

QbD-Based Investigation of Dermal Semisolid in situ Film-Forming Systems for Local Anaesthesia

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Purpose: The aim of our research work was to develop dermally applicable, lidocaine hydrochloride (LID-HCl)-containing semisolid in situ film-forming systems (FFSs) using the Quality by Design (QbD) approach to increase drug permeation into the skin.

Methods: Silicones were used to improve the properties of formulations and to increase the permeation through the skin. The QbD approach was applied to ensure quality-based development. With initial risk assessment, the critical material attributes (CMAs) and the critical process parameters (CPPs) were identified to ensure the required critical quality attributes (CQAs).

Results: During the initial risk assessment, four high-risk CQAs, namely in vitro drug release, in vitro drug permeation, drying properties, and mechanical properties, and three medium-risk CQAs, namely pH, viscosity, and film appearance were identified and investigated. Moreover, four high-risk CMAs were also considered during the formulation: permeation enhancing excipients, drying excipients, film-forming excipients, and emollients. During the experiments, LID-HCl influenced these critical parameters highly, thereby reducing the drying time. The formulation containing 25% silicone showed the best mechanical properties (49 mN skin adhesion, 20.3% film flexibility, 1.27 N film burst strength), which could predict better patient adherence. In addition, in vitro permeation studies showed that formulation containing 50% silicone has the fastest permeation rate. The flux of diffused API was 6.763 $\mu\text{g}/\text{cm}^2/\text{h}$, which is much higher compared to the silicone-free formulation (1.5734 $\mu\text{g}/\text{cm}^2/\text{h}$), and it can already be observed in the lower part of the dermis in 0.5 hour.

Conclusion: Our results show that LID-HCl has great influence on the critical parameters of FFSs. The silicone content can improve the applicability of formulations and has a favorable effect on the permeation rate of LID-HCl into the skin.

Keywords: in situ film-forming system, Quality by Design, formulation excipients, local anaesthesia

Introduction

Dermal local anaesthesia is a widely used method before a surgical procedure to decrease pain. Recently, research has focused on developing painless local anaesthetic treatment without needle insertion or injection. This non-invasive treatment can be used to decrease pain during a surgical intervention or chronic pain associated with neuralgia, arthritis or other severe medical diseases.^{1,2} Besides, it is an attractive alternative to injection in pediatrics.³

Lidocaine hydrochloride (LID-HCl) is one of the commonly used drugs during local anaesthesia.⁴ Lidocaine can relieve pain rapidly, but its effective time is short.

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Gels, sprays, creams, ointments, and patches are used as vehicles, but the barrier function of the skin limits the permeation of LID-HCl.^{5–7} It is a great challenge to reach the optimal permeation from these dermal preparations.⁸ The generally used dermal semisolid preparations, such as creams, ointments, and gels can be smeared and removed easily by movement and wetting.⁵ So a new drug delivery system may be required to enhance effectiveness and patient adherence.

The in situ film-forming system (FFS) is an innovative dermally applicable semisolid drug delivery system, which forms a film on the skin surface after application.^{9,10} FFSs contain non-volatile and volatile components. Non-volatile components include the active ingredients in matrix to provide the transport through the skin, while volatile components are responsible for film formation and enhanced drug permeation. Throughout the application process, volatile components evaporate, thereby an in situ formed film is left on the skin surface with a concentrated drug content, which promotes enhanced drug permeation.¹¹ The application of the FFS is convenient, the appearance is attractive, and the film formed after fast drying has good mechanical properties. With optimal compositions, these advantages can be exploited,¹² thus offering a promising choice in local anaesthesia.

To achieve optimal properties, volatile and non-volatile silicones are a good choice in FFSs.^{13–16} Silicones have a great effect on film-forming systems, for example, they ensure a “silky touch” feeling on the skin surface, have a softening feeling during the application, and they help the formulation to dry.¹⁷ The effects of silicones on critical attributes need to be considered during the formulation. Non-volatile silicones modify the mechanical attributes, thereby softer films can be formulated. Volatile silicones improve the film-forming ability, and more favorable drying time can be achieved.¹⁸ The optimal mechanical properties ensure that the films are retained on the skin surface for a longer time, thereby increasing exposure time. To improve patient adherence, films need to be removable painlessly, and the drying time needs to stay in a convenient range.

During the pharmaceutical development, it is essential to provide the appropriate quality of formulations. The International Council for Harmonization (ICH) guideline Q8 defines and sets the basis of the Quality by Design (QbD) approach.¹⁹ QbD is a systematic aspect, which ensures the optimal environment to reach the required properties. The method begins with identifying the quality

target product profile (QTPP), then helps to understand the critical quality attributes (CQAs), organizes them and ensures the control of critical materials attributes (CMA) and critical process parameters (CPPs) based on the risk assessment.^{20–22} QbD tools are applied to examine the most critical parameters.^{23,24} These tools are summarized in the ICH guideline Q9.²⁵

Based on our previous research, in situ FFSs could be a good choice to ensure painless local anaesthesia.¹⁸ The aim of this work was to develop LID-HCl-containing semisolid in situ FFSs using the QbD approach. The purpose of using QbD approach is to select the influencing attributes of the investigated system, which is essential for future development steps, such as defining product and process design space, and defining control strategy. Our study focuses on the formulation of three LID-HCl-containing compositions with or without silicones to investigate, on one hand, the effect of LID-HCl on the film-forming properties and on the other hand, the effect of formulations on the skin permeation of the active substance. The formulations were tested relative to each other and to blank FFSs.

Materials and Methods

Materials

Lidocaine hydrochloride was purchased from Hungaropharma Ltd. (Budapest, Hungary). Poly(vinyl alcohol) (87–90% hydrolyzed, average mol wt 30,000–70,000) was obtained from Sigma-Aldrich (Budapest, Hungary). Ethanol (96 per centum, Ph. Eur. 9.) was from Molar Chemicals Ltd. (Budapest, Hungary). Xantural[®] 180 Xanthan Gum was a product sample from CP Kelco A Huber Company. ST – Cyclomethicone 5-NF, Dimethiconol Blend 20, ST Elastomer 10, and 7–3101 Elastomer Blend HIP Emulsion were kindly provided by Dow Corning (Midland, Michigan, USA). Purified and deionized water was used (Milli-Q system, Millipore, Milford, MA, USA). Methyl parahydroxybenzoate (Ph. Eur. 9.) was supplied by Molar Chemicals Ltd. (Budapest, Hungary). Salvequick[®] sticking plaster was from Orkla Care AB (Solna, Sweden). PVA-based artificial skin was obtained from © 2018 Tattoo machine Webshop (Mátészalka, Hungary). Cellulose acetate filter (Porafil membrane filter, cellulose acetate, pore diameter: 0.45 µm) was purchased from Macherey-Nagel GmbH & Co. KG (Düren, Germany).

Excised human skin was obtained from Caucasian female patient by routine plastic surgery procedure of the Department of Dermatology and Allergology, University of Szeged. Tissue samples to be destroyed are considered to be hazardous waste, so ethical permission is not required for research on these tissue samples in Hungary according to the Act CLIV of 1997 on Health Section 210/A. The local ethical committee (Regional Ethics Committee for Human Biomedical Research, University of Szeged) has to be informed about the in vitro skin penetration studies (Notification document number: 83/2008).

Methods

Quality by Design Methodology

Definition of TPP and QTPP

The definition of the Target Product Profile (TPP) is the first step during the product formulation. It defines the target of our work. After that, the Quality Target Product Profile (QTPP) summarizes the quality characteristics of the target product. It is the basis of design. QTPP parameters include, for example, therapeutic indication, route of administration, dosage form and strength, etc. according to the relevant guidelines.^{19,24,26}

Definition of CQA, CMA, CPP

CQAs are derived from the QTPP. Based on prior knowledge, they potentially affect the quality of the product, for example, physical properties, solubility of active pharmaceutical ingredients (API) in the formulation, pH, viscosity, etc., which are clearly defined to provide the required product quality.¹⁹ After the determination of the quality attributes, the next step is to define the parameters which influence CQAs to provide the predefined quality. These are the critical material attributes (CMAs) and the critical process parameters (CPPs), which include properties of the API and excipients (eg, emollient, polymer), and

properties of the applied process (eg, type of technology, homogenization time and rate).^{18,27}

Risk Assessment: Quality Tools

Risk assessment is in the focus of the QbD approach. During risk management, the risks of the product quality are assessed, controlled, communicated, and reviewed. Quality tools such as the Ishikawa diagram, risk estimate matrix (REM) and Pareto analysis support and facilitate risk assessment. The Ishikawa diagram, which collects possible root causes and effects that have an influence on the quality. During the risk assessment, the next step was to select the critical parameters with Pareto analysis. This technique, which is also called ABC analysis, is used for the selection of risks that produce a significant effect. Categories A, B, and C of items have the highest, medium and the lowest influence on the quality of formulations, respectively. The REM presents the interdependence rating between QTPPs and quality attributes. Furthermore, the REM was used to define the connection between the quality attributes and CMAs, CPPs. The parameters were selected and the critical control points were defined with LeanQbD™ software (QbD Works LLC, Fremont, CA, USA).^{25,28}

Preparation of FFSs

Three different types of formulations were examined. Blank formulations were also formulated and investigated for better understanding of the effect of LID-HCl on FFSs. The compositions and the functions of different ingredients can be found in Table 1. The blank film formulations without active substance (F1 - F3) and film formulations containing 5% LID-HC (LF1 - LF3) were prepared. The first type of formulations (F1 - LF1) did not contain silicones, while the others (F2 - LF2, F3 - LF3) contained different volatile and non-volatile components.

Table 1 Composition of Blank FFSs and FFSs Containing LID-HCl

Composition	Function of the Excipient	F1	LF1	F2	LF2	F3	LF3
LID-HCl	Active pharmaceutical ingredient	-	+	-	+	-	+
Purified water with methyl parahydroxybenzoate	Solvent with preservative	+	+	+	+	+	+
Ethanol 96%	Drying, permeation enhancing	+	+	+	+	+	+
PVA	Film-forming, viscosity enhancing	+	+	+	+	+	+
Xanthan gum	Film-forming, viscosity enhancing	+	+	+	+	-	-
Dimethiconol Blend 20	Film-forming, emollient	-	-	+	+	-	-
ST-Elastomer 10	Film-forming, emollient	-	-	+	+	-	-
7-310I Elastomer Blend HIP Emulsion	Film-forming, emollient	-	-	-	-	+	+
ST-Cyclomethicone 5NF	Drying, permeation enhancing	-	-	+	+	+	+

ST – Cyclomethicone 5 – NF was the volatile silicone component to ensure the drying properties and to increase the permeation through the skin.^{18,29,30} Additional non-volatile silicones, Dimethiconol Blend 20, ST – Elastomer 10, and 7–3101 Elastomer Blend HIP Emulsion were added to F2, LF2 and F3, LF3, to modify film formation and rigidity of films.¹² Furthermore, they modify the appearance of the film, provide a “silky touch” feeling, protect and soften the skin.¹⁷ F2, LF2 contained 25% of silicones, and F3, LF3 had 50% of silicones in the formulations. Volatile silicone containing was the same in these compositions. PVA and Xanthan gum also enhance film formation and have viscosity increasing properties.^{12,18} Additionally, ethanol is a drying excipient and a permeation enhancer excipient as well.³⁰

LID-HCl was dissolved in Ethanol 96% and PVA was dissolved separately in purified water at 80°C under mixing. The two solutions were mixed at room temperature. Then, Xanthan gum was added to formulations F1, LF1 and F2, LF2 to ensure the required consistency. Finally, silicones were added slowly and mixed with a high shear mixer.

Characterization of the Critical Parameters of the Semisolid System

Investigation of Drying Properties

PVA-based artificial skin was used as model skin surface to detect the drying time of the preparations. When the formed film seemed to be dry, a microscope slide was used to touch the top of the film. If no marks were left on the slide, the film could be considered dry, and the elapsed time was the drying time. If the film left marks on the slide, the test was repeated until we got a dry film.^{18,31} Five parallel measurements were carried out. The results were calculated as means \pm SD.

Investigation of pH

Each 10 g sample was placed in a beaker, and a Testo 206 pH meter (Testo SE & Co. KGaA, Lenzkirch, Germany) was used to measure the pH. Three parallel measurements were carried out.

Rheological Investigation

Rheological measurements were carried out with a Physica MCR101 rheometer (Anton Paar GmbH, Graz, Austria) to investigate the properties of FFSs before drying, and the effect of LID-HCl on the rheological parameters. Parallel plate geometry PP25 was applied with a measuring gap of

0.1 mm. The blank FFSs were also studied. Flow curves were obtained during the examination. The shear rate was raised from 0.1 to 100 1/s (up-curve) and then reduced from 100 to 0.1 1/s (down-curve) in CR mode. The shearing time was 300s and the measurements were made at 32°C.³²

Characterization of the Critical Parameters of Films

Investigation of in vitro Drug Release

A Franz diffusion cell system (Logan Automated Dry heat sampling system) was applied to model drug release through a cellulose acetate synthetic membrane. Around 300 mg of each sample was used as the donor phase. The acceptor phase was thermostated phosphate buffer (PBS pH 7.4 \pm 0.15) at 32°C \pm 0.5°C. Drug release lasted 8 hours (sampling times: 0.5; 1; 2; 3; 4; 5; 6; and 8 h). The concentration of the drug was examined by high-performance liquid chromatography (HPLC) (Shimadzu Nexera X2 UHPLC, Kyoto, Japan).

HPLC was equipped with a C18 reverse-phase column (ZORBAX Eclipse XDB-C18, Phenomenex, Torrance, CA, USA) with 5 μ m, 4.6X150 mm dimension. The mobile phase was 0.1% phosphoric acid (solvent A):acetonitrile (solvent B) 90:10 in gradient mode. It was changed from 90:10 (A:B, v/v) to 40:60 (A:B, v/v) in 6 minutes then going back to 90:10 (v/v) between 6.1–10 minutes. The flow rate of 0.8 mL/min was set over 10 minutes, the column temperature and sample tray temperature were set to 25°C, and the detection was made at 230 nm. The injection volume was 5 μ L. The time of analysis was 10 min, and the retention time was 4.2 min.³² Four parallel measurements were carried out. The results were calculated as means \pm SD.

Investigation of in vitro Drug Permeation

Measurements of Drug Permeation with Franz Diffusion Cell System

A Franz diffusion cell system (Logan Automated Dry heat sampling system) was applied to model the permeation through ex vivo human heat-separated epidermis (HSE). The preparation of HSE was based on a procedure reported by Kligman and Christophers.³³ Around 300 mg of each sample was used as the donor phase. The acceptor phase was thermostated phosphate buffer (PBS pH 7.4 \pm 0.15) at 32°C \pm 0.5°C. Drug permeation through HSE lasted 24 hours (sampling times: 0.5; 1; 2; 4; 6; 12; 18; and 24 h). The concentration of the drug was examined by high-performance liquid chromatography (HPLC)

(Shimadzu Nexera X2 UHPLC, Kyoto, Japan). The method of the HPLC measurement was the same as for the investigation of in vitro drug release. Four parallel examinations were carried out. The results were calculated as means \pm SD.

Investigation of Drug Permeation with Raman Spectroscopy

Full thickness human subcutaneous fat free, abdominal skin was treated with LID-HCl-containing FFSs at room temperature. The skin sections were placed on filter papers that were soaked with phosphate-buffered saline solution. 200 mg of each preparation was placed on a 1x1 cm surface of the skin. The exposition time was 30 and 180 minutes. After the treatment, the films were pulled down and the residues were wiped. The treated skins were frozen and sectioned with a Leica CM1950 Cryostat (Leica Biosystems GmbH, Wetzlar, Germany). Aluminum-coated slides were used under the 15- μ m-thick cross-sections. Raman spectroscopic analysis was carried out with a Thermo Fisher DXR Dispersive Raman Spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) equipped with a CCD camera and a diode laser operating at 780 nm. Microscopic lens with 50X magnification was used. Measurements were made with a laser power of 24 mW and a slit width of 25 μ m. Skin mapping was captured of an area of 200X1,000 μ m, with a step size of 50 μ m vertically and horizontally. The OMNIC for Dispersive Raman 8.2 software package (Thermo Fisher Scientific) was used during instrument operation and evaluation. The untreated skin was also measured. The individual spectrum of each formulation was used as a reference when comparing the treated and non-treated skin.³⁴

Investigation of the Mechanical Parameters of Films with Texture Analyzer

TA.XT plus Texture Analyzer (Stable Micro Systems Ltd, Vienna Court, Lammas Road, Godalming, Surrey, UK. GU7 1YL) was used to carry out the measurements. Skin adhesion, film burst strength and film flexibility were characterized with different accessories. Four parallel measurements were carried out during each examination. The results were calculated as means \pm SD.

A 10x2 cm film was measured under the 90 Degree Peel Rig during the skin adhesion test to determine the mean peeling force (Pa) which can separate the film from the artificial skin surface. The applied test speed was 5 mm/s, while the distance was 50 mm. The mean peel

force was averaged from 10 mm to 45 mm during the evaluation. Sticking plaster was used as a reference.^{18,35}

Film Support Rig was used during the film burst strength and film flexibility tests. Burst strength (Pa) and resilience (%) were measured. Films with a diameter of 22 cm were made and placed into the film support rig. The compression mode was used for measuring film burst strength. Test speed, force, and target distance were 0.5 mm/sec, 100 g, and 1 mm, respectively. Similarly, the compression mode was applied for film flexibility with a test speed of 0.5 mm/sec, a force of 100 g and a distance of 1 mm. In both cases, human HSE was used as reference.^{18,36} The preparation of heat-separated epidermis was based on a procedure reported by Kligman and Christophers.³³

Investigation of Film Appearance

There was placed 0.2 g of each formulation on a 3x3-cm surface of the PVA-based artificial skin. After drying, the appearance was investigated visually.¹⁸

Statistical Analysis

The one-way ANOVA analysis of variance (Dunnett) with GraphPad Prism 8 for Windows software (GraphPad Software Inc., La Jolla, CA, USA) was applied to make the statistical analysis of results. More parallel measurements \pm SD were carried out. The differences were significant if $p < 0.0001$ **** $p < 0.001$ *** $p < 0.01$ ** $p < 0.05$ * versus the control.^{18,24}

Results and Discussion

Determination of QTPP and CQAs

As regards the TPP, the target was to formulate a semisolid, in situ film-forming system containing LID-HCl, with required properties for local anaesthetic therapy. Based on these, the QTPP of the FFS-containing LID-HCl encompasses therapeutic indication, route of administration, dosage form, dosage strength, site of activity, release profile, appearance of semisolid system, physical, chemical and microbiological stability, patient adherence increasing effect, mechanical properties of film and packaging material type. The CQAs originate from the QTPPs. In the present case, the composition is a semisolid in situ FFS, so the properties of both the semisolid compositions and the film must be considered. The Ishikawa diagram shows the parameters influencing the quality of the semisolid in situ film-forming system containing LID-HCl (Figure 1).^{25,37}

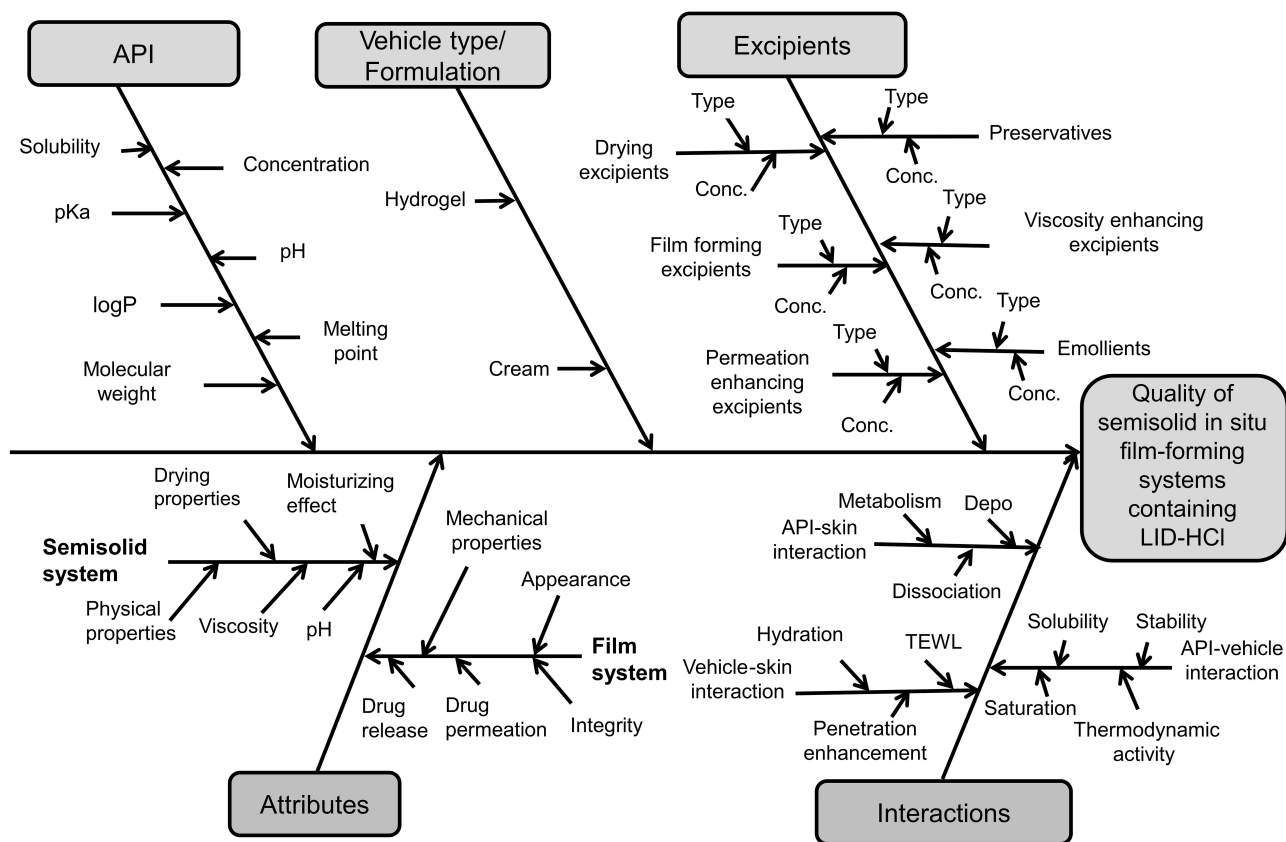


Figure 1 Parameters influencing the quality of FFSs containing LID-HCl.

The quality attributes of the semisolid system include physical properties, solubility of API in formulation, viscosity, pH, moisturizing effect, and drying properties. The quality attributes of the formed film include film appearance, integrity, mechanical properties, in vitro drug release and drug permeation. Tables 2 and 3 present the targets and justifications of QTPPs and CQAs.

Initial Risk Assessment

After defining the QTPPs and CQAs, the next step is to determine the CMAs and CPPs of the FFSs containing LID-HCl with risk assessment. Risk assessment refers to the estimate of the risks, related to the investigated semisolid and film systems. Table 4 shows the influencing factors as well as their impacts and occurrences on the target product.

After that, risk assessment tools were applied to determine the connection between the parameters. Firstly, the parameters were identified, and then we performed risk assessment and ranked the parameters based on their risk. The risk estimate matrix (REM) was used to evaluate the relationships between CQAs and QTPPs (Table 5).

A three-step scale was applied to rank the relationship between the CQA and QTPP parameters for the FFS containing LID-HCl, by assigning low (low-risk parameters), medium (medium risk parameters) and high (high-risk parameters) values to each of them. A 1(low)-3(medium)-9 (high) scale was used for the probability rating.

A Pareto chart (Figure 2) was constructed based on the results of the REM to rank and show the severity scores of CQAs, and to highlight the highly influenced parameters of product quality. The results show that four quality attributes have the highest influence on the quality of the target product with the highest severity score (>400), called Category A. These are in vitro drug release, in vitro drug permeation, drying properties, and film mechanical properties. Category B (severity score: 250–400) includes viscosity, pH, and film appearance. The last category of severity score is Category C (below 250), which has the quality attributes with the lowest influence on the target product.

The next REM (Table 6) was established to show the connection between CQAs and CPPs, CMAs. The evaluation was made by using the same scale (1-low, 3-medium,

Table 2 QTPPs of the FFS Containing LID-HCl

QTPP	Target	Justification
Therapeutic indication	Local anaesthetic	During local anaesthesia, superficial loss of sensation can be achieved, which is a good choice to avoid the adverse effects of injections during minor surface-skin surgical interventions and invasive procedures. It can decrease pain, itching, and irritation. ^{24,38}
Route of administration	Dermal	Non-invasive dermal delivery is a convenient and painless administration route compared to SC injections. ³⁹
Dosage form	Semisolid in situ film-forming system	Due to the advantages over other conventional dosage forms, fast drug release, resistance to washing and smearing can be achieved, which presumably increase the drug permeation rate. ^{12,40}
Dosage strength	5%	This concentration of LID-HCl is an effective dose as a local anaesthetic formulation. ^{32,41}
Site of activity	Deeper layer of the skin (dermis)	Regarding the local anaesthetic aim, the permeation of active ingredients into the deeper layer of the skin, such as the dermis, is required because of the location of skin nerves. ^{18,24}
Release profile	Fast drug release	Fast drug release is favorable to achieve the local anaesthetic effect as soon as possible. ⁴⁰
Appearance of semisolid system	Transparent or white, homogeneous	Aesthetic preparation needs to be formulated for good patient adherence. ^{12,18}
Stability (physical, chemical)	No visible sign of instability in the formulation at the time of preparation and after 3 months (at room temperature)	Physical and chemical stability, such as proper viscosity, pH and avoidance of phase separation are important for applicability. ¹⁸
Stability (microbiological)	Meets the property requirements of the pharmacopoeia for dermal systems	To meet the requirement for marketing authorization to provide the safety of formulations.
Patient adherence increasing effect	“Silky touch” feeling on the skin	To soften and hydrate the skin, improve comfort for patients, thereby providing patient adherence. ⁴²
Mechanical properties of film for skin application	Optimal structure of film, flexible, highly adherent, resistant film	Suitable mechanical properties are required to achieve optimal skin adhesion and flexible movement like that of the skin. Films need to be removed in one piece, easily, painlessly. ¹⁸
Packaging material type	Appropriate for the formulation type, well-closed	Because of the volatile components, well-closed package is required to avoid evaporation. ¹⁹

9-high). Eleven CMA and CPP parameters were screened to determine their influence on the CQAs during the formulation of FFSs containing LID-HCl. The influencing material parameters were viscosity and permeation enhancing excipients, drying excipients, film-forming excipients, preservatives, and emollients.

Mixing rate, mixing time, type of mixer, temperature of technology and type of technology were found to be the influencing process parameters. Based on the REM results, a Pareto chart (Figure 3) was generated showing the severity scores of CQAs. The most critical parameters (Category A) influencing the quality of FFS-containing LID-HCl have the highest severity scores (>20,000). These are the following parameters: permeation enhancing, drying, film-forming excipients, and emollients. Category B includes viscosity enhancer excipients and type of technology (severity scores are 10,000–20,000), these parameters have medium influence on the final product's quality. Category C has a low impact on the quality

of the FFS during the development (>10,000): mixing rate, temperature of technology, mixing time, type of mixer, and preservatives belong here.

According to the initial risk assessment, four highly influencing CQA parameters were identified, namely in vitro drug release, in vitro drug permeation, drying properties, and film mechanical properties. Moreover, three medium critical CQA parameters were also defined: viscosity, pH, and film appearance. These were the investigated parameters during the research work. The initial risk assessment also showed that the following four material parameters of the defined CPPs and CMAs had the highest influence on the target product: permeation enhancing excipients, drying excipients, film-forming excipients, and emollients. These parameters were considered during the development.

Figure 4 shows the result of the risk assessment during the formulation of FFSs containing LID-HCl based on the QbD approach.

Table 3 CQAs of the FFS Containing LID-HCl

CQA	Target	Justification
Semisolid system properties		
Physical properties (color, odor, appearance)	Translucent or slightly white appearance, homogeneous, clear, and odorless	To ensure patient adherence and stability. ¹⁸
Solubility of API in formulation	High (>90%)	Drug solubility provides a homogenous system. It is important to achieve a high concentration gradient to improve the permeation through the skin. ⁴³
Viscosity	Appropriate spreadability (range: 500–5,000 mPas)	To provide optimal application properties of the formulation and ensure the required stability. ³¹
pH	Optimal pH for dermal application (range: 4–8 pH)	Proper pH is an important parameter for dermal application for the safety and efficacy of use, to avoid irritation and to ensure the stability of formulation. ^{44,45}
Moisturizing effect	To increase skin hydration with 20% compared to the control	To increase skin hydration, to promote drug permeation. ⁴⁶
Drying properties	Convenient drying time (within 10 minutes)	Due to fast drying, smearing is avoided, thereby comfortable usability and resistance are ensured. ^{18,31}
Film properties		
Film appearance	Translucent or slightly white, homogeneous, compact film	Better patient adherence can be achieved with invisible, homogenous, not shiny, and resistant films. ¹²
Film integrity	Compact, resistant film on the skin surface	To ensure aesthetic appearance, and to be pulled down completely and easily. ³¹
Film mechanical properties	Optimal structure of film (Tg: under 80 °C), skin adhesion (mean peel range: 100–500 mN) compared to sticking plaster; film burst strength (range: under 5 N), film flexibility (range: above 25%) compared to heat-separated human epidermis	To provide the optimal structure of the film, optimal exposure time, good adhesion and film flexibility are essential. Burst strength and flexibility also allow following the skin movement. ¹⁸
In vitro drug release	30% in 0.5 hour	To provide fast effect, fast drug release is necessary.
In vitro drug permeation	Detected in the lower layer of the skin (epidermis, dermis) in 0.5 hour	The API penetrates into the dermis. ⁴⁷

Table 4 Summary of All the Parameters That Affect the FFS Containing LID-HCl

QTPPs	Impact	CQAs	CPPs and CMAs	Occurrence
Therapeutic indication	High	Physical properties (semisolid system)	Mixing rate	Medium
Route of administration	High	Solubility of API	Mixing time	Low
Dosage form	High	Viscosity	Type of mixer	Medium
Dosage strength	Medium	pH	Temperature of technology	High
Site of activity	High	Moisturizing effect	Type of technology	High
Release profile	High	Drying properties	Viscosity enhancing excipients	Medium
Appearance of semisolid system	Low	Film appearance	Permeation enhancing excipient	High
Stability (physical, chemical)	Medium	Film integrity	Preservatives	Low
Stability (microbiological)	Low	Film mechanical properties	Drying excipients	High
Patient adherence increasing effect	Medium	In vitro drug release	Film-forming excipients	High
Mechanical properties of film for skin application	High	In vivo drug permeation	Emollients	Medium
Type of packaging material	Medium			

Table 5 REM of QTPP and CQA Parameters, Low = Low Risk, Medium = Medium Risk, High= High-Risk Parameters

QTPP CQAs	Therapeutic Indication (H)	Route of Administration (H)	Dosage Form (H)	Dosage Strength (M)	Site of Activity (M)	Release Profile (H)	Appearance of Semisolid System (L)	Stability (Physical, Chemical) (M)	Stability (Microbiological) (L)	Patient Adherence Increasing Effect (M)	Mechanical Properties of Film for Skin Application (H)	Type of Packaging Material (M)
Physical properties (semisolid system)	Low	Low	Low	Low	Low	Low	High	High	High	Medium	Low	Medium
Solubility of API	Medium	Low	Low	High	Low	High	High	High	Medium	Low	Medium	Low
Viscosity	Low	High	High	Medium	Medium	Low	High	Medium	Medium	Medium	High	Medium
pH	Medium	High	High	High	Medium	Medium	Medium	Medium	High	Low	Low	Low
Moisturizing effect	Low	Medium	Medium	Low	Medium	Low	Low	Low	Low	High	Medium	Low
Drying properties	Medium	High	High	High	High	High	Low	Medium	Low	High	High	Medium
Film appearance	Low	Medium	High	Low	Low	Low	Medium	High	High	High	High	Low
Film integrity	Low	Medium	Medium	Low	Medium	Low	Low	High	Medium	High	High	Low
Film mechanical properties	High	High	High	Medium	Medium	Low	Low	High	High	High	High	Low
In vitro drug release	High	High	High	High	High	High	Low	High	High	Medium	High	Low
In vitro drug permeation	High	High	High	High	High	High	Low	High	High	Medium	High	Low

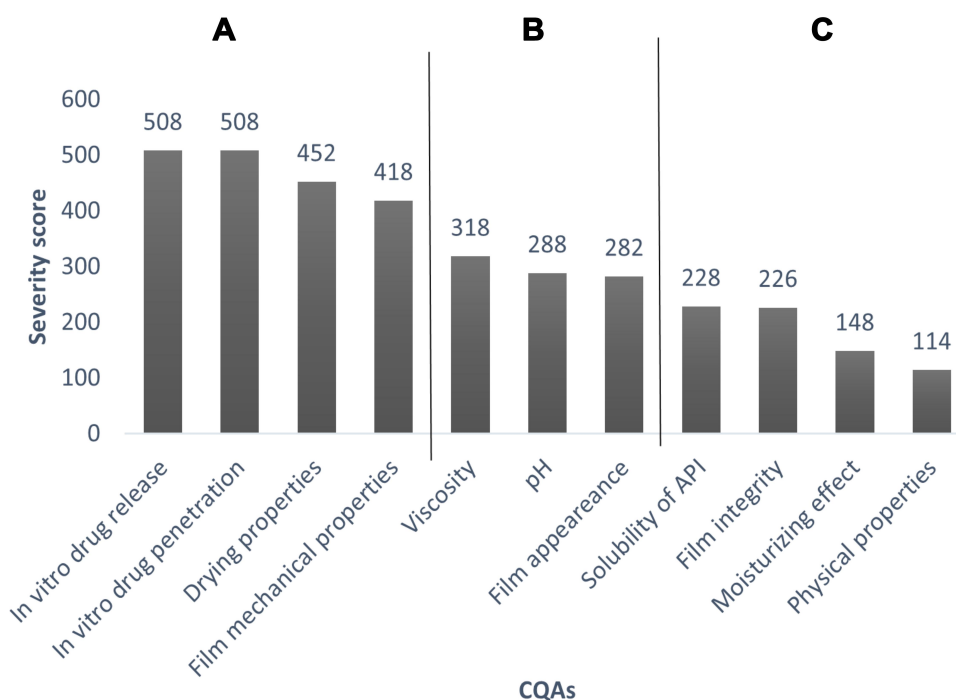


Figure 2 Pareto chart of CQA parameters; (A) high-risk parameters, (B) medium-risk parameters, (C) low-risk parameters.

Results of the Critical Parameters of the Semisolid System Drying Properties

As our previous work described, silicone content significantly decreases drying time.¹⁸ Additionally, a further examination was carried out to observe the effect of LID-HCl on this parameter. LID-HCl significantly decreased the drying time of all compositions, so it has favorable effect on the formulations. It was the most noticeable in the case of formulation LF2, where the values dropped from 10 minutes to 8.35 minutes (Figure 5). Formulations LF2 and LF3 met the requirement (10 minutes).

Results of pH of FFSs

The pH is an important attribute to provide safety and efficacy of use, and the stability of formulations. The results showed that all the formulations were in the optimal range of pH, thereby these are appropriate for dermal application. The LID-HCl content decreased the pH of the formulations. The values are presented in Table 7. However, the LID-HCl is a weak base, with 7.75 pKa. Below this pKa the ionized form of the drug is higher, than the base form, which predicts lower permeation rate through the SC, so the permeation enhancer silicones could be favorable for increasing permeability of SC.^{48,49}

Rheological Properties of FFSs

The three different types of formulations showed different rheological properties. In the flow curves, thixotropy was observed in all cases. Thixotropy was the lowest in the case of F1 and LF1. Based on the flow curves (Figure 6), both the LID-HCl content and the silicon amount increased the shear stress of the systems.

The viscosity value of F1 (608 mPas) and LF1 (718 mPas) was the lowest at 100 1/s at 32°C. F2 was 2070 mPas and LF2 was 2560 mPas. The highest viscosity was detected for F3 with 3540 mPas and for LF3 with 4770 mPas. The rheological measurements showed that the formulations met the requirements (Table 3), they are suitable for dermal use.

Results of the Critical Parameters of Films

In vitro Drug Release Studies

The in vitro drug release study was one of the most critical parameters in the case of risk assessment (Figure 3). The measurement was performed to examine the release profile of the active ingredient from the formulations. The release of LID-HCl was measured through a synthetic membrane, which was an artificial mixed cellulose ester membrane, for 8 hours (Figure 7). According to our target (Table 3), 30% of the API had to be released in 0.5 h. The results

Table 6 REM of CPPs/CMA and CQA Parameters, Low = Low Risk, Medium = Medium Risk, High= High-Risk Parameters

CMA, CPPs CQAs	Mixing Rate (M) CPP	Mixing Time (L) CPP	Type of Mixer (M) CPP	Temperature of Technology (H) CPP	Type of Technology (H) CPP	Viscosity Enhancing Excipients (M) CMA	Permeation Enhancing Excipients (H) CMA	Preserva tives (L) CMA	Drying Excipients (H) CMA	Film- Forming Excipients (H) CMA	Emollients (M) CMA
Physical properties (semisolid system)	High	Medium	High	High	High	High	Medium	Low	Medium	High	Medium
Solubility of API	High	High	Medium	High	High	Medium	High	Medium	Medium	Medium	Medium
Viscosity	High	Medium	Medium	High	High	High	Medium	Medium	Medium	Medium	Medium
pH	Low	Low	Low	Low	Low	High	Low	Low	Low	Medium	Low
Moisturizing effect	Low	Low	Low	Low	Low	High	Medium	Low	High	High	High
Drying properties	Low	Low	Low	Low	Low	Medium	High	Low	High	Medium	Medium
Film appearance	Low	Low	Low	Low	Medium	Medium	High	Low	High	High	Medium
Film integrity	Low	Low	Low	Low	Medium	Medium	High	Low	High	High	High
Film mechanical properties	Low	Low	Low	Low	Medium	Medium	High	Low	High	High	High
In vitro drug release	Low	Low	Low	Low	Medium	Medium	High	Low	High	High	High
In vitro drug permeation	Low	Low	Low	Low	Medium	Medium	High	Low	High	High	High

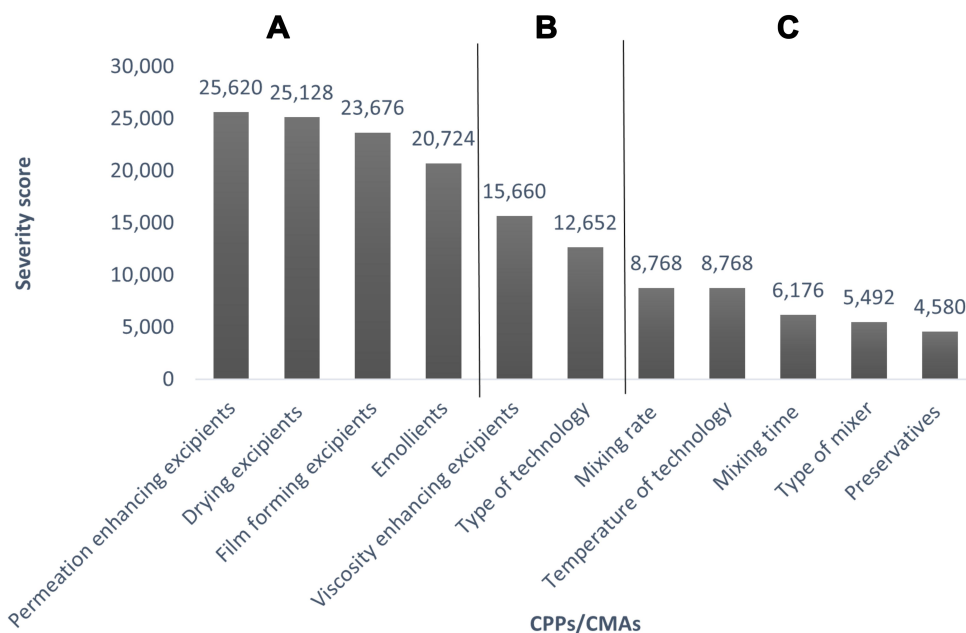


Figure 3 Pareto chart of CPP and CMA parameters; (A) high-risk parameters, (B) medium-risk parameters, (C) low-risk parameters.

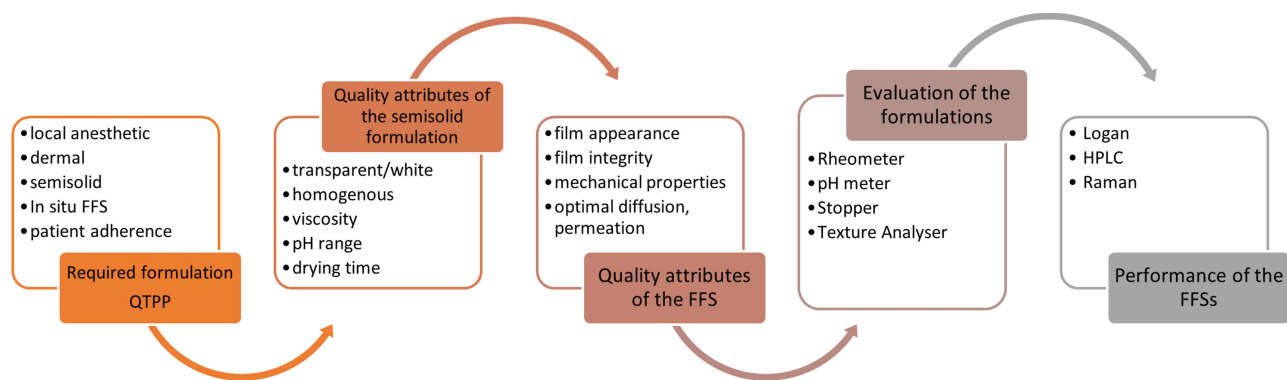


Figure 4 Process of research work.

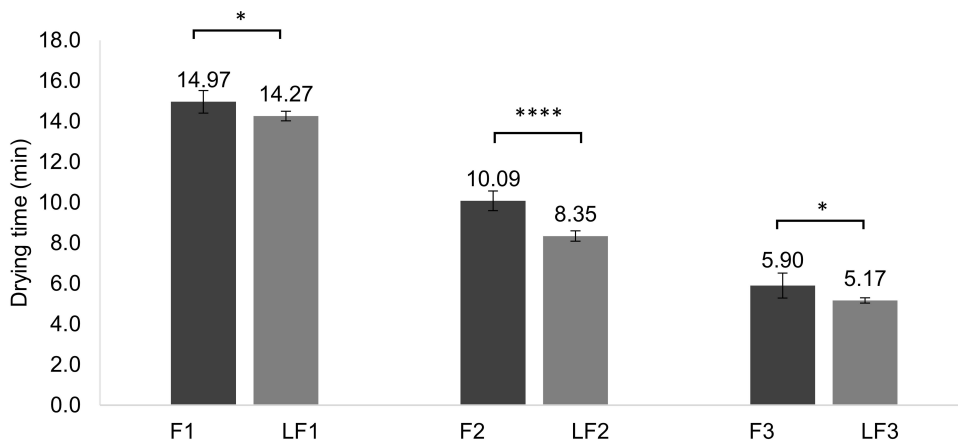


Figure 5 Comparison of the drying times of blank and LID-HCl-containing formulations; Mean \pm SD (n=5), ($p < 0.05$ * and $p < 0.0001$ **** vs blank formulation).

Table 7 pH Data of FFSs

	pH		pH
F1	5.70	LF1	5.40
F2	6.00	LF2	5.50
F3	6.00	LF3	5.37

showed that the diffused API was lower than 30% in 0.5 hour but more than 30% of LID-HCl was released in the case of LF2 and LF3 after 1 hour. After 3 hours, the

diffused amount of API was more than 60% from all formulations (Table 8).

In the case of LF3, the diffusion of API significantly increased in 0.5 hour. Later, the release profiles through this synthetic membrane were similar in all cases, so the different excipients have a similar effect on the drug release. However, the API released from the LF3 formulation faster, than from the other formulations, so it could be explained by the favourable effect of the 7–3101 Elastomer Blend HIP Emulsion in the composition.

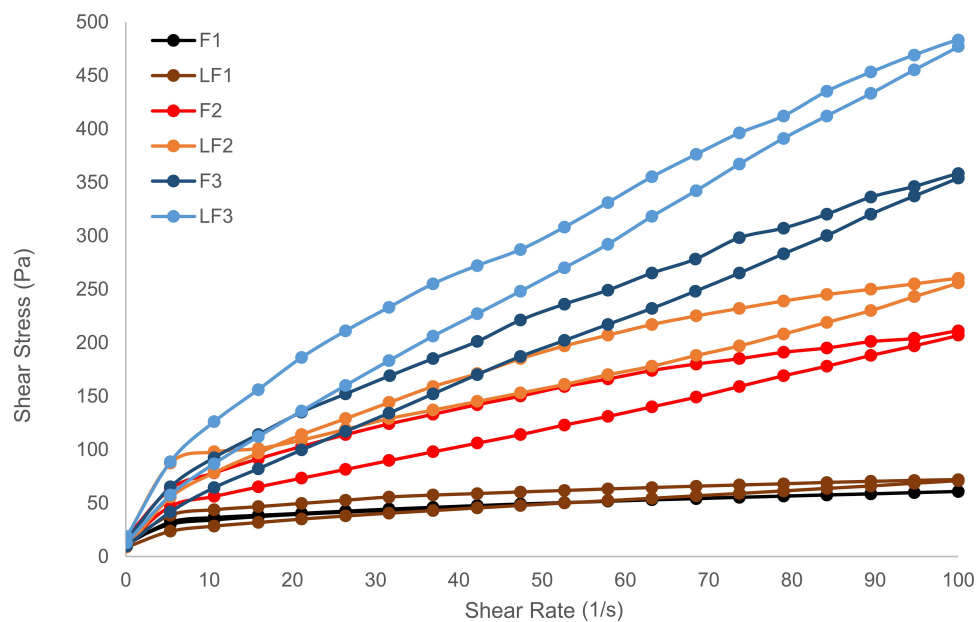
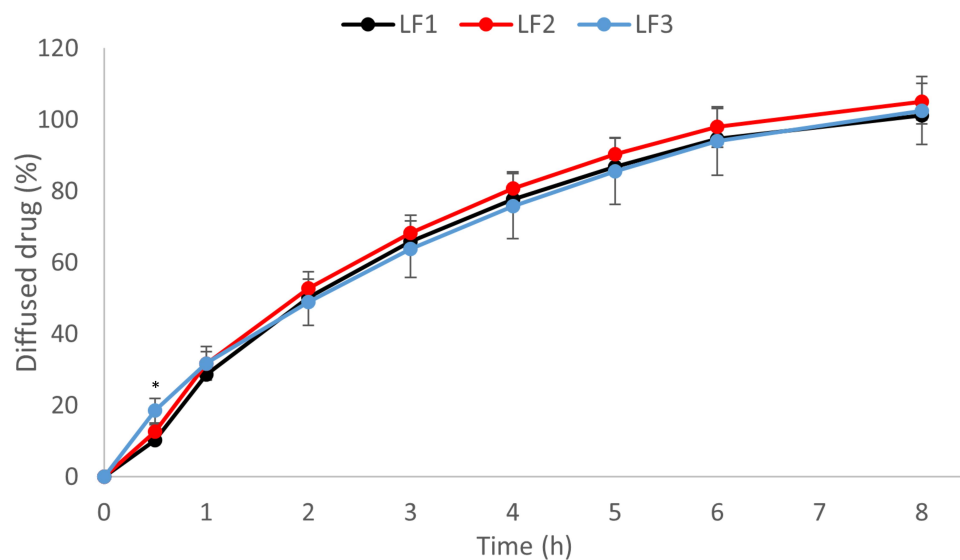
**Figure 6** Flow curves of FFSs.**Figure 7** In vitro drug release through cellulose acetate membrane; Mean \pm SD (n=4), (p < 0.05 *, LF3 vs LF1 and LF2).

Table 8 Mean Cumulative Amount of Diffused API (%) \pm SD (n=4) After 0.5; 1 and 3 Hours, ($p < 0.05$ *)

	0.5 h	1 h	3 h
LF1	10.24 \pm 0.54	28.57 \pm 1.24	65.84 \pm 1.88
LF2	12.59 \pm 2.01	31.63 \pm 3.35	68.27 \pm 4.90
LF3	18.50* \pm 3.45	31.75 \pm 4.78	63.72 \pm 7.91

In vitro Drug Permeation Studies

The in vitro drug permeation study consisted of two measurements. The permeation of LID-HCl was measured through HSE during 24 h in a Franz cell and completed with Raman spectroscopy, where the location of the API was detected in the skin layers.

Then, the mathematical evaluation was carried out. The rate of the permeation (flux) was calculated from the slope of the cumulative amounts of LID-HCl ($\mu\text{g}/\text{cm}^2$) permeated versus time (h) profiles (Table 9). LF1 and LF2 contained volatile silicone to increase the permeation rate through the skin. The results showed that ST-Cyclomethicone 5NF increased the permeation rate compared to LF1. In addition, the amount of volatile silicone was the same in both formulations, but the highest permeation rate was detected in the case of LF3. This could be explained by the additional effect of 7–3101 Elastomer Blend HIP Emulsion, and the fast drying of the formulation with prolonged drying mechanism.¹⁸

The in vitro skin permeation studies were also carried out with Raman spectroscopy. The correlation maps were established, which showed the distribution of LID-HCl-containing FFSs by using the appropriate spectra that fit to the treated skin spectra. The spectra of LID-HCl, blank formulations, and API-containing formulations were recorded. In this case, the spectra of API-containing formulations were used to make the distribution correlation maps, because these spectra indicate the presence of LID-HCl. The spectra of pure API could not be used because of the low intensity of LID-HCl in the formulations. A non-treated correlation map was used as a control during the evaluation. Figure 8 shows the recorded correlation maps of LF1 (A), LF2 (B), LF3 (C). The warmer color indicates a higher amount of the preparations in the different skin layers.

Table 9 Fluxes J ($\mu\text{g}/\text{cm}^2/\text{h}$) of Diffused API

	J ($\mu\text{g}/\text{cm}^2/\text{h}$)
LF1	1.5734
LF2	4.2924
LF3	6.763

The results showed that the LID-HCl-containing preparations were present in the different regions of the human skin. Formulation LF1 was found in the upper region of the human skin and formulation LF2 permeated into the epidermis and the upper part of the dermis after 3 hours. Formulation LF3 could already be observed in the lower part of the dermis after 0.5 hour. After 3 h the distribution of the formulation could be found in all skin layers as well.

Based on the results, the LF3 showed the fastest permeation rate, so the results of Raman mapping correlated with the measurements of the in vitro permeation study in a Franz cell.

Mechanical Properties of Films with Texture Analyzer

According to the risk assessment, the film mechanical properties are also critical parameters, which give important information about the usability of formulations (Figure 2). The optimal mechanical properties ensure patient adherence as well as long and durable application. Skin adhesion is required to increase the exposure time of API; however, if the skin adhesion value is too high, the removal of the film can be painful for the patients. Flexibility ensures that the film can imitate the movement of the skin, which is also required for durable use. If film burst strength is high, the structure of the film can be too rigid, but if the value is low, the film is not able to keep its integrity. During the measurements, we used sticking plaster as reference in the case of skin adhesion, and heat-separated epidermis in the case of flexibility and film burst strength.

In our previous study, it was obtained, that silicone content makes the films softer but less resistant.¹⁸ In this research, we examined the effect of API on the FFSs. As the results show (Figure 9A), skin adhesion highly increased due to the LID-HCl content in formulations LF1 and LF2. When these preparations were used, the parameters met our targets (Table 3). In the case LF3 the adhesion parameter was lower than expected.

The flexibility of films can be seen in Figure 9B. LF1 (27.2%) and LF2 (38.3%) met the requirement, while LF3 (20.3%) showed lower flexibility. In the case of LF1 and LF3, the API decreased the flexibility of the film; however, the flexibility of LF2 increased.

Film burst strength showed a significant increase when the formulation contained LID-HCl (Figure 9C). The burst strength of LF1 jumped from 4.91 N to 8.12 N, and thus its values were too high for our target. The other two films, LF2 (2.96 N) and LF3 (1.27 N) had optimal properties.

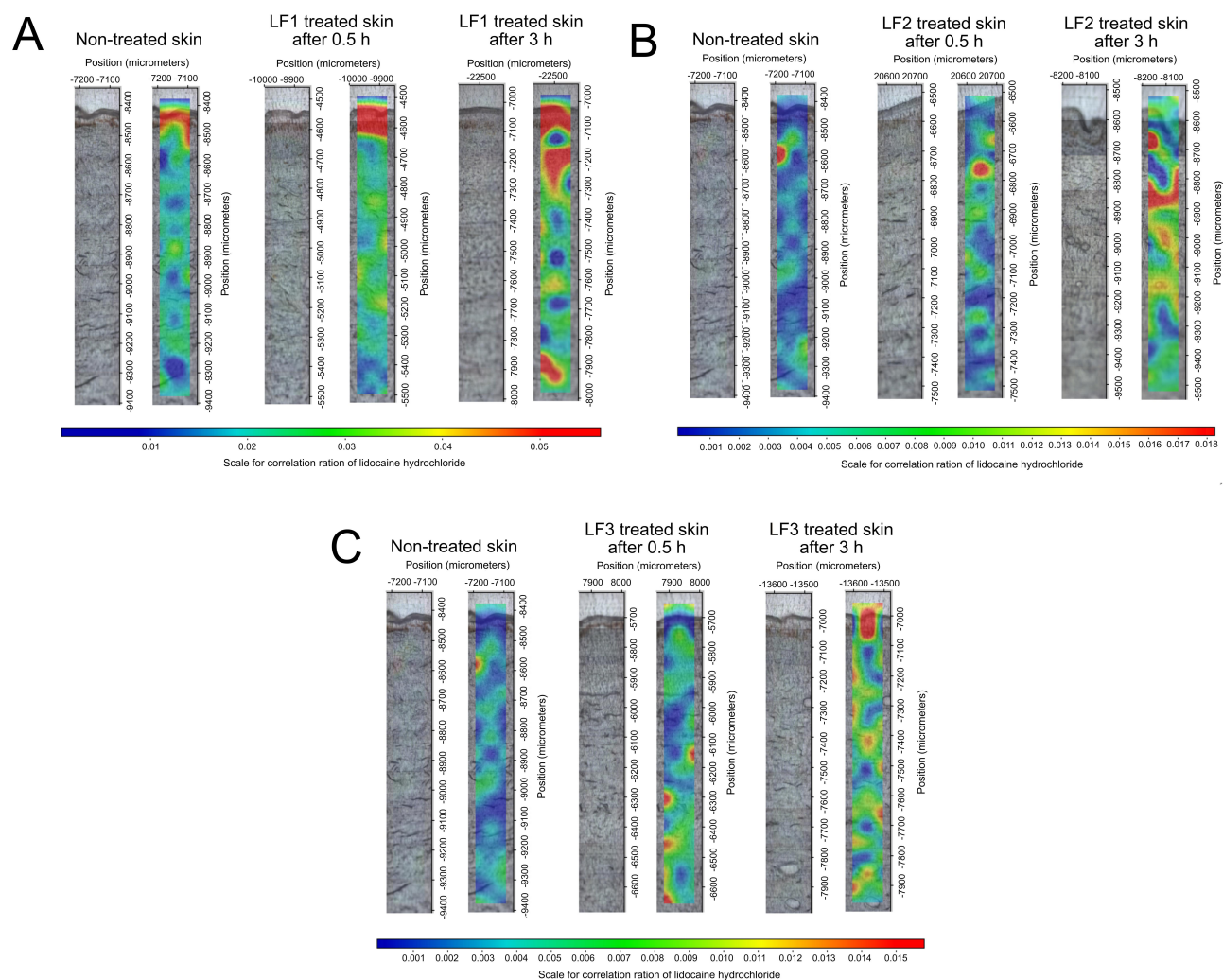


Figure 8 Raman correlation maps for the distribution of FFSs of (A) LF1, (B) LF2, and (C) LF3.

In conclusion, the API increased skin adhesion and film burst strength. The film flexibility of LF2 increased, while the flexibility of LF1 and LF3 decreased due to the API content. Based on the results, LF2 had the best mechanical properties, which could predict higher effect and better patient adherence.

Appearance of Films

The film appearance met our requirements (Table 3). After drying, translucent, slightly white, homogenous, and compact films were formed, which are appropriate for convenient application. There were no differences between the films formed by blank or LID-HCl-containing formulations.¹⁸

Conclusion

In this research work semisolid in situ FFSs containing LID-HCl were formulated using the QbD approach. Initial

risk assessment was applied to evaluate the critical parameters during the development. Based on the results of initial risk assessment, three compositions with or without API were formed and investigated. Initial risk assessment defined the CMAs and the CPPs to ensure the required CQAs. During the initial risk assessment, four CQAs, namely in vitro drug release, in vitro drug permeation, drying properties, and film mechanical properties were found to be highly critical attributes, and three CQAs, namely viscosity, pH, and film appearance were found to be medium critical attributes in the formulation of FFSs. These parameters were investigated. Furthermore, the effects of LID-HCl on these parameters were studied. The initial risk assessment also revealed that four factors, namely permeation enhancing excipients, drying excipients, film-forming excipients, and emollients were highly critical parameters for the CQAs.

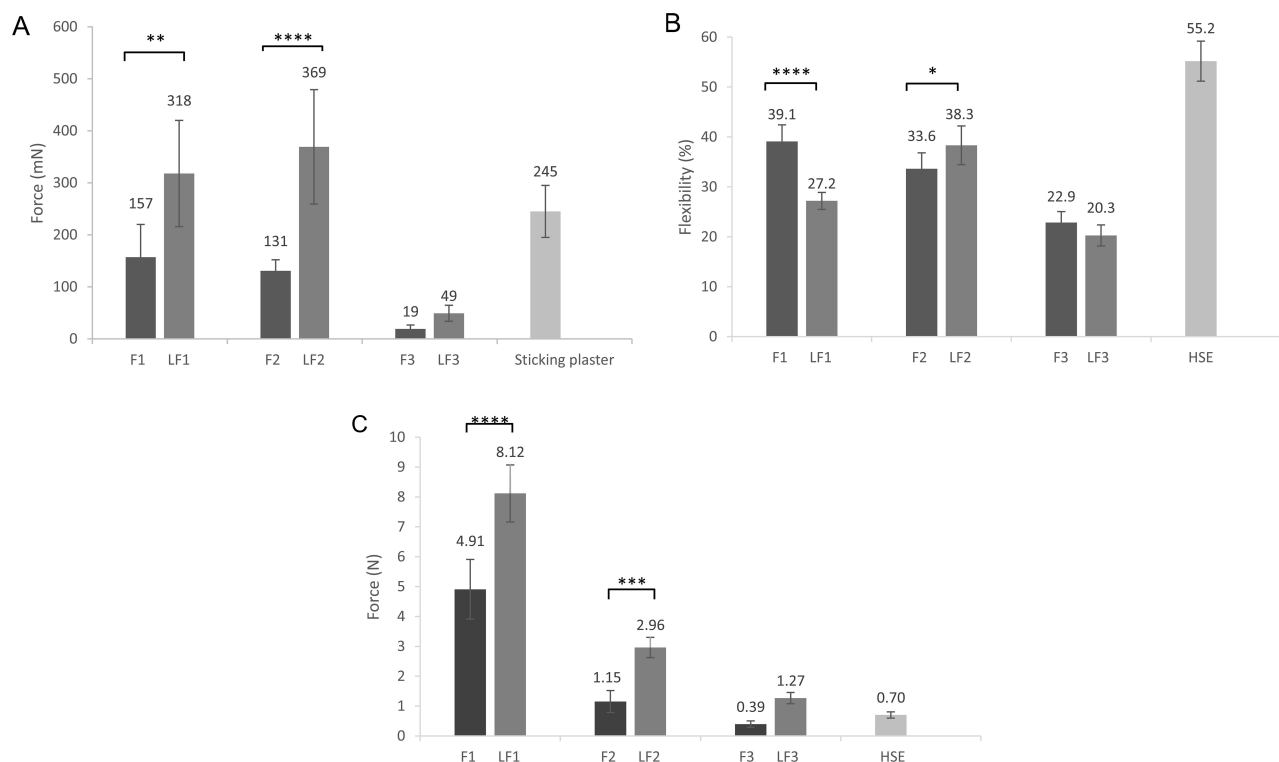


Figure 9 Mechanical properties of FFSs: (A) Skin adhesion, (B) film flexibility, (C) film burst strength; Mean \pm SD (n=4), ($p < 0.05$ *, $p < 0.01$ **, $p < 0.001$ ***, and $p < 0.0001$ **** vs blank formulation).

The results of in vitro drug release showed, there were no significant differences between the diffusion of the formulations after 3 hours, so the formulations have the same drug release profile. However, the LF3 showed significant increase in the diffusion of API in 0.5 hour, so it was released from the LF3 formulation faster, than from the other formulations. The results of in vitro permeation through the HSE showed that the silicone content increased the permeation

rate through the skin. The LF3 formulation had the highest permeation rate, which could be explained by the additional effect of non-volatile silicone in the composition, and the fast drying of the formulation with prolonged drying mechanism.¹⁸ The measurements of Raman spectroscopy revealed that the LID-HCl-containing preparations were present in the different regions of the human skin. LF3 showed deeper permeation into the skin and the rate of permeation was higher. The measurements of drying properties showed that LID-HCl decreased the drying time significantly. Mechanical properties give important information about the usability of films. Silicone content makes the films softer and less resistant; however, the API content modifies the mechanical properties of FFSs. The API increased the skin adhesion and film burst strength, and in the case of LF2, the film flexibility increased, too. Based on these, the formulation containing 25% silicone (LF2) showed the best mechanical properties, which could predict better patient adherence. In respect of pH, rheological parameters, and film appearance, all the three formulations met our requirement. Table 10 summarizes the applicability of FFSs considering our initial expectations (Tables 2 and 3).

In summary, LID-HCl has high influencing effect on the formulation properties. The silicone content has

Table 10 Summary of Applicability of FFSs Containing LID-HCl: Optimal: Exceptionally Good Result, Adequate: The Result Meets Our Requirement of Table 3, Inadequate: The Result Does Not Meet the Requirement of Table 3

Formulation Investigation	LF1	LF2	LF3
In vitro drug release	Optimal	Optimal	Optimal
In vitro permeation	Inadequate	Inadequate	Optimal
Drying properties	Adequate	Adequate	Optimal
Mechanical properties	Inadequate (too rigid)	Optimal	Adequate (too soft)
pH	Optimal	Optimal	Optimal
Viscosity	Optimal	Optimal	Optimal
Film appearance	Optimal	Optimal	Optimal

improved the effect on the permeation rate of API through the skin. Based on our results, formulations F2-LF2 have good mechanical properties, but the permeation rate need to be increased with addition of other permeation enhancers, and F3 - LF3 are appropriate delivery systems for LID-HCl, but the mechanical properties of film are required to improve.

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Disclosure

The authors report no conflicts of interest in this work.

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