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FORMULATIONDEVELOPMENT AND EVALUATION OF MUCOADHESIVE BUCCAL FILM OF METHYLDOPA

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ABSTRACT

The aim of the present study was to formulate the mucoadhesive buccal films and selection of most satisfactory formulation by in-vitro evaluation. Buccal delivery is considered to be an important alternative to the per-oral route for the systemic administration of drugs. The mucosa is relatively permeable, well supplied with both vascular and lymphatic drainage. Methyldopa is an anti-hypertensive drug with an oral bioavailability of 50% due to extensive first pass metabolism. Hence the present investigation was done to formulate mucoadhesive buccal films of Methyldopa with an objective to improve therapeutic efficacy, patient compliance, half-life and prepared films were evaluated for various physicochemical characteristics such as thickness, drug content uniformity, surface pH, and in vitro drug release etc. Ex vivo permeation studies of Methyldopa solution through porcine buccal mucosa showed 85.30 % absorption at the end of 30 mins. The mucoadhesive buccal films of methyldopa were prepared by solvent casting technique using various polymers. *In vitro* release studies were performed with pH 6.6 phosphate buffer solution. Good results were obtained both in physicochemical characteristics and *in vitro* studies. The *in vitro* release data were fit to different equations and kinetic models to explain release profiles. The kinetic models used were zero order, higuchi's and Hixon-Crowell model. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation F_5 (HPMC K-47 and PVP K-30). The correlation coefficient value (r) indicates the kinetic of drug release was zero order. The formulation was found to be right and suitable candidate for the formulation of methyldopa buccal film for therapeutic use.

Keywords: Methyldopa, buccal films, solvent casting technique, *in vitro* release studies, buccal mucosa, zero order.

INTRODUCTION

In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via buccal route, using bio-adhesive dosage forms offers such a novel route of drug administration. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. [1]The oral cavity is an attractive site for the administration of drugs because ofease of administration. Various dosage forms like Tablets, Capsules and Liquid orals are administered by oral route. In recent years, delivery of therapeutic agents through buccal mucosa has gained significant attention. Administration of the drug via the mucosal layer is novel method that can render treatment more effective and safe. There are opportunities for mucosal (local effect) and Transmucosal(systemic effect) drug administration. The mucosal administration of drugs is to achieve site-specific release of drugs on the mucosa, whereas, in the latter, transmucosal administration involves drug administration through mucosal barrier to reach the systemic circulation. Among the various transmucosal routes like nasal, rectal, vaginal, ocular, pulmonary and buccal routes, the buccal mucosa is an attractive alternative to the oral route of drug administration and it is a potential site for the delivery of drugs to the systemic circulation.[2]

Therapeutic agents administered through buccal mucosa enters directly to the systemic circulation and there by circumvent the first-pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route. Among these the buccal mucosa has several advantages like excellent accessibility, an expanse of smooth muscle, immobile mucosa, moderate permeability, less enzymatic activity and suitable for the administration of retentive dosage forms. Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer therapeutic agent to patients who cannot be dosed orally to prevent accidental swallowing. [3]

Mucoadhesive drug delivery

The concept of mucosal adhesive or mucoadhesive was introduced in to the controlled drug

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delivery area in the early 1980's.[4]The potential route of buccal mucosal route of drug administration was first recognized by Walton and others reported in detail on the kinetics of buccal mucosal absorption.[5,6,7] Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. Over the last two decades mucoadhesion becomes of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action (with in gastro intestinal tract) or systemic delivery, by retaining a formulation in intimate contact with absorption site (in the buccal cavity). Mucoadhesion may be defined as a state in which two materials, one of which mucus or a mucous membrane, is held together for extended period of time. [8] The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses liver and avoids pre-systemic elimination in the gastro intestinal tract and liver. The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that are subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract.[9]Buccal delivery offers a safer mode of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity.[10] A suitable buccal drug delivery system should possess good bio-adhesive properties, so that it can be retained in the oral cavity for the desired duration.[11]

Active Substances can be administered locally to treat oral diseases like periodontal disease, bacterial and fungal infections. A systemic action can be achieved via drug permeation through the mucosal epithelium.[12,13] Fast dissolving films recently have acquired great importance in the pharmaceutical industry due to their unique properties and specific advantages like no need of water for disintegration, accurate dosing, rapid onset of action, ease of transportability, ease of handling, pleasant taste and improved patient compliance.[14,15] Fast dissolving film is a type of drug delivery system, which when placed in the oral cavity it rapidly disintegrates and dissolves to release the medication for oral mucosal and intra-gastric absorption, without chewing and intake of water.[16,17] This technology evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers. These films have potential to deliver the drug systemically through intra-gastric, sublingual or buccal route of administration and also has been used for local action.[18,19]

The present research work was to formulate and evaluate mucoadhesive buccal films containing Methyldopa as a drug using different ratios of polymers to avoid hepatic first pass metabolism and to increase bioavailability of the drug.Drugs like Methyldopa has been selected as model drugbecause the drug shows promising pharmacokinetics and physiochemical properties required for novel control release dosages.Methyldopa isalpha-adrenergic agonist, psychoactive drug and sympatholytic or antihypertensive agent. It is effective in the treatment Hypertension (or high blood pressure), Gestationalhypertension (or pregnancy-induced hypertension) and pre-eclampsia. Methyldopa has molecular weight of 238.215gm/mol, oral bioavailability approximately 50%, protein binding is 70-76% and elimination half-life is 0.8-1hr. Thus, it was considered as a potential drug for buccal drug delivery.

MATERIALS AND METHODS

Methyldopa was obtained as gift sample from Yarrow chemicals, Mumbai, India. Hydroxypropyl methylcellulose K-47 (HPMC K-47) and polyvinylpyrrolidine K-30 (PVP K-30) were commercially obtained from S.D. Fine chemicals ltd. Mumbai. Poly Ethylene Glycol 6000 (PEG 6000) was obtained commercially from Reidel chemical Pvt. Ltd. New Delhi. Sodium carboxymethylcellulose was obtained from Lobachemie Pvt. Ltd. Mumbia and Ethyl cellulose was obtained from Qualikems fine chemi Pvt. Ltd. Vadodara. All other chemicals were of analytical grade, and water used in this assay was doubly distilled.

Analytical method

i. Determination of λ max

The absorption maxima were found to be 282 nm.

ii. Calibration curve of methyldopa

Calibration curve of methyldopa in 0.1 N HCl and phosphate buffer (pH 6.6) were obtained at 282 nm with UV-VISIBLE spectrophotometer. Using concentration and absorbance data, a calibration curve was obtained.

Pre formulation studies

The overall objective of the pre-formulation testing is to generate information useful to the formulator in developing stable and mucoadhesive buccal films.

FT- IR spectrum interpretation

The pure drug and polymers were subjected to FT-IR studies alone and in combination, to study the interference of polymers and drug.

PREPARATION OF METHYLDOPA MUCOADHESIVE FILMS

Buccal mucoadhesive films were prepared solvent casting method [20,21] using polymer or polymer blends along with the drug and a suitable solvent. HPMC K-47(250 mg for film I) was weighed accurately and added in 4 ml of ethanol. The contents in the beaker were stirred on magnetic stirrer for 15 min for swelling of polymer. Further 1 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then PEG 6000 was added to the polymer solution. Methyldopa (15 mg) was weighed and dissolved in 3 ml of ethanol and 1drop of Tween 80 in another beaker also the colouring and favoring agents were also added. The drug solution was added to the polymerdispersion. The whole mixture was mixed thoroughly with the help of a magneticstirrer. The glass mould of size 5×3 cm^2 was placed over a flat surface, which was ensured using spirit level. The drug-polymer mixture was poured into the glass mould. An inverted funnel was placed over the mould overnight for controlled evaporation of the solvent. The film was

removed from the mould and packed in wax paper and stored in a desiccator. On similar lines all films were prepared. Similarly, dummy films were prepared without adding drug. Composition of various methyldopa buccal films was given in Table 1.

Table 1: Composition of different mucoadhesive formulations containing methyldopa

Contents**	Formulation					
	I	II	III	IV	V	VI
Methyldopa	15	15	15	15	15	15
HPMC K 47	250	*	200	*	200	*
Na CMC	*	250	*	200	*	200
Ethyl cellulose	*	*	50	50	*	*
PVP K-30	*	*	*	*	50	50
PEG 6000	80	80	80	80	80	80
Ethanol	8	8	8	8	8	8
Tween 80	10	10	10	10	10	10
Col.	0.05	0.05	0.05	0.05	0.05	0.05
Flv.	0.05	0.05	0.05	0.05	0.05	0.05

EVALUATION:

Thickness Uniformity

The thickness of each film was measured using Digimatic Micrometer at six different positions of the film and the average was calculated[22] parameters are given under.

Swelling Study

Buccal films (n=3) were weighed individually (W1) and placed separately in petri dishes containing 5 mL of phosphate buffer (pH 6.6) solution. The dishes were stored at room temperature. Then, films were removed and excess surface water was removed carefully usingthe filter paper after specified time intervals. The swollen films were then again weighed (W2)and swelling index (SI) was calculated using the following formula (Eq. 1):[23,24] and results are given under.

SI (%) = (W2 –W1)/ W1 x 100……..(1)

Uniformity of Weight of the films

Films of size 2 x 2 cm^2 were cut. The weight of each film was taken usingShimadzu (Shimadzu Corporation, Kyoto, Japan) balance with 0.001 gram sensitivity and the weight variation of three films was calculated [22] and results are given below.

Surface pH

Buccal films were left to swell for 1 hr on the surface of the agar plate, prepared by dissolving 2% w/v agar in warmed phosphate buffer solution, pH 6.6 under stirringand then poured the solution into the petri dish till gelling/solidify at roomtemperature. The surface pH was measured by means of pH paper placed on the surface of the swollen film. The mean of three readings was recorded [25] andparameters are given below.

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 300 times, which is considered satisfactory to reveal good film properties.[26] The number of times of film could befolded at the same place without breaking gave the value of the folding endurance and results are given under.

This test was done on all the films for five times.

Drug Content Uniformity of films

The methyldopa buccal film unit of each formulation was dissolved in 250 ml of phosphate buffer (pH 6.6), then stirred and filtered. The amount of methyldopa wasdeterminedspectrophotometrically at λ_{max} 282 nm.[27] The average of drug contents of threefilms was taken as final reading. Concentrations of methyldopa were calculated from a standard calibration curve of methyldopa in phosphate buffer (pH 6.6) and parameters are given below.

In Vitro Drug Release Studies

The US Pharmacopeia XXIII rotating paddle method was used to study the drug release from thedesigned buccal mucoadhesive films. The dissolution medium consisted of 250 ml of phosphate buffer solution of pH 6.6. The release was performed at 37±0.5oC with a rotation speed 50 rpm.

The one side of the buccal film was attached to a 3 cm diameter glass disk with instant adhesive (cyanoacrylate adhesive). The film with glass disk was placed at the bottom of the dissolution vessel so that the film dosage form faced upright thereby allowing drug release only from the upper side of the film.[28] Samples of 5ml were withdrawn at pre-determined time intervals and replaced with fresh medium. The samples were filtered through 0.45-µm filter (Millipore Co.,Bedford, MA, USA) and analyzed after appropriate dilution by UV spectrophotometry (Systronic 2203 smart, India) at λ_{max} 282 nm. The release studies were conducted in triplicates and the mean values were plotted versus time and results are given under.

In vitro Residence Time

The *in vitro*residence time was determined using USPdisintegration apparatus. The disintegration medium was800 ml of pH 6.6 phosphate buffer (PB) maintained at 37±0.5°C.The segments of porcine buccal mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Threemucoadhesive films of each formulation were hydrated onone surface using pH 6.6 PB and the hydrated surface wasbrought into contact with the mucosal membrane. Theglass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the buffer solution at the lowest point and was out at thehighest point. The time required for complete erosion or detachment of the film from the mucosal surface wasrecorded [29,30] and parameters are given below.

Ex Vivo Drug permeation studies

Permeation studies were carried using the modified Franz diffusion cell of internal diameter of 2.5 cm. porcine oral mucosa was used as the model membrane. The buccal pouch of the freshly sacrificed pig was procured from the local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides and then washed in isotonic phosphate buffer of pH 6.6 and used immediately. The membrane was stabilized

before mounting in order to remove the solublecomponents. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 200 ml of isotonic phosphate buffer of pH 6.6 which was maintained at 37 ± 0.2º C and the hydrodynamics were maintained by stirring with a magnetic bead at 50 rpm [31,32] and results are given under.

Stability study [33]

Optimized medicated films were subjected to short term stability testing. Films were placed in a glass beaker lined with aluminum foil and maintained at 40±2°C and 75±5% RH for 2 month as per ICH guidelines. Changes in the appearance and drug content of the stored films were investigated after storage.

RESULTS AND DISCUSSION

The present study deals with the formulation of mucoadhesive buccal films of methyldopa which is used for the treatment of hypertension. The present study was intended to select the best possible polymer and excipient combinations to formulate the mucoadhesive buccal films of methyldopa. Films were prepared by solvent evaporation method. Different polymers such as HPMC K-47, Na CMC, ethylcellulose and PVP K-30 were used at different compositions. PEG 6000was used as plasticizer to enhance the flexibility of the film. All the films were prepared under identical conditions to minimize processing variables. Further these films were evaluated for various physical properties. The composition of various methyldopa mucoadhesive buccal films was given in table 8.

Thickness uniformity of films: All the drug-loaded films have uniform thickness throughout. The average thickness of all the films ranged between 0.175±0.0055 to 0.227±0.0071 which are in listed in table 10. The optimized F_6 film was found to have thickness of 0.175±0.0055mm.

Uniformity of weight of films: Drug loaded films (2 x 2 cm^2) were tested for uniformity of weight and the results are given in the Table 11. All the films were found uniform. Standard deviation of all the films ranged between0.2926 and 1.4167.The optimized F_6 film was found to have thickness of 20.45±1.4115mg.

Surface pH: Attempts were made to keep the surface pH as close to buccal/ salivary pH as possible. The surface pH of all films was within satisfactory limit of 7.0±1.5 [**32**] and hence no mucosal irritation was expected and ultimately achieved patient compliance (Table 04). These results suggested that the polymeric blend identified was suitable for oral application owing to the acceptable pH measurements.

Folding endurance: Films did not show any cracks even after folding formore than 200 times. Hence it was taken as the end point (Table 04). Folding endurance did notvary when the comparison was made between plain films and drug- loaded films.

Content uniformity of methyldopa films: The content uniformity tests arecommonly employed for unit dosage forms such as tablets, capsules etc. In order tomake sure about the uniform dispersion of drug in films, content uniformity testswere carried out. The drug content was analyzed at 282 nm. Corresponding blanks were used for the estimation of drug. The theoretical drug loading was 15mg in 2x2cm^2 films.

The results of content uniformity tests are expressed as AM ± SD and reportedin the Table 04. The results indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 81.93 to 88.72. All the formulations showedmore than 80% of the drug loading indicating much of the drug is not lost.

Swelling studies of the films: The swelling of the drug loaded films ofsize 2 x 2 cm^2 was studied up to 30 min in case of change in weight. The swelling of the films were observed in phosphate buffer solution (pH 6.6). The data for increase in weight due to swelling are given in the tables 05 to 17 for films I to VI, respectively. The entire data are shown in the figure 07. The order of % increase in weight is IV < III < II < VI < I < V. Swellingwas more pronounced in films V and I which contains HPMC K 47. Films IVshowed least swelling (weight basis), may be due to the presence of ethyl cellulose.

***In Vitro* Release Studies**

*In vitro*release studies of methyldopa films were carried out in phosphatebuffer solution, pH 6.6. The release data of methyldopa was carried out respectively from the films I to VI.The *in vitro* release data of methyldopa from all the films are compiled in the Table 06. Drug release profiles from all the films are shown in the Figure 08. Ethylcellulose retarded therelease rate of drug from HPMC films (films III and IV). PVP increased the drug release rate from HPMC films. The *in vitro* indicates that PVP increases the drug release rate from HPMC films though the effect is less in theinitial periods.

The results of drug release can be correlated with the percent moisture loss. Percent moisture loss is an indication of the capacity of polymer to retain moisture content. More the moisture retention in the films more could be the tendency of drug release.

Viscosity of the polymer also has its influence on the drug release rate. If the viscosity of the polymeric solution is more, then drug release rate will also be more.

Data of in vitro drug-release were fit into different equations and kinetic models to explain the release kinetics of methyldopa from these films. The release data of methyldopa from the film-V are processed into graphs as shown in the figures 09 and 10 to understand the linear relationship (kinetic principles), as models.The data of all the films were processed for regression analysis using MS-Excel statistical functions. The parameters and equations were obtained.

All values indicate that the regression values were higher with zero order and therefore the release kinetics of methyldopa followed zero order from all the films.

Release Mechanisms

To understand the release mechanisms of methyldopa, the data of *in vitro* drug release were fit into Higuchi's model and Hixon-Crowell cube root law model. The data of *in vitro* drug release from the film-V are fit into the models specified and the graphs are generated as shown in the figures 11 (Higuchi's model) and 12 (Hixson- Crowell model), as representative figures.

However the equations generated for all the films are shown in the table 07. Application of Hixon – Crowell cube root law, the equation $M_0^{1/3}$-$M^{1/3}$ = kt, provides information about the release mechanism, namely dissolution rate limited.

Application of Higuchi's equation ($M = K\ t^{1/2}$) provides information about the release mechanism, namely diffusion rate limited.

Perusal to Table 08 indicates that R^2 values are higher for Higuchi's modelcompared to Hixon – Crowell for all the films. Hence methyldopa release from the all the films followed diffusion rate controlled mechanism.

In Vitro Release Time

*In vitro*release time of methyldopa films were carried out in phosphate buffer solution, pH 6.6. The release data of methyldopa are given in the Tables 09 respectively for the films I to VI. The incorporation of the drug induced significantreduction of the residence time of various formulations. The enhanced erosion rate was observed with the non-ionic polymers (HPMC with PVP K_{30}). As the particleswells, the matrix experiences intra-matrix swelling forcewhich promotes disintegration and leaching of the drugleaving behind a highly porous matrix. Water influx weakens the network integrity of the polymer, thusinfluencing structural resistance of the swollen matrices,which in turn results in pronounced erosion of the lose gellayer (El-Khodairy, 2001).

The water-soluble hydrophilicpolymers like Na CMC dissolve rapidly and introduceporosity. The void volume is thus expected to be occupiedby the external solvent which diffuses into the film andthereby accelerate the dissolution of the gel (Samuelovet al., 1979). The*in vitro*residence time of the film was inorder of $F_4>F_3>F_2>F_1>F_6>F_5$.

Ex Vivo Drug permeation studies

Film-V out of six formulations prepared was considered as the bestformulation based on the *in vitro*release rate. Therefore, this formulation was selected for the*ex vivo* studies. The *ex vivo* permeation studies were conducted onthe buccal pouch of the freshly sacrificed pig was procured from the local slaughter house for the films-V. Data are recorded in the table 10. Each recording was an average of three determinations. About 85.30% of methyldopa waspermeated from film V within 30 min (figure 13).

Kinetics of permeation of methyldopa through Buccal pouch Mucosa

The absorption data for methyldopa (table 10) were processed into graphs (Figures 14 and 15) to understand the linear relationship i.e., kinetic principles. The data were processed for regression analysis and the equations were given in the table 10. A perusal to the table 10 indicated that the buccal absorption of methyldopa from buccal pouch mucosa followed first order from film-V.

In Vitro ex Vivo Correlation

The concept of *in vitro* - *ex vivo* correlation has been extensively used by pharmaceutical scientists. *In vitro*release studies and their correlation with *ex vivo* studies will be helpful to predict therapeutic efficiency of the dosage form. So correlation between *in vitro* release behavior of a drug and it's*ex vivo* absorption inbuccal mucosa must be demonstrated experimentally to reproduce therapeutic response.

In vitro release vs. *ex vivo* buccal mucosa permeation of methyldopa from film-V

The relevant data were taken from the table 10, for the *in vitro* release and *ex vivo* buccal absorption for the film-V. The data obtained were recorded in table 11. Further the data were regressed using MS-Excel statistical program. A perusal to the figure 16 indicated good correlation (0.9972) for film-V.

Stability study

The stability study of the formulation $F_6$was carried out at normal room conditions and 40±2°C and 75±5% RH for a period of two months. The films does not show any change in appearance and flexibility. The drug content and surface pH was found almost constant for up to two months. The in vitro dissolution time of the films after the stability study was also not found to be affected.

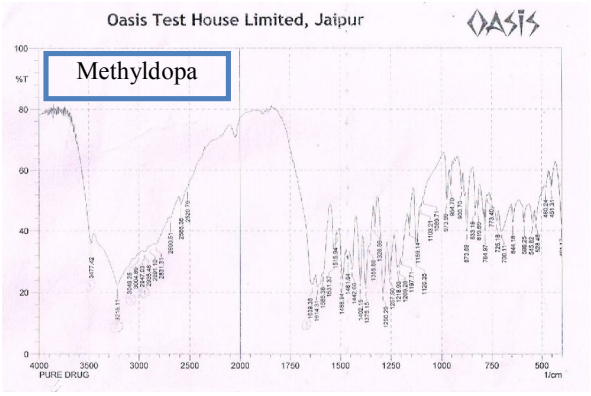

Figure 1: FT-IR spectrum of methyldopa

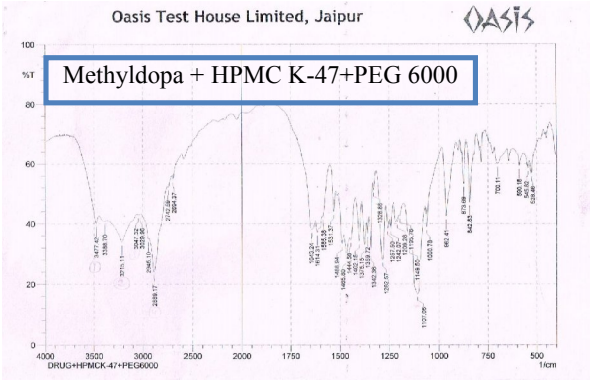

Figure 2: FT-IR spectrum of methyldopa, HPMC K 47 and PEG 6000

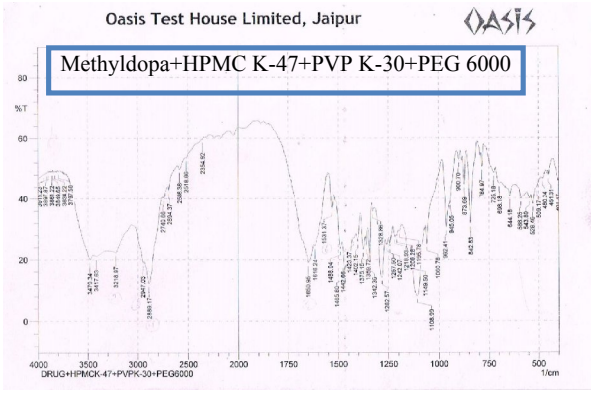

Figure 3: FT-IR spectrum of methyldopa, HPMC K 47, PVP K 30 and PEG 6000

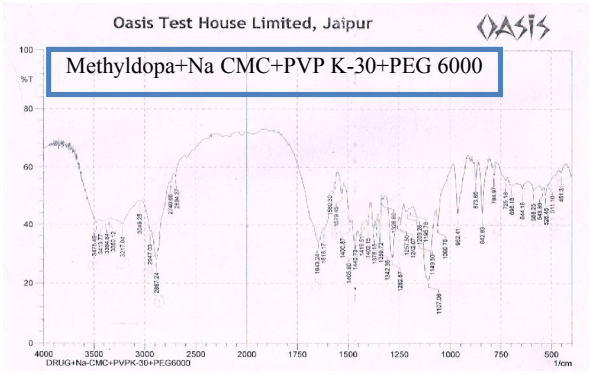

Figure 4: FT-IR spectrum of methyldopa, Na-CMC, PVP K 30 and PEG 6000

Table 2: Data for calibration curve of methyldopa in 0.1 N HCl at 282 nm

Sr. no.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	5	0.119
3.	10	0.226
4.	15	0.331
5.	20	0.447
6.	25	0.563
7.	30	0.672

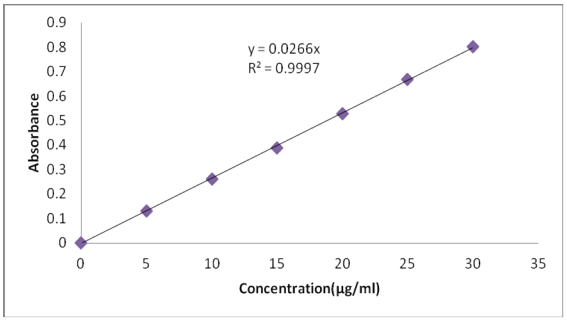

Figure 5: Calibration curve of methyldopa in 0.1 N HCL

Table 3: Data for calibration curve of methyldopa in phosphate buffer solution (pH 6.6) at 282 nm.

Sr. no.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	5	0.131
3.	10	0.262
4.	15	0.389
5.	20	0.529
6.	25	0.668
7.	30	0.801

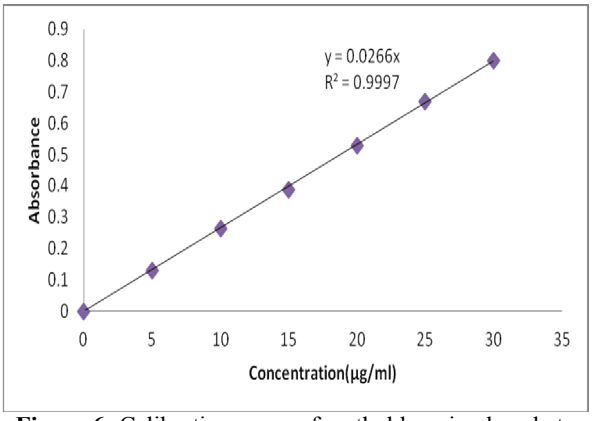

Figure 6: Calibration curve of methyldopa in phosphate buffer solution, pH 6.6

Table 4: Thickness, average weight, surface pH, folding endurance and drug content of mucoadhesive buccal films loaded with methyldopa

Sr. No.	Film code	Average thickness* (mm) AM±SD	Average weight,* (mg) AM±SD	pH ± SD	Folding Endurance	% Drug present
1.	I	0.202 ± 0.0028	15.60 ± 0.3827	7.53 ± 0.07	> 200	84.86 ± 0.3415
2.	II	0.195 ± 0.0042	17.20 ± 0.4182	7.19 ± 0.03	> 200	80.26 ± 0.3918
3.	III	0.213 ± 0.0054	21.52 ± 1.4327	7.42 ± 0.07	> 200	88.46 ± 4.3960
4.	IV	0.227 ± 0.0071	23.83 ± 1.5216	7.13 ± 0.09	> 200	86.46 ± 1.6641
5.	V	0.175 ± 0.0055	20.45 ± 1.4115	7.39 ± 0.08	> 200	87.87 ± 1.6641
6.	VI	0.185 ± 0.0087	23.90 ± 1.2764	7.22 ± 0.03	> 200	81.93 ± 2.2332

Table 5: Swelling studies of methyldopa films from I-IV Change in weight

Sr. no.	Time (min)	Weight of film I (mg) AM±SD	Weight of film II (mg) AM±SD	Weight of film III (mg) AM±SD	Weight of film IV (mg) AM±SD	Weight of film V (mg) AM±SD	Weight of film VI (mg) AM±SD
1.	0	15.60±0.1638	17.20±0.3166	21.52±0.9829	23.83±0.9952	20.45±1.1645	23.90±1.5683
2.	5	55.10±0.7322	70.76±5.7768	56.82±9.1809	50.86±8.9012	89.33±13.1087	96.83±6.6352
3.	10	81.70±1.9578	91.06±6.2243	72.00±8.3321	61.67±2.8321	123.06±12.1547	128.23±7.4298
4.	15	92.19±0.4693	106.70±5.4865	75.46±10.1744	67.50±6.6774	144.40±11.0573	144.67±7.2954
5.	20	104.45±1.8359	119.57±8.4682	85.43±4.9817	77.26±3.7581	159.03±12.1294	165.20±12.7812
6.	25	115.23±1.5287	135.60±6.0777	98.01±7.9186	86.17±5.3490	175.96±4.0758	180.45±12.1436
7.	30	120.45±1.3638	147.17±7.5654	103.33±4.1680	91.15±8.4751	180.19±3.1734	190.11±11.4698

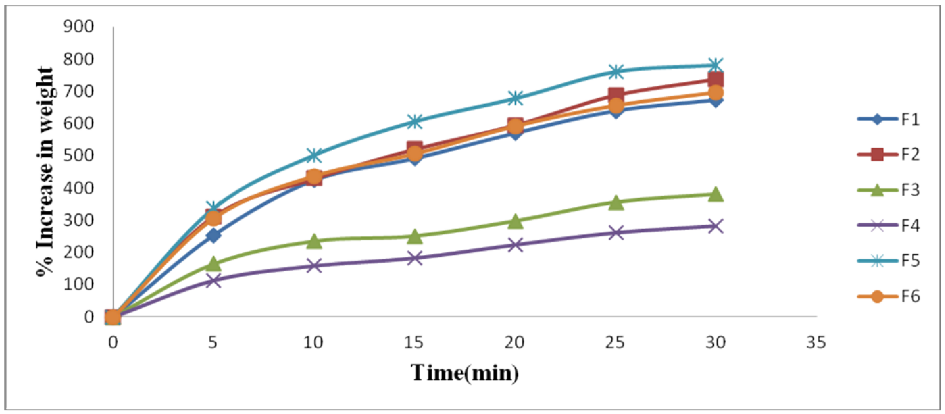

Figure 7: Swelling studies of methyldopa films- Change in weight in phosphate buffer in pH 6.6

Table 6: Compilation of*in vitro* release of methyldopa in 30 min

Sr. No	Film code	% drug released
1	I	59.67
2	II	50.48
3	III	48.52
4	IV	34.56
5	V	71.53
6	VI	58.59

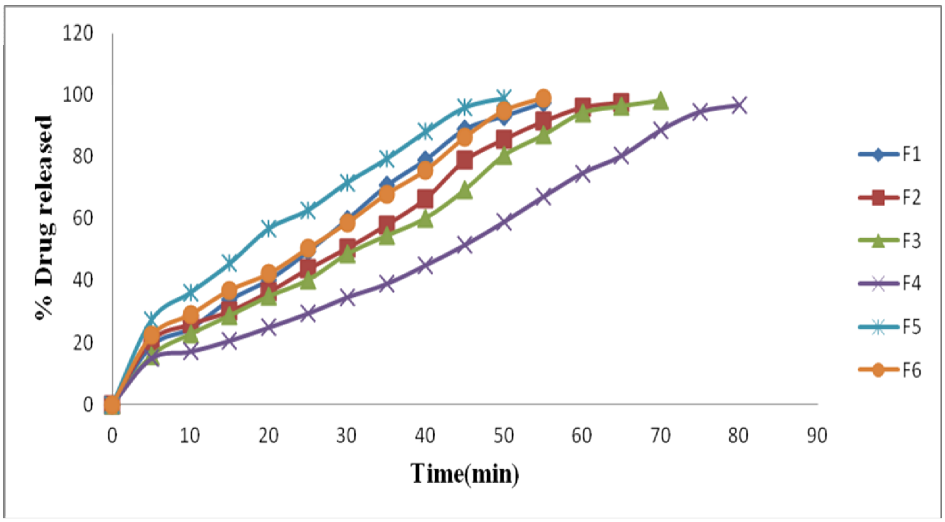

Figure 8: *In vitro* release of methyldopa from films I to VI

Kinetics of Drug Release (Zero and First Order)

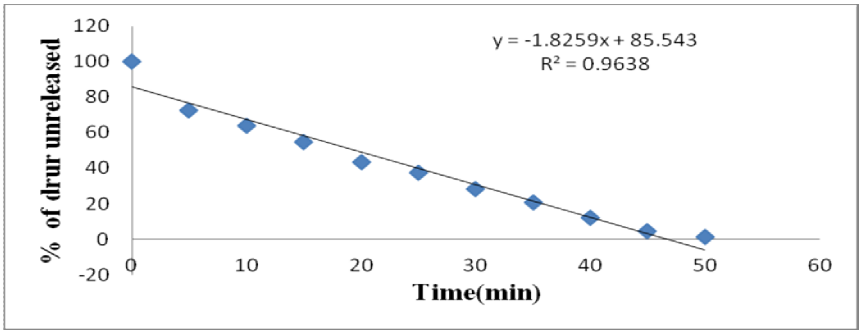

Figure 9:*in vitro* release of methyldopa from film-V in phosphate buffer (pH 6.6)

Zero order release

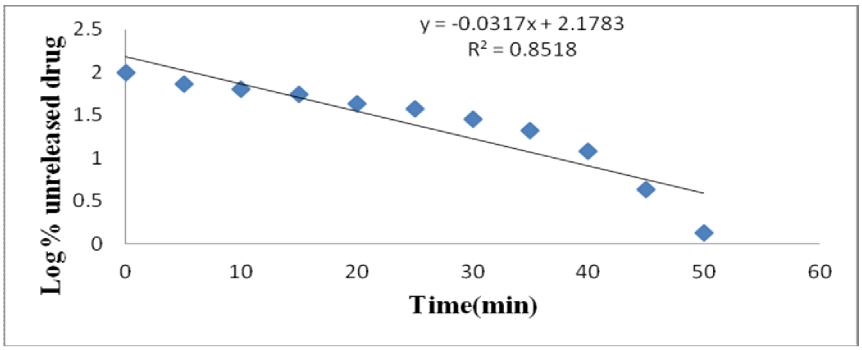

Figure 10: *in vitro* release of methyldopa from film-V in phosphate buffer (pH6.6).

First order release

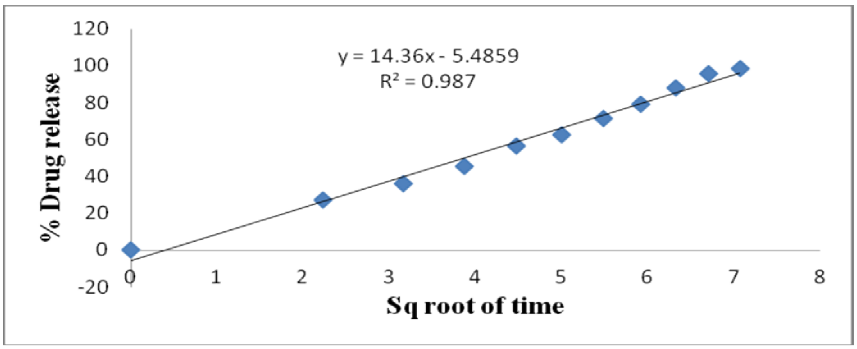

Figure 11: *In vitro* release of methyldopa from film-V in phosphate buffer (pH 6.6)

Higuchi's Release Model

Table 7: Fitting of the Hixon-Crowell cube root law for *in vitro* release of methyldopa from film-V.

Time in min M	$M_0^{1/3}$-$M^{1/3}$	K, $mg^{1/3}$/min
0	0.0000	0.0000
5	0.0965	0.0193
10	0.1330	0.0133
15	0.1753	0.0117
20	0.2333	0.0117
25	0.2679	0.0107
30	0.3275	0.0109
35	0.3905	0.0112
40	0.4835	0.0121
45	0.6221	0.0138
50	0.7293	0.0146

For film V (M_0 =0.880mg) Mean K= 0.0118

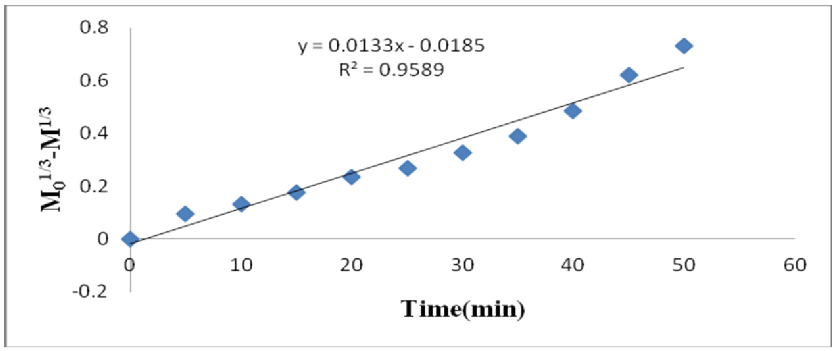

Figure 12: Fitting of the Hixon-Crowell cube root law for*in vitro* release ofmethyldopa from Film-V.

Table 8: Regression equations of *in vitro* release of methyldopa from films I - VI.

Film code	Hixon-Crowell model	Higuchi's model
I	y = 0.0115x - 0.0429 R² = 0.9588	y = 14.115x - 13.248 R² = 0.9468
II	y = 0.0098x - 0.0423 R² = 0.9486	y = 13.06x - 12.797 R² = 0.9432
III	y = 0.0097x - 0.0533 R² = 0.9434	y = 12.896x - 15.077 R² = 0.9439
IV	y = 0.0074x - 0.0578 R² = 0.9113	y = 10.533x - 14.451 R² = 0.8948
V	y = 0.0133x - 0.0185 R² = 0.9589	y = 14.36x - 5.4859 R² = 0.987
VI	y = 0.0113x - 0.0392 R² = 0.9114	y = 13.636x - 10.302 R² = 0.9533

Table 9: Data of *In vitro* release time of methyldopa from the films I-VI in the phosphate buffer solution, pH 6.6 at 37 ^{0} C.

Film code	In vitro release Time (min)
I.	70
II.	76
III.	83
IV.	120
V.	50
VI.	65

Table 10: *Ex Vivo*permeation of methyldopa in buccal pouch from film-V.

Time (min)	%Drug absorbed (mg)	Log % drug absorbed	% drug unabsorbed	Log % drug unabsorbed
0	0.00	0.000	100.00	2.000
10	45.02	1.653	54.98	1.740
20	72.59	1.860	27.41	1.438
30	85.30	1.765	14.70	1.167

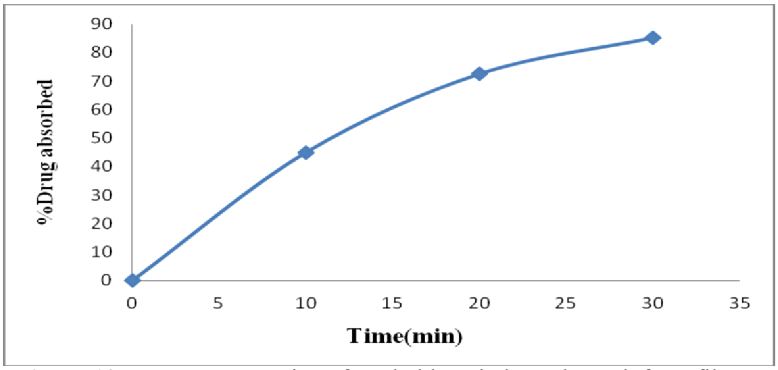

Figure 13: *Ex Vivo*permeation of methyldopa in buccal pouch from film-V

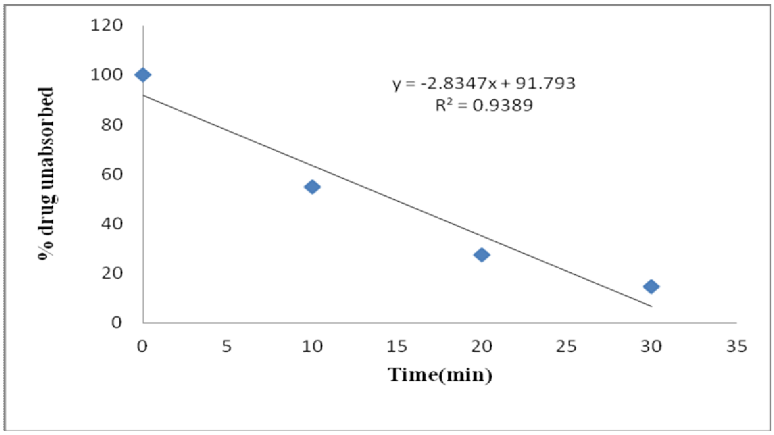

Figure 14: *Ex Vivo*permeation of methyldopa in buccal pouch from film-V
Zero order permeation

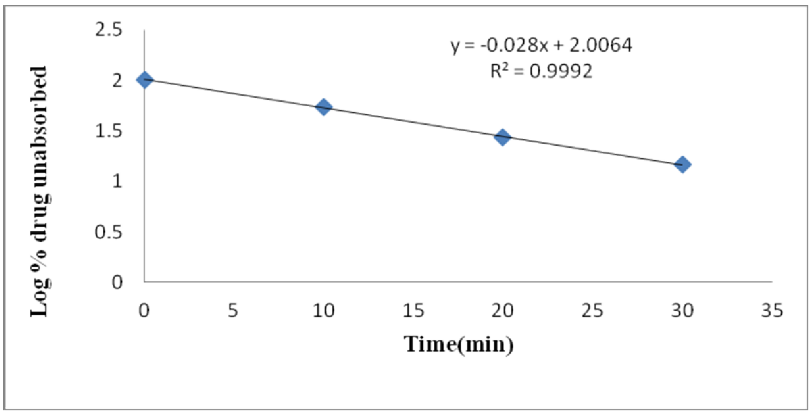

Figure 15: *Ex Vivo*permeation of methyldopa in buccal pouch from film-V
First order permeation

Table 11: *In vitro*release vs. *ex vivo*buccal mucosal permeation of methyldopa from film-V

Time (min)	*In vitro* drug Release (%)	Time (min)	*Ex vivo*drugAbsorption (%)
0	00.00	0	00.00
10	37.65	10	45.02
20	57.83	20	72.59
30	72.33	30	85.30

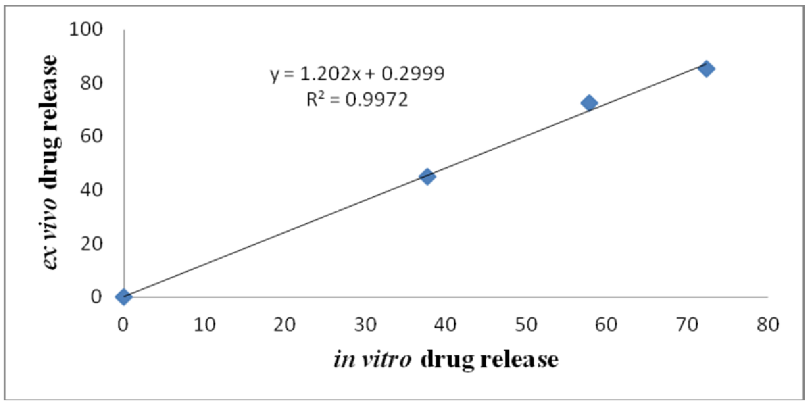

Figure 16: *In vitro* release Vs*ex vivo* buccal mucosal permeation of methyldopa from film-V

CONCLUSION

The results of the present study indicated that HPMC K-47and PVP K-30 could be used as a film forming polymer for formulation of mucoadhesive buccal films containing methyldopa. New buccal mucoadhesive film formulations containing methyldopa had been prepared with satisfactory physicochemical characterizations. On the basis of data obtained from in-vitro dissolution and ex-vivo permeation studies that F_6 is promising formulation suitable for the immediate release of methyldopa for the systemic use since they exhibited maximum drug release and permeation respectively. The formulation batch $F_6$was found to be stable for a period of one month at 40°C/75%RH.

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REFERENCES

1. Bhalodia R, Basu B, Garala K, Joshi B, Mehta K. Buccoadhesive drug delivery systems: A review. International Journal of Pharma and Bio Sciences.2010; 6(2): 1-32.
2. Velmurugan S, Deepika B, Nagaraju K, Vinushitha S. Formulation and *in vitro* evaluation of buccal tablets of piroxicam. Int. J. PharmTech Res. 2010; 2(3): 1958-1968.
3. Yamsani VV, Ramesh Gannu, Chandrasekhar Kolli, BhanojiRao ME, Yamsani MR. Development and *in virto*evaluation of buccoadhesive carvedilol tablets. Acta Pharm. 2007; 57: 185–197.
4. Salamat-Miller N, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Advanced Drug Delivery Reviews. 2005; 57: 1666–1691.
5. Pandit JK, Vemuri NM, Wahi SP, JayachandraBabu R. Mucosal Dosage Form of Ephedrine Hydrochloride using Gantrez-AN 139. Eastern Pharmacist 1993; 36:169-170.
6. Gupta A, Garg S, Khar RK. Mucoadhesive Buccal Drug Delivery System: A Review. Indian Drugs 1992;29(13):586-93.
7. Harris D, Robinson JR. Drug Delivery via Mucous Membrane of the Oral Cavity. J Pharm Sci 1992;81:1-10.
8. Smart JD, The basics and underlying mechanisms of mucoadhesion, Adv Drug Deliv Rev 2005; 57:1556-68.
9. Brahmankar DM, Jaiswal SB, Biopharmaceutics and pharmacokinetics a treatise. 1st edition. Delhi; VallabhPrakashan. 2003; 230-72.
10. Nakhat PD, Kondawar AA, Babla IV, Rathi LG, Yeole PG, Studies on buccoadhesive tablets of terbutaline sulphate Ind J Pharm Sci. 2000; 69 (4): 505-510.
11. Vishnu M. Patel, Bhupendra G Prajapati, Harsha V Patel, Karshanbhi M patel, Mucoadhesive bilayer tablets of propranolol hydrochloride. AAPS Pharm Sci Tech. 2007; 8(3): E1- E6.
12. S Nehal, G Garima. Advances in Biological research. 2011; 5: 291-303.
13. A NarasimhaRao,KSindhu. International Journal of Pharmacy and Biological Sciences. 2011; 3: 145-159.
14. AArun; C Amrish. International Journal of Chem Tech Research. 2010, 2, 576-583.
15. B Gavaskar, S Vijaya Kumar, G Sharan, Y Madhusudan. International Journal of Pharmacy and Pharmaceutical Sciences. 2011; 2(3): 29 -33.
16. VK Subash, GBasani, G Sharan,YMadhusudanRao. International journal of Pharmacy and Pharmaceuticalsciences. 2010; 2: 29-33.
17. RP Dixit, SP Puthli. Journal of Control Release. 2009; 139: 94-107.
18. SD Barnhart, MS Sloboda. Drug Delivery Technology. 2007; 7 (8): 34 – 37.
19. G Vijaykumar, P Ajaykumar, P Satishkumar, S Karunasri, K Raghavender, P Priya. World Journal of Medical Pharmaceutical and Biological Sciences. 2011; 1(1): 06-12.
20. C F Wong; K H Yuen and K KPeh, *Int J Pharm*, 1999; *178*(1): 11-22.
21. S Senel; G Ikinci; S Kas; A Yousefi-Rad; M F Sargon and A AHincal, *Int J Pharm*, 2000;*193*(2): 197-203.
22. Ahmed MG, Harish NM, Charyulu RN, Prabhu P. Formulation of chitosan- based ciprofloxacin and diclofenac film for periodontitis therapy. Trop JPharm Res 2009;8(1):33-41.
23. K G Desai and T M Kumar, *AAPS PharmSciTech*, 2004; *5*(3): e35.
24. S A Yehia; O N El-Gazayerly and E B Basalious, *Curr Drug Deliv*, 2009; *6*(1): 17-27.
25. Noha AN, Nabila AB, Fatima A, Ismail, Lobna MM. D esign and characterization of mucoadhesive buccal patches containingcetylpyridinium chloride. Acta Pharm 2003;53:199-212.
26. Khanna R, Agrawal SP, Ahuja A. Preparation and evaluation of buccal films of clotrimazole for oral Candida infections. Indian J P harm Sci1997; 59:299-305.
27. A Sood and R Panchagnula, *Int J Pharm*, **1998**; *175*:95-107.
28. H Okamoto; H Taguchi; K Iida and K Danjo, *J Control Release*, **2001**; *77*(3): 253-260.
29. El-Khodairy KA. Effect of physicochemical properties of the hydrophilic Gantrez matrix. *Alex. J. Pharm. Sci.* 2001; 15:35-40.
30. Samuelov Y, Donbrow M, Friedman M. Sustained release of drugs from ethyl cellulose-polyethylene glycol films andkinetics of drug release. *J. Pharm. Sci.,* 1979; 68:325-329.

31. Chandra Sekhar K, Naidu KVS, Vamshi Vishnu Y, Ramesh G, Kishan V, MadhusudanRao Y. Transbuccal delivery of chlorpheniramine maleate from mucoadhesive buccal patches. Drug Delivery 2008; 15(3): 185-91.
32. V M Patel; B G Prajapati; J K Patel and M M Patel, *Curr Drug Deliv*, 2006; *3*(3): 325-331.
33. David JM. International stability testing, Bufflo grove; Interpharm Press Inc: 1999.

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