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Development and evaluation of buccal film containing antihypertensive agent

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Abstract
The present study illustrates development of site specific delivery of metoprolol succinate in treatment of hypertension. Formulations were developed by utilizing polymers such as HPMC and Chitosan along with plasticizer (PEG-400) by solvent technique. The calibration curve of metoprolol succinate was developed in PBS pH 6.8 at 223 nm in the range of 5 to 25 µg/ml. Compatibility study were carried out by FT-IR and Differential scanning colorimetry. The formulations were evaluated for thickness, folding endurance, weight variation, drug content, percent moisture loss, percent moisture absorption, tensile strength, SEM. *In vitro* drug diffusion study was also carried out using franz diffusion cell with PBS pH 6.8 and the samples were analyzed by UV-spectrophotometrically at 223 nm. FT-IR and DSC study revealed no interaction between drug and polymers. Formulations shown good uniformity of drug content more than 90%, there is little effect on moisture loss test due to hydrophilic polymers. Formulations showed thickness within the range of 0.17 to 0.28 in (F1, F2) HPMC. Whereas with ethyl cellulose thickness found to be 0.30, 0.35 mm respectively. All formulation showed good tensile strength. By increasing the concentration of polymer in the formulation increases the tensile strength, and folding endurance. But with use of ethyl cellulose it decreases the tensile strength. The buccal film formulated with 1:1 and 2:1 ratios of EC and HPMC, EC and CHITOSAN predominantly occurred by a diffusional process. This method could be used as an effective alternative delivery system for Metoprolol succinate when compared with conventional tablet formulations.

Keywords: Metoprolol succinate, buccal film, physical characterization, *in vitro* diffusion, stability testing.

1. Introduction
Buccal delivery is defined as drug administration through the mucosal membranes lining the cheeks and as an attractive route for systemic delivery of drug with relative permeable with a rich of blood supply. It has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Drugs are absorbed into the systemic circulation. An expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Drugs are absorbed into the systemic circulation through the deep lingual or facial vein, internal jugular vein, and braciocephalic vein which bypasses drugs. Avoids hepatic first pass metabolism leading to high bioavailability amongst various routes of drug delivery, an oral route is perhaps the most preferred to the patient and clinicians alike [1]. The inherent problem associated with in some drug, can be solved by modifying the formulation. There are the need alternative routes for the systemic drug delivery drugs.

Buccal region is that part of the mouth bounded interiorly and laterally by the lips and the cheeks, posterior and medially by the teeth and/or gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums. The oral cavity comprises the oral mucosa situated within the dental arches framed on the top by the hard and soft palates and in the bottom by the tongue and floor of the mouth. The total surface area of the oral cavity is about 170 cm^2 in humans. The "buccal cavity" refers to that part of the oral cavity covering the inside of the cheek, whereas the "sublingual region" refers to that portion of the oral cavity underlying the tongue. In the oral cavity, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after damage [2].

Many antihypertensive drugs are used in the treatment of congestive heart failure, cardiac arrhythmias and angina pectoris. It exhibits poor bioavailability of 25-30% which undergoes to its high first pass metabolism. Hirlekar designed buccal drug delivery system for poorly soluble drugs [3].

Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms, because it has expanse of smooth muscle which is relatively immobile, abundant vascularization, rapid recovery time after exposure to stress and the near absence of langerhans cells [4].

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods and also enhances drug bioavailability because the mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding, in most cases, degradation by first-pass hepatic metabolism [5]. Drugs administered via the parenteral route gain direct access to the systemic circulation and produce effective plasma levels of drugs. However, this route is associated with pain on administration, formulations need to be sterile, and it is time consuming for doctors and patients. In addition certain health risks are associated with this route and include problems such as psychological distress and occasional allergies [2].

Hypertension is high blood pressure is a condition in which the blood pressure on the arteries is chronically elevated. With every heart beat, the heart pumps blood through the arteries to the rest of the body. Blood pressure is the force of blood that is pushing up against the walls of the blood vessels. If the pressure is too high, the heart has to work harder to pump, and this could lead to organ damage and several illnesses such as heart attack, strock, heart failure or renal failure. Hypertension is classified as, Primary (essential) hypertension Secondary hypertension; about 90–95% of cases are categorized as "primary hypertension," which means high blood pressure with no obvious medical cause. The remaining 5–10% of cases (Secondary hypertension) is caused by other conditions that affect the kidneys, arteries, heart or endocrine system. Hypertension is defined conventionally as a sustained increase in blood pressure 140/90 mmHg, criterion that characterizes group of patients whose risk of hypertension-related cardiovascular disease is high enough to merit medical attention. Actually, the risk of both fatal and nonfatal cardiovascular disease in adults is lowest with systolic blood pressures of less than 120 mmHg and diastolic BP less than 80 mmHg; these risks increase progressively with higher systolic and diastolic blood pressure [6].

Chitosan is a natural biocompatible and bio degradable polymer, extensively used in the development of mucoadhesive buccal drug delivery. Chitosan has an excellent film forming ability and better mucoadhesive property. The mucoadhesive property of Chitosan either due to its ability to form secondary chemical bonds such as hydrogen bonds or ionic interactions between the positively charged amino groups of chitosan and the negatively charged mucin. Apart from this chitosan has a cell binding and membrane permeation activity. HPMC is a semisynthetic cellulose derivative, biocompatible, has a variety of application in novel drug delivery systems including mucoadhesive property. The property of HPMC to form a strong, flexible film, made the polymer touse in this investigation. It is stable over a pH range of 3 to 11. Apart from this HPMC has the ability to absorb water and swell, so enhancing the thickness of the film, thus an ideal candidate for mucoadhesive buccal systems [7].

Metoprolol is a beta1-selective (cardio selective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, Metoprolol also inhibits beta2-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Because of these desired pharmacodynamic properties, Metoprolol is used popularly for management of hypertension [8].

2. Materials

Metoprolol succinatewas obtained as gift sample by Nicholas Piramal Ltd., Mumbai, India. HPMC K100 (Aldrich chemistry, Mumbai, India), Chitosan (Loba Chemie, Mumbai, India), Polythylene Glycol, Sodium Chloride, Methanol (Loba Chemie, Mumbai, India), Calcium Hydroxide (S.D. Fines, Mumbai, India). all other ingredients were of analytical grade.

3. Methods

3.1 Formulation: The Buccal film formulations were prepared in the laboratory using the polymer such as HPMC and chitosan with the use of plasticizer (PEG-400) by solvent casting method. Formulations were prepared by dissolving drug in distilled water (10 ml) then stirred it on magnetic stirrer with 30/min rpm. (For the preparation of EC based film, ethyl cellulose was dissolved in a 5 ml methanol). Both the solutions were mixed and plasticizer PEG 400 was also added stirred it well on magnetic stirrer (rpm 30/min). The above solution was allowed to stand for 30 min for deaeration. The solution was casted on a petridish (diameter 8.8cm) and dried at room temperature for 24 hr. And for chitosan base buccal film, make acetic acid 1% solution and dissolve chitosan for deacetalyztion. Same procedure follows as film of HPMC. Film was carefully removed from the petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose (2×2 mm^2 per film) containing of 4 mg of drug. The samples were stored in desiccators at relative humidity 30-35% until further analysis.

Table 1: Formulation Composition

2	F1	F2	F3	F4	F5	F6	F7	F8
Drug (mg)	4	4	4	4	4	4	4	4
HPMC K100 (gm)	0.2	0.3	0.2	0.3	–	–	–	–
CHITOSAN (gm)	–	–	–	–	0.2	0.3	0.2	0.3
PEG-400 (ml) (%w/w of polymers)	10%	10%	10%	10%	10%	10%	10%	10%
ETHYL CELLULOSE (gm)	-	-	2%	2%	-	-	2%	2%
Total solvent SOLVENTS (ml)	10	10	10	10	10	10	10	10

3.2 Thickness Uniformity
The thickness of films was measured by using Digimatic Micrometer (Mitutoyo, ABSOLUTE). The thickness of each film was determined at six different places and their average was calculated. The standard deviation of thickness was computed from the mean value [9].

3.3 Drug Content Uniformity
To check the uniformity of the drug in the film (2x 2 Sqcm^2), three films were taken out from each batch. Each film was then placed in volumetric flask containing 10ml of distilled water and shaken to extract the drug from film. One milliliter of above resulting solution was withdrawn, after suitable dilution with distilled water and analyzed UV-spectrophotometrically at 223 nm using distilled water as blank. The mean and standard deviation of drug content of three randomly selected films were calculated. The same procedure was adopted for all the batches and drug content was noted [10].

3.4 Weight Uniformity
Films (size of 2 x 2 mm^2) were cut from different areas of film. The weight of each film was taken and the weight variation of six films was calculated. The standard deviation of weight was computed from the mean value [11].

3.5 Folding Endurance
The folding endurance of the films was determined by repeatedly folding one film at the same place till it broke or folded up to 200 times, which is considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking give the value of the folding endurance. This test was done on all the batches for five times [12].

3.6 Percentage Moisture Loss Test
Percentage moisture loss test was determined by keeping the films (2 x 2 cm^2) in a desiccator containing anhydrous calcium chloride. After 3 days, the films were taken out, re-weighed and the percentage moisture loss was calculated using the following formula [13].

Percentage Moisture Loss= ((Initial weight -Final weight)/ Initial weight) x 100

3.7 Percentage Moisture Uptake/absorb
The weighed patches were kept in desiccators at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the film were reweighed and determine the percentage moisture uptake from the below mentioned formula.

Percentage moisture uptake = [Final weight-Initial weight/ Final weight] ×100

3.8 Tensile Strength and: Tensile strength of the Films was determined with "Texture analyzer" testing machine. It consists of two load cell grips. The lower one is fixed and upper one is movable. The test film of specific size was fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the films was taken directly from the dial reading. Same procedure was repeated for three times and standard deviation was calculated from mean values [14].

Tensile Strength = (breaking load /surface area)

3.9 Swelling index
Buccal films are weighed individually (W1) and placed separately in petri-dish containing phosphate buffer pH 6.8. The buccal films are then removed from the petri dish and excess surface water is removed using filter paper.
The buccal films are reweighed (W2) and swelling index (SI) was calculated as follows:

S.I. = (W2-W1)/W1

Whereas:
S.I. = Swelling index
W2 = Final weight
W1 = Initial weight

3.10 Surface pH of the buccal film- It was determined by the method described by Bottenberg *et al*. The buccal films were allowed to swell by keeping them in contact with 0.5 ml of double distilled water for 1 hour in glass tubes. The surface pH was then noted by bringing a combined glass electrode near the surface of the buccal film and allowing it to equilibrate for 1 minute.

3.11 *In vitro* diffusion study- *In vitro* diffusion study was performed by using modified franz diffusion cell across cellophane membrane. Phosphate buffer solution (PBS) of pH6.8 was used as medium for diffusion study. Buccal filmes of dimension 2x2 cm^2 were placed on the membrane, which was placed between donor and receptor compartments of Franz diffusion cell. Cellophane membrane was brought in contact with PBS of pH 6.8 filled in receptor compartment. Temperature was maintained at 37 ^{0}C with stirring at 50 rpm using amagnetic bead stirrer. 1ml of sample was withdrawn from a receptor compartment at pre-determined interval and was replaced with fresh PBS of pH 6.8. With suitable dilution, samples were measured for absorbance at 223 nm using UV visible spectrophotometer [12].

3.12 Stability Study-Stability studies were carried out on formulation, according to ICH guidelines by storing replicates of films (packaged in aluminum foil) in a humidity chamber, with a relative humidity of 75± 5% and a temperature of 40±0.5 °C. At periodic intervals the samples were taken out at 0, 15, 45 and 90 days and the period for their degradation of the film was checked. Samples were also analyzed for drug content [15].

3.13 Surface electron microscopy: The morphology of films were determined using SEM /JSM 5610 LV, Jeol Datum Ltd. Japan operated at an accelerating voltage of 10 kV [16].

4. Result and Discussion
4.1 Drug – excipients compatibility studies: As described in the methodology FT-IR studies were carried out on pure drugs and along with the polymer.IR spectra of drug and polymer in figures.

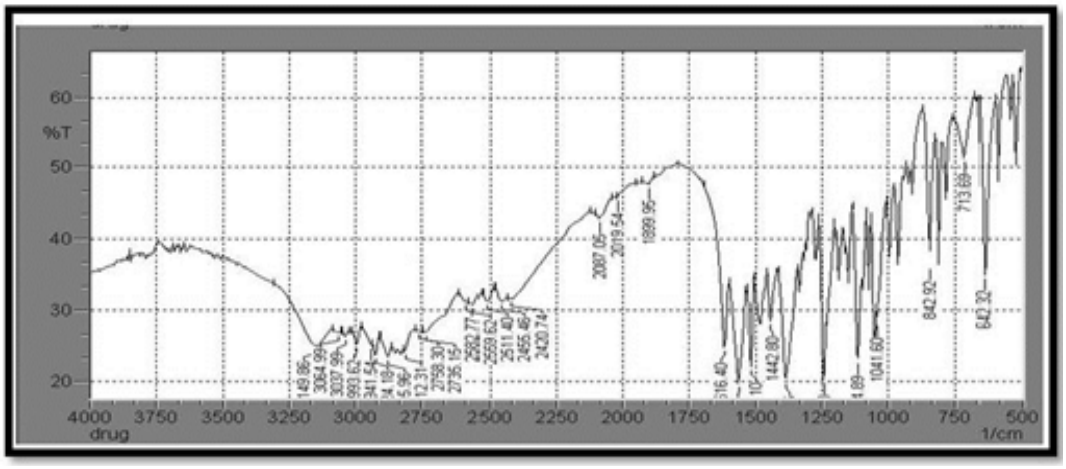

Fig 1: FTIR Spectra of Metoprolol succinate

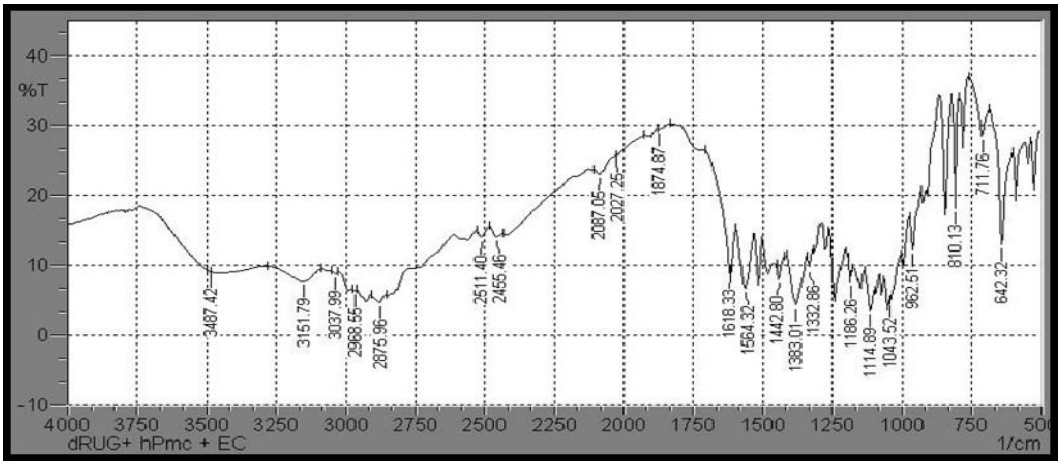

Fig 2: FTIR Spectra of drug, HPMC and ethyl cellulose

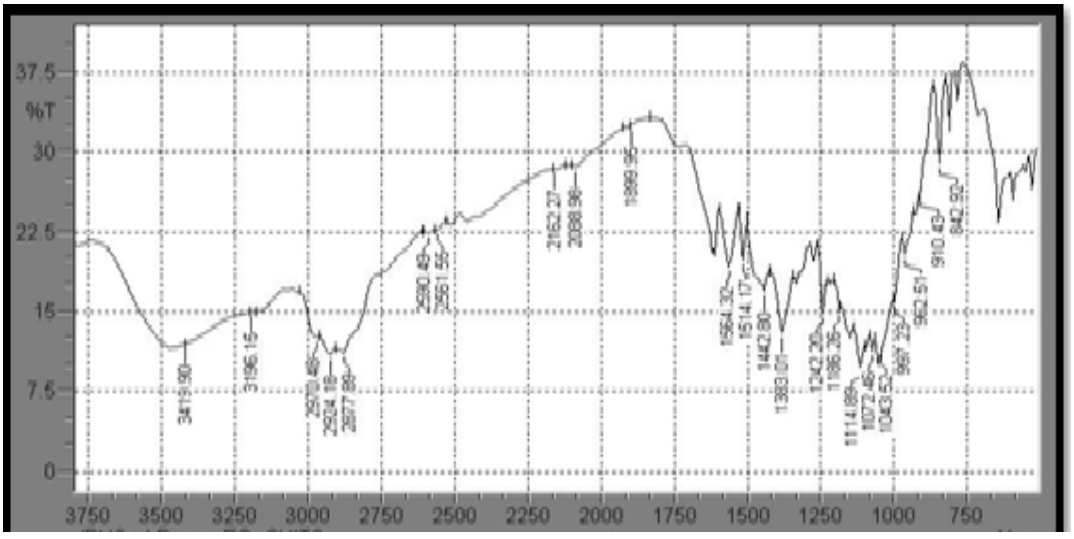

Fig 3: FTIR Spectra of metoprolol succinate, Chitosan and ethyl cellulose

4.2 Drug polymer compatibility: by Differential Scanning Colorimetry (DSC): The DSC thermogram of pure drug and polymer utilized in the system of formulations are presented in following figures

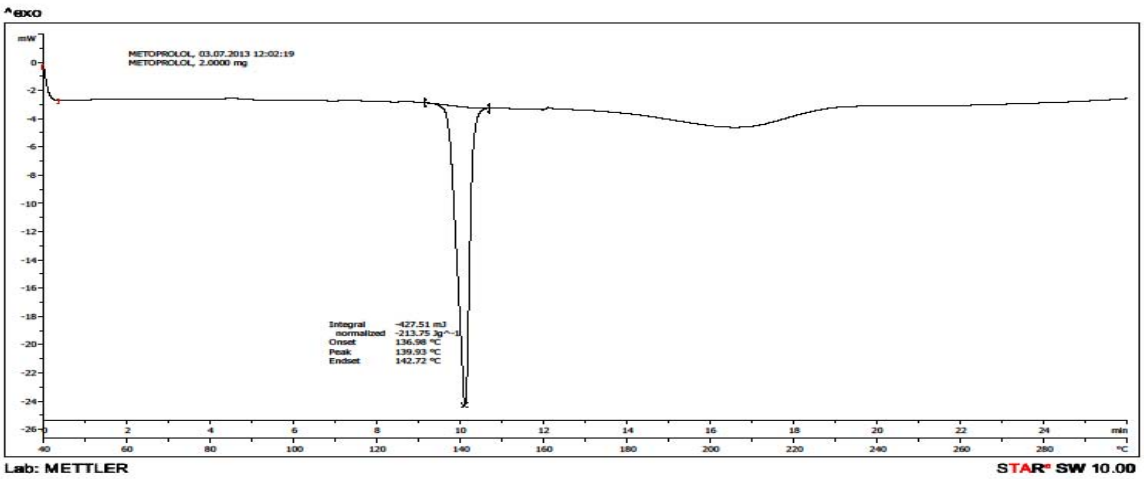

Fig 4: DSC thermogram of physical mixture of Metoprolol succinate and HPMC K100, ethylcellulose

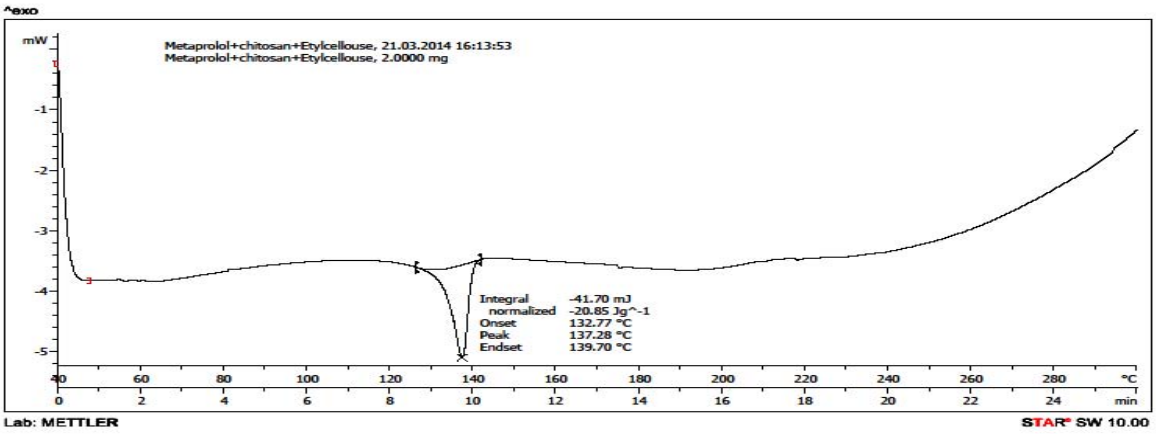

Fig 5: DSC thermogram of Drug, Chitosan and ethyl cellulose batch

Table 2: Physical Characterization of Developed Films

Code	F1	F2	F3	F4	F5	F6	F7	F8
Thickness (mm)	0.17 ±0.05	0.28 ±0.05	0.30 ±0.05	0.35 ±0.04	0.41 ±0.056	0.46 ±0.041	0.44 ±0.052	0.49 ±0.041
Drug content (%)	91.75 ±0.03	94.66 ±0.01	90 ±0.02	87.6 ±0.06	90.25 ±0.02	92.50 ±0.03	92 ±0.04	93.75 ±0.01
Weight (mg)	55±0.10	72±0.08	90±0.08	102±0.1	115±0.13	120±0.06	132±0.09	141±0.06
Folding endurance	268±2	285±3	256±1	250±2	230±2	210±2	200±2	190±3
Moisture loss (%)	5±0.7	6±0.8	3±0.3	2.5±0.09	8.05±1.0	8.09±0.12	5.9±1.02	5.07±1.4
Moisture abs. (%)	4±0.6	5.5±0.7	2.8±0.5	2.1±0.03	6.95±1.69	7.90±0.2	4.60±1.04	3.07±1.33
Tensile strength (Kg/cm^2)	2.3	2.6	1.6	1.4	1.5	1.7	1.2	1.01
(%) Swelling Index	10.1	8.3	6.3	5.5	15.1	12.3	7.4	3.8
pH	6.7	6.8	6.6	6.8	6.0	6.1	6.2	6.3

The drug loaded buccal film of metoprolol succinate with use PEG400 and polymers show change in the thickness of buccal film. Thickness of the developed formulations F1 to F4 formulation varied from 0.17±0.052 to 0.35±0.041mm (HPMC) whereas thickness of F5 to F8 (Chitosan) was found to be 0.41 to 0.49,which means as increase in concentration of polymer there was also increase in thickness of film which is within acceptable range. All film samples were found to be uniform within each formulation. Reliability of the process in the preview of getting uniform drug was confirmed by drug content analysis data. The mean drug content was found to be in the range of 3.48 to 3.76 mg and independent of solid content. No significant difference in drug content was noted when increase in polymer concentrations. The drug content uniformity values owed the fact that the process used in the study is capable of giving films with uniform drug content, with unsubstantial differences in targeted drug loading.

Weight of film formulation F1 (2%) & F2 (3%) shows 55±0.10 mg, 72±0.08 mg respectively. By use of ethyl cellulose weight of F3 and F4 formulation 90±0.083 mg and 102±012 mg. Buccal film of batch F5 (2%) and F6 (3%) Shows 115±0.137 mg and 120±0.063 mg, whereas by use of ethyl cellulose polymer in formulation F7 and F8 indicate 132±0.0989 mg and 141±0.0632 mg weight respectively, from

result it was showed that as concentration of polymer increases weight of buccal film also increases. If higher the weight variation, higher will be the variation in contents which make the formulation therapeutically unacceptable. It was observed that all the batches were uniform in weight and there was no significant difference in the weight of the individual formulations from the average value and the variations were all within normal limits.

Buccal film prepared using HPMC which is 268±2 to 285±3. Whereas folding endurance of HPMC (F3, F4) batch with ethyl cellulose shows 256±1.0, 250±2.0. Chitosan films shows folding endurance value (F5 and F6) 230±2.0, 210±2.5 respectively, along with ethyl cellulose as rate controlling membrane (F7, F8) about 200±2.10, 190±3.4, which showed good folding endurance and ensured good flexibility. This makes the system acceptable for movement of mouth, indicating good strength and elasticity. The presence of plasticizers in the form of PEG 400 imparts flexibility to the polymers. PEG 400 form hydrogen bond with polymers molecule thereby imparting flexibility to the film. The folding endurance values were found to be more than 200 which is considered satisfactory and reveals good film properties. Folding endurance test results indicate that the films would maintain the integrity with buccal mucosa when applied. Moisture loss in HPMC film found to be 5.0%, 6.0%, 3%, 2.5%. Whereas in chitosan 8.05%, 8.90%, 5.90%, 5.07%. Moisture absorbs F1 and F2 shows about 4%, 5.5%. And for F3, F4 shows 2.8 and 2.1.where as for F5, F6, F7 and F8 show about 6.95, 7.85, 4.60, and 3.07 respectively. It was due to increasing polymer concentration as such polymer are hygroscopic due to this it may absorb moisture.

Tensile strength with HPMC (F1) 2% (F2) 3%, was found to be 2.34±0.07, 2.64±0.03 respectively, while chitosan (F5)2%, (F6)3% show 1.53±0.03, 1.72±0.01 Kg/cm^2 respectively, which indicate that a concentration of polymer increases, the tensile strength also increases, but tensile strength of the buccal film prepared with of 2% ethyl cellulose in batch of HPMC (F2,F3) shows low tensile strength i.e1.65±0.01, 1.41± 0.03 Kg/cm^2 tensile strength, while with chitosan batch F7 show 1.20±0.01, and F8 show1.01±0.03 Kg/cm^2. Combination with another polymer changes the network of polymer so bonding of molecules to be affected, that must be taken into consideration during the determination of the tensile strength properties of the film.

The swelling index of the buccal film prepared with HPMC conc. 2% (F1), HPMC conc. 3% (F2) was found to be 10.1%, 8.3% resp. Swelling index for batch F3 and F4 showed 6.3% 5.5% and for formulation F6 and F7 shows 15.1%, 12.3%, respectively and batch F7 and F8 indicate 5.5% & 6.3%. Formulation F2 (contains HPMC and PEG) shows highest (15.1%) swellability due to the hygroscopic polymers and plasticizer. According to swelling, these polymers exhibited high swelling; the film weight increased from the original. Although the increase in surface area during swelling .It was found that the percentage swelling of decrease it may be due to poor water solubility of ethyl cellulose that may lead to resistance of the matrix network structure (hydrogen bond) to the movement of water molecule. From the results of the swelling study

Prepared formulation (with HPMC) F1 and F2 batch, which shows formulation 6.7, 6.8 pH, whereas with the use of ethyl cellulose in batch F3 and F4 batch pH was found to be 6.6, 6.8 resp. Also Chitosan F5 and F6 shows 6.0, 6.1 pH, and with the addition of ethyl cellulose pH found to be 6.2 and 6.3 for F7 and F8 batch.

Batch F1 with concentration 2% showed release after 100 min the release was found to be 91.23, where for batch F2 show 93.03% drug release at end of 100 min, with use of ethyl cellulose in F3 and F4 batch drug diffusion found to be 90%, 89.72% in 150 mins. For the chitosan base formulation (F5, F6) drug diffusion at end of 300 min was found to be 91%, 88.22%, while use of chitosan and ethyl cellulose (F7, F8) formulation show 90.%, 86.76% release respectively. *In vitro* drug diffusion study indicated that the release of drug varied from the formulation batches according to the type and concentration of polymers utilized. The concentration of HPMC and Chitosan was increases gradually the diffusion of drug was decreased. Whereas formulation contains polymer ethyl cellulose show control release.

Before placing buccal film in stability chamber, concentration of HPMC containing film F1, F2, F3, F4 was found to be 91.75%, 94.66%, 90%, 87.6 respectively, whereas after 90 day percent concentrations was found to be 85.3, 88.0, 85.39, 84.67 respectively. Results suggest that percent of drug degradation was found to be 6.39 & in F1, F2 batch 6.63% F2 batch 4.61% for F3 batch, 2.93% F4 in 90 days. Formulation F5 and F6 shows 82.45%, 80.05% drug contains and after 90 days concentration was founds to be 82.45% and 80.05% where degradation of drug to be 7.75% and 8.95%. Formulation F7 and F8 indicate 92%, 88% and after 90 days. It was found to be 86.33%, 82.78% respectively. Result of all SEM shows plain and uniform surface while texture of ethyl cellulose contain film shows the rough surface area.

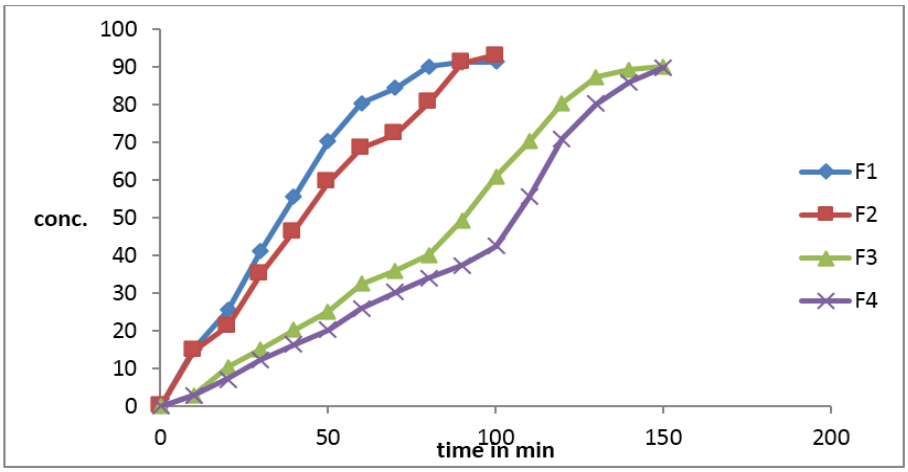

Fig 6: *In vitro* drug diffusion study of HPMC AND HPMC+EC

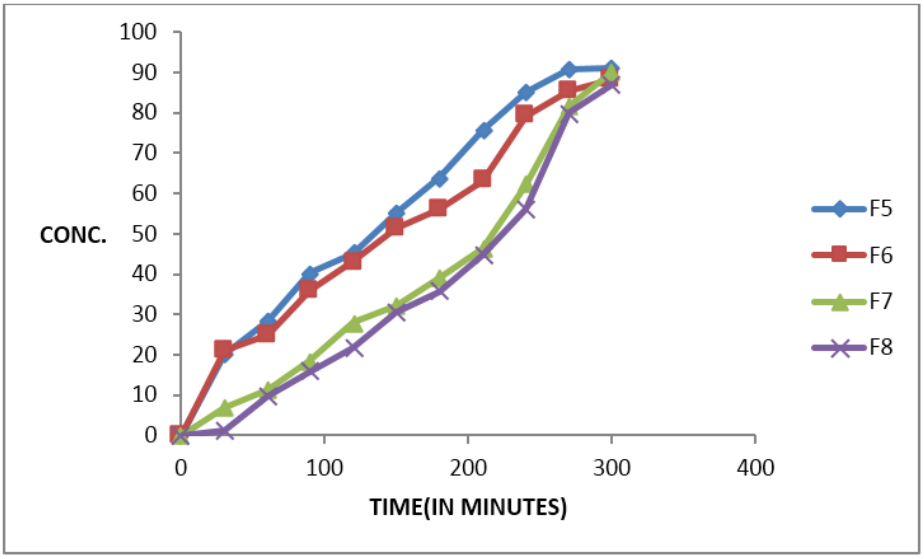

Fig 7: *In vitro* drug diffusion study of CHITOSAN AND CHITOSAN+EC

5. Conclusion

In conclusion, the formulated buccal films as a drug delivery system promising the approach which is mainly used for improving therapeutic efficacy of metoprolol succinate in the treatment of hypertension. The use of polymer such as chitosan, HPMC and plasticizer PEG-400 showed promising characteristics. From overall investigation data, it can be concluded that chitosan may be the best polymer to develop a stable mucoadhesive buccal film to deliver drug constantly. Design and development of such buccal film by chitosan may be highly beneficial which can deliver drug up to a period about 5 hrs duration. Hence can be the deliver the drug through buccal film at for sustains release. Hence chitosan polymer can be used as a means of improving drug delivery.

6. References

1. Sudhakar Y, Kuotsu K and Bandyopadhyay AK. Buccal bioadhseive drug delivery - a promising option for orally less efficient drugs. Journal of Controlled Release 2006; 10, 114(1):15-40.
2. Rathbone MJ, Hadgrft J. Absorption of drug from the human oral cavity. International Journal of Pharmaceutics 1991; 74:9-24.
3. Hirlekar RS, Kadam VJ. Design of buccal drug delivery system for a poorly soluble drug. Asian Journal of Pharmacy and Clinical Research 2009; 2(3):49-53.
4. Yajaman S, Ketousetuo K, Bandyopadhyay AK. Buccal bioadhesive drug delivery — A promising option for orally less efficient drugs: Review Article. Journal of Controlled Release 2006; 114:15–40.
5. Madhav NVS, Shakya AK, Shakya P, Singh K. Orotransmucosal Drug Delivery Systems: A Review. Journal of Controlled Release 2009; 140 (1):2–11.
6. Tripathi KD. Essentials of Medical pharmacology, Jaypee Brothers, New Delhi, 1988.
7. Shijith KV, Chandran SC, Premaletha K. A review on basics behind Development of mucoadhesive buccal drug delivery systems, International Journal of Biochemistry and Cell Biology 2013; 1(2):310-317.
8. James WH. Jennifer S. Metoprolol succinate extended release/hydrochlorothiazide combination tablets. Vasc Health Risk Manag 2007; 3(3):279–288.
9. Khairnar A, Jain P, Baviskar D, Jain D. Development of mucoadhesive buccal patch containing aceclofenac in-vitro evaluations. International Journal of Pharm Tech Research 2009; 1(4):978-81.
10. Mohamed H, Muaadh A, Mohamed Ali. Buccal mucoadhesive films containing antihypertensive Drug Journal of Chemical Pharm Research 2011; 3(6):665-686.
11. Komaragiri SD, Chandramouli FY, Vardhan RV, Vikram A, Aruna U. Formulation and characterization of atenolol fast dissolving film Indian journal of pharmaceutical science & research 2012; 2(2):58-62.
12. Alagusundaram M, Chengaiah B, Ramkanth S, Angalaparameswari S, Chetty SM. Formulation and evaluation of mucoadhesive buccal film of ranitidine. International Journal Pharm Technical Research 2009; 1(3):557-563.
13. Indira MY, Srujana KK. Mucoadhesive buccal films of glibenclamide. Development and evaluation. International Journal of Pharmacy 2011; 1(1):42-47.
14. Prabhushankar GL, Gopalkrishna B, Manjunatha KM, Girisha CH. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2(1):162-167.
15. Khanna R, Agrawal SP, Ahuja A. Preparation and evaluation of buccal films of clotrimazole for oral Candida infections. Indian Journal of Pharmaceutical Sciences 1997; 59:299-305.
16. Bottenberg P, Cleymact R, Muynck CD, Remon JP, Coomans & Michotte Y. Development and testing of bioadhseive fluoride containing slow release tablets for oral use. Journal of Pharmacy and Pharmacology 1991; 43(1):457-464.