Article info

Design and evaluation of sustained release mucoadhesive film of sumatriptan succinate containing grafted co-polymer as the platform

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Abstract

Purpose: The primary goal of this research is to improve the bioavailability and efficacy of Sumatriptan succinate by incorporating it in the mucoadhesive film for the treatment of migraine. Mucoadhesive film offers an excellent substitute to deliver the drug in the systemic circulation and eliminate the chance of first-pass metabolism.

Method: Using central composite design (CCD), various formulations were created by incorporating polymer, plasticizer, and water, and an optimized preparation was created using statistical screening. The optimization has been performed by applying a 3<sup>4</sup> factorial method based on dependent variables such as Drug content (%), Swelling index (%), Folding endurance (Number of times), and Mucoadhesive strength (g).

Results: The actual experimental values obtained were compared with those predicted by the mathematical models. Formulation S9 was selected as an optimized formulation because it showed the lowest standard deviation between predicted and actual values compared to other formulations. In the case of the S9 formulation, approximately 77.12% of the drug was released within 24 h, but initially, it showed burst release. In addition, the in-vitro release of pure drug suspension showed 99.32% drug release within 2 h. That signifies that the developed formulation provides sustained release due to presence of grafted co-polymer.

Conclusion: Formulation holding drug-loaded grafted film showed decent sustained and controlled drug release characteristics compared to a pure drug suspension. S9 formulation showed better results than other formulations in drug content, swelling index, folding endurance, and mucoadhesive strength, which is further used to treat migraine.

1. Introduction

Migraine is a conjoint neurological or chronic illness categorized by occasional attacks of severe headache enduring 4–72 h associated with vomiting, nausea, photophobia, and phonophobia. It is more common in women with symptoms such as depression, anxiety, and severe pain (Jensen and Stovner, 2008; Diener et al., 2019; Vetvik and MacGregor, 2017). This disease is more common in women, and 14.7 percent of adults in the United States suffer from migraine. The novel approach for the therapy identified cervical nerves and neuropeptides (Antonaci et al., 2016; Charles, 2018). Migraines usually have a family history and affect people aged...
18–50 years. This disease is rated the third most prevailing disorder (Ahmed, 2012; Steiner et al., 2003). In several works of literature, migraine problems are classified as common, classic, complicated, and variant and further classified as migraine with aura and migraine missing aura (Goadsby, 2012; Goadsby et al., 2009). Migraine with aura symptoms include headaches that last hours or days, as well as symptoms such as hyperactivity, hyperventilation, depression, and neck stiffness. Migraine without aura symptoms include headaches with definite features and associated symptoms such as pulsating quality, moderate to severe pain, photophobia, phonophobia, and so on (Goadsby et al., 2017; Carmona and Bruera, 2009). The oral route is one of the best-favoured routes for the administration of drugs, but the disadvantage for this route is solubility and first pass metabolism. The Mucoadhesive path can overcome this problem. Mucoadhesive films offer a noble marginal way to deliver the drug and reject the chance of first-pass metabolism (Muheem et al., 2016; Kermanizadeh et al., 2018). Additional advantages of mucoadhesive Buccal films are no water requirement for disintegration, avoiding first-pass metabolism, exact dosing, easiness of handling, pleasant taste, the speedy onset of action, and sustained or regulated release of drug (Senalty et al., 2010; Salehi and Boddohi, 2017). The grafted copolymer is defined as a series of macromolecules with one or more types of block molecule series attached to the core polymeric backbone chain as various side chains. For extended drug delivery systems, graft polymerization is one of the most convenient ways to use natural polysaccharides (Liechty et al., 2010; Vega-Hernandez et al., 2021; Bhosale et al., 2015).

Sumatriptan succinate, a 5-HT1B/1D receptor agonist in the triptans class, is used to treat migraines. The high first-pass metabolism accounts for approximately 15% of its bioavailability. (Iwasawa and Danjo, 2001; Negro et al., 2018).

A review of the literature revealed that buccal films are a superior dosage form for delivering drugs in exceptional cases when conventional dosage forms fail to treat the disease. So, if we can make a sustained release formulation of sumatriptan succinate by using grafted copolymer, it can solve the problem of bioavailability and patient compliance. The primary goal of this research is to improve the bioavailability and efficacy of Sumatriptan succinate. Mucoadhesive films are an excellent alternative for drug delivery that eliminates the possibility of first-pass metabolism.

2. Materials and methods

2.1. Materials

Sumatriptan succinate was purchased from Aurobindo pharmaceutical, India. HPMC was obtained from Coloorq Asia Pvt. Ltd., India. PEG was acquired from Molychem laboratory, India. Xanthan gum was procured from Purix global, India. Potassium persulphate was purchased from Loba Chemie Pvt. Ltd, India. Acrylamide was acquired from Sisco research laboratories Pvt. Ltd., India, and acetone were obtained from Merck Life science Pvt. Ltd., India. All other materials used for analysis were of analytical grade.

2.2. Synthesis of acrylamide grafted xanthan gum

500 mg Xanthan gum was taken in a beaker and liquefied with 75 ml of distilled water with continuous stirring. In another beaker, acrylamide (500–2000 mg) was dissolved in 25 ml of water with potassium persulphate (50–200 mg). The solution is mixed and the received aggregate is irradiated using a microwave for 120 s to produce numerous batches of grafted gum with a power supply (50–125 W). The temperature of the reaction was monitored by inserting the thermometer, and it was maintained less than 70 °C. After the final touch of microwave irradiation, its content is ultimately refrigerated and saved undisturbed for 24 h to complete the grafting reactions. A gel-like mass is formed by introducing an excess amount of acetone. The precipitate grafted copolymer was gathered and derided at 40 °C in a warm air oven for 24 h (Malviya et al., 2020; Kaity et al., 2013). The whole process is elaborated in the Fig. 1. The percentage of grafting efficiency is influenced by potassium persulphate, acrylamide, and microwave irradiation exposure time.

The % grafting (%G), % grafting efficiency (%GE) and % conversion (%C) were calculated using the following equations:

\[ %G = \frac{W_1 - W_0}{W_0} \times 100 \]

\[ %GE = \frac{W_1 - W_0}{W_2} \times 100 \]

\[ %C = \frac{W_1}{W_2} \times 100 \]

where, W0- amount of xanthan gum, W1- grafted copolymer, W2- amount of acrylamide.

2.3. Formulation optimization by CCD

Formulation optimization was performed with the Quality by Design approach (QbD) using CCD taking three variables into three levels (-1, 0, +1). The amount of grafted copolymer (50–150 mg), HPMC (200–400 mg), and PEG (100–300 mg) and formulation response were optimized as percentage drug content, folding endurance, mucoadhesive strength and percentage swelling index (Flaifel, 2020; Mukherjee et al., 2018).

2.3.1. Development of sumatriptan succinate loaded buccal films

Different concentrations of polymeric solution were selected based on CCD. The chosen polymeric solution grafted polyglycans, copolymer (HPMC), and PEG 400 was added and stirred on a magnetic stirrer at low rpm (about 1000 rpm) until a clear homogenous solution formed. The drug was mixed into the solution described above. The solution was then poured into a round petri dish. Initially, plates were dried at room temperature in a hot air oven. The dried film was sensibly removed, checked for any cracks, and cut into 1x1 cm diameter (Ahmed et al., 2020; Qureshi et al., 2020).

3. Characterization and evaluation of grafted gum and formulation

3.1. Characterization of grafted xanthan gum

3.1.1. Fourier transforms infrared spectroscopy (FTIR-8400S, Shimadzu, Japan)

An FTIR spectrum of xanthan gum, physical mixture and grafted xanthan gum was studied for compatibility studies. About 1 mg of drug was mixed with KBr and ground using mortar and pestle. The mixture was placed in a small die and pressed to prepare KBr pellets. The resultant thin disk was mounted in the holder of the spectrophotometer. The obtained spectrum was interpreted and compared to the spectrum of working standards (Puri et al., 2021).

3.1.2. Differential scanning calorimetry (DSC) analysis

The DSC curves of pure xanthan gum, grafted xanthan gum, and acrylamide/xanthan gum/potassium persulphate were generated by a differential scanning calorimeter (Q10, TA System, USA) at a
heating rate of 10 °C/min from 25 to 300 °C. Accurately amount of sample was taken in a standard pan and placed at the sample stage (Inderbir et al., 2018; El Assimi et al., 2019).

3.1.3. Scanning electron microscopy (SEM)
Using double-sided adhesive tape, grafted xanthan gum samples were mounted onto the stubs and then coated with gold–paladium alloy (10 nm thickness) using a fine coat ion sputter. The samples were analyzed for external morphology under scanning electron microscopy (Model: JSM 5200, Japan) (Rana and Murthy, 2013).

3.2. Evaluation and characterization of buccal film

3.2.1. Drug content uniformity
Mucoadhesive films were cut into small sizes and dissolved in 10 ml of an isotonic phosphate buffer (pH 6.8) for 6 h under occasional shaking. The resultant solution was filtered through a 0.45 μm Whatman filter paper. After proper dilution, the amount of drug was analyzed using a UV-spectrophotometer (Shimadzu, India). Percentage drug content was calculated using the following equation (Al-Dhubiab et al., 2016; Nair et al., 2020).

\[
% \text{ Drug content} = \frac{\text{Experimental drug content} - \text{drug content}}{\text{drug content}} \times 100
\]

3.2.2. Swelling index
A film was weighed on a pre-weighed coverslip (W1). Then placed, the film was in a Petri dish, and 20 ml of pH 6.8 phosphate buffer was added. After every-five minutes, the coverslip was removed and weighed up to 30 min (W2). The difference in the weights gives the weight increase due to absorption of water and swelling of film. The following equation determines the swelling index (Muzib and Kumari, 2011).

\[
% SI = \left( \frac{W2 - W1}{W1} \right) \times 100
\]

where SI is the swelling index of the film, W1 is the initial weight and W2 is the weight of the swelled mucoadhesive film.

3.2.3. Folding endurance
A small film strip was folded at the same spot repeatedly until it was torn apart. The folding endurance was determined by the number of folds required to break the film. A film is considered acceptable to reveal good quality patch properties when a film shows more than 200 times folded until it is torn (Avachat et al., 2013).

3.2.4. Mucoadhesive strength
Mucoadhesive studies were determined using a mucoadhesion test device based on the principle of double beam physical balance with 3 % w/v mucin solution. The device comprises a base and two small arms at both ends. To one side of the arm, a holding clip was fixed to which we could attach the buccal film while the free end of the film was attached to another clip attached to a suspended weight system. The film was attached, and the weight was increased gradually until the required force was acquired to break the film. The weights at which the film gets detached or breaks are

| Batch code | % Grafting | %Grafting efficiency | % Conversion |
|------------|------------|----------------------|-------------|
| A1         | 71.4       | 71.4                 | 171.4       |
| A2         | 79.2       | 79.2                 | 179.2       |
| A3         | 83.2       | 83.2                 | 183.2       |
| A4         | 75.8       | 75.8                 | 175.8       |
| A5         | 206.4      | 103.2                | 153.2       |
| A6         | 212.6      | 70.86                | 104.2       |
| A7         | 217.4      | 54.35                | 79.35       |
| A8         | 168.6      | 84.3                 | 134.3       |
| A9         | 221.6      | 110.8                | 160.8       |
| A10        | 48.4       | 96.8                 | 296.8       |
| A11        | 150.4      | 75.2                 | 125.2       |

Fig. 1. Schematic presentation of preparation of acrylamide grafted xanthan gum.
taken as the mucoadhesive strength of the film (Shaikh et al., 2011).

3.2.5. In-vitro drug release studies of buccal film

A Franz diffusion cell with a receptor compartment capacity of 20 ml was used for in vitro studies. The drug-loaded film was applied to the drug release membrane, and the receptor compartment of the diffusion mobile was filled with phosphate buffer pH 6.8. The entire assembly was fixed on a magnetic stirrer, and the temperature was kept at 37.0 ± 0.2 °C. Sample was withdrawn at time interval of 0.08, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 hrs. and analyzed for the drug by using a UV spectrophotometer (Singh et al., 2008; Jain et al., 2021).

3.2.6. Drug release kinetic studies

The results obtained from in vitro release research were analyzed and fitted in different equations like Zero-order, First-order, Higuchi’s version and Korsmeyer-Peppas equation (Taleuzzaman et al., 2021).

Fig. 2. A- FTIR spectrum of xanthan gum, B- FTIR spectrum of Physical mixture of xanthan gum, acrylamide, potassium persulphate, C- FTIR spectrum of grafted xanthan gum.
4. Result and discussion

4.1. Influence of amount of acrylamide on synthesis of grafted xanthan gum

The higher percentage of grafted polymer was obtained after a 120-second irradiation time, which increased the acrylamide and potassium persulfate levels to optimal levels. In Table 1, batch code A9 has the highest percentage of grafting efficiency in which the amount of acrylamide was 1000 mg, and initiator potassium persulfate was 150 mg. However, after the desired limit, prolonged exposure to microwave radiation and a high acrylamide concentration can break the strength of polysaccharides and help more homo polymerization than grafted polymer.

**Fig. 3.** A- DSC of pure xanthan gum, B- DSC of physical mixture of xanthan gum, acrylamide and potassium persulphate, C- DSC of grafted xanthan gum.
4.2. FTIR analysis

The vibration peak of OH stretching of xanthan gum powder was exhibited at 3348.54 cm\(^{-1}\). The C=O stretching peak was found at 1730.21 and 1599.04 cm\(^{-1}\), representing the structure of acetate and pyruvate in the xanthan gum molecule. However, the C–N stretching band indicated at 1408 cm\(^{-1}\), as shown in Fig. 2(A). There are no interactions among all excipients. So, the excipients are compatible, as shown in Fig. 2(B). In the case of grafted xanthan gum, bands 1658 and 1600.97 cm\(^{-1}\) are indicated in the first amide group (C–O stretching) and second amide group (N–H bending) of the amide group of acrylamides Fig. 2 (C). The peak of 3344.68 cm\(^{-1}\) in grafted xanthan gum is credited to the overlap of the O–H stretching band and the amide group N–H stretching band.

4.3. DSC analysis

The DSC analysis of xanthan gum, a physical mixture of xanthan gum, acrylamide, and potassium persulphate, and grafted xanthan gum is shown in Fig. 3. The thermogram of pure xanthan gum displayed a broad exothermic at 182\(^\circ\)C, the physical mixture showed a sharp peak of ceric ammonium at 212\(^\circ\)C, and acrylamide showed a small peak near 65\(^\circ\)C. DSC of grafted xanthan gum showed endothermic peaks on 70\(^\circ\)C, 168\(^\circ\)C, indicated the acrylamide, potassium persulphate and xanthan gum receptively. But grafted xanthan gum showed an exothermic peak at 261\(^\circ\)C.

Table 2

| Formulation code | Grafted xanthan gum (mg) | HPMC (mg) | PEG 400 (mg) | Drug content (%) | Swelling index (%) | Folding endurance (No. of time) | Mucoadhesive strength (g) |
|------------------|--------------------------|-----------|--------------|------------------|-------------------|-----------------------------|--------------------------|
| G1               | 150                      | 300       | 200          | 94.95            | 31.05             | 219                         | 13.15                    |
| G2               | 100                      | 400       | 200          | 96.16            | 49.50             | 342                         | 24.48                    |
| G3               | 150                      | 400       | 300          | 91.5             | 34.50             | 264                         | 16.29                    |
| G4               | 100                      | 300       | 200          | 99.19            | 42.40             | 302                         | 20.68                    |
| G5               | 50                       | 300       | 200          | 87.04            | 63.50             | 364                         | 31.41                    |
| G6               | 100                      | 300       | 200          | 98.99            | 44.10             | 297                         | 21.52                    |
| G7               | 100                      | 300       | 200          | 96.88            | 44.60             | 290                         | 21.95                    |
| G8               | 100                      | 200       | 200          | 97.82            | 38.15             | 274                         | 18.92                    |
| G9               | 50                       | 400       | 300          | 84.96            | 66.00             | 406                         | 32.74                    |
| G10              | 100                      | 300       | 300          | 95.41            | 43.60             | 312                         | 21.44                    |
| G11              | 150                      | 300       | 200          | 93.39            | 21.50             | 176                         | 10.28                    |
| G12              | 100                      | 300       | 100          | 95.08            | 45.10             | 285                         | 22.61                    |
| G13              | 150                      | 400       | 100          | 92.19            | 36.25             | 246                         | 17.29                    |
| G14              | 100                      | 300       | 200          | 99.32            | 42.70             | 296                         | 20.92                    |
| G15              | 100                      | 300       | 200          | 98.88            | 43.63             | 309                         | 21.17                    |
| G16              | 150                      | 200       | 300          | 91.37            | 26.55             | 192                         | 12.92                    |
| G17*             | 100                      | 300       | 200          | 99.73            | 44.80             | 314                         | 22.18                    |
| G18              | 50                       | 400       | 100          | 85.5             | 70.50             | 381                         | 35.04                    |
| G19              | 50                       | 200       | 300          | 84.42            | 59.90             | 349                         | 29.26                    |
| G20              | 50                       | 200       | 100          | 87.01            | 58.95             | 326                         | 29.13                    |

Fig. 4. SEM image of grafted xanthan gum.
Fig. 5. Effect of factors on % Drug content (A), % Swelling index (B), Folding endurance (C), and Mucoadhesive strength (D) contour plot.
4.4. SEM analysis

SEM images of Acrylamide grafted xanthan gum were observed. The grafted gum appeared lumpy with undulant sharp breaking points, indicating that the chemically modified xanthan gum appeared needle and brittle. SEM studies of Acrylamide based grafted xanthan gum are shown in Fig. 4.

4.5. Formulation optimization by CCD

Grafted xanthan gum showed a good result at 50–150 mg concentration, whereas films of HPMC in a range of 200–400 mg showed an excellent film. Still, if the quantity of HPMC is increased above 400 mg, the film was challenging to peel, whereas plasticizers in the range of 100–300 mg showed good film properties. Various formulations were organized by incorporating polymer, plasticizer, and water using CCD and optimized preparation was created by using statistical screening. The twenty runs of the experiment were estimated for the drug content (%), swelling index (%), folding endurance (no. of time), and mucoadhesive strength (g) are listed in Table 2.

4.5.1. Effect of variable on percentage drug content

Drug content = 98.32 + 3.45 * A − 0.37 * B − 0.55 * C − 0.013 * A * B + 0.053 * A * C + 0.42 * B * C − 6.65 * A ^ 2 − 0.34 * B ^ 2 − 0.18 * C ^ 2.

where A is the amount of grafted xanthan gum, B is the amount of HPMC, and C is the amount of plasticizer. The Model F-price of 45.01 implies the model is significant p < 0.0001. The percentage of drug content in the film is also affected by the concentration of grafted gum, HPMC, and plasticizer followed a direct relationship. Contour plot Fig. 5 (A).

4.5.2. Effect of variable on swelling index

The following polynomial equation prevailed from the model for swelling index.

Swelling index = 43.89−16.90 * A + 5.17 * B + 0.17 * C + 0.63 * A * B + 0.86 * A * C + 3.11 * B * C + 3.11 * A ^ 2 − 0.34 * B ^ 2 + 0.18 * C ^ 2.

The above-given calculation indicates that A (concentration of grafted xanthan gum) has a negative effect, and that B (concentration of HPMC) positively influences the swelling index. An increase in grafted xanthan gum quantity may decrease the degree of swelling of the film, and the swelling index of films decreases with an increase in the concentration of HPMC. The individual influence of factor A (grafted xanthan gum) and factor B (HPMC) can be further understood with the support of the contour plot in Fig. 5 (B).

4.5.3. Effect of variable on folding endurance

Folding endurance = +01.82−72.90 * A + 32.20 * B + 10.80 * C + 3.75 * A * B − 1.75 * A * C + 0.50 * B * C − 11.05 * A ^ 2 + 5.45 * B ^ 2 − 3.55 * C ^ 2.

Table 3

| Formulation code | Predicated value | Actual value |
|------------------|------------------|--------------|
|                  | Drug content     | Swelling index | Folding endurance | Mucoadhesive strength | Drug content | Swelling index | Folding endurance | Mucoadhesive strength |
| S1               | 92.23            | 55.60         | 325              | 27.61                | 87.23        | 59.78         | 335              | 31.89                |
| S2               | 97.07            | 32.79         | 236              | 15.30                | 95.45        | 36.89         | 249              | 13.46                |
| S3               | 97.95            | 41.25         | 299              | 19.97                | 94.96        | 45.9          | 287              | 24.89                |
| S4               | 90.86            | 62.00         | 372              | 30.43                | 91.49        | 68.23         | 350              | 28.29                |
| S5               | 92.73            | 58.32         | 348              | 28.69                | 90.72        | 57.32         | 369              | 33.8                 |
| S6               | 93.23            | 55.61         | 340              | 27.17                | 94.93        | 51.43         | 325              | 24.09                |
| S7               | 94.48            | 35.25         | 244              | 16.44                | 96.28        | 35.9          | 216              | 18.25                |
| S8               | 97.18            | 46.02         | 302              | 22.69                | 98.03        | 45.85         | 312              | 21.67                |
| S9               | **90.05**        | **58.70**     | **362**          | **28.77**            | **92.92**    | **55.98**     | **357**          | **32.98**            |
| S10              | 92.23            | 55.60         | 325              | 27.61                | 87.23        | 59.78         | 335              | 31.89                |

Fig. 6. FTIR spectrum of optimized Film.
The folding endurance was found to be advanced with an increasing concentration of HPMC and PEG 400. Apart from it, folding endurance was found to be decreased while growing the concentration of grafted xanthan gum. All the patches showed the excellent value of folding endurance—contour plot Fig. 5 (C).

### 4.5.4. Effect of variable on mucoadhesive strength

\[
\text{Mucoadhesive strength} = +21.45 - 8.77 \times A + 2.53 \times B - 0.17 \times C + 0.12 \times A \times B + 0.48 \times A \times C - 0.76 \times B \times C + 0.76 \times A^2 + 0.18 \times B^2 + 0.50 \times C^2.
\]

From the above equation, xanthan gum (A) has a negative effect, whereas HPMC (B) has a positive influence on mucoadhesive strength. The positive sign showed a directly proportional influence, while a negative sign showed an inversely proportional influence on the mucoadhesive strength. Therefore, mucoadhesive strength increases on growing HPMC quantity, whereas it decreases by increasing grafted xanthan gum’s attention. Contour plot Fig. 5 (D).

The resultant actual experimental values obtained were compared with those predicted by the mathematical models generated. Formulation S9 was selected as an optimized formulation because it showed the lowest standard deviation between predicted and actual values compared to other formulations (Table 3).

### 4.6. FTIR analysis

In the FTIR spectrum after film preparation the main peaks from sumatriptan succinate indicated at respective wave numbers i.e. S=O stretching (1089.02 cm\(^{-1}\)), C—S stretching (674.81 cm\(^{-1}\)), N—H stretching (3316.52 cm\(^{-1}\)) and C—N stretching (1287.92 cm\(^{-1}\), 1251.89 cm\(^{-1}\)). The peak of 3344.68 cm\(^{-1}\) in grafted xanthan gum is credited to the overlap of O—H stretching band and N—H stretching band of amide group. However, the

![Fig. 7. A- Comparative In vitro release profile, B- Zero order graph of formulation S9, C- First order graph of formulation S9, D- Higuchi order graph of formulation S9, E- Korsmeyer peppas order graph of formulation S9.](image)
In vitro release profile of pure drug suspension and drug containing grafted film formulation (S9). (Mean ± SD, n = 3).

| Time (hrs) | % Drug release of S9 formulation | % Drug release of Pure drug suspension |
|-----------|----------------------------------|---------------------------------------|
| 0.08      | 1.15 ± 0.23                      | 14.16 ± 0.13                          |
| 0.25      | 6.57 ± 0.18                      | 33.81 ± 0.34                          |
| 0.5       | 14.37 ± 0.11                     | 49.73 ± 0.2                           |
| 0.75      | 20.83 ± 0.23                     | 63.38 ± 0.23                          |
| 1         | 27.16 ± 0.21                     | 85.99 ± 0.54                          |
| 2         | 34.82 ± 0.14                     | 99.32 ± 0.46                          |
| 3         | 43.47 ± 0.17                     | 99.13 ± 0.47                          |
| 4         | 51.07 ± 0.34                     | 12.34 ± 0.49                          |
| 5         | 54.87 ± 0.33                     | 12.74 ± 0.41                          |
| 6         | 56.23 ± 0.15                     | 11.43 ± 0.49                          |
| 7         | 61.06 ± 0.42                     | 11.38 ± 0.49                          |
| 8         | 64.54 ± 0.12                     | 11.46 ± 0.49                          |
| 10        | 67.63 ± 0.88                     | 11.33 ± 0.49                          |
| 12        | 71.49 ± 0.43                     | 11.47 ± 0.49                          |
| 24        | 77.12 ± 0.53                     | 11.34 ± 0.49                          |

C–N stretching band indicated at 1408 cm⁻¹. HPMC indicated the peak at 3387.11 cm⁻¹, indicating OH vibrational and stretching C–O at 1058 cm⁻¹ (Fig. 6).

4.7. In vitro release studies

In vitro dissolution is used to measure the amount of drug released into the system/medium at a given time. When compared to a pure drug suspension, a formulation containing drug-loaded grafted film demonstrated good sustained and controlled drug release characteristics. In the case of the S9 formulation, about 77.12% of the drug was released within 24 h, but initially, it showed burst release. In addition, in vitro release of pure drug suspension showed 99.32% drug release within 2 hr. (Table 4).

The calculated regression coefficients for zero order, first order, and Higuchi models were found to be 0.66, 0.805, 0.899 and 0.887, it was found that the in vitro drug release kinetics of S9 were best explained by Higuchi models as the plot showed the highest linearity. The value of R² found to be 0.898 highest for the Higuchi model indicates sustained release of the drug (Fig. 7).

5. Conclusion

Mucoadhesive films offer a good substitute way to deliver the drug and eliminate the chance of first-pass metabolism. Therefore, we can make a sustain release formulation of sumatRIPTIN succinate by using grafted copolymer. It can solve the problem and increase patient compliance. The resultant actual experimental values obtained were compared with those predicted by the mathematical models generated. S9 was chosen as an optimised formulation because it had the lowest standard deviation between predicted and actual values when compared to other formulations. In the case of the S9 formulation, approximately 77.12% of the drug was released within 24 h, but initially, it showed burst release. In addition, in vitro release of pure drug suspension showed 99.32% drug release within 2 hr. Formulation holding drug-loaded grafted film showed decent characteristics of sustained and controlled drug release compared to a pure drug suspension.

Our research can be used to deliver in the form of sustained release for different types of drugs which having problem like first-pass metabolism. This research can also be used in future for better patient compliance, sustained or regulated release of drugs.
Liechty, W.B., Kryscio, D.R., Slaughter, B.V., Peppas, N.A., 2010. Polymers for drug delivery systems. Annu. Rev. Chem. Biomol. Eng. 1, 149–173. https://doi.org/10.1146/annurev-chembioeng-073009-100847. PMID: 22432577; PMCID: PMC3438887.

Malviya, R., Sharma, P.K., Dubey, S.K., 2020. Microwave facilitated green synthesis and characterization of acrylamide grafted copolymer of Kheri (Acacia chundra) Gum Polysaccharide. Natl. Prod. J. 10 (4), 467–487.

Muheem, A., Shakeel, M.A., Anwar, M., Mallick, N., et al., 2016. A review on the strategies for oral delivery of proteins and peptides and their clinical perspectives. Saudi Pharm J. 24 (4), 413–428. https://doi.org/10.1016/j sữa.2014.06.004. Epub 2014 Jun 16. PMID: 27330372; PMCID: PMC4906063.

Mukherjee, A., Banerjee, S., Halder, G., 2018. Parametric optimization of delignification of rice straw through central composite design approach towards application in grafting. J. Adv. Res. 14, 11–23. https://doi.org/10.1016/j.jare.2018.05.004. PMID: 30023132; PMCID: PMC6046610.

Muzib, Y.I., Kumari, K.S., 2011. Mucoadhesive buccal films of glibenclamide: development and evaluation. Int J Pharm Investig. 1 (1), 42–47. https://doi.org/10.4103/2230-973X.67628. PMID: 23071919; PMCID: PMC3465111.

Nair, A.B., Al-Dhubiab, B.E., Shah, J., Jacob, S., Saraiya, V., et al., 2020. Mucoadhesive buccal film of almotriptan improved therapeutic delivery in rabbit model. Saudi Pharm. J. 28 (2), 201–209.

Negro, A., Koverech, A., Martelletti, P., 2018. Serotonin receptor agonists in the acute treatment of migraine: a review on their therapeutic potential. J. Pain Res. 11, 515–526. https://doi.org/10.2147/JPR.S132833.

Puri, V., Sharma, A., Kumar, P., Singh, L., Huanbutta, K., 2021. Synthesis and characterization of Thiolated Gum Ghatti as a novel excipient: development of compression-coated mucoadhesive tablets of domperidone. ACS Omega 24, 15844–15854. https://doi.org/10.1021/acsomega.1c01328.

Qureshi, M.A., Nishat, N., Jadoun, S., Ansari, M.Z., 2020. Polysaccharide based superabsorbent hydrogels and their methods of synthesis: a review. Carbohydr. Polym. Technol. Appl. 1, 100014.

Rana, P., Murthy, R.S.R., 2013. Formulation and evaluation of mucoadhesive buccal films impregnated with carvedilol nanosuspension: a potential approach for delivery of drugs having high first-pass metabolism. Drug Deliv. 20 (5), 224–235. https://doi.org/10.3109/10717544.2013.779331.

Salehi, S., Boddohi, S., 2017. New formulation and approach for mucoadhesive buccal film of rizatRIPTAN benzoate. Prog. Biomater. 6 (4), 175–187.

Semalty, M., Semalty, M., Nautyal, U., 2010. Formulation and evaluation of mucoadhesive buccal films of enalapril maleate. Indian J. Pharm. Sci. 72 (5), 571–575. https://doi.org/10.4103/0250-474X.78522. PMID: 21694987; PMCID: PMC3116300.

Shaikh, R., Raj Singh, T.R., Garland, M.J., Woolfson, A.D., Donnelly, R.F., 2011. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 3 (1), 89–100. https://doi.org/10.4103/0975-7406.76478. PMID: 21430958; PMCID: PMC3053525.

Singh, S., Jain, S., Muthu, M.S., Tiwari, S., Tilak, R., 2008. Preparation and evaluation of buccal bioadhesive films containing clotrimazole. AAPS PharmSciTech 9 (2), 660–667.

Steiner, T.J., Scher, A.J., Stewart, W.F., Kolodner, K., Liberman, J., Lipton, R.B., 2003. The prevalence and disability burden of adult migraine in England and their relationships to age, gender, and ethnicity. Cephalalgia 7, 519–527. https://doi.org/10.1046/j.1468-2982.2003.00568.x. PMID: 12950377.

Taleluzzaman, M., Sartaj, A., Gupta, D.K., Gilani, S.J., Mirza, M.A., 2021. Phytosomal gel of Manjistha extract (MJE) formulated and optimized with central composite design of Quality by Design (QbD). J. Dispers. Sci. Technol. https://doi.org/10.1080/01974262.2013.80568.x. PMID: 12950377.

Vega-Hernández, M.A., Cano-Díaz, G.S., Vivaldo-Lima, E., Rosas-Aburto, A., Hernández-Luna, M.G., Martínez, A., Palacios-Aquísira, J., Mohammadi, Y., Penlidis, A., 2021. A review on the synthesis, characterization, and modeling of polymer grafting. Processes 9 (2), 375.

Vetvik, K.G., MacGregor, E.A., 2017. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol. 16 (1), 76–87. https://doi.org/10.1016/S1474-4422(16)30293-9. Epub 2016 Nov 9 PMID: 27836433.