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Research Article

FORMULATION AND EVALUATION OF BUCCAL PATCHES BY USING NATURAL GUM

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ABSTRACT

Present study focuses on isolation of Manilkara zapota seed gum and formulate buccal patches of lisinopril for improve bioavailability. Isolated gum study for various parameters like loss on drying, pH, tannin test, starch test, starch test, sucrose and fructose test, swelling index and viscosity. Buccal patches of lisinopril were prepared by using solvent casting method by using five different concentration of isolated gum. Buccal patches characterised on the basis ofThickness, Weight uniformity, folding endurance, swelling Studies, Surface pH Determination, Percentage Moisture loss, Drug content Uniformity, *Ex-Vivo* Mucoadhesive strength, *In Vitro* Drug Release,Ex- vivo permeation study. By compatibility study there is no chemical interaction between drug and excipients used. All prepared buccal patches were transparent, smooth, consistent and flexible. The surface pH of all formulations was found to be almost in neutral pH and no mucosal irritation was expected. The percentage moisture loss of optimised formulation (F4) was found to be 6.59 ± 0.54. Among all the formulations, F5 showed maximum swelling index. The optimized formulation F4 also showed satisfactory, Mucoadhesive strength (5.1kg/cm^2), drug content (98.6 ± 0.002 mg), *Ex-Vivo* permeation (80.5±0.5%). *In-Vitro* drug release of optimised formulation (F4) was found to be 96.5±0.07 at the end of 8 hrs.Drug release mechanism was determined by plotting release data to Higuchi and Korsmeyer-Peppas model. All the formulations are best fitted to Korsmeyer-Peppas model and according to this model the drug releases from theses patches s may be controlled by diffusion with super case-II transport. Stability study of selected optimised formulations was done as per ICH guidelines for 3 month, which revealed that no significant change with respect to the evaluations conducted before stability study.

Keywords: Manilkara Zapota Seed Gum, Buccal patches, Muoadhesion.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of drug delivery for achieving both systemic and local therapeutic effects. For many drugs, conventional oral formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamics profiles with an acceptable level of safety to the patient. However, oral drug delivery also presents some disadvantages because after oral administration, many drugs are subjected to pre-systemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability.[1]

On the other hand, the buccal region of oral cavity is an attractive target for administration of drug of choice. Other than the common advantages of novel drug delivery systems, buccal mucosa has several specific advantages like, faster and richer blood flow (2.4 mL / min / cm2) than other parts of oral region. Moreover, the permeability of the

buccal mucosa is 4 - 400 times greater than that of the skin. The mucus network of buccal mucosa carries a negative charge, which may play role in Mucoadhesion. Buccal drug delivery offers direct access to the systemic circulation through the external jugular vein, which bypass the drugs from the hepatic first-pass metabolism, leading to higher bioavailability. This drug delivery systems offer versatility in designing multidirectional or unidirectional drug release systems for local or systemic action.[2]

A number of Mucoadhesive devices have been developed in the recent years. However, buccal films offer greater flexibility and comfort than adhesive tablets. In addition, patches can overcome the problem of the relatively short residence time of oral gels on mucosa as these gels are easily washed away by salivary secretion. Also the patch can be easily applied to the wound surface that can control the healing more effectively. An ideal buccal patch should be flexible, elastic, and soft yet strong enough to withstand breakage due to stress from activities in the mouth. Moreover, it must also possess good Mucoadhesive strength so that it is retained in the mouth for the desired duration[3]

Various natural polymers are use as Mucoadhesive polymer includes pectin, chitosan, guar gum and karaya gum. These polymers of monosaccharide are inexpensive. They are highly stable, safe, non-toxic, hydrophilic and gel forming nature. Manilkara zapota (Linn.) P.Royen syn. is belonging to family sapotaceae which is used as a Mucoadhesive and sustain release polymer which extracted from fresh fruits of zapota.[4,5]

Lisinopril is an angiotensin converting enzyme (ACE) inhibitor that category is employed to treat high blood pressure, congestive heart failure (CHF) and to improve survival after a heart attack. Lisinopril belonging to class III as per BCS classification system, it means that it has high solubility and low permeability. Lisinopril is slowly and incompletely absorbed after oral administration. Its oral bioavailability just 25% hence attempt was made to formulate Mucoadhesive buccal patches of lisinopril to improve bioavailability and satisfactory drug release.[6,7]

2. MATERIAL AND METHOD

2.1 Materials

Lisinopril was supplied by Gsk Laboratories Limited (India).Manilkara zapota seed was naturally collected.

Propylene glycol, sucrolose and citric acid, Acetone were purchased from Modern science lab.Pvt. Ltd.(India). All chemicals and Solvent used were analytical grade.

Isolation and purification of gum

Gum was isolated from seeds using maceration techniques. 100gmSeed Powder was mix in Petrolium ether and kept aside for 5 hr. Seed powder 100 g was soaked in cold distilled water 500 ml and slurry was prepared. Then slurry was kept aside for one day. Then solution was heated on bunsen burner for 1 hr. After 1 day the mixture was filtered with the help of muslin cloth. The filtrate was centrifuged at 3000 rpm for 10 minutes.The supernatant was collected after centrifugation, and then double volume of acetone was added in it to precipitate the mucilage. The precipitate was washed with chloroform. The mucilage was then dried at 40 C to 45 C in hot air oven and then passed through mesh no. 120 and store in desiccators until used for further studies in powder.[8]

Pre-formulation study of Gum

Differential scanning calorimetry(DSC)

Thermogram of Manilkara zapota seed gum was obtained using differential scanning calorimeter(Figure1)Sample was kept in aluminium pan, sealed and heated at constant rate of 10°C/min over temperature range of 10 to 200°C. By purging nitrogen with flow rate of 10 ml/min inert atmosphere was maintained.[9]

Infrared spectroscopy

FTIR spectrum of Manilkara zapota seed gum was recorded (Figure2) and spectral interpretation was done. The characteristics IR absorption peaks of Natural gum were studied.[10]

Evaluation of Manilkara zapota seed gum

Loss on drying

The method adopted was that specified in the B.P 2004 for acacia. 1.0 g of the sample was transfer into each of several Petri dishes and then dried in an oven at 105°C until a constant weight was obtained. The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage.[11]

P^H Determination

pH was determined by shaking a 1%w/v solution of the sample in water for 5 min and the reading were noted by digital pH meter.[11]

Tannin test

To the10ml of 10%w/v solution, then 0.1ml of ferric chloride test solution was added to it. Gelatinous precipitate formed but neither a

precipitate nor liquid shows dark blue colour nor result was reported. [11]

Starch test
The 10 ml of 10%w/v solution was prepared. To it 0.1 ml of 0.005M Iodine was added.[11]

Sucrose and fructose test
To 1 ml of 10% w/v solution. To it the 4 ml of distilled water was added then to it 0.1 gm of resorcinol and 2 ml of hydrochloric acid was added. [11]

Swelling Index
A 1 gm of transferred to 100 ml measuring cylinder containing 90ml of water, shake well for 30 seconds and allow to stand for 24 hours, shaking gently on 3 occasions during this period .The sufficient water was added to produce 100 ml, mixed gently for 30 seconds, avoiding the entrapment of air, allow to stand for 5 hours and measured the volume of mucilage. The determination was repeated for three times. Average of four determinations is not less than 40.[11]

Viscosity
Viscosity of Manilkara zapota seed gum was determined using Brookfield viscometer.1 %(w/v) solution of gum.[11]

Pre-formulation study of Drug
Differential scanning calorimetry(DSC)
Thermogram of Lisinopril was obtained using differential scanning calorimeter(figure2). Sample was kept in aluminium pan, sealed and heated at constant rate of 10°C/min over temperature range of 10 to 200°C. By purging nitrogen with flow rate of 10 ml/min inert atmosphere was maintained.[12]

Infrared spectroscopy
FTIR spectrum of procured Lisinopril was recorded (Figure3) and spectral interpretation was done. The characteristics IR absorption peaks of Lisinopril were studied.[12]

Drug-excipients interaction study
To check out any possible interaction between drug and excipients used, compatibility study using DSC and FTIR was carried out. It was done using Fourier Transform Infrared Spectrophotometer using KBr pellet method. DSC thermo gram and FTIR spectra of physical mixtures of Lisinopril, citric acid, sucrolose and propylene glycol was recorded.

Preparation of Mucoadhesive buccal patches
Mucoadhesive buccal patches of lisinopril were prepared by using solvent casting technique.
The calculated amount of manilkara zapota seed gum (Table no. 1)dissolving in 10 mL warm water with stirring to produce solution and kept for 24 hr to remove all the air bubbles and form clear solution. Aqueous solution was prepared by dissolving Lisinopril (79.49 mg),citric acid (0.5 mg) and sucralose (0.5 mg) in 10 ml of distilled water with stirring to produce solution. The aqueous solutions of both mean gum solution and drug solution were mixed and stirred for 1 h. The solutions were cast on to 9 cm diameter of glass Petri plate and were dried in the oven at 45° C for one day. Drug loaded buccal patches upper Mucoadhesive layer containing drug and polymer the lower ethyl cellulose layer were also prepared by pouring the above polymeric solution on ethyl cellulose membrane. The backing membrane of ethyl cellulose (5%w/v) was fabricated by slowly pouring a solution containing 500mg of ethyl cellulose and 0.2 mL of Dibutyl pthalate (2% v/v) as plasticizer in 10 mL acetone in Petri plate of 9.0cm diameter. It was allowed to air dry for 1 hr .Patches without backing layer were used to evaluate mechanical properties and drug content uniformity where as patches with backing layer were used for studies like in vitro drug release, Ex vivo permeation study.[12]

Table 1: Composition of Lisinopril Buccal Patches

Ingredients	Drug:Polymerratio	Formulation code				
		F1	F2	F3	F4	F5
Lisinopril(mg)	1:3	79.49	79.49	79.49	79.49	79.49
Manilkara Zapota Seed Gum (mg)	1:5	150	180	210	240	270
Propylene Glycol(ml)	1:7	1	1	1	1	1
Citric Acid (mg)	1:9	0.5	0.5	0.5	0.5	0.5
Sucralose	2:1	0.5	0.5	0.5	0.5	0.5
Distilled water(ml)	2:3	10	10	10	10	10

Each patch contain 5 mg of lisinopril

Evaluation of physiochemical and mechanical properties of Mucoadhesive buccal patches

Physical evaluation

All the buccal patches were visually inspected for clarity, flexibility and surface texture.

Thickness, Weight Uniformity, Folding Endurance

Weight uniformity of the formulated patches was tested in 10 randomly selected patches from each Mucoadhesive buccal patches, was weighed individually on an analytical balance. Thickness was measured at three randomly selected spots using a micrometer screw gauge. Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times without breaking.[12]

Surface P^H Determination

Patches were placed in Petri plate containing 10 mL phosphate buffer (pH6.8) and the pH at the surface measured after 1, 2, 3, 4, 5,6,7,and 8 by placing the tip of the glass microelectrode of a digital pH meter close to the patch and allowing it to equilibrate for 1 min prior to recording. Experiments were performed in triplicate. The surface pH of the patches was determined in order to investigate the possibility of any side effects in the oral cavity. A acidic or alkaline pH is bound to cause irritation to the buccal mucosa, hence an attempt was made to keep the surface pH of the patch close to the neutral.[12]

Swelling Studies

The swelling index is important characteristics for Mucoadhesion. After determination of the original patch weight, the sample were allowed to swell on the surface of agar gel plate (2%,w/v). The agar gel plates were kept in an incubator at 37^0C. Increase in the weight of the patches was determined at preset time intervals of 1,2,3,4,5,6,7 and 8 hr and the percent swelling determined.[13]

$$S.I. = \frac{W2-W1}{W1} \times 100$$

Where- S.I. - swelling index

W1- weight of buccal patch before dipping into beaker

W2- weight of buccal patch after dipping in beaker & wiped

Percentage Moisture loss

The patches (n=3) were weighed individually and kept in a desiccators containing calcium chloride at 37°C for 24 hrs. The final weight was noted, when there was no change in the weight of individual patch. The percentage of moisture content was calculated as a difference between initial[12] and final weight with respect to final weight.[14]

The percentage moisture loss was calculated using following formula:

$$\text{Percent moisture loss} = \frac{\text{Initial weight} - \text{Final Weight}}{\text{Initial weight}} \times 100$$

Drug content Uniformity

Content uniformity is determined by estimating the API content in individual strip. Three patches from each formulation were took and individually dissolved in 50 ml of 6.8 pH phosphate buffer to give solutions of 10µg/ml concentration. These solutions were filtered and absorbance of each solution was recorded at 205 nm (λ max of Lisinopril) using the placebo patch (patch without drug) solution as a blank. The percentage drug content was determined. Mean of the percentage drug content and standard deviations was calculated. The Limit of content uniformity is 85-115%.[14]

Ex vivo Mucoadhesive strength

The force required to detach the attachment of Mucoadhesive patch from the mucosal surface was applied as a measure of the Mucoadhesive strength. This study was carried out on a specially fabricated physical balance assembly. Sheep buccal mucosa was glued on a dry Petri dish surface by placing the mucosal surface outward and it was moistened with few drops of simulated saliva (pH 6.8).The right side pan of the balance was replaced by a glass disc glued with a buccal patch of 4 cm diameter. The balance was adjusted for equal oscillation by keeping sufficient weight on the left pan. A weight of 5g (W1) was removed from the left pan, which lowered the pan and buccal patch was brought in contact with pre moistened mucosa for 5 min. Then weight was increased gently on the left pan until the attachment break (W2). The difference in weight (W1-W2) was taken as Mucoadhesive strength. The Mucoadhesive force was calculated from the following equation.

Mucoadhesive force (kg/m/s)= Mucoadhesive strength (g)/1000×Acceleration due to gravity

Here, acceleration due to gravity 9.8 m/s^{-1}. [14]

***In Vitro* Drug Release (Dissolution test)**

The United States Pharmacopeia (USP) XXIII-B rotating paddle method is used to study the drug release from the patches. The dissolution medium consisted of phosphate buffer pH 6.8.

The release is performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal patch is attached to the glass disk with instant adhesive material. The disk is allocated to the bottom of the dissolution vessel. Samples (5 ml) are withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through what man filter paper and analyzed for drug release after appropriate dilution.[15]

***Ex- Vivo* permeation study**

The fabricated Patch was placed on the Goat Buccal Mucosa and attached to the diffusion cell such that the cell's drug releasing surface towards the receptor compartment which was filled with phosphate buffer solution of pH 6.8 at 37±10C. The elution medium was stirred magnetically. The aliquots (5ml) were withdrawn at predetermined time intervals and replaced with same volume of phosphate buffer of pH 6.8. The samples were analyzed for drug content using UV spectrophotometer at 207 nm. [15]

Kinetics of drug release

Korsmeyer model

$M_t / M_\infty = kt^n$

Where, M_t/M_∞ is the fraction of drug released at time t; k is the kinetic constant correlated with the structural and geometrical properties of the dosage form; the diffusion exponent 'n' indicating the type of drug release mechanism depends on the polymer swelling characteristics and the relaxation rate at the swelling. Formulations with n value of 0.5 indicate Fickian diffusion release which occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. For formulations, values of0.5 < n < 1.0 indicate anomalous transport or non-Fickian release. For n = 1.0, the release mechanism belongs to case-II or zero-order relaxation release associated with stresses and state-transition in hydrophilic glassy polymers which swell or erode in water or biological fluids Formulations with n > 1.0indicate super case-II transport due to the combination of diffusion and polymer relaxation/dissolution.[16]

Stability study for F4

Stability studies of pharmaceutical products were done as per ICH guide lines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

Method: Selected formulations were stored at different storage conditions at elevated temperatures such as 40^{0}C ± 20 / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of thirty days and checked for physical changes, drug content and folding endurance, thickness drug release. Results were shown in **Table 8.16.**

RESULT AND DISCUSSION

Characterization of Gum

Differential scanning calorimetry (DSC***):*** As reflected by DSC thermogram shown in Figure.1, sharp peak was observed at 134.90^{0}C.

FTIR spectroscopy (Gum): FTIR spectrum of Manilkara zapota seed gum was recorded and spectral interpretation was done. The characteristics IR absorption peaks of Lisinopril at 3130cm^{-1} (N-H stretch 2^0 Secondary amine), 1750 cm $^{-1}$(C=O Carboxylic acid), 1621 (C=O stretch Amide), 1450 cm^{-1} (C=C stretching Aromatic) was there in drug sample spectrum; which confirmed the purity of Lisinopril shown in Figure.2.

Characterization of pure drug

Differential scanning calorimetry (DSC***):*** As reflected by DSC thermogram shown in Figure.3, sharp endothermic peak was observed at 159.33ºC corresponding to melting point of drug in crystalline form; reflecting purity of Lisinopril.

FTIR spectroscopy (Drug): FTIR spectrum of procured Lisinopril was recorded Figure.4, and spectral interpretation was done. The characteristics IR absorption peaks of Lisinopril at 3130cm^{-1} (N-H stretch 2^0 Secondary amine), 1750 cm^{-1}(C=O Carboxylic acid), 1621 (C=O stretchAmide), 1450 cm^{-1} (C=C stretching Aromatic) was there in drug sample spectrum; which confirmed the purity of Lisinopril.

Drug-excipients interaction study

To check out any possible interaction between drug and excipients used, compatibility study using DSC and FTIR was carried out. DSC results reflected similar thermal behaviour of physical mixture as that of pure drug. A sharp endothermic peak noted at 159.33°C in case of Lisinopril, indicative of its melting point (Figure.5). FTIR spectroscopic study results discovered no any new peak appearance or disappearance of existing peaks, discarding any chemical interaction probability amongst drug and polymer used. The characteristic peaks at 3130cm^{-1} (N-H stretch 2^0 Secondary amine), 1750 cm $^{-1}$(C=O Carboxylic acid), 1621 (C=O stretch Amide), 1450 cm^{-1} (C=C stretching Aromatic) were recognized in all spectra (Figure.6). All characteristic peaks of Lisinopril were experiential in physical mixture

spectrum. Thus, IR spectroscopy results depicted that Lisinopril was compatible with selected polymer, excipients and possess good stability.

All patches from F1-F5 were found to be smooth in nature and had good appearance.

The weight and thickness of patches were in ranges 17.8 ± 0.8 to 45.5 ± 0.8 mg and0.11 ± 0.0 to 45.5 ± 0.8 mm, respectively. Folding endurance ranged from 198 folding for formulation F1 to 271 folding for F5 indicating patches were highly flexible. Drug content of formulation varied from 82.4% ± 0.007 to 97.6% ± 0.036 indicating drug was dispersed uniformly throughout the patches. The moisture content loss (%) was found to be in the range of 16.8 ± 0.19 to 44.2 ± 0.07. It was found that there is negligible loss of moisture from patches .The surface pH of a patch should be close to that of saliva (i.e.5.8-7.1) since deviation from this pH may cause irritation to the oral mucosa. Value of surface pH for formulation F1 and F2 were in the range 6.6-6.7 indicating they are suitable for application to the oral mucosa given in Table 3.

Mucoadhesive strength

Mucoadhesive strength of patches was found to be maximum in F5 batch (5.2 gm) while minimum in case o1 batch F1 (3.2 gm) Mucoadhesive strength of the formulation increase with increase in concentration of the Mucoadhesive polymer. The complete detachment of patches from the mucosa was found satisfactory and is recorded in Table 4.

Swelling index

Swelling behaviour of a buccal drug delivery system is an important property for uniform and prolonged release of the drug. polymer swelling is an essential stage in the formation of a Mucoadhesive bond between hydrophilic matrix formulation and the mucosa. Swelling studies were performed to investigate the performance of the dosage form, swelling capacities and patch integrity after swelling. Maximum swelling was observed in batch F5 (80%) while batch F1 showed minimum swelling (59%).Maximum swelling percentage was observed for F5 batch because of more concentration of hydrophilic polymer and result recorded in Table 5, Figure 7.

***In Vitro* drug release studies (Dissolution test)**

The drug release time profile from different concentration of Manilkara zapota seed gum. In vitro drug release studies showed that release rate of drug increase with increasing concentration of hydrophilic polymer. The curve was obtained after plotting the cumulative amount of drug released from each formulation vs. time. The *in vitro* drug release studies showed maximum percentage drug release of 98.47% 4 hours of F1 batch, 98.89% for 5 hours of F2 batch, 96% for 7 hours of F3 batch, 97.2% for 8 hours of F4 batch, 88.6% for 8 hours of F5 batch. After 8 hours, the patch had lost their integrity and hence was not fit for further release study. Formulation F4 has 97.2% showed maximum release. While other formulations showed maximum amount of drug release in 4,5,7 hours respectively and less amount of drug release in 8 hr of F5 batch. Only F4 batch showed the maximum drug release in 8 hr. Result was recorded in Table 6,Figure 8.

***Ex Vivo* permeation study**

Hydrophilic polymer would leach out, thereby creating pores and channels for the drug to diffuse out of the patches. Further, an increase in the polymer concentration led to drug release over a prolonged period of time.*Ex Vivo* permeation study indicate shows a drug release profiles are shown in Table7,Figure 9.Drug release was successfully observed for all patches.

Release kinetics

The values of n in Korsmeyer-peppas model indicated that all the patches followed non-Fickian release mechanism. Non-Fickian release kinetics is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms. Therefore, the release of the drug from the formulated patches was controlled by swelling of the polymer, followed by diffusion through the swollen polymer and slow erosion of the polymer. Result was show in Table. 8, Figure10.

Stability study

Stability studies of the formulation F4 of Mucoadhesive buccal patches were conducted to determine the effect of formulation additive on the stability of the drug and also to determine the physical stability of the formulation. After the 3 months study, it was found that there was no change in appearance of the patch and negligible change in thickness. The folding endurance and drug content was decreased but not significantly .Result shown in Table 9.

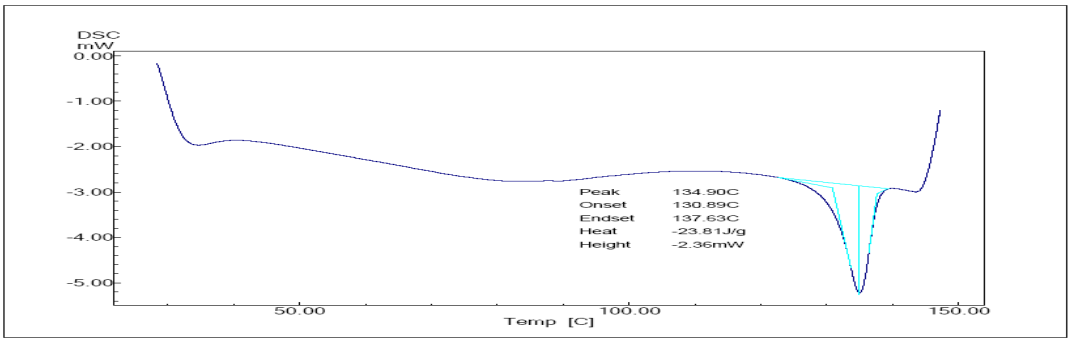

Fig. 1: Thermo gram of Manilkara Zapota Seed Gum

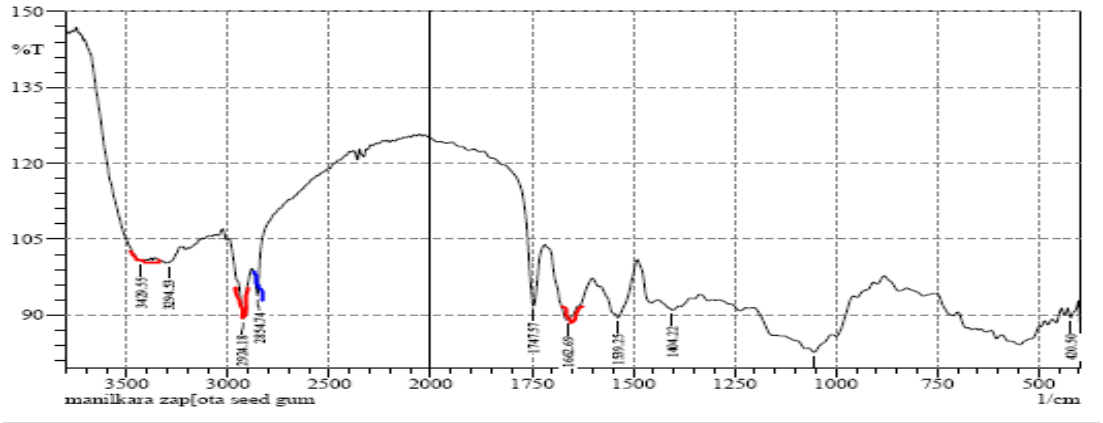

Fig. 2: IR Spectrum of isolated manilkara zapota seed gum

Table 2: Evaluation of Isolated Of Manilkara Zapota Seed Gum

S. No.	TEST	OBSERVATION	INFRERNCE
1	pH	6.8	
2	LOD	2.8%	-
3	Tannin	No dark blue color	Absent
4	Starch	No blue or brown color	Absent
5	Sucrose and Fructose	No yellow or pink color	Absent
6	Swelling power	35.28 ml	Passes the test(<40ml)
7	Gum (M.P)	Standard	Observed
8	Manilkara zapota seed gum	130^0C	129.6^0C

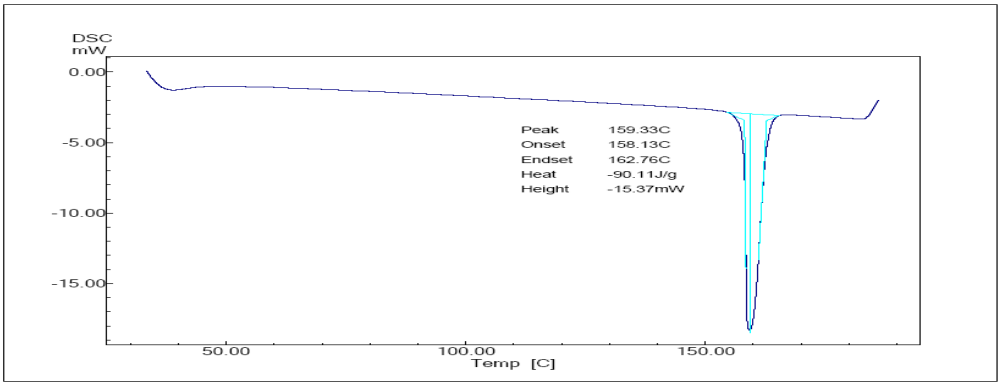

Fig. 3: Thermogram of pure drug Lisinopril

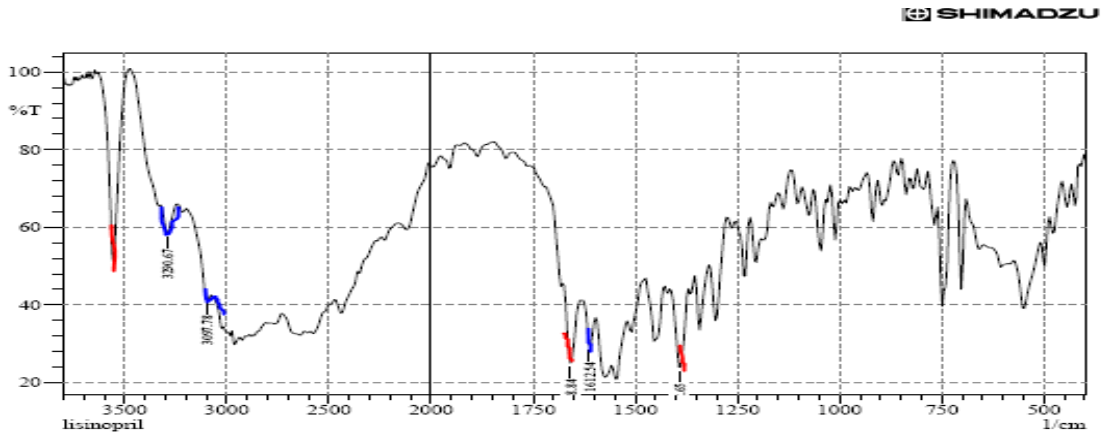

Fig. 4: IR Spectrum of Lisinopril (pure drug)

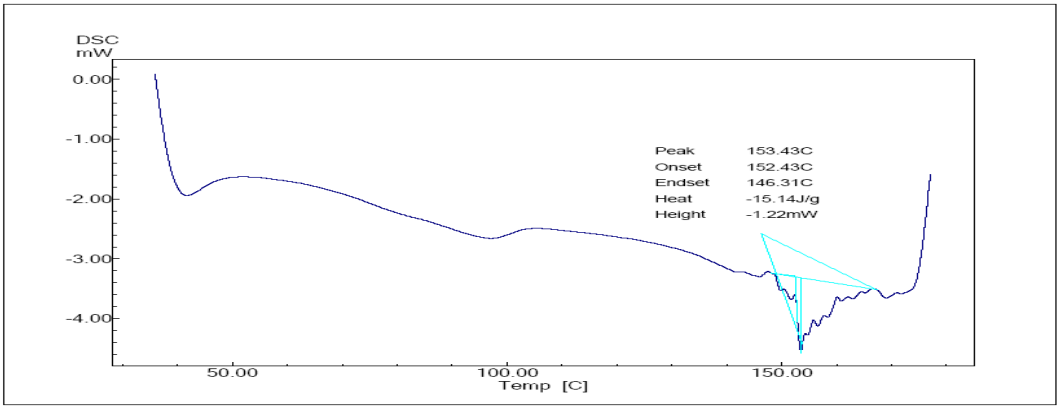

Fig. 5: Thermogram of Drug+Manilkara Zapota Seed Gum

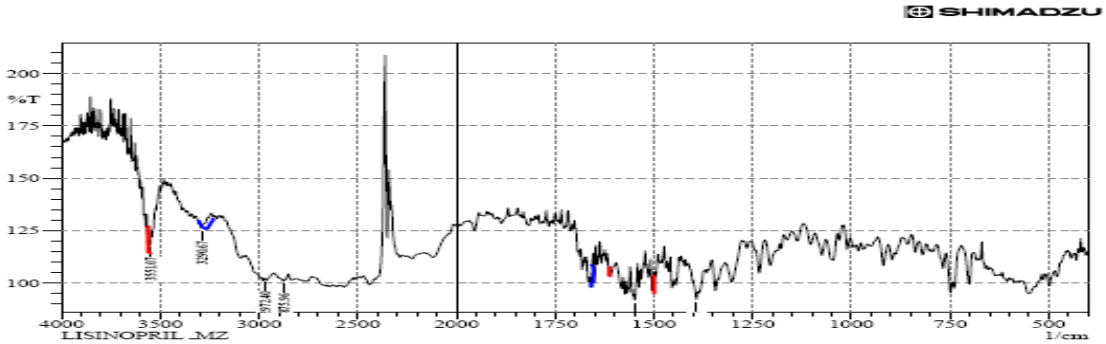

Fig. 6: FTIR Spectrum of Drug + Manilkara Zapota Seed Gum

Table 3: Physicochemical Evaluation Parameters of Lisinopril Buccal Patch

FC	Weight uniformity (mg)	Thickness (mm)	% moisture loss	Drug content uniformity (mg)	Folding endurance	Surface pH
F1	17.8 ± 0.8	0.11 ± 0.03	16.8 ± 0.19	82.4 ± 0.007	198 ± 0.8	6.7 ± 0.12
F2	20.1 ± 0.7	0.14 ± 0.01	20.8 ± 0.23	86.3 ± 0.005	220 ± 1.2	6.8 ± 0.12
F3	25.5 ± 1.2	0.16 ± 0.08	24.4 ± 0.15	95.4 ± 0.005	231 ± 0.8	6.7 ± 0.14
F4	30.8 ± 1.0	0.19 ± 0.07	29.4 ± 1.30	98.6 ± 0.002	251 ± 1.5	6.8 ± 0.21
F5	45.5 ± 0.8	0.22 ± 0.08	44.2 ± 0.07	97.9 ± 0.036	271 ± 1.9	6.6 ± 0.08

Table 4: Physicochemical Evaluation Parameters of Lisinopril Buccal Patch

FC	Mucoadhesive strength(gm)
F1	3.2
F2	4.1
F3	4.9
F4	5.1
F5	5.2

Table 5: Result of swelling study of batch F1-F5

Time in hrs.	% swelling index				
	F1	F2	F3	F4	F5
1	20.7±0.05	22.5± 0.07	24.1± 0.03	26.4± 0.08	27.4± 0.08
2	25.9± 0.05	28.7± 0.07	31.8± 0.03	30.8± 0.09	36 .4± 0.08
3	33.6± 0.05	36.8± 0.08	42.9± 0.03	34.7± 0.05	50.8± 0.07
4	39.6± 0.06	40.9± 0.03	47.01± 0.07	50.6± 0.04	54.3± 0.05
5		41.9± 0.04	46.9± 0.08	53.4± 0.03	56.5± 0.07
6		38.9± 0.06	39.3± 0.07	52.6± 0.04	58.6± 0.02
7				48.7± 0.05	55.6± 0.07
8				35.3± 0.06	53.4± 0.07

Table 6: Percent drug release of Lisinopril patches

Time (Hr)	F1	F2	F3	F4	F5
1	26.25±0.03	28.48±0.08	18.6±0.06	21.6±0.08	24.7±0.08
2	43.58±0.06	36±0.08	27.7±0.03	30.6±0.04	20.1±0.05
3	62.47±0.12	56.89±0.04	29.8±0.06	42.4±0.05	29.6±0.05
4	98.47±1.68	71.32.3±0.02	34.6±0.02	50.4±0.08	34.4±0.07
5		98.25±0.08	51.8±0.06	65.1±0.02	47.5±0.04
6			61.2±0.07	70.7±0.04	56.4±0.06
7			70.8±0.06	79.3±0.07	66.2±0.06
8			79.8±0.08	96.5±0.07	88.6±0.04

Table 7: Ex Vivo drug permeation studies

Time(Hr)	F1	F2	F3	F4	F5
1	14.4±0.3	18.4±0.3	20.4±0.3	25.4±0.3	23.4±0.3
2	17.4+0.3	20.1±0.4	30.8±0.6	36.4±0.5	29.4±0.7
3	22.4±0.3	24.4±0.4	36.4±0.3	42.3±0.3	35.6±0.5
4	31.3±0.4	35.6±0.3	45.7±0.2	53.1±0.2	42.4±0.3
5	36.2+0.4	44.6±0.5	57.3±0.5	62.3±0.5	54.3±0.3
6	44.1±0.2	53.2±0.4	62.2±0.4	68.8±0.6	64.5±0.3
7	54.6±0.3	60±0.3	67.6±0.1	74.4±0.4	70.5±0.2
8	62.2+0.5	69±0.5	74.7±0.4	80.5±0.5	77.06±0.5

Table 8: Kinetic parameters of Lisinopril buccal patch

FC	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	N
F1	0.981	0.967	0.936	0.939	0.941
F2	0.982	0.961	0.941	0.973	0.826
F3	0.968	0.934	0.911	0.901	0.654
F4	**0.996**	**0.906**	**0.968**	**0.997**	**0.675**
F5	0.946	0.846	0.872	0.878	0.670

Table 9: Evaluation of optimized batch F4 during stability studies at 40^0 C ± 2^0 C and 75% ± 5 RH

Parameters	0 Day	30 Days	60 Days	90 Days
Thickness(mm)	0.19 ± 0.07	0.17 ± 0.07	0.17 ± 0.09	0.16 ± 0.05
Folding endurance	251 ± 1.5	245 ± 1.6	240 ± 1.1	240 ± 1.8
Drug Content %	98.6 ± 0.002	98.6 ± 0.002	97.2 ± 0.04	97.2± 0.09

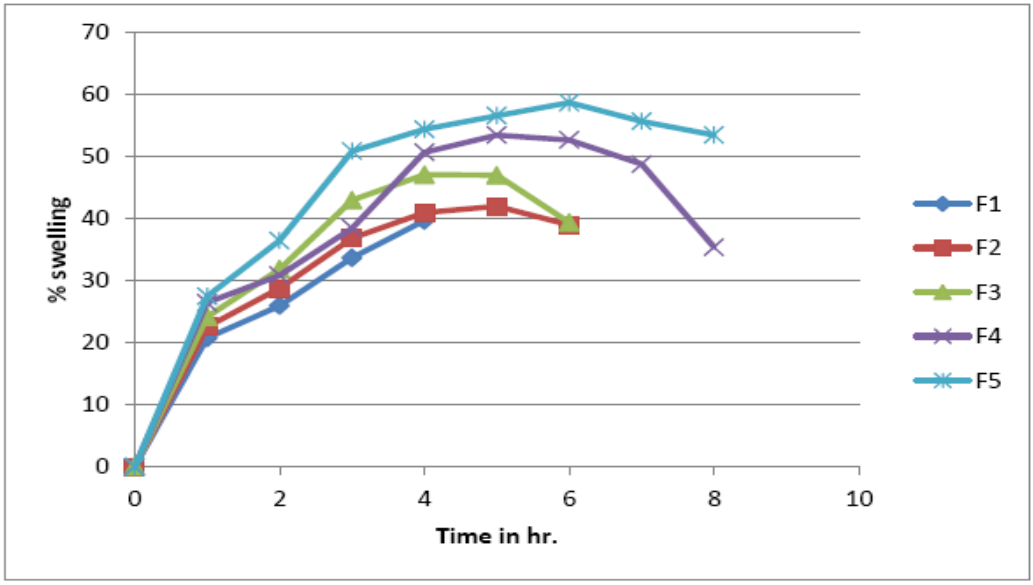

Fig. 7: Comparative study of swelling index of Lisinopril patches (F1-F5)

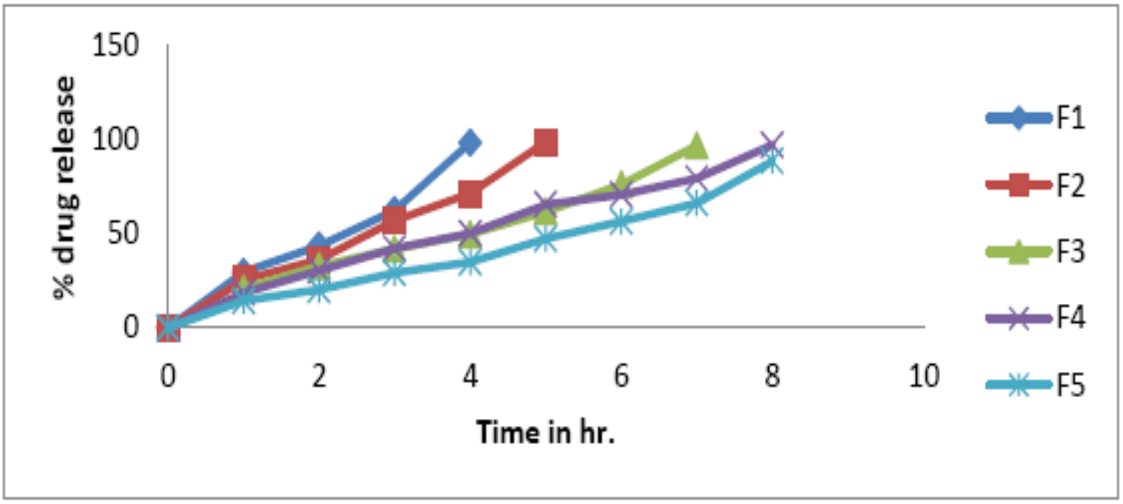

Fig. 8: Comparative in vitro drug profiles of Lisinopril patches (F1-F5)

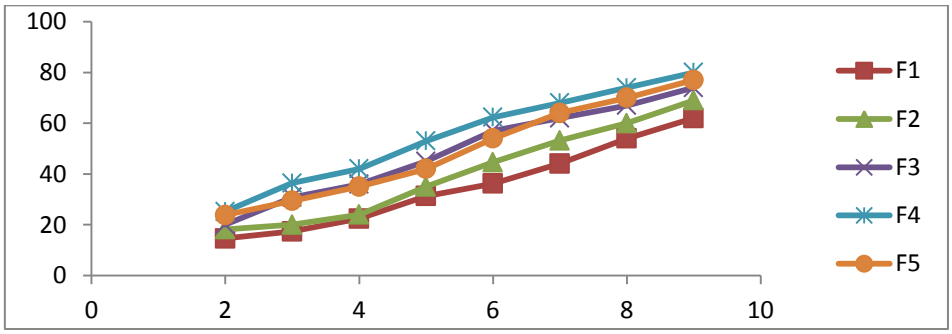

Fig. 9: Comparative Ex Vivo-permeation study of F1 – F5 buccal patches of Lisinopril

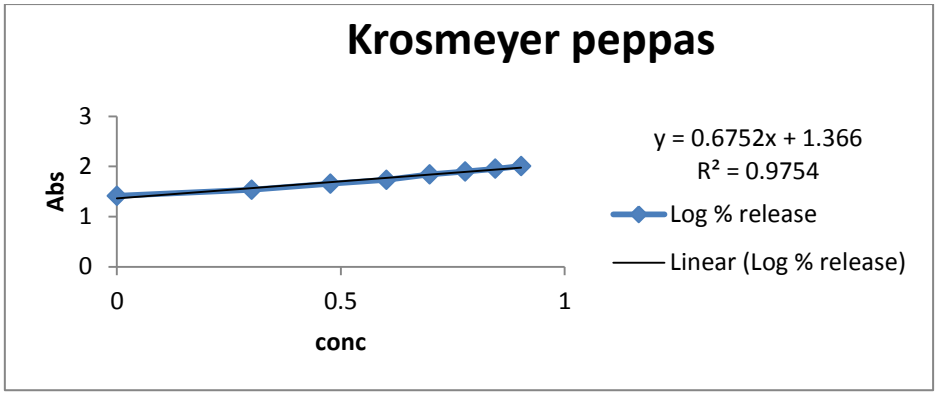

Fig. 10:Krosmeyer Peppas Graph (Optimize batch F4)

CONCLUSION

After application of optimization technique, it was found that the concentration of Manilkara zapota seed gum had significant effect on like % drug content, in vitro drug release, Ex Vivo permeation study and folding endurance. Manilkara zapota seed gum has good Mucoadhesive property as well as sustained release property.

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