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# Controlled Release of Benzocaine from Monomer and Copolymer Carriers in Synthetic Gastro-intestinal Media

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**Abstract:** New dosage forms able to control drug release in the gastro-intestinal media have been prepared and investigated in this paper. Two different type of medicinal agent bonding (MA), in our case Benzocaine (Bz), were chosen in order to examine drug release.

i) MA attached to ethylenic monomer (m,p-vinylbenzaldehyde), condensation reaction.

ii) The copolymer carrier (Cp) is obtained by copolymerizing this monomer.

These two carriers were well characterized by microanalysis, FTIR, DSC (Tg) and GPC (Ip) and the two fraction α and β were calculated from elemental analyses of Cp. The results showed good polydispersity and low average molecular weight. MA linked to an organic product by the azomethine function (C=N), hydrolytically sensitive, allowed controlled release of Bz, from the monomer carrier and from the bending Schiff bases groups. Theoretical and experimental analyses of controlled release of Bz kinetics from monomer and copolymer carriers were conducted for the case of contact with synthetic gastro-intestinal fluids at various pH (1,2; 6,0 and 8,0) at 37°C.

The process was found to be controlled by the nature of media (heterogeneous), which involved the preliminary hydrolysis, and the drug (Bz) diffusing out of structure of copolymer (Cp) to the external aqueous media.

The results obtained on the rate of delivery showed a clear difference between pH = 1,2 and pH = 6,0 and 8,0 based on:

i) The cation of p-aminoniumbenzoic acid ($PABAH^+$) release at pH = 1,2

ii) Bz release at pH = 6,0 and 8,0

**Keywords:** Benzocaine; Schiff Base; copolymer carrier; drug release; hydrolysis; diffusion.

## Introduction

Systemic treatment is often administered via the gastrointestinal tract, since many dosage forms are easy to swallow. For classical dosage forms the drug release generally follows the first-order reaction kinetics. The drug is liberated very rapidly from the form, and as a result the drug concentration in the gastrointestinal liquid and in the blood builds up to a maximum concentration and then falls exponentially until the next dose.

An undulating concentration figure of the drug is obtained, high concentrations alternating with low concentrations. In order to facilitate the treatment by reducing the number of taken doses, the active substance has to be formulated in such a way that its

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release is delayed and controlled. Moreover, the development of new systems able to release a controlled amount of drug over a defined period of time represents also an important pathway of drug effects optimization. These therapeutic systems offer important advantages over traditional dosage forms in diseases requiring the most constant possible blood levels over prolonged therapeutic duration: uniform blood levels are achieved, smaller total amounts of drug are needed, side effects are reduced and the therapy is optimized[1].

Many devices able to control the drug release have been prepared in various ways, following 3 mechanisms, namely: osmosis, polymer erosion and diffusion, the release being often controlled by more than one mechanism[2]. Another interesting way is to attach the drug to the polymer by means of a labile chemical bond.

As our paper is concerned with the last process i.e, attaching the drug to a biocompatible polymer, it is interesting to examine the results which have been obtained previously in the literature.

Various drugs have been attached to low molecular-weight polyethylene glycol: procaine[3], atropine[4], esters of salicylic acid[5], penicillin, aspirin, quinidine and atropine[6].
The organic function chosen for the polymer-drug bonding is very often, ester or carbonate and, sometimes acetal, because their hydrolysis in acidic or basic media are well-known in organic chemistry.

Another process applied more recently, is synthesizing monomer with pendant drug, and then polymerization of the obtained molecule[7-11]. Amines such as 5-amino-salicylic acid[12], 3-aminopyridine[10,11] para-amino benzoic acid[9], para-anisidine[13] and 2-aminothiazole[14] have been grafted on styrenic supports. The acrylic and methacrylic supports have been widely used for amine drugs such as theophylline[15], sulfanilamide[8], benzoic acid[16] and anilines model[17]. In these cases, the released drug depends on the hydrolysis of the function group of linkage.

In this context, we have chosen the Benzocaine (Bz) as anesthetic medical agent, grafted via azomethine bond on vinylbenzaldehyd to obtain the monomer carrier Im, which has been copolymerized with N-2-vinylpyrrolidone by a radical copolymerization.
Benzocaine (ethyl4-aminobenzoate), an ester with a long acting local anesthetic, has been used for the relief of local pain, among other disorders, as in buccal affections. It also acts on the synapses blocking the potential action[18].

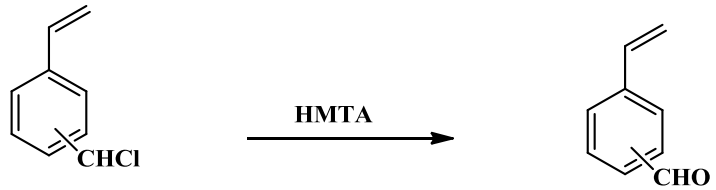
The kinetics of (Bz), released from Im and Cp, have been measured by using a double-beam UV spectrophotometer in different synthetic liquid at various pH (1,2; 6,0 and 8,0) and under the same conditions of temperature (37°C) and stirring (500 rpm).The results showed the cumulative percentages of drug released as function of the hydrolysis reaction of azomethine bond in first, and, the diffusion of MA from the structure of the carriers in second.

## Results and Discussion

### *Synthesis and characterization*

#### Synthesis of monomer Im : N-((m,p)- vinylbenzylidène)-benzocaine

(m,p)vinylbenzaldehyd VBA was synthesized previously following the Sommelet's method[19], as shown in scheme 1.



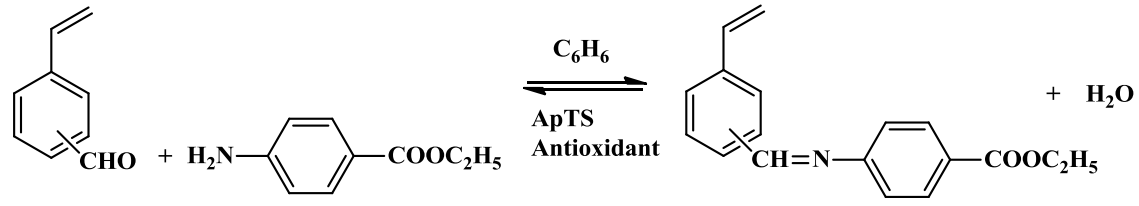

**CMS** **VBA**

**Scheme1**

The characteristics of VBA are as follows, they are in good agreement than those reported in reference[13]:

The principal IR bands are ($cm^{-1}$): 1705 (C=O), 2731 and 2825 (C-H aldehyde), 1605 (C=C aromatic) and 918 and 989 (C-H vinylic).

The monomer Im has been synthesized by using the general method described in the literature[7,9,20-24]. The scheme 2 shows the synthesis reaction of the monomer support of benzocaine.




**VBA** **Bz** **Im**

**Scheme2**

Characteristics of Im:

- Solid aspect, yellow powder, already described[14]
- Yield: 80%
- FTIR spectrum (Figure 1) σ ($cm^{-1}$): 1655 (C=N), 1707 (C=O, ester), 1450 and 1600 (C=C aromatic, stretching), 900-990 (C-H, vinylic), 1456 (-$CH_3$, bending), 2987 (-CH alkane, stretch).

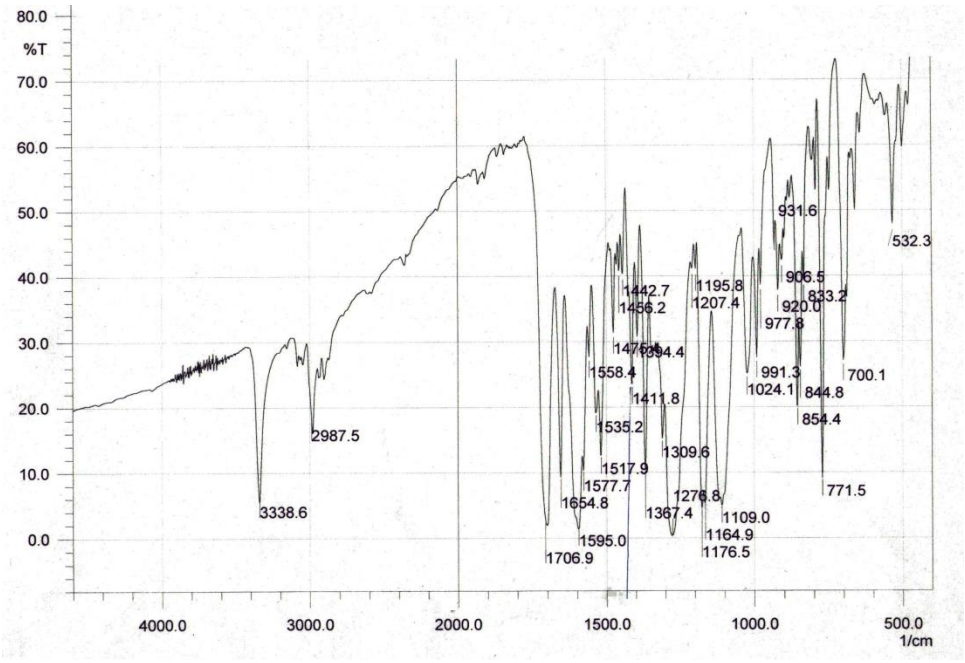
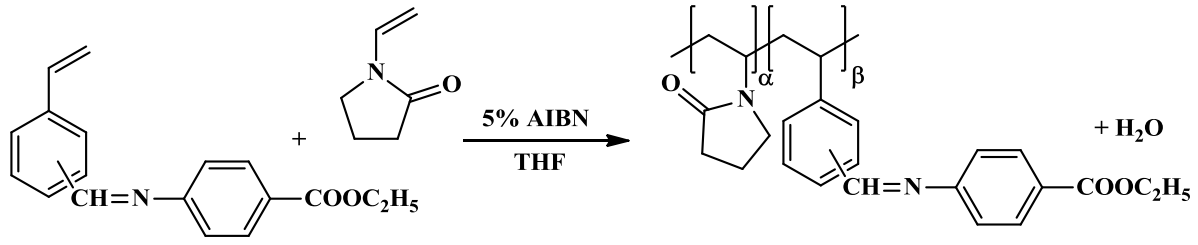



**Figure 1:** FTIR spectrum of Im

**Synthesis of copolymer: poly[N-(m,p)-vinylbenzylidène-benzocaine-co-N-2-vinylpyrrolidone], Cp**

The Cp was obtained by mixing 96% VP with 4% Im, dissolved in anhydrous tetrahydrofuran (THF) with 5% (W/W) of azobisisobutyronitrile (AIBN) as initiator, and placed in a glass tube (Scheme 3).




**Im** **VP** **---[$f_1$]$_\alpha$---[$f_2$]$_\beta$---**
**Cp**

**Scheme3**

The Cp characteristics are:

- Tg = 81±0,1°C (DSC) (glass transition temperature)
- $\bar{M}_n$ = 10500, $\bar{M}_w$ = 12800, Ip = 1.21
- Copolymerization rate: 84%
- Elemental analyses: %N : 10,84%

(This value enabled us to calculate $\mathbf{f_1}$ (89,3%) and $\mathbf{f_2}$ (10,7%), the Cp's molar fractions

- IR spectrum (Cp) (σ (cm-$^1$)): (Figure 2)

1670 (C=O*, VP), 1288,4 (C=C, aromatic),1423,4 and 1461,9 (C-O**, VP), 2889,2 and 2954,7 (-C-H, alkane, stretching), 1462 (-$CH_3$, bending), 1604,7 (C=C, aromatic, stretching).

*: imine band is masked by the C=O band of VP.

**:C =O Band of ester is masked by that of the VP.

We noted a vinylic band absence (out of plane bending) at 900-990cm$^{-1}$.

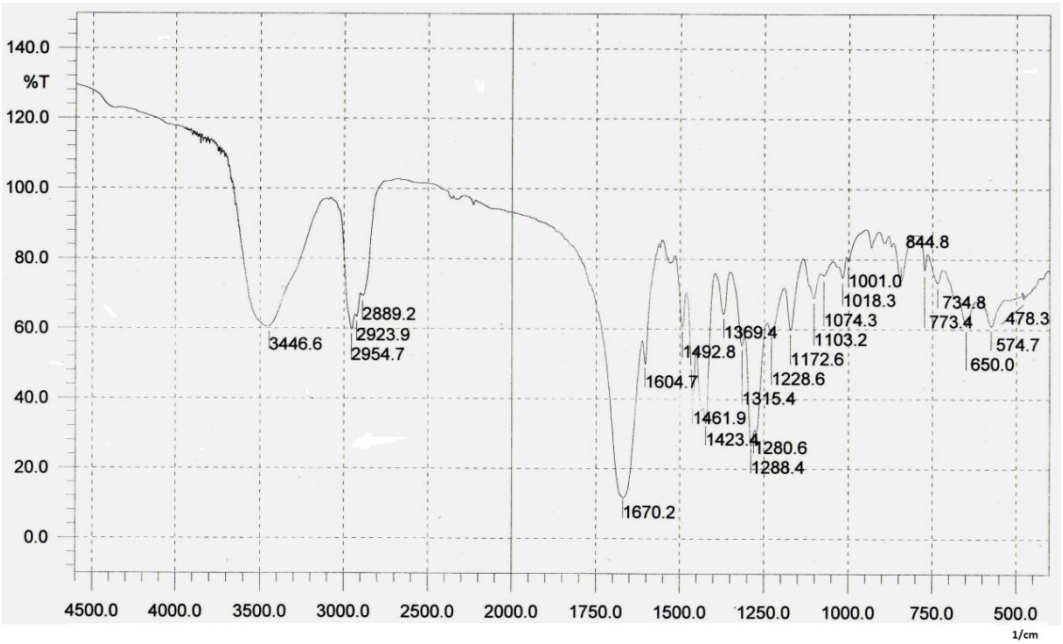



**Figure 2:** Cp FTIR spectrum

***Release study***

The test *"in vitro"* experiments conditions are carried out in a closed flask with a controlled stirring rate (500rpm). Im and Cp are insoluble in synthetic intestinal gastric liquids (100mL).Im and Cp in powder form are dispersed in pure form. Samples (1mL) of liquid were taken at intervals for analysis, after appropriate dilutions, using UV-Vis-2401PC-SHIMADZU spectrophotometer calibrated at $\lambda_{max}$ of Bz in studied pH. Figure 3 shows examples of UV absorption spectrum at different concentrations of Bz at pH=8.0.

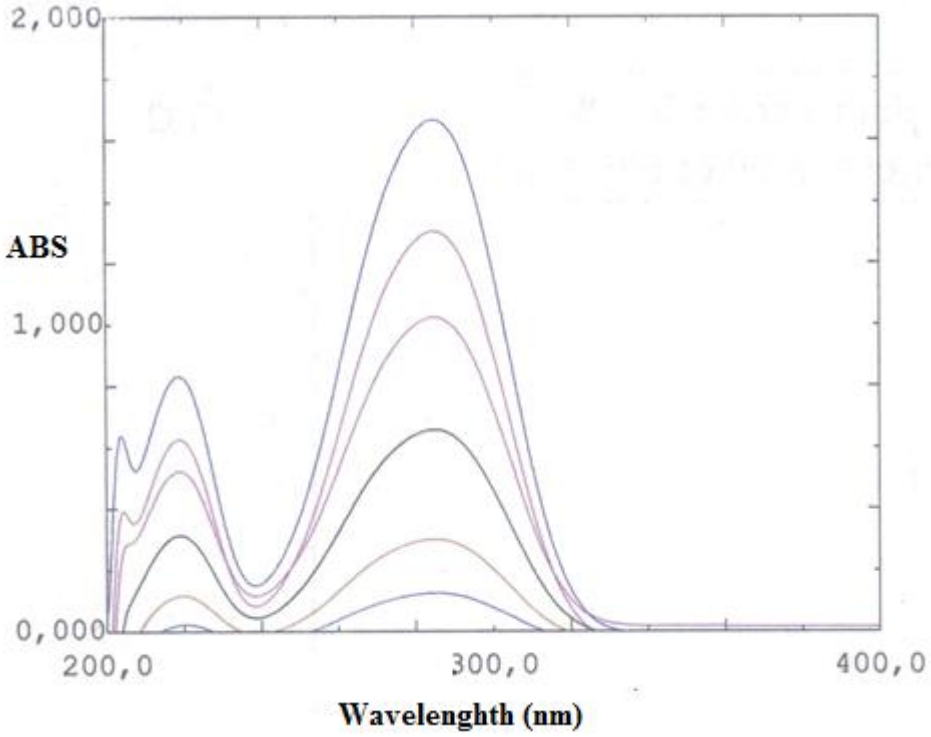



**Figure 3**: UV benzocaine spectra at pH =8,0 with different concentrations ($10^{-4}$; $8x10^{-5}$; $6x10^{-5}$; $4x10^{-5}$; $2x10^{-5}$; $1x10^{-5}$(mol/L) ).

The $\lambda_{max}$ and $\varepsilon_{max}$ values are given in table 1:

**Table 1:** $\lambda_{max}$ and $\varepsilon_{max}$ in pH = 1,2; 6 and 8.

| | Bz | | |
|---|---|---|---|
| | pH=1,2 | pH=6,0 | pH=8,0 |
| $\lambda_{max}$ (nm) | 226 | 285 | 285 |
| $\varepsilon_{max}$ l.mole$^{-1}$.cm$^{-1}$ | 13324 | 17190 | 16825 |

The Table 2 reports the percentage of the initial mass of drug grafted on Im and Cp and percentage of the initial mass of Bz in Im and Cp: copolymer indexed as follow:
$(\text{-VP})_{\alpha}\text{-(Im-)}_{\beta} \equiv \text{Cp}$

| | % Im/Cp | % Bz/Im | $m_{\text{total to release}}$ (mg) |
|---|---|---|---|
| Im | / | 58,42 | 58,42 |
| Cp | 23,15 | 58,42 | 13,52 |

- -(VP)- : vinylpyrrolidone: as comonomer
- -(Im)- : monomer Im.
- %Im/Cp: fraction of Im in Cp
- %Bz/Im : percentage of drug in Im
- $m_t$: total mass to release (mg)

When the monomer and Cp carriers (Im, Cp), in powder form, were soaked in simulated intestinalgastric liquids (pH = 1,2; 6 and 8), liberation of the drug was observed with typical kinetics as shown in fig. 4 and 5.

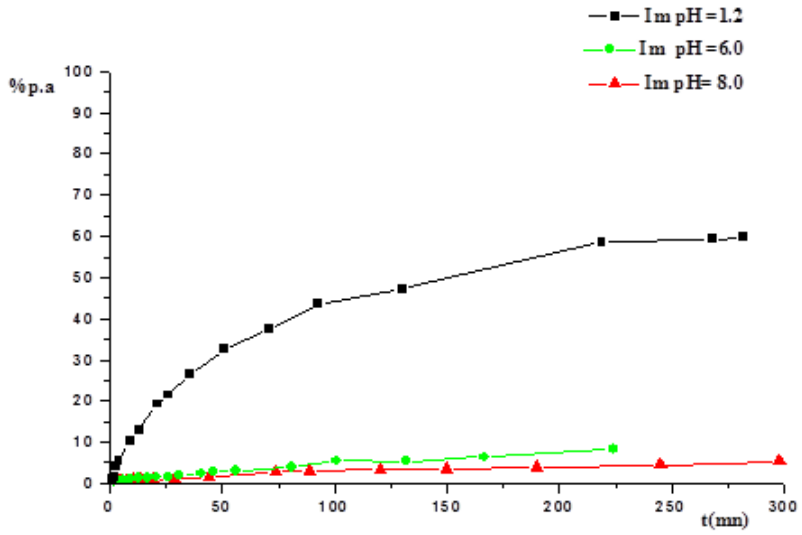



**Figure 4**: Percent released drug as function of time for Im at pH = 1,2; 6,0 and 8,0; T 37°C and Ω 500 rpm.

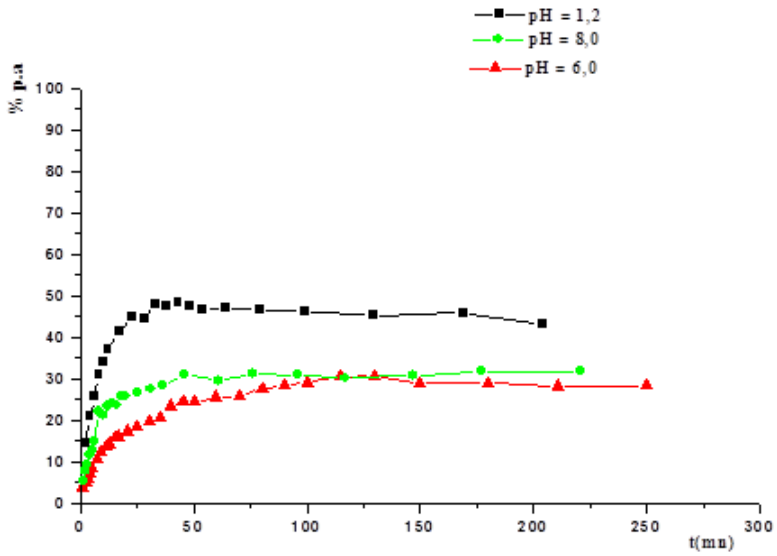



**Figure 5**: Percent released drug as function of time for Cp at pH = 1,2; 6,0 and 8,0; T 37°C and Ω 500 rpm.

To construe the results of the Bz released, it is necessary to consider:

•$PABAH^+$:cation of p-aminobenzoic acid

•The hydrophilic patterns (VP)

• The pK of benzocaine (Bz) (pK = 2,49)[25] and p-aminobenzoic acid(PABA) (pK = 4,9)[26] and there solubility.

It is clear that we have two different primary particles that are released during the hydrolysis of (Im) and (Cp).

1. At pH = 1,2 the majority of cation p-ammoniumbenzoic acid ($PABAH^+$) is released after hydrolysis of the imine function (Im) or groups "pendant" Schiff base of the copolymer (Cp) on one hand and the ester hydrolysis of the active ingredient (Bz) on the other hand.
2. At pH=6.0 and pH= 8,0 we have a benzocaine release; the ester function is not affected by hydrolysis at pH above

The results showed that the drug release from monomer in various experimental liquids at pH 6,0 and 8,0, is very slow than from the copolymer Cp (figure 6). As a matter of fact, the monomer is insoluble in this release medium, and by the prevention of the drug release by steric effect of the benzocaine (bulky molecule). The inhibiting action aiming at reach the delay effect is compromised for copolymer at low molecular weight and based of N-vinyl-2-pyrrolidone hydrophilic co-monomer.

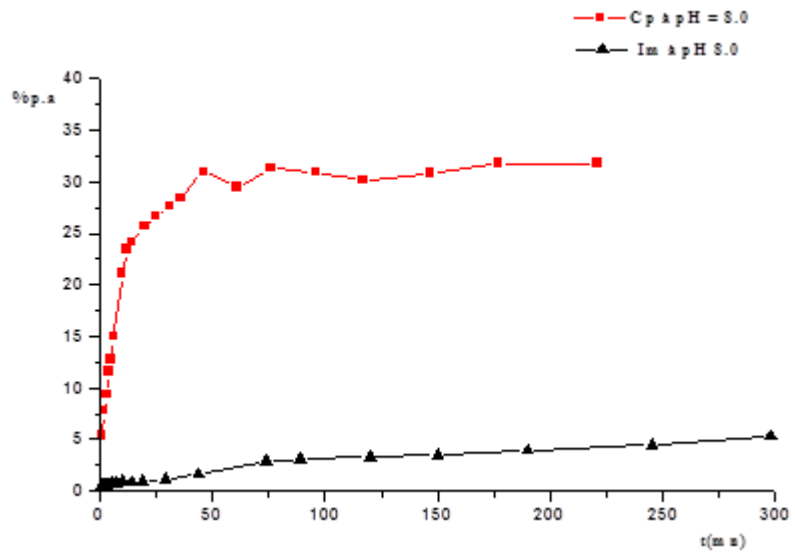



**Figure 6**: Percentage of benzocaine released from the copolymer Cp and Im at pH =8.0.

The release of cation p-ammoniumbenzoic acid ($PABAH^+$), produced from the hydrolysis of the ester function unstable with pH = 1,2, presents a release percentage a little higher than other pH[9]. Also, in acidic pH media, the high percentages of released drug are obtained because the hydrolysis of Schiff bases is rapid, reaches 60 % after two hours from Im and 50 % for Cp.

After study, it proved that this kinetics cannot be expressed or described by simple classical equations. The delivery diffusional appearance has been proved when the percentage of drug released has been plotted as function of a square root of time. In fact, a linear relationship is observed for short times (figure 7).

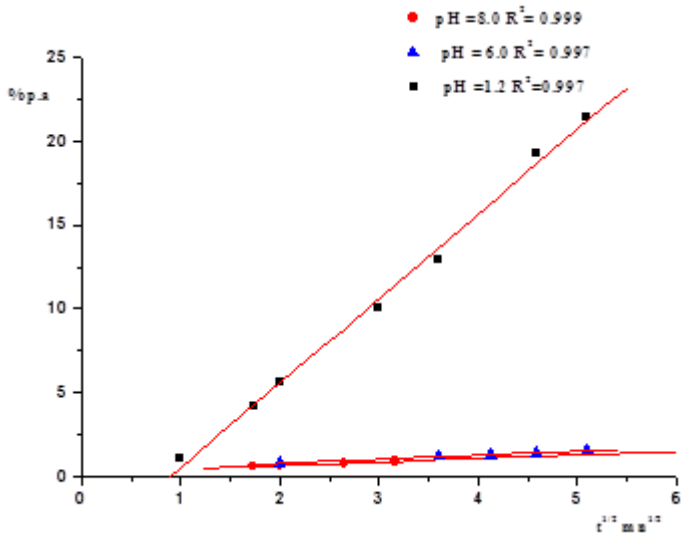



**Figure 7:** Benzocaine rate released from the Cp as function of the square root of time at pH = 1.2, 6.0 and 8.0

Nevertheless, the establishment of the Cranck mathematical model[27] able to describe the diffusion model according to the Fick's laws. The amounts of diffusing substance at time t $M_t$ compared to the amount of diffusing substance at infinite time (equilibrium) $M_\infty$ are determined by the following relation:

$$\text{(A)} \qquad \frac{M_\infty - M_t}{M_\infty} = \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{D.n^2.\pi^2.t}{R^2}\right)$$

where R is the macromolecule grains radius.
The different values of $M_\infty$ obtained from the graph of log(Mt/Mi) =f(t), are given in Table 3.

**Table3:** The amounts of benzocaîne delivery from a monomer and copolymer at infinite time in the various release media at the different pH.

| pH | | 1,2 | 6,0 | 8,0 |
|---|---|---|---|---|
| $M_\infty$ (Bz) mg | **Im** | 41 | 5,0 | 3,11 |
| | **Cp** | 7,275 | 4,849 | 4,483 |

However, it is very difficult or practically impossible to calculate the diffusivities because we don't know the dimensions of the grains of Im and Cp.

## Conclusion

This paper has paved the way to new oral galenic forms able to control the drug release in stomach. In this case, a pharmacologically active monomer or copolymer are prepared and soaked at pH = 1,2; 6,0 and 8,0. The drug release process of is very complicated because various matter transfers take place through the structure of Cp. No analytical solution can be found for this problem, numerical methods with finite differences have to be built in order to describe the whole process. When the copolymer carrier is in contact with

synthetic intestinalgastric, it becomes in gel form, because of the liquid transfer into the copolymer. On the other hand, a drug release is observed, which does not follow a classical kinetic equation, as the kinetics are partially controlled by diffusion. Several factors influence the drug release: the nature of the carriers, the rate of hydrolysis of imine function, the pH of the medium, and the molecular weight of the polymer support.

In order to carry out this reaction, benzocaine has been condensed with (m,p)-vinylbenzaldehyd to give a monomer carrier. This monomer carrier was copolymerized with N-vinyl-2-pyrrolidone. The heterogeneous drug release kinetics have been established for 3 different pH, and the results proved that benzocaine release is strongly affected by the pH media and, therefore the rate of hydrolysis of Schiff base.

The study shows that any process of diffusion through these insoluble structures must follow four main steps:

1- The setting in balance of the grains of the supports in the media with the formation of the water film around the grain
2- The liquid diffusion in the grain structure
3- Hydrolysis of the imine function of the monomer and its copolymer
4- Diffusion of the drug out of the supports

Finally, it is worth to mention that the work does not stop at this step. In this work, we also examined the inclusion of the obtained formulations i.e. monomer and copolymer in other polymeric supports using other techniques principally microencapsulation. The purpose is to get a large domain of release drug modification.

**Acknowledgements**

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## Experimental Section

### *Materials and equipments*

(VBA) (m,p) has been synthesized following the Sommelet's method from a mixture of (meta/para)-chloromethylstyrene: (60/40). Benzocaine 98 % of purity from Sigma, N-vinylpyrrolidone from Aldrich, analytical solvents (benzene, tetrahydrofuran, petrol ether, and absolute ethanol) used as received. The release media are composed of: HCl and NaCl for pH=1.2, $KH_2PO_4$ and NaOH for pH=6.0, HCl and Borax for pH=8.0, in accordance with US pharmacopeia [28].

The average molecular weights Mn and Mw of the copolymer Cp have been obtained by KNAUER apparatus, equipped with a set of columns Ultra-Styragel $10^{-4}$and $10^{-5}$ A° WATERS, using polystyrene as standards and tetrahydrofuran as solvent at a flow of 0.7mL/mn. The transition temperature of a copolymer has been measured by differential scanning calorimetry DSC 92 SETARAM apparatus. IR spectra have been recorded on dried KBr disks using SCHIMADZU FTIR-8300 apparatus. Microanalysis of copolymer has been established in the Central Analysis Service of CNRS Solaize (France).The UV–Vis spectra have been carried by UV-Vis-2401 PCSHIMADZU with double beams controlled by data processing, with thermostated cells.

***Synthesis of monomer and copolymer***

***Preparation of (m,p)-Vinylbenzaldehyd (VBA)***

VBA has been prepared from a commercial mixture of meta/para: 60/40 chloromethylstyrene (CMS), according to SOMMELET method [13]. 0,4mol (56,07g) of hexamethylenetetramine (HMTA) has been added to 0,4 mol (60,8g) of fresh distilled CMS which has been placed in a flask equipped with refrigerant, and then 125 mL of acetic acid has been introduced and diluted with125 mL of water. After adding some spangles of 4-tertiobutylcathecol, the mixture has been heated until reflux at 100°C during 2 hours under agitation. 100 mL of HCl has been added to the mixture and heated for 15 min. The organic phase is extracted with ether oxide and washed several times with $Na_2CO_3$ solution at 10 %and with pure water until neutrality. This phase was dried with $Na_2SO_4$ and concentrated by rotavapor. The obtained green oil of VBA has been distilled under vacuum (p = 1mmHg) and at65 °C of temperature.

***Preparation of N-(m,p)-Vinylbenzylidene)-benzocaine***

A dry 500mL 2-necked flask equipped with a magnetic stirrer and a Dean-Stark surmounted by a condenser, has been used for this synthesis. 77mmol of benzocaine were dissolved in 150mL of benzene in the presence of 2mg of 2,6-di-t-butyl catechol (antioxidant) and some traces of para toluenesulfonic acid (PTSA) as catalyst has been reacted under reflux. The mixture has been heated until boiling. After cooling, 77mmol of (m,p) vinylbenzaldehyd in 50mL of benzene has been added to the initial solution. The mixture has been heated until reflux at the azeotrope temperature (experimental T = 79,5 °C) in order to eliminate the produced water. After evaporation of the solvent, the residue has been recrystallized several times in absolute ethanol.

***Preparation of poly[N-(m,p)-vinylbenzylidène-benzocaine -co-N-2-vinylpyrrolidone]***

The obtained monomer (Im) has been copolymerized with N-2-vinylpyrrolidone (VP)at a ratio 4/96 of Im/VP, using 2,2-azo-bis-(isobutyronitrile) (AIBN, 5% on mass) as initiator and under nitrogen atmosphere, in tetrahydrofuran (THF) solution , at 65°C during 18 hours. The obtained copolymer has been purified by re-crystallization in THF/Petrol ether couple. Finally, the yellow powder of copolymer has been collected with 84 % of yield.

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