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ACTIVATED CARBON FROM FRUIT STONES AS IBUPROFEN CARRIER - ENCAPSULATION AND *IN VITRO* RELEASE STUDY

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Summary

Yaneva, Z. L., L. L. Bekirska, N. V. Georgieva, B. K. Derventlieva & I. D. Gandev, 2017. Activated carbon from fruit stones as ibuprofen carrier – encapsulation and *in vitro* release study. *Bulg. J. Vet. Med.*, **20**, Suppl. 1, 8–12.

The aim of the present study was to investigate the properties of Bulgarian activated carbon derived from fruit stones (ACFS) as a precursor for the development of ibuprofen (IBU) controlled release systems. The experimental data from the drug encapsulation kinetics study displayed satisfactory incorporation efficiency E = 67.7%. The *in vitro* release profile of the nonsteroidal anti-inflammatory drug established significant extend of prolonged IBU release from the loaded activated carbon. The experimental results were mathematically modelled.

Key words: activated carbon, ibuprofen, incorporation, release, mathematical modelling

INTRODUCTION

The development of innovative, controlled-release systems (CRS) for biologically active substances increasingly used in medicine, pharmaceuticals and agriculture, has been one of the top priority areas of scientific research in the field of medical chemistry over the last decade (Garrido-Herrera *et al.*, 2006).

The main qualitative indicators for assessing the effectiveness of CRS are the degree of incorporation and subsequent *in vitro* controlled release of the biologically active substance, which depend on the physico-chemical and mechanical properties of the composite, on the molecular characteristics and properties of the organic substances, and on the interaction between the carrier and the incorporated drug (Oh *et al.*, 2011; Azaïs *et al.*, 2006; Balau *et al.*, 2009; Huei *et al.*, 2016).

The efficiency of activated charcoal CRS and its proven antitoxic activity, due to its large specific surface area, high adsorption capacity and microporous structure, has provoked *in vitro* and *in vivo* studies on the potential of a variety of newly synthesized AC as precursors for the development of effective drug delivery systems (Oh *et al.*, 2011). McCary & Rybolt (2013) investigated the incorporation of acetaminophen into various porous carbon-containing materials and their sub-

sequent release. *In vitro* studies on sorption of metoprolol, pindolol, salbutamol, furosemide and clonidine on activated carbon demonstrated that although the drugs affinity for the carrier is in good agreement with their hydrophobicity, the desorption rate is not proportional to their hydrophilicity and was significantly influenced by the particle size (Roivas and Neuvonen, 1994). Effective use of activated charcoal as an oral adsorbent in the primary treatment of acute theophylline poisoning was investigated *in vitro* (Nakamura *et al.*, 2003). The study of Tominaga *et al.*, (2012) on new treatment with activated charcoal swabs showed a remarkable improvement without adverse side effects in the treatment of bacterial vaginosis.

The outline of this new priority area in medicinal chemistry, as well as the lack of researches applying alternative Bulgarian activated carbons as carriers of biologically active substances, provoked the objectives of the current research.

The aim of the present study was to perform laboratory analyzes and comparative studies on the properties of Bulgarian activated carbon derived from fruit stones (ACFS) as a precursor for the development of ibuprofen controlled release systems.

MATERIAL AND METHODS

Ibuprofen ($C_{13}H_{18}O_2$, ≥98%, HPLC), C_2H_5OH (analytical standard), HCl (reagent grade, 37%), NaOH (p.a.) and NaCl (p.a.) were supplied by Sigma-Aldrich®. The activated carbon derived from fruit stones by steam-gas activation (ACFS) was supplied by GANDEV-ELI-ILIYA GANDEV ET, Kamenovo Village, Bulgaria.

Ibuprofen concentrations were measured with UV-VIS spectrophotometer DR 5000 Hach Lange (Germany), supplied with 10 mm quartz cells. All spectra were recorded in the UV region at λ 257 nm with 2 nm slit width, 900 nm min^{-1} scan speed and very high smoothing.

Drug encapsulation

Ibuprofen encapsulation was carried out by agitating of ACFS with 60 mL of ibuprofen solution with initial concentration C_o 20 μg/mL at temperature T = 30 ± 2°C. The kinetics experiments were conducted in a standardized batch reactor (V 200 mL) with a two-bladed impeller at agitation rate n 200 rpm. The drug solutions were separated from the carrier by centrifugation with Heraeus Labofuge 200 (Thermo, Electron Corporation) and filtered using 0.45 μm membrane filters (LCW 916, Hach Lange, Germany). All experiments were carried out in triplicate, and the average values were taken to minimise random error. Blanks containing no drug and replicates of each sorption point were used for each series of experiments.

Drug release study

Ibuprofen release experiments were conducted by agitating 0.3 g dried IBU-loaded ACFS sample with 20 mL simulated gastric fluid solution, containing 0.1N HCl and 0.1N NaCl at pH 1.2 and temperature 37 °C in a Digital Waterbath WNB 22 (Memmert GmbH). The liquid phase concentrations of released IBU were determined spectrophotometrically at definite time intervals till equilibrium.

Non-linear regression analysis was employed to describe the encapsulation/release behavior of the studied system by means of various mathematical equations.

RESULTS AND DISCUSSION

Ibuprofen standard solutions were prepared in EtOH. The drug UV/VIS calibration curve in the concentration range C_o 20–200 µg/mL characterised with satisfactory linearity R^2=0.9950.

Kinetics of IBU encapsulation

The highest attained encapsulation capacity of the AC at pH = 7 towards the drug was 20.01 µg IBU/mg ACFS, which is equal to incorporation efficiency E = 67.7%. The experimental kinetics curve of IBU incorporation into ACFS (Fig. 1) displayed a significantly high encapsulation rate of the drug molecules during the first 40 min (Fig. 1–I), which characterized with the highest value of the rate constant k' = 0.5469 min^{-1}. Regarding the sorption mechanism, this stage represents the mass transfer of the drug molecules through the boundary layer around the solid particles. The second stage (Fig. 1–II) displays a gradient decrease in IBU liquid phase concentration, which could be attributed to diffusion of the organic molecules in the micro-/meso-pores of the carrier. The final section of the plot (Fig. 1–III) represents macropore intraparticle diffusion and the establishment of equilibrium.

Considering that ibuprofen is a weak carboxylic acid with pKa = 5.2, and that the experimentally determined point of zero charge of ACFS is pHPZC = 9.37, it could be concluded that at pH = 7 the carrier surface is positively charged, so one of the basic mechanisms determining ACFS affinity towards IBU is based on electrostatic interaction between the solid particles and the drug molecules.

In vitro ibuprofen release

The *in vitro* release behaviour of IBU in simulated gastric fluid (pH=1.2, T=37 °C) was investigated (Fig. 2). The highest release efficiency of approximately 90% was obtained for 20 h. The experimentally obtained release profile was described by four mathematical models (Table 1). According to the highest value of the correlation coefficient R^2 and the lowest values of SSE, MSE and RMSE (Table 1), it was established that the mixed-order model best represented the drug release beha-

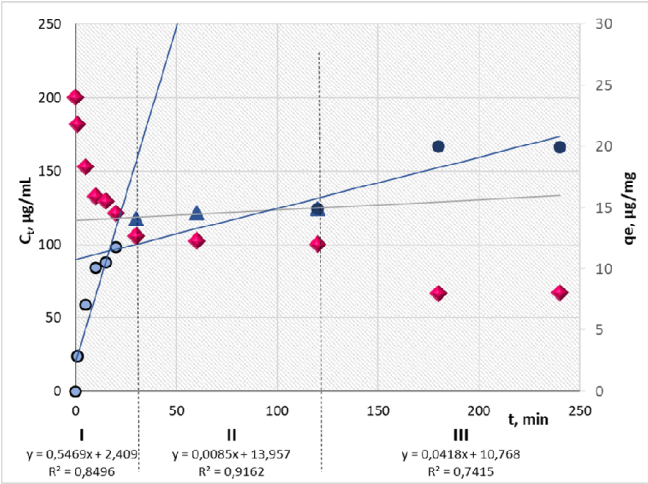

Fig. 1. Kinetics of ibuprofen encapsulation into ACFS.

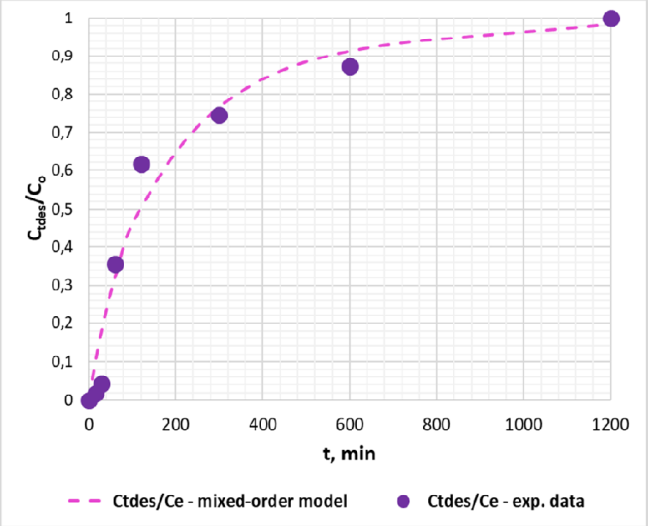

Fig. 2. Release profile of ibuprofen from ACFS-drug loaded particles.

Table 1. Release models, parameters and error function values

Desorption models, non-linear equation		Model parameters		Error functions	
Zero-order $C_t = k_o t$	(1)	K_o	0.144	R^2 SSE MSE RMSE	0.676 11502 1643.2 40.534
Higuchi $q_t = k_H t^{1/2}$	(2)	K_H	4.549	R^2 SSE MSE RMSE	0.866 2871.73 410.25 20.22
Mixed order $q = q_1 e\ ((1 - \exp(-k_1 1.t)/(1 - f_2 2.\exp(-k_1 1\ t))$	(3)	k_1 f_2	0.003 0.645	**R^2** **SSE** **MSE** **RMSE**	**0.967** **0.043** **0.007** **0.084**
Korsmeyer-Peppas $\frac{C_t}{C_o} = a.t^n$	(4)	α n	0.062 0.402	R^2 SSE MSE RMSE	0.892 0.123 0.021 0.143

viour. Consequently, IBU dissolution from the AC matrix was due to a mixed mechanism combining desorption and diffusion of the drug molecules.

The applicability of Korsmeyer-Peppas model could not be fully neglected due to the acceptable value of the regression coefficient (R2 ~ 0.89). The release exponent n of this model describes the drug release mechanism: Fick diffusion for n=0.5; non-Fickian diffusion for 0.5<n<0.1.

Thus, according to the value of n obtained in the present study, the probable

mechanism of IBU release is non-Fickian diffusion. This model is generally used to analyse the release of pharmaceutical polymeric dosage forms, when the release mechanism is not well known or when more than one type of release could be involved (Costa & Lobo, 2001).

CONCLUSION

The current study has provided insights into the encapsulation/release behaviour of the system ibuprofen/ACFS. The obtained ibuprofen release efficiency in simulated gastric fluid was significant and attained for a prolonged time period of 20 h. The results from the present study are essential as they could be applied during the development of innovative AC-based carrier systems for human and veterinary medicine.

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