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Formulation and evaluation of mucoadhesive buccal tablets of solifenacin

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ABSTRACT

Drug delivery via buccal route, using bioadhesive dosage forms offers such a novel route of drug administration. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route. The mucosal lining of oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has high patient acceptability compared to other non-oral routes of drug administration. In the present study, an attempt was made to design and evaluate mucoadhesive buccal tablets of solifenacin. Different formulations of solifenacin having polymers at different concentrations were prepared by direct compression method. Drug and polymer interactions were investigated by Fourier Transform Infrared (FTIR) and no interactions were detected with the used polymers. solifenacin pure drug was evaluated for preformulation parameters. Among all formulations F2 and F8 were optimized with drug release 98.6% and 99.6% respectively. But mucoadhesion time for F8 was less than F2 (<8hrs).hence F2 was considered as best formulation. Among nine formulations, formulation F2 containing HPMC KM4 (10%) exhibits in-vitro drug release of 98.6% in 8 hrs. All the formulations were subjected to post compression parameters and showed uniformity within limits. The optimized mucoadhesive buccal tablets were evaluated for weight variation, hardness, thickness, friability and drug content and were within specified limits. F2 was optimized based on sustained drug release at 98.6% in 8 hrs. The optimized buccoadhesive formulation followed zero-order kinetics and non-fickian release mechanism. Stability studies as per ICH guidelines showed that there were no significant changes in the drug content.

Keywords: Mucoadhesive , Sustained release , Buccal tablets, Solifenacin.

INTRODUCTION

In recent years the interest in novel route of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via buccal route, using bioadhesive dosage forms offers such a novel route of drug administration. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectables as carriers. Amongst various routes of drug delivery oral route is

perhaps the most preferred to the patient and the clinician alike. However this route presents some problems for a few drugs. The enzymes in the GI fluids, GIT-pH conditions and the enzymes bound to GIT membranes are a few factors responsible for the bioavailability problems. The blood that drains the GIT carries the drug directly to the liver leading to first-pass metabolism resulting in poor bioavailability. The inherent problems associated with the drug in some cases can be solved by modifying the formulation or by changing the routes of administration. Parenteral, mucosal and transdermal routes circumvent hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs[1]. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route[2]. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity. The mucosal lining of oral cavity offers some distinct advantages. It is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has high patient acceptability compared to other non-oral routes of drug administration[3].

BUCCAL DRUG DELIVERY SYSTEM

Oral Mucosal Sites

Within the oral mucosal cavity, delivery of drugs is classified into three categories

1. Sublingual delivery: is the administration of the drug via the sublingual mucosa to the systemic circulation.
2. Buccal delivery: is the administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation.
3. Local delivery: for the treatment of conditions of the oral cavity, principally ulcers, fungal conditions and periodontal disease.

Drug delivery via buccal route

Buccal delivery refers to drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingiva. Various advantages and other aspects of this route are elucidated of the following.

Advantages of mucoadhesive buccal drug delivery

Drug administration via the oral mucosa offers several advantages.

a. Flexibility in physical state, shape, size and surface.
b. Ease of administration and termination of therapy in emergency.
c. Permits localization of the drug for a prolonged period of time.
d. Administered to unconscious and trauma patients.

Disadvantages of buccal drug delivery system

Drug administration via buccal mucosa has certain limitations,

a) Drugs which irritate the oral mucosa have a bitter or unpleasant taste or odor cannot be administered by this route.
b) Drugs, which are unstable at buccal pH, cannot be administered by this route.
c) Only drugs with small dose requirements can be administered.
d) Surface area available for absorption is less[4].

AIM & OBJECTIVE

The aim of the present investigation is to design, formulate and evaluate bucco adhesive tablets of Solifenacin.

The objectives of the present work are as follows:

1. HPMC K4M and Sodium CMC and Xanthan gum will be selected as polymers for the preparation of muco adhesive buccal tablets.
2. Preformulation study will be done by FTIR spectroscopic method for drug polymer interaction.
3. To evaluate the prepared muco adhesive buccal tablets for various tablet evaluation parameters hardness, thickness, weight variation, friability, drug content uniformity, surface pH, swelling index, *in vitro* drug release study and Kinetic studies.

PREPARATION OF THE STANDARD CALIBRATION CURVES OF SOLIFENACIN

Standard calibration linearity curve of solifenacin in pH 6.8 Phosphate buffer

Solefinacin (100mg) was dissolved in small quantity of phosphate buffer and volume was made up to 100 ml in volumetric flask using Phosphate buffer pH 6.8. From this stock solution 10 ml was withdrawn and is diluted to 100ml in volumetric flask which gives the concentration of 100µg/ml. From this stock solution aliquots were withdrawn in volumetric flask to give

concentrations 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml. Absorbance of each solution was measured at 220 nm using Shimadzu UV- 1700 UV-Vis double beam spectrophotometer with Phosphate buffer pH 6.8 as a reference standard.

PRE FORMULATION STUDIES

Pre-formulation can be defined as an investigation of physical and chemical properties of a drug substance alone. The overall objective of pre-formulation studies is to generate information useful to the formulator in developing stable dosage forms.

COMPATIBILITY STUDIES USING FTIR

To investigate any possible interactions between the drug and excipients used, the FT-IR spectra of pure Solefinacin and its physical mixture with different excipients were carried out using thermo Electron Corporation (Agilent Technologies Cary 630 FTIR) spectrophotometer. The samples were prepared as KBr (potassium bromide) disks compressed under a pressure of 150 lbs. The wave number range is selected in between 500 - 3500cm^{-1}.

Method

1 mg of drug is mixed with the 100 mg of Spectroscopic grade of KBr and triturated for uniform mixing. The thin and transparent pellet is prepared by applying 150 lbs pressure. The prepared pellet is exposed to IR beam and spectra are recorded by using FT-IR.

FORMULATION DEVELOPMENT OF MUCOADHESIVE BUCCAL TABLETS OF SOLEFINACIN

Preparation by direct compression method

Direct compression method was employed to prepare buccal tablets of Solefinacin using HPMC K4M, Sodium CMC, Xanthan gum and as polymers. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula and were passed through #60 to get uniform particle size. The drug and all the ingredients except lubricants were taken on a butter paper with the help of a stainless steel spatula and the ingredients were mixed in the order of ascending weights and blended for 10 min in a porcelain mortar. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend of each formulation was compressed by using 8mm punch on a single stroke tablet punching machine[79]. The compression of tablets direct compression procedure involves 2 consecutive steps.

1. The mixture (150 mg) was compressed using an 8-mm, round-shaped flat punch in a single-stroke, multi-station tablet machine.
2. Next, the upper punch was raised and the backing layer of EC (50 mg) was then added on the above compact and the 2 layers were compressed to form buccal tablets. The buccal tablets were prepared using compositions as given in the following table: 3.5.a.

Composition of Mucoadhesive Tablets of Solefinacin

Table 3.5.a: Formulation table of solifenacin buccoadhesive tablets

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Solefinacin	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
HPMC K4M	5%	10%	15%	--	---	---	---	--	--
Sodium CMC	---	---	---	5%	10%	15%	---	---	---
Xanthum gum	---	---	---	---	---	---	5%	10%	15%
Aspartame	1	1	1	1	1	1	1	1	1
Mannitol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	4	4	4	4	4	4	4	4	4
Ethyl Cellulose	50	50	50	50	50	50	50	50	50

Total wt	200	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSION

Analytical method development

DETERMINATION OF λmax

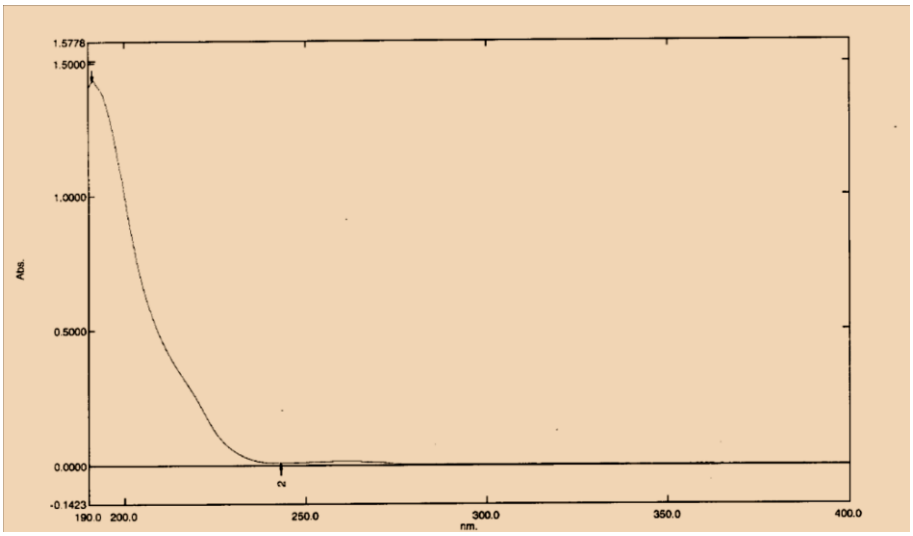

Fig .4.1.1.a Graph indicating λmax of solifenacin

Discussion

From the above graph, the maximum absorbance (λmax) peak was observed at 220nm

Standard Graph of solifenacin

The standard graph of Solifenacin has shown good linearity with R^2 values 0.9989 in pH 6.8 buffer, which suggests that it obeys the "Beer-Lambert's law".

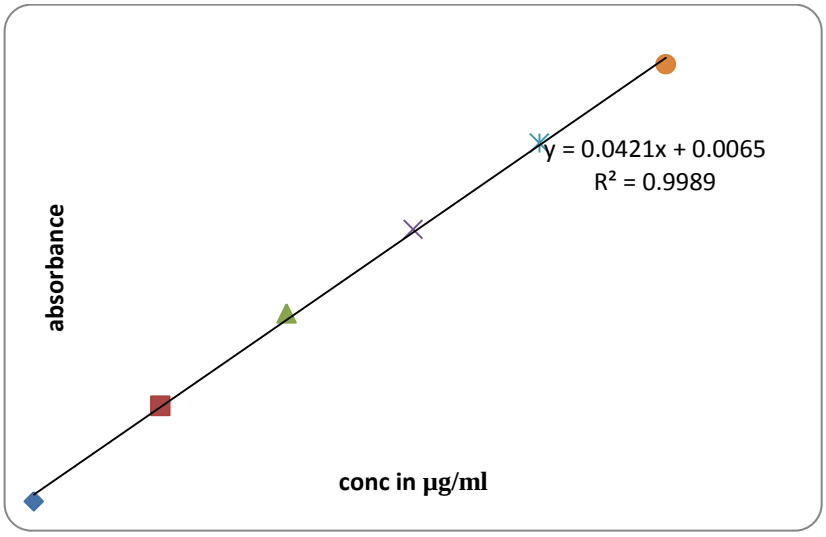

Figure 4.1.2.a. Standard graph of Solefinacin in 6.8 pH buffer

COMPATIBILITY STUDIES

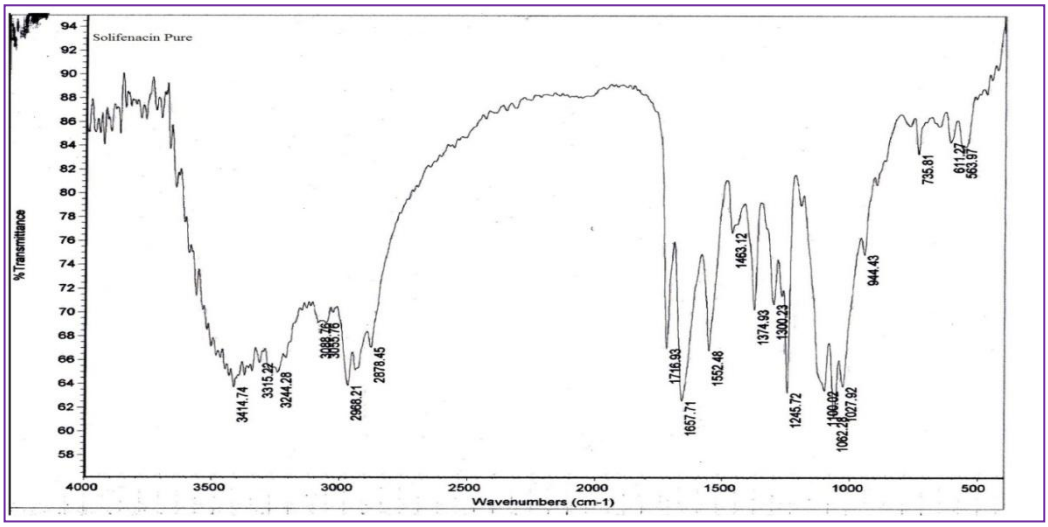

Fig no: 4.2.a FTIR Spectra of Solefinacin Pure drug

Fig no: 4.2.b. FTIR Spectra of solifenacin optimized

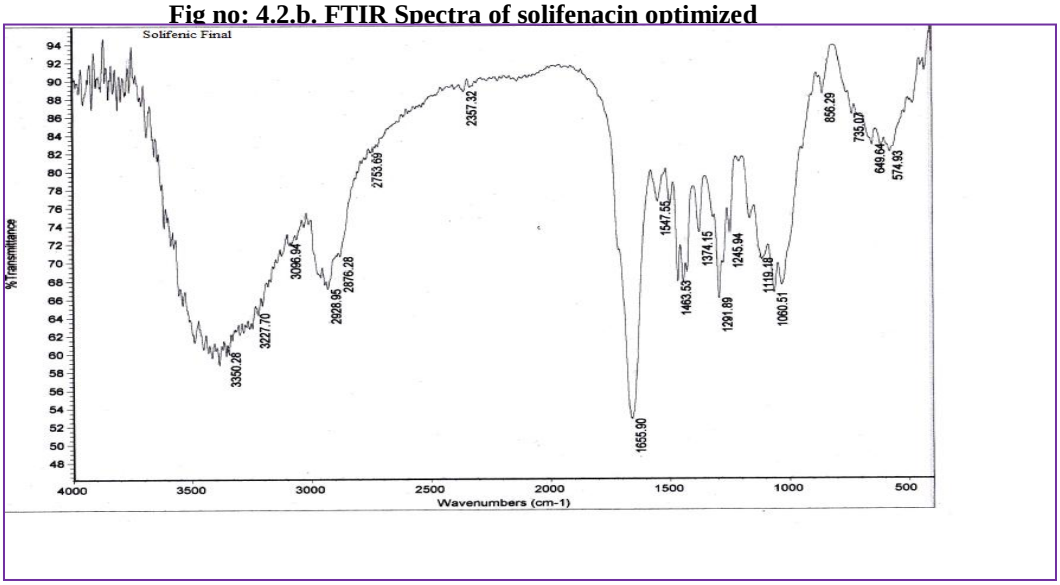

Fig no: 4.2.b. FTIR Spectra of solifenacin optimized

Inference

There is no significant change in the shift of major peaks of drug in the above graphs, hence there were no drug and excipient interactions found.

Evaluation of precompression parameters

The blends for Bucoadhesive tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausners ratio. Angle of repose was less than 30° and Carr's index values were less than 15 for the blend of all the batches indicating excellent to good flowability and compressibility. Hausner's ratio was less than 1.11 for all the batches indicating excellent flow properties.

Table: 4.3.a. Physical Properties of Pre-compression Blend

Formulatios	Angle of repose	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio	Flow property
F1	30.25	0.342	0.386	11.39896	1.128655	Good
F2	30.43	0.358	0.412	13.1068	1.150838	Good
F3	22.87	0.326	0.334	2.39521	1.02454	Excellent
F4	22.45	0.334	0.348	4.022989	1.041916	Excellent
F5	24.37	0.442	0.499	11.42285	1.128959	Excellent
F6	29.41	0.321	0.334	3.892216	1.040498	Good
F7	22.88	0.326	0.333	2.39531	1.02464	Excellent
F8	30.13	0.360	0.414	13.1071	1.1509	Good
F9	24.30	0.447	0.500	11.42687	1.1311	Excellent

Discussion

From the above pre-compression parameters it was clear evidence that powdered blend has Good flow properties and is suitable for direct compression.

Evaluation of post-compression parameters

Table no 4.4.a: Physical Evaluation of Bucoadhesive Tablets

F.Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)	pH	Mucoadhesion time(hrs)
F1	6.50 ±0.44	2.52±0.17	300.8±1.48	0.36	98.25±1.37	6.4	6
F2	6.60±0.31	2.57±0.25	299.4±0.54	0.39	99.48±0.80	6.6	8
F3	6.72±0.40	2.54±0.80	298.6±0.41	0.43	99.12±2.47	6.5	9
F4	6.86±0.55	2.50±0.20	298.8±1.64	0.12	100.22±0.88	6.6	5
F5	6.34±0.57	2.65±0.66	300.6±1.14	0.54	100.24±1.25	6.5	7
F6	6.49±0.30	2.63±0.25	298.2±0.83	0.58	99.53±1.87	6.3	9
F7	6.51±0.32	2.57±0.81	298.7±0.46	0.36	99.50±0.60	6.5	6
F8	6.53±0.35	2.58±0.80	298.9±0.64	0.39	99.32±0.87	6.4	7
F9	6.52±0.31	2.57±0.82	298.9±0.44	0.43	99.58±0.60	6.6	9

Discussion

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 44.a. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 298.2±0.83 and 300.8±1.48mg. The hardness of the tablets ranged from 6.34±0.57 to 6.86±0.55 kg/cm^2 and the friability values were less than 0.5% indicating that the Bucoadhesive tablets were compact and hard. The thickness of the tablets ranged from 2.52±0.17 to 2.65±0.66 mm. All the formulations satisfied the content of the drug as they contained 98 to 101 % of solefinacin and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Microenvironment pH study

Table:4.4.b. Results of Microenvironment pH study

F CODE	Surface pH
F1	6.4
F2	6.6
F3	6.5
F4	6.6
F5	6.5
F6	6.3
F7	6.5
F8	6.4
F9	6.6

Discussion

The surface pH of all formulations was found to be within ±1 units of neutral pH. The values are tabulated in the table no.4.4.b. Hence these formulations should not cause any irritation in buccal cavity.

Swelling Index

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	20.8	24.6	30.4	14.8	18.3	20.7	20.1	21.3	18.4
15	48.1	51	56.2	30.1	35.3	38.5	46.2	55.2	56.7
30	59.6	63.8	67.5	50.4	54.4	60.6	68.5	76.5	67.9
60	76.45	79.4	85.6	65.8	70.7	74.4	88.3	99.6	85.6

Discussion

The swelling behavior of a buccal adhesive system is an important properties uniform and prolonged release and effective mucoadhesion. The swelling index study indicated that the rate of swelling was directly proportional to Sodium alginate and polymer content. Swelling index was calculated with respect to time. The swelling index gives an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after moisture absorption. The results of present formulation were tabulated in the table no 4.4.c.

Mucoadhesion time

Table : 4.4.d. Effects of polymers on mucoadhesion time

Formulation Code	Mucoadhesion time(hrs)
F1	6
F2	8
F3	9
F4	5
F5	7
F6	9
F7	6
F8	7
F9	9

Discussion

The mucoadhesion time is important to know how long the tablet could able to stick to the buccal mucosa. This adhesion time relates to the release rate of drug. The bioadhesive tablet is important for good mucoadhesion. Bioadhesion characteristics are affected by the type and ratios of bioadhesive polymers the results were tabulated in the table no.4.4.d.

In-vitro drug release study

Table: 4.4.e. comparitive invitro dissolution study of solifenacin buccoadhesive tablets

TIME (HRS)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	17.6	9.8	7.2	21.3	20.6	19.8	21.3	20.6	79.8
2	39.8	17.2	15.0	34.9	30.4	25.1	34.9	30.4	25.1
3	52.31	23.80	20.9	48.6	42.6	33.6	48.6	42.6	33.6
4	70.61	45.6	33.8	52.1	54.1	48.2	52.1	54.1	48.2
5	86.3	60.1	58.0	74.8	68.7	56.1	74.8	68.7	56.1
6	98.2	70.8	65.1	98.5	85.9	68.5	97.3	77.4	68.5
7	----	89.0	79.3		99.6	74.2	-----	85.9	74.2
8	----	98.6	86.7			90.6	-----	99.6	80.6

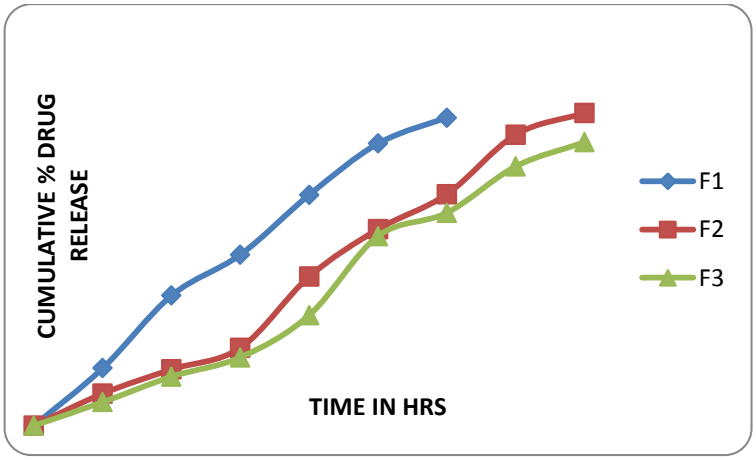

Figure: 4.4.c. *In-Vitro* Drug Release for Formulation F1, F2, F3

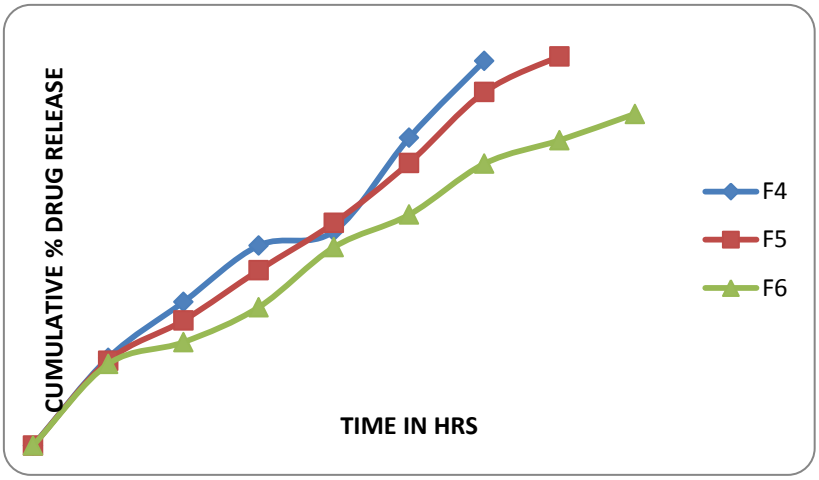

Figure: 4.4.d. *In-Vitro* Drug Release for Formulation F4, F5, F6

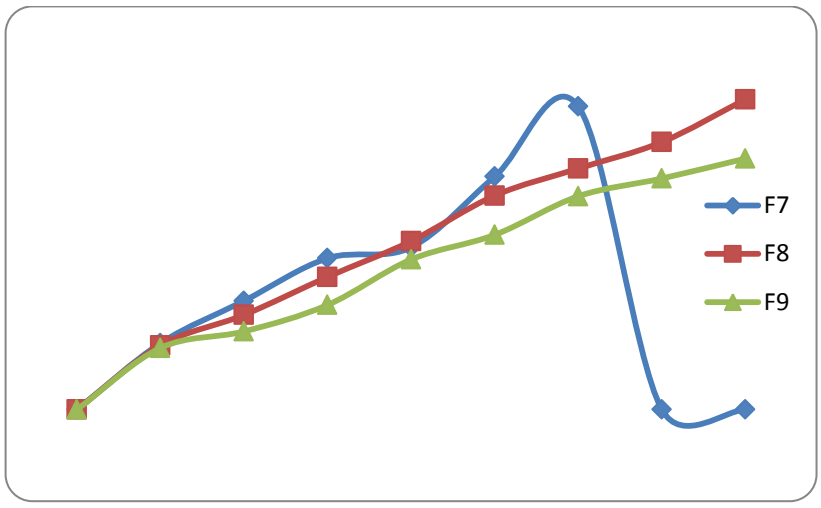

Figure: 4.4.e. *In-Vitro* Drug Release for Formulation F7, F8, F9

Discussion

The In-vitro drug release study has been done for various formulations (F1-F9). The different ratios of polymers were used. The results shown that as the proportion of polymers in the formulation increases, cumulative percent drug released was found to be reduced. Among the nine l batches, formulation F_1, F_4 and F_7 have released 98.2%, 98.5% and 97.2% drug release in 6th hr respectively, F2 and F8 formulations shows drug release of 98.6% and 99.6 respectively. Among all F2 and F8 were optimized based on sustained drug release and highest drug release at 98.6% and 99.6 respectively at 8th hr. But mucoadhesion time for F8 formulation was less than 8 hours so F2 was considered as best formulation.

kinetic analysis of dissolution data

Table: 4.5.b. Drug Release Kinetics for Optimized Formula F2

	ZERO	FIRST ORDER	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	12.725	0.1558	36.232	1.6729
Intercept	5.1333	2.2060	19.878	0.5685
R^2	0.9842	0.8441	0.8587	0.8286

Discussion

In-vitro drug release data of all the buccal tablet formulations was subjected to goodness of fit test by linear regression analysis according to zero order, first order, Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release. From the above data, it can be seen the formulation, F2 have displayed zero order release kinetics ('r^2 value of 0.9842).

From Peppas data, it is evident that the drug is released by non-Fickian diffusion mechanism. This is because as the proportion of polymers in the matrix increased there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer. Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional path lengths.

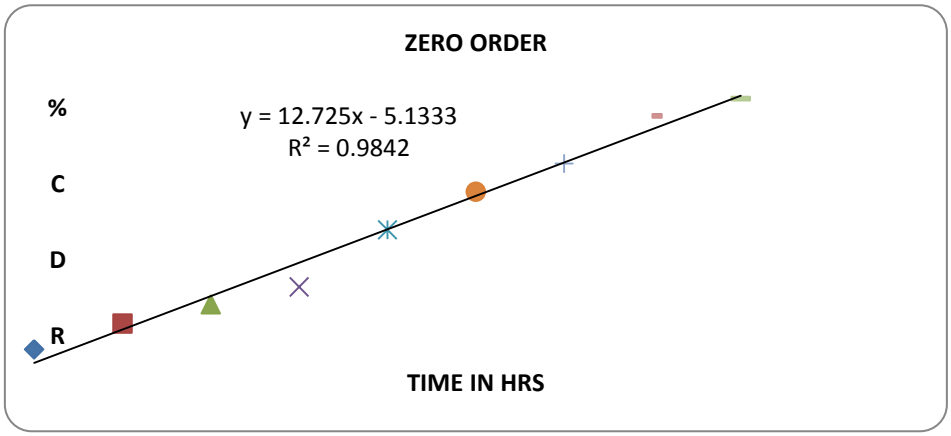

Figure : 4.5.a. Zero order kinetic graph for formula F2.

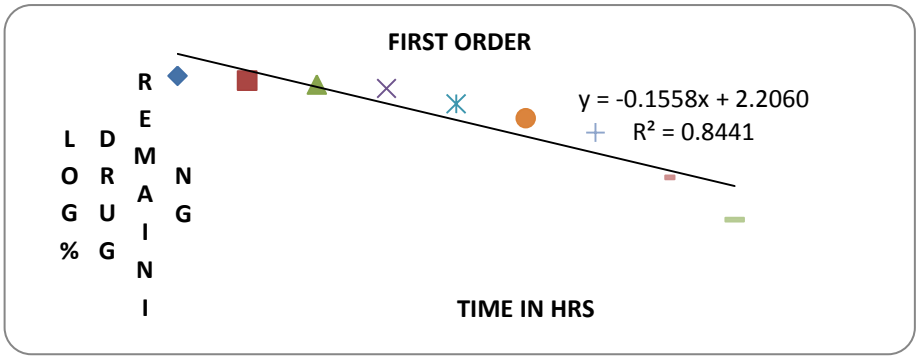

Figure : 4.5.b. First Order Kinetic Graph for Formula F2.

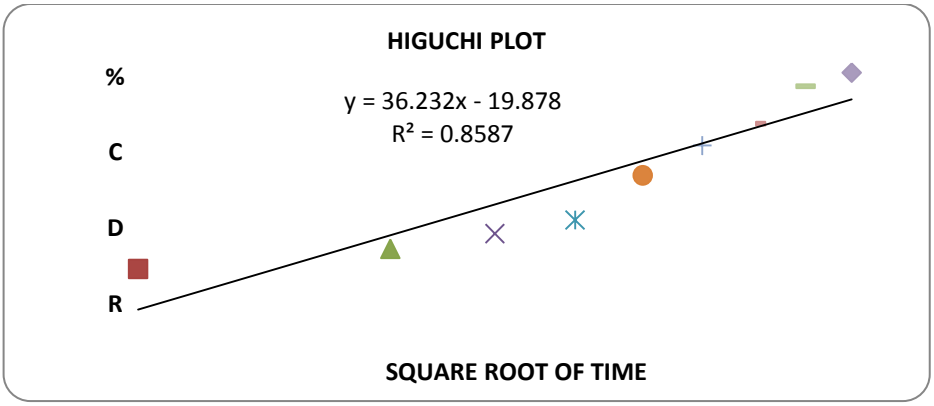

Figure: 4.5.c. Higuchi kinetic graph for formula F2.

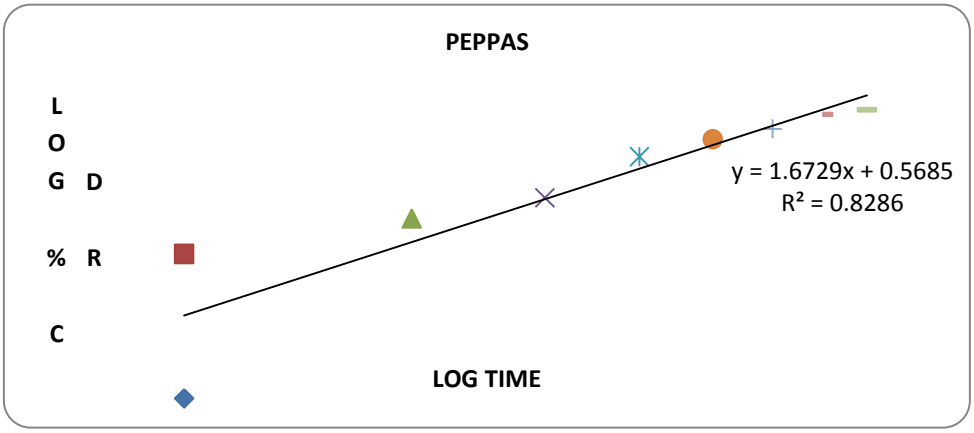

Figure: 4.5.d. Peppas kinetic graph for formula for F2.

STABILITY STUDIES

Table: 4.6.a. Stability studies of Solefinacin bucoadhesive tablet (F2) at room temperature

Time	Colour	Assay		Cumulative % drug release		Surface pH	
		25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH
First day	White	99.48	99.48	97.6	98.6	6.6	6.6
30 days	White	99.40	99.30	99.1	97.9	6.6	6.6
60 days	White	99.31	99.2	97.2	97.1	6.6	6.6
90 days	White	98.5	98.0	98	97.8	6.6	6.6

Discussion

Results from stability studies indicate that the formulated solefinacin bucoadhesive tablet are stable for a period of 3 months under 2 different conditions at 25±2^{0}c and 65±5%RH and 40±2^{0}c and 75±5%RH. There were no remarkable changes observed during the period of storage.

SUMMARY AND CONCLUSION

The aim of the study was to explore the drug delivery system of solifenacin for treatment of Overactive Bladder. Among all formulations F2 and F8 were optimized with drug release 98.6% and 99.6% respectively. But mucoadhesion time for F8 was less

than F2 (<8hrs).hence F2 was considered as best formulation. A satisfactory attempt was made to develop buccal drug delivery system of solifenacin and evaluate it. From the reproducibility results obtained by the executed experiments it can be concluded that: Influence of the formulation variables on hardness, drug uniformity, mucoadhesive strength, drug release is evident. Formulation F2 has successfully sustained the release of Solefinacin in buccal cavity, with great mucoadhesive strength. The formulation F2 showed good pre compression and post compression parameters and follows zero order and higuchi kinetics. After the Stability studies the optimized formulation doesnt show any remarkable change in drug release. Based on the all experiment results it can be concluded that Hydroxy propyl methyl cellulose containing buccal formulation would be the suitable candidate for mucoadhesive drug delivery of solifenacin with sustained release properties.

CONCLUSION

It can be concluded that solifenacin can certainly be administered through the oral mucosa. The designed buccoadhesive tablets can overcome the disadvantage of extensive first pass effect and low oral bioavailability of solifenacin. This increased and predictable availability of solifenacin from designed formulation may result in substantial dose reduction of the dosage form when the drug is administered through oral mucosa so that it will be economical to the patient. Further work is recommended to support its efficacy claims by pharmacokinetic and pharmacodynamic studies in human beings.

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