Evaluation of commercial arrowroot starch/CMC film for buccal drug delivery of glipizide

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Abstract

In the present work, commercial arrowroot starch (AR starch) has been successfully used as a base material with sodium salt of carboxy methyl cellulose (CMC) for buccal drug delivery system. Different ratio of CMC and AR starch has been prepared with constant ratio of drug. In our study, glipizide has been used as the drug for controlled drug delivery through buccal mucosa. Films were cast by solution casting method with glycerol as plasticizer. All the films were characterized for thickness, swelling index, moisture content, relative pH, drug content uniformity, compatibility of polymer and drug, surface morphology of films, muco adhesive property and in-vitro drug release study. Formulation F3 shows a residence time of 140 minutes with good mucoadhesive property, compatibility within polymers, drug content uniformity of $100 \pm 6.0\%$ and a controlled drug release among all the ratios.

Keywords: *arrowroot starch, buccal drug delivery, CMC, film, glipizide.*

1. Indroduction

The development of buccal drug delivery has been focused in recent years[1,2] due to the advantages like controlled drug delivery, compatibility, rapid termination, flexibility, comfort, ease in accessibility, most convenient, easy and painless administration[3,4,5]. First pass hepatic metabolism is avoided in buccal drug delivery system as it access directly into the systemic circulation through jugular vein which makes more bioavailability than gastrointestinal route of drug release[6]. Mucoadhesive polymers are widely used as the base material to carry the drug and adhere to the mucosal surface of the buccal cavity[7]. Mucoadhesion is a process in which mucous membrane and the polymer get adhered[8]. In buccal drug delivery system, drugs can be administered in many forms such as ointments, patches, tablets, gels and films, but films are widely used because of its long residence time, flexibility, thinness, comfort and patient's compliance[9].

Selection of suitable material is essential for the development of different drug dosage forms[10]. Many polymers such as polycarbophil, carbopol, hydroxy propyl methyl cellulose, hydroxy ethyl cellulose, alginate, sodium carboxymethyl cellulose, polyvinyl pyrrolidone and hydroxy propyl cellulose are widely used due to their mucoadhesion property, compatibility with drug, flexibility and film forming capacity[11-16]. The mechanism behind the interaction of mucus and mucoadhesive polymers results in physical entanglement, hydrogen bonding or Van-der-Waals attraction. The adhesion property mainly depends on the chemical groups present at the surface of the polymers such as hydroxyls, amines, amides and carboxyls[17-19] Cellulose derivatives are considered to be a promising material in terms of mucoadhesion property and hydrogen bonding ability with mucous membrane. It has been reported that carboxymethylcelullose has good mucoadhesive property than other cellulose derivatives. Since CMC is an anionic polymer it has the ability to form hydrogen bonding but other derivatives like hydroxypropylmethylcellulose, which is non-ionic neutral derivative has a moderate mucoadhesive property due to the absence of proton donating carboxyl groups which facilitates the formation of hydrogen bonds[20,21].

Starch is a natural biopolymer, which is widely available and low cost[22]. In drug delivery and tissue engineering starch have been widely used[23]. Starch films are usually brittle with more tackiness. Starch can be used as oral films when it is suitably formulated with mucoadhesive polymers like CMC, HPMC, chitosan[24,25]. In the case of starch, amylose and amylopectin content are crucial for its mechanical and thermal properties. Higher the amylose content, more strong the film will be. Amylopectin contributes to the flexibility of the film. Generally all kind of starches have about 25% of amylose and 75% of amylopectin content. Strength of the film, processability, ability to resist water and thermal stability depends upon the molecular weight.

When starch and CMC is blended it leads to improved mechanical properties in terms of increased tensile strength and decreased elongation at break[26,27]. CMC addition in starch increases the film forming properties of starch[28] and blending of starch and CMC results in clearer film without hazy appearance[29]. CMC/starch forms a biodegradable

film suitable for many applications such as edible film and coating, packaging and in some medical applications[26].

Glipizide is a second generation sulphonyl urea based drug which stimulates the β cells of pancreas to release insulin[30]. Glipizide is considered to be an antidiabetic drug with a biological half-life of 3 - 4 h, such a rapid absorbing drug will also have fast elimination rate[31,32]. Although glipizide is a widely consumed antidiabetic drug, it leads to gastrointestinal disturbance on chronic usage[33]. Therefore it is necessary to formulate a material which entraps glipizide and facilitates controlled and sustained drug release without affecting gastrointestinal track.

In this present study, commercially available Indian arrowroot starch, which is low cost, has been effectively used as a matrix material for buccal drug delivery system. Glipizide, an anti-diabetic drug is successfully incorporated in the film with carboxymethylcellulose and Indian arrowroot starch to evaluate the basic film property, drug delivery efficacy, stability of the film and mucoadhesion property for buccal film, in vitro residence time and in vitro drug release.

2. Experimental

2.1 Materials

Sodium salt of carboxymethylcellulose with medium viscosity was purchased from Sigma Aldrich, Arrowroot starch (curcuma angustifolia) was purchased from local market in Chennai (harvested between March-April 2017) and glycerol was purchased from Fischer Scientific. Double distilled water was used throughout the process. All the chemicals were used as purchased.

2.2 Amylose and amylopectin content of starch

Amylose and amylopectin content in the arrowroot starch sample was determined using standard iodine calorimetric method according to ISO 6647-2[34]. Percentage of amylose and amylopectin content was found to be 46.8% and 53.2% respectively.

2.3 Preparation of drug loaded CMC/AR starch film

Starch and CMC blends were formed with different weight ratios such as 100:0, 10:90, 30:70, 50:50, 70:30, 90:10 and 0:100 wt%. Starch was gelatinized with 30g of DI water at 90 °C for 15 minutes using magnetic stirrer with 300 rpm. CMC was dissolved in 100g of water and made to stir for 2 hours to form a homogeneous solution. Gelatinized starch solution was cooled to room temperature and was mixed with CMC solution and stirred for another

10 minutes after adding 0.5g of glycerol as the plasticizer. The above mixture was cast by solution casting method in a petri dish dried at 40 °C overnight in hot air oven. Different formulation of polymer and drug is given in the Table 1.

2.4 Film thickness and weight measurement

The films of blend and the plain CMC and starch were cut into 2cm × 2cm dimension and each formulation was weighed accurately with three specimens in each sample with the digital balance. The film thickness was measured using the (model Baker 10mm) dial thickness gauge K130/3, at minimum five different points[9].

2.5 Surface pH of films

Surface pH of the film was determined by preparing a film specimen of a dimension 2cm × 2cm and kept in the petri dish by wetting the film with 0.5ml of water and allowed to swell for 2 hours at room temperature, surface pH of the film was determined using pH paper. Acid or alkaline pH of the film may cause irritation to the mucosa therefore it is necessary to maintain the pH of the film around 7[35].

2.6 Swelling index

The swelling properties of blended films were measured by percentage swelling index. The film was cut into 2cm × 2cm dimension and its weight was measured accurately and denoted as W_1. Then the film was placed in the petri dish containing 5 ml of phosphate buffer solution with a pH of 6.8. The swollen film was removed from the petri dish carefully and was wiped with filter paper to remove the excess solvent from the film[1]. The weight of the film was weighed and denoted as W_2.

Swelling index was calculated by using the following Equation 1:

$$\%Swelling = \frac{W2 - W1}{W1} x100 \qquad (1)$$

Where, W_1 = initial weight of the film.

W_2 = weight of the swelled film.

2.7 Folding endurance

Folding endurance of the film was measured quantitatively by repeatedly folding a small strip with a dimension of 4cm × 1cm at 180° plane at the same place until it break or folded 300 times without breaking. The number of times film was folded without breaking is calculated and considered to be the measure of folding endurance[5].

Table 1. Formulation of AR starch/CMC blend system.

Ratio	CMC	Starch	Plasticizer	Drug	Formulation
100:0	4.00g	0.00g	0.5g	0.5g	PC
90:10	3.60g	0.40g	0.5g	0.5g	F1
70:30	2.80g	1.20g	0.5g	0.5g	F2
50:50	2.00g	2.00g	0.5g	0.5g	F3
30:70	1.20g	2.80g	0.5g	0.5g	F4
10:90	0.40g	3.60g	0.5g	0.5g	F5
0:100	0.00g	4.00g	0.5g	0.5g	PS

2.8 Moisture content

The amount of moisture present in the film samples can be determined by simple weight measurement. 2cm × 2cm dimension of each samples were cut and weighed as the initial weight (W_1). Then the samples were heated to 100 °C for nearly 2 hours to attain constant weight and it is considered as the final weight (W_2) of the sample. The percentage weight difference between W_1 and W_2 are the moisture content present in the film[36].

2.9 Drug content uniformity

The drug content uniformity was measured by taking three specimens from each sample with a dimension of 2cm × 2cm and dissolved in 100mL of phosphate buffer solution with a pH of 6.8 and was continuously stirred for 6 – 8 hours. The solution was filtered and diluted suitably and the drug content was measured in Varian Cary 50 UV spectrophotometer at an absorbance of 276nm[37]. Drug content uniformity is measured by the following equation-

Drug Content uniformity = experimental drug loading/ theoretical drug loading × 100.

2.10 Drug – polymer compatibility study

Drug and polymer interaction can be determined by using ATR-FTIR. The different formulation of blended film with drug content was analysed with the help of Attenuated total reflectance Fourier transform infrared spectroscopy of the model Bruker tensor 27 FTIR spectrometer (Bruker, Billerica, MA, USA) at a resolution of $4cm^{-1}$ over the wave number region of $4000 – 400cm^{-1}$ [15].

2.11 Mucoadhesive property

Mucoadhesion of polymer is important in buccal drug delivery system because it increases the residence time of the drug in the buccal cavity[38]. The buccal mucosa of goat was taken in phosphate buffer solution of pH 6.8 and the polymer film was adhered on to the surface of mucosa, buccal mucosa and the film was taped in a glass substrate within the beaker containing phosphate buffer and allowed to stir at an RPM of 200 at 37 °C using magnetic stirrer. Time taken by the film to detach from the mucosa is considered as the residence time and how long it attached to the mucosa gives the mucoadhesion property of the film[36].

2.12 Surface morphology studies

Surface morphology and the presence of drug in the polymer film were studied by scanning electron microscopy using the model Hitachi S3400-N (Tokyo, Japan). All the films were gold coated using sputter coater. Films were analysed at an accelerating voltage of 20.0 kV and at a resolution of 400μm.

2.13 In vitro drug release study

In vitro drug release study was performed by adhering the polymer film in the side walls of the beaker which contains phosphate buffer solution with a pH of 6.8, at a temperature of 37 °C. Assume that the drug releases from the film from one side only. Beaker was stirred gently in a magnetic stirrer and the buffer solution was sampled periodically in Varian Cary 50 UV spectrophotometer at 276nm to find the concentration of drug present in the sample. Solution withdrawn from the beaker was then replaced with the exact volume at each sampling[39].

3. Results and Discussion

3.1 Film thickness and weight measurement

Uniformity in film thickness is necessary because it is directly related to drug concentration and mucoadhesive property of the polymer. Plasticizer used in the formulation will affect the thickness of the film and sometimes even the polymer itself will increase the thickness of the film (polyvinylpyrrolidone). An ideal film for buccal drug delivery system should have an optimum thickness of around 0.05 to 1.0 mm[36,40]. Film thickness was measured at minimum five different points and mean standard deviation values has been calculated and is presented in Table.2. All films have a random thickness in the range of 0.22 – 0.32 mm irrespective of the ratio of polymers present in the film; it shows that polymer does not influence much in the thickness. PC, formulation measured a minimum thickness of 0.22mm and F1 shows a maximum thickness of 0.32mm.

Weight measurements are generally done to ensure the uniform drug loading in the sample. Weight variations should not be larger as it renders inconsistency of drug loading[41]. Weight of the film is measured using digital balance and mentioned in the Table 2. Weight of the film also varies according to the moisture content present in the samples. Formulation F2 and F3 has a maximum film weight of 5.32 and 5.30g respectively, this may be due to the presence of more moisture content in the film such as 24.6 ± 1.25% and 23.1± 0.72% for F2 and F3 respectively.

3.2 Swelling ratio

Swelling characteristic is one of the important factors which affect the mucoadhesive property of the polymers. The optimum amount of water uptake by the polymer film is essential in exhibiting mucoadhesive property[7]. Generally hydrophilic polymers will absorb more water and undergo dissolution by making pores, formation of such pores facilitates the diffusion of drug from the film[42]. Swelling is affected by structure of the polymer, temperature, swelling medium, ionic strength, pH of the environment and cross linking of network[43]. Polymers which have the ability to form hydrogen bonds can form a strong network structure, therefore penetration of water becomes difficult, and such hydrogen bond can be between polymer - polymer, polymer - plasticizer and polymer- drug[44,45]. In hydrophilic polymers like CMC swelling is mainly due to hydrogen bond formation between water and the polymer chain.

Starch contains readily available hydroxyl groups which attributes to the interaction of water and polymer chain for substantial hydrophilicity. Glycerol will also interact with polymer and water molecules, giving rise to hydrogen bonds and increase in swelling percentage[46]. In the present study constant amount of plasticizer and drug were used in all systems so, the interaction between drug - water and plasticizer - water does not influence much in swelling. PC formulation contain CMC, plasticizer and

Table 2. Physical properties of AR starch/CMC blend system.

Formulation	Thickness (mm)	Swelling (%)	Moisture (g)	Surface pH	Film weight (g)	Drug content Uniformity (%)	Folding Endurance (No)
PC	0.22± 0.01	dissolved	2.90± 0.05	6.9 ± 0.05	4.86± 0.05	102±1.5%	289 ± 1.4
F1	0.32± 0.02	487 ± 1.7	3.90± 0.05	6.4 ± 0.05	4.93± 0.06	104± 2.6%	302 ± 1.4
F2	0.23± 0.01	455 ± 1.7	24.6± 1.25	6.6 ± 0.08	5.31± 0.05	102± 5.5%	315 ± 2.3
F3	0.24± 0.01	433 ± 1.0	23.1± 0.72	6.7 ± 0.03	5.29± 0.03	100± 6.0%	294 ± 2.9
F4	0.28± 0.05	418 ± 2.3	15.0± 0.58	6.8 ± 0.10	5.09± 0.03	102± 5.2%	274 ± 3.0
F5	0.27± 0.03	408 ± 2.4	12.1± 0.44	6.6 ± 0.05	5.07± 0.05	100±10.2%	267 ± 1.4
PS	0.25± 0.51	355 ± 2.8	11.1± 0.72	6.9 ± 0.05	4.97± 0.05	104± 7.3%	252 ± 1.4

drug, it swells faster and dissolve completely in the buffer solution of pH 6.8 because the polymer interacts more with water than drug and plasticizer. In PS formulation (355 ± 2.8), which has AR starch, drug and plasticizer, has a considerable swelling percentage due to the interaction of AR starch with plasticizer and drug, therefore starch is not able to interact more with water to form hydrogen bond and does not dissolve so it swells in the presence of water. On increasing the percentage of AR starch in CMC, there is a gradual increase in swelling percentage in the formulations F1(487 ± 1.7), F2 (455 ± 1.7) and F3 (433 ± 1.0), this may be due to the synergistic interaction of CMC and AR starch with water in the film. In F4 (418 ± 2.3) and F5 (408 ± 2.4) swelling percentage tend to decrease as the less interacting AR starch has increased more (Table 2).

3.3 pH of the film

pH of the film is crucial in drug delivery system because the film should be compatible with the pH of the mucus surface which involved in absorbing the drug. pH is one of the factor which affects the mucoadhesion property of the polymer and therefore, optimum pH is necessary for required mucoadhesion[11,18]. pH of all the films are found to be in the range of saliva pH (6.5 - 6.8) and therefore it does not cause irritation at the place of administration[47]. pH of the film samples are given in the table.2.

3.4 Drug content uniformity

Drug content uniformity is important because it ensures that the drug is uniformly distributed throughout the film. The limit of drug content uniformity is likely to be between 85 – 115%[48]. Drug content for all the samples was found to be between 100 to 105(table.2).

3.5 Moisture content

Moisture content is essentially important as it helps in initial adhesion to the mucosa membrane. Optimum amount of moisture is needed to adhere the film to the mucosa membrane and excess moisture leads to tackiness in the film which leads to poor aesthetic appearance and difficulty in handling. CMC has more crystalline region than amorphous region in its molecular alignment. Therefore, it absorbs less moisture from the environment which appears in Formulation PC (CMC with drug) with least moisture content of 2.9 ± 0.05[16]. AR starch after gelatinization becomes more amorphous and has porous structure and absorbs more moisture compared to CMC which is exhibited in the formulation PS (AR starch with drug) with 11.1 ± 0.72 of moisture content[49]. Formulation F1 (3.9± 0.05), F2 (24.6 ± 1.25) and F3 (23.1± 0.72) shows a synergistic effect with the increased percentage of moisture with the gradual increment in the percentage of AR starch. Percentage of moisture present in the film samples was given in the Table 2.

3.6 Folding endurance

Folding endurance value is expressed in terms of number of times the film is folded without breaking. Folding endurance value indirectly gives the mechanical property of the film, higher the folding endurance value, higher is the flexibility of the film[50]. The synergistic effect of CMC and AR starch shows an increase in the flexibility of the film in the Formulation F1 and F2 with an increased folding endurance value of 302 and 315 respectively.

3.7 Drug – polymer compatibility study

Compatibility between polymer and the drug is studied through FTIR. The FTIR spectrum of pure glipizide drug is shown in the Figure 1A. A vibrational stretch at 3340cm⁻¹ is attributed to the N-H bond present in the drug; similarly 2918cm⁻¹, 1688cm⁻¹, 1651cm⁻¹ and 1529 cm⁻¹ are corresponding to C-H stretching vibration, C=O, C=N and N-H bending vibrations respectively[51] are observed. In Figure 1B, spectra of AR starch, CMC, and AR starch/CMC with drug are shown. AR starch film shows a stretching vibration at 3283cm⁻¹ due to the presence of hydroxyl group in AR starch as well as plasticizer (glycerol), 2928cm⁻¹ attributes to the presence of C-H in the system. Peaks at 1015cm⁻¹ and 854cm⁻¹ are corresponding to the C-O-C stretching and bending vibrations present in AR starch respectively[52].

CMC film shows a stretching vibration of hydroxyl group at 3276cm⁻¹ and presence of C-H bond shows a characteristic peak at 2923cm⁻¹. Vibrational stretching present at 1589cm⁻¹ attributes to the COO⁻ (carboxyl) group. A vibrational stretch at 1029cm⁻¹ attributes to the presence of C-O-C group in the film[53]. The blend film (starch-CMC with drug) shows no new characteristic peak in the spectrum, which means that CMC, AR starch and glipizide drug are compatible without forming bonds between them. Blend film shows a broad peak between 3800 and 3000cm⁻¹ due to the presence of hydroxyl group in AR starch, CMC, plasticizer and the stretching vibration of
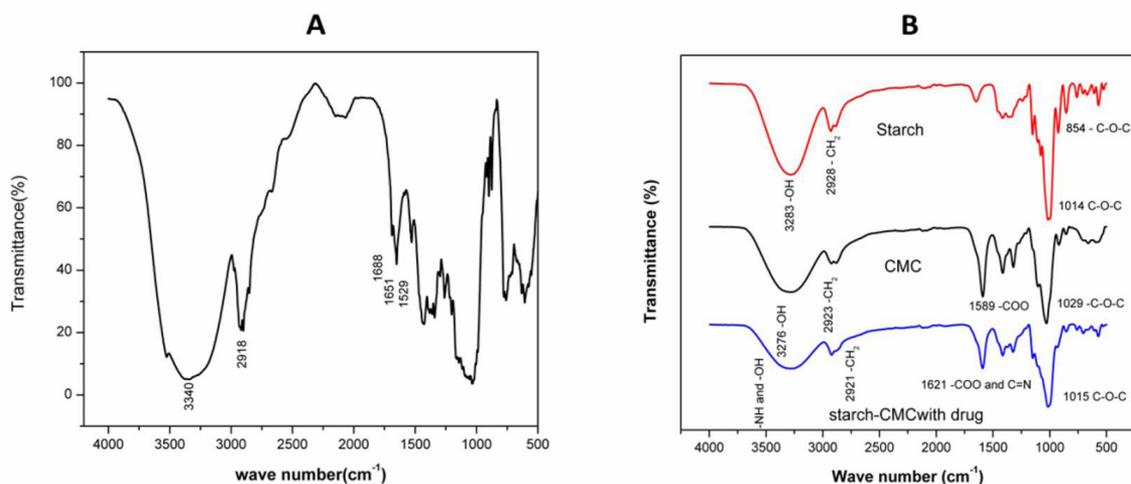
Figure 1. FTIR spectrum of glipizide (A), FTIR of starch, CMC and Starch-CMC and drug (B).
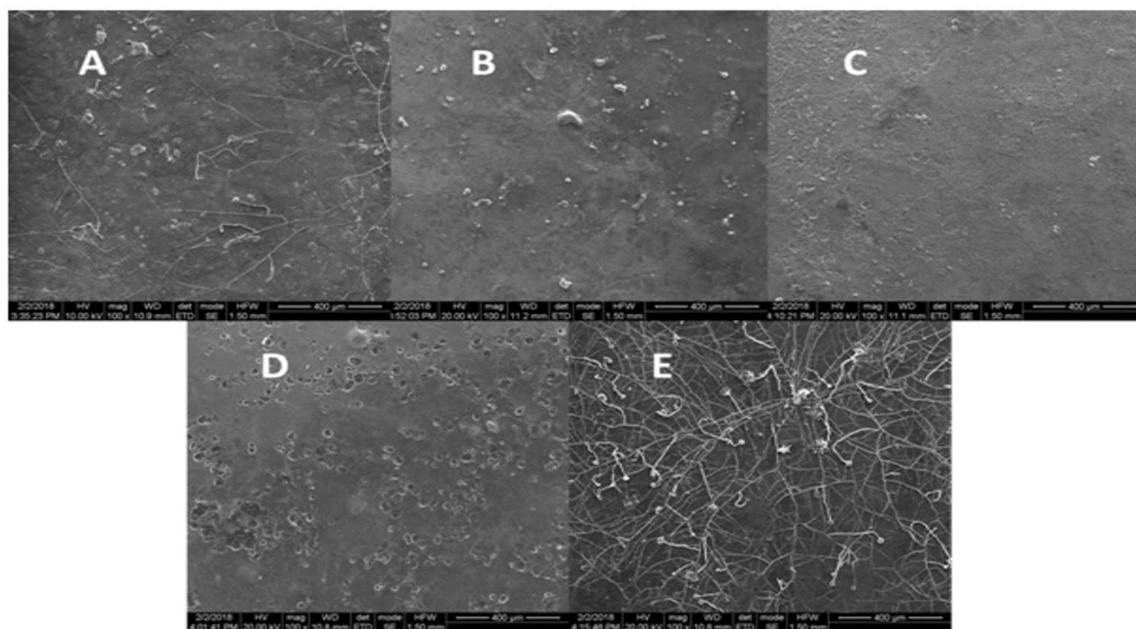

Figure 2. SEM image of different formulations F1(A), F2(B), F3(C), F4(D), F5(E).

N-H group present in glipizide drug also overlaps to obtain a broad peak. Peak at 2921cm^{-1} attributes to the C-H present in AR starch, CMC and the drug. Vibrational stretching at 1621cm^{-1} is corresponding to the overlap of C=N present in the drug and COO$^-$ group present in CMC. C-O-C stretching vibration in the spectrum is shown at 1015cm^{-1} due to the presence of AR starch and CMC. All peaks appear in the blend of AR starch – CMC with glipizide drug with minor shift in the corresponding peak values.

3.8 Scanning electron microscopy

Scanning electron microscopy is a useful tool to analyse the surface morphology and compatibility of the blend system. It is also useful in studying the dispersion of drug present in the blend composition. Formulation of F1(Figure 2A) and F5(Figure 2E) shows a brittle morphology in the image attributing to the lack of plasticizer and insufficient amount of AR

and CMC in F1 and F5 respectively, but the presence of drug was found to be homogenous in both the images. Figure 2B belongs to formulation F2, showing some agglomeration of drug in the surface but without any appearance of crack which may be due to the optimum percentage of plasticizer and adequate proportion of CMC and AR starch in the blend. Figure 2D also shows some agglomeration in the surface which belongs to F4 formulation. Figure 2C has optimum ratio of plasticizer, blend proportion and dispersion of drug is also homogenous which can be shown as smooth surface
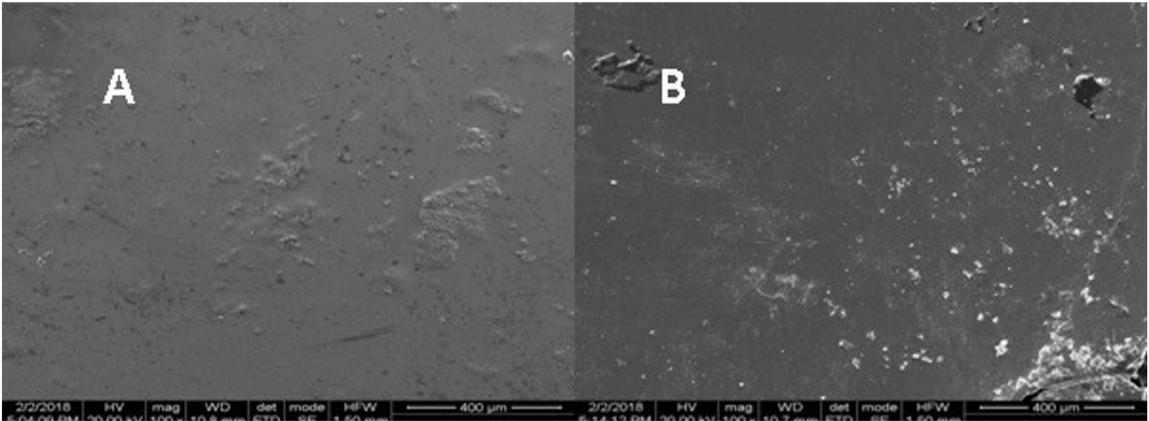
Figure 3. SEM image of Plain CMC with drug (A) and Plain AR starch with drug (B).
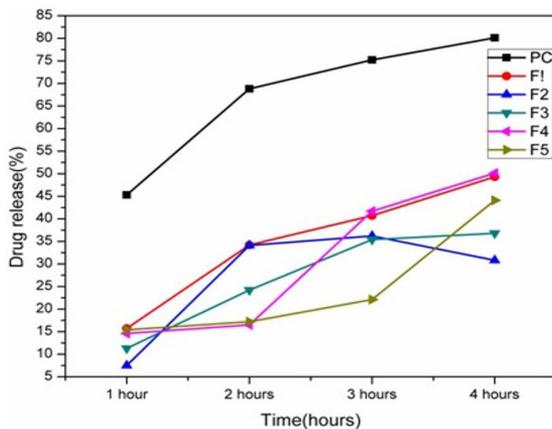

Figure 4. In-vitro drug release profile.

in the image, therefore F3 is considered as the optimum composition of polymer as well as the drug. Formulation PC and PS also shows some agglomeration of drug in the system which is shown in the Figure 3A and B.

3.9 Mucoadhesive property

Residence time of a film and mucoadhesive property is directly related to each other. In-vitro residence time of film in buccal mucosa of goat was examined and determined experimentally in minutes. F3 was found to have longest residence time of 140 ± 3 minutes and F5 has a least residence time of 30 ± 2 minutes. All the blend systems found to have mucoadhesive property with the mucosa membrane but the residence time differs between them according to the wt% of polymer present in the system. CMC was reported to be a mucoadhesive polymer by many research groups[12,54,55] therefore blend formulation with high proportion of CMC results in good mucoadhesive property. F1 and F2 initially swell faster when adhered to the surface of mucosa and dissolved within 80 ± 3 and 90 ± 3 minutes respectively. This may be due to the increased wt% of hydrophilic CMC present in the system. At the same time F4 and F5 loosen the bond strength from the mucosa membrane within 40 ± 2 and 30 ± 2 minutes

respectively because F4 and F5 has less proportion of CMC so the mucoadhesion property was low in those formulations. PS (AR starch with drug) has a residence time of less than 15 minutes, due to least mucoadhesive property of AR starch. F3 was found to have good mucoadhesive property and its residence time was 140 ± 3 minutes without dissolving in the buffer medium which attributes that F3 has an optimum composition of CMC and AR starch (50:50) as a mucoadhesive film.

3.10 In vitro drug release study

In-vitro drug release study was performed for 4 hours. Figure 4 demonstrates the drug release profile of different formulations. CMC has more affinity towards water than drug therefore it dissolves soon and releases the drug rapidly. This is also attributed in the swelling percentage of PC(dissolve). Formulation F1 (90:10) and F2 (70:30) shows a random release of drug which may be due to the presence of higher CMC ratio and non-uniform distribution of drug in the film and it is also confirmed by SEM image showing agglomeration and non-uniformity in the surface. PS has good interaction with CMC, drug, plasticizer, which helps in entrapping drug for sustained release. But, drug release percentage was unable to study for PS, as it adhered to the side walls of the beaker due to least mucoadhesive property. All blend system shows mucoadhesive property and controlled drug release due to the synergistic effect of PC and PS. From the graph it implies that F3 (50:50) shows a sustained drug release at each hour compared to that of all formulations. So, F3 can be considered as an optimum formulation of the blend system with respect to drug release profile and SEM image also supports by homogenous, uniform and smooth surface (Figure 2C). F4 and F5 exhibit a random release of drug similar to F1 and F2 showing that the drug is non-uniformly distributed in the film.

4. Conclusion

In the present work, drug release through gastrointestinal route has been avoided and buccal route has been suggested because glipizide leads to gastrointestinal disturbance. In order to increase the residence time without losing the

mucoadhesive property of CMC, AR starch is successfully blended with the constant ratio of antidiabetic drug, glipizide. Drug content uniformity of the films was found to be between 100 to 105%. FTIR shows the compatibility between drug and the polymer materials. The smooth surface of the films by SEM also supports the compatibility of polymer and drug. Formulation F3 (50:50) was found to have suitable swelling ratio, smooth surface morphology, good muco- adhesive property and sustained in-vitro drug release profile. Therefore, the blend of commercially available, low cost Indian arrowroot starch and CMC can be used as buccal film for drug delivery system with suitable drug.

5. Acknowledgements

6. References

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