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Review/Research

FABRICATION AND CHARACTERIZATION OF BUCCOADHESIVE GELS OF LEVETIRACETAM FOR TRANSMUCOSAL DRUG DELIVERY AND ASSAY BY USING UPLC

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Abstract

The purpose of the study is to fabricate and characterize buccoadhesive gels of levetiracetam for transmucosal drug delivery. Buccoadhesive dosage forms like buccoadhesive gels, tablets and films offer targeted site and controlled delivery of drugs through intrajugular vein. The dosage forms can be terminated from buccal cavity when ever required to avoid long exposure to drugs if therapeutic efficacy is attained, which is not possible with conventional dosage forms. Buccoadhesive dosage forms also bypasses the first pass metabolism. In this study different formulations of buccoadhesive gels containing levetiracetam were pepared and evaluated by performing invitro methods.

Keywords: Buccoadhesive gels, levetiracetam, transmucosal drug delivery, controlled delivery, intrajugular vein and first pass metabolism.

INTRODUCTION:

Most of the drugs are preferred to be administered via oral route due to low cost[1], ease of administration[2] and high level of patient compliance[3], which has many limitations. Such conventional oral/buccal dosage forms are modified to control release dosage forms to overcome

the limitations[4]. Buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms[2].

METHODOLOGY:

Fabrication of buccoadhesive gels[4]:

Buccoadhesive gels were prepared (Table 2) by dispersing an appropriate amount of the polymer in the distilled water, and allowing it to swell. The polymer solution was stirred to break the lumps formed during swelling. In another beaker, the drug was dissolved in the distilled water by simple mixing in a beaker. To this drug solution, polymer mixture was added, and thoroughly agitated until a clear gel was formed. 10% glycerol was added to avoid drying of gel.

Table 1: Composition of levetiracetam loaded buccoadhesive gels.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7
Drug (mg)	500	500	500	500	500	500	500
Sodium alginate (mg)	500	500	500	500	500	500	500
HPMC (mg)	---	100	300	500	---	---	---
Carbopol 934P (mg)	---	---	---	---	300	500	750
Glycerine	10%	10%	10%	10%	10%	10%	10%
Distilled water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

HPMC: Hydroxy Propyl Methyl Cellulose

Q.S: Quantity Sufficient

Characterization of buccoadhesive gel:

A. Physicochemical characterization of buccoadhesive gel[3]:

Determination of pH: 1g of gel were weighed and diluted 10 times with isopropyl alcohol. Then, pH of gels was measured with pH-meter[5].

Viscosity study: A Brookfield viscometer digital viscometer DVLV-II was used to measure the viscosity of gel formulation at 25°C. Spindle number 1 was rotated at 100 rpm[6].

Gelation and gel melting temperature: Gelation and gel melting were evaluated using a modified Miller and Donavan technique. 5ml aliquot of gel was transferred to the test tubes and sealed with aluminum foil. The tubes were immersed in a water bath at 4°C. The temperatures of the water bath was augmented by increment of 1°C and were allow equilibrating to 1 minute at each new setting. The samples were then examined for gelation, which was said to have occurred when the

meniscus no longer moved upon slanting the tube through 90°C. The gel melting temperature, the temperature, at which a gel starts flowing upon tilting through 90°C,was recorded[7].

Spreadability:

Spreadability was determined by an apparatus suggested by Muttimer et al., which was suitability modified in the laboratory and used for the study. It consisted of a wooden block which was provided by a pulley at one end. A rectangular ground glass plate was fixed on this block. An excess of gel (3gm) under study was placed on this ground plate. The gel was then sandwiched between this plate and another glass plate having the dimensions of the fixed ground plate and provided with the hook. A 1kg weight was place on the top of the two plates for 5 minute to expel air and to provide a uniform film of the gel between the plates. Excess of the gel was scrapped off from the edges. The top plate was then subjected to a pull of 50 gm, with the help of string attached to the hook and the time (in seconds) required by the top plate to cover the distance of 10 cm is noted. A shorter interval indicates better Spreadability. The Spreadability can be calculated using the formula[8]:

$$S = \frac{m.l}{t}$$

Where, S = Spreadability

m = weight tied to the upper slide

l = length of the glass slide

t = time

Adhesion strength measurement:

The adhesion force of gel were determined by means of adhesive force measuring device showing in fig 1, using tissue cut from mucosal area of rat hairless abdomen. The pieces of tissue stored frozen in phosphate buffer pH 6.8, and thawed to RT before use. At the time of testing, a section of rat skin secured to the upper glass vial (C) using a cyanoacrylate adhesive (E). The diameter of each exposed mucosal membrane was 1.5cm. The vials were equilibrated and maintained at 37°C for 10 min. Next, one vial with the section of the tissue (E) was connected to the balance (A) and other vial was the fixed on height adjustable pan (F). To expose tissue on this vial, a constant amount of 0.1 g gel (D) was applied. The height of vial was adjusted so that the gel could adhere to the mucosal tissue of both vials. Immediately, a constant force of 1N is applied for 10 min to ensure intimate

contact between tissues and the sample. The vial was then moved upwards at constant speed, and was connected to the balance. Weights were added at a constant rate to the other side of the modified balance of the used device until the two part vials were separated[9].

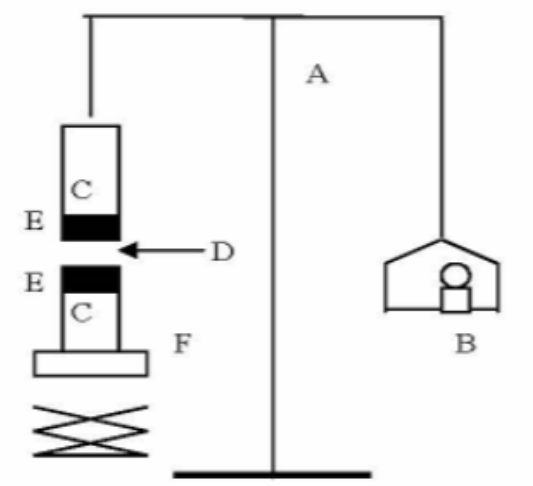

Fig. 1: Bioadhesive force measuring device: (A) modified balance; (B) Weights; (C) glass vial; (D) SA gel; (E) rat tissue; (F) height-adjustable pan.

The buccoadhesive force, expressed as the detachment stress in dyne/cm2, was determined from the surface of each formulation using the following equation. Detachment stress (dyne/ cm2) = m.g/A Where, m is the weight added to the balance in gm g is the acceleration due to gravity taken as 980cm.s2 and A is the area of tissue exposed.

B. Invitro permeation studies[10-15]

Construction of linear callibration graph of leveteracetam at wavelength of 209.

Buffer Preparation (6.8 pH):

Step1: preparation of 0.2M potassium dihydrogen phosphate (PDP):

Dissolve 27.218 grams of PDP in water and make it up to 1000 ml in a 1000ml volumetric flask.

Step 2: Preparation of 0.2M NaOH:

Dissolve 8grams of NaOH in water and make it up to 1000 ml in a 100ml volumetric flask

Step 3: Preparation pf 6.8 pH buffer:

Add 250 ml of 0.2M PDP into 1000ml volumetric flask.

Now add 112ml of 0.2M NaOH to the above 1000 ml volumetric flask, and make the final volume to 1000ml and mix well.

Preparation of drug stock solution by using 6.8pH buffer

Pipette out 10ml of the solution from the volumetric flask which contain 0.1g or 100mg of drug dissolved in buffer i.e.,0.1gram or 100mg in 100ml in another volumetric flask.

Make up 10ml solution by adding buffer water upto 100ml.

Then again pipette out 10ml of the solution from from the prepared solution and make it up to 100ml which gives 1mg/100ml concentration.

Now pipette out 1ml, 2ml, 3ml, 4ml, 5ml, 6ml, 7ml, 8ml, 9ml, 10ml of the solution separately, Mark them and add it to 10ml of volumetric flask and make it up to 10ml by adding the drug stock solution contains 100mg in 100ml.

***Invitro* diffusion studies:**

Diffusion studies were performed by using two raw eggs which was firstly emptied. Then two egg shells were taken and placed in a beaker containing 15ml of concentrated HCL. After keeping it for 20mins the egg shell was dissolved and membranes was separated and was taken into another beaker containing deionised water to remove the traces of acid. After that the first egg shell membrane was taken into petri plate containing 6.8 pH buffer and the other shell membrane was taken into petri plate containing deionised water.

Two Franz diffusion cell were taken and washed using acetone and one was filled with buffer and the other with deionised water along with magnetic bead at a temperature of 37 ± 0.5^{o}C degree Celsius on a magnetic stirrer. Egg shell membranes was cut into two by using surgical blade and was placed on the franz diffusion cell and the magnetic stirrer was switched on after sometime the film was added from the top of the franz diffusion cell and the samples were collected at regular time intervals using 1ml syringe. The study was performed for 8 hours and the absorbance of the collected samples was determined using UV Visible spectrophotometer.

C. **Organoleptic characters of buccoadhesive gels[5,8,10]:** Organoleptic characters of formulated buccoadhesive gels examined by physical evaluation
D. **Drug excipient compatibility[1,2,7]:** The studies were carried out by FTIR (Fourier transform infrared) analysis using physical mixture of drug and excipients.
E. Differential scanning calorimetry (DSC): The physical transitions (stability) studies are performed by DSC.

F. Assay by using UPLC: Assay was performed by using ultra performance liquid chromatography (UPLC). A method was developed by using solvent mixture for pure drug and the formulation sample tested for percentage assay.

G. Pharmacokinetics study[17]: The plasma concentration and time profile curve to contrasts the plasma level profiles of levetiracetam after oral administration of the marketed tablet and buccoadhesive gel (F7) formulations are shown in Table 6 and the various pharmacokinetic parameters are recorded. Buccoadhesive gel (F7) was applied both sides to the cheek of albino Wistar rats. A dose of marketed tablet as the oral suspension was given to rats to evaluate the disparity in pharmacokinetic parameters with the buccoadhesive gel (equivalent to marketed drug dose).

RESULTS:

pH of buccoadhesive gels: pH of all formulated gels are with in the range (6.7 t0 7.1) suitable with pH of saliva. pH of F2, F3, F6 and F7 are adequate (table 2).

Gelation temperature: Gelation temperature of all formulated gels are with in the range (36 to 39). Gelation temperature of F2, F6 and F7 are adequate (table 2)..

Viscosity study: Viscosity of all formulated gels are satisfactory, viscosity of F7 containing carbopol is found to be 2055±4.5 which is comparatively higher than other formulations (table 2).

Spreadability: Spreadability of all formulated gels are satisfactory, i.e in the range of 4.1±0.01 to 4.9±0.03. spreadability of F7 was adequate (table 2).

Adhesion strength: Buccoadhesive strength of F7 containing carbopol is found to be 0.55±0.04 which is comparatively higher than other formulations (table 2).

Table 2: Physicochemical characterization of buccoadhesive gels (mean±SD, n=6).

Formulation	pH	Gelation temperature oC	Viscosity at 100 RPM (cPs)	Spreadability (CM)	Adhesion strength
F1	6.7±0.05	39±0.5	1320±5.8	4.1±0.01	0.19±0.01
F2	6.8±0.04	37±0.05	1446±6.1	4.6±0.05	0.37±0.01
F3	6.8±0.03	36±0.04	1629±6.6	4.4±0.01	0.42±0.03
F4	6.9±0.05	38±0.06	1688±10	4.7±0.05	0.47±0.02
F5	7.1±0.04	38±0.05	1522±10	4.5±0.10	0.45±0.04
F6	6.8±0.03	37±0.5	1781±5.1	4.7±0.01	0.49±0.01
F7	6.8±0.03	37±0.5	2055±4.5	4.9±0.03	0.55±0.04

Standard graph using 6.8 ph phosphate buffer:

Serial dilutions of drug in 6.8pH phosphate buffer has shown satisfactory absorbance at wavelength 209 using UV VISIBLE Spectrophotometer. Upon plotting a graph between concentration (X axis) and absorbance (Y axis) given in table 3, linearity has shown with R^2 0.999.

***Invitro* diffusion studies:** Results of *Invitro* diffusion studies of all formulations (F1 to F9) in 6.8 pH phosphate buffer are given in table 4 and found to be satisfactory over 6 hours. Invitro diffusion profile of F7 is adequate.

Table 3: Absorbance values of known concentration of drug in 6.8 ph phosphate buffer

SL.NO	CONCENTRATION (µ/ml)	ABSORBANCE
	0	0
	1	0.109
	2	0.12
	3	0.133
	4	0.148
	5	0.161
	6	0.178
	7	0.19
	8	0.204
	9	0.219
	10	0.231

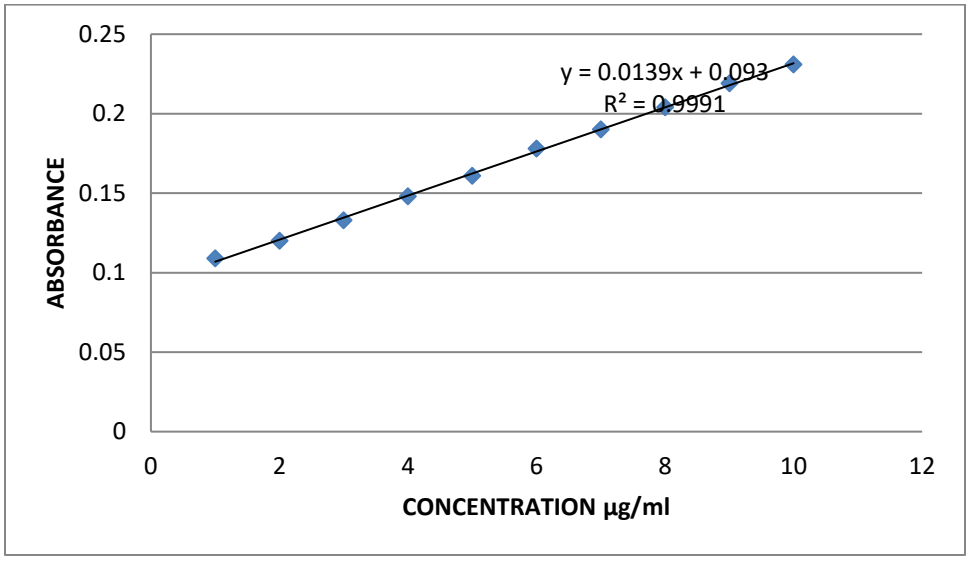

Fig 2: Standard graph of levetirecetam using 6.8 ph phosphate buffer

Table 4: percent Invitro diffusion studies of all formulations In 6.8 pH phosphate buffer (mean±SD, n=6).

SL.NO	TIME IN MIN	F1	F2	F3	F4	F5	F6	F7
	0	0	0	0	0	0	0	0
	15	5.22±0.03	4.7±0.10	4.2±0.5	4.07±0.06	4.3±1.0	4-1±0.02	3.8±0.01
	30	13±0.80	11.2±0.19	10.5±0.06	9.90±0.10	10.3±0.09	9.7±0.06	8.8±0.05
	60	21±0.10	19.9±0.12	16.1±0.24	12.3±0.44	16.6±0.80	15.1±0.81	12.6±0.10
	120	39±0.08	32.1±0.09	30.4±0.39	29.4±0.86	31.5±0.62	29.8±0.22	25.9±0.09
	180	52±0.22	49.3±0.07	45.9±0.82	41.4±0.51	45.2±0.06	42,2±0.25	39.8±0.52
	240	70±0.12	65.6±0.13	61.4±0.11	58.5±0.09	62.6±0.05	60.7±0.02	58.6±0.43
	300	81±0,27	79.2±0.12	74.4±0.81	72.6±0.65	78.1±0.59	75.6±0.11	71.2±0.51
	360	99±0.33	95±0.09	92±0.09	90±0.08	93±0.09	89±0.16	85±0.15

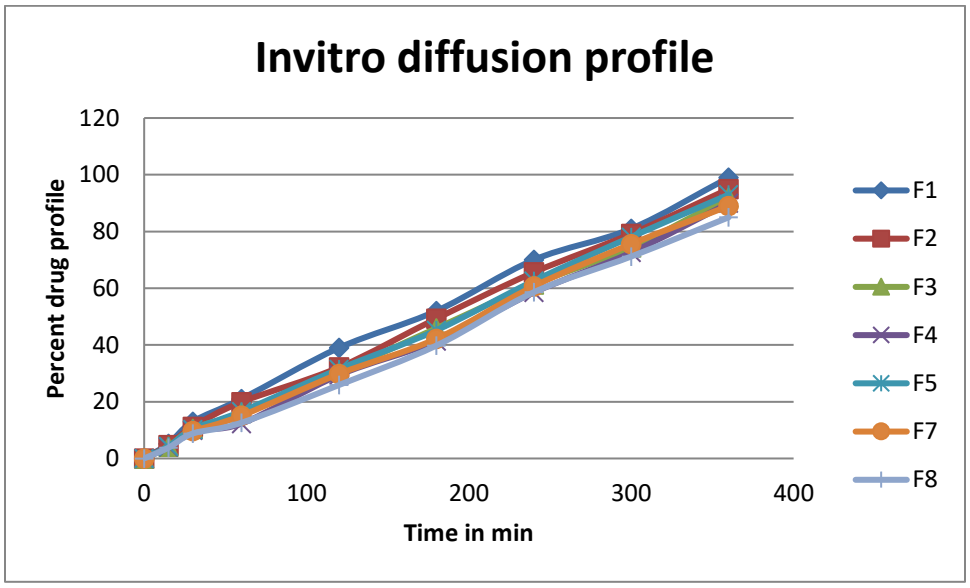

Fig 4: Invitro permeation profile of formulations F1 – F8

Organoleptic characters of prepared gels:

The organoleptic properties of all the formulations i.e F1 – F9 are found to be satisfactory. All the three formulations are palatable, where are the color of, F1 – F3 is Pale brown and translucent, F4 is brown and translucent, F5 to F7 is white. F1 is odorless and characteristic for F2 - F9. The results are given in table 5.

Table 5: Organoleptic characters of prepared gels:

SL.NO	FORMULATION	COLOR	ODOR	TASTE
1	F1	Pale brown and translucent	Odorless	Palatable
2	F2	Pale brown and translucent	Characteristic (gum like)	Palatable
3	F3	Pale brown and translucent	Characteristic (gum like)	Palatable
4	F4	brown and translucent	Characteristic (gum like)	Palatable
5	F5	White	Characteristic (gel like)	Palatable
6	F6	White	Characteristic (gel like)	Palatable
7	F7	White	Characteristic (gel like)	Palatable

Table 6: Comparative results of pharmacokinetic parameters (mean±SD, n=6)

Pharmacokinetic parameters	Marketed XR tablet (orally)	F7 Buccal
Tmax (h)	5	6
Cmax (µg/ml)	18.7	20.3
AUClast (µg.h/ml)	274	268
AUMClast (µg.h2 /ml)	295	282

Drug and exc[p[ent compatibility: The spectrum of drug and excipient compatibility are given in fig no 4 and 5.

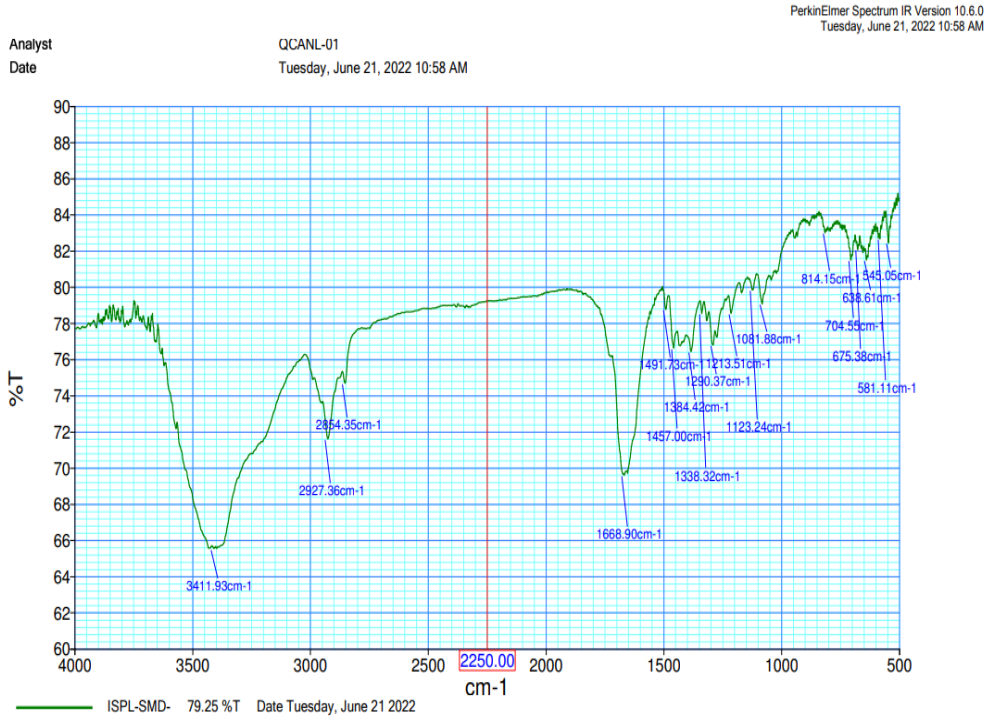

Fig 4: FTIR spectrum of pure drug

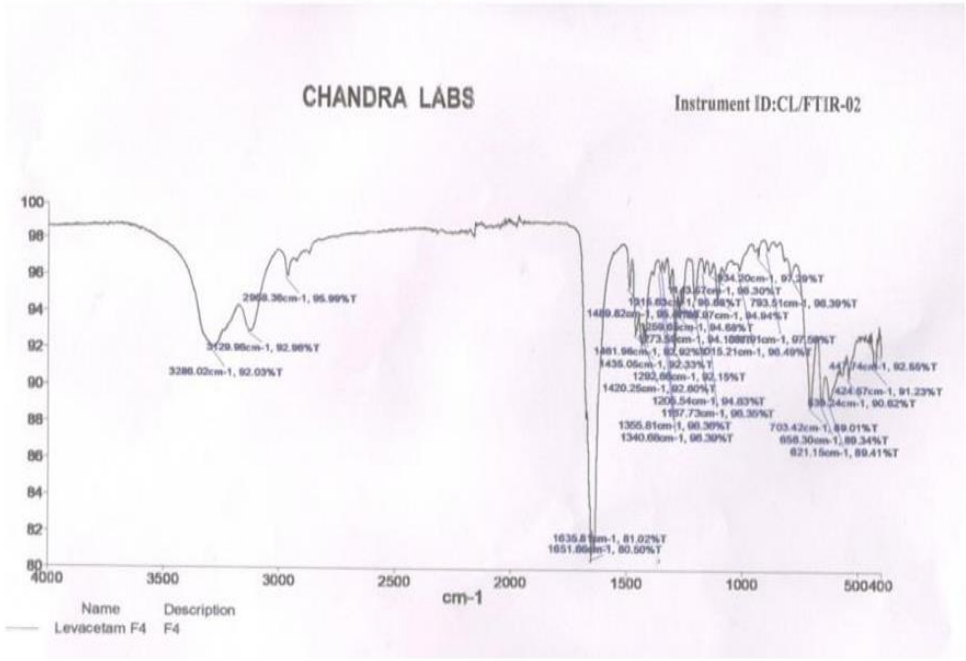

Fig 5: FTIR spectrum of F7 formulation.

Stability studies: The spectrum of DSC are given in fig 6 and 7.

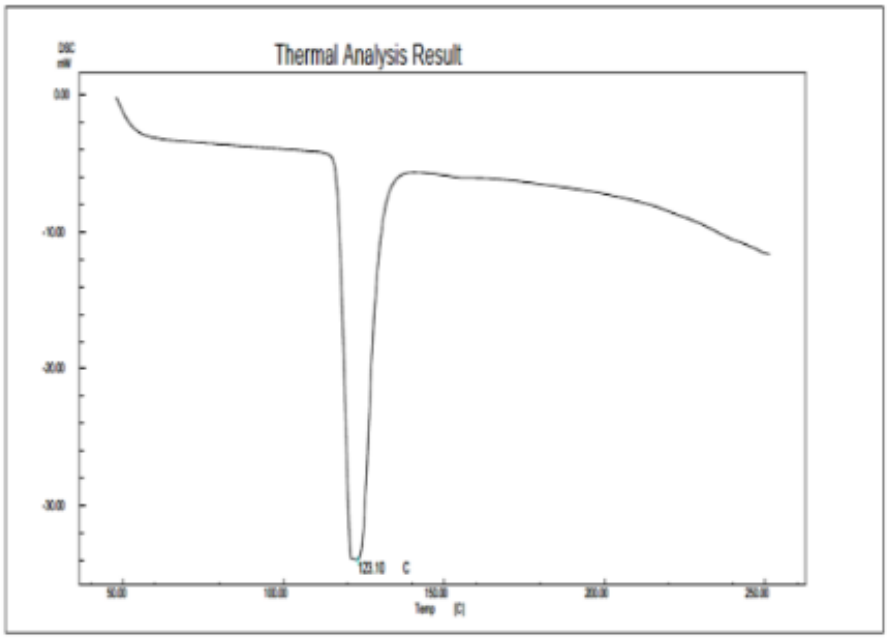

Fig 6: DSC of pure drug.

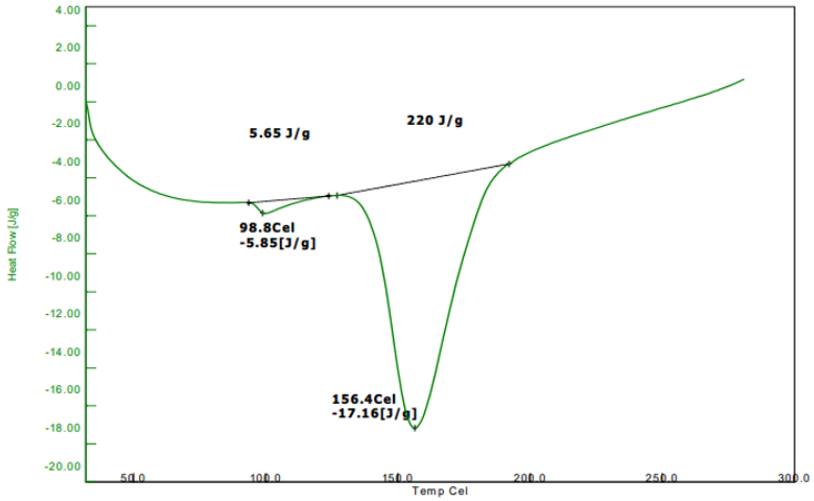

Fig 7: DSC of F7 formulation.

Assay by UPLC: Assay was performed by using ultra performance liquid chromatography and the chromatograms are given in fig 8 and 9.

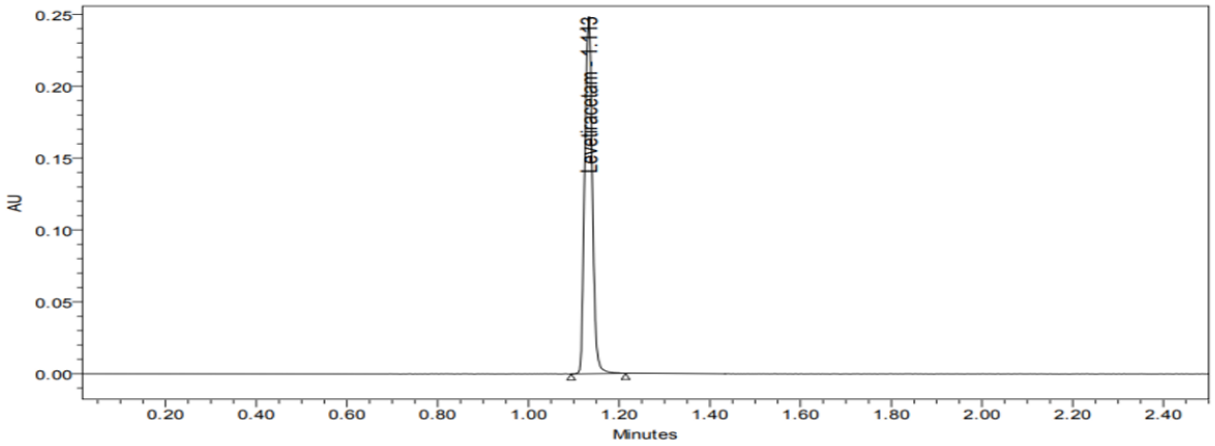

Fig 8: Optimized chromatogram of Levetiracetam.

Sl.no	Peak name	RT	Area	USP plate count	USP Tailing
1	Levetiracetam	1.113	1045602	2836	1.2

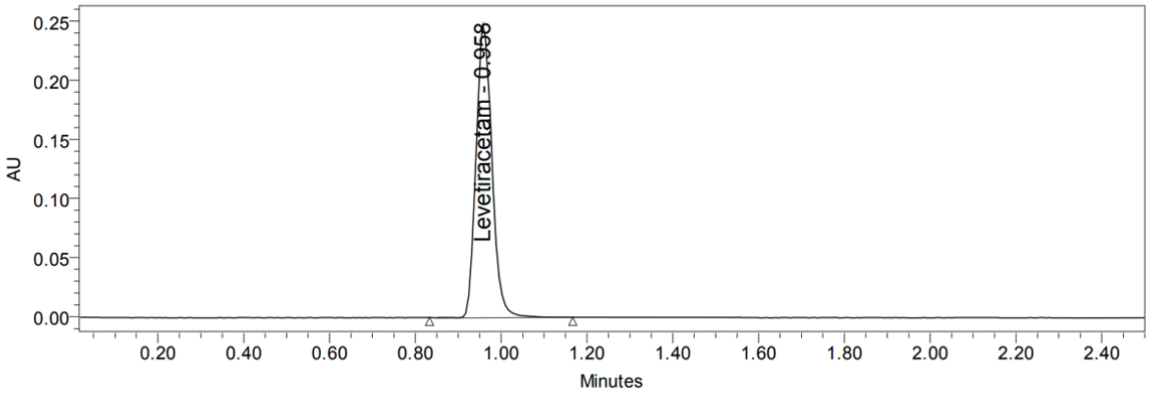

Fig 9: Optimized chromatogram of F7 formulation

Sl.no	Peak name	RT	Area	USP plate count	USP Tailing
1	F7	0.958	1039825	1004	1.39

Assay was obtained as 99.02% for Levetiracetam buccoadhesive gel using UPLC.

CONCLUSION:

The properties of buccoadhesive gels were enhanced after addition of polymers such as HPMC and carbopol using sodium alginate as control release polymer. Different characterization techniques were performed for all formulations which were found to in suitable range i.e with adequate stability, physicochemical characters, organoleptic characters, assay using UPLC and invitro permeation. pH of all formulated gels are with in the range (6.7 t0 7.1) suitable with pH of saliva. pH of F2, F3, F6 and F7 are adequate. Gelation temperature of all formulated gels are with in the range. Gelation temperature of F2, F6 and F7 are adequate. Viscosity of all formulated gels

are satisfactory, viscosity of F7 containing carbopol is found to be 2055±4.5 which is comparatively higher than other formulations. Spreadability of all formulated gels are satisfactory, i.e in the range of 4.1±0.01 to 4.9±0.03. spreadability of F7 was adequate. Buccoadhesive strength of F7 containing carbopol is found to be 0.55±0.04 which is comparatively higher than other formulations. Results of *Invitro* diffusion studies of F1 to F9 in 6.8 pH phosphate buffer are found to be satisfactory over 6 hours. Invitro diffusion profile of F7 is adequate.

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