Controlled Release of Drugs from Cellulosic Wound Bandage Using Silica Microsphere as Drug Encapsulator Module

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ARTICLE INFO	ABSTRACT
	Controlled-drug-releasing materials show promising applications in medicinal bandages. In addition, one could incorporate drugs to make such bandages more versatile. During this context, silica microparticles were synthesized, during presence of different drugs namely sodium diclofenac, linoleic acid and recienoleic acid. The morphological characterization shows formation of monodispersed, silica microparticles. FT-IR spectroscopy provided the interaction of the drug molecule at its hydroxide (OH) site with oxygen ions on the silica surface. UV–vis spectroscopy showed persistence of the different drugs signature, especially its R group, confirming its antimicrobial activity even after conjugation. Using zone-of-inhibition studies, the antimicrobial studies were done on two microorganisms, namely, Staphylococcus aureus and Escherichia coli. However, the encapsulator module showed controlled release of all drugs for the duration of 48 h. This work demonstrated an effective protocol to prepare antimicrobial patches for controlled drug delivery.

INTRODUCTION

Cellulosic fibers are natural polymers of vegetable origin, like cotton, linen, jute, ramie, hessian and sisal. (Mohamed and Hassabo, 2015; Visakh and Arao, 2015) Therefore, it would be useful to impart high performance properties to natural fibers. There are several ways to functionalize the natural fibers e.g. deposition and/or infiltration of functional polymeric materials onto/into the fiber surface, (Abo-Shosha *et al.,* 2009; Ibrahim *et al.,* 2013; Mohamed *et al.,* 2013; Mohamed *et al.,* 2013; Waly *et al.,* 2009; Waly *et al.,* 2012) using nanotechnology while preserving the inherent properties of the fiber, to modify the fiber surface by applying a nano-coating (Hassabo, 2011; Hassabo, 2014; Hassabo *et al.,* 2015; Hassabo *et al.,* 2014; Hassabo *et al.,* 2014; Mohamed *et al.,* 2014). Hybrid inorganic-organic polymers applied by the encapsulation process are well suited for this purpose (Hassabo, 2014; Hassabo *et al.,* 2015). Recently inorganic porous particles have been used to develop biocompatible polymers, which can be

used for drug storage (Bagshaw *et al.,* 1995; Huo *et al.,* 1995; Tanev *et al.,* 1994). Many various polymeric systems have been well studied as a drug carriers (Al-Karawi and Al-Daraji, 2010; Fiore *et al.,* 2010; Liu *et al.,* 2010; Manchanda *et al.,* 2010; Nada *et al.,* 2015; Shin *et al.,* 2009; Zheng *et al.,* 2010), such as polymer hydrogels (Liu *et al.,* 2010), PLGA nanoparticles (Manchanda *et al.,* 2010), polyvinyl alcohol and starch polymers (Al-Karawi and Al-Daraji, 2010). Silica microparticles was used to carry the drug, which is especially poorly water-soluble. Zhao *et al*. (Zheng *et al.,* 2010) have shown a drug, which has poor water solubility, and has been loaded onto polyethylene glycol/polylactic acid system to improve drug delivery. Shin *et al.* (Shin *et al.,* 2009) have used similar polymeric micellar combinations to load and deliver multiple drugs, simultaneously. Silica has biocompatible, biodegradable, and nontoxic natures, which make it safe to use (Nurdin and Purwasasmita, 2013). Furthermore, silicones have some unique properties including low surface energy, heat stability, high compressibility, low surface tension, hydrophobicity, good electric properties, low fire hazard and limited solubility in organics coupled with water insolubility (Abidi *et al.,* 2007; Mohamed *et al.,* 2013; Mohamed *et al.,* 2013).

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In addition, "smart delivery systems" is one of the challenging areas of research, which can design into new smart materials. Interesting in silica gel microcapsules prepared by interfacial polymerization in both oil-in-water (o/w) and water-in-oil (w/o) emulsions (Bean *et al.,* 2012), with much of the understanding of the chemistry concerned derived from studies of oil core systems. Bean et. al. have studied the formation of water-core/silica gel microcapsules prepared in a single-step procedure via interfacial polymerization of a surfactant stabilized water-in-oil emulsion, and characterize these materials by optical and electron microscopes (Bean *et al.,* 2012). During this research, synthesis of silica microparticles and loading of different drugs have been under taken. The particles have been studied for their antimicrobial properties using two different microorganisms, namely, Staphylococcus aureus and Escherichia coli.

EXPERIMENTAL

Materials

Tetraethyl orthosilicate $Si(OC_2H_5)_4$ (TEOS 99%), ammonium hydroxide solution (NH_4OH 25%), ethanol (99%), diclofenac sodium, linoleic acid and ricinoleic acid were purchased from Sigma Aldrich. Two bacterial strains from the Faculty of Agriculture, Cairo University, Egypt were employed. They include Escherichia coli (E. coli) as Gram-negative bacteria (G-ve) and Staphylococcus aureus (S. aureus) as Gram-positive bacteria (G+ve). Both of bacterial strains were selected as test cells because they are the most frequent bacteria in the wound infection to represent G+ve and G-ve bacteria, respectively. Fresh inoculants for antibacterial assessment were prepared on nutrient broth at 37°C for 24 hours.

Methods
Synthesis of silica microparticles

Standard Stöber method (Stöber *et al.,* 1968) for preparing silica micro-particles were selected to use during this research. In 250 ml Erlenmeyer flask, 15 ml ethanol (99%), 4 ml Deionized water (DI), 0.75 ml ammonia (25%). The molar ratio of C_2H_5OH: H_2O: NH_3 is 17.12: 55.5: 42.86 are mixed together and stirred for 30 minutes at 1000 rpm. 1.2 ml of TEOS (4.55 M) is added to the solution drop by drop, and the whole solution stirred at 1000 rpm for 3 h.

A whitish precipitate is obtained and then allowed to settle down using centrifuge at 3000 rpm for 3 min. After that, washing the precipitate by DI water and dried at 60°C.

Synthesis of conjugated Silica/Drug (Si:Drug) microparticles

Similar preparation as for silica micro-particles is used. In 250 ml Erlenmeyer flask, 15 ml ethanol (99%), 4 ml deionized water (DI), 0.75 ml ammonia (25%), in the molar ratio of C_2H_5OH: H_2O: NH_3 is 17.12: 55.5: 42.86. After 30 minutes stirring, 1.2 ml of TEOS is added (4.55M) to the solution. Drug (4 mg/ml) was additionally added simultaneously along with TEOS. Then the whole solution was stirred for 3h, and finally a whitish

precipitate is obtained. After centrifugation at 3000 rpm for 10 min., followed by washing and finally dried at 60 °C.

Release studies

Release studies are evaluated using the following procedure. Four samples (each 10 mg of Si: Drug suspended in 20 ml water, pH 6.5) are kept in individual test tubes. These tubes are kept on a simple shaker (multi Mix MTR-22) with specific program for shaking and rotation. At definite time, one test tube is removed from the shaker and subjected to centrifugation at 3000 rpm for 2 min. This is done to collect the released drug in water from the silica surface after definite time intervals (because silica micro particles settle at 3000 rpm, leaving only the released drug in the aqueous medium at supernatant level). After that, the filtrate was evaluated using UV–vis spectrometer to observe the signature of drug. The data is taken for duration of 48 h. The whole procedure is repeated four times to get the final values. This is done to ensure repeatability and correctness of the data.

Bandages/samples for antimicrobial release studies

Chemical spray technique was used to deposit a film onto substrate. The distance between nebulizer to substrate was 50 cm, the temperature of the substrate was maintained at 80°C, and the deposition time was 10 min. In this method, a solution of 100 mg Si: Drug composite in 10 ml of DI water is sprayed and deposited on the substrate. Control samples are also deposited using the same technique, for Drug (12 mg/10 ml) and for silica (88 mg/10 ml). The concentrations are decided using the drug loading studies. Similar samples were deposited on thin bandage cloth materials well.

Antimicrobial Testing

The disc diffusion method (Hassabo *et al.,* 2014) was used to assess the antimicrobial activity of all samples. Discs of 10 mm diameter from the samples are prepared. Nutrient agar plates were incubated with microbial culture. The thin film of Si: Drug coated on the surface of a cover slip by spraying was then gently placed with the help of a forceps on top of the agar plate containing the test organism. The plate is then incubated at 30°C for 72 h to observe increase in the zone of inhibition as the test compound is progressively released from the thin film surface. The inhabitation zone (distance from disc circumference in mm) is determined for each disc. These zones are measured and were reported in the units of diametric lengths. In the antibacterial assay, all data consisted of the means of at least three parallel experiments that the discrepancies among them were less than 5%.

Characterization of the Si/Drug microsphere

A release study of the oil from Si/Drug capsules was investigated through a UV-Vis spectrophotometer (300 UV-Vis, 50 ANALYTIKA JENA Spectrophotometer) operated between 300 and 800 nm with 2 nm resolution.

Fourier Transform Infrared (FT-IR, Shimadzu Systems) spectroscopes of the treated samples are recorded and analyzed.

Scanning electron microscope SEM analysis of the Si/Drug capsules was performed using a Hitachi, Japan. The average diameter of the Si and Si/Drug capsules nanoparticles is determined from the diameter of 100 nanoparticles found in several chosen areas in enlarged microphotographs.

Thermal behavior of Si and Si/Drug capsules was investigated using a thermo gravimetric analyzer (TGA). This is done by taking few mg of sample in the TGA chamber and the chamber is subjected to the temperature variation from 25°C to 800°C at the rate of 10°C/min in nitrogen atmosphere. The initial weight was considered as 100%.

RESULT AND DISCUSSION

Characterization of the Si/Drug microcapsules

Fig. 1 illustrates the possible interaction between silica particle and drug molecule. The lone pair of electrons of carboxyl oxygen of each drug could be made a partial bond with silica through a weak van-der-Waals force. Then, losing a proton from -OH group to be stabilized. The interaction is seen by the FT-IR analysis. The important point to mention here is that, the interaction was weak and that was is necessary to release the drug molecule in suitable medium.

FT-IR analysis

FT-IR study was carried out to confirm the compatibility between the Si nanoparticles and different Drug (Fig. 2). The typical signatures of silica are observed in bands at 798, 950 and 1050–1100 cm^{-1}. The bands at 950, 798 and 1070 cm^{-1} are due to Si-OH stretching, Si-O-Si symmetric and asymmetric stretching vibrations respectively (Basaldella and Legnoverde, 2010). The band near 1094 cm^{-1} was associated with the Si-O-Si stretching vibration. At 798 cm^{-1} there is a band are attributed to the ring structure of the SiO4 tetrahedral.

The 950 and 571 cm^{-1} bands are due to Si-O groups. The band at 440-480 cm^{-1} is of Si-O-Si bending vibration mode. The characteristic of diclofenac sodium exhibited distinctive peak at 1574.59 cm^{-1} is due to the aromatic stretching and the –COO asymmetric stretching, the peaks observed at 1504.2 and 1452.14 cm–1 are due to N-H deformation and C-N stretching, respectively. The IR spectra of diclofenac sodium exhibited distinctive peaks at 3386.39 cm^{-1} due to N-H stretching of the secondary amine, aromatic stretching-CH stretching at 2965 cm^{-1}. Ricinoleic acid has characteristic peak representing ester C=O group at 1724 cm^{-1}. This is due to the carbonyl group of carboxylic acid (–COO asymmetric stretching), the peaks observed at 2962 and 2887 cm^{-1} are due to C-H valence and O-H for alkane, respectively. In addition, there are other peaks at 2500 – 3300 and 1000-1100 cm^{-1} due to O-H stretching of the carboxylic acid and C-O-C respectively.

FT-IR spectra of linoleic acid show that, the region 1690-1710 (cm^{-1}) is a very strong peak. A strong band in this region is indicative of C=O stretch of the carboxylic acid in the linoleic acids. The sharp two peaks in region (2800-3000 cm^{-1}) indicate the presence of aliphatic hydrocarbon for CH stretch containing CH$_3$ and CH$_2$ groups. The moderate peak in the region above 3000 cm^{-1} was observed to confirm the presence of the double bond in the chemical structure.

The broadening and slight shifting of Si-OH (3200–3700 cm^{-1}) signatures in Si/Drug system, as compared to both silica and Drug, meaning that, it is due to the Drug.

In case of the FT-IR spectra of the Si/Drug, the peaks of Drugs are present in the Si/Drug. It was confirmed from above that there are no major shifting, as well as, there is no loss of fundamental peaks between the spectra of Drugs and Si/Drug with all other peaks normally present. Therefore, it can be concluded that there is no strong chemical interaction between Drug and Si/Drug.
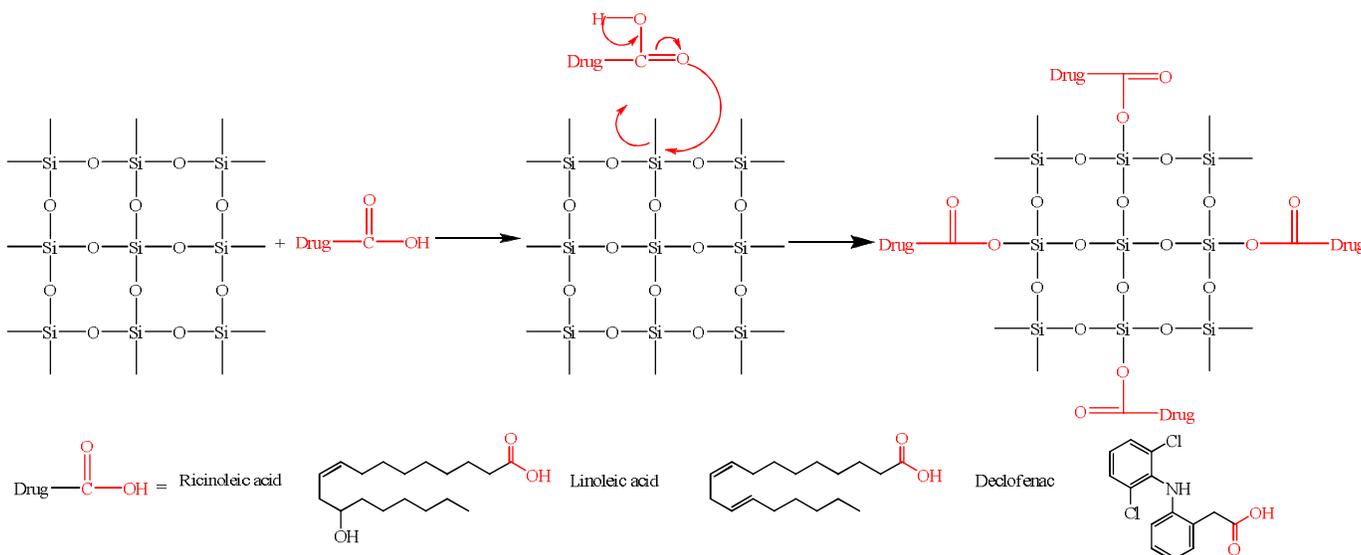

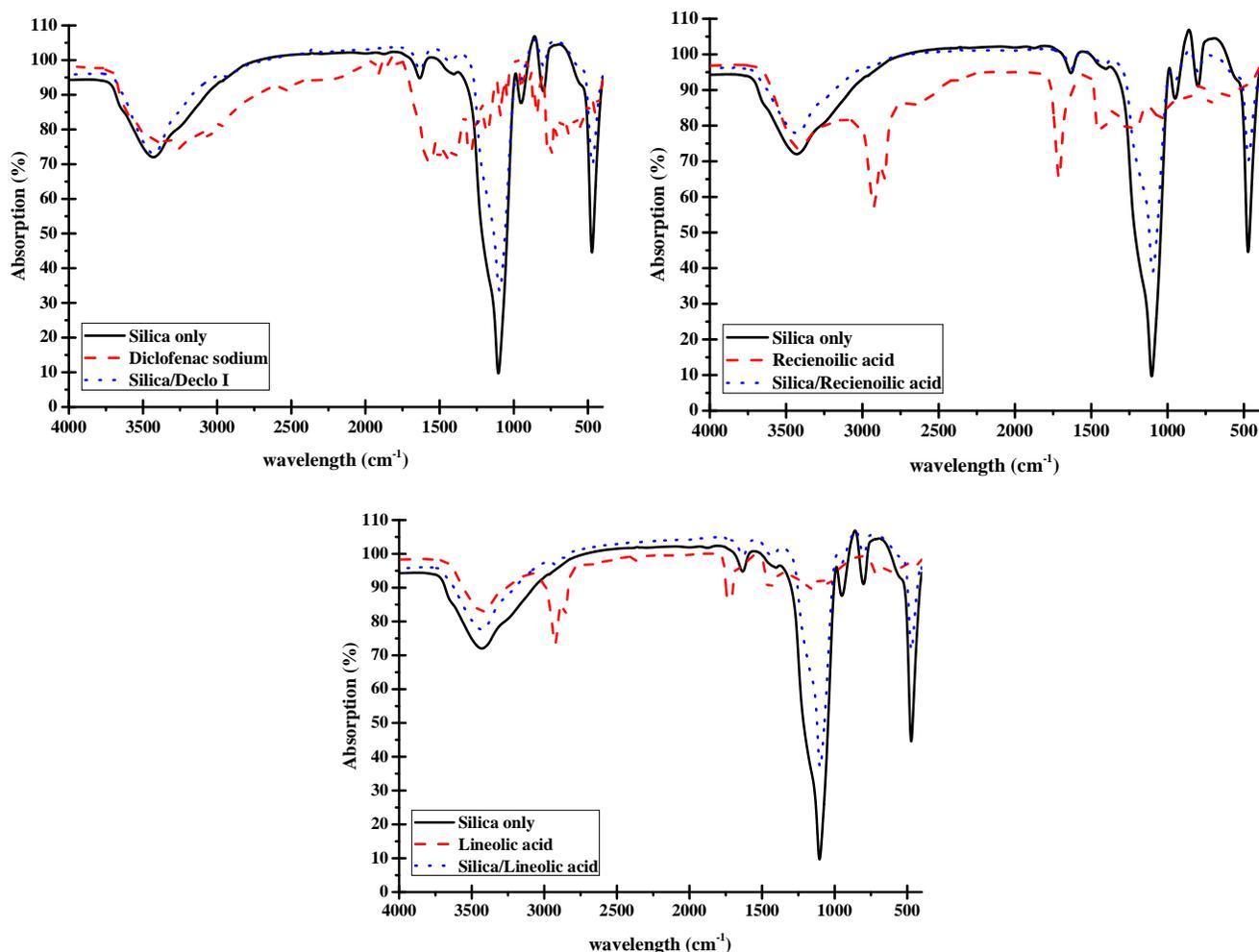**Fig. 1**: Possible interaction of silica particle with drug molecule

Fig. 2: FT-IR spectra of Si/Drugs, a) Si/Diclofinac sodium, b) Si/Recienolic acid and c) Si/Lineolic acid.

Surface and size analysis

The SEM was recorded in order to provide further confirmation on the encapsulation of Si/Drug. SEM-EDX spectra of Si only and Si/Drugs are shown in Fig. 3. The obtained SEM confirms the existence of drug inside the silica.

SEM images show that, the drug is clearly adsorbed on the silica surface, and the images showed silica particle size around 200 – 300 nm and silica was coated on the surface of the drugs, and Si/Drug particle size was around 1 μm. In addition, the image of silica only show that, the particles are uniformly spherical and homogeneity distributed. On the other hand, the image of silica/drug shows that the silica particles are agglomerated and rounded the drug particles. This agglomeration is due to the chemical structure, size and nature of both drug and silica particles.

Thermal analysis

Thermal behaviors of Si/Drugs are performed using TGA (Thermograms are shown in Fig. 4). The graph showed two weight

loss signatures (an onset of drop in graph), one at ~98°C and another at around 250 °C (with a lesser slope). The total weight drop was around 12% in the range of 25°C to 200°C.

Tudja et al (Tudja *et al.,* 2001) have been studying the thermal behavior of diclofenac sodium and they have found that the material started to decompose at around 98°C to yield a residue, which remain on the chamber walls till ~220°C. Hence, it revealed that in 100% of the sample, 12% is the diclofenac sodium contribution to the rest 88% is of silica particles.

The same behavior for both recienoleic acid and linoleic acid and their composites with silica are expected and confirmed with TGA as illustrated in Fig. 4, but both of composites are decomposed at earlier temperature than diclofenac ~68°C. In addition, silica/recienoleic acid show more thermal stability than silica/diclofenac and silica/linoleic acid, which may be attributed to presence of hydroxyl group, which may increase the thermal stability, by making chemical bonded with the silica particles.
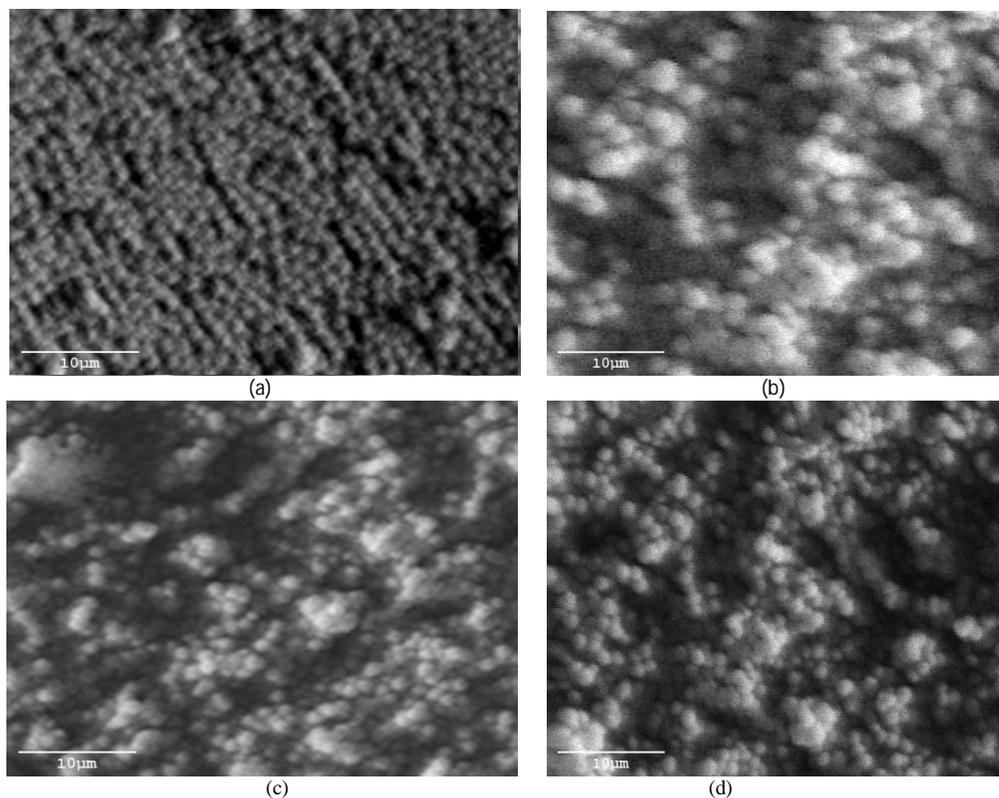
Fig. 3: SEM images of Silica and Silica/Druga) Silica only, b) Silica/Diclofenac, c) Silica/Recienoleic acid and d) Silica/Lineoleic acid.
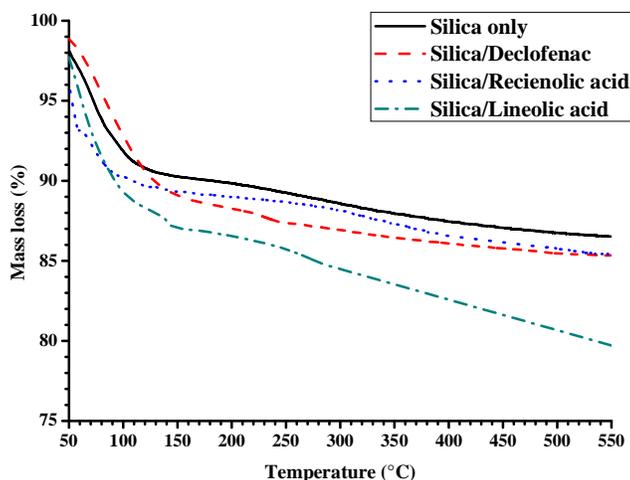

Fig. 4: Thermal gravimetric analysis (TGA) of silica and silica/drug.

Time-lapse Release of Drug Compound

Encapsulation of drugs into silica is important to decrease the amount of drug release into the body. To find out the level of drug release, the amount of the drug released at certain time can be detected.

Furthermore, in ideal encapsulation, all selected drugs will be trapped in the microcapsules, but it is still possible that there is drug bonded with surface or contained in microcapsule pores. The part of drug, which is not in the microcapsules, may lead to the detection of drug at normal pH (6.5). The result is shown in Fig. **5**, when microcapsules containing drug is

inserted, the excretion of drug from the microcapsules are observed. At pH 6.5, it is seen that the tested samples have succeeded in excreting all drugs with the greater amount and concentration. In case of Si/LA oil, by increasing the time the amount of LA oil increased gradually with constant rate till 24 h which reach (16 mg; 40%), after that, drug realizing rate was decreased, meaning for the next 24 h, the total released amount was 50%. For Si/RA oil, the excreted rate of RA oil after 12 h was reached 16 mg 60%.After that, increasing the time come with constant release rate of the RA oil from encapsulated silica microsphere to reach (27 mg; 67%) after 48 h.
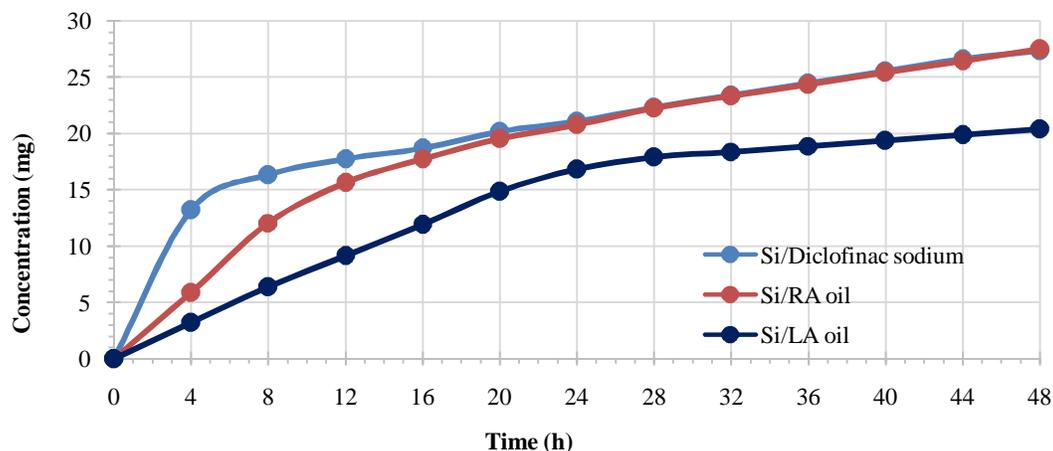
Fig. 5: Release profile of silica/diclofinac, silica/RA oil and silica/LA oil

Table 1: Zone of inhibition diameter of the Si: Drugs with an interaction with *Escherichia coli* (E. coli) and *Staphylococcus aureus* (S. aureus).

Drugs		Zone of inhibition diameter in mm					
		E. coli			S. aureus		
		24 h	48 h	72 h	24 h	48 h	72 h
Drug 1 Diclofenac Sodium	Drug 1 only	14.2	14.8	14.9	12.1	12.5	12.6
	Si/Drug 1	13.1	13.2	13.3	9.5	9.7	9.8
Drug 2 Linoleic acid	Drug 2 only	7.8	8.2	8.3	6.5	6.8	6.8
	Si/Drug 2	6.8	7.1	7.1	5.6	5.9	5.9
Drug 3 Ricinoleic acid	Drug 3 only	6.5	7.1	7.1	6.0	6.2	6.3
	Si/Drug 3	6.1	6.3	6.3	5.8	6.0	6.0

Si/diclofenac sodium has same behavior like Si/RA oil, however the drug released reached (16.4 mg; 41%) after 8h. The acidity becomes the main factor for the excretion of active drugs. In acid condition, the microcapsule tends to swell. The swelling will lead to the opening of enlarged microcapsule pores, so it increases the drugs coming out. After certain time, the drug tends to get stable. The stability arises due to the absence of drugs that comes out from the microcapsules. It is caused by the environment condition, which is no longer supporting the excretion of active substance.

This shows that the resulted microcapsules have already given a pretty good control that released efficiency of the drugs. With the same amount, all the three kind of used drugs without encapsulation will work for 120 minutes, while drug encapsulation in silica improve the work efficiency time till 48 h or longer.

Antibacterial Studies

For assessment of antimicrobial activity, samples were subjected to Disk Diffusion susceptibility test method. The antibacterial results and the zone of inhibition (in terms of mm of the diameter of the zone) is recorded in each case and summarized in **Table 1**.

As seen from the data for both bacterial strains, diclofenac Sodium, Linoleic acid and Ricinoleic acid samples show growth of both bacteria under them with inhibition zone, indicating that they can inhibit bacterial activity. In addition, all the Si/Drug samples inhibit bacterial growth as is evident from the absence of growth under all treated samples. As seen from the data

of all drugs, the data with control (Drug only) indicated that, each drug itself show a good efficacy for E. coli and S. aureus. Therefore, it was expected that, the Si/Drug could show better results, and that was confirmed with the data in **Table 1**. In addition, all drugs and Si/Drugs shows more inhibition zone on E. coli than S. aureus. Furthermore, for all drugs, the inhibition zone of the Si/Drug is smaller than drug only, and after 72 h is almost similar to that after 48 h. The zone of inhibition improved after 24 to 48 h.

This was good in comparison with their controls, wherein the zone was saturated at 24 h itself. The zone of inhibition after 24 h was small and slightly improved with time.

Antibacterial activity of all drugs, which is an anionic compound due to a presence of COO- in the solution and depend on the content of the carboxyl groups of the drug. Therefore, all Si/Drugs had more effective inhibition on E. coli than S. aureus. The fact was attributed to their different cell walls. S. aureus, a typical Gram-positive bacterium, its cell wall is fully composed of peptide polyglycogen.

The peptidoglycan layer is composed of networks with plenty of pores, which allow foreign molecules to come into the cell without difficulty. On the other hand, the cell wall of E. coli, a typical Gram-negative bacterium is made up of a thin membrane of peptide polyglycogen and an outer membrane constituted of lipopoly-saccharide, lipoprotein and phospholipids. Because of the bilayer structure, the outer membrane is a potential barrier against foreign molecules (Hassabo *et al.,* 2014).

CONCLUSION

Diclofenacsodium, linoleic acid and ricinoleic acid can be encapsulated into silica microcapsules, with less than 1 µm in size, increasing the possibility of the drug to be controlled released from silica microcapsules at pH condition 6.5 (skin pH), so the silica microcapsule has the potency to be used as drugs carrier and control its release behavior.

ACKNOWLEDGEMENTS

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