin (**Scheme** 1)which are two antiepileptic drugs were stabilized into a titania network. The aim of this work is established the drug release mechanism with the purpose to obtain local drug release systems into the brain.

According to the obtained results of the release profiles, it can be recommended the dose of drugs to be.



Scheme 1 Chemical structures of (a) Phenytoin (DPH) and (b) Valproic acid (VPA)

2. EXPERIMENTAL

2.1 Materials

Ethanol (Vetec, 96%), titanium butoxideTi(OBut)$_4$) (Aldrich, 98%),Valproic acid (Aldrich, 98 %), Phenytoin (Aldrich, 98%).

2.2 Methods

2.2.1 Samples preparation.

The encapsulation of valproic acid (VPA) or phenytoin (DPH) within a hydroxylated titania matrix was achieved in a single step using the sol-gel procedure. In **Table 1** are given the chemical precursor quantities and the molar rations used in the preparation of the TiO_2-VPA and TiO_2-DPH samples. TiO_2 reference was prepared under the same experimental conditions as the titania-drug samples.

The next procedure was carried out: the respective amount of VPA or DPH was dissolved in the adequate mixture of distillated water and ethanol, under stirring at room temperature. Then, titanium (IV) tetrabutoxide was added drop by drop to the drug solution in a lapse of 4 h.Thefinal mixture wasstirred at 25°Cuntil to complete theformation of the gel. Finally, the water and alcohol were removed with vacuum.Next the samples were dried at 30 °C for 8 h.

Table 1. Quantities of drug and Alkoxide:water:ethanol molar rations used to prepare antiepileptic drug-titania samples.

Samples	Drug quantity (mg)	Alkoxide: water: ethanolratio(mol)
TiO_2/DPH-50	50	1:16:8

TiO_2/DPH-100	100	1:16:8
TiO_2/DPH-250	250	1:16:8
TiO_2/VPA-200	200	1:8:8
TiO_2/VPA-400	400	1:8:8
TiO_2/VPA-800	800	1:8:8

2.2.2 Samples characterization.

Scanning Electron Microscopy(SEM). Morphology was analyzed by scanning electron microscopy (SEM JEOL-5600 LV) at 20kV. Samples were coated with a layer of gold of approximately 20 nm using an EMS 550 sputter coating.

2.2.3 "In vitro" drug release.

"In vitro" releasesmeasurements were performed at laboratory scale, according to the USP XXXVstandards [36]. The samples were suspended in 150 ml of hydrochloric acid (HCl) 0.1 N/tribasic sodium phosphate (Na_3HPO4) 2 M in a 3:1volume ratio (pH 6.8). The dissolution medium was kept under stirring at 50 rpm. All the experimentalmeasurementswere carried out at 37°C ± 0,2^{0}C. For VPA quantification an HPLC (SMARTLIN 2600 Konik with detector DAD) equipment with UV detector was used monitoring the signal at λ= 309. The DPH quantification was determinate by UV spectroscopy (UNICAM UV- 530). At determinedintervals of time an aliquot of 3 ml was removed from the release medium for spectroscopic measurement at λ=232 nm.After each measurement the aliquot was returned to the release medium.The experiments were made for duplicated. For each case a curve of calibration was previously built and it was used to quantify the released drug.

2.2.4 Encapsulation efficiency (E.E%) determination.

The amount of valproic acid (VPA) or phenytoin (DPH)loaded in the prepared samples wasdirectly estimated by dissolution of 5mg of each sample in 10 ml of phosphate-buffered saline (PBS) 0.1M at room temperature. After the dissolution the VPA amount release was determined by HPLC while the DPH amount was determined by ultraviolet spectroscopy.The encapsulation efficiency (E.E) was calculated using the following equation.

$$E.E\ (\%) = \frac{m_R}{m_T}\ x100 \qquad (1)$$

$m_{R=}$ mass of each drug released from titana and m_T= theoreticaldrug content.

2.2.5 Yield (Y%.).

The nanostructured materials (NM) yield determination (Y%) was calculated according to the following equation:

$$Y\ (\%) = \frac{m_p}{m + m_{Ref}}\ x100 \qquad (2)$$

m_p: is the total mass of the obtained drug-titania materials.

$m.$: is the mass of VPA orDPH used in each synthesis

$m._{Ref.}$is the massof titania without drug (a titania reference)

2.2.6 Data analysis

To analyze the "*in vitro*"release data various kinetic models were used to determine the release mechanism. The zero order rate equation (3) describes the systems where the drug release rate is independent of its concentration [37]. The first order equation (4) describes the release drug from systems where release rate is concentration dependent [38]. Higuchi [39] described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion equation (5). The Hixson-Crowell cube root law equation (6) describes the release from systems where there is a change in surface area and diameter of particles [40].

$$C = k_o t \qquad (3)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and *t* is the time.

$$LogC = LogCo - kt/\ 2.303 \qquad (4)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$Q = Kt^{1/2} \quad (5)$$

Where, K is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC}\, t \quad (6)$$

Where, *Qt* is the amount of drug released at a time *t*, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made: *cumulative % drug release vs. time* (zero order kinetic model); *log cumulative of % drug remaining vs. time* (first order kinetic model); cumulative *% drug release vs. square root of time* (Higuchi model) *log cumulative % drug release vs. log time* (Korsmeyer model) and *cube root of drug % remaining in matrix vs. time* (Hixson-Crowell cube root law).

2.2.7 Drug release mechanisms.

Korsmeyer [41, 42] derived a simple relationship which described drug release from a polymeric system Eq. (7). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$Mt/M\infty = Kt^n \quad (7)$$

Where Mt / M∞ isfraction of drug released at time *t*, *K* is the rate constant and *n* is the release exponent. The *n* value is used to characterize different release mechanisms (see **Table 2**).

Table 2. Diffusion exponent and solute release mechanism.

Diffusion exponent (n)	Overall solute diffusionmechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

3. RESULTS AND DISCUSSION

In a previous paper was reported the physical-chemistry characterization of all materials presented in this work [43].Table 3 summarizes the encapsulation efficiency and the yield of particles for all samples. From the table it is possible to determinethat there is an effect of the kind of the drug on the gelationtime. When VPA was encapsulated, the gelation time increased almost doubling that for VPA encapsulation. However, the drug amount did not have effect on the gelation time. In the case of DPH there is a maximum of Y% with sample containing 100 mg. A similar behavior was observed in the EE values. For the case of VPA encapsulation both the Y% and the EE % decrease as the VPA amount was increased. In this case low amount of drug can be dispersed in the complete network of titania. Larger amount of drug can block the pore mouth, this is not happen in the case of small ones.

Table 3. Yield and encapsulation efficiency % for all samples. Y (Yield) and E.E (Encapsulation efficiency).

Sample	Y (%)	EE (%)	Gelation time (h)
TiO_2/DPH-50	82±0.5	32±0.5	35
TiO_2/DPH-100	92±0.5	66±0.3	35
TiO_2/DPH-250	72±0.5	42±0.5	35
TiO_2/VPA-200	96±0.4	78±0.2	60
TiO_2/VPA-400	86±0.5	62±0.5	60

TiO_2/VPA-800	72±0.5	55±0.5	60

Figure 2 shows the SEM images for the different Drug-TiO_2 systems.Aggregates are observed and are formed by spheroidal particles, as a role the surface presents small roughness. The agglomerates have variable sizes. The materials have a size of about 400- 500 nm.

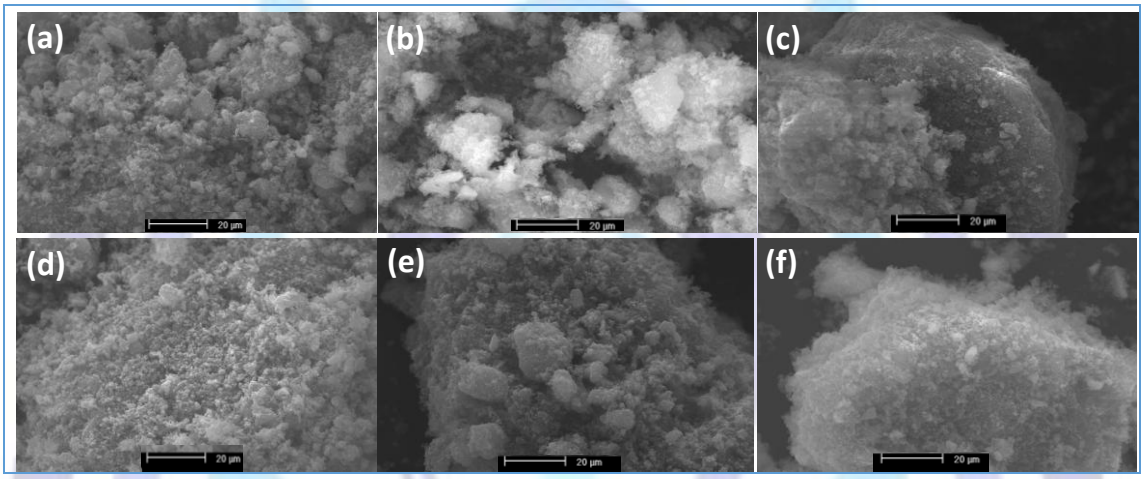


Figure 2. Scanning electron micrographs (SEM) of (a) TiO_2/VPA-200,)b) TiO_2/VPA-400, (c) TiO_2/VPA-800, (d) TiO_2/ DPH-50, (e) TiO_2/ DPH-100,(d) TiO_2/ DPH-250.

3.1 Kinetics studies

Release profiles for DPH and VPA are shown in figures 3 and 4 respectively. Both figures present at least two drug release stages. The first one is observed between 0-12 hours, and the second between 12 and 22 hours.

There is a direct effect of the E.E on the released drug amount. However samples prepared with the highest drug content did not present the highest release profile.However, the profiles obtained did not present burst, indicating an effective drug encapsulation into the TiO_2 matrix.

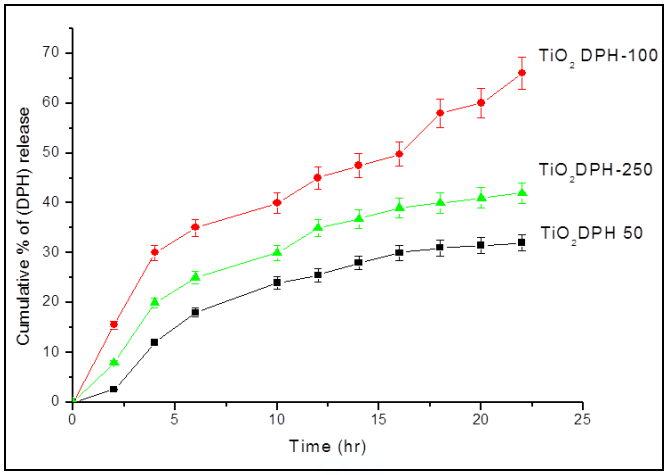


Figure 3. Release profiles of the nanostructured materials of TiO_2/DPH related to E.E.

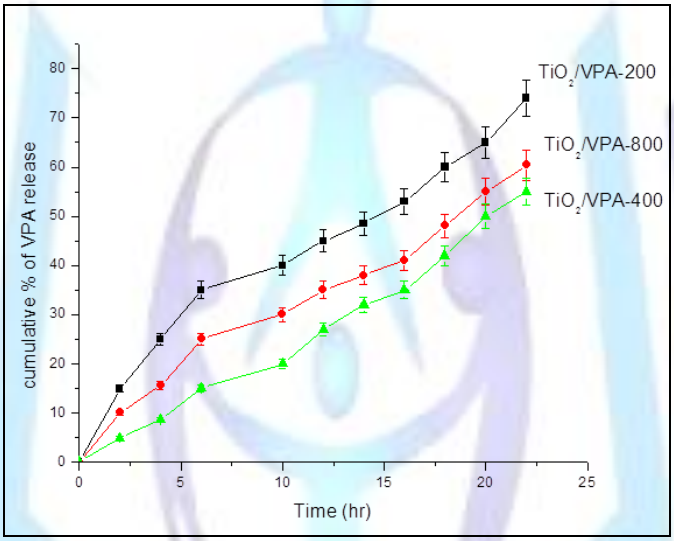


Figure 4. Release profiles of the nanostructured materials of TiO_2/VPA related to E.E.

Considering proper mechanisms such as zero order, first order, Higuchi and Hixson-Crowell cube-root model, was observed that the first order and the Hixson Crowell mechanism can be completely ruled out (Table 4) in comparison with the others. However, the observed fittingsobtained for the other mechanisms disagreement too. Data did not permit to select among of them. Another option was fitted the experimental data with the empirical Peppas equation to obtain the "*n*"exponent of the variable time. The "*n"* obtained valueswere around 0.13-0.22for the DHP and 0.30 for the VPA respectively. Theseresultsareextremely low and the correlation coefficients are not good. For these systems the "*n"* valuenot within the interval between 0.5 and 1.

Considering the results shown in Table 4 and the fact that releasing curves seem to present two stages was necessary to analysecombined mechanisms are operating. With the purpose to analyse this behaviour, the experimental release data were dividedin two parts, the first, between 0 and 10 hours and the second between 12 and 22 hours. It is to be noted that when was applied the Peppas approximation to each complete profile data,the “n” valuefor each onewasextremely low, in fact much lower than 0.4.

Table 4. Correlation Coefficients (r) for linear relationship of the proposed combined Kinetics of (0-22 h) of TiO_2/DPH and TiO_2/VPA.

Samples	Zero Order	First Order	Higuchi	Hixson Crowell	Korsmeyer-Peppa
	r^2	r^2	r^2	r^2	*“n”*
TiO_2/DPH-50	0.9270	0.9311	0.9278	0.8449	0.15
TiO_2/DPH-100	0.9806	0.9619	0.9409	0.8770	0.22
TiO_2/DPH-250	0.9568	0.9468	0.9060	0.8428	0.13

TiO_2/VPA-200	0.9666	0.9731	0.9065	0.8393	0.30
TiO_2/VPA-400	0.9822	0.9507	0.9320	0.8240	0.38
TiO_2/VPA-800	0.9497	0.9352	0.9197	0.8517	0.30

This data processing did not offer a clear definition of what mechanism is ruling the release process, however, the Peppas empirical equationapplied to each time interval (Table 5) gave the interesting following result:

Table 5. *"n"* obtained values from the experimental data for DPH and VPA.

Samples	***"n" value***	
	(0-10) h	(12-22) h
TiO_2/DPH-50	0.31	0.41
TiO_2/DPH-100	0.40	0.44
TiO_2/DPH-250	0.43	0.42
TiO_2/VPA-200	0.40	0.49
TiO_2/VPA-400	0.44	0.46
TiO_2/VPA-800	0.49	0.43

In both VPAand DPH systems, the whole process is not ruled by only one mechanism as is suggesting by the release profiles. However for the DPH system"n" is approximately constant. The difference between the behaviour of DPH and VPA consists that in the latter the beginning of the process is different to the first one. According to the release profiles the VPA systems seem to turn to a well-defined zero order mechanism and not to a fickeanmechanism.

The very low values of "n" indicate that an extra factor is competing, such as has been observed in hydrogels [44] where the geometry of the device is changing. However, this is not the case for the TiO_2which possesses a well-defined stiff spatial structure. TiO_2 is a porous and hydrophilic material that can be embedded by the water, thus the drug can be taken out by the solvent where controlled diffusion operates at the beginning but later the gradient becomes constant and system tend to zero order. It would be an explanation of experimental facts.

4. CONCLUSIONS

The release mechanism for both drug is not govern by only one mechanism. It was observed an initial fickean mechanism with subsequent deviation of the mechanism, indicating that other extra factor competed with such fickean mechanism. As titania is a porous and hydrophobic material it can absorbed water to extract the drug from the matrix. Peppas model suggests for both cases, the release mechanism is controlled by two parallel processes. The first is by diffusion of the drug through the matrix and the second is related to a gradient of constant diffusion by ingress of the solvent in the matrix. The best drug release profiles were for the TiO_2/DPH-100 (E.E, 66 %) and TiO_2/VPA-200 mg (E.E, 78 %) samples. TiO2/DPH (100 mg) and TiO2/VPA (200 mg) presented the best release profiles, which may have high potentials for in vivo applications.

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