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Formulation And Evaluation of Buccal Films of Entacapone

Ananthalakshmi Dara, Ravikrishna Velupula, Krishnaveni Janapareddi*
Department of Pharmaceutics, University College of Pharmaceutical Sciences (UCPSc),Kakatiya University, Warangal-506009, T.S, India
*Email : krishnaveni.janapareddi@gmail.com

ABSTRACT

The main objective of the present study is to formulate buccal films of Entacapone (ENT) for quick onset of action and avoid first pass effect thereby improving bioavailability. A series of buccal film formulations F1-F6 were prepared using HPMC E15 as a polymer, Dichloromethane and methanol (1:1) as casting solvents. The formulations were prepared by solvent casting method and evaluated for their physicochemical parameters such as weight variation, film thickness, pH, folding endurance, % swelling index, drug content, in vitro drug release and ex vivo permeation studies. The steady state flux (Jss) and enhancement ratio (ER) were calculated for optimized formulation (F6) by comparing with drug suspension. Entacapone was quantified by UV spectroscopy at λmax of 309 nm and DSC/FTIR study. The surface pH of all the films was found to be neutral pH. The optimized formulation (F6) showed satisfactory physico-mechanical parameters, physical stability and steady state flux (Jss) value of 205.51µg/cm²/h which was significantly high (3.26 folds) compared to drug suspension (63.97µg/cm²/h). The in vitro drug release of optimized formulation was found to be 93.9±1.82% in 8 hrs and it followed zero order kinetics governed by non- fickian mechanism.The results indicated that the buccal films of Entacapone would be a promising alternative to oral dosage forms for fast action and enhance its bioavailability by avoiding first pass effect.

Keywords: *Buccal Films, Entacapone, HPMC E-15, Solvent Casting method, Parkinson's disease.*

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INTRODUCTION

In recent years, the delivery of therapeutic agents through transmucosal routes has gained significant attention. Drug delivery via the buccal route using bioadhesive dosage forms offers a novel route of administration particularly in overcoming first pass metabolism and drug degradation in the GIT environment. Drug absorption through buccal mucosa is mainly followed by passive diffusion into the lipoid membrane. The drug is transported through the facial vein which then drains into the general circulation via the jugular vein, bypassing the liver and thereby sparing the drug from the first-pass metabolism [1]. The oral cavity is easily accessible for buccal delivery and could be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route [2, 3]. The other advantages of buccal drug delivery include: low enzymatic activity, suitable for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless drug administration. A suitable buccal drug delivery system should be flexible and should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. Buccal drug delivery system utilized bioadhesive polymers which will adhere to the buccal mucosa upon hydration and hence act as targeted or controlled release system [4]. Parkinson's is a most progressive neurodegenerative disorder which causes nerve cell damage in the brain, leads to reduced dopamine levels in the brain. The common symptoms of Parkinson's include tremor, rigidity, slowness of movement, and difficulty in walking. Entacapone (ENT) is a selective reversible inhibitor for the treatment of Parkinson's disease generally given in combination with Levodopa. It works by inhibiting a chemical messenger catechol-O-methyl transferase (COMT) which in turn helps in increasing the amount of dopamine in the body. Thus, an adequate amount of dopamine controls the brain to coordinate body movements and leading to greater relief from the symptoms of Parkinson's disease [5]. Entacapone is rapidly absorbed (approximately 1 hour). The absolute bioavailability following oral administration is 35% due its first pass metabolism. The biological half life of Entacapone is 0.4-0.7 hrs. The physicochemical properties of Entacapone, its low half life and low molecular weight (305.10 g/mol) make it suitable candidate for buccal delivery. Among the buccal formulations, the buccal films are most preferred over other formulations because of their flexibility and comfort and they are avoiding the

shorter residence time of oral gels, these are quickly removed. The films also protect the wound surface, which reduces the pain and treats the disease more effectively [6].Hence the present study is aimed to prepare and evaluate buccal films of Entacapone using bioadhesive polymers, in order to overcome the problems associated with oral administration.

MATERIAL AND METHODS

Materials

Entacapone was provided by the Aizant Drug Research Solution Pvt. Ltd.(Hyderabad,India), HPMC -E15, dichloromethane were purchased from Himedia Pvt. Ltd., (Mumbai, India)Propylene glycol and Methanol purchased from Finar Chemical Pvt. Ltd. (Ahmedabad, India). Potassium dihydrogen ortho phosphate and ortho phosphoric acidwere purchased from SD fine chemicals Ltd (Mumbai, India), Citric acid purchased from Merk Pharmaceutical Pvt. Ltd. (Hyderabad, India). Water used was ultrapure Millipore. All other reagents used in the study were of analytical grade.

PREFORMULATION STUDIES

Drug characterization by DSC and FT-IR

About5-10mg of the drug was taken in the pierced DSC aluminium pan and crimped, scanned in the temperature range of 50-300°C at a heating rate was 10°C/min, nitrogen served as purged gas. Empty aluminium pan, crimped was used as a reference cell. The DSC 4000, PerkinElmer instrument was used for this purpose [7].The pure drug, phospholipid and optimised formulation were analysed by FT-IR (Bruker FT- IR Tensor 27) spectroscopy by KBr disc method. The spectrum was obtained at a resolution of $4cm^{-1}$ between the frequency ranges of $4000\text{-}400cm^{-1}$[8].

Solubility studies

The solubility of Entacapone in methanol and phosphate buffers of pH 5.8, pH 6.8, and pH 7.4 was determined by the phase equilibrium method. An excess amount of the drug was taken into 10ml vials containing 5ml of phosphate buffer and the vials were closed with rubber caps and constantly agitated at 37ºc for 24 hrs using a rotary shaker. After 24hrs, the samples were withdrawn and the solution was filtered through a 0.2µm syringe filter and the drug solubilized was estimated UV spectrophotometrically by measuring the absorbance at 309 nm [9].

Construction of standard graph of Entacapone

The standard graph of clozapine was constructed in different solvents such as methanol, phosphate buffers of pH 5.8, 6.8 and 7.4 by using UV-visible spectrophotometer (Labindia, 3000+). The drug was dissolved in a solvent and the dilutions were made to get desired concentrations of 2, 4, 6, 8, 10, 12, 14, 16 and 18 µg/ml. The absorbance of samples was measured at 309 nm against blank. A standard graph was plotted between concentration and absorbance[10].

METHOD OF PREPARATION OF BUCCAL FILMS:

The buccal films of Entacapone were prepared by the solvent casting method. The composition of films was given in Table 1. The accurately weighed quantity of polymer was dissolved in methanol and dichloromethane mixture (1:1) by vertexing for 20 min. Then, the mixture was left for 2 hrs to allow the polymer to swell. The plasticizer, penetration enhancer and the weighed amount of drug were dissolved in a solvent and the solution was added to the polymer mixture. The solution was cast into a Petri dish ($70.83cm^2$) and dried at room temperature overnight. The dry films were cut into ($2x2\ cm^2$) square shaped sections [11].

Total area of Petridish =$70.83\ cm^2$
Drug required in $4\ cm^2$ =10 mg
Total drug loaded =177 mg

IN VITRO EVALUATION STUDIES OF BUCCAL FILMS:

Uniformity of weight:

Three films ($4cm^2$) of each formulation were weighed individually using an electronic balance and the average weight was calculated [12].

Film thickness:

Thickness of three films from each formulation was measured using vernier caliper. The thickness of films was measured at three different places of film and average was calculated [13].

Folding endurance

Folding endurance was determined by folding the film repeatedly at the same place until it broke.The number of times,the films could be folded without breaking was computed as the folding endurance value [14].

Surface pH

The bioadhesive films were allowed to swell by keeping them in 1 ml of phosphate buffer of pH 6.8 solution for 2hr at room temperature. The surface pH measurements were recorded using digital pH

meter(Global Systronics, India) up to 1hr at interval of every 5 min. The pH was measured by bringing the pH electrode in contact with surface of film and allowing it to equilibrate for 1 min. The experiment was performed in triplicate (*n=3*)[15].

Drug content

The drug content of the film was determined by taking the film (4 cm^2)containing 10mg of Entacapone and dissolved in 100 ml ethanol and phosphate buffer pH 6.8 mixture (1:4). The resultant solution was filtered through a whatman's filter paper and the content of Entacapone was estimated at suitable dilution spectrophotometrically at 309 nm[16].

***In vitro* drug release studies of buccal films**

The *in vitro* drug release studies were performed by using Franz diffusion cell a capacity of 20ml capacity and dialysis membrane (*1200-14000 Daltons*). The film of 4 cm^2 was mounted on the dialysis membrane which was placed between the donor and receptor compartment of the diffusion cell. The receptor compartment was filled with phosphate buffer pH 6.8 as release medium. The whole assembly was placed on the magnetic stirrer and the solution in the receptor compartment was stirred at 350rpm and the temperature was maintained at 37±0.5 . An aliquot of 2ml was withdrawn at predetermined time intervals up to 8 hrs and replaced with same amount of fresh phosphate buffer in order to maintain sink condition. Then, the samples we reanalyzed by UV- Visible spectrophotometer at 309nm at suitable dilution and the cumulative percent drug release was calculated [17].

Release kinetics and mechanism:

The data of *in vitro* drug release was fit into various kinetic equations like zero order, first order, Higuchi and Peppas equations and R^2 values were calculated to determine the release kinetics and mechanism of drug release from buccal films [17].

***EX VIVO* PERMEATION STUDIES:**

The *exvivo* permeation studies were performed using fresh porcine buccal mucosa and Franz diffusion cell with a diffusion area of 30.02 cm^2 and 20ml of receiver chamber potential. The freshly isolated porcine buccal mucosa was mounted on receiver compartment of diffusion cell and allowed to equilibrate for 30min in Phosphate buffer pH 6.8 at room temperature. The donor chamber was filled with test formulation and the entire set up was placed on magnetic stirrer and performed the experiment up to 8 hrs at 37 ± 0.2°C and 50rpm.The aliquots (2ml) were withdrawn at predetermined time intervals up to 8 hrs and replaced with same amount of fresh phosphate buffer. Then, the samples were analyzed at suitable dilution by using UV-visible spectrophotometer at 309nm [18]. The cumulative amount of drug permeated at different time points was calculated using the following formula.

$$Q = [C_n V + \sum_{i=1}^{n-1} C_i S] \quad (1)$$

Where, Q= Cumulative amount of drug permeated (µg); C_n= Concentration of drug (µg/ml) in n^{th} sample interval; V= Volume of Franz diffusion cell (20 ml), S= Sampling volume (2ml)

$\Sigma C_i S$ = Sum of drug concentration of sample (1 to n-1)

i =1 multiplied with sampling volume (S)

The cumulative amount of Entacapone permeated through excised porcine buccal mucosa was plotted as a function of time. The steady state flux (Jss, µg/cm^2/h) was calculated from the linear equation of the plot by regression.

The experiments were performed in triplicate (n=3) and the mean value was used to calculate the steady state flux(Jss) and permeability coefficient (P).

$$Jss = (dQ/dt)/A \quad (2)$$

$$P = Jss/C \quad (3)$$

Where,

Jss - Steady state flux ($mg.hrs^{-1}cm^{-2}$) ; **P-**Permeability coefficient (cm/h); **dQ/dt**- The slope obtained from the steady state portion of the curve; **C**-The concentration of drug in donor compartment (µg/cm^3) and A the area of diffusion (cm^2).

The enhancement ratio (ER) was calculated by dividing Jss of the respective formulation by Jss of the drug suspension.

Swelling Index

The initial weight of the film (without backing membrane) was determined using a digital balance (W0). Then the films were allowed to swell on the surface of a buffer medium (pH 6.8) plate as described under measurement of surface pH. The weight of the swollen film was determined (Wt) at predetermined time intervals for 5mins [19]. The experiment was performed in triplicate. The percent swelling index was calculated according to the following equation.

$$\% \text{ Swelling Index} = (W_t - W_0)/ W_0 \times 100$$

Where, W_0-initial weight of the film, W_t- weight of swollen film at **t** time

Stability studies

Stability study was carried out for optimized F6 films at two different storage conditions. One was normal room conditions and the other was 40°C/75% RH for 4 weeks.The films were packed in butter paper followed by aluminium foil and plastic tape. After 4 weeks the films were evaluated for physical appearance, surface pH, and drug content[20].

Drug-excipients compatibility studies of optimized formulation (F6)

The DSC/FT-IR analysis was used to assess the drug-excipients interactions of optimized formulation (F6). The study was performed for both physical mixture of optimized formulation without drug and with drug. The procedure followed was as described in section 2.2.1.

RESULTS AND DISCUSSION

Drug characterization by DSC and FT-IR

The DSC and FT-IR analysis of drug were used to determine the purity of drug. The DSC thermogram of pure Entacapone showed an endothermic peak at a temperature of 170.05ºC which is corresponding to the theoretical melting point (165-170ºC) of Entacapone. It indicates that the Entacapone is pure and crystalline in nature. The DSC thermogram of Entacapone was shown in Fig.1. The FT-IR Spectra (Fig.2) of Entacapone showed absorption at specified wavelengths for all the functional groups of Entacapone which indicates that the purity of drug.

Solubility studies of Entacapone

The solubility of Entacapone in Phosphate buffers of pH 5.8, 6.8 and 7.4 was found to be 0.0203±0.002, 0.0869±0.005 and 0.0284±0.003 mg/mL respectively (Fig.3). The highest solubility of drug was found to be in phosphate buffer pH 6.8. Hence, it was selected as solvent for further studies.

Construction of standard graph of Entacapone

The standard graphs of Entacapone in Methanol and phosphate buffers were found to be linear and a good correlation was obtained between the concentration ranges of 2-18 µg/ml. The R^2 values of all graphs were found to be in range of 0.996 to 0.998 indicates the good correlation between concentrations and absorbance. The standard graph of Entacapone in Phosphate buffer pH 6.8 was shown in Fig.4.

***In vitro* evaluation studies of buccal films**

All the fabricated buccal films were smooth and transparent with good flexibility. The prepared films were evaluated for all physicochemical parameters and their results were shown in Table 2. All the films were found to have thickness in the range of 0.19±0.07 mm to 0.54±0.05 mm. The weights of different films were found to be in the range 64.8±0.37 to 126.6±0.26 mg. The weight and thickness of the films were increased with increase in the concentration of polymer. However, in all the cases, the calculated standard deviation values are very low which suggest that the prepared films are uniform in weight and thickness. The Folding endurance of films was found to be in the range of 207.6±10.01 to 240.3±8.02. The folding endurance was increased from F1 to F6 films due to increased concentration of polymer and presence of plasticizer. The surface pH of the films was found to be between 6.3±0.21 to 6.7±0.07. The pH is close to the buccal pH of 6.8 indicating the films could be non-irritant to the buccal mucosa. The drug content results vary from 86.1±1.3 to 96.2±1.9%. It was observed that all the formulations were showed satisfactory in uniformity of drug content and all the physicochemical parameters were within the limits.

***In vitro* drug release studies**

The *in vitro* drug release studies revealed that the rate of drug release from buccal films was governed by the amount of the polymer. The formulation F6 showed rapid drug release i.e. 38.7±0.49% within 30 min and reached to highest release i.e. 93.90±1.82in 8hwhen compared to other formulations. Asthe polymer concentration was increased, the rate of drug release was also increased in this case. This might be due to rapid swelling and erosion of HPMC E15 when contact with medium. The cumulative percent drug release of all the formulations was shown in Table.3 and their release profiles were shown in Fig.5.

Release kinetics and mechanism

The *in vitro* drug release data of all the formulations was fitted to zero order, first order, Higuchi, and Peppas equations and values were given in the Table 4. From the results, the release kinetics of optimized F6 formulation was governed by non-fickian diffusion with zero order release (R^2 value-0.9879).

***Ex vivo* permeation studies for optimized formulation (F6)**

The *ex vivo* permeation studies were performed for optimized film formulation (F6). The steady state flux (Jss), permeation coefficient (Kp)and cumulative amount of drug permeated (Q)of F6 was found to be205.51µg/cm^2/h, 20.55 cm/h and 9574.37±162.02 µg respectively. The amount of drug permeated from buccal film (F6) was highest at all the time points compared to drug suspension. The F6 showed significantly high flux i.e. 3.26 folds ($p<0.0001$) to drug suspension(63.97 µg/cm^2/h). The high flux value

of F6 indicates the rapid and high permeation of drug through buccal mucosa due to rapid swelling and erosion of polymer and the addition of permeation enhancer. The permeation enhancer could open the pores of mucosa and facilitates the rapid drug permeation. The comparative permeation profiles of optimized formulation (F6) and drug suspension (DS) were shown in Fig.6 and the *ex vivo* permeation resultsweregiven in Table 5. The Flux, permeation coefficient (Kp) and Enhancement ratio (ER) of F6 and drug suspension were shown in Table 6.

Swelling Index

The proper swelling of a buccal film is essential for uniform release of drug and sufficient bio adhesion with buccal mucosa. The optimized formulation F6 showed swelling index of 53.44±1.75 within 20 min and reached to 97.8±2.83% within 60 min. The results were shown in the Table 7. The results indicated that the optimized F6 showed sufficient swelling when contact with buffer solution.

Stability Studies

From the results, it was observed that there was no considerable change was observed in drug physical appearance, surface pH and drug contentof F6 formulation up to 1 month. It indicated that the F6 formulation was found to be stable for 1 month.

Drug-excipient compatibility studies

DSC study of physical mixture of Entacapone showed a sharp endothermic peak at 168.02 °C, a shift in the peakwas very less when compared to peak of pure drug (170.05°C) which indicates the absence of drug-excipient interaction. The DSC thermogram of drug-physical mixture was shown in Fig.7.The FT-IR studies also showed the functional groups of the pure drug were retained in the spectra of the physical mixture. This indicates that there is no interaction between drug and excipients. The FT-IR spectra of drug-physical mixture were shown in Fig.8.

Table 1: Composition of the Entacapone buccal films:

Ingredients	F1	F2	F3	F4	F5	F6
Entacapone (mg)	177	177	177	177	177	177
HPMC E15 (mg)	500	600	800	1000	1500	2000
Dibutylpthalate(%)	0.1	0.1	0.1	0.1	0.1	0.1
Dichloromethane (ml)	15	15	15	15	15	15
Methanol(ml)	15	15	15	15	15	15
Citral (%)	0.1	0.2	0.3	0.4	0.5	0.6

F-Formulation; **HPMC-**Hydroxy Propyl Methyl Cellulose; **mg-**milligram; **ml-**millilitre

Table 2: Physicochemical parameters of Entacapone buccal films

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Surface pH	Drug content (%)
F1	64.8±0.37	0.19±0.07	207.6±10.01	6.3±0.21	86.1±1.3
F2	76.9±0.34	0.23±0.09	215.6±5.13	6.5±0.12	89.3±1.1
F3	82.3±0.33	0.24±0.08	216±10.26	6.5±0.14	87.9±1.7
F4	94.7±0.30	0.36±0.06	225.3±3.05	6.4±0.16	93.0±1.2
F5	104.8±0.29	0.50±0.01	231.6±3.08	6.6±0.12	94.3±1.5
F6	126.6±0.26	0.54±0.05	240.3±8.02	6.7±0.07	96.2±1.9

Each value represents mean±SD (*n=3*) and for 4cm² film; mg-milligram; **mm**-millimeter;**%**-percent

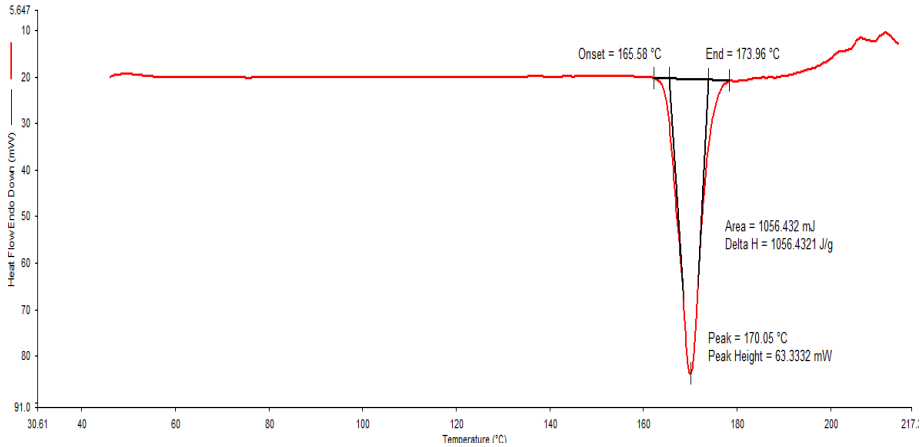

Fig. 1: DSC thermogram of Entacapone pure drug

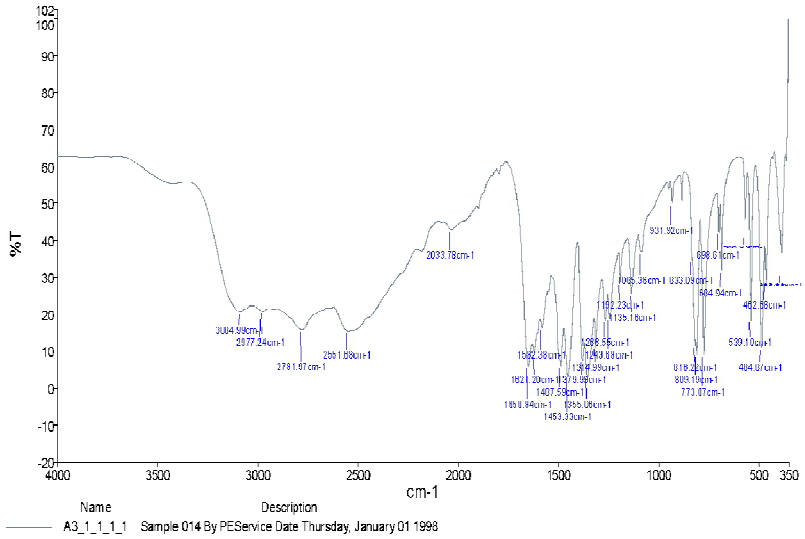

Fig. 2: FT-IR Spectra of Entacapone pure drug

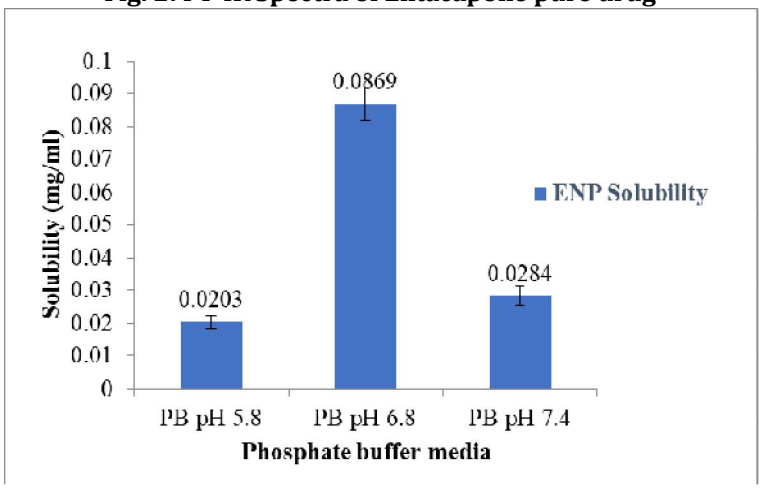

Fig.3: Solubility of Entacapone in different media

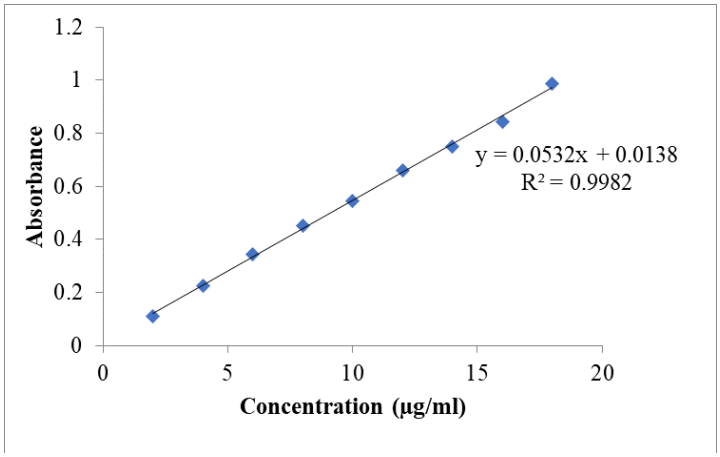

Fig.4: Standard graph of Entacapone in Phosphate buffer pH 6.8

Table.3: *In vitro* cumulative percent drug release of Entacapone buccal films

Time (hrs)	Cumulative percentage drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
0.5	2.75±0.12	11.67±0.26	13.5±0.28	17.8±0.32	16.5±0.38	38.7±0.49
1	8.94±0.24	13.87±0.31	24.06±0.34	21.7±0.37	30.9±0.44	45.8±0.52
2	19.86±0.34	28.32±0.37	26.4±0.40	28.5±0.42	48.2±0.49	58.1±0.59
3	31.18±0.39	30.82±0.45	32.8±0.47	41.3±0.48	59.6±0.53	67.2±0.61
4	50.66±0.40	43.18±0.48	37.7±0.53	47.2±0.57	68.1±0.59	71.8±0.68
5	57.7±0.46	50.72±0.51	49.83±0.57	60.3±0.59	69.6±0.63	76.5±0.75
6	65.5±0.51	60.51±0.54	59.7±0.60	66.4±0.62	76.1±0.67	82.4±0.89
7	69.5±0.57	67.9±0.61	66.8±0.63	73.0±0.66	77.9±0.72	92.2±0.92
8	72.3±0.64	69.6±0.67	70.7±0.69	80.4±0.74	82.5±0.79	93.9±1.82

Each value represents mean±SD (*n=3*)

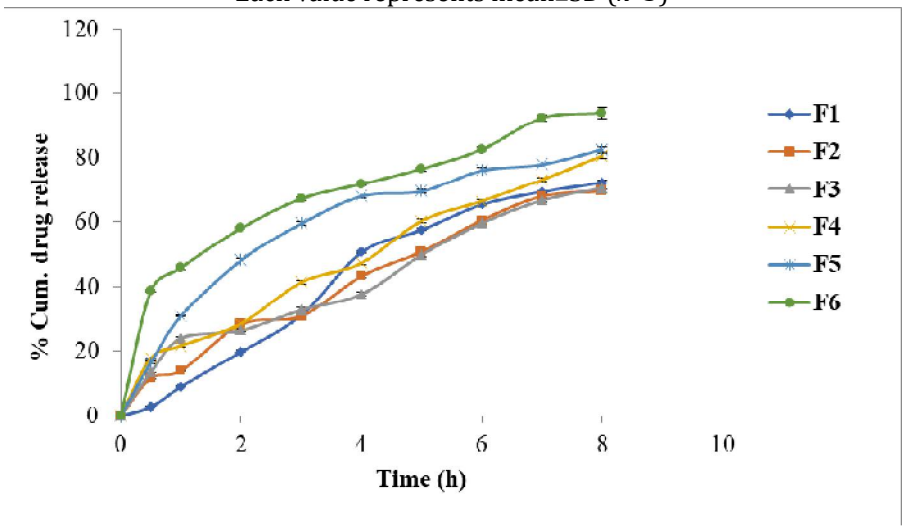

Fig.5: *In vitro* cumulative percent drug release profiles of Entacapone buccal films

Table.4: Release kinetics and mechanism of optimized buccal film (F6)

Formulation code	Mathematical models (Release kinetics)			
	Zero-order	First-order	Higuchi	Korsemeyer's Peppas
	R^2	R^2	R^2	R^2
F1	0.9617	0.9846	0.9264	0.9448
F2	0.9792	0.9871	0.9649	0.9778
F3	0.9678	0.9710	0.9577	0.9543
F4	0.8305	0.8887	0.966	0.9879
F5	0.8602	0.9700	0.9775	0.9598
F6	0.9879	0.9744	0.9765	0.9818

Table.5: The *ex vivo* permeation profiles of optimized buccal film (F6) and drug suspension (DS)

Time(hrs)	Amount of drug permeated (µg)	
	F6	DS
0	0	0
0.5	1839.60±114.02	408.67±11.30
1	2431.95±119.30	849.91±15.60
2	2923.83±122.41	1391.73±103.20
3	3855.80±137.22	1781.20±113.01
4	4848.40±149.06	1919.07±124.04
5	5340.94±152.09	2387.50±132.30
6	6740.15±155.01	2654.24±134.21
7	7572.37±158.02	2715.43±139.32
8	9574.37±162.02	3366.51±142.04

Each value represents mean±SD (*n=3*)

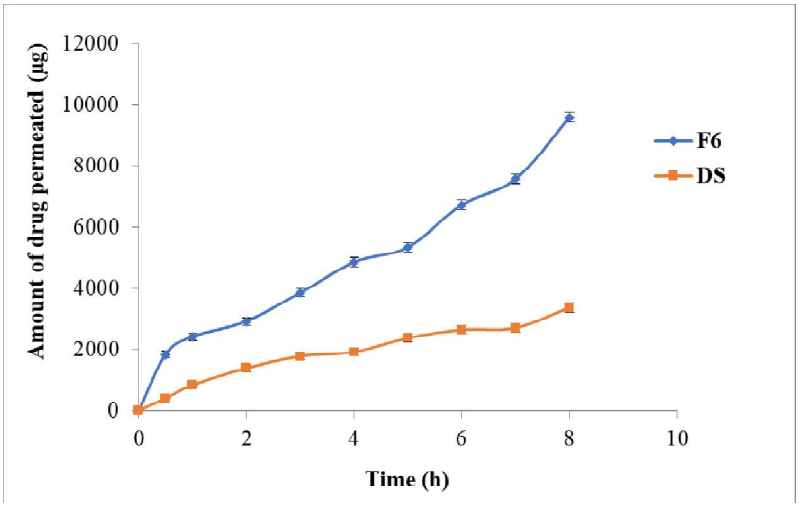

Fig.6: The comparative permeation profiles of optimized formulation (F6) and drug suspension

Table.6: Steady state flux (Jss), Permeation coefficient (Kp) and Enhancement ratio (ER) of optimized formulation (F6) and drug suspension

Formulation code	Flux (Jss) (µg/cm²/h)	Kp_x10^{-3} (cm/h)	Enhancement ratio
F6	205.51	20.55	3.26
Drug suspension	63.97	6.39	1

Table.7: % swelling index of optimized buccal film (F6)

Time (min)	% Swelling index
0	0
5	7.80±0.89
10	23.21±0.95
20	53.44±1.75
30	62.4±1.96
40	68.4±2.34
50	90.9±2.72
60	97.8±2.83

Each value represents mean±SD (*n=3*)

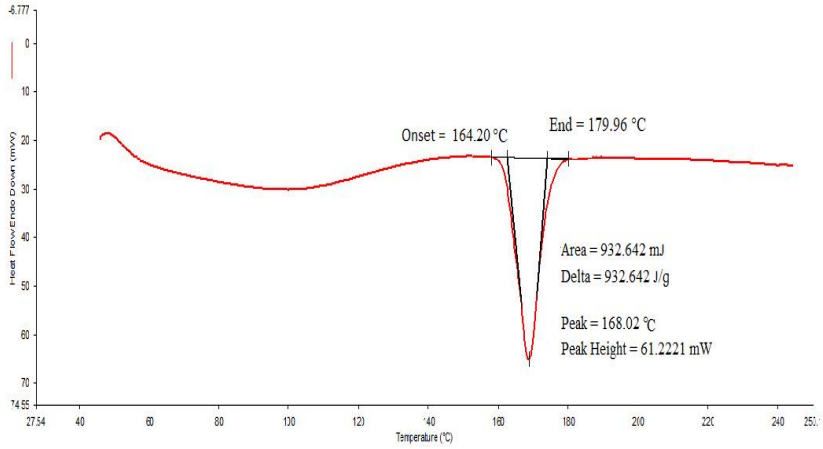

Fig.7: DSC thermogram of drug-physical mixture

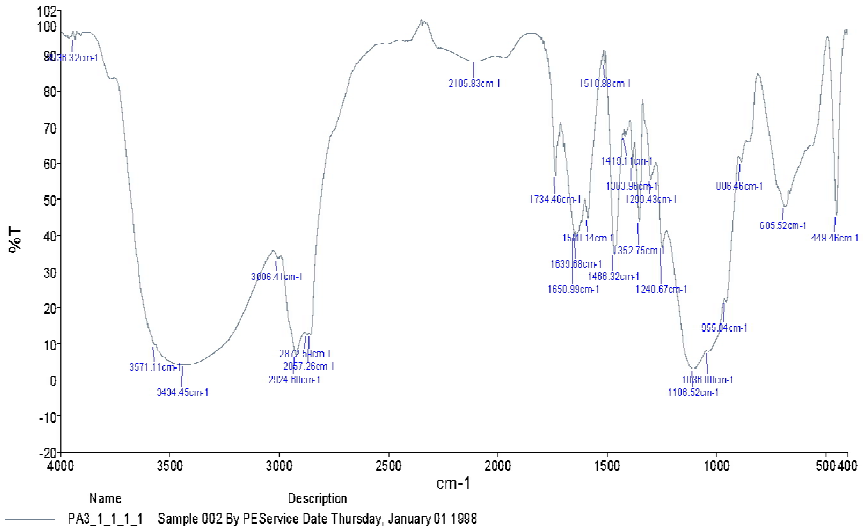

Fig.8: FT-IR spectra of drug-physical mixture

CONCLUSION

In the present study, the buccal films of Entacapone were prepared successfully by solvent casting method. The optimized buccal film (F6) composed of drug: HPMC E15 (1:10) in methanol and dichloromethane mixture (1:1) along with 0.1% of dibutylpthalate as plasticizer and 0.6% citral as permeation enhancer showed satisfactory physicochemical properties,good physical stability, highest percent drug release (93.9±1.82%) and followed zero order model of drug release and fairly good amount of drug permeation through the porcine buccal membrane in 8hrs. The formulation F6also showed significantly high flux i.e. 3.26 ($p<0.0001$) times more than that of drug suspension. Hence, the present study concludes that these erodible F6 buccal films of Entacapone can be very promising for effective doses to systemic circulation circumventing the hepatic first pass metabolism and enhances bioavailability.

CONFLICT OF INTEREST

The authors declared no conflict of interest

REFERNCES

1. Choudhury, Feroza K, Rosa M Rivero, Eduardo Blumwald, and Ron Mittler. (2017). "Reactive Oxygen Species, Abiotic Stress and Stress Combination." *The Plant Journal* 90 (5): 856–67.
2. Devic, Slobodan, Nada Tomic, Saad Aldelaijan, Francois DeBlois, Jan Seuntjens, Maria F Chan, and Dave Lewis. (2012). "Linearization of Dose–Response Curve of the Radiochromic Film Dosimetry System." *Medical Physics* 39 (8): 4850–57.
3. Gilhotra, Ritu M, Mohd Ikram, Sunny Srivastava, and Neeraj Gilhotra. (2014). "A Clinical Perspective on Mucoadhesive Buccal Drug Delivery Systems." *Journal of Biomedical Research* 28 (2): 81.
4. V. Ravi Krishna, Y. Madhusudhan Rao, P.Chinna Reddy, K. Sujatha. (2011). "Formulation and Invitro evaluation of Buccoadhesive tablets of Furosemide", *Int. J. Drug Dev. & Res.*, 3(4): 351-361
5. Md, Shadab, Shadabul Haque, Jasjeet Kaur Sahni, Sanjula Baboota, and Javed Ali. (2011). "New Non-Oral Drug Delivery Systems for Parkinson's Disease Treatment." *Expert Opinion on Drug Delivery* 8 (3): 359–74.
6. Reddy, B Venkateswara, and R K Reddy. (2015). "Formulation and Evaluation of Buccal Mucoadhesive Tablets of Glipizide." *World Journal of Pharmacy and Pharmaceutical Science* 4 (07): 1804–21.
7. Sichina, W J. (2000). "Use of DSC for the Characterization of Starches." *PerkinElmer Instruments*.
8. Ma, Hongdan, Dongyan Guo, Yu Fan, Jing Wang, Jiangxue Cheng, and Xiaofei Zhang. (2018). "Paeonol-Loaded Ethosomes as Transdermal Delivery Carriers: Design, Preparation and Evaluation." *Molecules* 23 (7): 1756.
9. M. Sunitha , A. Padma, B. Balaji, V. Ravi Krishna and M. Vamshi krishna (2014). "Formulation And Invitro Evaluation Of Buccal Mucoadhesive Tablets Of Chloropheneramine Maleate".*International Journal Of Pharmaceutical, Chemical And Biological Sciences,*4(3),774-784.
10. Ganesh. M, Ramesh. K, Madhusudan Rao. Y, Chandra Shekar. B. (2015). "Formulation, Characterization and in vitro Evaluation of Entacapone Solid Dispersions with Lipid Carriers by Using Spray Drying Method".*International Journal of Pharmaceutical Sciences and Drug Research,* 7(3): 235-243.
11. Sathish, D, S Himabindu, P Pavan Kumar, and Y Madhusudan Rao. (2013). "Preparation and Evaluation of Novel Expandable Drug Delivery System." *Journal of Pharmaceutical Research International*, 1079–93.
12. Devic, Slobodan, Nada Tomic, Saad Aldelaijan, Francois DeBlois, Jan Seuntjens, Maria F Chan, and Dave Lewis. (2012). "Linearization of Dose–Response Curve of the Radiochromic Film Dosimetry System." *Medical Physics* 39

(8): 4850–57.
13. Takeuchi, Yoshiko, Nozomi Ikeda, Kohei Tahara, and Hirofumi Takeuchi. (2020). "Mechanical Characteristics of Orally Disintegrating Films: Comparison of Folding Endurance and Tensile Properties." *International Journal of Pharmaceutics* 589: 119876.
14. Mohasin Lodhi, Akhilesh Dubey, Reema Narayan, Prabhakara Prabhu, and Sneh Priya. (2013). "Formulation and evaluation of buccal film of Ivabradine hydrochloride for the treatment of stable angina pectoris"*Int J Pharm Investig.*3(1): 47–53.
15. Shringirishi, Madhuri, Alok Mahor, Rishikesh Gupta, Sunil Kumar Prajapati, Kuldeep Bansal, and Prashant Kesharwani. (2017). "Fabrication and Characterization of Nifedipine Loaded β-Cyclodextrin Nanosponges: An in Vitro and in Vivo Evaluation." *Journal of Drug Delivery Science and Technology,* 41: 344–50.
16. Nagadeep, J., P. Kamaraj, and M. Arthanareeswari.(2019). "Gradient RP-HPLC method for the determination of potential impurities in dabigatran etexilate in bulk drug and capsule formulations." Arabian Journal of Chemistry 12, no. 8 : 3431-3443.
17. Jaishetty, Nagadeep, Kamaraj Palanisamy, and Arthanareeswari Maruthapillai. (2019). "Enantiometric Separation Of Sitagliptin In A Fixed Dose Combination Formula Of Sitagliptin And Metformin By A Chiral Liquid Chromatographic Method." Int J Pharm Pharm Sci 9; 23-29.
18. Jaishetty, Nagadeep, Kamaraj Palanisamy, Arthanareeswari Maruthapillai, and Rajamanohar Jaishetty. (2016)."Trace Level Quantification of the (−) 2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1, 1, 1-trifluoro-3-butyn-2-ol Genotoxic Impurity in Efavirenz Drug Substance and Drug Product Using LC–MS/MS." Scientia pharmaceutica 84, no. 3, 456-466.
19. Nagadeep, J., P. Kamaraj, M. Arthanareeswari, And P AVivekanand. (2021). Asian Journal of Chemistry 33, no. 2 (2021): 307-313.

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