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# DRUG RELEASE STUDIES OF AN ANTITHYROIDIAN FROM SYNTHESIZED AND CHARACTERISED MONOMER AND COPOLYMERS CARRIERS IN GASTRIC AND INTESTINAL MEDIA

**SOUMIA CHIRANI[*,a], CHAFI NAFA[a,b] and MESLI ABEDERREZZAK[a,b]**

Dept. of Pharmacy, Faculty of Medical Sciences, Djillali Liabes University of Sidi Bel-Abbes, ALGERIA
[a]Laboratory of Macromolecular Physical and Organic Chemistry, Djilali Liabes Universty, BP89 City El Arbi Ben m' hidi Sidi Bel-Abbes, ALGERIA
[b]Dept. of Chemistry, Djilali Liabes Universty, BP89 City El Arbi Ben m' hidi Sidi Bel-Abbes, ALGERIA

## ABSTRACT

Many researchers have reported clinical and laboratory parameters for prediction of remission in grave's disease during or after antithyroid drug therapy, there is no reliable one to assure the complete remission. However, in this current study, we were interested by one antithyroidian agent: 2-Aminothiazole in order to prepare controlled release formulations from this antithyroidian active agent. The release carriers are: one synthesized monomer; by the condensation of 2-Aminothiazole with (m.p.)-vinylbenzaldehyde; and its copolymers with N,N-dimethylacrylamide to get hydrosoluble systems. In these delivery systems, the active agent is spaced out from copolymer chain by phenyl group. The drug releases from these formulations were been studied *in vitro* and the late effect was measured in terms of the decrease of drug released percent as function of time obeying to diffusional kinetics.

**Key words**: Antithyroid drug, Drug release, Delivery vehicles, Diffusion.

## INTRODUCTION

Antithyroid drugs (ATD) have long been used for the drug therapy of graves' disease[1]. 2-Aminithiazole is among the first synthesized antithyroid drugs. It inhibits thyroperoxydase that catalyzes iodination and thyroid hormone biosynthesis.

We noted the great and recent interest in chemically grafting antithyroidian active agents on polymer chains; in order to increase thyroid drug release. Significant advances have been made in the development of drug delivery systems in order to increase the drug

[*]Author for correspondence; E-mail: chiranis@yahoo.fr

efficacy. These devices can control the drug release and can be obtained by different techniques[2,3].

A drug delivery system can be a matrix of polymer incorporating the active agent; the drug can be dispersed in the polymer or covalently linked to polymer backbone[4-11]. In the latest technique, the linkage of the drug to the polymer can be obtained either by a chemical modification of the polymer or by grafting the drug onto a monomer, which is polymerized or copolymerized. In this domain, the styrenic and acrylic polymers are widely used by the researchers[12,13] and some parameters such as geometry, functional group and group spacer can modify the drug release. The linkage between drug and polymer can be realized by various functions such as amide, carbonate, ester or imine functions[6,12,14-16]. We were interested in imine linkage because it can be easily hydrolyzed in all range of pH media and allows a grafting of amine-terminated drug precursors.

2-Aminothiazole inhibits the biosynthesis of thyroid hormone. So, our research is intended to use polymeric supports able to control the release of 2-Aminothiazole in the defined periods in order to increase its efficacy and reduce the undesirable effects, so we have:

- Synthesised a monomer "carrier": N-(m,p)-vinylbenzyliden-2-aminothiazole (Im) by condensation of our ATD agent to m,p-vinylbenzaldehyde (VBA) and its copolymers with N,N-dimethylacrylamide (DMA) in order to get hydrosoluble carriers. In this case, the drug is linked to a monomer (Im) with an imine function; and
- Studied the 2-Aminothiazole's release from monomer and copolymers carriers in gastric (pH = 1.2) and intestinal (pH = 8.0) media.

## EXPERIMENTAL

### Materials

(m,p)-vinylbenzaldehyde (VBA) was synthezised from a mixture of (meta/para)-chloromethylstyrene (60/40) and hexamethylentetramine (H.M.T.A) from* 2-Aminothiazole and tetrahydrofuran (THF) from Sigma Chemical and Labosi, respectively. Benzene (99.8%) and diethyl ether (99%) were provided from Prolabo.

### Synthesis of (m,p)-vinylbenzaldehyd (VBA)

VBA was prepared from a commercial mixture of meta/para : 60/40 chloromethyl-

styrene (CMS), according to Sommelet method[17]. 0.6 mol of hexamethylenetetramine (HMTA) is added to 0.3 mol of fresh distilled CMS, which is placed in a flask equipped with refrigerant, and then 125 mL of acetic acid is introduced and diluted with 125 mL of water. After adding some spangles of 4-tertiobutylcathecol, the mixture is heated under reflux at 100°C during 2 hours under agitation. 100 mL of HCl were added to the mixture and heated for 15 min. The organic phase was 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 was distilled under vacuum (p = 1 mmHg) and at 65°C of temperature.

**Synthesis of the monomer: N-(m,p) vinylbenzyliden-2-aminothiazole (Im)**

The Schiff base (Im) was prepared according to the following stepes (Scheme 1): the same quantities in mol of 2-Aminithiazole and VBA were dissolved in benzene with the presence of 4-tertiobutylcathecol and paratoluensulfonic acid (PTS) as an antioxidant and a catalyst respectively, in a flask equipped with Dean-Stark apparatus. The mixture was heated until reflux at the azeotrope temperature (experimental T = 79, 5°C) in order to eliminate the produced water. After filtration, the solvent (benzen) was been evaporated by rotavapor. After several re-crystallizations in chloroform, a yellow powder of Schiff base was collected giving 70% of yield.

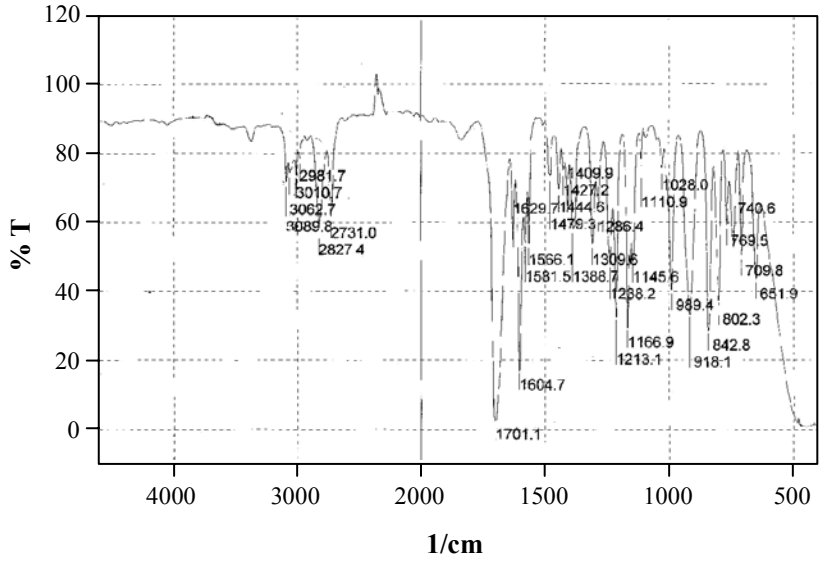



**Fig. 1: Infrared spectrum of (m,p)-vinylbenzaldehyde**

### Synthesis of copolymers

The obtained monomer (Schiff base) Im was copolymerized with N,N-dimethylacrylamide at a ratio 10/90 of Im/DMA under nitrogen atmosphere, without solvent, at 65°C during 95 minuts; with respectively two percentages (5% or 5‰) of initiator: AIBN (2,2-azo-bis-isobutyronitrile). The obtained copolymers ($Cp_1$ with 5% of AIBN and $Cp_2$ with 5‰ of AIBN) were purified by re-crystallization in the tetrahydrofuran/petroleum Ether couple (Scheme 2). Giving 80.20% and 72.52% of yield, respectively.

### Characterization methods

Fourier transform infrared spectroscopy (FTIR): the monomer (Im) and its copolymers spectra were registered on Schimadzu FTIR-8300 on dryed KBr disks.

The proton magnetic resonance ($^1$H NMR) spectrum of monomer was recorded using BRUCKER apparatus in deuterated dimethylsulfoxide $DMSOd_6$ as solvent at 300 MHz**.**

Microanalyses were been done in CNRS Microanalyses Center; Vernaison division (France).

Melting temperature of monomer was been taken by Tottoli Büchi 510 apparatus.

### *In vitro* drug dissolution tests

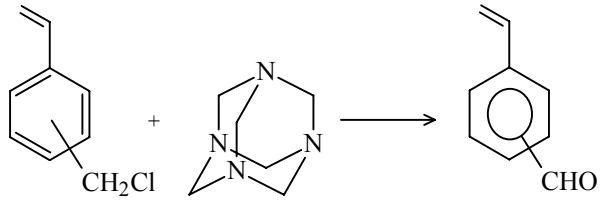
Release experiments were conducted in closed flask, kept at 37 ± 0.5°C and at controlled stirring rate of 500 rpm. At t = 0, 100 mg of monomer or copolymer, were soaked in 100 mL of buffered aqueous solution at pH = 1.2 or 8.0.

The release of 2-aminithiazole was followed by UV spectroscopy using UV-Vis-2401 PC-Shimadzu apparatus. The drug solutions were analyzed at $\lambda_{max}$ = 268 nm both in reconstituted gastric and intestinal media ($\varepsilon$ = 3038 $L.cm^{-1}.mol^{-1}$ in pH = 1,2 and $\varepsilon$ = 3420 $L.cm^{-1}.mol^{-1}$ in basic solutions (pH = 8.0)).

## RESULTS AND DISCUSSION

### Characterization of V. B. A and monomer carrier (Im)

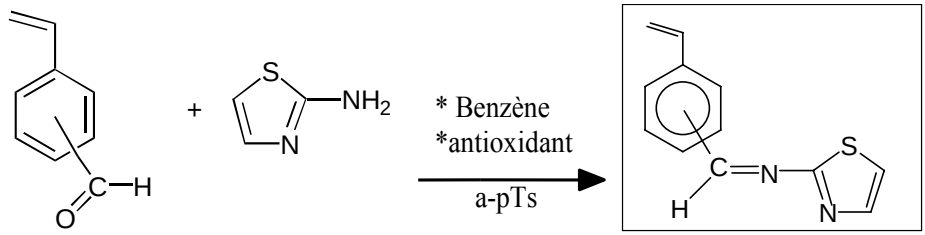
Synthesized V.B.A (Scheme 1) was characterized by FTIR and the most important bandes are: C O at 1701 $cm^{-1}$, CH (aldehyde) at 2731 $cm^{-1}$ and 2824 $cm^{-1}$, C=C (aromatic) at 1604 $cm^{-1}$ and C-H (vinylic) at 918 $cm^{-1}$ and 989 $cm^{-1}$.




C.M.S. H.M.T.A. V.B.A.

**Scheme 1**

However, we confirmed the purification of our monomer support of 2-Aminothiazole (Im) (Scheme 2) by several (C.C.M)'s chromatographies in ether/petrolium ether media with everal compositions (0% to 70% on Ether). Our synthezised monomer being apolar we've obtained only one and clear blot from 50% of diethyl ether.




**V.B.A** **p.a** monomère support(**Im**)

**Scheme 2**

Schiff's base (Im) microanalyses : $C_{12}H_{10}N_2S$ (214 g/mol):

| | **C%** | **S%** | **N%** | **S%** |
|---|---|---|---|---|
| **Im** | 61.74 | 16.78 | 14.16 | 16.78 |
| | 61.78 | 16.50 | 13.07 | 16.50 |

The infrared spectrum of Schiff base (Im) (Fig. 2) showed clearly the absence of C=O aldehyde band at 1701 $cm^{-1}$ and the principal FTIR absorption bands ($cm^{-1}$) are: C=N (imine): 1627.8; C-H (vinylic): 910.3-989.4; C-H(aromatic): 3172.7; C=C (aromatic): 1510.2.

The $^1H$ NMR spectrum of monomer (Im) (Fig. 3) in deuterated dimethyl sulfoxide (DMSO) gives the following proton signals δ (ppm): 5.20-5.30 for $CH_2$ (2d); 5.75-6.15 for $CH_2$=CH (2t); 6.50-7.55 for aromatic protons of thiazole ring; 8.45 for –CH=N- (s).

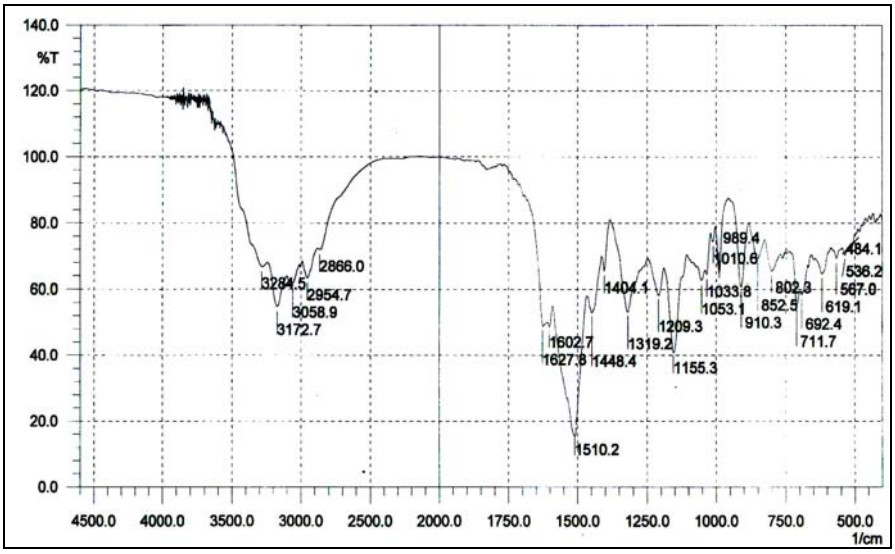



**Fig. 2: Infrared spectrum of monomer (Im)**

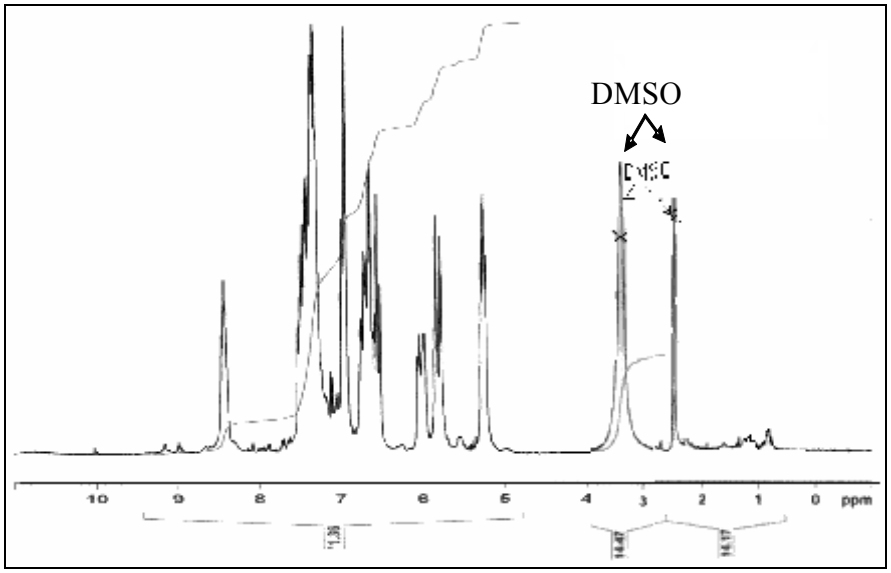
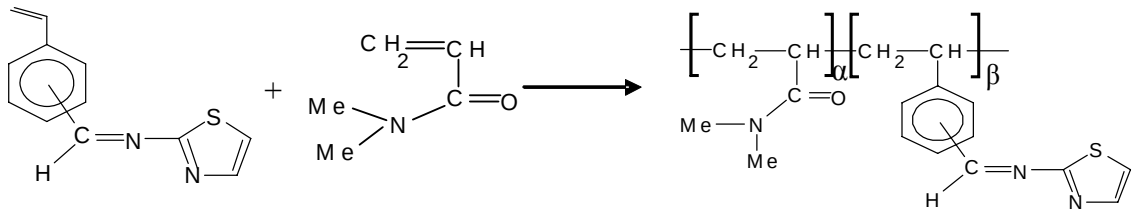



**Fig. 3: $^{1}$H NMR spectrum of monomer (Im)**

## Copolymers characterization

Copolymers $Cp_1$ and $Cp_2$ were prepared by the copolymerization's reaction between our synthezised monomer and D.M.A with 5% and 5‰ of AIBN as initiator, respectively. (Scheme 3).



**Scheme 3**

The FTIR spectra of copolymers (Fig. 4) showed the absence of vinylic band and the most important FTIR bands of copolymers are given in Table 1.

**Table 1: Principal IR bands of copolymers**

| | **v ($cm^{-1}$)** | |
|---|---|---|
| | **$Cp_1$** | **$Cp_2$** |
| C-H (-CH and $-CH_2$-) | 2852.5-2925.8 | 2850.6-2922.0 |
| C=O (amide) | 1627.8 | 1624.0 |
| C=C (aromatic) | 1504.4 | 1508.2 |
| C-H ($CH_3$) | 1400.2 | |
| C=N | Masqued with the large band C=O of the amide | |

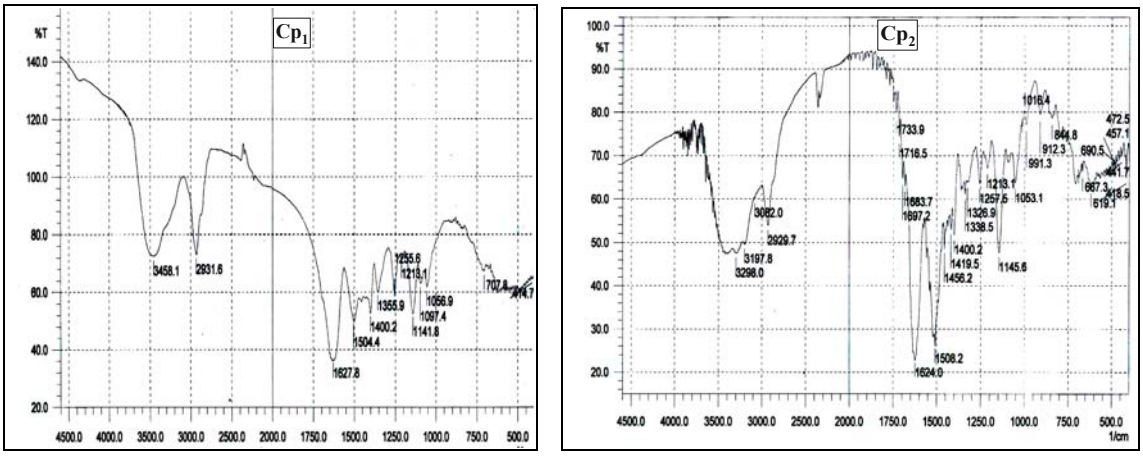



**Fig. 4: FTIR spectra of $Cp_1$ and $Cp_2$**

Copolymers' microanalyses' results are given in Table 2:

**Table 2:**

| Copolymer | C% Exp. | H% Exp. | N% Exp. | N% Exp. S% Exp. |
|---|---|---|---|---|
| $Cp_1$ | 54.34 | 08.22 | 12.64 | 01.65 |
| | 54.51 | 08.33 | 12.73 | 01.65 |
| $Cp_2$ | 58.09 | 06.37 | 13.46 | 09.01 |
| | 58.06 | 06.44 | 13.46 | 09.01 |

## Incorporation rates calculus α and β

Sulphur being the only one element existing only in the structural part of monomer, we have prefered to use its results in that calculations' example: considering the copolymer $Cp_2$ and having sulphur's percentage: S% = 09.01%, we can define the ratio: $0.0901 = 32\ \beta / (214\ \beta + 99.13\ \alpha)$ and $\alpha + \beta = 1$

Then: $\alpha = 0.586$ and $\beta = 0.414$

In the same way for the copolymer $Cp_1$: $\alpha = 0.9457$ and $\beta = 0.0543$.

## Drug release study

Kinetics of 2-Aminothiazole delivery from the monomer (Im) and its copolymers ($Cp_1$) and ($Cp_2$) *in vitro* in reconstituted gastric and intestinal media are illustrated in the following figures (Figs. 5 and 6):

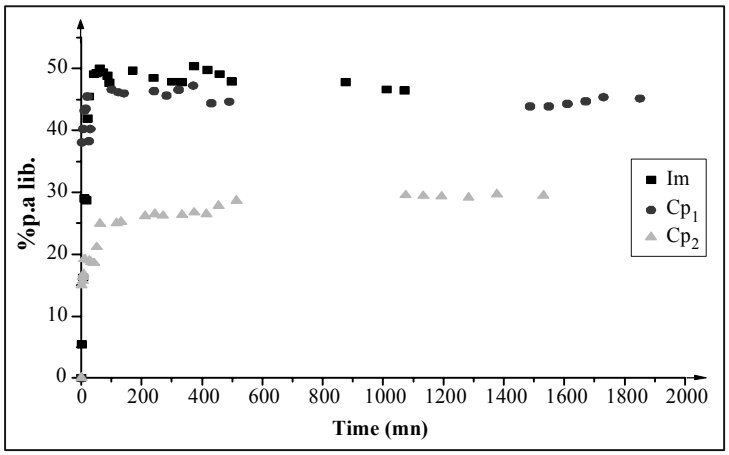



**Fig. 5: % of drug released as function of time in pH= 1.2 (37°C, 500 rpm)**

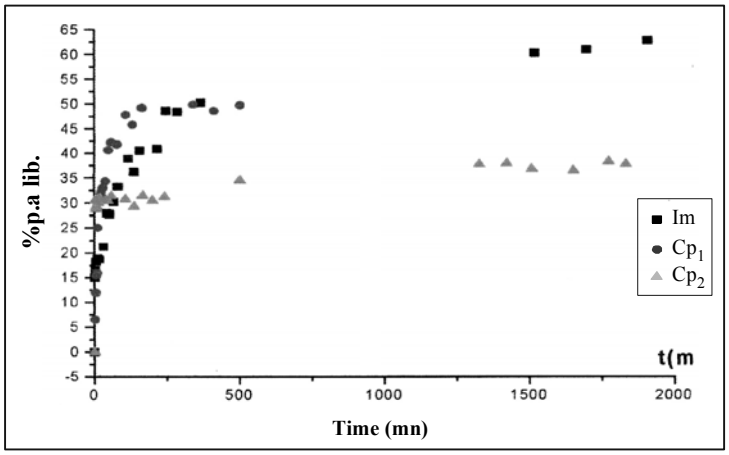



**Fig. 6: % of drug released as function of time in pH= 8 (37°C, 500 rpm)**

These results showed that the 2-Aminothiazole drug release from the monomer (Im) were faster than those from copolymer's ($Cp_1$) faster than those from copolymer's ($Cp_2$). After one hour, the percentage of released drug from (Im) reached 50% and only 45% and 25% for $Cp_1$ and $Cp_2$, respectively. This comment is in agreement with theory because the release from copolymer carriers includ additional step which is the diffusion throughout macromolecular structure. So, high percentages of drug released were obtained with easy hydrolysis of Schiff bases in acidic pH media.

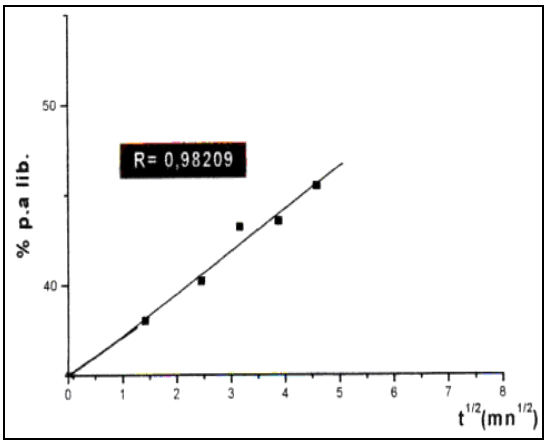



**Fig. 7: % of drug released from $Cp_1$ as function of square root of time in pH= 1.2 (37°C, 500 rpm)**

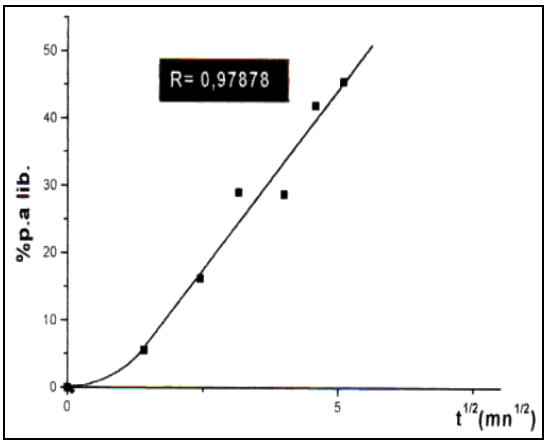



**Fig. 8: % of drug released from monomer as function of square root of time in pH = 1.2 (37°C, 500 rpm)**

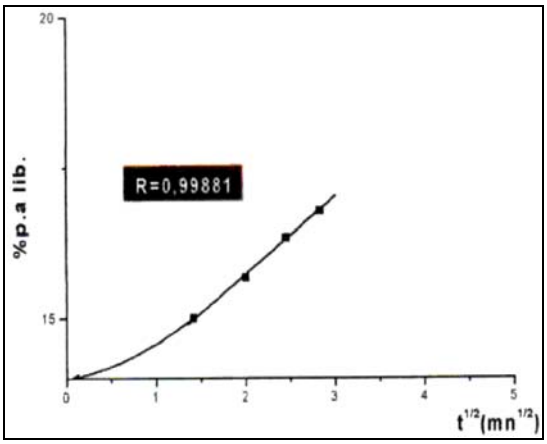



**Fig. 9: % of drug released from $Cp_2$ as function of square root of time in pH=1.2(37°C, 500 rpm)**

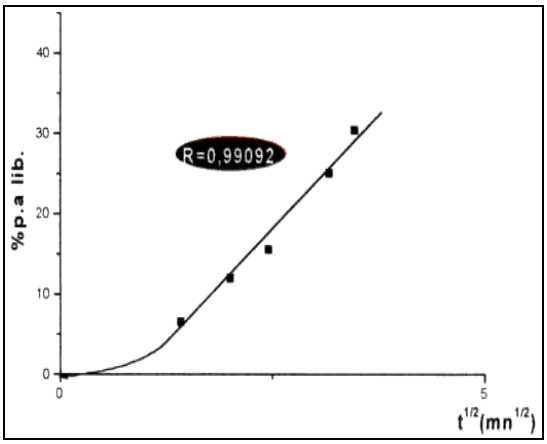



**Fig. 10: % of drug released from $Cp_1$ as function of square root of time in pH=8.0 (37°C, 500 rpm)**

These kinetics cannot be expressed by simple classical equations. The diffusional appearance of this delivery was demonstrated when the percentage of drug released was plotted as function of a square root of time. In fact, a linear relationship was observed for short times :

In this case, we deduced that the release kinetics were controlled by diffusion according to Fick's laws. On the Table 3 were reported the values of infinities weights of 2-Aminothiazole (ATD) with the percent released (Y%) at an infinity time, in both of gastric and intestinal media:

**Table 3: Values of infinities drug weights from monomer and copolymers in gastric and intestinal media**

| pH | Support | $m_\infty$ (ATD) (mg) | Initial ATD weight (mg) | Initial support weight (mg) | Y % |
|---|---|---|---|---|---|
| **pH = 1,2** | Im | 26.67 | 46.77 | 100.80 | 57.02 |
| | $Cp_1$ | 01.52 | 02.97 | 100.00 | 51.32 |
| | $Cp_2$ | 05.82 | 18.96 | 100.00 | 30.68 |
| **pH = 8** | Im | 30.03 | 46.73 | 100.70 | 64.26 |
| | $Cp_1$ | 01.51 | 02.97 | 100.00 | 50.74 |
| | $Cp_2$ | 07.59 | 18.96 | 100.00 | 40.01 |

From these results we deduced that; both in acidic and basic media; released drug percents were lower in the case of $Cp_2$ than $Cp_1$'s and than those of Im. Certainly it was due to them high mass which includes the hydrophilic co-monomer "dimethylacrylamide". The presence of DMA permits a rapid hydrolysis of the imine linkage. Concerning the drug release from copolymers, it was observed a notable burst effect particularly for $Cp_1$. This effect was due inevitably to its low mass and the high percentage of monomer support of drug which can be on the macromolecule chain extremities.

## CONCLUSION

In the present paper, 2-Aminothiazole was modified by grafting it on monomer based on (m,p)-vinylbenzaldehyde and copolymerization with dimethylacrylamide. The drug release from these formulations was studied in acidic (pH = 1,2) and basic (pH = 8) media and the results demonstrated that 2-Aminothiazole release was strongly affected by the copolymer supports. Then the results showed us the importance of the molecular mass of polymers on the drug release constant. Consequently, we can select a desired formulation on the base of the drug application. This study does not stop at this state and has a perspective which is the inclusion of the obtained formulations i.e. monomer and copolymer in other polymeric supports using other techniques principally microencapsulation in order to get a large domain of drug release modification; also, to use biodegradable polymers carriers in order to decrease the accumulation of these ones in tissues.

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