"TRANSMUCOSAL DELIVERY OF SITAGLIPTIN AND DAPAGLIFLOZIN FOR DIABETIC THERAPY THROUGH A MUCOADHESIVE BUCCAL PATCH COMPRIZING NATURAL POLYSACCHARIDES''

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ABSTRACT:
Study's purpose was to develop and assess a mucoadhesive buccal patch containing the combination of two antidiabetic drugs sitagliptin and dapagliflozin by using solvent casting method. For the manufacture of sitagliptin and dapagliflozin mucoadhesive buccal patch, a two-factor, three-level factorial design was used. sitagliptin and dapagliflozin buccal patch thickness, weight uniformity, surface pH and folding endurance, drug content uniformity, swelling index, moisture absorption, tensile strength and *invitro* drug release research were all analyzed. Ex vivo mucosal permeability, ex vivo mucoadhesion time, In vivo bioavailability study, and accelerated stability experiments were performed on the optimized formulation. Ex vivo mucoadhesion time 7.00 hr and drug release of sitagliptin 92.84±0.55 % and dapagliflozin 91.9±0.55 % respectively in six hours. A reduction in first pass metabolism, an increase in anti-diabetic activity, and a maximum permeation of 93.42±1.32% were all observed. In vivo bioavailability of sitagliptin and dapagliflozin buccal patch show significant results when compared to marketed tablet. As a result, it suggests a viable alternate drug delivery system for sitagliptin and dapagliflozin for the treat type 2 diabetes. The stability of formulations was tested which indicated that percentage drug release and mucoadhesion time exhibited variations within the limit up to 2 months of testing with acceptable slight variation. The buccal route is a preferred method of administration for systemic drug delivery because it provides the medication with direct access to the systemic circulation and has a high efficacy in the treatment of Type 2 diabetes.

Keywords: Buccal patch, sitagliptin, dapagliflozin, mucoadhesion, solvent casting, Ex-vivo drug release, In-vitro bioavailability study**.**

INTRODUCTION:

Over 171 million people worldwide already suffer with diabetes, and by 2030, that figure is predicted to double. Obesity and type 2 diabetes have become much more common over the last thirty years, and this has resulted in increased health care expenses and societal repercussions. The complex interplay of genetic and epigenetic predispositions, along with the equally intricate influence of societal variables that shape behavior and environmental dangers, is what leads to the underlying causes of the diabetes epidemic. Furthermore, some data point to

the possibility that the incidence of obesity in adults and children may level off or stabilize in some industrialized countries, which could lead to a decrease in incident type 2 diabetes (T2DM), as obesity remains a key risk factor for the disease.[1]

Parenteral, transdermal, and mucosal drug delivery are among the other administration techniques that can prevent hepatic first-pass metabolism and successfully maintain drug levels in the bloodstream. Drug plasma levels are effectively maintained using the parenteral approach, which supplies medication to the systemic circulation. This route is not selected, though, because administering it hurts. Transdermal administration of effective lipophilic medicinal products is often limited to barrier properties and slow delivery since it is not optimal for maintaining rapid blood levels. This mucosal method of administration bypasses the pre-systemic first-pass metabolism of the liver and gastrointestinal tract.

MATERIALS AND METHODS:

Materials: The API drugs sitagliptin and dapagliflozin are purchased from Unichem laboratories, Kolhapur and remaining all the chemicals used for the study was also purchased from the Unichem laboratories, Kolhapur.

Methods Preparation of Sitagliptin and Dapagliflozin buccal patch by solvent casting method: The solvent casting process was used to manufacture Sitagliptin and Dapagliflozin buccal mucoadhesive patches by using different concentration of chitosan solution. The chitosan solution was prepared using 1.5% (v/v) acetic acid in distilled water under occasional stirring for 48 hr. The resulting viscous chitosan solution was filtered through nylon gauze to remove debris and suspended particles. In 20 ml of chitosan solution, accurately weighed polyvinylpyrrolidone (PVP K-30) added as a plasticizer under constant stirring. Five minutes were given for the polymer and plasticizer filled beaker to settle. 5 % (v/v) propylene glycol was added as a permeation enhancer in the beaker with constant stirring. Then 50 mg of Sitagliptin and 5mg of Dapagliflozin were weighed and dissolved. The drug and the polymer solution were mixed. The entire solution was completely incorporated with the help of a magnetic stirrer and sonicator. The resultant solution was left overnight at room temperature to ensure a clear, bubble-free solution. A flat surface petriplates was rinsed with Glycerin. The petriplates was filled with the entire solution. To reduce unexpected evaporation, an upturned funnel was put over the petriplates and dried for 24 hours. After Drying remove the patches from petridish and cut into the $2cm^2$.

Pre formulation Study: Pre formulation studies were carried out to try and standardize a spectrophotometric method of measurement for both the drugs sitagliptin and dapagliflozin, as well as to try and standardize method possible for drug polymer interactions. Drug-polymer interaction was investigated using Fourier transform infrared (FTIR) spectra analysis and differential scanning calorimetry (DSC).

Spectroscopic Analysis:

Determination of λ max and calibration curve of sitagliptin: Freshly prepared 500ml of pH 6.8 phosphate buffer solution were transferred to a volumetric flask measuring 100 ml and added 10 mg of Sitagliptin into volumetric flask. A spectrophotometric method based on the measurement of absorbance at 200 to 400 of the UV region in 6.8 phosphate buffer solution has been used in the study for estimating sitagliptin.

Determination of λ max and calibration curve of dapagliflozin: A solution containing 100 ml of methanol and 10 mg of dapagliflozin were transferred to a volumetric flask measuring 100 ml. A spectrophotometric method based on the measurement of absorbance at 200 to 400 of the UV region in 6.8 phosphate buffer solution has been used in the study for estimating dapagliflozin.

Fourier Transforms Infrared Analysis: To evaluate the likely structural modification that occurred, an Agilent Technologies Cary 630 FTIR infrared spectroscopy study of the Sitagliptin and Dapagliflozin sample was conducted.

Drug Excipients Compatibility study: A study on the compatibility of drug excipients using Fourier transform infrared spectroscopy was conducted (FT-IR spectroscopy. Agilent Technology, carry 630 FTIR). Between 4,000 and 400 cm-1 of the sample were examined. The procedure consists of dispersing a mixture of drug, polymer and all other solid excipients (1:1:1) mixed well and then this solid mixture is kept in a stability chamber at 40°C and 75 RH for one month.

Differential Scanning Calorimetry: Pure drugs, polymers, and physical mixes have their DSC thermograms measured after being maintained at 40±2°C and 75±5% RH. All samples were placed in airtight aluminium pans. Heated at a 10°C per minute, and scanned between 30 and 200°C.

Experimental Design:

Table No.1: Formulation table of buccal patches

Formulation Code	Chitosan (%)	PVP K-30 (mg)	Propylene Glycol (%)	Sitagliptin (mg)	Dapagliflozin (mg)
BP1	1.5	50	5	50	5
BP2	2.5	50	5	50	5
BP3	1.5	150	5	50	5
BP4	2.5	150	5	50	5
BP5	1.5	100	5	50	5
BP6	2.5	100	5	50	5
BP7	2	50	5	50	5
BP8	2	150	5	50	5
BP9	2	100	5	50	5

A two-factor, three-level (3^2) factorial design for the sitagliptin mucoadhesive buccal patch was used to optimize the formulation.

Each of the 2 factors was evaluated at three different levels (low, medium, and high), and experimental trials were conducted with each of the nine possible combinations. For the buccal patch, the percentages of mucoadhesive time (Y_1) and cumulative drug release (Y_2) were chosen as the dependent variables, whilst the percentages of Plasticizer concentration (X_1) and Polymer concentration (X_2) were selected as the independent factors. The buccal patch was made using the same quantity of sitagliptin (50 mg) and dapagliflozin (5mg) in each of the nine batches. The 3^2 factorial design approach for the development of the sitagliptin and dapagliflozin mucoadhesive buccal patch's independent and dependent variables is shown as follows.[11]

Evaluation of Patches:

Weight Uniformity: According to the IP method, five patches with similar specifications were chosen from each formulation and subjected to a weight variation test on a digital balance. The average weight of five buccal patches was subtracted from the weight of each patch. The mean and standard deviation were established for every formulation. [39]

Thickness uniformity: A vernier caliper is used to measure the thickness of each patch five times (the center and the four comers).

Folding endurance: In order to show strength patch qualities, a single patch was folded manually up to 200 times, or repeatedly in the same area until it broke., the mean and SD were determined.

SurfacepH:

The pH was measured one minute after equilibration by placing an electrode in direct contact wit h the patch's surface.The patches were exposed to 1 ml of distilled water (pH 6.6 to 7.21) or one minute at room temperature.[45]

Drug Content Uniformity: A content uniformity test was carried out to ensure that both drugs were distributed uniformly across the patch. 100 ml of phosphate buffer was added in a 250 ml beaker when the patch was put on. Hold it for 12 hours to dissolve. A UV spectrophotometer set to 267 nm and 276nm was used to measure the amount of drug present in filtrate 70 ml after the solution had been filtered using whatman filter paper.[11&17]

Swelling study:

Preweighted, 1 cm^2 patches were immersed in 50 ml of distilled water to determine the swelling index of the patches.The strips were carefully removed after 5, 10, 30, and 60 minutes, washed with filter paperand then exactly weighedOverhydration can lead to an unanticipated reduction i n adhesive strength up to a certain point because of separation at the polymer tissue contact.The degree of moisture increases the adhesion. Adhesion is influenced by the rate and extent of patch hydration and swelling, which in turn affects the patch's ability to deliver medication. [22&49]

Tensile strength: The total weight required to break or rupture the dosage form was studied for the tensile strength. A 1x1 cm2 buccal patch, was fixed between the stationary and movable plate. The force required to break the film was calculated by measuring the total weight loaded in the string, and the weight that corresponds to break the patches was taken as tensile strength.[39]

Percentage moisture absorption: The moisture absorption test was carried out to ensure that the buccal patch was stable or undamaged. After the buccal patch was weighed, it was kept at a relative humidity range of 75 to 5% in a desiccator filled with 100 ml of a saturated aluminum chloride solution. Three days after the buccal patch was taken out, the weight was again measured. Using the following formula, the percentage of moisture absorption was determined.[44]

%Moisture absorption = (Final weight - Initial weight) / Initial weight * 100

***In-vitro* drug release:** The in-sure drug release across the buccal mucosa (goat) is performed using Fraz type glass diffusion cells at 37°C-40.2°C. Fresh buccal mucosa is mounted in between the donor and receptor compartments. The buccal patch should be applied with the compartments clamped together and the center facing the mucosa. The donor compartment

contains phosphate buffer pH 6.8. Using a UV-visible spectrophotometer, the absorbance of 2 ml samples was measured at predefined intervals.[35&49]

***Ex Vivo* Permeability Study:** Using a Franz diffusion cell, the degree and rate of Sitagliptin and Dapagliflozin mucosal penetration through the goat buccal mucosa were measured. There was 1cm^2 of effective diffusion area. Phosphate buffer solution, pH 6.4, was used to fill the receptor compartment (23 ml), which was kept at a constant 37±0.5 °C. At a speed of 50 rpm, a magnetic stirrer was utilized to reproduce the environment of the buccal cavity. The donor and receptor compartments of the diffusion cell were enclosed by a patch placed over the goat's buccal mucosal surface while it was covered. At regular intervals, one ml of receptor medium was removed and promptly replaced with an equal volume of PBS, pH 6.4. By measuring the quantity of both the drugs released into the receptor media with a UV-visible spectrophotometer at 267 nm and 276 nm in comparison to a control, the amount was determined.[10]

***Ex vivo* mucoadhesion time:** *Ex vivo* mucoadhesion tests were conducted after the patch was applied to freshly sliced goat buccal mucosa. With cyanoacrylate adhesive, the goat buccal mucosa was attached to the inside of a beaker. Each patch was cut into pieces of 2 cm^2, One side of each piece was moistened with 1 drop of isotonic phosphate buffer pH 6.8 and pasted to the buccal mucosa by applying a light force with a fingertip for 30 sec. The beaker was filled with 500 ml of isotonic phosphate buffer pH 6.8 and kept at 37 °C. After 2 minutes, 50 rpm stirring rate was applied to simulated the buccal cavity's environment and patch adhesion was monitored for 7 hours.[23]

***In vivo* bioavailability study:**

Preparation of rabbit plasma sample preparation:

The liquid-liquid extraction method was used to isolate Sitagliptin and Dapagliflozin in rabbit plasma. Blood samples were collected following oral Mucoadhesive Buccal Patch application of Sitagliptin and Dapagliflozin. Before application the animals were kept fasted for overnight 12 hr.) During fasting animals had free access to water) rabbit (n = 02, weighing 1-2kg). Blood samples (2mL) were collected into labelled heparinized-coated micro- centrifuge tubes containing perchloric acid to precipitate plasma protein. The samples were collected at an interval of 0.15, 0.30, 2, 4, 8, 12 hrs from marginal vein and vortexes for approximately 15 min followed by centrifuging at 3500 rpm. These samples then transferred into sample vials for injection.

Preparation of standard stock solutions (Marketed Tablet): The Sitagliptin and Dapagliflozin tablet 12.5mg was accurately weighed and transferred to 100mL volumetric flask. To this mobile phase was added to make up and sonicated for 15 min. The final volume was made up to 100mL with mobile phase and the solution was filtered through the membrane filter 0.22µ. The data was used to calculate $R^2$and linear regression equation.

Stability studies: Once the patches were deemed suitable, they were sealed in aluminum foil and incubated for two months at 37±0.5°C and 75 % relative humidity. At the one- and two-month marks, the appearance, mucoadhesion time and % drug release of the preserved patches were assessed; the data displayed was the mean of three conclusions. The patches' color, shape, and medication content were examined for any changes.[1]

RESULT AND DISCUSSION:

Pre formulation Study: Melting point of both the drugs was determined by using the digital melting point apparatus. The result was found to be 120^0C and 130^0C respectively.

Solubility Study:

The solubility's of both the drugs are as follows.

Table No.2: Solubility Study

Solvents	Sitagliptin Solubility	Dapagliflozin Solubility
Water	Freely Soluble	Sparingly Soluble
Phosphate Buffer 6.8	Freely Soluble	Freely Soluble
Methanol	Sparingly Soluble	Freely Soluble
Ethanol	Slightly Soluble	Freely Soluble
Propylene Glycol	Slightly Soluble	Freely Soluble

Spectroscopic Analysis :

The λ max of Sitagliptin was found to be 267 nm in 6.8 buffer by UV spectrophotometer.

The λmax of dapagliflozin was found to be 276 nm in 6.8 buffer by UV spectrophotometer.

Drug Excipient Compatibility Study:

This shows the compatibility of drugs and excipients utilizing FTIR spectra, so there is no proof of any incompatibility between the drugs and excipients.

Simultaneous estimation of SITA and DAPA:

Simultaneous estimation of sitagliptin and dapagliflozin involves measuring their absorbance at specific wavelengths to determine their concentration (Cx for SITA and Cy for DAPA) in a sample. At λ_1, SITA and DAPA absorbance's are 0.095 and 0.227 and absorptivity's are 0.0475 and 0.0908 respectively. The resulting total absorbance (A1) is 0.259. At λ_2, SITA and DAPA absorbance's are 0.155 and 0.176 and absorptivity's are 0.0775 and 0.0704 respectively. The resulting total absorbance (A_2) is 0.259. Using these data, the concentration of SITA and DAPA in the sample was calculated to be 20.65 and 4.47 respectively. The percentage recoveries of SITA and DAPA were 88.26 % and 89.58 %, indicating the method effectiveness in estimating the concentrations of these compounds in the sample. The Simultaneous estimation of sitagliptin and dapagliflozin involves analyzing their concentrations in a sample to determine their recovery percentages. The percentage recovery of sitagliptin is 88.26% and dapagliflozin is 89.58 %.

Differential Scanning Calorimetry:

The DSC thermogram of Sitagliptin, a onset of Sitagliptin is visible at 124.82°C. The thermogram of sitagliptin was worded in the temperature range of 10°C to 200°C indicates a broad endothermic peak of Sitagliptin is visible at 146.90°C The DSC thermogram of dapagliflozin, A onset of dapagliflozin is visible at 122.34°C. The endothermic peak of dapagliflozin is visible at 132.04°C. The DSC thermogram of PVP K-30, A onset of PVP K-30 is visible at 179.30°C. The broad endothermic peak of PVP K-30is visible at 193.65°C. A onset of chitosan is visible at 76.29°C. The broad endothermic peak of PVP K-30 is visible at 83.32°C. This indicates the drug is well melted at high temperature. The DSC thermogram of Sitagliptin, Dapagliflozin, chitosan and PVP K-30 mixture. A onset of Sitagliptin is visible at 127.35°C and peak of Dapagliflozin is visible at 214.45°C. This indicates the drug is well preserved in polymer mixture at high temperature. A broad endothermic peak of Dapagliflozin is visible at 217.14°C and a short peak of Sitagliptin is visible at 139.84°C and peak of Dapagliflozin is visible at 217.14°C. This slight shift of melting temperature indicates mixing of Sitagliptin, Dapagliflozin, with excipients.

Evaluation of Patches:

Weight Uniformity: For Each patch within relevant formulation type group, the weight uniformity values were uniform. The average weight of five buccal patches was deducted from

the weight of each patch, a range of 106.38 ±0.03 to 208.77 ±0.06 discovered. While the optimized batch BP4 208.77 ±0.06 because more PVP K 30 quantity. The mean and SD values for each formulation were determined.

Thickness Uniformity: Using a vernier caliper, the thickness of each patch is measured in five distinct places (the center and the four corners). The average thickness of buccal patches was found in the range of 0.51 ±0.013 to 0.59 ±0.04 The optimized batch BP4 shows 0.57±0.013 optimum result due to higher concentration of PVP K 30 used. For each formulation, the mean and SD values were determined.

Folding endurance: Even after more than 200 folds, the patch did not exhibit any cracks. As a result, it was considered the conclusion. folding endurance did not change One patch was manually folded 200 times, which was considered as being acceptable to promote patch qualities, or one patch was repeatedly folded until it broke. The range of the buccal patches' average Folding endurance was observed to be between 168±0.08 and 298±1 while the optimal batch BP4 displays a result of 298±1 in accordance with standards.[42]

Surface pH: Buccal patches are allowed one minute to swell in distilled water. An electrode is applied to the swollen patch to detect the surface pH. It was found between 6.43±0.05 to 6.7±0.02. The optimized batch BP4 shows 6.67±0.04 optimum result within the standard ranges.

Drug Content uniformity: It was discovered in the range of 83.51± 72 and 92.15±0.83. The optimized batch shows 92.15±0.83.

Swelling index study: The bioadhesion and drug release pattern of a formulation are controlled by its swelling behavior. The results of the current investigation showed that excessive hydration can decrease the bond between the bioadhesive patch and the mucosa by dilution of the functional groups that are necessary for the adhesive interaction.

Tensile strength: From taking 3 sequential readings and calculated the mean of 3 reading. The results are found to be as follows. Maximum Tensile strength is to be 277±0.027and the minimum reading is 215 ±0.04. The optimum batch shows the 277.84±0.067 reading.

Percentage moisture absorption:

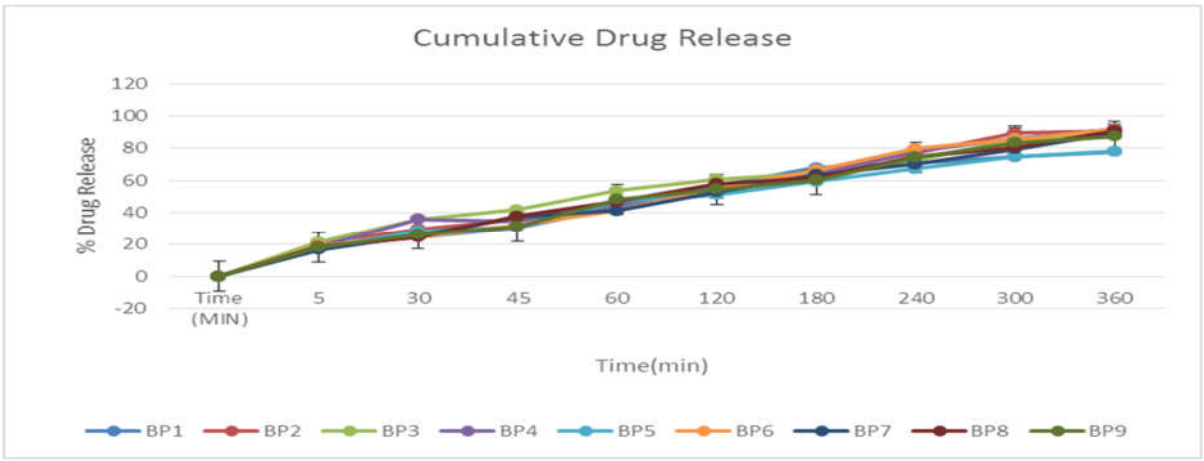
For three days, a study on moisture absorption was conducted. The percentage of moisture absorption (%) varies between 2.64±0.024 % and 5.5±0.013 %. The optimized shows the 2.7±0.019 % reading The formulation's low moisture level is greatly beneficial for preventing

microbiological contaminants and patch bulk. Once more, compositions with low moisture content remain stable rather than becoming an entirely dry and brittle layer The Sitagliptin and dapagliflozin buccal patches' low moisture absorption (%) can assist prevent hydrolytic breakdown, keeping the patches stable.

In-vitro drug release: The in vitro drug release pattern of Sitagliptin and dapagliflozin from prepared buccal patches. All of these buccal patches gradually delivered the drug over the course of 6 hours.

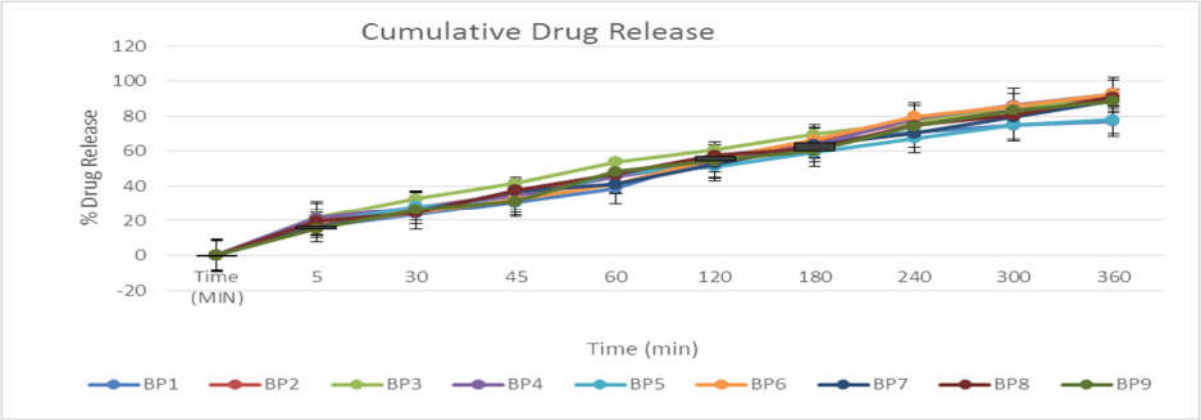
Among all formulations, the maximum drug release of Sitagliptin (92.84±0.55%) over a period of 6h was observed in the case of formulation batch BP4, while the minimum in vitro drug release of Sitagliptin (77.2±0.48%) over a period of 6 h was found in the case of formulation batch BP1.and for Dapagliflozin maximum drug release (91.90±0.55%) over a period of 6h was observed in the case of formulation batch BP4, while the minimum in vitro drug release (79.47±0.48%) over a period of 6 hr.

***Ex Vivo* permeability Study:** The percentage of drug permeated across porcine buccal mucosa was found to be a maximum of 93.42±1.32% for the optimized formulation BP4 at 6 Hrs of study. The satisfactory results were identified based on the duration to reach maximum drug permeation. The formulations reaching maximum drug release within their mucoadhesion time which was estimated earlier are selected for further study.



***Ex vivo* mucoadhesion time:** The results of mucoadhesion study were presented. The selected Formulations were studied for *ex vivo* mucoadhesion time and the duration of mucoadhesion time was found in between 4.25±0.065Hrs to 7±0.035 Hrs. This indicates the duration of

attachment with mucous membrane and period of effective drug release.The formulation BP4 showed optimum mucoadhesive time of 7±0.035 Hrs due to the high concentration of chitosan solution used as compared to BP2, BP4, BP6.



***In Vivo* Bioavailability Study:**

The in vivo bioavailability study of optimized batch was done on rabbits. The result of marketed formulation that is sitagliptin and dapagliflozin tablets.the above study it is quantify that Sitagliptin and Dapagliflozin concentrations into combination Mucoadhesive Buccal Patch shows the maximum plasma drug concentration and marketed sitaxa D tablet shows the minimum plasma drug concentration as compared to buccal patches in rabbit.

Stability Study:

The stability study was done for the optimized batch. After 30 days there are no significant changes in color & texture and shows 7±0.024 hr mucoadhesion time with 92.0±0.83 and 91.8±0.1 and after 60 days the result shows no significant changes in color & texture with 6.8±0.015 and 91.98±0.83 and 91.7±0.4 respectively.

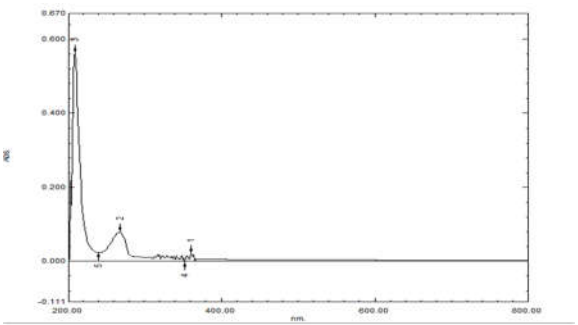


Fig No.8.1: UV spectrum of Sitagliptin

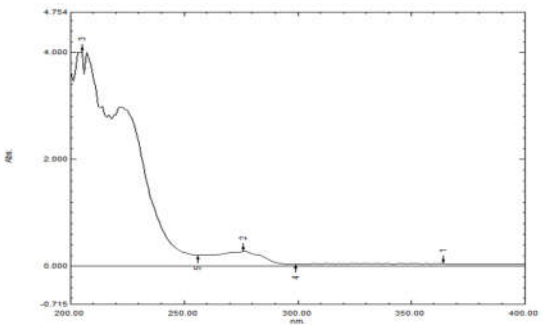


Fig. No.8.2 absorption spectrum of Dapagliflozin

FTIR:

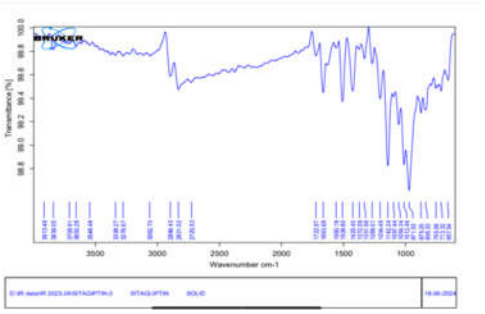


Fig.No.8.3: FTIR Spectra of Sitagliptin

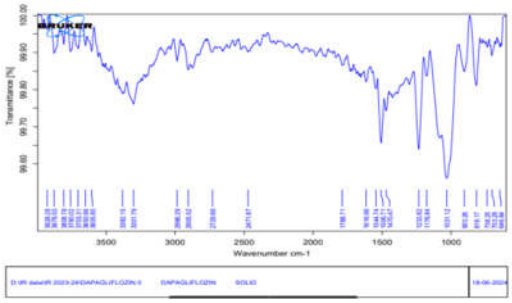


Fig.No.8.4: FTIR Spectra of Dapagliflozin

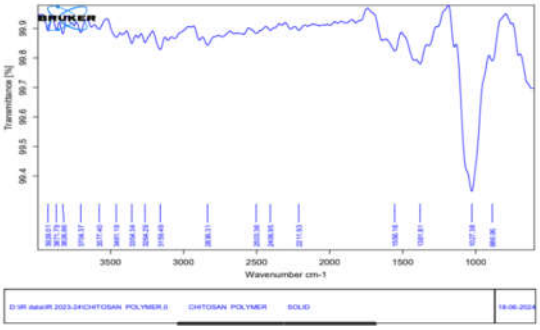


Fig.No.8.5: FTIR Spectra of Chitosan

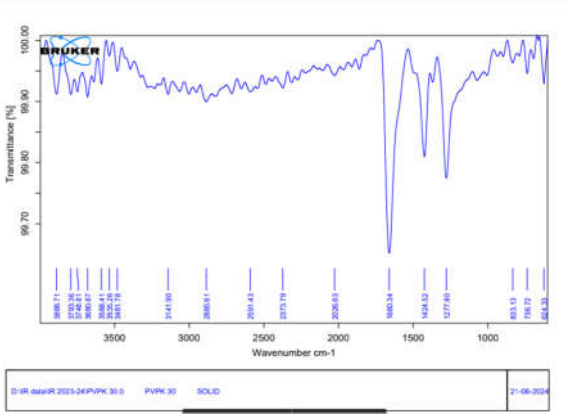


Fig.No.8.6: FTIR Spectra of PVP K 30

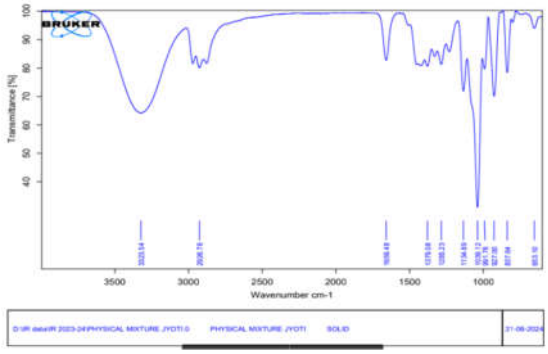


Fig.No.8.7: FTIR Spectra of Physical Mixture

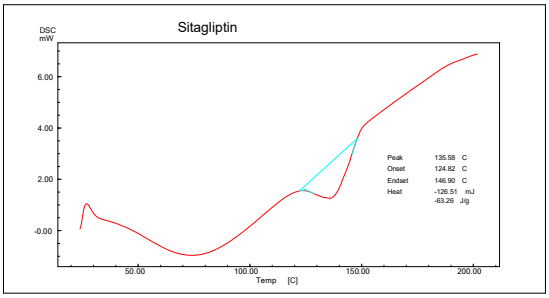


Fig.No.8.8: DSC of Sitagliptin

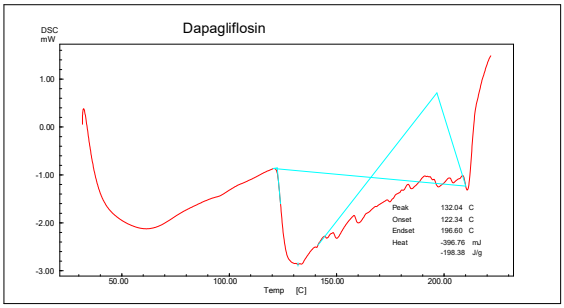


Fig.No.8.9: DSC of Dapagliflozin

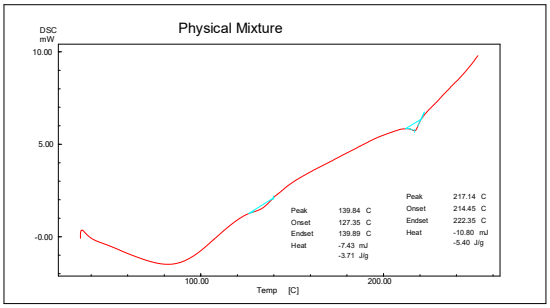


Fig.No.8.10: DSC of Physical Mixture

DSC: The DSC thermogram of Sitagliptin, Dapagliflozin, chitosan and PVP K-30 mixture. A onset of Sitagliptin is visible at 127.35°C and peak of Dapagliflozin is visible at 214.45°C. This indicates the drug is well preserved in polymer mixture at high temperature. The thermogram of sitagliptin ,dapagliflozin and chitosan and PVP K-30 mixture was worded in the temperature range of 10°C to 500°C indicates a broad endothermic peak of Dapagliflozin is visible at 217.14°C and a short peak of Sitagliptin is visible at 139.84°C and peak of Dapagliflozin is visible at 217.14°C. This slight shift of melting temperature indicates mixing ofSitagliptin,Dapagliflozin,withexcipient.

Experimental Design:

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. Response for given levels of each factor. Bydefault, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. Because BP4 exhibits optimum outcomes, it was clear that it is optimized batch according to analysis of DOE data.

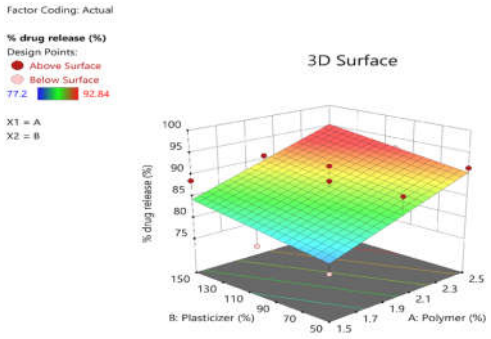


Fig.No.8.11: 3D plot for % CDR

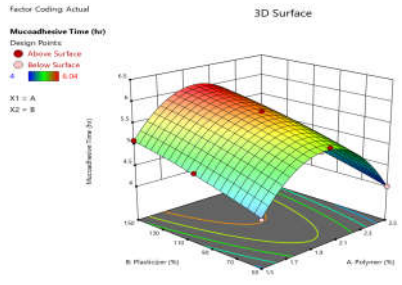


Fig.No.8.12:.3D plot for Mucoadhesion time

Table No.3: Evaluation test -

Batches Code	Weight Uniformity (mg)	Thickness Uniformity	Folding Endurance	Surface pH	Drug Content Uniformity (%)	Swelling Index	Tensile strength (g/cm^2)	Moisture Absorption (%)	Mucoadhesion time
BP1	106.38	0.51	168	6.53	83.51	18.95	215	5.5	4.25
BP2	109.70	0.56	245	6.49	91.04	17.84	261	2.64	6.48
BP3	205.18	0.56	185	6.45	86.44	18.62	231	4.7	5.10
BP4	208.77	0.57	298	6.67	92.15	17.10	277	2.7	7
BP5	155.21	0.58	173	6.7	85.67	18.83	228	5.4	4.78
BP6	158.33	0.59	267	6.60	91.68	17.42	270	2.57	6.73
BP7	108.13	0.53	198	6.50	89.34	18.56	246	3.7	5.35
BP8	207.04	0.54	225	6.50	90.21	18.19	256	3.4	6.04
BP9	156.27	0.55	214	6.43	89.98	18.51	252	3.5	5.78

Summary:

Diabetes mellitus is an ongoing medical condition that affects the proteins, fats, and carbohydrates are metabolized. The most common form of diabetes, known as type 2 diabetes or non-insulin dependent diabetes, is characterized by insulin resistance, relative insulin insufficiency, and hyperglycemia. A two-factor. 3-level (2^3) factorial design used for preparation of Sitagliptin Dapagliflozin mucoadhesive buccal patch. The Independent variables chosen for buccal patch were the percentage of Chitosan Solution and PVP K-30 whereas % CDR and mucoadhesive time were selected as the dependent variable. The preparation of Buccal patch using chitosan solution, PVPK-30 by solvent casting method. The thickness, weight uniformity, surface pH, folding endurance, drug content, swelling index, moisture absorption, tensile strength and in vitro drug release research of the buccal patches were studied. Ex vivo mucosal permeability, ex vivo mucoadhesion time, in vivo bioavailability and accelerated stability experiments were used to further analyze the optimized formulation of Sitagliptin and Dapagliflozin BP4.

Ex vivo mucoadhesion time was 7.00 hours, while the ex vivo permeation research yield an 93.42±1.32% result. In addition to delivering a maximum drug release of of sitagliptin 92.84±0.55 % and 86.39±0.52 of dapagliflozin within the allotted mucoadhesion period, the produced mucoadhesive Sitagliptin and Dapagliflozin buccal patches significantly increased antidiabetic efficacy and decreased first pass metabolism. The in vivo bioavailability study of Sitagliptin and Dapagliflozin buccal patch shows significant results as compared with standard Sitaxa D drug. So, it indicates a potential alternative drug delivery system for Sitagliptin and Dapagliflozin combination for the treatment of type 2 diabetes mellitus.

Conclusion:

This formulation's primary advantage is that it avoids first pass metabolism, allowing for a lower dosage of drug that is still effective. The melting point of sitagliptin and dapagliflozin is 120^0C and 130^0C. Solubility study indicate that both the drugs are soluble in phosphate buffer. From spectroscopic analysis lambda max of sita and dapa is 267 and 276 nm respectively. At λ1, SITA and DAPA absorbance's are 0.095 and 0.227 and absorptivity's are 0.0475 and 0.0908 respectively. The resulting total absorbance (A1) is 0.259. At λ2, SITA and DAPA absorbance's are 0.155 and 0.176 and absorptivity's are 0.0775 and 0.0704 respectively. The resulting total absorbance (A2) is 0.259. Using these data, the concentration of SITA and DAPA in the sample were calculated to be 20.65 and 4.47 respectively. The percentage recoveries of SITA and DAPA were 88.26 % and 89.58 %.

A 2^3factorial design for the Sitagliptin and dapagliflozin mucoadhesive buccal patch was used to optimize the formulation. Each of the 2 factors was evaluated at three different levels (low, medium, and high).A mucoadhesive buccal patch comprising 150 mg of PVP K-30 and 2.5 % solution of chitosan is considered as an optimized batch (BP4) and it shows good mucoadhesive times of 7.00 hours and drug release of sitagliptin 92.84±0.55 % and dapagliflozin 91.9±0.55 % respectivly in six hours, The weight uniformity of optimized batch (BP4) is 208.77 ±0.06, thickness is 0.57±0.013, and surface pH of that batch is 6.67±0.04. The folding endurance and tensile strength ranges are within the limits i.e 298±1 and 277±0.027 respectively.

The drug content uniformity which shows the equal distribution of the drug throughout the batch is 92.15±0.83. Swelling index of optimized batch is 17.10±0.62. The optimum batch (BP4) shows the least percentage of moisture absorbance 2.7±0.019 and maximum percentage of drug

permeation 93.42±1.32 according to the findings. Both in vitro and ex vivo tests yielded favorable results for the bioadhesive buccal patch for sitagliptin and dapagliflozin. Comparing sitagliptin and dapagliflozin buccal patch to other dosage forms of the same combination, in vivo bioavailability confirms that the buccal patch formulation has a considerable effective antidiabetic effect. Thus, it may be said that one of the alternatives for administering sitagliptin and dapagliflozin together is the buccal route.The stability study results confirmed that optimized batch BP4 does not show any large deviation in mucoadhesive time and cumulative drug release.

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