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Hydrophilic polymers influences the release of Clofarabine from the Clofarabine Mucoadhesive Buccal patches

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Abstract
Mucoadhesive drug delivery system interact with the mucus layer covering the mucosal epithelial surface, & mucin molecules that increase the residence time of the dosage form at the site of the absorption. Hence mucoadhesive drugs rapidly absorbed in mucus layer that increases bioavailability due to its considerable surface area. It was very critical concept to prepare mucoadhesive patches of Clofarabine which is used to treats acute lymphoblastic leukemia in pediatric and adult people with having a common side effect of Capillary leak syndrome (CLS) but this side effect along with other side effects minimizes by preparing Mucoadhesive buccal patches. We had prepared the mucoadhesive buccal patches by Solvent casting method using different concentrations of hydrophilic Polymers. Solubility of Clofarabine increases thrice by using beta-cyclodextrin for the formation of inclusion complexes. Using lower concentration of sodium alginate and higher concentration of cross povidone is used to release the drug from the buccal patches comparing to the concentration of HPMC and CMC. Maximum *In vitro* drug release 94% over a period of 8 h was observed by using higher concentration of Cross povidone for the preparation of a Mucoadhesive buccal patches. The use of hydrophilic polymers in the prepared Clofarabine buccal patches was able to substantially enhance the percentage of drug released from the patches, thereby increasing bioavailability.

Keywords: Capillary leak syndrome (CLS), Mucoadhesive drug delivery system, BCD, Solvent Casting method

Introduction
In this context, mucoadhesive drug delivery system interacts with the mucus layer and covered the mucosal epithelial surface & mucin, which increase the residence time of the dosage form at the site of the absorption. Therefore Mucoadhesive drug delivery system is considered as a part of Novel Drug Delivery system, which act as locally and topically increases the rate of bioavalability. Mucoadhesive drugs are rapidly absorbed in mucus that put forth the rate of bioavailability. Mucoadhesive drugs placed in mucosa that bypasses the first-pass hepatic metabolism and avoiding the degradation of gastrointestinal enzymes. The macro molecules like proteins and oligonucleotides are easily delivered in mucus membrane.
Since the early 1980, the concept of Mucoadhesion has gained considerable interest in pharmaceutical technology. The modified development that overcomes some obstacles like enzyme inhibitory & penetration enhancer properties which improve the patient compliance. Depending upon the route of administration, the mucoadhesive drugs are delivered in 7 different ways like Buccal, Sub lingual, Vaginal, Rectal, Nasal, Ocular and Gastro intestinal system which offer several advantages over other controlled oral controlled release systems by virtue of prolongation of residence of drug in GIT and Targeting & localization of the dosage form at a specific site. MDDS will serve both the purposes of sustain release & presence of dosage form at the site of absorption with Painless administration & avoid of first pass metabolism. Buccal delivery of drugs provides an attractive alternative to the per oral administration of drugs, particularly in overcoming deficiencies associated with the latter mode of administration. Various studies have been carried out to formulate a wide range of mucoadhesive buccal drug delivery devices, including tablets, films, and patches,

disks, ointments, and gels. Among these formulations, buccal patches are preferred owing to their good flexibility compared with tablets and more accurate dosing of the drug in comparison with gels and ointments. [1, 2]

Surface area of the mucosal is about 100 cm^2, and three are three different types of mucosal layer is found on tongue. The buccal epithelium is composed of multiple layers of cells which present between the deepest cells and the surface. Mucus is a translucent and viscid secretion which contains Water - 95%, Glycoprotein and lipids - 0.5-5% with Mineral salts - 1% and Free proteins - 0.5-1%. Buccal patches can be formulated to exhibit a systemic or local action. By the development of this novel technology, the release of the drugs takes place in oral cavity or in buccal mucosa that also give an advantage of avoiding the first pass effect **[3]**

Buccal patches are consisting of an impermeable backing layer, where the drug is reserved from which the drug is released in a controlled manner, and a bioadhesive surface for mucosal attachment.

Mucoadhesive patches are prepared by two methods like solvent casting and direct milling.

1. In the solvent casting method, the patches are prepared by casting the solution of the drug and polymers onto a backing layer which subsequently allowed the solvents to evaporate.
2. In the direct milling method, drug and polymers are homogenously mixed and compressed in a certain thickness with a desired size and shape, then cut or punched out. [4 - 6]

Advantages of the buccal patches

- Most significantly buccal patches improve the bioavailability of the drugs due to having considerable surface area.
- Buccal patches mainly avoiding drug metabolism in the liver that bypassing the First-Pass Effect due to drug directly enters the bloodstream.
- It enhances the effectiveness of the drug due to directly reaches the blood stream.
- Buccal patches dissolve quickly as drug immediately contact with saliva, so it gives rapid onset of action.
- So buccal patches give immediate therapeutic action.
- It should reduce side effects because of very low content of the drug used in the formulation.
- As drug bypasses the Digestive System it reduces the side effect like irritation, nausea and gastrointestinal discomfort.
- Buccal patches are very convenient because of light weight and easy to transport.
- Shelf medication is possible in case of use of Buccal patches.

Buccal patches are types of drug formulation that can help drugs enter the systemic circulation. They are made of mucoadhesive polymers, which have smooth surfaces and can release drugs in a controlled manner. To sustain the therapeutic effect, it is essential to extend the intimate association between active(s) and the membrane barrier of buccal tissue. Mostly proteins, peptides and some steroids are degraded easily on the GI tract so those drugs formulated as mucoadhesive buccal patches that not degraded by digestive fluid and the rate of drug absorption also not influenced by the gastric emptying rate.

Buccal Patches can shift the drug aside from the site of absorption hence decreasing the contact time and change in distribution kinetics of the drug. From the buccal patches drug easily released and permeate across the mucosal membrane to systemic circulation and also into sub mucosal epithelial layers unaffected by the impact of salivary flow, pH, electrolytes, and mucosal enzymes [7].

Aim of the project work

- Need to develop a process to prepare the Clofarabine buccal patches.
- As like parenteral preparation, drug directly administered to the blood stream from the mucus membrane.
- Improve the solubility of the drug Clofarabine by using the complexation process using beta-cyclodextrins(βCD) and Crospovidone
- Also determine in which ratio of the mixture of βCD-Clofarabine-Crospovidone for the Clofarabine buccal patches.
- Majority anticancer drugs induces Capillary leak syndrome (CLS) that also can be caused by the drug Clofarabine. But in buccal patches of Clofarabine contain fewer drugs as compaired to injectable preparation.
- That also avoids many side effects.

Materials

Clofarabine collected from Care Exim, Abhyankar Nagar, Nagpur, Maharashtra as gift sample, HPMC K30, Crospovidone, beta cyclodextrin purchased from Krishkan Chemicals, Thaltej Village, Ahmedabad, other ingredients like glycerine, PVA, sodium alginates collected from Sri Jayadev College of Pharmaceutical Sciences, Naharkanta, Odisha Laboratory. All ingredients used for my project work were in analytical grade.

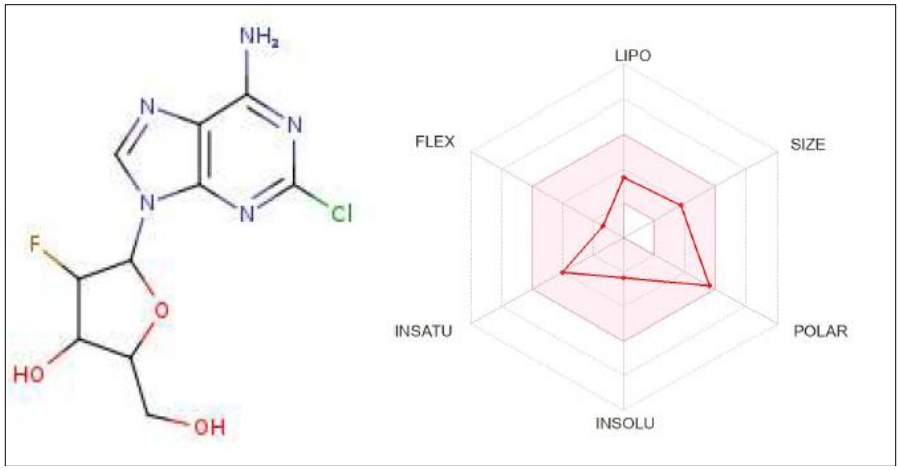

Fig 1: Structure Clofarabine

Clofarabine is a purine nucleoside antimetabolite used for treating relapsed or refractory acute lymphoblastic leukemia (ALL) in children after at least two other types of treatment have failed. Ongoing trials are assessing its efficacy for managing other cancers.

Methods

1. Enhancing the Solubility of Clofarabine by using B-Cyclodextrin

Taking 20 mg of Clofarabine mixed with B - Cyclodextrin in different proportion from 25% to 200% of weight of Clofarabine in 100ml of distilled water. Making the inclusion complexes of Clofarabine with beta- cyclodextrin· [8-9]

Table 1: Increasing BCD improves drug solubility through inclusion complex formation, reaching a plateau at 10-15 mg BCD.

Drug (mg)	BCD (mg)	Inclusion complexes	Solubility of Drugs (mg/ml)
10	0	10	0.15
10	2.5	12.5	0.19
10	5	15	0.23
10	7.5	17.5	0.25
10	10	20	0.3
10	15	25	0.3
10	20	30	0.29

2. Analytical methods for Clofarabine estimation

A. Standard curve using UV

Standard solutions of Clofarabine were prepared (5-30 µg/ml) in saline phosphate buffer. The absorbance was measured at 263 nm and calibration curve was constructed.

B. Standard curve using HPLC

Another set of standard solutions of Clofarabine was prepared (5-50µg/ml) in mobile phase. HPLC analysis of Clofarabine was performed using a 2000 pump set at flow rate of 1 ml/min, a Spectra UV 2075 detector set at 263nm. Samples were injected using an injector at 20µl capacity per injection was used. The column used was 4.6 mm, 5.0µm particle size and a mobile phase of methanol: water: glacial acetic acid (70:30:0.3). 221 the calibration curve was obtained from the area of peak measured.

3. Drug Polymer interaction studied by FTIR study

Clofarabine FTIR spectra Figure 1 show peaks indicating O-H (around 3460 cm^{-1}), N-H (around 3107 cm^{-1}),Ar-CH(3042 cm^{-1}) , CH_2(CH cm^{-1}), Beta NH_2(1708), (C=C (around 1621 cm^{-1}), C=N (around 1550 cm^{-1}), C-O (around 1055 cm^{-1}), C-F (around 1305 cm^{-1}), C-N (around 1288 cm^{-1}), and C-Cl (around 710 cm^{-1}) stretching and bending vibration.

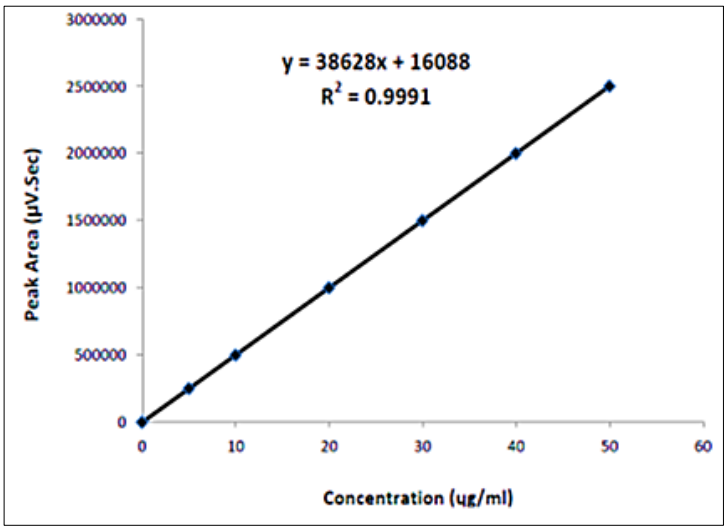

Fig 2: FTIR study of Clofarabine alone

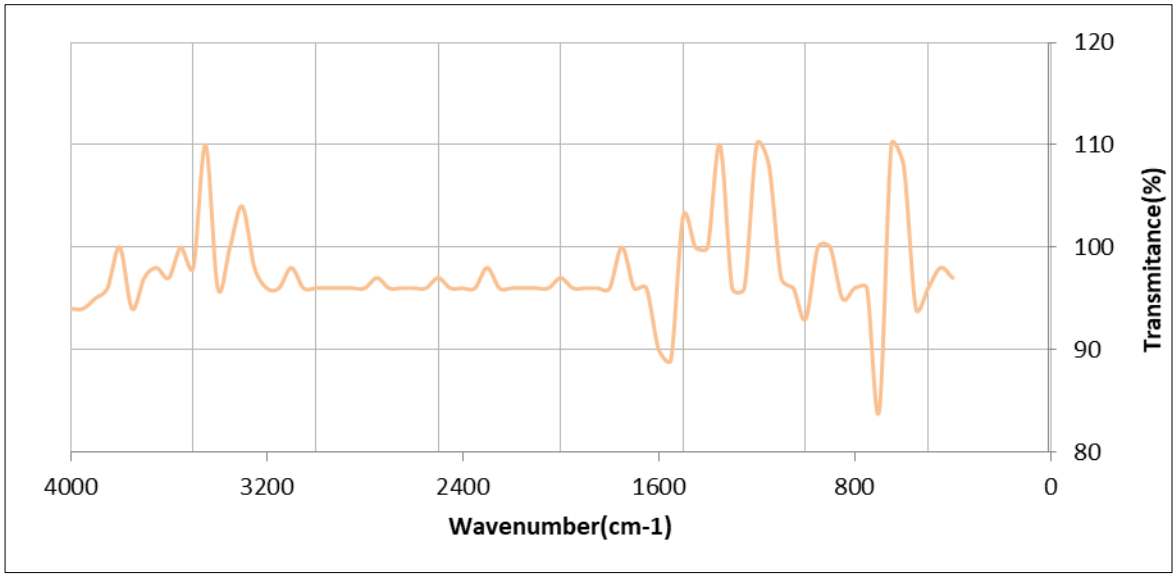

Fig 3: FTIR Study of Drug + Sodium alginate

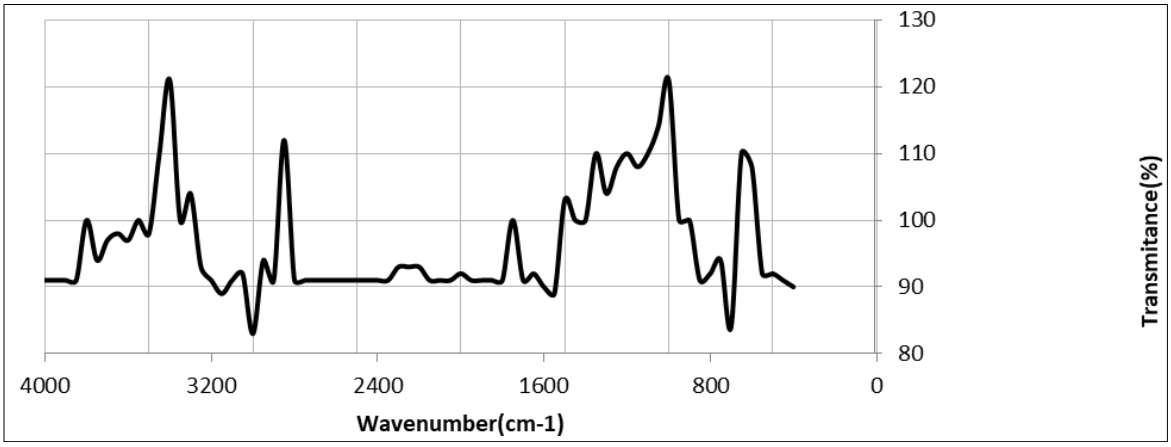

Fig 4: FTIR Study of Drug + HPMC

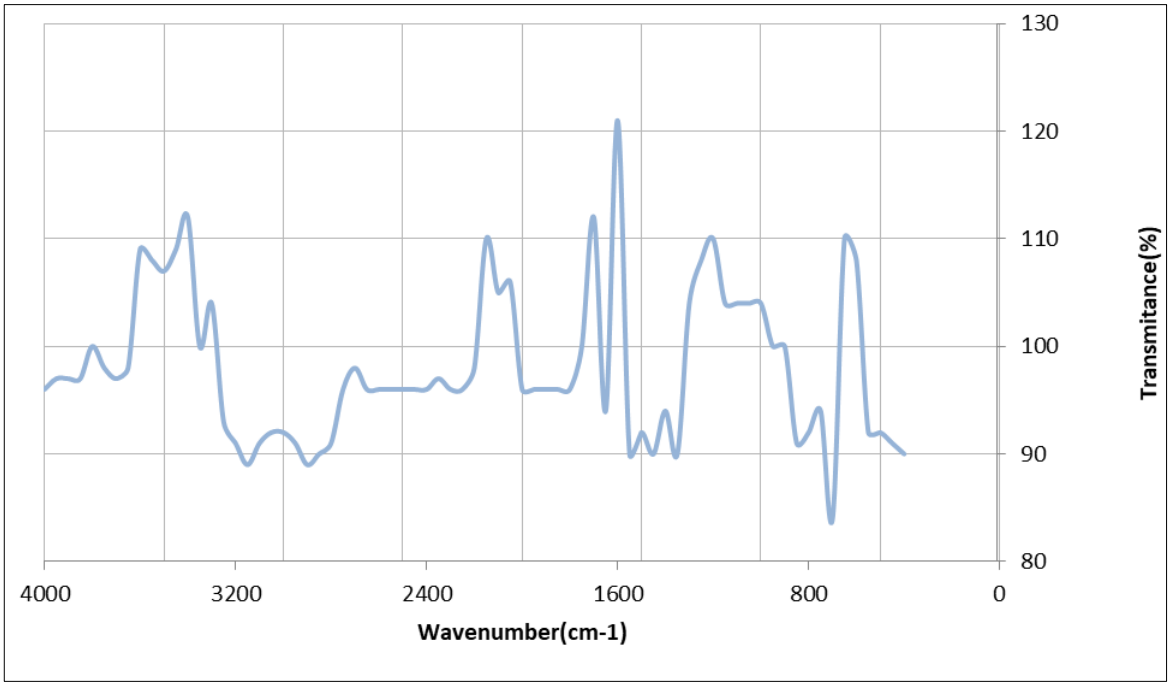

Fig 5: FTIR Study of Drug + Cross-povidone

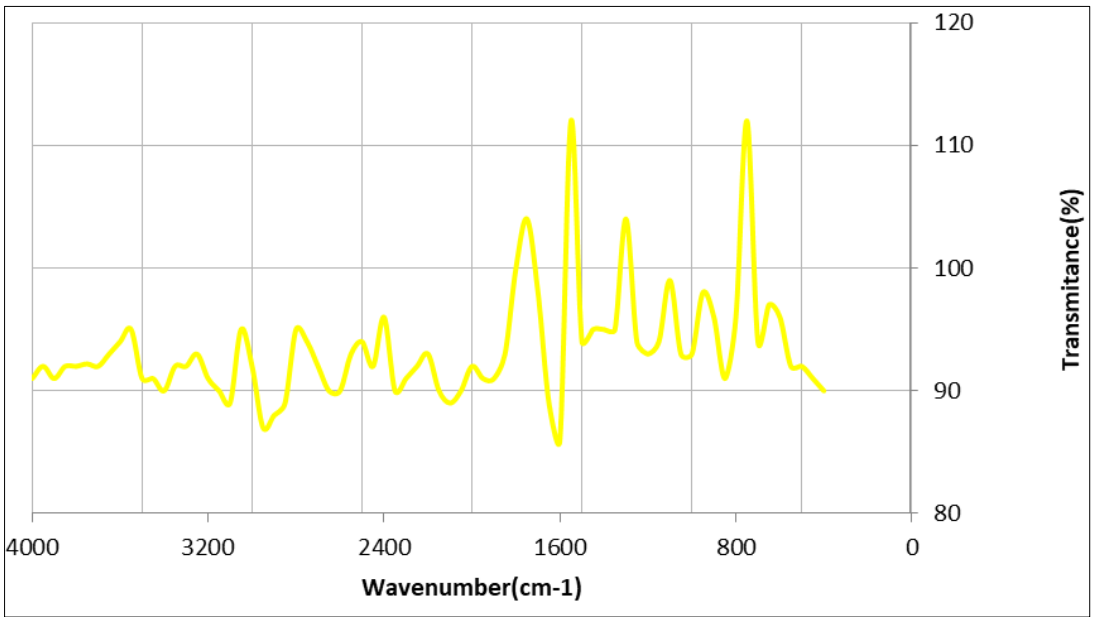

Fig 6: FTIR Study of Drug + CMC

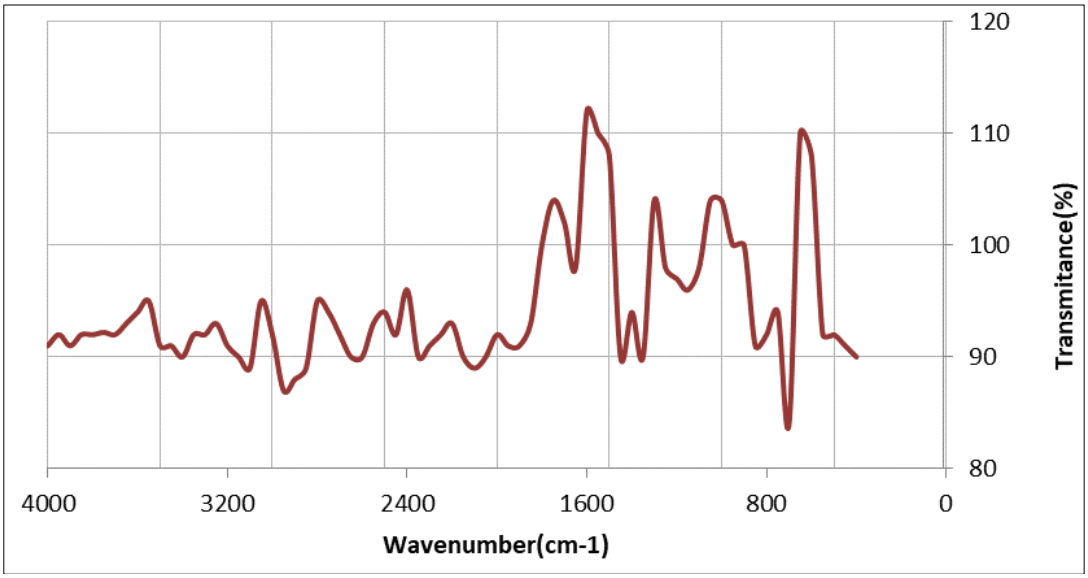

Fig 7: This FTIR spectrum shows transmittance (%) versus wavenumber (cm^{-1}), highlighting key absorption bands that identify the sample's chemical bonds and functional groups.

FTIR spectra shown in Figure 2, 3, 4 & 5 indicate that drug showing all the peaks in the prominent manner even though combined with the different polymers which clearly indicates polymers are not reacting with the drugs, we had concluded that all the polymers are compatible with the Clofarabine drugs.

4. Preparation of Clofarabine Buccal patches

Clofarabine buccal patches prepared by using of different proportions of combinations of sodium alginate from 300 mg to 400 mg, HPMC K30 from 100 mg to 200 mg, Crospovidone from 100 mg to 200 mg and Carboxy methyl cellulose from 100 mg to 200 mg with containing Clofarabine 20 mg were prepared using a 54-cm^2 petri dish by solvent casting technique. Glycerin was incorporated as a plasticizer at a concentration of 10% w/w of dry weight of polymers. Backing membrane was casted by pouring 4% w/v aqueous solution of PVA on aluminum foil in petri dishes at 42 °C and left for 10 hr. Phosphate buffer saline, pH 6.8, was used as solvent in the casting method. [10]

40 mg of Clofarabine inclusion complexes was incorporated in mixtures containing different ratios and combinations of polymers and plasticizer. The matrices were prepared by pouring 20 ml of the homogeneous solutions on the PVA-aluminum foil backing membrane. Then, these buccal patches were dried at 42 °C in an incubator. After 24 h, the dried patches were removed from the petri dishes and kept in desiccators until use.

Table 2: The table lists twelve formulations with different amounts of Sodium Alginate, HPMC K30, Cross Povidone, and Carboxymethyl Cellulose, each containing 40 mg of Clofarabine inclusion complex. These variations help optimize the drug delivery system.

Formulation	Sodium Alginate	HPMC K30	Cross povidone	Carboxymethyl Cellulose	1:1Clofarabine Inclusion complex
F 1	400	100	-	-	40
F 2	350	150	-	-	40
F 3	300	200	-	-	40
F 4	400	-	100	-	40
F 5	350	-	150	-	40
F 6	300	-	200	-	40
F 7	400	-	-	100	40
F 8	350	-	-	150	40
F 9	300	-	-	200	40
F 10	200	100	100	100	40
F 11	275	75	75	75	40
F 12	350	50	50	50	40

Evaluation of the Clofarabine Buccal patches

1. Patches Weight and Thickness

The weight of each prepared Patches was measured using a digital balance among the three Patches of every formulation and the average weight was calculated. Similarly the thickness of each Patches was measured using a micrometer screw gauge at different points of the Patches and the average was calculated. [12]

2. Folding Endurance

Folding endurance of the Patches was premeditated by repeatedly folding one Patches at the same place till it broke or folded up to 300 times manually. The number of times the Patches could be folded at the same place until it breaks gives you value of folding endurance. [13]

3. Tensile Strength

It is defined as the resistance of the material to a force tending to tear it separately and is identified as the maximum stress in the stress-strain curve. Patches were held between two clamps positioned at a distance of 3 cm and were pulled by the top clamp at a rate of 100 mm/m, the force and elongation were measured when the Patches broke. It was calculated by the replicate. It is given by the following equation, [14, 15]

$$\text{Tensile strength} = \text{Force at break (N)} / \text{Cross - sectional area of the Patches } (mm2).$$

4. Elongation Break

The elongation at break is a measurement of the maximum deformation the Patches can undergo before tearing apart. It is calculated using the following equation. [16]

$$\text{Elongation at break} = \text{Increase in length of break} / \text{Initial Patches length} \times 100$$

5. Determination of Drug Content

The drug contents in the buccal patches were determined by dissolving 1 cm2 patch in 100 ml phosphate buffer saline solution and shaken vigorously for 24 h at room temperature. These solutions were filtered through Whatman filter paper (No. 42). Spectrophotometrically determining the drug content using a UV-VIS spectrophotometer at 263 nm against a blank. The drug content was estimated from the calibration curve, which was constructed between 1 and 5 µg/ml concentration ranges. [17]

The method was validated for linearity, accuracy, and precision. The regression equation for the calibration curve was

$$Y = 0.048X + 0.002,\ R2 = 0.9990.$$

6. Determination of Moisture Content and Moisture Absorption

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed.[18] The moisture content (%) was determined by calculating moisture loss (%) using the formula:

$$\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The buccal patches were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of aluminum chloride, which maintains 76% and 86% relative humidity (RH).

7. *In vitro* release study

The *In vitro* drug release study was carried out using a Franz diffusion cell. The effective diffusion area was 1.8 cm^2. The receptor compartment (40 ml) was filled with phosphate buffer saline (PBS), pH 6.8. The patches were applied under occlusion on the dialysis membrane fitted between the donor and receptor compartments of the diffusion cell. The drug release was performed at 37±0.5 °C, at a stirring speed of 50 rpm using a magnetic stirrer. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of Clofarabine released into the receptor medium was quantified by using UV-visible spectrophotometer at 263 nm against a blank. [19, 20]

Results and Discussion

Clofarabine patches were prepared by using an inclusion complex. 20 mg Clofarabine buccal patches were prepared whose weight was varies from 1000 mg to 1107 mg. We had chosen the optimized formulation which was in the range of 1005 mg and 1024 mg.

Table 3: The formulations exhibit uniform weight, consistent thickness, good folding endurance, and high drug content, indicating stable and mechanically strong patches.

Formulations	Weight variation (gm)	Thickness (mm)	Folding endurance	Drug content (%)	Moisture content (%)
F 1	1.03±0.06	~ 0.34	81	99	1.3
F 2	1.09±0.03	~ 0.36	83	98	1.4
F 3	1.10±0.06	~ 0.37	88	99	1.7
F 4	1.03±0.05	~ 0.33	80	98	1.2
F 5	1.02±0.04	~ 0.33	80	99	1.1
F 6	1.00±0.05	~ 0.34	83	99	1.1
F 7	1.09±0.07	~ 0.38	83	98	1.4
F 8	1.07±0.08	~ 0.36	84	98	1.6
F 9	1.10±0.09	~ 0.35	82	98	1.6
F 10	1.10±0.09	~ 0.36	80	99	1.3
F 11	1.11±0.07	~ 0.34	93	99	1.6
F 12	1.02±0.08	~ 0.39	86	99	1.7

Thickness was found to vary from 0.3 to 0.4 mm. we had selected from our prepared formulation which were 33mm and 34 mm.

Folding endurance for patches were in the range of 80 to 85 was due to use of sodium alginate, we concluded that as we had use less alginate and more cross povidone having less folding endurance.

Drug release perfectly from the Clofarabine patches, all drugs were easily releases from the prepared Clofarabine patches that mostly 99% of the drug released.

Moisture content of the buccal patches were range from 1% to 2%, we found that due to use of less content sodium alginate and high content of Crospovidone having less moisture. The *In vitro* drug release pattern of Clofarabine from formulated buccal patches is shown in Figure 6. All of these buccal patches slowly released the drug, incorporated and sustained over a period of 8 h.

The drug release from buccal patches varied with respect to the polymer composition and nature. An increase in drug release from the buccal patches was found with increasing concentration of polymers that are more hydrophilic in nature. Among all formulations, the maximum *In vitro* drug release 94% over a period of 8 h was observed in the case of formulation no. F 6, while the minimum *In vitro* drug release (80%) over a period of 8 h was found in the case of formulation no. F 3, the *In vitro* drug release was more sustained for the Clofarabine buccal patches which were composed with high proportion of HPMC

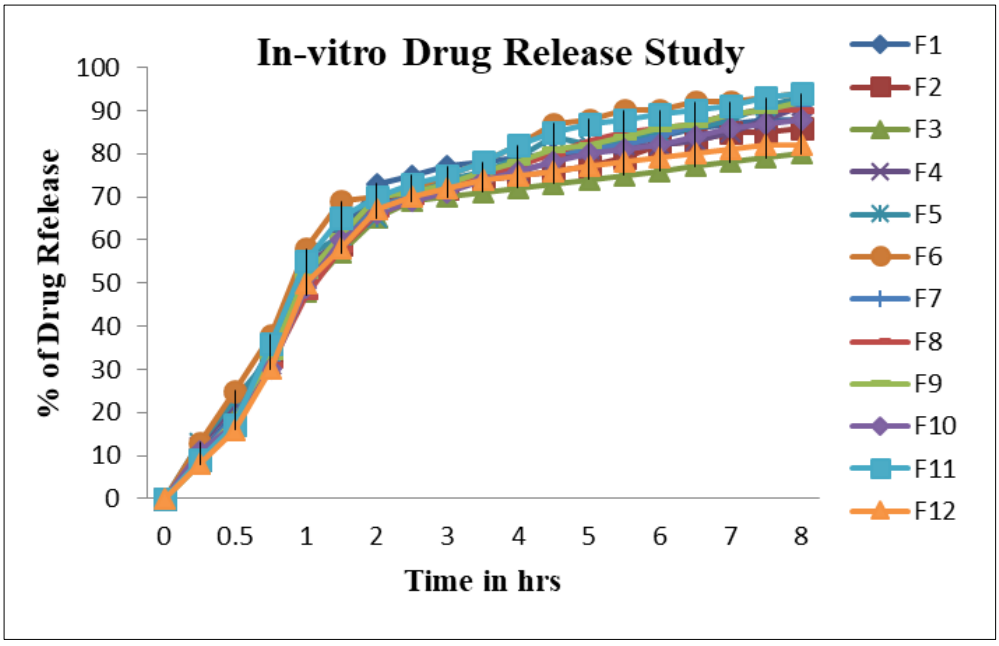

Fig 6: *In-vitro* Drug release from Clofarabine Buccal patches

Conclusion

Clofarabine buccal patches were prepared by using different polymers like sodium alginate, Hydroxy Propyl Methyl Cellulose (HPMC), Crospovidone (CP) and Carboxy methyl Cellulose (CMC) in various proportions and combinations showed satisfactory Using lower concentration of sodium alginate and higher concentration of cross povidone is used to release the drug from the buccal patches comparing to the concentration of HPMC and CMC. Whereas concluded that with increasing HPMC the release of the drug decreases from the buccal patches. Also we had concluded by taking the combination of all polymers like higher concentration of Crospovidone and lower concentration of Sodium alginate, HPMC and CMC also increases the *In-vitro* drug release from the Clofarabine mucoadhesive buccal patches. Solubility of the drug increases thrice by using beta-cyclodextrin for the formation of inclusion complexes. The use of hydrophilic polymers in the prepared Clofarabine buccal patches was able to substantially enhance the

percentage of drug released from the patches, thereby increasing bioavailability.

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