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Research Article

DESIGN, DEVELOPMENT AND EVALUATION OF MUCOADHESIVE PATCHES OF REPAGLINIDE FOR BUCCAL DELIVERY

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Abstract

The buccal region offers an attractive route of administration for systemic drug delivery. The aim of the present study was to develop the mucoadhesive buccal patches of Repaglinide by solvent casting method using the polymers like chitosan, PVP K-30 and propyleneglycol as plasticiser. Repaglinide is an anti-diabetic drug in the class of medications known as meglitinides. It is having an oral bioavailability of 56% and half-life of 1 hour. It undergoes hepatic first pass metabolism. All the formulations were examined for film thickness, weight variation, drug content, percentage moisture loss, and percentage moisture absorption, surface pH, folding endurance, tensile strength, *in vitro* and *in vivo* residence time and in vitro release. All prepared buccal patches were smooth and flexible. The surface pH of all formulation showed to be neutral. *In vitro* release studies were conducted for Repaglinide loaded patches in phosphate buffer (pH, 6.8) solution. The formulation C_5 R_2 showed optimum tensile strength which indicates less probability of rupture. Stability studies were performed for optimised formulation and showed no appreciable change in physical structure and in drug content. Data of *in vitro* release from patches were fit to different equations and kinetic models to explain release profiles. Kinetic models used were zero and first-order equations, Higuchi, and Korsmeyer-Peppas models. The selected patches were further studied for temperature dependant stability studies for three months. It was found that the drug loss was less through the patches stored for three months.

Key Words: Bio adhesive strength, Buccal patches, *in vitro* release, Repaglinide,

Introduction

Amongst the various routes of administration tried so far in the novel drug delivery systems, localized drug delivery to tissues of the oral cavity has been investigated for the treatment of periodontal disease, bacterial and

fungal infection. Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action. Repaglinide is an anti-diabetic drug in the class of medications known as meglitinides. It is having an oral bioavailability of 56% and Half-life of 1 hour. It is used as the suitable candidate because of its low therapeutic dose and hepatic first pass metabolism. In addition, it should release the drug in a predictable manner to elicit the required therapeutic response. Drug delivery through the buccal mucosa offers a novel route of drug administration. Bio adhesion may be defined as the state in which two materials, at least one of which is of a biological nature, are held together for extend periods of time by interfacial forces. If the adhesive attachment is to a mucous coat, then the phenomenon is known as mucoadhesion. It causes bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism. Buccal adhesive patches are modified release dosage form that has potential to provide controlled drug delivery from 1 to 24 hrs. They adhere to buccal mucosa for extended period of time. Various synthetic polymers are under investigation or the buccal drug delivery. In the current work the various polymers used are chitosan, PVP K-30 and propylene glycol is used as plasticizer. Chitosan is a cheap nontoxic biodegradable polymer, widely available in Indian coastal areas and gives wide opportunities for development of better drug delivery systems.

Materials and Methods:

Repaglinide was purchased from yarrow chem products, Mumbai. Chitosan was obtained from yarrow chem. Pdts, Mumbai. PVP K 30, PVA and HPMC were obtained from HiMedia laboratories Pvt.ltd, Mumbai. Propylene glycol and acetic acid was purchased from Nice Chemicals Pvt. Ltd, Cochin.

Methods

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 the placebo patches

The plain polymeric patches were prepared by solvent casting technique. Acetic acid solution 1.5% 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 was added at different ratios to get different combinations of

patches. Propylene glycol was added as plasticizer. The polymers were weighed accurately and dissolved properly. The required quantity of propylene glycol was added. This polymeric solution was kept overnight to remove air bubbles, and then it was added uniformly to a petriplate containing mercury as substrate. The plate was then kept in an oven at 45^0C for 24 hours. After drying the film was peeled off with a sharp blade and kept in a self-sealed cover.

Table-1: Composition of various prepared buccal films with different polymers.

FORMULATION	CHITOSAN	PVP K-30	PROPYLENE GLYCOL
C_1	0.8	0.2	5
C_2	0.8	0.3	5
C_3	0.8	0.4	5
C_4	0.8	0.6	5
C_5	1	0.6	5
C_6	0.8	0.6	5
C_7	0.6	0.6	5
C_8	0.4	0.6	5

Preparation of drug loaded patches

The plain polymeric patches were prepared by solvent casting technique. acetic acid solution 1.5% 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 was 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 45^0C for 24 hours. After drying the film was peeled off with a sharp blade and kept in a self-sealed cover.

Table2.Composition of drug loaded patches.

Formulation	Dose of Repaglinide	Chitosan	PVP K-30	Propylene glycol
C_4R_1	15	0.8	0.6	5
C_4R_2	10	0.8	0.6	5
C_4R_3	5	0.8	0.6	5
C_4R_4	2	0.8	0.6	5
C_5R_1	15	1	0.6	5
C_5R_2	10	1	0.6	5
C_5R_3	5	1	0.6	5
C_5R_4	2	1	0.6	5

Formulation of ethyl cellulose backing membrane:[10]

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. The composition of ethyl cellulose backing membrane is as follows.

Table3: Formula of ingredients ethyl cellulose backing membrane.

Sl no	Ingredients	Concentration
1	Ethyl cellulose	4%w/w
2	Glycerol	10%w/w of polymer weight
3	Alchohol:Toluene(1:4)	QS to 100 ml

Evaluation of patches

Physical Appearance and Surface Texture: Physical appearance and surface texture evaluation includes visual inspection and evaluation of texture by feel and touch.

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.

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

SD% = % swelling by diameter method

D_t = diameter of swollen patch after time t

D_o = original patch diameter.

Folding Endurance:

The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance.Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 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 it solidified 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:

i. 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:

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

ii. 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 (RH). 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. Glassbottle (length =5cm, narrow mouth with internal diameter =0.8cm) 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 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 oneside 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.

$$\text{Percent elongation at break} = \frac{L_B - L_0}{L_0} \times 100$$

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

L_0 = original length of the specimen in cm.

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

Evaluation of Drug Loaded Patches:

Drug Content Determination: [2]

The weight of whole patch was determined and cut in to $2cm^2$. 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.

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

***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 100 rpm. A 2× 2 cm 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.

Bio-adhesive Strength of Selected Patches:

The tensile strength required to detach the polymeric patch from the mucosal surface was applied as measure of the bioadhesive performance. The apparatus was locally assembled and was a modification of the physical balance. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by small stainless steel lamina vertically suspended. At the same side, a platform was maintained in the bottom in order to fix the model mucosal membrane. The bovine cheek pouch excised and washed was fixed to the platform. The mucoadhesive patch was fixed of $3cm^2$, was fixed to the stainless steel lamina using an adhesive. The exposed patch surface was moistened with 1ml of isotonic phosphate buffer for 30 seconds for initial hydration and swelling. The platform was then raised upward until the hydrated patch was brought into the contact with the mucosal surface. A preload of 20gms was placed over the stainless steel lamina for 3 minutes as initial pressure. And then weights were slowly increased on the right pan, till the patch detaches from the mucosal membrane. Force required detaching the patch from the mucosa give the bioadhesive strength of the mucoadhesive patch. The procedure is repeated for 3 times for each patch and mean value of the 3-trials was taken for each set of formulation. After each measurement the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before taking reading.

Bio adhesive force, $F = \frac{(W_w \times G)}{A}$

A - Surface area of the patch(cm2)

Ww - Weight applied (g)

G - Acceleration due to gravity (cm/s^2)

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 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.

Results and Discussion

Drug Estimation:

Calibration curves of Repaglinide in methanol and phosphate buffer (pH 6.8) solutions were obtained at 281 nm with UV spectrophotometer. Beer's law obeyed to construct the calibration curve was in the concentration range of 2-10µg/ml.

Drug – Polymer Compatability:

IR spectra of Repaglinide alone and its combination with polymers. An IR spectrum of Repaglinide showed the peaks 3331.07cm-1 (N-H, str), 2953.02cm-1 (C=C str), 1678.07cm-1 (C=O str), and 1529.55cm-1 (Ar-NO2 str). These peaks can be considered as characteristic peaks of repaglinide and were not affected and prominently observed in IR spectra of along Repaglinide with polymers.

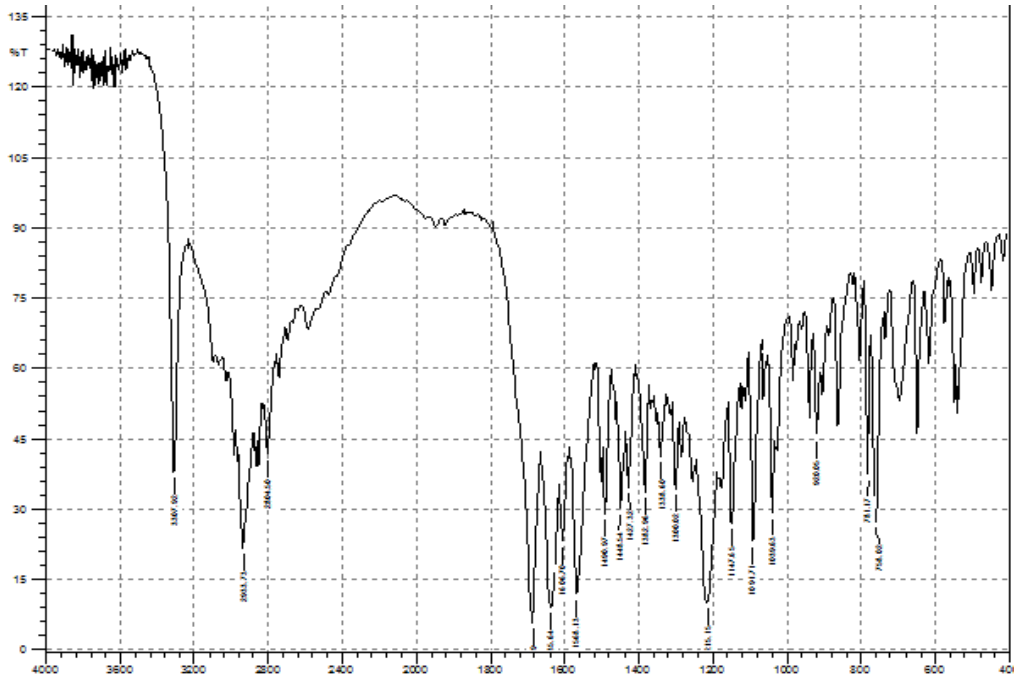


Fig.1-IR spectrum of Repaglinide.

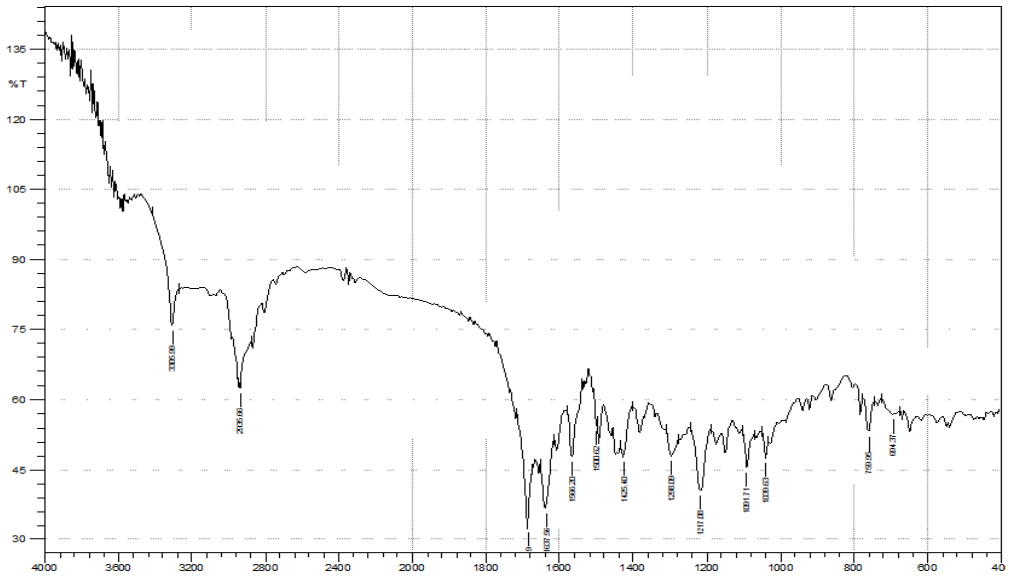


Fig.2-IR spectrum of Repaglinide +Chitosan+PVP

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_4, C_5 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 smoothsurfaced. 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. The weights of the patches range from mg to mg.Results indicated that group-IV (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_4 and C_5 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.

Table-4: Physical evaluation of formulation C_1-C_8.

Formulation code	Texture	Thickness	Weight variation (g)	Folding endurance	Swelling index(5hr)	Surface pH
C_1	Brittle	0.27±1.25	0.030±0.81	94±1.13	16.3±4.1	5.7
C_2	Less flexible	0.261±1.4	0.033±0.76	115±1.1	25.5±3.9	6.7
C_3	Less flexible	0.27±1.2	0.032±0.57	187±1.5	53.8±2.9	6.4
C_4	flexible	0.27±1.1	0.026±0.23	209±1.1	62.5±1.9	6.8
C_5	flexible	0.29±1.05	0.023±0.25	215±1.3	43.7±1.7	7
C_6	flexible	0.26±1.04	0.039±0.50	200±2.5	37.5±2.9	6.4
C_7	Less flexible	0.23±1.4	0.027±0.43	185±2.3	40.1±3.6	6.5
C_8	Less flexible	0.24±1.3	0.029±0.32	180±2.0	38.6±3.8	6.4

Folding endurance:

Films which showed folding endurance above 200 were selected for drug loading. Thusformulations C_4 and C_5 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 indicate its compatibility with buccal pH.

Moisture content & moisture absorption studies:

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.

Table-5: mechanical evaluation of formulation C_1-C_8.

Formulation code	Moisture content	Moisture absorption	Vapour transmission rate ($gcm^{-2}h^{-1}$)	Tensile strength (N/m2)	Percentage elongation at break
C_1	0.97%±0.02	0.98%±0.017	$1.4\times10^2 \pm 0.75\times10^2$	1.5±0.25	15%± 8.4
C_2	0.97%±0.02	0.98%±0.076	$1.45\times10^2 \pm 0.8\times10^2$	1.5±0.35	15%±8.5
C_3	1.4%±0.025	0.98%±0.017	$1.5\times10^2 \pm 0.75\times10^2$	2.5±0.16	33%±8.4
C_4	1.5%±0.06	1.78%±0.009	$4.1\times10^2 \pm 0.82\times10^2$	3.0±0.15	40%±8.6
C_5	1.4%±0.10	0.98%±0.002	$4.6\times10^2 \pm 0.80\times10^2$	3.8±0.16	46%±7.3
C_6	1.2%±0.10	0.98%±0.017	$2.7\times10^2 \pm 0.75\times10^2$	2.5±0.11	27%±7.9
C_7	1.01%±0.02	0.88%±0.003	$2.5\times10^2 \pm 0.73\times10^2$	2.5±0.17	25%±7.3
C_8	0.98%±0.02	0.55%±0.009	$1.4\times10^2 \pm 0.73\times10^2$	1.5±0.14	16%±8.3

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 filmswas 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 C_4 and C_5 that contain higher concentration of chitosan showed the highest transmission rate of $4.1\times10^2 \pm 0.82\times10^2$ and $4.6\times10^2 \pm 0.80\times10^2$($g\ cm^{-2}h^{-1}$) respectively (table5).

Tensile strength:

Tensile strength measures the strength of film as a diametric tension or tearing force. It is measured in gm or N/m^2. The tensile strengths of patches were studied. The tensile strengths of patches were in the order of $C_4 > C_3 > C_2 >$

C_1 in group I. This indicates chitosan and polyvinyl pyrollidone produce effective cross-linking. Among all the patches studied patch C4 and C5 showed highest tensile strength and patch C_1 showed lowest tensile strength.

Percent elongation at break:

The elongation at break test provides an indication of the strength and elasticity of the film which is reflected by the elongation of the break. Films suitable for buccal application should preferably be strong but flexible. The evaluation of C4, C5 formulations in each group showed highest elongation in formulations.

Evaluation of Drug Loaded Patches:

Drug content determination: [2]

The content uniformity test was performed by adding the drug containing buccal patches was added to 100 ml of phosphate buffer (PB) pH 6.8 contained in a 250 ml beaker was placed on temperature controlled magnetic stirrer maintained at 37 °C. The medium was stirred at 300 rpm with a magnetic bead for 3 h. Then the solution was filtered through 0.45 µm membrane filter and the filtrate was examined for the drug content at 281 nm using UV-Spectrophotometer.

Table 6: Percentage dug loading

Formulation Code	Dose of Repaglinide	Percentage Drug loading
C_4R_1	15	45.54
C_4R_2	10	58.76
C_4R_3	5	41.25
C_4R_4	2	33.74
C_5R_1	15	43.10
C_5R_2	10	60.88
C_5R_3	5	46.72
C_5R_4	2	49.50

In vitro drug release:

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 C_4R_2 and C_5R_2. Combinations C_4 and C_5 showed release up to 8hr. The maximum release was shown by formulation C_4R_2 and C_5R_2. Thus formulations C_4R_2 and C_5R_2 from each combination which showed maximum percentage loading and drug release were selected for further studies.

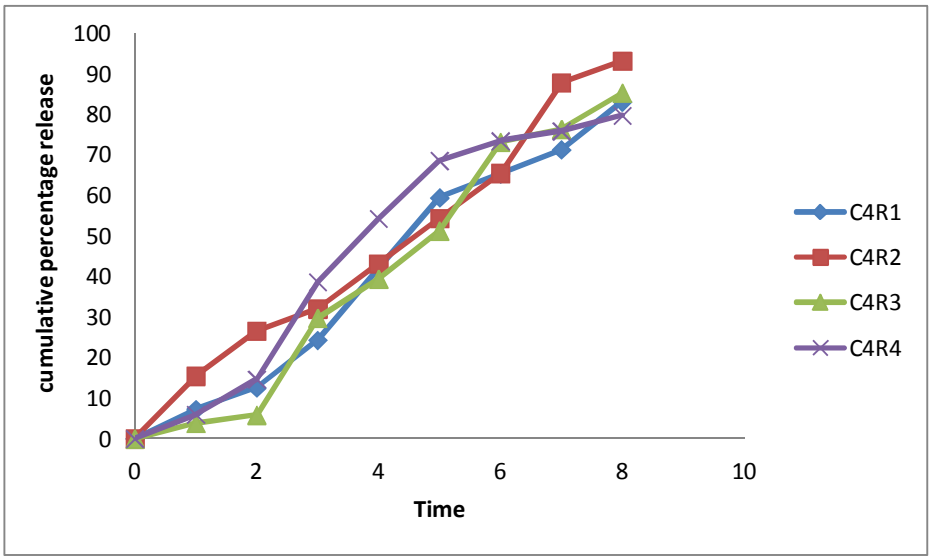


Fig.5- _in vitro_ release of Repaglinide from buccal patches of C_4R_1 - C_4R_4

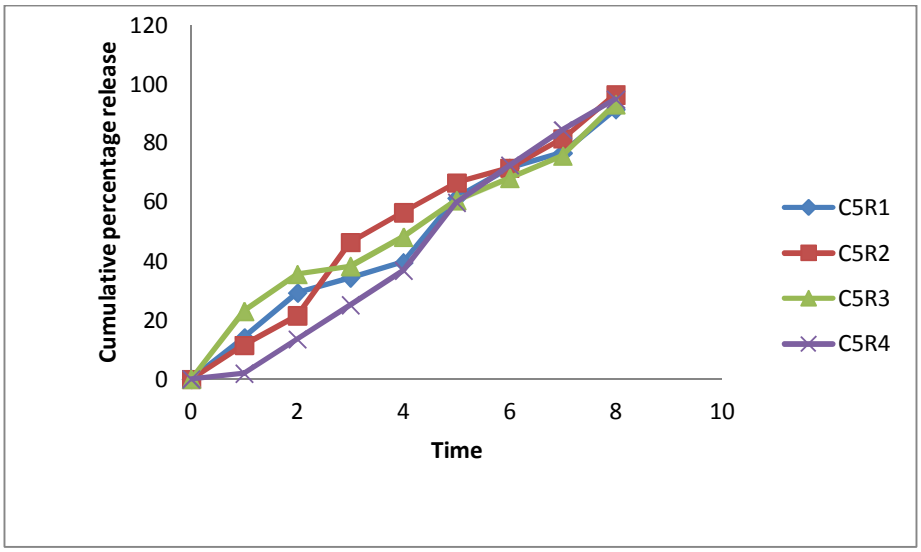
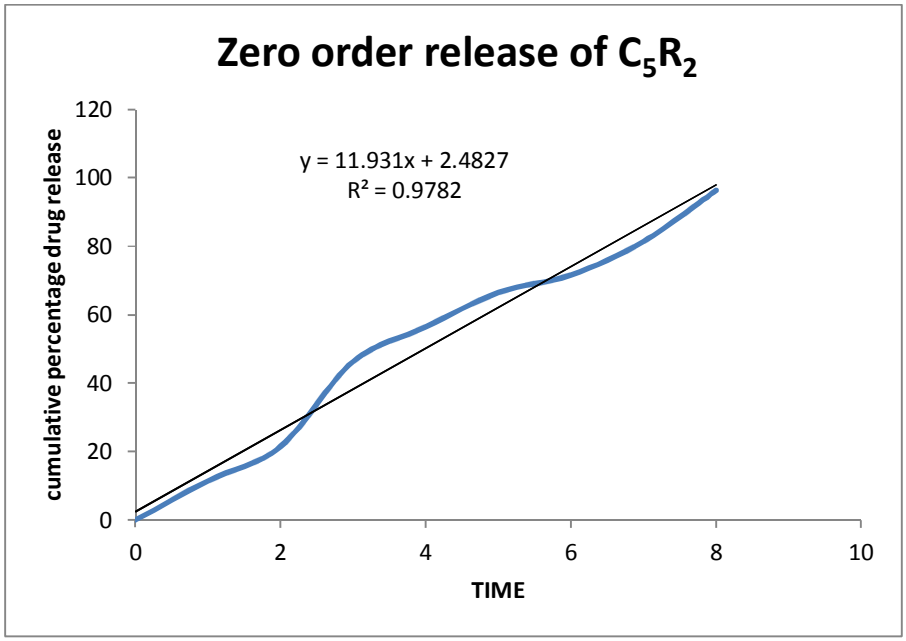


Fig.6- _in vitro_ release of Repaglinide from buccal patches of C_5R_1 – C_5R_4

Drug Release Kinetic Study: Formulation C5R2 shows zero order drug release kinetics .It shows R^2 value of 0.9782.



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 C_4R_2 is showed in the

(Table 6). 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-7: Bio-adhesive strength of selected patches.

Formulation code	Bioadhesive strength (N)
C_4R_2	5.201±0.15
C_5R_2	6.588±0.13

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 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.

Conclusion

Among the various polymeric combinations, the combination C_5R_2 was found to be most suitable. The formulation C_5R_2 comprising polymers 1% chitosan, PVP K 30 fulfil the requirement of good buccal film. It showed highest bioadhesive strength. Stability studies also showed satisfactory results. It follows *in vitro* drug release up to 96.45% for 8hr.Thus from the present study it can be concluded that, bucco adhesive system for Repaglinide with chitosan1%, PVP K-30 meet the ideal requirement for buccal devices which can be good way to bypass the extensive hepatic first pass metabolism and increase bioavailability.

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