NOVA SCHOOL OF SCIENCE & TECHNOLOGY

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LABORATÓRIO ASSOCIADO PARA A QUÍMICA VERDE

Ionic and Aerogel Levothyroxine formulations with improved bioavailability properties

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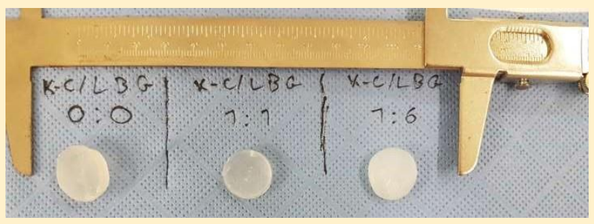
Introduction

Biopolymers are polymers produced from natural sources, chemically synthesized from biological material and or fully biosynthesized by microorganisms. They have an unique strength in their application for drug delivery, which allows for a new breakthrough in the formulation of novel drug delivery systems that enhance therapy and treatment. This can be achieved by functionalizing the surface of polymeric particles. Ionic liquids have gained increasing attention as clean and multifunctional solvents for a variety of applications. The main function of polymeric carriers is to transport the drugs to the required site of action while protecting the drugs from interaction with other molecules. In this work the mixture of kappa-carrageenan with locust bean gum (60%/40%) is used. Levothyroxine is the main thyroid hormone in circulation, can be administered orally as sodium salt, is used exclusively for the treatment of various forms of hypothyroidism. Active Pharmaceutical Ingredients (APIs) used in drug formulations are usually found in their crystalline form to maximize their purity, thermal stability, and bioavailability. However, these solid forms have a number of limitations, such as low water solubility, polymorphism, and difficulty in crossing lipid layers due to their insufficient lipophilicity. Pure compounds, salts and all kinds of pharmaceuticals and drug candidates can undergo polymorphism. Chloride ions remain the most commonly used anionic ion counterions for forming salts as APIs, while sodium ions are more commonly used for forming salts from acidic molecules.

Biopolymers` aerogels

Synthesis

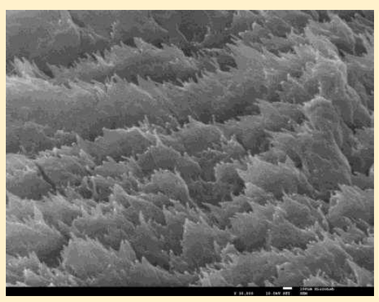
Mixture of KCAR_LBG → Addition of IL [EOMIM][Br] → Solvent Exchange water->ethanol



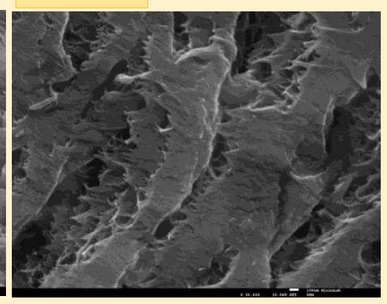
KCAR_LBG 0:0 KCAR_LBG 1:1 KCAR_LBG 1:6

Characterization

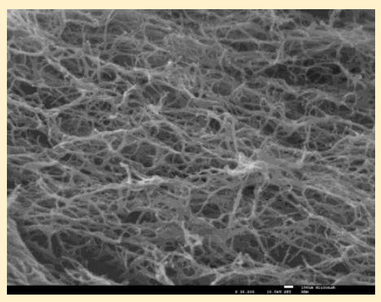
SEM



KCAR_LBG_T4



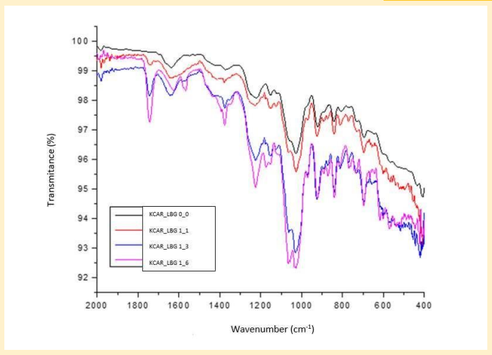
KCAR_LBG_f_1_1



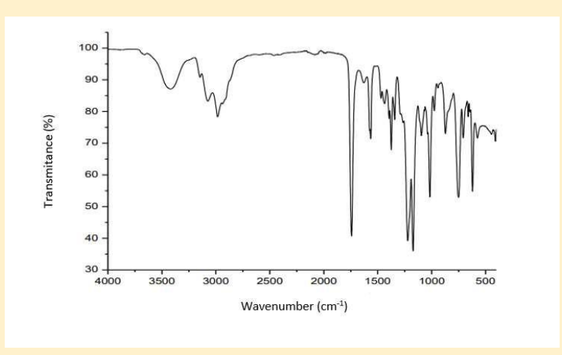
KCAR_LBG_f_1_6

SEM images of κ-carrageenan-locust bean gum dried gels synthesized with different compositions of the ionic liquid [EOMIM][Br].
The network structures of samples produced without [EOMIM][Br] and with the addition of 50% (m/m) of this ionic liquid presented a more dense fiber structure. The dried gel synthesized with the addition of an ionic liquid excess (300% (m/m)) exhibited a more visible interconnected fiber web structure containing a broad pore distribution including meso and macropores.

FTIR-ATR



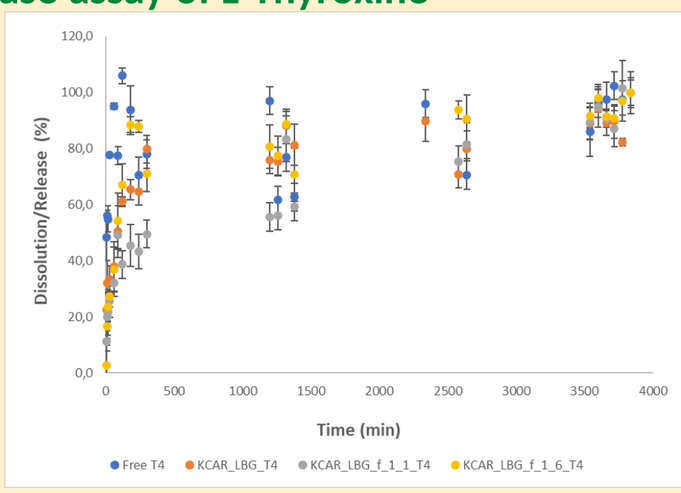
KCAR_LBG with different IL's ratios



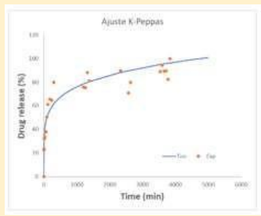
Ionic Liquid [EOMIM][Br]

The spectra on the left shows the FTIR spectra of the biopolymer mixture KCAR_LBG for the different IL ratios. These measurements serve to confirm the characteristic bands of the KCAR_LBG composite functionalized with the IL [EOMIM][Br]. The sample identified in the figure as KCAR_LBG does not have the presence of IL thus allowing a comparison of band intensities to be possible. The band at 1750 cm^{-1} corresponds to the carbonyl C=O bond which is a representative band of IL [EOMIM][Br] and it can be seen that in the 1:3 and 1:6 ratios these bands have an higher intensity compared to the KCAR_LBG and 1:1 ratio samples. The band related to the imidazolium rings on IL can also be observed close to the wavenumber of 1600 cm^{-1}.

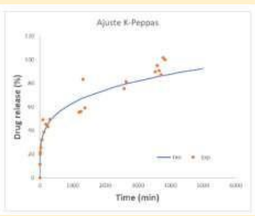
Release assay of L-Thyroxine



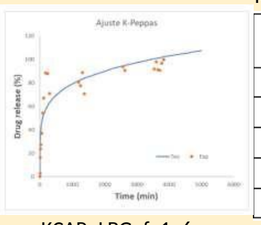
Phosphate Buffer pH 7.4 T=37°C



KCAR_LBG_T4



KCAR_LBG_f_1_1



KCAR_LBG_f_1_6

K-Peppas and Higuchi kinetic parameters for the release of levothyroxine

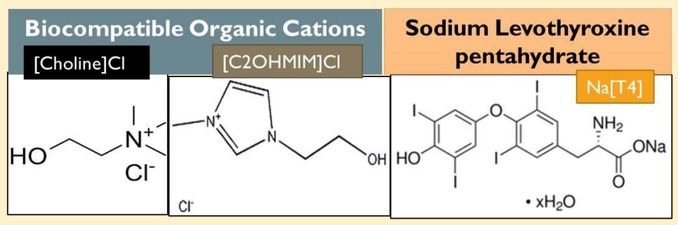
Samples	K-Peppas			Higuchi	
	R^2	$k(min^{-1})$	n	R^2	$k(min^{-1})$
KCAR_LBG_T4	0,331	29,28195	0,0609	0,2256	0,1942
KCAR_LBG_0_0	0,8933	17,38201	0,1939	0,7629	0,8129
KCAR_LBG_1_1	0,939	10,86926	0,2668	0,9241	1,2598
KCAR_LBG_1_6	0,7075	8,014935	0,4265	0,6504	1,2598

The matrixes KCAR_LBG, KCAR_LBG_f_1_1 and KCAR_LBG_f_1_6 were impregnated respectively with 79.5 % (m/m), 67.5 % (m/m) and 53.1 % (m/m) of levothyroxine. The amount of levothyroxine that could be loaded in the three different aerogel matrixes differs substantially. The presence of ionic liquid apparently does not promote the adsorption capacity of the drug and, the higher macroporosity observed on sample KCAR_LBG_f_1_6 may also be interfering with the process. Apparently, this matrix is less able to retain the drug inside the porous structure.
The release profiles of levothyroxine at physiologic pH 7.4 for the composites KCAR_LBG_T4, KCAR_LBG_f_1_1_T4 and KCAR_LBG_f_1_6_T4 samples are shown above. The release plateau is reached in about 3500 min (2 ½ days) corresponding to around 17 %, 19 % and 35 % of the total loaded levothyroxine in each composite, respectively. Matrixes decompose in up to 5 days and consequently the total amount of drug is released.
In the table able are presented the correlation factors (R2) determined through the adjustment of the two kinetic models more adjustable to the release curves: i) log C vs log t (K. Peppas) and ii) C vs t 0.5 (Higuchi), where C represents the percentage of drug in solution at time t (released) and where t represents the time in minutes.
For all composites the best fitting is achieved with the Korsmeyer and Peppas model with a good correlation factor (R2). Since the matrixes present some swellable degree it was considered that the K. Peppas kinetic model would best represent the release mechanism of levothyroxine from composites. The kinetic parameters determined for drug release through K. Peppas and Higuchi models are also presented in the table. The parameter k is the Korsmeyer release constant and n is an empirical parameter that characterizes the release mechanism. The n values of Korsmeyer- Peppas are mostly less than 0.5 suggesting the release mechanism was governed by diffusion.

API-ILs based L-Thyroxine

Biocompatible Organic Cations: [Choline]Cl, [C2OHMIM]Cl

Sodium Levothyroxine pentahydrate: Na[T4]



Synthesis

ANIONIC EXCHANGE REACTION [CATION]Cl + Na [T4] —Ethanol, rt, 24h→ [CATION][T4] + NaCl

Based on the literature it is proven that this method improves the bioavailability of drugs. In this reaction 2 biocompatible organic cations, C2OHMIM and choline chloride, were used. The reaction worked and the samples were characterized by HNMR. Positive results were obtained with this reaction, the reaction with the choline chloride cation had a yield of 65% and the reaction with C2OHMIM 68%. The solubility tests were performed in water at 37°C. It can be seen an increase up to 4-5 times compared to the starting levothyroxine.

Water Solubility studies

Compounds	Solubility (g/L) 37°C
Na[T4]	0.153
[Cholin][T4]	~0.476
[C2OHMIM][T4]	~0.476

Levothyroxine loaded into aerogel

Aerogel - Supercritical drying:

- Pressure: 140 bar
- Temperature: 40°C
- Time: 2 h

→ Levothyroxine loading using a saturated levothyroxine solution in DMSO →

Highlights

- Successful preparation of levothyroxine loaded aerogel
- New API ILs based levothyroxine have been developed
- Significantly improvement of water solubility at 37°C (4 to 5 times comparing with original API)

References

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Acknowledgements

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