(TRANS)DERMAL FILM-FORMING SYSTEMS: CHALLENGES IN DESIGN AND CHARACTERIZATION OF AN INNOVATIVE PRODUCT

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Topical route of drug application offers a range of possibilities, but often with poor patient adherence. Development of formulations that form a discrete film upon application compiles the advantages of (trans)dermal patches and conventional liquid or semisolid topical dosage forms, leading to efficient drug penetration with less frequent use. However, development and characterization of these systems is challenging, and the current draft guideline of the European Medicines Agency (EMA) has opened additional questions (1). Optimal selection of film-forming polymers (often from the groups of vinyl alcohols, silicones or methacrylates), volatile and non-volatile solvents, plasticizers and/or penetration enhancers, usually requires assistance of an experimental design, along with a holistic QbD concept. Active pharmaceutical ingredient's (API) solubility must be sufficient in both volatile and non-volatile excipients, leading to its transient supersaturation, without crystallization (2). Thus, non-volatile excipients generate a matrix film structure that enhances drug delivery into deeper skin layers, without compromising skin barrier integrity. Undoubtedly, when aiming for transdermal delivery, the API itself must meet certain requirements (logP=1-3, MW<500 Da), with the formulation pH set to 7-10. As critical quality attributes (CQAs) of film-forming systems, film drying time, flexibility, integrity and skin substantivity are commonly defined. For volatile solvent-based topical products, EMA's draft guideline introduced a need to describe transformation/metamorphosis of the drug product on administration. Unfortunately, no specific characterization method is recommended. Hence, the researchers apply a range of techniques: from sophisticated (localized nanothermal analysis, photothermal microspectroscopy), combination of established (rheology, tribology, texture analysis), to development of customized protocols.

References

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(TRANS)DERMALNI FILM-FORMIRAJUĆI SISTEMI: IZAZOVI U DIZAJNU I KARAKTERIZACIJI INOVATIVNOG PROIZVODA

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Dermalni put primene lekova nudi brojne mogućnosti, ali je često praćen nezadovoljavajućom adherencom. Razvoj sistema koji nakon primene obrazuju diskretan film na koži, spaja prednosti (trans)dermalnih flastera i konvencionalnih farmaceutskih oblika za primenu na koži, tečne ili polučvrste konzistencije, nudeći efikasnu penetraciju uz manje učestalu primenu. Međutim, njihov razvoj i karakterizacija praćena je mnogim izazovima, a važeći nacrt vodiča Evropske agencije za lekove (EMA) otvorio je i neka nova pitanja (1). Optimalan izbor film-formirajućih polimera (često iz grupe vinilalkohola, silikona ili metakrilata), isparljive i neisparljive frakcije rastvarača, plastifikatora i/ili ubrzivača penetracije, obično zahteva pomoć eksperimentalnog dizajna, a svakako holistički QbD koncept. Lekovita supstanca mora biti u dovoljnoj meri rastvorljiva kako u isparljivim, tako i u neisparljivim ekscipijensima, pružajući stanje supersaturacije nakon obrazovanja filma, bez kristalizacije (2). Na taj način, neisparljivi ekscipijensi obrazuju svojevrsnu matriks strukturu filma, koja olakšava transport lekovite supstance u dublje slojeve kože, bez narušavanja integriteta kožne barijere. Naravno, kada je reč o transdermalnoj isporuci, i sama lekovita supstanca mora ispuniti određene zahteve (logP 1-3, Mr < 500 Da), a pH formulacije bi trebalo da se nađe u opsegu 7-10. Kao uobičajeni kritični atributi kvaliteta (CQA) ovih sistema prepoznati su vreme sušenja, fleksibilnost, integritet filma i supstantivnost na koži. Nacrt vodiča EMA uvodi potrebu za ispitivanjem transformacije (metamorfoze) formulacije tokom/nakon primene na kožu. Nažalost, preporučena metodologija nije navedena, te istraživači primenjuju čitav niz tehnika, od sofisticiranih (lokalizovana nanotermalna analiza, fototermalna mikrospektroskopija), preko kombinacije etabliranih (reološka, tribološka, teksturna analiza), do razvoja posebno prilagođenih protokola.

Literatura

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