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Design And Development Of Mucoadhesive Buccal Patches

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Abstract: Mucoadhesive patches of Sexagliptin containing 1 mg of drug were prepared successfully using HPMC (15 and 47 cps), PVA, and ethylcellulose polymers in different combinations and there were total six films were prepared. Optimized formula was evaluated and drug release pattern was studied. Water soluble polymers showed highest release compared to water insoluble polymers. More over the viscosity of the polymer also affects the drug release pattern. Formulations followed the zero order kinetics and Higuchi's model for drug release. In vivo absorption of drug in rabbits found that 80.14% within 30 min from the optimized formula. The in vitro-in vivo correlations (IVIVC) was attempted for the release and absorption of Sexagliptin from the patches. The correlation coefficient for patch BP-V was 0.996.

Index Terms - Mucoadhesive patches, Sexagliptin, HPMC, zero order kinetics and Higuchi's model

I. INTRODUCTION

Nowadays, requirement of design and development of novel dosage form is created to improve patient compliance, safety and efficacy. Buccal film is novel film technology which is fulfilled all these requirements. Buccal film is administered through buccal drug delivery system. Buccal film is small in size, dose, easily administered so that it is more palatable and acceptable dosage from than other buccal drug delivery system like wafers, lozenges, microparticles, gel, tablets. Buccal film is effective dosage form which improves bioavailability as it bypasses first pass metabolism. It is satisfactorily adhered to buccal layer of oral cavity so it is more convenient than other dosage form. It is cost effective, biodegradable, fast absorption, elegant, easy to handle, non irritating and no requirement of swallowing of drug henceforth it is more accepted dosage form by geriatric and pediatric patients.(Jagtap V, 2020).

1.1 Advantages of Buccal Film (Jagtap V, 2020).

- No risk of chocking.
- No need of chewing and swallowing.
- Rapid onset of action and minimum side effects.
- Accurate dosing compared to liquid dosage form.
- Taste masking is possible.
- Good mouth feel and good stability.
- Requires less excipient.
- Ease of transportation, storage and consumer handling.
- More Economical
- Ease of administration to pediatric, geriatric patients. Also to patients who are mentally retarded, disabled or non cooperative.

- Prolongs residence time of dosage form at site of absorption. So improves bioavailability.
- Drug can be protected from degradation in GI tract and acidic environment.
- Buccal film has large surface area that leads rapid disintegration and dissolution in oral cavity.

1.2 Disadvantages of Buccal Film (Jagtap V, 2020).

- Saliva is continuously secreted into the oral cavity diluting drugs at the site of absorption resulting in low drug concentrations at the surface of the absorbing membrane. Instinctively swallowing of saliva results in a maximum part of dissolved or suspended released drug being removed from the site of absorption. Moreover, there is risk that the delivery system itself would be swallowed.

- Drug characteristics can make boundary for use of the oral cavity as a site for drug delivery. Taste, irritancy, allergy and adverse properties such as discoloration or erosion of the teeth can limit the drug candidate list for buccal route. Conventional type of buccal drug delivery systems did not allow the patient to concomitantly eat, drink or in some during talk.

1.3 Ideal Characteristics of Drug to be selected (Jagtap V, 2020):-

- No Bitter Taste
- Dose lower than 20mg.
- Low molecular weight
- Good stability in water and saliva.
- Ability to permeate oral mucosal tissue

1.4 Theories of Mucoadhesion (Rajaram DM, 2017)

There are five different theories, which explain phenomenon of mucoadhesion:

- **Electronic theory**

This theory is based on fact that both mucus layer and biological materials have opposing electrical charges that able to create double electronic layer at the edge and thus helps in determination of *mucoadhesive* strength.

- **Wetting theory**

Liquid or less viscous molecules enter into mucosal surface and fix themselves by counteracting the surface tension at the interface. This property relates to contact angle, wetting and spread ability capacity of molecule. (Figure 2) Contact angle (θ) and interfacial tension (γ) can be determined from following equation:

$\gamma SG = \gamma SL + \gamma LG\cos S = \gamma SG – (\gamma SL - \gamma LG)$

Where γLG is liquid–gas surface tension, γSL is solid–liquid surface tension and γSG is solid–gas surface tension.

- **Diffusion Theory**

This theory suggests that *mucoadhesive* polymer diffuses into mucus layer by breaking glycoprotein chain network. This diffusion is time dependent and depends on diffusion coefficients and molecular weight of both phases.

- **Adsorption Theory**

Weak Vander Waals forces and hydrogen bond mediated adhesion involved in adsoption theory is most accepted theory of mechanism of mucoadhesion. It involves primary and secondary bonding in exhibiting semi permanent surface interactions.

- **Fracture Theory**

This is the second most accepted theory, which explains the forces required to detach the two surfaces following adhesion. This force is called as tensile stress or fracture strength and can be determined by following equation:

Sm= Fm/Ao
Where Sm: Tensile stress, Fm: maximum force of detachment
andAo: surface area
OR
Sf= (gcE/c) ½

Where Sf: fracture strength, gc: fracture energy (Wr + Wi = work done to produce new fracture surfaces + irreversible work of adhesion), E: Young's modulus of elasticity and c: critical crack length.

Each and every theory is equally important to describe the mucoadhesion process. There is a possibility that there will be initial wetting of the mucin, and then diffusion of the polymer into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion.

2. PREPARATION OF SAXAGLIPTIN BUCCAL FILMS: -

SOLVENT CASTING METHOD:

Solvent casting method was employed for the preparation of the buccal patches. Water soluble, water insoluble polymers and mix of polymers used in the formulations are as shown in Table 1.

Table 1 Formulations of Sexagliptin Buccal Patches

Ingredients	Formulations					
	BP-I	BP-II	BP-III	BP-IV	BP-V	BP-VI
Sexagliptin (mg)	15	15	15	15	15	15
HPMC, 15cps (mg)	250	-	200	-	200	-
PVP (mg)	-	-	-	-	50	50
Ethyl cellulose (mg)	-	-	50	50	-	-
HPMC, 47cps (mg)	-	250	-	200	-	200
Glycerin, 3drops, (mg)	88.2	88.2	88.2	88.2	88.2	88.2
Ethanol (ml)	8	8	8	8	8	8
Tween 80, 1drop, (mg)	10.5	10.5	10.5	10.5	10.5	10.5

Method :-

90% ethanol and 3 drops of glycerin were added. In another beaker, 3 ml of ethanol and 1 drop of Tween 80 and Sexagliptin (15 mg) were added followed by stirring for 15 min with aid of magnetic stirrer. Both the mixtures were mixed, poured in to glass mould having a size of 5x3 cm2 placed on flat surface, which was ensured by a spirit level. Controlled evaporation of the solvent, by placing an inverted funnel for overnight, was allowed. The mucoadhesive film was removed from the mould and packed in wax paper and stored in a desiccators. Similarly, all the formulations were prepared followed by dummy patches too. In this article, the word 'film' is used to represent the preparation of 5x3 cm2 size and the word 'patch' is for other sizes.

3. Result & Discussion

3.1 Physical Characteristics of Patches:

The buccal patches were found to be of good strength, smooth surfaced, and translucent in nature. Uniform distribution of drug and polymer was observed.

3.2 Thickness Uniformity of Films:

Uniform thickness was found throughout the formulations. Standard deviation was ranged between0.0026 and 0.0089 mm.

3.3 Uniformity of Weight of Patches:

Drug loaded patches (1x1 cm^2) were tested for uniformity of weight. All the patches were found uniform. Standard deviation of all the patches ranged between 0.2926 and 1.4167 mg.

3.4 Swelling Studies of the Patches:

The observed data for all formulations showed an increase in weight with increase in swelling as shown in Fig. 10.1. The order of % increase is represented as BP IV < BP III < BP II < BP VI < BP I < BP V. Formulation containing HPMC and PVP (BP V) had shown highest swelling, this is due to water soluble nature of the polymers. Formulation BP IV had shown the least swelling as it contained water insoluble polymer ethyl cellulose. However, overall percentage swelling was lowso that the patches will not cause any discomfort to the patients.

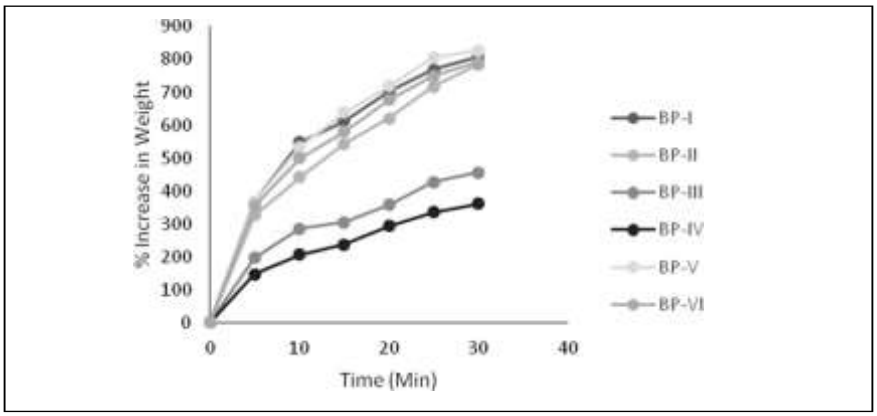


Fig 1 Swelling Studies of the Patches

3.5 Tensile Strength:

A universal tensile strength testing machine was used to determine the tensile strength of loaded and unloaded patches. By observing the data, the order of the patches for tensile strength was observed as BP IV > BP II > BP III > BP I > BP VI >BP V. Strength of patches mainly depends on the polymeric crosslinking. The highest crosslinking was found with formulation BP IV containing HPMC and ethylcellulose,indicating HPMC has the capability of effective crosslinking with ethylcellulose. Patches BP-V had shown less strength may be less crosslinking and hydrogen bonding between drug and polymer.

3.6 Percentage Elongation:

Percentage elongation was determined using Universal tensile strength testing machine for the blank and drug loaded patches. The order of percentage elongation of the patches is IV > III > II > I >VI > V. The percentage elongation of drug loaded patches is in the order of IV >II > III > I > VI > V. By observing the data, it can be concluded that HPMC shown effective crosslinking. The drug loaded patches have shown higher percent of elongation compared to unloaded patches, which may be due to hydrogen bonding between drug and polymer. From observation, BP IV formulation has shown highest % of elongation of 28.47 ± 0.98. This may be due to highest cross linkage of HPMC and ethylcellulose.

3.7 Percentage Moisture Loss:

It becomes more significant as the formulation comprised of hygroscopic components. The release of drug mainly depends on the water intake capacity of patches and solubility of polymers. Formulations containing water insoluble polymers shown least moisture loss i.e, BP III and BP IV. Formulations containing water soluble polymers exhibited highest moisture loss i.e, BP I and IV.

3.8 Surface pH:

The property pH of the patches was found to be 7 ± 0.3 unit difference. As such no mucosal irritation is expected with the pH created at the environment of application, which lead to the convenience of the patient.

3.9 Folding Endurance:

Loaded films didn't show any breaks even after multiple foldings up to 300 times. The comparison was made with loaded and unloaded films and found no difference.

3.10 Content Uniformity of Sexagliptin:

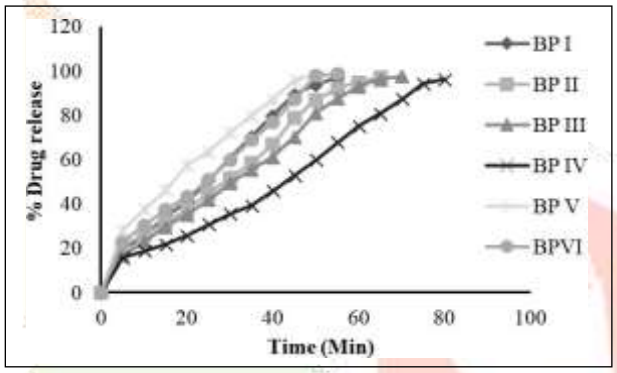
The results of content uniformity test analysed at 270.6 nm indicated that drug was uniformly distributed with the recovery up to 89 %. All the formulated patcheshave shown > 80 % of drug loading which indicates minimum loss of the drug.

3.11 Viscosity:

Use of ethyl cellulose as copolymer in formulation BPIV had shown highest viscosity compared to other formulations. Formulation BP I showed very least viscosity, this may be due to dispersion of polymer in ethanol. Viscosity of the polymeric solution is inversely

3.12 In Vitro Release Studies:

Drug release pattern was studied using phosphate buffer solution, pH 6.6 at temperature of 37 ^{o}C for all formulated buccal patches. Sampling interval was five minutes. Drug release profiles of all the formulations are shownin Fig. 2. Several observations were drawn. It was foundthat with increase in viscosity (HPMC) there was a decrease in drug release. HPMC of different viscosities have shown difference in the release pattern because of viscosity. Increase in drug release was observed in the formulation containing PVP when compared with the patches containing HPMC alone. Analysing the results indicated that percent moisture loss, swelling properties, and viscosity have an impact on release



pattern in their own way. Based on drug release pattern, it was considered to optimize the BP–V, as the highest drug release of 98% in 50 min was obtained.

Fig. 2: % Drug release patterns from formulations

Table 2: Comparison of Orders of In Vitro Release of Sexagliptin from the Patches

Patch Code	Regression equations for in vitro release in phosphate buffer pH6.6	
	Zero order	First order
BP I	y = -1.769x + 93.20 R^2 = 0.988	Log y = -0.024x + 2.120 R^2 = 0.887
BP II	y = -1.469x + 91.40 R^2 = 0.982	Log y = -0.023x + 2.194 R^2 = 0.882
BP III	y = -1.393x + 92.71 R^2 = 0.988	Log y = -0.024x + 2.218 R^2 = 0.87
BP IV	y = -1.176x + 97.08 R^2 = 0.988	Log y = -0.013x + 2.128 R^2 = 0.823
BP V	y = -1.814x + 84.44 R^2 = 0.957	Log y =-0.032x + 2.150 R^2 = 0.881
BP VI	y = -1.719x + 90.69 R^2 = 0.984	Log y = -0.031x + 2.124 R^2 = 0.776

The results of drug release were fitted into various mathematical models such as zero order and first order to understand the kinetics patterns of formulations. The results are tabulated as shown in Table 2. It is observed that R^2 values for all formulations are higher with zero order when compared to first order. It confirms that drug release follows zero order releasepattern.

3.13 Release Mechanisms:

To study the drug release mechanisms, the results were fitted with Hixon-Crowell cube root law model and Higuchi's model. Regression values for all formulations are tabulated in Table 3. Perusal to the Table 3, it can be concluded that the drug release was diffusion rate limited.

Table 3: Comparison of Regression Values of Mathematical Models

Patch code	Hixon-Crowell model	Higuchi's model
I	y = 0.011x - 0.042 R^2 = 0.959	y = 14.17x - 12.89 R^2 = 0.949
II	y = 0.009x - 0.049 R^2 = 0.943	y = 13.04x - 12.02 R^2 = 0.947
III	y = 0.009x - 0.049 R^2 = 0.949	y = 12.88x - 14.30 R^2 = 0.949
IV	y = 0.007x - 0.053 R^2 = 0.913	y = 11.75x - 8.206 R^2 = 0.988
V	y = 0.013x - 0.01 R^2 = 0.966	y = 14.26x - 4.469 R^2 = 0.990
VI	y = 0.012x - 0.048 R^2 = 0.905	y = 13.81x - 10.07 R^2 = 0.953

3.14 In Vivo Absorption of Sexagliptin in Rabbit Buccal Mucosa from Patches:

Based on the results of all the tests including releaserate, BP V was taken as the optimized formula for invivo studies in rabbits. The strategy utilized for this objective was the estimation of disappearance of thedrug from the loaded patches.

Each value was an average of three readings. About84.59% of Sexagliptin was absorbed from patch V within 30 min (Fig. 3).

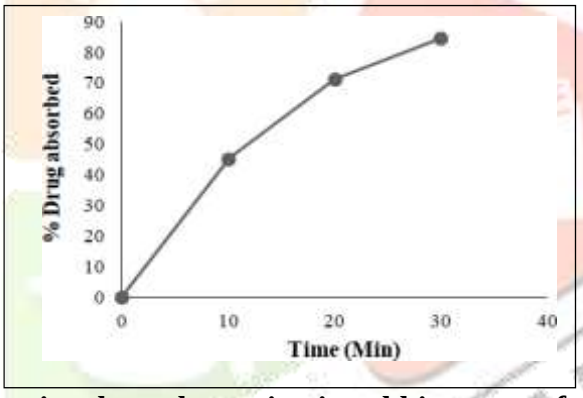


Fig. 3: In-vivo drug absorption in rabbit mucosa from BP V

3.15 Ageing:

Stability studies were carried out as per ICH guidelines.Differences in the drug content for stored patches were investigated and recorded after three determinations. Drug content analysed spectrophotometrically. Percentage decline in drug content for all patches was also calculated and reported. Results indicate that the drug loss is less in the patches stored for six months. Satisfactory characteristics were found without much changes over a period for optimized formula.

4. Conclusion

Mucoadhesive patches of Sexagliptin containing 1 mg of drug were prepared successfully using HPMC (15 and 47 cps), PVA, and ethylcellulose polymers in different combinations and there were total six films were prepared. Optimized formula was evaluated and drug release pattern was studied. Water soluble polymers showed highest release compared to water insoluble polymers. More over the viscosity of the polymer also affects the drug release pattern. Formulations followed the zero order kinetics and Higuchi's model for drug release. In vivo absorption of drug in rabbits found that 80.14% within 30 min from the optimized formula. The in vitro-in vivo correlations (IVIVC) was attempted for the release and absorption of Sexagliptin from the patches. The correlation coefficient for patch BP-V was 0.996.

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