JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

PREPARATION AND EVALUATION OF TRIPLE LAYER DUAL RELEASE BUCCAL PATCHES OF ATENOLOL

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ABSTRACT

In this research triple layer buccal patch composed of immediate, sustained and backing layer for delivering the medicament venlafaxine hydrochloride(show oral bioavailability 40%) for the treatment of depression by two actions HPMC E15 composed immediate layer provide instant action and release of drug upto 1 hour then sustained release layer composed of guar gum provide sustained action upto next 7 hours. Triple layer buccal patches for the delivery of atenolol using HPMC E15 and guar gum polymers in various proportions and combinations were fabricated by solvent casting technique. Various physicomechanical parameters like weight variation, thickness, folding endurance, drug content, moisture content, SEM study, moisture absorption, and various ex vivo mucoadhesion parameters like mucoadhesive strength, force of adhesion, and bond strength were evaluated.

Keywords:-
HPMC E15, Atenolol, mucoadhesion, triple layer

INTRODUCTION

One of the most valuable methods of administration for systemic and local drugs actions is 'Buccal administration' of drugs. The natural or synthetic polymer adhesion tissues are titled as bio-adhesion and are integrated among mucus membrane and polymer labelled as mucoadhesion. Goblet cells are present in mucus membrane comprised of glycoprotein mucin for secretion of mucus. Buccal mucosa exhibits a rationally flat and steady surface for the settlement of Mucoadhesive dosage form. The extent of drug that can be integrated is restricted by the size inadequacy of the buccal dosage form. The appropriate dose for buccal dosage forms suggested for daily necessity is 25 mg or less, considered valuable for patients. Drug with small half-life, needing sustained or organized release demonstrating poor aqueous solubility and may be efficaciously distributed through the buccal mucosa.

The categories mentioned for distribution of drug moieties in oral mucosa are listed as:

(i) Sublingual

(ii) Buccal

(iii) Local

For overcoming inadequacies like high first pass metabolism, and drug degradation in the harsh gastrointestinal environment made buccal delivery of drugs a substitute to the conventional oral route of drug administration. Maximum valuable results given by buccal drugs because of plentiful blood supplied to oral mucosa. Concentration gradient is accountable for transference of drugs in saliva. A suitable buccal drug delivery should be flexible and possess good bio-adhesive properties. The drug released in a controlled

and predictable manner to elicit the required therapeutic response. The efficiency of mucoadhesive preparation is dependent upon the polymer composition used in preparing buccal patches. The benefits of buccal patches are easy exclusion, low enzymatic activity, and unproblematic administration of patch, ability to comprise permeation enhancer or enzyme inhibitor or pH changer.

ORAL MUCOSA:

The outmost stratum of oral mucosa is comprised of a stratified squamous epithelium. Beneath squamous epithelium exists a basement membrane and a lamina propria. The deepest layer of oral mucosa is the sub mucosa. The epithelium is similar to stratified squamous epithelia found in the rest of the body. The sublingual epithelium comprises of less cell layers than the buccal mucosa epithelium around (40-50) cell layers dense. The thickness depends on site the buccal mucosa measures at 500-800µm, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingival measure at about 100-200µm.

Environment of Buccal Mucosa Role of Saliva:

(1) Saliva has moisturizes nature for buccal dosage forms

(2) It has protecting fluid for all the muscles of oral cavity

(3) Continuous mineralization is another feature of the saliva.

Role of Mucus:

(1) The human mucus composed of carbohydrates and protein. They provide lubricating effect.

(2) They responsible for adhesion dosage forms with buccal mucosa.

Permeability of Drugs through Buccal Mucosa:

The potential routes of drug absorption through the oral mucosa are;

(i)Trans-cellular

(ii)Para-cellular

Ideal Drug Candidates for Buccal Drug Delivery System:

(1) The drugs used for buccal drug delivery which are absorbed only by process of passive diffusion

(2) They should have no odour and molecular weight of drugs should be between 200-500 Daltons

(3) The having lipophilic and hydrophilic nature can be suitably incorporated in buccal dosage forms

(4) The tasteless and persistent pH drugs are perfect for buccal drug delivery systems

Buccal adhesive polymers:

Adhesives are materials which are used to attach things. The numerous physiochemical features of bio-adhesive polymers including hydrophilicity, hydrogen bond-forming groups, elasticity for inter permeation with mucus and epithelial muscle, and visco-elasticity.

Perfect Polymer Features for Buccoadhesive Drug Delivery System

(1) It is easy to integrate in different sorts of dosage forms.

(2) It should be unaffected by different types of conditions like change in PH and food.

(3) It should be inert and harmonious with the environment.

(4) It should adhere quickly to moist tissue surface and should possess some site specificity.

Polymer Selection Criteria for Buccal Patches:

(1) It has to companionable with oral mucosal membrane.

(2) They have narrow delivery through tissues and polymer should have higher molecular weight.

Benefits of Buccal Drug Delivery System:

Drug administered by means of buccal mucosa have numerous diverse benefits.

(1) The buccal delivery benefits by more blood supply towards oral cavity.

(2) First pass effect avoided because drugs directly absorbed from oral mucosa.

(3) The usage of buccal dosage forms is easier than others. They can be discontinued if toxic effects appeared.

(4) The side effects decreased and improved patient compliance.

(5) The peptide molecules that not suitable for delivering through oral route can easily administered by buccal mucosa. Buccal delivery system have capacity to withstand environmental conditions and sustained delivery of drugs possible.

Disadvantages:

The disadvantages of buccal drug delivery system are:

(1) The dilution of the drug takes places by the uninterrupted excretion of the saliva.

(2) Drugs with large potency dosage are problematic to be given by buccal route.

(3) The unintentional removal of dosage form happens by incessant swallowing of saliva probable loss of medication.

(4) Lesser area of the oral cavity available for drug absorption.

(5) Drugs which annoy the mucosa or have an acrimonious flavor not appropriate.

(6) Barrier properties of the mucosa.

(7) Drugs which are unstable at buccal pH cannot be administered.

MATERIALS AND METHODS

Basically as per its name triple layer buccal patches comprises of three different layers kept over one-another where every layer has its distinct release pattern or function. First layer (top of patch) was an immediate release layer which can release the drug immediately when applied onto the buccal area. Second layer was sustained release layer from where released drug shall reach to first layer. Then third layer was backing layer which can prevent drug release into the oral cavity and thus allows unidirectional release towards buccal mucosa. All three layers were prepared by solvent casting method. First backing layer was prepared then sustained layer and at last immediate release layer was solvent casted above the sustained release layer. Thus, all these layered were combined to achieve tri layered duo release buccal patches of Atenolol.

Solvent casting method involved prepared a solution or homogenous dispersion of drug, polymers and other excipients (plasticizer, additives) and a solvent (water or other desired solvent) followed by pouring or casting it into mould or petri plate and subsequent drying to evaporate solvent leading to formation of a film.

Preparation of backing layer

Prepared by using solvent casting technique in which the solution of ethyl cellulose, dibutylpthllate and acetone was casted into petri plate and air dried over night at room temperature.

Preparation of sustained release layer

Selected quantities of polymer and drug, plasticizer, and water were mixed and formed a solution and casted over the previously prepared backing layer and dried at 45^{o}C in hot air oven overnight.

Preparation for immediate release layer

Aqueous solution of desired ratio of drug, polymer, plasticizers and other excipients was prepared and casted over the previously prepared sustained release layer and dried in an oven at 45^{o}C overnight.

Before direct preparing triple layer patch

Before preparing triple layer directly first individuals layers of different drug and polymers ratio were prepared and evaluated for different parameters then the best immediate and sustained formulation were incorporated into triple layer patch.

Preliminary trials formulation for immediate layer patch

Preliminary trials of buccal patches of HPMC E15 for the purpose of immediate release layer in triple layer patch were performed with three different formulations I1, I2, I3 given in Table.

Trial formulations of HPMC E15 polymer.

Ingredients	Trial Formulations		
	I1	**I2**	**I3**
HPMC E15	100 mg	150 mg	200 mg
PEG 400	40% polymer weight (w/w)	40% polymer weight (w/w)	40% polymer weight (w/w)
Water	15 ml	15 ml	15 ml

Preliminary trials formulation for sustained layer patch

Preliminary trials of buccal patches of guar gum for the purpose of sustained release layer in triple layer patch were performed with three different formulations S1, S2, S3 given in Table

Preliminary trials formulations of guar gum.

Ingredients	Trial Formulations		
	S1	**S2**	**S3**
Guar Gum	50 mg	100 mg	150 mg
Glycerol	40% polymer weight w/w	40% polymer weight w/w	40% polymer weight w/w
Water	20ml	20ml	20ml

Preliminary trials formulation for backing membrane patch

Preliminary trials of buccal patches of ethyl cellulose for backing layer in triple layer patch were performed with three different formulations B1, B2, B3 given in Table

Preliminary trials formulations of ethyl cellulose

Ingredients	Trial Formulations		
	B1	**B2**	**B3**
Ethyl Cellulose	100 mg	200 mg	300 mg
Acetone: IPA	20ml	20ml	20ml
Dibutyl pthallate	20% polymer weight w/w	20% polymer weight w/w	20% polymer weight w/w

Evaluation Parameters:

Thickness

Thickness of patches of each formulation was measured with vernier to measure the uniformity of film thickness which is a factor toward the accuracy of dose of the film. Film size of 2 by 2 cm^2 and n=3 means measured in three films).

Surface morphology

Scanning electron microscopy were used to be determined the surface morphology of triple layer patch with the resolution power dried patch mounted on one stub using double side adhesive tape and coated with gold palladium alloy using fine coat sputter.Then sample was analyzed in carl zeiss in different magnification of 1000X, 2000X, 5000X and 10000X.

Weight variation

Individual patches were weighed of each formulation in digital balance then average weight calculated with standard deviation. Film size of 2 by 2 cm^2 and n=3 means measured in three films.

Surface pH measurement

Surface pH was measured to evaluate the possible damage to mucus by the films.Samples were immersed in phosphate buffer (pH=6.8) for 2 h. Samples were taken out and the pH of each film was recorded by placing the probe of pH meter in contact with the wet sample Film size of 2 by 2 cm^2 and n=3 means measured in three films.

Folding endurance-

Patches were manually folded repeatedly at the same place until it cracked. Numbers of folds were noted before patch broke (Salehi *et al* 2017). Film size of 2 by 2 cm^2 and n=3 means measured in three films.

Drug content uniformity

Patches of 20mm diameter were cut from three different places from the casted patch. Each patch was placed in 100ml volumetric flask and dissolved in phosphate buffer pH 6.8. (2ml) and diluted it with phosphate buffer up to 10ml to make concentration of 5ug/ml. The absorbance of diluted sample was measured at 225nm in a UV-visible spectrophotometer. Then the ratio drug content was known by using standard plot and repeat procedure for other films. Film size of 2 by 2 cm^2 and n=3 means measured in three films).

***In vitro* drug release study**

USP dissolution type 5 apparatus was used under sink conditions 37^oC and 50 rpm. A solo patch was positioned in 500ml pH 6.8phosphate buffer. Patch was applied on glass disc in such a way that mucoadhesive film of the patch was in connection with the dissolution medium and backing layer was fixed on disk. Samples were taken at required time intervals, diluted appropriately and absorbances were measured in a UV-visible spectrophotometer. Film size of 2 by 2 cm^2 and n=3 means measured in three films.

***Ex vivo* mucoadhesion time**

Buccal patch was applied on a freshly cut buccal mucosa of goat. Buccal mucosa was tied on to a glass slide and patch was wetted with 1 drop of pH 6.8 phosphate buffer and pasted on buccal mucosa slide put on beaker simulate the assembly at 50 rpm time by which patch is collapsed or deadhered from it is noted. Film size of 2 by 2 cm^2 and n=3 means measured in three films.

***Ex vivo* permeation study of patch**

Permeation of drug from the patches across goat mucosa membrane studied with the help of Franz diffusion cell apparatus using phosphate buffer 6.8 as medium. Buccal mucosa placed between donor and receptor compartment. Total volume in receptor compartment was 7.5ml. Strip of patch placed on buccal mucosa. Draw the sample at every regular interval of time that is 5min, 10min, 15min, 120min up to 8 hours and analysed via UV spectrophotometer (Hanif *et al* 2017). Film size of 2 by 2 cm^2 and n=3 means measured in three films.