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Bioadhesive Buccal Tablets of Aminophylline by Direct Compression Method

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Abstract
Buccal administration of drugs which exhibit a low oral bioavailability is a useful method to achieve higher bioavailability. The objective of present research work is to design and evaluate the prolong release bioadhesive buccal tablet of Aminophylline with goal to increase the bioavalability, reduce dosing frequency and improve patient compliance. Aminophylline is ethylenediamine salt of theophylline. Buccal tablets of aminophylline were prepared by direct compression using different bioadhesive polymers such as HPMC K4M and Carbopol 934-P. The prepared tablets were subjected to post friability, Hardness thickness, weight variation, drug content and swelling index, bioadhesive strength, *In-vitro* drug release.
Keywords: Aminophylline, HPMC, direct compression method, Swelling index, *in-vitro* drug release.

1. Introduction

Sublingual tablet and chewing gum are widely used systems but upon their administration a large proportion of the administered dose can be swallowed before being absorbed (Benowitz & Savanapridi 1987). It is proposed that a sustained release bioadhesive tablet can help to avoid this undesirable effect and also exhibit a longer duration of action. Buccal delivery of drug, as an alternative to the oral route of drug administration, is a subject of growing interest because of its numerous advantages such as good accessibility, robustness of epithelium, facile removal of dosage form in case of need, relatively low enzymatic activity, prevent drug degradation in gastrointestinal tract and avoid hepatic first-pass metabolismIn the last decade considerable interest has been focused on buccal drug delivery systems(Burgalassi & Rassing 1996, Ghosh & Pfister 2005, Bruschi & Freitas 2005, Madhav & Singh 2009) using the oral mucosal cavity as an attractive administration route. Several advantages (Mizrahi & Domb 2008) such as relative permeability, robustness and short recovery after stress or damage are related to mucous membrane. However, oral mucosa has been considered advantageous to the oral route because they bypass the hepatic first-pass effect and pre-systemic metabolism into the gastrointestinal track. Furthermore, drug absorption can be discontinued in the case of toxic effects by discharging the formulation from the buccal cavity (Miller & Johnston 2005). Bioadhesive formulations have been developed to enhance the bioavailability (Wong & Peh 1999, Choi & Kim2000) of drugs that undergo substantial first-pass hepatic effect and to control the drug release to a constant rate (Choi & Kim 2000). Aminophylline is ethylenediamine salt of theophylline. Theophylline stimulates the Central Nervous Systeme, skeletal muscles and cardiac muscle. It also relaxes certain smooth muscles in the bronchi through PDE3 inhibition, produces diuresis, and causes an increase in gastric secretion.

2. Materials and Method

2.1. Materials

Aminophylline was received as gift sample from Sandoz Pharma Ltd, Mumbai. Hydroxypropyl methylcellulose (HPMC K-4M) was obtained from Loba chemicals, Mumbai and Carbopol 934-P and Mannitol was obtained from S.D. Fine Chemicals, Mumbai. Magnesium stearate was obtained Signet Chemicals, Mumbai, India. All other ingredients were further used without purification of analytical grade.

2.2 Experimental Methods

2.2.1 Compatibility Studies

2.2.1.1 FTIR Studies

The drug-excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infrared spectra of pure drug and mixture of drug and excipients were recorded. A base line correction was made using dried potassium bromide and then the spectra of the drug mixture, drug polymer mixture, formulation mixture and potassium bromide were recorded on FTIR.

2.2.1.2 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed using Schimazdu DSC 60 instrument. The samples were hermatically sealed in aluminium pans and heated over the temperature range 35 ^{0}C to 300 ^{0}C with heating rate of 10 ^{0}C/min. The inert atmosphere was provided by purging nitrogen gas flowing at 10 ml/min.

2.2.2 Formulation of bioadhesive buccal tablets

Buccal tablets containing aminophylline were prepared by direct compression method. The ingredients of the core layer were weighed accurately and mixed by trituration in a glass mortar and pestle for 15 minutes. All the ingredients were screened through the sieve no. 100. The above mixture was then compressed using 8 mm punch on 8 stages rotary tablet compression machine. In order to obtain constant tablet weight the Mannitol was added as filler excipient in the core layer. After compression of tablets, the upper punch was removed carefully without disturbing the set up and mixed ingredients.

2.2.3 Evaluation of bioadhesive buccal tablets

2.2.3.1 Weight Variation

Eight tablets from each formulation (F1 to F8) were weighed using an electronic balance and the average weight was calculated. The weight variation test for all the formulations complies with the IP limit (± 10%).

2.2.3.2 Hardness

Tablets required certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation. (Singh & Ahuja, 2002).

2.2.3.3 Friability

Ten tablets were weighed (Wo) and placed in the Roche friabilator and was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were dedusted and weighed again (W). The percentage friability was measured using the following formula. (Madgulkar & Pokharkar 2008).

$$\text{Percentage friability} = 1 - (W/Wo) \times 100$$

Where, Wo = Initial weight of tablet

W = Weight of tablets after revolution

2.2.3.4 Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a vernier caliper. The average values were calculated.

2.2.3.5 Determination of tablet swelling index

Tablets were weighed (W1) and placed individually in Petri dishes containing 20 ml of distilled water. The dishes were stored at room temperature. After 30, 60, 120 and 240 min, the discs were removed and the excess water on their surface was carefully removed using filter paper. The swollen discs were reweighed (W2) and the index of swelling was calculated by the following formula: (Boyapally & Douroumis 2010).

$$\text{Swelling index} = W2 - W1/\ W1$$

2.2.3.6 Surface pH Study

The tablet is allowed to swell by keeping it in contact with 1 mL of phosphate buffer (pH 6.8) for 2 hours at room temperature. The pH is determined by bringing the electrode into contact with the tablet surface and allowing to equilibrating for 1 minute .The experiment was repeated thrice and data. (Owens& Sakr 2005).

2.2.3.7 Bioadhesion strength

The *in-vitro* bioadhesive strength study was done and the results are shown in the Table 03. On the modified physical balance and measure the force (N) required detaching of the tablet. The bioadhesion characteristics were affected by concentration of the bioadhesive polymers. Increase in concentration of the polymer increases bioadhesive strength of formulation.

2.2.3.8 Drug content

The drug content is determined for obtaining the amount and percentage of drug retained in the dosage unit of particular tablet lot. It is done by assay on application of suitable analytical procedure that is developed initially meant to give the stated amount of percentage of active drug that the dosage unit comprises. The percentage of drug content should comply with the specification of stated amounts in the individual monographs in the pharmacopoeias by any suitable analytical procedure. The drug that belongs to reported in the monographs to have contains not less than 98.5 % and not more than the equivalent of 101.0 % as per USP of stated amount of the drug.

2.2.3.9 *In vitro* drug release studies

USP dissolution apparatus with paddle was used for the in vitro dissolution studies of bioadhesive tablets with a simple modification. A two-end open glass cylinder of 3 cm diameter and 10 cm length was taken. The prepared bioadhesive tablet was placed by applying a moderate pressure this was then tied to one end of the cylinder, taking care to place the tablet inside the cylinder. This cylinder was then placed on the surface of dissolution medium (900 ml of phosphate buffer pH 6.8) maintained at 37 ± 0.5 ◦C at 100 rpm for 8 h. At specified time intervals, 5 ml samples were withdrawn and immediately replaced with an equal quantity of fresh buffer. The samples were filtered and analysed after appropriate dilution by UV spectrophotometry at 271 nm.

2.2.4 Stability of buccal tablets

Stability of buccal tablets was performed for optimized formulation in normal human saliva. Human saliva was

collected from humans and filtered through filter paper. Buccal tablets were placed in distinct petridishes containing 5 mL of human saliva and placed in a temperature-controlled oven for 6 hr at 37°C ± 0.2°C. At regular time intervals (0, 2, 4, and 6 hr), the buccal tablets were examined for change in colour, surface area and integrity. The experiment was repeated in triplicate (n = 3). (Bhanja & Das2010).

3.0 Result and Discussion:

3.1 Compatibility studies

3.1.1 FTIR Studies

The incompatibility between the drug and excipients were studied by FTIR spectroscopy. The results indicate that there was no chemical incompatibility between drug and excipients used in the formulation. (Figure 1)

3.1.2 Differential Scanning Calorimetry (DSC)

Thermogram of Aminophylline HPMC, carbopol gave only one endotherm peaks, which are close to their melting temperature indicating that mixing of the Aminophylline in the excipients. The physical mixture formulation showed peak with reduced intensity suggests decrease in crystallinity of pure Aminophylline. (Figure 2)

3.2 Evaluation of bioadhesive buccal tablet

3.2.1 Weight variation test

Tablets were randomly selected from each batch and individually weighed using digital balance. The weight variation test was conducted for each batch of all formulations F1 to F8 as per I.P and the results are shown in (Table 2). The weight variation test for all the formulations complies with the IP limit (± 10%).

3.2.2 Hardness test

The adequate tablet hardness is necessary requisite for consumer acceptance and handling. The measured hardness of the tablets of each batch of all formulations i.e. F1 to F8 were ranged about 6.0 to 8 .0 Kg/cm2 and the results are shown in (Table 2).

3.2.3 Friability test

The friability test for all the formulations were done as per the standard procedure I.P. The results of the friability test were tabulated in (Table 2). The data indicates that the friability was less than 1% in all formulations ensuring that the tablets were mechanically stable. (Velmurugan & Vinushitha2010).

3.2.4 Thickness

The thickness of the tablets was found to be almost uniform in all formulations F1 to F8. The thickness was found to be in the range of 4.0 to 5.0 mm. None of the formulations (F1 to F8) showed a deviation. Hence, it is concluded that all the formulations complied the thickness and the results are shown in (Table 2).

3.2.5 Swelling Index

Swelling index of all the formulations F1 to F8 was found to be 22.6 to 71.1, which is matched with reported values. Hence, it was shown in. (Table 3)

3.2.6 Surface pH

Surface pH of all the formulations F1 to F8 was found to be 6.2 to 6.8, which is well within the limit of acceptable salivary pH range of 6.2 to 6.9. Hence, it was concluded that all formulations could not produce any local irritation to the mucosal surface. (Table 3)

3.2.7 Bioadhesive strength

The *in vitro* bioadhesive strength study was performed and the results are shown in the (Table 3). On the modified physical balance and measure the force (N) required detaching the tablet. The bioadhesion characteristics were affected by the concentration of the bioadhesive polymers. Increase in concentration of polymer increases bioadhesive strength of formulation. The formulations (F1, F2, F3 & F4) with HPMCK4M and Mannitol showed the bioadhesive strengths of 29.5gm, 31.4gm, 34.5gm and 35.8gm respectively. The formulations (F5, F6, F7 & F8) with Carbopol 934p and Mannitol showed the bioadhesive strengths of, 27.6 gm., 30.5gm, 32.5gm and 34.1gm respectively. (Figure 5)

3.2.8 Drug content

The drug content of each batch of all the formulations (F1 to F8) was evaluated as per the standard protocol. The results indicate that the percentage of drug content was found to be 98.00% to 101.00%. Hence it is concluded that all the formulations are following acceptable limits as per Indian Pharmacopoeia i.e. ± 5%. (Table 2)

3.2.9 *In Vitro* release studies

All the prepared buccal tablets were evaluated for the % cumulative drug release and drug release profile was shown in (figure 4). The formulation F4 release the drug near about 98.96 % at the end of 8 hrs this indicate that F4 formulation containing different polymer ratio could be fit for the Buccal tablet. So the drug release profile of formulation F4 was found Maximum at the end of 8 hrs. (Table 3)

3.3 Stability of buccal tablets

At regular time intervals (0, 2, 4, and 6 hr), the buccal tablets were examined for change in colour (no change), surface area (8.11 to 8.39 mm) no Collapsing and thickness is 4-5 (Table 4)

4. Conclusion

Development of bioadhesive buccal drug delivery of Aminophylline is one of the alternative routes of administration. In this present study F4 formulation comprises of Aminophylline and HPMC K4M (1:3) showed optimum drug release and satisfactory bioadhesive properties. Thus the study revealed that the Aminophylline buccal tablets showed good bioadhesion time with sustained release of drug for more than 8 hours. The optimized formulation also showed satisfactory surface pH and physical parameters satisfactory stability and comfortability in the oral cavity. From the results of present investigation it can be concluded that Aminophylline can certainly be administered through the oral mucosa and HPMC K4M is suitable for development of bioadhesive buccal system.

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Table 1. Composition of Aminophylline bioadhesive buccal tablets.

Formulation	D : P	Drug	HPMC K4M	Carbopol 934P	Mannitol	Mg stearate
F1	1:0.50	50mg	25mg	-	223mg	2mg
F2	1:1	50 mg	50mg	-	198mg	2mg
F3	1:2	50 mg	100mg	-	148mg	2mg
F4	1:3	50 mg	150mg	-	98mg	2mg
F5	1:0.50	50 mg	-	25mg	223mg	2mg
F6	1:1	50 mg	-	50mg	198mg	2mg
F7	1:2	50 mg	-	100mg	148mg	2mg
F8	1:3	50 mg	-	150mg	98mg	2mg

Table 2. Evaluation of Aminophylline bioadhesive buccal tablets

Formulation	Weight Variation (mg)	Hardeness (Kg/cm^2)	Thickness (mm)	Friability (%)	Drug Content(%)
F1	300.4 ± 2.18	7.18 ± 0.15	4.49 ± 0.06	0.39 ± 0.05	98.42
F2	298.1 ± 1.33	6.98 ± 0.18	4.44 ± 0.05	0.34 ± 0.15	98.89
F3	300.1 ± 2.08	7.34 ± 0.16	4.48 ± 0.06	0.41 ± 0.08	98.99
F4	298.4 ± 2.14	6.92 ± 0.19	4.54 ± 0.04	0.44 ± 0.13	99.43
F5	300.1 ± 1.09	7.08 ± 0.29	4.47 ± 0.01	0.42 ± 0.08	98.96
F6	298.3 ± 1.45	7.16 ± 0.15	4.52 ± 0.03	0.34 ± 0.22	98.99
F7	299.4 ± 1.52	7.04 ± 0.23	4.45 ± 0.02	0.36 ± 0.05	98.81
F8	299.3 ± 2.14	7.16 ± 0.15	4.49 ± 0.02	0.47 ± 0.05	99.40

Table 3. Evaluation of Aminophylline bioadhesive buccal tablets

Formulation	Drug release (%)	Bioadhesive Strength (gm)	Surface PH	Swelling Index (%)
F1	83.96 ±1.61	29.5	6.2	22.6 ± 1.9
F2	85.36 ±1.20	31.4	6.8	27.7 ± 0.4
F3	84.36 ±1.34	34.5	6.4	39.2 ± 1.3
F4	98.96 ±1.00	35.8	6.2	31.8 ± 0.3
F5	82.46 ±1.20	27.6	6.3	62.9 ± .83
F6	78.65 ±1.49	30.5	6.7	71.1 ± 0.3
F7	85.34 ±1.49	32.5	6.5	57.4 ± 1.7
F8	81.35 ±1.61	34.1	6.2	29.3 ± 1.9

Table 4. Stability data of buccal tablets in normal human saliva

Time (hrs)	Colour change	Thickness (mm)	Change in shape Diameter (mm)	Collapsing
0	No	4.54 ± 0.01	8.11 ± 0.01	No
1	No	4.60 ± 0.01	8.19 ± 0.01	No
2	No	4.71 ± 0.01	8.38 ± 0.01	No
4	No	4.90 ± 0.01	8.39 ± 0.01	No
6	No	4.94 ± 0.01	8.37 ± 0.01	No

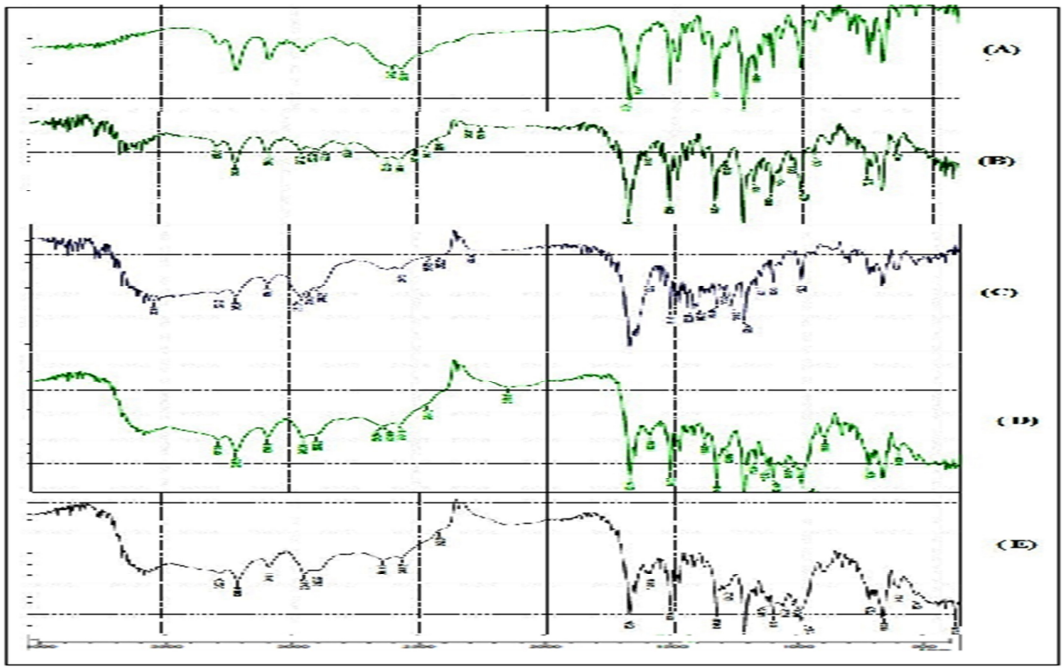

Figure 1. FTIR of pure Aminophylline (A), Aminophylline + HPMC (B), Aminophylline + carbopol (C), Aminophylline + Mannitol (D), and Drug + all exciepients (E).

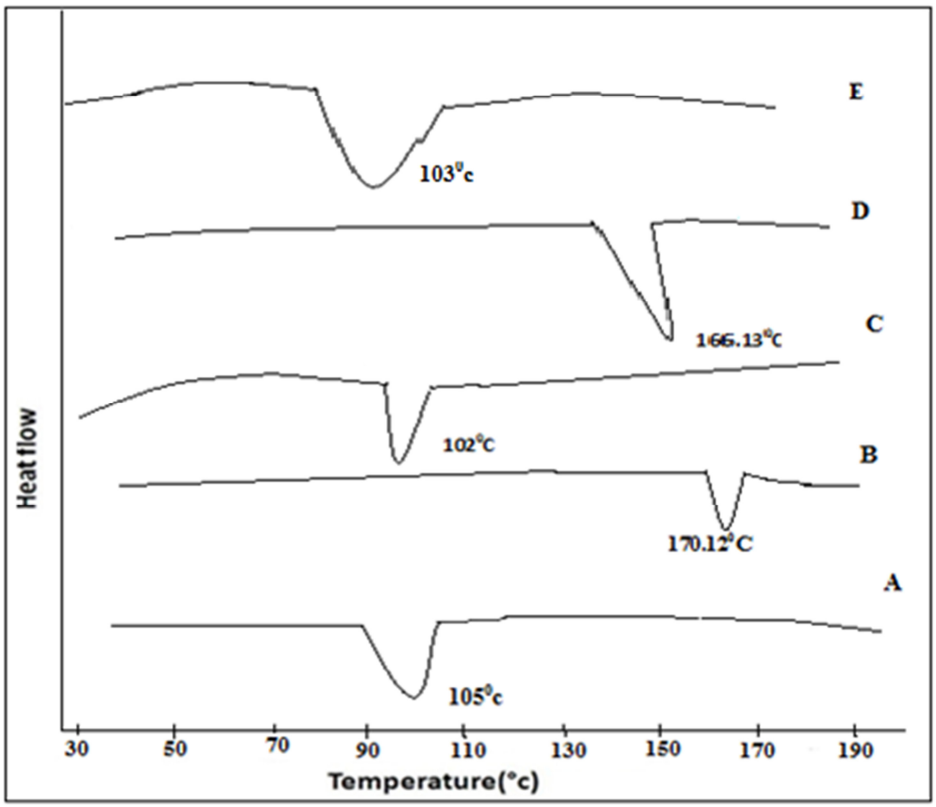

Figure 2. DSC of pure Aminophylline (A), HPMC (B), carbopol (C), Mannitol (D), and Drug + all exciepients (E).

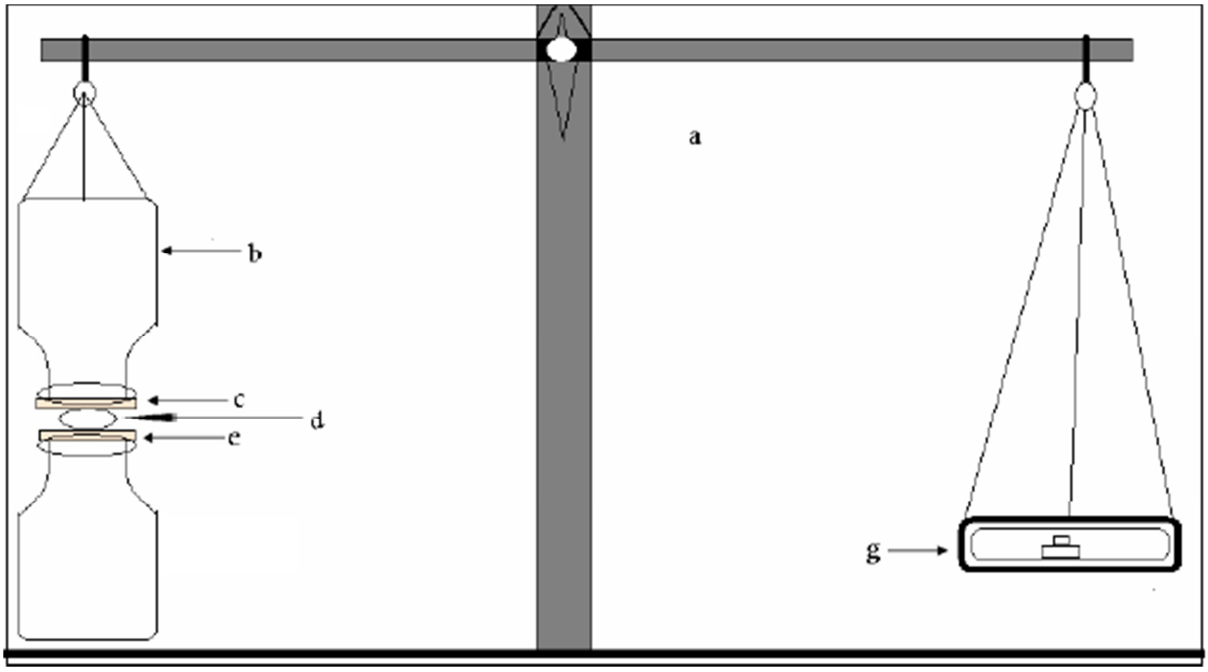

Figure 3. Measurement of bioadhesive strength
a- scale; b-glass vial; c-sheep buccal mucosa; d- bioadhesive tablet;
e- Adjustable pan; g-weight

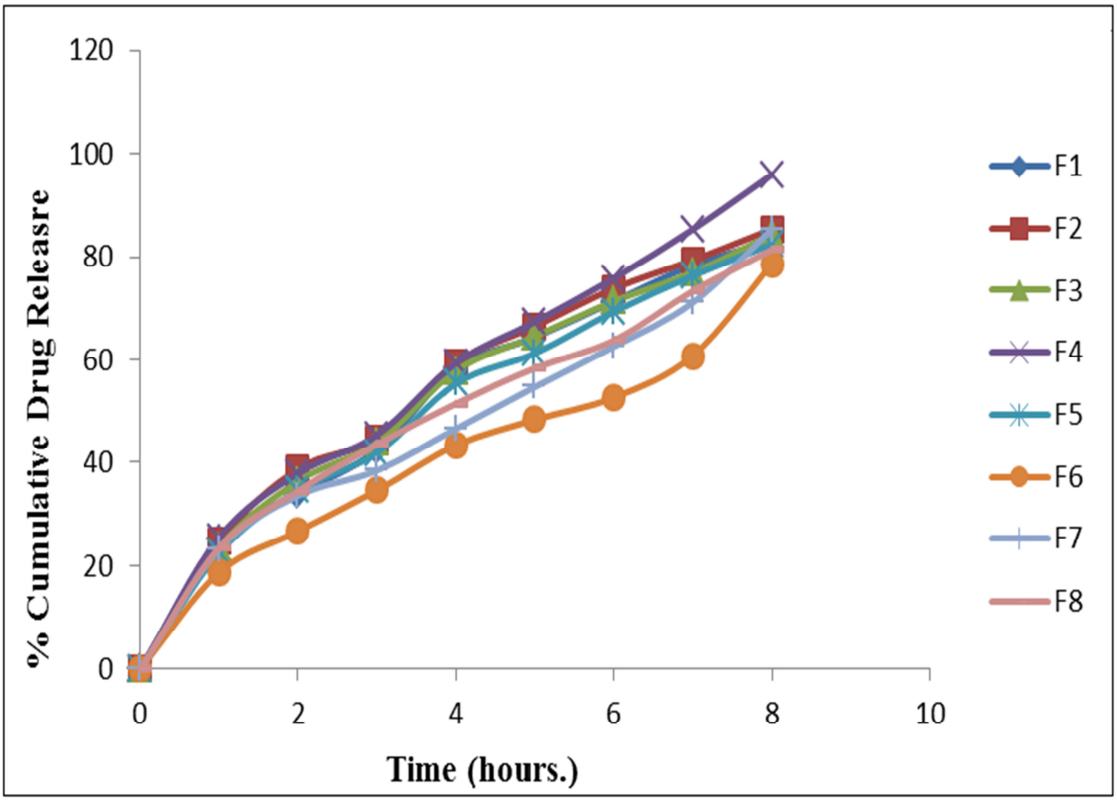

Figure 4. *In-vitro* drug release profiles of formulations

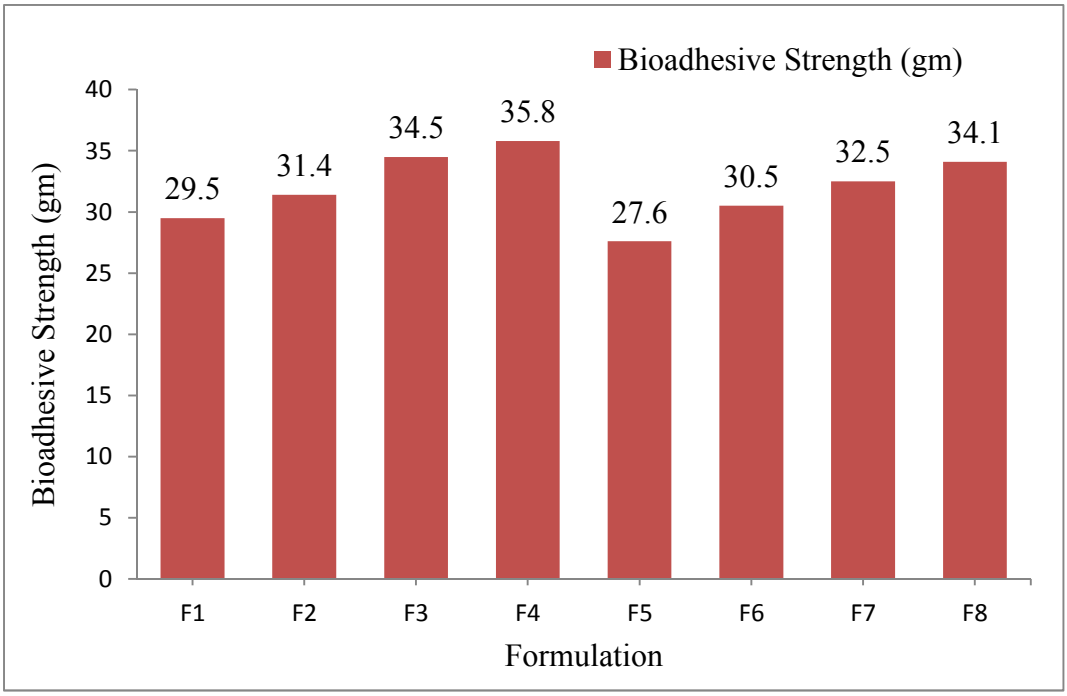

Figure 5. Bioadhesive strength of all the formulation

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