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FORMULATION AND EVALUATION OF BUCCAL PATCHES FOR DELIVERY OF DICLOFENAC DIETHYLAMINE AS A MODEL DRUG

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ABSTRACT

Diclofenac diethylamine is a non-steroidal anti-inflammatory drug. Here diclofenac diethylamine used as a model drug. This drug is given here as a buccal patch dosage form. In which the main aim is to increase the bioavailability and better absorption, without any first pass metabolism. This dosage form is very much reliable for those patients, who is unconscious, require fast action, and cannot swallow smoothly. This dosage form directly absorbs through the buccal mucosa and avoid enzyme metabolism also. The patches were evaluated by weight uniformity, moisture gain, moisture loss, physical appearance, thickness uniformity, drug content uniformity and *in vitro* release study.

KEYWORDS: Diclofenac Diethylamine, Model Drug, Buccal Patch, Gelatin, PEG 400, HPMC, Glutaraldehyde.

INTRODUCTION

Mucoadhesive term if we split then, muco = mucus, and adhesive= adhere. So, upper portion of the mucus which is adhere known as mucoadhesive. And this mucus membrane covers the mucosal epithelial surface as well as mucin molecule, which helps the dosage form residence time to increase in its absorption site. Actually, the mucus membranes are present in our body in various locations - buccal, sublingual, rectum, stomach, nasal etc. among those sites the effective and convenient site is buccal cavity.

This mucoadhesive drug delivery system is a controlled release drug delivery system. When the drug absorbed and delivered to the body through the buccal mucosa placed in oral cavity, this type of drug delivery system is known as Buccal Drug Delivery System. In our oral cavity the dug formulation is given for attaching into the buccal section, situated in between upper gums and cheek. In this type of drug delivery system avoid acid or enzyme metabolism, it is also a pain less administration and permeation rate are faster than transdermal drug delivery system. This formulation can be administered to the unconscious patient also. This type of drug delivery system has been chosen because of its direct action without attending first pass metabolism in our body.[1]

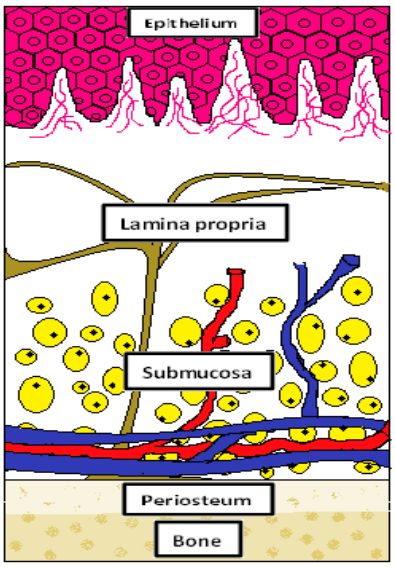

Figure 1: Anatomy of oral mucosa.

The main thing is to attach the formulation into buccal section by interacting with the mucus and the polymer made formulation patch system. This is possible due to mucus layer structural characteristics and polymer properties. Actually, this adhesion property given to the formulation because of the avoiding swallowing unfortunately in any case and, to release the drug through the mucus layer continuously at a constant rate.[2]

Promotion of mucoadhesive drug delivery system has achieved because of site specific drug delivery through blood vessels and lymph vessels.

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) used as tooth ache, analgesic, arthritis, gives relief from pain. Diethylammonium is the salt of diclofenac (diclofenac diethylamine). It is used for first line therapy for acute and chronic pain.

If the dosage form given orally this will goes for first pass metabolism and the half of the given dose will reach and act on the site of action. For this reason, an alternative process has been established, which bypass hepatic first pass metabolism and directly goes to the systematic circulation. The drug, Diclofenac diethylamine if we use for buccal drug delivery system, the dose will be minimal. Because excessive dose will create patient uncomfortable in his/her mouth, it may sometime irritate also.

MATERIALS AND METHODS

MATERIALS

Gelatin, Polyethyline glycol-400, Hydroxy propyl methyl cellulose, Gluteraldehyde were purchased from Loba Chemie. Diclofenac diethylamine purchased from Yarrow Chem Pvt. Ltd. Mumbai. All chemicals and reagents used were of analytical grade.

METHODS

Preparation of formulations of Diclofenac diethylamine buccal patches

Preparation of buccal patches

Buccal patches were prepared[3] by dissolving Diclofenac diethylamine, gelatine and PEG 400 in distilled water into a beaker by applying heat on heating plate. Before put the beaker over the heating plate the ingredients must be mixed properly with a clean glass rod. The molten gelatine mixture was cast on a glass slide of 8cm x 2cm. Gelatine was allowed to set at room temperature. The slides were placed inside a vacuum desiccator for drying 24 hours. After that the dried patches were removed from the slide and 2cm x 2cm pieces were cut with a pair of sterilized scissors.[4] Then aqueous solution of Glutaraldehyde (1%w/v) was prepared in a 100 ml beaker. The pieces of the patches were placed in previously chilled glutaraldehyde solution. After the stipulated time as per the formulation design the patches were washed twice with chilled distilled water to remove the glutaraldehyde residue. Then the patches were dried at room temperature in vacuum desiccators. HPMC K4M, 0.5gm was dispersed by stirring in 10 ml warm water followed by cooling in refrigerator at 4^0C to prepare a transparent viscous solution. The HPMC solution was spread over the patch. The patches coated with HPMC layer were dried at room temperature overnight.[5] The drug and dose of buccal patches are selected only for model experiment purposes.

Table 1: Formulations of buccal patches.

Ingredients	F1	F2	F3
Diclofenac diethylamine	10 mg	10 mg	10 mg
Gelatin	1 g	1 g	1 g
PEG 400	0.5 g	1 g	0.5 g
Distilled water	5 ml	5 ml	5 ml
Glutaraldehyde	1%	1%	2%
Glycerin	0.5 g	0.5 g	0.5 g
HPMC	0.5 g	0.5 g	0.5 g
Time of cross-linking	4min	4min	4min

EVALUATION OF THE PATCHES BY PHYSICAL TESTS

Weight uniformity

The patches were dried in vacuum desiccators at room temperature (30^0C) for 4 hours before testing. An area of 2cm × 2cm was cut and the dry weight of the patch was determined.

Physical appearance

All the prepared patches were visually inspected for colour, clarity and smoothness.

Moisture Gain

The accurately weighed films were kept in desiccators at room temperature (25^0-30^0C) for 24 hours, containing saturated solution of potassium chloride in order to maintain a RH of 80-85%. After 24 hours the films were taken out and weighed again.[6]

Thickness and Flatness

Three strips (longitudinal) were cut out from each patch and the thickness was measured using screw gauge – one from the centre and two from either side. One of the patches was placed between two slides and thickness (d1) was measured. The thickness (d2) of two slides without any patch was measured similarly by screw-gauge. The thickness of the patch was finally determined from the equation,[7]

$$d = d1 - d2$$

Finally, the standard deviation was calculated and the reading was plotted in (table 4). The formula of standard deviation is:

$$S = \sqrt{\frac{\sum(x_i - \bar{x})^2}{n-1}}$$

Drug Content estimation

The buccal film of each formulation was cut-out in three equal parts and placed in a 50 ml phosphate buffer (pH6.8). The contents were stirred till 24 h followed by filtration. The filtrate is suitably diluted and the absorbance was measured at 282 nm by using UV Spectrophotometer. The mean of three films was taken as drug content.[8]

***In-vitro* release study of Diclofenac diethylamine across semi-permeable membrane**

A patch of 1.5cm x 1.5cm was cut and the HPMC side was placed on a semipermeable membrane followed by slight press. The membrane was fitted with the opening of a Keshary-Chien apparatus so that it was facing towards the receptor chamber. The receptor chamber was filled with 50 ml distilled water (receptor medium). The semipermeable membrane just touched the medium. The temperature was maintained from awater bath maintained at 37±0.5^{0}C. Samples of 5ml each were taken out through the port of the apparatus and fresh 5ml medium was replenished to maintain the volume of the receptor medium. The medium was constantly stirred with a magnetic stirrer. The samples were placed in UV spectrophotometer to measure the absorbance.

RESULTS AND DISCUSSION

Results of physical tests

Weights of patches

Weights of the patches (2cm × 2cm) were determined in triplicate and the average weight was reported in Table2.

Table 2: Results of weight uniformity measurements of the buccal patches.

Formulation	Weight (gm)[MEAN]	
	Reading 1	Reading 2
F1	0.1942	0.1876
F2	0.1673	0.1792
F3	0.1762	0.1829

Moisture gain study of the patches

The initial and final weights of the patches were taken after maintaining a condition of 30^{0}C, RH 80-90% for 24hrs and the percentage of moisture uptake was calculated by the following formula:

$$\%\ Moisture\ uptake = \frac{Final\ Weight - Initial\ Weight}{Initial\ Weight} \times 100\%$$

Table 3: Results of Moisture gain measurements of the buccal patches.

Formulation	Mean ± SD
F1	4.42± 0.015
F2	2.86±0.007
F3	3.50±0.014

(Mean ±SD, n = 3)

Physical appearance

The dried patches were photographed against a black background. The patches appeared as transparent, very pale yellow, thin membrane.

Thickness and flatness

After complete drying, those patches were cut into three equal pieces when attach to the slide, at that time by the help of a screw gage measure the size of both slide and patch. Next the patch removed from the slide and measures the thickness of the slide. Then sublimation had done from slide with patch to slide without patch. In this way per formulation 3 readings were enlisted. And then mean was calculated of that sublimation result of 3 readings of a particular batch.

Table 4: Thickness of buccal patches (Diclofenac diethylamine)

Formulation No.	Thickness (mm)± SD
F1	0.40±0.07
F2	0.70±0.04
F3	0.76±0.15

(Mean ±SD, n = 3)

Drug content

Table 5: Drug content of buccal patches (Diclofenac diethylamine)

Formulation	Drug content (mg)
F1	0.2619
F2	0.4041
F3	0.3342

(Mean ±SD, n = 3)

***In vitro* release study**

The release study of Diclofenac diethylamine buccal pathches were continued up to 240 minutes of three formulations. The release data of all formulated patches were shown in the figure (Fig. 2).

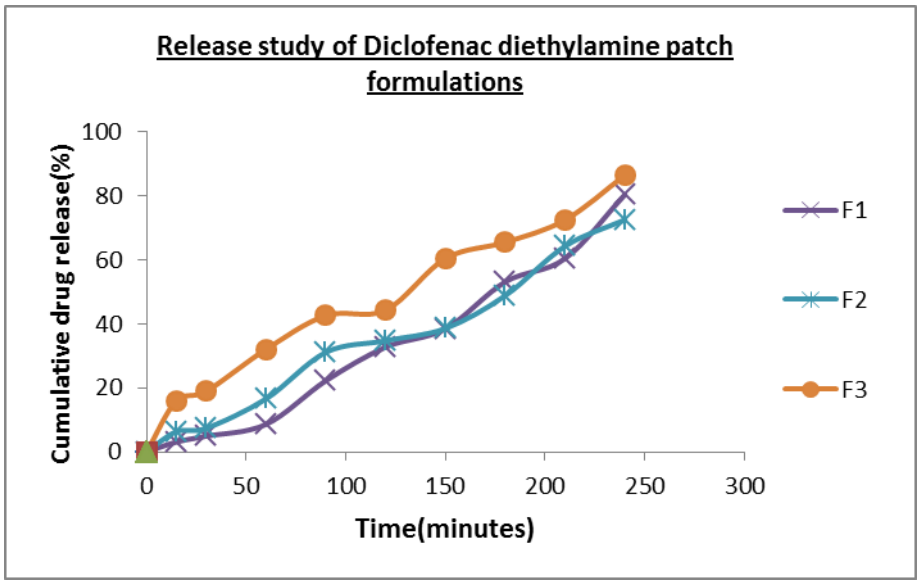

Fig.2: Release profile of various formulations of Diclofenac diethylamine buccal patches.

CONCLUSION

From the present investigation, it can be concluded that such buccal patches of diclofenac diethylamine (used as model drug) may provide sustained buccal delivery for prolonged periods, which can be a good way to bypass the extensive hepatic first-pass metabolism. Though, long term stability study and clinical trial is required for future development of this dosage form.

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AUTHORS CONTRIBUTIONS

Experimental design contribution to Debjani Das and Niladri Ghosal. Paper writing contribution to Dr. Sudipta Das and Niladri Ghosal.

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