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Mucoadhesive Buccal Patches and Use of Natural Polymer in Its Preparation – A Review

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Abstract: Natural polymers have recently gained importance in pharmaceutical field. Mucoadhesive polymers are used to improve drug delivery by enhancing the dosage form's contact time and residence time with the mucous membranes. Mucoadhesion may be defined as the process where polymers attach to biological substrate or a synthetic or natural macromolecule, to mucus or an epithelial surface. When the biological substrate is attached to a mucosal layer then this phenomenon is known as mucoadhesion. The substrate possessing bioadhesive polymer can help in drug delivery for a prolonged period of time at a specific delivery site. The studies of mucoadhesive polymers provide a good approach of mucoadhesion and some factors which have the ability to affect the mucoadhesive properties of a polymer. Both natural and synthetic polymers are used for the preparation of mucoadhesive buccal patches. Various natural polymers which can be used in mucoadhesive buccal patches are chitosan, sodium alginate, tragacanth, gelatin and guar gum etc. Chitosan, a derivative form of chitin, is a naturally occurring biopolymer and have a large number of pharmaceutical applications.
Key word: Mucoadhesive buccal patch, Natural polymer, Mucoadhesion.

INTRODUCTION

Various routes of drug delivery such as oral, parental, transdermal, nasal are used to deliver the drugs to the systemic circulation. Among these routes, oral route is most preferred by the patient and by the clinician. Drug delivery by per-oral administration arise some problems such as hepatic first pass metabolism and enzymatic degradation within the GI tract. For certain class of drugs, these problems can be overcome by their administration through buccal mucosa. Therefore, absorptive buccal mucosa is considered as potential sites for drug admistration[1].

Buccoadhesive drug delivery is an important route of drug administration and has comprehensively been investigated by many researchers. The buccal route has been preferred due to avoidance of first pass metabolism and possibility of being accessible for controlled and sustained drug release [2]. Various dosage forms for the buccal delivery of drugs can broadly be categorized as conventional matrix tablets, gels, films, patches, strips and ointment systems. The uses of various polymeric patches for buccal drug delivery are broadly investigated. Introducing various polymeric systems has been comprehensively employed in the modification of the drug release. Coating and matrix formation can be employed for protection of various solid dosage forms like tablets, pellets, granules and powders. [3]

Buccoadhesive patch should be flexible, elastic, soft and strong to withstand breakage due to stress from

mouth activities. Buccal patches also show good buccoadhesive strength so that it can be retained in the mouth for a desired duration. There are critical and essential evaluation of buccal patches such as mucoadhesion, swelling properties and mechanical properties. [4]

Buccal patches are preferred over adhesive tablets in respect of its flexibility and patients comforts. Bioadhesive polymers are used to control the buccal drug delivery due to their ability to localize the dosage form in specific regions to enhance drug bioavailability.

Chitosan is one of the natural polymers, which is being widely used. Chitosan is composed of glucosamine and N-acetyl glucosamine which are also constituent of mammalian tissue. It is non toxic, biocompatible and biodegradable polymer. This polymer is considered for its film as well as matrix forming abilities. Chitosan is also used as enzyme inhibitor as well as permeation enhancer properties[5].

Attractiveness of Buccoadhesive drug delivery system: - [6]

a) It permits the localization of the delivery system.
b) Patients are well adapted to oral administration of drugs.
c) Patient acceptance and compliance is good compared to other drug delivery system.
d) Its ability to easily recover after local treatment is prominent.
e) Allows a wide range of formulations that can be used e.g. buccoadhesive patches and ointments.

Advantages of buccoadhesive drug delivery: - [7]

Drug administration via the buccoadhesive drug delivery offers several advantages such as:-

a) Drug is easily administered and extinction of therapy in emergency can be facilitated.
b) Drug release for prolonged period of time.
c) In unconscious and trauma patient's drug can be administered.
d) Drugs bypass first pass metabolism so increases bioavailability.
e) Some drugs that are unstable in acidic environment of stomach can be administered by buccal delivery.
f) Drug absorption by the passive diffusion.
g) Flexibility in physical state, shape, size and surface.
h) Maximized absorption rate due to close contact with the absorbing membrane.
i) Rapid onset of action.

Limitations of buccoadhesive drug delivery: - [8]

There are some limitations of buccal drug delivery system such as-

a) Drugs which are unstable at buccal pH cannot be administered.
b) Drugs which have a bitter taste or unpleasant taste or an obnoxious odor or irritate the mucosa cannot be administered by this route.
c) Drug required with small dose can only be administered.
d) Those drugs which are absorbed by passive diffusion can only be administered by this route.
e) Eating and drinking may become restricted.

Various mucoadhesive polymers can broadly be categorized as follow: [9]

(I) Synthetic polymers:

1. Cellulose derivatives (Methylcellulose, Ethyl cellulose, Hydroxy ethyl cellulose, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose, Sodium carboxy methylcellulose).
2. Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
3. Poly hydroxyl ethyl methylacrylate.
4. Poly ethylene oxide.
5. Poly vinyl pyrrolidone.
6. Poly vinyl alcohol.

(II) Natural polymers:

1. Tragacanth
2. Sodium alginate
3. Guar gum
4. Xanthan gum
5. Soluble starch
6. Gelatin
7. Chitosan

Following natural polymers are reported to have been used in preparation of mucoadhesive buccal patches:-

Chitosan

Chitosan a derivative form of chitin is a naturally occurring biopolymer. Chitosan is a linear polysaccharide composed of randomly distributed β-(1-4)-linked D-glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (acetylated unit). Commercial chitosan is derived from the shells of shrimp and other sea crustaceans, including Pandalus borealis. [10]

Properties of chitosan

1. Used in trans-dermal drug delivery.
2. Mucoadhesive nature
3. Chitosan ability to produce many different form when.
4. In drug delivery, it shows positive charge under acidic conditions.

5. Chitosan is insoluble in neutral and basic environments.
6. Chitosan may form many translational metal ions.
7. Ability to attach itself to other molecules.
8. Ability of specific cellular action for target drugs.
9. It has bacteriostatic and fungistatic effect. [11]

Advantage of chitosan

Chitosan have good biocompatibility and low toxicity that makes it a good pharmaceutical excipient in both conventional and novel applications. [12]

Application of chitosan

Various applications of chitosan and its derivatives in pharmaceutical field:

1. It is a good diluent for direct compression of tablets formulation.
2. It is used as binder for wet granulation.
3. Chitosan shows controlled release of drugs from tablets, granules and in film.
4. It increases viscosity in solutions during hydrogels preparation.
5. Chitosan improves the dissolution of poorly soluble drugs and enhance the absorption of drug in nasal and oral drug delivery system.
6. A novel mucoadhesive polymer used for transmucosal drug delivery system.
7. Microcrystalline chitosan has high capacity for retaining water so this is advantageous in development of slow release formulation, formulation of gels that control drug release.
8. The hydrophilic nature of microcrystalline chitosan aid in, controlling rate of drug release for mucoadhesive formulations in stomach.
9. The cationic form of chitosan polymer has potential for DNA complexation and could be useful for non viral vectors for gene therapy. Chitosan protects DNA against DNAase degradation. [13-19]

Guar gum

Guar gum is naturally occurring form of galactomannan and also called guaran[20]. It is primarily ground endosperm of guar beans. Guar gum contains about 80% galactomannan, 12% water, 5% protein, 2% acid soluble ash, and 0.7% fat. The molecular weight of guar gum is approximately 1 million that give high viscosity in solution. The high viscosity of guar gum is due to its long chain structure and high molecular weight. Guar gum is a polysaccharide composed of the sugars galactose and mannose. [21-23]

Properties of guar gum

Guar gum is rapidly soluble in cold and hot water but insoluble in many organic solvents. Guar gum has excellent properties such as emulsifying agent, thickening, stabilizing and film forming agent. Guar gum has ability to control rheology by water phase management. The viscosity of guar gum is affected by temperature, pH, salts and other solids [24]. Guar gum is used in colon delivery due to its drug release retarding property. Guar gum has also susceptable to microbial degradation in the large intestine. [25]

Pharmaceutical Application

In the pharmaceutical industry guar gum is used as binder or as disintegrates in tablets. It is also used in some bulk-forming laxatives. In cosmetics and toiletries industries, guar gum is applicable as thickener in toothpastes and conditioner in shampoos.

Tragacanth

Tragacanth is a natural gum obtained from the dried juice of several species of the genus Astragalus, including A. adscendens, A. gummifer, A. brachycalyx and A. tragacanthus. [26-27] Tragacanth gum is a viscous, odorless, tasteless and water-soluble mixture of polysaccharides.

Pharmaceutical application of Tragacanth

1. It is used as adhesive agent for tablets and pills.
2. Tragacanth used as emulsifying oil droplets in creams, paste and lotions.
3. Used as thickening agent. [28]

Sodium alginate

Alginic acid or alginate is an anionic polysaccharide, also called as algin and obtained in the cell walls of brown algae. It has ability of binding with water and forming a viscous gum. Alginic acid is capable of absorbing 200-300 times its own weight in water when water extracted from alginate. [29] Alginate is mainly extracted from seaweed. Alginic acid is mainly produced by two bacterial genera such as Pseudomonas and Azotobacter. These play an important role in the preparation of its biosynthesis pathway. [30]

Sodium alginate is the sodium salt of alginic acid. Its formula is $NaC_6H_7O_6$. Sodium alginate is a gum which extracted from the cell walls of brown algae. Sodium alginate is slowly soluble in water and insoluble in ethanol and ether.

Pharmaceutical application of sodium alginate

1. It is flavorless gum and used to increase viscosity in the food industry.
2. It is used as emulsifier.
3. Used in indigestion tablets and the preparation of dental impressions.
4. It is used for pulling radioactive toxins from the body because of their good chelating property.
5. It is also used in immobilizing enzymes by inclusion. [31-32]

Table 1:- Buccal dosage forms formulated using natural polymer

S. No.	Natural polymer	Drug	Dosage form
1.	Chitosan	Propranolol hydrochloride, Metoprolol tartarate, Cetylpyridinium chloride, Curcumin, Propranolol hydrochloride, Resperidone, Salbutamol sulphate, Verapamil HCL , Lornoxica	Buccal film,[33] Bioadhesive bilayered patches,[34] Mucoadhesive buccal patches,[35] Mucoadhesive buccal patches,[36] Mucoadhesive buccal patches,[37] Mucoadhesive buccal patches,[38] Mucoadhesive buccal patches,[39] Mucoadhesive buccal patches,[40] Buccal patches [41]
2.	Gelatin	Sumatriptan succinate, Aceclofenac	Mucoadhesive bilayered patches,[42] Mucoadhesive buccal patch [43]
3.	Guar gum	Diltiazem hydrochloride	Mucoadhesive buccal tablets [44]
4.	Sodium alginate	Diltiazem hydrochloride, Methotrexate	Mucoadhesive buccal tablets, [44] Buccal mucoadhesive patches [45]
5.	Xanthan gum	Tizanidine hydrochloride	Mucoadhesive buccal tablets [46]

RESEARCH WORK

R. Chaudhary et al. (2010) formulated buccal patches with drug (methotrexate) by solvent casting method. Drug was loaded after dispersion in 5ml phosphate buffer. Drug was added in polymeric dispersion of buccal patch formulation with continuous stirring. When drug was homogenously dispersed or dissolved solution was poured in petridish. The backing membrane was prepared by dissolving ethyl cellulose (5%) in mixture of acetone and isopropyl alcohol (60:40). Glycerol (5%) was added as plasticizer. The patches were evaluated for weight uniformity, thickness, swelling index, surface pH, mucoadhesive strength and mucoadhesive time and folding endurance. Use of sodium alginate with carbopol-934 in presence of glycerol (plasticizer) showed promising results. *In vitro* drug release was found to be 82% through cellophane membrane and 70.78 % through buccal mucosa with suitable mucoadhesive strength and mucoadhesive time. [45]

R. NG. Rao et al. (2010) prepared buccal patches of montelukast sodium by solvent casting technique. The patches were prepared by using polymers such as hydroxyethyl cellulose (HEC), sodium carboxymethylcellulose (NaCMC), eudragit RL-100 and polyvinylpyrrolidone K-30 (PVP K-30). Propylene glycol (PG) was used as plasticizer. Polymer was dissolved in ethanol (95%) with continuous stirring. Montelukast sodium was incorporated in the polymeric solutions after levigation with 0.1ml of PG. The thickness and folding endurance of the prepared patches was in the range of 0.266 to 0.326 mm. Folding endurance of all prepared patches was > 250. The results of swelling index between the range of 30.03 - 44.27 %, and the surface pH was in the range of buccal region pH. The *in vitro* residence time for all the prepared patches was found to be between 3.20 - 5.59 hrs. The bursting strength of patches was in the range of 4.166 to 5.733 Kg/cm^2. *In vitro* drug release was in the range of 68.83 - 92.22 % in 8 hrs. [47]

B. Manasa et al. (2010) prepared the mucoadhesive buccal patch of resperidone by using hydroxy propyl methyl cellulose (HPMC 47cps & 15 cps), chitoson, poly vinyl alcohol, poly vinyl pyrilodine polymer and using solvent casting method. HPMC polymer (200 mg) was weighed accurately and placed in 3 ml of ethanol was added and stirred the dispersion. Then 3 drops (0.0882gm) of glycerin were added to the polymer solution. Resperidone (10 mg) was weighed and dissolved in 3 ml of ethanol and 3 drops of tween 80 in an another beaker. The patches were evaluated for their thickness, content and weight uniformity, folding endurance, swelling index, tensile strength and surface pH. *In vitro* drug release studies of resperidone-loaded patches in phosphate buffer (pH 6.6) was found in the range of 67.32% to 98.28 in 60 min. [38]

B. Basu et al. (2010) prepared the mucoadhesive buccal patches of pimozide by using HPMC (15 & 47 cps), carbopol 934, poly vinyl alcohol (PVA) and poly vinyl pyrolidone. By Using FTIR and UV spectroscopic methods it was confirmed that pimozide

and the used polymers do not show any interaction. The patches were evaluated for their thickness, folding endurance, weight uniformity, content uniformity, swelling behaviour, tensile strength and surface pH study. *In vitro* drug release studies of pimozide-loaded patches in phosphate buffer (pH 6.6) was in the range of 55.32 % to 97.49 % in 60 min. *In vivo* absorption of pimozide patches was in ranged from 47.96 % to 83.42 % in 60 min in human volunteers. *In vivo* studies in rabbits showed 85.97% of drug absorption from HPMC-15 cps patch in 60 min. There are good correlations between *in vitro* release and *in vivo* absorption of pimozide was observed. [48]

Dharani et al. (2010) developed the buccal patch by solvent-casting technique using hydroxy propyl methyl cellulose E15 (HPMC E15) and 20 ml of (1:1) solvent mixture of dichloromethane and methanol was added. Propylene glycol was added to this mixture. Ondansetron hydrochloride was dissolved in 5 ml of solvent mixture, added to the polymer solution and mixed well. Patches were carried out in oven placed for drying in 8 hrs. [49]

R.S. Patel et al. (2009) prepared mucoadhesive buccal patch of salbutamol sulphate by using PVA (10% w/v), chitosan (1% w/v) and PVP (5% w/v) solution in water which were mixed together in a determined ratio and stirred continuously until a clear solution was obtained. Then polyethylene glycol 400 (PEG-400) (2% w/w) was mixed uniformly to obtained a clear viscous liquid. This solution was taken in a petridish and dried in an oven maintained at 40°C till a flexible patch was formed. The patches were 10 mm in diameter and 0.4 ± 0.02 mm in thickness. The mass ranged from 33.4 to 35.1 mg. The surface pH of all formulations was within the desirable range 5.5 – 6.5. The medicated patches showed higher radial swelling compared to plain patches. The swelling values after 5 hrs were 31± 2.4 % and 29.8± 2.2 % respectively. [39]

R.S. Hirlekar et al. (2009) prepared the mucoadhesive buccal patch by carvedilol methyl-β-cyclodextrin (CAR-MβCD). Complex equivalent to 6.25 mg of CAR was mixed with 7.5 mg of carbopol 974P, 15 mg of sodium carboxymethylcellulose, 63.25mg of directly compressible lactose, 5 mg of PVP K-30, 2 mg of talc and 1 mg of magnesium stearate. The complex showed complete drug release as compared to 32.8% and 42.7% from plain drug and physical mixture respectively in 60 min. The plain drug showed sharp endothermic peak at 118^0C. MβCD showed a broad endothermic peak in the range of 100-120^0C due the release of water molecule. FTIR spectra of CAR characteristic bands at 1253, 1502 and 2922 cm^{-1} corresponding to aromatic secondary C-N vibrations, C-C multiple bond stretching and C-H stretching of aromatic ring respectively. Plain patch showed good mucoadhesive strength of 18gm. [50]

D. Baviskar et al. (2009) prepared the mucoadhesive buccal patch of aceclofenac by solvent casting method using polymer like gelatin, poly sodium carboxymetylcellulose (Na CMC) and poly vinyl alcohol. Eight formulations were prepared by varying the concentration of poly Na CMC and evaluated for various parameters like weight variation, patch thickness, volume entrapment efficiency and measurement of elongation at break, folding endurance, *in vitro* mucoadhesive time, and *in vitro* release and stability study. The formulation containing aceclofenac 6%, gelatin 4.5%, poly Na CMC 5.5%, propylene glycol 5%, poly vinyl alcohol 2.5% and distilled water up to 100%, showed a release of 88.4% after 8 hrs. The aceclofenac stability studies were performed at 40 ± 2^0C / 75 ± 5% relative humidity. [43]

S.V. Deshmane et al. (2009) prepared the mucoadhesive buccal patch of verapamil HCl by using chitosan with polyvinylpyrrolidone K-30 (PVP K-30). The polymeric solution of chitosan was prepared using 1.5% (V/V) acetic acid in distilled water with occasional stirring for 48 hrs. The drug release characteristic was increased on use of a water-soluble hydrophilic additive PVP K-30 into the chitosan solution under constant stirring. Propylene glycol (5%, V/V) was used as plasticizer. The solution was poured into a glass petridish having 6 cm diameter. The amount of drug to dissolve in petridish was such that patch of 10 mm diameter size containing 50 mg of verapamil HCl. The swelling percentage was found to be function of solubility of drug and PVP K-30. The mucoadhesive strength, vapour transmission and *in vitro* release of water soluble drug through water insoluble chitosan base matrix were found satisfactorily. The physical appearance of buccal patch was examined by scanning electron microscopy. [40]

C. S. Kolli et al. (2008) prepared the mucoadhesive buccal patch by solvent costing methods and taken 10 g of prochlorperazine (PCPZ) maleate in a conical flask; 100 ml of 5 % w/v sodium bicarbonate solution was added, kept for shaking for 30 min on rotary shaker. Diethyl ether, 50 ml was added and kept for shaking for 15 min. *In vitro* flux of PCPZ was calculated to be 2.14 ± 0.01 µg and buccal absorption was also demonstrated *in vivo* in human volunteers. *In vitro* drug release and moisture absorbed was governed by HPMC content. Increasing concentration of HPMC delayed the drug release. The mechanical properties, tensile strength (10.28 ± 2.27 kg mm^{-2}) and elongation

at break reveal that the formulations were found to be strong but not brittle. The results indicate that suitable bioadhesive buccal patches of PCPZ with desired permeability and suitable mechanical properties could be prepared. [51]

CONCLUSION

Mucoadhesive buccal patches have been recently gained importance in drug delivery. The use of natural polymers is increasing in buccal patches formulation. A lot of work is still going on all around the world on mucoadhesive buccal patches using various natural polymer. This review is an effort to summarize the work done till date and to show the future pathway of mucoadhesive buccal patches preparation using natural polymer.

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