WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 10, 806-817. Research Article ISSN 2277– 7105

FORMULATION AND IN-VITRO EVALUATION OF DISSOLVING BUCCAL FILMS OF LOVASTATIN

Manju Rani* and Bhag Chand

Department of Pharmaceutics, Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), University of Delhi, Pushp Vihar, sector - 3, New Delhi-110017, India.

Article Received on
13 July 2017,

Revised on 02 August 2017,
Accepted on 23 August 2017

DOI: 10.20959/wjpr201710-9363

***Corresponding Author**
Manju Rani
Department of Pharmaceutics, Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), University of Delhi, Pushp Vihar, sector - 3, New Delhi-110017, India.

ABSTRACT

The purpose of this investigation was to develop "Dissolving muco-adhesive buccal films" of lovastatin by solvent casting technique to deliver lovastatin into blood via buccal mucosa and to bypass its first pass metabolim and also to improve the bioavailability of the drug using muco-adhesive polymers and PEG400 as plasticizer. Mucoadhesive polymer[1] such as Hydroxy Propyl Methyl Cellulose E5 (HPMC), Polyvinyl alcohol(PVA), Polyvinyl pyrollidine(PVP), Carboxy methyl cellulose(CMC), Carbopol 934 and Chitosan were used for the film. Prepared films were carried out for *in vitro* evaluation tests such as weight variation, film thickness, folding endurance, drug content, mucoadhesive strength[2] force of adhesion, bond strength, disintegration studies and dissolution studies. Attenuated total reflectance (ATR), Differential Scanning Calorimetry (DSC) and X-ray powder diffraction (XRD) analysis revealed no Interaction between drug and polymers. Results revealed that buccal film containing HPMC 5% (w/v) and PEG400 40% (w/w of dry polymer weight) shows maximum dissolution and comply all the characteristics of buccal films. Thus, this study suggests that "dissolving mucoadhesive buccal films" can act as a potential for buccal delivery of poorly water soluble hypolipidemic drug lovastatin.

KEYWORDS: Mucoadhesive polymers; Lovastatin; Buccal films.

INTRODUCTION

Oral route is most preferred route of drug administration but solubility and first pass metabolism sensitivity of drug are important characteristic to be accepted by this route.

Parental rout is painful drug administration system. Topical drugs are limited for topical or local treatment only.

High molecular weight drugs, poor skin penetrating drugs, poor water insoluble drugs, and extensive first pass metabolism prone drugs need alternative routes. *Mucoadhesive* route is becoming popular alternative for most of the drugs.

Mucoadhesive drug delivery system through *Buccal*, sublingual, rectal and nasal mucosa can be faster and systemic mode of non-invasive drug administration to bypass first pass metabolism. Faster delivery and enhanced bio availability of drugs is observed through *mucoadhesive* administration[3] Buccal route is preferred mostly for the drugs which have poor solubility, dissolution and bioavailability and for the drugs which show high hepatic first pass metabolism. Buccal route is the most convenient route as it is noninvasive and more patient compliance. This is because the buccal mucosa is highly vascularized and the drugs are directly absorbed into blood stream and shows immediate action. Moreover this route can be used for both local and systemic effects. As the drug directly reaches the blood, the dose can be minimized.[4] Several buccal adhesive delivery devices have been developed such as tablet, wafers, gels and films. Overall, a muco-adhesive buccal film offers several benefits due to its small size, thickness and improved patient compliance compared to tablets and gels. Buccal films offer more surface area and offers rapid disintegration and rapid absorption. The muco-adhesive buccal films adhere to the buccal mucosa and then the films are disintegrated after hydrating in saliva and release the drug. As the film adhered to buccal mucosa the released drug has more chances to get firstly absorb into the blood stream through mucosal layer.[5]

Lovastatin is a potent cholesterol-lowering agent that belongs to the class of medications called statins[6] According to BCS classifications it is a class II drug with low solubility and high permeability. Lovastatin is absorbed from the gastrointestinal tract and <5% of the oral dose reaches the general circulation as active inhibitors. Lovastatin undergoes extensive first-pass metabolism so the availability of the drug in the system is low and variable. Enhancement of the bioavailability of Lovastatin can reduce the dose required to elicit the same pharmacological action and hence reduce the side-effects associated with the drug. lovastatin also causes irritation to gastric mucosa. Thus delivering lovastatin through buccal route would increase the bioavailability as the first pass metabolism would be bypassed. Dissolving Buccal film is the better option to deliver lovastatin through buccal route because

by incorporating lovastatin into water soluble polymer matrix will also enhance its water solubility, stability and bioavailability.

MATERIALS AND METHODS

Materials

Lovastatin USP was obtained as a gift sample from Sterling®Biotech Limited, Gujrat, India. Hydroxy Propyl Methyl Cellulose E5 (HPMC), Polyvinyl alcohol(PVA), Polyvinyl pyrollidine(PVP), Carboxy methyl cellulose(CMC), Carbopol 934, (medium viscosity) Chitosan, Poly ethylene glycol 400 (PEG400), Ethanol were purchased from Central Drug House, Lab Reagents, New Delhi, India.

Method

Preparation of Dissolving Buccal Films

Hydrophilic polymers was dissolved in 10ml of hot water in one beaker and Lovastatin, PEG 400 were dissolved in 7ml of 95% ethanol in another beaker, stirred continuously in magnetic stirrer about 45mins.

Drug solution was then added to the polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass petridish and was dried at room temperature for about 48hrs. The dried film was carefully removed from the petridish and was cut into size required for testing. The films were stored in air tight plastic bags.

Further a series of placebo dissolving buccal films were prepared with varying concentration of polymer, plasticizer and co-solvent. Afterwards films were gently peeled off and each of them were evaluated for their following physical properties are Detachability from Petri plates, Non-Stickiness, Uniformity, Flexibility, Transparency/Appearance, Tensile strength, Brittleness

Dissolving Buccal Films Formulation

Based on the physical properties and mucoadhesive strength, a series of buccal films were prepared with varying concentration of polymers, plasticizer and ethanol as solvent. For all formulations the amount of Lovastatin were same i.e. 10 mg. The formulations were summarized in the table 1.

Table 1: Various dissolving buccal film formulations.

Formulation code	Polymer	Polymer conc.w/v (mg)	PEG400 conc.w/w	Ethanol	Distilled water
F1	HPMC	250	40%	7ml	10ml
F2	HPMC	500	40%	7ml	10ml
F3	HPMC	1000	40%	7ml	10ml
F4	PVA	250	40%	7ml	10ml
F5	PVA	500	40%	7ml	10ml
F6	PVA	1000	40%	7ml	10ml
F7	Chitosan	200	40%	7ml	10ml
F8	Chitosan	300	40%	7ml	10ml

***In Vitro* Evaluation of Dissolving Buccal Films**

Weight variation

Ten films were randomly selected and their average weight was obtained. Individual films were weighed and compared with the average weight for the deviation.

Thickness

The thickness of film can be measured by micrometer screw gauge at different strategic locations (at least 5 locations). This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film.

Folding endurance test

Folding endurance is determined by repeated folding of the film at the same place till the film breaks. The number of the times of the film is folded without breaking is computed as the folding endurance value

Surface pH

The surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since strong acidic or alkaline pH may cause irritation to the buccal mucosa. The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 1 h. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1.0 min.

Determination of Mucoadhesive Strength, Force of adhesion &Bond strength

It was determined by Modified Wilhemy Plate Method.

Modified Wilhelm Plate Method

A small glass plate (2 cm) was coated by film of test mucoadhesive agent using a rubber band. The egg white was collected from hen eggs and kept in a suitable container and the temperature was maintained at 37 °C. The composition and viscosity of egg white is similar to that of mucus.[3,8]

Table 2: Composition of Egg White and Mucus.

	water	Glycoprotein	Mineral salts	carbohydrate	Viscosity
Mucus	95%	0.5-5%	1%	0.5-1%	12-15Pa-s
EGG White	90-95%	<10%	-	<1%	12-18Pa-s

Nylon thread was attached at one end of the glass plate and the other end of thread was attached to the left arm of physical balance. It was allowed undisturbed for 5 min. Provision was given to raise the weight from the right arm of balance. At specified intervals, weight was added to completely detach the coated glass plate from egg white and the force required to completely pull the plate out of the egg white was determined under experimental condition. Three plates were tested for each material and the average weights required was calculated.

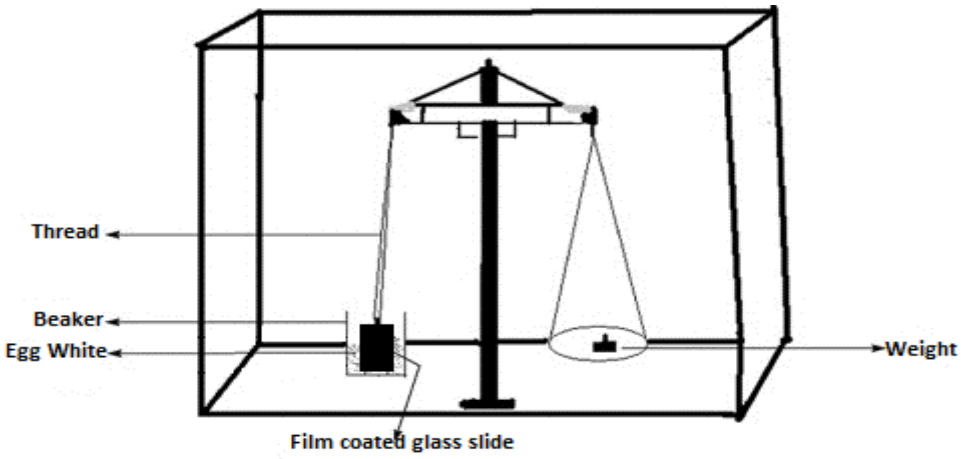


Fig. 1 Apparatus to determine mucoadhesion *in vitro*, using Modified Wilhemy's technique.

Force of adhesion and Bond strength were calculated by following equations:

Force of adhesion (N) = mucoadhesive strength (g) × 9.8/1000

Bond Strength (Nm^{-2}) = force of adhesion/film surface area

Disintegration test

In-vitro disintegration time was determined visually in a petridish containing 25 ml of pH 6.8phosphate buffer with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrate.

Drug Content

Drug content studies were carried out for F2, F5 and F7 formulation of Dissolving buccal films. Dissolving film of size 4cm² was taken and transferred into a graduated glass stoppered flask containing 10ml of methanol. It is then stirred continuously to completely dissolve the film. The solution is then suitably diluted and absorbance values were measured in a UV spectrophotometer at 237nm. The average of three films was taken as final reading.

***In vitro* drug release study**

The drug release studies were performed with USP dissolution test apparatus. (Paddle method). The USP dissolution apparatus was thermo stated at the temperature of 37±10C and stirred at rate of 75 rpm in a 500ml dissolution medium of pH 6.8 phosphate buffer. The aliquots of 5 ml were withdrawn at the time interval of every 15mins and replaced with equal volume of dissolution medium. The sink condition was maintained throughout the study. The samples were analyzed at 237 nm in a UV-VIS Spectrometer and cumulative amount of drug release at various time intervals was calculated.

Compatibility studies

The drug-polymer compatibility was confirmed by taking IR spectrum of drug, polymer and physical mixture of drug-polymer proved that the excipients were compatible with the Lovastatin.

RESULT AND DISCUSSION

Optimization of Polymers

The Placebo films were prepared using HPME E5, PVP, PVA, Chitosan, Carbopol 934, CMC, Sodium Alginate as polymers in various amounts. The characteristics of films were evaluated as follows:

Table 3: characteristics of films prepared using various polymers.

Sr. no.	Polymer	Amount	Remarks
1	HPMC	250	Good
2		500	Very good
3		1000	Very good
4	PVA	250	Sticky
5		500	Very sticky
6		1000	Peel off problem
7	PVP	250	Good
8		500	Very good
9		1000	Very good
10	Sodium Alginate	250	Very weak
11		500	Pale yellow in colour
12		1000	Yellow in colour
13	CMC	250	Brittle
14		500	Very brittle
15		1000	Very brittle
16	Carbopol 934	250	Peel off problem
17		500	Sticky and Peel off problem
18		1000	Sticky and Peel off problem
19	Chitosan	200	Very good
20		300	good

Thus films having very good and good characteristics were selected for further studies.

Preparation of film formulations

All the film formulations containing HPMC-E5, PVA, chitosan, and PEG400 as plasticizer were readily prepared by solvent casting method.

Evaluation of Prepared Films

From the results of the tests for physical characterization conducted, it is observed that the weight and thickness of all film samples were uniform within each formulation. Films formulated from HPMC E5 and CHITOSAN were smooth, flexible and transparent/ translucent whereas those prepared from PVA were slightly rough in texture, heavier and translucent. All film formulations exhibited good folding endurance. It is summarized as follows:

Table 4: Physical characteristics of films.

Formu-lation code	Polymer	Appearance	Weight Variation (mg)±SD	Thickness (mm)	Folding Endurance	Surface pH
F1	HPMC2.5%	Transparent	36.69±0.59	0.14±0.004	120±2	6.55±.036
F2	HPMC 5%	Transparent	55.93±2.14	0.176±0.011	111.33±3.05	6.77±0.13
F3	HPMC10%	Translucent	74.67±1.6	0.197±0.015	94.66±4.16	6.55±0.04
F4	PVA 2.5%	Translucent	39.65±0.41	0.155±0.007	124±2	6.61±0.06
F5	PVA5%	Translucent	59.32±0.79	0.194±0.005	115.66±2.08	6.62±0.16
F6	PVA 10%	Translucent	80.1±0.38	0.22±.007	96±2	6.60±0.1
F7	Chitosan2%	Translucent	31.63±0.49	0.27±0.015	143.33±2.08	6.21±0.02
F8	Chitosan3%	Translucent	57.05±1.12	0.35±0.026	143.66±1.52	6.27±0.03

Surface pH

An acidic or alkaline pH of administered dosage forms can irritate the oral mucosa. The measured surface pH was found to be close to neutral in all the formulations which means that they have less potential to irritate the oral mucosa and therefore they should be fairly comfortable.

***In vitro* Disintegration test**

All the formulations showed *in vitro* disintegration (table 5) within 4minutes.

Table 5: Disintegration time of buccal film formulations.

Sr.no.	Formulation code	Polymer	*In vitro* disintegration Time (sec)
1	F1	HPMC 2.5%	85±3
2	F2	HPMC 5%	95.66±2.51
3	F3	HPMC 10%	118±3
4	F4	PVA 2.5%	93±2
5	F5	PVA5%	129.66±7.23
6	F6	PVA10%	163.33±4.16
7	F7	Chitosan 2%	157.66±2.51
8	F8	Chitosan 3%	208±3

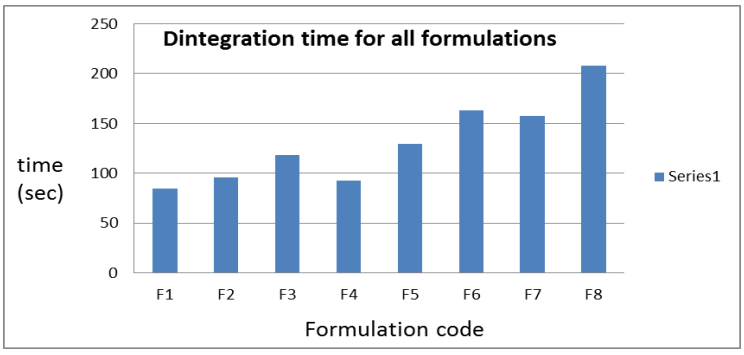


Fig. 2: Disintegration time for dissolving buccal film formulations.

Mucoadhesive Strength, Force of adhesion and Bond strength

From the results it was found that the mucoadhesion of film increases with increase in concentration of polymer. The optimize concentrations were found to be F2 (HPMC 5%), F5 (PVA 5%) and F7 (CHITOSAN 2%). Above these concentrations of respective polymer there was no more considerable increase in mucoadhesion.

Thus formulations F2, F5 and F7 were taken for further optimization.

Table 6: Mucoadhesive strength, Force of adhesion and bond strength.

Sr.no.	Formulation code	Polymer	Mucoadhesive Strength (g)	Force of Adhesion(N)	Bond strength(Nm^{-2})
1	F1	HPMC2.5%	5	0.049	61.25
2	F2	HPMC 5%	6.5	0.063	79.625
3	F3	HPMC 10%	6.7	0.065	82
4	F4	PVA 2.5%	6	0.058	73.5
5	F5	PVA5%	10	0.098	122.5
6	F6	PVA 10%	9.5	0.093	116.37
7	F7	Chitosan2%	5.2	0.05	63.625
8	F8	Chitosan3%	5	0.049	61.25

Drug content: Each buccal film formulation showed drug content more than 95%.

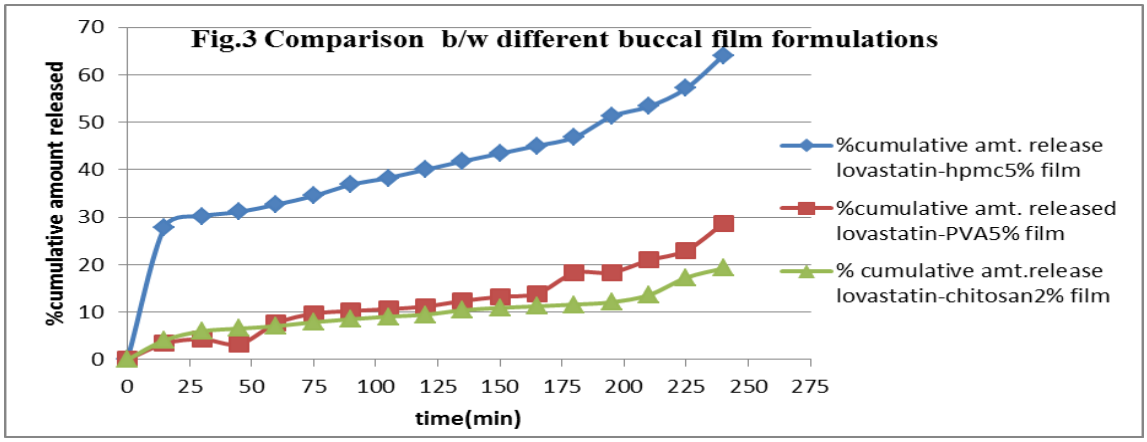
Table 7: % Drug content of dissolving buccal film formulations.

Formulation (dissolving buccal films)	% drug content
F2(lovastatin-HPMC5%)	97.45±0.687
F5(lovastatin-PVA5%)	96.81±0.795
F7(lovastatin-Chitosan2%)	97.82±0.168

***In vitro* drug release study**

Cumulative percentage drug release of the three dissolving buccal film formulations F2 (lovastatin-HPMC 5%), F5 (lovastatin-PVA 5%) and F7 (lovastatin-CHITOSAN 2%) at pH 6.8 were found to be 64.08, 28.7 and 19.24 respectively. And among the three dissolving buccal film formulations; Formulation F2[lovastatin-HPMC5%] shows highest cumulative percentage release.

% Cumulative Drug Release Comparison between Dissolving Buccal Film Formulations.



Compatibility Studies

Attenuated total reflectance (ATR), Differential Scanning Calorimetry (DSC) and X-ray powder diffraction (XRD) analysis revealed no interaction between drug and polymers.

The results are shown in the figures below.

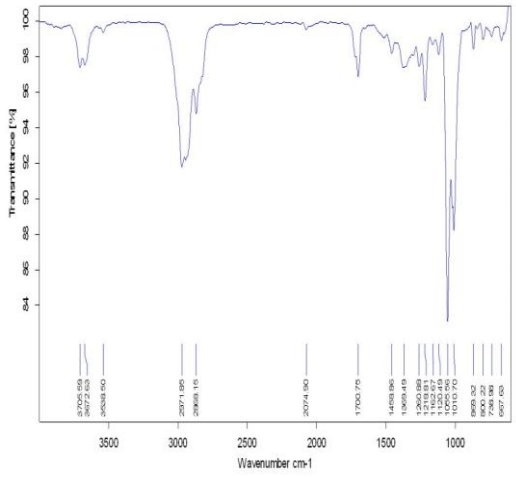


Fig .4: ATR of lovastatin.

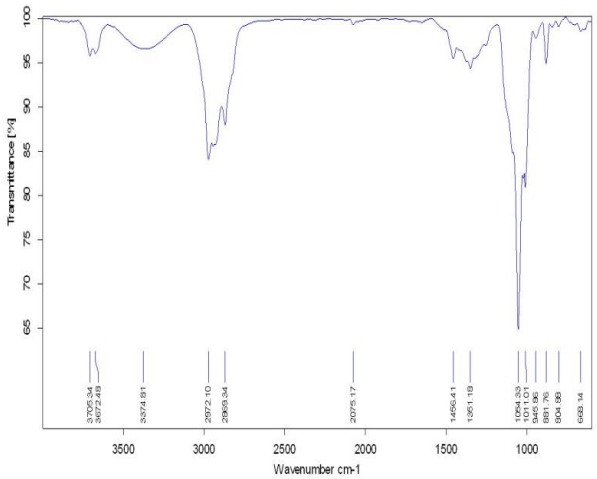


Fig. 5: ATR of lovastatin-HPMC film.

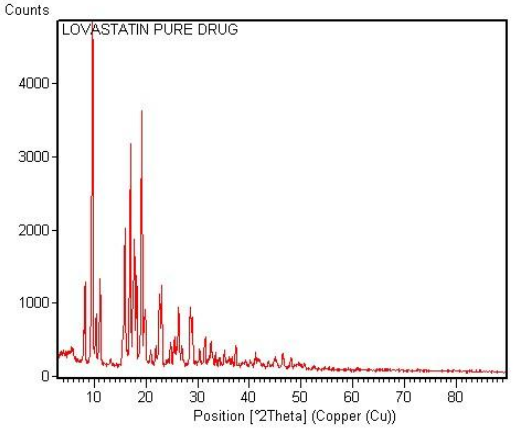


Fig. 6: XRD of lovastatin.

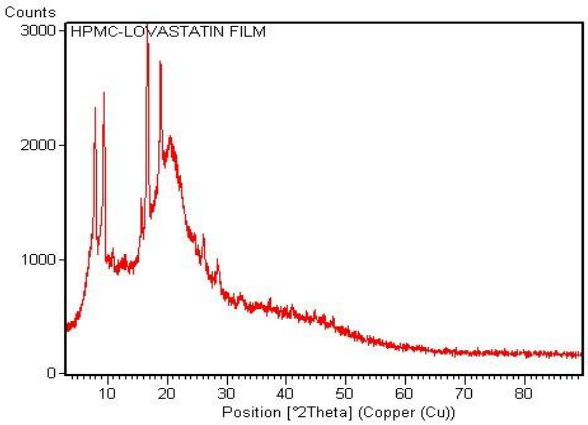


Fig. 7: XRD of lovastatin-HPMC film.

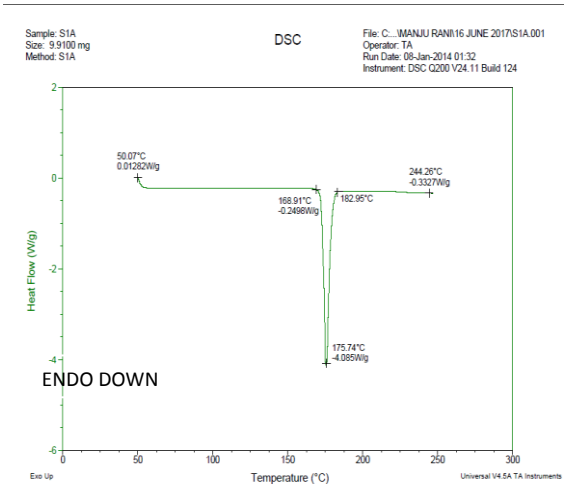


Fig. 8: DSC of lovastatin.

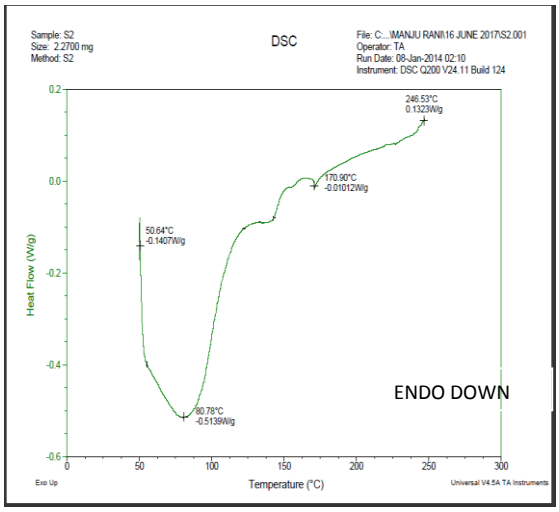


Fig. 9: DSC of lovastatin-HPMC film.

CONCLUSION

The in-vitro dissolution studies showed higher cumulative percentage drug release for "Dissolving Buccal Films of Lovastatin formulations" as compared to pure drug. The results indicate that "Dissolving Buccal Films formulation" have a potential to increase release and bypass the first pass effect of poorly water soluble drugs such as Lovastatin. However, In-vivo studies are needed to ensure increased bioavailability. Hence "the Dissolving Buccal Films" are distinctive and commercially feasible approach for optimal delivery of the poorly water soluble and poorly bioavailable drugs.

ACKNOWLEDGMENTS

The authors are grateful to all the faculty of Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR) who has been the guiding force and motivation behind the project. The

authors are also thankful to the University Science Instrumentation Center (USIC), University of Delhi, New Delhi, for providing necessary facilities for the conduct of study.

REFERENCES

1. Hanif M, Zaman M, Chaurasiya V. Polymers used in buccal film: a review. *Des Monomers Polym*, 2015; 18(2): 105-111. doi:10.1080/15685551.2014.971389.
2. Yu T, Andrews GP, Jones DS. Mucoadhesion and Characterization of Mucoadhesive Properties, 2014. doi:10.1007/978-1-4614-9524-6.
3. Rajaram DM, Laxman SD. Buccal Mucoadhesive Films : A Review, 2017; 8(1): 31-38.
4. B RM, Murthy VSN, A PR, Gattu DK. Molecular Pharmaceutics & Organic Process Research Buccal Film Drug Delivery System-An Innovative and Emerging Technology, 2013; 1(3): 1-6. doi:10.4172/2329-9053.1000107.
5. P CR, Chaitanya KSC, Y MR. A review on bioadhesive buccal drug delivery systems : current status of formulation and evaluation methods, 2011; 19(6).
6. Pushpa H, Priyata H, K ND, Onya N, Vijayalakshmi A. Screening of lovastatin (HMG-CoA reductase inhibitor) from edible wild mushrooms, 2016; 6(6): 190-196. doi:10.5943/cream/6/3/6.
7. Carvalho FC, Bruschi ML, Evangelista RC, Palmira M, Gremião D. Mucoadhesive drug delivery systems, 2010; 46(2008): 1-18.
8. Ketelaere B De. PROCESSING, PRODUCTS, AND FOOD SAFETY The assessment of viscosity measurements on the albumen of consumption eggs as an indicator for freshness, 1970; 2699-2703. doi:10.3382/ps.2008-00520.