IJBPAS, March, 2024, 13(3): 1066-1085

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

EXECUTION OF QBD TECHNIQUE IN SEMISOLID DOSAGE FORM FOR TOPICAL DRUG DELIVERY

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Received 4th Feb. 2023; Revised 15th March 2023; Accepted 4th April 2023; Available online 1st March 2024

https://doi.org/10.31032/IJBPAS/2024/13.3.7623

ABSTRACT

The quality of any pharmaceutical product is always considered to be an important concern from the time when the pharmaceutical field came into existence. When a product is being developed by a pharmaceutical manufacturer, the testing and evaluation process of that product turns out to be very expensive as well as it is quite a time taking process also. The assurance and belief that the pharmaceutical product manufactured is of the requisite quality and efficacy in terms of its final output can be brought up with the implementation of Quality by Design (QbD) methodology. The topical formulations have been used from many decades which possess a semisolid character and comprises of gel, ointments, creams etc. The topical drug delivery in an optimum manner requires an important prerequisite of maintaining the therapeutic level of the drug throughout the time period of treatment. The requirement of QbD technique in a process development is encouraged by many pharmaceutical manufacturers in the present time as this could be used efficiently in identifying the parameters which generally affect the quality as well as efficacy of a pharmaceutical product. The primary QbD elements such as quality target product profile, critical

quality attributes, critical material attributes, critical process parameters have been used during the manufacturing of the product so that the required profile of the product could be achieved.

Keywords: Quality by Design (QbD), Topical drug delivery, Semisolid dosage form, QbD tools, Advantages, Quality target product profile, Critical quality attributes, Critical material attributes, Critical process parameter

INTRODUCTION

Skin infections are observed due to bacterial, fungal, etc. exposure and it leads to the redness and swelling **[1-4]**. It could be efficiently treated with the help of topical formulations in which the formulation is being applied on the site topically. Such type of drug delivery systems is known as topical drug delivery system and the delivery of drug through this system have the pharmacological action on the superficial part of the skin or within the skin **[5]**. Many semisolid formulations have been extensively used since time for delivering the drug topically such as gels, creams, lotions, ointments etc. **[6-9]**. Beside these, few other formulations have been remained in existence when talking about the topical systems such as sprays, foams, medicated powders, solutions as well as medical adhesive systems **[10]**. Absorption of a drug molecule of lower dose is limited to a smaller area of skin **[11]**.

Some of the prominent advantages of the topical drug delivery system are highlighted below:

- The evasion of first pass liver metabolism **[12]**
- High spreading ability rate and ease of use **[13]**
- Patient compliance is enhanced **[14]**
- Self-medication could also be involved **[15]**
- Site specific drug delivery **[16]**
- Discontinuation of the medication is feasible **[17]**
- Drugs with diminutive biological half-lives are appropriate candidate **[18]**
- Avoidance of fluctuation in the drug levels **[19]**

Topical drug delivery system has some limitations like i) Irritation of the skin or allergic reaction at the site of application is observed in some events; ii) Emergence of contact dermatitis in some cases; iii) Difficulty in the penetration of poorly permeable drugs through the dermal route; and iv) Large particle size drugs could not penetrate the dermal route.

The ObD technique plays an important role in overcoming all the above said limitations and

its implementation becomes crucial to produce a desired quality product. It results in the improvement of the standard of manufacturing process and establishes the optimum conditions for the development of therapeutic products with the presence of high quality and desired clinical results.

The various aspects that have been focused in this review paper are the important attributes which are related to topical formulations which effect the therapeutic performance and quality of such kind of pharmaceutical preparations. The different components of QbD have been discussed related to the semisolid topical preparations.

Barrier properties of skin

The biggest challenge faced by the formulation scientists who are involved in the problem in delivering a therapeutically effective amount of drug through the different layers of skin **[20]**. In the development of topical formulations, both of the active and passive drug delivery plays a key role. The skin acts as a tough barrier in delivering the drug through the topical and transdermal route of drug delivery. The outer most layer of the epidermis which is Stratum corneum, comprises of dead and enucleated keratinocytes which is in the form of multiple layers and seem to be a mortar like structure. This layer is reported to have 15-20 µm thickness **[21]**. To protect from the invasion of harmful pathogens, the stratum corneum provides a strong protection to the body**.** The water concentration gradient is reduced from 75% in the viable epidermis layer to below 30% on the surface. In the transportation of a drug molecule through the surface of skin, both the hydrophilic and lipophillic pathways play a major role. The drugs which are poorly soluble pose a greater problem in being penetrated through the skin. The size which the drug molecule bears also has a vital role in its drug penetration through the skin. It has been reported in the previous literatures that the lipophillic and small sized drug molecules have a much higher capability to cross the skin and penetrates quite easily. On the other hand, the drug molecule which possesses a larger size and is hydrophilic in nature is not easily penetrated because such kind of drug molecules has low permeability in the stratum corneum **[22]**. It is important to emphasize here that all of the current marketed topical drug products have a hydrophilic nature.

Mechanisms involved in drug penetration through the topical route

The penetration of the drug molecule from the formulation through the skin is affected by mainly three considerable factors. The prime factor is the physicochemical property of the drug molecule which it possesses; the next

factor is the type of formulation and lastly the method of delivery of the drug molecule is also a significant factor. There are mainly three pathways through which a particular drug molecule which is delivered via topical route gets penetrated into the different layers of skin. The three pathways of the drug penetration are the Follicular route, Transcellular route and Intercellular route **[23, 24]**.

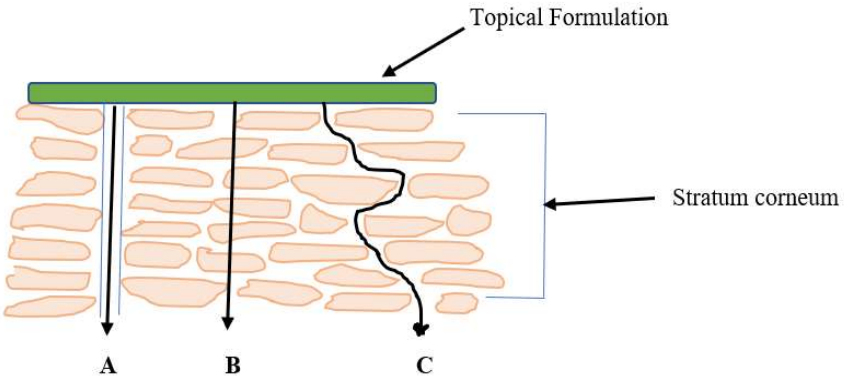

Figure 1: Depiction of the three pathways of drug penetration from a topical formulation: A: *Follicular route, B: Transcellular route, C: Intercellular route* [25]

Nano formulations and their effectiveness in the topical drug delivery:

Nanocarriers forms an important means to deliver the drug molecule topically and these generally vary in the size from 1 to 100 nm. The drug molecules are being entrapped or encapsulated in these nanocarriers which are none other than particles or globules in structure. This drug delivery system has also been used to deliver the drugs into the deep situated tissues of skin and in enhancing the topical effects of drug locally. The achievement of systemic therapeutic effects of the drug is also resulted through nanocarriers. Nanoemulsion, nanoparticles, liposomes, dendrimers, ethosomes, aquasomes, niosomes are some important examples of nanocarriers used in the topical drug delivery **[26]**.

Quality by testing (QbT)

The quality of the ingredients/components used in the manufacturing of formulation is of utmost importance and during its manufacturing, this quality could be verified by employing the technique of QbT which is referred to as Quality by testing. The components or ingredients which is to be used in the manufacturing process can be used only if they confirm the FDA approved specifications along with the requirements of the manufacturer and adherence of the USP

standards. The quality and the superiority of the product is based on the protocols followed during the manufacturing process and also the strict adherence of the specifications used. The final product after manufacturing is extensively tested by using the technique of QbT which further confirms the quality as well as the fineness of the manufactured product. It is required to mention here that the technique of QbT is a time taking method, involves a lot of efforts and further it is a costly technique also **[27]**.

Quality by Design (QbD)

QbD technique holds with it an influential idea which tells that **"**The quality cannot be tested in the product, but it should be built into the product". QbD is a technique which is an organized technique which involves some risk with it but it is believed to be a proactive tactic in the development of pharmaceutical products according to the ICH Q8 guidelines **[28]**. The implication of QbD is based on some predefined objectives and the thorough understanding of process involved which is built on the scientific principles and quality risk management. The present time needs the strict adherence of QbD technique by all of the leading pharmaceutical manufacturers in an innovative way in order to progress in this competitive era.

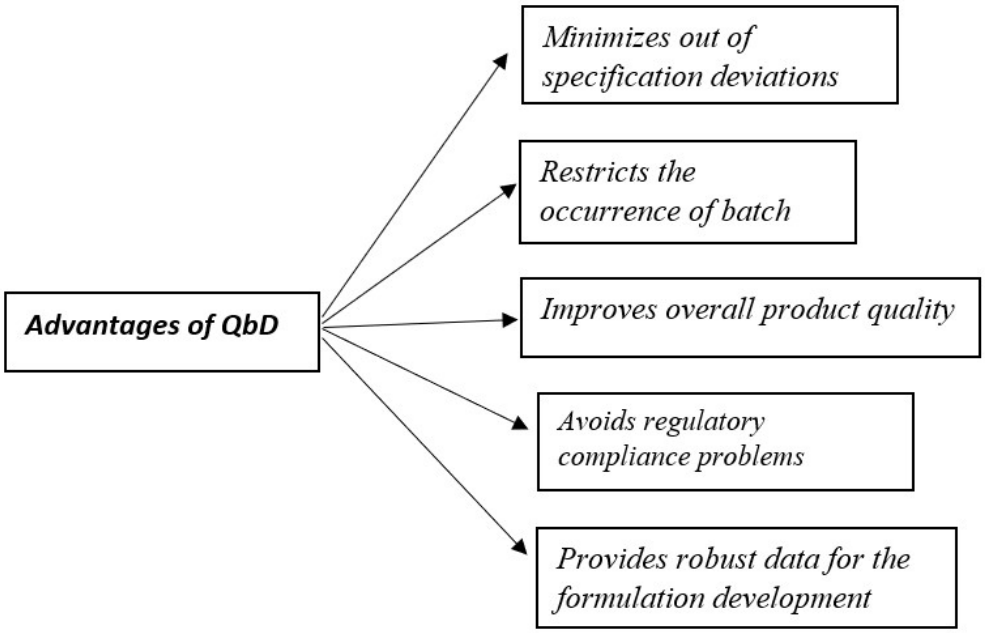

Figure 2: Advantages of QbD in formulation development

Elements of QbD

The most commonly recognized QbD elements comprise of the following components*:*

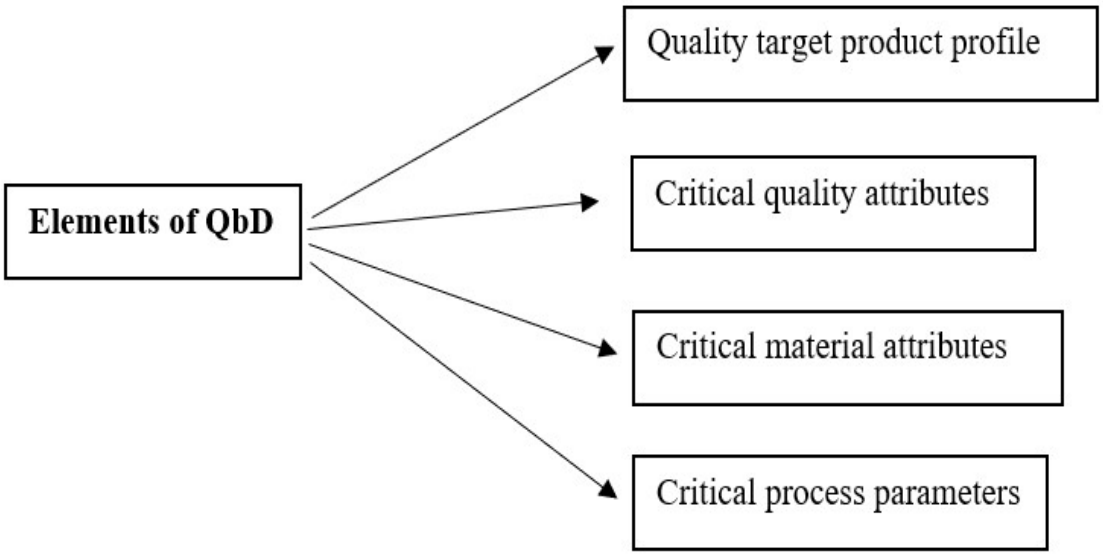

Figure 3: Elements of QbD

The quality target product profile (QTPP) comprises of form of a dose, delivery systems, dosage strength(s), container and closure system used for the packaging of final drug product, etc. The characteristics of drug with respect to its quality to be achieved are summarized in QTPP. It further provides a strong evidence that the product which is being manufactured will be reached in its final stage with all the required qualities and standards **[29]**.

The chemical, physical, biological or microbiological properties of an output material including the final drug product are comprised of the critical quality attributes (CQAs). With respect to the safety and effectiveness of the drug product, CQA is an important prerequisite and must be deliberately followed **[30]**.

When considering the input materials, their physical, chemical, biological and microbiological properties are comprised in the critical material attributes which is generally referred to as CMAs. The critical material attributes must be in the acceptable limit or the range of distribution so that the targeted quality of drug molecule as well as the excipients must be accomplished **[31, 32]**.

Quality, description, appearance, contamination, assay as well yield of the end product is also determined by the critical process parameters (CPPs) which has been followed in the earlier stage of production as well as during the process **[33]**.

'Risk assessment' (RA), 'Design of experiments' (DOE) and the Process analytical technology (PAT) are the important tool of the QbD technique **[34]**. When focusing on the first tool which is the Risk assessment, it involves some steps like identifying the potential risks, the analysis of these risks and at a later stage, the evaluation of that risk is being done. The foremost stage in this is the Risk assessment in the sequence of quality risk management process and then, the risk control and risk review are also included. Minimization of the level of risk is the prime objective of risk control. In establishing a relation between the factors responsible for affecting a process and the output of that process, the design of experiment is done and found to be an effective technique. It is a decisive step to recognize optimal conditions, CMAs, CPPs, and the ultimate design space. The performance and the quality of raw materials, in process materials and the final product is established by the Process analytical technology which further confirms the production of an end product that constantly imitates to establish quality and the required performance standards **[35-37]**.

Implementation of QbD in the development of topical semisolid formulation

A certain series of steps must be followed in the manufacturing of topical formulations that are based on the concept of QbD techniques to achieve a desired final product. The preliminary step is to identify the QTPPs to achieve the desired performance of the product along with the implementation of QbD in product development **[38]**. The next step which has to be followed after the identification of OTPP is to identify the CQAs followed by CMAs and CPPs. Arrangement of a setup and execution of DoE to link CMA and CPPs to CQAs is also required to illustrate that how these parameters impact the QTPP. Afterwards, a process design space should be defined, which will lead to an end product with the selected QTPP. The final step will be to recognize and control the causes of variability within the excipients and the manufacturing process. A continuous process of screening is followed diligently which will result into the improvisation of the manufacturing process and also validate consistently the quality of the product.

CQAs of topical semisolid dosage form [39]

When referring to a drug product, the integral component of this drug product is known as the CQAs. The quality attributes of a therapeutic product are very much dependent upon these CQAs only. To confirm the quality of the product that is desired, various types of

physical, chemical, biological, or microbiological properties must be within a suitable limit or range. It could be emphasized here that a thorough monitoring of all of the CQAs could definitely result into a consistent product with its optimum performance. The CQAs are influenced by different elements of the drug product, thus there are different types of CQAs which are associated with the drug, excipient as well as the packaging components etc.

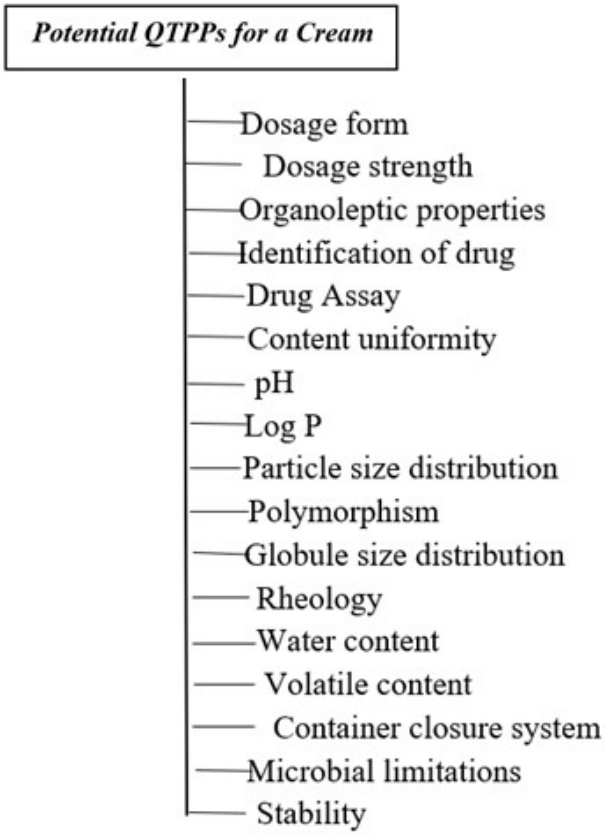

Figure 4: Example of potential QTPPs for a semisolid dosage form

Particle size

The particle size is a very important attribute in the design of a topical formulation where an Active Pharmaceutical Ingredient (API) is to be suspended in a semi solid preparation and to achieve the desired final product, the particle size has to be vigilantly selected. The selected particle size must not be changed throughout the process otherwise it will be resulted into certain problems like variability in the bioavailability of the drug from the semisolid dosage form. The change in the particle size of drug suspension is possible due to phase separation or aggregation or it may also occur due to polymerization or coagulation. The change in particle size can

also possibly result into grittiness in the final product which will again result into the problem of patient compliance **[40]**.

Globule size

When consideration is given to the emulsion preparations, then the size of globule is an important parameter and a change in size of the globule may cause certain kind of stability issues in the final product. Drug release profile may also get modified if occurrence of change in the globule size is observed. The previous literatures have also reported the problems of drug entrapment alteration and a different partitioning behavior of the used API. Instability issues have also been seen due to the change in globule size. The manufacturing processes such as the rate of mixing of ingredients, temperature and the order of addition of excipients can have foremost influences on the globule size development and must be considered **[41]**.

Organoleptic properties

These properties include the qualitative description of drug product such as its color, smell, texture etc. The color of the final product is a significant factor which helps in achieving the patient satisfaction. A change in color is susceptible during the storage of product. Implication of quantitative tests should be established to set the satisfactory criteria for the color variation.

Drug identification and assay

The assay of a drug affects clinical effectiveness of the drug product and the acceptable limits are between 90-110%.

Polymorphism

The physicochemical properties like aqueous solubility, stability, melting point, density, texture and processing behavior of polymorphs of the same drug could get changed with the alteration in the form of the drug molecule. Additionally, a presumption could be established here that the different polymorphic forms of the same active ingredient may result into a modification in the shape and size which results into the modification of the microstructure of the system. This can lead to a change in skin permeation and the retention behavior **[42, 43]**.

pH

The pH of the product is a crucial factor in the overall design of the topical formulation. Solubility of some ingredients used in topical preparations could be dependent on pH. Thus, any change in pH throughout a product's shelf life may modify the solubility and bioavailability of the API, which may affect the overall therapeutic performance of the product. Some other properties that could get affected by change in the pH are stability, viscosity, zeta potential, droplet size, size

distribution, electrostatic interactions etc. Hence, the alteration in pH should be strictly controlled throughout the process to get a desired final product **[44, 45]**.

Rheological properties

Rheological properties have an influence on release of drug from the topical formulation, skin permeation and skin retention of the dosage forms. Rheological behavior varies for different topical dosage forms and effect the stability of formulation, physical appearance and performance during the shelf life of the product. Rheological properties of the formulation are a combination of CMSs and CPPs **[46, 47]**.

Evaporation of volatile materials

Topical formulations with different percentages of water and volatile substances can be separated into different types of dosage forms. For instance, as ointments are required to be retained longer on the skin, low evaporation rates are desired, which can be provided by high polyethylene glycol or mineral oil content. On the other hand, gels get evaporated more rapidly due to a higher proportion of water and alcohol. Evaporation of volatiles such as water and alcohol from a formulation could lead to stiffening and changes in the microstructure of the formulation. Loss of water and volatiles can lead to changes in solubility of the active ingredients in the formulation which may further lead to change in the retention time of formulation and drug permeation efficiency **[48]**. Thus, the proportion of volatile excipients in topical products could be a CQA affecting factor. Evaporation can also be affected by CMAs such as the type and quantity of the volatile ingredients.

Container and Closure system

The topical semisolid formulations are packed in different dispenser systems such as jars, tubes and different type of pumps. The selection of container depends upon the flow property or the viscosity of the product. The different dispensing modes may exert different shear force on the product that may become a reason of alteration in the microstructure of the formulation. If there will be an alteration in the microstructure, then it could lead to a changed performance of the product. The degradation of product due to the interaction with container is fairly common in the topical formulations as these types of preparations are high in water content and this becomes a reason of product degradation **[49]**. According to the FDA stability guidelines, stability should be examined in the actual dispenser form that is probable to be marketed when pilot batches are evaluated during product development.

CMAs

The qualitative and quantitative data of drug and excipients both are measured as raw material attribute. In the manufacturing of dosage form, the selection of an appropriate source of drug (API) is the most important step. The quality and purity of the procured API must be thoroughly evaluated along with the temperature of storage, shelf life and stability tests during processing. Thus, the selection of the source of the API is an essential step in the development of pharmaceutical formulations **[50]**. If in a certain formulation, the proportion of APIs are low, the physical characterization is defined by the excipients which contributes to the major part of the formulations. The role of excipients is important in overall altering the performance of an API when the formulation has to be applied on the skin. Both of the quality and stability aspects of the drug in the final product can be affected by the use of different grades of excipients. The next factor to be considered is the inclusion of impurity **[51]**. The presence of impurity in the drug or excipient could lead to an adverse effect on the performance of the final product. Thus, the evaluation of impurity is essential throughout the manufacturing of a desired pharmaceutical product **[52]**.

CPPs

The design of an optimal manufacturing process requires the careful measurement of all the factors such as equipment, facilities, material transfer, manufacturing variables, and QTPP. The major variables that must be considered in the manufacturing of semisolid formulations are the type of mixer, mixing/homogenization time, the mechanical energy input as well as temperature **[53]**. The process parameters using these linked factors need to be recognized and sensibly controlled so that the batch to batch variation could be evaluated. The maintenance and selection of temperature during manufacturing process is also an important factor and it is required to maintain the stability of formulation components including the drug and excipients **[54]**. The factors like dissolution and dispersion of the components is also dependent upon temperature. The consistency of the final prepared semisolid dosage form varies with change in the heating or cooling rate during the manufacturing of the product. Additional heating during processing can lead to degradation of ingredients while inadequate heat can cause drug solubility issues, thus resulting into the product failure **[55]**.

Type of mixer

It is worth to mention here that the shape and size of the mixing tank, its capacity as well as capability to uphold the anticipated

temperature results into the required homogeneity of the product. To achieve a product with uniform distribution, correct combination of tank and mixture blade is required. Hard plastic blades such as teflon blades are recommended by the FDA as these material causes nominal harm to the wall of the tank. The acceptance criteria for content uniformity are usually set at ±0.5% across the top, middle and bottom sample from the tank.

Mixing speed and time

The mixing speed and mixing time are both critical parameters that need to be precisely controlled along with suitable mixers and programmable logic controllers during the manufacturing of the semisolid products. During manufacturing of gels, low shear mixing is characteristically required in order to preserve the viscosity of the product, while emulsification typically requires high shear rates to attain the ideal droplet size. The mixing time can be optimized by identifying the minimum time for dissolution of the components and maximum time to achieve desired viscosity. Over mixing may lead to structural interruption of polymeric gels which can be characterized by a drastic drop in emulsion viscosity, thus it requires to be controlled. Therefore, the mixing speed and time are CPPs that can impact the QAs of the final product **[56]**. Some of the topical formulations based on QbD technique are listed in **Table 1**.

Table 1: Details of topical formulations based on QbD

Name of Drug	Pharmacological Category	Type of Formulation	Objective	Inference	Ref
Itraconazole	Antifungal	Microemulsion based hydrogel	Product Development with probable CQA	Prepared formulation after application of qbd technique was found to be much superior in comparison with the conventional formulation in the treatment of topical infections.	[57]
Fusidic acid	Antibiotic	*In situ* gel	To design and to evaluate the potential use of an *In Situ* gel for topical delivery of fusidic acid	The prepared formulation consisting of fusidic acid showed excellent antimicrobial and wound healing effects and found to be a preferable substitute to the commercially existing cream.	[58]
Levocetirizine	Antihistaminic	Emulgel	Preparation, design and evaluation of levocetirizine loaded emulgel for the treatment of atopic dermatitis	After the conduction of histopathological and biochemical studies, much better therapeutic potential was observed in the qbd applied formulation.	[59]
Voriconazole	Antifungal	Nanostructured lipid carriers (NLCs)	To diminish the incidence and rate of associated adverse	Excellent properties observed in the prepared NLCs gel in targeting the	[60]

			effects during the oral administration of formulation.	**skin and could become a potential choice in comparison with the conventional forms in the case of topical fungal infections.**	
Lidocaine and Prilocaine	**Local anesthetics**	**Microemulsion**	**Modification in the *In Vivo* efficacy of eutectic mixture of lidocaine and prilocaine microemulsion.**	**The topical delivery of lidocaine and prilocaine has been enhanced in a much advanced way through the development of qbd based microemulsion formulation and found to be an excellent alternative to the conventional forms.**	**[61]**
Ketoconazole	**Antifungal**	**Cubosomes**	**Development of cubosomes with lower concentrations of Surfactants**	**Cubosomes with loading of ketoconazole along with the presence of much lesser surfactant concentration was successfully developed which could prove to be an outstanding means for the topical drug delivery.**	**[62]**
Resveratrol	**Antioxidant**	**Polymeric micelles**	**Improvisation in the permeability of drug with respect to scaly and psoriatic skin with the presence of inflammation.**	**An indication in the improved use of the prepared formulation through a significant reduction in the score, serum cytokines level as well as hyperkeratosis.**	**[63]**
Aceclofenac	**NASIDs**	**Gel containing Solid dispersion**	**Development of aceclofenac topical gel consisting of solid dispersion employing QbD technique**	**Absence of skin irritation along with exceptional anti-inflammatory property is observed in the prepared formulation when compared with a marketed gel.**	**[64]**
Luliconazole	**Antifungal**	**Liquid crystalline nanoparticles**	**Elimination of the limitations of Luliconazole conventional dosage forms through QbD technique.**	**The prepared LCNP resulted into an increased skin permeation rate in the delivery of topical antifungal drugs and found to be an effective carrier system.**	**[65]**
Methotrexate	**Anticancer**	**Nanoparticle**	**Development and Characterization of Zein (Natural Polymer) containing nanoparticles for achieving a controlled manner of drug.**	**Improvisation in the chemotherapeutic potential of Methotrexate loaded nanoparticle formulation along with an enhanced extent of drug release.**	**[66]**
Diflunisal	**NSAIDs**	**Nanostructured lipid carriers(NLCs)**	**To improve the penetration and concentration of drug at the site of application**	**This has resulted into a higher concentration of drug in dermis and the penetration was also improved reaching till the deeper layers of skin.**	**[67]**
Acyclovir	**Antiviral**	**Microemulsion**	**Formulation of a safe, efficacious and stable dosage form**	**Microemulsions of Acyclovir by QbD approach were found to be a promising approach and proved to be a safe and stable dosage forms.**	**[68]**

Aceclofenac	**NSAIDs**	**Microemulsion**	**To develop a topical formulation and to avoid the complications associated with oral route.**	**The developed QbD based microemulsion has found to possess a great potential for topical delivery of drug and in overcoming the complications of oral route.**	**[69]**
Desoximetasone	**Corticosteroids**	**Niosome**	**Employment of QbD principles in designing a non-ionic surfactant based niosomal formulation.**	**The optimized formulation was found to efficiently deliver a hydrophilic or a hydrophobic drug to the target site with much improved stability and efficacy.**	**[70]**
Gamma Oryzanol	**Natural- Antioxidant**	**Niosome**	**To achieve the optimization of niosomal formulation by means of the QbD approach**	**The optimized niosomal formulation resulted into a drastic increase in the *Ex Vivo* permeation rate and the drug retention in the dermal layer was also found to be excellent.**	**[71]**

CONCLUSION

The associated demerits of QbT create a base for the establishment and popularization of QbD techniques in the pharmaceutical manufacturing. The assessment and identification of the material and process attributes leads to production of desired product. By employing this technique, the manufacturer can achieve the desired quality and therapeutically efficient product. The topical dosage forms have become the primary choice in the present era due to its noninvasive, patient friendly and site-specific drug delivery. The development of topical semisolid dosage by using QbD technique is a promising attempt to minimize the cost and time of manufacturing.

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