Section 1: 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...
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, Mw = 13000-23000 g.mol⁻¹) from Sigma, PBS w (Mn=1850 g/mol) from Aldrich. Chloroform: (Teb=61.2°C, formula CHCl₃, M =119, 38 g/mol) From Aldrich.

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 is 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 phenolphthaleine determines the equilibrium of the acid-base dosage. Mn=1850 g/mol (Eq. 1).

\[
[\text{COOH}] = \frac{(V-V_0)\text{[NaOH]}}{M_{n\text{PBS}}} 
\]

\[(1)\]

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, ø=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 CaCl₂.

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-

Tween 80 (polyethylene glycol sorbitan monoooleate was obtained from Sigma-Aldich (USA)). Dichloromethane DCM (Teb=39.6°C, formula CH₂Cl₂, M = 84,93g/mol at purity of >98%); Polyethylene glycol sorbitan monooleate (T80); PMMA, Mw = 350,000 g mol⁻¹ from Aldrich. Chloroform: (Teb=61.2°C, formula CHCl₃, M =119, 38 g/mol) From Aldrich.
The loading efficiency (AMO\textsubscript{loaded} %) and the encapsulation efficiency (Yield %) were determined after the extraction in an appropriate solvent according to the following equations (Eqs. 2-3):

\[
\text{AMO}_{\text{loaded}} (\%) = \frac{\text{mass of AMO extracted}}{\text{mass of microparticles}} \times 100 \quad (2)
\]

\[
\text{Yield} (\%) = \frac{\text{mass of AMO extracted}}{\text{initial mass of AMO}} \times 100 \quad (3)
\]

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.Boulsmail 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

2401 PC, Chimadzu, Japan). The loading efficiency (AMO\textsubscript{loaded} %) and the encapsulation efficiency (Yield %) were determined after the extraction in an appropriate solvent according to the following equations (Eqs. 2-3):
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 triplicate. Several mathematical 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).
\[
d_{10} = \frac{\sum n_i d_i}{\sum n_i}
\]
\[
d_{32} = \frac{\sum n_i d_i^3}{\sum n_i d_i}
\]
\[
d_{43} = \frac{\sum n_i d_i^4}{\sum n_i d_i^3}
\]
Dispersion was calculated as ratio \( \delta = \frac{d_{43}}{d_{10}} \), which \( \delta \) represent an index of the population \( \delta \) (Eq. 7).
\[
\delta = \frac{d_{43}}{d_{10}}
\]

**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 active agent from microparticles. The latter 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 characteristics 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 \( \delta \) 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:

![Infrared spectra of PMMA (a), pure amoxicillin (b)](image-url)
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 size 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 (d32) 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 is 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 (d32) between 62.45 and 151.39 μm with PBS (Fig. 5a, 6a). The percentage of AMO encapsulated 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 (d32) increases, when the rate of the organic phase (B%) increases, also, with a percentage of 8% = 2.81, small microspheres of diameter d32 = 78.25 μm are obtained, and for B% = 5.62, d32 = 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 microspheres are decreased with d32 = 54.03 μm for B% = 11.21.

A better content of microspheres of active substance prepared with DCM (amoxicicilic 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 (amoxicicilic 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 CH₂, CH₃: 2929, O-C=O: 1720.

PBS: ester C=O: (1716-1732); CH₂- (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 Amoxicilin: 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

<table>
<thead>
<tr>
<th>Code</th>
<th>Polymer matrix</th>
<th>Emulsifier</th>
<th>Parameter of organic phase A (%)</th>
<th>Parameter of organic phase B (%)</th>
<th>Parameter of aqueous phase C (%)</th>
<th>Speed (rpm)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABP</td>
<td>PBS</td>
<td>PVA</td>
<td>31</td>
<td>5.62</td>
<td>0.72</td>
<td>600</td>
<td>DCM</td>
</tr>
<tr>
<td>ABT</td>
<td>PBS</td>
<td>T80</td>
<td>50</td>
<td>3.75</td>
<td>1</td>
<td>600</td>
<td>DCM</td>
</tr>
<tr>
<td>APP1</td>
<td>PMMA</td>
<td>PVA</td>
<td>31</td>
<td>5.62</td>
<td>0.72</td>
<td>600</td>
<td>DCM</td>
</tr>
<tr>
<td>APP2</td>
<td>PMMA</td>
<td>PVA</td>
<td>62</td>
<td>5.62</td>
<td>0.72</td>
<td>600</td>
<td>DCM</td>
</tr>
<tr>
<td>APP3</td>
<td>PMMA</td>
<td>PVA</td>
<td>31</td>
<td>2.81</td>
<td>0.72</td>
<td>600</td>
<td>DCM</td>
</tr>
<tr>
<td>APP4</td>
<td>PMMA</td>
<td>PVA</td>
<td>31</td>
<td>11.21</td>
<td>0.72</td>
<td>600</td>
<td>DCM</td>
</tr>
<tr>
<td>APT1</td>
<td>PMMA</td>
<td>T80</td>
<td>50</td>
<td>3.75</td>
<td>1</td>
<td>600</td>
<td>DCM</td>
</tr>
<tr>
<td>APT2</td>
<td>PMMA</td>
<td>T80</td>
<td>50</td>
<td>3.75</td>
<td>1</td>
<td>400</td>
<td>DCM</td>
</tr>
<tr>
<td>APT3</td>
<td>PMMA</td>
<td>T80</td>
<td>50</td>
<td>3.75</td>
<td>1</td>
<td>800</td>
<td>DCM</td>
</tr>
<tr>
<td>APT4</td>
<td>PMMA</td>
<td>T80</td>
<td>50</td>
<td>3.75</td>
<td>1</td>
<td>600</td>
<td>CHCl3</td>
</tr>
</tbody>
</table>

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

Table 2: Formulation processing condition of microspheres

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

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

<table>
<thead>
<tr>
<th>Speed (rpm)</th>
<th>(d_{32}) (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>287.8</td>
</tr>
<tr>
<td>600</td>
<td>171.05</td>
</tr>
<tr>
<td>800</td>
<td>131.11</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Code</th>
<th>Hixon - Crowell</th>
<th>Higuchi</th>
<th>Korsmeyer-Peppas</th>
<th>Best fit mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>APT4</td>
<td>0.0021</td>
<td>0.9034</td>
<td>1.5312</td>
<td>0.9745</td>
</tr>
<tr>
<td>ABP</td>
<td>0.0049</td>
<td>0.8606</td>
<td>2.9815</td>
<td>0.9956</td>
</tr>
<tr>
<td>APT1</td>
<td>0.0070</td>
<td>0.9537</td>
<td>1.1925</td>
<td>0.9612</td>
</tr>
<tr>
<td>APT2</td>
<td>0.0012</td>
<td>0.9850</td>
<td>0.5668</td>
<td>0.9834</td>
</tr>
<tr>
<td>APT3</td>
<td>0.0006</td>
<td>0.6600</td>
<td>1.9237</td>
<td>0.9726</td>
</tr>
<tr>
<td>APP1</td>
<td>0.0014</td>
<td>0.9395</td>
<td>2.0582</td>
<td>0.9805</td>
</tr>
<tr>
<td>APP3</td>
<td>0.0014</td>
<td>0.8623</td>
<td>3.8781</td>
<td>0.9846</td>
</tr>
<tr>
<td>APP4</td>
<td>0.0011</td>
<td>0.9210</td>
<td>1.1800</td>
<td>0.9328</td>
</tr>
</tbody>
</table>
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-crowell 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: \( M_t^{1/3} = k_{bc}t + M_r \)

Higuchi: \( M_t = k_{bc}t^{1/2} \)

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

Where, \( M_t \) is the mass of drug dissolved in time \( t \); \( k_{bc}, k_5 \) and \( k_{KP} \) are, respectively the Higuchi’s, the Hixon–Crowell’s and Korsmeyer-Peppas’s release constants; and \( n \) the release exponent that indicates of the mechanism of release (Korsmeyer and Peppas, 1983; Higuchi, 1963).

\( n \leq 0.5 \) corresponds to a Fickien diffusion mechanism, 

\( 0.5 < n < 1 \) non-Fickien material transport, 

\( n = 1 \): Transport II (Relaxation) case, 

\( n > 1 \): Super-II Transport Case II

The Hixon–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 \( r^2 \), the Higuchi model seems to be the model for APT4, ABP, APT3 and APP3 formulations with \( r^2 \) 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 \((r^2 = 0.97)\) 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 \((R^2 = 0.98)\) assumes that the drug release is limited by the dissolution rate of the particles.

CONCLUSIONS

Microencapsulation of amoxicillin was performed using two different matrices: 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, CICH3), 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 \( \mu \)m with PVA and 131.11 to 287.8 \( \mu \)m with Tween 80, PBS's microparticles in the range 62.45 \( \mu \)m with PVA and 151.39 \( \mu \)m 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.

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