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Currant Review On Co-Crystals For Topical Drug Delivery

[1]Anuja A. Suryawanshi, [2]Dr. J. P. Rai

School of Pharmacy LNCT University, Bhopal (M.P.)

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Abstract

Topical drug delivery systems have a rich history, evolving from ancient ointments to sophisticated modern formulations designed to treat various skin disorders and systemic conditions. Recently, co-crystal technology has emerged as a significant advancement in pharmaceutical science, offering the potential to enhance the physicochemical properties of drugs used in topical applications. Co-crystals, which are crystalline structures, composed of two or more molecules, can improve drug solubility, stability, and bioavailability without affecting the drug's pharmacological properties. This review article explores the development and application of topical drug delivery systems, highlighting the advantages and challenges associated with topical administration. It also discusses the role of co-crystals in enhancing the effectiveness of topical treatments by modifying drug properties. The integration of these technologies represents a promising approach to overcoming limitations in current treatments and advancing patient care.

Keywords: Topical drug delivery, Co-crystals, Pharmaceutical technology, Drug solubility, Drug stability, Skin disorders, Drug bioavailability, Topical formulations, Co-crystal technology, Drug delivery systems.

Introduction

Topical drugs have a long history. Thousands of years ago, ointments and salves made from animal, mineral, or plant extracts were commonly used in Egyptians, Chinese and Babylonians to cure a wide range of ailments (Lima *et al*., 2021; Roberts *et al*., 2021). Before 2000 BC, emplastra appeared in China, which maybe the original transdermal patch (Pastore *et al*., 2015). Topical drug delivery systems have been shown to overcome difficulties in drug delivery, especially orally. Over the last decades the treatment of illness has been accomplished by administrating drugs to human body via various routes namely oral, sublingual, rectal, parental, topical, inhalation etc. Topical delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorders like acne or the cutaneous manifestations of a general disease like psoriasis with the intent of containing the pharmacological or other effect of the drug to the surface of the skin or within the skin. Semi-solid formulation in all their diversity dominate the system for topical delivery, but foams, spray, medicated powders, solution, and even medicated adhesive systems are in use (Surver and Davis, 2002). Co-crystals, a well-known but understudied family of crystalline solids, have piqued the interest of crystal engineers and pharmaceutical scientists in the recent decades and the pre-formulation stage currently includes the drug development process. Co-crystallization has proven a valuable strategy in the design of pharmaceutical materials with desired properties since the advent of crystal engineering (Trask *et al*., 2006). The co-crystals technique is unique in that it has no effect on the drug's pharmacological qualities, but it may improve its efficacy, also bioavailability and number of physicochemical characteristics including solubility (Yoshimura *et al*., 2017), stability (Jasani *et al*., 2018), dissolution, melting point and Permeability (Sanphui *et al*., 2015; Dai *et al*., 2016)

Topical drug delivery

A topical drug delivery system is a local drug delivery system for the delivery of topical drugs through the skin for the treatment of skin disorders. These systems are commonly used for local skin infections. Formulations are available in different forms, from solid to semi-solid to liquid. If the drug substance in solution has a favorable lipid/water partition and it is a non-electrolyte, the absorption of the drug is improved through the skin (Hardenia *et al*., 2014). A topical medicine delivery system is a way to deliver a drug that's applied onto a particular part of the body, generally the skin, to treat colorful nourishment (Myers, 1992).

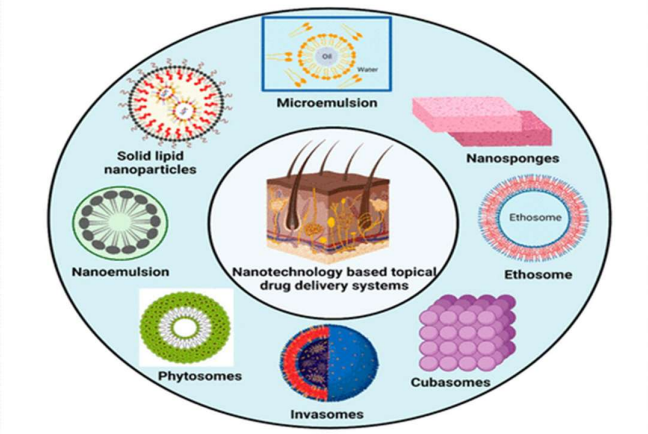

Figure 1: Various nanocarriers employed in topical drug delivery

Advantages

Avoidance of first pass metabolism.Convenient and easy to apply.Avoid of risk.Inconveniences of intravenous therapy and of the varied conditions of absorption like Ph changes presence of enzymes gastric emptying time etc.Achievement of efficacy with lower total daily dosage of drug by continuous drug input.Avoid fluctuation of drug levels inter- and intrapatent variations (Kanawade and Gowekar, 2021).

Disadvantages

Possibility of local skin irritation at the site of application.Contact dermatitis due to some drug may occur.Some drugs with poor permeability are difficult to penetrate via the skin.Drugs with larger particle sizes are difficult to penetrate.Possibility of allergenic reactions.Drugs with a very small plasma concentration can be used for action (Kute and Saudagar, 2013).

Structure of the skin

The skin is a largemulti-layered organ, skin serves as a hedge against physical, chemical, attack. Some accoutrements similar as nickel ions, mustard gas, oleoresins, from Rhus Toxicodendron, generally known as bane ivy, can access the hedge, but utmost of the substance can not. The skin act as thermostat in maintain body temperature, securities the body from irruption by microorganism, protects againstultra-violet shafts, and play a part in the regulation of blood pressure (Patel *et al*., 2016).

Layers of the skin

Epidermis: The epidermis is the thin, external subcaste of the skin that's visible to the eye works to give protection for the body. The epidermis subcaste provides a hedge to infection from environmental pathogens and regulates the quantum of water released from the body into the atmosphere through trans epidermal water loss. Epidermis contains cells that produce color and cover vulnerable system. Epidermis layers- stratum corneum (wanton cell subcaste), It's made up of three layers in thicker corridor stratum granulosum(grainy subcaste), stratum lucidum (Clear subcaste), stratum spinosum(prickly subcaste). The stratum corneum is responsible for the hedge function of the skin and behaves as a primary hedge to the percutaneous immersion (Lakshmi *et al*., 2017; Sajid *et al*., 2015).

Dermis: The next layer of skin in the dermis is a thick and elastic layer of fibrous tissue mainly composed of collagen elastin and fibrillin that gives the skin its suppleness and strength. The dermis contains nerve endings sweat glands sebaceous glands hair follicles and blood vessels9. The dermis is a collagen-rich vascular connective tissue containing mucopolysaccharides collectively known as the stroma (Chandel *et al*., 2013)

Hypodermis: The dermis is the inner layer of the skin. It is the layer of contact between the skin and underlying body tissues such as muscles and bones. The sweat glands, sebaceous glands, and hair follicles enclose themselves in the epidermis, but they originate in the dermis. Sweat glands secrete a dilute salt solution onto the surface of the skin. The evaporation of this dilute salt solution cools the skin, which is important for regulating body and skin temperature. These routes are found throughout the body. The amount of (soft) diluent produced depends on the ambient temperature, the amount of heat generated by skeletal muscle activity, and various emotional factors. Sebum is an oily liquid that is secreted in the hair follicles and from there to the surface of the skin (Sowmya *et al*., 2015)

Skin Accessories: Sweat glands produces sweat of pH 4-6.8 and absorbs medicines, secretes proteins, lipids and antibodies. Its function is to control heat.

Hair Follicles: They've sebaceous glands which produces sebum and includes glycerides, cholesterol and squalene.

Classification of topical drug delivery systems

Solid preparation: Topical Powders, Plasters Ointments, poultices.

Semi solid preparation: Creams, Poultices, Gels, Pastes, ointment.
Liquid preparation: Liniment, Lotions, solution, tinctures, Emulsions, Suspensions, Paints.
Miscellaneous preparation: Transdermal drug delivery systems, Tapes and Gauzes, Rubbing alcohols, Liquid cleanser, and Topical aerosol (Bani and Bhardwaj, 2021).

Pathways of medicine immersion through the skin

Trans follicular route- Trans follicular route is the shortest pathway that medicine has to follow the systemic rotation that provides a large area for prolixity of medicine. Mortal skin contains 40- 70 hair follicles, 200 to 250 sweat glands on every sq.cm. of skin area. Substantially water answerable substance are diffused briskly through accessories than that of other layers.

Transcellular route- Medicine delivering through this route passes from corneocytes which has largely doused keratin creating hydrophilic pathway. The medicine passes through the corneocytes of stratum corneum.

Intercellular route- Intracellular region is filled with lipid rich unformed material. In Intracellular pathway the medicine diffuses through the nonstop lipid matrix present between the cells (Subhash and Sopan, 2023).

Treatment Approaches for Various Disorders Using Topical Drug Delivery

The skin controls the entry and exit of many chemicals, preventing moisture loss and controlling body temperature to preserve balance as homeostasis within the body. Various skin disorders treated by the topical delivery approach are mentioned below.

Acne: The skin condition that affects a person's appearance and is accompanied by chronic inflammation of the sebaceous glands, usually in the back and face area,is termed acne (Tan and Bhate, 2015; Dessinioti and Katsambas, 2010). The factors responsible for acne development are, namely, colonization of propionibacterium acnes, excessive androgen levels, proinflammatory cytokine release, and abnormal keratinization of the sebaceous glands (Poomanee *et al*., 2018). The liposomal hydrogel (3DP-NH), using reverse phase evaporation techniques and containing Cryptotanshinone (CPT), was formulated for pimples. Three-dimensional (3D) printing technologies have the ability to facilitate the personalized treatment of acne (Eady *et al*., 2003).

Atopic Dermatitis: Atopic dermatitis (AD) or eczema is a skin condition with chronic inflammation that exhibits signs of extreme swelling, oozing in patients, itching, and redness (Boneberger *et al*., 2010; Devillers and Oranje, 2006). Compared with the current topical therapeutic drugs in AD, the overall experimental findings indicate that this novel topical platform can provide better efficacy in AD treatment (Badihi *et al*., 2020).

Melanoma: The deadliest type of skin cancer is melanoma, and its successful treatment is possible in the initial stage with the help of surgery alone and has a higher rate of survival. However, the survival rates decrease considerably after metastasis (Singh *et al*., 2017; Tracey and Vij, 2019). Therefore, the topical application of chemotherapy is an effective route for successful skin cancer treatment (Luo and Shen, 2017; Brys *et al*., 2016).

Psoriasis: Psoriasis is a long-term inflammatory multifactorial skin disorder condition driven by hyperproliferative epidermis responses due to the development and hyperactivation of immature keratinocytes (Gudjonsson *et al*., 2004; Cornell, 1992). Topically applied Carbopol-based liposomal gel, coencapsulated with curcumin and ibrutinib, was prepared by Jain and his team for the synergistic approach to enhance the efficacy against psoriasis (Jain *et al*., 2022).

Vitiligo: Depigmentation of skin accompanied by macules of white color without melanocytes is called vitiligo (Doppalapudi *et al*., 2017; Hann *et al*., 1991). It can severely impact a person psychologically and can even cause suicidal thoughts (George and Burks, 1955). The topical formulation of an ethosome-based hydrogel loaded with methoxsalen was fabricated to treat this particular condition. Accumulating ethosomal formulation in dermal and epidermal layers resulted in increased skin permeation. Thus, the formulation improved percutaneous penetration of methoxsalen; therefore, it can be employed for vitiligo treatment (Garg *et al*., 2016).

Challenges of developing topical drug delivery system

The challenge of developing a successful topical product stems from the several requirements that a formulation must meet (Bhowmik, 2012):

Container Selection and Product Stability: Depending on the properties of the combined ingredients, a dispensing container will be chosen (i.e., tube, jar, can, etc.) to provide a stable physicochemical environment that protects the active compound(s) from chemical degradation. The formulation can be a liquid or semi-solid, monophasic or multiphasic.

Skin Penetration: Skin penetration is the primary challenge to deliver the bioactive agents into the skin that follows Fick's first law of diffusion, which states the transfer rate of solutes as a function of the concentration of the various ingredients, the size of the surface area to be treated and the permeability of the skin (Sultana *et al*., 2014).

Cosmetic Acceptability: In today's self-image conscious world, patients are looking for topical products that are not only safe and effective, but also cosmetically acceptable and easy to apply. Acne patients are mainly comprised of teenagers or young adults, and therefore, products that offer convenience and are minimally disruptive to daily routines increase the

level of compliance, and ultimately, the efficacy of the topical therapy. This may require formulations that spread easily, or in the case of facial acne, the ideal formulation should leave minimal residue or oiliness.

Co-crystal

Cocrystal is a crystalline structure composed of at least two components, where the components may be atoms, ions or molecules (Stahly, 2009). This definition is sometimes extended to specify that the components be solid in their pure forms at ambient conditions (Ter *et al*., 2009). However, it has been argued that this separation based on ambient phase is arbitrary (Bond, 2007).Co-crystals are the preparation which helps to improve physicochemical properties of many pharmaceuticals. Physicochemical properties involves dissolution rate, solubility, chemical stability, and moisture uptakes influence therapeutic efficacy values.

Definition of Co-crystal: Co-crystals can be defined per the USFDA as "crystalline material composed of two or more different molecules, one of which is the active pharmaceutical ingredient, in a defined stoichiometric ratio within the same crystal lattice that is associated by non-ionic and non-covalent bonds" (Sakhiya and Borkhataria, 2024).

Advantages

Co-crystals are the stable crystalline form as compared to amorphous dosage form. Co-crystals increased solubility thus increased bioavailability. Co-crystalization technique can be used for purification. Co-crystals improve the product quality by improving stability (Sanju, 2022).

Disadvantages

It is difficult to scale up co-crystals. Co-crystal formation is not appropriate in thermo-labile drug. There is a chances of impurities if polymer use are not biocompatible. A large number of experiment are necessary to measure the ternary phase diagram. In some methods of co-crystals formation there is chances of formation of large amount of environmental pollution.

Physico-chemical properties

Melting point: So many APIs are in liquid form at room temperature due to their low melting point but cocrystal has ability to alter their melting point so that it can persist in solid for at room temperature. Melting point is the physical property of solids substance, which is used to determine the purity of the product with sharp melts and narrow ranges (Abourahma *et al*., 2011).

Solubility: The solubility of any APIs is the most important characteristics for their absorption. Solubility can also decide how much amount can be absorbed through GIT. So many APIs has low solubility due to which less absorption thorough GIT but it can be overcome by Cocrystallization method for example:- IND-SAC Cocrystal. A cocrystal will have a different solubility as compared to either of the starting materials due to the altered underlying crystal structure (Bavishi and Borkhataria, 2016).

Bioavailability: So many drugs has less bioavailability due many reasons in which solubility is also a reason for their fluctuation in bioavailability by Cocrystallization we can enhance their solubility & enhance the bioavailability of respective drug. Cocrystals have potential to enhance the delivery and clinical performance of drug/medicine by modulating drug solubility, pharmacokinetics, and bioavailability. The approach of cocrystallization is particularly important in situations where the cocrystal transforms rapidly to a low-solubility form of the drug and is unable to maintain desired solubility levels necessary to ensure optimal absorption (Stanton *et al*., 2010).

Stability: It is also imperative study has to be done during the development of new dosage formulation. Different stability studied like chemical stability, thermal stability, solution stability and photostability should be performed during development of pharmaceutical cocrystals (Schultheiss and Newman, 2009).

Method of Preparation of Co-crystal

1. Spray Drying Method: Spray – drying is a well-known process that has been used for several pharmaceutical applications such as micro and nano particles for pulmonary delivery, solid dispersions, viral vectors, and pure drug particles.The cocrystals nucleate and grow within highly supersaturated regions of the drug substance due to rapid solvent evaporation and solidification of the generated droplets, the presence of coformer and the drug – coformer interactions in the liquid phase. For drug-conformer incongruent solubility system, where pure cocrystal can't be formed using solvent evaporation method, cocrystallization using spray drying method can be used as an alternative method. Thus, spray drying method can supply a novel atmosphere for the preparation and scale-up of Cocrystals (Vehring, 2008).

2. Grinding Method: In this techniques materials are mixed, pressed and crushed in a mortar and pestle or in mill in general aspects this technique provides particle size reduction but in case of co-crystallization these method is viable for solid-state grinding along with liquid state grinding (Diwan, 2020).

a. Dry (Neat) Grinding: It is also known as mechanochemical grinding or solid-state grinding. Dry grinding can be accomplished in a variety of ways, including mechanical grinding with a ball mill mixture, vibratory milling, or manual grinding with a motor and pestle. The dry grinding procedure results in the creation of cocrystals. The author indicated

that the properties of piroxicam co-crystal and formed orodispersible tablets had been adjusted, resulting in faster disintegration and a higher dissolution rate (Aitipamula and Vangala, 2017).

b. Wet Grinding (Liquid- assisted grinding): Liquid-assisted grinding (LAG) is a modification of the solidstate grinding procedure that involves the addition of a small amount of solvent. The additional solvent acts as a catalyst in the creation of co-crystals. When compared to the solvent evaporation approach, this method is more favorable because it requires less time and less solvent. The disadvantage of this procedure is that it requires a large amount of solvent for preparation (Gadade and Pekamwar, 2016).

3. Solvent Evaporation Technique: This is the most common and dependable procedure for producing co-crystals. The medication and coformer are chosen and dissolved in a shared solvent at an appropriate stoichiometric ratio before being evaporated at room temperature to produce co-crystals (Aakeroy *et al*., 2003).

4. Slurrying: Slurry crystallization is a simple technique that involves adding solvent to the API as well as a suitable coformer. The physical stability of the crystallization solvent to co-crystals and its solid former mostly influences the choice of this procedure. The creation of co-crystals is accomplished by adding coformer to the solution and stirring it. The solvent is subsequently evaporated at room temperature to obtain cocrystals, which can then be characterized by PXRD (Alatas *et al*., 2015).

5. Hot Melt Extrusion Method: In hot melt extrusion technique, the Cocrystals area unit ready by heating the drug and co-formers with intense intermixture that improved the surface contacts while not use of solvent. The restrictions of this methodology embrace each coformer and API ought to be compatible in liquefied kind and not used for unstable medicine. Hot-Melt Extrusion method is a method that combined cocrystal formation and drug-formulation process, exhibit a simpler way to manufacture a drug product, involve not only drug and coformer, but also an inert matrix (Li *et al*., 2017).

6. Supercritical fluid atomization method: Supercritical fluids use offers additional advantages compared to the classical cocrystalproduction methods. Co-crystallization with supercritical solvent (CSS) is a method where an API and a co-crystal former are mixed together by magnetic stirring after being pressurized by supercritical CO2 in a highpressure vessel (Padrela *et al*., 2010).

Characterization

Fourier transform infrared spectroscopy: IR spectroscopy was employed to determine the probably interaction between drug and conformer. The samples were dispersed in KBr paller and scanned using Shimadzu IR spectrophotometer between 4000-4000cm-1 with resolution of $4cm^{-1}$ (Pindelska *et al*., 2017)

Differential scanning calorimetry: The thermal behavior of drug alone and co-crystal was determined by Differential scanning calorimetric studies by mattlet Toledo DSC 8229 Module.Weighed samples were heated in aluminum pans at rate of 5º C/min from 0 to 300ºC temperature range, under a nitrogen stream. The instrument was calibrated using medium and empty aluminum pan was used as a reference (Jingkang *et al*., 2007).

Raman spectroscopy: Raman spectroscopy is an analytical method to differentiate between polymorphs, salts, cocrystals, solid solutions and hydrated salts, since the sample preparation uses only small quantity of substance. It is also a non-destructive approach for characterizing compounds, provided that the frequency of the transmitted Raman radiation is small. In particular, Raman spectra are useful for cocrystallization, because the oscillations in the cocrystals are different from the initial materials (Elbagerma *et al*., 2010).

Scanning electron microscopic studies: An electron microscope called a SEM scans the material using an electron beam. The atoms that make up the sample interact with the electrons to produce signals that provide information about the surface topography of the sample. Using double-sided tape and a vacuum, specimens were placed to a metal sample holder with a 12 mm diameter and coated with gold-palladium. The co-crystal micrograph and particle size are calculated using it (Kiang *et al*., 2009).

Applications of co-crystals

Compared to other solid-state modification techniques employed by pharmaceutical industry, cocrystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution (Vishweshwar *et al*., 2006; Peterson *et al*., 2006). Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization (Trask, 2007).

Conclusion

The development of topical drug delivery systems and co-crystals represents significant advancements in pharmaceutical science. While challenges remain, ongoing research and technological innovations continue to enhance the efficacy, safety, and acceptability of these therapeutic approaches.

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