Materials Research Express

PAPER

Chitosan-sodium lauryl sulfate/Eudragit S100 beads loaded with 5-fluorouracil: Influence of solvent and duration of crosslinking on physicochemical properties

Saravanan Muniyandy, Lui Mei Yi, Aruna Santhagunam and Lay Hong Chuah

1 Department of Pharmacy, Fatima College of Health Sciences, PO Box 24162 Al Maqam, Al Ain, United Arab Emirates
2 School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, 46150 Bandar Sunway, Selangor Darul Ehsan, Malaysia
3 Centre of Nanotechnology, Indian Institute of Technology, Roorkee, Uttarakhand 247667, India

E-mail: drmsaravanan@gmail.com

Keywords: Chitosan, sodium lauryl sulfate, Eudragit S100, 5-fluorouracil, ionotropic gelation, drug loading, sustained release.

Abstract

Chitosan beads loaded with 5-fluorouracil (5-FU) were prepared by ionotropic gelation using sodium lauryl sulfate (SLS) as a crosslinking agent in presences of Eudragit S100. The objective was to improve the loading and sustained release of 5-FU. The influence of the solvent system, counter ion concentration, crosslinking time, and addition of Eudragit on particle size, drug loading, entrapment efficiency (E.E.), and in vitro release was investigated. The beads were also characterized by scanning electron microscopy, Fourier transform infrared (FTIR), and thermogravimetric analysis (TGA). Spherical beads were produced with at least 2% SLS, and the resultant particle size was smaller with higher SLS concentration. FTIR has confirmed the incorporation of 5-FU and the electrostatic interaction involved in the formation of chitosan/SLS/Eudragit beads. TGA graph has shown a sharp weight loss between 225 °C and 250 °C in beads prepared with an alcoholic crosslinking solution. The amorphous nature of the entrapped drug was also revealed in the TGA. All batches exhibited 5-FU burst release within 30 min, and beads prepared with 2% SLS/Eudragit has displayed a sustained release up to 4 h in a dissolution medium of increasing pH. Further, the E.E. of 5-FU was increased with hydroalcoholic solvent, lower SLS concentration, and shorter crosslinking time.

1. Introduction

Chitosan is derived from alkaline deacetylation of chitin, a naturally occurring polysaccharide readily available in marine crustaceans. Consisting of 2-amino-2-deoxy-β-D-glucan monomers, these primary amine groups afford a cationic nature to chitosan polymer chains. Chitosan is insoluble in neutral or basic pH but soluble in aqueous acetic acid solutions; hence, using a hazardous organic solvent is unnecessary. Excellent biocompatibility and low toxicity are its other main advantages. Chitosan beads are capable of controlled release of drug and thus implicate a great potential in sustained drug delivery [1]. Chitosan beads/micro and nanoparticles are prepared with different crosslinking agents such as glutaraldehyde and trisodium polyphosphate and sodium lauryl sulfate (SLS).

Ionotropic gelation is one of the many techniques available in preparing chitosan beads and relies on the electrostatic interaction between oppositely charged molecules. In 1989, Bodmeier et al reported [2] the production of chitosan/tripolyphosphate (TPP) particles by introducing chitosan droplets into the TPP counter ion solution, which inspired a series of investigations on this system. Chang et al used a high voltage electrostatic field to extrude chitosan droplets into mixtures with varying ratios of TPP and sodium hydroxide (NaOH) to produce beads with different membrane structures [3]. The entrapment efficiency (E.E. %) of the model drug, 5-fluorouracil (5-FU), was observed to be very low, particularly for beads prepared from TPP alone. Also,
Table 1. Formulae for different batches of 5-FU-loaded chitosan beads.

| Batch | Chitosan (g) | 1% v/v acetic acid (mL) | 5-FU (g) | SLS (%) | Eudragit (%) | Solvent* | Cross-linking time (h) |
|-------|-------------|-------------------------|---------|---------|-------------|----------|----------------------|
| 1     | 1.5         | 100                     | 1.5     | 1       | 1           | AQ       | 1                    |
| 2     | 1.5         | 100                     | 1.5     | 1       | 1           | HA       | 1                    |
| 3     | 1.5         | 100                     | 1.5     | 1       | 1           | AL       | 1                    |
| 4     | 1.5         | 100                     | 1.5     | 2       | 2           | AQ       | 1                    |
| 5     | 1.5         | 100                     | 1.5     | 2       | 2           | AL       | 1                    |
| 6     | 1.5         | 100                     | 1.5     | 2       | 2           | AL       | 2                    |
| 7     | 1.5         | 100                     | 1.5     | 2       | —           | AL       | 1                    |
| 8     | 1.5         | 100                     | 1.5     | 2       | —           | AL       | 2                    |

* AQ = Eudragit (AQ) + SDS (AQ); HA = Eudragit (EtOH) + SDS (AQ); AL = Eudragit (EtOH) + SDS (EtOH).

approximately 80% of the loaded 5-FU was released in the phosphate buffer solution (pH 7.4) within 30 min, indicating a lack of sustained-release [3].

The use of other multivalent anions was also explored as potential crosslinking agents. Berthold et al (1996) used sodium sulfate to prepare chitosan beads [4], but the resultant particles had weak mechanical strength. El-Gibaly et al used sodium lauryl sulfate (SLS) to produce melatonin-loaded chitosan beads [5]. The prepared particles were buoyant in simulated gastric fluid and showed a trend of decreasing E.E. % and slower drug release rate with higher SLS concentration. Further, El-Nahas et al prepared floating chitosan beads from 2% SLS, capable of sustained release with only 70% of loaded trimetazidine released at 12 h in 0.1M HCl dissolution medium [6].

5-FU is a hydrophilic drug with a pKa of 8 [7] and reported to have reduced loading in chitosan beads/microspheres along with and burst release [3, 8, 9]. It is an antimitabolite commonly used in treating gastric and colorectal cancer, generally administered as an intravenous infusion due to its extremely short half-life of 11 min. Besides, it also has saturable pharmacokinetics that makes it the most suitable candidate for sustained drug delivery [10]. This study aims to achieve better 5-FU loading in the chitosan beads with sustained-release characteristics using a non-toxic crosslinking agent such as SLS. Chitosan-SLS beads are selected due to their simplicity and flexibility in the manufacturing process. Very scanty information is available in the literature about the chitosan-SLS beads [11], and none available for 5FU loaded chitosan-SLS beads. Several variables were investigated in this investigation: solvent system (aqueous, hydroalcoholic, alcoholic), counter ion concentration, crosslinking time, and presence of Eudragit. Toxic crosslinking agents such as glutaraldehyde are avoided in the present investigation.

Alcoholic-based solvents were tested because 5-FU exhibits lower solubility in alcohol compared to water [12, 13], and thus it was hypothesized that an alcoholic-based solvent would improve E.E. %. Chitosan beads were prepared via ionotropic gelation in a one-step process by the dropwise introduction of the polymeric solution into mixtures with different ratios of SLS and Eudragit S100. Eudragit S100 was gifted by Jebsen & Jebsen Chemicals (M) Sdn Bhd, Selangor, Malaysia. SLS was obtained from R&M Chemicals (UK). 5-FU and tris (hydroxymethyl) aminomethane were purchased from Easybuyer Ltd (China) and Merck (Germany), respectively. Sodium hydroxide, sodium chloride, glacial acetic acid, and ethyl alcohol were obtained from Systerm, Malaysia. All other chemicals used were of analytical grade.

2. Methodology

2.1 Materials

Chitosan from shrimp shells, in the form of flakes, practical grade, Brookfield viscosity > 200,000 cps, and anhydrous sodium acetate were purchased from Sigma-Aldrich (USA). Eudragit S100 was gifted by Jebsen & Jebsen Chemicals (M) Sdn Bhd, Selangor, Malaysia. SLS was obtained from R&M Chemicals (UK). 5-FU and tris (hydroxymethyl) aminomethane were purchased from Easybuyer Ltd (China) and Merck (Germany), respectively. Sodium hydroxide, sodium chloride, glacial acetic acid, and ethyl alcohol were obtained from Systerm, Malaysia. All other chemicals used were of analytical grade.

2.2 Preparation of beads

Eight batches of 5-FU-loaded chitosan beads were prepared according to the formulae in table 1. The different solvent systems were attained by dissolving the solute in its respective solvent as follows: Eudragit aqueous (AQ) was prepared by dissolving Eudragit in 50 ml of 1M NaOH, then adjusting the pH to 8.5 with 1M HCl and further to pH 7.5 with 10% v/v acetic acid and making the volume up to 100 ml by water. Eudragit alcoholic (EtOH) solution was prepared by dissolving Eudragit in 96% ethyl alcohol, whereas SLS (AQ) and SLS (EtOH) were prepared by dissolving SLS in distilled water and 96% ethyl alcohol, respectively. The 1.5% w/v chitosan
solution was prepared by dissolving 1.5 g chitosan in 100 ml of 1% v/v acetic acid solution. Next, 1.5 g 5-FU was added to the chitosan solution and stirred at 800 rpm for 30 min. The polymeric solution was introduced dropwise using a 25 ml syringe fitted with a 21G needle into a mixture of 50:50 ml (1:1 ratio) SLS: Eudragit to form the beads. The distance between the needle tip and the top of the crosslinking solution was fixed at 6 cm, and a magnetic stirrer was used to stir the mixture to prevent particle aggregation. The chitosan solution was introduced within 30 min, and the beads were left to react in the crosslinking solution for the specified time. The beads were collected by filtration with nylon mesh, washed twice with distilled water, and dried at 40 °C for 24 h. The unloaded beads were prepared in the same manner except without the addition of 5-FU.

2.3 Appearance, morphology and particle size analysis
The physical appearance of fresh and dried beads was compared, and photographs were taken for each batch using the Sony Alpha DSLR-A290 camera. Randomly selected beads were observed under bright-field phase-contrast microscopy at 20x magnification using the Olympus BX41 microscope equipped with a camera. The height and width of each particle were measured using the imaging software supplied by Olympus, and the average particle size and standard deviation were determined. For field emission scanning electron microscopy (FESEM), a SU8010 microscope (Hitachi, Japan) was used to observe the surface morphology and shape of the dried microcapsules. The samples were fixed in stubs using double-faced copper adhesive tape and were coated with a thin layer of platinum using a Q150R S rotary-pumped sputter coating system (Quorum Technologies, UK) before being observed.

2.4 Determination of drug loading and entrapment efficiency
For each batch, 100 mg of beads were dispersed in 20 ml 1M NaOH [15(Ohya et al., 1994)]. After 12 h, 20 ml distilled water was added, and the solution was subjected to sonication with a Hielscher UIP500hd ultrasonic homogenizer at 60% amplitude for 1 min to rupture the microspheres. Next, the solution was filtered through a Whatman filter paper. After dilution, 5-FU content was analyzed using the UV–visible Spectrophotometer (Shimadzu, UV-1800) at Amax 270 nm [9]. This procedure was repeated in triplicate for each batch. The standard and blank solution was prepared and analyzed in the same way except by dissolving 50 mg 5-FU plus 50 mg unloaded beads (from batch 5) for the standard solution while 50 mg unloaded beads (from batch 5) was dispersed for the blank solution. EE% was calculated as follows:

\[
\text{EE} (%) = \frac{\text{Actual drug content (mg)}}{\text{Theoretical drug content (mg)}} \times 100
\]

2.5 Fourier transform infrared (FT-IR) spectral studies
A sufficient amount of sample was crushed with pestle and mortar. The IR spectra of 5-FU, chitosan, SLS, Eudragit, loaded and unloaded beads were taken over 500–3000 cm\(^{-1}\) in the Varian 640 FT-IR spectrophotometer using an attenuated total reflection accessory made up of diamond crystal. The Varian Resolutions Pro software analyzed the IR spectra.

2.6 Thermogravimetric analysis
The thermal properties of samples were analyzed on a thermogravimetric analyzer (TGA Q50, TA Instruments, USA). Three milligrams of sample was heated in a sealed aluminum pan at the rate of 25 °C min\(^{-1}\) up from 20 °C–600 °C under a constant nitrogen flow of 20 ml min\(^{-1}\).

2.7 In vitro release studies
The dissolution medium of pH 1.2 was prepared by dissolving 2 g sodium chloride and 31.6 ml 1M HCl in distilled water and making up the volume in a 1000 ml volumetric flask. For each batch, a weighed amount of beads containing 25 mg 5-FU (calculated based on drug loading) was dispersed in 250 ml dissolution medium pH 1.2 for two h to mimic gastric pH and emptying time. This mixture was left to incubate at 37 °C ± 0.5 °C and 50 rpm in a shaking water bath. After two h, 1.14 g tris(hydroxymethyl) aminomethane and 0.885 g anhydrous sodium acetate was added to the dissolution medium to achieve pH 7.2. At the determined interval, 2 ml of sample was withdrawn, and an equal volume of dissolution medium was replaced to the beaker. The amount of drug in the dissolution was determined at 270 nm by UV-Vis spectrophotometry (Shimadzu, UV-1800).
3. Results and discussion

3.1 Preparation of beads

Chitosan beads were formed by ionotropic gelation based on electrostatic interactions between the cationic chitosan and a multivalent anion as a crosslinking agent, SLS. When chitosan is dissolved in acetic acid solution, the nitrogen atom on primary amine groups of chitosan is protonated by hydrogen atom from acetic acid, resulting in the formation of NH$_3^+$ groups [3]. Conversely, SLS has a sulfate group (SO$_4^-$) in its anionic form. The NH$_3^+$ from chitosan and SO$_4^-$ from SLS interact through inter- and intra-molecular electrostatic interactions, giving rise to a water-insoluble sulphonate salt precipitates as a spherical particle [5, 6].

3.2 Appearance, morphology and particle size analysis

Figure 1 shows the photograph of fresh/wet 5-FU-loaded beads, and photomicrographs of the dried bead are shown in figure 2. The average height and width of beads from each batch are as in table 2. All formulation batches have formed beautiful spherical beads, as shown in figure 1. Beads prepared from aqueous solvent (batch 1 and 4) have a clear, transparent, spherical appearance while those from hydroalcoholic and alcoholic solvent (batch 2, 3, 5, 6, 7, and 8) were opaque, white and spherical (figure 1).

After drying, only beads from 2% SLS and Eudragit in alcohol have (batch 5 and 6) formed distinct, free-flowing spherical particles, while beads from batch 1 to 4, were agglomerated, non-spherical and were not free-flowing. At 20x magnification, beads prepared from 1% SLS had a sheet-like appearance instead of a distinct spherical outlook compared to beads from 2% SLS with a definite spherical shape (figure 2). Batch 7 and 8 beads prepared without Eudragit were not spherical. All these observations evidence the requirement of alcohol and Eudragit to make spherical SLS crosslinked chitosan beads.

The sizes of various beads were given in table 2. Irrespective of the solvent system, beads prepared from 1% SLS formed bigger beads ranging from 3061–3322 μm in height compared to beads from 2% SLS creating smaller beads ranging from 1577–2323 μm in height. A higher concentration of SLS leads to a higher degree of crosslinking, pulling the polymeric network closer together and decreasing particle size [3]. FESEM pictures of batch 1, 5, and 6 dried beads are given in figures 3(A)–3(C), respectively. Except batch 5, no other batches have shown spherical geometry. Batch 5 has retained the spherical geometry even after drying, possibly due to enough % of chitosan to form a solid matrix after crosslinking. Other batches either formed film (figure 3(A)) or folding (figure 3(C)) like structure after drying. Different surface morphology was observed on the beads based on the solvent system. Beads prepared with aqueous (figure 4(A)) and hydroalcoholic (figure 4(D)) solvent has shown folding like structure on the surface. In contrast, alcohol made beads have shown discontinuous surface coating (figure 4(C), 4(E), and 4(F)), probably due to the deposition of Eudragit during the drying of the beads. Interestingly, crystalline-like structures (figure 4(B)), perhaps due to crystallization of polymers at the interface, were seen on the surface of the beads prepared with hydroalcoholic solvent. These beads have also shown the highest drug loading. We could not understand the exact reason for this, however, could be due to less migration of drug from chitosan beads to the hydroalcoholic crosslinking agent contains Eudragit and SLS.

3.3 Drug loading and entrapment efficiency

Table 2 reports the theoretical and actual drug loading and EE% for each batch. The influences of different variables on EE are illustrated in the bar chart (figure 5). In terms of the solvent system with 1% SLS and Eudragit, the highest drug loading and EE% was achieved in hydroalcoholic than the alcoholic and aqueous (lowest loading) solvent systems (figure 5). The low EE% in an aqueous solvent may be attributed to the diffusion of 5-FU from inside the beads to the external aqueous phase, due to its high water solubility (1 in 80) [12, 13].

Further, the washing process with distilled water may contribute to 5-FU loss. Adjusting the pH of the crosslinking solution to 7.5, to minimize 5-FU ionization (acidic drug; pKa 8) and water solubility did not improve EE% significantly. The EE% is higher in the hydroalcoholic, and alcoholic-based solvent due to a smaller driving force for diffusion since 5-FU is only very slightly soluble [13] in alcohol (1 in 170). However, the EE% is still poor because 5-FU exists in the unionised form in acidic pH (in the chitosan solution) and may still diffuse to the external alcoholic phase of the crosslinkers solution. In contrast, beads prepared with 2% aqueous SLS/Eudragit (Batch 4) has shown better loading than the one prepared with 2% alcoholic SLS/Eudragit (Batch 5). It could be due to less size of beads prepared in alcoholic solution; larger surface area might have caused more drug loss from these beads.

Besides that, the EE% decreases as SLS concentration increases, and this supports literature data from El-Gibaly et al [5]. The higher SLS concentration leads to greater crosslinking and gel volume contraction, expelling water from the polymeric network. As water is extruded, there is a connective loss initially entrapped 5-FU, resulting in lower EE% [5]. Also, the EE% was lower with two h reaction time. It could be due to the high...
aqueous solubility of 5-FU, such that a longer crosslinking time provided a more extended period for more 5-FU to partition to the external phase [16]. The addition of Eudragit improved EE% slightly from 9.0% to 10.1% because Eudragit is solubilized in the solvent phase hindering the diffusion of 5-FU out from the beads.

Figure 1. General appearance of freshly prepared and wet beads of batch 1 to 8. All beads were spherical and discrete. Not to scale.
Figure 2. Photomicrographs of dried beads from batch 1 to 8 under bright-field contrast microscopy at 20x magnification.

Table 2. Theoretical and actual drug loading, percentage entrapment efficiency and mean height and width (including standard deviation, SD) of beads from batch 1 to 8.

| Batch | Yield (g) | Theoretical drug loading (mg) | Actual drug loading (mg) | Entrapment efficiency (EE%) | Mean height (μm) (n = 6 ± SD) | Mean width (μm) (n = 6 ± SD) |
|-------|-----------|-------------------------------|--------------------------|----------------------------|-------------------------------|-------------------------------|
| 1     | 3.0177    | 50                            | 11.38                    | 22.8                       | 3081.60 ± 469.80             | 1862.68 ± 342.96             |
| 2     | 2.4841    | 50                            | 17.41                    | 34.8                       | 3061.68 ± 373.03             | 2684.70 ± 242.03             |
| 3     | 2.4645    | 50                            | 13.76                    | 27.5                       | 3322.35 ± 277.32             | 3071.75 ± 392.66             |
| 4     | 3.5604    | 50                            | 9.23                     | 18.5                       | 2323.15 ± 221.06             | 2192.78 ± 280.33             |
| 5     | 3.3160    | 50                            | 6.89                     | 13.8                       | 1698.68 ± 160.17             | 1303.50 ± 167.10             |
| 6     | 2.6045    | 50                            | 5.05                     | 10.1                       | 1577.90 ± 86.03              | 1344.55 ± 172.83             |
| 7     | 2.4363    | 50                            | 6.12                     | 12.2                       | 1929.20 ± 10.18              | 1526.85 ± 25.67              |
| 8     | 2.6080    | 50                            | 4.51                     | 9.0                        | 1685.60 ± 148.07             | 1402.58 ± 234.25             |
3.4 FT-IR spectra analysis
The IR spectra of 5-FU, chitosan, SLS, and Eudragit are shown in figure 6, whereas the IR spectra of unloaded and 5-FU-loaded beads from each batch are shown in figures 7 and 8, respectively. FT-IR analysis was used to confirm the formation of a complex between SLS and chitosan molecules. The primary amine group of chitosan had a characteristic N–H bending peak at 1652 cm$^{-1}$, while the IR spectra of unbound SLS showed two characteristic peaks of asymmetric and symmetric SO$_2$ stretch at 1222 cm$^{-1}$ and 1085 cm$^{-1}$ respectively (figure 6)\cite{11}. When compared to the IR spectra of unloaded beads (figure 7), the N–H bending peak of unbound chitosan disappeared. Additionally, the SO$_2$ stretch peaks were shifted to a lower field ranging from 1192–1219 cm$^{-1}$ and 1062–1079 cm$^{-1}$ across all batches\cite{11}. This matched a similar shift from insulin/SLS salt complex established by Dai and Dong\cite{17}. Hence, this confirmed the electrostatic interaction between the NH$_3^+$ group of chitosan and SO$_4^{2-}$ group of SLS\cite{6,11}. Besides that, two characteristic peaks of Eudragit at 1725 cm$^{-1}$

[Figure 3. FESEM of 5-FU loaded chitosan beads of batch 1 (A), 5 (B) and 6 (C). Except batch 5 and 6 all other beads were not spherical.]
Figure 4. Surface morphology of 5-FU loaded beads of batch 1 (A), 2 (B), 3 (C), 4 (D), 5 (E) and 6 (F).

Figure 5. Effect of different variables on percentage entrapment efficiency.
and 1154 cm\(^{-1}\) also appeared in the IR spectra of unloaded beads from batch 1 to 6, implying that Eudragit was incorporated into the chitosan polymeric matrix \([14]\). These peaks were absent in beads of Batch 7 and 8, which were prepared without Eudragit.

The incorporation of 5-FU was also confirmed by FT-IR analysis. The IR spectra (figure 6) of unbound chitosan had a characteristic N–H stretching peak at 2927 cm\(^{-1}\), while 5-FU had a characteristic C=O stretching band at 1715 cm\(^{-1}\) \([8]\). In comparison to IR spectra of loaded beads (figure 8), the chitosan N–H stretching peak was present in all batches varying from 2921–2927 cm\(^{-1}\), confirming that the polymeric matrix was made from chitosan. Additionally, in all batches except batch 4, a new peak appeared at wavenumber ranging from 1700–1719 cm\(^{-1}\), representing C=O stretching of 5-FU, signifying that 5-FU was successfully entrapped in the polymeric network. Because the C=O stretching peak was not significantly shifted to another field, this implied...
that 5-FU did not experience any chemical changes during incorporation into the beads [8]. The lack of characteristic C=O stretching peak in Batch 4 could be owing to low drug loading in the analyzed microsphere as well as the amorphous nature of the entrapped drug. FT-IR of Batch 1 also shown a similar pattern as batch 4 as both are prepared from aqueous crosslinking solution.

3.1. Thermal analysis
TGA of unloaded beads were given in the supplementary figures 1 and 2. Batches prepared with 2% SLS/Eudragit in alcoholic crosslinking solution (Batch 2, 3, 5–8) have shown a sharp weight loss (about 30% to 45%) between 210 °C and 240 °C indicating thermal degradation at this point. It could be due to the crystalline nature of chitosan due to complexation with SLS/Eudragit in the presence of alcohol. A similar observation is reported by Yalman et al. [18] in bone putty made up of chitosan-g-stearic acid. In contrast, aqueous crosslinked beads (batch 1 and 4) have shown 10 to 20% weight loss around 120 °C indicated loss of absorbed water and also shown gradual thermal degradation (about 30% weight loss) between 200 °C and 300 °C [19] indicating better thermal stability than the alcohol-based beads.

5-FU has shown a sharp weight loss from 240 to 300 °C, indicating its melting point at 281 °C [8]. A similar weight loss was observed in the physical mixture of chitosan and 5-FU, as shown in supplementary figures (available online at stacks.iop.org/MRX/7/115402/mmedia). The TGA pattern of Batch 2 (hydro alcoholic) has a sharp 45% weight loss between 200 °C and 300 °C suggesting the crystalline nature of the bead. This observation is also supported by the SEM observation, as indicated in figure 4. All drug-loaded batches have shown similar TGA pattern of unloaded beads suggesting amorphous as well as low % of drug loading.

3.6 In vitro release studies
The effect of different variables: solvent system, SLS concentration, crosslinking time, and presence of Eudragit on the 5-FU release rate from the beads are shown in figures 9, 10, 11 and 12, respectively. Drug release from chitosan beads relies on the penetration of dissolution medium into the particle, swelling of the polymeric matrix, and subsequent dissolution and diffusion of entrapped drug through the swollen matrix [2]. Because chitosan exhibits high swelling in acidic pH, there is a burst release of 5-FU in dissolution medium pH 1.2 from all batches [8]. All beads did not show sustained drug release lasting longer than 4 h.

In terms of the solvent system (figure 9), beads prepared from aqueous solvent displayed the fastest drug release, followed by the hydroalcoholic and alcoholic solvent. However, beads prepared from higher SLS concentration exhibited a slower release rate (figure 10) due to reduced chain mobility caused by the denser polymeric network. As a result, the prepared beads were more rigid and stable, with a lower tendency to swell. The higher polymeric density also imposed a longer diffusion path length to the external environment, thus
Figure 9. Effect of different solvent system on release profile of 5-FU from beads (batch 1 to 3).

Figure 10. Effect of SLS concentration on release profile of 5-FU from beads (batch 1 and 4).

Figure 11. Effect of cross-linking time on release profile of 5-FU from beads (batch 5 and 6).
resulting in a slower 5-FU release rate [6]. Conversely, the rate of 5-FU release was faster with a shorter reaction time of 1 h (figure 11). A shorter crosslinking time leads to a looser gel structure, allowing easier penetration of dissolution medium and subsequently quicker dissolution and diffusion of the entrapped drug, lead to faster drug release [20]. The presence of Eudragit marginally slowed the 5-FU release rate from beads (figure 12). As Eudragit dissolves only above pH7, its presence in the polymeric matrix delays diffusion of dissolution medium into the chitosan matrix and thus leads to a slower 5-FU release.

4. Conclusion

Chitosan/SLS/Eudragit beads were prepared by ionotropic gelation. At least 2% SLS was required to produce beads with a distinct spherical appearance. Compared to aqueous solvent, alcoholic and hydroalcoholic solvents were able to improve EE%. The presence of Eudragit marginally improved EE% while slowing the 5-FU release rate. However, all batches did not display sustained-release beyond four h. The EE% of 5-FU can be improved with alcoholic-based solvent, lower SLS concentration, and shorter reaction time, but with the cost of a faster 5-FU release rate. Therefore, further studies are required to find a balance between the factors involved in order to achieve higher EE% while retaining sustained-release characteristics. This study revealed the feasibility of making 5-FU loaded chitosan beads, which could be useful in treating cancers in the upper part of gastrointestinal cancer.

ORCID iDs

Saravanan Muniyandy https://orcid.org/0000-0002-6295-5676

References

[1] Agnihotri S A, Mallikarjuna N N and Aminabhavi T M 2004 Recent advances on chitosan-based micro- and nanoparticles in drug delivery J. Controlled Release 100 5–28
[2] Bodmeier R, Oh K H and Pramar Y 1989 Preparation and evaluation of drug-containing chitosan beads Drug Dev. Ind. Pharm. 15 1475–94.
[3] Chang S A, Niu G C, Kuo S M and Chen S F 2007 Preparation and preliminary characterization of concentric multi-walled chitosan microspheres Journal of Biomedical Materials Research A. 81 554–66.
[4] Berthold A, Cremer K and Kreuter J 1996 Preparation and characterization of chitosan microspheres as drug carrier for prednisolone sodium phosphate as model for anti-inflammatory drugs J. Controlled Release 39 17–25
[5] El-Gibaly I, Meki A M and Abdel-Ghaffar S K 2003 Novel B melatonin-loaded chitosan microcapsules: in vitro characterization and antiapoptosis efficacy for aflatoxin B1-induced apoptosis in rat liver Int. J. Pharm. 260 5–22
[6] El-Nahas H M and Hosny K M 2011 Chitosan-based floating microspheres of trimetazidin dihydrochloride; preparation and in vitro characterization Indian Journal of Pharmaceutical Science. 73 397–403
[7] Justyna W, Andrzej N and Beata L 2019 5-Fluorouracil-Complete Insight into its natural and ionised forms Molecules 24 3683
[8] Bhat S K, Keshavaya J, Kulkarni V H, Reddy V K R, Kulkarni P V and Kulkarni A R 2012 Preparation and characterization of cross-linked chitosan microspheres for the colonic delivery of 5-Fluorouracil J. Appl. Polym. Sci. 125 1736–44
[9] Zhou Z, Cao D, Liu L, Liu Q, Zhao Y, Zeng W, Yi Q, Yang Z and Zhou J 2013 Fabrication and properties of Gelatin/Chitosan microspheres loaded with 5-Fluorouracil Journal of Macromolecular Science, Part B: Physics, 52 973–83
[10] Zhang C, Li G, Wang Y, Cui F, Zhang J and Huang Q 2012 Preparation and characterization of 5-fluorouracil-loaded PLLA-PEG/PEG nanoparticles by a novel supercritical CO2 technique Int. J. Pharm. 436 272–81
[11] Elsayed A, Al-Remawi M, Qinna N, Farouk A, Al-Sou`od K A and Badwan A 2011 Chitosan-sodium lauryl sulfate nanoparticles as a carrier system for the in vivo delivery of oral insulin AAPS PharmSciTech. 12 958–64.
[12] Zorrilla-Veloz R I, Stelzer T and López-Mejías V 2018 Measurement and correlation of the solubility of 5-fluorouracil in pure and binary solvents J. Chem. Eng. Data 63 3809–17
[13] Hsu L S F and Marrs T C 1980 Determination of 5-fluorouracil in human plasma by high-pressure ion-exchange chromatography Ann. Clin. Biochem. 17 272–6
[14] Thakral N K, Ray A R and Majumdar D K 2010 Eudragit S-100 entrapped chitosan microspheres of valdecoxib for colon cancer Journal of Material Science: Materials in Medicine 21 2691–7
[15] Ohya Y, Shiratani M, Kobayashi H and Ouchi T 1994 Release behavior of 5-fluorouracil from chitosan-gel nanospheres immobilizing 5-fluorouracil coated with polysaccharides and their cell specific cytotoxicity J. Macromol. Sci., Part A 31 629–42
[16] Panos I, Acosta N and Heras A 2008 New drug delivery systems based on chitosan Curr Drug Discovery and Technology 5 333–41.
[17] Dai W G and Dong L C 2007 Characterization of physicochemical and biological properties of an insulin/lauryl sulfate complex formed by hydrophobic ion pairing Int. J. Pharm. 336 58–66
[18] Yalman V, Çelik E, Arslan O, Alkan F, Türkşügül N L, Şirin H T, Arslan A K and Demirbilek M 2020 A study on bone tissue engineering: Injectable chitosan-g-stearic acid putty Technol. Health Care 28 227–39
[19] Pereira M A V, Fonseca G D, Silva-Júnior A A, Fernandes-Pedrosa M F, de Moura M, de F V, Barbosa E G, Gomes A P B and dos Santos K S CR 2014 Compatibility study between chitosan and pharmaceutical excipients used in solid dosage forms In Journal of Thermal Analysis and Calorimetry. 116 1091–100
[20] Shiraishi S, Imai T and Otagiri M 1993 Controlled release of indomethacin by chitosan-polyelectrolyte complex: optimization and in vivo/in vitro evaluation J. Controlled Release 25 217–25