



Preparation of Biodegradable Polymeric Blend Microspheres of Soy Protein Isolate/Guar Gum and Release Studies of Tolterodine Drug

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ABSTRACT

The blend microspheres based on soy protein isolate (SPI) and guar gum (GG) were prepared by solution blending and then cross-linked with Ca^{2+} ion, and their function as drug carrier was explored as well. The effects of SPI/GG blend composition on the structures of microspheres were studied. Fourier transform infrared results suggested that miscibility was driven by strong hydrogen bonding. Morphological properties of the microspheres were studied by scanning electron microscopic analysis. Thermal properties and crystallinity of the microspheres were characterized using differential scanning calorimetry and X-ray diffraction techniques, respectively. The controlled release function of the complex microspheres was verified using tolterodine as a model drug, that is, the swelling and drug release were affected by (pH-7.4) condition. Dissolution experiments were performed at 37°C in phosphate buffer solution (pH-7.4).

Key words: Soy protein isolate, Guar gum, Microspheres, Blend, Drug-delivery system.

1. INTRODUCTION

Biocompatible natural polymers such as polysaccharides and proteins, such as chitosan [1], alginate [2], cellulose [3], soy protein [4], zein [5], casein [6], and so on, are potentially available as the biomedical materials [7], and especially has been developed as the carrier of oral drugs. Microspheres are currently a typical form of drug carrier [8]. The drugs are encapsulated and taken by microspheres to mask taste and odor, to enhance stability, to improve gastrointestinal tolerance, and to provide sustained release after oral administration [9]. Depending on the nature of the components, the microspheres may be sensitive to pH variance of tissues in the human body [10]. Furthermore, the loaded drugs can be controlled-released as the microspheres swell under given pH, and settle at the target sites of effective absorption, and prolongs the duration of activity by selectively adhering of microspheres [5]. In addition, the bioactivity of other components in microspheres may facilitate the curative effect or reduce the side effect of drugs [4]. Especially, the miscible blends can be used to adjust the behavior of drug release depending on the properties of components as well as

the compositions in whole blend and the interaction between components, and especially produced the function of the pulsatile chronotherapeutics and the controlled profiles of drug release [11].

Biocompatible alginate can be ionically cross-linked in the presence of multivalent cations [12], and induced the gelation, which was already used to produce many kinds of biomedical materials, such as hydrogel [13], microspheres [5,8-10], microcapsule [14], membrane [15], and fiber [16]. The soy protein isolate (SPI) - based microspheres cross-linked with Ca^{2+} and exhibited controlled release function due to the sensitivity of $\text{Ca}^{2+}/\text{COO}^-$ linkage to pH and other ion. It is well known that the linkage between Ca^{2+} and COO^- can be only stable in acidic condition. Guar gum (GG) is galactomannan, derived from guar (*Cyamopsis tetragonolobus*) kernels which belong to family Leguminosae. The solution of GG in water has the highest viscosity amongst all the natural polysaccharide discovered till the date. Further, it has better bio-degradability and bio-compatibility. Due to these properties, GG finds application in various industries like textile, food, petrochemical, mining,

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paper, explosive, etc. But due to uncontrollable rate of viscosity, uncontrollable rate of hydration, instability of its solution for a long time and susceptibility to microbial contamination restricts its use in pharmaceutical industries. To overcome this drawback, GG should be chemically modified. Modified GG is widely used in pharmaceutical application due to its viscosity enhancing properties. GG its derivatives and its blending with natural polymers are used as binders and disintegrate in tablet and also used as a control release agent for the drug [17]. Soy protein is a plant protein to favor the health of the human being and can be thermoplastic-processed and solvent-cast as biomedical materials. The possible benefits of soy protein include lowering cholesterol, anti-carcinogenic effects of Bowman-Birk, and protective effects against obesity, diabetes, irritants of the digestive tract, bone, and kidney diseases [18]. On the basis of the bioactivity of soy protein, the soy protein plastics prepared by melt-processing [19] and further modification of chemical cross-linking [20] showed great potential applications as tissue engineering scaffold [21] and drug-delivery system [20]. In addition, the soy protein-based membrane was also used as drug carrier and wound dressing material [22]. To further improve the bio function and properties, the blending with other biocompatible polymers, such as chitin [23] and chitosan [24], cellulose [25], and poly (ethylene glycol), was attempted, and especially produced a new form material of hydrogel for drug delivery. The blend materials had enhancing mechanical properties [23] and inherited the bioactivities of added components [24], which benefited the application of tissue engineering [24]. However, as we know, the microsphere of drug carrier containing soy protein has not been developed so far.

Hence, in the present study, authors prepared SPI/GG blend microspheres loaded tolterodine and studied the effect of various factors *viz.*, SPI, GG, tolterodine, concentration on the swelling properties and drug release profiles and results are presented here.

2. EXPERIMENTAL

2.1. Materials

SPI powder was obtained from Honeyville Food Products, Salt Lake City, Utah, USA. According to the manufacturer, SPI supplied consisted of 90% protein, 4% fat, about 5% ash, and 1% remaining unknown constituents. GG was purchased from SD-Fine Chemicals, Mumbai. Calcium chloride was procured from Qualigens Fine Chemicals, Mumbai. Tolterodine was supplied by Sun Pharma India Ltd., Mumbai. Double distilled water was used to prepare the polymeric blend microspheres.

2.2. Methods

2.2.1. Preparation method of blend microspheres

SPI was dispersed in distilled water at room temperature, and then basified with 10 wt% NaOH

aqueous solution to produce a viscous liquid of pH 9-10 containing 3% SPI. Meanwhile, GG was also dissolved in distilled water to obtain a solution containing 3 wt% GG. Subsequently, the resultant SPI and GG solutions were mixed by the weight ratio of 1:1, 1:2 and 3:1, respectively, In the mixing solution, the weight ratios of SPI vs.GG were consistent with the weight ratios of SPI and GG solution as mixing, namely the SPI content in the total weight of SPI and GG were 25, 50, 75 wt%, respectively. The mixing solutions were mechanically stirred at room temperature for 2 h to result in a homogeneous dispersion of SPI and GG components. At last, the complex microspheres formed by injecting the mixing solutions into 10% wt CaCl₂ aqueous solutions using the syringe equipped with nozzle as well as cross-linking -COOH groups in SPI and GG molecules in the aqueous solution are containing Ca²⁺ for 30 min. The obtained microspheres were washed with distilled water to remove the free ion attached onto the surface and existed into internal holes. According to the SPI content in the solid, the microspheres were coded as SG-1 (25 wt% SPI), SG-2 (50 wt% SPI), and SG-3 (75 wt% SPI). The drug-loaded microspheres were prepared as follows, and the tolterodine was mixed with the SPI/GG mixing solution with weight ratio of 1:1, in which the SG-2 microspheres with best miscibility was used while the content of tolterodine is 20 parts with regards to the 100 parts of the whole solid of SPI and GG. Subsequently, the mixing solution containing tolterodine was cross-linked by Ca²⁺ and then produced the drug-loaded microspheres. All the drug-loaded microspheres were washed by distilled water to remove the drug attached onto the surface and then dried before the study of drug release.

2.4. Characterization

2.4.1. Fourier transform infrared (FTIR)

FTIR spectra were recorded on a Bomem MB-3000 FTIR spectrometer (Canada). The SPI and GG powder were taken with the method of KBr pellet and scanned in the range of 4000-400 cm⁻¹.

2.4.2. X-ray diffraction (XRD)

XRD patterns were recorded on A Siemens D 5000 powder X-ray diffractometer using Cu K α (1.54056 Å) radiation (35 kV, 30 mA). All the powder samples were mounted on a sample holder and scanned from 2° to 60° in 2 θ at a speed of 10 min⁻¹.

2.4.3. Scanning electron microscopic (SEM) studies

The surfaces of microspheres were photographed using a software controlled digital scanning electron microscope (JEOL JSM 5410) with 20 kV as the accelerating voltage. All the microspheres were frozen in liquid nitrogen while some were fractured immediately, and then they were freeze-dried for further characterization.

2.4.4. Drug - release studies

The tolterodine was selected for the experiments of drug release because its ultraviolet (UV) absorption cannot be overlapped with the components of blend microspheres. Similar to the swelling tests again, pH value of 7.4 was adjusted, and the experiments carried out at this pH. The drug-loaded SG-2 microspheres were used to study the drug release in vitro as follows. The drug-loaded microspheres (0.5 g) were incubated into 45 mL solution with various pH at 20°C. After the given intervals, the 5 mL solution was removed for determining the release content of the drug, which was obtained from the absorbance at 286 nm measured on a UV-VIS spectrophotometer (LABINDIA, V-3000⁺). Subsequently, the 5 mL fresh buffer solution was supplied to keep the total volume of 45mL solutions.

3. RESULTS AND DISCUSSION

3.1. FTIR Analysis (Interaction between SPI and GG Components)

Usually, the good miscibility in the blend is driven by the intermolecular hydrogen bond among components. Before discussing the interaction between components, the groups that possibly form hydrogen bonds must be identified. The FTIR spectra of GG and SPI powder were shown in Figure 1.

Except for the double peaks at 3448 and 3340 cm⁻¹ assigned to O-H and N-H stretching vibrations, the SPI powder had two characteristic peaks at 1660 (amide I) and 1588 cm⁻¹ (amide II), which can reflect the formation or cleavage of hydrogen bonds. The O-H groups in GG can also anticipate into hydrogen bonding and its stretching vibration located at 3450 cm⁻¹. In addition, the -COOH group can be cross-linked with Ca²⁺, which constructs the structure of microspheres and plays a stabilizing role. The -COOH has asymmetrical and symmetrical stretching vibrations located at 1660 and 1588 cm⁻¹ respectively;

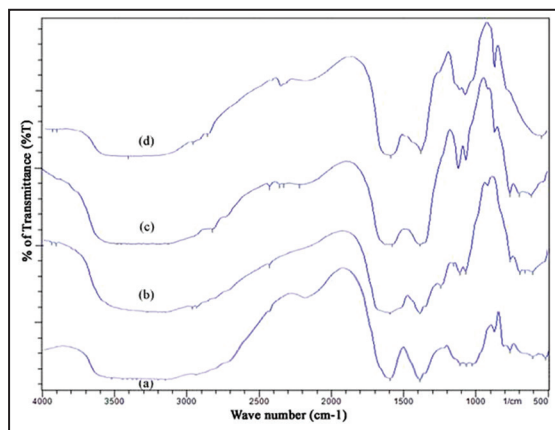


Figure 1: Fourier transform infrared spectra of: (a) Pure guar gum, (b) Pure soy protein isolate, (c) SG microspheres with drug (d) SG microspheres without drug.

the former is stronger and wider while the latter is sharp.

FTIR spectra of the freeze-dried microspheres with different SPI and GG content and their blend microspheres with and without drug loaded were shown in Figure 1. After the SG microspheres formed by the Ca²⁺ cross-linking, the absorption of O-H stretching vibration at 3450 cm⁻¹ of pure GG powder was shifted down to 3379 cm⁻¹, indicating that there existed stronger hydrogen bonding. Meanwhile, the cross-linking of Ca²⁺ caused two peaks assigned to asymmetrical and symmetrical stretching vibration of -COOH approached each other after ionization (from -COO⁻) and located at 1660 and 1588 cm⁻¹. The changes of SPI content in complex microspheres can be observed by the intensity changes of the characteristic peak of SPI component, namely the intensities of peaks at 1660 and 1588 cm⁻¹ assigned to GG component decreased. Introducing SPI containing N-H groups resulted in the shift of absorption above 3000 cm⁻¹ to high wave number for the complex microspheres, shown as the peak position at 3450 cm⁻¹ in FTIR spectra of (b) microspheres. Meanwhile, the C=O stretching vibration assigned to SPI shifted to low wavenumber of 1660 cm⁻¹ in contrast to SPI powder, indicating that the SPI component in (c) microspheres participated in the formation of hydrogen bonds.

3.2. Differential Scanning Calorimetry

Differential scanning calorimetry tracings of the tolterodine: (a), SG blend microspheres (b) and tolterodine drug loaded SG microspheres (25% of SPI [SG1] and 50% of SPI [SG2]) are displayed in Figure 2. The onset melting peak of tolterodine was observed at 100°C (pure drug). However, no characteristic peak of drug in the drug loaded (SG1 and SG2) and plain SG blend microspheres, suggesting that the drug particles are molecularly dispersed in the polymer matrix.

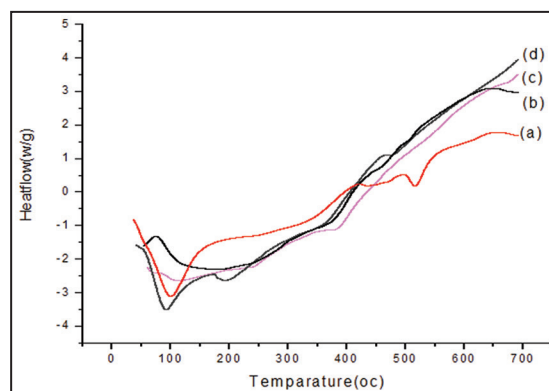


Figure 2: Differential scanning calorimetry thermograms of pure drug (a), pure blend (b) and drug loaded blend microspheres at 25% of soy protein isolate (SPI) (c), and at 50% of SPI (d), respectively.

3.3. XRD Analysis

XRD analysis provides a clue about the crystallinity of drugs in the SG blend microspheres. The XRD patterns of: (a) pure tolterodine drug, (b) SG blend microspheres without drug, and tolterodine-loaded SG blend microspheres of, (c) SG1(25% of SPI), (d) SG2 (50% of SPI), (e) SG3 (75% of SPI) microspheres are presented in Figure 3. Pure tolterodine drug (a) peaks observed at 2θ of 12.9° and 22.0° are due to crystalline nature of drug, whereas these peaks were not observed in drug loaded SG microspheres (c, d, and e) and plain SG microspheres (b). This indicates that the tolterodine drug particles are dispersed at the molecular level in the polymer matrix. Hence, no crystalline nature of the drug was observed in the case of drug loaded microspheres.

3.4. Scanning Electron Microscopy

Figure 4 shows the SEM images of free surfaces of with and without drug loaded microspheres. The difference of miscibility between GG and SPI components can be deduced by comparing the structural changes. When in Figure 4a, the SG-1 microspheres showed a rougher surface in Figure 4b because introducing SPI destroyed the original structure of SG component it looks like a smooth surface. However, when SPI component increased up to 50 wt%, a still more smooth surface was observed for the SG-2 microspheres, but the [Figure 4c], indicates the highest miscibility between GG and SPI components under such weight ratio. As the SPI became the dominant component, a coarse surface reappeared for the SG-3 microspheres containing 75 wt% SPI, shown as an alveolate structure in Figure 4d.

3.5. In Vitro Release Studies

To understand the release patterns of tolterodine of all the formulations prepared, we performed in vitro release studies in a phosphate buffered saline (pH-7.4)

at 37°C . These experiments were performed in triplicate and the results presented are averages. The release profiles of the formulations loaded with 5, 10, 15 and 20 w/w% tolterodine are graphically shown in Figure 5.

3.5.1. Effect of SPI content

Release profiles of SG microspheres prepared with different amounts of SPI are displayed in Figure 5a. It was found that SG polymeric blend microspheres produced up to 76-94% cumulative release in 12 h. The increase in drug release could be due to the fact that during dissolution, microspheres might have systematically swollen with an increasing amount of SPI (hydrophilic) due to the formation of loosely cross-linked network chains of SPI. Thus, a relaxation type response of the polymeric chains might be possible due to stresses induced by the surrounding solvent medium during the dissolution, resulting in an increase of chain dimension (radius of gyration) of the polymer; leading to increase in the molecular volume of hydrated polymer due to increased swelling of SPI component of the polymer matrix, thereby reducing the void volume of the matrix. Notice that the nature of release profiles showed almost similar trend in all the formulations containing different amounts of SPI, indicating that swelling SPI has established a linear relationship with the release profiles.

3.5.2. Effect of GG content

Release profiles of SG microspheres prepared with different amounts of GG are displayed in Figure 5b. It was found that SG polymeric blend microspheres produced up to 60-80% cumulative release in 12 h. The increase in drug release could be due to the fact that during dissolution, microspheres might have systematically swollen but with an increasing amount of GG (hydrophilic) the swelling nature is little bit less in these cases. Comparatively with increase of GG

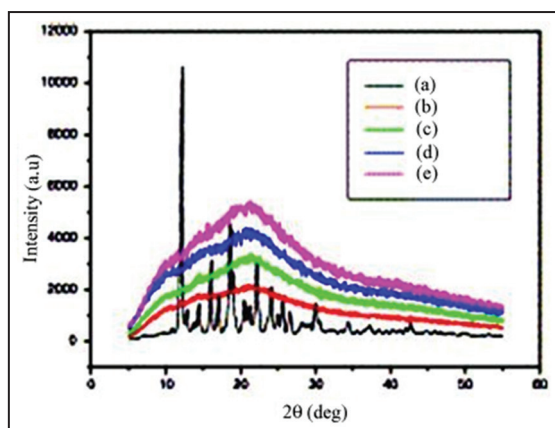


Figure 3: X-ray diffraction: (a) Pure tolterodine drug, (b) SG blend microspheres without drug, and tolterodine-loaded SG blend microspheres of (c) SG-1 (25% of soy protein isolate [SPI]), (d) SG-2 (50% of SPI) (e) SG-3 (75% of SPI).

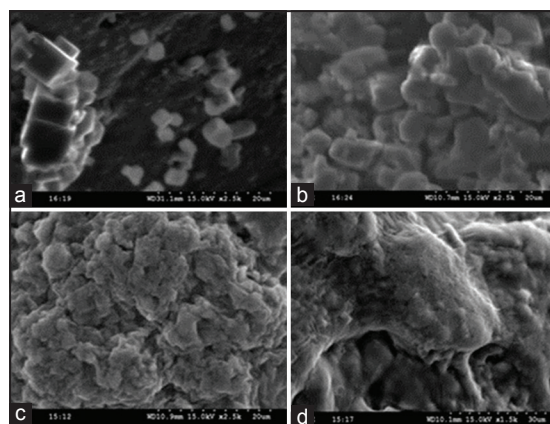


Figure 4: Scanning electron microscopic images of the surfaces of pure SG microspheres (a), and drug loaded (b, c and d) blend microspheres of SG-1 (25% of soy protein isolate [SPI]), SG-2 (50% of SPI) and SG3 (75% of SPI), respectively.

content the drug release decreased. This may be due to less swelling nature of GG when compared with SPI. This is evident from the Figure 5b.

3.5.3. Effect of drug content

The other parameter that affects the tolterodine release is its concentration, for this purpose the authors prepared the microspheres by varying drug content (5-20 w/w% using). The effect of drug concentration on release profiles is shown in Figure 5b. The Figure 5c illustrates that the drug release from SG polymeric blend microspheres increases with an increase in drug content. The cumulative release (%) of the microspheres containing 20% drug showed 100% release within the studied period of time (12 h), whereas the microspheres containing 5% drug showed 68% release in 12 h. Higher initial load of the drug causes the faster movement of water penetration on surface of the microspheres, this further facilitates the relaxation of the polymer chains.

3.6. Drug Release Kinetics

Drug release kinetics was analyzed by plotting the cumulative release data versus time by fitting to the following empirical equation [26].

$$(M_t/M_\infty) = kt^n \quad (1)$$

Here, M_t/M_∞ represents the fractional drug release at time t , k is a constant characteristic of the drug, polymer system, and “ n ” is an empirical parameter characterizing the release mechanism. Using the least squares procedure, we have calculated the values of “ n ”

and “ k ” for all the formulations developed. If $n=0.5$, drug diffuses and release out of the polymer matrix following a Fickian diffusion or case I. For $n>0.5$, anomalous or non-Fickian transport occurs. If $n=0.5$, non-Fickian or Case II release kinetics is prevalent. The intermediary values on “ n ” ranging between 0.5 and 1 indicate the anomalous transport [27].

In the present research, the values of “ k ” and “ n ” show a dependence on the extent of cross-linking, % drug loading, and SPI content. Values of “ n ” for microspheres prepared by using the varying amounts of SPI and GG keeping tolterodine constant have ranged from 0.345 to 0.547, producing a slight deviation from the Fickian mode of transport. The tolterodine loaded microspheres have “ n ” values ranging from 0.335 to 0.547 giving a shift from erosion type release to swelling-sustained non-Fickian transport. Correlation coefficients, r , obtained while fitting the release data fall in the range 0.957-0.976, but non-Fickian trends are due to a reduction in the regions of low microviscosity and closure of micro-cavities in the swollen state of the matrix. Similar findings have been observed elsewhere [28] wherein, the effect of different polymer ratios on the dissolution kinetics was investigated. The “ n ” value for formulations containing different amounts of SPI, Tolterodine, and GG is 0.5, which indicates the non-Fickian diffusion transport, i.e., a slight deviation from the Fickian trend.

4. CONCLUSIONS

In summary, a potential drug-delivery system based on GG and SPI is developed, which combines of GG

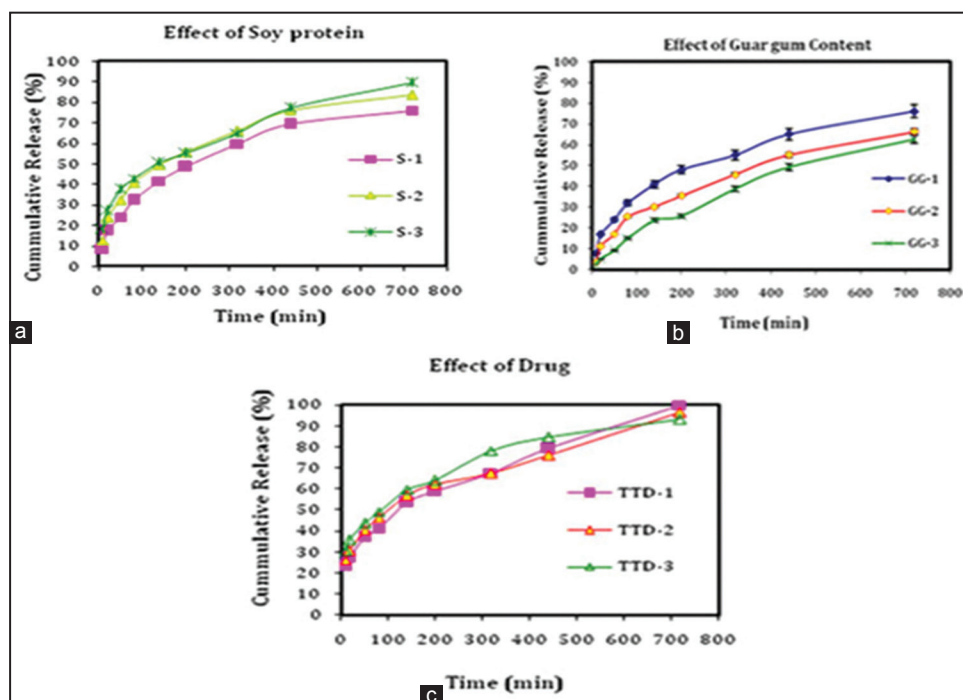


Figure 5: (a) Effect of soy protein, (b) effect of guar gum, (c) effect of tolterodine drug TTD-1 (20%), TTD-2 (10%) and TTD-3 (5%) on TTD release.

with the bioactivity of SPI. This system shows a form of microspheres and is stabilized by the cross-linking of Ca^{2+} . The best miscible microspheres contain the weight ratio of SPI and GG by 1:1, and present a uniform and smooth structure.

Furthermore, the strong interaction among components, like hydrogen bonding, is the main driving force to promoting the miscibility. Different from the rapid cleavage of pure GG microspheres in the conditions of pH 7.4. Tolterodine release through the modified microspheres continued up to 10 h. Such complex microspheres may be helpful to facilitate the prompt release of drugs in the of detrusor overactivity (DO, contraction of the muscular bladder wall) in the human body (pH 7.4).

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***Bibliographical Sketch**



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