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Characterization of Biocompatible Nanocomposite based on Silica, Dextran and Lidocaine

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Abstract

A silica/dextran/lidocaine nanocomposite (SiO/DEX/LID) was synthesized using acid-catalyzed sol-gel process. The resulting material was characterised using diffuse reflectance infrared Fourier transform spectroscopic analysis, diffusive reflectance spectroscopy in UV–Vis range, X-ray photoelectron spectroscopy and nitrogen adsorption method. LID was found to interact with the silica/dextran nanocomposite (SiO/DEX) via hydrogen bond formation between the carbonyl group of LID and SiO/DEX network. Analysis of nanocomposite with help of the series of complementary techniques ruled out the possibility of interaction between LID and the silica modified surface through the nitrogen atoms of the drug molecule. The findings reveal the potential of SiO/DEX/LID nanocomposite for being used in the preparation of medical patches for wounds and burns healing.

Keywords: Sol-gel; Dextran; Lidocaine; Nanocomposite; DRIFT; DRS

Introduction

Over the past decades, intense research was dedicated to the development of novel transdermal drug delivery systems (TDDS) to enhance the anaesthetic effect of drugs [1,2]. In most cases, the formulations used for local anaesthesia are solutions or gels, with their main disadvantage of lack of stability, necessary exposure time and adhesion to the skin causing overall reduction of contact time and efficacy. These problems may be overcome by using bioadhesive films for topical applications. Patches offer advantages over conventional parenteral or oral routes [3]. Nowadays, scientists' efforts are focused on improving TDDS, that is, on prolonging the period of time of the anaesthetic effect, increasing bioavailability and efficacy.

Anilide-type local anaesthetics are widely used in medical practice for all types of local anaesthesia [4,5]. Lidocaine, 2-(diethylamino)-N-(2, 6-dimethylphenyl) acetamide hydrochloride is applied for infiltration, epidural and spinal anaesthesia in surgery and for thermal anaesthesia of mucous tunics in stomatology, ophthalmology, urology, pulmonology and other fields of medicine [5]. Also, LID is used as a high-performance antiarrhythmic drug in cardiology [6]. The interest in lidocaine has noticeably arisen after appearance of the new form of remedy delivery through the skin, that is transdermal matrix system of local activity [1,7,8]. The amide bond in the structure of lidocaine provides more prolonged anaesthetic effect in comparison with ester-type analogs [4]. The development of a transdermal drug delivery film to control the prolonged release of a water soluble anaesthetic like, e.g., lidocaine, is a promising research route nowadays.

A few reports describe the use of a chitosan-alginate composite [9], poly(acrylic acid) and poly(methacrylic acid) polymer complexes [10] as transdermal drug-delivery dosage forms of lidocaine. The silica sol-gel matrices are often used as a versatile support for biomolecules in applications such as drug carriers [11,12] because of their advantages such as high dispersion, developed and available surface, the ability to adjust the surface properties over a wide range, high chemical purity, physiological biocompatibility, chemical inertness, physical rigidity, higher mechanical strength, enhanced thermal stability and negligible swelling in aqueous solution [13]. Logically it follows that the controlled modification of the adsorptive properties of silica surface by biopolymers can potentially improve their compatibility and affinity towards bio-compounds.

As a biopolymer forming matrix, dextran advantages include biodegradability, water solubility, chemical inertness, biocompatibility and good film forming property [14]. Dextran also decreases the inflammatory reaction and swelling around the wound. In addition, it has already been established that this biopolymer can increase the therapeutic efficacy of local anaesthetics [15]. The adsorption on silica surface and the formation of different types of adsorptive complexes owing to diverse functional groups can stabilize certain conformations of lidocaine as *cis*- or *trans*-forms, influencing the bioavailability and efficiency of anaesthetics. To improve a transdermal drug delivery system, that is, to prolong the period of time of its anaesthetic effect, greater understanding of the different mechanisms of chemical interactions are required.

In the present study, we developed a novel drug delivery nanocomposite system based on silica, dextran and lidocaine. The silica material was prepared by sol-gel with a polysaccharide dextran modification. The functionalized silica sol-gel obtained so was then combined with water soluble anaesthetic lidocaine to obtain a SiO/DEX/LID nanocomposite material. The resulting material was thoroughly characterized using diffuse reflectance infrared Fourier transform spectroscopic analysis (DRIFT), diffusive reflectance spectroscopy in the UV–Vis range (DRS), X-ray photoelectron spectroscopy (XPS) and nitrogen adsorption. These spectroscopic tools will allow to inspect in detail the interaction between LID and the silica matrix.

Materials and Methods

Materials

Lidocaine hydrochloride monohydrate (≥ 99%), dextran sulphate sodium salt (40 kDa), tetraethyl orthosilicate (TEOS98%, GC) were

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obtained from Sigma-Aldrich (Sintra, Portugal). Hydrochloric acid (37%, ACS grade) was supplied by Fisher Scientific (Porto Salvo, Portugal). Ethanol (96%) was purchased from AGA (Prior Velho, Portugal). Ultra pure water was used throughout the study.

Preparation of systems based on silica, dextran and lidocaine

Silica sol was prepared via acid-catalysed sol-gel process which has been fully described in Buckley and Greenblatt work [16]. Briefly, silica was obtained from a mixture of TEOS, ethanol and water in a 1:4:16 molar ratio. Ethanol (15.5 ml) was mixed with TEOS (15 ml). The solution was stirred. Distilled water (19 ml) was mixed with 2 drops of concentrated hydrochloric acid. Then this acidic solution was poured into the TEOS/ethanol solution in the flask under stirring. The obtained solution was heated up to 60°C and stirred during 1.5 hours. After 1.5 hours of heating, the solution was stirred for 4 hours at 500 rpm. The silica sol was further kept for aging for about 24 hours. After aging, 5 ml of silica sol-gel solution was placed in a Petri dish and dried at room temperature, then ground and used for characterization.

To prepare the SiO_2/DEX nanocomposite, a given amount of dextran (21.8 mg) was first dissolved in distilled water which was then added to 5 ml of silica sol-gel solution. The mixture was then shaken for 45 minutes under 400 rpm. Then, the suspension was placed in a Petri dish and dried at room temperature, then ground and used for characterization.

As for the SiO/DEX/LID nanocomposite, it was prepared as following: a given amount of dextran (87.2 mg) was first dissolved in distilled water which was then added to 20 ml of silica sol-gel solution, followed by the addition of water solution of lidocaine (204 mg in 6 ml of water). The mixture was then shaken for 45 minutes under 400 rpm. SiO/DEX/LID system was placed in Petri dish and dried at room temperature, then ground and used for characterization.

Characterizations

Nitrogen adsorption: The surface structure parameters were calculated from the N_2 adsorption/desorption isotherms, which were obtained at -195.8°C with an automated apparatus (*ASAP 2420, V2.09,* Micromeritics, Norcross, GA, USA) at the Laboratorio de Sólidos Porosos (Servicios Centrales de Apoyo a la Investigación, Universidad de Málaga). The total mass of powder present during the analysis was typically 0.128–0.196 g. The samples were first outgassed at room temperature for 12 hours under vacuum to a final pressure of 1-2 microns of Hg and then the isotherms were measured over the relative pressure range of (P_S/P_o) from 0.01 to 0.991 and back. The BET specific surface area (S_{BET}) and the volume of monolayer coverage were determined using the Brunauer-Emmett-Teller (BET) equation. The pore volume versus diameter distribution was calculated using the Barrett-Joyner-Halenda (BJH) method [17,18].

Diffuse reflectance infrared Fourier transform spectroscopy (DRIFT): Diffuse reflectance infrared Fourier transform (DRIFT) spectroscopic analysis was performed in a JASCO 6800 spectrometer coupled to a Termo Spectra-Tech 0030-005 diffuse reflectance accessory. The infrared absorption spectra of the samples were measured at room temperature in the wave number range of 4000-400 cm^{-1}. The samples were examined as fine powders which were mixed with pulverized KBr in the ratio 1:2 sample powder to KBr, respectively.

Diffusive reflectance spectroscopy (DRS): The optical absorption spectra on the UV–Vis range were obtained with a Jasco V-560 UV–Vis spectrophotometer, equipped with an integrating sphere attachment (JASCO ISV-469). The various spectra were recorded in diffuse reflectance.

X-ray photoelectron spectroscopy (XPS): For XPS measurements the samples were subjected to a pressure of 5 tons/cm^2 to produce clear homogeneous pellets with d=10 mm, h=1 mm. XPS was performed on Kratos Axis Ultra HSA equipment with VISION software for data acquisition and CASAXPS software for data analysis at the Laboratory for Surface Analysis (LAS) at the Materials Centre of the University of Porto (CEMUP). The analysis was carried out with a monochromatic Al Kα X-ray source (1486.7 eV), operating at 15 kV (90W), in FAT mode (Fixed Analyser Transmission), with a pass energy of 40 eV and a pass of 0.1 eV for regions and 80 eV of pass energy and 1.0 eV of step for survey. The signal from carbon C (1s) at 285 eV was used as an internal reference to correct the energy. All spectra were fitted assuming a Shirley baseline.

Results and Discussion

The porosity characteristics of obtained silica, silica modified by dextran and ternary system SiO/DEX/LID were calculated from adsorption/desorption curves by Nitrogen adsorption method. Parameters characterizing the porosity of the silica, i.e., specific surface area (S_{BET}), average pore diameter (d_{pore}) and total pore volume ($V_{\Sigma pore}$) are given in Table 1.

The surface area (S_{BET}) of unmodified silica SiO (592 m^2/g) is much larger than that of silica modified by biopolymer SiO/DEX (341 m^2/g). The pore volume ($V_{\Sigma pore}$) of the unmodified silica is larger than that of the silica modified by dextran. However, the average pore diameter (d_{pore}) of modified silica (34 Å) is slightly larger than that of the unmodified sample (27.6 Å), which can be explained by the migration of segments of polymer chains into the pores. Adding LID to the SiO/DEX system resulted in complete destruction of the pore structure. The pores were most probably filled with the organic and a non-porous material was obtained as result.

Silica, SiO/DEX and SiO/DEX/LID nanocomposites were further analyzed using DRIFT spectroscopic analysis. In the spectra of silica and of silica modified by dextran (Figure 1, spectra 1 and 2), the deformation band at 1630 cm^{-1} can be attributed to the adsorbed water. The bands at 1085 and 800 cm^{-1} are assigned to the asymmetrical and symmetrical stretching vibrations of Si-O, respectively, of the Si-O-Si network [19,20]. The band at 956 cm^{-1} can be attributed to (Si-O) of silanol groups [21].

The spectrum of the individual hydrochloride lidocaine sample is also displayed in Figure 1 (spectrum 3). The band at 1672 cm^{-1} can be assigned to the stretching vibrations of C=O ($\nu_{C=O}$) of the amide group (amide I) in lidocaine. The band at 1656 cm^{-1} corresponds to the deformation vibrations of bond CNH (δ_{CNH}) of the amine group. The band at 1544 cm^{-1} can be attributed to the sum of stretching vibrations of C-N and bending vibrations of N-H ($\nu_{CN}+\delta_{NH}$) of the amide group (amide II), and the band at 1250 cm^{-1} to the stretching vibrations of C-N-H (ν_{CNH}) (amide III). It is in line with the reported in literature [22,23]. In the infrared spectrum of the corresponding ternary system (Figure 1, spectrum 4), the main bands from lidocaine are observed. The bands amide I and amide II are shifted to 1677 and 1534 cm^{-1}, respectively. It is clearly distinguishable that LID interacts with silica-dextran network through these functional groups. Table 2 summarizes the results of IR-spectroscopic investigation. The shifts of amide I and amide II bands can result from a strong rearrangement of chemical bonds in amide group, which is confirmed by the rotational isomerism of the molecule [24]. The amide I band shift towards higher wavenumber after obtaining the ternary system can indicate the possibility of a hydrogen bond interaction between the LID and the modified silica

N	Sample	S_{BET}, m^2/g	d_{pore}, Å	$V_{\sum pore}$, cm^3/g
1	SiO	592	27.6	0.322
2	SiO/DEX	341	34.0	0.211

Table 1: Porous structure of the modified silica in terms of specific surface area (SBET), average pore diameter (dpore) and total pore volume (V∑pore).

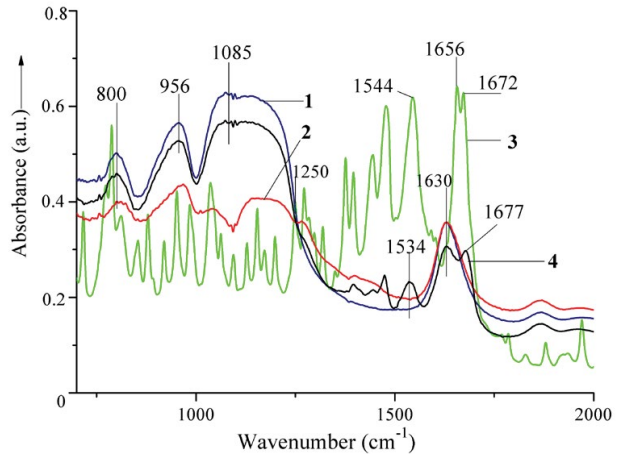

Figure 1: DRIFT spectra: 1 - silica, 2 - silica modified by dextran, 3 - LID, 4 - ternary system SiO/DEX/LID.

surface via electron donation of carbonyl group C=O to the silica-dextran network. Whereas the shift of band amide II to low-frequency region is evidence of the reduction of the double bond between N and the carbonyl carbon of C(O)–N bond of lidocaine on SiO/DEX surface. Probably, the molecule of lidocaine in adsorptive complex is mainly in *cis*-like conformation, since the location of the band amide I closely matches the adsorption band of lidocaine *cis*-conformation ($n_{C=O}$ at 1682 cm^{-1}) following the data of McMaster et al. work [25].

In order to get additional information about adsorptive complexes of LID in the ternary system, further investigations were performed with use of DRS method. For the UV–Vis spectra of the studied systems, the absorption maxima may be assigned to one of the following transitions: $\pi \rightarrow \pi^*$ from the aromatic centres, $n \rightarrow \pi^*$ from the carbonylated systems, $\pi \rightarrow \sigma^*$ from the nitrogen electrons in the amine groups, or $n \rightarrow \pi^*$ from the oxygen electrons in the drugs [26,27].

In the case of neat lidocaine, the absorption band is centered at 273 nm (Figure 2, spectrum 1). This band is shifted to 267 nm in the ternary system (Figure 2, spectrum 4). As the maximum absorption bands were shifted to lower wavenumbers than in the neat compound, it means that hypsochromic effect takes place ($n \rightarrow \pi^*$ transition from the oxygen electrons of carbonyl group in the drug) [28]. The medium of the ternary system SiO/DEX/LID is more polarized than that of the neat LID. This polarity could be the result of an increase in the flow of electrons between the LID and the SiO/DEX system. Thus, as the polarity increases, the $\pi \rightarrow \pi^*$ transitions tend to undergo a bathochromic shift, and the $n \rightarrow \pi^*$ transitions undergo a hypsochromic one. The hypsochromic effect is due to inductive effect of carbonyl oxygen in amide bond of lidocaine. The blue shift of lidocaine can be explained as hydrogen bond formation between the carbonyl group and the SiO/DEX surface [26]. The decrease in the absorbance of ultraviolet light in ternary systems compared to neat lidocaine can be assigned to the stability and the hypsochromicity of the nanocomposites. Lidocaine in ternary systems absorbs less ultraviolet light since it interacts (forms

Main bands	Wavenumber (cm^{-1})		Δv (cm^{-1})
	Lidocaine hydrochloride monohydrate	SiO/DEX/LID Dried at room T	
Amide I ($v_{C=O}$)	1672	1677	+5
Amide II ($v_{CN+\delta NH}$)	1544	1534	–10

Table 2: Assignments of IR bands of amide I and amide II in LID samples and measured shifts in wavenumber.

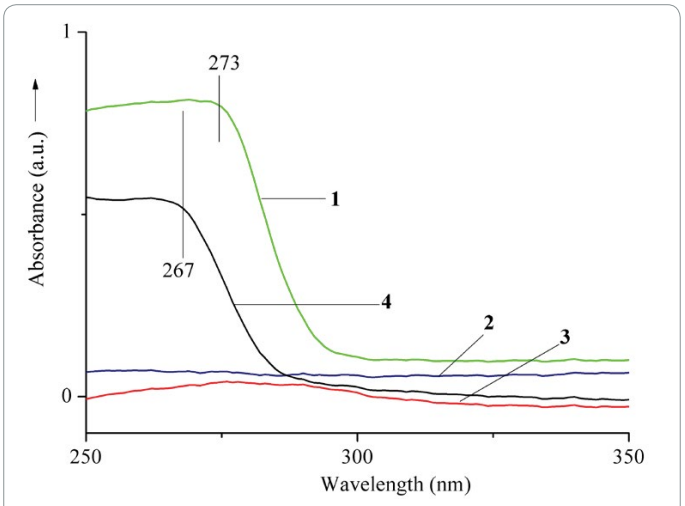

Figure 2: UV spectra: 1 - LID, 2 - SiO, 3 - SiO/DEX, 4 - ternary system SiO/DEX/LID.

hydrogen bonds) with SiO/DEX surface and therefore is not free to absorb light.

To find additional evidence of the potential interactions between the drug and the silica framework in ternary system, SiO/DEX/LID was analyzed with help of X-ray photoelectron spectroscopy. For SiO, SiO/DEX and SiO/DEX/LID samples the Si2p region showed only a single peak centered at ~103 eV, which corresponds to the tetrahedrally coordinated Si atoms in oxidation state 4+ [29,30]. Regarding the oxygen states for samples, at least two different O species were observed with binding energies of the O1s level at ~530 and ~532 eV. As the contribution from the Si-O moieties from the bulk silica dominates, the high resolution O (1s) signal could not be monitored using XPS. Table 3 displays the binding energy and full width at half maximum (FWHM) for N (1s) signal for neat lidocaine and ternary system. According to the data, there are no essential changes in binding energy and FWHM for N (1s) signal for neat drug and corresponding system. It can then be concluded that there is no possibility of interaction between LID and silica modified surface through the nitrogen of drug molecule.

Conclusions

Nanocomposites based on silica, dextran and lidocaine (LID) were synthesized using a sol-gel approach. For these materials we have shown that diffuse reflectance infrared Fourier transform spectroscopic analysis, diffusive reflectance spectroscopy in UV–Vis range and X-ray photoelectron spectroscopy represent a powerful set of tools extremely adequate for investigating the interaction between LID and the silica matrix. Analyses of the nanocomposites with the help of those complementary techniques showed that interaction between drug and silica modified surface takes place, almost exclusively via hydrogen bond formation between the carbonyl group of LID and SIO/

Sample	N (1s) signal	
	Binding energy (eV)	FWHM (eV)
Lidocaine (neat)	400.0/402.1	1.31/1.37
SiO/DEX/LID	400.2/402.4	1.50/1.48

Table 3: Data recovered from XPS analysis: binding energy and FWHM of the high resolution N (1 s) signal.

DEX network. Such information is very important for the generation of novel drug delivery systems based on composite materials from silica and dextran.

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References

1. Davies PS, Galer BS (2004) Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. Drugs 64: 937-947.
2. Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, et al. (2012) Drug delivery systems: An updated review. Int J Pharm Investig 2: 2-11.
3. Shingade GM, Aamer Q, Sabale PM, Grampurohit ND, Gadhave MV, et al. (2012) Review on: Recent trend on transdermal drug delivery system. JDDT 2: 66-75.
4. Mahadik KR, Kuchekar BS, Deshmukh KR (2009) Concise organic pharmaceutical chemistry (13th edn.). Nirali Publication, India.
5. Klein JA (2000) Tumescent technique: tumescent anesthesia & microcannular liposuction.
6. Strichartz GR, Berde CB (1994) Local anesthetics. In Miller RD (ed.) Anesthesia (4th edn.), Churchill Livingstone, New York, USA.
7. Meier T, Wasner G, Faust M, Kuntzer T, Ochsner F, et al. (2003) Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. Pain 106: 151-158.
8. Comer AM, Lamb HM (2000) Lidocaine patch 5%. Drugs 59: 245-249.
9. Albertini B, Di Sabatino M, Calonghi N, Rodriguez L, Passerini N (2013) Novel multifunctional platforms for potential treatment of cutaneous wounds: development and in vitro characterization. Int J Pharm 440: 238-249.
10. Sánchez-Leija RJ, Pojman JA, Luna-Bárcenas G, Mota-Morales JD (2014) Controlled release of lidocaine hydrochloride from polymerized drug-based deep-eutectic solvents. J Mater Chem B 2: 7495-7501.
11. Morais EC, Correa GG, Brambilla R, Dos Santos JH, Fisch AG (2013) Selective silica-based sorbent materials synthesized by molecular imprinting for adsorption of pharmaceuticals in aqueous matrices. J Sep Sci 36: 636-643.
12. Barbe C, Bartlett J, Kong L, Finnie K, Lin HQ, et al. (2004) Silica particles: a novel drug-delivery system. Adv Mater 16: 1959-1966.
13. Li Z, Barnes JC, Bosoy A, Stoddart JF, Zink JI (2012) Mesoporous silica nanoparticles in biomedical applications. Chem Soc Rev 41: 2590-2605.
14. Satvekar RK, Rohiwal SS, Raut AV, Karande VA, Tiwale BM, et al. (2014) A silica-dextran nanocomposite as a novel matrix for immobilization of horseradish peroxidase, and its application to sensing hydrogen peroxide. Microchim Acta 181: 71-77.
15. Armstrong DN, Kingsnorth AN (1986) Local anaesthesia in inguinal herniorrhaphy: influence of dextran and saline solutions on duration of action of bupivacaine. Ann R Coll Surg Engl 68: 207-208.
16. Buckley AM, Greenblatt M (1994) The sol-gel preparation of silica gels. J Chem Educ 71: 599-602.
17. Gregg SJ, Sing KSW, Salzberg HW (1967) Adsorption, surface area and porosity. J Electrochem Soc 114: 279.
18. Brunauer S, Emmett PH, Teller E (1938) Adsorption of gases in multimolecular layers. J Am Chem Soc 60: 309-319.
19. Krol DM, Lierop JGV (1984) The densification of monolithic gels. J Non-Cryst Solids 63: 131-144.
20. Gonzales-Oliver CJR, James PF, Rawson H (1982) Silica and silica–titania glasses prepared by the sol–gel process. J Non-Cryst Solids 48: 129-152.
21. Li X, King TA (1996) Spectroscopic studies of sol-gel-derived organically modified silicates. J Non-Cryst Solids 204: 235-242.
22. http://riodb01.ibase.aist.go.jp/sdbs/
23. Bellamy LJ (1975) The infra-red spectra of complex molecules. Wiley, New York, USA.
24. Barton D, Ollis WD (1979) Comprehensive organic chemistry. Pergamon, Oxford.
25. McMaster PD, Noris VJ, Stankard CE, Byrnes EW, Guzzo PR (1991) The solution conformation of lidocaine analogues. Pharm Res 8: 1013-1020.
26. Silverstein RM, Bassler GC, Morill TC (1991) Spectrometric identification of organic compounds (5th edn.), John Wiley & Sons Inc, New York, USA.
27. Williams DH, Fleming I (1989) Spectroscopic methods in organic chemistry. McGraw Hill, Maidenhead.
28. Hesse M, Meier H, Zeeh B (2008) Spectroscopic methods in organic chemistry. Thieme, New York.
29. Moulder JF, Stickle WF, Sobol PE, Bomben KD (1992) Handbook of X-ray Photoelectron Spectroscopy. Perkin–Elmer Corporation, USA.
30. Grunthaner FJ, Grunthaner PJ, Vasguez R, Lewis B, Maserjian J, et al. (1979) Local atomic and electronic structure of oxide/GaAs and SiO2/Si interfaces using high-resolution XPS. J Vac Sci Technol 16: 1443-1453.