Mechanism Based on Formulation Development of Moxifloxacin

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Introduction

The other less likely techniques are membrane contractor, coacervation and solvent injection method [Gordillo-Galeano & Mora-Huertas *et al*, 2018]. In membrane contactor method, active ingredient is dispersed in the molten mixture of lipids and then pressurized to pass through a porous hydrophobic membrane (typically 0.05µm pore diameter) to the aqueous phase containing the stabilizing agent. The lipid forms droplets and precipitate in the form of SLN or NLC, once the aqueous phase is cooled to room temperature [Charcosset *et al*, 2005]. In the coacervation method, precipitation of free fatty acids from their micelles is carried out in the presence of surfactants [Battaglia *et al*, 2010]. In solvent injection technique, prerequisite is an organic solvent completely miscible with water. Lipids and the active ingredient are dissolved in organic solvent then injected under stirring in the aqueous solution containing stabilizing agent. This process will make rapid migration of the organic solvent into the water and precipitation of lipid particles [Schubert & Muller-Goymann, 2003].

QBD IN DRUG DEVELOPMENT

The quality by design (QbD) in pharmaceutical product development is novel and now being main focus area in regulated market scenario. International regulatory bodies such as International Conference on Harmonization and United States Food and Drug Administration (USFDA) have emphasized on principles and applications of QbD in pharmaceutical development in their guidance for the industry. QbD principles, when implemented, lead to a robust product development, and hence, prompt approval. It also reduces exhaustive validation exercises and risk related to post-approval changes (Bastogne, 2017; Pramod *et al*, 2016; Yu & Woodcock, 2015; Yu *et al*, 2014, Yu, 2008). QbD approach begins with predefined objectives and emphasizes product and process understanding and control based on sound science and quality risk management.

The goal includes the following:

1. Achieving meaningful product quality specifications based on clinical performance
2. Increasing process capability and reducing defects by enhancing product and process design, understanding, and control
3. To increase product development and manufacturing efficiencies
4. To enhance root cause analysis and postapproval change management Pharmaceutical development studies should be based on scientific approach. An understanding on product and its manufacturing process is a prerequisite requirement for successful product development. The knowledge should be based on sound scientific principles [Guidance for Industry Q8, 2009].

Pharmaceutical development should include the following elements:

Figure: QbD approach to formulation development

Under QbD, these goals can often be achieved by linking product quality to the desired clinical performance and then designing a robust formulation and manufacturing process to consistently deliver the desired product quality. Mathematical models (one the most critical tool in QbD) are useful throughout the product lifecycle including design space establishment and control.

LITERATURE REVIEW

POLOXAMER USE IN IN-SITU GEL SYSTEMS

Poloxamers have been used alone or in combination with other polymers such as

methylcellulose, HPMC and sodium carboxymethylcellulose (Na CMC) to improve bio adhesive nature of the gel components, thereby improving the retention of the drug in the pre-corneal area, thereby facilitating the reservoir effect of the cornea for pilocarpine [Shastri et al, 2010 a & b; El-Kamel, 2002; Desai & Blanchard, 1998).

HYBRID SYSTEMS (COMBINATION OF TWO OF MORE DELIVERY SYSTEMS)

Solid lipid nanoparticles are being explored in almost every research area (ie, transdermal, mucosal, intramuscular and ocular drug administration). However, for certain applications (especially dermal, transdermal, mucosal), these systems possess unsuitable rheological properties. Therefore, it should be further processed it as a semi-solid formulations to provide precise, spatial and temporal control [Desfrançois et al, 2018]. Hybrid systems are referred to as formulation prepared using combination of two or more delivery systems in order to achieve desired CQAS to have synergistic effect.

MOXIFLOXACIN: OCULAR FORMULATION DEVELOPMENT

Fluoroquinolones are powerful treatment options for preventing potentially sight- threatening bacterial infections and moxifloxacin that provides high lipophilicity for enhanced corneal penetration with high aqueous solubility at physiological pH. [Robertson et al, 2005].

Quality Target Product Profile (QTPP)

It is building block of development. It is related to quality, safety, and efficacy of the pharmaceutical product. It includes:

- Intended use in clinical setting, route of administration, dosage form, delivery systems.
- Dosage strength(s).
- Container closure system.
- Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics
- (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed.
- Drug product quality criteria (e.g., sterility, purity, stability, and drug release) appropriate for the intended marketed product.

Critical Quality Attributes (CQA)

A CQA is any property (may be physical, chemical, biological, or microbiological property or characteristic) that can impact quality of final drug product. To ensure a quality product, it should be within an appropriate limit, range, or distribution. Potential drug product CQAs derived from the quality target product profile and/or prior knowledge is used to guide the product and process development. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.

Risk Assessments

Risk assessment is a science-based process that can help in identifying potential material attributes and process parameters to impact product CQAs. Risk assessment is typically performed early in the pharmaceutical development process and is repeated as more information becomes available and greater knowledge is obtained. ICH Q9 quality risk management mentions it as “the manufacturing and use of a drug product, including its components, necessarily entail some degree of risk”. The evaluation should be based on scientific knowledge, which is linked to the patient safety. This study is carried out before any kind of development studies in order to identify potentially high-risk formulation and process variables which ultimately impact the quality of the drug product. The purpose is to prioritize the studies where uncertainty is involved. This also forms building block of control strategy as it identifies the criticality of variables in order to impact formulation or process parameters. The list of common risk assessment tools as follows:

- Basic risk management facilitation methods (flowcharts, check sheets, etc.)
- Fault tree analysis
- Risk ranking and filtering
- Preliminary hazard analysis

- Hazard analysis and critical control points
- Failure mode effects analysis
- Failure mode, effects, and criticality analysis
- Hazard operability analysis
- Supporting statistical tools

Prior knowledge helps in risk assessment process. It is defined as a familiarity with someone or something with past experience or skills acquired through experience or education information, facts, descriptions. It is also associated with ownership and confidentiality and not available in public domain. Hence, it constitutes understanding of process, proprietary information, or skill that is acquired through previous studies.

OBJECTIVE

The objective of study includes

- Development of a sustained release ocular delivery of fluoroqinolones that provides extended delivery of drug into the aqueous humour for longer period of time as well maintain therapeutic concentration throughout the dosing regimen.
- Evaluation of formulation strategy as per QbD principle for optimization of formulation and process components.
- Establishing the performance of selected formulation based on *in vitro* characterization in Pharamacodynamic model.

PLAN OF WORK

Plan of work includes:

1 Preparation of hybrid nano-dispersed system (SLNs dispersed in *in-situ* gel) of moxifloxacin using cold homogenization technique

2 Formulation development as per QbD principles

a) *Defining QTPP & CQAs*

b) ***Initial risk assessment and screening*** to identify high risk components

c) ***Understanding high risk components*** through DoE approach

d) ***Optimization and design space generation*** meeting all CQAs (critical quality attributes) i.e, total drug content; entrapment efficiency; particle size and size distribution; zeta potential

e) Assessment of ***design space formulation for topical application attributes*** i.e, permeation enhancement, gel strength evaluation, gelling temperature

3 Selection of optimum ***sterilization method***

4 Microbiological, Safety and Pharmacodynamic effectiveness of formulation. It includes:

a) ***In vitro*** **antibacterial activity** by cylinder plate method in terms of zone of inhibition.

b) **Safety studies:**

i. ***Acute dermal toxicity*** as per OECD guideline 405

ii. ***Acute ocular toxicity*** as per OECD guideline 404

iii. ***Chronic repeat eye instillation*** irritation/corrosion testing in rabbits.

5 ***Proof of concept studies using*** fluorescence microscopy to confirm the passage of SLNs across corneal barrier and delivery to the internal eye, for the treatment of corneal infection

ANALYTICAL METHOD DEVELOPMENT

Standard plot of MOX was prepared in methanol, triple distilled water (TDW) and simulated tear fluid (STF). Stock solutions of MOX (equivalent to moxifloxacain base) were prepared in each of the solvents and were serially diluted to obtain concentrations ranging from 1-10 □ g/mL for triple distilled water and simulated tear fluid. The samples were then analyzed spectrophotometrically at the wavelength maxima (λmax) of 295, 289 and 288 nm using respective solvents as blank. The observed absorbances for the respective dilutions were plotted against corresponding concentrations and straight line. The mean of extinction coefficient, of drug was then calculatedand used for determination of MOX in unknown solution

Drug Excipient Compatibility Studies

Estimation of drug-excipient interactions is a crucial step in preformulation studies of drug development to achieve consistent stability, bioavailability and manufacturability of solid dosage

forms. A compatibility study was carried out with drug: excipient in 1:1 ratio. Drug excipients mixed in 1:1 ratio were triturated in mortar and pestle to ensure complete mixing. The mixture thus obtained was packed in glass vial and kept under stability conditions 40□C/ 75% RH & 30□C/65% RH for 4 weeks. Vials were physically examined for colour change after 4 weeks.

FORMULATIONS DEVELOPMENT

The steps involved in manufacturing process are shown in figure 10. Lipid and surfactant were heated in a vessel using hot plate magnetic stirrer. MOX was dispersed in a small quantity of water. Drug solution was added slowly to the molten lipid surfactant mixture under constant magnetic stirring. The mixture was allowed to congeal under stirring until the water was completely evaporated. The solid mass was scrapped off and dried in vacuum oven overnight at 40°C. The dried mass was sifted using sieve ASTM # 30.

Stabilizer was dissolved in water under magnetic stirring. Solid dispersion prepared was added to stabilizer solution under high speed homogenization using ultra turrex for 5 - 15 minutes. The dispersion obtained was passed through HPH at variable pressure & cycles to achieve desired particle size distribution.

RESULTS & DISCUSSION DEVELOPMENT OF SPECTROPHOTOMETRIC METHOD

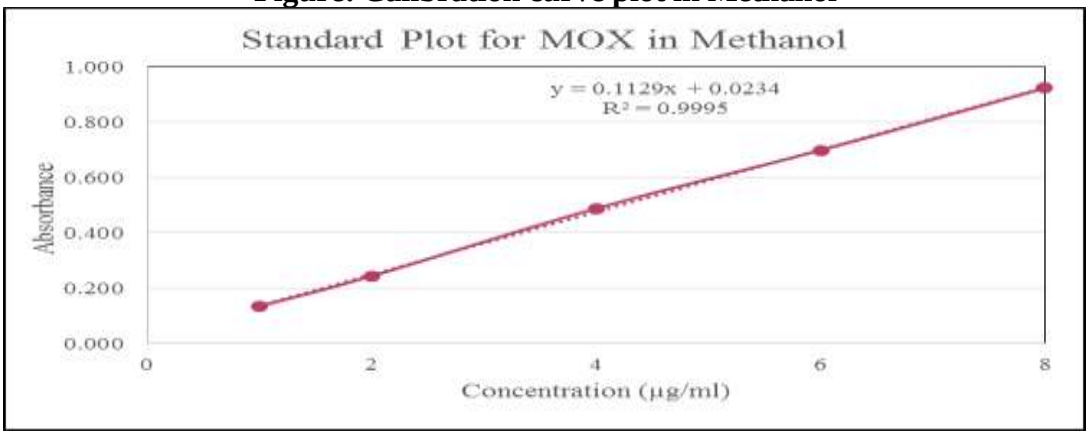
The standard stock solutions of MOX was prepared by dissolving 50 mg of drug in 100 ml of respective diluent (Methanol, TDW & STF) in volumetric flask. Suitable dilutions were prepared to get dilutions of 1-10 µg/ml). Since, Beer-Lambert law is applicable only for diluted solution; care was taken to keep maximum absorbance ~1.000. The absorption maxima, ranges slope; intercept is given in Table.

Table : Results of method development carrier out for MOX in Methanol, TDM and STF

Parameter	Methanol	TDM	STF
Absorbance maxima (λmax) (nm)	295	289	288
Range (µg/ml)	1-8	1-10	1-10
Equation	0.1129x +0.0234	0.1051x + 0.0015	0.1053x + 0.0056
Slope	0.1129	0.1051	1.1053
Intercept	0.0234	0.0015	0.0056
Regression coefficient (r^2)	0.9995	0.9999	0.9999
Mean Absorbance range	0.134 – 0.923	0.104 – 1.053	0.107 – 1.060

MOX showed linear relationship between absorbance and concentration as per Beer- Lambert law in the studied media with regression coefficient >0.999. There is slight increase in absorptivity observed in methanolic solution. Therefore, maximum concentration was capped at 8 µg/ml in order to have maximum absorbance ~1.000. The data in line with literature reported values and hence, can be taken for estimation of drug in respective media [Al Omari *et al*, 2014]. The calibration curve plots are shown in Figure 13 -15.

Figure: Calibration curve plot in Methanol



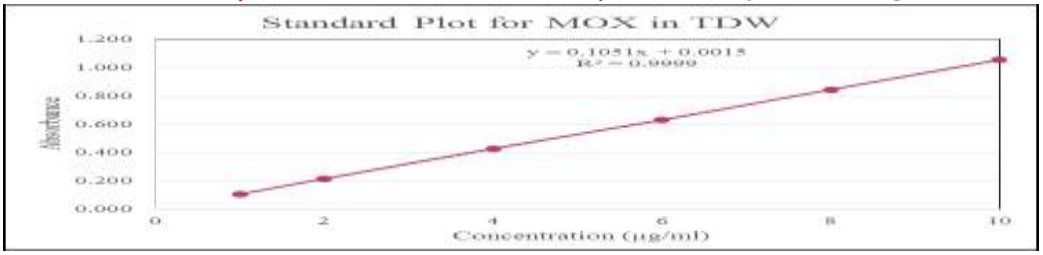


Figure: Calibration curve plot in TDW

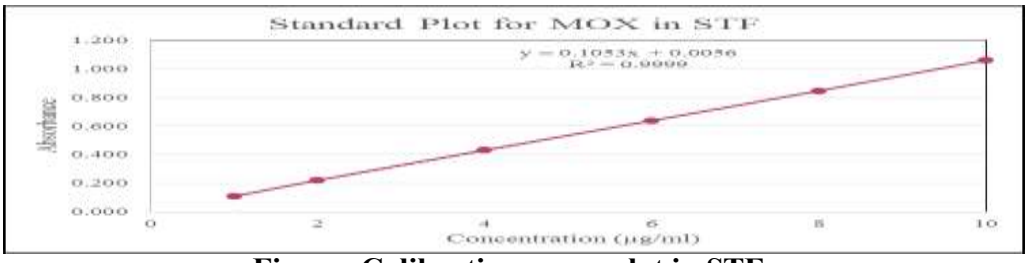


Figure: Calibration curve plot in STF

FORMULATION DEVELOPMENT

SLN production by cold homogenization is preferred technique for hydrophilic drugs. It avoids or minimizes the melting of the lipid and thereby minimizes the loss of hydrophilic drugs to the aqueous phase. Researchers have used this technique for preparation of SLNs of Propranolol Hydrochloride, *Houttuynia cordata (H. cordata)* extract toad venom extract, vinorelbine bitartrate [Sharif Makhmal Zadeh *et al*, 2018; Kim *et al*, 2017; Zhang *et al*, 2013; Wan *et al*, 2008; You *et al*, 2007]. However, this technique has been limited explored in terms of understanding impact of formulations & process variables on CQAs.

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