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Review Article

In vitro, ex vivo and in vivo studies on anti-hypertensive-loaded transdermal and buccal patches

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Abstract

The occurrence of hypertension is increasing slowly among urban and rural segments of the Indian population, irrespective of gender. It can affect quality of life and also lead to mortality under serious circumstances. Although several oral anti-hypertensive medications are available in the Indian market, the management of hypertension is reported to be poor. Anti-hypertensive-based transdermal or buccal patches may be necessary for patients where oral or parental route of administration is not possible or when no better control is achievable. Apart from Catapres®/TTS, no other transdermal or buccal film of anti-hypertensive could be identified in the global market to date. However, the literature survey of published research articles since 2004 in the specialized databases of Elsevier, PubMed, and Cambridge using the keywords such as “anti-hypertensive”, “buccal”, and “transdermal” reveals more than 30 studies on fabrication, *in vitro*, and *ex vivo* characterization of transdermal and buccal films of anti-hypertensive agents. Among these, only 10 articles presented *in vivo* studies in animal models with no studies on human volunteers. Few reported stability studies as per ICH guidelines and skin irritation studies. The present review article aims to reflect on the polymers, plasticizers, and penetration enhancers employed, outcomes of different studies on drug release, diffusion, and permeation, identify limitations and weaknesses of the reported studies, emphasize future research directions, and establish the potential reasons for not finding another successful anti-hypertensive loaded transdermal or buccal patch being launched.

Keywords: Anti-hypertensive, buccal, *ex vivo* permeation, *in vitro* drug release, *in vivo* studies, transdermal

Introduction

According to the WHO, high blood pressure or hypertension is one of the major causes of premature death globally. With estimated cases of more than a billion, hypertension is one of the most serious non-communicable diseases and risk factors contributing to morbidity¹. Globally, only 21% of hypertensive patients were reported to have blood pressure under control in 2021. Approximately 90 million women and more than 100 million men worldwide suffer from hypertension-associated disability-adjusted life years (DALYs)².

According to the National Family Health Survey (NFHS-5) reports of 2019–2021, hypertension was found to affect 24% in men and 21% of women in India, up from 19% and 17%, respectively, observed in the 2015–16 survey cycle^{3,4}. The rate of hypertension control in India is dismal with <10% of the country's rural and 5% of its urban hypertensive population having their blood pressure (BP) managed^{2,4}.

Anti-hypertensive drugs can be broadly divided into six groups according to prescribed data. These are calcium channel blockers, angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, alpha-blockers, and alpha agonists⁵. Out of these various categories, in the Indian context, calcium channel blockers are most employed and combination therapy with different anti-hypertensive molecules is also a common strategy for proper control of hypertension⁶.

In the management of chronic hypertension, oral route is the route of choice for administering anti-hypertensive drugs. In cases of hospitalized patients or persons with erratic fluctuations of blood pressure, intravenous therapy is recommended. In special cases, when oral and regular parenteral administration is not possible or for better management of blood pressure, anti-hypertensive-based transdermal or buccal patches may be necessary^{7,8}.

There are inherent advantages of designing transdermal and buccal patches of anti-hypertensive medications owing to their specific physicochemical and

pharmacokinetic properties and also their desired therapeutic efficacy with respect to lag time, onset and duration of action, frequency of administration ⁹. The characteristics which justify transmucosal dosage form development for anti-hypertensive drugs includes:

1. Low molecular weight and lipophilic nature. Examples are amlodipine (Molecular weight: 408.87; pKa: 8.7), verapamil (Molecular weight: 454.6; pKa: 8.75), telmisartan (Molecular weight: 514.6; pKa: 3.62), losartan potassium (Molecular weight: 461; pKa: 4.9) ^{10,11}
2. Susceptibility to extensive first-pass metabolism in the liver e.g. propranolol, alprenolol, verapamil ^{11,12}
3. Due to its short elimination half-life of 3-4 h, more frequent oral dosing is necessary to maintain the therapeutically effective plasma concentration. Examples are propranolol ($t_{1/2}$: 3 h), metoprolol ($t_{1/2}$: 3 h), bupranolol ($t_{1/2}$: 2 h), losartan potassium ($t_{1/2}$: 2 h) ^{11,13}
4. Low oral bioavailability of most of the drugs due to pre-systemic metabolism, varying between 10-35% as seen with bupranolol, losartan potassium, valsartan, carvedilol ^{12,13}

Marketed anti-hypertensive drug-loaded transdermal formulation is clonidine-based Transdermal Therapeutic system (Brand name: Catapres-TTS®, Dose: 0.1,0.2,0.3 mg/d, Surface area: 3.5, 7.0, 10.5 cm², Dosage frequency: once weekly, Steady-state plasma concentrations: 0.4 ng/ml, 0.8 ng/ml, 1.1 ng/ml, Manufacturer: Boehringer Ingelheim, U.S since 1985) ¹⁴.

No other transdermal or buccal films could be found in the global or Indian market with anti-hypertensive drugs of any pharmacological category. However, in literature, several studies (more than 30) have been reported in the last 20 years involving fabrication, *in vitro*, and *ex vivo* characterization of transdermal and buccal films of anti-hypertensive agents. No comprehensive summary of the various studies conducted so far by different research groups is available. The present review article aims to compile the outcomes of various studies conducted so far and elucidate the potential reasons of the failure of products of such studies to reach the market and be commercially available.

For the literature survey, research articles published from 2004 to 2024 from Elsevier, PubMed, and Cambridge were considered. The selected keywords were “anti-hypertensive”, “buccal films/patches”, “transdermal patches”, “transmucosal”, “natural polymers in development of buccal/transdermal films”, “synthetic polymers in development of buccal/transdermal films”, “penetration enhancers used in buccal/transdermal films”, and “plasticizers used in buccal/transdermal films”. The keywords were used either singly or in combination to find the most relevant studies. Articles from Springer, information from the Internet, and Online published articles from Medscape were also reviewed for the purpose.

Transdermal and Buccal Patches: Potential Route for Anti-Hypertensive Drugs

There are certain potential advantages and benefits of using transdermal and buccal patches over other dosage forms which include ¹⁵⁻¹⁹

- (a) The gastrointestinal transit process, with its potential for exposure to enzymatic and pH-mediated breakdown, can be avoided by using transdermal and buccal routes.
- (b) Direct drug delivery into systemic circulation via transdermal and buccal patches is a painless and non-invasive method.
- (c) Compared to other administration methods, the buccal film achieves a relatively rapid onset of action with fewer side effects.
- (d) Buccal film increases bioavailability when a low concentration of API is used because of direct contact and adhesion, which causes the film to stay at the application site for a long time.
- (e) Easy route for children, unconscious, and bedridden patients.
- (f) Enables self-medication.

Transderm-Scop with scopolamine used to cure motion sickness, was the first commercially available transdermal drug delivery (TDD) system ¹⁷. Table 1 lists some of the well-known FDA-approved buccal and transdermal patches, available commercially for the last 10 years.

TABLE 1: List of FDA approved and marketed transdermal and buccal patches: (From 2014 to date)

Drug (Brand name)	Dosage form	Year of approval	Manufacturer	Therapeutic category	Ref
Buprenorphine and naloxone (Bunavail®)	Buccal	2014	BioDelivery Sciences International Inc.	Opioid analgesic	20
Asenapine (Secuado®)	Transdermal	2019	Hisamitsu Pharmaceutical Co., Inc. Noven C.A.N.	Antipsychotic	21
Levonorgestrel and ethinyl estradiol (Twirla®)	Transdermal	2020	Agile Therapeutics	Contraception	22
Fentanyl (Fenspar®)	Transdermal	2021	Sparsha Pharma International Pvt. Ltd.	Chronic pain	23
Donepezil (Adlarity® / Aricept®)	Transdermal	2022	Corium LLC/Eisai Co. Ltd.	Alzheimer's disease	24

Components of Transdermal and Buccal Patches of Anti-Hypertensive Agents: Literature Survey

Transdermal and buccal patches consist of active pharmaceutical ingredients (APIs), mucoadhesive polymers, plasticizers, permeation enhancers which are discussed below^{17,19}.

(a) Active pharmaceutical ingredients: Drugs can belong to any of the classes of Biopharmaceutical Classification System (BCS). Examples are losartan potassium (angiotensin II receptor antagonists) (Class III), captopril (ACE inhibitors) (Class I), metoprolol tartrate (Class I), propranolol hydrochloride (Class I), atenolol (beta blockers) (Class III), Carvedilol (mixed alpha beta blockers) (Class II) etc^{17,18}.

(b) Mucoadhesive polymers/Film formers: A mucoadhesive polymer is thought to be one of the main formulation components for the development of a transdermal and buccal delivery system. Numerous hydrophilic and /or hydrophobic polymers have been used as film-forming agents, either alone or in combination to improve bioadhesion. Examples are hydroxypropyl methylcellulose/Methocel

K4M/15M/100M, Eudragit RL/RS 100, ethyl cellulose (EC), polyvinyl pyrrolidone K30/K90 (PVP), Carbopol 934P, polyvinyl alcohol (PVA), chitosan, etc^{17,19}.

(c) Plasticizers: Plasticizers are added to increase patch strength and flexibility and decrease fragility and brittleness. The purpose of plasticizer is to prevent inter-polymeric chain interactions by acting as a barrier between them. Plasticizer may affect drug release behavior. Examples are glycerine, propylene glycol, poly ethylene glycol, Citroflex etc.^{19,25}.

(d) Permeation enhancer: Penetration across stratum corneum/buccal mucosa is thought to be the limiting factor to systemic absorption in the development of the transdermal and buccal patches. Permeation enhancers facilitate drug permeation across the abovementioned physiological barriers. Examples are dimethyl sulfoxide, Tween 80, propylene glycol, menthol, cineole, etc.²⁵.

Table 2 provides a comprehensive list of different polymers/film formers, plasticizers and penetration enhancers used in fabrication of anti-hypertensive loaded transdermal and buccal patches in last 20 years.

TABLE 2: Comprehensive list of components of anti-hypertensive-loaded transdermal and buccal patches

Sl. no.	Active pharmaceutical ingredient (Transdermal/ Buccal)	Polymers and/or film formers	Plasticizer	Permeation enhancer	Ref
1.	Losartan potassium (Transdermal)	Eudragit®E100, PVP K30, succinic acid	Citroflex	-	26
2.	Losartan potassium (Fast dissolving buccal film)	HPMC K15M, PVP K30, Pectin, Aspartame, Lactose	Glycerine, Propylene glycol (PG)	-	27
3.	Losartan potassium (Transdermal)	Eudragit RS100, Eudragit RL100, Methocel K 100M. Soya lecithin	PG	Tween 80	28
4.	Captopril (Fast Dissolving Film)	HPMC E5/Sodium carboxy methyl cellulose (SCMC), Methyl Cellulose (MC), PVP, PVA	PEG 400 and glycerin	-	29
5.	Ramipril (Buccal)	PVA, Sodium alginate (SA), HPMC 5	PEG 400	-	30
6.	Losartan potassium (Transdermal)	PVP K30, HPMC K100, Ethyl cellulose (EC), and Chitosan	Castor oil	PG	31
7.	Metoprolol tartrate (Transdermal)	PVP K30, PVA	Glycerin	DMSO or Tween 80	32
8.	Carvedilol (Buccal)	HPMC K4M, HPMC K15M, MC and Carbopol 940P, Eudragit RSPO	PG	-	33
9.	Propranolol hydrochloride (Transdermal)	Chitosan	Glycerine	Cineole/ menthol/oleic acid/ PG/ Tween 80	34
10.	Atenolol (Buccal)	Randomly methylated beta cyclodextrin (RAMEB) (for complex formation), PVA, HPMC/Methocel E5, EC	Citroflex A4	-	35

In-Vitro Drug Release and Ex-Vivo Permeation Studies on Transdermal and Buccal Patches of Anti-Hypertensive Drugs: Literature Survey of Last 20 Years

Mane et. al. (2022) studied the effect of HPMC, EC, Eudragit L100, aspartame, PVA, dimethyl sulphoxide as a permeation enhancer on *in vitro* drug release using Franz diffusion cell of losartan potassium from buccal patch. Studies showed 95.13% drug release in 5 h³⁶.

Haju et. al. (2021) studied *in vitro* drug release and diffusion, *ex vivo* permeation (through goat buccal mucosa) of cilnidipine from buccal patch prepared from HPMC E15, HPMC K4M and propylene glycol. In 24 h, *in vitro* release and diffusion studies showed 95.18% release and 82.64% diffusion respectively with *ex vivo* permeation of 76.34%³⁷.

In their studies, **Sadique et. al. (2020)** reported the *in vitro* drug release of losartan potassium from fast-dissolving buccal film prepared from HPMC K15M, glycerine, propylene glycol, sodium starch glycolate and other additives. Studies exhibited 88.56% drug release in 5 min²⁷.

Ericksa et.al. (2020) investigated the impact of hydrophobic polymer, Eudragit E100 and hydrophilic polymer, PVP K30, succinic acid as a permeation enhancer and Citroflex as a plasticizer on bioadhesion, post wetting-bioadhesion, *in vitro* release, *ex vivo* permeation of losartan potassium from transdermal patch, employing solid microneedles as physical penetration enhancer. *In vitro* drug release studies of patches using apparatus USP V indicated $93.11 \pm 2.11\%$ drug to be released in 4 h from the optimum formulation, simultaneously via diffusion and erosion mechanisms, as best correlation was obtained with the kinetic models of Higuchi and Korsmeyer-Peppas. Bioadhesion and post wetting-bioadhesion studies done using a Texture Analyser with human skin samples obtained from abdominoplasty revealed a reduction in post wetting adhesion force from 1063.05 ± 60.33 gf to 995.9 ± 72.53 gf²⁶.

Anil et. al. (2018) conducted *in vitro* drug release, *in vitro* drug diffusion and *ex vivo* permeation (through porcine buccal mucosa) studies of ramipril from buccal patch prepared from PVA, sodium alginate, HPMC 5, PEG 400. Within 8 h, 98% drug was released *in vitro*. *In vitro* drug diffusion and *ex vivo* permeation studies revealed 97.02% diffusion and 94.87% permeation within 6 h³⁰.

In vitro drug release studies of losartan potassium from fast dissolving buccal film using HPMC 5 cps, saccharin sodium, sodium starch glycolate, glycerol as a plasticizer and menthol as a permeation enhancer showed 96.8% drug release in 5 min³⁸.

Singh et. al. (2018) observed the *in vitro* drug release and *ex vivo* permeation (through porcine buccal mucosa) profiles of losartan potassium from buccal patch made from PVA, chitosan, EC, dibutyl phthalate, propylene glycol. In 8 h, 98.48% drug was released *in vitro* and *ex vivo* permeation studies showed 79.98% drug permeation³⁹.

In vitro diffusion studies of losartan potassium from matrix type transdermal patch using PVP K30, EC, HPMC, chitosan, polyethylene glycol (PEG 400) as a permeation enhancer, castor oil as a plasticizer showed 80.41% drug to be released in 10 h. Physicochemical and stability studies were conducted but no permeation data or data on skin irritation have been reported³¹.

In their studies, **Verma et. al. (2016)** explored the *in vitro* drug release and *ex vivo* permeation (through mice abdominal skin) behaviors of losartan potassium from transdermal patch prepared from HPMC, Carbopol 940, PVP and PEG 400. Studies exhibited 93.41% drug release and 70.65% drug permeation over 8 h⁴⁰.

Malipeddi et. al. (2016) fabricated a transdermal patch of metoprolol tartrate with PVP K30, PVA, glycerin and dimethyl sulfoxide (DMSO) as a penetration enhancer and studied *in vitro* drug release and *ex vivo* permeation (through rat abdominal skin). Studies reported 65.5% drug release and 53% permeation in 24 h. Permeation followed zero-order kinetics, and the release mechanism was diffusion rate-controlled. No skin irritation was observed with the patches³².

Ikram et. al. (2015) viewed the impact of HPMC K100M, PVP K30, EC, and propylene glycol on a buccal patch with losartan potassium with respect to *in vitro* drug release using USP 23 Type-2 rotating paddle dissolution test apparatus. In 8 h, maximum drug release occurred⁴¹.

In vitro release studies of metoprolol succinate from buccal patch using HPMC K100M, EC, and propylene glycol showed 93.03% drug release after 100 min⁴².

In a study conducted by **Omray et. al. (2014)**, *in vitro* drug release studies exhibited 69.3% release in 8 h from diltiazem hydrochloride-loaded transdermal patch containing PVP, Carbopol 934P, carboxy methyl cellulose, PEG 400, and Tween 60 as a permeation enhancer. The release pattern followed zero order kinetics⁴³.

In vitro release studies of polymethylmethacrylate (PMMA)-EC transdermal patches of losartan potassium demonstrated 76.5% release in 24 h⁴⁴.

Meher et. al. (2013) investigated the effects of HPMC K4M, HPMC K15M, methylcellulose, Carbopol 940, and Eudragit RSPO on *in vitro* drug release and *ex vivo* permeation (through goat buccal mucosa) of carvedilol from the buccal patch. In 12 h, *in vitro* drug release studies showed 88% drug release and *ex vivo* permeation of 80%³³.

In vitro drug release and *ex vivo* permeation studies of losartan potassium from fast-dissolving buccal film using PVA, maltodextrin, mannitol, cross povidone, propylene glycol, and citric acid as permeation enhancer showed 98.99% drug release and 89.42% drug permeation in 10 min using porcine oral mucosal membrane⁴⁵.

Jain et. al. (2012) reported *in vitro* release and *ex vivo* permeation of losartan potassium through rat skin from EC-PVP patches with Tween 80 as a permeation enhancer. In 24 h, *in vitro* release studies showed 90.28%

release and *ex vivo* permeation of 71.25%. Drug release conformed to Higuchi model⁴⁶.

Propranolol hydrochloride-loaded transdermal patch fabricated with chitosan, glycerine, propylene glycol and cineole demonstrated *in vitro* release of 70.4% drug release and *ex vivo* permeation of 60.6% (through abdominal portion of Wistar rats) in 8 h³⁴.

Bagchi et. al. (2010) reported *in vitro* drug release of 100% and 79.74% drug permeation in 36 h across abdominal skin of young albino rat with losartan potassium loaded transdermal patches of EC-PVP K30-HPMC. Skin irritation studies in male healthy rabbits found the patches to be non-irritant⁴⁷.

Shivhare et. al. (2010) investigated the *in vitro* bioadhesion (using goat cheek pouch), *in vitro* release and *ex vivo* permeation (through goat buccal mucosa) of losartan potassium-based buccal patch made from HPMC K15M, Eudragit RL100 and glycerol. *In vitro* release and *ex vivo* permeation studies indicated 96.54% release and 79.98% drug permeation in 6 h. Bioadhesive strength was found to be 64.23 ± 0.23 g in 10 min⁴⁸.

In their studies, **Adhikari et. al. (2010)** researched the *in vitro* drug release and *ex vivo* permeation (through porcine buccal mucosa) of atenolol from buccal patch formulated from sodium alginate, Carbopol 934P, HPMC and glycerine. Studies exhibited 72.03% release and 70.17% drug permeation in 24 h⁴⁹.

In vitro release and *ex vivo* permeation (through porcine buccal mucosa) studies of enalapril maleate buccal patches of hydroxyethyl cellulose, sodium carboxymethyl cellulose, PG demonstrated 96.35% release in more than 2 h and 82.48% permeation after 10 h⁵⁰.

In vitro release studies of randomly methylated beta cyclodextrin (RAMEB) (for complex formation)-PVA buccal patches of atenolol exhibited 90% release within 1 h³⁵.

In Vivo Studies on Transdermal and Buccal Patches of Anti-Hypertensive Drugs Over the Last 20 Years

To date, ten studies reported *in vivo* investigations on buccal/transdermal patches containing propranolol hydrochloride, trandolapril, diltiazem hydrochloride, losartan potassium, nitrendipine, atenolol, labetalol hydrochloride, and metoprolol tartrate for evaluation of pharmacodynamics and pharmacokinetic parameters^{28,51,52-59}.

In the study of **Kurcubic et. al. (2023)**, one group of hypertensive albino rats (simulated saliva-induced hypertension) was administered mucoadhesive buccal patches of propranolol hydrochloride for 24 h consisting of HPMC (0.5%), polyethylene oxide polymer (PEO) (3.5%), PVA (1.5%) and PG (3.0%). Significant lowering of blood pressure from 190 mmHg to 160 mmHg was observed in 4 h. Pharmacokinetics values are reported as: $C_{max} = 4.22 \pm 0.66$ µg/ml, $t_{max} = 1.33 \pm 0.52$ h, $AUC_{0-24h} = 66.13 \pm 18.03$ µg.h/ml, $AUC_{0-\infty} = 111.82 \pm 39.04$ µg.h/ml, $t_{1/2} = 17.41 \pm 7.38$ h. Relative bioavailability was

found to be 99.98% compared to oral tablet as a standard formulation. *In vitro* release studies showed the total amount of drug to be released in 240 mins with 45% permeation⁵¹.

In the study of **Jaiswal et. al., 2023**, transdermal patches of trandolapril consisting of Eudragit NM 30 D, glycerine, and oleic acid [20:0.5:3.5] were applied in hypertensive Wistar albino rats (hypertension induced by giving 0.8% v/v formalin solution for 24 h). *In vitro* studies exhibited 89.16% drug release in 24 h with *ex vivo* permeation of 87.42%. The optimum formulation showed C_{max} of 749.19 ± 4.91 ng/ml, t_{max} of 6.66 ± 0.94 h, AUC_{0-t} of 8690.43 ± 28.26 ng h/ml, $AUC_{0-\infty}$ of 9555.17 ± 26.32 ng h/ml and $t_{1/2}$ of 6.11 ± 0.64 h⁵².

To date, two studies reported *in vivo* investigations on transdermal patches containing losartan potassium, where different protocols were followed to induce hypertension in male adult Wistar rats and Sprague-Dawley rats by subcutaneous injection of methylprednisolone acetate (MPA) (20 mg/kg/w) for 2 weeks and clipping renal artery and nephrectomy (right kidney) respectively^{28,53}. In the first study,²⁸ two groups of hypertensive animals (drug-induced hypertension maintained over 72 h) were given Eudragit RL 100 and Eudragit RS 100 ethosomal (made of soy-lecithin) patches in the abdominal area, and significant lowering of blood pressure to almost normal value was observed in 48 h with Eudragit RL 100 patch. The same patch showed $92.41 \pm 1.98\%$ drug release in 72 h during *in vitro* studies. The patch demonstrated satisfactory stability at 4°C and 60% relative humidity. The optimum patch in the second study⁵³, consisting of Eudragit RL 100 and Eudragit RS 100 in the ratio of 1:1 lowered blood pressure from 160 mmHg to almost normal value, 11 h post-application of the patch and remained stable till 24 h in nephrectomized rats. Almost 75-80% of drug release was reported in 48 h during *in vitro* release studies from the optimum formulation.

Another study reported *in vivo* investigations on buccal patches containing losartan potassium, where hypertension was induced in white rabbits by an intramuscular injection of ketamine HCl (40 mg/kg) and xylazine (10 mg/kg) for 4 h. Here, two groups of hypertensive animals (drug-induced hypertension) were given two buccal patches with HPMC K15M/Sodium carboxymethyl cellulose-Carbopol 934P-PEG 400 (0.3:0.7:1) in the buccal pouch of the rabbit for 4.5 h. The two optimum formulations showed C_{max} of 183.22 ± 3.049 ng/ml, 191.06 ± 2.215 ng/ml, t_{max} of 1.5 ± 0.32 h, 1.5 ± 0.26 h, $AUC_{0-\infty}$ of 509.43 ± 4.427 and 528.72 ± 1.628 ng-h/ml. Good *in vitro-in vivo* correlation (Level A) was observed with both the optimum formulations with r^2 values > 0.99 ⁵⁴.

Buccal patches of diltiazem hydrochloride were administered to white rabbits for 4.5 h where hypertension was induced by intramuscular injection of a 1:5 mixture of xylazine (1.9 mg/kg) and ketamine (9.3 mg/kg). The optimum patch was developed with SCMC, hydroxy propyl cellulose (HPC) in the ratio of 2:1 and PEG 400. Relative bioavailability (%) compared to oral commercial sustained release tablet (Altiazem® SR) as a

reference formulation was 165.2. Other pharmacokinetic parameters were found to be $C_{\max}$ as 195.58 ± 11.65 ng/ml, $t_{\max}$ as 3.00 ± 0.00 h, and AUC_{0-10} as 1206.27 ± 137.61 ng h/ml, $AUC_{0-\infty}$ as 1527.98 ± 378.22 ng h/ml. The same patch showed about 85.5% drug release and permeation of 71.66% in 7 h using a chicken pouch membrane and followed Korsmeyer-Peppas kinetics (Fickian diffusion). A good correlation was also obtained in this case between *in vitro* drug release and *in vitro* drug permeation. Only *in vivo* residence time/ mean residence time (MRT) was estimated in healthy male adult volunteers, aged between 27 and 40 years. MRT was reported to be 6.84 ± 2.5 h⁵⁵.

In the study of **Mittal et. al., 2009**, Wistar albino rats were given transdermal patches of nitrendipine for 24 h (fructose solution-induced hypertension) consisting of Eudragit E PO, PVP K 30 [4:6] and oleic acid as a permeation enhancer in the shaven abdominal area and significant lowering of blood pressure from 172.83 mmHg to 107.43 mmHg could be seen. Pharmacokinetics values are obtained as $C_{\max}$ and $t_{\max}$ of 816 ± 10.33 ng/ml and 12 h respectively, AUC_{0-t} of 31263 ± 436.13 ng h/ml. High AUC values indicate increased bioavailability of the drug. The same patch showed 94.67% drug release in 48 h and 82.62% drug permeation across human cadaver skin. There was no skin irritation with the application of the patch indicating the safety of the adhesive as well as the drug by transdermal route⁵⁶.

In the study of Gupta et. al., 2006, EC: HPMC-based transdermal patch (4:6) of atenolol was given in the inner pinna (ear skin) (hypertension induced by subcutaneous injection of 10 % fructose solution) of Wistar albino rats) for 28 h and an effective plasma concentration of 100.2 ± 0.50 ng/ml was detected in 7 h, AUC_{0-28} of 2260 ng h/ml was observed⁵⁷.

In the study of **Aqil et. al., 2005**, a constant and steady decline in blood pressure in rats (hypertension induced by subcutaneous injection of 2% normal saline) was noticed from 173.16 mmHg to 124.66 mmHg i.e 28% reduction in blood pressure over 48 h from labetalol hydrochloride-loaded transdermal patch composed of Eudragit RL 100, Eudragit RS 100 (7.5:4.5). The optimum formulation followed Higuchi kinetics and showed 90.26% drug release in 48 h and 85.19% drug permeation in 24 h through abdominal skin of the albino rat. The authors proposed shelf-life stability of a maximum of 3 years at ambient conditions for the developed transdermal system⁵⁸.

Eudragit-RL 100-polyvinyl acetate (PVAc) (8:2) transdermal patches of metoprolol tartarate, containing menthol as a permeation enhancer when applied on Wistar male albino rats (methylprednisolone acetate-induced hypertension maintained over 48 h) produced a significant drop in blood pressure from 175.46 mmHg to 101.33 mmHg. From the optimum patch, 95.04% drug release and 90.38% drug permeation (through albino rat abdominal skin) occurred in 48 h. In skin irritation studies, irritation potential was determined to be < 2, confirming the non-irritant nature of the patch components. Moreover, the authors predicted 2-year

shelf-life for the patch under normal storage conditions⁵⁹.

In Vivo Studies on Transdermal Patches and Buccal Films of Non-Anti-Hypertensive Drugs

In this section, *in vivo* investigations on buccal/transdermal patches containing clozapine, zidovudine, benztropine mesylate, tizanidine, zolmitriptan succinate, pramipexole, dapoxetine hydrochloride and lamivudine for evaluation of pharmacodynamics and pharmacokinetic parameters are being reported⁶⁰⁻⁶⁷.

Qadir et al., 2025 studied skin sensitivity probability and pharmacodynamic parameters in male albino Wistar rats following the administration of clozapine-loaded transdermal matrix patches, consisting of Eudragit RS 100, PEG 400, and oleic acid. A flux value of $147.376 \mu\text{g}/\text{cm}^2/\text{h}$ and a cumulative percentage release of 94.87% were obtained in 24 h. With the optimized patch containing 50 mg of drug, a maximum plasma concentration of 38.396 ng/ml was attained in 28.96 h, and the total AUC was determined to be 1625.500 ng-h/ml. The fabricated patch was found to be safe for the skin. The predicted shelf life was almost 2.5 years⁶⁰.

In their study, Sabareesh et al, 2024, developed HPMC E15-chitosan transethosomal patches of zidovudine from its nanoethosomal dispersion made of phospholipids and cholesterol. Drug penetration was increased significantly from the marketed formulation as evident from high permeation coefficient value and flux values of $2.56 \text{ mg}/\text{cm}^2/\text{h}$ and $0.494 \text{ mg}/\text{cm}^2/\text{h}$ respectively. Bioavailability studies showed superior performance as AUC was 189 times more than the commercial product⁶¹.

In the study of **Chabru et. al., 2023**, four groups of Wistar albino rats were given transdermal patches of benztropine mesylate for 72 h consisting of polyacrylates, polysiloxanes, and polyisobutylene and ethyl acetate on the dorsal skin surface area. This patch exhibited 54.82% drug permeation in 72 h through rat skin during *ex vivo* studies. Pharmacokinetics values are reported as $C_{\max}$ of 274.28 ± 21.23 ng/ml, $t_{\max}$ as 12 ± 4.82 h, $t_{1/2}$ as 73.54 ± 8.63 h, K_e of $0.009 \pm 0.04 \text{ h}^{-1}$, AUC_{0-72} as $9.661 \pm 1.19 \mu\text{g}/\text{ml.h}$, $AUC_{0-\infty}$ as $20.314 \pm 1.32 \mu\text{g}/\text{ml.h}$ ⁶².

Arpa et. al., 2023 studied *in vivo* release profile and determined the pharmacokinetic parameters of tizanidine-loaded buccal patch of chitosan azelate in female rabbits. *In vitro* drug release exhibited 100% drug release within approximately 60 min and drug permeation. Various *in vitro* and *in vivo* parameters were obtained as follows: flux (J_{ss}) ($\mu\text{g cm}^{-2}\text{h}^{-1}$) = 12.120 ± 0.595 , permeability (t_{0-8}) = $9.98 \pm 1.71\%$, permeability (t_{0-24}) = $54.70 \pm 7.22\%$, $C_{\max}$ = 145.84 ± 27.97 ng/ml, $t_{\max}$ = 4 h, AUC_{0-8} = 3 times higher, and AUC_{0-12} = 2 times higher than orally administered commercial product (tizanidine tablet, Sirdalud®)⁶³.

In vivo studies of zolmitriptan succinate-loaded buccal film in rabbits produced $C_{\max}$ of 57.36 ± 7 ng/ml, $t_{\max}$ of 60 min, AUC_{0-t} of 7427.5 min ng/ml, $AUC_{0-\infty}$ of 11285.70 min ng/ml, MRT_{0-t} of 133.55 min. Histopathological studies with the films revealed no signs of cytotoxicity or

necrosis on application to the buccal mucosa. The buccal films were composed of agarose, guar gum, and glycerol. The study dealt also with the significance of the combination of both physical and chemical techniques on the flux enhancement of the *ex vivo* permeation of the drug⁶⁴.

In their studies, **Singhal et. al. (2021)** viewed the outcome of PVP K 90 (20% w/v), glycerol (5% w/v) and PG (5% w/v) with *in vivo* studies on pramipexole-loaded one-compartment and two-compartment iontophoretic patch were carried out in male Wistar rats. Cumulative permeation (nmol/cm²), skin deposition (nmol/cm²), Total delivery (nmol/cm²), and delivery efficiency (DE) (%) were found to be 350.19 ± 51.62, 330.19 ± 113.73, 680.39 ± 124.90, and 6.8 respectively from one compartment system (20 µmol PRA + 184 µmol NaCl). From a two-compartment system (20 µmol PRA + 16 µmol NaCl), cumulative permeation (nmol/cm²), skin deposition (nmol/cm²), total delivery (nmol/cm²), delivery efficiency (DE) (%) were found to be 1269.64 ± 178.52, 133.44 ± 24.22, 1403.08 ± 180.16, 14.0 respectively⁶⁵.

Aldawsari et. al. (2020) explored *in vivo* profile in male Wistar rats of dapoxetine hydrochloride loaded fast mouth dissolving buccal film of HPMC E5, maltodextrin. C_{max} of 344.34±49.96 ng/ml, t_{max} of 0.50s, AUC₀₋₂₄ of 1568.83±145.34 ng.hr/ml, AUC_{0-∞} of 1701.923±161.27 ng.hr/ml, relative bioavailability of 191.25% compared to standard oral formulation were reported⁶⁶.

In vivo pharmacokinetic behaviors of lamivudine from transdermal patch prepared from methylcellulose was studied in albino male rabbits. From *in vivo* pharmacokinetics studies, t_{max} of 6.79 ± 3.73 h, C_{max} of 0.55 ± 0.23 mg/ml, AUC_{0-last} of 30.14 ± 9.99 mg.h/ml, AUC_{0-∞} of 54.04 ± 13.18 mg.h/ml, K_{el} of 0.008 ± 0.004 h⁻¹ and t_{1/2} of 116.55 ± 74.64 h were reported. After stability studies, it has been concluded that the patches would remain stable for 3 months at 40°C and 75% relative humidity. Skin irritation studies did not reveal any signs of erythema or itching or inflammation on the rabbit skin⁶⁷.

Conclusion and Future Prospects

Comprehensive literature survey and compilation of outcomes of the studies revealed that among 30 studies conducted so far on anti-hypertensive-loaded transdermal and buccal patches, only ten studies reported *in vivo* data in animals with none in humans, twelve studies reported skin irritation studies of the developed films in animal models and eight studies reported stability studies on the developed films as per ICH guidelines. The shelf-life predicted from accelerated stability studies indicated that the films may be stored for a minimum of 1 month to a maximum of 3 years at conditions varying from 25±2°C/60±5% relative humidity to 40±2°C/75±5% relative humidity. A wide range of values exists as different studies reported stability studies being conducted for different periods. Although no conclusive decision can be reached regarding the stability of the polymeric films/patches, the polymeric compositions employed in the studies may

be considered for the development of stable formulations. Regarding skin irritation/sensitivity potential or irritation to the buccal mucosa, the polymeric compositions, permeation enhancers, and/or plasticizers may be regarded as non-irritant, thus confirming their use for future *in vivo* studies. However, there is a huge gap in terms of *in vivo* studies on either anti-hypertensive or non-anti-hypertensive in animal models. *In vivo* studies on humans are rare. Therefore, insufficient stability data and *in vivo* data in animals, and lack of human data with respect to skin irritation potential and *in vivo* pharmacokinetic and pharmacodynamic parameters may be responsible for the failure of successful translation of a product from research laboratory to market. Limited *in vivo* studies of both anti-hypertensive-loaded and non-anti-hypertensive-loaded buccal/transdermal patches, in rats or rabbits indicate the superiority of the transmucosal drug delivery systems over conventional oral dosage forms in achieving therapeutically effective plasma concentrations of drugs to clinically significant outcomes. These revelations will guide future studies on anti-hypertensive-loaded transdermal and buccal patches with special emphasis on the complete formulation development starting from the judicious selection of polymers, plasticizers, and penetration enhancers, *in vitro*, *ex vivo*, to *in vivo* characterization of the products in animals and human volunteers, including stability studies as per ICH guidelines, to predict shelf-life of the formulations. Efforts in the proper direction will successfully deliver a technologically and economically feasible, safe, and effective transdermal and buccal patch for anti-hypertensive drugs in the market.

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