RESEARCH ARTICLE

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Potato Starch Edible Films as Environmentally Friendly Carriers for Model Drug: In vitro Release Study

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Starch is a vital plant polymer used in thousands of food and non-food products. Researchers have made great efforts over the past 20 years to develop ingredients based on nature which enhance starch texture and nutritional values. Starch has many non-food applications, ranging from body care to medicinal applications, among its uses in other foodstuffs. Since starch is sustainable and environmentally friendly material, in many chemical applications, including plastics, detergents and glues, it can serve as a good substitute for fossil-fuel components. This work aims to introduce edible starch films-based carriers for supporting the release of fluorescein as a model drug. Physical modification for potato starch carriers (PSS) was done by incorporating glycerol and low-density polyethylene (LDPE) molecules. Fluorescein dye was incorporated in edible films to investigate the amount of release by UV-vis technique. It was found that PSS-LDPE is spread better than LDPE at physiological temperature and PSS dissolution is also appropriate at this temperature. While PSS formed faster edible film than LDPE and PSS-LDPE, it decayed within 3 days. The amounts of dye released from PSS and PSS-LDPE films were higher than that of fluorescein dispersed in starch suspension in buffer solution (pH 7.5) at 37°C.

Introduction

The continuous release of drugs from polymeric carriers plays a vital role in therapeutic treatment of several diseases [**1**]. Synthetic polymers like polyethylene has been applied as a drug carrier in diverse forms such as tubes, implantable chambers, and capsules [**1**]. Although polyethylene was found suitable as a carrier for bioactive materials, its decay lifetime is very long reach up to 1000 years, this causes in many problems for the environment like marine, since polyethylene kill many living organisms present in sea [**1, 2**]. Plastic edibility could be chemical or biological, the latter is a natural process in which the decay of materials results from the action of naturally occurring microorganisms such as bacteria, fungi or algae [**3-6**]. These organisms could break down plastic into non-plastic and nontoxic basic substances like water, carbon dioxide, methane and biological molecules. This is commonly known as biodegradation, which is not important in the first step of biological decay of polyethylene, which has a good resistance to microorganisms [**3,5**]. The photo-oxidation is a key first decay step for non-hydrolysable materials such as polyethylene, it increases the amount of low molecular weight material by breaking bonds and increasing the surface area. In the second decay step, microorganisms may utilize the biotic decay products and low molecular weight polymer [**3,5-8**].

Comparatively inert polymers like polyethylene might convert to edible polymer via coupling hydrolysable polymer to its backbone, starch could be used for this purpose [**3,7,8**]. Beside starch, the well-prepared formulation consisting of a transition-metal salt and thermal stabilizer, can also be used as additives for polyethylene [**3,8**]. The key role of starch in the consumption of microorganisms has been found to provide greater permeability of oxygen. The matrix will be hollowed, and the volume / surface ratio will increase. The facilitated release of decay products from the samples is another consequence of the increased matrix permeability. This is most obvious when the decay is performed in an aqueous environment [**3**]. Polyethylene starch blends are also susceptible to macro bio-edibility, which is caused by organisms bigger than bacteria such as insects and animals [**3**].

Starch is naturally occurring macromolecule, an abundantly existing, and cheap carbohydrate polymer. Due to these advantageous properties, there has been substantial investigation for studying such a biodegradable material [**9**]. The starch's macromolecular structure comprises two types of chains: linear amylose and branched amylopectin. The macromolecular structure of starch usually has approximately 80 percent amylopectin and up to 20 percent amylose per weight, according to the botanical source [**9-**

11], however starch with 80 percent of amylose could be obtained [**11**]. Although native starches have been widely used for food products, the physical properties of this biopolymer are still not completely understood [**12,13**]. The restriction of utilizing natural starches in several applications is due to their unpredictable behaviour under variation of external environment like the pH and temperature [**12**]. Moreover, native starches from different botanical sources have been investigated by numerous of researchers and revealed to have functional drawbacks as pharmaceutical excipients [**14**]. These disadvantages include restricted compressibility, lowered solubility in water, poor flow properties, and minimal paste strength [**14-16**]. For example, drug tablets formulated with high content of native starch are usually friable, weak, and tend to cap [**16,17**]. To resolve these difficulties, native starch can be swiftly altered by employing specific procedures to improve the functionality of starches as excipients for pharmaceutical usage [**16,18,19**].

Despite the success of water-soluble polymers as solid dispersion transports, numerous procedures for the formulation of solid dispersal are used, including solvent, physical mixture, fusion, kneading, super critical fluid and fusion methods [**20**]. But an edible film prepared from polysaccharides was recently introduced [**21**], in order to improve dissolution rate of drugs.

The aim of this work is to introduce modified starch film as a suitable edible carrier compared with physical mixing method. Fluorescein dye was used as a model drug to investigate the release characteristics from the both methods. Fluorescein dye was chosen in this study due to its photosensitivity and its application as drug with a long history of usage for evaluating retinal blood flow in ophthalmology [**22**].

Experimental

Materials

All materials have been used as received without further purification. Starch from potato, soluble (PSS) supplied by Sigma-Aldrich, UK was used as the film-forming module to provide an incessant edible film, with or without low density polyethylene (LDPE) (Ras Lanuf Co.), high density polyethylene (HDPE) (Ras Lanuf Co.). Glycerol (Sigma) was used as a plasticizer. Clay (was gifted by Dr. Fares Fathi, Geology department at the University of Benghazi, Libya) was used as filler. Distilled water and ethanol (Sigma) were used as solvents for the filmogenic solutions. Carbon tetra chloride (Alpha). Sodium chloride (Sigma). Fluorescein (Sigma). Sodium hydroxide (Sigma)

Making HDPE film

High density polyethylene (HDPE) film was applied in this work as a control. The HDPE film was prepared by melting 10 grams of polymer under 75ºC for about 30 minutes with mixing after that the polymer melt was poured in aluminium container was cut into 12 × 2 centimetres rectangle.

Making LDPE film

Low density polyethylene (LDPE) film was prepared by dissolving 5 grams of LDPE in specific volume of carbon tetra chloride, and then the suspension was put under reflux. Finally, the filmogenic solution poured in aluminium container.

Making edible films

The edible films were prepared according to procedure taken from literature, with slight modification [**23**]. Briefly, 0.025 grams of clay were suspended in distilled water for 60 minutes and left to rest overnight, then the suspension blended with 2.5 grams of PSS : LDPE mixture with variation (4:0 and 4:3), then 2 grams of hydrochloric acid was added to ensure the complete dissolving of polymer, after that the solution was neutralized by adding 2 grams of sodium hydroxide, hence the solution was mixed with 2 grams of glycerol, and distilled water in order to complete about 34 grams of solution. After homogenization, this solution was heated at 70 ºC under stirring until gelatinous starch was formed. According to the casting technique, a specific content of filmogenic solution was poured onto squared glass plates (10 × 10 cm^2) to obtain smooth, unbroken and constant thickness films, followed by drying in desiccator at room temperature for approximately 72 hours. The drying process was continued until a constant weight was obtained. 0.25 grams of fluorescein were added to each film when in vitro dye release study was carried out.

The cloud point temperature measurements

The lower critical solution temperature (LCST) measurements were carried out using 1 mg/mL dispersions of PSS, PSS-LDPE, and LDPE. The prepared films were stirred in proper solvent for 16 hours at 5ºC. The percent of optical transmittance of the dispersions was measured by a Cecil 7400 SERIES UV-Visible spectrophotometer. The temperature of the dispersion was measured by a temperature probe. The transmittance was recorded at 560 nm. Absorbance data points were taken as a function of temperature and recorded up to 70ºC.

Films edibility experiment

The edibility of prepared films, without dye, was investigated according to a protocol published elsewhere [**1**]. Concisely, 5 centimetres pieces were cut, precisely weighed, and placed in flasks beside with 20 mL of aqueous solution. The flasks were shaken at 50 RPM. For each time point, one flask for one group was given labelled number (n = 8 for each group). At programmed time intervals, the flask was detached from the shaker and the contents were emptied onto filter paper. The film was separated and dried till a constant weight was gained. The original weight of the film sample minus the dried weight at the sampling time was the weight loss due to edibility of the films, so percent weight loss was expressed as percent edibility. The percent of weight loss [%] was determined using an OHAUS electronic balance. Finally, mass loss was recorded as a

function of time and directly obtained in the form of a graph. This graph was fitted to an exponential function via Graph Pad Prism Software®, hence the weight loss lifetime was determined.

In vitro dye release studies

Physical mixture of polymer powder

Physical mixture of PSS powder was used to compare release with the starch films. This was done by gentle mixing of specific portion of dye and PSS powder with ceramic mortar and 10 minutes pestle. Then 50 mg of the resulting mixture was applied for the release study.

PSS-Fluorescein / PSS-LDPE-Fluorescein films

The release experiment was taken from literature with slight modification [**1**]. Polymer film loaded with fluorescein dye was used for this purpose. Each piece of film weighing 1 gram was cut and then placed in a vial containing 900 ml of buffer solution (pH = 7.5) maintained at 37ºC. The vials were shaken at 50 oscillations per minute. At each time interval, 10 mL of solution was removed and analysed for the dye content using a UV/VIS Cecil 7400 SERIES spectrophotometer set at 490 nm, the wavelength at the maximum absorbance of fluorescein molecule. In order to maintain the sink conditions, the dissolution medium was replaced with 10 mL of buffer solution at each time interval.

Results and discussion

The phase transition of polymers used as drug carriers may be a trigger to the change of temperature to acquire thermo-responsiveness [**24**]. The important factor for thermo-responsive phenomenon is the change of the hydration state of polymeric solution, and consequently a change in the hydrophilic–lyophilic balance (HLB) against the temperature [**24**]. The lower critical solution temperature (LCST), which is the temperature below which the polymer in solution is completely miscible, could be determined by altering the temperature throughout the upper critical solution temperature (UCST), a phase transition leading to swelling [**24**]. A good model of thermo-responsive polymers is poly(N-isopropylacrylamide) (PNIPAM), which undergoes a phase transition at LCST equal to 32°C, and this value could be improved to be nearby to the body temperature (37°C) via the insertion of hydrophobic moieties to the PNIPAM backbone [**25**]. As the LCST of a carrier polymer is among room temperature and body temperature, the polymer is sensitive to the physiological temperature [**26**]. Below the LCST, the polymeric carrier is in a swollen state, which is expected to cause faster diffusion of the drug out from the polymer matrix. Above the LCST, the carrier marginally swells and the diffusion of drug out of that matrix might be reduced [**24**]. Similarly, the thermo-responsive behaviour of biopolymer like starch can be enhanced either by blending the polysaccharide with a synthetic polymer like polyethylene or small molecule like glycerol.

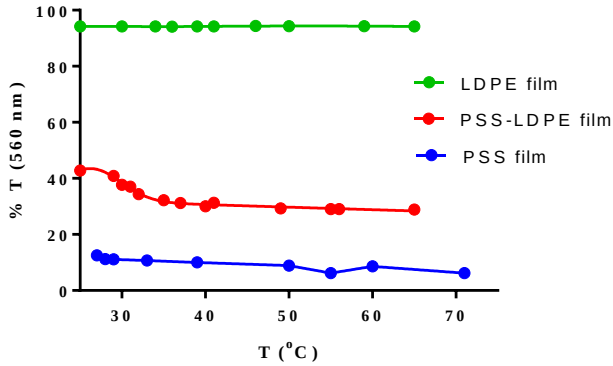


Fig. 1. Transmittance changes for 10 mg/mL dispersions of PSS, LDPE and PSS-LDPE films.

Fig. 1 depicts the temperature dependence on the percent of transmittance (% T) of PSS, PSS-LDPE, and LDPE films dispersed in aqueous solution, from these thermographs the LCST for each polymer is determined. As it can be seen the transmittance of low-density polyethylene do not exhibit any change as the temperature is raised. So that its LCST cannot be predicted in aqueous system. On contrary, the starch-polyethylene suspension (PSS-LDPE) displays thermo-responsive behaviour and its transmittance markedly decreased by increasing the temperature given LCST at 33ºC. Interestingly, the thermo-responsive behaviour for PSS suspension is fluctuated, since it gives two critical temperatures 30 and 55ºC. This suggests that the PSS-LDPE is dispersed better than the LDPE at physiological temperature and dissolving of PSS at this temperature is also acceptable. The performance of PSS-LDPE could be attributed to the hydrophobic part of polyethylene.

Films edibility

The mass loss of films was achieved on the rectangle-shaped HDPE film as a control, LDPE film, LDPE containing 75% of starch (PSS-LDPE film), and plasticized starch film (PSS), see **Fig. 2**. This experiment was to mainly examine the disparity of decay kinetics because of the variation of starch content and kind of plastic. The decay process was evaluated via mass loss. Before immersion the sample in aqueous solution, the polymer samples were characterized by weighing and recording their initial mass using an electronic balance with a resolution of 0.1mg. After one day of immersion, the samples were pulled and cleaned to ensure complete removal of soil/mud. Samples were then placed in an area with enough ventilation for natural drying. The dried degraded samples were weighed using the same electronic balance as carried out before starting decay. Then, the percentage of mass loss of respective sample was measured as follows:

$$\%\ Mass\ loss = \frac{M_i - M_f}{M_i}\ x\ 100 \qquad (1)$$

where, M_i is the initial mass (i.e., mass before decay) and M_f is the final mass (i.e., mass after decay).

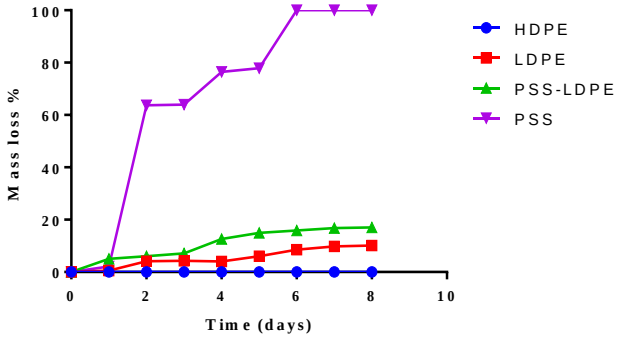


Fig. 2. Edibility study for HDPE film as a control, LDPE film containing 75% of starch, and plasticized starch film (PSS).

As it can be seen from **Fig. 2**, HDPE film showed no apparent mass loss over the period of study, the percent of mass loss was fixed at 0 %. This result agrees with the fact that the pure HDPE is technically non-degradable, and there should not be any mass loss. Practically the LDPE film demonstrated 10 % mass loss. While the PSS-LDPE film demonstrated mass loss of 17 %. Interestingly, the PSS film displayed 100% mass loss. These results reveal that the presence of starch enhances the decay kinetics and thus increases mass loss. This could be because of the hydrophilic behaviour of starch that has been reasoned in several studies [**4**]. The starch being hydrophilic in nature retains moisture that contributes to the decay of the polymer. The adding of the starch into the LDPE, the higher the moisture content that causes quicker decay. The films gross morphology was observed to be changed physically. The presence of starch in LDPE film led to surface roughness of the samples because of increasing in the decay (see **Fig. 3**). The weight loss and change in physical appearance of the sample in the aqueous solution could be proposed as an evidence of biodegradation of this polymer in such an open environment. The results specify that the incorporation of hydrophilic starch into hydrophobic LDPE enhances the hydrophilicity and degradability of the overall blend. Similar decay phenomena of the LDPE incorporated with starch were observed in some other studies [**4**]. Consequently, the decay behaviour of the starch mixed LDPE polymer could be modulated by manipulating the starch content in the polymer. Indeed, the polymer should be developed with fundamentally a controlled decay characteristic while maintaining the required strength of the polymeric object during its designed lifetime for a desired application.

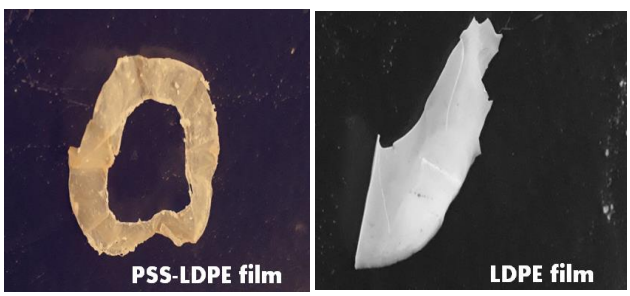


Fig. 3. Shows digital photos for LDPE and PSS-LDPE films, respectively.

Figs. 4-6 show the experimental kinetic study and its mathematical fitting for LDPE, PSS-LDPE, and PSS films decay in aqueous solution determined by monitoring the variation in mass loss as a function of time in days scale, the experiments were done at room temperature at natural pH values.

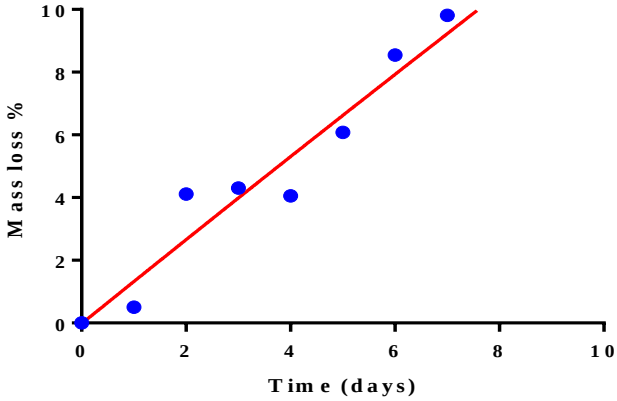


Fig. 4. Kinetic plot for LDPE film decay determined by mass loss. (Experiment was done at 25 ºC and pH 7.5 and experimental data were mathematically fitted by one phase decay).

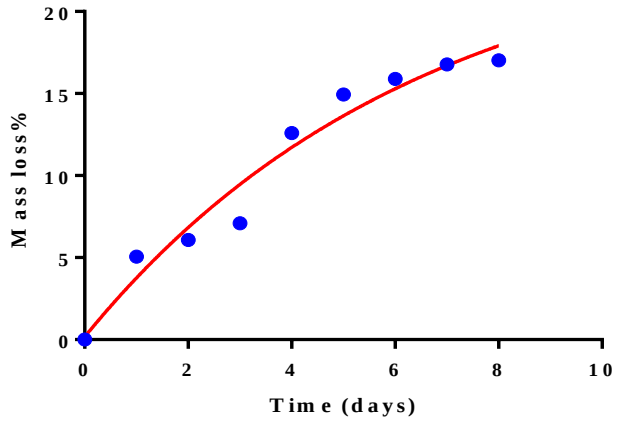


Fig. 5. Kinetic plot for PSS-LDPE decay determined by mass loss. (Experiment was done at 25 ºC and pH 7.5 and experimental data were mathematically fitted by one phase decay).

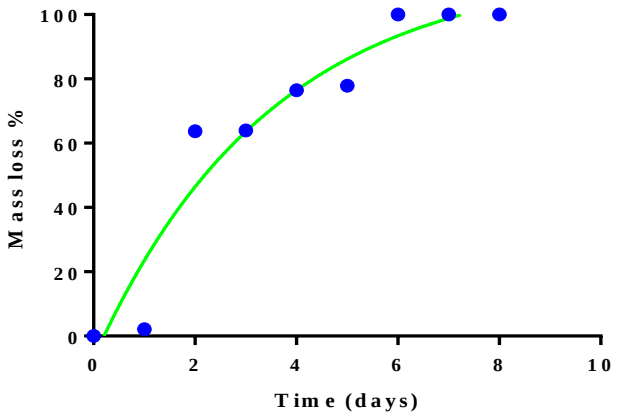


Fig. 6. Kinetic plot for Starch-G decay determined by mass loss. (Experiment was done at 25ºC and pH 7.5 and experimental data were mathematically fitted by one phase decay).

Table 1 displays decay lifetime (τ) and its parameters for LDPE, PSS-LDPE and PSS decay in aqueous solution, at 25 °C and natural pH values. The decay lifetime was determined using the mass loss method. A one phase decay model was used to fit the kinetic data; hence the decay lifetime and its parameters were generated:

$$(Mass\ loss\ \%)_t = (Mass\ loss)_0(1 - e^{-\frac{t}{\tau}}) \quad (2)$$

where $(Mass\ loss\ \%)_t$ is the percent of mass loss as a function of time t, $(Mass\ loss\ \%)_0$ is the percent at zero time and τ is the decay lifetime.

Table 1. Decay lifetime and its parameters for polymers decay determined by mass loss.

System	K (day^{-1})	$t_{½}$ (days)	τ (days)	R^2
LDPE	5.4 x 10^{-3}	128.5	185	0.9487
PSS-LDPE	1.5x 10^{-1}	4.459	6	0.9623
PSS	2.9 x 10^{-1}	2.413	3	0.9237

Data in **Figs. 4-6** and **Table 1** illustrate that the one phase decay model is a good fit for experimental data as its corresponding R^2 value is considerably high (between ~0.92 and 0.96). The percentage of mass loss values of all polymers were found to be time dependent. It was noted that the decay lifetime for LDPE reached to 185 days, dramatically decreased to 6 days in PSS-LDPE, further decline was recorded to PSS film (3 days). This suggests that the presence of potato starch enhanced the edibility of films, this was accompanied by a quench in the decay lifetime values.

In-vitro dye release study

The in vitro release of fluorescein dye in films and physical mixtures are shown in **Fig. 7**. Less than 5 ppm of dye was released from starch microparticles suspensions (PSS+Fl) after 100 minutes. This little release could be attributed to low solubility and crystallinity of fluorescein dye in aqueous suspensions. In contrast, the concentrations of dye released from PSS-Fl and PSS-LDPE-Fl films were 20 and 15 ppm, respectively. This enhance in the amount of release might be credited to the addition of plasticizer (Glycerol) which led to improve the dye solubility and therefore the quantity of release from films in aqueous in buffer solution (pH 7.5) at 37°C. Once associated with the high release concentration for PSS-Fl because of high hydrophilicity as a result of more OH groups. The OH groups of starch solvate the dye molecule via forming hydrogen bonds with the OH groups of fluorescein, for the PSS-LDPE-Fl film the dye release revealed a lower ability to be rejected from the film. This was explained to the enhancement in film hydrophobicity as a result of incorporation polyethylene. The hydrophilic dye is surrounded by hydrophobic environment which lower the solvation of fluorescein, as a result small quantity of dye will be released. To sum up the amount of model drug release could be controlled by modifying the hydrophilic starch with polyethylene. This summary is consistent with the results obtained in a similar work concerned with polyethylene starch extrudates. It was found that modifying starch with polyethylene was useful for carrying bioactive materials like drug, but its non-edibility poses a problem which could be controlled by the amount of loaded starch in the matrix [**1**].

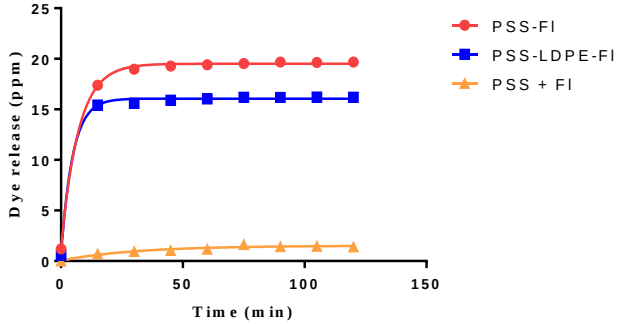
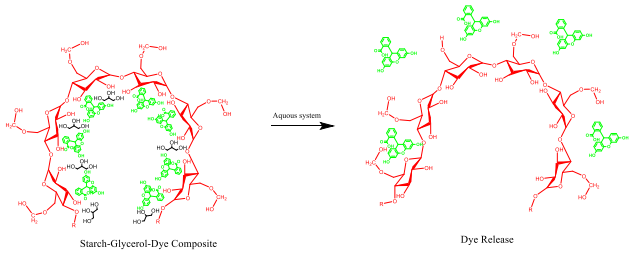


Fig. 7. Kinetic plots for fluorescein release for dye dispersed in starch (PSS+Fl), PSS-Fl film, and PSS-LDPE-Fl film. (Experiment was done at 37 °C and pH 7.5.

The role of glycerol-dye-starch solvation in fluorescein release is depicted in **Scheme 1**.



Scheme. 1. Representation a mechanism of fluorescein release from starch film.

Conclusion

Starch content and modification processes of polyethylene play important roles in decay properties of the starch-mixed LDPE synthetic polymer, thus providing the opportunity to modulate the polymer properties for drug release. The spectrophotometric investigation showed that fluorescein release from films was considerably higher than that of the physical mixtures of dye in PSS suspension. A lower release amount was detected for PSS-LDPE-Fl than that of PSS-Fl which was ascribed to the hydrophobic behaviour of synthetic polymer.

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Conflicts of interest
There are no conflicts to declare.

Keywords

Starch film, edibility, release, kinetic

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Authors biography

Fateh Eltaboni received the B.Sc. degree in Chemistry from University of Benghazi (Libya) in 2003 and M.Sc. degree in Physical Chemistry from the same university in 2006, then he received the PhD degree in Physical Chemistry from the University of Sheffield (UK) in 2013 he worked as a post-doc researcher in bacterial polymers (Kroto Research Institute (UK) until the end of 2013. He and his co-authors now with the Laboratory for Polymeric Materials & Nanocomposites.

Graphical abstract

Graphical representation of edible thin film loaded with model drug (●). The thin film is crosslinked by glycerol (….) which dissolve immediately in the aqueous solution. For mathematical study the release of model drug is investigated as a function of time.