CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

DEVELOPING AND ASSESSING BUCCALPATCHES WITH ANTI-DIABETIC DRUG

Medapati Ramya Sri, L.Devakmma
Geethanjali College of Pharmacy, JNTUH, Telangana

Article Received: January 2023 **Accepted:** January 2023 **Published:** February 2023

Abstract:
Metformin is a biguanide antihyperglycemic agent and first-line pharmacotherapy used in the management of type II diabetes. The present investigation is concerned with the development of the metformin HCl buccal films, which were designed to prolong the buccalresidence time, to increase penetration through buccal mucosa and thus increase the bioavailability and its half-life. Various formulations were developed by using release rate controlling film forming polymers like HPMC 5cps and HPMC 50cps in various combinations using plasticizer PEG 400. The prepared films were evaluated for number of parameters like physical appearance and surface texture, weight uniformity, thickness ofthe films, folding endurance, swelling index, tensile strength, drug excipients interaction study, content uniformity, in-vitro drug release study. The FTIR studies indicate that Metformin HCl showed complete entrapment within the polymer carrier bonding is suggested and there was no chemical interaction. From all the formulations, F8 shows maximum drug release at the ends of 8 hr and chosen as optimized formulation and which follows zero order release with super case II transport mechanism.

Keywords: *Metformin HCl, HPMC, FTIR, super case II transport.*

Corresponding author:
Medapati Ramya Sri,
Dept: Pharmaceutics,
Geethanjali College of Pharmacy,
Cheeryal, Medchel,
Hyderabad, Telangana.
India.E-mail: ramyasri.race@gmail.com

QR code

Please cite this article in press Medapati Ramya Sri et al. ***Developing And Assessing BuccalPatches With Anti-Diabetic Drug****., Indo Am. J. P. Sci, 2023; 10 (02).*

INTRODUCTION:

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucous membrane are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocularand oral cavity) offer distinct advantages over oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and depending on the particular drug, a better enzymatic flora for the drug absorption[1]. Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease(gum infection), bacterial and fungal infection. Over the decades mucoadhesion has become popular for its potential to optimize localized drug deliveryby retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site (e.g. buccal cavity). Well defined bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time [2, 3, 4]. The biological surface can be epithelial tissue or it can be the mucous membrane adhere on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion. The use of mucoadhesive polymers in buccal drug delivery has a greater application[3].Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route drug delivery provides the direct entry to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability [5, 6, 7]. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action[8,9,10].

Metformin is considered an antihyperglycemic drug because it lowers blood glucoseconcentrations in type II diabetes without causing hypoglycemia. It is commonly describedas an "insulin sensitizer", leading to a decrease in insulin resistance and a clinically significant reduction of plasma fasting insulin levels. Another well-known benefit of thisdrug is modest weight loss, making it an effective choice for obese patients type II diabetes. IUPAC Name is 1-carbamimidamido-N, N-dimethylmethanimidamide hydrochloride. Chemical Formula $C_4H_{12}ClN_5$.

The main aim of the present study to enhance the mucoadhesive formulation that uses buccal mucosa as a new route ofmedication administration for drug delivery, to develop and asses brand-new buccal patches with anti-diabetic characteristics.

MATERIALS

Table. No.1 Materials and Source

Sl. No.	Materials	Source
1	Metformin HCl	BMR chemicals, Hyderabad.
2	HPMC 5cps	Loba Chemical Pvt. Ltd., Mumbai.
3	HPMC 50cps	Loba Chemical Pvt. Ltd., Mumbai.
4	PEG 400	SD Fine Chem., Mumbai.
5	Methanol	Narmada chemicals, Hyderabad.

METHODOLOGY:

Preformulation studies:

Preformulation testing is the initial phase in the improvement of dose types of a drug substance. It is one of the critical essential being developed of any drug delivery system. It tends to be characterized as an examination of physical and synthetic properties of a medicament substance alone and when joined with excipients.

Characterization of the medicament is an essential advance at the preformulation period of item improvement taken after by concentrate the properties of the excipients and their similarity. The general goal of preformulation testing is to produce data valuable to the formulator in creating steady and bioavailable measurements frames, which can be mass- produced. The following are the various preformulation studies

Solubility:
Solubility of Metformin HCl was determined in Methanol, Ethanol, 0.1N HCl, pH 7.4 and pH 6.8 phosphate buffers. Solubility studies were performed by taking excess amount of Metformin HCl in different beakers containing the solvents. The mixtures were shaken for 48hrs in rotary shaker. The solutions were centrifuged for 10mins at 1000 rpm and supernatant were analyzed at 232 nm.

Drug-excipients interaction study of films:

There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The technique employed in this study to know drug-excipients interactions is IR spectroscopy; IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug Metformin HCl and formulations were scanned by using Jasco FTIR 410, by a thin film method.

Analytical methods for the estimation of Metformin HCl:

Preparation Of Reagents

A. Potassium Dihyrogen Phosphate (0.2M)
27.218 gm of potassium dihyrogen phosphate is dissolved in distilled waterand makeup to 1000 ml with the same.

B. Sodium Hydroxide Solution (0.2M)
8 gm of sodium hydroxide was dissolved in 1000 ml of distilled water.

C. Phosphate buffer pH 6.8
50 ml of 0.2M of potassium dihydrogen phosphate solution and 22.4ml of 0.2Msodium hydroxide solution were mixed and made up to 200 ml with distilled water.

Determination of λ max for Metformin HCl
10mg of Metformin HCl was dissolved in 3ml of methanol and made upto 10ml with 6.8 pH buffers so as to get a stock solution of 1000 µg/ml concentration. From this 1ml solution was withdrawn and diluted to 10ml with same to get a concentration of 100µg/ml (SS-II). From this stock solution pipette out 0.5 ml of the solution and makeup the volume to 10ml using same buffer to get the concentration of 5µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of standard calibration curve of Metformin HCl
The standard calibration curve for Metformin HCl was prepared using pH 6.8phosphate buffer.

Standard solution 10 mg of Metformin HCl was dissolved in 3ml of methanol and made upto 10 ml with pH 6.8 phosphate buffer to give a concentration of 1000 µg/ml.

Stock solution
From standard solution take 1ml of solution in 10 ml volumetric flask. The volume was made up to mark with pH 6.8 phosphate buffer to produce concentration 100 µg/ml of Metformin HCl respectively. From the working standard solution take 0.1, 0.2, 0.3, 0.4, 0.5, 0.ml of the solution and make upto the mark with 6.8 pH buffer to get the concentrations of 1,2, 3, 4, 5, and 6 µg/ml.

The absorbance data for standard calibration curve and plotted graphically. The standard calibration curve yields a straight line, which shows that drug obeys Beer's law in the concentration range of 1-6 µg/ml.

Metformin HCl Buccal Patches:
Initially, polymer was dissolved in methanol under constant stirring till clear solution was obtained. Then to this solution, 4 drops of propylene glycol was added. To this solution Metformin HCl was added by stirring. The resultant solution was then poured on the petri dish of area 44.156 sq.cm and allowed to dry undisturbed at room temperature. The dried film was cut into discs of 2x2 cm (4sq.cm of area) diameter. The compositions of films are reported in table.

Table.No.2: Formulation Details of Drug Incorporated Buccal Films.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Metformin HCl	40	40	40	40	40	40	40	**40**
HPMC 5cps	150	300	450	600	-	-	-	**-**
HPMC 50cps	-	-	-	-	150	300	450	**600**
PEG 400 (ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	**0.3**
Methanol (ml)	5	5	5	5	5	5	5	**5**

Note: 4 sq.cm buccal films containing 40 mg of Metformin HCl.

Evaluation of films

Evaluation of Metformin HCl buccal films

The Metformin HCl buccal films were evaluated for the following properties:

Physical appearance and surface texture of film:

This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.

Weight uniformity of films:

Three films of the size 4sq.cm were weighed individually using digital balance and the average weights were calculated.

Thickness of films:

Thickness of the films was measured using screw gauge with a least count of 0.01 mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken.

Folding endurance of films:

The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding films at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

Swelling index of films:

The swelling index of the films was determined by immersing preweighed film of size in 50 ml water. The films were taken out carefully at 0.5, 1, 2 upto 3hrs. intervals, blotted with filter paper and weighed accurately.

he swelling index calculated by,

$$\% \text{ Swelling Index} = \frac{\text{Wet weight} - \text{Dry weight}}{\text{Wet weight}} \times 100$$

Surface pH of films:

Surface pH was determined by the films were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH papernear the surface of films and allowing equilibrate for 1 min.

Tensile strength of films:

Tensile strength of the film was determined with digital tensile strength tester (Tinius-Olsen). The sensitivity range of the machine is 1-10 Newton's. It consists of two load cell grips. The lower one was fixed and upper one was movable. The test film of size ($1x4\ cm^2$) was fixed between these cell grips and force was applied till it breaks. The tensile strength of the film was directly taken from the dial reading in Newton's, which was converted into kilogram.

Drug content uniformity study of films:

The films were tested for drug content uniformity by UV-Spectrophotometric method. Films of 4sq.cm were cut from three different places from the casted films. Each film was placed in 100 ml volumetric flask and dissolved in pH 6.8 phosphate buffer and 1 ml is taken and diluted with pH 6.8 phosphate buffer upto 10 ml. The absorbance of the solution was measured

at 232 nm using UV/visible spectrophotometer (Shimadzu UV- 1700). The percentage drug content was determined using the standard graph and the same procedure was repeated for three films.

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. The moisture content (%) was determined by calculating moisture loss (%) using the formula:

Moisture Content (%) = Initial weight – Final weight/Initial weight*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). After 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula:

Moisture Absorption (%) = Final weight – Initial weight/Initial weight*100

***In-vitro* drug release of films:**

In-vitro release studies were carried out by attaching dialysis membrane, prepared buccal films containing drug was placed inside donor compartment which is agitated continuously using magnetic stirrer at 50 rpm and then temperature was maintained at 37 ± 0.5ºC. Receptor compartment consist of 40 ml of pH 6.8 phosphate buffer, sample of 1 ml were withdrawn at periodic intervals from receptor compartment and replaced with fresh pH 6.8 phosphate buffer immediately, and drug release was analyzed spectrophotometrically at 232 nm. Release rate was studied for all prepared formulations.

\

Drug Release Kinetics:

In order to predict and correlate the release behavior of Metformin HCl from different patches, it is necessary to fit into a suitable mathematical model. The *in vitro* Metformin HCl release data from buccal patches were evaluated kinetically using various mathematical models like zero-order, first-order, Higuchi, and Koresmeyer–Peppas model equations.

Zero-Order Kinetics

$F = K_0 t$, where F represents the fraction of drug released in time t, and K_0 is the zero-order release constant.

First-Order Kinetics

$\ln (1 - F) = -K_1 t$, where F represents the fraction of drug released in time t, and K_1 is the first-order release constant.

Higuchi Model

$F = K_H t^{1/2}$, where F represents the fraction of drug released in time t, and K_H is the Higuchi dissolution constant.

Koresmeyer–Peppas Model

$F = K_p t^n$, where F represents the fraction of drug released in time t, K_p is the Koresmeyer– Peppas release rate constant, and n is the diffusion exponent.

RESULTS AND DISCUSSION:

Preformulation studies:

Solubility studies:

Table.3: Solubility studies of Metformin HCl

Solvents	Solubility studies(µg/ml)
Water	1.025
0.1 N HCl	0.743
6.8 pH buffer	0.654
7.4 pH buffer	0.524

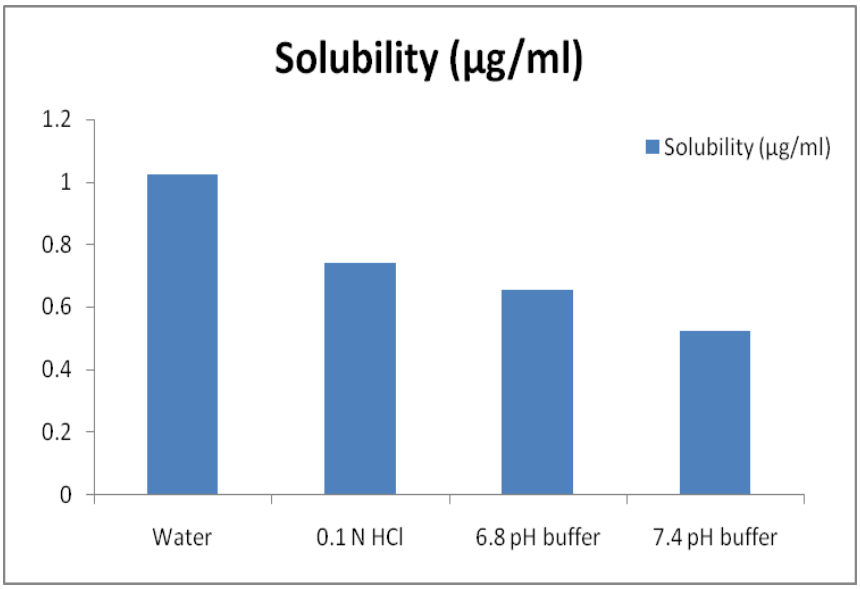

Fig 1 : Solubility studies of Metformin HCl

Discussion: From the solubility studies it was observed that Metformin HCl was found tobe more soluble in water and 0.1 N HCl among buffers.

UV SPECTRUM OF Metformin HCl:

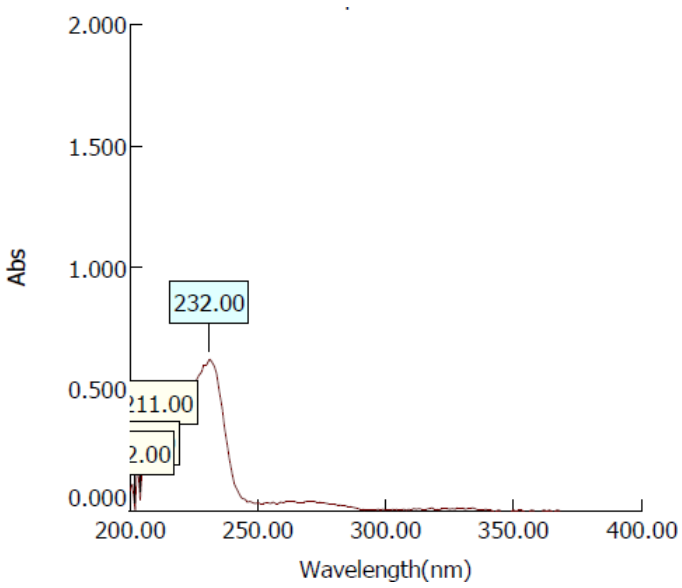

Fig 2: UV Spectrum of Metformin HCL

Discussion:

A solution of Metformin HCl containing the conc. 10 µg/ ml was prepared in 0.1 N HCl buffer and UV spectrum was taken using PG Instruments T60 double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm. The maximum absorbance was found to be at 232 nm.

Calibration Curve of Metformin HCl in 0.1 N HCl

Table 4: Calibration Curve of Metformin HCl in 0.1 N HCl Buffer

Concentration (µg/mL)	Absorbance
0	0
5	0.168
10	0.311
15	0.473
20	0.637
25	0.792
30	0.924

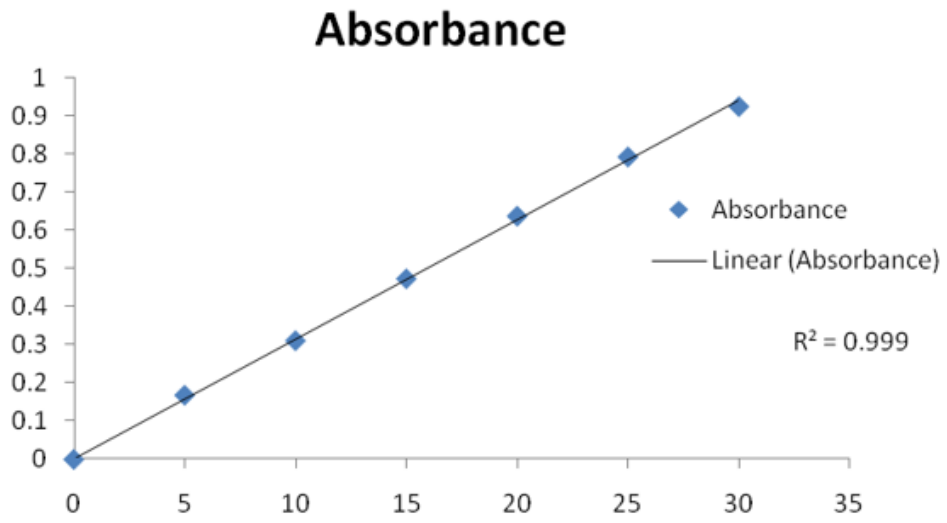

Fig 3: Standard calibration curve of Metformin HCl in 0.1 N HCl BufferDrug-excipients interaction studies:

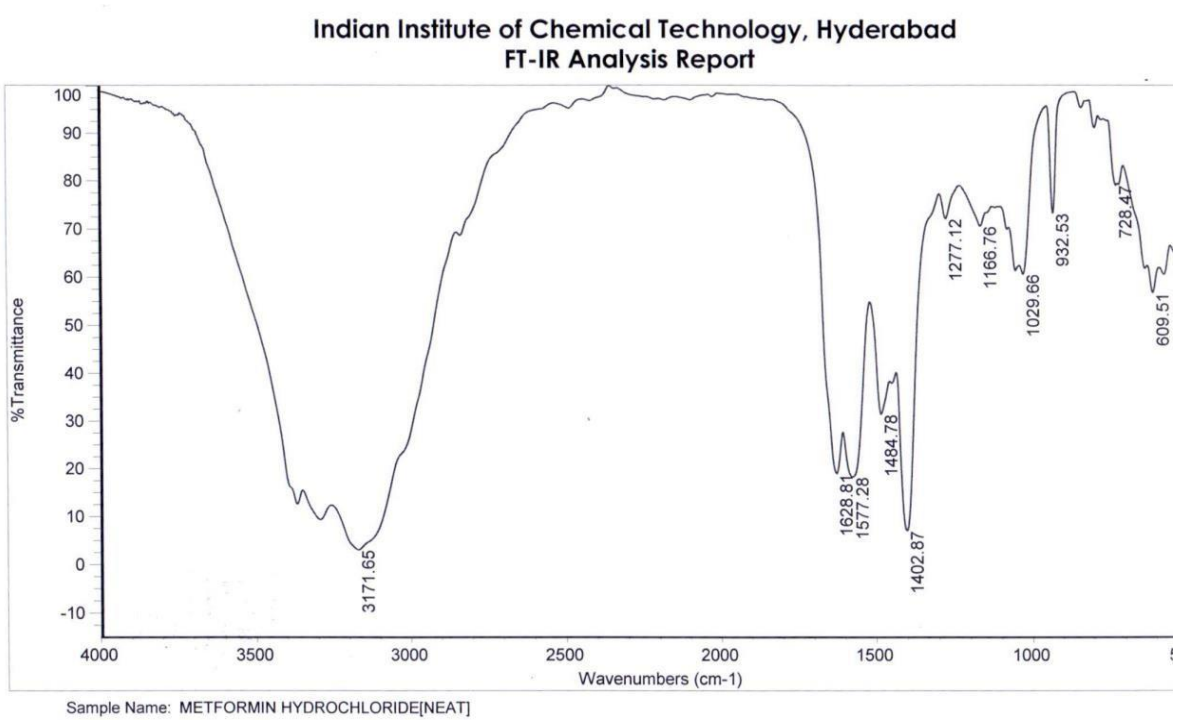

Fig 4: FTIR Spectra of Metformin HCl (pure drug)

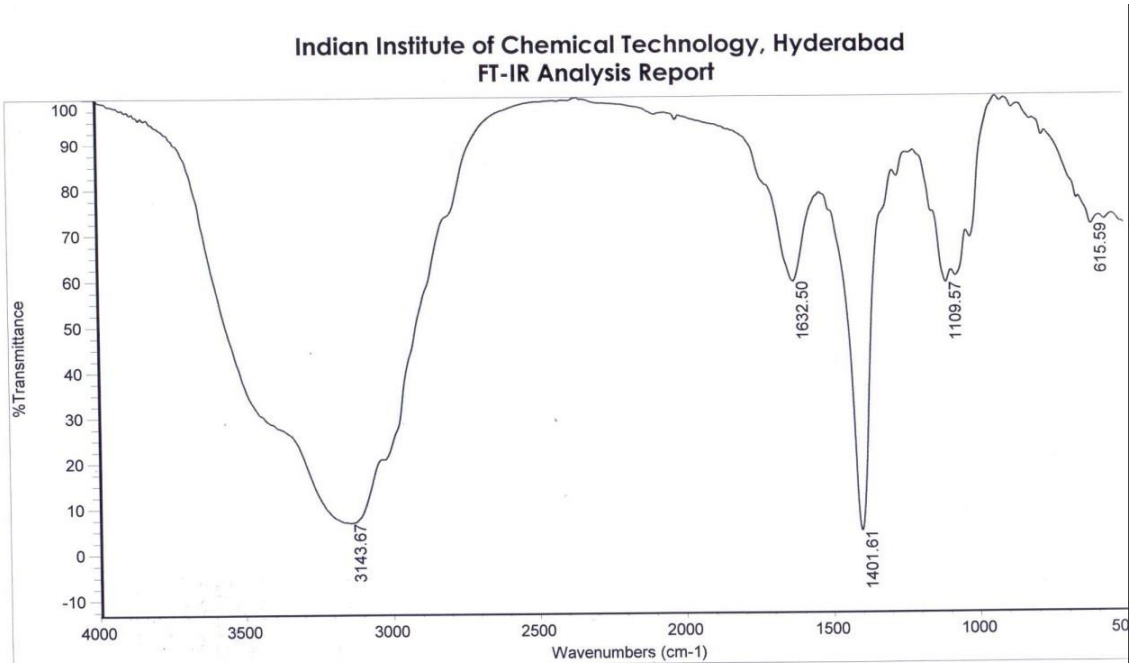

Fig 5: FTIR Spectra of optimized formulation

Discussion:
From the compatibility studies it was concluded that the functional groups that were present in the pure drug were also found in the optimized formulation with very minute changes, from this we can conclude that the drug and excipients have no interactions.

Physical appearance and surface texture of films:
These parameters were checked simply with visual inspection of films and by feel or touch. The observation reveals that the films are having smooth surface and they are elegant in appearance.

Weight uniformity of films:
The weight of the films was determined using digital balance and the average weight of all films was given in table.

Folding endurance of films:
The folding endurance gives the idea of flexible nature of films. The folding endurance was measured manually, films were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the films exhibited good physical and mechanical properties and the average folding endurance of all films

Surface pH of films:
Surface pH was determined by bring the films in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min and the average surface pH of all films was given in Table.

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymer, the surface pH of the buccal films was determined to optimize both drug permeation and mucoadhesion. Attempts were made tokeep the surface pH as close to buccal /salivary pH as possible, by the proper selection of the polymer for developing the buccal films. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of prepared films.

Table.5: Evaluations of Buccal Films

Formulation code	Thickness (mm)	Folding endurance	Surface pH	Weight variation (%)
F1	0.20	158	6.8	1.09
F2	0.11	169	6.2	2.97
F3	0.16	175	6.8	1.56
F4	0.19	162	6.5	1.87
F5	0.18	129	6.8	2.28
F6	0.12	168	6.8	2.04
F7	0.26	183	6.9	1.75
F8	0.18	195	6.7	1.09

Swelling index of films:
The swelling index of the films was determined by immersing preweighed film of size 10 mm in 50 ml water. The films were taken out from petridish carefully at 0.5, 1, 2, upto 3hrsintervals, blotted with filter paper and weighed accurately and the average swelling index of all films was given in Table.

From all these films F8 formulation buccal film films shows high percent swelling index.

Tensile strength of films:
The tensile strength of all the films were evaluated by using standard tensile strength tester and the average tensile strength of all films was given in Table. In all the cases the calculated standard deviation values are very low which suggest that,the prepared films shows uniform tensile strength.

Drug content uniformity of films:
Metformin HCl buccal films prepared with various polymers were subjected to the evaluation for uniform dispersion of drug throughout the film. In each case three films were used and the average drug content was calculated, the results were shown in Table-. The drug was dispersed in the range of 96 to 102 %. Suggesting that drug was uniformly dispersed throughout all prepared films.

Table.6: Evaluation of Metformin HCl Buccal Patches

FC	Avg. Swelling index (%)	Moisture content(%)	Moisture absorption (%)	Tensile strength	Drug content (%)
F1	12.76	1.76	4.09	3.83	97.98
F2	19.86	1.07	3.87	4.26	96.16
F3	25.02	1.32	4.56	4.79	96.09
F4	35.85	1.08	3.46	5.02	99.78
F5	19.67	0.98	4.23	3.76	101.45
F6	29.72	1.05	3.09	4.98	98.75
F7	42.98	0.89	3.42	5.13	100.65
F8	48.76	1.02	3.96	6.24	97.53

***In-vitro* drug release of films:**

The detailed *in-vitro* drug release data were plotted between percent drug released from the formulation and time as shown in Fig.

The present study indicates a good potential of erodible mucoadhesive buccal films containing Metformin HCl for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. The result of the present study shows that therapeutic levels of Metformin HCl can be delivered buccally. It may be concluded that the formulations F8 shows promising controlled drug release.

Table.7: Drug release data of Metformin HCl buccal films

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	**0**
0.5	40.87	42.85	33.25	22.87	45.87	47.98	42.76	**27.58**
1	53.98	54.98	41.78	42.98	63.09	51.25	55.98	**36.64**
2	65.89	66.98	53.78	59.72	75.25	62.56	63.86	**45.12**
3	76.09	74.09	66.98	68.24	79.16	73.85	71.64	**54.74**
4	88.25	83.45	72.04	82.57	85.64	82.34	79.98	**67.46**
5	95.02	90.56	87.59	91.56	92.45	90.65	86.09	**76.97**
6		97.56	99.56	96.52		97.09	90.56	**85.09**
7							96.76	**91.64**
8								**99.45**

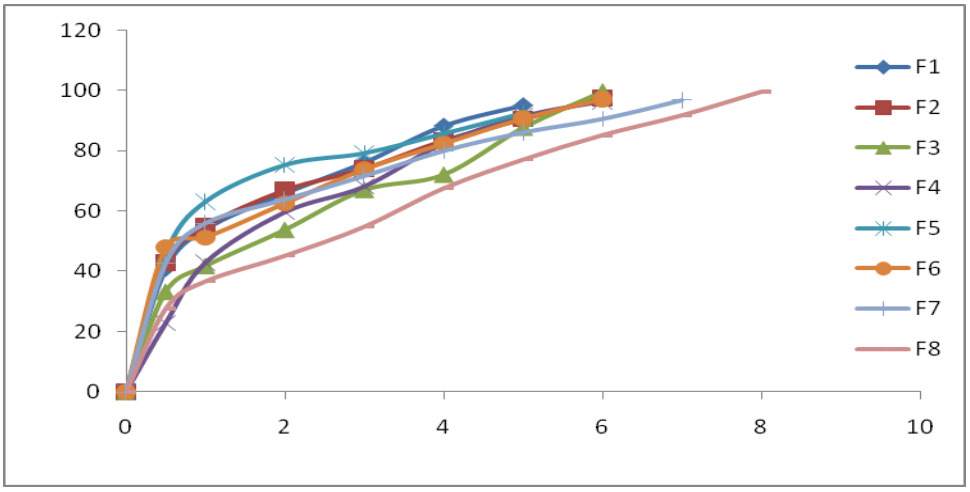

Fig 6: Invitro Drug Release of Formulations (F1-F8)

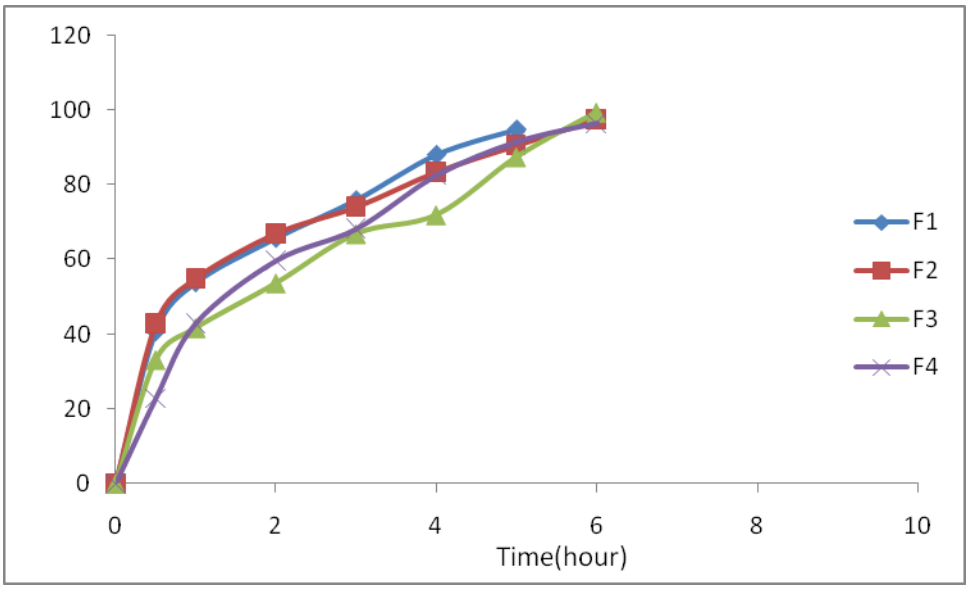

Fig 7: Invitro Drug Release of Formulations (F1-F4)

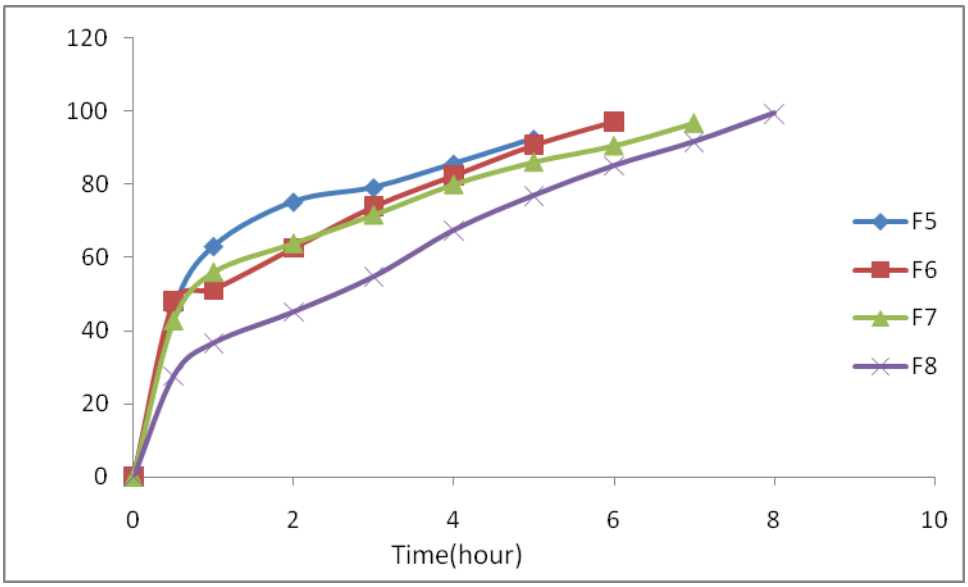

Fig 8: Invitro Drug Release of Formulations (F5-F8)

Discussion:

Total eight formulations was formulated by HPMC 5cps and HPMC 50cps in four different concentrations. From all the formulations, F8 shows maximum drug release at the ends of 8 hr and chosen as optimized formulation. So the drug release kinetics were performed for the optimized formulation (F8)

Kinetic Data of Metformin Hcl Mucoadhesive Buccal Films:Zero Order:

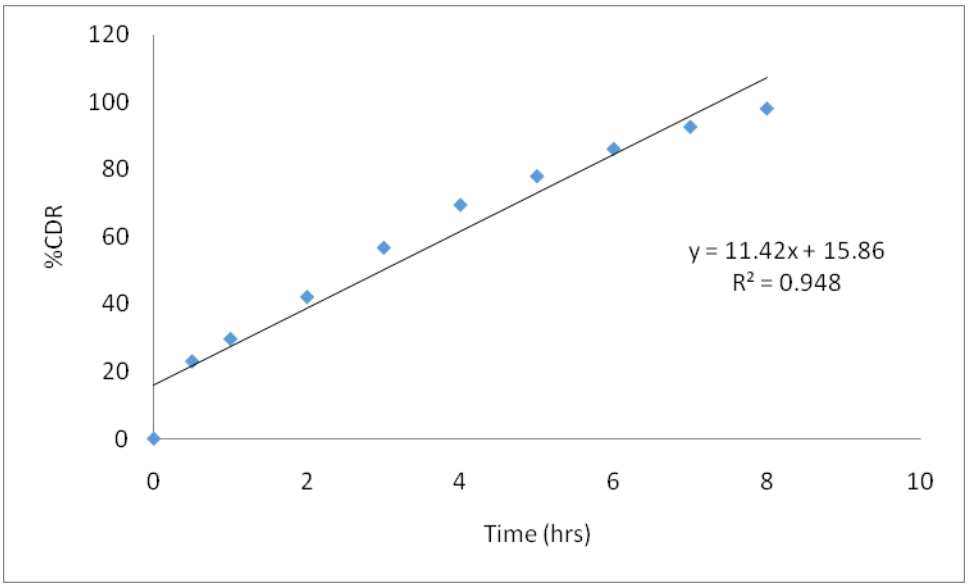

Fig 9: Zero order of F8 formualtion

First Ordeer:

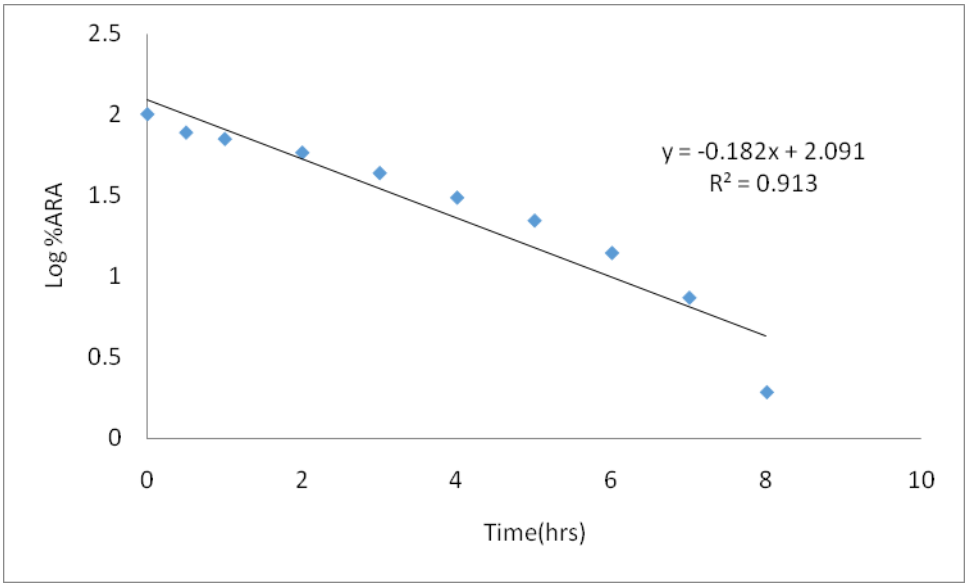

Fig 10: First order of F8 formualtion

Higuchi Plot:

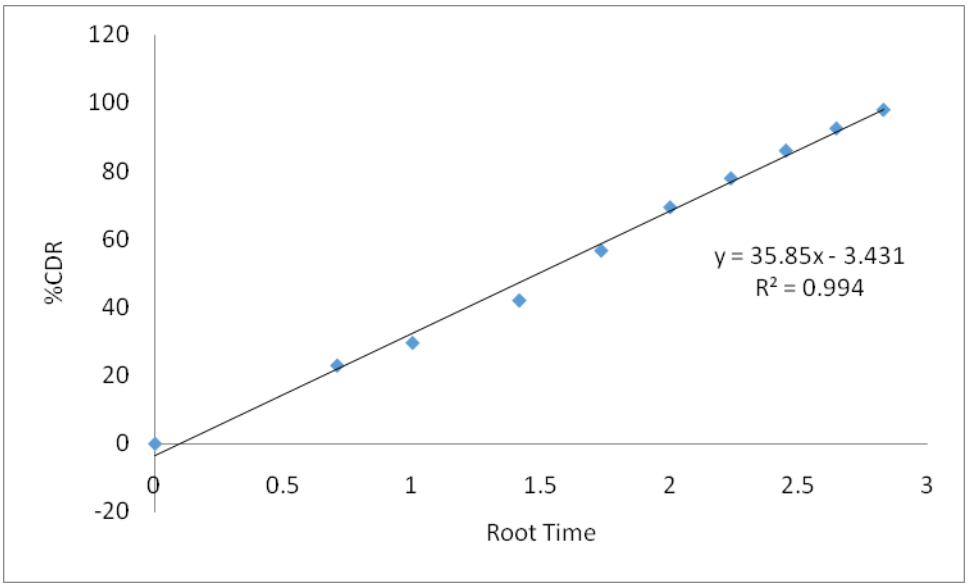

Fig 11: Higuchi plot of F8 formualtion

Peppas Plot:

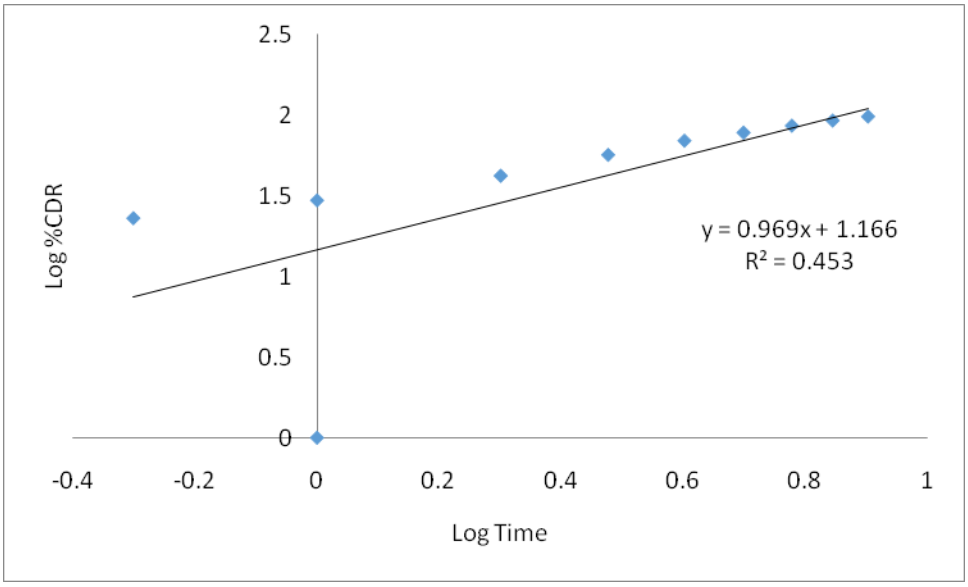

Fig 12: Peppas plot of F8 formualtion

Table.No.8. Kinetic Models and Values

R^2 values					n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer - Peppas**	**Korsmeyer-Peppas (n)**
F8	**0.948**	**0.913**	**0.994**	**0.453**	**0.969**

The invitro dissolution data for best formulation F8 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F8 shows R^2 value 0.948. As its value nearer to the '1' it is conformed as it follows the Zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport. The 'n' value is 0.969 for the optimised formulation (F8) i.e., n >0.89 which indicatesSuper case II transport.

SUMMARY

Recently the buccal patch has been increasingly used for administration of drug mainly because of advantages like the drug is directly available to the systemic circulation, avoidance of first pass metabolism and easy removal of patch from the site etc.

Among the various drug delivery systems development buccal drug delivery system is one by which one can improve the bioavailability of the drug by avoiding hepatic metabolism.

The prepared patches were evaluated for number of parameters like physical appearance and surface texture, weight uniformity, thickness of the patches, folding endurance, swelling index, tensile strength, drug excipients interaction study, content uniformity, *in-vitro* drug release study.

The results are quoted in different section of chapter-from the result of various evaluation parameters, we can summarize:

- The patches prepared were checked visually for its appearance and surface texture. All the prepared patches were of smooth surface and elegant texture.
- Percentage weight variation of all the prepared patches using different concentration are in between 1.09 to 2.97%.
- The patches show thickness values in between 0.11 to 0.26 mm.
- The patches show folding endurance values are below 150 to 200.
- The patches show swelling index values in between 12.76 to 48.76 %.
- Similarly surface pH of all the patches prepared is ranging in between 6.2 to 6.9pH.
- The tensile strength of all the patches prepared is ranging in between 3.76 to 6.24 Kg/cm^2 respectively.
- The FTIR studies indicate that Metformin showed complete entrapment within the polymer carrier bonding is suggested and there were no chemical interaction.
- Similarly, the patches are also subjected to drug content uniformity study and it lies in between 96 to 101 %, which suggest that uniform dispersion throughout the buccal patches.
- Finally the *in-vitro* drug release study was carried out for all the patches and release profile were subjected to various kinetic equations like Higuchi diffusion equation and Peppas exponential equation. The regression coefficient values of this kinetic equation are very nearer to one (1) suggesting that plots are fairly linear and slope values of the Peppas equation is (>0.89) suggest that drug was released by Super case II transport mechanism.

CONCLUSION:

The aforementioned findings lead to the conclusion that buccal patches can be used to administer metformin. Using various formulation factors, the medication release patternfrom these patches may be changed.

REFERENCES:

[1] Shidhaye SS, et al. Mucoadhesive bilayered patches for administration of sumatriptan. AAPS pharm sci tech. 2009; 9(3): 1-13.

[2] Giradkar KP, et al. Design development and in vitro evaluation of bioadhesive dosage form for

buccal route. International journal of pharma research & development. 2010; 2: 1-24.
[3] Amir H, et al. Systemic drug delivery via the buccal mucosal route, Pharmaceutical technology. 2001; 1-27.
[4] Fatima AA, Chukwuka UK. Development and in-vitro evaluation of matrix-type transdermal patches of losartan potassium. Universal Journal of Pharmaceutical Research. 2017; 2(2): 16-20.
[5] Steward A, et al. The Effect of Enhancers on the Buccal Absorption of Hybrid (BDBB) Alpha-Interferon.IntJ Pharm. 1994; 104: 145–149.
[6] Al-kaf AGA, Othman AM. Pharmacosomes: an Updated review, Universal Journal of Pharmaceutical Research. 2017; 2(1): 30-33.
[7] Mishra S. A Review articl: Recent Approaches in buccal patches, the pharma innovation. 2012;7(2):78-86.
[8] AJ Hoogstraate, et al. Diffusion Rates and Transport Pathways of FITC-Labelled Model Compounds through Buccal Epithelium, Proc. Int. Symp. Contr. Rel. Bioact.Mater. 1993;20:234–235.
[9] Bhartee P, Kapil Kumar. Buccal drug delivery system: a tool for the effective delivery of pharmaceuticals. Universal Journal of Pharmaceutical Research. 2017; 2(3): 19-24.
[10] Ryan FD, Paul AM, Agnieszka AZ, David W. Design and physicochemical characterization of a bioadhesive patch for dose controlled topical delivery of imiquimod. Int J Pharm. 2006;307:3 18-25. [11] Shafiullah D, Pramodkumar TM, Shivakumar HG. Formulation and evaluation of chlorhexidine mucoadhesive drug delivery systems. Ind Drugs. 2006;43(2): 122-5.
[12] Diojad RC, Manvi FV, Malleshwarrao VSN, Patel PS. Buccoadhesive drug delivery system of isosorbide dinitrate: Formulation and evaluation. Ind J Pharm Sci. 2006;68(6):744-8.