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Research Paper

Design And Characterization of Mucoadhesive Buccal Patches of Repaglinide

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ABSTRACT:
Repaglinide is an antidiabetic drug which belongs to the class of Meglitinides .the main aim of the study is to develop and characterise mucoadhesive buccal patches of Repaglinide to avoid first pass metabolism. The patches were prepared by solvent casting method and characterised for folding endurance,thickness,drug content,surface pH ,tensile strength, bioadhesive strength, in vitro drug release study etc. In vitro dissolution studies are conducted by using phosphate buffer 6.8 pH. The buccal patches were prepared by using the polymers chitosan, poly vinyl pyrrolidone, Hydroxyl propyl methyl cellulose, poly vinyl alcohol.Propylene glycol is used as plasticiser. The result of the study indicates tensile strength of patches were between 1.82-2.1N/m2. Folding endurance is between 189 to 245.Patches thickness were from 0.27-0.33mm .The swelling index is between 22.7 to 56.7. Bio adhesion time was from 4-6 hours. Buccal patches prepared with chitosan, PVP K-30, HPMC were exhibit prolong release for more than 8 hours. It is having case II transport mechanism. The drug release rate of all the formulation were analysed for Zero order, First order, Higuchi and Peppas equation. All the formulation follows case II transport and anomalous mechanism.

Keywords: *Muco adhesion, Buccal Patch, Repaglinide, in vitro dissolution study.*

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I. INTRODUCTION:

Buccal patches are systems that may range from simple erodible and non-erodible adhesive films to more sophisticated systems, which can be designed to provide either unidirectional or multidirectional release of the drug. Bio adhesive formulations have a wide scope of applications for both systemic and local effects of drugs. The oral trans mucosal drug delivery bypasses liver and avoids pre-systemic elimination in the GI tract and liver. Buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route been preferred due to avoidance of first pass metabolism and possibility of being accessible for controlled and sustained drug release. Bucco adhesive patch should be flexible, elastic, soft and strong to withstand breakage due to stress and mouth activities. Buccal patches also show good buccoadhesive strength so that it can be retained in the mouth for a desired duration. There are critical and essential evaluations of buccalpatches such as muco adhesion, swelling properties.

II. MATERIALS AND METHODS:

Repaglinide and Chitosan were purchased from Yarrow Chem products, Mumbai.PVP K-30, PVA and HPMC were obtained from Hi Media laboratories Pvt.ltd, Mumbai. Propylene glycol and acetic acid was purchased from Nice chemicals Pvt. Ltd, Cochin.

Drug- Polymer Compatibility:Drug –polymer interaction was observed by IR spectrophotometry. An FTIR study of pure drug Repaglinide, pure polymers and physical mixture of drug and polymers were performed by KBr pellet technique

Preparation of drug loaded patches:

The plain polymeric patches were prepared by solvent casting technique. 1.5% acetic acid solution was prepared in which weighed quantity of chitosan was properly dissolved. The solution was filtered through muslin cloth to remove debris. Different polymers like PVP K 30, PVA, and HPMC were added at different ratios to get different combinations of patches. Propylene glycol was added as plasticizer. The polymers were weighed accurately and dissolved properly. 5%w/v of propylene glycol was added. Required quantity of Repaglinide was added and

stirred well for uniform mixing. This polymeric solution was kept overnight to remove air bubbles and then it was added uniformly to a petri plate containing mercury as substrate. The plate was then kept in an oven at 450C for 24 hours. After drying the film was peeled off with a sharp blade and kept in a self-sealed cover. The ethyl cellulose backing membrane was prepared by casting technique. Ethyl cellulose was soaked in 20 ml of alcohol-toluene mixture and kept for 24 hours. To this remaining quantity of solvent and glycerol in required amount was added and mixed thoroughly using mechanical stirrer till finally dispersed thick solution is obtained. This solution was poured on plain glass mould lined with aluminium foil, the solution was then dried immediately in an oven at 40ºC.

Tableno:1Formulation of patch

FORMULATION	CHITOSAN	PVP K-30	PROPYLENE GLYCOL	HPMC	PVA
C_1	1	0.6	5	0.2	-
C_2	1	0.6	5	0.4	-
C_3	1	0.6	5	0.6	-
C_4	1	0.6	5	0.8	-
C_5	1	0.6	5	-	0.2
C_6	1	0.6	5	-	0.4
C_7	1	0.6	5	-	0.6
C_8	1	0.6	5	-	0.8

Sl.no	INGREDIENTS	CONCENTRATION
1	Ethyl cellulose	4% w/w
2	Glycerol	10%w/w of polymer weight
3	Alcohol:Toluene(1:4)	Q.s to 100ml

EVALUATION OF PATCHES

Weight Variation:

Ten patches of 1cm2 were weighed individually and average of those of those patches measured.

Thickness:

The thickness of the patch was measured using screw gauge with a least count of 0.01mm at different spots of the patches. The thickness was measured at five different spots of the patch and average was taken.

Percent Swelling Index:

The polymeric patches are cut in to small patches of 1.5cm diameter. This patch was placed on the surface of the agar plate and the diameter at different time intervals where taken up to 5hrs and the percentage swelling index was calculated using the formula,

$$SD\% = \frac{Dt - Do \times 100}{Do}$$

SD% = swelling by diameter method

Dt = diameter of swollen patch after time t

Do = original patch diameter.

Folding Endurance:

Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance.

Surface pH:

Buccal patches were left to swell for 1 hour on the surface of the agar plate, the agar plate prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.6 under stirring and the solution was poured into the

petridish, it was allowed to stand until itsolidified to form a gel at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

Moisture Content & Moisture Absorption Studies:

Moisture Content:

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After three days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss using the formula:

$$\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Moisture Absorption:

The buccal patches were weighed accurately and placed in the desiccators containing 100ml of saturated solution of aluminium chloride, which maintains 76% relative humidity. After three days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula:

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Water Vapour Transmission Rate (VTR):

Vapour transmission method was employed for determination of vapour transmission from the patch. Glass bottle filled with 2g anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim, was used in the study. The patch was fixed over the adhesive and the assembly was placed in constant humidity chamber, prepared using saturated solution of ammonium chloride
and maintained at 37±20C. The difference in weight after three days was calculated. The vapour transmission rate was obtained as follow.

$$\text{Vapour transmission rate (VTR)} = \frac{\text{(Amount of moisture transmitted)}}{\text{Area} \times \text{Time}}$$

Tensile Strength:

The tensile strength of buccal patch refers to tension or force required to tear of the patch apart into two pieces. The instrument used to measure the tensile strength designed in our laboratory especially for this project work. The instrument is a modification of chemical balance. One pan of the balance was replaced with one metallic plate having a hook for attaching the film. The equilibrium of the balance was adjusted by adding weight to the
right pan of the balance. The instrument was modified in such a way that the patch can be fixed up between two hooks of horizontal beams to hold the test film. A film of 2.5cm length was attached to one side hook of the balance and the other side hook was attached to plate fixed up to the pan. The weights are added to the other side pan of the balance. Thus, tensile strength,

$$T = \frac{M \times g}{B \times t} \quad \text{Dynes/cm}^2$$

T= force at break/ initial cross-sectional area of sample.

Where, m= mass in grams

g = acceleration due to gravity 980 cm/sec²

b = breadth of the specimen in cm

t = thickness of sample in cm.

Percent Elongation at Break:

The percent elongation at break is defined as the elongation at the moment of rupture of the specimen divided by the initial gauge length of the specimen and multiplying by 100.

$$\text{Percent elongation at break} = \frac{LB - L0}{L0} \times 100$$

LB = length of the specimen in cm when it breaks.

L0 = original length of the specimen in cm.

The instrument and procedure is similar to that used for tensile strength.

Drug content determination

The weight of whole patch was determined and cut in to 2cm2. For determining the drug content, a single piece of patch was taken and crushed in a mortar using pestle. Methanol was added and triturated to completely dissolve the drug, it was then diluted to 100ml. The solution was filtered. The absorbance of the solution was measured using UV spectrophotometer at 281 nm and the drug loading was calculated. Percentage drug loading was calculated using formula.(Table-2).

$$\text{Percentage drug loading} = \frac{\text{Practical loading}}{\text{Theoretical drug loading}} \times 100$$

In vitro release:
The in vitro release study was carried out using USP dissolution apparatus type 2 in 400ml phosphate buffer pH 6.8 at 50 rpm. A 2 cm2 patch was taken and attached to a glass slide in order to prevent floating of patch over the dissolution media. The in vitro release study was carried out for 8 hours. 5ml of samples were withdrawn at various times interval, replacing with fresh medium each interval, absorbance of the samples were measured at 281nm, and the cumulative percentage release was calculated.(fig.4&5)
Bio-adhesive strength of selected patches:
In general, the strength of mucoadhesion is affected by various factors such as contact time with mucus, swelling rate of the polymer and the biological membrane used in the study. The bio-adhesive strength of the selected formulations is showed in the table 6. The highest bio adhesive strength was showed by formulation C12R2, which was 9.1N. It indicate that, HPMC base have good bio adhesion properties in combination with chitosan and PVP.
Stability study of selected patches:
Patches that were placed in specified temperature and humidity conditions for stability studies were withdrawn every week and analysed for their drug content. Percentage drug present in the patches was determined spectrometrically. It was found that the drug loss was less through the patches stored for one month. The patches were also observed for their appearance and texture. The patches prepared using chitosan, PVP and HPMC combination showed satisfactory characteristics without being influenced by ageing. Drug Release Kinetic Study: To describe the kinetics of the drug release from the buccal patches the data were treated on the basis of mathematical models such as zero-order, first order, Higuchi, Korsmeyer- Peppas models.

III. RESULTS AND DISCUSSION:

Drug – Polymer Compatability:
IR spectra of Repaglinide alone and its combination with polymers. An IR spectrum of Repaglinide showed the peaks 3307.92 cm-1 (N-H, str), 2933.73 cm-1 (O-H gp), 1217.08 cm-1 (C=O str), and 1637.56 cm-1 (C=O str). These peaks can be considered as characteristic peaks of Repaglinide and were not affected and prominently observed in IR spectra of Repaglinide with polymers.(fig no:1,2,3)

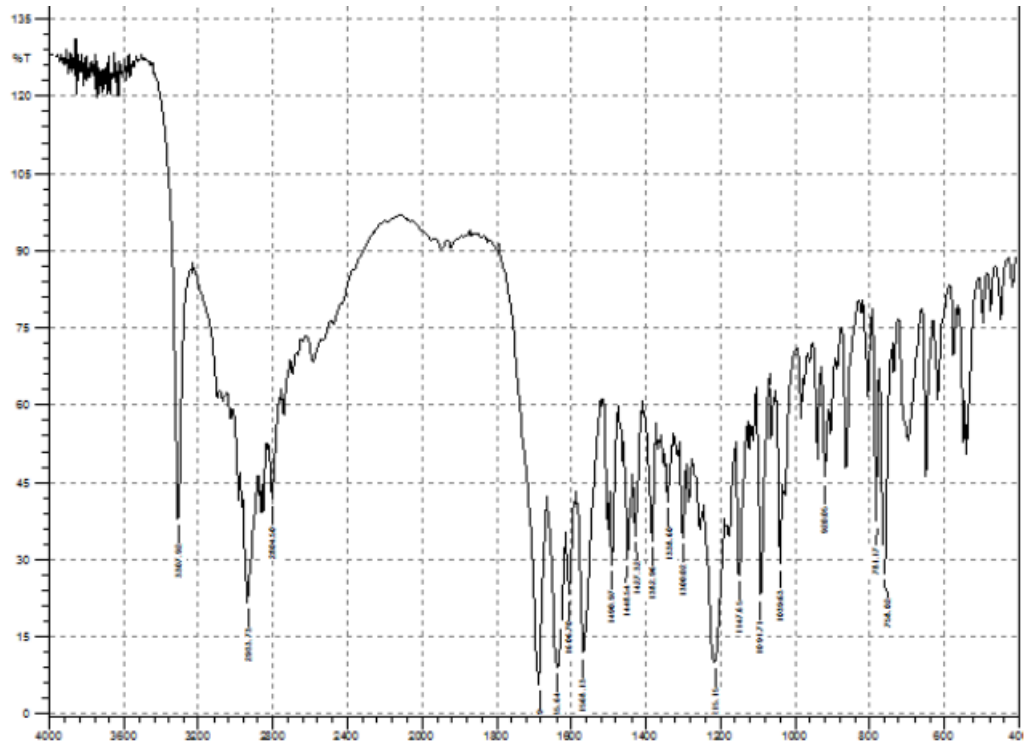

Fig no: 1 Repaglinide pure drug

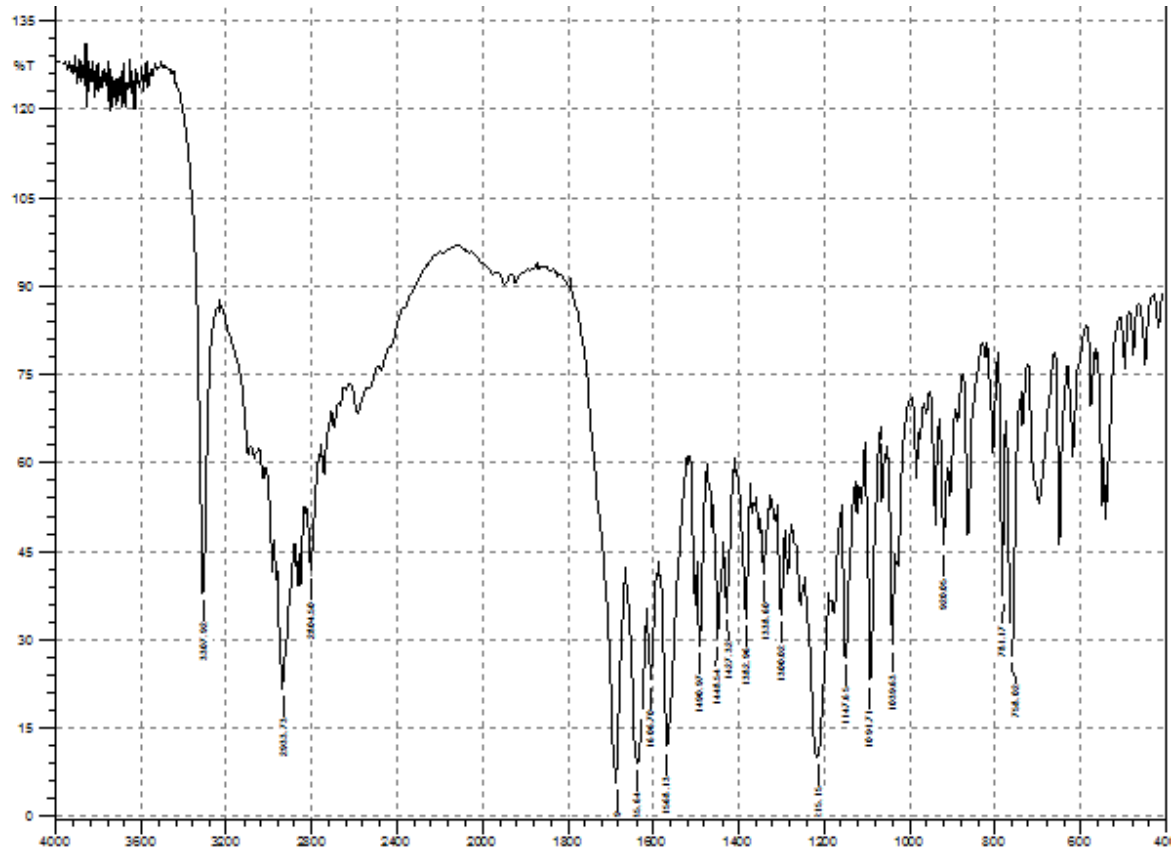

Fig no: 2 Repaglinide + chitosan+PVP+PVA

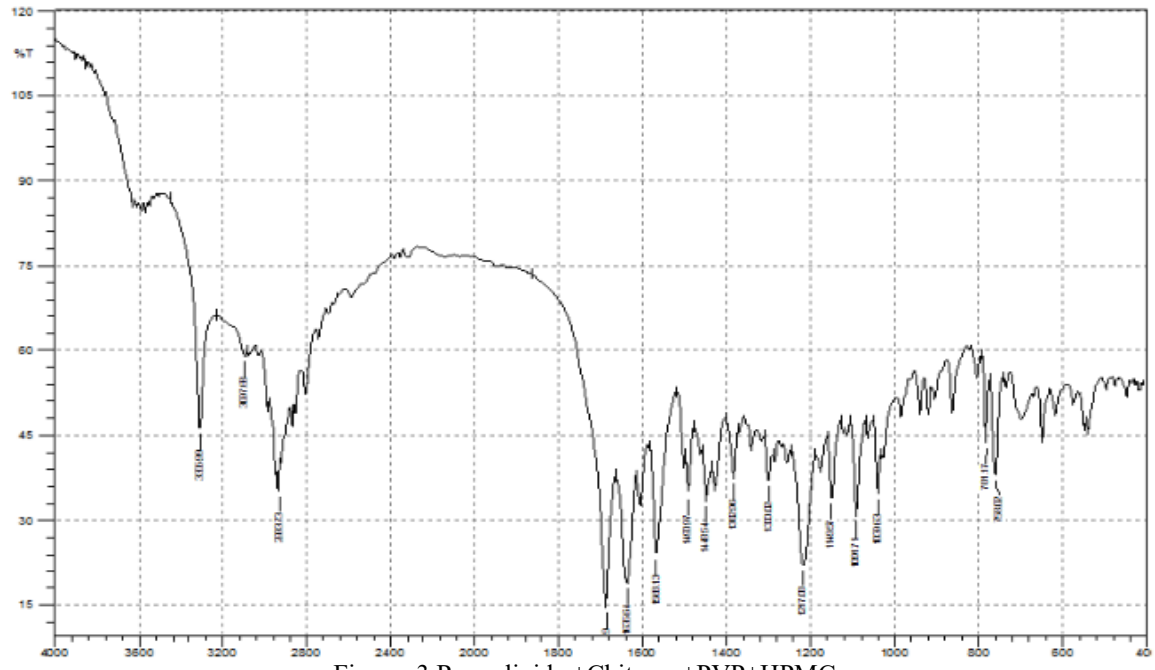

Fig no: 3 Repaglinide +Chitosan+PVP+HPMC

Preparation of the Patches:

The prepared patches were evaluated for physical and mechanical parameters. Based on the results of physical evaluation one patch from each group was selected as right candidate for drug loading. Thus formulations C_2, C_6 were selected which showed satisfactory results. The selected formulations were loaded with different doses of drug Repaglinide.

Evaluation of the Patches

Physical appearance and surface texture:[12]

All the prepared patches were translucent and visually smooth surfaced. A few numbers of patches were brittle and less flexible. All other formulations were smooth and flexible in nature.

Weight variation: [12]

The average weight of film from each group of formulation was reported by taking the weights five times for standard deviation. Results indicated that group-III (Chitosan, PVP, HPMC) have the least mass among the different formulations.

Thickness:

The thickness of films varied from 0.24±0.01mm to0.27±1.3mm. Group I having highest thickness while group IV having least among all formulations.

Swelling index:

Any polymer with good swelling property is expected to be a good candidate for bioadhesive application. Among all formulations from each group C_{12} and C_{16} showed more pronounced percentage swelling index. It was observed that there was proportionate increase in swelling of film as the increase in concentration of film.

Folding endurance:

Films which showed folding endurance above 200 were selected for drug loading. Thus formulations C_{12} and $C_{16}$from each group was selected which showed maximum folding endurance. The results indicate that an increase in polymer concentration increased the folding endurance.

Surface pH:

The surface pH of all the films exhibited uniformity in their values and they were found to be in neutral pH and indicates its compatibility with buccal pH

Table no;1 Evaluation of the Patches

Formulation Code	Texture	Thickness	Weight variation	Folding Endurance	Swelling index(5hr)	Surface p^H
C_1	smooth	0.27	0.08	189	22.7	7
C_2	smooth	0.29	0.075	205	38.7	6.8
C_3	smooth	0.29	.046	210	40.5	6.8
C_4	smooth	0.35	0.032	225	44.6	7
C_5	smooth	0.37	0.029	245	56.5	7
C_6	smooth	0.29	0.035	232	40.9	7
C_7	smooth	0.31	0.035	219	39.3	7
C_8	smooth	0.33	0.033	224	33.9	7

MECHANICAL EVALUATION OF FORMULATION.

Moisture content:

The percentage of moisture content was varied between. in most cases, the moisture content was found to increase with increase in concentration of polymers that are more hydrophilic in nature. Low moisture content in the formulations helps them to remain stable from being a completely dried and brittle film.

Moisture absorption: 14

In the present study the moisture absorption capacity of the films were determined as follows. Three 1cm diameter films were cut out and weighed accurately then the films were placed in desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccator at 79.5 %. After 3 days the films were removed, weighed and percentage moisture absorption was calculated. Average percentage moisture absorption of three films was found.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Water vapour transmission rate:

In this study, the vapour transmission rate of the formulation C12 and C16 that contain higher concentration of chitosan showed the highest transmission rate of 4.1×102 ± 0.82×102 and 4.6×102 ± 0.80×102(g cm-2h-1) respectively

Invitro drug relase

The release data of Repaglinide from all the patches are calculated and the graph of cumulative percentage release vs. time for each combination is shown in fig.5, fig.6.All the formulations of chitosan, PVP combination showed release up to8hr. The maximum percentage release was shown by formulation C2R2 and C6R2. Combinations C2 and C6showed release up to 8hr. The maximum release was shown by formulation C2R2 and C6R2. Thus formulations C2R2 and C6R2 from each combination which showed maximum percentage loading and drug release were selected for further studies.

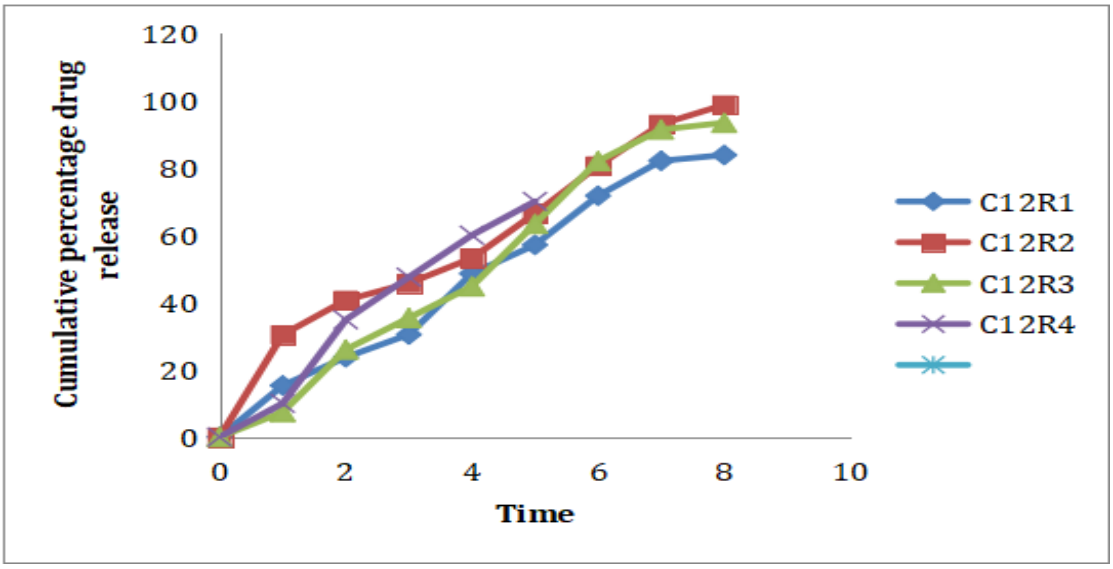

Fig no :4 *In vitro* dissolution study on C2R2

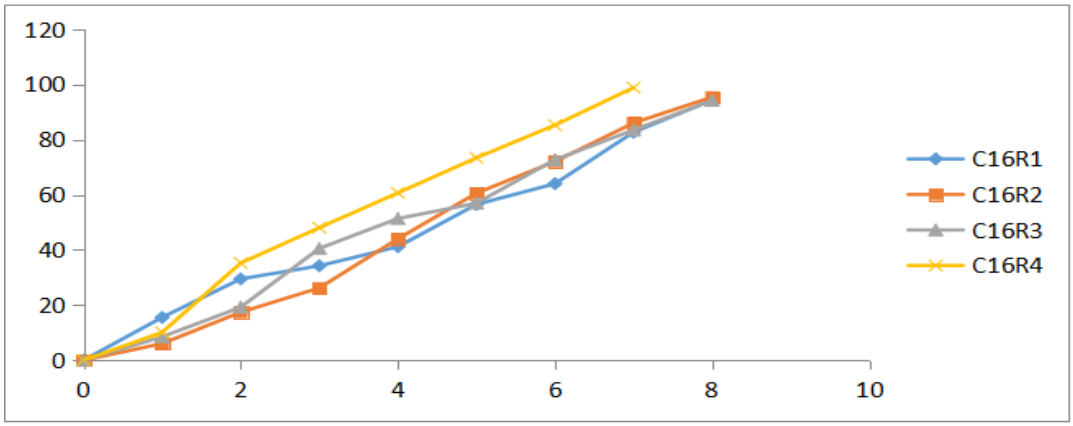

Fig no: 5 *In vitro* dissolution study on C6R2

Drug Release Kinetic Study:

Formulation C2R2 shows zero order drug release kinetics .It shows R2 value of 0.9678.

Bio-adhesive strength of selected patches. (Table.3)

In general, the strength of mucoadhesion is affected by various factors such as contact time with mucus, swelling rate of the polymer and the biological membrane used in the study. The bio-adhesive strength of the selected formulations C12R2

The highest bioadhesive strength was showed by formulation, which was 6.588 N. It indicate that increase in the concentration of chitosan increases bioadhesion properties**.**

Table no3; Bioadhesive strenght of the patch

Formulation code	Bioadhesive strength (N)
C_2R_2	5.201±0.15
C_6R_2	6.588±0.13

Patches that were placed in specified temperature and humidity conditions for stability studies were withdrawn every week and analysed for their drug content. Percentage drug present in the patches was determined spectrometrically. It was found that the drug loss was less through the patches stored for three month. The patches were also observed for their appearance and texture. The patches prepared using chitosan(1%), PVP combination showed satisfactory characteristics without being influenced by ageing.

Formulation Code	Zero Code	Higuchi model	Peppas model	
C2R2	0.9678	0.9554	0.9467	n=0.5
C6R2	0.9906	0.8586	0.9958	n=1.5

Statistical analysis:

All the data were statistically analysed using Instat Graph Pad software. P value (< 0.05) considered as significant.

IV. CONCLUSION

Repaglinide is an antidiabetic drug which belongs to the class of Meglitinides .the main aim of the study is to develop and characterise mucoadhesive buccal patches of Repaglinide to avoid first pass metabolism. The patches were prepared by solvent casting method and characterised for folding endurance,thickness,drug content,surface pH ,tensile strength, bioadhesive strength, in vitro drug release study etc. In vitro dissolution studies are conducted by using phosphate buffer 6.8 pH. The buccal patches were prepared by using the polymers chitosan, poly vinyl pyrrolidone, Hydroxyl propyl methyl cellulose, poly vinyl alcohol.Propylene glycol is used as plasticiser. The result of the study indicates tensile strength of patches were between 1.82-2.1N/m2. Folding endurance is between 189 to 245.Patches thickness were from 0.27-0.33mm .The swelling index is between 22.7 to 56.7. Bio adhesion time was from 4-6 hours. Buccal patches prepared with chitosan, PVP K-30, HPMC were exhibit prolong release for more than 8 hours. It is having case II transport mechanism. The drug release rate of all the formulation were analysed for Zero order,First order,Higuchi and Peppas equation. All the formulation follows case II transport and anomalous mechanism**.**

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