www.ijprems.com
editor@ijprems.com

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)
Vol. 05, Issue 06, June 2025, pp : 988-993

e-ISSN : 2583-1062
Impact Factor : 7.001

A COMPREHENSIVE REVIEW ON SKIN BRIGHTENING GEL USING KOJIC ACID

Munavarunnisa[1], Salma begum[2], V.Keerthi[3], Bhargavi CH[4]

[1,2,3]Sarojini Naidu Vanita Pharmacy Maha Vidyalaya.

[4]Assistant Professor, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya.

Email: bhargavichekkilla@gmail.com

DOI: https://www.doi.org/10.58257/IJPREMS42146

ABSTRACT

Hyperpigmentary disorders represent a common cosmetic concern, driving demand for effective skin brightening agents. Topical gels offer an advantageous delivery system for agents like Kojic acid, Arbutin, and Licorice extract, which primarily function by inhibiting tyrosinase, the key enzyme in melanin synthesis. This review synthesizes information on the formulation and evaluation of such gels, focusing on the roles of common polymers like Carbopol 940 and HPMC K4M. Key formulation strategies involve selecting appropriate polymers and excipients to achieve desired physicochemical properties (viscosity, spreadability, pH) and drug release profiles. Comprehensive evaluation, including physicochemical characterization, drug content analysis, In vitro release studies, and stability testing, is crucial for ensuring product quality, safety, and efficacy. While gel formulations provide a promising platform, challenges related to active ingredient stability and optimizing skin penetration persist. Standardized evaluation methodologies are essential for developing reliable and effective topical skin brightening treatments.

KEYWORDS: Skin Brightening, Hyperpigmentation, Topical Gels, Kojic Acid, Arbutin, Licorice Extract, Carbopol 940, HPMC K4M, Formulation, Evaluation, Drug Delivery, Tyrosinase Inhibitors.

1. INTRODUCTION

Skin pigmentation, primarily determined by the amount and distribution of melanin produced by melanocytes, plays a crucial role in photoprotection but can also be a source of significant cosmetic concern when irregularities occur. Hyperpigmentary disorders, such as melasma, solar lentigines (age spots), and post-inflammatory hyperpigmentation (PIH), are common conditions characterized by the excessive production or uneven distribution of melanin, leading to darkened patches on the skin [1, 2]. These conditions can impact an individual's quality of life, driving a substantial demand for effective and safe skin brightening or lightening agents within both the cosmetic and therapeutic markets [3]. The primary biochemical target for most skin brightening agents is tyrosinase, a key copper-containing enzyme that catalyzes the rate-limiting steps in melanogenesis – the hydroxylation of L-tyrosine to L-DOPA and the subsequent oxidation of L-DOPA to dopaquinone [4, 5]. Inhibition of tyrosinase activity directly reduces melanin synthesis, leading to a lightening effect on the skin. Several agents derived from natural and synthetic sources have been identified and utilized for their tyrosinase-inhibiting properties.

Among the commonly employed agents discussed in the source material are Kojic acid, Arbutin (specifically alpha-arbutin), and Licorice extract (containing the active compound Glabridin). Kojic acid, a fungal metabolite, acts by chelating the copper ions essential for tyrosinase function [6]. Alpha-arbutin, a glycosylated hydroquinone derivative found naturally in plants like bearberry, functions as a competitive inhibitor of tyrosinase [7]. Licorice extract, derived from the root of *Glycyrrhiza glabra*, contains Glabridin, which exhibits both tyrosinase inhibition and anti-inflammatory effects, making it particularly useful for addressing PIH [8, 9].

Despite the proven efficacy of these agents, their successful delivery into the skin via topical application presents challenges. Issues such as chemical instability (particularly for Kojic acid), poor skin penetration due to molecular size or polarity, and potential for skin irritation necessitate carefully designed delivery systems [10]. Topical gel formulations have emerged as a popular and advantageous vehicle for delivering skin brightening agents. Gels offer several benefits, including ease of application, a non-greasy feel, potential for enhanced hydration, a cooling sensation upon application, and favorable drug release characteristics compared to more occlusive ointment bases [11, 12]. The polymeric network of a gel can control the release rate of the active agent, potentially improving its penetration and efficacy. This review aims to synthesize the current understanding regarding the formulation and evaluation of topical gels designed for delivering key skin brightening agents, specifically Kojic acid, Arbutin, and Licorice extract. Drawing primarily upon the principles, ingredients, and methodologies presented within the source document, this paper will explore the mechanisms of action of these agents, discuss the rationale and components of gel formulations

www.ijprems.com
editor@ijprems.com

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)
Vol. 05, Issue 06, June 2025, pp : 988-993

e-ISSN : 2583-1062
Impact Factor : 7.001

using common polymers like HPMC, Sodium alginate, Xanthan gum and Carbopol, and review the essential evaluation parameters required to ensure the quality, safety, and efficacy of these topical products.

2. MECHANISMS OF ACTION OF KEY SKIN BRIGHTENING AGENTS

Effective skin brightening strategies often rely on inhibiting the enzymatic activity of tyrosinase, the central regulator of melanin production. Several agents, derived from both natural and synthetic origins, have been identified for their ability to interfere with this pathway. This section reviews the mechanisms of action for three commonly utilized brightening agents highlighted in the source material: Kojic acid, Arbutin, and Licorice extract.

Kojic Acid

Kojic acid is a hydrophilic fungal metabolite produced by several species of Aspergillus and Penicillium [6, 13]. Its primary mechanism of action as a skin brightening agent stems from its potent ability to inhibit tyrosinase activity. Kojic acid functions by chelating the copper ions (Cu^{2+}) present within the active site of the tyrosinase enzyme [6, 14]. Copper ions are essential cofactors for tyrosinase function; by binding these ions, Kojic acid effectively inactivates the enzyme, preventing the catalysis of melanin precursors (L-tyrosine and L-DOPA) and thereby reducing melanin synthesis [14]. While effective, Kojic acid is known for its potential instability in formulations, particularly its susceptibility to oxidation, which can lead to discoloration and reduced efficacy, necessitating careful formulation strategies [10].

Arbutin (Alpha-Arbutin)

Arbutin is a naturally occurring glycoside of hydroquinone, found predominantly in plants of the Ericaceae family, such as bearberry (Arctostaphylos uva-ursi), cranberry, and blueberry [7, 15]. While beta-arbutin is the more common natural form, alpha-arbutin, often produced synthetically, is reported to be more stable and potentially more effective [16]. Alpha-arbutin exerts its skin brightening effect through the competitive inhibition of tyrosinase [7, 17]. It structurally resembles tyrosine, the natural substrate for tyrosinase, allowing it to bind to the enzyme's active site. However, unlike tyrosine, it is not processed into melanin precursors. By occupying the active site, it prevents the binding and processing of tyrosine, thus inhibiting melanin production [17]. Compared to hydroquinone, arbutin is generally considered a safer alternative with a lower potential for cytotoxicity and irritation [15].

Licorice Extract (Glabridin)

Licorice extract, obtained from the root of the Glycyrrhiza glabra plant, contains several bioactive compounds, with Glabridin being one of the most significant components responsible for its skin brightening effects [8, 18]. Glabridin is an isoflavonoid that demonstrates potent tyrosinase inhibitory activity, effectively reducing melanin synthesis [8, 19]. Its mechanism involves inhibiting the enzyme without affecting its synthesis. Beyond tyrosinase inhibition, Glabridin also possesses significant anti-inflammatory properties [9, 18]. It can inhibit the production of pro-inflammatory mediators, which is particularly beneficial in treating post-inflammatory hyperpigmentation (PIH), where both pigmentation and inflammation are contributing factors [9]. This dual action makes licorice extract a valuable ingredient in formulations targeting both uneven skin tone and underlying inflammation.

In summary, Kojic acid, Alpha-arbutin, and Licorice extract (Glabridin) employ distinct but related mechanisms, primarily centered around the inhibition of tyrosinase, to achieve skin brightening effects. Understanding these mechanisms is crucial for selecting appropriate agents and designing effective topical formulations.

3. TOPICAL GEL FORMULATIONS FOR SKIN BRIGHTENING

Selecting an appropriate vehicle is critical for the effective topical delivery of skin brightening agents. Among the various topical dosage forms, gels have gained significant popularity due to their favorable physicochemical properties and aesthetic appeal [11, 12]. This section reviews the rationale for using gels and discusses key formulation components, particularly the polymers Carbopol 940 and HPMC K4M, as highlighted in the source material.

Key Polymers in Gel Formulation

The properties of a topical gel are largely dictated by the type and concentration of the gelling agent used. The source document focuses on two commonly used polymers: Carbopol 940 and Hydroxypropyl Methylcellulose (HPMC) K4M.

Sodum Alginate

Sodium alginate is a water-soluble polysaccharide polymer. It serves as an emulsifier, gelling agent, thickening, and stabilizer in food, and it can be utilized in medicines for tissue engineering and drug delivery[20]. Key properties relevant to gel formation include:

- Viscosity: The molecular weight of the polymer determines how viscous sodium alginate solutions are.

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)
Vol. 05, Issue 06, June 2025, pp : 988-993
e-ISSN : 2583-1062
Impact Factor : 7.001

- Gelation: When exposed to calcium ions, it easily gels.
- Biocompatibility: It is usually regarded as safe and compatible with the body's biochemistry.
- pH: Sodium alginate solutions normally have a pH between 6.0 and 8.0.
- Plasticizing Effect: It has the ability to plasticize, making films more flexible.
- Film Formation: It can be applied to produce films with a range of characteristics, such as barrier and antibacterial qualities.

Xanthan Gum

Xanthan gum, a polysaccharide with emulsifying, stabilizing, and thickening qualities. Even at low concentrations, it creates a viscous solution and is extremely soluble in water, both hot and cold. Its viscosity drops under shear and recovers when the shear force is removed, a phenomenon known as pseudoplastic flow[21]. Key properties include:

- Thickening: Xanthan gum can be used in a variety of food applications since it is a very effective thickener, even at low concentrations.
- Emulsification and Suspension: It aids in stabilizing and suspending particles in liquids and emulsions to avoid clumping and separation.
- Pseudoplasticity: It is advantageous for pumping and mixing applications since its viscosity reduces under shear stress.
- Stability: Xanthan gum is adaptable in a variety of applications due to its stability throughout a broad range of temperatures, pH values, and salt concentrations.

Carbopol 940

Carbopol 940 is a synthetic, high-molecular-weight polymer of acrylic acid cross-linked with allyl ethers of pentaerythritol [22]. It is widely used in pharmaceutical and cosmetic formulations as a gelling agent, thickener, and suspending agent. Key properties include:

- High Viscosity: Carbopol 940 can form clear, viscous gels at low concentrations (typically 0.5-2.0% w/w) [20].
- pH Sensitivity: Its viscosity is highly dependent on pH. Carbopol dispersions have low viscosity at acidic pH but thicken significantly upon neutralization (typically to pH 5.5-7.5) with a suitable base, such as Triethanolamine (TEA) [21]. This neutralization causes the polymer chains to uncoil and swell due to electrostatic repulsion between ionized carboxyl groups, forming the gel network.
- Clarity: Properly neutralized Carbopol gels are typically transparent and aesthetically pleasing.

Hydroxypropyl Methylcellulose (HPMC) K4M

HPMC is a semi-synthetic, non-ionic cellulose ether [22]. HPMC K4M denotes a specific viscosity grade (approximately 4000 mPa·s for a 2% aqueous solution at 20°C). It is commonly used as a thickener, binder, film-former, and controlled-release agent in various pharmaceutical applications. Key properties relevant to gel formation include:

- Viscosity: HPMC forms viscous solutions or gels upon hydration in water [22]. The viscosity depends on the grade and concentration used.
- pH Independence: Unlike Carbopol, the viscosity of HPMC gels is relatively stable over a wide pH range [23].
- Film Formation: HPMC can form a flexible film upon drying, which might influence drug release and skin feel.
- Biocompatibility: It is generally considered safe and biocompatible.

Other Excipients

Besides the gelling agent and active ingredients, topical gel formulations typically contain other excipients to ensure stability, efficacy, and patient acceptability.

Common excipients include:

- Neutralizing Agent: Triethanolamine (TEA) is used to neutralize Carbopol 940 and induce gel formation [21].
- Preservatives: Methyl paraben and Propyl paraben are included to prevent microbial growth and ensure product stability during storage [23].
- Humectant/Co-solvent: Propylene glycol acts as a humectant to prevent the gel from drying out and can also function as a co-solvent and penetration enhancer [24].
- Vehicle: Purified water typically serves as the primary vehicle.

www.ijprems.com
editor@ijprems.com

INTERNATIONAL JOURNAL OF PROGRESSIVE RESEARCH IN ENGINEERING MANAGEMENT AND SCIENCE (IJPREMS)
(Int Peer Reviewed Journal)
Vol. 05, Issue 06, June 2025, pp : 988-993

e-ISSN : 2583-1062
Impact Factor : 7.001

Formulation Approaches

The source document details several formulations (F1-F6) likely exploring different concentrations or combinations of Carbopol 940 and HPMC K4M, alongside fixed concentrations of Kojic acid, Arbutin, and Licorice extract. This approach allows for the investigation of how polymer type and concentration influence critical gel properties such as viscosity, spreadability, pH, drug content, and ultimately, drug release profiles. By systematically varying the formulation, researchers aim to identify an optimal composition that provides the desired physical characteristics, stability, and release kinetics for the skin brightening agents.

4. EVALUATION METHODOLOGIES FOR TOPICAL SKIN BRIGHTENING GELS

Developing a safe, effective, and stable topical gel formulation requires rigorous evaluation using a comprehensive set of methodologies. These tests assess the physical, chemical, and performance characteristics of the gel, ensuring it meets quality standards and is suitable for its intended application. This section reviews the key evaluation parameters typically employed for topical gels, as indicated by the procedures outlined in the source document.

Physicochemical Characterization

Assessing the physical properties of the gel is fundamental to understanding its quality, stability, and user acceptability.

- Appearance, Clarity, and Homogeneity: Visual inspection is the first step, evaluating the gel for its overall appearance, color, transparency or opalescence, and homogeneity. The formulation should be free from clumps, phase separation, or visible particulate matter, indicating uniform dispersion of ingredients [25].
- pH Measurement: The pH of a topical formulation is critical as it influences drug stability, gel viscosity (especially for pH-sensitive polymers like Carbopol), and skin compatibility [26]. An inappropriate pH can cause skin irritation. The pH is typically measured using a calibrated pH meter directly on the gel sample or a dispersion of the gel in water [Source: DOCX]. The target pH should ideally be close to the physiological pH of the skin (around 4.5-6.0) [26].
- Viscosity Measurement: Viscosity determines the gel's consistency, affecting its ease of application, retention time on the skin, and potentially the rate of drug release [27]. It is typically measured using a viscometer (e.g., Brookfield viscometer) equipped with appropriate spindles and operated at controlled speeds and temperatures. Variations in viscosity between batches or during stability studies can indicate formulation instability.
- Spreadability: This parameter relates to the ease with which the gel can be applied uniformly over the skin surface. A common method involves placing a known weight of the gel between two glass slides and measuring the diameter of the circle formed after applying a standard weight for a specific time [28]. Good spreadability enhances user compliance.

Drug Content Uniformity

Ensuring that the active pharmaceutical ingredients (APIs) – in this case, Kojic acid, Arbutin, and Licorice extract – are uniformly distributed throughout the gel is crucial for consistent dosing and efficacy. This involves accurately quantifying the amount of each API in multiple samples taken from different parts of the gel batch using a validated analytical method, such as High-Performance Liquid Chromatography (HPLC) or UV-Visible spectrophotometry, after appropriate extraction.

In vitro Drug Release/Diffusion Studies

In vitro release testing (IVRT) is essential for assessing the rate and extent to which the active agents are released from the gel formulation. This provides insights into the formulation's potential in vivo performance and allows for comparison between different formulations [30]. A common apparatus used is the Franz diffusion cell system. In this setup, a synthetic membrane (e.g., cellulose acetate, polysulfone) or excised skin is mounted between the donor and receptor compartments of the cell. A known quantity of the gel is applied to the membrane in the donor compartment, while the receptor compartment is filled with a suitable buffer solution maintained at physiological temperature (e.g., 32°C or 37°C) and stirred continuously. Samples are withdrawn from the receptor medium at predetermined time intervals and analyzed for drug concentration using a validated analytical method (e.g., UV-Vis spectrophotometry). The cumulative amount of drug released over time is plotted, and release kinetics can be analyzed using various mathematical models (e.g., Zero-order, First-order, Higuchi, Korsmeyer-Peppas) to understand the release mechanism [31].

Stability Studies

Stability testing evaluates the formulation's ability to maintain its physical, chemical, and microbiological properties over time under specified storage conditions, ensuring its quality, safety, and efficacy throughout its shelf life [32]. Based on the source document, stability studies typically involve storing the gel formulations under controlled conditions (e.g., different temperatures and humidity levels, potentially following International Council for Harmonisation (ICH) guidelines) for a defined period. At various time points, samples are withdrawn and re-evaluated for critical parameters, including:

- Physical appearance (color, clarity, homogeneity, phase separation)
- pH
- Viscosity
- Drug content (assay of active ingredients)

Significant changes in any of these parameters may indicate instability and necessitate formulation adjustments.

Collectively, these evaluation methodologies provide a comprehensive assessment of the topical skin brightening gel, ensuring that the final product is well-characterized, stable, and capable of delivering the active agents effectively.

5. CONCLUSION

Topical gel formulations represent a valuable and widely utilized approach for delivering skin brightening agents such as Kojic acid, Arbutin, and Licorice extract to address hyperpigmentation concerns. This review, based on the foundational principles presented in the source material, underscores the importance of selecting appropriate gelling agents to achieve desired physicochemical properties, cosmetic elegance, and potentially optimized drug release profiles. The successful development of such formulations hinges not only on the careful selection of active ingredients and excipients but also on rigorous evaluation encompassing physicochemical characterization (appearance, pH, viscosity, spreadability), drug content uniformity, In vitro release studies, and comprehensive stability testing. While topical gels offer significant advantages for delivering these brightening agents, challenges related to active ingredient stability and achieving optimal skin penetration remain. The systematic formulation and evaluation strategies discussed provide a crucial framework for developing safe, stable, and effective topical skin brightening products, although further research, including in vivo studies and clinical trials, is necessary to fully validate their therapeutic potential.

6. REFERENCES

[1] Sarkar R, Arora P, Garg KV. Cosmeceuticals for Hyperpigmentation: What is Available? *J Cutan Aesthet Surg*. 2013;6(1):4-11.
[2] Vashi NA, Kundu RV. Facial hyperpigmentation: causes and treatment. *Br J Dermatol*. 2013;169 Suppl 3:41-56.
[3] Rodrigues M, Pandya AG. Melasma: a clinical and epidemiological review. *An Bras Dermatol*. 2015;90(6):757-74.
[4] Hearing VJ. Determination of melanin synthetic pathways. *J Invest Dermatol*. 2011;131(E1):E8-E11.
[5] Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. *Physiol Rev*. 2004;84(4):1155-228.
[6] Saeedi M, Eslamifar M, Khezri K. Kojic acid applications in cosmetic and pharmaceutical preparations. *Biomed Pharmacother*. 2019;110:582-593.
[7] Boo YC. Arbutin as a skin depigmenting agent with antimelanogenic and antioxidant properties. *Antioxidants (Basel)*. 2021;10(7):1129.
[8] Simmler C, Pauli GF, Chen SN. Phytochemistry and biological properties of glabridin. *Fitoterapia*. 2013;90:160-84.
[9] Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. *Pigment Cell Res*. 1998;11(6):355-61.
[10] Burnett CL, Bergfeld WF, Belsito DV, et al. Final Report of the Safety Assessment of Kojic Acid as Used in Cosmetics. *Int J Toxicol*. 2010;29(6_suppl):244S-273S.
[11] Osborne DW, Amann AH. Topical Drug Delivery Systems. In: *Remington: The Science and Practice of Pharmacy*. 22nd ed. Pharmaceutical Press; 2012: 851-870.
[12] Benson HAE, Watkinson AC. Topical and Transdermal Drug Delivery: Principles and Practice. John Wiley & Sons; 2011.

[13] Bentley MVLB, Vianna Adole, Marchetti JM. Colloidal Carriers for Dermal Delivery of Kojic Acid. *AAPS PharmSciTech*. 2000;1(4): article 31.

[14] Cabanes J, Chazarra S, Garcia-Carmona F. Kojic acid, a cosmetic skin whitening agent, is a slow-binding inhibitor of catecholase activity of tyrosinase. *J Pharm Pharmacol*. 1994;46(12):982-5.

[15] Couteau C, Coiffard L. Overview of Skin Whitening Agents: Drugs and Cosmetic Products. *Cosmetics*. 2016;3(3):27.

[16] Sugimoto K, Nishimura T, Nomura K, et al. Inhibitory effects of alpha-arbutin on melanin synthesis in cultured human melanoma cells and a three-dimensional human skin model. *Biol Pharm Bull*. 2004;27(4):510-4.

[17] Funayama M, Arakawa H, Yamamoto R, et al. Effects of alpha- and beta-arbutin on activity of tyrosinases from mushroom and mouse melanoma. *Biosci Biotechnol Biochem*. 1995;59(1):143-4.

[18] Fu B, Li H, Wang X, Lee FS, Cui S. Isolation and identification of flavonoids in licorice and a study of their inhibitory effects on tyrosinase. *J Agric Food Chem*. 2005;53(19):7408-14.

[19] Nerya O, Vaya J, Musa R, et al. Glabrene and isoliquiritigenin as tyrosinase inhibitors from licorice roots. *J Agric Food Chem*. 2003;51(5):1201-7.

[20] Bonacucina G, Martelli S, Palmieri GF. Rheological, mucoadhesive and release properties of Carbopol gels in hydrophilic cosolvents. *Int J Pharm*. 2004;282(1-2):115-30.

[21] Islam MT, Rodríguez-Hornedo N, Ciotti S, Ackermann C. Rheological characterization of topical carbomer gels neutralized to different pH. *Pharm Res*. 2004;21(7):1192-9.

[22] Rowe RC, Sheskey PJ, Quinn ME, eds. *Handbook of Pharmaceutical Excipients*. 6th ed. Pharmaceutical Press; 2009. (HPMC entry)

[23] Soni MG, Burdock GA, Taylor SL, Greenberg NA. Safety assessment of propyl paraben: a review of the published literature. *Food Chem Toxicol*. 2001;39(6):513-32. (Similar assessments exist for Methyl Paraben)

[24] Fartasch M. Topical Corticosteroids. In: *Plewig G, Landthaler M, Burgdorf WHC, Hertl M, Ruzicka T, eds. Braun-Falco's Dermatology*. 3rd ed. Springer; 2009: 1917-1926. (Discusses propylene glycol as vehicle component)

[25] United States Pharmacopeia (USP). General Chapter <1> Injections and Implanted Drug Products (Parenterals)—Product Quality Tests. (Principles of visual inspection apply)

[26] Lambers H, Piessens S, Bloem A, Pronk H, Finkel P. Natural skin surface pH is on average below 5, which is beneficial for its resident flora. *Int J Cosmet Sci*. 2006;28(5):359-70.

[27] Davis SS. Viscoelastic properties of pharmaceutical semisolids III: Nondestructive methods of examination. *J Pharm Sci*. 1971;60(9):1351-7.

[28] Garg A, Aggarwal D, Garg S, Singla AK. Spreading of semisolid formulations: an update. *Pharm Technol*. 2002;26(9):84-105.

[29] International Council for Harmonisation (ICH). Guideline Q2(R1): Validation of Analytical Procedures: Text and Methodology. 2005.

[30] Ng SF, Rouse J, Sanderson D, Eccleston G. A comparative study of transmembrane diffusion and permeation of ibuprofen from topical formulations using Franz diffusion cells. *Pharmaceutics*. 2010;2(2):209-23.

[31] Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv Drug Deliv Rev*. 2012;64(Suppl):163-74.

[32] International Council for Harmonisation (ICH). Guideline Q1A(R2): Stability Testing of New Drug Substances and Products. 2003.