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Acyclovir release from its composites with silica as a function of the silica matrix modification and the drug loading

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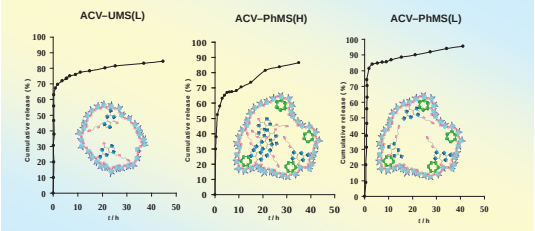
Acyclovir release from its composites with unmodified silica at pH 1.6 and 7.4 follows zero order kinetics for two days. Modification of the silica matrix with phenyl groups leads to dramatic decrease in the drug release level at pH 7.4 compared with pH 1.6 as well as to heterogeneous phase state of acyclovir in the phenyl modified composite with high loading of the drug.



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Acyclovir or 9-[(2-hydroxyethoxy)methyl]guanine (ACV) is a commonly used antiviral drug for the treatment of highly contagious herpes simplex virus infections affecting 65–90% of the adult population worldwide.[1,2] However, efficiency of the ACV therapy *via* parenteral or oral route is rather low, so multiple administration or large dose of the drug is required to achieve therapeutic concentration in the blood, which results in side effects.[2,3] This indicates the need for development of new ACV formulations capable of its controlled and sustained release, which will be more effective, safe and patient compliant.

Drug–silica composites represent a promising solution for oral delivery with improved pharmaceutical and consumer properties.[4–7] Various technologies and materials employed in new dosage forms of ACV are described in reviews,[8–10] including 'soft' materials, such as natural and synthetic polymers or liposomes, which are biologically relevant though susceptible to destruction due to environmental factors like mechanical action, temperature or enzymes. Colloidal silica has advantages over the 'soft' materials in the oral drug formulations due to its unique combination of physicochemical properties, like mechanical and thermal ones, photostability, tunable structure as well as textural and morphological characteristics, accompanied by valuable biological properties, such as biodegradability, biocompatibility, stability to enzymatic and microbial attacks, which in particular make it a safe food additive.[11] Nevertheless, the works devoted to the use of colloidal silica as a carrier for ACV are scarce. Examples include employment of colloidal silica (aerosol) as an excipient in orally disintegrating ACV tablets,[12] use of silica gel itself as an alternative to ACV cream[13] and the ACV sol–gel encapsulation into silica nanoparticles resulting in new corneal implant for the controlled release of the drug for 10 days after the corneal transplantation,[14] with enhanced effectivity compared to free ACV incorporated directly into hydrogel constructs. Other examples represent the synthesis of magnetic core–silica shell ACV-loaded nanoparticles[15] as a delivery system with good capacity for the drug storage and sustained release, as well as mesoporous silica nanoparticles (MSNs) functionalized by various organic groups related to the glycosaminoglycan structure and loaded by ACV,[16] with greater antiviral effect of ACV having been observed for the ACV–MSN–SO_3 composite compared to free ACV.

In this work, ACV composites with phenyl modified silica (PhMS) as well as unmodified silica (UMS) with two different drug loadings were synthesized using sol–gel technique (for details, see Online Supplementary Materials). The choice of these silica materials originated from the purine aromatic system and acid–base groups of ACV, which could interact with the matrices and influence the release kinetics. Hereinafter, the ACV–UMS composites with low and high drug loading values of 18.4 and 36.5 mg g^{-1} are designated as ACV–UMS(L) and ACV–UMS(H), respectively, while the ACV–PhMS ones with the loading values of 18.3 and 34.7 mg g^{-1} are correspondingly designated as ACV–PhMS(L) and ACV–PhMS(H).

In vitro release profiles of ACV from the composites into buffer media with pH values of 1.6 mimicking gastric juice and 7.4 typical of small intestine are presented in Figure 1 (for details, see Online Supplementary Materials). Irrespective of the surface chemistry of silica matrix and pH, the release was accompanied by significant burst effect, namely initial fast drug liberation in a short period. For both the ACV–UMS composites as well as the ACV–PhMS(L) one, long-term sustained release is observed up to 48 h. Employment of various kinetic models, namely the zero order, the first order, the Korsmeyer–Peppas and the Hixson–Crowell ones[7] (for details, see Online Supplementary Materials) revealed, that after the burst effect identified using our approach,[17] the release of ACV followed the zero order kinetics with a correlation coefficient $R^2 > 0.96$ and was controlled by anomalous diffusion, because the values of the Korsmeyer–Peppas diffusion exponent, which indicated the mechanism of the process,[18] were $0.53 < n < 0.90$ (Table 1). According to this mechanism, the release originates from two simultaneous processes, namely disintegration/degradation of the silica matrix and drug diffusion. The good fit of the kinetic profiles to the Hixson–Crowell model confirms the disintegration/degradation of the silica matrices. This mechanism has been found for the release of different drugs encapsulated in various silica

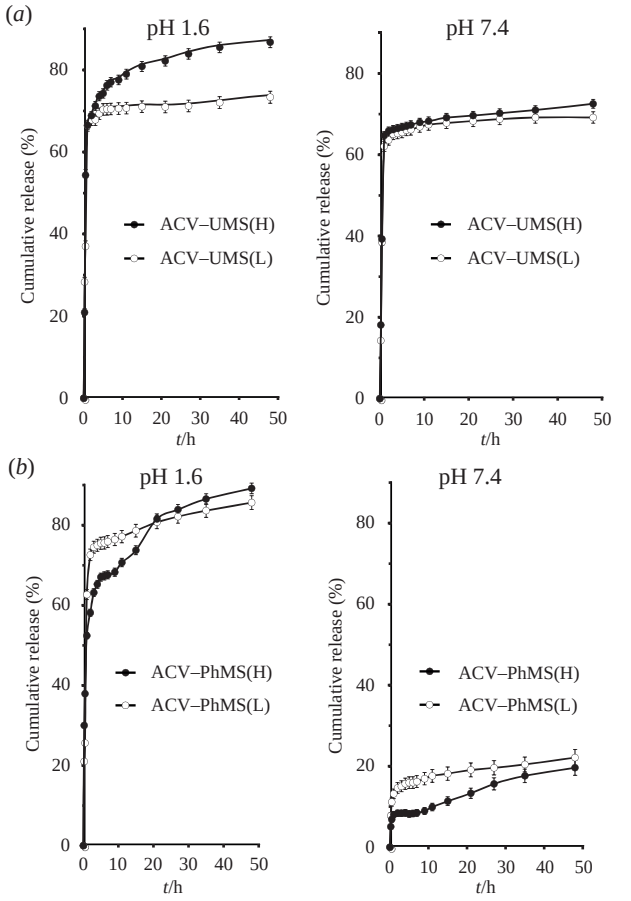

Figure 1 Release profiles of ACV from the synthesized composites at pH 1.6 and 7.4. The data are an average of three measurements ± SD.

materials.[17,19,20] Visual observation revealed an increase in turbidity of the medium after a few hours of the ACV release.

The results in Table 1 demonstrate that the release rate from ACV–PhMS(L) is higher than the one from ACV–UMS(L). Numerous studies testify that the introduction of organic functional groups into silica results in the formation of less structured matrices,[21,22] which are prone to more rapid degradation, especially in the case of phenyl-modified silica.[23] It is likely that this factor promotes the faster drug liberation from ACV–PhMS.

Also it was found that the release rate increased with the ACV loading in the ACV–UMS composites, the higher amount of encapsulated drug made the composite structure more brittle. It is known, that the more drug is present in a silica composite, the greater destruction it brings to the network of siloxane bonds and the composite structure.[17,24]

The release profiles from ACV–PhMS(H) exhibit a complex pattern regardless of pH. Specifically, after the burst effect, a pronounced plateau followed by gradual liberation tending to the next plateau is observed. Maxima are absent on the release curves from ACV–PhMS(L) and the ACV–UMS composites. It was suggested that the indicated behavior might be associated with the ACV state in the composites, namely its heterogeneity. To clarity this, the composites were investigated by differential scanning calorimetry (DSC) and powder X-ray diffraction (XRD) (for details, see Online Supplementary Materials). DSC thermograms of ACV and the composites reveal the following (Figure 2). The curve of crystalline ACV contains four peaks: (i) broad endothermic one at 108.0 °C associated with loss of moisture, (ii) small endothermic peak centered at 176.1 °C supposedly assigned to the transition from the form I to form IV of ACV, (iii) strong endothermic peak centered at 257.2 °C associated with melting of the form IV and (iv) exothermic peak at 260.0 °C, which testifies to decomposition of the drug.[25,26] The thermograms of both the ACV–UMS composites and ACV–PhMS(L) demonstrate only broad endothermic peaks in the 25–135 °C range associated with their dehydration. The absence of peaks related to ACV indicates that the drug has lost its crystal structure and is mainly molecularly dispersed in the composites. However, the thermogram of ACV–PhMS(H) exhibits a small endothermic peak at 262.5 °C followed by the small exothermic one at 264.3 °C, which are assigned to the ACV melting and decomposition, respectively. These peaks confirm that the drug in the composite preserves partially or completely its crystalline structure. The DSC results were confirmed by the powder XRD data, namely the reflexes associated with crystalline ACV[25,26] appear only in the XRD pattern of ACV–PhMS(H) (Figure S1, Online Supplementary Materials).

Table 1 Burst effect, burst time and kinetic parameters of the ACV release from ACV–silica composites into buffer solutions as calculated using different kinetic models (k_0 and k_1 in mg h^{-1}, k in h^{-n} and $k_{H–C}$ in h$^{-1/3}$). Estimated error for k_0 and k is 4%, the error for k_1 and $k_{H–C}$ is 6–8%.

Models and parameters	pH	ACV–UMS(L)	ACV–UMS(H)	ACV–PhMS(L)	ACV–PhMS(H)
Zero order	1.6	k_0 = 0.068	k_0 = 0.122	k_0 = 0.145	–
		R^2 = 0.9689	R^2 = 0.9692	R^2 = 0.9659	
$Q_t = Q_0 + k_0 t$	7.4	k_0 = 0.073	k_0 = 0.081	k_0 = 0.108	
		R^2 = 0.9654	R^2 = 0.9600	R^2 = 0.9688	
First order	1.6	k_1 = 0.0074	k_1 = 0.0027	k_1 = 0.0110	–
		R^2 = 0.8965	R^2 = 0.9053	R^2 = 0.9428	
$Q_t = Q_0 \cdot e^{-k_1 t}$	7.4	k_1 = 0.0013	k_1 = 0.0007	k_1 = 0.0059	
		R^2 = 0.9370	R^2 = 0.9018	R^2 = 0.8374	
Korsmeyer–Peppas	1.6	k = 5.98	k = 13.11	k = 12.53	–
		n = 0.55	n = 0.80	n = 0.90	
		R^2 = 0.9524	R^2 = 0.9674	R^2 = 0.9691	
$\frac{M_t}{M_\infty} = kt^n \left(\frac{M_t}{M_\infty} \leqslant 0.6\right)$	7.4	k = 7.97	k = 8.19	k = 10.85	
		n = 0.53	n = 0.56	n = 0.85	
		R^2 = 0.9578	R^2 = 0.9582	R^2 = 0.9792	
Hixson–Crowell	1.6	$k_{H–C}$ = 0.003	$k_{H–C}$ = 0.006	$k_{H–C}$ = 0.013	–
		R^2 = 0.9840	R^2 = 0.9907	R^2 = 0.9765	
$Q_0^{1/3} - Q_t^{1/3} = k_{H–C} t$	7.4	$k_{H–C}$ = 0.002	$k_{H–C}$ = 0.002	$k_{H–C}$ = 0.011	
		R^2 = 0.9788	R^2 = 0.9866	R^2 = 0.9885	
Burst effect (%)	1.6	63.4	67.6	75.7	52.0
Burst time/h		2	3	3	1
Burst effect (%)	7.4	62.0	68.4	80.1	40.1
Burst time/h		4	3	6	0.5

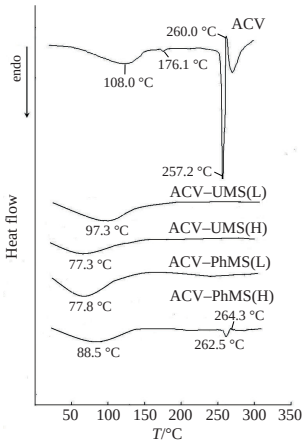

Figure 2 DSC thermograms of crystalline ACV and the synthesized composites.

The phase state of a drug encapsulated in a porous matrix is known to depend on the pore size and the loading.[27] For estimation of pore size in the synthesized composites, the pore size distribution for the UMS and PhMS matrices prepared under the same conditions was determined using N_2 adsorption–desorprion (for details, see Online Supplementary Materials). The obtained data demonstrated that the modification of silica matrix with phenyl groups, contrary to general regularity of a decrease in pore size after incorporation of organic groups into a silica matrix, led to formation of PhMS matrix with higher pore size than the UMS one, the average pore size were 2.5 and 3.5 nm, respectively. It is possible that the large plane phenyl groups incorporated act as spacers to prevent the pores from collapse upon drying the matrix, which can lead to the formation of pores with larger size. It was found,[28] that the drug nifedipine spatially constrained within pores of an average size ~2.4 nm existed in an amorphous state, while for crystallization a space larger than ~3.4 nm in diameter (if spherical) was theoretically predicted.[28] Thus, it may be suggested that in ACV–PhMS(H) the amount of loaded ACV and the matrix pore size promote crystallization of the drug. The ACV molecules oriented due to their π–π interaction with phenyl groups of the matrix serve as centers of crystallization. However, the crystallization is impossible with low drug loading, in this case the interaction of ACV with PhMS is obviously more favorable than the formation of crystals, therefore in ACV–PhMS(L) the drug is amorphous. The pore size in the ACV–UMS composites is too small to allow the ACV crystallization. Thus, the complex release profiles of ACV–PhMS(H) may result from coexistence of amorphous and crystalline ACV phases in the composite. The slow dissolving crystalline drug reduces the release rate, whereas amorphous ACV is liberated faster.[29]

Note, that the level of released ACV from the ACV–PhMS composites in neutral medium dramatically decreases as compared with the acidic one, presumably due to stronger interaction between the phenyl modified matrix and ACV in its neutral form at pH 7.4.[2] This would lead to a significant fluctuation of the drug concentration in different segments of gastrointestinal tract.

In summary, the investigated ACV–silica composites, except ACV–PhMS(H), represent a promising platform for the development of new oral ACV formulations. The composites are capable of controlled release of the drug for two days in the media mimicking biological fluids in gastrointestinal tract. Modification of the silica matrix with phenyl groups and the ACV loading significantly affect the release kinetics of the drug from the sol–gel composites. For this reason, the composites based on PhMS can not be considered for further development of the oral drug formulations. Nevertheless, the effect of pH-dependent ACV release from the composite with PhMS was found promising for development of pH-triggered drug formulations based on modified silica.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.09.038.

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