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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLET OF IRBESARTAN

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ABSTRACT

The aim of present investigation was formulation and evaluation of mucoadhesive buccal tablet of Irbesartan to study the effect of different polymers on release profile of drug for prolonged release. In this study mucoadhesive buccal tablet were prepared by direct compression method. Various rheological characteristics of the powder bed like bulk density, compressibility index, and angle of repose were evaluated and studied. Mucoadhesive buccal tablets were compressed on a 8 station mini press using 8 mm flat faced punches and were all assessed for weight variation, hardness, thickness, percent swelling index, mucoadhesive strength and in vitro release of the drug by using USP TDT 08L dissolution testing apparatus method II using a paddle at 50 rpm. Data was optimized by using 3^2 full factorial design by using software named as design expert and with the help of kinetic study. The stability studies showed that there is no decrease in the drug content of all formulations for the period of 2months.

KEYWORD: Buccal tablet, Irbesartan, Xanthan gum, Carbopol 934.

INTRODUCTION

Among all dosage forms, oral route is more preferred to patient. The per oral route of administration of drug has disadvantages of hepatic first pass metabolism and enzymatic degradation within the GI tract, that eliminate oral administration of certain classes of drugs like peptides and proteins. Trans-mucosal routes of drug delivery offer distinct advantages over per oral administration for systemic drug delivery. The buccal mucosa lines the inner cheek, and Buccal formulation are placed in the mouth between the upper gingivae (gums) andcheek to treat local and systemic conditions. The Buccal route provides one of the

potential routes for typically large, hydrophilicand unstable proteins, oligonucleotides and polysaccharides, as wellas conventional small drug molecules. The oral cavity has been usedas a site for local and systemic drug delivery.[2]

The buccal region of oral cavity is an attractive site for the delivery of drugs owing to the ease of the administration. Buccal drug delivery involves the administration of desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and trans-mucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation.[3]

Mucoadhesive drug delivery systems[4]

These may be defined as drug delivery systems which utilize the property of bio-adhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body forextended periods of time. These drug delivery systems are adhered to the mucous layer that covers a mucosal tissue.

The term mucoadhesion can be considered to refer to a sub group of bio-adhesion and, more specifically, to the case when the formulation interacts with the mucous layer that covers a mucosal tissue. The mucosal layer lines a number of regions of the body including gastrointestinal tract, urogenital tract, airway, ear, nose and eye.

Hypertension is also referred as high blood pressure. It is condition in which arteries have persistently had high blood pressure.Every time human heart beat, pump blood to whole body through the arteries. The main goal of treatment of hypertension is tolower blood pressure less than 140/90.This can be possible by giving ant hypertensionmedication.Thismedication can be given by various routes.In recent years,delivery of therapeutic agents through various trans-mucosalroutes has gained significant attention for the local and systemic delivery of therapeutic peptides and other drugs that are subjected to first pass metabolism or unstable within the rest of the gastrointestinal tract. Absorption of therapeutic agentfrom the oral cavityprovides a direct entry of such agent into systemic circulation, thereby avoiding the first pass hepatic metabolism and gastrointestinal degradation. However buccal route of drug delivery has received much more attention because of its unique advantages over oral trans mucosal route such as easy accessibility, patient compliance rapid cellular recovery following

local stress and ability to with stand environmental extreme like change sin pH, temperature etc. Irbesartan, a nonpeptide tetrazole derivative, is an angiotensin receptor blocker used mainly for the treatment of hypertension. Irbesartan is a antihypertensive drug that has low solubility, so buccal route is excellent for the systemic delivery, there by rendering great bioavailability by using different mucoadhesive polymer such as xanthan gum and carbopol 934.

MATERIALS AND METHODS

Material

Irbesartan was provided as gift sample from mylan laboratories sinner. Xanthan gum, Carbopol 934, Mannitol, Magnesium stearate, Talc, Lactose.

Ingredient used in formulation

Table No.1: Ingredient used in formulation.

Sr.No	Name of ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	Irbesartan	75	75	75	75	75	75	75	75	75
2	Xanthan gum	30	30	30	35	35	35	40	40	40
3	Carbopol 934	20	25	30	20	25	30	20	25	30
4	Mannitol	10	10	10	10	10	10	10	10	10
5	Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
6	Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
7	Lactose	110	105	100	105	100	95	100	95	160

Preformulation studies[5]

Preformulation studies on the obtained sample of drug for identification and compatibility studies were performed.

Characterization of the Drug

Organoleptic properties

The sample of Irbesartan was studied for organoleptic properties such as colour, odour and appearance.

Melting point

The melting points of Irbesartan were determined by melting point apparatus. Observed value was compared with the reported value.

Drug excipient compatibility study[6]

Drug excipient compatibility was performed by liquid Fourier Transform infrared. It was performed by mixing drug with excipient in equal proportion and then IR spectrum was noted for mixture using NaCl cell. Small amount of the mixture was placed on the sample cell, the cell was then filtered in sample holder, spectra were scanned over a frequency range 4000-400cm^{-1} with FTIR instrument and the spectral analysis were done.

Preparation of Mucoadhesive buccal tablet (By Direct compression method)

1. Weighing of ingredients
2. Milling of drug and Excipients
3. Mixing of drug and Excipients
4. Tablet compression

Evaluation of Mucoadhesive Buccal Tablets

Hardness test[7, 8]

Hardness test was conducted for three tablets from each batch and average values were calculated.

Weight variation test

Weight variation test was performed for ten tablets from each batch using an electronic balance and average values were calculated.

Thickness

The thicknesses of buccal tablets were determined using digital micrometer (Digital Caliper, Aerospace, India). Ten individual tablets from each batch were used and the average thickness was calculated.

Friability test[5]

Friability of twenty randomly selected tablets from each formulation were determined by using the Roche type friabilator.

In Vitro drug release for Irbesartan tablet[5]

The drug release profile was studied using USP dissolution testing apparatus method II using a paddle at 50 rpm. 500ml dissolution fluid, pH 6.8 phosphate buffer, was used and a temperature of 37 ±0.5°C was maintained. 5ml aliquots at 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12 h respectively were pipette out and the same volume was replaced with pH

6.8phosphate buffer. Absorbance was measured at λmax244nm and from which percentage of Irbesartan was calculated using calibration curve.

In vitro mucoadhesive strength[5]

In vitromucoadhesive strength of tablet was measured with goat Oral mucosa, using a modified physical balance. On one side of the balance, a rubber closure tied with thread was attached and on other side empty polythene bag was attached. Goat oral mucosa was obtained from a local slaughter house and stored in a phosphate buffer pH 6.8 upon collection. The experiments were performed within 3 h of collection of oral mucosa which has been separated from sheep stomach. The goat stomach mucosa was fixed to the opening of the glass vial with thread and then placed in a beaker, well packed. Phosphate buffer pH 6.8 was added into the beaker up to the upper surface of the buccal mucosa to maintained oral mucosal viability during the experiment. The tablet was sticked to the rubber closure with cyanoacrylate glue, then the beaker was raised slowly until contact between goat oral mucosa and tablet was established. A preload of 5 gm was placed on the clamp for 5 min (preload time) to establish adhesion bonding between tablet and goat oral mucosa. The preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp and water was then added in the polythene bag by pipette in drop-wise manner, at a constant rate. The weight of water required to detach tablet from stomach mucosa was noted as in vitro mucoadhesive strength, and these experiments were repeated with fresh mucosa in an identical manner. The modified physical balance for *in vitro* mucoadhesive strength determination consisting of polythene bag (on one side) and rubber closure for attachment of tablet (on other side).

Swelling Study[9]

Buccal tablet are weighed individually (W1) and placed separately in petri dishes containing phosphate buffer pH 6.8 for 8 hrs at regular interval of time (1, 2, 4, 6 and 8 hr) and The tablet are removed from the petri dishes and excess surface water is removed using filter paper. The tablet are weighed (W2) and swelling index (SI) is calculated as follows

$$SI = (W2-W1)/W1$$

Drug content uniformity[10, 11]

Ten tablets were accurately weighed and powder crushed in a glass pestle mortar. An accurately weighed amount equivalent to 5 mg of pure drug was taken, and the assay was performed UV spectrophotometer.

Optimization by 3^2 factorial designs[12]

Optimization is the key parameter in the development of any product factorial designs used to evaluate two or more factors simultaneously interactions can be determined in the factorial design. A study in which two factors and three levels are involved is called as 3^2 factorial design. For the present work 3^2 factorial design selected and 2 factors were evaluated at three possible levels by formulating all possible 9 formulation combination which are shown in table 3.

Formulation code assigned to the batches

$X_{1=}$ Xanthan gum

$X_{2=}$ Carbopol 934

Table 2: Design summary.

Factor	Name	Unit	Type	Min.	Max.	-1 actual	+1 actual	Mean	Std. Dev.
A	Xanthan gum	%	Numeric	30	40	-1.00	1.00	35	10.32
B	Carbopol934	%	Numeric	20	30	-1.00	1.00	25	11.25

Xanthan gum and carbopol 934 are independent variable used in the formulation. They are mucoadhesive polymer to increase the residence time of formulation in oral cavity and also show their effect on mucoadhesive strength, swelling inedx, in vitro drug release.

Independent variable

$X_{1=}$ Xanthan gum

$X_{2=}$ Carbopol 934

Dependent variable

Y1= Drug release

Y2= Swelling index

Y3= Mucoadhesive strength

RESULT AND DISCUSSION

Preformulation study

Organoleptic Properties

The organoleptic properties of Irbesartan such as appearance crystalline, white colour odorless powder complying with the description that is found in the literature.

Melting Point

The melting point of Irbesartan matches with the values found in literature 180-181^{0}c Melting point of Irbesartan was observed 178-182^{0}c performed in triplicate.

Solubility

Solubility of Irbesartan was checked in various solvents soluble in methanol, choloform, sparingly soluble in ethanol, insoluble in water.

COMPATIBILITY STUDY

Infra-red spectrum

The FTIR spectrum of pure Irbesartan showed peaks in wave numbers (cm-1) which corresponds to the functional group present in the structure of the drug. FT-IR spectrum of Irbesartan is shown in figure. And interpretation of FT-IR spectrum is given in Table. From the below observation we conclude that the given sample was Irbesartan.

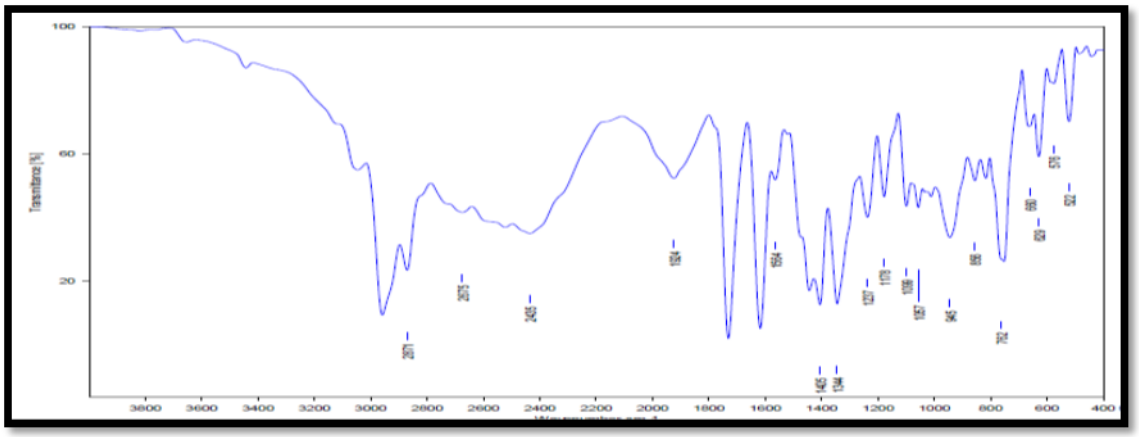

Figure 1: FT-IR Spectrum of Irbesartan.

Fourier transform infra-red spectroscopy (FTIR)

Infra-red spectra of drug and polymers showed matching peck with the drug spectra. The data obtained from the IR spectra showed no evidence of the interaction between the drug and the polymer studies. All the major characteristics peckes of the drug were present in the drug polymer combination spectra which indicate compatibility of drug with the polymers.

Drug + xanthan gum

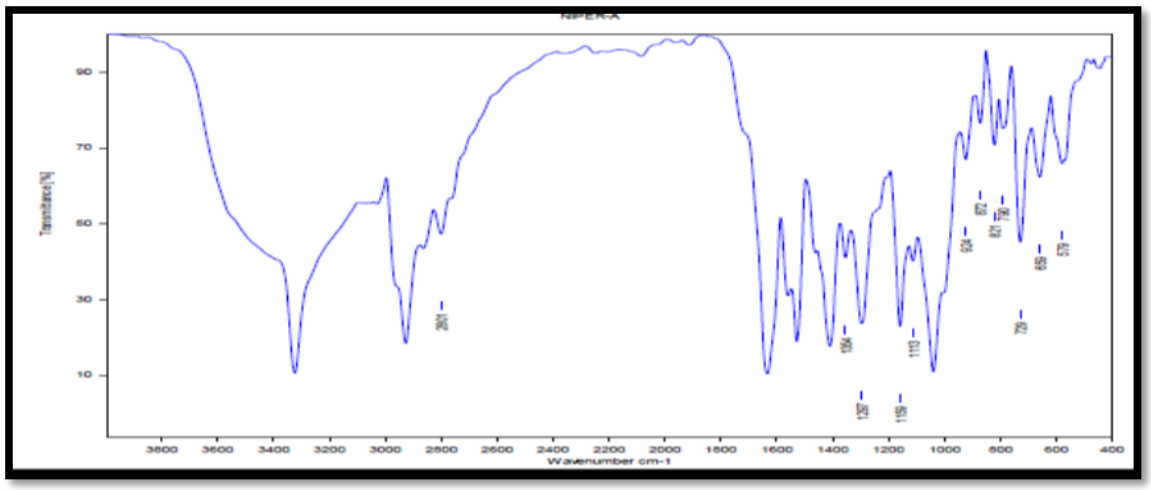

Figure 2: FTIR Spectrum of Drug + xanthan gum.

Drug + Carbopol 934

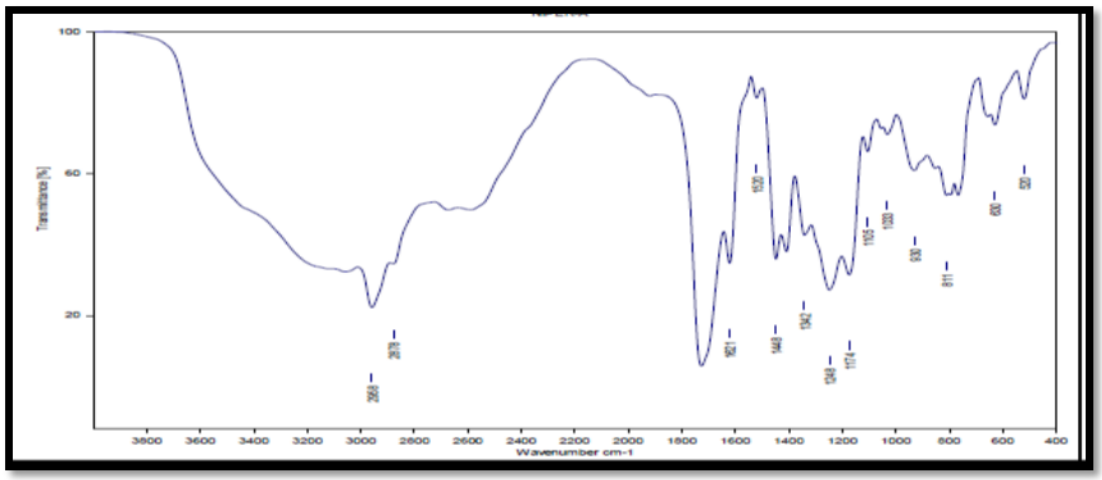

Figure 3: FTIR Spectrum of Drug + Carbopol Mixture.

Pre-compression parameters

Table 3: Pre compression parameters for Mucoadhesive buccal tablet.

Formulation code	Angle of repose(^{0}) Mean ±S.D*	Bulk density(g/ml) Mean ±S.D*	Tapped density(g/ml) Mean ±S.D*	Carr's index (%) Mean ±S.D*	Hausner's ratio Mean ±S.D*
F_1	25.90 ± 0.75	0.3125 ± 0.001	0.3428 ± 0.23	9.12 ±0.56	1.09 ± 0.40
F_2	25.56 ± 0.52	0.3869 ± 0.001	0.4238 ± 0.50	8.32 ±0.47	1.09 ±0.56
F_3	27.34 ± 0.72	0.3721 ± 0.002	0.4524 ± 0.59	10.1 ±0.56	1.13 ± 0.72
F_4	28.37 ± 0.83	0.3968 ± 0.004	0.4596 ± 0.70	8.16 ±0.68	1.06 ± 0.64
F_5	27.43 ± 0.25	0.3906 ± 0.001	0.4350 ± 0.40	11.9 ±0.72	1.2 ± 0.70
F_6	29.42 ± 0.70	0.3980 ± 0.001	0.4612 ± 0.55	14.05±0.62	1.11 ± 0.64
F_7	28.12 ± 0.62	0.3947 ± 0.005	0.4328 ± 0.84	19.02 ±0.74	1.14 ± 0.65

F_8	26.80 ± 0.85	0.3850 ± 0.004	0.4417 ± 0.45	13.32 ±0.73	1.18 ± 0.74
F_9	27.52 ± 0.44	0.3973 ± 0.002	0.4125 ± 0.74	13.56 ±0.67	1.17 ± 0.45

***n=6**

Post compression parameters

Table 4: Post compression parameters for Mucoadhesive buccal tablet.

Formulation code	Hardness (Kg/cm2)*	Thickness (mm)*	Friability (%)*	Weight variation (mg)*	pH*	Drug content (%)*
F_1	6.55 ±0.44	2.50± 0.17	0.30 ±0.50	248± 0.40	6.7± 0.20	90.36 ±0.65
F_2	6.60 ±0.31	2.53 ±0.25	0.39 ±0.40	249±0.60	6.6± 0.3	93.75 ±0.85
F_3	6.70 ±0.40	2.57 ±0.80	0.43 ±0.55	255± 0.80	6.7 ±0.37	92.45 ±0.45
F_4	6.86 ±0.55	2.50 ±0.20	0.12 ±0.30	250 ±0.70	6.8 ±0.50	94.85 ±0.73
F_5	6.34 ±0.57	2.65 ±0.66	0.54 ±0.46	248 ±0.32	6.6 ±0.26	97.65 ±0.42
F_6	6.49 ±0.30	2.63 ±0.25	0.58 ±0.55	250 ±0.45	6.8 ±0.36	99.22± 0.78
F_7	6.51 ±0.32	2.57± 0.81	0.36± 0.35	252± 0.30	6.7 ±0.34	96.75 ±0.34
F_8	6.53 ±0.35	2.58 ±0.80	0.39 ±0.40	250 ±0.70	6.6 ±0.30	98.56 ±0.56
F_9	6.52± 0.55	2.57 ±0.55	0.43 ±0.45	249 ±0.72	6.8 ±0.21	95.23 ±0.96

***n=6**

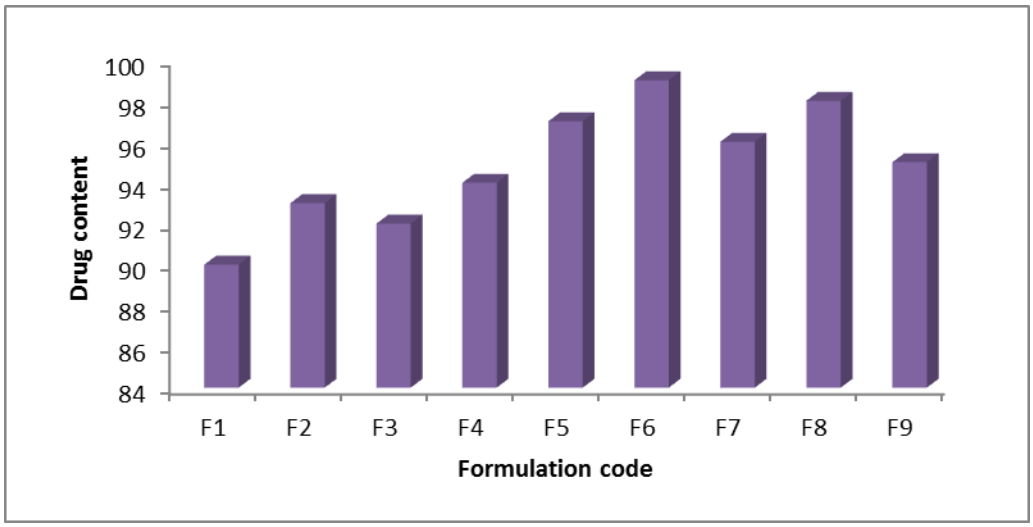

Figure 4: Graphical presentation of drug content.

Swelling Study

The swelling index of Irbesartan tablets for a period for 12 h is shown. The water uptake nature of the polymer is one of the important properties that affect the onset of swelling. Swelling has been increases with increase in amount of xanthan gum and carbopol 934.

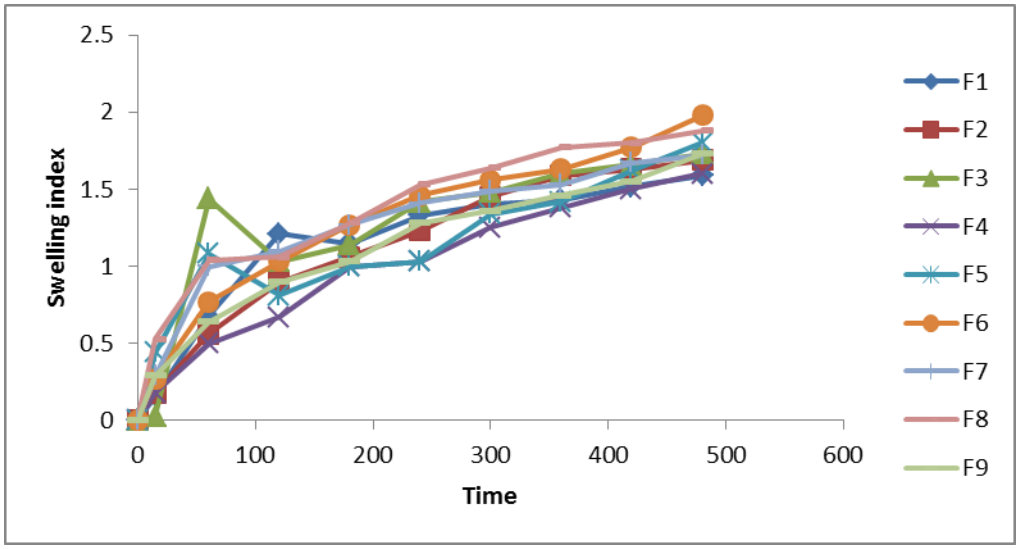

Figure 5: Graphical Presentation of swelling index.

In-Vitro Dissolution Study

In -Vitro drug Release Studies of Irbesartan buccal tablets were determined using USP type II apparatus. The drug release was found to vary according to the ratio of mucoadhesive polymers. Amongst all formulation F6 showed maximum drug release of 97.33% after 12 hrs of study and also showed better contact with biological membrane containing xanthan gum and carbopol.

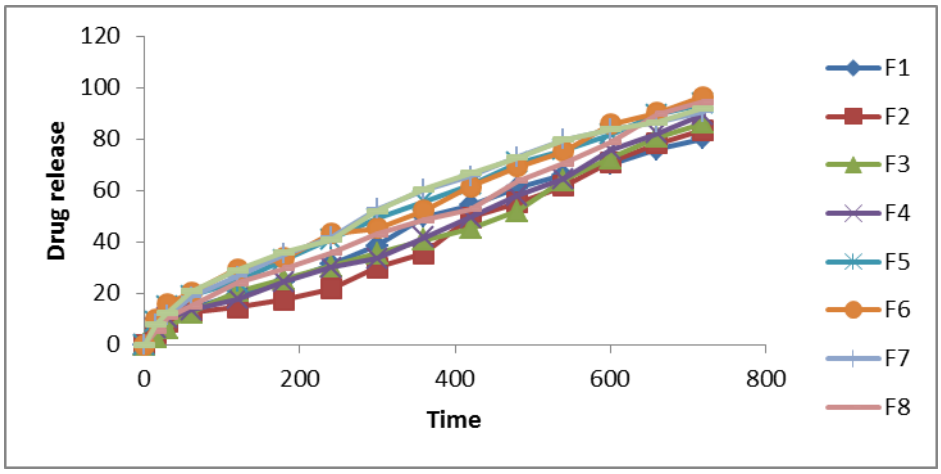

Figure 6: Graphical presentation of In-vitro drug release.

Mucoadhesive strength

The highest bioadhesion strength was possessed by the formulation F6 containing xanthan gum and carbopol 934. Increase in the concentration of xanthan gum and carbopol 934 increases bioadhesion strength.

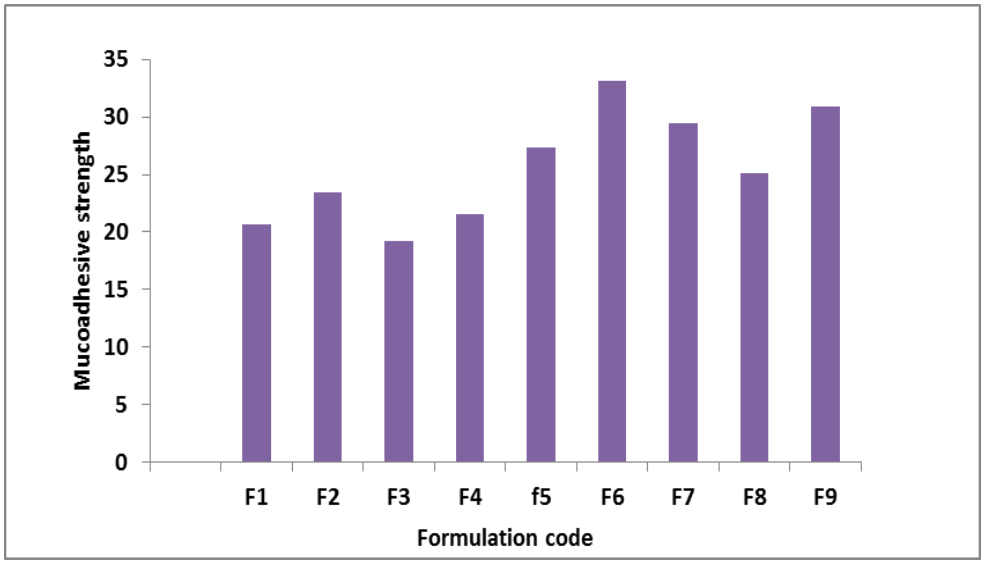

Figure 7: Graphical presentation of Mucoadhesive strength.

Optimization

A 3^2 full factorial design was selected and 2 factors were evaluated at 2 levels, respectively. The percentage of xanthan gum (X1) and carbopol 934 (X2) were selected as independent variables and dependent variables drug release, swelling index, mucoadhesive strength. The data obtainedwere treated using design expert software and analyzed statistically using analysis of variance (ANOVA).

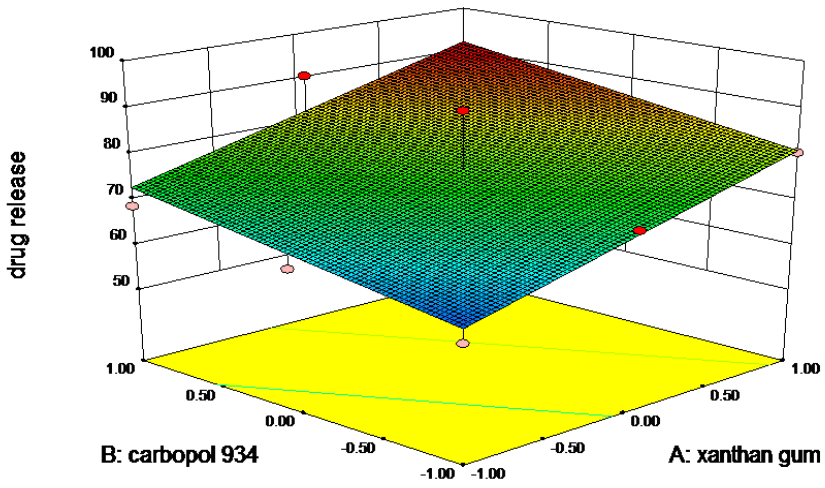

Figure 8: surface response plot showing effect of xanthan gum and carbopol 934 on drug release.

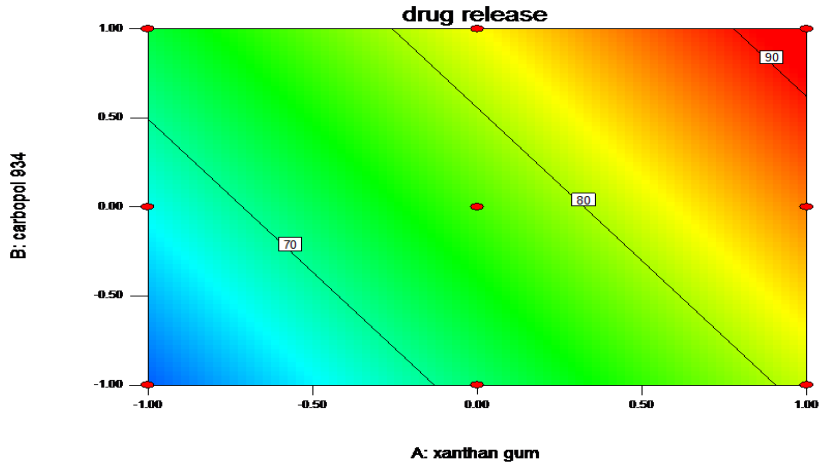

Figure 9: Counter plot showing effect of xanthan gum and carbopol 934 on drug release.

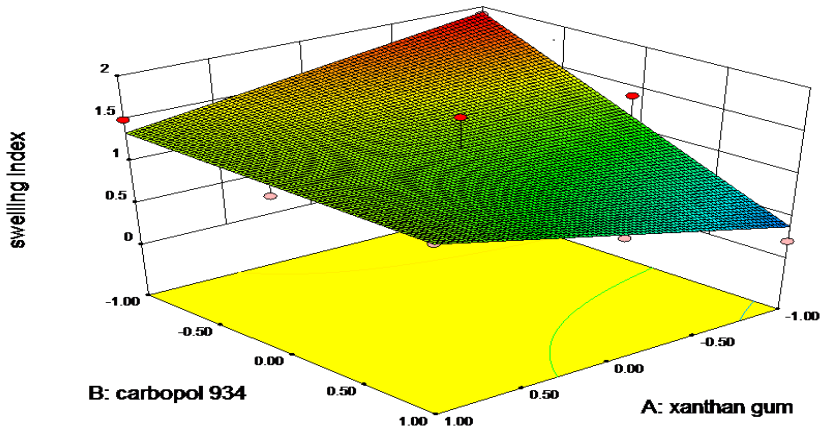

Figure 10: Surface response plot showing effect of xanthan gum and carbopol 934 on swelling index.

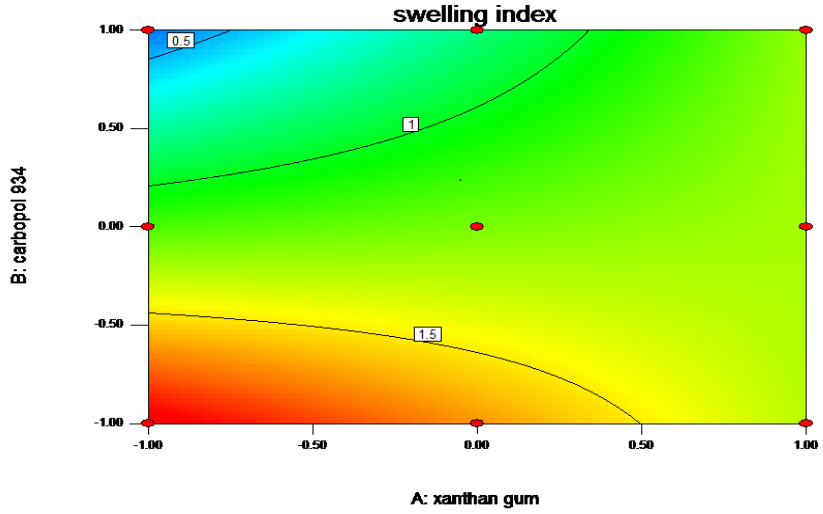

Figure 11: Counter plot showing effect of xanthan gum and carbopol 934 on swelling index.

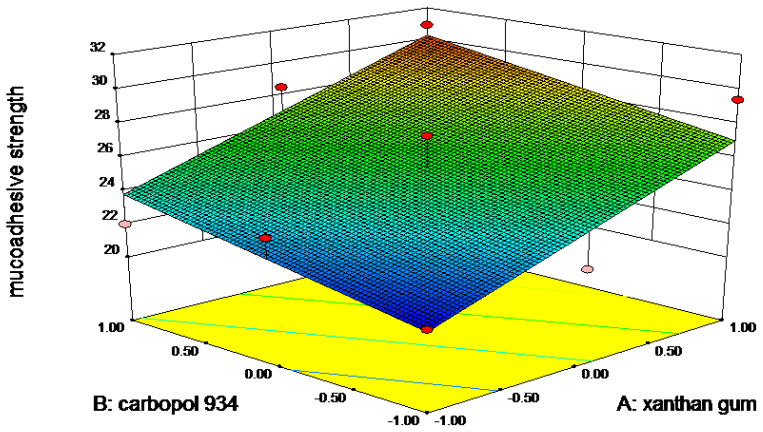

Figure 12: surface response plot showing effect of xanthan gum and carbopol 934 on mucoadhesive strength.

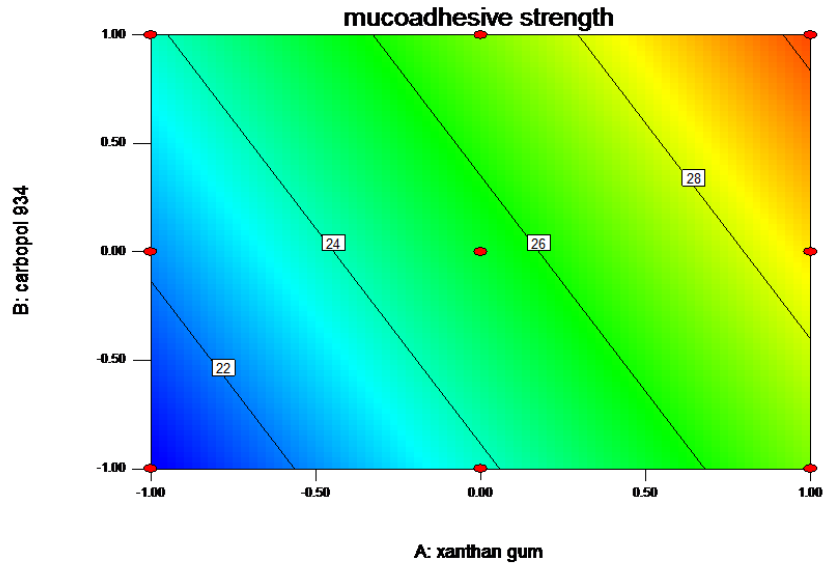

Figure 13: Counter plot showing effect of xanthan gum and carbopol 934 on mucoadhesive strength.

From design expert batch of Xanthan gum and carbopol 934 was found to be optimized. From this data **F_6**was selected as optimized formulation.

Kinetic Data

Table 5: R^2 values of Korsemayer'speppas model kinetics.

Batch	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
R^2	0.995	0.901	0.920	0.955	0.933	0.945	0.976	0.943	0.518

Stability studies of Mucoadhesive buccal tablet of Irbesartan

Table 6: Stability study of optimized formulation.

Sr .No.	Observations	Before Stability	Stability testing interval days	
			1 months	2 months
1.	**General appearance**			
	Color	No change	No change	No change
	Odor	No change	No change	No change
2.	pH	6.7	6.8	6.7
3.	Drug release	97.33	97.10	96.56
4.	Drug content	99.23	99.05	98.85

Optimized formulation **F_6** at 25 ^{0}c temperature was found to be stable up to 2 months. There was no significant change in appearance, drug release, and drug content.

CONCLUSION

It was planned in this investigation to formulate and evaluate mucoadhesive buccal tablet of Irbesartan to release the drug in buccal cavity for extended period of time in order to avoid first pass metabolism to reduce the dosing frequency and to improve the patient compliant.Experiments were conducted to investigate the influence of polymer like xanthan gum and carbopol 934 bioadhesion strength and release kinetic of mucoadhesive tablet of Irbesartan. In vitro dissolution studies were conducted in apparatus II at 50 rpm for 12 hr. Drug content of all formulation were found to be more than 99.22%. The pH of all mucoadhesive formulation was in between 6.7 to 6.8. In vitro drug release result of all the formulation were conducted for 12 hrs of all tablet formulation **F_1 -F_9.** The formulations **F_6** were taken as an optimized batch.It can be seen that by increasing the concentration of xanthan gum and carbopol 934 in the formulation, the drug release rate was found to be increased. The in vitrorelease kinetic indicate that all the formulation show anomalous or non-fickian diffusion. The drug release occurs probably by diffusion, erosion and dissolution follows.The data was statically analyzed and mechanism of release kinetic studied. All the studies were conducted at least 6 times and average was computed and tabulated.

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