Review Article

Polymers in Matrix Type Transdermal Patch

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Received: 24-12-2021; **Revised:** 21-02-2022; **Accepted:** 28-02-2022; **Published on:** 15-03-2022.

ABSTRACT

Transdermal drug delivery is the administration of therapeutic agents through intact skin for systemic effect. Polymers are the backbone of the matrix-type transdermal patches. Based on the nature of origin, these polymers can be Natural, Semi-synthetic, and Synthetic polymers. Several experimental results have revealed the fact that in the case of the fabrication of matrix-type patches, the use of a polymeric blend becomes more effective than the use of a single polymer to control the rate of drug release from the patch. In this context, the selection of an appropriate combination of polymers becomes very crucial to modulate the rate and extent of release of drugs from matrix-type patches. It is essential to have sound knowledge of the inherent properties of different polymers for the selection of an appropriate combination of polymers to achieve the controlled drug release from the matrix-type patches. This article assembles comprehensive up-to-date information on various categories of polymers and polymer blends being used for the development of matrix type patches, the inherent characteristics of these different categories of polymers, and their impact on physio-mechanical properties as well as the rate of drug release from drug-loaded patches.

Keywords: Eudragit, Ethyl cellulose, HPMC, Higuchi model, matrix type patch, Polymer, PVP, Transdermal.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2022.v73i01.014

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v73i01.014

INTRODUCTION

Transdermal patches are rate-controlled drug delivery systems designed to deliver a therapeutically effective amount of drug into systemic circulation across the stratum corneum at a predetermined time and controlled rate. Depending on the method of incorporation of the drug, patches can be either of the drug-in-adhesive type, matrix type, or reservoir type. In matrix patches, the drug is dispersed homogeneously within an organic polymer matrix which may be hydrophilic or lipophilic.[1-6] Drug molecules can elute out of the matrix by first dissolving in the surrounding polymer and then diffusion through the polymer structure. Drug solids present in the layer closer to the surface of the device are first to elute and when this layer becomes depleted then the drugs in the next layer begin to dissolve and elute gradually. Therefore, it leads to the formation of a drug depletion zone with defined thickness. The thickness of the drug depletion zone increases continuously as more drug solids elute out of the matrix leading to the inward advancement of the interface of the drug depletion zone further into the core of the patch. The rate of drug release from diffusion-controlled matrix type of patches is time-dependent and is defined at a steady-state by the Higuchi model which can be represented by Equation 1 as follows:

$$\frac{Q}{t^{1/2}} = (2ACD)^{1/2} \quad \text{--------(1)}$$

Where, C= Drug solubility in the polymer which is the drug concentration in the system

A= Initial loading dose in polymer matrix

D= Diffusivity of drug molecules in polymer matrix

Q= Cumulative % of drug release.

The release from the matrix type of patch is thus controlled by loading dose, the solubility of the drug in polymer, and the diffusivity of the drug in the polymer matrix.[7,8]

Minitran® (Nitroglycerin)(Bausch Health Companies Inc.), Emsam® (Selegiline) (Somerset Pharmaceutical Ltd.), Exelon® (Rivastigmine)(Novartis) are some examples of commercially available matrix type diffusion-controlled transdermal patches.[5,6]

Polymers play a very crucial role in controlling drug release from the transdermal patch. The higher proportion of hydrophilic polymer in patches provides rapid release of the higher percentage of the drug (burst effect) which leads to difficulty in controlling the rate of release of the drug over a prolonged duration. Alternatively, the use of a more hydrophobic polymer leads to insufficient drug release from the patch, leading to a sub-optimal therapeutic effect. A balance between hydrophilicity and hydrophobicity of polymer or polymer blend is essential for effective modulation of drug release from patches.

The present review assembles comprehensive up-to-date information on the suitability of various types of polymers being used for the fabrication of matrix-type patches. In the review, a novel attempt was taken to establish the correlation between the inherent properties of various widely used polymers to develop matrix-type patches and the impact of these intrinsic characteristics of polymers on the various physio-mechanical properties and drug release profiles of the formulated drug-loaded patches.[9-11] For a better understanding of these correlations, it is essential to have sufficient knowledge of the nature of different widely used polymers, the origin of polymers, properties of polymers, and drug release mechanism exhibited by different types of polymers, which have been aptly described here for the first time.

CLASSIFICATION OF POLYMERS IN MATRIX TYPE TRANSDERMAL PATCHES

Polymers constitute the heart of TDDS, which control the release of the drug from the device. The polymer matrix can be prepared by dispersion of the drug in a liquid or solid-state polymer base. Polymers used in TDDS should have good stability and compatibility with the drug and other components of the system and they should provide predictable and reproducible drug release.[12,13]

The polymers employed in the fabrication of TDDS can be classified as follows:

1. Natural polymers: e.g. xanthan gum, sodium alginate, chitosan, mucilage of *Ficus carica* fruit, etc.

2. Semi-synthetic polymers: e.g. hydroxypropyl methylcellulose (HPMC), ethyl cellulose (EC), carboxymethylcellulose (CMC), and other cellulosic derivatives, etc.

3. Synthetic polymers: e.g. polyvinyl alcohol, polyvinyl chloride, polyethylene, polypropylene, polyacrylate, polyamide, polyurea, polyvinylpyrrolidone, polymethylmethacrylate, etc.[1-3]

NATURAL POLYMERS IN MATRIX PATCHES

Xanthan gum

Xanthan gum (XG) is obtained by the fermentation of *Xanthomonas campestris* found on leaf surfaces of green vegetables. It is a high molecular weight polysaccharide gum containing D-glucose and D-mannose as the dominant hexose units, along with D - glucuronic acid, and is prepared as the sodium, potassium, or calcium salt. XG remains stable in both acidic as well as in alkaline conditions due to its rigid structure and is resistant to any pH change. It is highly pseudoplastic, which ensures good pourability thereby enabling easy casting of drug-polymer dispersion on to mold for the fabrication of a matrix type of patch.[14,15]

Gorle et al. (2017) formulated a matrix patch of paracetamol using two different polymers i.e. XG and HPMC E5. PEG 400 was used as the plasticizer. XG was used as a release retarding polymer. The findings of the in vitro release study suggested that an increase in the concentration of XG release rate decreased. XG-based patches showed an extended drug release of 98.65% over a period of 12 hrs.[15] Abu- Huwaij and coworkers (2010) formulated nicotine-loaded mucoadhesive patches using XG and Carbopol 934. The fabricated patches showed acceptable swelling behavior, adhesive properties, and drug release. XG-based patches exhibited sustained and almost complete release in 10 has compared to Carbopol based patches which showed only 39% release of nicotine in 10 hrs. Moreover, it was found that the acid-base reaction of nicotine with Carbopol was relatively stronger than its reaction with XG, which in turn depicted the unsuitability of medicated Carbopol based patches for controlled drug delivery.[14]

Sodium alginate (SA)

Sodium alginate consists of the sodium salt of alginic acid, which is a mixture of polychronic acid composed of residues of D- mannuronic acid and L- glucuronic acid. It is extracted from brown seaweeds (Phaeophyceae). The alginic acid is extracted from the seaweed in alkaline conditions, then precipitated and subjected to an ion-exchange process.[16] Lefnaoui et al. (2017) formulated matrix-type transdermal drug delivery systems of ketotifen fumarate (KF) with chitosan–alginate polyelectrolyte complex (PEC). Propylene glycol (PG) was used as a plasticizer; Tween 80 and Span 20 were used as permeability enhancers. The in-vitro skin permeation data revealed Tween 80 to be an effective permeation enhancer in the optimization of transdermal films for sustained KF release. The polymeric composition corresponding to CTS: ALG in the ratio of 1:1, was found to be most suitable with 2.12 ± 0.17 mg/cm^2 of KF permeated after 24 h. Almost complete drug release was observed in 24h and drug release data fitted to Korsmeyer–Peppas indicated diffusion-mediated non-Fickian transport.[17]

Ficus carica fruit mucilage

The naturally occurring fruit mucilage of *Ficus carica* has gained popularity as a matrix-forming polymer in the fabrication of transdermal patches owing to its non-irritating and non-toxic properties and its compatibility with skin. Moreover, several experimental studies have revealed that the release of drugs from the patch can be delayed in a controlled manner with the increase in the proportion of *Ficus carica* fruit mucilage.[18-21] Rangari *et al.* (2012) formulated matrix-type transdermal patches of pioglitazone HCl by employing various proportions of *Ficus carica* fruit mucilage. Improvement in mechanical properties of prepared patches was observed with the increase in the proportion of fruit mucilage. The highest tensile strength and folding endurance values were found to be 0.334 ± 0.09 N/mm^2 and 95 ± 1.4 in the case of a patch containing the highest proportion of fruit mucilage (10% w/w). Moreover, it was also observed that the mucilage patch containing the highest proportion of fruit mucilage retarded the release profile from the matrix and was found to release 92.6 % drug after 48 hrs.[21]

Chitosan

Chitosan is one of the most important naturally occurring polymers, which is chemically (1,4)-2-amino-2-deoxy- β-D-glucan. It is produced by alkaline N-deacetylation of chitin, which is the main component of the shells of crab, shrimp, and krill. The increased popularity of chitosan in the field of transdermal drug delivery may be attributed to its exceptional properties including non-cytotoxicity, biocompatibility, non-allergenic behavior, and film-forming ability.[22-24] Allena et al. (2012) formulated a sustained-release transdermal patch of metformin hydrochloride using chitosan and HPMC. Dibutyl phthalate was used as the plasticizer. It was observed that formulation containing chitosan and HPMC at a ratio of 5:1 demonstrated 95.89% drug release at the end of 24 hours and the release kinetics followed zero order.[25]

SEMISYNTHETIC POLYMERS IN MATRIX PATCHES

Hydroxypropyl methylcellulose (HPMC)

HPMC, a semi-synthetic polymer belongs to the category of hydrophilic and swellable polymer. Apart from its extensive application in oral controlled drug delivery, HPMC has also been explored to fabricate a matrix type of transdermal patches. HPMC has the potential to yield clear films due to the adequate solubility of polar drugs in the polymer. A phenomenon namely the burst effect has been observed in the case of matrices of HPMC without a rate-controlling membrane. HPMC chain dissolution from the matrix surface involves two distinguishable steps. The first step involves changes in the entanglement of individual polymer chains at the matrix surface, which depends on the rate of hydration. The second step involves the diffusion of drug molecules from the surface of the polymeric matrix structure to the bulk of the medium.[26-29]

Guyot et al. (2000) formulated an adhesive matrix for transdermal delivery of propranolol by employing two different polymers HPMC and polyisobutylene. Ucecryl polymer, an acrylic polymer was employed as an outer rate-controlling membrane. Propylene glycol used as a plasticizer was found to have a positive effect on the release rate of the drug. Moreover, it was observed that in the case of HPMC matrices without a rate-controlling membrane (12 mm thick Ucecryl layer) more than 70% of the initial drug load was released within the first hour whereas release from the coated matrices became more regular (reduction of the burst effect) and slow.[30] Garala et al. (2009) designed a transdermal therapeutic system of tramadol HCl using HPMC-Eudragit S100 (ES100) matrix film. Different trials were carried out by employing the concept of factorial design to optimize the proportion of HPMC and ES-100 required for the development of a sustained-release medicated patch. Drug release from the patch containing the lowest amount of HPMC (325mg) and the highest amount of Eudragit (525 mg) was found to be lowest at 58.96 ± 0.42 mg in 12 hrs. The maximum percentage of drug release (i.e. 80.25 %) was observed from the patch containing the higher proportion of the hydrophilic polymer, HPMC (i.e. 525 mg). Clopidogrel bisulfate has a short elimination half-life (7-8 hrs), low oral bioavailability (50%), undergoes extensive first-pass metabolism (85%) and frequent high doses (75 mg) are required to maintain the therapeutic level. TDDS matrix patches of clopidogrel bisulfate were formulated from HPMC, PVP, and EC by solvent evaporation technique for improvement of bioavailability of the drug and reduction of toxic effects. A drug diffusion study showed a maximum release of 90.06 % of drug from a patch containing HPMC and PVP at a ratio of 2 :1 in 24 hrs.[31]

Ethylcellulose (EC)

EC is a water-insoluble polymer used in controlled release dosage forms. As it cannot undergo swelling, EC compatibility becomes a key factor in such systems, as release kinetics would depend largely on the porosity of the hydrophobic compact. Although EC is considered insoluble, it can take up water. This is because of its hydrogen bonding capability with water. Drug release from a porous, hydrophobic polymeric drug delivery system occurs when the drug dissolves in the bulk fluid entering through the pores and diffuses out into the bulk through media-filled pores. Thus, the geometry and structure of the pore network are important. The Higuchi model has failed to explain drug release at drug loading levels below the percolation threshold. Below the percolation threshold, incomplete drug release is observed presumably due to the limited accessibility of several drug particles to the dissolution medium since they are encapsulated by water-insoluble polymeric materials. When the EC-based matrix patch comes into contact with an in vitro study fluid, thermodynamically compatible with the polymer, the fluid is absorbed into the polymer matrix which initiates the polymer chain dissolution process at a very slow rate. It is well known that the addition of a hydrophilic component to an insoluble film former increases the release rate constant. This may be due to the dissolution of the aqueous soluble component of the film, which leads to in situ formation of pores and a decrease in mean diffusion path length for the drug molecule to be released. Molecular diffusion through polymers is an effective, simple, and reliable means of attaining sustained/controlled release of a variety of active agents.[32-35]

Idress et al. (2014) attempted to formulate a matrix patch of flurbiprofen by employing EC as matrix former. Propylene glycol (PG) or dibutyl phthalate (DBP) was used as plasticizer and Span 20, Tween 20, sodium lauryl sulfate (SLS), isopropyl myristate (IPM) or ethanol (EtOH) were employed as permeation enhancer. The drug release from patches followed the Higuchi model where maximum drug permeation from the patch containing EC as matrix-forming polymer, DBP as plasticizer, and IPM as penetration enhancer was found to be 903 µg in 48 hrs.[36] Mukherjee et al. (2005) developed a suitable matrix type TDDS of dexamethasone using blends of two different polymeric combinations, PVP and EC and Eudragit with

PVP. In vitro dissolution studies showed that the drug distribution in the matrix was homogeneous and the SEM photographs corroborated the fact. The formulations of PVP: EC provided slower and more sustained release of drug than the PVP : Eudragit formulations during skin permeation studies and the formulation PVP:EC (1:5) was found to provide the slowest release of drug. Mean cumulative amount of drug permeating from the PVP:EC (1:5) patch after 20 h was found to be 0.080 mg/cm^2.[34] Shaker et al. (2013) formulated lornoxicam (LX) matrix patches by employing different ratios of two polymer combinations i.e ethyl cellulose and Eudragit E100 (E100) and ethyl cellulose and PVP. Iso propyl myristate (IPM) and oleic acid were used as plasticizers. The maximum flux values observed for the patches containing EC: E100 (1:1) + 20%IPM and EC: PVP (1:1.6) + 10 % oleic acid were found to be 43.124±3.9 (µg/cm^2/h) and 21.7±0.35 (µg/cm^2/h) respectively. Therefore, both the polymer combinations containing suitable plasticizer could be used for developing matrix type TDDS exhibiting controlled drug release.[37]

SYNTHETIC POLYMERS IN MATRIX PATCHES

Eudragit (acrylic acid polymer)

Eudragits are copolymers of methacrylic acid which can be either water-soluble such as Eudragit L,S, and E or insoluble like Eudragit RS, RL. Eudragit RL 100, Eudragit RS 100, Eudragit NE 40D, E-100 etc. have been used in various studies to formulate transdermal patches. All of these different grades of Eudragit are hydrophobic in nature.[38] A detailed comparative profile for different grades of Eudragit polymers commonly used in a matrix type of patches is presented in Table 1.

Table 1: Properties of Different Grades of Eudragits Used in Matrix Patches [39-42]

POLYMER	ERL 100	ERS 100	E- NE 40D	E100
Effect on the drug release profile	Enhanced drug release or flux as compared to ERS 100	Retards drug release / flux	Retards drug release from patch.	Retards drug release and flux
Solubility in organic solvents	Methanol:acetone (20:80), Ethanol: acetone (6:4). Ethanol, Chloroform, Dichloromethane: methanol (1:1) Dichloromethane:ethanol (1:1)	Soluble mainly in chloroform, ethanol	Soluble in acetone, methanol	Soluble in acetone, alcohol, chloroform
Drug	Carvedilol	Glibenclamide	Sotalol	Ondansetron
Performance of optimized formulation	Maximum flux found to be 300 µg/cm^2 in 24 h from patch containing ERL100 and ERS100 in the ratio of 8:2.	The maximum cumulative amount of drug permeation (254.58 ± 15.52 µg) was observed in case of patch containing ERL:ERS at a ratio of 4:1	Effect of Release Promoter (RP) (adipic acid) was studied on the formulation containing ERL 100: NE40D as 343 : 860 (in mg) since it showed slowest release. The released amount of sotalol was increased to 1200 µg/ cm^2 in 8 h due to the addition of RP.	Patch containing Eudragit E100: PVP at a ratio of 5:1 along with succinic acid as release promoter exhibited highest % of drug release i.e. 57.27 % in 8 hrs.
Reference	Udhumansha Ubaidulla et al.	S. Mutalik, N. Udupa	Ozge inal, Evren algin yapar et al.	David et al.

Baviskar et al.(2014) designed a matrix-type transdermal drug delivery system of lornoxicam with ethyl cellulose: polyvinylpyrrolidone and Eudragit RL 100: Eudragit RS 100 in different ratios with propylene glycol as plasticizer (5%) and Tween 80 as permeation enhancer using the solvent evaporation. technique. It was found that ethyl cellulose: Polyvinylpyrrolidone and Eudragit RL 100: Eudragit RS 100 can be successfully utilized for formulating transdermal patches of lornoxicam to sustain its release characteristics and to avoid disadvantages of oral routes. ERL 100; ERS 100 and EC;PVP were employed at three different ratio i.e. 4:6; 5:5; 6:4. Optimized patches containing EC:PVP in the ratio of 4:6 and ERL100 : ERS100 as 6:4 exhibited maximum (311.04 µg/cm^2 and 306.32 µg/cm^2, respectively) cumulative amount of drug permeated in 24 h following Higuchi kinetics. The patches also exhibited greater values of tensile strength (0.538 ± 0.063 kg/mm^2 and 0.509 ± 0.059 kg/mm^2, respectively). The data indicate the patches to be strong and flexible. Thus, higher proportion of ERL 100 resulted in better drug permeation profile.[43] Chandak et al.(2010) developed a matrix-type transdermal formulation of pentazocine using Eudragit RL/RS. Folding endurance values of matrix films were found within 100 and 150, indicating good strength and elasticity. The endurance values decreased with the increase in Eudragit RS content of the matrix films. Moreover, moisture uptake was found

to decrease with decreasing content of Eudragit RL (permeable) in the matrix In-vitro drug release study revealed that, with an increase in the proportion of Eudragit RS (slightly permeable) type polymer, $t_{1/2}$ increases and release rate constant decreases. The rate constant was found to be highest (6.548 $h^{-1/2}$) in the case of a formulation containing only ERL100 and it decreased to 2.282 $h^{-1/2}$ in patch containing only ERS100. The formulated patches were found to follow Higuchi release kinetics.[38] Jafri et al. (2019) attempted to develop lamotrigine matrix patch by employing Eudragit RS100 as a rate-controlling polymer and DuroTak® 387-2510 as an adhesive. The impact of the addition of different permeation enhancers (PE) such as oleic acid, lemon oil, and aloe vera on permeation profile was studied. A formulation consisting of oleic acid as PE exhibited a maximum flux of 0.916 mg/cm^2/h.[44]

Polyvinyl pyrrolidone (PVP)

Polyvinyl pyrrolidone (PVP) is basically a water-soluble polymer obtained by the polymerization reaction of monomer namely N-vinyl pyrrolidone. PVP is a water-soluble, inert, non-toxic, biocompatible and biodegradable polymer. These advantages render PVP a versatile ingredient in the formulation development of broad conventional to controlled drug delivery systems. PVP is also found to be suitable for transdermal patches due to its inherent film-forming characteristics. However, the challenges associated with the use of PVP include its inherent hydrophilicity and hygroscopicity issues. Due to this hygroscopic nature, PVP films exhibit high water vapor absorption which in turn leads to microbial contamination thereby making the medicated patches practically unusable or even harmful. To overcome these issues and to improve the properties and performance, PVP was blended with EC.[45,46]

Sadashivaiah et al.(2008) fabricated transdermal patches loaded with haloperidol, by using PVP K30 and EC as film-forming polymers. To produce films at different PVP/EC ratios (from 1:4 to 4:1 *w*/*w*), dibutyl phthalate and hyaluronidase (4% *w*/*w*) were added as plasticizers and permeation enhancers, respectively. The drug release rate increased by increasing the concentration of hydrophilic PVP in the EC films since the addition of the hydrophilic polymer to the insoluble EC led to the formation of pores in the film in contact with the dissolution medium. The higher dissolution rate of haloperidol was also attributed to the PVP anti-nucleating effect, as also indicated in another study. The patch containing PVP: EC in the ratio of 2:1 exhibited the highest cumulative % of drug release of 88.35% lasting one day.[47] Gupta et al. (2003) attempted to develop matrix patches of diltiazem by employing various ratios of PVP and EC. Dibutyl phthalate was used as a plasticizer. A comparison of the average rate constants revealed lower rates of release of the drug from the patches containing PVP: EC in the ratios of 3:2, 2:1, and 1:2. Amongst the three patches, the formulation with PVP: EC at 1:2 exhibited a much more satisfactory release profile towards zero-order kinetics with a cumulative drug release of 3.9117 µg in 24 hrs.[48] PVP was also blended with polymerized rosin, a solid resin naturally obtained from pine trees, poorly evaluated for transdermal delivery despite its good film-forming property. Moreover, Satturwar et al.(2005) fabricated a matrix patch of diltiazem hydrochloride by loading it in PVP/resin films (4: 6, 3:7, and 2:8 *w*/*w*). It was observed that the moisture content and the water absorption capacity of patches increased by increasing the concentration of the hydrophilic PVP. The formulation containing polymerized rosin and PVP at a ratio of 6:4 exhibited the highest tensile strength of 0.393 ± 0.06 N/mm^2 The in vitro drug permeation tests proved that the permeation of the drug across the skin improved by increasing the PVP concentration in the formulation. The formulation containing polymerized rosin and PVP at a ratio of 6:4 exhibited the highest cumulative amount of drug permeation of 26.23 µg after 24 hours.[49] Arora et al. (2015) formulated a transdermal patch containing diclofenac as a drug and a combination of EC and PVP as polymers. Only 50% of the drug was released in 24 hrs for the patch containing PVP: EC at a ratio of 1:2. Drug release was found to follow zero-order kinetics. Increase in proportion of EC retarded drug release.[50]

POLYMER BLENDS IN TDDS MATRIX PATCHES

It is evident from several studies that the use of a blend of polymers leads to the creation of several diffusion pathways to achieve desired steady and sustained drug release profile from patches as compared to the use of a single polymer in a matrix type of patches. In this context, a blending of polymer becomes the only option as there is a report of burst release when the hydrophilic polymer is used. Alternatively, sufficient therapeutic concentration, required to elicit the pharmacological action, is difficult to achieve in the case of patches containing only hydrophobic polymer. Therefore, a blend of polymers becomes effective to enable the controlled release of drugs from the matrix patches. Moreover, proper selection of polymer blend and optimum ratio of the constituents may produce patches of desirable physio-mechanical properties, especially folding endurance, tensile strength, water vapor transmission rate, etc. Some of the commonly employed blends that have been used in the fabrication of matrix patches are described in the following section.

Cellulosic Blends in Matrix Patches

Ekapol Limpongsa and Kraisri Umprayn (2008) developed diltiazem hydrochloride transdermal drug delivery systems. The mechanical properties of blank films prepared from various ratios of HPMC and EC with and without plasticizer were characterized. Two different plasticizers namely dibutyl phthalate and triethyl citrate were used in the study. Plasticization of hydrophilic polymers like HPMC with a hydrophobic plasticizer provided a higher strength as compared to those of the hydrophilic polymer film plasticized with a hydrophilic plasticizer. The addition of EC into the HPMC film resulted in a lower tensile strength, percent elongation at break, and Young's modulus. Therefore, the presence of EC might have been responsible

for the lower strength and elongation when compared to HPMC alone. This may be attributed to the hydrophobic nature of EC owing to the presence of a long-chain of anhydrous glucose unit (AGU) linked together with acetal linkage. However, it was observed that plasticization with dibutyl phthalate (DBP) produced higher strength but lower elongation as compared to triethyl citrate. In this study, the influence of the addition of permeation enhancers including isopropyl myristate (IPM), isopropyl palmitate (IPP), N-methyl-2-pyrrolidone, oleic acid, polyethylene glycol 400, propylene glycol, and Tween 80 on permeation was evaluated. Finally, it was concluded that the patch composed of HPMC; EC at a ratio of 8:2 with 30% DBP as a plasticizer and 10% IPM, IPP, or Tween 80 and loaded with 25% diltiazem HCl was found to fulfill the goals of the formulation. The mentioned optimized patch with 10% IPP as permeation enhancer showed the maximum cumulative permeation of diltiazem HCl i.e. 2.5 mg/cm^2 in 12 hrs.[51] Parthasarathi. et al. fabricated the matrix-type transdermal patches bearing naproxen using various ratios of EC and HPMC (2:8; 8:2; 4:6; 6:4). The combination of EC and HPMC in a ratio of 2:8 and 4:6 showed the highest cumulative drug release i.e. 2400 and 2200 µg/cm^2 respectively in 24 hrs. From the release studies, it was observed that increasing the proportion of HPMC enhanced the cumulative amount of drug release owing to the hydrophilic nature of HPMC. The decrease in drug release rate from films containing more lipophilic polymer combinations may be attributed to the relatively hydrophobic nature of polymer which has less affinity for water, thereby resulting in a lowering of thermodynamic activity of the drug in the film and consecutive drug release. Moreover, it was also observed that the tensile strength of formulated patches increased with increase in the proportion of ethylcellulose and the highest tensile strength (2.84 kg/cm^2) was observed in case of patch containing EC: HPMC at a ratio of 8:2. [52]

Cellulosic-Acrylic Blends in Matrix Patches

Vijaya et al. (2012) formulated amitriptyline hydrochloride matrix patches involving Eudragit RL 100 and HPMC polymers. Dibutyl phthalate was used as a plasticizer. The data obtained from in vitro drug release study revealed that the patch containing Eudragit RL 100 and HPMC at a ratio of 2:1 produced the highest drug release of 98 ±1.03% in 24 h. Drug release followed the Higuchi model with a diffusion-controlled mechanism.[53]

Thenge et al. (2010) formulated matrix type transdermal patch of lercanidipine using Eudragit RS 100 – HPMC and Eudragit RS 100 – EC. In this study, propylene glycol was used as a penetration enhancer and dibutyl phthalate was used as plasticizer. It was also observed that the folding endurance value of prepared patches increased with an increase in EC content in patches and maximum folding endurance was found to be 250 in the case of a patch containing ERS100:EC at a ratio of 3:7. Eudragit RS 100 – HPMC (at a ratio of 3:7) containing patches were found to be more suitable and released 96.23 % of the drug over a period of 24 hours following zero-order kinetics.[54] Gannu et al. (2007) formulated nitrendipine matrix patches composed of a blend of Eudragit RL 100 and hydroxypropyl methylcellulose in the ratios of 5:0, 4:1, 3:2, 2:3, 1:4 and a blend of Eudragit RS 100 and hydroxypropyl methylcellulose in the same ratios. All formulations contained 6 % v/w of carvone as penetration enhancer and 15% v/w of propylene glycol as a plasticizer. The formulation containing ERL100: HPMC at a ratio of 2:3 exhibited the highest cumulative drug permeation of 2300 µg/cm^2 in 24 hrs. Moreover, the in vitro drug release study also revealed the highest cumulative percentage of drug release (89.29%) in 24 hrs.[55] Shafique et al. (2021) attempted to develop a transdermal drug delivery system (TDDS) containing ketoprofen (KTF) and pregabalin (PGB). In this study, the hydrophilic polymer (HPMC) and hydrophobic polymers (Eudragit L-100 and ethylcellulose) were employed for the formulation of transdermal patches. Propylene glycol and oleic acid were used as permeation enhancers and PEG-400 was employed as a plasticizer. In vitro drug permeation studies exhibited more than 97% and 95% release of PGB and KTF, respectively. Moreover, this study also revealed that in the case of pregabalin patches containing HPMC and EC, higher permeation was observed when the proportion of HPMC was kept higher than the EC. Similarly, the patches containing HPMC and Eudragit L-100 exhibited higher permeation when the proportion of Eudragit L-100 was kept lower as compared to that of HPMC. A similar pattern was observed with the release of ketoprofen from the two types of patches.[56]

EC-PVP Blends in Matrix Patches

Mukherjee et al. (2004) formulated dexamethasone transdermal patches where a comparison was made between Povidone-ethyl cellulose and Povidone-Eudragit combination and higher drug release occurred from Eudragit containing patches due to the formation of larger cavities in comparatively hydrophilic polymeric network enabling faster diffusion of drug. From PVP-EC patches cumulative percentage of the drug that permeated following zero-order kinetics was 50 µg/cm^2 in 24 hours. Thus, for controlled drug release, PVP– EC polymers are better suited over PVP–Eudragit combination for the development of TDDS of dexamethasone.[34] Yousuf et al. (2020) formulated matrix type transdermal patches of ketotifen fumarate where the patch containing PVP and EC in ratio of 1:1was found to be suitable which released 76.49% drug at the end of 24 hours.[57] Rastogi et al. (2015) fabricated glibenclamide matrix type patch by employing EC and PVP K-30 at various ratios. Olive oil and mustard oil were used as a penetration enhancer. Di-butyl phthalate was used as plasticizer. Formulation containing EC: PVP K-30 at a ratio of 8:2 and 10%w/w of olive oil exhibited the highest % of drug release of 94.22±2.93 in 12 hrs. and flux was found to be 311.4±3.68 µg/cm^2/h.[58]

MISCELLANEOUS POLYMER BLENDS IN MATRIX PATCHES

Shah et al. (2010) formulated patches of papaverine hydrochloride by the solvent casting method using ethyl cellulose: PVP, PVA: PVP, and Eudragit RL-100: Eudragit RS-

100 using different ratios. Propylene glycol was used as a plasticizer and DMSO was used as permeation enhancer. It was observed that the formulation containing PVA: PVP at a ratio of 2: 1 exhibited the highest cumulative % drug release of 49.83 % in 24 hrs.[59]

Vijaya R et al. (2015) formulated repaglinide matrix patch by employing a blend of Eudragit E100 and polyvinylpyrrolidone (PVP). The films were prepared by solvent evaporation technique. Effect of plasticizer concentration (20, 30, and 40%w/w), penetration enhancers (menthol and oleic acid) on drug release and permeation were studied. The in-vitro drug release study revealed that formulation containing 30 % w/w propylene glycol as plasticizer in the film exhibited higher drug release of 93.26 % in 14 h and the release was found to follow Higuchi kinetics with diffusion mediated mechanism. The formulation containing Eudragit E100 and PVP (7:3) along with 5% menthol as enhancer exhibited highest flux of 0.019 mg/cm^2/hr.[60] Akram et al. (2018) fabricated transdermal matrix patches of glimepiride using polymeric blend of ERL100 and ERS 100. Dibutyl phthalate was used as plasticizer. Five different PE (isopropyl myristate [IPM], Span® 80, Tween® 20, eucalyptus oil, and limonene) were added at three different concentrations of polymer (2%, 5%, and 10% w/w) in order to enhance permeation through rabbit skin. The in-vitro drug permeation study revealed that the formulation containing ERL100: ERS100 at a ratio of 7:3 and 10% w/w of IPM as PE exhibited the maximum flux of 51.763 µg/cm^2/hr, and the enhancement effect of different enhancers on glimepiride permeation through rabbit skin was found to be in the rank order of IPM > eucalyptus oil > Span® 80 >Tween® 20> limonene.[61] Thus, discussion on the various polymer blends used in the fabrication of matrix type transdermal patches has laid down some key points which can guide formulation development scientists in the future in the selection of the right polymer blend for a matrix patch. Among various semi-synthetic polymers, HPMC belongs to the category of swellable and hydrophilic polymer. From several studies, it has been observed that it is difficult to control the release rate of drug by employing HPMC alone without any rate-controlling membrane due to the burst release phenomenon. Moreover, moisture absorption study has revealed that the percentage moisture absorption of patches increases with the increase in the proportion of polymers like HPMC or PVP, which in turn leads to the increase in the possibility of microbial attack or microbial contamination. Moreover, the physio-mechanical characteristics of patches containing HPMC in higher proportion are inferior.[62-70] Therefore, HPMC should be combined with suitable other polymers to produce patches of desirable physio-mechanical characteristics and release profiles. Similarly, EC should be blended with a hydrophilic polymer such as PVP to achieve good control over the release profile so that a sufficient amount of drug is released to elicit the required therapeutic action. It has also been observed that PVP plays a significant role in improving the physio-mechanical properties such as tensile strength, folding endurance, etc. Among the acrylic polymers commonly investigated in the fabrication of matrix patches, Eudragit RL 100 has been found to promote a drug release profile as compared to ERS-100. The reason can be attributed to the fact that ERL-100 contains a higher proportion of hydrophilic quaternary ammonium group which is responsible for the swelling of the film and the generation of high ionic repulsive force with the incorporated ionized drug molecule thereby, enhancing the diffusivity and the corresponding release profile of drug from patches. ERL 100 is also reported to improve the physio mechanical properties of the patches.[71-77]

CONCLUSION

Polymers are the backbone of the transdermal drug delivery system. As per the results obtained from the in-vitro drug release studies of patches that have been reported in the literature, it can be concluded that the use of a combination of polymers is more effective than the use of a single polymer to achieve the satisfactorily controlled drug release profile. In this context, some factors those need to be considered include a selection of appropriate polymer blend, compatibility of the polymer blend with drug and other components such as plasticizers, penetration enhancers, etc., and determination of the optimum ratio of polymer blend that results in the formation of flexible transdermal patches having sufficient physio-mechanical properties. Patches containing this optimized ratio of polymer blend must be capable to release the drug in a controlled manner for a prolonged period of time. The present article aims to compile up-to-date information on the exact drug release mechanism followed by different types of polymers at the molecular level, advantages of using polymer blend over a single polymer to design transdermal patches, instances of polymer blend reported to fabricate suitable transdermal patches.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.