Indomethacin Release Behavior from pH-and Thermo-responsive Alginate –Ca^{2+} Containing Poly(N-isopropylacrylamide) semi-IPN Beads

Jun Shi[1,2], Natália Alves[1,2] and João F. Mano[1,2]
1.3B´s Research Group – Biomaterials, Biodegradables and Biomimetics, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal.
2.Polymer Engineering Department, University of Minho, Campus de Azurém, 4800-058 Guimarães, Portugal.

Statement of Purpose:

Intelligent hydrogels, which can change their swelling behavior and other properties in response to environmental stimuli, have attracted great interest not only because of their unique properties but also their hydrogel potential for significant technological and biomedical application. Among these, temperature and/or pH responsive systems have been potential candidates because these factors could be the most available environment in the human body.

In this work, the pH /temperature sensitive release of indomathcin, a model drug, from semi-interpenetrated networks, IPN, hydrogel beads composed of alginate and poly(-isopropylacrylamide), PNIPAAM, is reported. Such formulations intend to combine the pH responsive property of alginate and the temperature sensitivity of PNIPAAM to obtain a smart drug delivery system.

Methods:

N-isopropylacrylamide (Acros Chem.), ammonium persulfate (Sigma Chem.), N, N, N´, N´-tetramethylethylenediamine (Sigma Chem.), Sodium alginate (low viscosity, 250cps, Sigma Chem.) and indomethacin (Fluka Chem.) were used as received.

Preparation of alginate-PNIPAAM beads: Alginate, PNIPAAM (previously synthesized), small amount of NaCl and 20% of indomethacine were dissolved in distilled water. The solution was then dropped into 1.5% $CaCl_2$ solution and allowed to harden for 30min.

Determination of indomethacin encapsulation efficiency of beads: The beads (10mg) were put into 100ml of SBF (pH 7.4) and maintained stirring for 48 h. The amount of free indomethacin was determined in clear supernatant by UV spectrophotometry at 329 nm.

In vitro release studies: Beads (10 mg) were suspended in 50 ml of SBF (pH 7.4 or 2.1) solution. This dissolution medium was stirred at 50 rpm in a horizontal laboratory shaker and maintained at 37°C or 25°C. Samples (2 ml) were periodically removed and the volume of each sample was replaced by the same volume of fresh medium. The amount of released indomethacin was analyzed with a spectrophotometer at 329 nm.

Results / Discussion:

Four kinds of beads with different PNIPAAM content were prepared in our study. It can be seen from Table 1 that the loading content of the resultant beads are about 15%. pH- and temperature- sensitive release behaviors of indomethacin could be observed with all beads prepared (Figures 1 and 2).

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Table1 Drug loading content and loading efficiency of semi-IPN beads.

Samples	Percent of PNIPAAM(%)	Drug percent (feed, %)	Drug content (mg/10mg beads)	Loading content (%)	Loading efficiency (%)
a	0	20	1.19	14.4	72
b	25	20	1.25	15	75
c	33	20	1.26	15.2	76
d	14	20	1.21	14.6	73
e	43	20	1.24	15	75

Figure 1 show that from sample b only a negligible amount of indomethacin was released at pH 2.1, while at 7.4 pH more than 90% of the total drug in the beads was gradually released within about 3h. The results are consistent with the swelling results of the beads which reveal the increase of swelling at 7.4 pH. Temperature-dependent release profiles from sample e showed in Figure 2 demonstrated that the beads exhibit high release rate at higher temperature assigned to the sol-gel transition occurring in PNIPAAM above ~32 ºC.

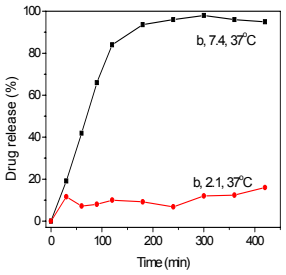

Figure 1 pH value-dependent release profiles at 37°C from b measured at 2.1 pH and 7.4 pH.

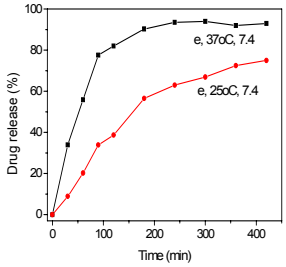

Figure 2 Temperature-dependent release profiles at 7.4 pH from e measured at 25°C and 37°C.

Conclusions:

A new pH /temperature sensitive drug delivery system, based on semi- IPN hydrogel beads composed of alginate and PNIPAAM, was proposed. Drug release results using indomethacine demonstrated that this semi- IPN system could be used in effective pH /temperature responsive drug delivery devices. The drug release profile could be controlled by changing the temperature and is also sensitive to the magnitude of swelling in semi- IPN hydrogel beads at different pH value.

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