Chemistry International 4(2) (2018) 120-129

International Scientific Organization
http://iscientific.org/
Chemistry International
www.bosaljournals.com/chemint/

Controlled release of amoxicillin from PMMA and poly(butylsuccinate) microspheres

Imene Boukhouya, Hicham Bakouri, Ilham Abdelmalek, Meriem Imene Amrane and Kaddour Guemra*

Laboratory of Organic Physical and Macromolecular Chemistry, Faculty of Exact Sciences,
Djillali Liabes University, Sidi Bel-Abbes, Algeria
*Corresponding author's E. mail: guemra_2@yahoo.fr

A R T I C L E I N F O

Article type:
Research article
Article history:
Received October 2017
Accepted March 2018
April 2018 Issue
Keywords:
Amoxicillin
Microparticles
Biodegradable polymer matrix
Solvent evaporation method
Kinetic study

A B S T R A C T

This work focus on the study and the elaboration of microspheres based on amoxicillin (AMO), those microspheres were prepared through the oil/water emulsion evaporation technique. Polybutylene succinate (PBS) and Poly(methylmethacrylate) (PMMA) polymeric matrix were used with Tween 80 (T80) and Polyvinyl alcohol (PVA) as emulsifiers. These polymeric systems were analyzed by SEM, FTIR and optical microscopy. The conditions of the microspheres forming were varied and the preparation was performed by changing different parameters such as: the nature of the polymer, the stirring speed, organic solvent, surfactant nature, and concentration, which allows the study of their effect on encapsulation efficiency and drug release kinetics. These parameters affect strongly the size of microspheres, the drug content and the drug release, the latter is settled in an artificially reconstituted media of pH = 1.2 transcribed from the stomachal medium.

© 2018 International Scientific Organization: All rights reserved.

Capsule Summary: Poly(butylsuccinate) was synthesized and oxidized in order to calculate its mass in number by the end group assay method; the microspheres prepared are characterized, kinetic study of release of amoxicillin.

Cite This Article As: I. Boukhouya, H. Bakouri, I. Abdelmalek, M. I. Amrane and K. Guemra. Controlled release of amoxicillin from PMMA and poly(Butylsuccinate) microspheres. Chemistry International 4(2) (2018) 120-129.

INTRODUCTION

Generally speaking, microencapsulation is based on trapping fine solid or liquid particles within a membrane. This technology allows the preparation of materials with interesting properties that can be applied in the pharmaceutical industry (Phytane et al., 2010; Wang et al., 2005) and so many other fields (Arshady, 1993; Diaf et al., 2012). One of the particularities of this method is that it permits the preservation of sensitive substances. In pharmacology, it is used to control and modify the drug release (Thombre and Cardinal, 2004). According to research works, scientists are much more attracted to work on the preparation of microspheres with biodegradable and biocompatible polymers origins, particularly for sustained drug delivery of pharmaceuticals (Freiberg et al., 2004). Lately, the interest of their application keeps increasing in the pharmaceutical industry (Singh et al., 1998; Pengd et al., 2007), agriculture (Dosled et al., 1999; Quaglia et al., 2001), and in environmental engineering (Petr et al., 2011). In addition, several reports on the microencapsulation have been developed for example, the microencapsulation of flavors, such as interfacial polycondensation (Kobaslijad and Mcquade, 2006), spray drying (Apintanopong and Noomhorn, 2003; Odziomek et al., 2012), complex

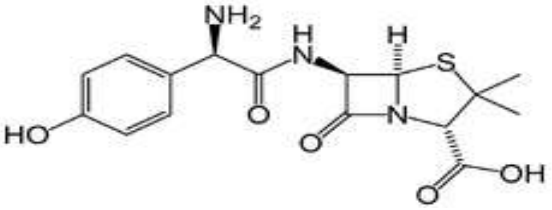
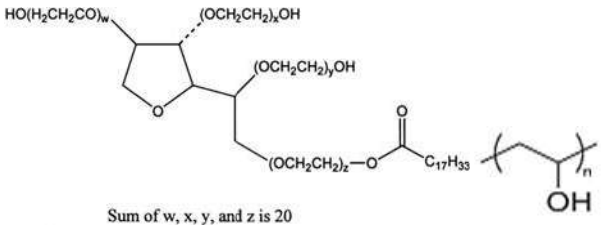


Fig. 1: Chemical structure of amoxicillin (AMO)



Tween 80 PVA

Fig. 2: Structures of emulsifiers

coacervation (Hwaya et al., year, interfacial solvent exchange (Yeo and Park, 2004) and in water/oil emulsion solvent diffusion (Berchane et al., 2007).

Numerous microsphere preparation techniques exists, among them, solvent evaporation method is the most used. In fact, various parameters affect it, for example: solvent evaporation rate, polymer solubility, drugs and excipients in emulsion phase, dispersion stirring rate, viscosity, polymer solubility, drug quantities, physico-chemical properties and concentration of the stabilizers (Abdelmalek et al., 2014).

In this work, amoxicillin microspheres were prepared through the solvent evaporation technique. The PMMA polymer as an important commercial plastic and an odorless, tasteless, and nontoxic polymer, is allowed to be used to sustain drug release from oral delivery system, this step can be realized either by formation of a matrix or an insoluble but permeable film (Shukl and Kiwari, 2012; Song et al., 2012). So many biodegradable polyesters have been applied successfully used as a result of their ease of manufacturing and desirable characteristics. Moreover, PBS as biodegradable polyesters can be prepared by simple polycondensation method from Succinic acid and Butanediol. PBS is a polymer which possesse excellent mechanical properties.

MATERIAL AND METHODS

In the present study amoxicillin is chosen as model drug. AMO (α-amino-p-hydroxybenzyl -penicillin) is a moderate-spectrum β-lactam antibiotics used to treat bacterial infections caused by susceptible microorganisms; it was purchased from Sigma Aldrich. Polyvinyl alcohol (PVA, 87-89% hydrolyzed, M_w = 13000-23000 g.mol^{-1}) from Sigma, Tween 80 (polyethylene glycol sorbitan monooleate was obtained from Sigma-Aldich (USA)). Dichloromethane DCM (Teb=39.6°C, formula CH_2Cl_2. M = 84,93g/mol at purity of >98%); Polyethylene glycol sorbitan monooleate (T80); PMMA, M_w = 350.000 g mol^{-1}) from Aldrich. Chloroform: (T_{eb}=61,2°C, formula $CHCl_3$, M =119, 38 g/mol) From Aldrich.

PBS was synthesized and characterized: (0.12 mole of butanediol in the presence of 0.1 mole of Succinic acid is reacted in a 100 cc two-necked flask equipped with a condenser in presence of 1 to 2% of Titanium isopropoxide. The mixture is then maintained at reflux (180°C) under a stream of nitrogen for two hours with vigorous stirring. In order to remove the residual monomers, the polymer obtained is heated at 200 °C in a 100 cc flask for three hours under high vacuum using a vacuum pump (max = 103 mm Hg).(Chirani et al., 2017).

PBS was oxidized with succinic anhydride in pyridine in order to calculate its mass in number by the end group assay method. The determination of the carboxylic acid functions of PBS is carried out by simple and reproducible acid-base test, 0.1 g of PBS are dissolved in 5 ml of absolute ethanol. The mixture is well stirred and the solution is dosed with 0.05N NaOH prepared with NaOH crystals dissolved in ethanol. The phenolphtaleine determines the equilibrium of the acid-base dosage. Mn=1850 g/mol (Eq. 1).

$$[COOH] = \frac{(V-V0)[NaOH]}{Mn_{PBS}} \quad (1)$$

Microspheres preparation

All microspheres were ready prepared by the emulsion solvent diffusion method, the effect of formulation and processing parameters on microspheres characteristics were investigated by varying active agent/polymer matrix, polymer /solvent, nature and concentration of surfactant and stirring speed. The active agent (AMO) and polymer (PBS or PMMA) were dissolved in 32 g of Dichloromethane DCM (% Poly /solvent=3.75 and 5.62), (%AMO/Poly =30, 50 weight %) and heated under slight reflux (30-35°C) and stirred to get homogenization, at the same time, the emulsifier was dissolved in de-ionized water (0.72% by PVA and 1 mass % by T80) of the emulsifier under stirring and heating. The organic phase was emulsified with the aqueous continuous phase in glass reactor (600ml, ⌀=80mm) under mechanical stirring (400,600 and 800 rpm) for 4h to complete solvent evaporation. The solidified micro-spheres were filtered, washed three times with distilled water and were vacuum-dried in desiccator of $CaCl_2$.

Microspheres characterization

Determination of the encapsulation efficiency

The active agent (AMO) content in microspheres was determined by dissolving 100 mg of microspheres in a sealed bottle containing 10 ml of absolute ethanol under stirring with rotation speed of 250 rpm for 24 h at 25°C. The resulting solution was analyzed by UV-VIS spectroscopy (UV-

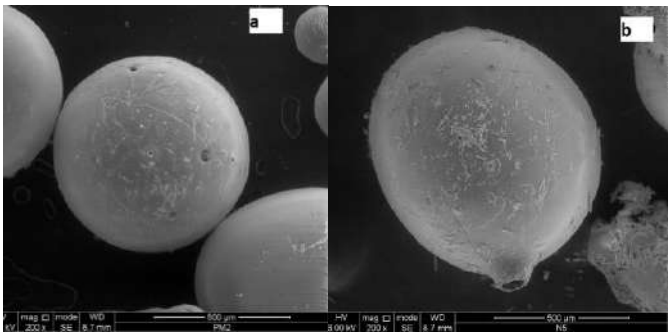


Fig. 3: SEM of spherical microspheres (a: APP1, b: APT1)

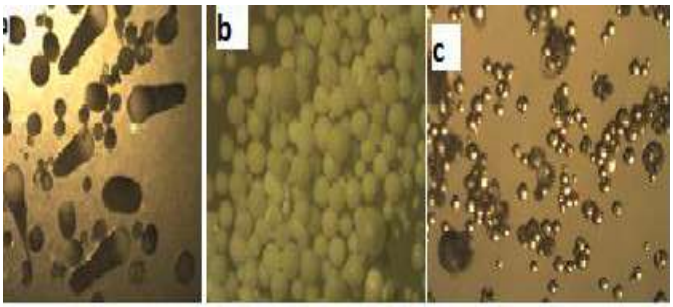


Fig. 4: Microscopic images of amoxicillin loaded PMMA's particles (a: 400 rpm,b: 600 rpm, c: 800 rpm)

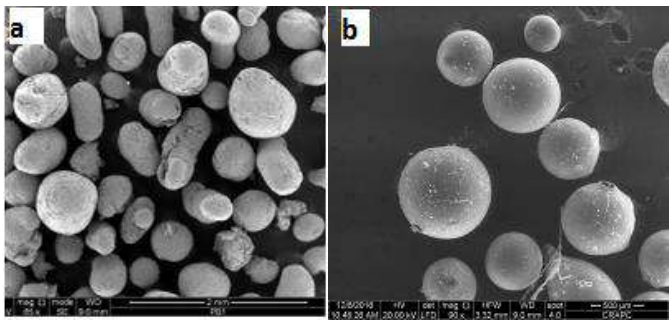


Fig. 5: SEM micrographs of the loaded microspheres

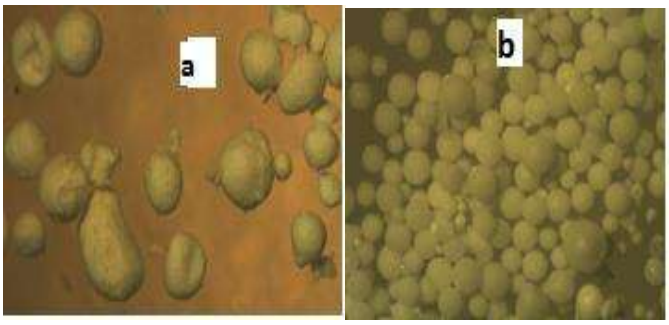


Fig. 6: Microscopic images of: a: ABP, b: APP1

2401 PC, Chimadzu, Japan). The loading efficiency (AMO_{loaded} %) and the encapsulation efficiency (Yield %) were determined after the extraction in an appropriate solvent according to the following equations (Eqs. 2-3):

$$AMO_{loaded}\,(\%) = \frac{\text{mass of AMO extrated}}{\text{mass of microparticules}} * 100 \qquad (2)$$

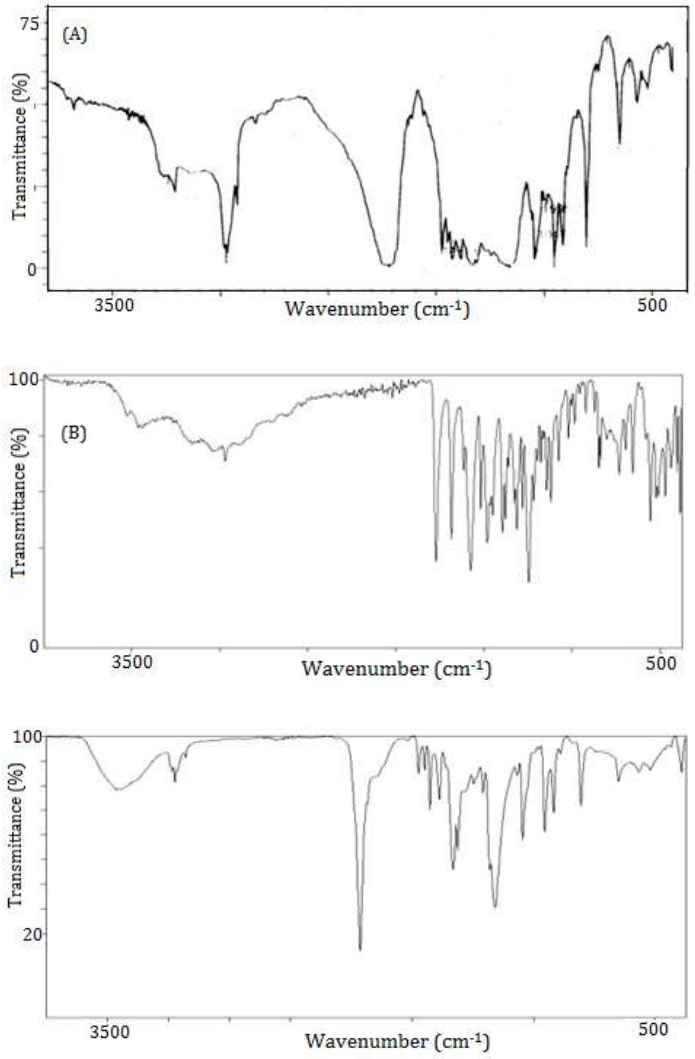


Fig. 7: Infrared spectra of PBS (a), pure amoxicillin (b) and microspheres loaded (ABP) (c)

$$\text{Yield}\,(\%) = \frac{\text{mass of AMO extraced}}{\text{initial mass of AMO}} * 100 \qquad (3)$$

Scanning Electron Microscopy (SEM)

Surface morphology was determined by the method SEM (Jetage & Travedet, 2000). The chap and surface morphology of microparticles were characterized by scanning electron microscopy (SEM) using Quanta 200 (FEI, France) at Bordeaux Center Imaging, Bordeaux-1 university at 50 Pas under 12 KV of accelerated voltage and Society with Action Center of Research Scientific and Technique in Analysis and Expertise Physico-Chemical S.P.A.C.E.A.P. C.Bou-Ismail TIPAZA Algeria. Microparticles were deposited on double-scotched carbon film fixed on a stub with low vacuum 60 Pascal (15 and 20 KV).

Particle Size

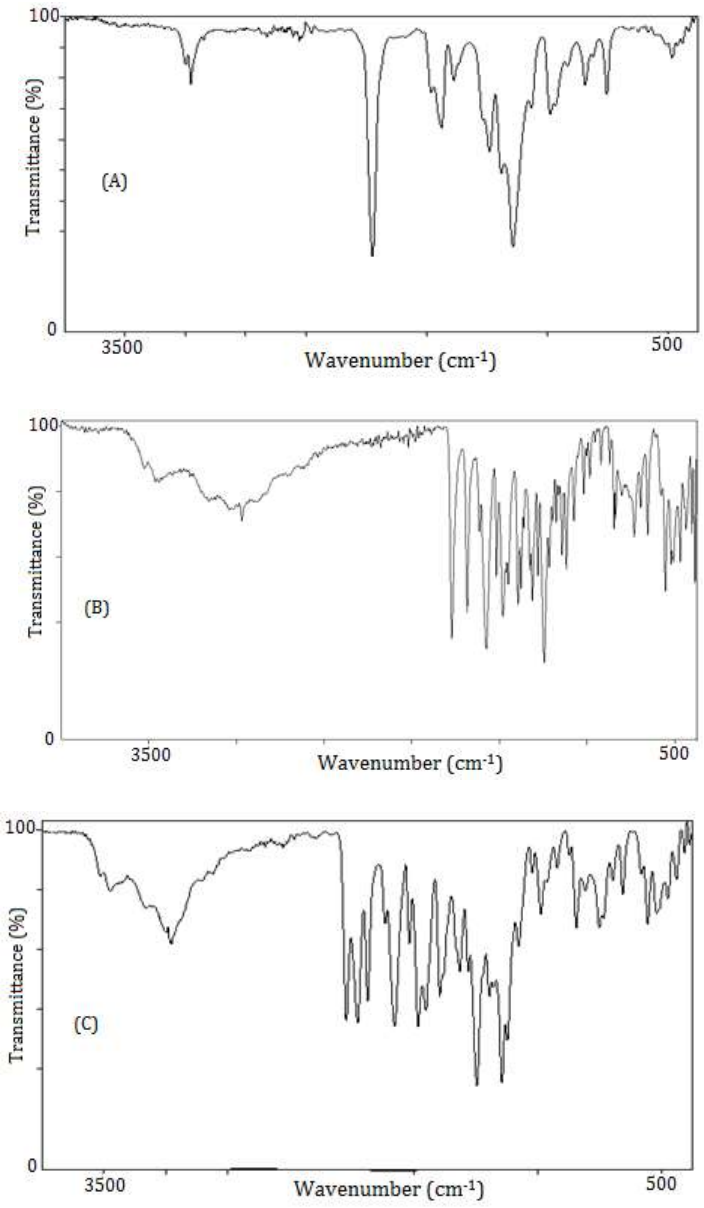


Fig. 8: Infrared spectra of PMMA (a), pure amoxicillin (b)

In this part, an optical microscopy (OPTIKA 4083.B1) was used to define the mean particle size and size distribution of the active agent microspheres. Furthermore, the analysis of 500 of the microspheres was performed for all the steps of the preparation, their mean diameters were determined subsequently. The obtained microspheres were determined in triplate. Several mathematic formula (Kczmarski and Bellot, 2003; Chirani et al., 2017) were used to calculate different characteristic parameters such as: the mean diameters (d_{10}, d_{32} and d_{43}), size distribution, d_{10} number mean diameter, d_{32} the diameter of sauter, (the volume-surface mean), d_{43} the weight mean diameter (the volume mean diameters) (Eq. 4-6).

$$d_{10} = \sum_i n_i d_i / \sum_i d_i \quad (4)$$

$$d_{32} = \sum_i n_i d_i^3 / \sum n_i d_i \quad (5)$$

$$d_{43} = \sum_i n_i d_i^4 / \sum_i n_i d_i^3 \quad (6)$$

Dispersion was calculated as ratio $\delta = d_{43}/d_{10}$, which δ represent an index of the population δ (Eq. 7).

$$\delta = d_{43}/d_{10} \quad (7)$$

In vitro drug release studies

In order to prohibit the passage of the microparticles while the ascent of the solution, an in vitro drug release study was performed, thus, a cylindrical double-wall glass reactor armed with fritted glass via an immersed extremity in solution was used. Study of the microspheres in solution was followed next by kinetic releases of actives agent from microparticles. The latters were studied by a UV-Visible spectrometer type 2401.PC Schmadzu, equipped with a compartment thermostat at the range of 37±0.3°C.

First, (100 mg) of microparticles were taken and soaked in an acidic media (pH=1.2) in 100mL of buffer solution, the solution was then stirred magnetically at a rotation speed of 500 rpm. Next, 1mL of the resulting acid solution was used to perform the dosage of released active agent. The calibration of the UV apparatus was realized before each analysis at the maximum wavelength of active agent (Deshmukh et al., 2013).

RESULTS AND DISCUSSION

Microspheres characterization

Table.3 resumes the principal character-ristics of the obtained microparticles, the mean diameter, the percentage of active agent loaded microparticles and the encapsulation yield obtained by extractions are all demonstrated. Results in table.3 confirms the dependence of the loadings efficiency and yields on the nature of polymer, the emulsifier, and the parameter of organic phase and stirring speed, solvent used in the formulation.

The obtained values of the yield and the drug loaded proves that the best formulation corresponds to APP4 (the best drug loads and the best yield); also the dispersion δ doesn't overrun 1.66.

The morphology of the prepared surfactants PVA and T80 are different (Fig. 5.a), PVA microspheres appears spherical homogeneous and smaller than T80 ones, which has a rough and porous surface (Fig. 5.b). The fact that the surface of the particles obtained with the T80 is much rougher with larger pores in the surface is explained by the variation in the emulsifier's chemical structures. The average diameter of the skip (d_{32}) of PBS microspheres is 62.45µm with PVA and 151.39µm with T80. The average diameter of the skip (d_{32}) of PMMA is in the range of 54.03-128.13µm with PVA and the range of 131.11-287.8µm with T80 and PVA, gives a high loaded than T80 (Li et al., 2008).

The diversity in the mixing speed should improve the level of encapsulated dynamic material, the same diameters are not necessary for the microspheres arranged under these same working states APT1, APT2, APT3 (poly:

PMMA, emulsifier: T80, a% = 50, B% = 3.75 and C% = 1). The characteristics of the microspheres is in fact influenced by the expansion of the mixing stirring speed from 400 rpm to 600 rpm and 800 rpm, the mean diameter of Sauter being mined by 287.8 µm at 171.05 µm and 147.69 µm, and the dispersion (δ) progresses from 1.30 to 1.17 and should 1.14, the emulsion will be increased, their provided vitality of the framework can be increased, thus, we observe that the global surface of the droplet increase, which is to be studied in our results of the inertial rupture hypothesis for isotropic turbulence (Hinze et al., 1995), it is clear as in Table 3, that the speed of agitation increases results in decreasing mean diameters of microspheres.

In the obtained results, it is demonstrated clearly that the nature of the polymer affect the efficiency of the encapsulation and the characteristics of the microspheres. PMMA microspheres (Fig. 5-b, 6-b) are smaller in size (d_{32}) ranging from (54.03-128.13) µm with PVA and (131.11-287.8) µm with T80 and with a less porous surface. The active agent content is between 14.31% and 37.94% and seems to be the best. (Fig. 5-a) confirms that there are no spherical system matrices with porous and rough surface and in the size (d_{32}) between 62.45 and 151.39 µm with PBS (Fig.5a, 6a). The percentage of AMO encap-sulated in theses samples is ranged between 12.08% with T80 and 17.65% with PVA. The obtained results are explained by the affinity between the molecules of the drug and PMMA, which may result in a more colocalization in PMMA than in PBS, thereafter, the water will penetrate less into droplets of PMMA and thus the transfer of the active ingredient to the continuous phase during the emulsion is also low compared to the large pore of PBS (Fig. 6a).

The interaction between the polymer matrix and the drug-enveloped molecules may be explain that, in which, the polarity and the size of the microspheres play an important role. It is known that the % of polymer is increased by the size of the microspheres. However, in our results, the size of the microspheres (d_{32}) increases, when the rate of the organic phase (B%) increases, also, with a percentage of B% = 2.81, small microspheres of diameter d_{32} = 78.25 µm are obtained, and for B% = 5.62, d_{32} = 128.13 µm are even obtained (Table 2). These obtained results justify the work of Hwissa (Hwissa et al., 2013, Yang et al., 2000), also the size of the microparticles are decreased with d_{32} = 54.03 µm for B% = 11.21.

A better content of microspheres of active substance prepared with DCM (amoxicillic charge = 36.25%) is demonstrated, with small sizes of the corresponding microspheres (d32 = 147.69 µm). However, large sizes of corresponding microspheres (d32 = 171.05 µm) were obtained with chloroform (amoxicillic charge = 17.22%). In this work, the important role of the solvent is well clear, the latter influence in the diffusion phenomena of the active ingredient during its evaporation. In addition, DCM permit a rapid solidification of micro-droplets and trapping of the active ingredient, for the simple reason that it evaporates faster that chloroform.

In the characterization part, infrared spectroscopy was used to compare the spectrums of microspheres with active agent (AMO) and polymer matrix (PMMA, PBS) (fig.07, 08). Therefore, the effective presence of similar characteristics bands microspheres is demonstrated.

FT-IR spectrum ν (cm^{-1}): PMMA: 990-1200 is the characteristic band of group ester C-O-C, terminal CH_3, CH_2: 2929, O-C=O: 1720.

PBS: ester C=O: (1716-1732); CH_2- (2945-2956); ester C-O-C: (1100- 1200); terminal O-H (3429-3552).

We identified the IR bands of AMO in microparticles at the same wavelength: 1370 cm^{-1} for the N-C aromatic band, 1730 cm^{-1} and 2950 cm^{-1} for C=O and 2090 cm^{-1} of O-H carboxylic acid vibration, bending of S-C at 3500 cm^{-1} of amine function and 3400 cm^{-1} vibration of alcohol functions.

Drug release from microparticles

It is well known that the microspheres prepared by simple emulsion evaporation, exhibit an initial release by bursting effect due to a substance encapsulated on the surface. In vitro release of $AMOH^+$ (three different pK values presents in Amoxicillin: 2.4 (carboxyl), 7.4 (amine) and 9.6 (phenol) (Basic et al., 2007; Abdelmalek et al., 2014) from the formulations was compared at pH = 1.2 simulating stomach medium, the results obtained from dissolution studies of drug are shown in fig.09, 10, 11, 12 and 13.

The microspheres manufactured by PMMA (128,13 µm) contain more active agent, but its release is the weakest and the slowest, these results can be interpreted by the polymeric structure of the microspheres, effectively the SEM photos of the PMMA microspheres have a smooth, pore-free surface as opposed to the porous PBS microspheres which are more porous. The mobility of the active agent is naturally easier in the porous systems. The cumulative release is more speed from the smaller microspheres prepared with PBS' (62.45µm).

The results show that in the gastric medium the active agent is released more rapidly from the Chloroform microspheres. Although, the size of these microspheres is larger than the size of the DCM microspheres, this result can be related to the internal structure of the microparticles made with chloroform and which may contain open cavities and pores allowing faster release.

Increasing the amount of polymer from 2.81 to 11.21 decreases the rate of release of the active agent due to the lower porosity of the microsphere surface. The release of the active agent is inversely proportional to the size of microspheres (Gabor et al., 2015). It has been reported that for smaller microspheres, a larger effective surface produces a larger number of drug molecules in the surface of the microspheres, which leads to a faster release of the drug (Abdelmalek et al., 2014).

It was reported that for the smaller microspheres, a larger effective area produces a greater number of drug molecules in the surface of the microspheres, which leading

Table 1: Formulation processing condition of microspheres

Code	Polymerr matrix	Emulsifier	Parameter of organic phase A (%)	Parameter of organic phase B (%)	Parameter of aqueous phase C (%)	Speed (rpm)	Solvent
ABP	PBS	PVA	31	5.62	0.72	600	DCM
ABT	PBS	T80	50	3.75	1	600	DCM
APP1	PMMA	PVA	31	5.62	0.72	600	DCM
APP2	PMMA	PVA	62	5.62	0.72	600	DCM
APP3	PMMA	PVA	31	2.81	0.72	600	DCM
APP4	PMMA	PVA	31	11.21	0.72	600	DCM
APT1	PMMA	T80	50	3.75	1	600	DCM
APT2	PMMA	T80	50	3.75	1	400	DCM
APT3	PMMA	T80	50	3.75	1	800	DCM
APT4	PMMA	T80	50	3.75	1	600	$CHCl_3$

A%= $\frac{active\ agent}{polymer}$, B%= $\frac{polymer}{DCM}$, C%= $\frac{\text{emulsifier}}{water}$, A%, B% and C% are massic compositions.

Table 2: Formulation processing condition of microspheres

Code	AMO_{loade} %	Yield %	d_{10} (µm)	d_{32} (µm)	d_{43} (µm)	Dispersion (δ)
ABP	17.65	33.33	64.12	62.45	94.81	1.48
ABT	12.08	24.11	131.7	151.39	180.12	1.36
APP1	14.31	59.51	99.95	128.13	143.31	1.43
APP2	32.55	82.92	59.63	64.25	91.74	1.54
APP3	15.87	77.42	53.66	78.95	88.9	1.66
APP4	27.94	87.05	47.57	54.03	59.9	1.26
APT1	36.25	57.22	133.67	147.69	156.79	1.17
APT2	27.7	42.34	230.58	287.8	301.6	1.30
APT3	27.37	51.81	118.9	131.11	135.53	1.14
APT4	17.22	26.66	157.89	171.05	188.01	1.19

Table 3: The evolution of d_{32} with the speed of agitation

Speed (rpm)	400	600	800
d_{32} (µm)	287.8	171.05	131.11

Table 4: Results of data analysis of drug release kinetics (Correlation coefficient, n he release exponent of Korsmeyer-Peppas (r2) and constant (K)

Code	Hixon - Crowell		Higuchi		Korsmeyer-Peppas			Best fit mode
	K	R^2	K	R^2	K	n	R^2	
APT4	0.0021	0.9034	1.5312	0,9745	0.0021	0.29	0.9544	Higuchi
ABP	0.0049	0.8606	2.9815	0.0.9956	0.0.0195	0.0.52	0.9915	Higuchi
APT1	0.0070	0.9537	1.1925	0.0.9612	0.0.0033	0,0.82	0.974	Korsmeyer-Peppas
APT2	0.0012	0.9850	0.5668	0,0.9834	0.0.0009	0,0.67	0.9718	Hixon-Crowell
APT3	0.0006	0.6600	1.9237	0,0.9726	0.0.021	0.0.29	0.9544	Higuchi
APP1	0.0014	0.9395	2.0582	0,0.9805	0.0.077	0,0.83	0.9845	Korsmeyer-Peppas
APP3	0.0014	0.8623	3.8781	0,0.9846	0.0.174	0,0.74	0.9798	Higuchi
APP4	0.0011	0.9210	1.1800	0,0.9328	0.0.056	00.955	0.9884	Korsmeyer Peppas

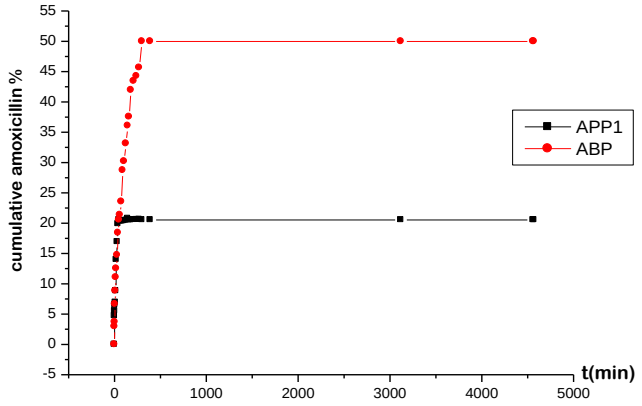


Fig. 9: Release profiles of amoxicillin from microspheres (APP1 and ABP1) (PMMA, PBS) (with DCM, emulsifier: PVA, speed stirring = 600 rpm, A%=31, B%=5.62, C%=0.72, 6bladed).

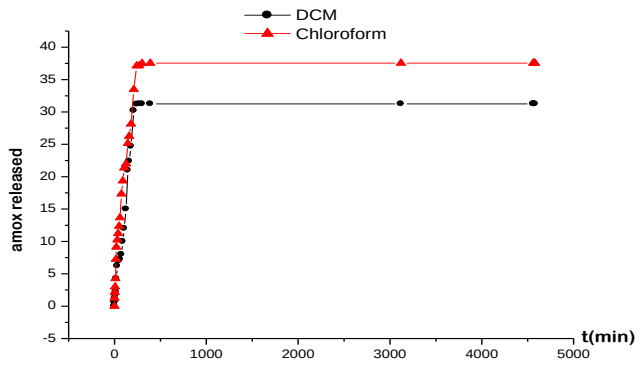


Fig. 10: Release profiles of amoxicillin from microspheres (APT1, APT4) DCM, chloroform, (with, speed stirring 600 rpm, emulsifier: T80, A%=50.0, B%=5.62, C%=0.50, 6 bladed).

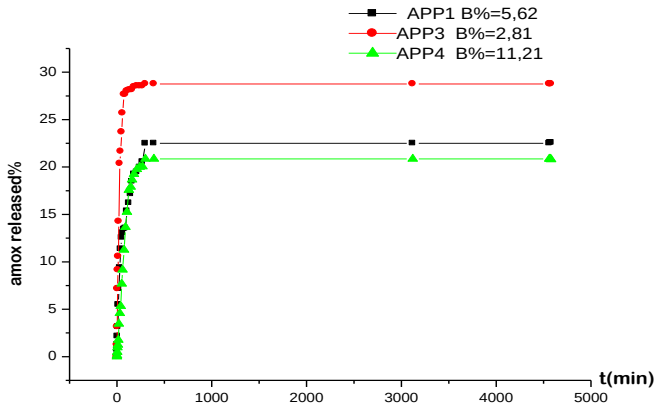


Fig. 11: Release profiles of amoxicillin from microspheres (APP1, APP3, APP4) (B%= 5.62, 2.81, 11.21) (with DCM, emulsifier: PVA, speed stirring = 600 rpm, A%=31, C%=0.72, 6 bladed).

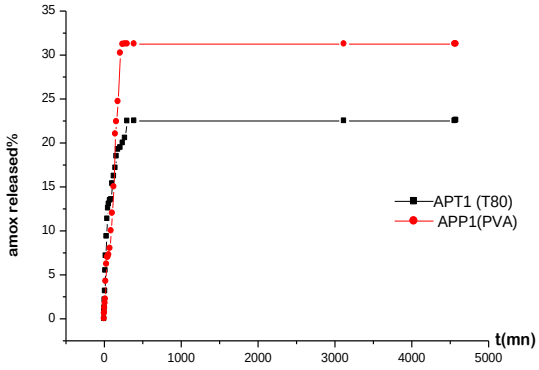


Fig. 12: Release profiles of amoxicillin from microspheres (APP1, APT1): PVA, T80 (with 600 rpm, DCM, 6bladed).

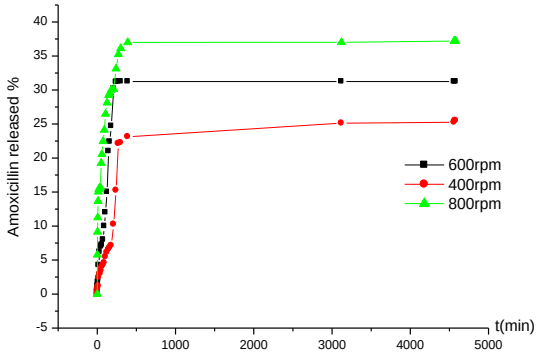


Fig. 13: Release profiles of amoxicillin from microspheres (APT1, APT2, APT3) speed stirring = 600, 400, 800 rpm (with DCM, emulsifier: T80, B%=5.62, A%=50, C%=0.5, 6bladed).

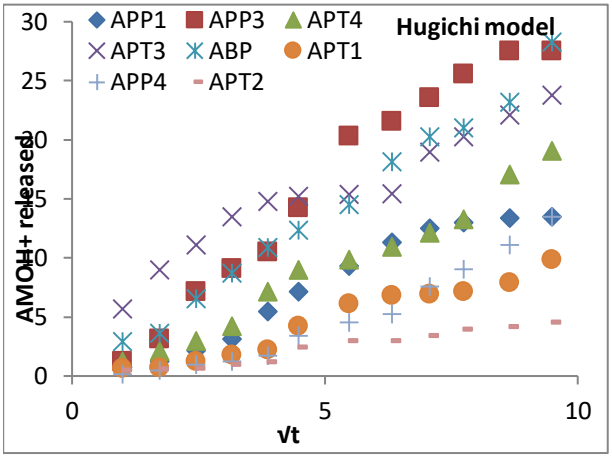


Fig. 14: Higuchi plots of AMO release **%** from microspheres

to a faster drug release (Deshmukh et al., 2013). However, it was reported that for the smaller microspheres, a larger effective area produces a greater number of drug molecules

in the surface of the microspheres (Yunpeng et al., 2013; Zang et al., 2013).

Mathematical analysis

In this part, in order to determine the AMO release mechanism from the elaborated systems, mathematical models were tested; the results are represented graphically and summarized in values in Table 4. The models tested for established kinetics are respectively: Hixon-crowel model and the two mathematical models most used by pharmacists to describe the release of the active principles of matrix systems: Higuchi and Korsmeyer-Peppas model (Tahara et al.1995).

Hixon-Crowell: $M_t^{1/3} = k_S.t + M_r$ (8)

Higuchi: $M_t = k_H.t^{1/2}$ (9)

Korsmeyer-Peppas : $\frac{M_t}{M_\infty} = K_{KP} t^n$ (10)

Where, M_t is the mass of drug dissolved in time t; K_H, K_S and K_{KP} are, respectively the Higuchi's, the Hixson–Crowell's and Korsmeyer-Pepppas's release constants; and *n* the release exponent that indicates of the mechanism of release (Korsmeyer and Peppas, 1983; Higuchi, 1963).

n ≤ 0.5 corresponds to a Fickien diffusion mechanism,

0.5 <n <1non-Fickien material transport,

n = 1: Transport II (Relaxation) case,

n> 1: Super-II Transport Case II

The Hixson–Crowell model assumes that the drug release is limited by the dissolution rate of the particles, and not by diffusion through the polymer matrix (Hixon et al.1931; Chirani et al.2017). We have noted that the value of the Higuchi release constant (kH) varies from 0.12 nm / 2 to 8.15 nm / 2; the results presented in Table 4 and on the basis of the correlation coefficient (r2), the Higuchi model seems to be the model for APT4, ABP, APT3 and APP3 formulations with r2 greater than 0.97; The results showed that the AMO release mechanism is regulated by Fickien diffusion in these microparticles by the fact that the exponent n <0.5.

However, the model that represents more drug diffusivity in matrices system APT1, APP4 and APP1 systems is the Korsmeyer-Peppas model (r2 = 0.97) and since in system trios n> 0.5 the diffusion is abnormal and may include both diffusion and erosion phenomena due to polymer dissolution. For the APT2 microspheres, it seems that the most representative model of the AMO release mechanism in this case is Hixon-Crowel model (R2 = 0.98) assumes that the drug release is limited by the dissolution rate of the particles.

CONCLUSIONS

Microencap-sulation of amoxicillin was performed using two different matrixes: Synthesized PBS and PMMA, the process was realized via the oil/water emulsion evaporation technique. The obtained results in this study confirms the effect of the physico-chemical parameters (polymer nature and concentration, stirring speed (400, 600, 800 rpm), organic solvent (DCM, $ClCH_3$), surfactant nature (T80, PVA) plays an important role on the elaborated micro- particles and their characteristics, including their quality, size, shape, and their morphology, the drug loaded and on the drug delivery of the active encapsulated agent in the stomach medium. The microspheres were analyzed via Scanning Electron Microscopy (SEM), perfectly spherical microspheres of PMMA were obtained with smooth and porous surfaces, while slightly spherical shapes with rough and porous surface were resulted from PBS, also large ranges of size has been obtained (the mean diameter d_{32} of Sauter for formulation of PMMA in the range of 54.03 to 128 µm with PVA and 131.11 to 287.8 µm with Tween 80, PBS's microparticles in the range 62.45 µm with PVA and 151.39µm with T80). According the release kinetic studies APT1, , APP1, APP4 and APP3 confirms the following of the diffusion as the principal mechanism for drug release. However, APT2 present the Hixon-Crowell release model while ABP, APT4 and APT3 followed Higuchi matrix model.

REFERENCES

Abdelmalek, I., Svahn, I., Mesli, S., Simonneaux, G., Mesli, A., 2014. Formu- lation, evaluation and microbiolo-gical activity of ampicillin and amoxicillin microspheres, Journal of Materials and Environmental Science 5(6), 1799-1807.

Apintanapong, M., Noomhorn, A., 2003. The use of spray drying to microen-capsulate 2- acetyl-1-pyrroline, a major flavour component of aromatic rice. International Journal of Food Science and Technology 38, 95-102.

Arshady, R., 1993. Microencapsules for food. Journal of Microencapsulation 10(4), 413-435.

Babič, S., Horvat, A.J.M., Pavlović, D.M., Kaštelan-Macan, M., 2007. Determination of pKa values of active pharmaceutical ingredients. Trends in Analytical Chemistry 26(11), 1043–1061 .

Berchane, N.S., Carson, K.H., Rice-Ficht, A.C., Andrews, M.J., 2007. Effect of mean diameter and polydispersity of PLG microspheres on drug release: Experiment and theory. International Journal of Pharmaceutics 337, (1-2), 118–126.

Chirani, S., lebig, M.O., Bouameur, S., Mouffok, M., chirani, N., Chafi, N., Guemra, K., 2017. Elaboration of Microspheres' Capsules Based on Ethylcellulose and Synthesized Poly (Butylsuccinate) as Biodegradable Matrices for Drug Delivery of an Antithyroidian Agent. Indian journal of Pharmaceutical Education and Research 5, 1-12.

Deshmukh, V., Warad, SH., Solunke, R., lWalunj, SH., Palve, SH., Jagdale, G., 2013. microspheres: as new drug delivery sysytemworld. Journal of Pharmacy and Pharmaceutical Sciences 2, 2278–4357.

Diaf, K., El Bahri, Z., Chafi, N., Belarbi, L., and Mesli, A., 2012. Ethylcellulose, polycaprolactone, and Eudragit matrices

for controlled release of piroxicam from tablets and microspheres. Chemical Papers 66, 779–786.

Dosled, C.C., Dailey, O.D. Jr., Mullinix B.G. Jr., 1999. Polymeric Microcapsules of Alachlorand Metolachlor: Preparation and Evaluation of Controlled-Release Properties. Journal of Agricultural and Food Chemistry 47, 2908-2913.

Freiberg, S., Zhu, X.X., 2004. Polymer microspheres for controlled drug release. International Journal of Pharmaceutics 282(1), 118, doi:10.1016 04.013.

Gabor, F., Ertl, B., Wirth, M., Mallinger, R., 1999. Ketoprofen-poly(D,L-lactic-co-gly-colic acid) microspheres influence of manufacturing parameters and type of polymer on the release characteristics Journal of Microencapsulation 16 1, DOI: 10.1080/026520499289266

Higuchi, T., 1963. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences 52, 1145–1149. DOI: 10.1002/ jps.2600521210.

Hinze J. O., 1955. Fundamentals of the hydrodynamic mechanism of splitting in dispersion processes. J AIChE Journal 1(3), 289-295.

Hixson, A.W., Crowell, J.H., 1931. Dependence of reaction velocity upon surface and agitation. Industrial And Engineering Chemistry 23(10), 923-31.

Hwang, D.S., Waite, J.H., Tirrell, M., 2010. Promotion of osteoblast proliferation on complex coacervation-based hyaluronic acid recombinant mussel adhesive protein coatings on Titanium. Biomaterials 31, 1080–1084.

Hwisa, N.T., Katakam, P., Chandu, B.R., Adiki, S.K., 2013. Solvent evaporation techniques as promising advancement in microencapsulation. Biolological Medicinal Chemistry 1, 8–22.

Jégat, C., Taverdet, T.L., 2000. Stirring speed influence study on the microencapsulation process and on the drug release from microcapsules. Polymer Bulletin 44, 345.

Kaczmarski, K., Bellot, J.Ch., 2003. Effect of particle-size distribution and particle porosity changes on mass transfer kinetics. Acta Chromatographica 13, 22-37.

Kobašlija, M., McQuade, D.T., 2006. Polyurea microcapsules from oil-in-oil emulsions via interfacial polymerization. Macromolecules 39(19), 6371-6375.

Korsmeyer, R.W., Peppas, N.A., 1983. Macromolecularand modeling aspects of swelling-controlled systems. In T.J. Roseman and S. Z. Mansdorf (Eds.), Controlled release delivery systems, New York, NY, USA: MarcelDekker, Pp 77–90.

Li, M., Rouaud, O., Poncelet, D., 2008. Microencapsulation by solvent evaporation: state of the art for process engineering approaches. International Journal of Pharmaceutics 363, 26-39.

Mehta, R.C., Thanoo, B.C., DeLuca. P.P., 1996. Peptide containing microspheres from low molecular weight and hydrophilic poly (d, l-lactide-co-glycolide). Journal of Controlled Release 41, 249.

Odziomek, M., Sosnowski, T.R., Gradoń L., 2012. Conception, preparation and properties of functional carrier particles for pulmonary drug delivery. International Journal of Pharmaceutics 433, 51–59.

Peng, D., Huang, K., Liu, Y., Liu S., 2007. Preparation of novel polymeric microspheres for controlled release of finasteride. International Journal of Pharmaceutics 342, 82–86.

Petr, S., Marek, K., Vladimir, S., Kucharczyk, P., 2011. Factors influencing encapsulation efficiency of biologically active compound into PLA submicroparticles, Proceedings of the 2nd international conference on Mathematical Models for Engineering Science, and proceedings of the 2nd international conference on Development, Energy, Environment, Economics, and proceedings of the 2nd international conference on Communication and Management in Technological Innovation and Academic Globalization. World Scientific and Engineering Academy and Society (WSEAS), pp. 170-174.

Phutane, P., Shidhaye, S., Lotlikar, V., Ghule, A., Sutar, S., Kadam, V., 2010. In vitro evaluation of novel sustained release microspheres of glipizide prepared by the emulsion solvent diffusion-evaporation method. Journal of Pharma 2(1), 35-41.

Quaglia, F., Barbato, F., De Rosa, G., Granata, E., Miro, A., La Rotonda, M.I., 2001. Reduction of the environmental impact of pesticides: waxymicrospheres encapsu lating the insecticide carbaryl. Journal of Agricultural and Food Chemistry 49,(10), 4808-4012.

Shukla, R.K., Tiwari, A., 2012. Applications and recent advances in delivering drugs to the colon. Carbohydrate polymers 88, 399–416.

Singh, M., O'Hagan, D., 1998. The preparation and characterization of polymeric antigen delivery systems for oral administration. Advanced Drug Delivery Reviews 34, 285-304.

Song, X., Chen, F., Liu, F., 2012. Preparation and characterization of alkyl ketene dimer (AKD) modified cellulose composite membrane. Carbohydrate Polymers 88(2), 417-421.

Tahara, K., Yamamoto, K., Nishihata, T., 1995. Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. Journal of Control Release 35, 59-66.

Thombre, A.G., Cardinal, J., 2004. in: Swarbick J, Boylan J C (eds). Marcel Dekker, Encyclopedia of pharmaceutical technology, New York. 1990, 61-88.

Urbán-Morlán, Z., Mendoza-Elvira, S.E., Hernández-Cerón, R.S., Alcalá-Alcalá, S., Ramírez-Mendoza, H., Ciprián-Carrasco, A., Piñón-Segundo, E., Quintanar-Guerrero, D., 2015. Preparation of ethyl cellulose nanoparticles by solvent-displacement using the conventional method and a recirculation system. Journal of the Mexican Chemical Society 59, 173-180.

Wang, S.H., Zhang, L.C., Lin, F., Sa, X.Y., Zuo, J.B., Shao, Q.X., 2005. Controlled release of levonorgestrel from biodegradable poly (D, L- lactide-co-glycolide) microspheres: in vitro and In vivo studie. International Journal of Pharmaceutics 301(1), 217-225.

Yang, C.Y., Tsay, S.Y., Tsiang, R.C., 2000. An enhanced process for encapsulating aspirin in ethyl cellulose microcapsules by solvent evaporation in an o/w emulsion. Journal of Microencapsulation 17, 269-277.

Yeo, Y., Park, K., 2004. A new microen-capsulation method using an ultrasonic atomizer based on interfacial solvent exchange,Journal of Controlled Release 100, 379-388.

Yunpeng, C., Yinghui, C., Xiaoyun, H., Zhenguo, L., Weien, Y., 2013. Porous microsphere and its applications. Internatinal Journalof Nanomedicine 8, 1111-1120.

Zang, Z., Sun, A., Long, L., 2013. Effect of physicochemical properties of drugs on morphology and release of microspheres. Journal of Medical and Biological Engineering 3(4), 293-308.

Visit us at: http://bosaljournals.com/chemint/
Submissions are accepted at: editorci@bosaljournals.com