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Research Article

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FORMULATION AND EVALUTION OF TERBUTALINE SULPHATE BUCCAL PATCHES BY USING HPMC K4M, HPMC E15 POLYMERS

*Middela Karthik and Dr. Reddy Sunil

Warangal Telangana India 506001.

INTRODUCTION

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*Corresponding Author Middela Karthik Warangal Telangana India 506001. Buccal route of drug delivery is a good alternative, amongst the various routes of drug delivery.^[1] Buccal drug delivery is most advantageous because it abundant blood supply in buccal mucosa, bypassing the hepatic first pass effect and accessibility.^[2] However, for oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration.^[3] Oral cavity has

been investigated for number of applications including the treatment of periodontal disease bacterial and fungal infection, aphthous and dental stomatitis. Over the last two decades mucoadhesion has become of interest for its systemic delivery by retaining a formulation intimate contact with buccal cavity.^[4] The term bio adhesion has been used to define the attachment of a synthetic natural macromolecule to a biological tissue for an extended period of time. When a substrate is a mucosal system adheres and interacts primarily with the mucus layer, this phenomenon being referred to as mucoadhesion.^[5] The adhesive properties of such drug delivery platforms can reduce the enzymatic degradation due to the increased intimacy between the delivery vehicle and the absorbing membrane.^[6] The use of mucoadhesive polymers in buccal drug delivery has a greater application. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability.^[7]

Advantages

- Bypass of the gastrointestinal tract and hepatic portal system, increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first metabolism.
- Improved patient compliance due to the elimination of associated pain with injections; administration of drugs in unconscious or incapacitated patients.
- Sustained drug delivery.
- A relatively rapid onset of action can be achieved relative to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Increased ease of drug administration.^[8]

Disadvantages

- Limited absorption area- the total surface area of the membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm2 represents non-keratinized tissues, including buccal membrane.^[9]
- The barriers such as saliva, mucus, membrane coating granules, basement membrane etc retard the rate and extent of drug absorption through the buccal mucosa.^[10]
- Continuous secretion of the saliva(0.5-2 l/day)leads to subsequent dilution of the drug.^[11]
- The hazard of choking by involuntarily swallowing the delivery system is a concern.
- Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and ultimately the involuntary removal of the dosage form.^[12]

Structure & Design of Buccal Dosage Form Structure and design

Drug delivery designed for the buccal mucosa contains a polymeric adhesive component. When in contact with the saliva, the adhesive attaches to the mucosa causing immediate and rapid drug delivery. Transmucosal drug delivery systems can be unidirectional or bidirectional. Unidirectional patches release the drug only into the mucosa, while bi-directional patches release the drug in both the mucosa and the mouth. The buccal patch is designed in either a matrix configuration with drug, adhesive and additives mixed together, or a reservoir system that contains a cavity for the drug and additives separate from the additives. An impermeable backing is applied to control the direction of drug delivery, to reduce patch deformation and disintegration while in the mouth; and to prevent drug loss. Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.



Components or structural features of oral cavity

Figure no. 1: Anatomical structure of Oral Cavity (Anterior View) Figure no:-2 structure of buccal mucosa.

Buccal dosage form for buccal delivery

In the past decades, to till now, different drug delivery systems intended for buccal administration have been developed. The most common buccal dosage forms are tablets and patches. Such type of form must be of a small size and a suitable geometry so as to not interfere with physiological function of the mouth, even after their hydration in the oral cavity. One of the requirements is that they do not adhere too tightly because it is undesirable to exert too much force to remove the formulation/ dosage form after use, otherwise the mucosa could be injured. An alternative is the use of formulations that dissolve or disintegrate completely during the application period. Moreover, in the case of Transmucosal administration, Drug release should be unidirectional (towards the mucosa), and the release into the saliva should be avoided.

Matrix type

The buccal patch designed in a matrix configuration contains drug, adhesive and additives mixed together.

Reservoir types

The buccal patch designed in a reservoir system contains a cavity for the drug and additives separate from the adhesive. An impermeable backing is applied to control the direction of drug delivery; to reduce patch deformation and disintegration while in the mouth; and to

prevent drug loss. Additionally, the patch can be constructed to undergo minimal degradation in the mouth, or can be designed to dissolve almost immediately.

Patches

Patches are laminated and generally consist of an impermeable backing layer and a drugcontaining layer that has mucoadhesive properties and from which the drug is released in a controlled manner. Moreover, buccal patches for systemic delivery of tyrotropin-releasing hormone, octreotide, oxytocin, buserelin, calcitonin and leuenkephalinhave been studied.

Novel drug delivery system

Novel drug delivery systems, such as lipophilic gel, buccal spray and phospholipids vesicles have been recently proposed to deliver peptides via the buccal route. A novel liquid aerosol formulation (Oralin, Generex Biotechnology) has been already developed. This system allows precise insulin dose delivery via a metered dose inhaler in the form of fine aerosolized droplets directed into the mouth. This oral aerosol formulation is rapidly absorbed through the buccal mucosal epithelium and it provides the plasma insulin levels necessary to control postprandial glucose rise in diabetic patients. This novel, pain-free, oral insulin formulation has a number of advantages including rapid absorption, a simple (user-friendly) administration technique, precise dosing control (comparable to injection within one unit) and bolus delivery of drug.^[13]



Figure 3: Schematic representation of different matrix tablets for buccal delivery. Arrows indicate the direction of drug release.

Buccal drug delivery system

A delivery system designed to deliver drug systemically or locally via buccal mucosa. Buccal delivery refers to the drug release which can occur when a dosage form is placed in the outer vestibule between the buccal mucosa and gingival.^[14]

Buccal dosage forms

• **Buccal mucoadhesive tablets:** Buccal mucoadhesive tablets are dry dosage form that have to be moistened prior to placing in contact with buccal mucosa. Example: a double

layer tablet, consisting of adhesive matrix layer of hydroxyl propyl celluloseand polyacrylic acid with an innr core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate).

Active ingredient	Polymers used	Investigators [Ref.]
Baclofen	NaMC, Na alginate and Methocel K15M	Basani et al.51
Carvedilol	HPMC K4M and CP 934P	Pandey et al.52
Carvedilol	HPMC K4M, HPMC K15M and CP 934	Yamsani et al.53
Chlorhexidine diacetate	Chitosan and Na alginate	Giunchedi et al.54
Chlorpheniramine maleate	Hakea gum from Hakea gibbos	Alur et al.55
Flurbiprofen	HPMC K15M, HEC, CP971 and Carbomer 940	Perioli et al.57
Itraconazole	Eudragit 100M, HPMC K4M and CP 934P	Madgulkaret al.58
Miconazole nitrate	CP 934, HPMC K4M and PVP K30	Madgulkar et al.59
Morphine sulfate	HPMC K100M, CP 910 and Eudragit RSPM	Anlar et al.60
Nicotine	CP 934 and HPC	Park and Munday 61
Nifedipine	CMC, CP 934P, HPMC, PVP K30 and PVA	Varshosaz et al.62
Omeprazole	Na alginate, HPMC	Choi and Kim63
Ondansetron	HPMC 15 cps, CP 934, Na alginate and NaCMC.	Hassan <i>et al</i> .64
Oxytocin	Mucilage of Diospyros peregrina fruit	Metia et al.65
Piroxicam	HPMC K4M and CP934	Velmurugan et al.66
Pravastatin Na	PVP K-30 and Pluronic F127 and EC	Shidhaye et al.67
Prednisolone	HPMC, CP 934 and NaCMC	Samani et al.68

 Table 1: List of Investigated Buccal Mucoadhesive Tablets.

• **Patches and Films:** Buccal patches consist of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required oval shape. A novel mucosal adhesive film called "Zilactin" – consisting of an alcoholic solution of hydroxy propyl cellulose andthree organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hours even when it is challenged with fluids.^[15]

Table 2: List of Investigated Buccal Mucoadhesive Patches.

Active ingredient	Polymers used	Investigators [Ref.]
Aceclofenac	Gelatin, Poly Na CMC and PVA.	Khairnar et al.74
Atenolol	CP 934P, HPMC and NaCMC	Adhikari et al.75
Carvedilol	HPMC, CP934, Eudragit RS 100, and EC	Thimmasetty et al.76
Carvedilol	HPMC E15 and HPC JF	Vishnu et al.77
Cetylpyridium chloride	PVA, HEC, or chitosan	Nafee et al.30
Hydrochlorothiazide	EC and HPMC	Attama et al. 78
Ibuprofen	NaCMC and PVP	Perioli et al.79
Insulin	NaCMC-DVP	Sahni et al.80
Methotrexate	HPMC K4M, Na alginate, NaCMC, CP 934, PVA and PVP K-30	Bhanja et al.81
Metoprolol tartrate	Eudragit NE40D with HPMC, Na CMC or CP	Wong et al.82
Miconazole	HPMC, NaCMC, Chitosan, HECand PVA.	Nafee et al.31

Semisolid Preparations (Ointment and Gels)

Bioadhesive gels or ointment have less patient acceptability than solid bioadhesive dosage form and most of the dosage forms are used only for localized drug therapy within the oral cavity. one of the original oral mucoadhesive delivery systems- "orabase"- consists of finely ground pectin, gelatin and sodium carboxy methylcellulose dispersed in a poly (ethleene) and a ground pectin, gelatin and sodium carboxy methylcellulose dispersed in poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes.^[16]

Active ingredient	Polymers used	Investigators [Ref.]
Insulin	Pluronic F-127gel, oleic acid, eicosapentaenoic acid and docosahexaenoic acid.	Morishita <i>et al</i> . 96
Itraconazole	2-ethylmethyl-2 pyrrolidone, Polaxamer 188 and CP 934	Kumar.K et al.117
Nystatin	Chitosan	Rasool et al.118
Triamcinolone acetonide	Polaxamer 407 and CP 934	Shin et al. 97

Table 3: List of Investigated	Buccal	Mucoa	dhesive	Gels.
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• Powders

Hydroxpropyl cellulose and beclomethasone in powder form when sprayed onto the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hours.^[17]

Buccal Mucoadhesive Marketed Products

Table 4 shows the commercially available list buccal dosage forms, the commercially administered steroid are methyl testosterone propionate and testosterone propionate.

Cyclodextrins are used as additives to enhance the absorption of these steroidal hormones Prochlorperazine and oxytocin are also found to be effective when administered in the formbuccal devices.

Brand name	Active ingredient	Bioadhesive polymer	Dosage form	Company	
Aphtach	Triamcinolone acetonide	HPC, PAA	Tablet	Teijin Ltd	
Puccestom	Prochlorporazina	Xanthan gum, Povidone,	Tablat	Reckitt Benkiser Plc	
Duccastem	Fiochioiperazine	Locust bean gum	Tablet		
Oralin–Generex	Insulin	Unknown	solution	Generex Biotechnology	
Louriad	Miconazola	Unknown	Tablet	Bio Alliance Pharma	
Laurrau	Witcollazole	UIKIIOWII	Tablet	(Phase III trials)	
Stright SP	Tastostarona	Carbomer 934P,	Tablet	Ardana Bioscience Ltd	
Strain SK	Testosterone	Hypromellose,	Tablet		
Suscard	Glyceryl trinitrate	Hypromellose	Tablet	Forest Laboratories	

Mechanism of buccal absorption

Buccal drug absorption occurs by passive diffusion of the nonionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophilic the drug molecule, the more readily it is absorbed. The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. The linear relationship between salivary secretion and time is given as follows: where,

$$\frac{-dm}{dt} = \frac{KC}{ViVt}$$

- M Mass of drug in mouth at time t
- K Proportionality constant
- C Concentration of drug in mouth at time
- Vi- The volume of solution put into mouth cavity and Vt- Salivary secretion rate

Factors affecting buccal absorption

The oral cavity are a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption.

1. Membrane Factors

This involves degree of keratinization, surface area available for absorption, mucus layer of salivary pellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.

2. Environmental Factors

A.) **Saliva:** The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film affect the rate of buccal absorption.

B.) Salivary glands: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.

C.) Movement of buccal tissues: Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing.^[18]

Composition of buccal patches

A. Active Pharmaceutical ingredient (API)

The buccal film technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose molecules are difficult to be incorporated in buccal film. Generally 5% w/w to 30% w/w of active pharmaceutical ingredients can be incorporated in the buccal patches.^[19]

B. Polymers (adhesive layer)

Polymer hydration and swelling properties probably play the main role. The polymer hydration and consequently the mucus dehydration could cause an increase in mucous cohesive properties that promote mucoadhesion. Swelling should favor polymer chain flexibility and interpenetration between polymer and mucin chains. So, depending on the type of formulation, polymers with different characteristics have to be considered. Examples:

Hydroxy ethylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, carbopol and other mucoadhesive polymers.^[20]

C. Diluents: Lactose DC is selected as diluent for its high aqueous solubility, its flavouring characteristics and its physico-mechanical properties, which make it suitable for direct compression. Other example: microcrystalline starch and starch.

D. Sweetening agents: Sucralose, aspartame, mannitol, etc.

E. Flavouring agents: Menthol, vanillin, clove oil, Peppermint oil, cinnamon oil, spearmint oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and etc.^[21]

F. Backing layer: Ethyl cellulose, etc.

G. Penetration enhancer: Cyano acrylate, EDTA, Ctric acid etc.

H. Plasticizers: PEG-100, 400, propylene glycol, etc.^[22]

Method of preparation

Two methods used to prepare adhesive patches include.

Solvent casting

In this, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation, a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry. The solvent casting method is simple, but suffers from some disadvantages, including long processing time, high cost and environmental concerns due to the solvents used. These drawbacks can be overcome by the hot-melt extrusion method.^[23]



Figure 4: Pictorial diagram of Solvent casting method.

Direct milling

In this, patches are manufactured without the use of solvents (solvent-free). Drug and excipients are mechanically mixed by direct milling or by kneading, usually without the presence of any liquids. After the mixing process, the resultant material is rolled on a release liner until the desired thickness is achieved. An impermeable backing membrane may also be applied to control the direction of drug release, prevent drug loss and minimize deformation and disintegration of the device during application period.^[24] While there are only minor or even no differences in patch performance between patches fabricated with the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues.^[25]



Figure 5: Pictorial diagram of Direct milling method.

List of drug delivered via buccal route: In an effort to determine the feasibility of buccal route as a novel route of drug delivery, several drugs have been studied. The variation in class of compounds illustrates that the pharmaceutical industries have an alternative and novel routes of administration for existing drugs.^[26]

- Active Ingredients:
- ➤ Acitretin
- Acyclovir
- ➤ Arecoline
- Buprenorpine
- ➢ Carbamazepine
- Chitosan
- Chlorpheniramine maleate
- > Metronidazole
- Morphine sulphate
- > Nicotine

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- ➢ Nifedipine
- ➢ Omeprazole
- > Oxytocin
- > Piroxicam
- Ergotamine tartrate (etc).

Evaluation Surface pH

The surface pH of the buccal patch was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature and pH was note down by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute.^[27]

Swelling studies

Weight and area increase due to swelling were measured. Weight increase due to swelling: A drug-loaded patch of 1x1 cm2 was weighed on a preweighed cover slip. It was kept in a petridish and 50 ml of phosphate buffer, pH 6.6 was added. After every five minutes, the cover slip was removed and weighed upto 30 minutes. The difference in the weights gives the weight increase due to absorption of water and swelling of patch. Area increase due to swelling: A drug loaded patch size of 1x1 cm2 was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. 50ml of phosphate buffer, pH 6.6, was poured into the petridish. An increase in the length and breadth of the patch was noted at 5 min intervals for 60 min and area was calculated.^[28] The percent swelling, %S, was calculated using the following equation:

Xt - Xo %S = x 100 Xo

Where Xt is the weight or area of the swollen patch after time t Xo is the original patch weight or area at zero time.

Thickness measurements

The thickness of each film is measured at five different locations (centre and four corners) using an electronic digital micrometer.

Morphological characters

Morphological characters are studied by using scanning electron microscope (SEM).^[29]

Palatability test

Palatability study is conducted on the basis of taste, after bitterness and physical appearance. All the batches are rated A,B and C grades as per the criteria. When the formulation scores at least one A grade, formulation is considered as average. When the formulation score two a geade then it would be considered as good and the one with all three A grade it would be the very good formulation.^[30] Grades: A = very good, B = good, C = poor.

Folding endurance

The test is performed by repeated folding of the film at the same place until film failure. A maximum of 300 times is sometimes reported as a limit to the test and the value is reported as the number of times the film can be folded prior to rupture.^[31]

In vitro drug release

The United States Pharmacopeia (USP) XXIII rotating paddle method used to study the drug Release from the bilayered and multilayered patches. The dissolution medium consisted of phosphate buffer pH 6.8. The release was performed at $37^{0}C \pm 0.50^{0}C$, with a rotation speed of 50 rpm. The backing layer of buccal patches attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples filtered through whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at suitable nm.^[32]

In vitro drug permeation

The in vitro buccal drug permeation study of Drugs through the buccal mucosa (sheep and rabbit) performed using Keshary-Chien/Franz type glass diffusion cell at $37^{\circ}C \pm 0.2^{\circ}C$. Fresh buccal mucosa mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa and the compartments clamped together. The donor compartment filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment

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was filled with phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment maintained by stirring with a magnetic bead at 50 rpm. A one ml sample can be withdrawn at predetermined time intervals and analyzed for drug content at suitable nm using a UVspectrophotometer.^[33]



Figure 6: Franz diffusion cell.

Stability study in Human saliva

Stability study of fast dissolving films is carried out for all the batches according to ICH guidelines. After predetermined time intervals, the films are evaluated for the drug content, disintegration time and physical appearance. The stability study of optimized mucoadhesive patch formulation was performed at 40° C, $37 \pm 5^{\circ}$ C & $75\pm5\%$ RH for three months. The value of all parameter after three months remain same as their values and minor changes occur in value of volume entrapment efficiency, % elongation & % drug release after 8 hour which was considerable.^[34,35]

Ex vivo mucoadhesive strength

A modified balance method used for determining the ex vivo mucoadhesive strength. Fresh buccal mucosa (sheep and rabbit) obtained, used within 2 hours of slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane washed with distilled water and then with phosphate buffer pH 6.8 at 370C. The buccal mucosa cut

into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The two sides of the balance made equal before the study, by keeping a 5 g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37°C \pm 1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive.^[36]



Figure 7: Measurement of Mucoadhesive Strength.

AIM AND OBJECTIVE OF STUDY

The purpose of this study was to develop formulations and systematically evaluate in-vitro performances of mucoadhesive patches of Terbutaline sulphate using different polymer and chose the polymer to develop the release of drug in immediate and sustained manner.

The buccal route has a relatively robust mucosa, has the advantage of allowing excellent accessibility and reasonable patient compliance. Within the oral mucosal cavity, the buccal region offers attractive route of administration for local or systemic drug delivery. The mucosa has a rich blood supply and it is relatively permeable. Recently interest has been focused on the delivery of drug to or via mucous membrane by the use of mucoadhesive

material, several mucoadhesive formulations are available under development and drug delivery via buccal mucosa is gaining importance of a novel route of drug administration.

Terbutaline sulphate is a selective $\beta 2$ adrenceptor agonist widely used in the acute and longterm treatment of bronchial asthma, chronic bronchitis, emphysema and other chronic obstructive lung diseases with reversible bronchial hyper reactivity. Terbutaline sulphate is a short-acting bronchorelaxant which can be given orally, par-enterally or by inhalation. Orally administered terbuta-line is absorbed incompletely. Terbutaline sulphate undergoes high first pass metabolism in the gut wall and liver and the bioavailability is only 15%. Peak plasma levels are 1.2 µg/ml for every mg of an oral dose, reached within 2–3 h. After inhalation, only about 10%–20% of inhaled dose reaches the lungs and the rest is swallowed. There are also reports about the harmful effects of aerosol bronchodilator therapy. Hence, there is a need to develop controlled drug delivery systems which can overcome the first pass effect, reduce the frequency of dosing and improve bioavailability.

The buccal region, within the oral cavity, offers an attractive route of administration for systemic drug delivery.^[38] Consequently, buccal drug delivery requires the use of mucoadhesive polymers as these dosage forms should ideally adhere to the mucosa and withstand salivation, tongue movement and swallowing for a significant period of time.

Objective of the Study

The objectives of present investigation are:

- To design a suitable buccal mucoadhesive patches for terbutaline sulphate using mucoadhesive polymers.
- Terbutaline sulphate buccal patches were prepared by solvent casting technique
- Evaluation of patches for the physical integrity and *in vitro* release.
- Preliminary *in vivo* studies for a short duration.

LITERATURE REVIEW

• Shalini Mishra, G. Kumar, P. Kothiyal^[37], Buccal drug delivery leads direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Buccal route is an attractive route of administration `for systemic drug delivery. This article aims to review the recent developments in the buccal adhesive drug delivery systems to provide basic principles to

the young scientists, which will be useful to circumvent the difficulties associated with the formulation design.

- Farheen Fiza et. al^[38], Drugs that are administered via the buccal mucosa directly enter the systemic circulation, thereby avoiding hepatic first-pass metabolism. Therefore, this administration route is useful for improving the bioavailability of drugs that are subject to an extensive first-pass effect when delivered orally. For the oral mucosal route of drug administration, various types of dosage forms can be prepared. A sublingual tablet can afford rapid drug absorption and a prompt pharmacological effect; however, the duration of delivery is short owing to the inevitable loss of a large proportion of the administered dose due to swallowing. To avoid such losses, a patch can be formulated that is located on the buccal mucosa of the oral cavity.
- Sanket Sharma, R. Yogananda^[39], Buccal administration of drug provides a convenient route of administration for both systemic and local drug actions. The preferred site for retentive oral transmucosal delivery systems and for sustained and controlled release delivery device is the buccal mucosa. Direct access to the systemic circulation through the internal jugular vein bypasses drug from the hepatic first pass metabolism leading to high bioavailability. The objective of this article is to review the developments in buccal adhesive drug delivery system as patches.
- **N.Vidyasagar et. al**^[40], this review article is to describe the buccal drug delivery system of different dosage forms such as patches (films) and general considerations in formulation, types of buccal drug delivery dosage forms and describing different categories of drugs and their applications.
- Nishan N. Bobade et. al,^[41] In this paper main focus on oral mucosa, pathway, barriers to penetration of drug, different dosage forms, evaluation methods; this will be useful to circumvent the difficulties associated with the formulation design.
- **Pradeep Kumar et. al**,^[42] This article aims to review the recent developments in the buccal adhesive drug delivery systems to provide basic principles to the young scientists, which will be useful to circumvent the difficulties associated with the formulation design.

- **Kinesh V. Patel et. al**,^[43] This article reviews current status of various buccal bioadhesive dosage forms such as tablets, patches, hydrogels and chewing gums and describes the strategies to improve permeation of drugs through the Buccal mucosa. Recent innovations in the dosage form development and in vivo and in vitro mucoadhesion testing methods has also been focused. Lastly, different dissolution testing methods for buccoadhesive dosage forms developed by different researchers have also been discussed.
- **Peeush Singhal et. al,**^[44] Develop and optimize formulations of mucoadhesive patches of Terbutaline sul-phate. The patches were prepared by the solvent casting method using Hydroxyl propyl methyl cellulose(HPMC cps50) as basic polymer and Carbopol 934, Eudragit RL 100 and Ethyl cellulose were taken in various ratios and 6 different formulations were made.
- Gururaj SK, Praveen Kumar GM, Divakar Goli, Upendra Kulkarni^[45], prepare the buccal patches of terbutaline sulphate, the bronchodilator having oral bioavailability of 10.8%, using polymers like sodium alginate, carbopol-934P, PVA and PVP in various proportions while glycerin as a plasticizer.
- Singh S. Soni R et. al^[46], prepare and evaluate buccal bioadhesive films of salbutamol sulphate (SS) for the treatment of asthma. The films were designed to release the drug for a prolonged period of time so as to reduce the frequency of administration of the available conventional dosage forms of SS. The different proportions of sodium carboxymethylcellulose (SCMC) and Carbopol 940P (CP 940P) were used for the preparation of films. Carbopol was used to incorporate the desired bioadhesiveness in the films.
- Patel, Rajesh Singh; Poddar, S. S. et. al,^[47] present study was concerned with the preparation and evaluation of mucoadhesive buccal patches for the controlled systemic delivery of Salbutamol sulphate to avoid first pass hepatic metabolism.
- N.G. Raghavendra Rao and Keyur Patel^[48] Develop and optimize formulations of mucoadhesive patches of Ropinirole. The Ropinirole is a non-ergoline dopamine agonist with high relative specificity and full intrinsic activity at the D2 and D3 dopamine receptor subtypes.

- Sharma, P; Hamsa, V,^[49] Buccal mucoadhesive patches of terbutaline sulphate were prepared as an alternative dosage form using six polymers in different combinations and proportions. The backing membrane wasmade of a polyglassine sheet or ethylcellulose.
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MATERIALS AND EQUIPMENTS

Chemicals And Equipments used.

S.NO	MATERIALS	SUPPLIER	
1	Terbutaline Sulphate	Sigma-Aldrich India, Mumbai	
2	Hpmc K4m (Mg)	Colorcon India, Mumbai	
3	Hpmc E15	Evonik Industries	
4	Carbopol-971p	S.D.Fine Chemicals	
5	Peg 400	S.D.Fine Chemicals	
6	6 Dichloromethane (Ml) S.D.Fine Chemicals		
7	Ethanol (Ml)	S.D.Fine Chemicals	

S. NO	EQUIPMENT NAME	SOURCE
1	Digital Weighing Machine	Shimadzu Aty 244
C	Uv-Vis Double Beam	Elico Sl 159 Double Beam
Δ	Spectrophotometer	Spectrophotometer
3	Keshry Diffusion Cell	Anchor, Mumbai
4	Magnetic Stirrer	Erweka
5	Usp Dissolution Apparatus	Lab India Ds 8000
6	Tray Dryer	Sisco
7	Bath Sonicator	Wensar

Table 6: List of equipments used.

DRUG PROFILE

Name: Terbutaline Sulphate.

Description: A selective beta-2 adrenergic agonist used as a bronchodilator and tocolytic.

Structure



IUPAC Name: 5-[2-(tert-butylamino)-1-hydroxyethyl]benzene-1,3-diol. Chemical Formula: C₁₂H₁₉NO₃ Molecular weight: 225.28

CLINICAL PHARMACOLOGY

Pharmacodynamics

Terbutaline is a relatively selective beta2-adrenergic bronchodilator that has little or no effect on alpha-adrenergic receptors. The drug has exerts a preferential effect on beta2-adrenergic receptors but stimulates beta-adrenergic receptors less selectively than relatively selective beta2-agonists. Terbutaline appears to have a greater stimulating effect on beta-receptors of the bronchial, vascular and uterine smooth muscles (beta2 receptors) than on the betareceptors of the heart (beta1 receptors). This drug relaxes smooth muscle and inhibits uterine contractions, but may also cause some cardiostimulatory effects and CNS stimulation.

Mechanism of Action

The pharmacologic effects of terbutaline are at least in part attributable to stimulation through beta-adrenergic receptors of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic- 3',5'- adenosine monophosphate (c-AMP). Increased c-AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Pharmacokinetics

Absorption: Approximately 30-50% if administered orally and well absorbed subcutaneously.

Route of elimination

About 90% of the drug was excreted in the urine at 96 hours after subcutaneous administration, with about 60% of this being unchanged drug. It appears that the sulfate conjugate is a major metabolite of terbutaline and urinary excretion is the primary route of elimination.

Half life: 5.5-5.9 hours.

Indications

For the prevention and reversal of bronchospasm in patients 12 years of age and older with reversible, obstructive airway disease, as well as symptomatic management of reversible bronchospasm associated with bronchitis and emphysema. Also used acute IV and sub-Q therapy in selected women to inhibit uterine contractions in preterm labor (tocolysis) and prolong gestation when beneficial.

Uses

Terbutaline is used as a fast-acting bronchodilator (often used as a short-term asthma treatment) and as a tocolytic to delay premature labor. The inhaled form of terbutaline starts working within 15 minutes and can last up to 6 hours.

Terbutaline as a treatment for premature labor is an off-label use not approved by the FDA. It is a pregnancy category 'B' medication and is routinely prescribed to stop contractions. After successful intravenous tocolysis, little evidence exists that oral terbutaline is effective. However, following uterine inversion in the third stage of pregnancy, Terbutaline (or either Halothane or magnesium sulfate) can be utilized to relax the uterus if necessary prior to uterine replacement.

POLYMER PROFILE

1. Hypromellose

Hypromellose is a semi synthetic, inert, viscoelastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments. Hypromellose is a partly O-methylated and O-(2- hydroxypropylated) cellulose. Odorless and tasteless, white or creamy-white fibrous or granular powder. Acidity/alkalinity pH is .5–8.0 for a 1% w/w aqueous solution. Hypromellose in an aqueous solution, unlike methylcellulose, exhibits a thermal gelation property. That is, when the solution heats up to a critical temperature, the solution congeals into a non-flowable but semi-flexible mass. Typically, this critical (congealing) temperature is inversely related to both the solution concentration of HPMC and the concentration of the methoxy group within the HPMC molecule (which in turn depends on both the degree of substitution of the methoxy group, the lower the critical temperature. Its is used as a tablet binder and as a matrix for use in extended-release tablet formulations. As a film forming agent at the concentrations of 2–20% w/w to coat the tablets. As an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

CARBOPOL 971 NFPOLYMERS

Carbopol polymers are polymers of acrylic acid cross-linked with polyalkenyl ethers or divinyl glycol. They are produced from primary polymer particles of about 0.2 to 6.0 micron average diameter. The flocculated agglomerates cannot be broken into the ultimate particles when produced. Each particle can be viewed as a network structure of polymer chains interconnected via cross-linking¹. *Carbopol polymers* are offered as fluffy, white, drypowders (100% effective).

The carboxyl groups provided by the acrylic acid backbone of the polymer are responsible for many of the product benefits. Carbopol polymers have an average equivalent weight of 76 per. Carbopol 71G, 971 P, 974 P are cross-linked with allyl penta erythritol and polymerized in ethyl acetate. Polycarbophil is cross-linked polymer in divinyl glycol and polymerized in solvent benzene. All the polymers fabricated in ethyl acetate are neutralized by 1-3% potassium hydroxide. Though Carbopol 971 P and Carbopol 974 P are manufactured by same

process under similar conditions, the difference in them is that Carbopol 971 P has slightly lower level of cross-linking agent than Carbopol 974 P. Carbopol 71 G is the granular form Carbopol grade.

Polyethylene Glycol

Polyethylene Glycol is a Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant. Its chemical name is α -Hydro- ω -hydroxypoly(oxy-1,2-ethanediyl), PEG, PEO, or POE refers to an oligomer or polymer of ethylene oxide. The three names are chemically synonymous, but historically PEG has tended to refer to oligomers and polymers with a molecular mass below 20,000 g/mol, PEO to polymers with a molecular mass above 20,000 g/mol and POE to a polymer of any molecular mass.^[2] PEG and PEO are liquids or low-melting solids, depending on their molecular weights. PEGs are prepared by polymerization of ethylene oxide and are commercially available over a wide range of molecular weights from 300 g/mol to 10,000,000 g/mol. While PEG and PEO with different molecular weights find use in different applications and have different physical properties (e.g. viscosity) due to chain length effects, their chemical properties are nearly identical. Different forms of PEG are also available, depending on the initiator used for the polymerization process – the most common initiator is a monofunctional methyl ether PEG, or methoxypoly(ethylene glycol), abbreviated mPEG. Lower-molecular-weight PEGs are also available as purer oligomers, referred to as monodisperse, uniform, or discrete. Very high purity PEG has recently been shown to be crystalline, allowing determination of a crystal structure by x-ray diffraction.

METHODOLOGY

Preformulation studies

Pre-formulation testing is the first step in the rationale development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when in combined with excipients. The overall objective of the pre-formulation testing is to generate information useful to the formulator in developing stable and bio availability dosage forms which can be mass produced.

The goals of pre-formulation studies are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish it's compatibility with different excipients.

Hence, pre-formulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies.

Characterization of Terbutaline sulphate

A. Melting point determination

The melting point of Terbutaline sulphate was determined by using meltingpoint apparatus.

B. UV spectroscopy

Preparation of Stock Solution: 100 mg of Terbutaline sulphate was taken in a 100 ml volumetric flask. To that 5 ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with 6.8 PH phosphate buffer solutions.

- From the above solution 1 ml is diluted to 10 ml with, 6.8 PH phosphate buffer solutions to give 100 µg /ml concentration.
- From the above solution 1 ml is diluted to 10 ml with, 6.8 PH phosphate buffer solutions to give 10 μg /ml concentration.
- The prepared solution i.e., 10 μg/ml concentration was scanned for λ_{max} from 200-400 nm in UV/Visible spectrophotometer.

C. Determination of solubility of Terbutaline sulphate

A saturated solution of TBS was prepared by shaking an excess amount in 2 ml phosphate buffer pH 6.6/distilled water at $25 \pm 10^{\circ}$ C room temperature for 24 h. The saturated solution was withdrawn, filtered and analyzed at 276 nm using UV visible spectrophotometer (Shimadzu 1601, Japan).

Drug-excipients interaction study of patches

There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The technique employed in this study to know drug-excipients interactions is IR spectroscopy; IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug Terbutaline sulphate and formulations were scanned by using Jasco FTIR 410, by a thin film method.

Surface pH

Buccal patches were left to swell for 1 hour in phosphate buffer of pH 6.8 in a petredish. The surface pH was measured by pH meter placed on the surface of the swollen patch. The mean of three readings was recorded.

Drug Content Uniformity of Patches

The patches were tested for the content uniformity. A patch of size $1X1 \text{ cm}^2$ was cut and placed in a 100 ml volumetric flask containing 100ml pH 6.8 phosphate buffer solutions. The contents were kept for 24 hours to complete dissolve the patch. After making proper dilution to the stock solution if necessary, the absorbance of the solution was measured against the corresponding blank solution at 276 nm.

Measurement of Mucoadhesive strength

The goat mucosal membrane was used as the model membrane and isotonic phosphate buffer pH 6.8 was used as the moistening fluid. The goat mucosal membrane was then stuck on to the inner surface of the beaker using suitable glue such that mucosal surface faces upwards. Then the phosphate buffer pH 6.8 was added in to beaker such that the buffer is contacted with the mucosal membrane. Two sides of the balance were made equal before the study, by keeping a 5 g weight on the left side. A beaker containing mucosal membrane was kept below the right hand set up of the balance. The patch was stuck on to a lower flat side of arm balance. 25 μ l of phosphate buffer pH 6.8 was added to the mucosal surface. Five grams weight from the left pan was removed. This lowered arm balance assembly along with patch over the membrane with weight of 5 g. This was kept undisturbed for 3 min. Then the weights on the left hand side were slowly added till the patch just separated from the membrane surface. The excess weight on the left pan i.e. total weight minus 5 g was taken as adhesive strength.

Measurement of Mucoadhesive Time

The mucoadhesive performance of the buccal patch was evaluated using goat buccal tissue. The time for patch to detach from the goat buccal tissue in a well-stirred beaker were used to assess the mucoadhesive performance. The fresh goat buccal tissue was fixed on the side of the beaker with glue. Before addition of the buffer, the patch was attached to goat buccal tissue by applying light force with fingertip for 20 second. The beaker was then filled with 800 ml phosphate buffer and kept at 37°. A stirring rate of 50 rpm were used to simulate buccal and saliva movement. The time for the patch to detach from the goat buccal tissue was recorded as the mucoadhesion time.

Folding endurance: Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times, which is considered

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satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance.

Tensile strength of patches

Tensile strength of the patch was determined with digital tensile strength tester (Tinius-Olsen). The sensitivity range of the machine is 1-10 Newton's. It consists of two load cell grips. The lower one was fixed and upper one was movable. The test patch of size (1x4 cm2) was fixed between these cell grips and force was applied till it breaks. The tensile strength of the patch was directly taken from the dial reading in Newton's, which was converted into kilogram.



Fig. 8: Tensile Strenth Tester.

In-Vitro Release Studies of Terbutaline sulphate patches in Phosphate Buffer (pH 6.8)

In-vitro release studies were carried out by attaching sigma dialysis membrane to one end of the open cylinder which acted as donor compartment prepared buccal patches containing drug was placed inside donor compartment which is agitated continuously using magnetic stirrer and then temperature was maintained at $37 \pm 1^{\circ}$ C. Receptor compartment consist of 100 ml of pH 6.8 phosphate buffer, sample of 2 ml were withdrawn at periodic intervals from receptor compartment and replaced with fresh pH 6.8 phosphate buffer immediately and drug release was analyzed spectrophotometrically at 276 nm. Release rate was studied for all prepared formulations.

Kinetic of drug release

The result of in-vitro dissolution studies of buccal patches were fitted with various kinetics models, like zero order (% cumulative drug release vs. time), Higu-chi's model (% cumulative drug release vs. square root of time) but these models failed to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the disso-lution data were also fitted to well-known Korsmeyer and Peppas semiempirical model to ascertain the me-chanism of drug release. log (Mt/M ∞) = logk + n logt Where, M ∞ is the amount of drug release after infinite time; k is the release rate constant which considers structural and geometric characteristics of the buccal patches; and n is the diffusional exponent; indicative of the mechanism of drug release. Table 8 shows an anal-ysis of diffusional release mechanism obtained by vari-ous value of n. The criteria for selecting the most ap-propriate model were chosen on the basis of goodness of fit test. The data were processed for regression analysis using MS EXCEL statistical function.

n value	Mechanism
n≤0.5	Quasi-fickian diffusion
0.5	fickian diffusion
0.5≤n≤1.0	Anomalous(non-fickian) diffusion
n≥1.0	Non –fickian super case II
1	Non –fickian case II

Table 7: Anal-ysis of diffusional release mechanism obtained by various value of n.

Table: Release Mechanism with Variation of n Values.

Stability studies

The optimized patches were stored at 45 ± 0.5 °C in hot air oven, over period of three month. At the end of three month patches were tested for drug content and *in-vitro* release profiles. Stability studies were conducted as per ICH guidelines. Samples were taken at 30th days intervals for drug content and *in-vitro* release estimation. The drug content and *in-vitro* release results were suggesting that there was no significant change in drug content and *in-vitro vitro* drug release.

Method of Preparation

Buccal patches of Terbutalin Sulphate were formulated by using solvent casting technique. Buccal patches were prepared using different grades of HPMC polymers and Carbopol 974P. Polyethylene glycol (PEG) was used as a plasticizer. Dichloromethane: Methanol in 1:1 ratio was used as the solvent system. Model dose of drug (15 mg per patch of 1x1 cm²) was weighed and dissolved in part of the solvent. Required amount of polymer was added slowly in drug solution and it was allowed to stand for complete swelling.

Polyethylene glycol was added to final solution. The resultant solution was set aside for 2 hrs to remove entrapped air and poured into glass petriplate. The Petri plates were kept on horizontal surface and covered with inverted funnel to allow controlled evaporation of solvent at room temperature till a flexible patch was formed. The formed patches were removed carefully, cut to size, wrapped in aluminum foil and stored in desiccators. Patches with any imperfections, entrapped air, differing in weight were excluded from further studies.

INCREDIENTS	BATCH CODE									
INGREDIENTS	F1	F2	F3	F4	<i>F</i> 5	F6	F7	F8	F9	F10
Terbutaline Sulphate	15	15	15	15	15	15	15	15	15	15
HPMC K4M	50		62.5		75		87.5		100	
HPMC E15		50		62.5		75		87.5		100
CARBOPOL 974P	50	50	37.5	37.5	25	25	12.5	12.5		
PEG 400 (%)	5	5	5	5	5	5	5	5	5	5
METHANOL +	10	10	10	10	10	10	10	10	10	10
DICHLOROMETHANE (1:1)	10	10	10	10	10	10	10	10	10	10

Table 8: Formulation of Buccal Patches.

RESULTS AND DISCUSSION

A. Preformulation studies

a. Melting point determination:

The melting points were found to be in the range of 246-248°C.

The reported melting point is 247°C.

b. Calibration curve of Terbutaline

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The absorbance values obtained are shown in **table 9**. Using concentration and absorbance data, a beer and lambert's plot was obtained. The plot is given the **figure 9**.

S. NO.	CONCENTRATION(µg/ml)	ABSORBANCE
1	0	0
2	2	0.185
3	4	0.345
4	6	0.526
5	8	0.722
6	10	0.907

 Table 9: Standard calibration curve of Terbutaline.



Figure no 9: Calibration curve.

C. Solubility determination

The solubility of terbutaline sulphate in water and phosphate buffer (pH 6.6) was found to be 252 ± 0.12 g/l and 239.27 ± 0.325 g/l, respectively. The apparent partition coefficient of terbutaline sulphate in an octanol, phosphate buffer (pH 6.8) system was found to be 0.051 ± 0.62 .

FTIR Studies

Drug polymer interactions were studied by FT-IR spectroscopy. One to 2mg of Terbutaline sulphate, polymer and physical mixtures of samples were weighed and mixed properly with Potassium bromide to a uniform mixture. A small quantity of the powder was compressed

into a thin semi transparent pellet by applying pressure. The IR spectrum of the pellet from 450-4000 cm¹ was recorded taking air as the reference and compared to study any interference.



Fig. 10: FT-IR spectra of Terbutaline sulphate.



Fig. 11: FT-IR spectra of Optimised formula (F-5).

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Physical appearance and surface texture of patches

These parameters were checked simply with visual inspection of patches and by feel or touch. The observation reveals that the patches are having smooth surface and they are elegant in appearance.

Weight uniformity of patches

The weight of the patches was determined using digital balance and the average weight of all patches was given in **Table 10**.

Thickness of patches

The thickness of the patches was measured using screw gauge and the average thickness of all patches was given in **Table 10**.

Folding endurance of patches

The folding endurance gives the idea of flexible nature of patches. The folding endurance was measured manually, patches were folded repeatedly till it broke and it was considered as the end point. The folding endurance was found optimum and the patches exhibited good physical and mechanical properties and the average folding endurance of all patches was given in **Table 10**.

Swelling index of patches

The swelling index of the patches was determined by immersing preweighed patch of size 10 mm in 50 ml water. The patches were taken out from petridish carefully at 5, 10 upto and 30 min. intervals, blotted with filter paper and weighed accurately and the average swelling index of all patches was given in **Table 10**.

Surface pH of patches

Surface pH was determined by bring the patches in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of patches and allowing equilibrate for 1 min and the average surface pH of all patches was given in **Table 10**.

Tensile strength of patches

The tensile strength of all the patches were evaluated by using standard tensile strength tester and the average tensile strength of all patches was given in **Table 10**.

Drug content uniformity of patches

Terbutaline sulphate buccal patches prepared with various polymers were subjected to the valuation for uniform dispersion of drug throughout the patch. In each case three patches were used and the average drug content was calculated, the results were shown in **Table-10**.

Formulation code	Thickness (mm)	Weight variation (mg)	Drug content Uniformity (mg)	Folding endurance	Tensile strength(N/m ²)	Swelling index (hr)	Surface pH	Muco adhesive strength (gm)	Muco adhesive time (min)
F1	0.26 ± 1.2	129.24 ± 1.2	92.41±0.1	78 ± 2	0.75	15.25	4.5	8.189	273
F2	0.25 ± 1.5	128.50 ± 1.8	94.28 ± 0.5	76 ±1	0.73	20.54	5.8	7.569	289
F3	0.27±1.8	128.98 ± 1.2	93.45±0.6	77±2	0.73	21.65	5.9	8.123	255
F4	0.28±1.3	129.87±1.4	94.9±03	77±9	0.75	23.31	5.7	7.664	249
F5	0.25±1.4	129.7±1.9	99.76±0.8	78±4	0.76	24.2	6.8	8.991	299
F6	0.29±1.5	129.09±1.1	94.5±.3	76±3	0.75	23.9	5.7	6.792	218
F7	0.26±1.4	126.97 ± 1.8	93.55±0.4	73 ±1	0.74	21.54	5.9	6.889	244
F8	0.27±1.8	127.54±1.2	94.28 ±0.44	72±2	0.72	22.31	6.2	7.356	263
F9	0.26±1.3	129.87±1.4	95.77±0.61	71±5	0.71	24.29	6.7	7.423	258
F10	0.29±1.4	128.97±1.9	96.92±032	82±4	0.72	27.12	6.4	7.887	229

Table 10: Physicochemical evaluation data of Terbutaline Buccal Patches.

Table 11: In vitro diffusion studies.

Time		Cumulative % drug release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0	0	0	0	0	0	0	0	0	0	0
1	34.8	32.2	29.8	26.5	24.4	22.9	20.28	18.9	29.9	33.56
2	53.2	49.2	47.4	45.7	43.9	41.3	38.26	41.3	51.3	51.4
4	72.1	71.9	68.43	66.12	63.5	56.9	49.37	56.9	66.9	70.22
6	89.2	86.7	79.31	77.91	74.2	70.2	62.37	70.2	79.2	82.49
10	98.2	94.4	89.5	87.23	83.4	78.7	78.2	88.9	93.1	96.74
12	100	100	98.56	97.61	92.79	83.03	83.03	93.03	98.03	99.03
24			100	100	99.86	96.49	96.49	100.49	100	100

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Figure no. 12 Dissolution Profiles.

KINETIC STUDIES

Table 12: Kinetic studies.

S.NO	time	log T	Square root of Time	%CR	%Drug remaining	log %CR	log% drug retained	cube root of %drug remaining
1	0	0	0	0	100	0	2	4.641589
2	1	0	1	24.4	75.6	1.38739	1.878522	4.228379
3	2	0.30103	1.414214	43.9	56.1	1.642465	1.748963	3.828138
4	4	0.60206	2	63.5	36.5	1.802774	1.562293	3.317144
5	6	0.778151	2.44949	74.2	25.8	1.870404	1.41162	2.95488
6	10	1	3.162278	83.4	16.6	1.921166	1.220108	2.550954
7	12	1.079181	3.464102	92.79	7.21	1.967501	0.857935	1.931872
8	24	1.380211	4.898979	99.86	0.14	1.999392	-0.85387	0.519249

Drug Releasing Kinetics of F5.

Table 12.1: Drug Releasing Kinetics of F5.

Formulation	Zero	First order	Higuchi	Kores mayer	Hixovcrowell
	order R ²	R ²	R ²	peppas R ²	R ²
F5	0.677	0.971	0.913	0.919	0.959

STABILITY STUDIES

Formulation Code	Trail no	Initial	1 st Month	2 nd Month	3 rd Month
F5	Trail-1	98.86	98.34	98.33	98.33
F5	Trail-2	98.52	98.35	98.35	98.34
F5	Trail-3	98.61	98.33	98.33	98.32

Table 13: Drug Content Data of Stability	study of Op	timized Formulation.
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CONCLUSION

From the present research work that is development and evaluation of Terbutaline Sulphate patches for buccal drug delivery, The patches prepared were elegant in appearance and smooth surface. The weights, thicknesses, tensile strength. folding endurance, drug content uniformity of patches shows uniformity in all formulations and surface pH lies in between 4.5-6.8 the optimized buccal patch F5 with HPMC K4M shows 6.8 whereas buccal patch F6 with HPMC E15 shows 5.7, mucoadhesive adhesive strenght of F5 shows 8.99gm whereas F6 shows 6.792gm, mucoadhesive time of F5 is 299min whereas F6 is 218 min. FTIR studies indicates no drug-excipients interaction between the drug and excipients used in the formulations F1-F10. The drug was distributed throughout the patch uniformly. The invitro-diffusion studies shows more than 85% of the drug was released from all the formulations at the end of 24 hrs, but formulation F5 shows 99.86 whereas F6 shows 96.49. In short term stability studies indicate there were no significant changes in the drug content and *in-vitro* drug release for the period of three month. From the result and conclusion of the research work we can summarize that Terbutaline Sulphate can be delivered via buccal route.

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