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Hypromellose-based films and film-forming systems for topical application: current status and perspective in drug delivery

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Abstract

Films and film-forming systems (FFS) are increasingly recognized for their potential as convenient carriers for precise and efficient drug delivery to or *via* the skin and mucous membranes. Among them, those based on hypromellose as a film-forming polymer demonstrate many favorable characteristics. To better understand the role of hypromellose in topical films and film-forming drug delivery systems, this review presents physicochemical characteristics and film-forming performances of different types of hypromellose. Furthermore, the review encompasses relevant studies demonstrating the broad application of hypromellose as a film-forming agent in films and FFS for dermal, oromucosal, vaginal, ocular, and nasal application, reflecting the growing interest of researchers in this field. It also highlights the observed advantages of hypromellose over other film-forming polymers and implies future development of films and FFS in general.

Key words: film, film-forming systems, drug delivery, hypromellose, topical application

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Introduction

The development of films and FFS as topical dosage forms represents a significant advancement in drug delivery, allowing for targeted and efficient treatment. Films and FFS show differences in their application manner: films are pre-formed and applied directly, whereas FFS create a film on the application site (*in situ*) through solvent evaporation. Common ingredients in both dosage forms are film-forming polymers, non-volatile solvents (plasticizers), and active ingredients. In addition, FFS contain volatile organic solvents, which are removed from pre-formed films by drying. Polymers provide structure, while plasticizers ensure the flexibility of the film. Active ingredients can be incorporated as a dispersion or solution within the polymer matrix. Additional ingredients, such as permeation enhancers, saliva-stimulating agents, colorants, and sweeteners, could be added to improve drug delivery performances for a particular administration route or patient acceptance (1-3).

In situ FFS and films offer several advantages over traditional topical preparations. They provide targeted delivery to inaccessible sites (e.g., oral, nasal, ocular, vaginal mucosa) where the application of solid dosage forms (e.g., orodispersible tablets, vaginal tablets) and semi-solids is challenging, improving drug onset, reducing dosing frequency, and enhancing drug efficacy. In systemic applications, they ensure consistent plasma drug concentrations *via* drug crystallization prevention, prolonged contact with the skin/mucosa and sustained release of the active substance, beneficial for drugs with short half-lives needing frequent dosing, hence maximizing therapeutic efficacy. In addition, they could effectively minimize drug side effects and metabolism by proteolytic enzymes. Mucoadhesion of thin films and FFS on mucous membranes or their non-sticky nature, bioadhesion and easy removal from the skin, improve patient comfort compared to rough, sticky patches, ointments, creams and gels. Non-invasive application and ease of handling enhance patient adherence to therapy, contributing to greater therapeutic success (1-4).

Despite their advantages, films and FFS have some limitations. Films typically cannot contain drug doses larger than 10 mg, limiting their application for drugs requiring higher dosages. They are also less suitable for drugs with long half-lives because the sustained release mechanism of thin films may not effectively match the drug's pharmacokinetics, potentially leading to either inadequate drug levels or accumulation in the body over time and increased risk of side effects. Incorporating hydrophilic drugs into films may not achieve systemic therapeutic levels due to inadequate skin/mucous membrane penetration. Variations in skin and mucosal barrier functions between individuals and intraindividual variability, particularly with age, can affect the consistent delivery of drugs *via* topical dosage forms including films. Additionally, the drug penetration, permeation and absorption from both pre-formed and *in situ* formed films could be affected significantly by the conditions at the application site, such as hydration and temperature, which can influence its effectiveness. Moreover, films have been associated with potential local adverse reactions like itching, erythema, or swelling, which may affect patient comfort and adherence to treatment. These factors may underscore the

considerations needed when utilizing films and FFS for drug delivery, and therefore these aspects must be carefully considered during pharmaceutical development (4).

Both film and FFS carriers can be based on a single polymer or a mixture of polymers. Polymers' ability to produce a thin, flexible, transparent, and mechanically resistant film is crucial for formulation's substantivity at the application site and drug delivery performance (2, 4, 5). Polymers act not only as film-forming agents, but also as drug release controllers. Additionally, polymers may prevent crystallization of the active pharmaceutical ingredient and crystal growth (3). The variety in polymer types has enabled the modification of key characteristics of films and FFS, such as drug release rate, bioadhesive properties, and mechanical strength of films. Consequently, in order to maximize the potential of polymers in the development of films and FFS, it appears that an extensive knowledge of their chemistry, rheology, and physicochemical properties is required (1).

Polymers used for film formation can be classified into three main groups based on their origin and chemical nature: natural, semi-synthetic, and synthetic polymers (3). Polysaccharides, particularly natural ones, have been at the forefront of drug delivery research due to their advantageous qualities. These include non-toxicity, biocompatibility, biodegradability, polyfunctionality, bioadhesion capability, environmental friendliness, as well as sustainability and renewability (6). Being the most prevalent biopolymer in nature, cellulose is a renewable and biodegradable material that serves as a consolidating agent in bacteria and plants. Cellulose is a linear polysaccharide consisting of repeated units of cellobiose, a mixture of two anhydroglucose rings connected by a β-1,4 glycosidic bond (7). However, natural polymers have several drawbacks, including a risk of microbial contamination, low mechanical strength, decreased viscosity during storage, and an unregulated rate of hydration (6). Cellulose, being inherently hydrophilic, water-insoluble, and having poor film-forming capacity and high crystallinity, cannot be used in its natural state. Therefore, cellulose derivatives such as hypromellose, carmellose, methylcellulose, ethylcellulose, hydroxypropylcellulose and hydroxyethylcellulose have been developed to overcome these limitations and enhance their utility in various biomedical applications (7). Recently, hypromellose has gained importance as a film-forming polymer in *in situ* FFS and films for topical applications (i.e., skin, mucous membranes) (8-16). The United States Food and Drug Administration (FDA) has classified hypromellose as a generally recognized as safe (GRAS) additive. Hypromellose has received FDA approval for use as a food additive and as a pharmaceutical excipient (17). In both types of products, dietary supplements and drugs, hypromellose is traditionally used as an emulsifier, film-forming agent in solid oral dosage forms, protective colloid, stabilizer, and suspending agent, or to increase the viscosity of liquid and semi-solid formulations (18). Hypromellose is a pharmaceutical excipient that can have various functions depending on the route of administration and the dosage form: dispersing agent, binder, viscosity-increasing agent, film-forming agent, or polymer matrix (17). Hypromellose is widely used in oral and topical formulations. In pharmaceutical preparations for oral administration, hypromellose is predominantly used

as a binder in tablets, for tablet coating, and as a matrix in sustained-release tablets. At concentrations of 2–5% w/w, it can be used as a binder in wet or dry granulation processes. Aqueous solutions of hypromellose at concentrations of 2% to 25% w/w are used for tablet coating solutions. For this purpose, lower viscosity hypromellose is used for making aqueous solutions for tablet coating, while higher viscosity hypromellose is used with organic solvents. It is also used in liquid preparations for oral administration as a suspending and/or viscosity-increasing agent at concentrations of 0.25% to 5% (17). Some types are used in concentrations of 10% to 80% w/w to form monolithic matrices for achieving sustained release of active substances. In amorphous solid dispersions, hypromellose stabilizes poorly soluble drugs and enhances bioavailability by preventing their crystallization. In conventional topical formulations such as creams and gels, hypromellose serves as an emulsifier, suspending agent and/or thickener. Aqueous solutions of hypromellose exhibit greater transparency compared to methylcellulose, making them a more common choice in ophthalmic formulations like eye drops and artificial tears. In commercial nasal formulations, such as nasal drops and nasal sprays, hypromellose is used as a viscosity-increasing agent at a concentration of 0.1%. It is also used as an adhesive in transdermal patches. Hypromellose is also considered a mucoadhesive excipient in orodispersible tablets to prolong residence time in the oral cavity (17). Hypromellose, as a film-forming agent, can form films with moderate bioadhesive properties within concentration range from 2% to 20%. This makes it suitable for controlled or delayed drug release applications, producing a lightweight, non-greasy film with a smooth texture (1). Films containing hypromellose exhibit moderate tensile strength, moisture and oxygen barrier properties, elasticity, transparency, and resistance to oils and fats (4). As a hygroscopic polymer, hypromellose attracts and retains water, which can enhance dispersion and lubricity, as well as providing a comfortable feel when applied to the skin (2).

Hypromellose offers advantages in ease of formulation because it has minimal interaction with other substances, unlike polymers such as povidone, chitosan and acrylate copolymers, which are more prone to forming bonds or complexes. Economically, hypromellose is less expensive than synthetic polymers such as polymethacrylates copolymers (Eudragit®), which are costly due to their complex synthesis and specialized applications. In addition, hypromellose is considered sustainable because it is derived from cellulose, a renewable resource, and is biodegradable, unlike synthetic polymers such as Eudragit® and polyvinyl alcohol, which are made from petrochemical sources and have a higher environmental impact. Films and FFS containing hypromellose have a balanced performance, offering optimal mechanical properties, adhesion and flexibility, whereas other polymers usually stand out with specific properties, with Eudragit® offering superior mechanical properties, and chitosan or alginate offering exceptional adhesion properties (2, 5, 19).

Physicochemical characteristics of hypromellose

Hypromellose (Figure 1) is a semi-synthetic ether of cellulose. Specifically, it represents a modification of alkaline cellulose, which occurs when purified wood pulp is treated with sodium hydroxide solution. The methoxy group (-OCH_3) and hydroxypropoxy group (-$OCH_2CH(CH_3)OH$) are introduced into the molecule by treating alkaline cellulose with methyl chloride and propylene oxide, respectively. The current edition of the European Pharmacopoeia (Ph. Eur.) describes hypromellose (hydroxypropylmethylcellulose) as partially O-methylated and O-(2-hydroxypropylated) cellulose (17, 20).

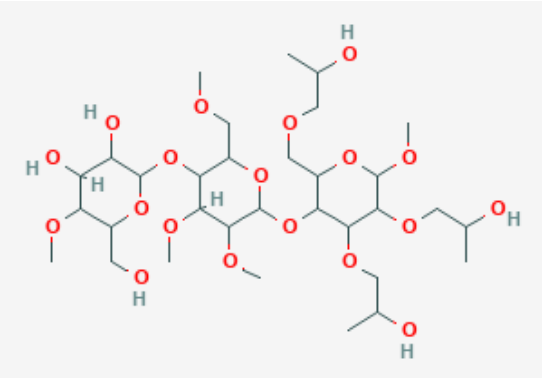

Figure 1. Chemical structure of hypromellose (21)
Slika 1. Hemijska struktura hipromeloze (21)

Both Ph. Eur. and the United States Pharmacopeia (USP) classify four types of hypromellose based on the relative content of methoxy and hydroxypropoxy groups, denoted as hypromellose 1828, hypromellose 2208, hypromellose 2906, and hypromellose 2910. The first two digits indicate the percentage of methoxy groups, while the last two digits indicate the percentage of hydroxypropoxy groups, determined after drying at 105 °C for 2 hours. Exact substitution degree limits defining each type of hypromellose are provided in Table I (20, 22).

Table I Content of methoxy and hydroxypropoxy groups in hypromellose of different substitution degrees according to Ph. Eur. 11.0 (20)

Tabela I Udeo metoksi i hidroksipropoksi grupa u hipromelozi različitog stepena supstitucije prema Ph. Eur. 11.0 (20)

Substitution degree	% methoxy groups	% hydroxypropoxy groups
1828	16.5 – 20.0	23.0 – 32.0
2208	19.0 – 24.0	4.0 – 12.0
2906	27.0 – 30.0	4.0 – 7.5
2910	28.0 – 30.0	7.0 – 12.0

On the market, hypromellose is available under various commercial names, such as Methocel® (DuPont, USA), Metolose® and Pharmacoat® (Shin-Etsu Chemical Company, Japan), and Benecel® (Ashland, Netherlands). There is also a new type of hypromellose called Affinisol® (DuPont, USA), which offers enhanced solubility for poorly soluble drug substances in formulations resulting from thermally demanding processes, such as melt extrusion (19). Methocel® brand hypromelloses are designated with letter codes J, K, F, and E, according to the pharmacopoeial classification based on the degree of substitution (1828, 2208, 2906, and 2910, respectively). The number following the letter code refers to the viscosity (expressed in mPa·s) of a 2% aqueous solution of hypromellose at 20 °C, with the letter "C" indicating a multiplier of 100, or the letter "M" indicating a multiplier of 1000. Different suffixes, such as "LV" or "CR", are used to identify specific types of hypromellose, indicating low viscosity hypromellose or hypromellose for controlled release of the active substance, respectively. "Premium" products are those that meet USP requirements and are suitable for tablet coating. For example, Methocel® E5 Premium LV represents an E-type cellulose ether, and the viscosity of a 2% aqueous solution of this polymer at 20 °C is around 5 mPa·s, indicating very low viscosity and compliance with the USP requirements. The viscosity of the polymer solution is directly proportional to the average molecular weight of the polymer. Therefore, the viscosity information provided by the supplier can offer some insight into the average molecular weight of hypromellose (18). The molecular weight of hypromellose varies and usually ranges from about 10000 g mol^{-1} to 1500000 g mol^{-1} (17). Ph. Eur. lists viscosity and the degree of substitution as functional characteristics of this excipient when used as a binding agent, viscosity enhancer, and film-forming agent. However, when used as a matrix-forming agent in extended-release tablets, in addition to the previously mentioned characteristics, the distribution of molecular weight, particle size distribution, and flowability are also identified as functional characteristics of hypromellose (20).

Hypromellose is a white powder with possible traces of yellow or gray color, but without a distinct odor or taste. It belongs to the group of amorphous polymers, meaning it does not have a clearly defined crystalline structure. This amorphous nature of hypromellose is often considered desirable in pharmaceutical formulations because it can contribute to increased solubility and bioavailability of active substances. Thanks to its nonionic nature, hypromellose poses a lower risk of potential interactions with other excipients and active substances. Additionally, it is particularly important for drug release that the hypromellose matrix remains unaffected by the pH of fluids in the gastrointestinal tract. This characteristic is crucial, considering that the polymer should remain unchanged under the influence of electrolytes and proteins/enzymes in bodily fluids (18, 19).

Hypromellose dissolves in cold water, forming viscous, colloidal solutions. However, it is practically insoluble in hot water, chloroform, ethanol, anhydrous ethanol, ether, and toluene. Nonetheless, dissolution can be achieved in mixtures of ethanol and dichloromethane, methanol and dichloromethane, as well as in mixtures of water and alcohols (e.g., ethyl and isopropyl alcohol). Some types of hypromellose are also soluble

in mixtures of water and acetone, dichloromethane and isopropanol, and other organic solvents (17). The interaction of water molecules with the hydroxypropoxy groups of hypromellose can occur through hydrogen bonds, while so-called water "cages" are formed near the hydrophobic methoxy groups. This means that in the hydrophobic regions, the hydrogen bonds between water molecules are more rigid in terms of their rotation. Therefore, at lower temperatures, the hypromellose/water system is transparent, and the water molecules near the hydrophobic methoxy groups are organized into ordered structures. As the temperature rises, the kinetic energy of the system increases, and these hydrogen bonds gradually weaken until the water "cages" break and the methoxy groups are exposed to the environment. When the hydrophobic methoxy groups are in close proximity in the presence of water, they can engage in attractive hydrophobic interactions, contributing to the formation of a "physical network." This network consists of hypromellose chains linked through the described hydrophobic associations between methoxy groups. The cloud point is the temperature at which this phase transition occurs, and it often tends to decrease as the degree of substitution increases, due to favorable hydrophobic associations (18).

According to Ph. Eur., the expected pH value for a 2% aqueous solution of hypromellose ranges from 5 to 8 (20). It is important to note that hypromellose is hygroscopic and capable of absorbing moisture from the environment, which can affect its consistency and stability over time. Hygroscopicity depends on several factors, including chemical structure, molecular weight, and environmental conditions. In situations where precise moisture control is crucial during product development, it is necessary to consider the hygroscopic characteristics of hypromellose (17).

Despite its hygroscopic nature, hypromellose is generally considered a stable excipient. Hypromellose solutions are stable in the pH range of 3 to 11. Aqueous solutions of hypromellose undergo a reversible sol-gel transformation during heating and cooling processes. The gelation temperature varies between 50 °C and 90 °C, depending on the type and concentration of hypromellose. Below the gelation point, the viscosity of the solution decreases as the temperature rises, while above the gelation point the viscosity increases with increasing temperature. After cooling, the coagulated polymer can be redispersed by mixing. Aqueous solutions of hypromellose are relatively stable in the presence of enzymes, meaning that the viscosity of these solutions remains unchanged during long-term storage. However, aqueous solutions of hypromellose are susceptible to microbiological contamination, so it is often necessary to add a preservative to ensure microbiological stability over extended periods (17).

Hypromellose-based films and FFS as topical drug delivery carriers

In the context of films and FFS, topical application encompasses diverse methods, including (trans)dermal, oromucosal, vaginal, ocular, and nasal applications. Dermal and transdermal drug delivery is intended for localized treatment (often used to manage skin wounds or infections) or, occasionally, for systemic effects. Oromucosal drug delivery

includes administration across the buccal mucosa or using orodispersible films that dissolve in the oral cavity to achieve systemic effects. Vaginal drug delivery involves delivery of the drug to the vaginal mucosa for local treatment or infection prevention. Ocular administration targets surface treatment of eye conditions like glaucoma, while nasal drug delivery could be explored for delivering active substances to the brain. Various formulations of FFS and films for drug delivery following topical application have been investigated in prior research, as illustrated in Table II, with a specific emphasis on significant findings concerning hypromellose.

Table II Summary of studies on hypromellose-based drug delivery films and FFS

Tabela II Pregled studija o filmovima i FFS na bazi hipromeloze za isporuku lekovitih supstanci

Hypromellose type	Hypromellose concentration	Solvent	Active pharmaceutical ingredient	Key findings	References
Dermal and transdermal drug delivery					
Hypromellose 90SH (viscosity 15,000 mPa·s) (Shin-Etsu Chemical Co., Japan)	1% (w/w)	Water and ethanol	Miconazole nitrate	High miconazole nitrate release (up to 70%) from films for dermal antifungal treatments	(8)
Hypromellose (mw 10,000 g mol^{-1}) (Sigma Aldrich, Germany)	n.s.*	Water	Copper nanowires	High antibacterial efficacy of the hypromellose film against *E. coli* and *S. aureus*	(24)
Hypromellose (10,000 - 18,000 mPa·s) (Colorcon, UK)	4% (w/v)	Water and ethanol	*Ocimum basilicum* L. extract	Significant increase in films' antioxidant activity	(25)
Methocel® E4M CR, K4M CR and E10M CR Premium EP (Colorcon, UK)	n.s.	Isotonic phosphate-buffered saline	Horseradish peroxidase	Hypromellose E10M provides the greatest resistance and prolonged protein release	(26)
Hypromellose 2910 (Sigma-Aldrich, Germany)	0.4 – 1.6% (w/w)	Water	Curcumin	The initial rapid release initiates curcumin delivery at the wound site	(9)
Hypromellose E5 (Onimax, Thailand)	1 – 5%	Water and ethanol	*Piper nigrum* L. oil	Hypromellose E5 exhibited superior characteristics compared to PVP K30 in FFS	(29)

Metolose® 90SH-4000 (Shin-Etsu Chemical Co., Japan)	10 or 20% (w/w)	Water	Tramadol	Confirmed tramadol analgesic effect from hydrogel film	(27)
Hypromellose K15M (Biodeals Pharma, India)	n.s.	Water and ethanol	Telmisartan	Maximized dissolution of the poorly soluble telmisartan from films comprising triethanolamine	(28)
Hypromellose E5 (Onimax, Thailand)	n.s.	Water and ethanol	Nicotine	Controlled nicotine release and enhanced permeation through porcine skin	(10)
Oromucosal drug delivery					
Hypromellose (Colorcon, UK)	3% (w/w)	Water	Meloxicam	The films did not achieve the desired disintegration time and drug release	(36)
Walocel® HM 6 PA 2910, HM 50 PA 2910 and HM 4.000 PA 2910 (DowWolff Cellulosics, Germany) Metolose® 65SH-1500 (Syntapharm, Germany) Pharmacoat® 615 (Shin Etsu Chemical Co., Japan)	1.96 – 10.67%	1:1 mixture of water and ethanol 96%	Caffeine or caffeine citrate	Faster dissolution of orodispersible films based on hypromellose with caffeine/caffeine citrate compared to other polymers	(37)
Hypromellose (15 mPa·s or 50 mPa·s) (CDH Laboratories, India)	0.5 – 2% (w/v)	Water	Levocetirizine dihydrochloride	Orodispersible films exhibited faster onset of action compared to conventional tablets in treating allergic conditions	(39)
Hypromellose (Sigma Chemical Co., USA)	n.s.	Water	Donepezil hydrochloride	Rapid *in vitro* drug release and superior palatability	(40)

Hypromellose (Sigma Aldrich, Germany)	5 – 10%	Water and methanol	Escitalopram	Rapid *in vitro* drug release from orodispersible films	(41)
Hypromellose E15 (Colorcon, USA)	0.5 – 2% (w/w)	Water	Peanut skin extract	High and immediate release of phenolic compounds from hypromellose films	(12)
Hypromellose E5 or hypromellose E15 (Loba Chemie, India)	0.5 – 1% (w/v)	Water and methanol	Lercanidipine	Increased *in vitro* release of lercanidipine and *ex vivo* permeation through porcine buccal mucosa	(42)
Metolose® 90SH-4000 (Shin-Etsu Chemical Co., Japan)	1.5% (w/w)	Deionized water	Chlorhexidine	High hygroscopicity and swelling, promising prolonged mucosal retention	(11)
Vaginal drug delivery					
Methocel® K 100 M (Colorcon, UK)	n.s.	Water and methanol	Tenofovir	The addition of zein to hypromellose film provided sustained drug release for 120 h	(15)
Hypromellose (4000 mPa·s)	19.1%	Water	Dapivirine	Potent anti-HIV activity demonstrated *ex vivo* (human cervical explant tissue)	(16)
Methocel® E5 Premium LV, (DOW chemicals, USA)	6% (w/w)	Water	Tenofovir	Effectively reduce HIV-1 infection *ex vivo* (human ectocervical tissues)	(53)
Hypromellose E15 (B.S.T., India)	n.s.	Water	Abacavir	Higher plasma concentrations of abacavir compared to intravenous administration from the 3rd hour onwards	(54)

Ocular drug delivery					
Hypromellose (mw 1261.45 g mol^{-1} and viscosity 4,000 mPa·s) (Sigma Aldrich, UK)	0.5 – 1.5%	Water	Timolol maleate	Combining hypromellose with hyaluronic acid provide a more controlled and sustained drug release profile	(48)
Nasal drug delivery					
Methocel® E50 premium LV (Colorcon, China)	1 – 3% w/w	Water	Donepezil hydrochloride	Enhanced *ex vivo* donepezil permeation through rabbit nasal mucosa	(13)

*n.s. – not specified

Dermal and transdermal drug delivery

Films and FFS have been investigated for the local treatment of skin conditions such as psoriasis, eczema, infections, and other dermatological issues. Moreover, there are examples of films and FFS designed to allow drug absorption through the skin directly into systemic circulation, bypassing first-pass metabolism and enabling prolonged drug action by forming a drug reservoir in the skin (2, 4, 5, 23). Hypromellose has primarily been used as a film-forming polymer in formulations for dermal and transdermal delivery, particularly considered for wound healing, fungal infections, and pain relief (Table II).

Films made from hypromellose or hydroxyethylcellulose were evaluated regarding the *in vitro* release of miconazole nitrate and their mechanical characteristics (stretchability, adhesion, moisture behavior). The films that were prepared (one with hypromellose (1%) and the other two with hydroxyethylcellulose (2% and 3%)), were glossy or transparent. Mechanical testing revealed that hypromellose-based films were less elastic than hydroxyethylcellulose-based ones. According to the results of the films' water vapor absorption capacity and water vapor loss, the hypromellose film dried more slowly during the solvent evaporation process in comparison to the hydroxyethylcellulose films. Moreover, the films made with hydroxyethylcellulose had a substantially lower amount of volatile components, indicating that this polymer was more promising for the film carrier preparation. Using a Franz diffusion cell with a synthetic membrane and an acceptor medium at pH 7.4, the *in vitro* release of miconazole nitrate from the films was assessed. The release of miconazole nitrate was lower from hypromellose-based films, probably due to miconazole nitrate's low solubility in water, while the release from hydroxyethylcellulose-based ones was higher, yielding a release rate of up to 70% (8).

In order to create an antibacterial nanocomposite film with copper nanowires (very thin copper threads, generally with widths of a few nanometers) in wound treatment, hypromellose was used as a film-forming agent and macrogol 6000 as a plasticizer. With

human dermal fibroblasts, this film demonstrated excellent biocompatibility at low bactericidal concentrations (MBC). Because of their shape and larger effective size, which prevents them from penetrating cells and decreases their surface area when compared to spherical particles, nanowires exhibit lower cytotoxicity than previously studied copper nanoparticles, which showed higher cytotoxicity. This could be because of their reduced ability to cause oxidative stress and the production of reactive oxygen species (ROS). The film's antibacterial qualities were thoroughly assessed *in vitro*, demonstrating its effectiveness against both Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria when the film had 4.8% mass fraction of copper nanowires (24).

With the goal of promoting wound healing, hypromellose was used as the film-forming agent and basil (*Ocimum basilicum* L.) extract (OB) was added to the films. By employing the casting procedure, polymeric films were made using 4% hypromellose, 1% glycerol, and varying amounts of OB (15% and 30% in relation to the mass of hypromellose), whereas placebo films were made with just hypromellose and glycerol. The macroscopic homogeneity, transparency, flexibility, and break resistance of the films were observed. Furthermore, the films demonstrated significant hydrophilicity and dissolving ability in aqueous vehicles because of the polar character of hypromellose. Their water vapor permeability was also satisfactory, with a slight decrease after incorporation of the extract. Their swelling ability was good. Crucially, significantly increased antioxidant capabilities of the OB-loaded films compared to the placebo film were demonstrated (25).

The potential of hypromellose as a film-forming agent was examined in order to guarantee the continuous release of growth factors in the treatment of wounds. Since growth factors are frequently macromolecular compounds (fibroblast growth factor, molecular weight 16 000 g mol^{-1}, and vascular endothelial growth factor, molecular weight 45 000 g mol^{-1}), hypromellose film upon hydration forms a viscous gel that can effectively slow down the release of topically applied growth factors. The study used three different forms of Methocel® hypromellose (E4M CR, K4M CR and E10M CR Premium EP), and a model protein horseradish peroxidase (HRP) (1% w/w HRP, molecular weight 40 000 g mol^{-1}) was incorporated into films. This model protein was applied to wound dressing covers (Melolin) and its *in vitro* release was quantified using Franz diffusion cells. The protein was shown to leak rapidly at first, then gradually over the course of five hours. Melolin usage considerably reduced the rate of initial release but had no effect on sustained release ($p < 0.05$). Hypromellose E10M gels exhibits greater resistance to HRP release following hydration because of its higher molecular weight as opposed to E4M. HRP release from the same formulations did not significantly differ from the release profile of basic fibroblast growth factor from films on Melolin substrate made from hypromellose E4M, indicating that HRP may in fact be a suitable model for *in vitro* testing of basic fibroblast growth factor release from hypromellose films (26).

Mayet et al.'s study (9) focused on creating and analyzing films based on hypromellose combined with chitosan, with interpenetrated polymer networks in order to

promote wound healing. The films were made using citric acid and genipin, which was utilized as a chitosan cross-linking agent. Curcumin was used as the model active substance. The optimized films with 3% chitosan and 0.4% hypromellose were selected due to their excellent rheological (viscosity at a shear rate of 100 s^{-1}: 62.53 MPa) and mechanical properties (yield stress: 38.59 Pa). Curcumin *in vitro* release results revealed that 1.1 mg was released within the first hour, whereas *ex vivo* permeation studies through isolated rat skin delivered 2.23 mg of curcumin during the same period, indicating that the lipophilic nature of the skin has a significant influence on curcumin release. Moreover, mechanical characterisation and tensile strength study demonstrated that the film properties are highly influenced by the concentration of polymers and the degree of cross-linking. Films with more cross-linking had better mechanical characteristics, such as a higher Young's modulus, making them stiffer and tougher. Higher cross-linking, then, decreases penetration ability, since a denser network structure is formed.

Saingam et al. tested FFS containing hypromellose and povidone at concentrations ranging from 1–5% as carriers for black pepper oil (*Piper nigrum* L.). In order to maximize the local effect of piperine in reducing pain sensation at the application site, the formulations also contained plasticizers (propylene glycol and polyethylene glycol 400) and additives such methyl salicylate and menthol. The formulation which consisted of 2% hypromellose, 3% methyl salicylate, 1% menthol, 0.02% black pepper oil, 1% propylene glycol, 52% ethanol, and 40.98% water demonstrated the best characteristics (pH, film drying time, and physical features (transparency, film thickness, and film surface)) (29).

Hydrogel films based on hypromellose were developed and characterized for use as patches for transdermal delivery of tramadol hydrochloride (TRA) as a systemic painkiller, in order to discover alternatives to the current oral therapy for peripheral neuropathy. Hypromellose was crosslinked using electron beam irradiation for film preparation, thus avoiding toxic crosslinking additives. The hydrogel film demonstrated great transparency and elasticity comparable to commercial wound dressings (View gel®, TAIHO Pharmaceutical Co., Japan). Depending on the ionizing radiation dose used for hypromellose crosslinking, different amounts of TRA were released and penetrated through the hydrogel sheets. Additionally, a dose-dependent analgesic effect in mice was verified. This work highlights the potential use of TRA-loaded hypromellose hydrogel films as a novel dosage form and substitute for the current oral therapy for peripheral neuropathy (27).

The study by Panda et al. (28) investigated the influence of different plasticizers (propylene glycol, polyethylene glycol 400, dimethyl sulfoxide and triethanolamine) on the crystal structure of telmisartan in *in situ* formed films from FFS with hypromellose as the main film-forming polymer with a mass ratio three times that of telmisartan. The results of polarised light microscopy (PLM), scanning electron microscopy (SEM) and X-ray diffraction (XRD) analyses showed high compatibility between hypromellose, plasticizers and telmisartan, with no phase separation observed during solvent evaporation leading to film formation. Most remarkably, films containing triethanolamine

as plasticizer showed a smooth surface, even in the submicron range. PLM and SEM results did not reveal any appreciable degradation of the films' microstructure following 6 weeks of exposure to stress conditions at 40 °C and 75% RH. Furthermore, the amorphization of telmisartan in the films was significantly facilitated by the plasticizer triethanolamine.

In the study by Pichayakorn et al., (10) hypromellose was combined with deproteinated natural latex and either glycerin or dibutyl phthalate as plasticizers to create FFS for transdermal nicotine delivery. Each polymer film dispersion had a pH of 7–8, and a smooth texture, without any agglomeration. Together with film formation time, other positive qualities were viscosity and spreadability, which were further reduced by the addition of ethanol. Two stages were visible in the *in vitro* release of nicotine from the film-forming mechanisms. Similar to the release of nicotine from concentrated solutions, the first phase entailed fast release over a period of 3–4 hours. Slow release then happened during *in situ* film creation, which researchers were able to visually confirm. FFS including glycerol showed higher *in vitro* nicotine penetration into porcine skin than those containing dibutyl phthalate. The integrity of the films *in situ* was impacted by the addition of ethanol, which also increased nicotine absorption. The *Higuchi* model verified that the kinetics of nicotine release and its penetration through the skin followed a diffusion mechanism. These formulations didn't significantly irritate the skin and were safe; however, for stability, they have to be kept in tightly sealed containers at 4 °C.

Oromucosal drug delivery

Orodispersible films and mucoadhesive buccal films represent two types of formulations for oromucosal administration (Table II). Orodispersible films rapidly hydrate with saliva upon placement on the tongue, facilitating the quick release of active pharmaceutical ingredients from the dosage form. These films enable drugs to bypass first-pass metabolism by being absorbed through the oral mucosa, thereby potentially enhancing drug bioavailability. Mucoadhesive buccal films are applied to the inside of the oral cavity for local or systemic drug delivery, providing extended retention time in the mouth. They facilitate gradual drug absorption and reduce gastrointestinal interactions. These films are flexible, easy to use, well-accepted by patients, and capable of withstanding mechanical stresses, making them the preferred dosage forms for buccal administration. Most polymers used as mucoadhesives are hydrophilic polymers that swell and interact with mucin in the buccal mucosa. Examples of swelling polymers include hypromellose, hydroxypropylcellulose, hydroxyethylcellulose, carmellose sodium, povidone (poly(vinyl pyrrolidone)) and chitosan (4, 30-35).

In the study by Jadach et al., (36) two types of orodispersible films were prepared using the solvent casting method. Hypromellose or sodium alginate were used as film-forming polymers, and crospovidone or microcrystalline cellulose were used as disintegrants. Meloxicam, a drug used to treat rheumatic diseases in children and adults, was added as a model active substance, glycerol as a plasticizer, and aspartame as a

sweetener. The evaluation of the prepared films was based on appearance description, mass uniformity measurement, disintegration time, meloxicam content, film wettability, and water content. The films had a similar appearance, drug content close to the theoretical value, and water content of less than 10%, regardless of the polymer or disintegrant ratio. The *in vitro* release results of meloxicam from the films showed that the release was influenced by the type of polymer, while the type of disintegrant had no effect. The average amounts of meloxicam released after 15 minutes from films with alginate were 17.1 ± 9.4% and 17.4 ± 10.2%, while the values for films with hypromellose were significantly lower (4.7 ± 0.4% and 5.2 ± 0.6%) when crospovidone or microcrystalline cellulose were used, respectively, confirming that the obtained gel films did not function as fast-dissolving drug delivery systems. Furthermore, the disintegration time for both alginate-based and hypromellose-based films, which was longer than 30 seconds, indicated that changes in the film composition (e.g., adding other disintegrants such as crosslinked cellulose, sodium starch glycolate, or crosslinked starch) were necessary.

Garsuch et al.'s study (37) compared the efficacy of hypromellose with carmellose, polyethylene glycol and polyvinyl alcohol copolymer, and sodium alginate in the production of orodispersible films. Along with polymers, the films contained plasticizers (sorbitol and 85% glycerol), surfactants (polysorbate 80 and dodecyl polyethylene oxide-23 ether), and saliva-stimulating agent (citric acid). Films were prepared with and without caffeine and caffeine citrate as model active substances. The dissolution of the films was studied by measuring the time required for a drop of distilled water to dissolve the film and create a hole in it. The films were also characterized by dynamic moisture sorption analysis. All films dissolved within 40 seconds. Films containing active substances dissolved more slowly than corresponding placebo formulations. The fastest dissolution was achieved with films made of carmellose (placebo < 5 s, with active substance < 10 s). The dissolution times for orodispersible films with caffeine from carmellose and hypromellose differed significantly ($\alpha = 0.05$). However, dynamic moisture absorption studies showed higher values for films with carmellose, which were sticky and difficult to handle, so films with hypromellose were more suitable as they dissolved quickly, were easy to handle and were not sticky.

Tedesco et al. investigated films based on hypromellose, gelatin, and their mixtures as matrices for orodispersible films. They investigated five formulations prepared by casting in which hypromellose was added to an aqueous gelatin solution in the following ratios: 0:100, 25:75, 50:50, 75:25, 100:0, with a total polymer mass of 2 g/100 g of solution for film formation. Sorbitol was added to the films as a plasticizer. The films were then characterized, including by SEM, FTIR, DSC, mechanical properties, contact angle, dissolution time and bioadhesive properties. In the blends, a less compact cross-sectional structure was observed in scanning electron micrographs compared to isolated polymer films. The addition of hypromellose increased the elongation, hydrophilicity and bioadhesive properties while reducing the *in vitro* film dissolution/disintegration time.

However, the polymer mixture did not exhibit synergistic behavior, in contrast to the initial assumption (38).

Hypromellose was utilized as a film-forming agent either independently or in combination with polyvinyl alcohol in the study conducted by Prabhu et al. (39). The study examined levocetirizine dihydrochloride-containing orodispersible films for the rapid symptomatic relief of seasonal and perennial allergic rhinitis. They passed the physical evaluation, which provided satisfactory results, in terms of weight uniformity, thickness, folding durability, content uniformity, surface pH, percentage elongation, and tensile strength. Formulations underwent disintegration tests, *in vitro* release studies of levocetirizine, and *in vivo* studies in rats. Rapidly dissolving films of levocetirizine dihydrochloride with hypromellose showed a significant increase in dissolution rate compared to conventional tablets. Studies conducted *in vivo* on rats using haloperidol-induced catalepsy, milk-induced leukocytosis, and nose provocation verified that levocetirizine dihydrochloride films exhibit faster onset of action compared to conventional tablets.

The preparation of orodispersible films containing donepezil hydrochloride for the treatment of Alzheimer's disease was studied by Liew et al. (40). A blend of hydrophilic polymers (hypromellose, corn starch, macrogol, lactose monohydrate, and crospovidone) was used to make the films, along with artificial sweeteners such sucrose, aspartame, and sodium saccharin, and pineapple flavor. *In vitro* release studies showed that 80% of donepezil hydrochloride was released within 5 minutes, with an average disintegration time of 44 seconds. The flexibility test results indicated that the films maintained their integrity for the first 40 folds, after which they broke, demonstrating satisfactory mechanical characteristics for patient use. The average *in situ* disintegration time in the volunteers' mouths was 49 seconds. Films containing 7 mg of sucralose were found to be superior compared to films with saccharin and aspartame in terms of taste, aftertaste, mouthfeel, and acceptance. Additionally, the films were stable for at least 6 months when stored at 40 °C and 75% relative humidity.

Mushtaque et al. conducted the design and optimization of orodispersible films with escitalopram using central composite response surface methodology with Design-Expert® software. The software generated six optimized formulations which were prepared by the solvent casting method. Besides escitalopram (5 mg), the films contained hypromellose, macrogol 400, croscarmellose, sodium lauryl sulfate, vanillin, citric acid, water, and methanol, with only the concentrations of hypromellose (5–10%) and macrogol (0.5–2%) varying, while the other substances were used in the same amounts. The developed formulations were evaluated based on weight variation, drug-excipient interactions, dryness/stickiness test, thickness, percentage elongation, swelling index, disintegration, folding endurance, surface pH, content uniformity, assay, moisture uptake, stability, and organoleptic properties. A validated spectrophotometric method was used to determine the content of escitalopram in the films. Films with 10% hypromellose exhibited unsatisfactory properties, such as an uneven surface and insufficient drug content, which meant that they did not meet the quality criteria. In contrast, films with 5% hypromellose

showed the best overall performance, including optimal thickness and acceptable elongation. All tested formulations showed satisfactory *in vitro* release of escitalopram (about 90.91%–92.42% drug release was observed within 1.5–2 minutes). It was found that increasing the concentration of the plasticizer (macrogol) slightly increased the drug release time (41).

Tedesco et al. studied the formulation of orodispersible films based on hypromellose combined with gelatin, using peanut shell extract that contained a variety of bioactive ingredients, including procyanidins, quercetin, rutin, daidzein, genistein, and trans-resveratrol. Using the solvent casting method, films were made with different extract concentrations (20 and 30 g/100 g solvent for film formation) and polymer ratios (100:0, 25:75, 50:50, 75:25, 0:100). Insoluble complexes were seen in formulations with a high gelatin content, most likely as a result of gelatin and polyphenol cross-linking. Increasing the extract content facilitated the inter- and intramolecular interaction between gelatin and hypromellose in formulations where the concentration of gelatin was equal to or lower than hypromellose. A 20% extract-containing hypromellose film without gelatin showed a dispersion time of 17.87 ± 1.77 s, elongation of 4.97 ± 0.41%, contact angle of 67.17 ± 0.41°, and strength of 26.63 ± 1.89 MPa. Accelerated stability testing (at 30 °C and 40 °C over 3 months) revealed that the films kept 60% of the total phenolic compounds, and *in vitro* release tests revealed 80% release of phenolic compounds after 5 minutes (12).

Chonkar et al. aimed to develop orodispersible films using hypromellose, which included lerkanidipine nanoparticles. These nanoparticles were prepared from a nanosuspension using the evaporative antisolvent precipitation method. Two nanosuspensions containing polyethylene glycol 400 and D-alpha-tocopheryl polyethylene glycol succinate 1000 as stabilizers were chosen for film incorporation. The optimized films' mechanical, chemical, and physical characteristics met the necessary criteria. The polymeric matrix of the films had nanoparticles distributed uniformly, as demonstrated by SEM and FTIR. Leerkanidipine's weakly crystalline nature was validated by the results of DSC and XRD. On the other hand, hypromellose crystals were created by thermal processing of the film, which led to the inclusion of amorphous lerkanidipine nanoparticles into the polymer matrix. Superior dissolution and permeation properties of the nanoparticles were confirmed by *in vitro* dissolution studies, and approximately 6.5 times higher *ex vivo* permeation of lerkanidipine from the formulation through porcine buccal mucosa was observed (42).

Wojtyłko et al. reported the development of films using hypromellose, in combination with either gellan gum or gelatin, containing chlorhexidine and designed to function as a mucosal patch for the potential treatment of oral cavity inflammation (11). Water loss assessment (gelatin films 92.94 ± 0.04%; gellan gum films 93.71 ± 0.50%), swelling capacity (gelatin 570.2%; gellan gum 837.7%), hygroscopicity, and tear resistance (time to break gelatin films 106 ± 9 min; gellan gum films 170 ± 17 min) were the characteristics of the obtained placebo films. Placebo hypromellose-gellan gum films exhibited greater water loss, swelling capacity, tear resistance, and hygroscopicity

compared to films where hypromellose was combined with gelatin. In addition, it was shown that translucent, flexible polymeric films containing chlorhexidine can be made by combining hypromellose with gellan gum or gelatin. High hygroscopicity and swelling capacity were seen in all of the chlorhexidine films that were evaluated, and there was no apparent difference in these characteristics before and after the addition of the active ingredient. In contrast, hypromellose/gellan gum-containing formulations were found to be more effective at producing films that remained at the application site for a longer period of time, which made them more appropriate for use as local patches compared to hypromellose/gelatin-based formulations.

Vaginal drug delivery

Vaginal films are thin, polymeric solid dosage forms applied directly to the vaginal mucosa for the release of active substances (e.g., microbicides) (Table II). These films typically dissolve upon contact with vaginal fluid, releasing the drug directly onto the tissue. Advantages of vaginal films include fast and precise dosing, discreet application without an applicator, reduced final product volume, and the ability to stabilize drugs sensitive to degradation in aqueous environments. Additionally, vaginal films have shown high acceptability among women compared to other vaginal formulations such as vaginal gels, foams, and pessaries (49-52).

The Notario-Pérez et al. study (15) optimized vaginal films for tenofovir's prolonged release in expectation of their potential use in the prevention of HIV transmission during sexual activity. Both a hydrophilic polymer (hypromellose) and an amphiphilic polymer (zein) were taken into consideration for the preparation of vaginal films. By adding a plasticizer (glycerol, polyethylene glycol 400, tributyl citrate or oleic acid) to a polymer solution in a mixture of water and methanol, changes in the characteristics of the film were also assessed. Non-adhesive silicone molds were used in the solvent casting process to create the films. The films' mechanical, chemical, and physical properties were determined. *In vitro* release of tenofovir from the films, their bioadhesive ability, and water capture (expressed as the percentage of the weight of water of the total film weight) in simulated vaginal fluid were also assessed. In addition to having the required mechanical properties, the 1:5 ratio of hypromellose and zein films, along with the 40% by weight addition of polyethylene glycol, was able to release tenofovir over a 120-hour period while adhering to biological tissues.

The use of dapivirine, a reverse transcriptase inhibitor and anti-HIV drug, as a fast-dissolving vaginal film for HIV prophylaxis was studied by Akil et al. The films were made using the solvent casting method and included hypromellose 4000, propylene glycol, macrogol 8000, glycerol, and dapivirine (1.25 mg/film and 0.05 mg/film). The resulting films' physicochemical parameters, such as their water content, mechanical properties, lactobacilli compatibility, *in vitro* permeability, and bioactivity on human cervical tissue samples, were assessed. Both *in vitro* and *ex vivo* tests confirmed the dapivirine-containing film's anti-HIV properties. Importantly, the investigated physical

and chemical properties of the film, as well as its bioactivity, were maintained over a period of 18 months (16).

Fast dissolving thin vaginal films were developed by Patel et al. to administer tenofovir (20 and 40 mg), an adenosine nucleotide analog that could be used in HSV-2 and HIV therapy. Using hypromellose, hydroxyethylcellulose, carmellose sodium, glycerol, sodium hydroxide, and water, placebo films and films with low- (20 mg) and high-dose (40 mg) of tenofovir were prepared using the solvent casting method. The high dose of tenofovir was effectively incorporated into the film, releasing more than 50% of tenofovir within 15 minutes. *Ex vivo* evaluation on human ectocervical tissues (explants) from pre-menopausal women showed a reduction in HIV-1 infection after the application of tenofovir film. After two weeks of repeated exposure, the safety of the films was confirmed in macaques, who showed minimal changes in vaginal pH, neutrophil influx, microbiome disturbance, and tissue disruption (53).

In the study by Ghosal et al., (54) vaginal films containing abacavir, a potent nucleoside reverse transcriptase inhibitor, were developed and optimized. Using hypromellose and povidone in ratios of 1:1, 1:3, 2:1, 3:1, 9:1, polysorbate 80, and glycerol, vaginal films were produced *via* the solvent casting technique. Along with the morphological characteristics of the films, a variety of physicochemical properties were assessed, including the drug content, film thickness, tensile strength, percent elongation at break, drug-polymer interaction, swelling capacity, folding endurance, bioadhesion, pH value, and moisture content. The films showed advantageous physicochemical characteristics. *In vitro* drug release studies showed that the combination of hypromellose and povidone could control the release of abacavir through vaginal films. Higher amounts of povidone in the formulation resulted in improved abacavir release rates (films with the highest povidone content released 99% of abacavir within 3 hours, while films with the lowest content released 97% of abacavir within 6 hours). During *in vivo* studies in rabbits, systemic absorption of abacavir was observed, while the films remained intact in the vagina for an extended period without causing signs of irritation.

Ocular drug delivery

Due to the specific anatomy of the eye, which includes the blood-ocular barrier and the eye's resistance to external chemicals, distributing drugs in the eye is challenging. Ocular films can extend contact with ocular tissue, overcoming the limitations of eye drops, such as the rapid removal from the precorneal cavity due to the tear flow and the nasolacrimal drainage. Ocular films are sterile preparations with a solid or semi-solid consistency, specifically shaped and sized for ocular application. They consist of a polymeric base that may or may not contain drugs, which are incorporated as a dispersion or solution within the polymer matrix. These films enable extended drug release and reduce dosing frequency, thereby enhancing therapeutic efficacy. They are increasingly important for local or systemic therapy of eye diseases such as glaucoma or macular degeneration, offering increased drug bioavailability in the eyes and minimizing systemic side effects through targeted action on ocular tissues (44-47).

So far, only a few studies have considered the use of hypromellose in the formulation of FFS for ocular drug delivery. Using ofloxacin as a model drug, different polymers including hypromellose were explored for the manufacture of films intended for ocular use in the study conducted by Patel et al. (14). Hypromellose, polyvinyl alcohol, hydroxypropylcellulose, and polymethacrylate copolymer (Eudragit® RL100) were used in the formulation of the films, either separately or in combination with povidone. Water or ethanol were used as the solvent, and glycerol or dibutyl phthalate as the plasticizer. Films containing only hypromellose showed less favorable mechanical properties compared to other polymers, but better water vapor permeability. In combination with povidone, however, both the mechanical properties (elongation at break, folding endurance, and tensile strength) and water vapor permeability were significantly improved. The films were sterilized by exposure to UV radiation. In irritation tests on albino rabbits' eyes, the films exhibited no symptoms of irritation, redness, swelling, or cloudiness even 24 hours after film removal.

In order to achieve prolonged drug retention in the eye for glaucoma therapy, Tighsazzadeh et al. looked into the development of polymeric films as prospective delivery vehicles for timolol maleate. The prepared films contained hypromellose and hyaluronic acid, either separately or in combination, and glycerol, besides the active ingredient. After preliminary optimization involving transparency and ease of handling assessments, the formulations underwent characterization for their physicochemical properties. According to swelling studies, hyaluronic acid-containing films had a significantly higher swelling capacity than hypromellose-containing films. This finding had a direct impact on the timolol maleate release profiles, indicating that hyaluronic acid is a suitable polymer for controlled drug delivery to the eye. When mechanical and mucoadhesive characteristics were evaluated, films containing hyaluronic acid showed higher elasticity and adhesiveness, while films containing hypromellose demonstrated higher resistance to breaking. The films' mechanical properties were not considerably impacted by UV sterilization. According to *in vitro* release tests, hyaluronic acid films showed prolonged release (maximum cumulative drug release over 8 hours); in contrast, hypromellose films showed maximum release within 2 hours as a result of fast swelling and polymer erosion (48).

Nasal drug delivery

To overcome the limitations of conventional nasal dosage forms, such as nasal drops and nasal sprays, which have short retention times due to mucociliary clearance, nasal films tailored to the dimensions of the olfactory region are being developed. These films aim to prolong residence time in the nasal cavity and enhance drug absorption, enabling non-invasive delivery of drugs from the nose to the brain. This approach has the potential to significantly advance therapy for neurodegenerative diseases and other conditions requiring drug delivery to the central nervous system *via* nasal administration (13, 43). Papakyriakopoulou et al.'s work focused on the development and optimization of nasal films containing donepezil chloride as a possible Alzheimer's disease treatment.

Nasal films with hypromellose E50, polyethylene glycol 400 as a plasticizer, and methyl-β-cyclodextrin as a permeation enhancer were prepared and characterized using *in vitro* and *ex vivo* methods. The impact of particular parameters on the flexibility of the film and the profile of donepezil chloride penetration through the rabbit nasal mucosa were studied using an experimental design. Utilizing a central composite design with three levels of variation, 17 tests were carried out in triplicate. The prepared films demonstrated good consistency in terms of thickness (19.6 ± 1.9 μm – 170.8 ± 11.5 μm), donepezil chloride content (90.0 ± 1.6% – 99.8 ± 4.9%), and stability during storage, minimal residual moisture (< 3%), and acceptable swelling and mucoadhesive characteristics. An optimal composition consisting of 1.5% hypromellose, 1.7% polyethylene glycol 400, and 0.8% methyl-β-cyclodextrin was chosen using response surface methodology to produce a flexible nasal film with the highest achievable donepezil chloride permeability ($J_{\text{nasal mucosa}}$ = 1.82 ± 0.000 μg/cm^2/min) (13).

Conclusion

The use of hypromellose as a film-forming pharmaceutical excipient in topical films and FFS has already demonstrated significant advantages in drug delivery. Hypromellose facilitates the formation of stable, homogeneous, and biocompatible films suitable for application on skin and mucous membranes (oral, vaginal, ocular, and nasal). Dermal, transdermal and oromucosal drug delivery are more frequently studied compared to vaginal, ocular, and nasal routes due to easier access and application, reduced risk of infection and irritation, larger surface areas for drug absorption, and thus broader therapeutic use. Additionally, these routes facilitate practical application and clinical trials, making them more attractive for research. The increased interest is seen in researching films compared to FFS, as carriers for small molecules and substances with limited solubility. Such studies primarily focus on the application of drugs for local action, as observed in skin or vaginal drug delivery. On the other hand, orodispersible films are being investigated for systemic delivery of active substances. Studies so far have demonstrated that the importance of hypromellose as a film-forming agent lies in its ability to control the release of active substances, enhance their bioavailability, and exhibit bioadhesive/mucoadhesive properties. However, hypromellose does have its disadvantages, such as slow dissolution, poor mechanical properties of films, high viscosity in solution making handling difficult, and sensitivity to moisture affecting stability. These challenges may necessitate the introduction and optimisation of other excipients, such as plasticizers (e.g., macrogol 400, macrogol 6000, glycerol, propylene glycol, sorbitol) and secondary polymers (e.g., chitosan, gellan gum, gelatin, polyvinyl alcohol, povidone, hyaluronic acid, zein), to improve film and FFS performances and expand new therapeutic possibilities.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

Sandra Milinković: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Visualization, Writing - original draft.

Ljiljana Đekić: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Visualization, Supervision, Writing - review & editing.

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Filmovi i film-formirajući sistemi na bazi hipromeloze za topikalnu primenu: trenutni značaj i perspektiva u isporuci lekovitih supstanci

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Kratak sadržaj

Filmovi i film-formirajući sistemi (FFS) sve više se ističu kao pogodni nosači za preciznu i efikasnu isporuku aktivnih supstanci na ili preko kože i sluzokože. Među njima, oni koji sadrže hipromelozu kao film-formirajući polimer pokazuju mnoge povoljne karakteristike. Kako bi se bolje razumela uloga hipromeloze u filmovima i FFS za topikalnu primenu, ovaj pregled prikazuje fizičko-hemijske karakteristike i sposobnost formiranja filmova različitih tipova hipromeloze. U nastavku, pregled obuhvata relevantne studije koje prikazuju široku primenu hipromeloze kao sredstva za formiranje filma u filmovima i FFS za dermalnu, oromukozalnu, vaginalnu, okularnu i nazalnu primenu, odražavajući rastući interes istraživača u ovoj oblasti. Takođe, naglašava prednosti hipromeloze u poređenju sa drugim film-formirajućim polimerima, kao i potencijal za celokupan budući razvoj filmova i FFS.

Ključne reči: film, film-formirajući sistemi, isporuka lekovitih supstanci, hipromeloza, topikalna primena