

Research Article

Physical stability of different chitosan salts in matrix tablet formulations

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ABSTRACT

This study aimed to evaluate the physical stability of chitosan (CS) and its salt forms, including chitosan glycolate (CGY) and chitosan lactate (CL), as diluent in matrix tablets for the modified-release dosage form. Caffeine, theophylline, and theobromine were selected as model drugs in this study because of its similarity in chemical structure but difference in solubility. *In vitro* drug release, hardness, and tablet weight of the drug-loaded matrix tablets made of CS or CS salts were assessed after preparation and 6 months of storage for physical stability monitoring. After 6 months under the accelerated storage condition, the hardness of the CS and CS salt matrix tablets without drug increased, whereas the hardness of the drug-loaded matrix tablets decreased. After 6 months, the weight gain of the CS matrix tablets was approximately 2.63% to 4.97%. In addition, storage of the CGY and CL matrix tablets for 6 months significantly caused rapid drug release. Results show that the application of CS as tablet excipient should be closely monitored and evaluated because of its low stability and hygroscopic property.

1. INTRODUCTION

Chitosan (CS) is a positively charged polysaccharide comprising copolymers of glucosamine ($\beta(1-4)$ -linked 2-amino-2-deoxy-D-glucose) and *N*-acetylglucosamine (2-acetamido-2-deoxy-D-glucose). CS is obtained after the deacetylation of chitin obtained from the exoskeletons of crustaceans after demineralization and deproteinization treatments¹. Recently, there has been growing interest in the use of CS as drug release controller and other pharmaceutical excipients in various pharmaceutical dosage forms, for instance, matrix tablets, compression-coated tablets, film-coated tablets, and nano/microparticles¹⁻⁵. Nevertheless, native CS in base form has been rarely used because of its low water solubility. Consequently, CS was modified into several salt forms to improve its solubility⁶⁻⁸. In pharmaceutical tablet formulation, CS and its salts have been widely utilized as binder in the wet/dry granulation process, lubricant, tablet diluent, film coating material, and controlled drug release agent⁹⁻¹². Apart from its application as pharmaceutical excipient, established human exposure to CS has occurred through

its use as a dietary supplement in preparations for obesity and hypercholesterolemia^{13,14}. Even though CS and its salts have been applied as pharmaceutical excipient for a long time, information about the physical stability of CS is still lacking. Thus, the information about the physical stability of CS and its salts would help formulators aware and concern about using CS in various pharmaceutical dosage forms.

This study aimed to evaluate the physical stability of CS and its salts, including chitosan

glycolate (CGY) and chitosan lactate (CL) (Figure 1), in matrix tablet dosage forms. *In vitro* drug release profiles, hardness, and tablet weight of drug-loaded matrix tablets made of CS or CS salts were assessed after preparation and 6 months of storage. Two molecular weights (MW) of CS, i.e., 45 and 200 kDa, with the degree of deacetylation of 87% to 89% were used. Three structurally similar drugs, namely, caffeine, theophylline, and theobromine (Figure 2) were selected as model drugs in this study because of their difference in solubility.

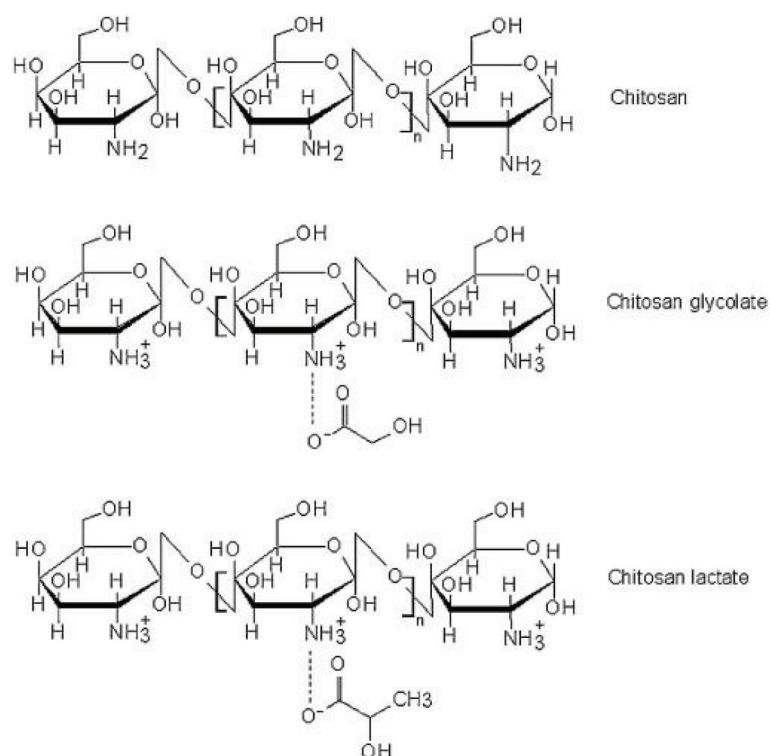


Figure 1. Chemical structures of chitosan (CS), chitosan glycolate (CGY), and chitosan lactate (CL)

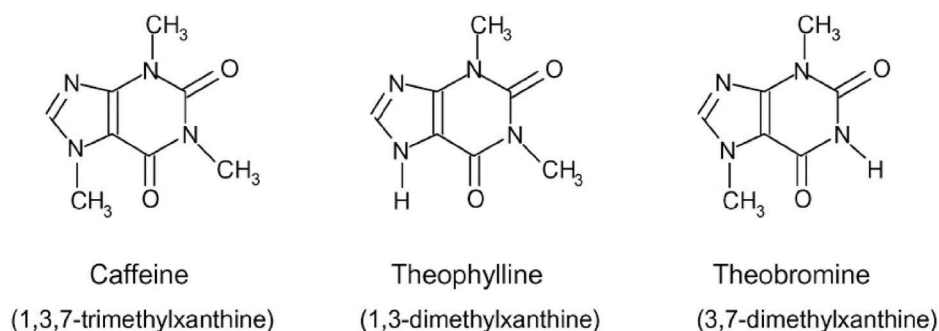


Figure 2. Illustration of the chemical structures of caffeine, theophylline, and theobromine

2. MATERIALS AND METHODS

2.1. Materials

CS with the degree of deacetylation of 87% to 89% and MW of 45 kDa (CS45) and 200 kDa (CS200) was purchased from Seafresh Co. Ltd., Thailand (lot numbers COA050507 and COA240702, respectively). Caffeine was obtained from BASF (Thai) Co.Ltd., Thailand. Theophylline and theobromine were purchased from Sigma Aldrich, USA. All excipients were of pharmaceutical grade, and other chemicals were of reagent grade.

2.2. Preparation of CGY and CL

CGY and CL were prepared by the spray drying technique, as described in a previous report¹⁵. Briefly, CS flakes were dissolved in either glycolic acid or lactic acid solution. Then, the CS solutions were spray-dried using a spray dryer (model SD-60, Labplant, UK) under the following conditions: inlet temperature of 140 °C, outlet temperature of 80 °C to 90 °C, and feeding rate of 5 mL/min. The obtained powders were collected and kept in a desiccator. Successful CS salt modification was confirmed by Fourier transform infrared spectroscopy, as reported in a previous study¹⁶.

2.3. Preparation of drug-loaded matrix tablets made of CS or CS salts

Two hundred milligrams of CS or CS salts mixed with 100 mg of the model drug (caffeine, theophylline, or theobromine) were compressed into tablets using a hydraulic press (Specac Inc., UK) at a fixed compression force of 2 tons and dwelling time of 20 s using a 9.5-mm diameter flat-faced punch set. The compressed tablets were kept in a desiccator at ambient temperature before further investigation. The compressed tablets were also kept in a stability chamber under the accelerated storage condition (45 °C, 75% relative humidity) for 6 months for physical stability monitoring.

2.4. Physical properties of drug-loaded matrix tablets made of CS or CS salts

The thickness and diameter of the matrix tablets were measured using a caliper (Dial Thickness Gauge, Mitutoyo, Japan). The tablet

hardness was measured on the first day and after 6-month storage using a texture analyzer (model TA-XT plus, Stable Micro System, UK) in compression mode. The images of the tablets containing CS and CS salts were recorded on the first day and after 6-month storage.

2.5. Weight change

The change in tablet weight was monitored to observe the hygroscopicity of CS and CS salts as the excipient in matrix tablets. After the preparation of the tablets, the initial weight (W_1) was recorded using an analytical balance (model AG204, Mettler-Toledo, Switzerland). Then, the prepared tablets were kept in a stability chamber for 6 months and weighed again (W_2). The percentage of weight increase due to absorbed ambient humidity was estimated using Eq. (1):

$$\text{Weight change} = \left[\frac{(W_2 - W_1)}{W_1} \right] \times 100 \quad (1)$$

2.6. *In vitro* release studies

The drug release behavior of the drug-loaded matrix tablets containing CS or its salts was investigated using the USP dissolution apparatus I (model Dissolutest, Prolabo, France) equipped with baskets, which was operated at a speed of 100 rpm and equilibrated to 37 ± 0.5 °C. The release studies were initially performed in pH 1.2 simulated gastric fluid (without pepsin) of the USP for 2 h, which was then replaced with pH 6.8 Tris buffer to simulate the intestinal conditions for the following hours. The samples (5 mL) were taken at various time intervals, i.e., 5 min, 10 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, and 24 h. Then, the amount of drug released was measured by a UV–visible spectrophotometer (model Lambda 2, Perkin Elmer, Germany) at maximum wavelengths of 272, 270, and 272 nm for caffeine, theophylline, and theobromine, respectively. Each *in vitro* release study was performed in triplicate.

2.7. Statistical analysis

Analysis of variance and Levene's test for homogeneity of variance were performed using SPSS version 10.1 for Windows (SPSS Inc., USA). Post hoc testing ($p < 0.05$) of the multiple comparisons

was performed using either the Scheffé or Games–Howell test depending on whether Levene’s test was insignificant or significant, respectively¹⁷.

3. RESULTS AND DISCUSSION

3.1 Physical properties and appearance of drug-loaded matrix tablets containing CS or its salts

The hardness properties of the matrix tablets containing CS or its salts are shown in Figure 3a. The hardness of all tablets was between 3.5 kg and 18.7 kg. For CS with the same MW, CGY matrix tablets exhibited higher hardness than CS and CL matrix tablets. This finding can be attributed to the chemical structure of CGY that contains the hydroxyl group, which might interact with the amine group of other CS units and then yield hydrogen bonds. By contrast, CL contains the CH₃ group, which might cause steric hindrance that interferes with the interaction between polymer chains (Figure 1). This result is consistent with that of our previous study, in which the CGY matrix tablets exhibited higher tablet hardness and tablet strength than the CS, CL, chitosan aspartate, and chitosan glutamate matrix tablets¹⁸. Furthermore, the addition of model drugs (caffeine, theophylline, or theobromine) in the tablets containing CS or CS salts distinctly increased tablet hardness. This is likely due to the compressibility and compactibility of the active drugs, as also mentioned in other reports^{19,20}. Moreover, in the case of CS and CGY, the tablets made of low MW (45 kDa) with no drug exhibited higher hardness than those made of high MW (200 kDa). The results of this study are consistent with those of previous studies^{18,21}, which show that CS with high MW has high viscosity, resulting in large particles of the spray-dried product that lead to low hardness of the resultant tablets.

After 6 months of storage in the stability chamber, the blank matrix tablets containing CS salts were six times harder (from 100% to 600%), as presented in Figure 3b and 4. This finding can

be attributed to the fact that CS is hygroscopic in nature, which means that it has a high capability to form the hydrogen bond (formed with both the hydroxyl and amino groups) with water. This phenomenon was previously reported in other studies^{22,23}, which explained that a moisture content of 6% (w/w) or higher improves the particle binding property, resulting in tablets with high hardness. Therefore, the hardness of the blank matrix tablets was dramatically increased. By contrast, polymer–polymer interaction was hindered by the drug molecules in the drug-loaded matrix tablets, resulting in a stable tablet hardness during 6 months of storage. Finally, the weight of the tablets containing CS salts is more stable than that of the tablets containing CS. This finding can be attributed to the modification of active moieties in the chemical structure of CS, which can prevent the interaction of polymer with water molecules in the air²⁴.

3.2. Weight change

The percentage of weight change after 6 months of storage of the matrix tablets containing CS and CS salts was monitored to evaluate the hygroscopic property of CS and its salts as the excipient in solid dosage forms. The initial weight of all matrix tablets ranged from 203.13 mg to 224.75 mg. As illustrated in Figure 5, the weight of the CS matrix tablets (CS45K and CS200K) was 2.6% to 5% greater than that of the CS salt matrix tablets after 6 months of storage. The weight change of matrix tablets containing CS was consistent with the tablet hardness results; CS can absorb moisture during storage, resulting in low physical hardness²⁵. In addition, the weight of matrix tablets containing CS salts with/without drug increased after storage. The exception is the weight of theophylline-loaded matrix tablets containing CL, which decreased after storage. This finding can be attributed to the fact that lactic acid has a low boiling point (122 °C), resulting in the evaporation of lactic acid during the long storage period²⁶.

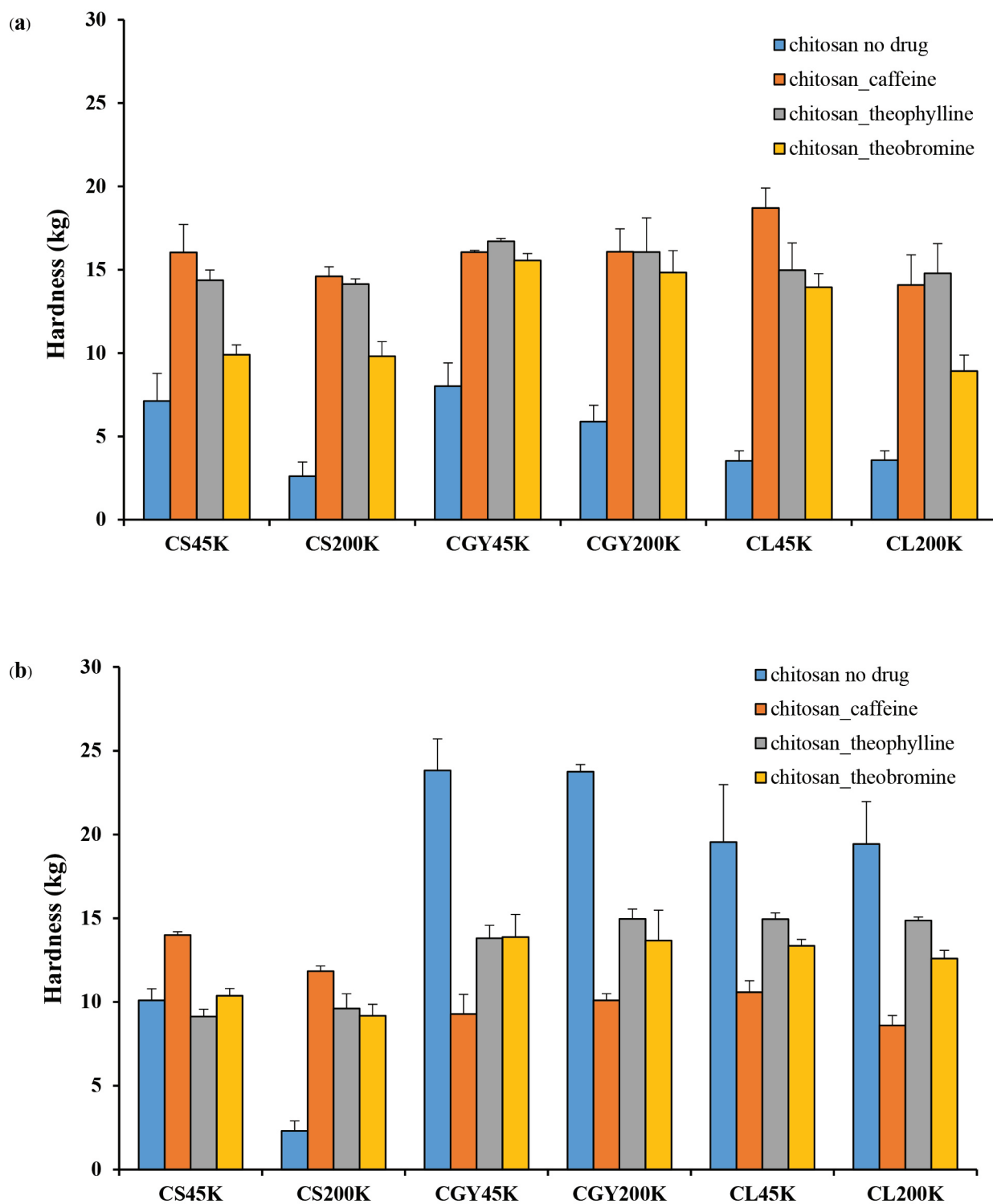


Figure 3. Tablet hardness of matrix tablets containing CS or CS salts (a) on the first day and (b) after 6 months of storage.

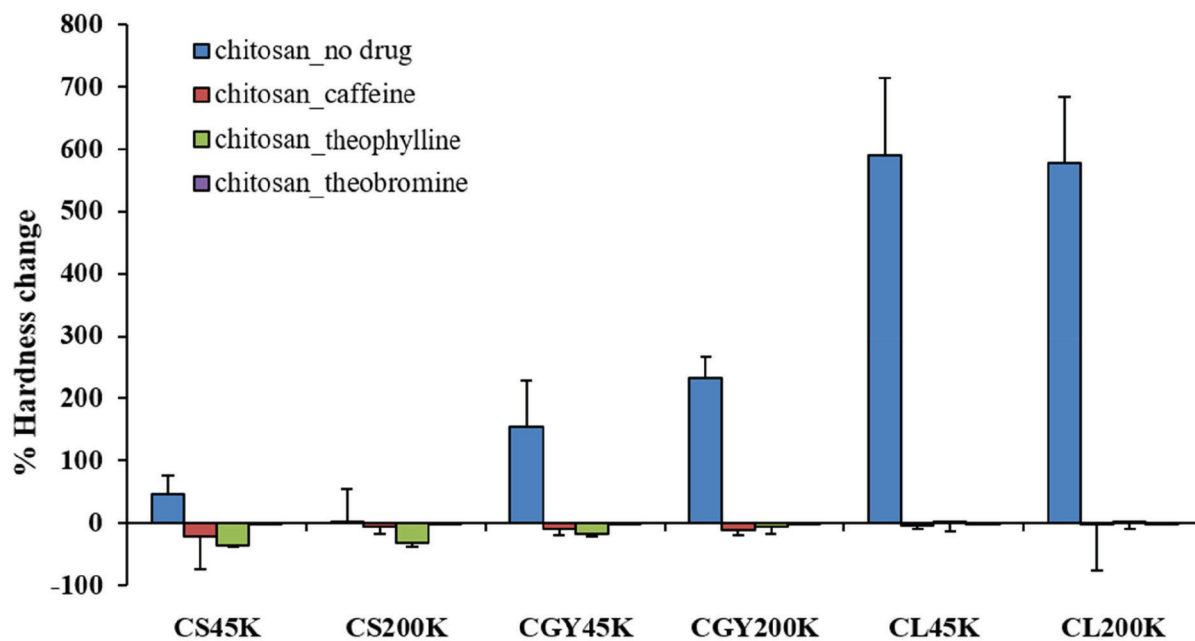


Figure 4. Percentage of tablet hardness change after 6 months of storage of matrix tablets made of CS or CS salts

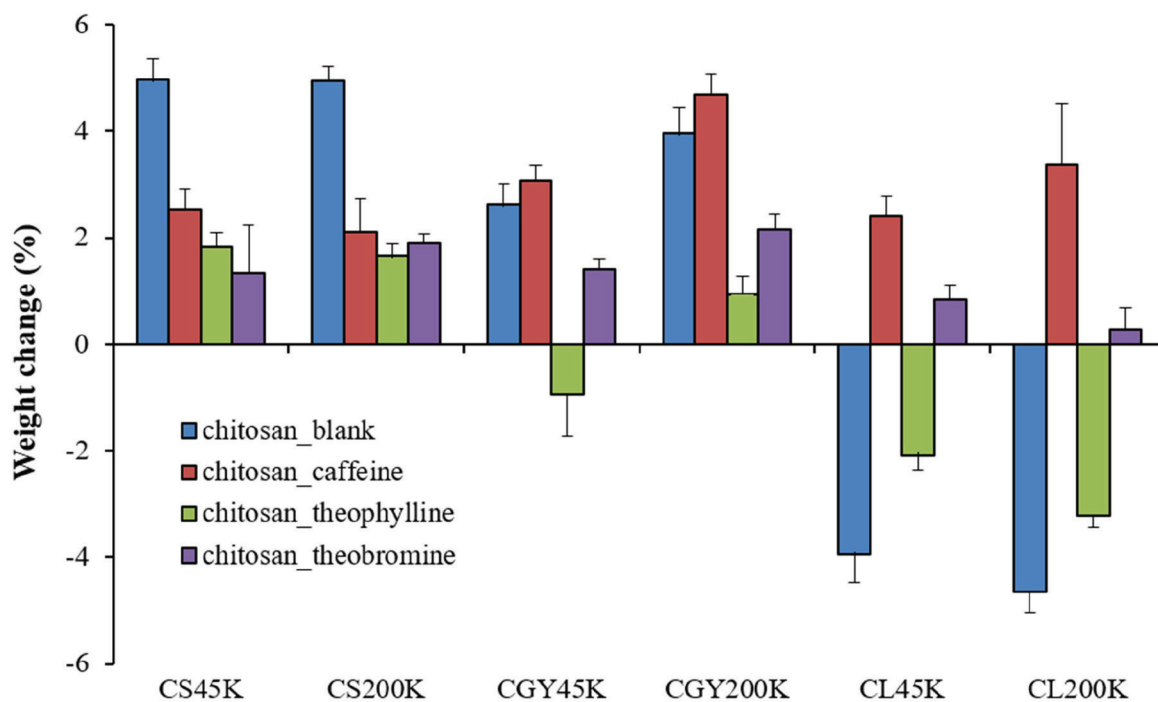


Figure 5. Percentage of weight change of blank and drug-loaded matrix tablets made of CS or CS salts after 6 months of storage

3.3 *In vitro* release studies

Drug release from the matrix tablets made of CS, CGY, and CL (MW of 45 and 200 kDa) was tested. Three model drugs with similar structure (i.e., caffeine, theophylline, and theobromine) were selected in this study because of their difference in solubility. According to a previous study, the solubility of caffeine is higher than that of theophylline; meanwhile, theobromine has the lowest solubility²⁷. Figure 6 shows the *in vitro* caffeine release from matrix tablets containing different CS salts. Notably, the release of caffeine from the tablets stored for 6 months was slower than that of freshly prepared tablets. CS in salt forms (CL and CGY) could extend drug release, compared with native CS. When loaded with theophylline (Figure 7), CS and its salts with high MW (i.e., 200 kDa) retarded drug release better than those with low MW (i.e., 45 kDa). After 6 months of storage, theophylline release from CS and CGY was fast. For the drug with the lowest solubility in this study, i.e., theobromine, drug release

from the matrix tablets made of CS, both 45 and 200 kDa, on the first day and after 6 months of storage were not statistically different (Figure 8). The slowest theobromine release was observed when using 45 kDa CL and 45 kDa CGY. It can also be concluded that the type of CS salts and MW influenced the drug release behavior. The 6 months of storage of the matrix tablets altered the drug release behavior of the tablets made of CS and CS salts. This finding can be attributed to the fact that CL and CGY were not chemically stable under the accelerated storage condition. When the tablets were stored for 6 months, color change of the tablets containing CS salts was observed (data not shown)¹⁸. In addition, drug release from the tablets containing CS salts (CL and CGY) was slower than that from the tablets containing CS. This phenomenon can be attributed to the previously reported finding that the particles of CS salts could swell to larger sizes than the particles of CS², which could lead to the slow penetration of the water molecules into the tablets.

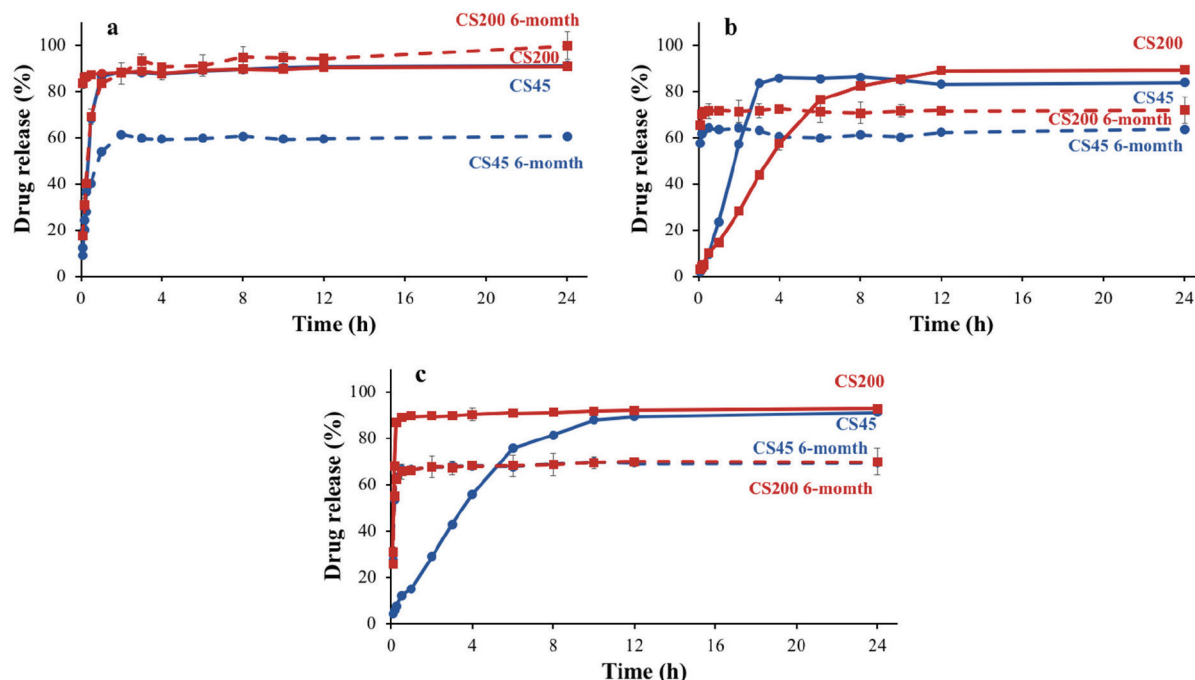


Figure 6. *In vitro* caffeine release from matrix tablets containing (a) CS, (b) CL, and (c) CGY

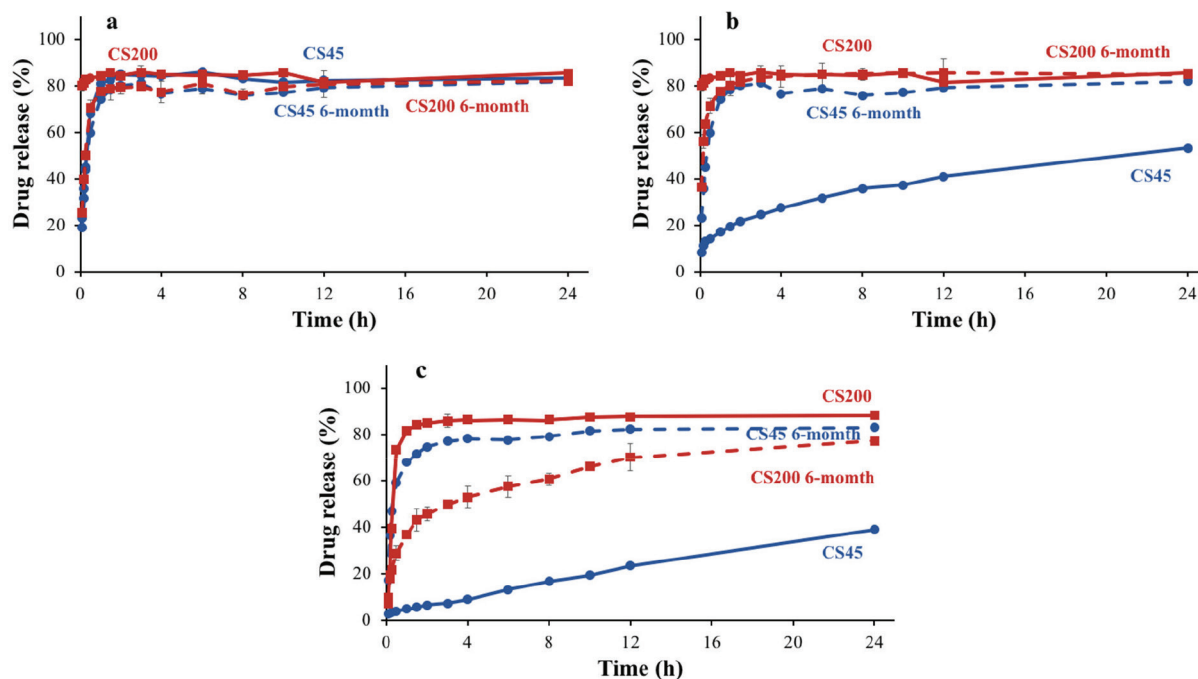


Figure 7. *In vitro* theophylline release from matrix tablets containing (a) CS, (b) CL, and (c) CGY

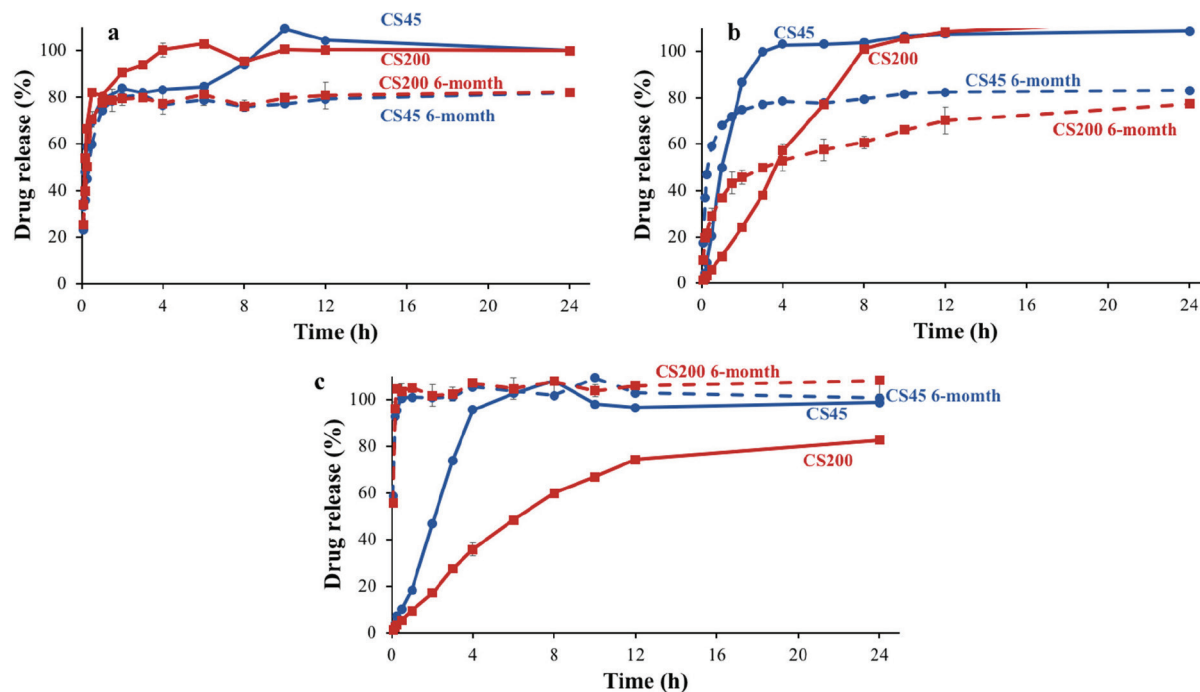


Figure 8. *In vitro* theobromine release from matrix tablets containing (a) CS, (b) CL, and (c) CGY

4. CONCLUSION

The physical properties of the blank and drug-loaded matrix tablets containing CS or its salts were altered after 6 months of storage. The blank matrix tablets made of CS and CS salts were likely to be harder than the drug-loaded matrix tablets made of CS and CS salts, and the weight of most tablets increased. *In vitro* drug release was also affected by aging of the polymer. The drug tends to be released slower from the matrix tablets made of CS salts than from the matrix tablets made of CS after storage for 6 months. This finding can be attributed to the hygroscopic nature of CS, which means that it has a high capability to form the hydrogen bond with water. Thus, when using a high proportion of CS, either base or salt form, as a tablet excipient, its physical stability that could influence the drug release behavior should be considered

Conflict of interest (If any)

The authors declare no conflicts of interest arising in this research.

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