



Molecular Imprinted-Polymer as a Controlled Release Material for Tramadol



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Abstract

The free-radical polymerization method was used to prepare crosslinked polymers as tramadol carriers for the controlled release process. The polymers were based mainly on ethylene glycol dimethacrylate (EGDMA) and methacrylic acid (MAA) in two different molar levels: 15 and 13. These two polymers represented the non-imprinted polymers (NIPs). Other corresponding polymers were prepared by adding tramadol hydrochloride during the synthesis that was removed at the end of the preparation process to produce tramadol-imprinted polymers (TIPs). The four polymers were loaded with tramadol for testing their *in vitro* release at various parameters such as soaking times, pH, and temperatures. The effect of molar ratio and imprinting process on tramadol release was studied. FTIR, TGA, and UV –absorption techniques were used to investigate the prepared and loaded polymers and the releasing process. More physical interactions were observed between the loaded tramadol and the matrix in TIPs than in NIPs. TIP with a molar ratio of crosslinker to polymer equals 13 demonstrated the highest control of releasing tramadol over 12-hour.

Keywords: Tramadol; imprinted polymer; controlled-release; crosslinked polymer; UV –absorption.

1. Introduction

Molecular imprinting technology is a viable synthetic approach to material design that has strong molecular identification of specific molecules. These designed materials, known as molecularly imprinted polymers (MIPs), mimic natural recognition entities such as antibodies and biological receptors. They are able to recognize both biological and chemical molecules including pollutants, drugs, amino acids, nucleotides, proteins, and many others [1,2]. The imprinting process includes functional monomers, template molecules, crosslinking agent, initiator, and a porogenic solvent [3]. Complexes or self-assemblies arise between the functional monomers and the template molecules. These complexes are

fixed by adding the crosslinker and initiator to originate the free radical polymerization reaction. The amount of crosslinking agent contributes to the rigidity of the matrix and therefore, the fixation of the complexes. The last step in the imprinting process is the removal of the template molecules from the polymeric matrix through washing by a solvent. The formed cavities are complementary to the template molecules in their shape, size, and position of the functional groups [4,5].

Most common functional monomers used are vinyl carboxylic acids, vinyl sulphonic acids, and vinyl heteroaromatic bases, such as acrylic acid, methacrylic acid, trifluoromethyl acrylic acid, 1-vinylimidazole, acrylamide, 4-vinylpyridine, 2-

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acrylamido-2-methylpropane sulphonic acid, 2-hydroxyethylmethacrylate, etc. Typical crosslinkers are ethylene glycol dimethacrylate, trimethylolpropane trimethacrylate, and pentaerythritol triacrylate, divinylbenzene, etc. Solvents, that are responsible for both bringing all the components in one phase and creating the porous structure in the polymeric matrix, include toluene, chloroform, dichloromethane, and acetonitrile. Azobisisobutyronitrile or benzoyl peroxide is used as an initiator in the imprinting process [6-8]. Molecular imprinting materials are involved in a lot of fields such as solid-phase extraction [9], catalysis [10], sensors [11], disease diagnosis [12], membranes [13] and drug release [14].

Tramadol is a synthetic painkiller drug used to treat mild-to-moderate pain. It is an efficient medicine to relieve dangerous situations when less powerful medications cannot do. However, tramadol is an addictive drug, and, accordingly, its prescription, dispensing, and use must be strictly controlled [15,16].

In this paper, molecular imprinted and non-imprinted polymers were prepared via free radical polymerization reaction and loaded with tramadol hydrochloride. The effects of the imprinting process and the molar ratio of ethylene glycol dimethacrylate (crosslinker) to the methacrylic acid (functional monomer) components on the controlled release of tramadol from the loaded polymers at different soaking times, pH, and temperature were examined.

2. Experimental

2.1. Material

Methacrylic acid (MAA) was obtained from Merck Co. (USA) and distilled in vacuum prior to its use in order to remove the stabilizer. Ethylene glycol dimethacrylate (EGDMA) and benzoyl peroxide (BP) of reagent grade were purchased from Sigma-Aldrich (Germany). Tramadol HCl, manufactured by Grunenthal Co., Germany, was kindly supplied by Minapharm Pharmaceuticals (MIPH), Egypt. Chloroform of chemical grade was used. The chemical structures of the used materials are presented in **Fig. 1**.

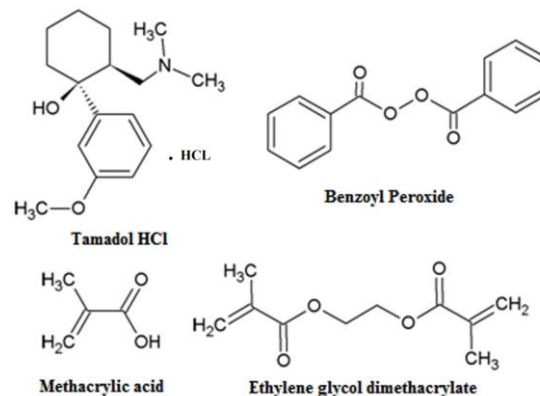


Fig. 1. Materials used in the synthesis of imprinted and non-imprinted polymers.

2.2. Methodology

2.2.1. Synthesis of tramadol-imprinted and non-imprinted polymers [17]

The free-radical polymerization method was used to synthesize four polymers based on poly(methacrylic acid-co-ethylene glycol dimethacrylate) [poly(MAA-co-EGDMA)]. Two non-imprinted poly(MAA-co-EGDMA), NIP13 and NIP15, were prepared using molar ratios of EGDMA to MMA equal 13 and 15, respectively. Other two corresponding tramadol-imprinted poly(MAA-co-EGDMA) symbolized TIP13 and TIP15 were synthesized.

The tramadol-imprinted polymers (TIP15 and TIP13) were prepared as represented in **Fig. 2**. Firstly, 0.5 mmol tramadol was dissolved in 6 ml chloroform in a glass tube, followed by addition of 1.00 mmol or 1.15 mmol MAA as a functional monomer and 15 mmol EGDMA as a cross-linker, respectively. Finally, 0.41 mmol BP dissolved in 2ml chloroform was added to the glass tube to initiate the free-radical polymerization reaction. The reactants in the glass tube were subjected to ultra-sonication for 30 min, purged with nitrogen for 2 min, and then, sealed. The glass tube was placed in a water bath at 80°C for 7h to allow the initiation of the polymerization reaction, after which a solid and rigid bulky material was obtained. The tube was removed from the water bath and left overnight to cool at room temperature. The rigid material was extracted from the tube and ground into fine powders using mortar and pestle. The crushed powders were sieved to below 212 μ m, washed with 10% acetic acid followed by methanol, and then with distilled water

to remove the tramadol. The other two non-imprinted polymers (NIP15 and NIP13) were prepared following the same procedure as mentioned above without the addition of tramadol.

2.2.2. Loading tramadol into the prepared polymers

Tramadol was loaded into 1g of the prepared TIPs and NIPs samples by performing the following procedure. TIPs or NIPs samples were soaked for 3h in a tramadol solution of 4 mg/L, i.e., initial concentration (C_i) at pH 7. At the end of the soaking time, the final concentration of tramadol in the solution (C_f) was estimated. The loaded-tramadol (LT) in TIPs or NIPs was determined in mg/g by using the following equation:

$$LT = C_i - C_f \dots\dots\dots 1$$

2.2.3. In vitro tramadol release estimation

The loaded-TIPs (L-TIPs) or loaded-NIPs (L-NIPs) were soaked in the desired solution. The percentage of the released tramadol (RT%) to the intended solution can be calculated by the following equation:

$$RT\% = \frac{C_f}{LT} \times 100 \dots\dots\dots 2$$

Where C_f is the final concentration of tramadol in the solution after soaking (in mg/L).

The effects of time, pH, and temperature on the release of tramadol from the different tramadol-loaded polymers (TIPs and NIPs) were in vitro investigated. These effects were studied by following the released tramadol from 0.25 g TIP or NIP at different time intervals, at different temperature degrees (room temp. 20 °C and 37 °C), and at different pH values (3.6, 7, and 9.8).

Estimation of loaded tramadol into the polymers or released tramadol from the polymers was carried out as previously reported [18], where standard solutions of different tramadol concentrations were prepared and their UV-vis absorption curves were recorded. The absorbances at the band 197 nm were considered and a calibration curve was constructed to estimate the concentration of unknown tramadol solutions.

2.3. Characterization techniques

TGA and DTG analysis: The thermal analysis was performed using Shimadzu TGA-50

thermogravimetric analyzer, Columbia, EUA, in nitrogen atmosphere at 10 °C/min heating rate in the range from room temperature to 600 °C.

FTIR spectroscopy: Fourier transform infrared (FTIR) spectra of the prepared samples were recorded by JASCO FTIR 6100 in the range of 4000–400 cm⁻¹ with 4 cm⁻¹ resolution and 50 scans with a scanning speed 2mm/sec.

UV-vis measurement: The UV-vis absorption spectra of solutions containing tramadol were measured using double beam spectrophotometer (JASCO Corp. V-570, Rel-OO, Japan) in the range 190-1100 nm. Quartz cells were used as holders for the liquid samples. The obtained data were drawn in the range 190-375 nm as no significant changes are noticed above 375 nm.

3. Results & discussion

3.1. Thermal characteristics

Fig. 3 shows the TGA and DTG curves of tramadol with both loaded-TIP15 and loaded-NIP15, and loaded-TIP13 and loaded-NIP13. It can be seen that tramadol decomposes at a maximum degradation temperature (T_d) of 257 °C. The mass loss above 100°C to below 182°C can be attributed to adsorbed moisture [19]. **Fig. 3 b** and **d** shows that tramadol decomposes in only one stage starting at about 182 °C with a maximum decomposition peak at 257°C. On the other hand, samples (TIP15 – TIP13) and (NIP15 – NIP13) loaded with tramadol have shown several decomposition peaks. The first is for the decomposition of the loaded-tramadol that overlaps with the degradation of the tramadol curve at about 257 °C for loaded-(NIP15 – NIP13) (**Fig. 3 b** and **d**, respectively). However, tramadol decomposition has been shifted to higher temperatures for loaded-(TIP15 – TIP13) (**Fig. 3 b** and **d**, respectively). This higher shift for the degradation temperatures of tramadol in TIPs than in NIPs may be attributed to the more heat energy dissipated in breaking of the non-covalent interactions between the trapped tramadol molecules within the specific network sites. The observed two other degradations at higher temperatures for TIP15 – TIP13 and NIP15 – NIP13 are related to the decomposition of the polymeric matrix.

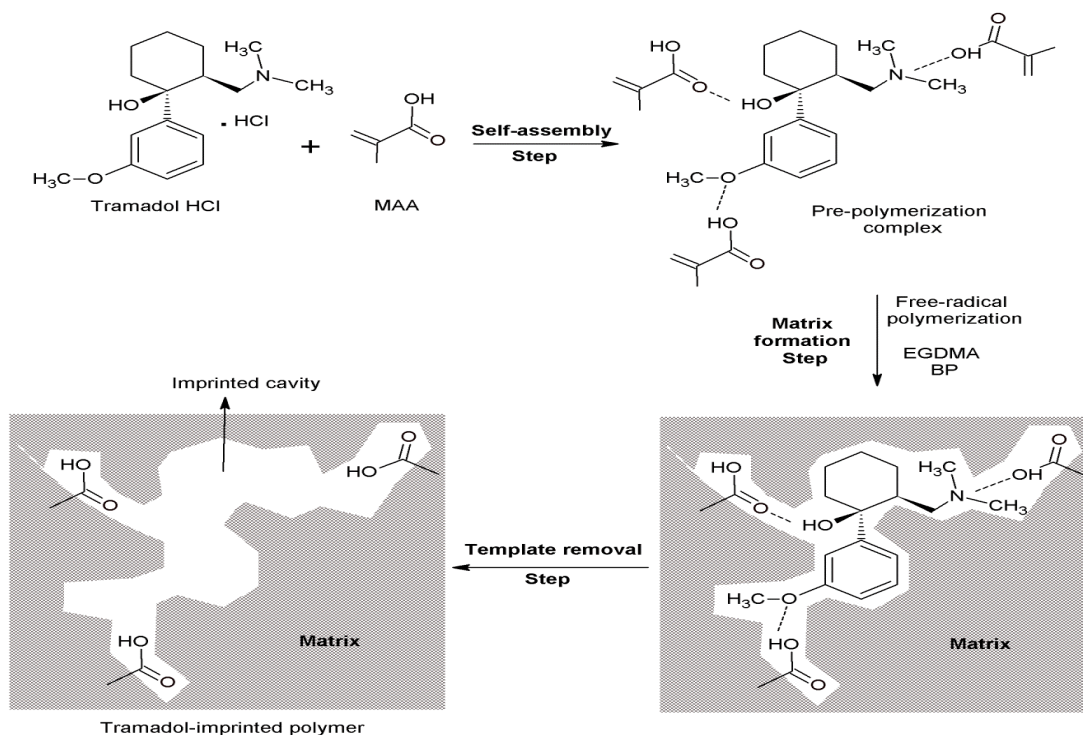


Fig. 2. Synthesis of the tramadol-imprinted polymers.

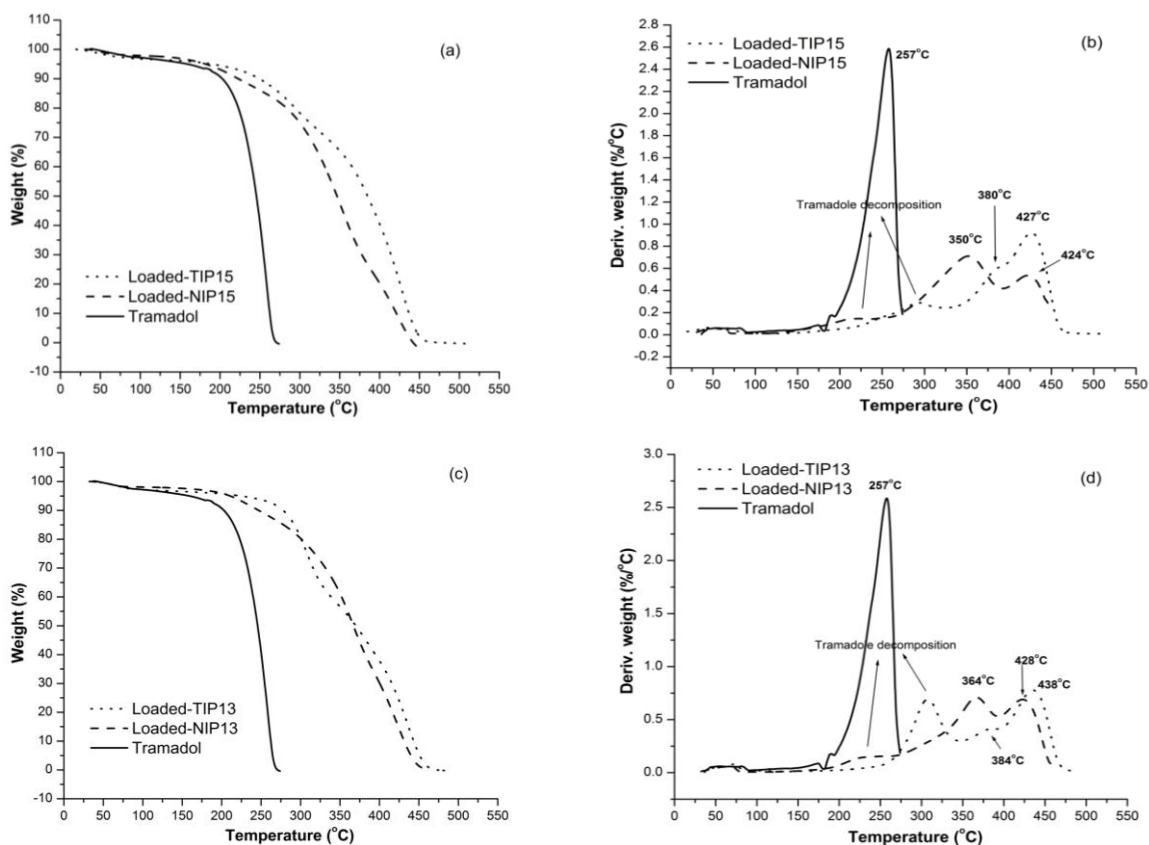


Fig. 3. TGA and DTG curves of; tramadol, L-TIP4 and L-NIP4 (a and b), respectively, and tramadol, L-TIP5 and L-NIP5 (c and d), respectively.

3.2. FTIR measurements

Fig. 4 a and **b** shows the FTIR of tramadol sample with (NIP15, L-NIP15, and L-TIP15) and (NIP13, L-NIP13, and L-TIP13), respectively. The spectrum of tramadol sample shows its principal bands at 2935 cm^{-1} and 2843 cm^{-1} (aliphatic C-H ν), 3304 cm^{-1} (O-H ν), 3048 cm^{-1} and 3007 cm^{-1} (aromatic C-H ν), 1603 cm^{-1} and 1583 cm^{-1} (C=C ν), bands from 1040 cm^{-1} to 1286 cm^{-1} (C-O ν and C-N ν), and 1470 cm^{-1} and 773 cm^{-1} (C-H δ) [20]. The spectra of NIP15 and NIP13 samples show the carbonyl and hydroxyl bands of the polymer matrix at ($1727\text{ cm}^{-1} - 1716\text{ cm}^{-1}$) and ($3439\text{ cm}^{-1} - 3427\text{ cm}^{-1}$), respectively. These two bands are shifted to lower wavenumbers in L-NIP15 and L-NIP13 spectra. The shift continues further to lower values in the spectra of L-TIP15 and L-TIP13 samples. This behavior can be attributed to the physical interactions originated between the carboxylic and ester groups in the cross-linked polymers and the OH and tertiary amine in tramadol [21,22]. The greater shifts in the carbonyl and hydroxyl bands may indicate the higher interactions in L-TIPs than in L-NIPs.

3.3. Controlled-release study of tramadol from L-TIPs and L-NIPs

3.3.1. Effect of soaking time

TIPs and NIPs were loaded with tramadol by soaking 1g in 4 mgL^{-1} tramadol solution (C_i) for 3 h under stirring. Due to the difference in the ability of the prepared polymers to absorb the tramadol contained in the solution, the UV-vis absorption spectra of the tramadol solution was performed and the absorbance was correlated with the calibration curve [18] to determine the concentration of tramadol retained in the solutions (C_f). The absorbances of TIP15 and NIP15 immersed solutions at $\lambda\ 197\text{ nm}$ were found to be 0.434 and 0.281, respectively. They were correlated with the calibration curve to determine C_f . The loaded-tramadol (LT) in TIP15 and NIP15 was determined using eq. 1 to be 3.060 and 1.955 (mg/g), respectively (**Fig. 5a** on the dashed line). However, LT in TIP13 and NIP13 was determined to be 3.608 mg/g at absorbance ($\lambda\ 197\text{ nm}$) 0.509 and 2.091 mg/g at absorbance ($\lambda\ 197\text{ nm}$) 0.300, respectively (**Fig. 5b** on the dashed line).

Fig. 5a shows the UV-vis absorption spectra of the dissolution medium after the immersion of L-NIP15 loaded by 1.955 mg/g with tramadol and L-TIP15 loaded by 3.060 mg/g with tramadol at different time intervals. **Fig. 5b** shows the UV-vis absorption spectra of the dissolution medium after the

immersion of L-NIP13 loaded by 2.091 mg/g with tramadol and L-TIP13 loaded by 3.608 mg/g with tramadol at different time intervals. The spectra reflect the released tramadol from L-NIPs and L-TIPs over time. In general, the absorption intensity at 197 nm wavelength increases with time, which means that more tramadol is released from L-TIPs and L-NIPs over time.

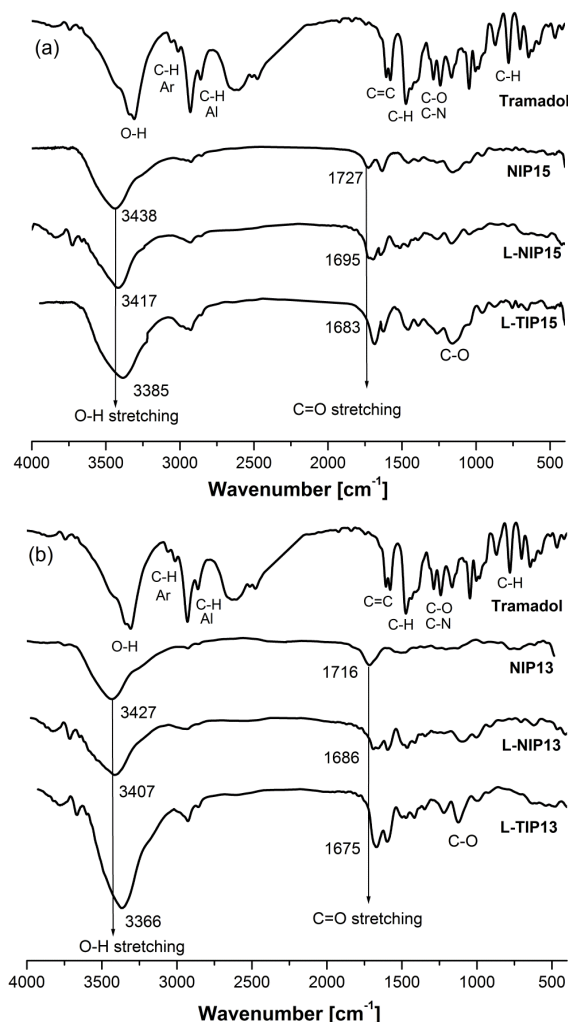


Fig. 4. FTIR spectra of tramadol sample with NIP15, L-TIP15, and L-NIP15 (a) and NIP13, L-TIP13, and L-NIP13 (b).

Fig. 6 shows the RT% of L-TIPs and L-NIPs at all time intervals calculated from eq. 2 and plotted against time. L-NIPs showed a high release of tramadol which is mostly released after 6 hours of immersion. However, L-TIPs exhibited gradual release of the loaded tramadol over a longer time. The initial and rapid release of tramadol in L-NIPs and L-TIPs at the early hours is attributed to the physical adsorption or the non-specific interactions. However, the slower release rate for L-TIPs, which

takes a longer time to reach the maximum release, can be attributed to the strong interaction with tramadol at the specific binding sites.

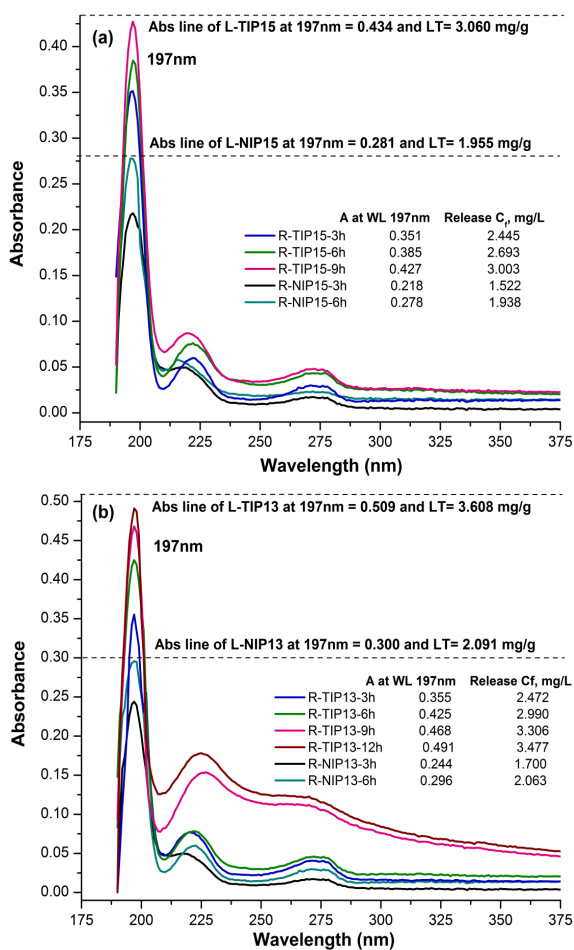


Fig. 5. UV-vis absorption spectra of the dissolution medium (pH 7) after immersion of L-NIP15 and L-TIP15 (a) and L-NIP13 and L-TIP13 (b) for different time intervals.

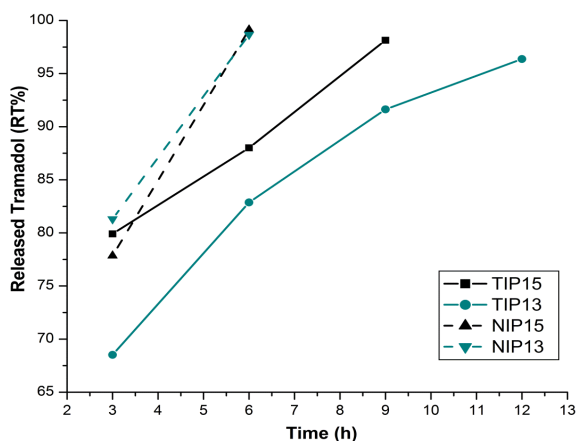


Fig. 6. The released tramadol % (RT%) from L-TIPs and L-NIPs measured in a dissolution medium of pH 7 for different time intervals.

The amount of released-tramadol from L-TIPs and L-NIPs is plotted against time in **Fig. 7**. This chart shows that about 99% of the loaded tramadol in L-NIPs was released after 6h while 83% to 88% were released from L-TIPs after the same time. Despite that, L-TIPs released more tramadol 2.69 mg (L-TIP15) and 2.99 mg (L-TIP13) after 6h than L-NIPs - 1.94 mg (L-NIP15) and 2.06 mg (L-NIP13). This more release of tramadol can be assigned to the higher tramadol capacity of L-TIPs than that of L-NIPs. Moreover, a more controllable release of tramadol was observed for L-TIP13 than L-TIP15 (Fig.4), where L-TIP13 needs 12 hours to release 96% of the loaded tramadol while L-TIP15 needs 9h to release 99%.

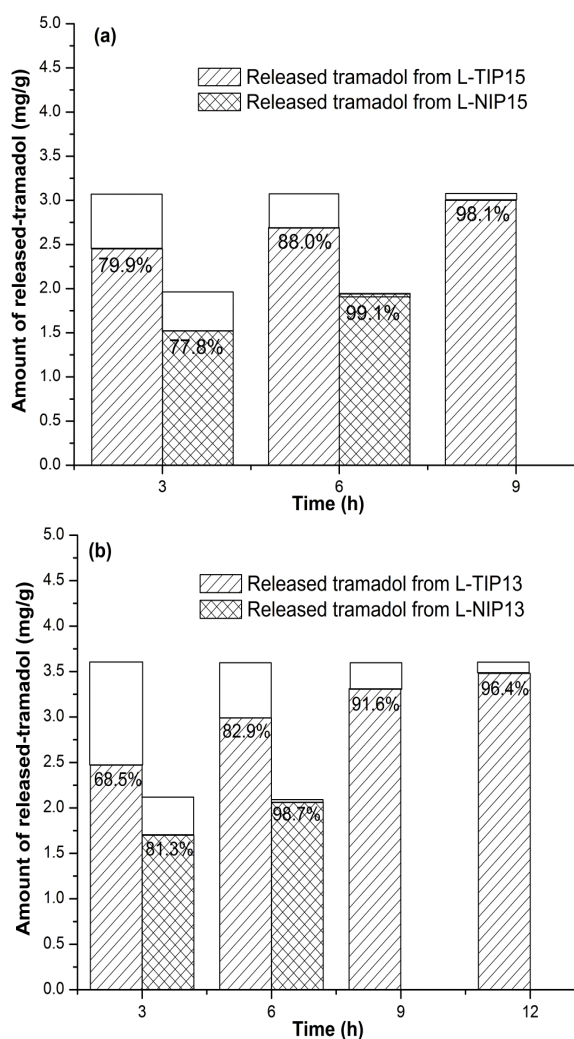


Fig. 7. The amount of released tramadol from 1g (a) L-TIP15 and L-NIP15 and (b) L-TIP13 and L-NIP13 in the dissolution medium (pH 7) for different time intervals.

3.3.2. Effect of pH

L-TIPs and L-NIPs samples were immersed in solutions of different pH ranges to study the effect of pH on the tramadol-release. **Fig. 8a** shows the UV-vis absorption spectra of dissolution media of pH (3.6, 7, and 9.8) after the immersion of the L-NIP15 sample, loaded with 1.955 mg/g tramadol, and L-TIP15 sample, loaded with 3.060 mg/g tramadol and soaked for 3h. **Fig. 8b** shows the UV-vis absorption spectra of the dissolution media of pH (3.6, 7, and 9.8) after the immersion of the L-NIP13 sample, loaded with 2.091 mg/g tramadol, and L-TIP13 sample, loaded with 3.608 mg/g tramadol and soaked for 3h. The spectra of both L-TIPs and L-NIPs samples showed intense absorbances at acidic pH 3.6 followed by pH 7 and least intense at pH 9.8. The absorbance intensities at acidic medium (pH3.6) correspond to 2.661 mg, 1.755 mg, 2.769 mg, and 2.013 mg for L-TIP15, L-NIP15, L-TIP13, and L-NIP13, respectively. These results indicate that tramadol is more released in the acidic medium than the neutral or alkaline ones.

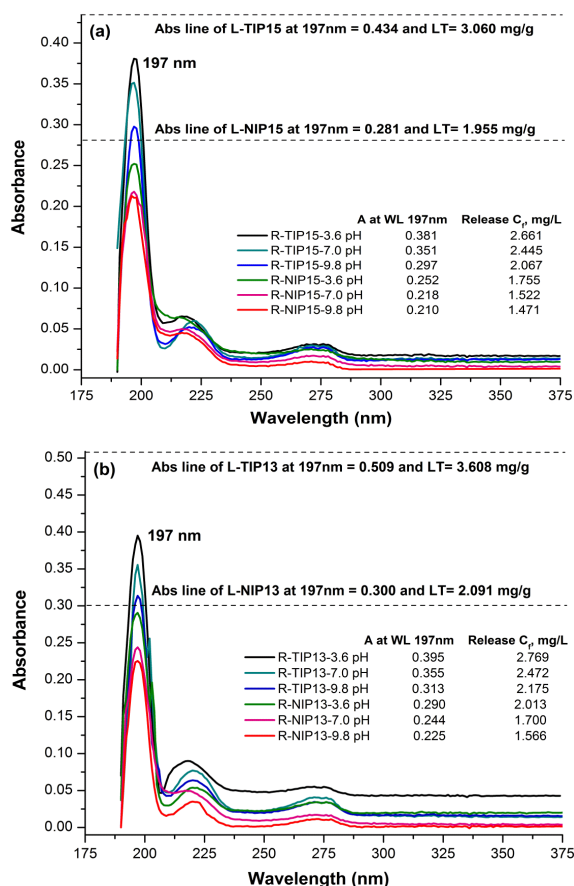


Fig. 8. UV-vis absorption spectra of the dissolution medium after immersion of L-NIP15 and L-TIP15 samples (a) and L-NIP13 and L-TIP13 samples (b) for 3h at different pH values.

The released percentage (RT%) of tramadol from L-TIPs and L-NIPs samples at different pH values were calculated using eq. 2 and plotted in **Fig. 9**. The effect of pH on the RT% of tramadol from L-TIPs and L-NIPs after being immersed for 3 h can be easily evaluated from this figure. For the loaded imprinted polymer, samples L-TIP15 and L-TIP13, the RT% is higher in the acidic medium (86.9% and 76.7, respectively) than the neutral (79.9% and 68.5%, respectively) and alkaline (67.5% and 60.35%, respectively) media. The same trend was observed for the non-imprinted polymers, L-NIP15, and L-NIP13, where RT% is higher in the acidic medium (89.7% and 96.2%, respectively) than the neutral (77.8% and 81.3%, respectively) and alkaline (75.2% and 74.9, respectively) media. It can be observed that the highest release is at pH 3.6 for both L-TIPs and L-NIPs while the slowest release is observed at pH 9.8. This can be assigned to the higher solubility of tramadol in acidic pH than in alkaline pH. The faster release of tramadol into the acidic medium is mainly based on the degree of ionization of tramadol ($pK_a=9.41$) [17].

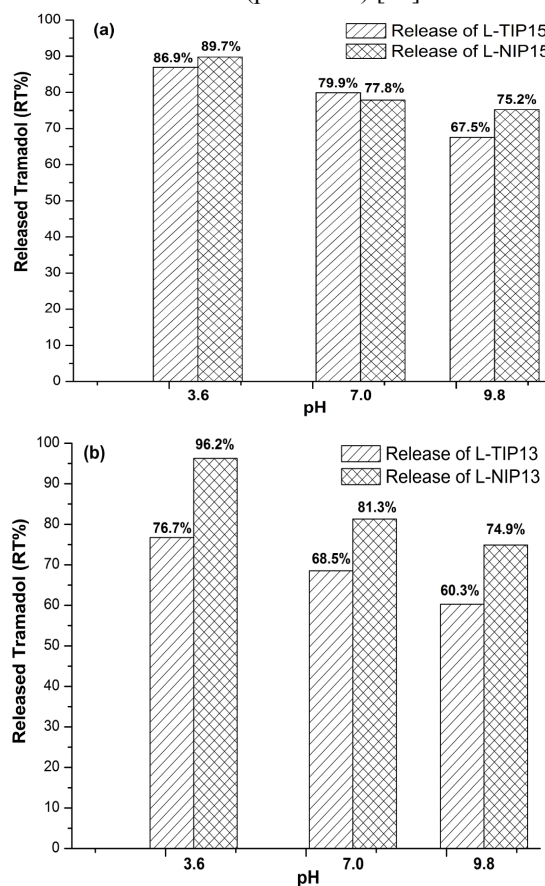


Fig. 9. Effect of pH on the RT % from L-TIP15 and L-NIP15 samples (a) and L-TIP13 and L-NIP13 samples (b) after being immersed for 3 h.

3.3.2. Effect of heat

Fig. 10a shows the UV-vis absorption spectra of the dissolution medium after the immersion of L-TIP15 and L-NIP15 samples at different temperature degrees (room temperature $\sim 20^\circ\text{C}$ and 37°C). **Fig. 10b** shows the UV-vis absorption spectra of the dissolution medium after the immersion of L-TIP13 and L-NIP13 samples at different temperature degrees (room temperature $\sim 20^\circ\text{C}$ and 37°C). The spectra show higher absorbances at 37°C than at room temperature. The absorbances at 197 nm for the dissolution media of immersed L-TIP and L-NIP samples correspond to the released tramadol. These absorbances were correlated with the calibration curve to estimate the concentration of the solution (C_r) and calculate the RT% using eq. 2. L-TIP15 and L-TIP13 samples, originally loaded with 3.06 mg/g and 3.608 mg/g tramadol, release 2.445 mg and 2.472 mg at 20°C , respectively.

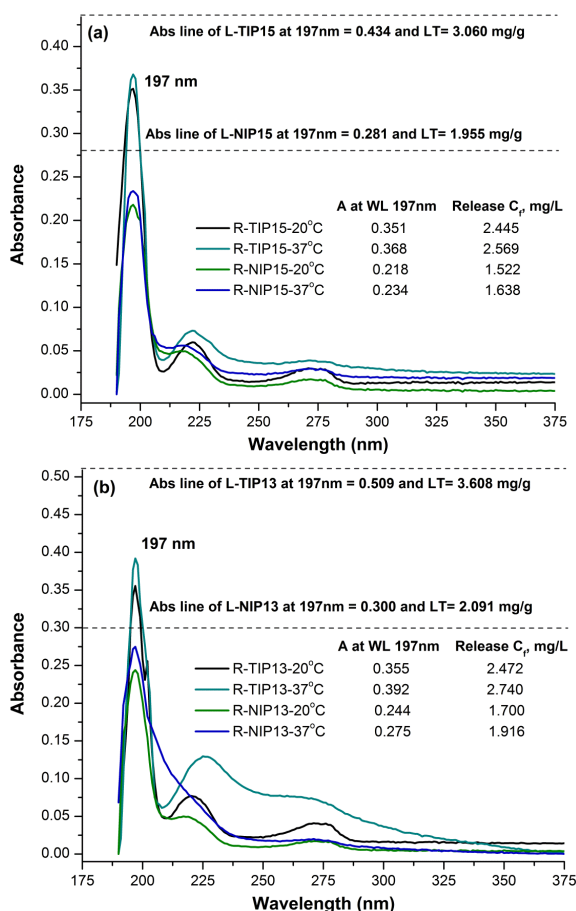


Fig. 10. UV-vis absorption spectra of the dissolution medium after immersion of L-TIP15 and L-NIP15 samples (a) and L-TIP13 and L-NIP13 samples (b) for 3h at 20°C and 37°C .

Higher tramadol release is observed at 37°C to reach 2.569 mg and 2.740 mg, respectively. The same trend can be observed for L-NIP15 and L-NIP13 originally loaded with 1.955 mg/g and 2.091 mg/g tramadol, respectively. These samples release 1.522 mg and 1.700 mg at 20°C and 1.638 mg and 1.916 mg at 37°C , respectively.

The plots in **Fig. 11** show the effect of temperature on RT% from L-TIP and L-NIP samples. RT% increases from 79.9% to 83.9% (for L-TIP15) and from 68.5% to 75.9% (for L-TIP13) by raising the temperature from 20°C to 37°C . In the same way, the RT% increases from 77.8% to 83.8% (for L-NIP15) and from 81.3% to 91.6% (for L-NIP13) by elevating the temperature from 20°C to 37°C . This behavior can be attributed to the breaking down of the physical interactions between tramadol and functional groups in polymers caused by excessive heat. Therefore, the higher the temperature, the greater the amount of released tramadol (RT%).

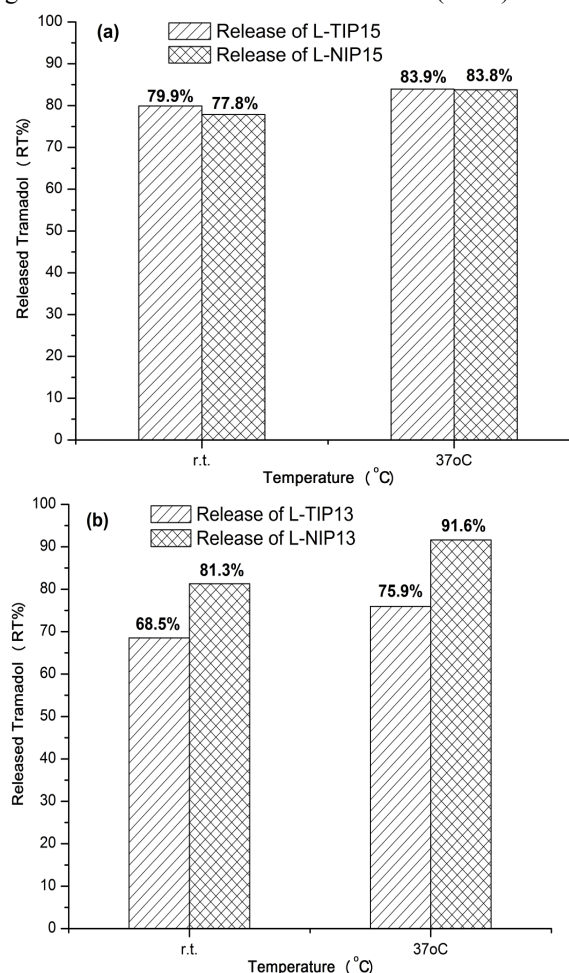


Fig. 11. Effect of temperature on the RT% from L-TIP15 and L-NIP15 (a) and from L-TIP13 and L-NIP13 (b) after being immersed for 3h at 20°C and 37°C .

4. Conclusion

Tramadol-imprinted and non-imprinted polymers were synthesized using two molar ratios of the crosslinker to the functional monomer equal 15 and 13. The prepared polymers were then loaded with tramadol. The effect of molar ratio and imprinting process on tramadol release was studied in different pH media, temperature, and soaking time. 3.06 mg and 3.608 mg tramadol can be loaded in 1 g TIP15 and TIP13, respectively, while 1.955 mg and 2.091 mg can be loaded in 1 g NIP15 and NIP13, respectively. The greater amount of tramadol loading in the imprinted polymers than in the non-imprinted ones may be due to the specific sites originated by the imprinting process together with the non-specific sites. The molar ratio of 13 exhibited higher loading than 15. TGA and FTIR analysis showed that greater physical interactions were generated between the loaded tramadol with imprinted polymers than with non-imprinted polymers. The release of tramadol is slower from imprinted polymers than from non-imprinted polymers because of the strong interaction with tramadol at the specific binding sites. Imprinted polymer with a molar ratio of 13 showed more controllable tramadol release over 12 hours than imprinted polymer with a molar ratio of 15 which extracted its loaded tramadol over 9 hours. 96.2% of the loaded tramadol in TIP13 was released into the acidic medium after 3 h while only 81.3% and 74.9% were released in the neutral and alkaline media. The fastest tramadol release into the acidic medium is due to the higher solubility of tramadol in acidic than in alkaline pH. Also, the rise in heat increased the tramadol released from L-TIP13 from 81.3% at room temperature to 91.6% at 37°C. The elevated temperature caused the breaking down of the physical interactions between tramadol and functional groups in polymers.

Conflicts of interest

There are no conflicts to declare.

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