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Development of drug adsorbates onto soluble inorganic silicate glass surface: example with acetaminophen

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Abstract A ternary melt-derived inorganic glass system (Igl) of composition corresponding to $62SiO_2$, $35Na_2O$, $3Al_2O_3$ (wt.%) has been formulated and studied as a drug carrier. The $[Al_2O_3/Na_2O]$ ratio is less than one and the aluminium ion is a network former that retards the glass dissolution. The processing conditions lead to a brittle, easily grinding, amorphous product. The Igl structure was proven by IR-spectroscopy, energy-dispersive spectrometry, X-ray diffraction, scanning electron microscopy. A very important fact established is that the Igl corrosion (dissolution) is pH-dependent. Inorganic glass system was transformed into model acetaminophen (APH) adsorbate (APH/Igla 1:1(w/w)) with mild experimental conditions and evaluated as a drug carrier. No interactions between Igl and APH during the processing were proven. Besides, APH settles onto the glass surface as crystalline phase. A lower extent of corrosion, apparent solubility and delayed in vitro APH release from the adsorbate in water and artificial gastric juice in comparison to the samples untreated drug and APH/Iglm physical mixture were established. It is hypothesized that the glass decomposition products, formed into contact with a solvent, initiate interactions with APH at the glass/solution interface. Similar behaviour of the Igl and its drug adsorbates could be expected in gastro-intestinal tract.

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Introduction

The finding that certain Na_2O–CaO–P_2O_5–SiO_2 soluble glasses are "bioactive" and bond to living bone and tissues marks the beginning of intensive research into development of new biomaterials from glasses or ceramics for implantation. The bioactive glass materials, usually referred to as "bioglasses", show a marked surface reactivity in solution leading to the formation of a biologically active hydroxycarbonate apatite layer [1, 2]. In the early 1980's a new research tendency emerged, namely to study bioglass compositions as drug carriers [3]. The unique bioglass properties, e.g. amorphous structure and nanoscale particle size distribution, surface reactivity when in contact with buffered or physiological solutions and pH-dependent dissolution, arouse concern as one could expect an improvement of the in vivo drug dissolution, activity and safety. The first dosage forms with melt-derived bioglass carriers—implants, oral bolus tablets and pellets, were developed with trace elements for ruminant animals [4, 5]. Kendall et al. [6, 7] found that the control of the chemical composition and granularity of the glass material allowed a long term supply of the included trace elements. The melting stage in the traditional synthesis of inorganic bioglasses, however, does not allow inclusion of organic drugs into the glass melts. In an attempt to overcome the problem, Vallet-Regi et al. [8, 9] studied mixtures of bioglasses with gentamicin and ibuprofen. They observed a prolonged drug release in animals.

There are, however, few data concerning drug adsorbate formation onto inorganic glasses [10]. Our hypothesis is

that inorganic glasses of appropriate composition, structure and pH-dependent dissolution possess a potential to be transformed into drug adsorbates of variable drug release in media simulating the gastro-intestinal fluids. A technological approach based on drug crystallization onto glass surface under mild experimental conditions could be applied to organic drug loading.

Thus, the aim of the present study was: (i) to process a melt-derived SiO_2, Na_2O, Al_2O_3 inorganic silicate glass system (Igl), and (ii) to develop a model inorganic silicate glass /acetaminophen (APH) drug adsorbate (APH/Igla) in order to evaluate the applicability of the Igl as drug carrier.

Materials and methods

Materials

Quartz sand-A1 was purchased from Kaolin (Senovo, Bulgaria), anhydrous sodium carbonate p.a. was purchased from Solovay (Devnya, Bulgaria), aluminium oxide Brockmann Grade II basic p.a. from (Roanal, Budapest, Hungary); potassium dihydrogen phosphate (analytical grade) and disodium hydrogen phosphate dihydrate (analytical grade) as buffer substances from Fluka, Buchs, Switzerland; APH (pharmaceutical grade, European Pharmacopoeia, 5th Ed.) was kindly donated by Sopharma (Sofia, Bulgaria).

Synthesis of soluble silicate glass of $62SiO_2$, $35Na_2O$, $3Al_2O_3$ (wt.%) composition (Igl)

The appropriate amounts of raw materials: quartz sand, sodium carbonate and aluminium oxide were mixed and homogenised in a mortar and placed in corundum crucibles. Melting was carried out in a supercantal furnace at 1250 °C for 1 h. The glass melt was rapidly fritted in water.

Characterization of the Igl in vitro dissolution (corrosion)

Glass pieces were crushed in an agate mortar. After crushing the glass powder was sieved (sieve mesh diameter 0.200 mm). A sample of 200 mg glass powder was transferred into 100 mL dissolution medium (0.1 M HCl or distilled water) placed in a 250 mL beaker. Four samples were prepared and left at room temperature for 2 h. They were occasionally shaken. Samples of 50.0 mL were withdrawn at 30, 60, 90 and 120 min and treated as described in [2] for gravimetric estimation of the dissolved glass amount.

The corrosion behaviour of the APH/Igl models was determined as described above. The amount of the sample weighed (400 mg) was equivalent to 200 mg glass.

Preparation of the model acetaminophen/glass adsorbate (APH/Igla)

The acetaminophen/glass adsorbate was prepared in 1:1 (w/w) ratio. An appropriate amount of Igl was dispersed, under stirring (magnetic stirrer), in the APH solution in 95% ethanol placed in a round bottom flask. The obtained suspension was stirred additionally for 1 h at room temperature. The solvent was evaporated at 50 °C in a Rotavapor R-114 (Buechi, Switzerland). The solid residue was dried overnight over P_2O_5, pulverized and passed through a 0.2 mm screen. The corresponding physical mixture (APH/Iglm) was prepared in a mortar by co-mixing of both components for 10 min and treated as described above for the adsorbate.

APH loading efficiency—50 mg samples of APH/Igla or APH/Iglm, respectively were dispersed in 50 mL water by shaking. The dispersion was filtered and the drug concentration in the filtrate was determined by UV spectroscopy at 244 nm. Sample of 25 mg pure Igl was treated as described above and used as a blank. The experiment is carried out in triplicate.

X-ray analysis

The samples were characterized by X-ray powder diffraction (TUR-M-62 diffractometer (Germany), Cu-Kα radiation). X-ray diffracted quanta were collected at equal θ steps of 0.01° within a time interval of 10 s for every angular step.

IR spectroscopy

Apparatus SPECORD 71 IR (Germany). The samples were prepared as KBr disks containing around 1% APH. The spectra were registered over the wave number region 4700–400 cm^{-1} at a resolution of 4 cm^{-1}.

Scanning Electron Microscopy–Energy-dispersive spectrometry (SEM–EDS)

Analyses were carried out using Hitachi S-4100 Apparatus (Hitachi Ltd., Tokyo, Japan) and a beryllium specimen holder with 30°-tilt. The electron probe diameter was around 13 nm. Energy-dispersive spectrometry (EDS) spectra were recorded at an accelerating voltage of 100 kV, with an energy resolution of 25 keV per channel.

Scanning Electron Microscopy (SEM)

Scanning electron micrographs were obtained using Hitachi S-4100 (Hitachi Ltd., Tokyo, Japan) apparatus.

Apparent equilibrium solubility

About 50 mg APH/Igla or APH/Iglm, equivalent to 25 mg untreated APH (excess amount) or Igl, were placed in vials with glass stoppers together with 5 mL water or 0.1 M HCl (artificial gastric juice) and shaken in a thermoregulated water bath at 22 ± 0.5 °C until equilibrium was reached. The APH concentration was determined in a filtered sample by UV spectrometry at 244 nm. A Igl sample, treated as described above, was used as a blank.

Dissolution screening

About 15 mg of APH/Igla or APH/Iglm samples equivalent to 7.5 mg APH were placed in a volumetric flask of 100.0 mL and dispersed in water. The samples were shaken for 15 min. The concentration of the dissolved APH was determined, after filtration, by UV spectrometry at 244 nm (UV-spectrophotometer Hewlett-Packard-8452A, USA). 7.5 mg Igl sample was treated as described above for the model preparations and used as a blank solution.

In vitro dissolution profile of acetaminophen models

The dissolution test was carried out according to the European Pharmacopoeia 5th Ed. using Dissolution apparatus II (paddle method, Dissolution Tester ERWEKA-DT600, Erweka, Germany). The amount of the sample was 400 mg (equivalent to 200 mg pure APH). The acceptor medium was 500.0 mL distilled water or 0.1 M HCl (artificial gastric juice); the rotation speed was 50 rpm and the temperature 37 ± 0.5 °C. The APH concentration in the withdrawn and filtered samples was determined by UV spectrometry at 244 nm (UV-spectrophotometer Hewlett-Packard-8452A, USA). A parallel dissolution test was carried out with a sample of untreated Igl (200 mg). The withdrawn samples at each time interval were used as blank.

Results and discussion

Processing and characterization of a soluble inorganic silicate glass

In order to prepare a glass system of strengthened structure and pH-dependent dissolution we attempted to modify the classical soda–lime–silica glass by introducing Al_2O_3. There are data reporting that the position and the function of the Al^{3+} ion in the glass structure depend on the [Al_2O_3/Na_2O] ratio [11]. At ratios below one, the trivalent aluminium ions are incorporated into the glass network as tetrahedral groups [AlO_4] and act as network formers. The glass structure is strengthened and the glass dissolution is decreased and prolonged. Having in mind the above considerations we have formulated a ternary Igl of chemical composition corresponding to 62SiO_2, 35Na_2O, 3Al_2O_3 (wt.%). It is worth noting that the [Al_2O_3/Na_2O] ratio in the new glass is less than one and the oxides weight participation get into the glass forming region of the ternary phase diagram (Fig. 1).

Processing of the SiO_2–Na_2O–Al_2O_3 glass system was carried out under such conditions as to yield a brittle, easy to pulverize amorphous product. To prevent the formation of crystal nuclei as well as to stop any process of crystallization, the hot oxides melt was rapidly quenched in cold water.

The X-ray pattern of the Igl presented in Fig. 2, curve 1, shows no indication of crystallinity and is typical of amorphous solids. The SEM picture of the Igl (Fig. 3) confirms the glass amorphous state. Small regions of microheterogeneity, however, can be distinguished. Such phenomena are probably due to the fritting process included in the glass preparation.

The suggested structural configuration of the melt-derived alkali aluminosilicate glass (Igl) is presented in Fig. 4. The trivalent aluminium ion is surrounded by oxygen atoms in tetrahedral arrangement.

The IR spectrum of the Igl (Fig. 5) confirms the existence of aluminium tetrahedral structures in the glass. The strong band at 785 cm^{-1} can be ascribed to the symmetric stretching vibrations of the Al–O bond of the [AlO_4] tetrahedral group [12]. The IR spectrum reveals also the characteristic vibration frequencies of the other main functional groups in the Igl. The strong asymmetric Si–O stretching vibrations appear at 1100 cm^{-1} and are characteristic of the Si–O–Si group in the glass. The absorption

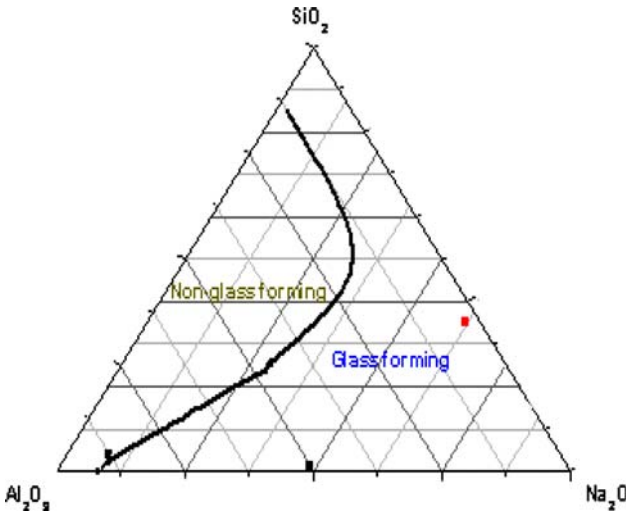

Fig. 1 Ternary phase diagram of the system SiO_2–Na_2O–Al_2O_3

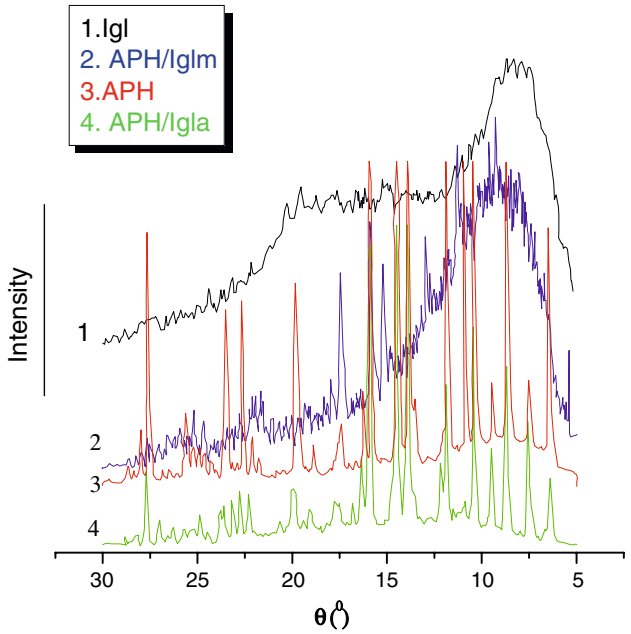

Fig. 2 X-ray powder diffraction patterns of: (1). Igl; (2). APH/Iglm; (3). APH and (4). APH/Igla

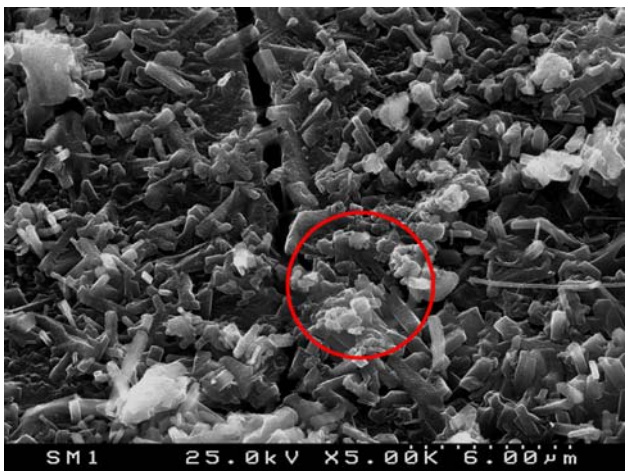

Fig. 3 SEM photograph of the SiO_2–Na_2O–Al_2O_3 inorganic glass system

band in the finger print region at 830 cm^{-1} can be assigned to the Si–OH groups.

In addition, the constituent elements of the glass were proved also by EDS using an energy dispersive X-ray analyzer (EDXA) attached to a scanning electron microscope (SEM). The method provides a very reliable identification of the characteristic elements of the analysed glass specimen, because the specific energy or wavelength of the generated X-rays are dependent on the interaction between the energetic monochromatic electrons from a stationary impinging electron beam and the electrons in the atoms of

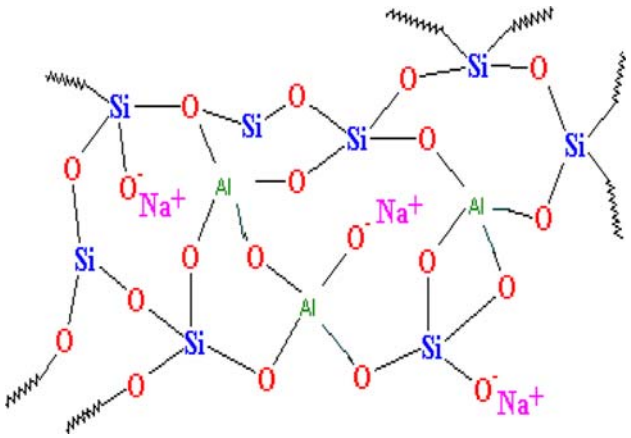

Fig. 4 Suggested structural configuration of the Igl

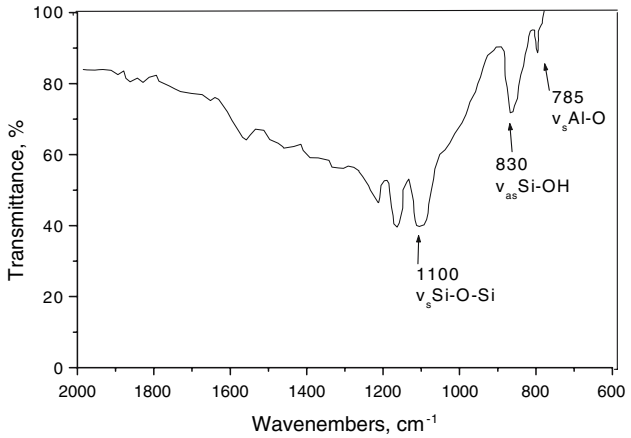

Fig. 5 IR spectrum of SiO_2–Na_2O–Al_2O_3 inorganic glass

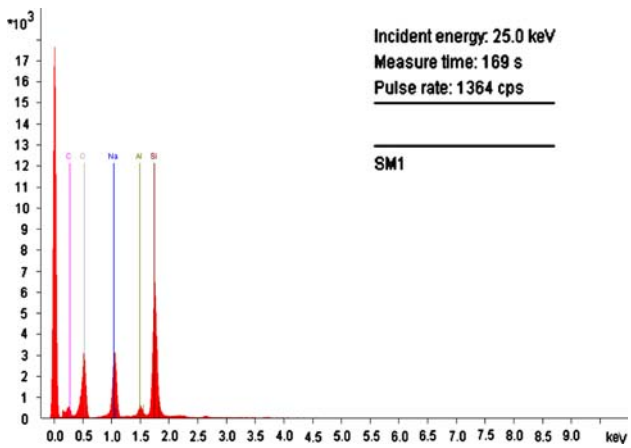

Fig. 6 SEM–EDS image of SiO_2–Na_2O–Al_2O_3 inorganic glass

the specimen [9]. The SEM–EDS picture (Fig. 6) features the peaks for Si, Al and Na related to the glass element composition.

In vitro corrosion (dissolution) of the Igl

There are many reports about the in vitro or in vivo reactions that occur at the glass interface when the SiO_2-based glass material comes in contact with aqueous media or physiologic fluids [13]. In general, these reactions are specified as glass corrosion, dissolution or leaching of the bioglass. The liquid media are usually named as "leaching" solutions. The process is a very complex and time dependent. The main initial reaction stages assumed for Igl when getting in contact with aqueous media are presented in Scheme 1. The dissolution begins with rapid exchange of Na cations, acting as Igl network modifier, with H^+ or H_3O^+ from the solvent. The next step is splitting of Si–O–Si bonds at the glass/solution interface and formation of a rich in soluble silanols (Si $(OH)_4$) layer. After that, condensation and repolymerization of silanols on the glass surface take place.

The available literature data about binary glass systems [14] show evidence that the in vitro dissolution process runs very similarly in "leaching" solutions of pH ranging from 1.0 to 9.0. That is why, it was very important to establish if the dissolution process of the ternary Igl system was pH-dependent.

Our results indicate that the Igl behaviour in 0.1 M HCl and in distilled water (Fig. 7) is very different. The Igl dissolves rapidly in 0.1 M HCl—the maximum dissolved amount is reached after 60 min. Unlike, the process runs in water slowly and uniformly—the final amount at the 120th minute dissolved is about 1.8 times lower than that in 0.1 M HCl.

Such a finding is of particular interest because a similar pH-dependent dissolution of Igl could also be expected in vivo in the gastro-intestinal tract.

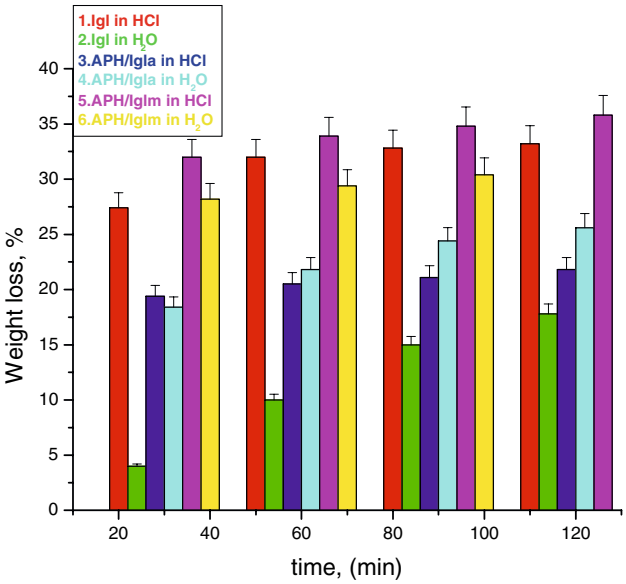

Fig. 7 Corrosion (dissolution) behaviour of Igl and APH/Igl model preparations in 0.1 M HCl and in water

The fact that Igl dissolves more easily and rapidly in HCl than in water is not surprising. Obviously, the high concentration of hydrogen ions in the acidic solution facilitates the exchange between sodium ions from the Igl and hydronium ions from the immersion acidic solution [2].

Suggestions about the lower value of the weight loss in water can be found in the publication of Douglas and El-Shamy [14]. The authors report that the sodium ions of Na_2O–Al_2O_3–SiO_2 ternary glasses remain immobilized on the glass surface sites and are hindered from passing into solution at pH of the medium above 5.0. The phenomenon is probably related to the difference in the solvation energy of sodium and hydrogen ions.

Scheme 1 Initial time depending steps in the process of Igl dissolution (after [1])

Step 1

Rapid exchange of the Na cations of the glass network modifier with H^+ or H_3O^+ from solution

$$\equiv Si\text{-}O\text{-}Na^+ + H^+ + OH^- \longrightarrow \equiv Si\text{-}OH^+ + Na^+ (solution) + OH^-$$

Step 2

Split of Si-O-Si bonds and formation of a layer rich of soluble silanols - Si $(OH)_4$ at the glass /solution interface

$$\equiv Si\text{-}O\text{-}Si + H_2O \longrightarrow \equiv Si\text{-}OH + OH - Si\equiv$$

Step 3

Condensation and repolymerization of silanols on the glass surface

$$\begin{matrix} & O & & O & & & O & O & \\ O & - & Si & - & OH + HO & - & Si & - & O \\ & O & & O & & & O & O & \end{matrix} \longrightarrow O - Si - O - Si - O + H_2O$$

Characterization of the acetaminophen/glass adsorbate (APH/Igla)

The main advantages of the technological approach used to prepare the APH/Igl adsorbate are: (i) mild process conditions (e.g., evaporation of the solvent ethanol under vacuum); and (ii) all the dissolved APH crystallizes rapidly on the surface of the glass particles as it has been confirmed by the test for efficiency of APH loading onto Igl carrier.

It is worth noting that APH does not transform into amorphous state during adsorbate processing. The X-ray diffractogram of the APH/Igla shows the main crystalline peaks for the untreated APH (Fig. 2, curves 4 and 3). Some of the characteristic peaks, however, are missing in the diffractogram of the APH/Iglm (Fig. 2, curve 2). The sample is partially crystalline, probably, as a result of very weak interactions due to the co-grinding of APH and Igl [15].

On the other hand, the IR study revealed that the spectrum of the adsorbate, similarly to that of the corresponding physical mixture, overlays the spectra of the pure drug and the glass, respectively (Fig. 8, curve 1 and curve 2 and Fig. 5).

Thus, the strong correlation found between the results from the X-ray diffraction and IR spectroscopy rules out any assumption for drug/carrier interactions occuring in the process of drug adsorbate preparation.

Corrosion (dissolution) study

The corrosion experiments were carried out with APH/Igla and APH/Iglm in an attempt to elucidate the APH influence on Igl dissolution.

It is hypothesised that, when the particles of the drug adsorbate come into contact with an aqueous medium, glass corrosion begins and the glass decomposition products initiate interactions with APH at the glass/solution interface. The corrosion study of the models (Figs. 7 and 9) supports a similar hypothesis.

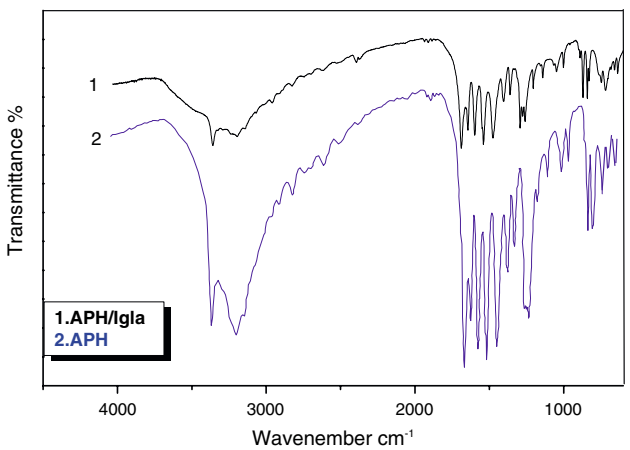

Fig. 8 IR spectra of: (1). APH/Igla; (2). APH

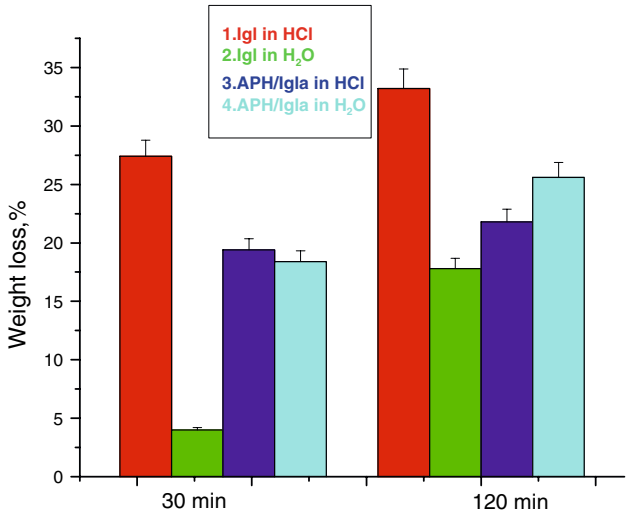

Fig. 9 Corrosion (dissolution) behaviour of Igl and APH/Igl adsorbate in 0.1 M HCl and in water

It was found that APH has a marked impact on the Igl durability. The final weight loss of the drug adsorbate is considerably smaller than that of the untreated glass in both media (Fig. 9). The higher value of the adsorbate weight loss in water than in 0.1 M HCl is due to the fact that APH is more soluble in water than in acidic medium. The weight loss values for the model physical mixture are very close in both media and they are not an arithmetic sum of the weight losses of both components.

Accounting for the fact that in the process of drug adsorbate development a physical adsorption of drug molecules and/or crystalline particles onto the surface of the amorphous Igl carrier takes place, it can be assumed that the lower degree of corrosion of the adsorbate, as compared to the untreated Igl and the APH/Iglm, is due to impeded access to the glass contact surface. Moreover, suppressed drug molecular mobility on the glass surface could also be assumed, as a result of physicochemical interactions between the Igl and APH in the "leaching" solution. As regards the greater amount of APH depleted into aqueous solution, it can be assumed that APH reacts in water with the depleted sodium ions and transforms into more soluble sodium phenolate. In a hydrochloric acid medium such an interaction is restricted.

Dissolution properties of APH included in APH/Igl models

The preliminary fast screening of the dissolution properties of APH from the drug/Igl models (Table 1) showed that: (i)

Table 1 Dissolution screening and equilibrium solubility in 0.1 M HCl and in water of APH/Igl models

APH/Igl models	Dissolution screening (mg/100 mL)		Apparent equilibrium solubility (mg/mL)	
	HCl	H_2O	HCl	H_2O
Untreated APH	6.6 ± 0.09	6.2 ± 0.03	19.42 ± 0.02	18.65 ± 0.15
APH /Igla	5.7 ± 0.1	5.8 ± 0.07	16.43 ± 0.02	16 ± 0.15
APH /Iglm	6.97 ± 0.1	6.74 ± 0.11	20.19 ± 0.06	19.6 ± 0.05

the amount of the dissolved drug does not depend on the nature of the dissolution medium, (ii) Igl in form of physical mixture does not influence APH solubility, and (iii) dissolution of APH from the adsorbate is relatively lower as compared to that of the untreated APH and APH/Iglm samples.

The results of the apparent equilibrium solubility study (Table 1) confirm the "screening" data. The adsorbate shows approximately 15% lower solubility than the untreated APH and APH/Iglm in both media. This finding can be related to the sample structure and to the APH/Igl interactions at the glass/solution interface, as it was already discussed above.

The in vitro dissolution profiles obtained in 0.1 M HCl and in water are presented in Fig. 10. The results show that: (i) APH dissolves completely from all samples in both media within a time interval from 15 to about 90 min; (ii) the APH dissolution depends on the kind of the sample and does not depend on the nature of the dissolution medium; (iii) the profile of the drug adsorbate is the lowest and the total amount of drug is released within 90 min; the dissolution rate is approximately 3 times slower than that of the non treated drug.

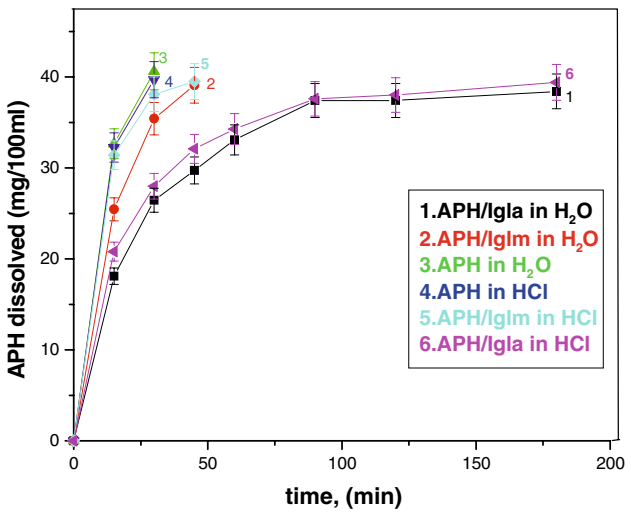

Fig. 10 In vitro dissolution profiles of APH/Igl models in 0.1 M HCl and in water

Conclusions

Application of inorganic melt-derived glasses as drug carriers could be a rational technological approach to formation of drug adsorbates.

The established correlation between the corrosion behaviour, apparent solubility and dissolution of APH/Igl adsorbate proves the ability of the amorphous Igl carrier to delay APH in vitro dissolution in water and artificial gastric juice. Similar behaviour of the Igl and its drug adsorbates could be expected in vivo in the gastro-intestinal tract.

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