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Formulation & Evaluation of Buccal Patch For Treatment of Diabetes

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Abstract

The present study aimed to design and evaluate a buccal patch for the transmucosal delivery of nateglinide, a hypoglycemic agent, to provide a non-invasive and patient-friendly alternative for diabetes management. A solvent casting method was employed to prepare buccal patches using a combination of polymers like HPMC, HPMC K4M, PVA. The optimized patch (DF3) exhibited a drug release of 93.32% over 09 hours. The buccal patch was found to showed good bioadhesion. This study demonstrates the potential of the developed buccal patch as a promising transmucosal delivery system for nateglinide, offering a convenient and effective treatment option for diabetes management.

Keywords: Transmucosal**,** hypoglycemic, bioadhesion, nateglinide, solvent casting method.

Introduction:

Non–insulin dependent diabetes mellitus (NIDDM), also known as type 2 (formerly referred to as adult-onset diabetes mellitus); in which resistance to endogenous insulin action is developed by target tissues due to alterations in cell receptors[1] and is characterized by progressive deterioration of normal pancreatic b-cell function. In the early stages of the disease, the b -cells of the pancreatic islets compensate for decreased insulin sensitivity by increasing insulin secretion. [2] As the disease progresses, b-cell decomposition with impaired insulin secretion follows and sensitivity to insulin continues to decrease.[3]

Nateglinide [N-(trans-4-isopropyl cyclo hexyl carbonyl)-D-phenyl alanine] is a novel, highly physiologic, glucose regulator recently approved for the treatment of type-2 diabetes mellitus. Nateglinide has a rapid onset and short duration of insulinotropic action that results in reduction of glucose level.[4-9]

Buccal delivery of drug is an alternate to the conventional method of drug administration to overcome problems such as high hepatic first pass metabolism. It is a safer method of drug administration since drug absorption can be easily terminated in case of toxicity by removing the dosage form from the buccal cavity. Considering the low patient compliance of rectal, vaginal, sublingual, & nasal drug delivery for control drug release, the buccal mucosa has rich blood supply & its relatively permeable & rapid onset of action can be achieved.[10]

MATERIALS

Nateglinide was purchased from Yarrow Chemical Pvt. Ltd., Mumbai, HPMC K4M, HPMC were procured from Merck Limited, Mumbai. Poly vinyl alcohol (PVA), Ethanol were obtained from S.D Fine chemicals, India, Propylene glycol was purchased from Fischer Scientific Chemicals, Mumbai. All the solvents and chemicals were used analytical grade.

Methods:

Buccal patches of Nateglinide containing different proportion of HPMC, HPMC K4M, PVA were prepared by solvent casting method. The measured amounts of polymers & Nateglinide were dissolved in water &ethanol respectively. 10% w/w propylene glycol was included to polymeric solution. Both polymeric solution and drug solution were mixed. The solution was blended occasionally to get glue like consistency [11]. The drug and polymer blend mixture was poured in petridish and kept aside for evaporation of solvent. Inverted funnel is kept on petriplate for controlling the rate of evaporation of solvent. After clear examination, the dried patches were taken, inspected for any air pockets and cut into 4cm^2 size & packed in an aluminium foil. [12]

Table 1: Composition of formulation of mucoadhesive buccal patches of Nateglinide:

Formulation batch	Drug (mg)	HPMC (%W/V)	HPMC K4M(%W/V)	PVA (%W/V)	Propylene glycol (%W/W)
DF1	60	1	3	0.5	10
DF2	60	1	2	1	10
DF3	60	1	2	1.5	10

Evaluation of patches:

Weight variation

Three films of 4 cm2 size were cut randomly, individually the patch were weighed on electronic balance and the mean weight was calculated.

Thickness of patch

The thickness of patch was directly related to drug content uniformity so it was essential to find uniformity in the thickness of the film. It can be measured by Vernier Calipers. The thickness was measured at different spots of the patch and average was taken as film thickness.

Drug content

Spectrophotometric method was used to assess the uniformity of drug distribution through measuring drug content at different parts of the same film. Three 4 cm2 of each film were weighed individually, dissolved in 20 ml methanol, and the solution was then filtered through filter paper and the concentration of Nateglinide was measured spectrophotometrically at 216 nm. Each preparation was tested in triplicates, and the percentage drug content was calculated from the following equation,

$$\% \text{ Drug content} = \frac{\text{Actual amount}}{\text{Theoretical amount}} \times 100$$

Folding Endurance

The folding endurance of the patch was used to estimate the mechanical strength of the patch to withstand the folding or the ability to withstand the brittleness. It was measured by repeatedly folding a patch at the same line before it breaks. The folding endurance was the number of times the film was folded without breaking. Higher the folding endurance value greater was the strength of the patch **[13].**

Swelling property

Phosphate buffer pH 6.8 was prepared to check the swelling property of the patch. The initial weight of the patch was determined and placed in the pre weighed stainless steel mesh. The system was dipped in the Phosphate buffer pH 6.8. The increase in the weight of the patch was noted by weighing the system at regular intervals **[13].** The degree of swelling was determined by the formula,

$$\textbf{Degree of swelling} = \frac{[\text{Final weight (Wt)} - \text{Initial weight (Wo)}]}{[\text{Initial weight (Wo)}]} \times 100$$

Surface pH

Patch was slightly wet with help of water. The pH was measured by bringing the electrode in contact with the surface of the patch. The study was performed on three patch of each formulation and average was taken. **[13,14]**

Ex vivo mucoadhesion time

The ex vivo mucoadhesion/retention time of the oral buccoadhesive films was determined using goat cheek mucosa. Goat check pouch of size 2 x 2 cm^2 was cut and pasted on the inner side of the beaker using double-sided adhesive tape. The film of size 4 cm2 was cut, and its surface was made wet using a drop of Phosphate buffer pH 6.8. Films were pasted on the surface of the goat pouch by applying a gentle force for 10 sec. Phosphate buffer pH 6.8. (500 ml), maintained at 37 ±1°C, was poured into the beaker and stirred at 150 rpm to simulate buccal conditions. All the experiments were performed in triplicate **[15].**

Ex- vivo mucoadhesive strength:

The fresh sheep buccal mucosa separated and washed with phosphate buffer (pH 6.8). A piece of gingival mucosa is tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial is tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch is stuck to the lower side of a rubber stopper with cyanoacrylate adhesive. Two pans of the balance are balanced with a 5-g weight. The 5-g weight is removed from the left hand side pan, which loaded the pan attached with the patch over the mucosa. The balance is kept in this position for 5 minutes of contact time. The water is added slowly at 100 drops/min to the right hand side pan until the patch detached from the mucosal surface.[16] The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength. [17,18]

$$\text{Mucoadhesive force (kg/m/s)} = \frac{\text{Mucoadhesive strength}}{1000} \times \text{acceleration due to gravity}$$

In vitro dissolution test

The patch was pasted on to the inner side of the vessel using double side adhesive tape. Dissolution was carried out by using pH 6.8 Phosphate buffer as dissolution medium. A suitable volume of the sample was withdrawn at every 1 hour. The dissolution parameter was maintained as below

Apparatus: USP Type II paddle, Medium: 900 ml of Phosphate buffer pH 6.8, Speed: 50 RPM, Temperature: 37^{o}C ± 0.5^{o}C, Time: 8 hours, Sampling interval: 1hr.

The absorbance of the resulting solution was measured by UV spectrometer at 216nm [19,20].

Result:

DF1, DF2, DF3 are the drug containing patches & composition of this patches are given in table no.1. All this three patches are evaluated for various parameters & result are given below.

Table no-2: Weight Variation, Thickness, Folding endurance, Mucoadhesive strength of patches

Batch Code	Weight (mg) n=3	Thickness (mm) (n=3)	Folding endurance(n=3)	Mucoadhesive strength(g) (n=3)
DF1	102.32 ± 0.6	0.89 ± 0.33	207 ± 16	31.2±0.471
DF2	126.46± 0.3	1.10 ± 0.89	235 ± 19	32.6±0.154
DF3	132.89 ± 0.7	1.19± 0.57	276 ± 15	35.9±0.213

Appearance of the film

The overall appearance was found to be clear and transparency was good which showed that the drug has distributed uniformly.

Weight variation

Three films of size 4 cm2 were cut randomly, individually the patches were weighed on electronic balance and the mean weight was calculated. Weight of patches was ranging from102.32 ± 0.6 to 132.89 ± 0.7mg. Weight of patches was found to be increasing proportion of polymer. The results were shown in table 2.

Thickness of patch

Thickness of all the patches was found to be in the range of 0.89 ± 0.33 to 1.19 ± 0.57mm. As the total amount of polymer increases the thickness of the patches were found to be increased. The results were shown in table 2.

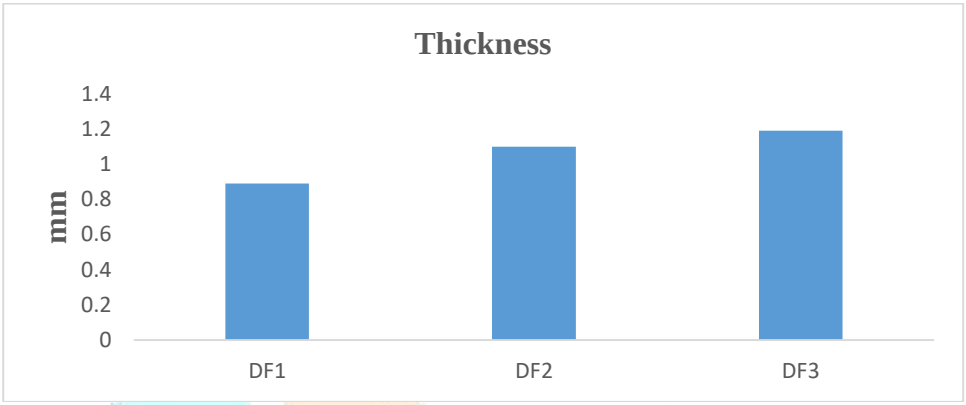

Fig-1: Thickness of patches

Folding Endurance

Folding endurance is the index of ease of handling the patches. As the amount of polymer increases the folding endurance was found to be increased. Folding endurance for the patches was found to be 207 ± 16 to 260 ± 15. All patches exhibited folding endurance above 200 proving the flexible nature of the patch. The results were shown in table 2.

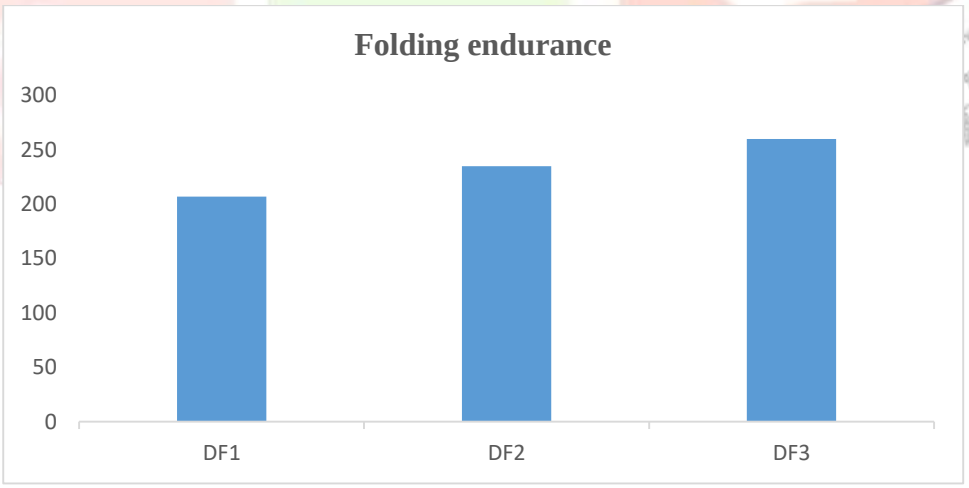

Fig-2: Folding endurance of patches

Mucoadhesive strength: The bioadhesive quality of Nateglinide films was pleasing for keeping them in buccal cavity. It was watched that HPMC particles were small and higher in amount thus gave more noteworthy surface territory to contact with the bodily fluid film. [73]

On collection of HPMC K4M the bioadhesive quality was upgraded which may be caused by design of hydrogen bond and vander-waal forces. The information was introduced in the table no-2 . Mucoadhesive strength of the patches were ranging from 31.2±0.471to 35.9±0.213. The most extreme buccoadhesive quality was acquired in DF3 Batch.

Table no-3: Drug content, Surface pH, Swelling index, Mucoadhesion time of patches

Batch Code	Drug content (%) n=3	Surface pH (n=3)	Swelling index (%) (n=3)	Mucoadhesion time (min) (n=3)
DF1	98.15 ± 0.8	6.5 ± 0.01	52.19 ± 4.5	560 ± 13
DF2	98.57 ± 0.6	6.8 ± 0.02	89.78 ± 3.4	530 ± 17
DF3	99.10 ± 0.9	6.4 ± 0.01	95.46 ± 2.2	580 ± 12

Drug content

All the batches of the patches contain 98.15 ± 0.8 to 99.10 ± 0.9 % of drug which indicate that there is no loss of drug during preparation of the patch. All the batches of the patches exhibit drug content within limit 98 to 99 % which is within the desirable range due to the equal distribution of drug in the solution. The results were shown in table 3.

Surface pH

Surface pH for all batches was between 6.4 ± 0.01 to 6.8 ± 0.02 which were due to pH of the drug solution as well as the polymer, hence no mucosal irritations was expected and ultimately achieves patient compliance. The results were shown in table 3.

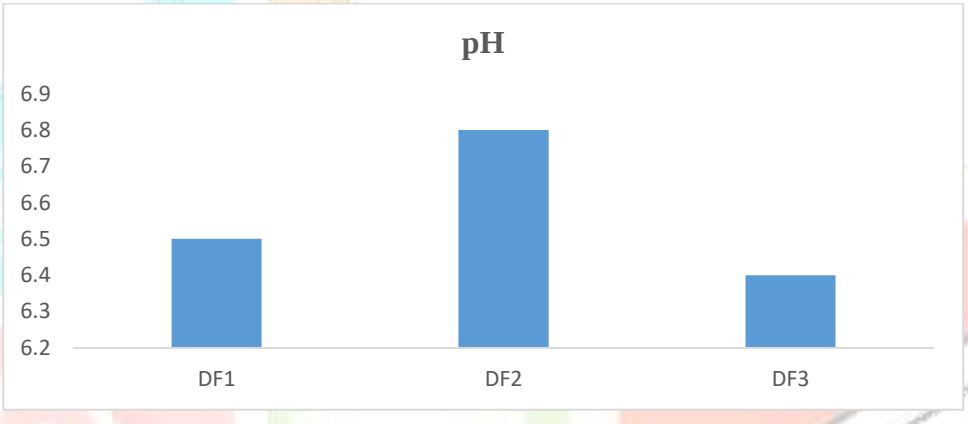

Fig-3: pH of patches

Swelling property

Swelling index shows the moisture uptake and swelling behavior of buccal patches. All the patches were subjected to swelling studies. The results indicated that all the patches exhibited appreciable swelling nature. The swelling index increasing with polymer concentration for HPMC K4M. Also it increases with increasing content of PVA. The results were shown in table 3.

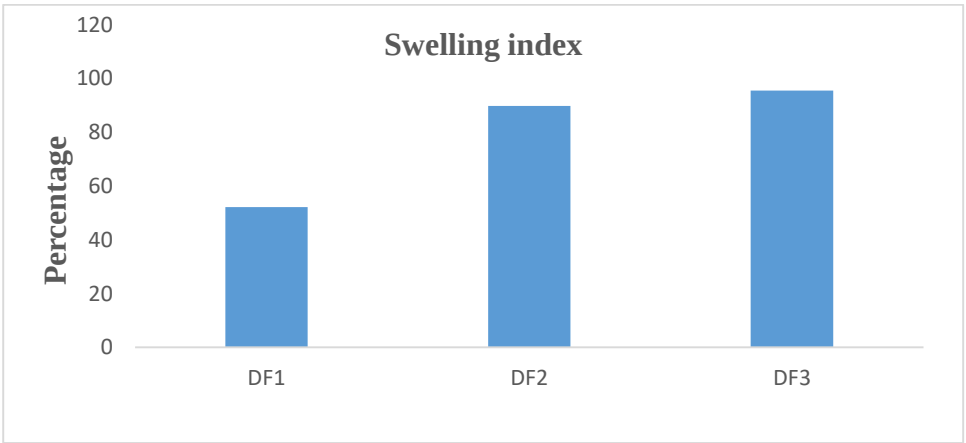

Fig-4:Swelling index of patches

Ex vivo mucoadhesion time

Mucoadhesion time of the patches were ranging from 530 ± 17 to 580 ± 12 min. It shows that increasing in HPMC K4M concentration increases the mucoadhesion time significantly. The results were shown in table 3.

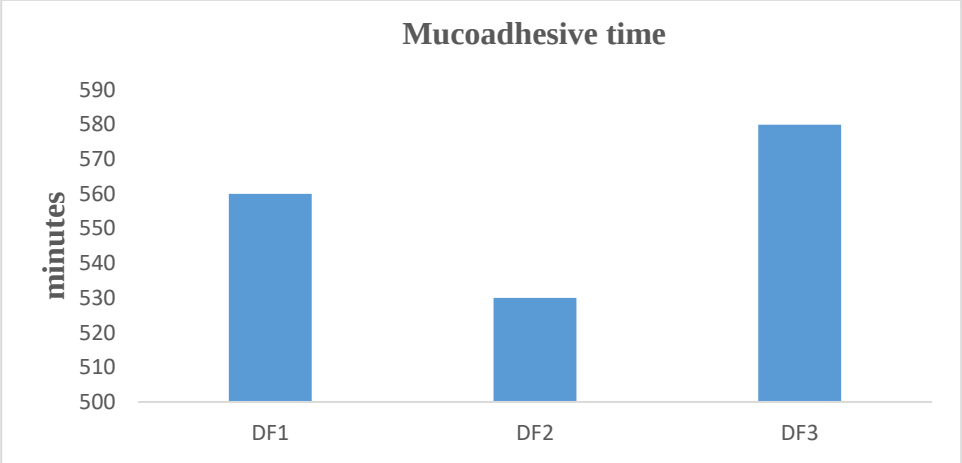

Fig-5: Mucoadhesive time of patches

In vitro dissolution test

The *in vitro* drug release studies were done for all three batches in Phosphate buffer pH 6.8 using Dissolution apparatus USP type II. The release data were given in the table 4.

Dissolution Parameters

Dissolution medium: Phosphate buffer pH 6.8 (900ml)

Paddle speed: 50 rpm

Apparatus: Dissolution apparatus USP type II

Temperature: 37ºC ± 0.5ºC

Withdrawal time: 9h with 1h interval

Volume withdraw: 2ml

Table no - 4: Cumulative percentage drug release of patches

Time (hours)	**Cumulative percent drug release**		
	DF1	**DF2**	**DF3**
1	12.72	11.41	13.64
2	21.02	20.02	22.21
3	33.43	31.56	32.37
4	48.24	45.78	41.05
5	58.55	52.68	50.54
6	67.74	66.95	60.24
7	77.52	75.86	76.77
8	84.59	82.45	85.71
9	92.22	91.56	93.32

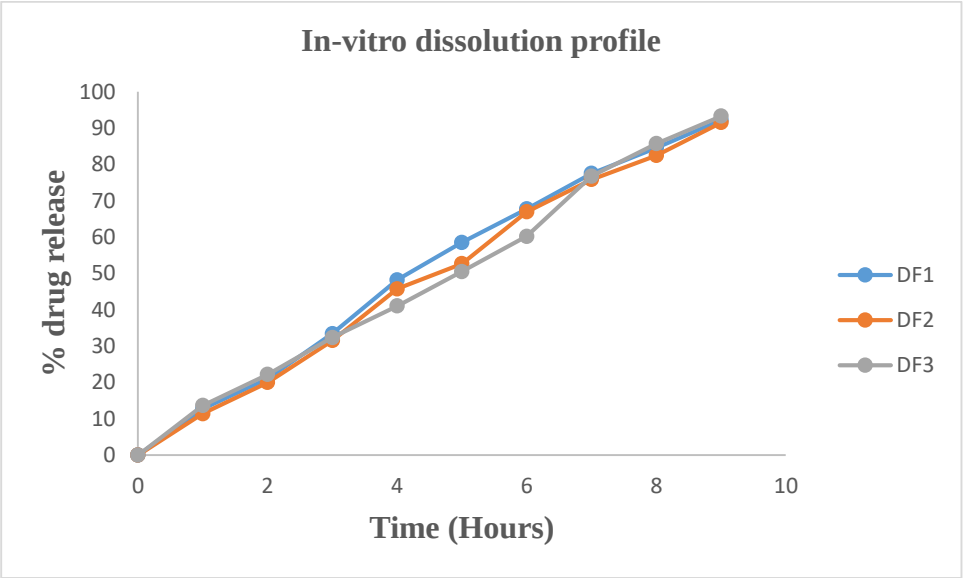

Fig- 6:% cumulative drug release at different time intervals

- The table presents the results of the in vitro drug release study for formulations DF1, DF2, DF3 at various time intervals. The cumulative drug release percentages are recorded over time to assess the release profile of the formulations.
- As time progresses, the cumulative drug release increases for all formulations. Formulations DF1, DF2, DF3and DF3 exhibit cumulative drug release percentages ranging from 11.41% to 93.32% at different time intervals.
- At the 1 hour mark, all formulations show a low cumulative drug release, with DF3 having the highest release percentage at 19.64 ± %.
- By the 2 hours mark, the cumulative drug release increases further for all formulations, with DF3 showing the highest release at 22.21%.
- At the 3 hours mark, DF1 exhibits the highest cumulative drug release at 33.43 %, followed closely by DF3 at 32.37%.
- The drug release continues to increase over time, with the highest cumulative drug release percentages observed at the 9 hours mark. DF3 exhibits the highest release at 93.32%, followed by DF1 at 92.22%.
- The results indicate that the formulations differ in their drug release profiles. DF3 consistently shows higher cumulative drug release percentages compared to the other formulations at each time interval.

Conclusion

The present study was aimed to develop a mucoadhesive buccal patches for the delivery of Nateglinide. This research work also studied exploration of some mucoadhesive polymers for mucoadhesive buccal patch formulation. Mucoadhesive patches were prepared by using selected drug with various polymers and evaluated for mucoadhesive strength, ex-vivo mucoadhesion ,folding endurance, in vitro dissolution, swelling studies, weight, thickness, drug content, surface pH. All three optimised batches of formulations were investigated & betters result were obtained. The mucoadhesive buccal patch displayed effective sustain drug release in an in-vitro environment.

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