



BUCCOADHESIVE DRUG DELIVERY SYSTEM

Snehal Khade*, Dr. Vijaya Barge², Dr. Ashok Bhosale.

PDEA's Shankarrao Ursal College of Pharmacy And Research Centre Kharadi, Pune.

Abstract:

The primary focus on the oral conveyance of the vast majority of the medications as potential restorative specialists is their broad presystemic digestion, insecurity in acidic climate coming about into insufficient and unpredictable oral assimilation. Parenteral course of organization is the lone set up course that defeats this load of disadvantages related with these orally wasteful medications. In any case, these plans are exorbitant, have most restless consistence, require rehashed organization, notwithstanding the other perilous impacts related with this course. Buccal cavity was observed to be the most helpful and effectively available site for the conveyance of remedial specialists for both neighborhood and fundamental conveyance as retentive measurements structures. Buccoadhesive medication conveyance is moderately new medication conveyance system; in this conventional polymers are supplanted by clever bioadhesive polymers, for example, Thiomers and lectins and so forth to defeat impediment of customary polymer. Buccoadhesive trademark are factor of both bioadhesive polymer and the medium in which the polymer live. It is the goal of this article to audit buccoadhesive medication conveyance by talking about the design, porousness of buccal mucosa, component of buccoadhesion, novel bioadhesive polymers, buccoadhesive dose structure and their assessment, late advances in buccoadhesive medication conveyance framework.

KEY WORDS: bioadhesive, theories, oral ingestion, Buccal depression and so on

1. INTRODUCTION

Bioadhesion can be characterize as a wonder of interfacial sub-atomic appealing powers in the surfaces of organic substrate and the normal or engineered polymers, which permits the polymer to hold fast to natural surfaces for a drawn out timeframe. Among the different courses of medication conveyance the oral course is maybe the most liked by the patient and clinicians the same. [1] The oral course favored course for the organization of restorative specialist because of minimal expense, simplicity of organization and significant

degree of patient consistence. In any case, huge hindrances force for the peroral organization of medications, like hepatic first pass digestion and medication corruption inside the GI parcel forbidding the oral organization of specific classes of medications particularly biologics for example peptides and proteins. Thus, other absorptive mucosae are being considered as likely locales for drug organization including the mucosal covering of the nasal, rectal, vaginal, visual, and oral hole. Among these, conveyance of medications to the oral depression has drawn specifically consideration because of its potential for high tolerant consistence and exceptional physiological provisions. Inside the oral mucosal cavity, the conveyance of medications is grouped into two classifications: (1) neighborhood conveyance and (2) foundational conveyance either by means of buccal or sublingual mucosa. [2]

2. Bioadhesive delivery of drug system in oral cavity

2.1 Sublingual delivery, which is systemic delivery of drugs through the mucosal membrane lining the floor of the mouth,

2.2 Buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and

2.3 Local delivery, which is drug delivery into the oral cavity. [1]

3. Buccoadhesive drug delivery system

Other than the low surface area available for drug absorption in the buccal cavity, the retention of the dosage form at the site of absorption is another factor which determines the success or failure of buccoadhesive drug delivery system. The utilization of buccoadhesive system is essential to maintain an intimate and prolonged contact of the formulation with the oral mucosa allowing a longer duration for absorption. [2]

3.2 Advantages of buccal bioadhesive drug delivery system

- Termination of therapy is possible.
- Permits localization of drug to the oral cavity for extended period of time.
- Ease of administration, good patient compliance
- Avoids first pass metabolism.
- Reduction of dose can be achieved.
- Selective use of therapeutic agents like peptides, proteins, and ionized species can be achieved.

- Drugs which are unstable in acidic environment of stomach or destroyed by the alkaline environment of intestine can be given by this route.
- Administration of drug with poor bioavailability.
- It follows passive diffusion.
- Administration of drugs with short half life.
- Prolongation of contact time with mucosa.
- There is no requirement of medical practitioner to apply the dosage form.
- It not hinders the talking function of patient.
- The buccal mucosa is relatively permeable with a rich blood supply, as comparison to other mucosal tissue.
- Flexibility in shifting the position of the drug in buccal cavity (in case of buccal film).

3.3 Disadvantages of buccoadhesive drug delivery system

- Eating and drinking may become restricted.
- By mistake system can be swallowed (in case of buccal tablet, buccal film).
- Saliva takes some drug into GIT.
- Drug which irritate mucosa or have a bitter or unpleasant taste or an obnoxious odour cannot be administered by this route.
- Drugs which are unstable at buccal pH cannot be administered by this route.
- Only those drugs are absorbed by passive diffusion can be administered by this route. ^[3]

4. Buccal drug delivery and Buccoadhesivity

In the development of these buccal drug delivery systems, buccoadhesion of the device is a key element. The term 'buccoadhesive' is commonly used for material that binds to the mucin layer of a biological membrane. Buccoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosae. ^[4]

4.1 Mechanism of Buccoadhesion

Buccoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Buccoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Buccoadhesion has the following mechanism-

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon)
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration). ^[5]

5. Buccoadhesive Polymer

Buccoadhesive polymers are water soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agent. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to replace. ^[7]

5.2 Ideal characteristics of buccoadhesive polymer

The buccoadhesive polymers should possess following characteristics.

- Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
- It should have good spread ability, wetting, swelling and solubility and biodegradability properties.
- It should have biocompatible pH and should possess good visco-elastic properties.
- It should be adhere quickly to buccal mucosa and should sufficient mechanical strength.
- It should possess peel, tensile and shear strengths at the bioadhesive range.
- It must be easily available and its cost should not be high.

- It should show bioadhesive properties in both dry and liquid state.
- It should demonstrate local enzyme inhibition and penetration enhancement properties.
- It should acceptable shelf life.
- It should have optimum molecular weight.
- It should possess adhesively active groups.
- It should have required spatial conformation.
- It should be sufficiently cross-linked but not to the degree of suppression of bond forming groups.

6. MATERIALS AND METHODS

6.1 PREPARATION OF BUCCOADHESIVE TABLET OF ACYCLOVIR

All the ingredients including drug, polymer and excipient were weighed accurately according to batch formulae. Then all ingredients except lubricant were mixed in order of ascending weight and blended for 10 min in mortal and pestle. After uniform mixing of ingredients, lubricant was added and again mixed for 10 min and compressed in to tablet of 310 mg using 10 mm round flat punches on multi-station punch tablet compression machine

TABLE 6.1.1 FORMULATION OF BUCCOADHESIVE TABLET OF ACYCLOVIR

| Sr. No. | Name of Ingredient | F 1 | F 2 | F 3 | F 4 | F 5 | F 6 |
|---------|----------------------------|------|-----|------|-----|------|-----|
| 1. | Acyclovir | 200 | 200 | 200 | 200 | 200 | 200 |
| 2. | Carbopol 940P | 15 | 15 | 15 | 15 | 15 | 15 |
| 3. | HPMC K13M | 7.5 | 15 | 22.5 | 30 | 37.5 | 45 |
| 4. | Microcrystalline cellulose | 82.5 | 75 | 67.5 | 60 | 52.5 | 45 |
| 5. | Talc | 5 | 5 | 5 | 5 | 5 | 5 |
| 6. | Total | 310 | 310 | 310 | 310 | 310 | 310 |

6.2 PREFORMULATION STUDY

6.2.1 Study of Organoleptic properties of pure drug

Acyclovir was tested for organoleptic properties such as appearance, taste, odour, colour etc.

6.2.2 Determination of λ_{\max} and calibration curve of drug

6.2.2.1 Determination of λ_{\max}

Acyclovir 100 mg was dissolved in 100 ml of phosphate buffer of pH 6.8, 10 ml was pipetted out from the above solution and it was diluted to 100 ml to get the concentration of 100 $\mu\text{g/ml}$. From this, 1 ml solution was pipette out and further diluted to 10 ml to obtain the concentration of 10 $\mu\text{g/ml}$. It was scanned for maximum absorbance by UV-spectrophotometer (Shimadzu, Japan) in range of 200-400 nm using phosphate buffer of pH 6.8.

6.2.2.2 Preparation of standard calibration curve of acyclovir

Accurately weighed 100 mg of Acyclovir was dissolved in 100 ml phosphate buffer of pH 6.8 in 100 ml volumetric flask. From this 10 ml solution was pipette out and further diluted to 100 ml. This solution was used as stock solution Aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml and 1 ml of working standards solution were transferred in to series of 10 ml volumetric flask. Then adjust volume up to 10 ml with phosphate buffer of pH 6.8. The concentration of these solution was 2 $\mu\text{g/ml}$, 4 $\mu\text{g/ml}$, 6 $\mu\text{g/ml}$, 8 $\mu\text{g/ml}$, 10 $\mu\text{g/ml}$. Finally, the absorbance of each sample was measured at 253 nm against blank phosphate buffer of pH 6.8. Standard curve of concentration vs. absorbance was plotted.

6.3 PRECOMPRESSION PARAMETERS

6.3.1 Bulk Density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by,

$$D_b = M/V_0$$

Where, M is the mass of powder

V_0 is the Bulk volume of the powder.

6.3.2 Tapped Density (D_t)

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by,

$$D_b = M/V_t$$

Where, M is the mass of powder

V_t is the tapped volume of the powder.

6.3.3 Angle of Repose

The frictional forces in a loose powder can be measured by the angle of repose, θ . This is the maximum angle possible between the surface of a pile of powder and the horizontal plane and it is given as,

$$\theta = \tan^{-1} h/r$$

Where, θ is the angle of repose

h is the height in cm

r is the radius

6.3.4 Carr's Index

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I = D_t - D_b / D_t \times 100$$

Where, D_t is the tapped density of the powder.

D_b is the bulk density of the powder.

6.3.5 Hausener ratio

It is the ratio of tapped density to the bulk density.

$$\text{Hausner ratio} = D_t / D_b$$

Where, D_t is tapped density

D_b is bulk density

7. EVALUTION OF TABLET

7.1 Thickness of tablet

Thickness of tablet is important for uniformity of tablet. Three tablets were taken and thickness was measured using Vernier calipers. The tablet thickness should control within $\pm 5\%$ variation of standard value

7.2 Hardness of tablet

The Pfizer hardness tester was used to determine the tablet hardness. The tablet was held along its oblong axis in between two jaws of tester. At this point, reading should be zero kg/cm^2 . Then constant force was applied until the tablet fractured. The value at this point was noted in kg/cm^2 .

7.3 Friability of tablet

Friability was evaluated by means of friability test apparatus known as Roache friabilator. Twenty preweighed tablet were placed in the friabilator and then operated at 25 rpm for 4 minutes. The tablets were then removed and weighed again. The difference in the two weights was used to calculate friability.

$$F = 100 \times [1 - W/W_0]$$

Where, W_0 is initial weight W is final weight

7.4 Weight variation test

Ten tablets were weighed individually, then calculate the average weight and comparing individual tablet weight to average weight of tablet. The tablets pass the test if not more than two tablets are outside the percentage limit.

Table 7.4.1 : Weight variation tolerances for tablet

| Average weight of tablet | % Deviation |
|------------------------------------|-------------|
| 80 mg or less | 10 % |
| More than 80 mg & less than 250 mg | 7.5 % |
| 250 mg or more | 1.1 % |

7.5 Drug content uniformity

Take five tablets randomly from each formulation, crush in mortar and pestle. Then take powder equivalent to 200 mg acyclovir and dissolved into 200 ml phosphate buffer of pH 6.8. Then this solution was further diluted to get the solution of 10 ppm. Finally Analyzed spectrophotometrically at 253nm. using UV visible spectrophotometer (Shimadzu, Japan) against phosphate buffer of pH 6.8 as blank.

7.6 Surface pH study

The surface pH of buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to buccal mucosa. The tablet was allowed to swell by keeping it in contact with 1 ml distilled water for 2 h at room temp. The pH was measured by bringing the electrode in contact with the surface of tablet and allowing it to equilibrate for 1 min.

7.8 Bioadhesion strength and bioadhesion time

Bioadhesive strength of the buccal tablets was measured on the “Modified Physical Balance method”. The method used goat buccal membrane as the model mucosal membrane. The fresh goat buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of mucosa was tied to the glass slide which was moistened with phosphate buffer pH 6.8. The tablet was stuck to the lower side of another glass slide with glue. The both pans were balanced by adding an appropriate weight on the left- hand pan.

The glass slide with mucosa was placed with appropriate support, so that the tablet touches the mucosa. On the side of balance powder (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The weight required to detach the tablet from the mucosal surface gave the bioadhesive strength. The experiment was performed in triplicate and average value was calculated. Bioadhesive strength was assessed in terms of weight [gm] required to detach from membrane.

Bioadhesion strength which was measured as force of adhesion in Newton by using formula.

$$\text{Force of adhesion (N)} = \text{Mucoadhesive strength} \times 9.81 / 100$$

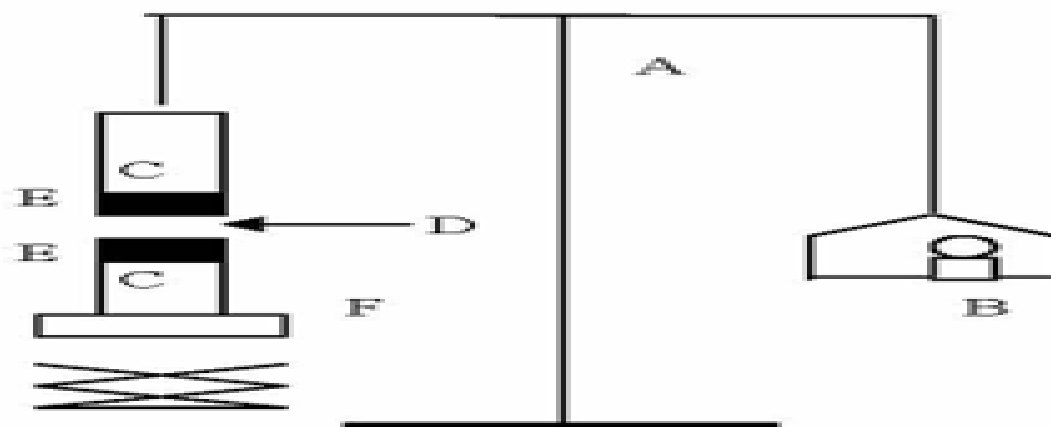


Fig. : Modified physical balance for determination of bioadhesive strength

7.9 Bioadhesion time determination⁴⁹

The *ex-vivo* mucoadhesion time was examined after application of the buccal tablet on freshly cut goat buccal mucosa. The fresh goat buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8 and kept at $37 \pm 1^\circ\text{C}$. After 2 minutes, stirring was applied slowly to simulate the buccal cavity environment and tablet adhesion was monitored for 8 h. The time for the tablet to detach from the goat buccal mucosa was recorded as the mucoadhesion time.

7.10 In-vitro dissolution study

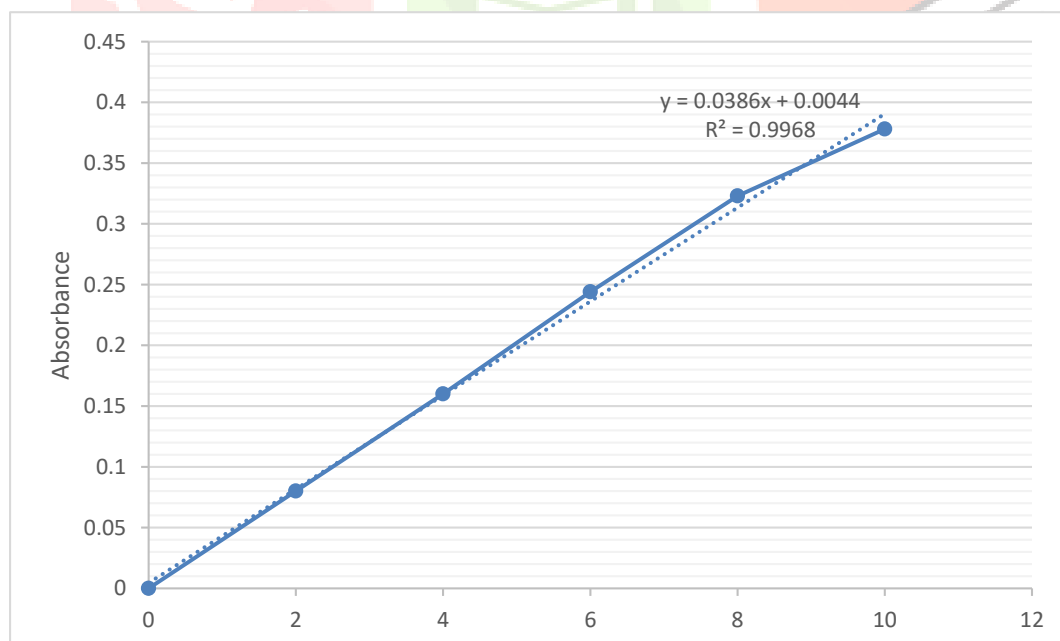
Dissolution studies were performed using USP type II apparatus and phosphate buffer pH 6.8 at 50 rpm and $37 \pm 0.5^\circ\text{C}$. Aliquots of 1ml of each sample were withdrawn periodically at suitable time interval and volume was replaced with equivalent amount of same dissolution medium. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by UV spectrophotometer (Shimadzu, Japan) at 253 nm.

RESULTS AND DISCUSSION**8.1 PREFORMULATION STUDY****8.1.1 Organoleptic properties of drug**

| Characters | Inference |
|---------------|---------------------|
| Appearance | Crystalline powder |
| Colour | White or colourless |
| Odour | Odourless |
| Melting point | 254- 257 ° C |

8.1.2 Preparation of standard calibration curve of acyclovir

| Sr. No. | Concentration (µg/ml) | Absorbance (at 253 nm) |
|---------|-----------------------|------------------------|
| 1 | 0 | 0.00 |
| 2 | 2 | 0.080 |
| 3 | 4 | 0.160 |
| 4 | 6 | 0.244 |
| 5 | 8 | 0.323 |
| 6 | 10 | 0.378 |

**Fig.8.2 : Calibration curve of acyclovir in phosphate buffer of pH 6.8**

The correlation coefficient (R^2) = 0.996

From the graph it is showed that it follows Beer-Lambort's law.

8.3 Precompression parameter

Table 10.3: Precompression parameter of formulations

| Formulation | Bulk density (gm/cm ³) | Tapped density(gm/cm ³) | Carr's index | Hausner ratio | Angle of repose (θ) |
|-------------|------------------------------------|-------------------------------------|--------------|---------------|---------------------------|
| F1 | 0.47±0.023 | 0.52±0.019 | 13.99 | 1.19 | 30 ⁰ .55'±0.36 |
| F2 | 0.41±0.011 | 0.47±0.023 | 12.76 | 1.27 | 28 ⁰ .80'±0.33 |
| F3 | 0.47±0.023 | 0.58±0.028 | 12.98 | 1.13 | 27 ⁰ .90'±2.01 |
| F4 | 0.41±0.011 | 0.56±0.017 | 13.34 | 1.15 | 30 ⁰ .77'±0.68 |

8.4 Post compression parameter

Table 8.4: Post compression parameter of formulation

| Formulation | Hardness (kg/cm ²) | Thickness (mm) | Friability (%) | Weight variation (mg) | Drug content (%) | Surface pH |
|-------------|--------------------------------|----------------|----------------|-----------------------|------------------|------------|
| F1 | 5.46±0.20 | 3.21 ±0.02 | 0.37±0.04 | 307.86±1.89 | 97.03±1.62 | 5.89±0.04 |
| F2 | 5.43±0.35 | 3.19 ± 0.05 | 0.44±0.02 | 305.61±3.42 | 95.89±1.63 | 5.72±0.04 |
| F3 | 5.53±0.30 | 3.20 ± 0.03 | 0.58±0.03 | 305.66±4.07 | 96.33±1.68 | 6.66±0.42 |
| F4 | 5.3±0.20 | 3.16 ± 0.04 | 0.57±0.02 | 305.31±5.72 | 95.56±1.87 | 6.78±0.05 |

8.5 Bioadhesive strength and bioadhesive time of formulation

Table 8.5: Bioadhesive strength and bioadhesion time of different formulations.

| Formulation | Bioadhesive strength (gm) | Bioadhesion force (N) | Bioadhesion time (h) |
|-------------|---------------------------|-----------------------|----------------------|
| F1 | 5.13 | 0.49 | 6.10 |
| F2 | 7.21 | 0.68 | 7.30 |
| F3 | 10.98 | 1.07 | 8.10 |
| F4 | 9.80 | 0.96 | 7.35 |

8.6 Dissolution study

Table 8.6.1 : Average cumulative percentage of drug released of formulations

| Time (h) | Average cumulative percentage of drug released from | | | |
|-------------|---|-------|-------|-------|
| | F1 | F2 | F3 | F4 |
| 1 | 24.79 | 20.54 | 13.41 | 11.21 |
| 2 | 38.41 | 33.62 | 21.98 | 18.49 |
| 4 | 54.38 | 49.43 | 35.13 | 30.14 |
| 6 | 69.15 | 64.25 | 51.10 | 44.12 |
| 8 | 85.24 | 77.54 | 66.98 | 51.10 |
| 10 | 95.21 | 86.37 | 82.41 | 71.59 |
| 12 | - | 94.78 | 90.18 | 78.35 |

Drug release studies were made to determine whether the release of the drug is slow enough, i.e., which polymer ratio is enough to sustain the release of the drug for 8 h. As we increases the ratio of HPMC K13M in the formulation, there is more swelling were observed which also responsible for the drug release and it also sustained the drug release at the 8 h. The drug release in F1 and F2 formulation is 95.21% and 94.78% respectively but there is initial abrupt bursting effect. Drug release in formulation F3 and F4 decreases with increases concentration of HPMC K13M. Drug release in formulation F3 is 94.26% which sustained at 12 h.

Therefore, optimized formulation was F3 having the polymer ratio 1:1.5 [Carbopol 940P: HPMC K13]. From, the comparison study of all formulation it was concluded that the order of drug release among formulations was found to be $F3 > F2 > F1 > F4$

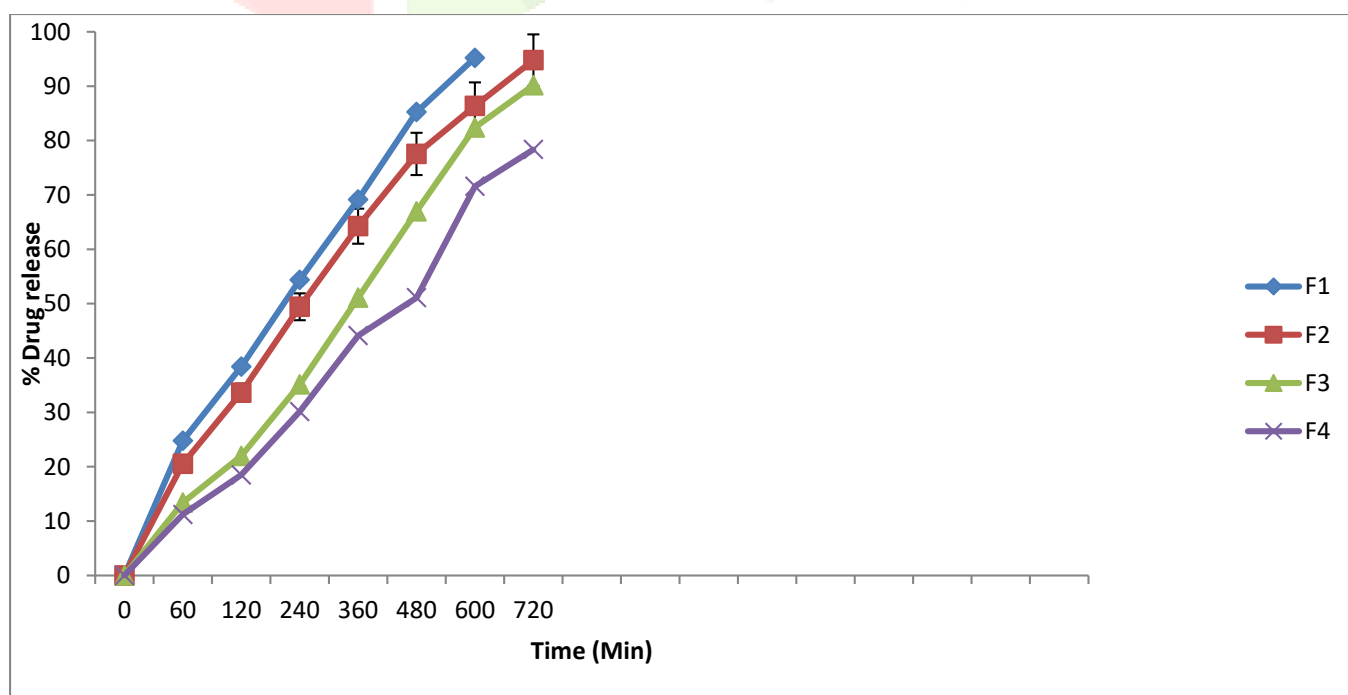


Fig. 8.6 : Cumulative percent drug release profiles of formulations F1-F4

8.7 Drug release kinetics of formulations

The drug release data of the selected formulation (F3) was fitted to various models like zero order, first order, Higuchi's model, Hixon Crowell and Korsmeyer's model. The Kinetic model fitting of drug release data was done with the help of Microsoft excel based software PCP-Disso v2.08. The calculated slope, the intercept and R^2 are shown in Table 7.9. Formulation (F3) was best fitted for Hixon Crowell model with regression value ' R^2 ' of 0.9544. Slope value suggested that the release captopril from floating tablets followed Case-II transport mechanism. Formulation (F3) follows zero order release kinetics with regression value ' R^2 ' of 0.9934.

Table 8.7 : Drug release kinetic of selected formulation (F3)

| Model | R^2 | Slope | Intercept |
|------------------------|--------|--------|-----------|
| Zero order | 0.9934 | 12.66 | 0.0651 |
| First order | 0.8563 | 0.1968 | 0.7010 |
| Hixon Crowell | 0.9544 | 1.1229 | 1.9409 |
| Korsmeyer-Peppas model | 0.3451 | 1.0121 | 1.2093 |
| Higuchi model | 0.9530 | 0.0245 | 0.5708 |

CONCLUSION

From the present study it was concluded that the buccoadhesive drug delivery system of acyclovir was deliver the drug in sustained release manner, for 8 h. Also it successfully avoids the extensive first pass metabolism and improves the bioavailability of Acyclovir. It was also found that Carbopol 940P and HPMC K13M can be promising polymers for buccoadhesive drug delivery systems and also as we increases the ratio of HPMC K13M in the formulation there is decrease in the drug release rate of Acyclovir. The optimized formulation sustained the release up to 8 h, followed Zero order kinetics while the drug release mechanism was found to be case II transport, controlled by diffusion through the swollen matrix. Sustained drug release with adhesion time of about 8 h and good bioadhesive strength was observed in case of optimized formulation. The swollen tablet also maintained its physical integrity during the drug release study.

Recent advances in buccoadhesive drug delivery systems:

Recently buccoadhesive formulation may provide to be an alternative to the conventional oral medication as they can readily attached to the buccal cavity retained for longer period of time and removed at any time. Buccoadhesive drug delivery system using matrix tablets, lms, layered systems, discs, microspheres, ointment and hydrogel system has been studied and reported by several research groups.

Garala K. *et al* developed and optimized in situ gel for the treatment of periodontal disease. Temperature-sensitive in situ gel containing 0.1% w/v Chlorhexidine hydrochloride was formulated by cold method using different polymers. Result of evaluation parameters revealed that the drug release, gelation temperature was considerably decrease with increasing $t_{50\%}$ as the concentration of each polymer was increased.^[16]

Suresh P. K. *et al* described the formulation of ciprofloxacin loaded cubic phase gels, a biodegradable, bioadhesive, biocompatible delivery system and their characterization for drug content, drug loading efficiency, gelation temp, gel melting temp, ph, bioadhesive force, viscosity, gel strength, swelling and drug release profile. The drug release kinetics revealed best fit with Higuchi's equation for all the formulations, indicating the drug release by diffusion.^[11]

Vijaybhaskar D. *et al* prepared mucoadhesive gels for the treatment of oral submucous fibrosis, which provide effect for the extended periods of time. Stress was given for improvised local action of the drug with the addition of mucoadhesive polymer in the formulation. Curcumin was taken as a model drug as it exhibits profound anti-turmeric and anti-mutagenic activity. The formulation containing equal mixture of NaCMC and HEC as base showed good in-vitro release and good adhesion to oral mucosa. The *In-Vivo* studies were carried out into two phases using 18 mice, in first phase OSF was induced in mice using marketed Gutkha preparation and formulation into a mucoadhesive gel form and applying to mice oral mucosa with the help of cotton buds for a period of six months and in second phase, treatment was carried

out following the above method using Curcumin formulation. Histopathological observation reported that there was considerable induction of OSF and excellent treatment results on Curcumin usage.^[14]

Finì A., Bergamante V., Ceschel C.G. studied *in vitro/ex vivo* buccal release of Chlorhexidine (CHX) from nine mucoadhesive aqueous gels, as well as their physiochemical and mucoadhesive properties. The combination of HPMC or HPC with CMC showed slower drug release when compared to each of the individual polymers. An accurate selection and combination of the materials allow the design of different pharmaceutical forms suitable for different purposes, by simply modifying the formulation composition.^[17]

Ramadan E. *et al* incorporated Metronidazole (MTZ) (anaerobic antibacterial agent) into different bioadhesive matrices including gels and films using Carbopol 934p(4%), chitosan(3%), and HPMC(3%). The effects of selected MTZ formulations on the healing rate of experimentally induced periodontitis in guinea pigs were estimated and histological compared between treated and control groups (Metronidazole gel).^[18]

Yellanki S.K., Singh J. and Manvi F.V. prepared six batches of MTZ gels using natural biodegradable polymers chitosan, guar gum and locust bean gum in variable concentrations. The results revealed that the surface pH was within the range of neutral pH. The best formulation in terms of cumulative percent drug release along with bioadhesion was formulation F₃ (Chitosan 3% w/v) with 78.23% drug release.^[13]

Shah D. *et al* developed a mucoadhesive film for the treatment of Leukoplakia (pre stage of oral cancer) by using Lycopene as a model drug, so that higher concentration was achieved in buccal cavity. As the film was intended for local effect, no drug release was performed. Solvent casting method was selected for film preparation. Lycopene is completely water insoluble, while other excipient are completely water soluble, so uniform film formulation is a major challenge. Viscosity of vehicle, thickness of the film, tensile strength, bending strength, film swelling, erosion properties and *ex vivo* mucoadhesion time and forces were the criteria to optimize the film formulation using propylene glycol as plasticizer.^[10]

Jelvehdari M. *et al* investigated the properties of Carbopol 934P polymeric system in water miscible co-solvents such as glycerin and alcohol. Benzocaine mucosal gel formulation is prepared by Carbopol as a gelling agent was applied in the treatment of dental pain. Neutralization of pH in various concentrations of Carbopol gels resulted in increased viscosity. A relationship between the viscosity and bioadhesive strength was shown in the neutralized Carbopol gels. On the other hand, the result indicated that increasing the amount of water, elasticity and release rate was increased. The result showed that diffusion of benzocaine from oromucosal gel and commercial sample followed Higuchi's law.^[15]

Perioli L. *et al* prepared mucoadhesive tablets using different mixture of cellulose and polyacrylic derivatives in order to obtain new formulation containing MTZ for periodontal disease treatment. All tablets were characterized by swelling studies, *ex vivo* and *in vivo* mucoadhesive time, *ex vivo* mucoadhesion force, *in vitro* and *in vivo* release. The best mucoadhesive performance and the best *in vitro* drug release profile were achieved by using HEC and Carbomer 940 in 2:2 ratio. The optimized tablet,

containing 20 mg of MTZ, released the drug over 12 hr period with buccal concentration always higher than its MIC.^[19]

Doshi *et al* prepared pharmaceutical dental gel preparation comprised of MTZ, CHX gluconate and local anesthetic as the active ingredient, glycol as the solvent medium, carboxyvinyl polymer, cross linked polymer of acrylic acid copolymerized with polyalkylsucrose as a gelling agent.^[20]

Okamoto H. *et al* examined the penetration rate of Lidocaine (LC) through excised oral mucosa from hamster cheek pouch and the in vitro release rate of LC from film dosage forms with hydroxypropylcellulose (HPC) as a film base. Addition of glycyrrhizic acid (GL) to the HPC films increased the LC release rate almost GL-content-dependently, while an optimum GL content was observed for the LC penetration rate. No LC penetration was observed from an acidic aqueous solution (pH 3.4) of LC, suggesting only unionized LC can substantially penetrate through the mucosa.^[21]

Senela S. *et al* prepared gels (at 1 or 2% concentration) or film forms of chitosan containing 0.1 or 0.2% Chlorhexidine and their in vitro release properties were studied. The antifungal activity of chitosan itself as well as the various formulations containing Chlorhexidine was also examined. Release of Chlorhexidine from gels was maintained for 3 h. A prolonged release was observed with film formulations. No lag-time was observed in release of Chlorhexidine from either gels or films. The highest antifungal activity was obtained with 2% chitosan gel containing 0.1% Chlorhexidine.^[22]

Kumar M. *et al* formulated Choline salicylate as a lozenge tablet to provide prolonged relief from pain associated with mouth ulcers. The lozenges were prepared using mannitol as base and gelatin dispersion as binder. Lozenge tablet formulation can provide an attractive alternative formulation in the alleviation of pain in recurrent aphthous mucosal ulcers.^[23]

References

1. Nishan NB, et al. A review on buccal drug delivery system. International journal of pharmacy and pharmaceutical science research 2013; 3(1): 35-40.
2. Viral KFP, et al. Advances in oral transmucosal drug delivery. Journal of controlled release 2011; 153: 106-116.
3. Vyas SP and Khar KR. Controlled drug delivery concepts and advances. 1st ed. Vallabh prakashan 2002; 258-298.
4. Sandeep SL, et al. mucoadhesive drug delivery system. Indo-global journal of pharmaceutical sciences 2011; 3(1): 243-251.
5. Pranshu T, et al. mucoadhesive drug delivery, mechanism and methods of evaluation. International journal of Pharma and bio sciences 2011; 2(1): 458.
6. Sarvan K, et al. Comprehensive review on buccal delivery. International journal of pharmacy. Int J Pharm 2012; 2(1): 205-217.
7. Doijad RC, Kapoor D, Dr. Manvi FV. Nanoparticulate DDS for Prednisolone Design and Characterization. 31st Annual meet and exposition of CRS Honolulu 2004:12-16.

8. Gandhi P, Patel M. A review article on mucoadhesive buccal drug delivery system. Int J Pharm Res Development. 2011; 3(5): 159 – 173.
9. Bhalodia R, Basu B. Buccoadhesive drug delivery systems: a review. Int J pharm bio sci 2010;1(2): 1-32.
10. Doijad RC, Patil S, Dr. Manvi FV. A study of Buccal Tablets of Glipizide Development and Evaluation. F.I.P. 2003:77-84.
11. Singh S, Singh R. Buccal Mucosa as a route for Drug Delivery: Mechanism, Design and Evaluation. Res J Pharm Bio Chem Sci 2011; 2(3): 358.
12. John D. Smart. The basics and underlying mechanisms of mucoadhesion. Adv Drug Delivery 2005;1-12.
13. Jain NK. Controlled release and Novel Drug Delivery. 1st edition. CBS publishers and Distributors New Delhi.1997, pp. 353-370.

