Research Article

Formulation and Evluation of Mucoadhesive Buccal Tablets of Naratriptan Hydrochloride

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ABSTRACT

Migraine is characterized by episodes of head ache that is often throbbing and may be severe. In migraine attacks are usually associated with nausea, vomiting, or sensitivity to light, sound, or movement and the attacks typically last 4 to 72 hours. The last decade has witnessed the advent of Naratriptan and the Ftriptan class of 5-HT1B/1D receptor agonists which have well established efficacy in treating migraine. Tablets o f Naratriptan Hydrochloride were prepared by direct compression method using bio adhesive polymers like Carbopol 934p, Methocel K4M, Methocel K15M and Sodium Car boxy methyl cellulose. The physical characteristics, swelling index, surface pH, and in-vitro bio adhesion strength and in-vitro release of formulated tablets were shown to be dependent on characteristics and composition of bio adhesive materials used. The modified in-vitro assembly was used to measure and compare the bio adhesive strength of tablets using sheep buccal mucosa as a model tissue. The maximum bio adhesive strength was observed in tablets formulated with Carbopol 934P alone and strength decreases with its content. The tablets were evaluated for in vitro release in pH 6.2 phosphate buffer up to 10 hours using standardized apparatus. All the formulations followed non- Fickian release mechanism. Carbopol 934P and Methocel K4m in the ratio of 1:1 can be used to design effective and stable buccoadhesive tablets of Naratriptan Hydrochloride.

Key words: Muccoadhesive tablet, Naratriptan Hydrochloride, Swelling, Bio adhesion.

INTRODUCTION:[1-9]

Extensive efforts have been made recently on targeting a drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery. The concept of mucosal- adhesive or muccoadhesive was introduced into the controlled drug delivery in the early 1980's. Muccoadhesive are synthetic or natural polymers, which interact with the mucus layer covering the mucosal epithelial surface and mucin molecules constituting a major part of mucus. Muccoadhesive systems render the treatment more effective and safe not only for topical disorders but also for systemic problems.

Bio adhesion

For drug delivery purposes, the term bio adhesion implies attachment of a drug carrier system to a specified biological surface. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as Mucoadhesion. Leung and Robinson described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer.

A bio adhesive is defined as a substance that is capable of interacting with biological materials and being retained on them or holding them together for extended period of time. Bio adhesives are classified into three types based on phenomenological observation, rather than on the mechanisms of bio adhesion.

Type I: Bio adhesion is characterised by adhesion occurring between biological objects without involvement of artificial material. Eg: Cell fusion and Cell aggregation.

Type II: Bio adhesion can be represented by cell adhesion onto culture dishes or adhesion to a variety of substances including metals, woods and other synthetic materials.

Type III: Bio adhesion can be described as adhesion of artificial substances to biological substrates such as adhesion of polymers to skin or other soft tissues.

EXPERIMENTAL WORK[10-20]

METHODOLOGY

Construction of Standard Graph of Naratriptan HCl

100mg of Naratriptan Hydrochloridewas accurately weighed and dissolved in 100ml of phosphate buffer 6.2 to obtain a concentration of 1000µg/ml. From the above solution 10ml was withdrawn and diluted to 100ml to obtain a concentration of 100µg/ml. From this stock solution aliquots of 1ml, 2ml, 3ml,4ml, 5ml and 6ml were diluted in 50ml volumetric flask with phosphate buffer to give concentrations in range of 2µgm/ml to 12µgm/ml respectively, absorbance was measured at 265nm.

Preformulation studies

MICROMERITIC PROPERTIES

Angle of repose: Ten grams of the granules was placed in a plugged glass funnel which had a distance of 10cm from the flat surface. The granules were then allowed to flow through the funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (*h*) formed as well as the radius of the heap (*r*) was noted. The angle of repose (θ) was calculated as

$$\tan \theta = h/r$$

Bulk density and Tapped density: Bulk and tapped densities were measured by using 10ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated.

$$\text{Bulk density} = M / V_0$$

Where M= mass of the powder;

V_0=bulk volume of the powder.

$$\text{Tap density} = M / Vr$$

Where M = mass of the powder,

Vr = final tapping volume of the powder.

Drug– excipient compatibility studies

Infrared spectra were taken by using KBr pellet technique using a Shimadzu FT-IR 8300 Spectrophotometer in the wavelength region of 4000 to 400 cm−1. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients or formulation) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

Carr's index: Compressibility index (Ci) or Carr's index value of microspheres was computed according to the following equation:

$$CI = (Td - Bd)/ Td$$

Hausner's ratio: Hausner's ratio of microparticles was determined by comparing the tapped density to the bulk density using the equation:

$$HR = Td/Bd$$

POST-COMPRESSION STUDIES

Thickness:

Twenty tablets from the representative sample were randomly taken and individual tabletthickness was measured by using vernier caliper. Average thickness and standarddeviation values were calculated.

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

%Friability was calculated as follows

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

where W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing. Friability values below 0.8% are generally acceptable.

Weight Variation Test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100/ W_A$$

As the total tablet weight was 250 mg, according to IP 1996, out of twenty tablets ±7.5 % variation can be allowed for not more than two tablets.
According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

v) Drug Content (Assay)
The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 3 tested tablets lies within the range of 90% to 110% of the standard amount.
Three tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to average weight of three tablets of Eletriptanwas transferred to a 100 ml volumetric flask containing 6.8 pH Phosphte buffer solution and the volume was made upto the mark. From this 10ml was taken and shaken by mechanical means using centrifuge at 3000rpm for 30min. Then it was filtered throughwhatman filter paper. From this resulted solution 1 ml was taken, diluted to 10 ml with 6.8 pH Phosphate buffer solution and absorbance was measured against blank at 250 nm.

***In vitro* dissolution studies**
- The dissolution testing of Naratriptan Hcl tablets was carried out using a USP Type II dissolution apparatus (Shimadzu) at 37±0.5 °C in 900 ml phosphate buffer pH 6.8 and a speed of 75 rev. /min.

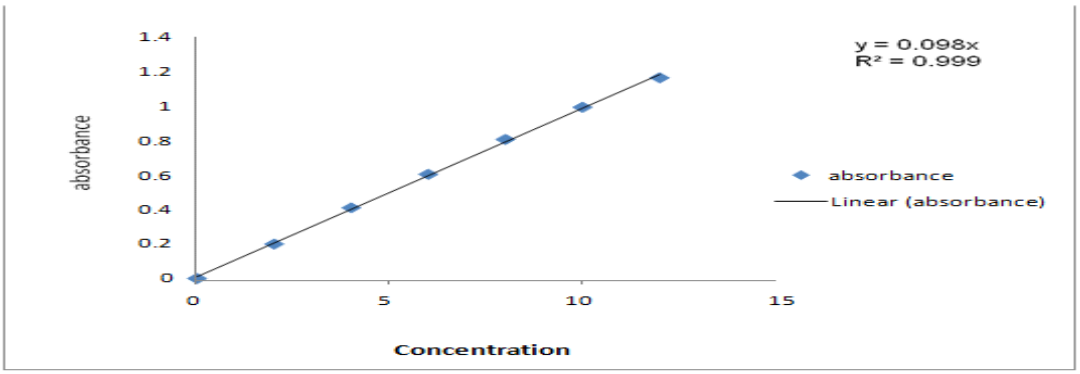
***In vitro* bioadhesion testing**
- In vitro bioadhesion studies were carried out using sheep buccal mucosa and modified two- armed balance. The left pan of physical balance was removed. To the left arm of balance, a thick thread of suitable length was hung. To the free end of thread attach a glass stopper of circular base (diameter 2.5cm). A clean 250ml beaker was placed below the glass stopper. In the centre of beaker, a cork (3.5cm diameter) along with sheep buccal mucosa attached to it was placed. Isotonic phosphate buffer pH (6.6) was added until it grazed of mucosal surface (around100ml). The isotonic buffer was maintained at 37°c. The sides of the balance were then
  - Balanced so that right hand side was exactly 6.55g heavier than left.
  - From the bioadhesive strength, Force of Adhesion was calculated as,
  - **Force of Adhesion (N)= Bioadhesion×9.81/1000**

Table 1: Formulation chart of Bioadhesive tablets (Total weight of tablet is 171 mg)

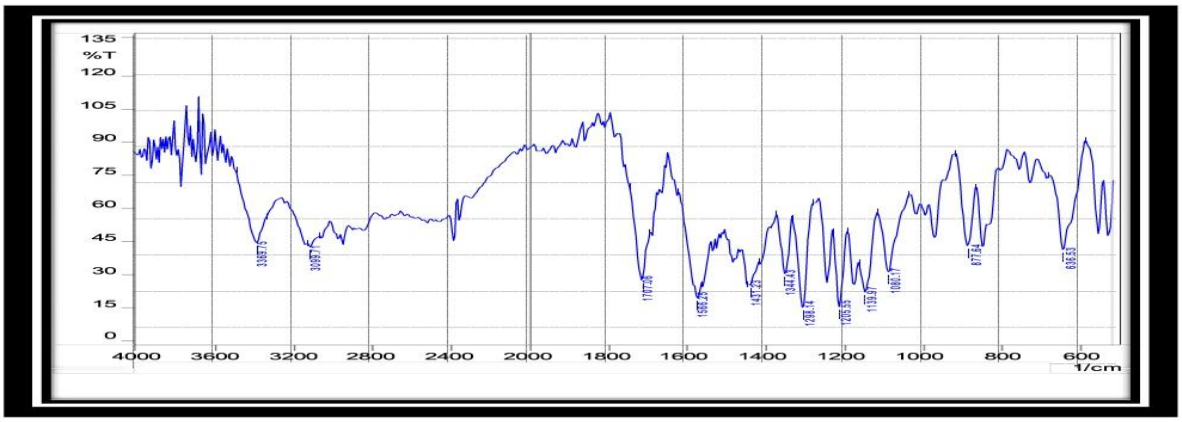
Formulation code	Naratriptn	Carbopol934p	Hpmck4m	Hpmck15	Na- cmc	Mg- stearate	Ethyl cellulose
F1	25mg	95mg	*	*	*	1mg	50mg
F2	25mg	47.5mg	47.5mg	*	*	1mg	50mg
F3	25mg	23.75mg	71.25mg	*	*	1mg	50mg
F4	25mg	71.25mg	23.75mg	*	*	1mg	50mg
F5	25mg	47.5mg	*	47.5mg	*	1mg	50mg
F6	25mg	23.75mg	*	71.25mg	*	1mg	50mg
F7	25mg	71.25mg	*	23.75mg	*	1mg	50mg
F8	25mg	47.5mg	*	*	47.5mg	1mg	50mg
F9	25mg	23.75mg	*	*	71.25mg	1mg	50mg
F10	25mg	71.25mg	*	*	23.75mg	1mg	50mg

RESULTS AND DISCUSSIONS
Pre Formulation Studies
Construction of Std. Calibration Curve

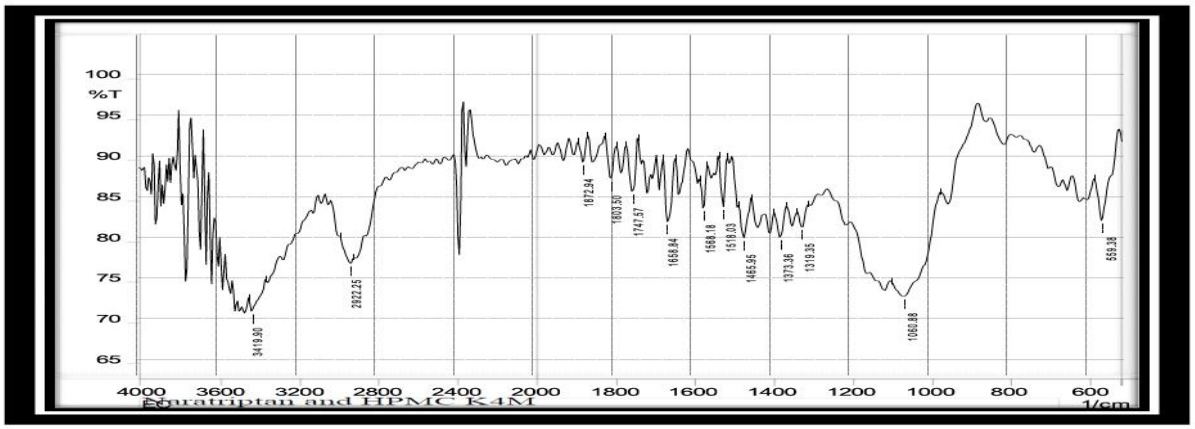
SL.NO	VOL OF SSII IN ML	VOL MADE UPTO	CONC IN µg/ml	ABSORBANCE AT 265nm
1	0	50 ml	0	0.00
2	1	50ml	2	0.198
3	2	50ml	4	0.407
4	3	50ml	6	0.600
5	4	50ml	8	0.801
6	5	50ml	10	0.986
7	6	50ml	12	1.156



FT-IR Studies
IR Spectra for Pure Drug



IR Spectra for Drug & HPMC K4 M



Result of FT-IR spectra of Naratriptan Hydrochloride& Carbopol

Drug/polymer	CH cm^{-1}	C=C cm^{-1}	C-C cm^{-1}	N-H cm^{-1}	C-N cm^{-1}	S=O cm^{-1}	C-H cm^{-1}	C=O cm^{-1}	C-O cm^{-1}	OH cm^{-1}
Naratriptan	3099.71	1566.25	1431.23	3369.75	1344.43	1139.97	-------	-------	-------	-------
HPMC K4 M	-------	-------	-------	-------	-------	-------	2956.97	1705.13	1168.90	2956.97
Naratriptan+HPMC k4 M	3099.71	1564.32	1431.23	3369.75	1344.43	1139.97	2933.83	1705.13	1168.90	2933.83

Evaluation of Pre Compression Parameters

Formulation Code	Bulk Density	Tapped Density	Carrs index	Hausners Ratio	Angle of Repose
F1	0.525	0.65	19.23	1.23	23.45
F2	0.524	0.62	15.48	1.18	19.65
F3	0.526	0.64	17.81	1.21	22.35
F4	0.564	0.63	10.47	1.11	20.69
F5	0.540	0.67	19.40	1.24	20.82
F6	0.523	0.64	18.28	1.22	20.72
F7	0.541	0.67	19.25	1.23	20.89
F8	0.532	0.69	22.89	1.29	20.78
F9	0.56	0.68	17.69	1.21	22.62
F10	0.565	0.63	10.31	1.11	20.86

Evaluation of Post Compression Parameters

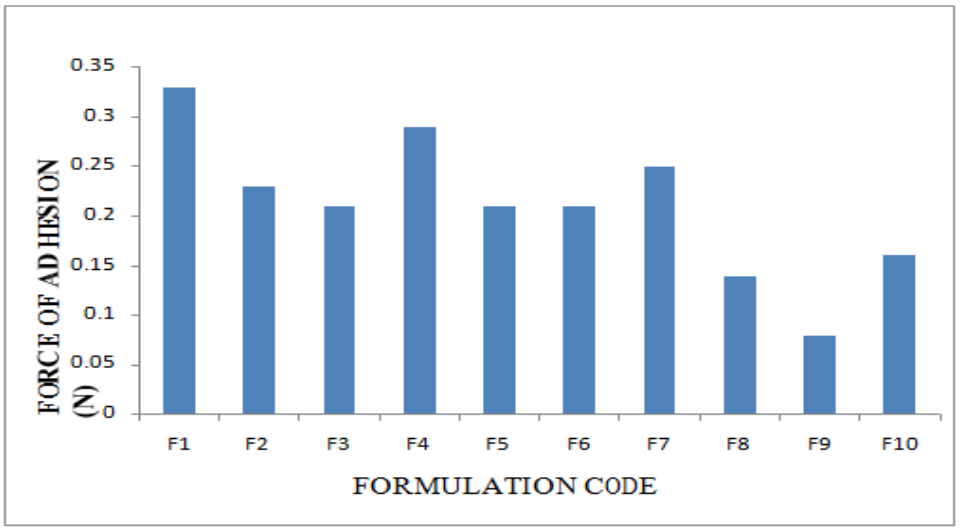
Formulation Code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness (Kg/cm^2)	%Drug content
F1	2.41	200.65	0.16	5.4	98.19
F2	2.45	199.6	0.18	5.5	99.69
F3	2.43	199.46	0.17	5.3	99.77
F4	2.35	198.97	0.25	5.6	100.38
F5	2.54	200.46	0.22	5.3	99.38
F6	2.60	201.6	0.3	6.0	96.5
F7	2.63	199.76	0.48	5.6	99.49
F8	2.72	200.82	0.25	5.5	98.17
F9	2.46	199.60	0.84	5.0	99.38
F10	2.42	199.2	0.23	5.2	98.23

% Swelling Index Profile

	PERCENTAGE (%) SWELLING INDEX				
Formulation code	0.5 hour	1 hour	2 hour	4 hour	6 hour
F1	50.01±0.098	90.71±1.10	90.71±1.10	260±0.78	275.00±1.89
F2	42.12±0.084	77.04±1.51	170.96±1.99	200±2.12	220.05±2.22
F3	36.98±1.01	65.14±1.33	135.96±1.33	175.59±1.12	180.07±1.11
F4	46.14±0.088	82.96±0.052	185.58±1.01	225.54±1.23	250.20±1.99
F5	338.36±0.99	72.16±1.05	162.04±1.21	193.66±1.34	213.16±2.01
F6	34.31±0.65	59.53±0.78	130.42±1.57	171.33±0.95	177.00±0.00
F7	42.61±0.95	77.96±1.01	179.0±0.58	217.18±1.04	240.01±1.11
F8	55.66±1.16	100.56±1.47	219.84±1.99	267.53±2.01	280.00±1.66
F9	60.12±0.69	110.03±0.95	225.17±0.49	283.19±1.41	295.00±1.59
F10	57.34±0.28	105.16±0.95	221.08±0.27	277.50±2.26	289.00±0.00

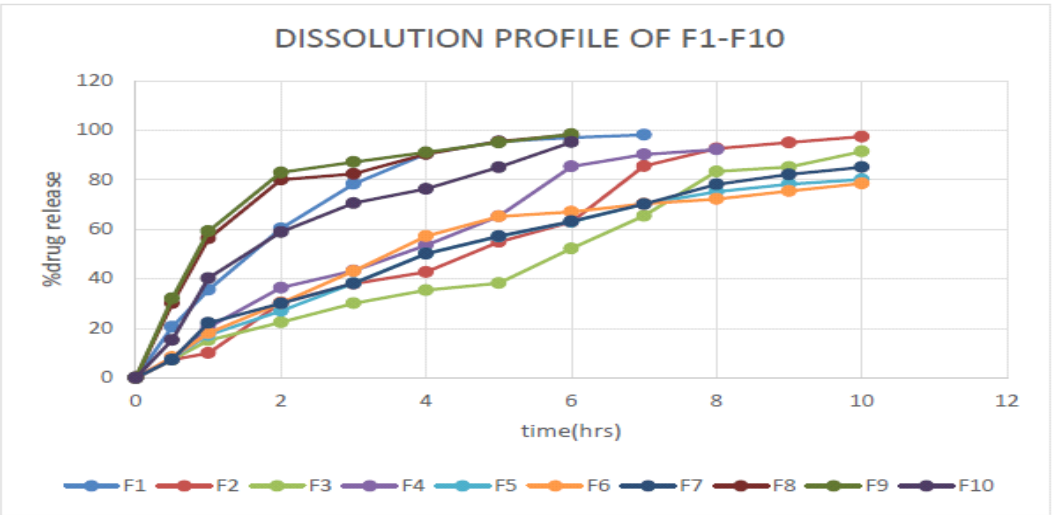
Evaluation of Force Adhesion

FORMULATION CODE	FORCE OF ADHESION (N)
F1	0.33
F2	0.23
F3	0.21
F4	0.29
F5	0.21
F6	0.21
F7	0.25
F8	0.14
F9	0.08
F10	0.16



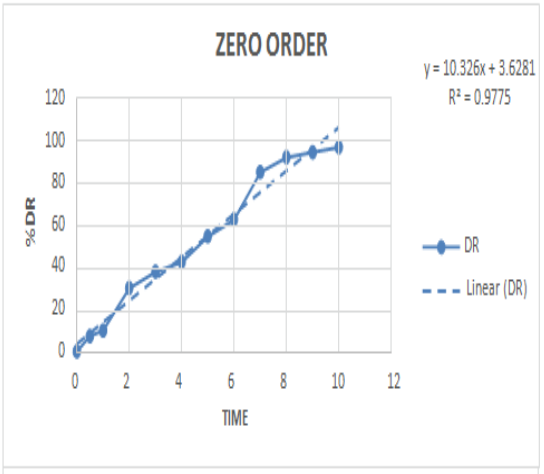
In Vitro Cumulative Percentage Drug Release Data

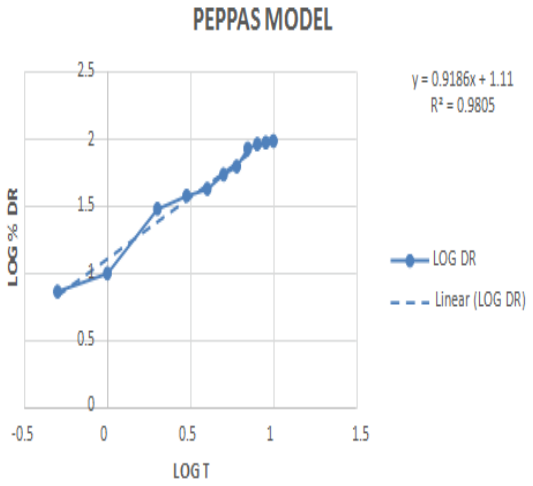
Time(hr)	% drug release									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
0.5	20.61	7.32	7.34	7.56	8.11	8.33	7.35	30.12	32.10	15.29
1	35.56	10.01	15.14	20.33	17.26	18.09	22.16	56.23	59.24	40.23
2	60.29	30.27	22.41	36.41	27.02	30.18	30.05	80.01	82.92	58.86
3	78.31	37.99	30.11	43.26	38.17	43.11	38.17	82.34	87.17	70.58
4	90.53	42.73	35.38	53.56	50.14	57.24	50.12	90.37	91.06	76.28
5	95.40	54.86	38.22	65.26	57.05	65.17	57.21	95.40	95.03	85.04
6	97.06	62.91	52.25	85.38	63.05	67.05	63.20	98.19	98.33	95.18
7	98.15	85.53	65.40	90.21	70.22	70.27	70.18	-	-	-
8	-	92.61	83.35	92.22	75.15	72.18	78.13	-	-	-
9	-	95.00	85.13	-	78.21	75.42	82.15	-	-	-
10	-	97.40	91.40	-	80.14	78.49	85.05	-	-	-

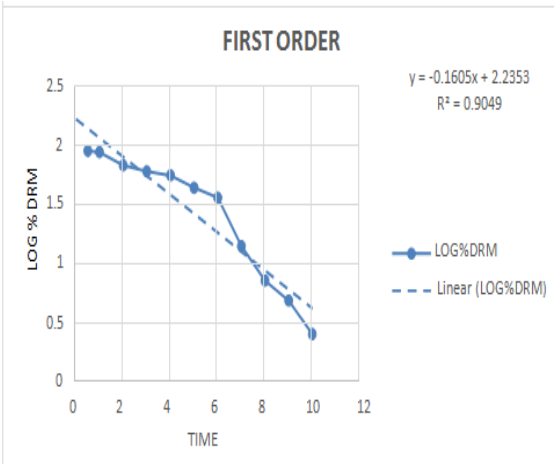


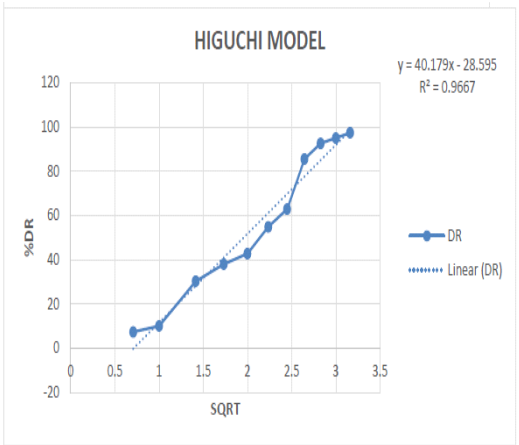
Kinetic Data Analysis of Optimized Formulation (F2)

Formulation code	Mathematical models (Kinetics)				
	Zero order	First order	Higuchi	Peppas	
F2	r^2	r^2	r^2	r^2	'n' value
	0.9775	0.9049	0.9667	0.9805	1.11









CONCLUSION

The main objective of the present study was to formulate and evaluate the controlled release buccal tablets of Naratriptan Hydrochloride. Carbopol, HPMC K4M, HPMC,K15M and NaCMC were selected as buccoadhesive polymers on the basis of their matrix forming properties and mucoadhesiveness .The prepared tablets were evaluated for various parameters such as compatibility studies, drug content, weight variation ,hardness, thickness, friability, swelling studies, microenvironment pH, *in vitro* drug release studies, *in vitro* mucoadhesion strength and Release rate kinetics. From the FT-IR spectra it was observed that similar characteristic peaks appear with minor differences (within limit) for the drug and its formulations. Hence it may be concluded that there was no chemical interaction between the drug and excipients used. *In vitro* drug release studies revealed that F2 formulation shows 97% drug release in 10 Hrs. Kinetic data of optimized formulation (F2) reveals that it follows first order kinetics and non fickanian diffusion & follows super case 2 transport(n>1).

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