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RESEARCH ARTICLE

Adaptation of hard gelatin capsules for oral delivery of aqueous radiopharmaceuticals

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Abstract

Purpose Oral administration of Iodine^{-131} (I^{-131}) solutions causes high risk of contamination for patients and dispensers. The objective of the study was to adapt hard gelatin capsules (HGCs) for filling with radiopharmaceutical solutions without deformation.

Methods Polystyrene (PS) internally lining films with different thicknesses were used to protect HGCs. The insulated HGCs were evaluated for their physicochemical characteristics and rupturing time in different dissolution media. HGCs internally lined with PS were examined for withstand loading with different volumes and radioactivities of I^{-131} solutions. Radioactivity release was studied in deionized water and acidic media. Quality control of released I^{-131} was inspected for radiochemical purities.

Results There was a directly proportion between PS lining thickness and stability of HGCs after filling with 500 μl aqueous methylene blue solution. HGCs internally lined with PS 100 μm thickness withstand deformation for > two months; however showed fast in-vitro rupturing time in different dissolution media. Internally lined HGCs loaded with different volumes and radioactivities of I^{-131} solutions resisted for one week without radioactive leakage. Yet, revealed complete release of I^{-131} after 20 min in dissolution media with great radiochemical purity.

Conclusion The study promises safely I^{-131} aqueous solution delivery via adapted HGCs.

Keywords Hard gelatin capsules · Iodine^{-131} solution · Polystyrene · Adaptation · Lining

Abbreviations

FT-IR	Fourier transform infrared spectroscopy
GC-MS	Gas chromatography-mass spectroscopy
HGCs	Hard gelatin capsules
I^{-131}	Radioactive Iodine^{-131} solutions
MB	Methylene blue
PS	Polystyrene

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Introduction

Radiopharmaceuticals are a heterogeneous class of medicinal products characterized by containing one or more radioactive isotopes. Those isotopes decay spontaneously with the emission of ionizing radiation that is used for various medical purposes [1, 2]. Iodine^{-131} radionuclide (I^{-131}) ($t_{1/2}$ = 8.04d), as an example, has important applications in nuclear medicine; especially it is the drug of choice for the diagnosis and treatment of thyroid carcinoma. Sodium iodide (I^{-131}) is produced in aqueous solution form, which is supplied mainly as oral solutions. However, liquid radiopharmaceutical preparations have suffered from certain disadvantages. Primarily, potential health hazards have been presented from the risk of radioactive contamination of patients and dispensers handling

I^{-131} solutions, in addition to the loss of radioactivity. Alternatively, encapsulated I^{-131} within a hard gelatin shell minimizes volatility, spillage and reduces contamination and exposure risks [3]. On the other hand, the volume of radioactive solution should be so small, with the constrain of the administration of small dose of I^{-131} radionuclide, to avoid the challenge of capsule deformation because of the aqueous solution present; in spite of filling with a carrier substance (adsorbent) such as sodium phosphate [1, 4].

Thus, when a large amount of radioiodine activity is prescribed, the patient may have to swallow multiple capsules of small volume diluted solutions or increase the concentration of the very small volume, which is very expensive for reprocessing the cyclotron with more cost-effective dosage form for the patient [5]. Therefore, there is a continued demand for adaptation of HGCs to hold higher volumes of aqueous radioactive pharmaceutical solutions, in a form which is easier to be standardize, safer for handling [6].

However, filling of aqueous solution into HGCs was confronted with many barriers. Hydrophilic substances may be formulated into a capsule filling material, but should be kept at/or below 10% [7]. Water is a potent plasticizer for gelatin, that the entropy of mixing of water with gelatin is lower than 0.5. Consequently, even small amounts of water decrease the glass transition temperature of gelatin [8]. This molecular interaction causes stiffness changes in the gelatin. Hence, compatibility between the fill mass and the gelatin shell of the capsules become a problem in case of using large amounts of amphiphilic or hydrophilic excipients.

Previously, Howard and Alexander (1964) had tried to administer radioactive materials by adsorbing the aqueous solution of radioactive material on a porous, non-toxic foamed gelatin sponge plug, which was inserted in a HGC. However, the it showed loss of radioactivity due to the decay, as the filled capsule had to be placed in a desiccator for complete drying over a period of two hours [9]. Recently, Takada and Murakami (2005), succeeded to safely incorporate aqueous solution of glycyrrhizin disodium to be encapsulated in HGCs for controlled-release colon targeted delivery, by lining with an ethyl cellulose film inside of the gelatin capsules [10].

Other trial for preparation of Sodium Iodide I^{-131} solution USP in HGCs dosage form was designed by HICON™ (2008); where the kit included one large HGC and one small HGC for each dose prepared. The small capsule containing 300 mg of anhydrous dibasic sodium phosphate USP, as absorbing agent, was inserted into the large capsule. The required volume of Sodium Iodide I^{131} solution USP (maximum 150 μL) was injected into the center of the closed small capsule; finally, the large capsule was closed with its cap (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021305s016lbl.pdf).

Polystyrene (PS) a hard, hydrophobic, stiff, inexpensive synthetic resin produced by the polymerization of styrene that is widely employed in the food-service industry [11]. Polystyrene sulfonate is used as potassium binder in acute and chronic kidney disease for people with hyperkalemia (abnormal high blood serum potassium levels [12]. Iconomopoulou et al., (2005) have used polystyrene–divinyl benzene beads as controlled release carriers for liquid biocides [13]. As well, Patil et al., (2006) have designed porous PS beads as carriers for self-emulsifying system containing loratadine [14].

In recent decades, global efforts have been made in the purpose of developing drug delivery systems (DDSs) for radiopharmaceuticals administration [15]. In the study, HGC shells internally lined with PS polymeric film was developed, evaluated and optimized; for adaptation to be filled with aqueous solutions for delivering radiopharmaceuticals (I^{-131}) with highest safety and stability measurements. Aiming in safely increasing the volume and consequently the radioactive dose administered, with compliance of cancer patients undergoing oral radiotherapy regimen. As well safely handling concerning the workers and distributers.

Methodology

Materials

Empty Hard gelatin capsule shells (size 0) were kindly given as a gift by Capsugel, Colmar/Strasbourg, France; Polystyrene (PS) polymer powder was purchased from Sigma Aldrich; Methylene blue was purchased from Sigma Aldrich; No-carrier-added sodium iodide^{-131} (NCA NaI^{-131}, 10 mCi/mL (37 MBq/mL) in 0.1 N NaOH) was a gift from Radioisotope Production Facility (RPF), Inshas, Egypt. Whatman paper number 1: international LTD was purchased from Merck Company, Germany. All other reagents are of analytical grade.

Experimental

Internally lining of HGCs with polystyrene film

Different concentrations of PS solutions (5, 10, 20%*w*/*v*) were prepared using xylene as solvent. 500 μl of PS solutions were poured into the body and cap of HGCs, then the capsules' parts were inverted (to ensure complete lining). The lined gelatin shells were left to dry for 24 h. Then, xylene traces were washed away several times with methanol until completely disappeared, following a method adopted previously [16].

Evaluation of xylene traces in polystyrene lining using GC–MS spectrometry

Gas chromatography-mass spectroscopy (GC-MS) analysis was performed for the evaluation of xylene traces in polystyrene lining, using Perkin Elmer/auto system XL with Turbo mass, USA, following the conditions adopted previously [17].

The mass spectrometer acquisition was performed in full-scan from 40 to 210 m/z to determine the characteristic ions and the retention times for identification of any xylene traces in PS samples. GC-MS data was obtained in the form of % abundance vs. mass spectrum (*m/z*).

Characterization of the prepared HGCs internally lined with polystyrene

FT-IR spectroscopy Fourier transform infrared spectroscopy (FT-IR) (Shimadzu 8400S, Lab Wrench, Japan) was employed within the spectral region of 400–4000 cm^{-1}, for the interpretation of any conformational and structural changes that might be undergone for proteins in HGCs and/or PS during lining process [18].

Determination of polystyrene lining thickness The thickness values of different PS internally lining films of HGC shells were determined at different points of the HGC shells, using (Zwick Roell Tensile Testing Proline, Germany); and calculated by the following equation:

$$\text{The thickness of PS internally lining films of HGC shells} = \text{The thickness of internally lined HGC shells} - \text{The thickness of non-lined HGC shells}$$

The results were expressed as the mean ± SD of 6 samples.

Determination of capsule hardness The hardness of the non-lined and the different PS internally lined HGCs were obtained according to the method reported by Cilurzo et al., 2005 [19], using tensile testing apparatus (Zwick Roell Tensile Testing Proline, Germany). Each capsule was compressed at the constant rate of 10 mm/min until the shell was broken or completely compressed. The work required to deform the capsule was determined. The results were expressed as the mean ± SD of 6 samples.

Effect of polystyrene film thickness on HGCs tolerance for water incorporation

Five different volumes of 2%*w*/*v* methylene blue (MB) aqueous solution (10, 25, 50, 100, 250, 500 μl) were filled into the non-lined and the different PS internally lined HGCs; in order to evaluate the tolerance of the capsules for water incorporation. As well, the maximum amounts of aqueous solutions that could be filled in the capsule without causing any leakage or capsule deformation were determined.

Effects of dissolution medium and polystyrene film thickness on the in-vitro rupture time of the capsule shells

Determination of rupture time of HGCs was achieved based on MB released from non-lined and the different PS internally lined HGCs, using a USP apparatus-2 paddles dissolution tester [20]. In the study, 100 μl of 2%*w*/*v* MB was filled into capsules and placed in 100 ml dissolution medium kept at 37 °C with stirring speed of 100 rpm. Deionized water, 0.1 N HCl buffer and phosphate buffer pH 7.4 were used as dissolution media. At predetermined time intervals, one ml sample of dissolution medium was withdrawn and replaced with fresh media. Samples were analyzed for released MB spectrophotometrically at λ_{664nm} using UV/visible spectroscopy (Jasco spectrophotometer, Japan). Results were expressed as rupture time (min) of HGCs for MB released in three replicates.

Examination for radioactive leakage

Loading of I^{-131} solutions with different volumes and the same radioactivity The selected HGCs based on results of previous tests were examined for loading with different volumes of the radioactive solution of I^{-131} (50, 200, 500 μL) having the same radioactivity (200 μCi / 7.4 MBq). Each of the loaded capsules were placed in 10 mL empty glass vials and the radioactive leakage for one week was examined by Gamma-ray spectrometry using a 8192 Tennelec Multichannel Analyzer coupled with a high purity germanium (HPGe) coaxial detector (USA) calibrated with a mixed source of: ^{155}Eu (86.5 and 105.3 keV), ^{57}Co (122.1 and 136.5 keV), ^{137}Cs (661.6 keV), ^{54}Mn (834.8 keV), and ^{65}Zn (1115.5 keV). The results were taken as mean of three replicates.

Loading of I^{-131} solution of different radioactivities and the same volumes The selected HGCs were examined for loading with 100 μl of radioactive I^{-131} solutions having different radioactivities (1, 2, 3 mCi/ 37, 74, 111 MBq). The loaded capsules were placed in 10 mL empty glass vials and examined for radioactive leakage for 1 week using the same condition in 2.2.6.1.

Radioactivity release study in different release media

The release of I^{-131} from selected HGCs in different release media was estimated. The capsules, filled with 100 μL of 1 mCi/37 MBq I^{-131}, were placed in 10 mL deionized water or acidic buffer solution (pH 1.2), at 37 °C and stirred using magnetic stirrer at 100 rpm. Samples (5 μL) of the release medium were withdrawn and measured for radioactivity content versus time.

Radiochemical purity of the radioactive I^{-131} loaded HGCs

Radiochemical purity was determined by the ascending paper chromatography method. At 2 cm above the lower edge of 13 cm length and 2 cm width paper sheet of Whatman paper no.1; suitable portion of the I^{-131} solution sample was positioned and left to dry, then the paper was developed using fresh 70% *v*/v methanol as mobile phase. After complete development, paper sheet was removed, dried, and was counted by radiochromatogram with NaI (Tl) detector, Canbirra, USA. The percentage of radiochemical purity was calculated as the ratio of the radioactivity of free I^{-131} to the total activity multiplied by 100 [21, 22].

Examination of radiation stability of the capsule shell

Radiation stability of the capsule shell was performed by loading selected HGCs with ^{131}I of different radioactivities (10, 20, 50 mCi/ 370, 740, 1850 MBq). The loaded capsules were placed in 10 mL empty glass vials and examined for deformation and radioactive leakage for 24 h using the same condition in 2.2.6.1.

Statistical analysis

All data were expressed as mean standard deviation (±SD) and were analyzed by using the Statistical Package for Social Sciences (SPSS) (IBM SPSS, v 20.0 software, Inc., Chicago IL, USA), by applying One Way ANOVA followed by Post Hock (Dunnett) test for multiple comparative test with non-lined HGCs (F1). Probability at significance level of ($p < 0.05$) was considered as statistically significant.

Results

Evaluation of xylene traces in polystyrene lining using GC–MS spectrometry

Evidently, the *m*/*z* value of 106 corresponded to the molecular weight of xylene is obvious in the GC-Mass spectra (Fig. 1). However, GC-Mass chromatogram of dried PS sample indicates absence of the characteristic band for xylene at 106 m/z. the results indicate the absence of any xylene traces in the PS sample used for lining of HGCs using xylene as solvent.

Characterization of the prepared HGCs internally lined with polystyrene

FT-IR spectroscopy

The FT-IR spectra of HGCs, PS and HGCs internally lined with PS are shown in Fig. 2. The FT-IR spectrum of HGCs (Fig. 2a) shows characteristic bands of gelatin at 3342.13, 2923.71, 1641.72 and 1549.64 cm^{-1}, corresponding to amide-A peak (N–H stretching coupled with the hydrogen bond of a carbonyl group in a peptide chain), amide-B peak (the asymmetric stretching vibration of alkenyl C–H and $NH3^{+}$), amide-I peak (the C=O stretching vibration of the peptide linkages) and amide-II peak (the N–H and the C–N stretching vibration), respectively.

The FT-IR spectrum of PS shows its characteristic band of four peaks at 3000–3100 cm^{-1} corresponding to aromatic C–H & = C–H, followed by a band of 2931.80, 2916.37 and 2850.79 cm^{-1} peaks corresponding to -C-H groups, as well, **the** aromatic ring mono-substitution peak at 1944.25 cm^{-1}, and a band of three peaks corresponding to the aromatic -

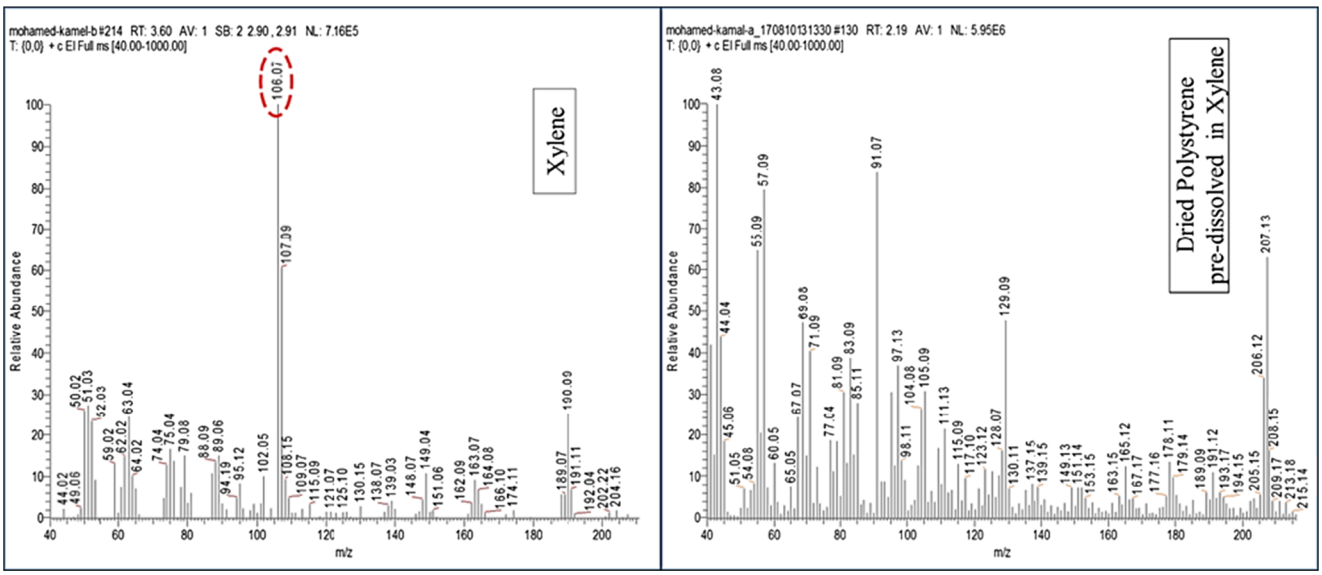


Fig. 1 GC-Mass chromatograms of xylene and polystyrene for determination of xylene traces in the PS lined HGCs

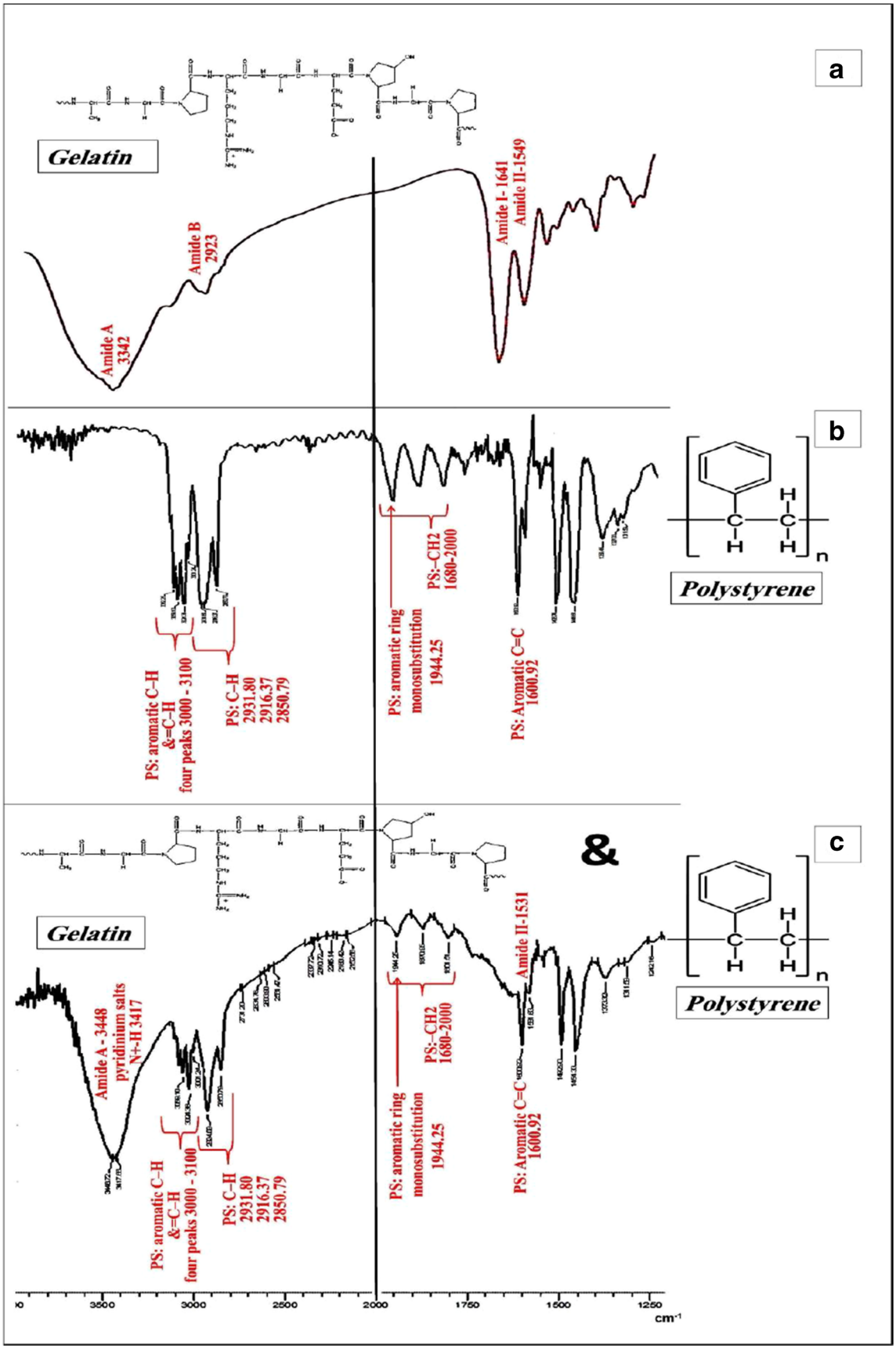


Fig. 2 The FT-IR spectra of (**a**) hard gelatin capsules, (**b**) polystyrene and **(C)** hard gelatin capsules internally lined with polystyrene

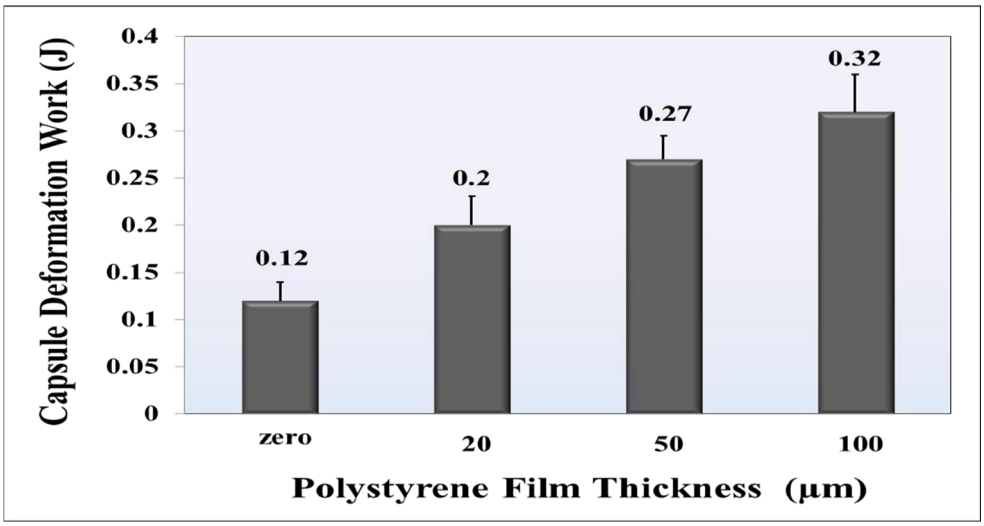


Fig. 3 Effect of polystyrene lining thickness of on the hardness of hard gelatin capsules

CH_2 at1680–2000 cm^{-1}, in addition to the characteristic peak of the aromatic -C=C at 1600.92 cm^{-1}, Fig. 2b.

The FT-IR spectrum of internally lined HGCs with PS shows the characteristic bands of PS, however, Fig. 2c illustrates shifting in the characteristic peak of amide A of HGCs to higher wave numbers (3448 cm^{-1}) and that of amide II to 1531 cm^{-1}. In addition a characteristic band of pyridinium salts (N+) (hydrogen bonds H) stretching is shown at 3417 cm^{-1} [23].

Determination of polystyrene lining thickness

The thickness of different PS films of HGC internally lined shells were observed to be uniformly distributed within different points of the same capsule lining The film thickness was directly proportion to PS concentration used in the coating solutions; as the thickness were 20, 50 and 100 µm for PS solutions of 5, 10 and 20% *w/v* concentrations, respectively.

Determination of capsule hardness

All capsules submitted to hardness testing were completely deformed without rupture of hard shells. The hardness of HGCs could be interpreted as capsule deforming work (J) [24]. Comparing to capsule deforming works of non-lined HGC shells (0.12 J), significant increase in the hardness ($p < 0.001$) of HGCs internally lined with PS films, which was interpreted as increase in capsule deforming works (0.2, 0.27 and 0.32 J) and is directly proportion to film thickness (20, 50 and 100 µm), respectively, Fig. 3.

Effect of polystyrene film thickness on HGCs tolerance for water incorporation

The tolerability of HGCs to be filled with aqueous solution could be interpreted as the onset of MB solution leakage, Table 1. The non-lined capsules showed leakage after only 3.5 min (0.0025 days) from the least

Table 1 Effect of Polystyrene film thickness on HGCs tolerance for water incorporation; expressed as onset of MB solution leakage

PS film Thickness (µm)	Onset time for leakage (*days*) after filling of HGCs with different volumes of MB solutions					
	10 µl	25 µl	50 µl	100 µl	250 µl	500 µl
Zero	0.0025 ± 0.0007	$0.0021^{a} \pm 0.0003$	$0.0018^{b} \pm 0.0004$	$0.0014^{b} \pm 0.0004$	0^{b}	0^{b}
20	$7^{C} \pm 0.2$	$5.75^{C} \pm 0.3$	$3.5^{C} \pm 0.25$	$1.38^{C} \pm 0.4$	$0.75^{C} \pm 0.06$	$0.5^{C} \pm 0.04$
50	$45^{C} \pm 3$	$39^{C} \pm 4$	$31^{C} \pm 2$	$25^{C} \pm 2.6$	$12^{C} \pm 1.5$	$5^{C} \pm 1.3$
100	$106^{C} \pm 6$	$101^{C} \pm 4$	$95^{C} \pm 5$	$91^{C} \pm 5$	$83^{C} \pm 3$	$76^{C} \pm 4$

Statistical Analysis by applying One Way ANOVA

a = significant differences ($p<0.05$)

b = significant differences ($p<0.01$)

c = significant differences ($p<0.001$)

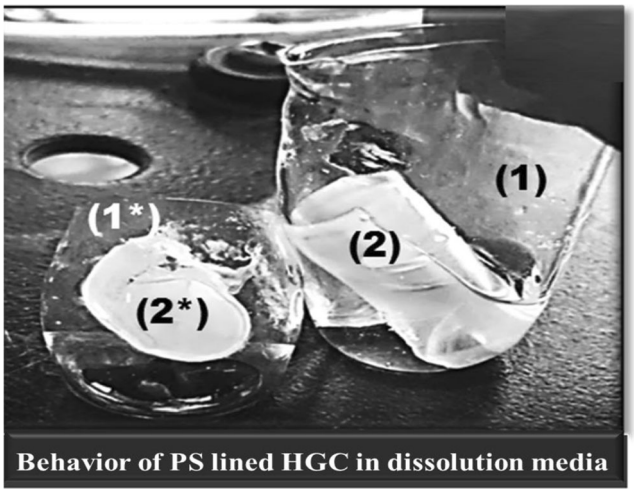


Fig. 4 Photograph of the behavior of polystyrene internally lined hard gelatin capsules in aqueous dissolution medium at 37 °C. (1) The swelled body of HGC shell. (1*) The swelled cap of HGC shell. (2) The internally lining PS films of the body of HGC shell remained intact at the end of the experiment. (2*) The internally lining PS films of the cap of HGC shell remained intact at the end of the experiment

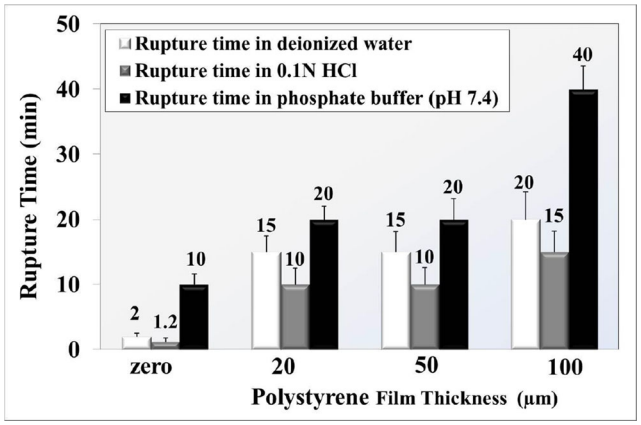


Fig. 6 Effect of polystyrene lining thickness on for in-vitro rupture time

incorporated volume of MB solution (10 µl), where the onset of leakage decreased with increase in the incorporated volume of MB solution reaching abrupt leakage (0 min) for 500 µl MB.

On the other hand, there was highly significant difference between the tolerability of non-lined HGCs to hold MB aqueous solution and that of internally lined ones. The tolerance of PS lined HGCs to be filled with aqueous solution was gradually increased with the increase in PS film thickness (100 > 50 > 20 µm); reached to its optimum tolerance for HGCs internally lined with 100 µm PS film thickness, ($p < 0.001$) compared with that of non-lined HGCs.

Effects of dissolution medium and polystyrene film thickness on the in-vitro rupture time of the capsule shells

Figure 4 shows the dissolution behavior of PS internally lined HGCs in dissolution medium at 37 °C. It is clear that initially, HGCs shells swell and become softer, followed by slipping of the capsule body from the cap, with complete release of HGCs contents, Fig. 4 (1 and 1*). However, the internally lining PS films withstand the dissolution process and remain intact at the end of the experiment, Fig. 4 (2 and 2*). An observation that postulates the possibility of its in-vivo excretion unchanged in faeces as opened 'ghost capsule'.

Figure 5a and 6 show the dissolution performance, tested as rupture time, of non-lined HGCs and PS internally lined HGCs in deionized water at 37 °C. Lag times for rupture of HGCs are observed, which is a minimum for non-lined HGCs and increases with increase in PS lining thickness. Significant differences were computed

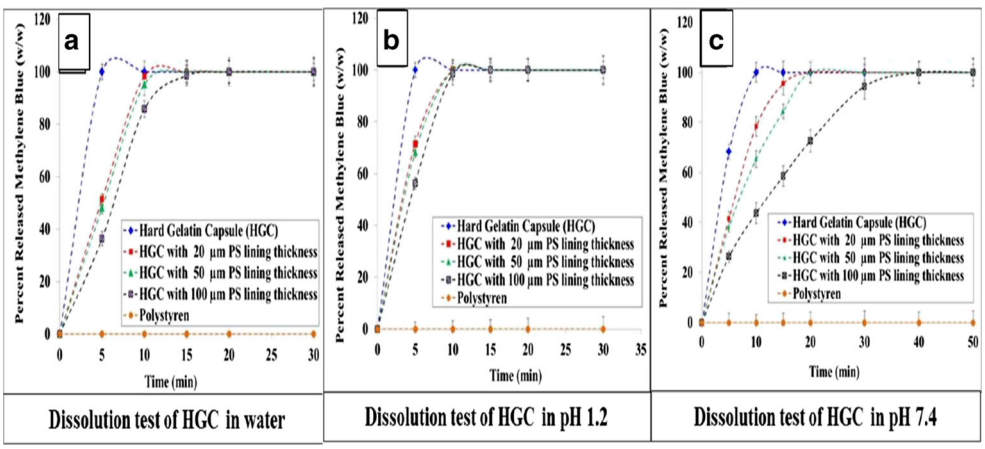


Fig. 5 The dissolution profile of polystyrene internally lined hard gelatin capsules (**a**) in deionized water (**b**) in 0.1NHCL (pH = 1.2) (**c**) in Phosphate buffer (pH = 7.4)

Table 2 Percent released I^{-131} radioactivity in different release media

Time (minutes)	% Released I^{-131} radioactivity	
	in deionized water	in acidic buffer solution (pH 1.2)
1	3.31 ± 0.31	15.41 ± 0.88
5	44.22 ± 1.45	56.35 ± 3.23
10	69.54 ± 3.78	92.91 ± 4.12
15	89.13 ± 4.89	99.22 ± 5.32
20	99.2 ± 4.35	99.23 ± 5.67
25	99.3 ± 4.77	99.41 ± 5.34
30	99.3 ± 5.34	99.45 ± 5.26
45	99.5 ± 5.23	99.51 ± 5.78
60	99.5 ± 5.67	99.62 ± 5.51

for rupture times of HGCs with PS lining thickness of 20 and 50 μm ($p < 0.01$), while for HGCs with PS lining thickness of 100 μm was ($p < 0.001$), compared with that of non-lined HGCs

The dissolution behaviors of the non-lined HGCs and PS internally lined HGCs in dissolution media of different pH values (1.2 and 7.4) are illustrated in Figures 5b, c and 6. In acidic pH, the rupture time was shorter than that in deionized water, indicating significantly faster dissolution rats compared with that in deionized water ($p < 0.001$), Figs. 5b and 6. However, in phosphate buffer (pH 7.4), prolonged rupture times of HGC shells are observed compare with that in deionized water ($p < 0.001$), Figs. 5c and 6. The dissolution behavior of the tested HGCs in dissolution media could be arranged in the same order as in deionized water, where rupture time was minimum for non-lined HGCs and increased with increase in PS lining thickness.

Examination for radioactive leakage

Loading of I^{-131} solutions with different volumes and the same radioactivity

The loaded capsule, with different volumes containing the same radioactivity of I^{-131} solution, showed high intact stability for one week without showing any radioactive release.

Loading of I^{-131} solution with different radioactivities and the same volumes

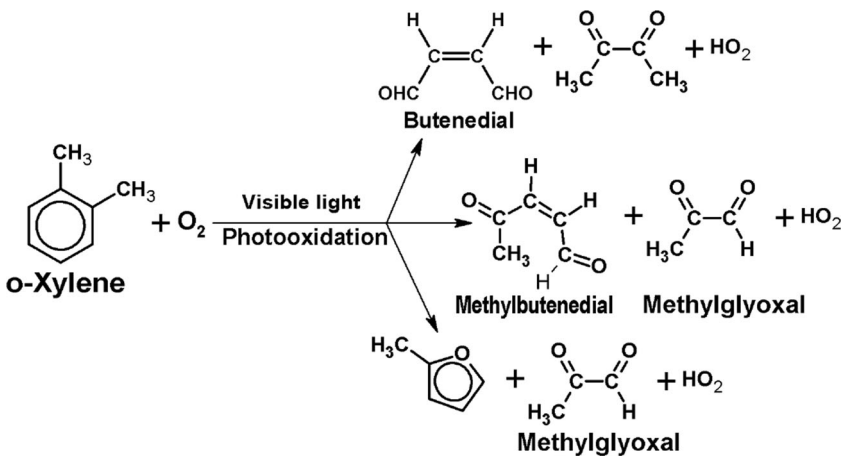
The loaded capsule with I^{-131} solution with different radioactivities and the same volumes showed high intact stability for one week without showing any radioactive release.

Radioactivity release study in different release media

The prepared capsules with 20% lining PS solution (100 μm thickness) were examined for I^{-131} release in deionized water as well as in acidic buffer solution (pH 1.2) for 1 h. The results revealed approximately complete release of I^{-131} after 20 min (> 99%) in deionized water, while recognized approximately complete release of I^{-131} after 15 min (> 99%) in acidic buffer solution (pH 1.2), Table 2.

Radiochemical purity of the I^{-131} capsule

Radiochemical purity is determined by the ascending paper chromatography method. The R_f for different chemical iodine species were: R_f of $I^- = 0.85$, R_f of $IO_3^- = 0.45$, R_f $IO_4^- = 0$. Figure 8 illustrates a typical radiochromatogram of free I^{-131} which indicates radiochemical purity of I^{-131} solution >95%.



Scheme 1 Photo-oxidation of xylene under condition of oxygen and visible light with the formation of reactive aldehydic byproducts

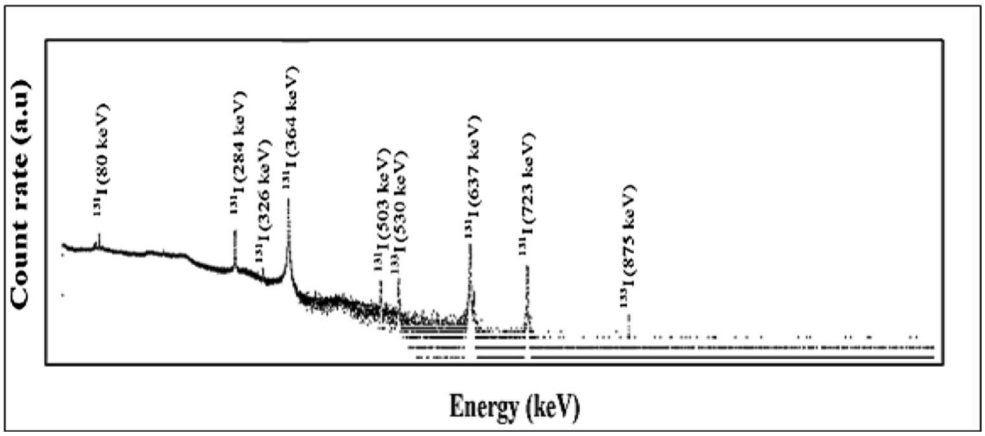


Fig. 7 A typical γ-ray spectrum of I^{-131} solution

Examination of radiation stability of the capsule shell

The loaded capsules with I^{-131} of different radioactivities showed high intact stability for 24 h without showing any deformation or radioactive release.

Discussion

The HGCs were successfully lined with no traces of xylene solvent as shown in GC-Mass results. The absence of the specific band for xylene at 106 m/z, in chromatogram of dried PS lined sample, could be explained in a consequence of very low affinity of PS towards xylene which was clarified previously [25].

The remarked unchanged values of PS characteristic peaks in FTIR analysis may be recognized to the reproducible procedure used in the process of HGCs lining, which kept the assembly of PS structure, Fig. 2b.

On the other hand, the shifting of absorption band of amide A peak, characteristic to gelatin, to higher wave numbers, Fig. 2c, may be attributed to crosslinking of the amide chains in gelatin of HGCs as a function of xylene used as a solvent for PS internal lining. Early, Shepson et al (1984) have suggest that oxidative cleavage of xylene under free radical conditions may be a pathway for the formation of reactive aldehydic metabolites [26], Scheme 1. Consequently, the generated aldehyde molecules are responsible for HGCs cross linking [27]. A result that clarified the appearance of pyridinium salts (hydrogen bonds) N + -H stretching at 3417 cm^{-1}.

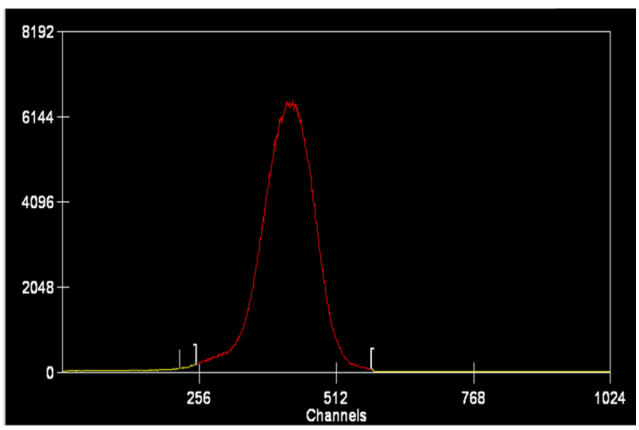


Fig. 8 Radiochromatogram of free I^{-131} in I^{-131} solution

Despite PS films have brittle to ductile behavior [28]; however, the predictable crosslinking effect of xylene to the free amino groups of gelatin as a result of the generated aldehyde groups [27], might explain the increase in hardness with PS lining of HGC shells. The observed relation between hardness of HGCs and film thickness, Fig. 3, could be clarified by the relation between the rate of evaporation of xylene solvent in the process of HGCs lining with PS and the solution viscosity, that is a function of polymer concentration dependence [29].

The results also revealed the dependence of the onset of MB aqueous solution leakage from HGCs on PS film thickness, Table 1. The results agreed with those suggested by Ellis and Smith (2008). Where the authors have established that, the permeability and diffusion of PS film are sensitive to film thickness, and that PS film permeability to water has the value of 0.35–0.41cm^3. mm /(m^2. Day. atm) [28] . This might explain the increase in onset of MB aqueous solution leakage from PS lined HGCs with increase in the film thickness.

The slower in-vitro rupture time (disintegration/dissolution) of PS lined HGCs, which increased with increase in lining thickness, was attributable to crosslinking effect of xylene, used as solvent in PS solution Fig. 4, (1 and 1*), to polypeptide chains which hindered the water to get into the HGC shells [30], confirming the results suggested in water incorporation tolerance study. The results agreed with the data reported previously, where the dissolution of HGCs and consequently the bioavailability of its contents were stated to be affected by different types of crosslinkers [31].

In case of using deionized water as dissolution medium, Figs. 5a and 6, the observed delay in the in-vitro rupture time of the HGCs shells could be returned to the cross-linking of the gelatin during dissolution test causing formation of rubbery water-

insoluble membranes known as pellicles which might act as a barrier preventing the fill from being released [24, 32].

Previous studies have shown that, the minimum solubility of gelatin has been found at its isoelectric point; which has designated the pH value of pure protein in salt-free water. Certainly, the gels have been shrunk when pH was close to the isoelectric point of gelatin gels (type-B gelatin in the study has an isoelectric point (IP) ≈ 5.5) and have been swelled when pH changed [33, 34]. A hypothesis that could explain the obtained results of faster in-vitro rupture time (disintegration/dissolution) of HGCs in the acidic dissolution medium, Figs. 5b and 6.

In the study, the prolonged rupture times of HGC shells in phosphate buffer (pH 7.4). The greater relative ionic strength of phosphate buffer has been reported previously to prolong considerably the swelling behavior and disintegration time of HGCs (in-vitro rupture time), this could be related to the degree of ionization of the solution; the authors have been attributed this phenomenon to the formation of ion pairs between network charges and ions in solution [35, 36].

The high intact stability for one week of the loaded capsules without showing any radioactive release confirmed that obtained in PS internally lined HGCs tolerance study for water incorporation. The obtained results might be promising for safe handling and dispensing of radioactive aqueous therapeutics in HGCs dosage forms. Moreover, these results also can prove the use of low radioactive concentration of I^{-131} in larger volumes as more dilute solutions, with the verification of the product stability and avoidance of solution radiolysis. Instead of increasing the concentration of small volumes, which is expensive procedure for compensate patient requirements; with the financial advances for I^{-131} capsule producers. The obtained results confirmed that established previously in the in-vitro study of rupture time of the capsule shells. The indicated radionuclidic and radiochemical purity of I^{-131} product solution >99.9%, Figs. 7 and 8, are totally matching with the accepted criteria of pharmacopeia proving its safe use for human [37, 38].

Conclusion

The study evaluated the possibility of using polystyrene (PS) internal lining to adapt HGCs for oral delivery of aqueous solutions. High intact HGCs stability for one week was established, without exhibiting radioactive leakage, for loaded insulated HGCs with different volumes and radioactivities of I^{-131} solutions. The results encourage the use of the studied insulated HGCs in hospitals for the filling with radiopharmaceutical preparations as aqueous I^{-131}. Hence, the study gave promising results for safely increasing the volume and consequently the radionuclide dose administered, with compliance and safety of cancer patients undergoing oral radiotherapy regimen as well as dispensers. The study added great value for adaptation of hard gelatin capsules for delivery of any aqueous solution without any harm or deformation and with very economic and simple method. Scaling up the research results as a product in the market may cause a revolutionary impact on patients compliance and pharmaceutical industry.

Compliance with ethical standards

Conflict of interest None.

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