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FORMULATION AND EVALUATION OF BUCCO-ADHESIVE TABLET OF ANTI-DIABETIC AGENT.

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Abstract: - The goal of this work was to investigate and describe mucoadhesive buccal tablets of pioglitazone hydrochloride utilising a variety of bioadhesive polymers in combination, including sodium alginate, carbopol, HPMC K4M, and HPMC K15M. TEN formulations were created with various polymer concentrations and combinations of two polymers in each formulation. Individual polymers make up formulations F1 to F4. F5 to F10 were made up of two polymer combinations. Physicochemical criteria such as hardness, thickness uniformity, weight fluctuation, and surface pH were assessed on the produced tablets. The bioadhesive strength and in-vitro drug release of the produced tablets were also tested. In vitro bioadhesive strength and release tests revealed that formulation F2, which had individual polymer and medication, had the best drug release (97.51%) and bioadhesive strength. The FTIR measurements revealed no evidence of interaction between polymer and drug.

Keywords: - Pioglitazone Hydrochloride, Bioadhesion, HPMC K4M, HPMC K15M, Carbopol 934P, Sodium Alginate.

Introduction: -

Buccal drug delivery is a compelling alternative to oral medication administration, especially in terms of resolving the drawbacks of the latter. By giving the medicine via buccal route, problems like first pass metabolism and drug degradation in the GIT can be avoided. Furthermore, the oral cavity is conveniently accessible for self-medication, and toxicity can be quickly eliminated by removing the dose form from the buccal cavity. [(8)] This method can also be used to give drugs to people who are unable to take them orally. At least three of the following are required for successful buccal medication administration using a buccal adhesive system: (a) a bioadhesive to keep the system in the mouth cavity and optimise the amount of intimate contact with the drug; (b) a buccal adhesive system to keep the mucosa (b) a vehicle for releasing the medicine at an acceptable rate under the conditions in the mouth, and (c) techniques for overcoming the oral mucosa's limited permeability. Buccal adhesive drug delivery stems extend the duration spent in the mouth and operate as controlled-release dosage forms. [(26, 27)] Because the buccal mucosa is less permeable than the sublingual mucosa, it is a better candidate for extended drug administration. [(47)] Furthermore, the medicine is very well tolerated, and it can be applied, targeted, and removed at any moment during the treatment period. Due to the shorter half-life of pioglitazone hydrochloride, it is advantageous to solve the

problem of frequent dosage (3-5 h). Continual release of the increased bioavailability of the medicine results in a significant reduction in the dose and, as a result, dose-related side effects. [22,25] As a result, the current study attempted to manufacture a mucoadhesive buccal tablet for Pioglitazone hydrochloride utilising several polymer mixes in order to avoid substantial first-pass metabolism, stomach degradation, and the potentially fatal side effect of liver damage. [31,32]

Materials and Method: -

Materials

USV Private Limited, Mumbai, provided a free sample of pioglitazone hydrochloride. Colorcon, Goa, provided a free sample of Hydroxy Propyl Methyl Cellulose K15M, Hydroxy Propyl Methyl Cellulose K4M. Loba Chemicals in Mumbai, provided Sodium alginate and Carbopol 934. All of the other reagents were of analytical grade.

Methods

Selection of Active Pharmaceutical Agent

Pioglitazone hydrochloride is the hydrochloride salt version of the drug. It belongs to the thiazolidinediones class of drugs that reduce blood sugar levels. It can be used alone or in combination with other medications to treat type 2 diabetes. It enhances insulin sensitivity in muscle and adipose tissue and inhibits hepatic gluconeogenesis, as well as improving glycemic management and lowering insulin levels in the blood. It works by restoring the body's insulin sensitivity, a common hormone that helps maintain blood sugar levels.

Formulation of Mucoadhesive Buccal Tablets

In a glass mortar, the drug, polymers, and excipients were homogeneously combined for 15 minutes. The combination (250 mg) was then compacted in a single stroke using a 9 mm biconcave punch on a station rotary machine (The Rimek Mini Press-1).

Formula for the preparation of pioglitazone hydrochloride bucco-adhesive tablets.

Ingredient's	Formulation Code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Pioglitazone HCl	30	30	30	30	30	30	30	30	30	30
HPMC K15 M	100	-	-	-	50	-	-	50	50	-
HPMC K4M	-	100	-	-	50	50	-	-	-	50
Carbapol	-	-	100	-	-	50	50	50	-	-
Sodium alginate	-	-	-	100	-	-	50	-	50	50
Mannitol	100	100	100	100	100	100	100	100	100	100
Menthol	5	5	5	5	5	5	5	5	5	5
Disodium saccharin	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5

EVALUATION OF BUCCO-ADHESIVE TABLET

DRUG AND POLYMER COMPATIBILITY STUDIES

An infrared spectrophotometer was used to record the drug's FTIR spectrum (Shimadzu Affinity-1). In the frequency range of 400-4000 cm-1, the IR spectrum of the medication, polymers, and their physical combination was recorded. The observed peaks were then logged and compared to the drug's standard FTIR.

CALIBRATION CURVE OF PIOGLITAZONE HCL IN 6.8 PHOSPHATE BUFFER

10 mg of Pioglitazone HCl was dissolved in a tiny amount of phosphate buffer (pH 6.8) and used to make a volume of 100ml. To acquire solutions in the conc., repeated dilutions of the stock solution were performed. The concentrations range from 2 to 20 g/ml. A UV-visible spectrophotometer was used to test the solution's absorbance at 242 nm. Conc. V/s absorbance was displayed on a graph.

CALIBRATION CURVE FOR PIOGLITAZONE HCL IN 7.4 PHOSPHATE BUFFER

The same was used to dilute 10 mg of Pioglitazone HCl in a little amount of phosphate buffer (pH 7.4) and make up to 100ml. To acquire solutions in the conc., repeated dilutions of the stock solution were performed. The concentrations range from 2 to 20 g/ml. A UV-visible spectrophotometer was used to test the solution's absorbance at 274 nm. Conc. V/s absorbance was displayed on a graph.

PRECOMPRESSION STUDY

Angle of Repose - On rotation, the angle of repose is the greatest angle formed by the powder plane with the horizontal surface. Angle of repose is useful in determining particle flow parameters, which may be linked to packing densities and particle mechanical arrangements. Fixing the funnel and free-standing cone method was used to estimate the angle of powder repose. The granules were taken after being properly weighed. The funnel's height was then modified so that the funnel's tip just touched the granules' peak. Granules were permitted to freely flow through the funnel onto the surfaces. The powder cone's diameter and angle of repose were measured.

Determination of Bulk density – The volume and weight of preserved bulk powder can be measured and the apparent bulk density assessed by pouring it into a graduated measuring cylinder using a big funnel. The following formula is used to calculate bulk density:

$$\text{Bulk Density} = \frac{\text{Weight}}{\text{Bulk Volume (Vo)}}$$

Where,

V_o – Bulk Volume

Determination of Tapped density - The volume and weight of preserved powder can be measured by putting it into a graduated measuring cylinder with a big funnel and tapping it 100 times on a wooden plank. The following formula can be used to determine tapped density.

$$\text{Tapped Density} = \frac{\text{Weight}}{\text{Tapped Volume (Vt)}}$$

Where,
V_t – Tapped Volume

Compressibility Index (or) Carr' index (I) – Carr devised an indirect method of determining powder flow from bulk densities. Compressibility percentages are a direct indicator of the powder's potential arch and stability. The Carr's index of each prepared formulation was calculated.

Hausner's ratio – The ratio between tapped density and bulk density is used to calculate Hausner's ratio, which reveals the flow qualities of the powder. This ratio was shown to be related to inter particle friction by Hausner and could thus be used to predict powder flow parameters.

POST COMPRESSION STUDY

Thickness

Using a Digital Thickness Tester, the thickness of three randomly selected tablets from each formulation was measured in millimetres.

Weight Variation Test

Twenty tablets are chosen at random and weighed individually in a single pan electronic balance, with the average weight determined. According to IP, no more than two individual weights should differ by more than 5% from the average weight, and none should differ by more than twice that percentage.

Hardness Test

The tablet was held between two jaws, one fixed and the other movable. The scale was set to zero, and the load was steadily increased until the tablet broke. The hardness of the tablet is determined by the load at that moment. For the hardness test, three tablets from each batch are utilised, and the findings are given in Kg/cm2.

Friability Test

20 pre-weighed tablet samples are inserted in the friabilator, which is subsequently turned 100 times (4 min). After that, the tablets are dusted and reweighed. Compressed tablets with a weight loss of less than 0.5 to 1.0 percent are generally regarded as acceptable.

Determination of Drug Content

Ten tablets are weighed and then crushed in a mortar to make powder. In a 100 ml volumetric flask, a quantity of powder weighing equivalent to 10 mg of medication was introduced, along with 6.8 Phosphate buffer. The solution is filtered using a membrane filter (0.45m), and 10 ml of the filtrate is transferred to a 100 ml volumetric flask, where 6.8 phosphate buffer is added to make up the final volume. The absorbance is then measured using a UV Visible spectrometer at 242 nm. The total amount of medication in a single tablet is then computed.

Surface pH

The pH of the buccal tablets' surroundings (surface pH) was measured to see if there were any negative effects from the pH change in vivo. Because an acidic or alkaline pH can irritate the buccal mucosa, keeping the surface pH as close to neutral as possible was decided. For this, a composite glass electrode was used. The pill was allowed to swell for 2 hours at room temperature after being in contact with 5 mL of distilled

water (pH 6.5 0.05). The pH was determined by placing the electrode on the tablet surface and allowing it to equilibrate for 1 minute.

Mucoadhesive Strength

A modified physical balance was used to assess the tablet's muco-adhesive strength. The fresh goat buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of the animal's death. Phosphate buffer pH 6.8 and cut into a 3 cm piece An inverted 50ml beaker was placed in the centre of a 250ml beaker containing phosphate buffer, and a piece of buccal mucosa was stuck on it (pH 6.8). A cyanoacrylate adhesive was used to stick the tablet to the lower side of the glass vial. With a 5 gm weight on the right-hand side pan of the balance, two pans were balanced. The right-hand side pan was lowered along with the tablet over the mucosa after a 5 gram weight was removed from it. The For a total of 5 minutes, the balance was held in this position. Water was introduced to the right-hand side pan gently (100 drops/min.) until the patch separated from the mucosal surface. The muco-adhesive strength was determined by the weight in grammes required to remove the tablet from the mucosal surfaces. The weight required to separate the pill from the mucosal surface (goat buccal mucosa) is used to determine muco-adhesive strength. The muco-adhesive strength was used to compute the following parameters.

Force of adhesion (N) = (Bioadhesive strength/1000) × 9.81

***IN - VITRO* DRUG RELEASE STUDIES**

The USP Type II (paddle) dissolution test Apparatus was used to test the dissolution characteristics of the prepared bucco-adhesive tablets of Pioglitazone hydrochloride for 8 hours.

Method: The dissolution vessel was filled with 500 mL of 6.8 phosphate buffer, and the medium temperature was set to 37°C 0.5°C. Each dissolution tank contains one tablet from a different batch, with the paddle rotating at 50 rpm. For up to 8 hours, 10 ml of sample is removed at predetermined intervals of one hour and replaced with the same volume of new medium. In a volumetric flask, the removed material is diluted to 10 mL and filtered using a 0.45 membrane filter. The drug content of the resulting samples is determined using a UV-Visible spectrophotometer at 242 nm.

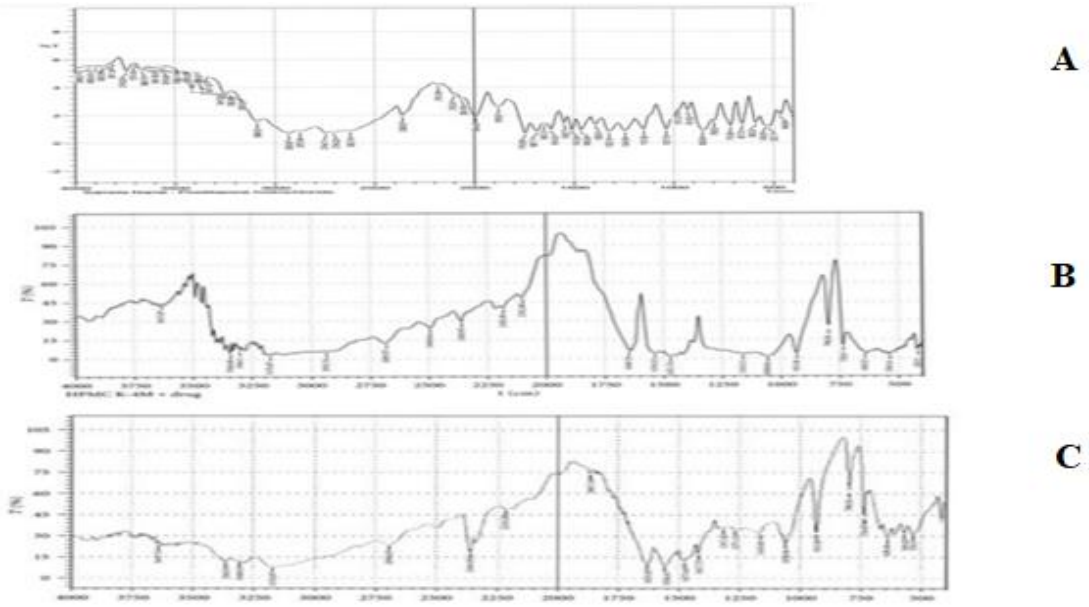
DETERMINATION OF SWELLING INDEX

One tablet was weighed and placed in a beaker containing 200 ml of medium for each formulation batch. The tablet should be taken from the media after each interval and weighed again for up to 8 hours, with the results recorded.

RESULTS AND DISCUSSION

EVALUATION OF BUCCO-ADHESIVE TABLET

Drug and polymer compatibility studies



Graph no. 1 – FTIR of Pioglitazone Hydrochloride and physical mixtures with polymers

A – FTIR of Pioglitazone Hydrochloride

B – FTIR of Pioglitazone Hydrochloride + HPMC K4M.

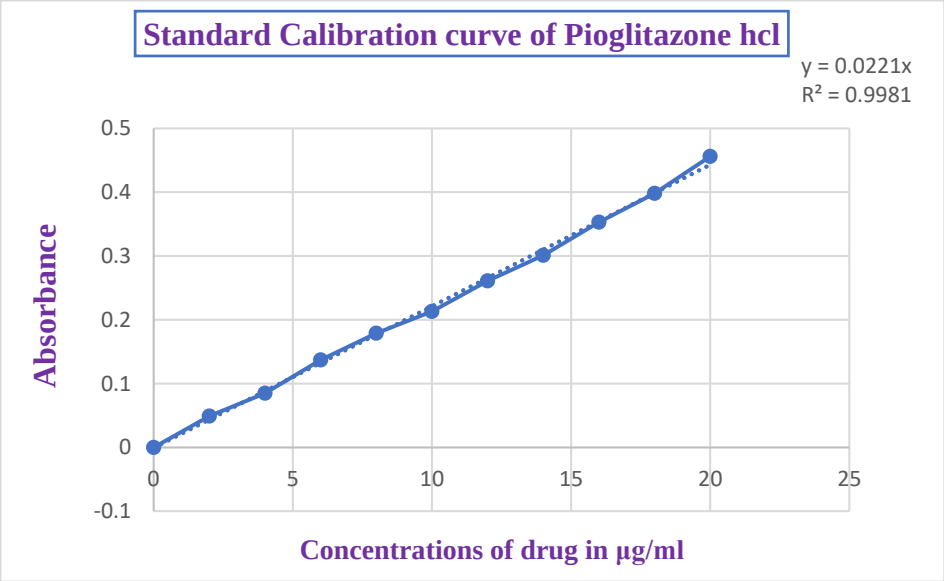
C – FTIR of Pioglitazone Hydrochloride + HHPMC K15M.

The results of FTIR study shows that, the drug was not found to show any interactions with the polymers i.e., HPMC K4M. and HPMC K15M. Hence, we can use the chosen polymers for further study.

CALIBRATION CURVE OF PIOGLITAZONE HCL IN 6.8 PHOSPHATE BUFFER

Concentrations (µg/mL)	Absorbance
0	0
2	0.049
4	0.085
6	0.137
8	0.179
10	0.213
12	0.261
14	0.301

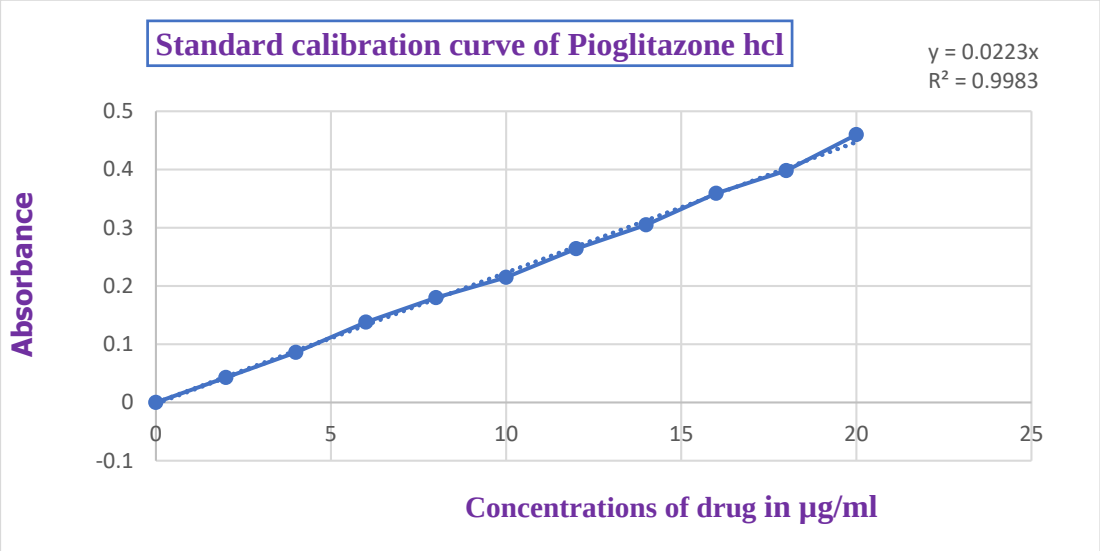
16	0.353
18	0.398
20	0.456



Graph No. 2 Calibration Curve of Pioglitazone Hcl In 6.8 Phosphate Buffer

CALIBRATION CURVE FOR PIOGLITAZONE HCL IN 7.4 PHOSPHATE BUFFER

Concentrations (µg/mL)	Absorbance
0	0
2	0.043
4	0.086
6	0.138
8	0.18
10	0.215
12	0.264
14	0.305
16	0.359
18	0.398
20	0.46



Graph No. 3 Calibration Curve of Pioglitazone HCl in 7.4 Phosphate Buffer

The calibration curve of Pioglitazone HCl shows the R^2 value which is equal to 0.9995 nearly a straight line which shows that the study follows bbeerlaw.

PRECOMPRESSION STUDY

Table no. 1 – Pre – compression study

Batch	Bulk Density (g/cm^3 ± SD)	Tapped Density (g/cm^3 ± SD)	Carr's Index (% ± SD)	Hausner's Ratio (± SD)	Angle of Repose (θ ± SD)
F1	0.460 ± 0.002	0.525 ± 0.010	12.52 ± 0.78	1.14 ± 0.05	31.25 ± 1.17
F2	0.458 ± 0.008	0.520 ± 0.009	12.24 ± 0.96	1.14 ± 0.04	31.40 ± 1.09
F3	0.465 ± 0.005	0.544 ± 0.021	14.39 ± 0.71	1.16 ± 0.05	32.59 ± 1.46
F4	0.450 ± 0.012	0.515 ± 0.024	12.32 ± 0.75	1.14 ± 0.03	31.41 ± 1.18
F5	0.451 ± 0.006	0.522 ± 0.009	13.10 ± 0.68	1.15 ± 0.02	31.56 ± 1.23
F6	0.440 ± 0.011	0.518 ± 0.023	13.77 ± 0.56	1.16 ± 0.05	32.15 ± 1.41
F7	0.445 ± 0.009	0.511 ± 0.008	13.81 ± 0.44	1.16 ± 0.07	31.58 ± 1.34
F8	0.458 ± 0.013	0.529 ± 0.019	12.76 ± 0.90	1.14 ± 0.09	33.05 ± 1.04
F9	0.465± 0.005	0.538 ± 0.012	12.17 ± 0.84	1.13 ± 0.08	32.45 ± 1.19
F10	0.462± 0.002	0.525 ± 0.007	13.71 ± 0.49	1.15 ± 0.03	31.43 ± 1.20

n =3

POST COMPRESSION STUDY

Table no. 2 – Post–compression study.

Batch	Wt. variation (± SD)	Hardness (± SD)	Diameter (± SD)	Thickness (± SD)	Friability (± SD)	Drug Content
F1	249.96±0.598	5±0.051	9.013±0.156	2.730±0.010	0.36±0.0025	86.20±2.34
F2	249.81±0.601	4.6±0.059	9.014±0.156	2.741±0.005	0.40±0.0018	93.81±1.45
F3	249.82±0.564	4.6±0.058	9.014±0.156	2.745±0.018	0.52±0.0019	91.48±143
F4	249.76±0.578	5±0.054	9.014±0.156	2.752±0.013	0.36±0.0025	83.68±1.43
F5	249.87±0.503	5±0.055	9.013±0.156	2.744±0.011	0.38±0.0021	91.46±1.46
F6	250.56±0.616	4.8±0.059	9.014±0.156	2.739±0.008	0.41±0.0025	91.13±086
F7	249.78±0.548	5±0.057	9.014±0.156	2.748±0.017	0.40±0.0018	90.57±067
F8	249.43±0.532	4.8±0.055	9.013±0.156	2.752±0.015	0.39±0.0017	88.72±1.54
F9	250.12±0.628	5.16±0.05	9.013±0.156	2.748±0.019	0.42±0.009	91.03±1.38
F10	250.21±0.637	5.12±0.05	9.013±0.156	2.745±0.018	0.36±0.0025	90.38±2.35

n = 3

The **Average Weight** of all Bucco-adhesive tablets within formulation was found to be uniform. This indicates uniform filling of the die cavity during tablet compression.

The **Hardness** of all Bucco-adhesive tablets was found to be in the range of 5±0.051to 5.12±0.05 kg/cm2. This ensures good mechanical strength.

The **Thickness** of all Bucco-adhesive tablets was found in the range of 2.730±0.010 to 2. .745±0.018mm. There were no marked variations in the thickness of all formulations indicating uniform behavior of powder throughout the compression process.

The **Friability** of all Bucco-adhesive tablets was found to be in the raof nge 0.36±0.0025 to 0.36±0.0025 which indicates the goflowabilityity.

The **Drug Content** of all formulations was found to be between 86.20±2.34 to 90.38±2.35. The values ensure good uniformity of drug content in the tablet.

Bioadhesive Parameters

Table no. 3. Surface pH, Mucoadhesive strength, Force of adhesion

Batch	Surface pH	Drug Content (%)	Mucoadhesive strength (gms)	Force of adhesion (N)
F1	6.68±0.13	86.20±2.34	08.52±0.76	0.08±0.1
F2	6.56±0.11	93.81±1.45	11.69±0.24	0.10±0.1
F3	6.48±0.16	91.48±143	09.54±0.75	0.09±0,2
F4	6.44±0.13	83.68±1.43	08.96±0.88	0.08±0.1
F5	6.74±0.15	91.46±1.46	11.28±0.88	0.11±0.1
F6	7.3±0.22	91.13±086	04.13±0.30	0.04±0.2
F7	6.44±0.13	90.57±067	05.67±0.32	0.05±0.2
F8	6.34±0.18	88.72±1.54	08.02±0.85	0.07±0.1
F9	7.07±0.15	91.03±1.38	10.56±0.35	0.105±0.3
F10	6.40±0.15	90.38±2.35	14.21±0.71	0.14±0.2

n=3

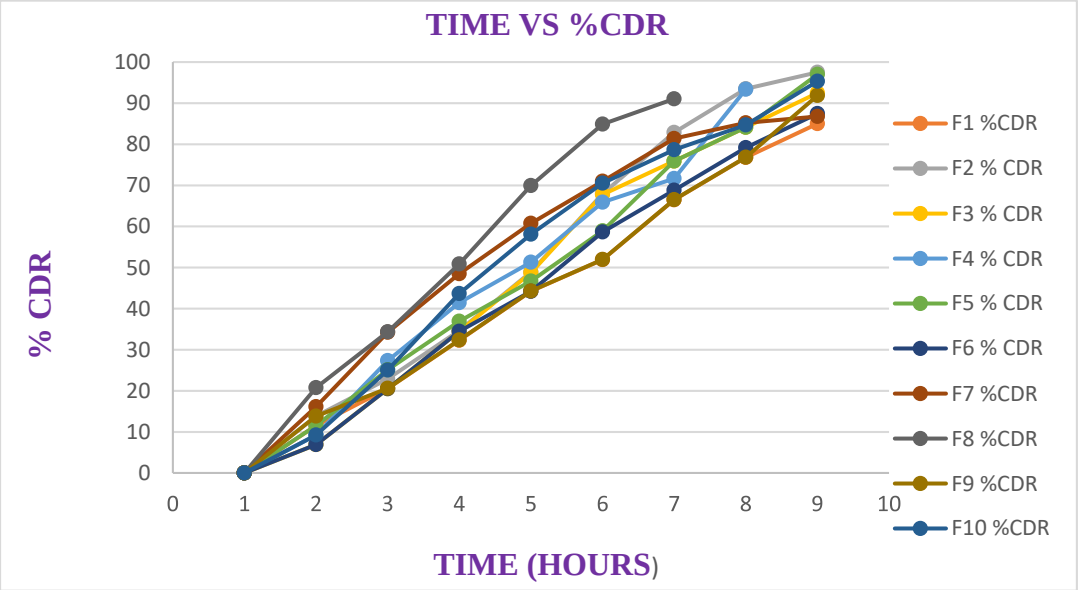
In- Vitro Drug Release Study

Table No. 4. In vitro drug release study

TIME (HRS)	CUMULATIVE % DRUG RELEASE									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	11.53± 0.198	13.846± 0.169	6.92± 0.165	9.23± 0.191	11.53± 0.175	6.92± 0.198	16.15± 0.195	20.76± 0.191	13.84± 0.188	9.23± 0.165
2	20.58± 0.185	22.895± 0.199	20.49± 0.178	27.33± 0.175	25.11± 0.188	20.49± 0.191	34.25± 0.197	34.34± 0.195	20.63± 0.165	25.06± 0.178
3	32.3± 0.191	34.66± 0.181	34.47± 0.191	41.44± **0.**184	36.92± 0.176	34.47± 0.195	48.5± 0.181	50.85± 0.197	32.35± 0.176	43.66± 0.195
4	44.25± 0.198	48.914± 0.187	48.73± 0.195	51.31± 0.189	46.69± 0.198	44.2± 0.178	60.76± 0.179	69.95± 0.191	44.29± 0.188	58.09± 0.156

5	51.9± 0.198	67.963± 0.195	67.78± 0.178	65.88± 0.175	58.91± 0.191	58.64± 0.185	70.99± 0.156	84.88± 0.181	51.94± 0.185	70.54± 0.189
6	66.47± 0.179	82.85± 0.173	75.88± 0.199	71.67± 0.165	75.88± 0.195	68.82± 0.198	81.4± 0.186	91.04± 0.176	66.51± 0.196	78.68± 0.179
7	76.78 ± 0.177	93.484± 0.189	84.11± 0.181	93.39± 0.159	84.11± 0.165	79.18± 0.169	85.2± 0.169		76.83± 0.185	84.7± 0.191
8	85.02± 0.165	97.511± 0.189	92.48± 0.177		97.01± 0.177	87.46± 0.191	86.78± 0.188		91.85± 0.195	95.33± 0.177

n=3



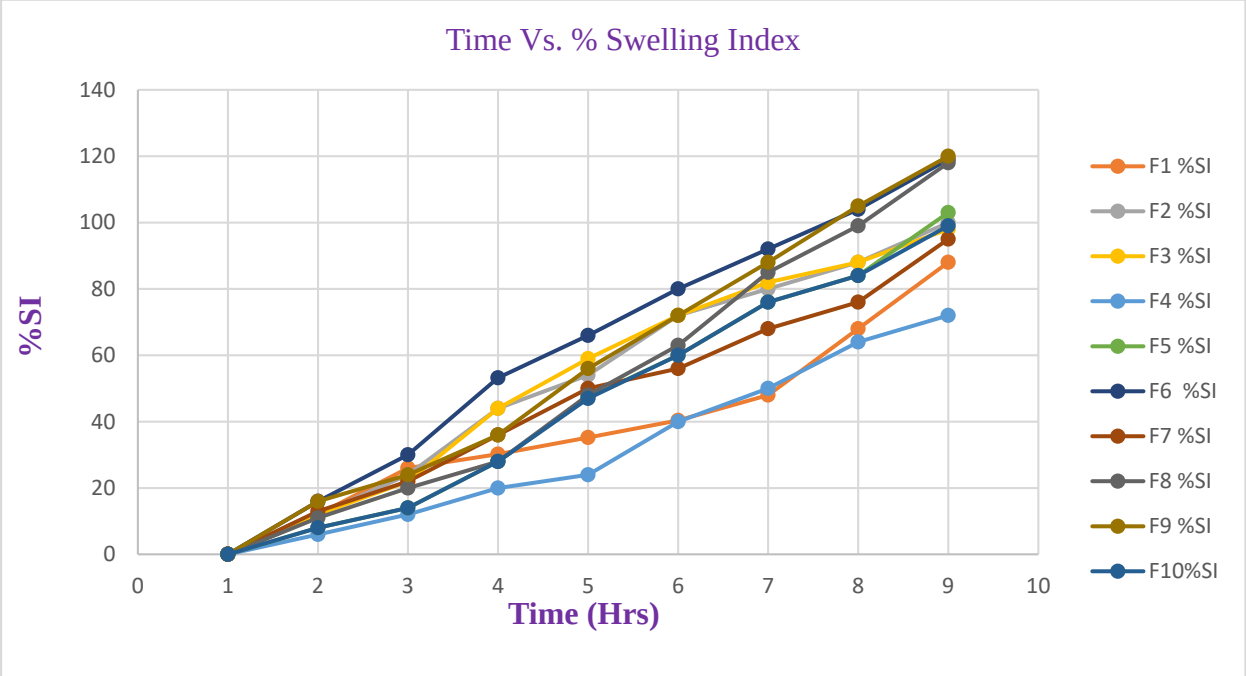
Graph No. 4 Time Vs. % CDR

DETERMINATION OF SWELLING INDEX

Table no. 5 – % Swelling Index

Time	F1 ± SD	F2 ± SD	F3 ± SD	F4 ± SD	F5±SD	F6 ± SD	F7 ± SD	F8 ± SD	F9± SD	F10±SD
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	12 ± 0.895	12 ± 0.895	12 ± 0.895	6 ± 0.895	8 ± 0.895	16 ± 0.895	13 ± 0.895	11 ± 0.895	16 ± 0.895	8 ± 0.895
2	26 ± 0.605	24 ± 0.895	22 ± 0.895	12 ± 0.895	14 ± 0.895	30 ± 0.895	22 ± 0.895	20 ± 0.895	24 ± 0.895	14 ± 0.895
3	30.2 ± 0.712	44 ± 0.895	44 ± 0.895	20 ± 0.895	28 ± 0.895	53.2 ± 0.895	36 ± 0.895	28 ± 0.895	36 ± 0.895	28 ± 0.895
4	35.2 ± 0.887	54 ± 0.895	59 ± 0.895	24 ± 0.895	47.2 ± 0.895	66 ± 0.895	50 ± 0.895	48 ± 0.895	56 ± 0.895	47 ± 0.895
5	40.4 ± 0.568	72 ± 0.895	72 ± 0.895	40 ± 0.895	60 ± 0.895	80 ± 0.895	56 ± 0.895	63 ± 0.895	72 ± 0.895	60 ± 0.895
6	48.4 ± 0.897	80 ± 0.895	82 ± 0.895	50 ± 0.895	76 ± 0.895	92 ± 0.895	68 ± 0.895	85 ± 0.895	88 ± 0.895	76 ± 0.895
7	68 ± 0.689	88 ± 0.895	88 ± 0.895	64 ± 0.895	84 ± 0.895	104 ± 0.895	76 ± 0.895	99 ± 0.895	105 ± 0.895	84 ± 0.895
8	88 ± 0.895	100 ± 0.895	1 ± 0.895	72 ± 0.895	103 ± 0.895	119 ± 0.895	95 ± 0.895	118 ± 0.895	120 ± 0.895	99 ± 0.895

n=3



Graph No. 5 % SI Index

CONCLUSION

The literature review on the buccal drug delivery technique suggests that it is effective for medicines with low molecular weight, low dosage, and considerable first-pass metabolism. Pioglitazone hydrochloride is an anti-diabetic medication with low molecular weight, low dose, strong biphasic solubility, and substantial first-pass metabolism, making it a good candidate for use in the buccal mucoadhesive drug delivery method. A review of the literature on HPMC, carbopol, and chitosan polymers found that they exhibit strong bioadhesive characteristics. The FT-IR validated the purity of the medication. The medicine and the polymers did not interact in any way. HPMC K4M, HPMC K15M, Carbopol, and Sodium alginate in various amounts were used to make buccoadhesive tablets containing pioglitazone hydrochloride.

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