



Literature Studies on Preparation and Evaluation of Buccal Patches

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Accepted on: 19-01-2014; Finalized on: 31-03-2014.

ABSTRACT

There is need to develop a dosage form that bypasses first pass metabolism and GI degradation. Oral cavity provide route for the administration of therapeutic agent for local as well as systemic delivery, so that first pass metabolism and GI degradation can be avoided. For the preparation of patches commonly used technique is solvent casting technique. This review article deals with various studies on formulation and evaluation of buccal patch.

Keywords: Buccal patch, solvent casting technique.

INTRODUCTION

In pharmaceutical area, patches are gained importance due to novel, patient convenient. As compared to tablet, patches has small in size, thin which increases patient compliance. Patch can exert local as well as systemic action. The release pattern of the drug is depending upon fabrication of the patch which give drug release to the mucosal side or oral cavity. Patch releasing drug towards the buccal mucosa exhibit the advantage of avoiding the first pass effect by directing absorption through the venous system that drains from the cheek.¹

Buccal patch is modified release dosage form, a nondissolving thin matrix composed of one or more polymers, drug and other excipients. The controlled release pattern of the drug from patch is depends on the type of the polymers present which bond to the oral mucosa. It gives unidirectional release, maybe towards oral mucosa, towards oral cavity or both i.e bidirectional.²

VARIOUS STUDIES ON BUCCAL PATCHES

Pongjanyakul T. *et al.*,³ formulated alginate-magnesium aluminium silicate films for buccal delivery of nicotine. Nicotine (NCT) containing the dispersion of Sodium alginate-magnesium aluminium silicate (SA-MAS) were prepared at different pHs and evaluated. The particle size and zeta potential, NCT adsorbed by MAS, and flow behaviour were characterized before film casting. After casting of the film, investigation of physicochemical properties, NCT content, *in vitro* bioadhesive property, and NCT release and permeation of the NCT-loaded SA-MAS films were carried out. Change in particle size and flow behaviour was due to the incorporation of NCT into SA-MAS. At pH 5 film having highest NCT content due to non-significant loss of NCT during drying. This finding suggests that the NCT-loaded SA-MAS films composed of numerous NCT-MAS complexes as micro reservoirs demonstrated a strong potential for use as a buccal delivery system.

Nafee N *et al.*,⁴ prepared patches with sodium carboxymethylcellulose, chitosan, polyvinyl alcohol, hydroxyethylcellulose, and HPMC. Optimum release behaviour was shown with patches containing 10% PVA and 5% PVP. The drug concentration at salivary level upto 6 hr was studied *in vivo*. On the contrary, *in vivo* release of the commercial oral gel product resulted in a burst and transient release of miconazole, which diminished sharply after the first hour of application. 6 months storage did not affect the elastic properties of patch, however, enhanced release rates were observed due to marked changes in the crystal habit of the drug.

Bhanja S. *et al.*,⁵ formulated and evaluated a buccal patch of methotrexate. Buccal patch was made up of drug with sodium alginate along with sodium carboxymethylcellulose, polyvinyl pyrrolidone, carbopol 934, and ethyl cellulose as backing membrane. Patch was fabricated by solvent casting method. The patches were also evaluated for film weight uniformity, thickness, swelling index, surface pH, mucoadhesive strength, mucoadhesive time and folding endurance. A combination of sodium alginate with carbopol 934 and glycerol as plasticizer, gives promising results. The optimum patches exhibits an *In-vitro* drug release of 82% through cellophane membrane and 70.78% in 8hrs through buccal mucosa with satisfactory mucoadhesive strength and mucoadhesive time.

Okamoto H. *et al.*,⁶ developed polymer patch dosage form of Lidocaine (LC) for buccal administration. He used HPMC as patch base and glycyrrhizin acid was added to increase release rate. A significant relationship between the penetration rate of LC and the release rate of unionized LC was found, suggesting that the *in vitro* dissolution study is a useful tool to predict the penetration rate taking the unionized drug fraction into consideration.

Nozaki Y. *et al.*,⁷ studied *in vitro/ in vivo* correlation of transmucosal controlled systemic delivery of isobarbide



dinitrate (ISDN). He used beagle dogs for transmucosal drug delivery. The cumulative absorption profile and pharmacokinetic profile were monitored and correlated with *in vitro* dissolution study, the correlation was found to be 1:1. The systemic bioavailability of ISDN following transmucosal delivery through the oral mucosa can be modulated by controlling the ratio of ISDN loading in the fast- and sustained-release layers (F/S) as well as ISDN content in sustained-release layer. The effect was demonstrated in both *in vitro* and *in vivo* studies, which attained an *in vitro* / *in vivo* correlation of 1:1.

Perumal V et al.,⁸ prepared and evaluated monolayered patch with drug and polymer of opposite solubilities. He used hydrophilic drug propranolol HCl and hydrophobic polymer such as eudragid 100 and chitosan. The optimum concentration of drug: eudragid: chitosan was found to be 1:10:0.5. Films were prepared by emulsification and casted by a new approach using a silicone-molded tray with individual wells. Films were evaluated uniform and reproducible drug content ($100.71 \pm 2.66\%$), thickness (0.442 ± 0.030 mm), mucoadhesivity (401.40 ± 30.73 mN) and a controlled drug release profile. Along with that films were also evaluated for surface pH mechanical strength.

Dharani S et al.,⁹ prepared and evaluated mucoadhesive buccal patches of ondansetron HCl. He used HPMC E 15 as main polymer for preparation of buccal patch using solvent casting method. He formulates the optimum patch having 2500 mg of HPMC E15. Permeation of OND was calculated *ex vivo* using porcine buccal membrane. Buccal films were developed by solvent-casting technique using Hydroxy Propyl Methyl Cellulose (HPMC E15) as mucoadhesive polymer. The patches were evaluated for weight variation, thickness variation, surface pH, moisture absorption, *in vitro* residence time, mechanical properties, *in vitro* release, *ex vivo* permeation studies and drug content uniformity.

Juliano C et al.,¹⁰ prepared six different film formulations, mono- or double-layered, containing 5 or 10 mg of chlorhexidine diacetate, respectively, and alginate and/or hydroxypropylmethylcellulose and/or chitosan as excipients, were prepared by a casting-solvent evaporation technique and characterized in terms of drug content, morphology (scanning electron microscopy), drug release behaviour, and swelling properties. They studied *in vivo* concentrations of chlorhexidine diacetate in saliva were evaluated after application of a selected formulation on the oral mucosa of healthy volunteers. The solvent casting method used for preparing soft, flexible, and easily handy. Some prepared formulations showed favourable *in vitro* drug release rates and swelling properties. The behaviour of a selected formulation, chosen on the basis of its *in vitro* release results, was preliminarily investigated *in vivo* after application in the oral cavity of healthy volunteers. The films were well tolerated and the salivary chlorhexidine concentrations were maintained above the minimum inhibitory concentration for *Candida albicans* for almost

3h. These preliminary results indicate that polymeric films can represent a valid vehicle for buccal delivery of antifungal/antimicrobial drugs.

Patel V et al.,¹¹ designed and characterized the chitosan-containing mucoadhesive buccal patches of propranolol hydrochloride. Mucoadhesive buccal patches containing propranolol hydrochloride were prepared using the solvent casting method. Chitosan was used as bioadhesive polymer and different ratios of chitosan to PVP K-30 were used. The patches were evaluated like weight variation, drug content uniformity, folding endurance, *ex vivo* mucoadhesion strength, *ex vivo* mucoadhesion time, surface pH, *in vitro* drug release, and *in vitro* buccal permeation study. Controlled drug release was studied for a period of 7h. The mechanism of drug release was found to be non-Fickian diffusion and followed the first-order kinetics. Incorporation of PVP K-30 generally enhanced the release rate. Swelling index was proportional to the concentration of PVP K-30. Optimized patches showed satisfactory bioadhesive strength of 9.6 ± 2.0 g, and *ex vivo* mucoadhesion time of 272 minutes. The surface pH of all patches was between 5.7 and 6.3 and hence patches should not cause irritation in the buccal cavity. Patches containing 10 mg of drug had higher bioadhesive strength with sustained drug release as compared to patches containing 20 mg of drug. Good correlation was observed between the *in vitro* drug release and *in vitro* drug permeation with a correlation coefficient of 0.9364. Stability study of optimized patches was done in human saliva and it was found that both drug and buccal patches were stable.

Ahn J.S et al.,¹² studied release of triamcinolone acetonide from mucoadhesive polymer composed of chitosan and poly (acrylic acid) *in vitro*. A complex composed of chitosan and poly (acrylic acid) (PAA) was prepared by template polymerization of acrylic acid in the presence of chitosan. Triamcinolone acetonide (TAA) was loaded into the chitosan/PAA polymer complex film. TAA was evenly dispersed in chitosan/PAA polymer complex film without interaction with polymer complex. Release behaviour of TAA from the mucoadhesive polymer film was dependent on time, pH, loading content of drug, and chitosan/PAA ratio. The analysis of the drug release from the mucoadhesive film showed that TAA might be released from the chitosan/PAA polymer complex film through non-Fickian diffusion mechanism.

Akpa P.A. et al.,¹³ studied buccoadhesive delivery system of hydrochlorothiazide formulated with ethyl cellulose hydroxypropylmethylcellulose interpolymer complex. The buccoadhesive and *in vitro* release properties of patches formulated with ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) interpolymer complexes of different ratios were studied. The patches containing hydrochlorothiazide (HCTZ) were prepared by casting and thereafter, evaluated using the following parameters: diameter, thickness, swelling behaviour, buccoadhesive strength, drug content analysis and *in vitro* release studies. The release of HCTZ from the patches was

studied in phosphate buffer (pH 7.5). The result of the study indicated that 1:2 ratio of EC and HPMC gave the highest buccoadhesive strength. All the patches had uniform diameters but varied thicknesses with their areas ranging from 2.06 to 2.16 cm². The area swelling ratio (ASR) indicated that the patches did not swell up to two times their initial areas, with the batch containing 3:2 ratio of EC and HPMC possessing the highest ASR. Higuchi's analysis of the release mechanism indicated that the release of HCTZ from the patches formulated with 1:1 and 2:1 ratios of EC and HPMC predominantly occurred by a diffusional process. This method could be used as an effective alternative delivery system for HCTZ compared with conventional tablet formulations.

Kim T.H. et al.,¹⁴ studied and evaluated mucoadhesive polymer film composed of Carbopol, Poloxamer and Hydroxypropylmethylcellulose. Using the casting method blend of film consisting of Carbopol, poloxamer, and hydroxypropylmethylcellulose (HPMC) was prepared and characterized. Triamcinolone acetonide (TAA) was loaded into Carbopol/poloxamer/HPMC polymer blend film. Carbonyl band of Carbopol in Carbopol/poloxamer/HPMC shifted to longer wavenumber than that of Carbopol in Carbopol/poloxamer due to the hydrogen bonding among Carbopol, poloxamer, and HPMC. Tan δ peak assigned to glass transition temperature (T_g) of HPMC shifted to low temperature due to increased flexibility caused by increased poloxamer content in polymer blend films. Swelling ratio of Carbopol/poloxamer/HPMC films was lowest in Carbopol/poloxamer/HPMC at mixing ratio of 35/30/35 (wt/wt/wt). Adhesive force of Carbopol/poloxamer/HPMC films increased with increasing HPMC content in Carbopol/poloxamer/HPMC polymer blend film and increasing hydroxypropyl group content in HPMC due to hydrophobic property of HPMC although bioadhesive force was highest at mixing ratio of 35/30/35 (wt/wt/wt). Release of TAA from TAA-loaded Carbopol/poloxamer/HPMC polymer blend film in vitro increased with increasing loading content of drug.

Singh A. et al.,¹⁵ prepared and evaluated buccal formulation for triamcinolone. Mucoadhesive films of Triamcinolone Acetonide composed of Carbopol 934 and Hydroxypropylmethylcellulose (HPMC) were developed by solvent casting method. The films were evaluated for swelling study, surface pH, bio-adhesive strength, in vitro residence time, in vitro drug permeation study, and In vitro drug release study. In vitro drug permeation study showed that 3 % menthol gave 20% permeation than 6% menthol. In vitro studies revealed that optimum buccal patches gave low swelling index, longer mucoadhesion and intermediate mucoadhesive strength. In conclusion,

This formulation is proposed as a good formula. It is suggested that in the development of buccal drug delivery system swelling behaviour and duration if mucoadhesion determined by in vitro study is critical factor in the selection of satisfactory formulation.

Koland M. et al.,¹⁶ designed and characterized mucoadhesive films of Losartan Potassium for buccal delivery. Mucoadhesive buccal films of losartan potassium were prepared using hydroxypropyl methylcellulose (HPMC) and retardant polymers ethyl cellulose (EC) or eudragit RS100. Ex vivo permeation studies of losartan potassium solution through porcine buccal mucosa showed 90.2 % absorption at the end of 2 hours. The films were subjected to physical evaluation such as uniformity of thickness, weight, drug content, and folding endurance, and tensile strength, elongation at break, surface pH and mucoadhesive strength. Films were flexible and those formulated from EC were smooth whereas those prepared from Eudragit were slightly rough in texture. The mucoadhesive force, swelling index, tensile strength and percentage elongation at break was higher for those formulations containing higher percentage of HPMC. In vitro drug release studies reveal that all films exhibited sustained release in the range of 90.10 to 97.40% for a period of 6h. The data was subjected to kinetic analysis which indicated nonfiction diffusion. Ex vivo permeation studies through porcine buccal mucosa indicate that films containing higher percentage of the mucoadhesive polymer HPMC showed slower permeation of the drug for 6-7 h.

Bazigha K A. R. et al.,¹⁷ studied in vitro evaluation of miconazole mucoadhesive buccal films. Five different film formulations containing 20 mg of miconazole nitrate, drug solubilizers (propylene glycol 10% w/w, polyethylene glycol 3% w/w, tween 20 6% w/w, and oleic acid 5%w/w) and chitosan as film forming polymer, had been prepared by a casting solvent evaporation technique and characterized in terms of weight uniformity, film thickness, surface pH, swelling capacity, in vitro drug release and in vitro microbiological effectiveness against *Candida albicans* in comparison to a reference. Thickness of the prepared films ranged from 0.11 to 0.23 mm and the film weight ranged from 152.5 to 188 mg, where the surface pH values of all films were in the range 5.84-6.63 which is favourable for oral mucosa. Optimum release behaviour and acceptable elasticity were exhibited by film containing propylene glycol 10% w/w. The swelling percent of the selected film after 6h reached 32.1%. The drug release mechanism was found to follow Fickian diffusion. The antifungal activity of the selected film was significantly ($p < 0.05$) superior to the reference miconazole oral gel (Daktarin®). Mucoadhesive chitosan buccal film for the topical delivery of miconazole nitrate could be a successful mean for the management of oral candidiasis. These preliminary results indicate that the selected film formulation (MC 0.524 mg/cm², PG 10% w/w and chitosan 2% w/w) can represent a valid mean for the management of oral candidiasis.

Panigrahi L. et al.,¹⁸ studied and evaluated mucoadhesive buccal patches of Salbutamol sulphate. The prepared patches from polyvinyl alcohol (PVA) Hydroxy propyl alcohol (HPMC) and chitosan carbapol polyvinyl pyrrolidone. The prepared patches were evaluated for

tensile strength swelling and bioadhesive characteristics for both plane and medicated patches. Increasing in swelling was found in medicated patch than plane patch. This suggests that Salbutamol sulphate modified the way of water is bound to the polymer. The decrease residual time was found to be with polyvinyl alcohol and chitosan containing film. High drug release was found from the film containing polyvinyl alcohol than HPMC. The non ionic polymer PVA showed good mucoadhesive and swelling characteristics. Medicated PVA patches maintained a satisfactory residence time in the buccal cavity and ensure zero order drug release which made them good candidate for buccal route.

Lopez C.R. et al.,¹⁹ designed and evaluated chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. Bilaminated films were produced by a casting/solvent evaporation technique and bilayered tablets were obtained by direct compression. The mucoadhesive layer was composed of a mixture of drug and chitosan, with or without an anionic cross linking polymer (polycarbophil, sodium alginate, gellan gum), and the backing layer was made of ethyl cellulose. The double-layered structure design was expected to provide drug delivery in a unidirectional fashion to the mucosa and avoid loss of drug due to wash-out with saliva. Using nifedipine and propranolol hydrochloride as slightly and highly water-soluble model drugs, respectively, it was demonstrated that these new devices show promising potential for use in controlled delivery of drugs to the oral cavity. The uncross linked chitosan-containing devices absorbed a large quantity of water, gelled and then eroded, allowing drug release. The bilaminated films showed a sustained drug release in a phosphate buffer (pH 6.4). Furthermore, tablets that displayed controlled swelling and drug release and adequate adhesivity were produced by in situ cross linking the chitosan with polycarbophil.

Rodrigues L.B.²⁰ studied *in vitro* release and characterization of chitosan films as Dexamethasone carrier. They produced mono and bilayer chitosan films containing Dexamethasone as a drug carrier for controlled release. The chitosan drug-loaded films were produced by a casting/solvent evaporation technique using 2% acetic acid solution and distilled water and they were dried at room temperature. These films were characterized by release and swelling studies, DSC and FTIR. The total profile for water absorption was similar for the types of films developed. FTIR analysis showed little change in the band position of the OH and NH stretching from dexamethasone and chitosan, respectively. DSC analysis from belayed film indicates that the dexamethasone peak was shifted from 256 to 2400C. These results suggested an interaction between hydroxyl and amino groups of chitosan and hydroxyl groups of dexamethasone. In the drug release studies it was observed 89.6% release from the monolayer film in 8h and 84% from the bilayer film in 4 weeks. These results

suggested that the chitosan sheet prepared in this study is a promising delivery carrier for dexamethasone.

Verma N et al.,²¹ prepared mucoadhesive buccal patches containing carvedilol. Mucoadhesive patches for the delivery of carvedilol were prepared using chitosan, a cationic polymer. Solvent casting technique was used for the purpose of preparation of buccal patches. Different physico-chemical properties like content uniformity, thickness, surface pH, radial swelling, residence time and bioadhesive force were determined. *In vitro* drug release was carried out in USP dissolution apparatus. For in-vitro residence time, all patches, except patches containing 2% w/v chitosan remained attached to the mucosal surface till complete erosion. Maximum bioadhesion was recorded for C-1 (1% w/v chitosan), followed by the C-3 (3% w/v chitosan), then C-2 (2% w/v chitosan). The *in vitro* drug release within 1h from C-1, C-2 and C-3 patches was 10.96%, 15.42% and 12.32% respectively, and after 8h it was found 37.77%, 50.23%, and 42.87% respectively. Nonstorage patches released 50.23% after 8h, whereas patches stored for 4 months released 40.1% drugs in the same period.

Vamshi V. Y²² developed mucoadhesive patches for buccal administration of carvedilol. A buccal patch for systemic administration of carvedilol in the oral cavity has been developed using two different mucoadhesive polymers. The formulations were tested for *in vitro* drug permeation studies, buccal absorption test, *in vitro* release studies, moisture absorption studies and *in vitro* bioadhesion studies. The physicochemical interactions between carvedilol and polymers were investigated by Fourier transform infrared (FTIR) Spectroscopy. According to FTIR the drug did not show any evidence of an interaction with the polymers used and was present in an unchanged state. XRD studies reveal that the drug is in crystalline state in the polymer matrix. The results indicate that suitable bioadhesive buccal patches with desired permeability could be prepared. Bioavailability studies in healthy pigs reveal that carvedilol has got good buccal absorption. The bioavailability of carvedilol from buccal patches has increased 2.29 folds when compared to that of oral solution. The formulation AC5 (HPMC E15) shows 84.85 + 0.089% release and 38.69 + 6.61% permeated through porcine buccal membrane in 4h. The basic pharmacokinetic parameters like the C_{max} , T_{max} and AUC_{total} were calculated and showed statistically significant difference ($P < 0.05$) when given by buccal route compared to that of oral solution.

Luana Peroli²³ developed of mucoadhesive patches for buccal administration of ibuprofen. The films were evaluated in terms of swelling, mucoadhesion and organoleptic characteristics. The best film, containing polyvinylpyrrolidone (PVP) as film-forming polymer and carboxymethylcellulose sodium salt (NaCMC) as mucoadhesive polymer, was loaded with ibuprofen as a model compound and in vitro and in vivo release studies were performed. Statistical investigation of in vitro release revealed that the diffusion process was the main



drug release mechanism and the Higuchi's model provided the best fit. In vivo studies showed the presence of ibuprofen in saliva (range 70 – 210 Ag/ml) for 5h and no irritation was observed.

Isabel Diaz del Consuelo²⁴ evaluated bioadhesive films for buccal delivery of fentanyl. The goals of this work were to develop bioadhesive films for the buccal delivery of fentanyl, and to evaluate their performance in vitro using the pig oesophageal model. Films were made with polyvinylpyrrolidone (PVP) of two different molecular weights: PVP K30 and PVP K90. Delivery of fentanyl was determined across full-thickness mucosa and across heat-separated epithelium (where the permeability barrier was shown to be located). The influence of film pH was investigated, and it was found that fentanyl permeation increased with increasing pH (i.e., when a higher percentage of the unionized fraction of drug was present). However, at the pH values studied, fentanyl was predominantly ionized suggesting that transport pathways offering a hydrophilic, or polar, environment across the mucosa were available. The transport rates achieved from the PVP films providing the highest delivery suggest that a buccal system of only 1–2 cm² in surface area could achieve a therapeutic effect equivalent to a 10 cm² transdermal patch, with a much shorter lag-time.

Mohamed S.²⁵ formulated and evaluated bioadhesive patch for buccal delivery of tizanidine (THCI). A monolayered buccal patch was prepared containing THCI using the emulsification solvent evaporation method. Fourteen formulations were prepared using the polymers Eudragits RS 100 or Eudragits RL100 and chitosan. Polymer solutions in acetone were combined with a THCI aqueous solution (in some cases containing chitosan) by homogenization at 9000 rpm for 2 min in the presence of trimethyl citrate as plasticizer and cast in novel Teflon molds. Physicochemical properties such as film thickness, in vitro drug release and in vitro mucoadhesion were evaluated after which permeation across sheep buccal mucosa was examined inter of flux and lag time. Formulations prepared using a Eudragit polymer alone exhibited satisfactory physicochemical properties but lacked a gradual in vitro drug release pattern. Incorporation of chitosan into formulations resulted in the formation of a porous structure which did exhibit gradual release of drug.

S. Singh²⁶ prepared and evaluated buccal bioadhesive films containing clotrimazole for oral candidiasis. The film was designed to release the drug at a concentration above the minimum inhibitory concentration for a prolonged period of time so as to reduce the frequency of administration of the available conventional dosage forms. The different proportions of sodium carboxymethylcellulose and carbopol 974P (CP 974P) were used for the preparation of films. Carbopol was used to incorporate the desired bioadhesiveness in the films. The films were prepared by solvent casting method and evaluated for bioadhesion, in vitro drug release and

effectiveness against *Candida albicans*. In vitro drug release from the film was determined using a modified Franz diffusion cell while bioadhesiveness was evaluated with a modified two-arm balance using rabbit intestinal mucosa as a model tissue. Films containing 5% CP 974P of the total polymer were found to be the best with moderate swelling along with favourable bioadhesion force, residence time and in vitro drug release. The microbiological studies revealed that drug released from the film could inhibit the growth of *C. Albicans* for 6h. The drug release mechanism was found to follow non-Fickian diffusion.

Mario Jug²⁷ developed low methoxy amidated pectin (AMP)-based mucoadhesive patches for buccal delivery of triclosan and effect of cyclodextrin complexation. The integrity of AMP matrix was improved by addition of 20% (w/w) Carbopol (CAR). The efficiency of cyclodextrin-epichlorhydrin polymer (EPI CD) and anionic carboxy methylated-cyclodextrin-epichlorhydrin polymer (CMEPI CD) in optimization of TR solubility and release from such a matrix was investigated and confronted to that of parent-cyclodextrin (CD). Loading of TR/CD co-ground complex into AMP/CAR matrix resulted in a biphasic release profile which was sensitive upon the hydration degree of the matrix, due to lower solubilising efficiency of CD, while the drug release from patches loaded with TR/EPICD complex was significantly faster with a constant release rate. Microbiological studies evidenced faster onset and more pronounced antibacterial action of TR/EPICD loaded patches, clearly demonstrating their good therapeutic potential in eradication of *Streptococcus* mutants, a carcinogenic bacteria, from the oral cavity.

Cristina Cavallari²⁸ prepared mucoadhesive multiparticulate patch for the intrabuccal controlled delivery of lidocaine. The aim of the present study was to prepare and evaluate patches for the controlled release of lidocaine in the oral cavity. Mucoadhesive buccal patches, containing 8 mg/cm² lidocaine base, were formulated and developed by solvent casting method technique, using a number of different bio-adhesive and film-forming semi-synthetic and synthetic polymers (Carbopol, Poloxamer, different type Methocel) and plasticizers (PEG 400, triethyl citrate); the patches were evaluated for bioadhesion, in vitro drug release and permeation using a modified Franz diffusion cell. A lidocaine/Compritol solid dispersion in the form of microspheres, embedded inside the patch, alone or together with free lidocaine, was also examined to prolong the drug release. The effects of the composition were evaluated considering a number of technological parameters and the release of the drug. All the formulations tested offer a variety of drug release mechanisms, obtaining a quick or delayed or prolonged anaesthetic local activity with simple changes of the formulation parameters.

Amelia M. Avachat²⁹ developed and evaluated tamarind seed xyloglucan-based mucoadhesive buccal films of



Rizatriptan benzoate (RB). Films were developed using xyloglucon, a novel polymer obtained from tamarind seed (TSX). Three dependent variables considered were tensile strength, bioadhesion force and drug release. DSC analysis revealed no interaction between drug and polymers. *Ex vivo* diffusion studies were carried out using Franz diffusion cell, while bioadhesive properties were evaluated using texture analyzer with porcine buccal mucosa as model tissue. Results revealed that bilayer film containing 4% (w/v) TSX and 0.5% (w/v) CP in the drug layer and 1% (w/v) ethyl cellulose in backing layer demonstrated diffusion of 93.45% through the porcine buccal mucosa. Thus, an attempt of formulating a stable mucoadhesive buccal film of RB for treatment of migraine using novel polysaccharide polymer TSX was made by optimization technique. TSX showed good film forming property as well as satisfactory bioadhesion with carbopol 934 than carbopol 934 alone. Thus, cheap and abundantly available natural polysaccharide TSX could be a promising vehicle for systemic delivery of a soluble drug like RB through buccal route. The *in vitro* studies have shown that this is a potential drug delivery system for RB with considerable good stability and release profile.

Surya N. Ratha Adhikari³¹ formulated and evaluated buccal patches for delivery of atenolol. Buccal patches for the delivery of atenolol using sodium alginate with various hydrophilic polymers like carbopol 934P, sodium carboxymethyl cellulose, and hydroxypropylmethylcellulose in various proportions and combinations were fabricated by solvent casting technique. Various physicochemical parameters like weight variation, thickness, folding endurance, drug content, moisture content, moisture absorption, and various *ex vivo* mucoadhesion parameters like mucoadhesive strength, force of adhesion, and bond strength were evaluated. An *in vitro* drug release study was designed, and it was carried out using commercial semipermeable membrane. All these fabricated patches were sustained for 24h and obeyed first-order release kinetics. *Ex vivo* drug permeation study was also performed using porcine buccal mucosa, and various drug permeation parameters like flux and lag time were determined.

S. Burgalassi³² developed mucoadhesive buccal patches releasing benzydamine and lidocaine. The drugs were used as hydrochlorides, or, to reduce their solubility and improve their release characteristics, as salts with pectin or polyacrylic acid. A LDC-tannic acid complex was also prepared and tested. After an initial screening of mucoadhesive polymers, tamarind gum (TG), a polysaccharide obtained from the seeds of *Tamarindus indica*, was selected as the adhesive component. *In vitro* tests, carried out on a cell line of human buccal epithelial origin, indicated a very low sensitivity for TG. The patches, prepared by compressing appropriate mixtures containing the drug salts/complexes, lactose and TG, were tested *in vitro* for mucoadhesion and drug release, and *in vivo* on human volunteers for retention and release of BNZ. The

devices containing the salts of BNZ with pectin and polyacrylic acid, and the complex of LDC with tannic acid showed zero-order release kinetics *in vitro*. The patches adhered for over 8h to the upper gums of the volunteers, and were perfectly tolerated. BNZ hydrochloride was released *in vivo* and *in vitro* with practically identical profiles. The mucoadhesive patches tested in this study may constitute a promising system for drug administration to the oral cavity. The model drugs, BNZ and LDC, were released at a fast rate and with diffusive kinetics when used as the hydrochlorides. *In vitro* tests revealed that release could be satisfactorily controlled by using the drugs in the form of less soluble salts/complexes with PCT, PAA or TA. Dry-coating with TG, tested in the case of the BNZ-PCT patches, was another effective technique for controlling release. The validity of the release tests *in vitro* was demonstrated by the coincidence of the *in vitro* and *in vivo* release profiles of BNZ-HCl.

David Vetchya et al., determined dependencies among *in vitro* and *in vivo* properties of prepared mucoadhesive buccal films using multivariate data analysis. There are no standardized methods for buccal patch evaluation, which limits the possibility of comparison of obtained data and evaluation of the significance of influence of formulation and process variables on properties of resulting films. The used principal component analysis, together with a partial least squares regression provided an unique insight into the effects of *in vitro* parameters of mucoadhesive buccal films on their *in vivo* properties and into interdependencies among the studied variables. Eight various mucoadhesive buccal films based on mucoadhesive polymers (carmellose, polyethylene oxide) were prepared using a solvent casting method or a method of impregnation, respectively. An ethylcellulose (EC) or hydrophobic blend of white beeswax and white petrolatum were used as a backing layer. The addition of polyethylene oxide (PEO) prolonged the *in vivo* film residence time (from $53.24 \pm 5.38 - 74.18 \pm 5.13$ min to $71.05 \pm 3.15 - 98.12 \pm 1.75$ min), and even more when combined with an ethylcellulose backing layer (98.12 ± 1.75 min) and also improved the film's appearance. Tested non-woven textile shortened the *in vivo* film residence time (from $74.18 \pm 5.13 - 98.12 \pm 1.75$ min to $53.24 \pm 5.38 - 81.00 \pm 8.47$ min) and generally worsened the film's appearance. Mucoadhesive buccal films (MBF) with a hydrophobic backing layer were associated with increased frequency of adverse effects. The use of principal component analysis, together with a partial least squares regression provided an insight in the effect of *in vitro* parameters of prepared MBFs on their *in vivo* properties and about interdependencies among the studied variables, which would have been very difficult to detect using other statistical procedures. It can be concluded from the obtained results that the tested non-woven textile shortened the *in vivo* film residence time even more in combination with an EC backing layer and worsened the film's appearance. In contrast, the addition of PEO prolonged the *in vivo* film residence time, and



even more so when combined with an EC backing layer and improved the film's appearance. MBFs with a hydrophobic backing layer and tested non-woven textile were significantly more often detached by the mechanism of gradual peeling of the backing layer. MBFs with a hydrophobic backing layer were also associated with increased frequency of adverse effects (feeling of discomfort in the mouth, a pressure sensation, and an aftertaste sensation) compared to the films with an EC backing layer. Pressure sensation and aftertaste sensation generally resulted in a reduction of *in vivo* film residence time. The only instance in which no adverse feelings affecting *in vivo* film residence time were observed was after the application of a film with an EC backing layer which contained PEO, and did not contain tested non-woven textile. This same film also exhibited the most prolonged *in vivo* film residence time. Finally, the ability to predict the *in vivo* film residence time particularly in samples with a high or low film residence time on the basis of the laboratory *in vitro* assessment was confirmed.³³

Rewathi R. Shiledar et al., formulate and evaluate xanthum gum based bilayer mucoadhesive buccal patch of zolmitriptan (ZTM). Along with xanthum gum (XG) hydroxypropyl methylcellulose E-15 was used as film former and polyvinyl alcohol (PVA) was incorporated which increased the tensile strength of the patches. The effect of the concentration of polymers such as XG and PVA was studied with the help of *in vitro* drug release ex vivo mucoadhesive strength and swelling index. Initially optimized formulation shows drug release up to 43.15% within 15 min, followed by sustained release profile over 5h. 4% dimethyl sulfoxide enhanced drug permeability by 3.29 folds, transported 29.10% of drug after 5h and showed no buccal mucosal damage after histopathological studies. In conclusion, XG can be used as a potential drug release modifier and mucoadhesive polymer for successful formulation of zolmitriptan buccal patches. The results have shown that XG has potential to modify drug release rate and shows good bioadhesion, in combination with 1% PVA and 3% HPMC E-15; 0.2% XG. Hence this natural polysaccharide which is economic and abundantly available can be used as a potential drug release modifier and mucoadhesive polymer for successful formulation of ZMT bilayered mucoadhesive buccal patches, which may prevent hepatic metabolism to a large possible extent. But use of penetration enhancer is necessary to achieve maximum permeation of drug through buccal mucosa. From the present study one can conclude that XG based mucoadhesive buccal patches of ZMT can be successfully prepared with considerable good stability and tolerability. But future *in vivo* studies is necessary to confirm permeation and retention of these patches.³⁴

J. Ravi Kumar Reddy et al., developed and *in-vivo* characterized novel transbuccal formulations of Amiloride hydrochloride. AMHCL patches were prepared by solvent casting method, using hydroxypropyl methyl cellulose

(HPMC), Carbopol, Chitosan, and polyvinylpyrrolidone-K30 (PVP). Tablets were prepared by direct compression method, using sodium carboxy methyl cellulose (SCMC), HPMC K100, sodium alginate, Carbopol 934 P, Eudragit RL 100, PVP and ethyl cellulose (EC) as a backing layer. The both formulations were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, swelling behaviour, tensile strength, buccoadhesive strength, surface pH and *in vitro* release studies. Data of *in vitro* release from both patches and tablets were fit to different equations and kinetic models to explain release profiles. *In vivo* drug release studies in rabbits showed 91.65% of drug release from HPMC-Chitosan patch, while it was 82.63e90.21% release from sodium alginate-SCMC buccal tablets. Good correlation among *in vitro* release and *in vivo* release of AMHCL was observed in both formulations. The satisfactory results were obtained in all prepared formulations and based on the results, it can be concluded, Amiloride hydrochloride oral mucoadhesive buccal formulations which can be used mainly in minimizing dose and mainly help to improve the patient compliance and Amiloride hydrochloride is a drug of choice for delivery through the control release via buccal route.³⁵

CONCLUSION

There should be improvement in current treatment in case of safety and efficacy. Buccal drug delivery system bypass the GI tract and hepatic portal system, Increases bioavailability of drug, Patient compliance, Though less permeable than the sublingual area, the buccal mucosa is well vascularised, and drug can rapidly absorbed into the venous system underneath the oral mucosa, Lower intersubject variability than TDDS, The large contact surface of the oral cavity contributes to rapid and extensive drug absorption. Patches are gained importance in pharmaceutical areas due to novel, patient friendly and convenient product. Due to their small size and thickness, they have improved patient compliance, compared to tablets. Moreover, since mucoadhesion implies attachment to the buccal mucosa, patch can be formulated to exhibit a systemic or local action. Due to the versatility of the manufacturing processes, the release can be oriented either towards the buccal mucosa or towards the oral cavity. Patch releasing drug towards the buccal mucosa exhibit the advantage of avoiding the first pass effect by directing absorption through the venous system that drains from the cheek. Buccal patch is a nondissolving thin matrix modified release dosage form composed of one or more polymer patch or layers, containing the drug and/or other excipients. The patch may contain a mucoadhesive polymer layer which bonds to the oral mucosa, for controlled release of the drug into the oral mucosa (unidirectional release), oral cavity (unidirectional release), or both (bidirectional release). The patch is removed from the mouth and disposed of after a specified time. However, the need for safe and effective buccal permeation/absorption enhancers is a

crucial component for a prospective future in the area of buccal drug delivery.

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Source of Support: Nil, Conflict of Interest: None.