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Original Article

Design and Development of Oxyclozanide Chewable Tablet Formulation Employing Quality by Design Approach

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ABSTRACT

Background: The focus of this research was to identify undiscovered knowledge associated with the production of oxyclozanide tablets utilizing Quality by Design (QbD) in order to develop an ideal formulation that would guarantee constant product quality. The modern approach to formulation design and optimization essentially entails QbD which is a systemic method of pharmaceutical development and comprises of the design and development of formulations as well as manufacturing processes to meet the target product quality. **Materials and Methods:** Pre-formulation studies on excipient flow properties, compactibility and tabletability profiles, identification of Critical Process Parameters (CPP) and Critical Quality Attributes (CQA) were carried out. An experimental design was adopted to investigate the effect of formulation and process variables (compression force, super-disintegrant type and concentration) on the CQAs using Modde Pro 12.1. The obtained results were used to generate a Design Space (DS) based on the study data. **Results:** Preformulation studies carried out on the core excipients used, gave an understanding to their tabletability and compactibility. Process parameters such a compaction force and formulation variables such as super-disintegrant concentration were studied within the framework of Quality by Design (QbD) and the new optimized formulation derived was tested and confirmed to be within the design space generated. **Conclusion:** At the end of the study, the aim was achieved; which was to implement pre-formulation studies and QbD to design a formulation containing Oxyclozanide (API) with a combination of excipients.

Keywords: Quality by Design (QbD), Oxyclozanide, Chewable tablet, Compactibility, Tabletability.

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INTRODUCTION

Pharmaceuticals are essential for both human and animal health. Despite the biological similarities in both humans and animals, drug development in veterinary medicine faces many challenges related to anatomical, physiological, and behavioural diversities and biochemical factors.[1] Veterinary drug products come in a variety of dosage forms, including tablets, suspensions and injectables.[2,3]

Pharmaceutical product development has been considered to be a complex process starting from the formulation through to the finalized product. These processes involve multivariate interactions between the input material and process conditions that are essential for product quality, safety and efficacy.[4] Recently, more science-based and systematic approaches have been used to ensure improved product quality. Within this science-based framework, current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines highlight the concept of Quality by Design (QbD).[5]

According to ICH Q8, 2008, QbD is a methodical, risk-based, and scientific approach to pharmaceutical product development and quality management. Rather than being a regulatory requirement for all formulation development, QbD is a special set of principles that can be used to build pharmaceutical products and processes that are founded on research.[6,7] QbD is aimed at ensuring the quality of a product during its shelf-life and understanding how the overall desired quality of a drug product is influenced by process parameters and formulation variables. A QbD-based study begins with determining the Target Product Profile (TPP) and then its quality, which combined is defined as the Quality Target Product Profile (QTPP).[7]

After the QTPP is defined, parameters that influence the QTPP critically are identified. They are the attributes of the final product that ought to be assured while manufacturing, also referred to as Critical Quality Attributes (CQAs). CQAs are highly dependent on the Critical Process Parameters (CPPs) during manufacturing

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Table 1: Quality Target Product Profile (QTPP).

Specification	Target product profile
Dosage form	Chewable tablet (immediate release)
Tablet weight	500 ≤ weight mg ≥ 505
Weight variation	± 5%
Disintegration	Less than 2 min in distilled water
Hardness	< 115 N
Friability	< 1%
Shape	Round flat faced

as well as the Critical Material Attributes (CMAs) of excipients incorporated in the formulation. Identification of CQAs and CPPs helps to obtain a design space and ensure that the manufacturing process is consistent with producing the same product quality over time by operating inside the predetermined design space, therefore ingraining quality into the final product.[4-7]

Tablets are the most common pharmaceutical dosage form and they are generally formed by powder compression (i.e., compaction) through the application of a certain amount of force. This begins with the powders volume being reduced, resulting in a smaller separation distance between particle surfaces, and then, inter-particle bonds are formed. The phrase "powder compressibility" refers to a powder's propensity to reduce in volume, a trait that is often measured by parameters obtained from compression equations.[8] The relationship between compression force and tablet tensile strength is one of the methods used to describe a powder's cohering ability. Compactibility and the tabletability have commonly been described in the literature as the correlation between tensile strength and porosity and tensile strength and compaction pressure, correspondingly.[9,10]

Oxyclozanide (OXY) was chosen as the active pharmaceutical ingredient in this study, which is a salicylamide anthelmintic drug used in veterinary medicine for the control of fascioliasis in farm animals.[11,12] Although tablet dosage forms are widespread in veterinary practice, the advantages of tablets are reduced because of the uncertainty in acceptability by animals and time consumption.[13,14]

Oxyclozanide has been marketed in tablet form; however, the dosage of 10-15mg/Kg of body weight would result in a larger total tablet weight rendering it difficult for a single animal to swallow, and therefore, chewable tablets could be a better alternative.[14,15]

Tablets that need to be chewed prior to ingestion are called chewable tablets. When chewed, chewable tablets dissolve in the mouth and can be ingested with or without water.[16] To enhance the palatability of the tablet, natural or synthetic sweeteners are commonly used. Mannitol is frequently used as an excipient in chewable tablets because of its non-hygroscopic nature, which is required in moisture-sensitive drugs.[17]

The objective of the study was to evaluate and understand the compatibility and tablet ability of the functional excipients in formulation development. The application of the QbD approach assisted in developing a robust chewable tablet formulation with fast disintegration, and acceptable hardness and friability.

MATERIALS AND METHODS

Materials

Oxyclozanide was kindly gifted by Sanovel ilac (Turkey), Mannogem® EZ Spray Dried was purchased from SPI pharma (U.S.A). Pearlitol® 25°C was purchased from Roquette (France). Kollidon® CL, Kollidon® CL-SF, Kollidon® VA 64 Fine and Ludiflash® were obtained as generous gifts from BASF (Germany). Polyplasdone™ XL 10 was purchased from Ashland (U.S.A). L-HPC® LH-21 was purchased from Shin-Etsu (Japan). Magnesium stearate was bought from Peter Greven (Germany).

Pre-compression Parameters and Powder Characterization

Morphological Studies and Powder Surface Area Determination

The morphology of Oxyclozanide and the excipients used were assessed by light microscopy. Images were taken at 20x and 40x magnification. The specific surface area measurement of some powder mixtures using the Brunauer-Emmett-Teller (BET) method was outsourced to Yildiz Teknik, Istanbul, Turkey.

Determination of Powder Flow and Density

Powder flow properties such as the bulk density, tapped density, Angle of Repose, Carr's Compressibility Index and Hausner Ratio of all the powders used in the formulation were determined according to USP methods.[18-21]

Angle of Repose

The angle of repose (θ) was manually computed from the measurement of the height (h) and the radius (r) of the heap (half of powder area diameter) using a Vernier caliper. The calculation was done according to the equation:

$$\theta = \text{Tan-1}\ \{\tfrac{h}{r}\} \qquad (1)$$

Bulk density

The bulk density (g/mL) was determined by pouring a certain amount of powder into a 100 mL graduated cylinder. The bulk density was calculated using the following equation:

$$P_{bulk} = \tfrac{M}{V_0} \qquad (2)$$

Table 2: Composition of oxyclozanide chewable tablets. Each formulation containing 50 mg of oxyclozanide.

Code	Mannogem® EZ Spray Dried (mg)	Kollidon® VA 64 Fine (mg)	L-HPC® LH-21 (mg)	Kollidon® CL (mg)	Kollidon® CL-SF (mg)	Polyplasdone™ XL-10 (mg)	Force (kN)
F1	409.5	22.5	0	18	0	0	5
F2	396	22.5	0	18	13.5	0	5
F3	387	22.5	0	18	22.5	0	5
F4	396	22.5	0	18	0	13.5	5
F5	387	22.5	0	18	0	22.5	5
F6	414	22.5	0	0	13.5	0	5
F7	405	22.5	0	0	22.5	0	5
F8	414	22.5	0	0	0	13.5	5
F9	405	22.5	0	0	0	22.5	5
F10	436.5	0	13.5	0	0	0	5
F11	427.5	0	22.5	0	0	0	5
F12	409.5	22.5	0	18	0	0	10
F13	396	22.5	0	18	13.5	0	10
F14	387	22.5	0	18	22.5	0	10
F15	396	22.5	0	18	0	13.5	10
F16	387	22.5	0	18	0	22.5	10
F17	414	22.5	0	0	13.5	0	10
F18	405	22.5	0	0	22.5	0	10
F19	414	22.5	0	0	0	13.5	10
F20	405	22.5	0	0	0	22.5	10
F21	436.5	0	13.5	0	0	0	10
F22	427.5	0	22.5	0	0	0	10

Table 3: Compaction Data Analysis at 5 and 10 kN. Relative standard deviations are denoted in parentheses.

Powders	Force	σ_t (MPa)[a]	ε (%)[b]	Py (MPa)[c]	ER in–die (%)[d]	RD in-die[e]	SSA (cm^3)[f]
OXY+LUD	5	0.809	19.1	66.5 (±0.01)	8.4 (±0.00)	0.809	2.5849
OXY+ MANN	5	0.758	24.1	74.3 (±0.01)	8.3 (±0.02)	0.759	2.4523
OXY+ PEARL	5	0.661	21.3	80.1 (±0.01)	5.9 (±0.05)	0.794	2.8775
OXY+LUD	10	1.896	11.2	82.7 (±0.01)	8.6 (±0.00)	0.888	2.5849
OXY+ MANN	10	1.753	15.3	101.2 (±0.01)	10.1 (±0.02)	0.847	2.4523
OXY+ PEARL	10	1.584	12.9	101.3 (±0.01)	7.1 (±0.05)	0.871	2.8775

[a]Tensile strength ($n = 5$). [b]Porosity ($n = 5$).[c]Heckel yield pressure ($n = 5$).[d]In-die elastic recovery ($n = 5$).[e]In-die relative density.[f]Specific surface area.

Where M is the powder mass (g) and V_0 is the initial volume.

Tapped density

The tapped density (g/mL) was determined by placing a 100 mL glass cylinder on the ERWEKA® tapped volumeter (GMBH SVM 203, Germany) that was tapped at certain intervals until a constant volume was reached. This parameter was calculated using the following equation:

$$P_{tapped} = \frac{M}{V_t} \quad (3)$$

Where M is the powder mass (g) and V_t is the tapped volume.

The bulk and tapped densities were used to calculated the Carr's Index and Hausner Ratio of the excipients in order to assess their compressibility.

Study Design

In this study the Quality Target Product Profile (QTPP) was set as highlighted in Table 1 and Design of Experiment (DoE) was carried out to analyze the effect of the process and formulation

variables on the critical quality attributes of oxyclozanide chewable veterinary tablets. The experimental data set consisting of 22 formulations is shown in Table 2. The effect of super-disintegrant type (Polyplasdone® XL-10 and Kollidon® CL-SF) as well as super-disintegrant concentrations (3% and 5%) were evaluated. The process variables tested were compaction forces set at 5 kN and 10 kN. The experimental data produced were used for software training.

CMAs and CPPs were regarded as the inputs (independent variables), while QTPPs (hardness, disintegration time, and friability) were considered as the outputs (dependent variables). The effect of super-disintegrant type, super-disintegrant amount and the impact of compression force on the target product profile as seen in were analyzed using QbD analysis software (Modde Pro 12.1).

Compaction Data Analysis

A portion of this study was conducted in order to understand the powder behaviour of the core materials under pressure using the in-die method. The data presented in Table 3 was obtained digitally from a compaction simulator (Stylcam 200R, Medelpharm, France) equipped with data acquisition software (Analis, version 2.01, Medelpharm). The core materials analyzed were (Oxyclozanide+Ludiflash®), (Oxyclozanide+Kollidon® VA 64 Fine+ Mannogem® EZ Spray Dried), and (Oxyclozanide+Pearlitol® 25 C +Kollidon VA 64 Fine). Each mixture contained mannitol or a mannitol-based filler, and this portion of the study was done to assess the compressibility and tabletability of the prepared formulations.

The Heckel equation was used to derive compression profiles.[22] The initial powder bed height, which was determined by the powder weight and mass in-die, was used to calculate the elastic recovery in-die. In accordance with the existing literature, the in-die yield Pressure (Py) was estimated as the reciprocal of the slope of the linear portion (R^2> 0.999) of the Heckel plot.[23]

Powder Blending

All formulation excipients were accurately weighed according to the values presented in Table 2 and manually mixed for 10 min. Each batch was lubricated with 1% magnesium stearate and mixed for approximately 2 min.

Formation of compacts

Tablets were compressed (*n* tablets were kN and 10 kN using a compaction simulator fitted with Euro B 11.28 mm round, flat-faced punches. A Fette102i rotary press was simulated during compression cycles at 10 rpm compression speed.

Post-compression Parameters

All formulations were evaluated for hardness, friability, weight variation, thickness and disintegration time.

Hardness

The tablets hardness was measured by (ERWEKA TBH 225, Germany) hardness tester and expressed as a mean value and standard deviation ($n = 6$).

Friability

Ten tablets from each batch were selected and accurately weighed using a digital balance (Mettler Toledo AB204-S/FACT) and placed in the plastic chamber of the friability tester (ERWEKA TA 220, Germany). The chamber was attached to a motor revolving at 25 rpm for 4 min. The tablets were de-dusted, re-weighed, and the percentage weight loss was then calculated.

Weight Variation

Ten tablets from each batch selected randomly were accurately weighed individually, and then the average and standard deviation were calculated for each batch.

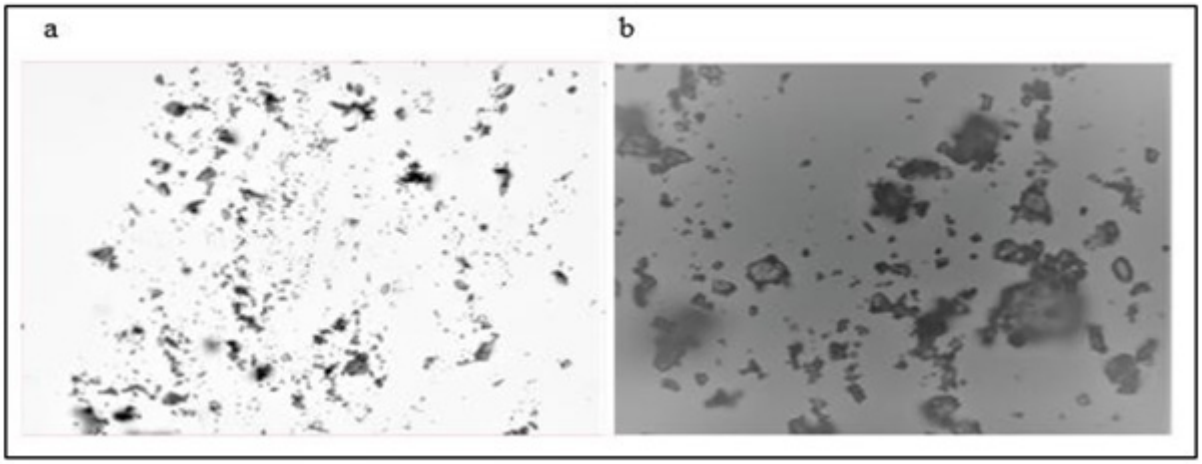

Figure 1: Microscopic image of Oxyclozanide at 20X (a) and 40X (b) magnification.

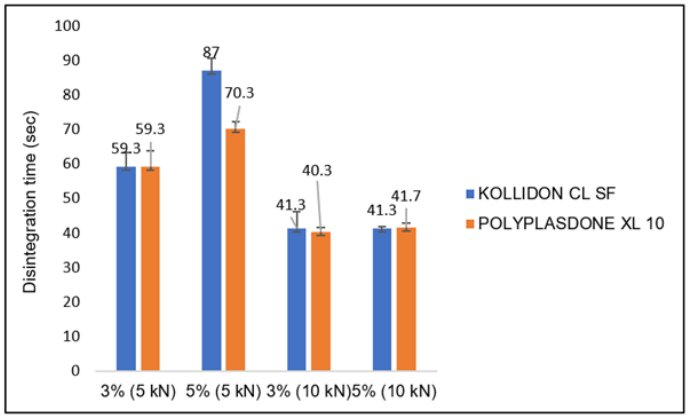

Figure 2: Effect of super-disintegrant type and concentration on disintegration time.

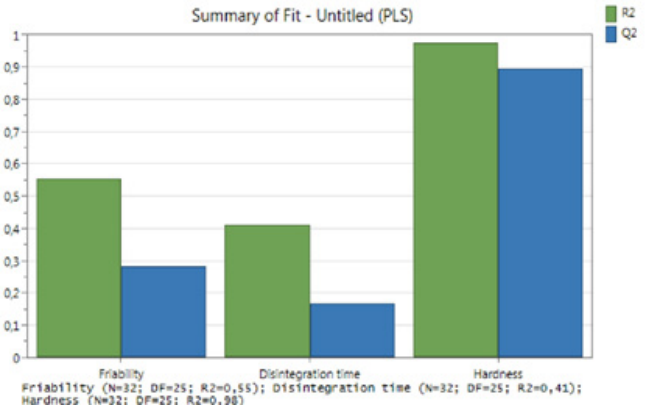

Figure 3: Analysis of model fit according to ANOVA test.

In vitro Disintegration Test

The disintegration time for three tablets of each formulation was determined using a disintegration apparatus (ERWEKA GmbH ZT 322, Germany). Tablets were individually placed in each tube immersed in a 600 mL beaker of distilled water (37°C). The mean and standard deviation were calculated.

Development of Design Space and Optimization

Experimental data were analyzed with Modde Pro 12.1 to establish a design space. Modde investigates the response factors in detail as a function of the variables. The Analysis of the Variance (ANOVA) test confirmed the credibility of the design of experiment. An R^2 (coefficient of determination) of 0.5 indicates a model with relatively low significance in terms of ANOVA. For a model to be significant or excellent, the Q2 (the model's predictive power) should be higher than 0.1 or 0.5, respectively. A decent model should also have an R2 and Q2 difference that is less than 0.3.[24]

Input factors (super-disintegrant type and amount, and compression force) were the qualitative and quantitative variables. The output (responses) resulted from post compaction quality control tests, where the parameters included hardness, friability and disintegration time. Partial Least Squares (PLS) regression was used to fit a mathematical model for each response. A 4D Design space plot was generated to show the probability of failure percentage (%) for the shown factor combinations. The lowest probability of failure point was selected from the graph and tested.

RESULTS

Pre-compression Parameters and Powder Characterization

Microscopic image of oxyclozanide at 20x and 40x captured by a light microscope as seen in Figure 1 showed oxyclozanide is a very fine powder with easy electrostatic formation during processing. Powder flow and density properties of individual raw materials were measured and calculated. Hausner ratio and Carr's index results for Mannogem® EZ Spray Dried, Kollidon® CL, and Ludiflash® were within the ranges of 1.2-1.6 and 25-36% respectively. This indicates passable to very poor flow property range. Oxyclozanide, Pearlitol® 25 C, Kollidon® CL SF, Polyplasdone™ XL-10, and Kollidon® VA 64-Fine were within 1.5-1.9 for Hausner ratio and their Carr's index were all above 38%.

Compaction Data Analysis

Table 3 show the compaction data results, which include the parameters that describe the compressibility and tablet ability of the core materials used in the chewable tablet formulation. A directly proportional correlation between tensile strength and compaction force is observed in the results, as well as a directly proportional relationship between yield pressure and compaction force.[8,25]

Three powder mixtures tested for compressibility and densification under pressure utilizing Heckel analysis. Oxy+Ludiflash showed the lowest yield pressure at 5 kN and 10 kN, respectively, which reflects its ability to deform plastically (<80 MPa) at low pressure and produce a coherent tablet with 0.809 MPa and 1.896 MPa tensile strength. Oxy+Mannogem exhibited plastic deformation at 5kN then brittle fracture at 10kN.

Table 4: List of Model fit summary according to ANOVA test.

Responses	R^2	R^2 Adj	Q^2	SDY	RSD
Friability	0.554053	0.447026	0.28163	2.09389	1.55706
Disintegration time	0.41109	0.269751	0.1699	128.094	109.462
Hardness	0.975849	0.970053	0.896094	35.979	6.22622

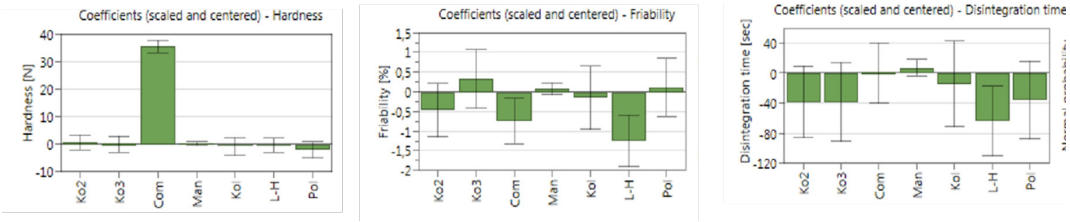

Figure 4: Coefficient plots for the PLS models displaying their confidence intervals.

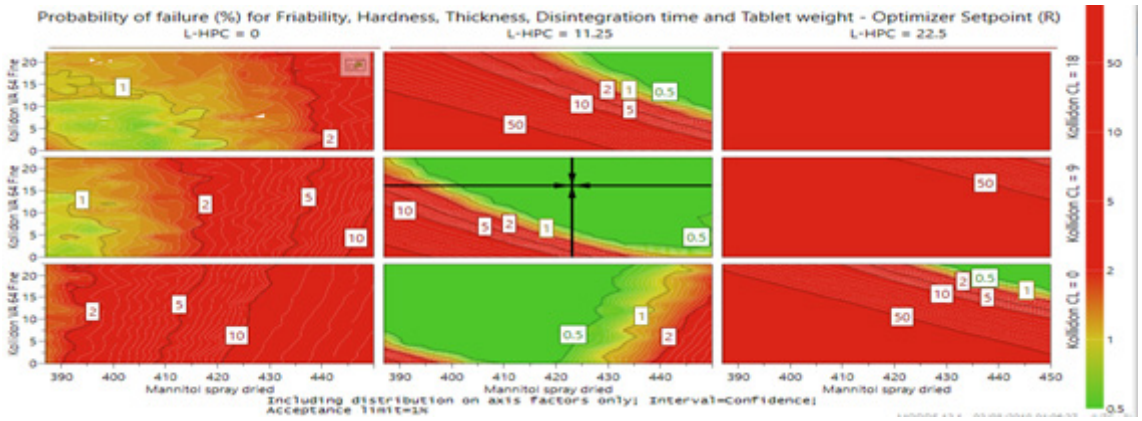

Figure 5: 4D Design space with set point obtained from Modde 12.1.

Oxy+Pearlitol granules showed the highest yield pressure, which indicates less plasticity and more brittle behaviour. This may be due to the granule preparation method (wet granulation), which yields denser granules with low intra-granular porosity and high solid fraction producing the weakest tablets in terms of tensile strength at the two forces.[26,27]

Post-compression Results

All formulations were within acceptable limits for weight variation and disintegration time, while formulations compressed at 10 kN were within limits for friability. As demonstrated in Figure 2, 3% and 5% of super-disintegrant were examined for their impact on the disintegration times under various compaction forces. Generally, the relationship between compaction force and disintegration time is influenced by the super-disintegrant concentration.[28] However, in most formulations, the disintegration time reduced as the compaction force increased. For both super-disintegrants, Kollidon® CL-SF and Polyplasdone™ XL-10, the disintegration time shortened with increased compression force.

The results represented in Figure 3 show that the disintegration time of the tablets not only varied based on the type of disintegrant but also due to the different concentrations of the disintegrant used. However, the effect of the type can only be seen at 5% concentration and 5 kN compression force, where Polyplasdone™ XL-10 showed better performance compared to Kollidon® CL-SF. This could be due to the slight difference in particle size (25-40 µm for Polyplasdone™ XL-10 and 30-50 µm for Kollidon® CL-SF), thus facilitating faster water absorbance.

Modelling of Experimental Design

The Analysis of Variance (ANOVA) test confirmed the credibility of the design of experiment illustrated in Table 4 and Figure 3. According to the model fitting results, it is observed that compaction force is the variable that affects hardness the most. Kollidon® CL, Kollidon® CL SF, Polyplasdone™ XL 10 and L-HPC® LH-21 (Ko2, Ko3, Pol, L-H) all significantly affect the disintegration time. Compaction force as well as L-HPC LH-21 both show notable effect on friability.

The response goals for the optimizer was given and the initial set point was selected according to log(D) and the likelihood of percentage failure. Figure 4 represents the adjusted regression coefficient values for the model equation. The histograms demonstrate the importance and relevance of how variables have an impact on the responses. A term is considered to be significant when y = 0 is far from the starting point. Additionally, there is a level of uncertainty that does not go beyond y = 0.[29-32]

Development of Design Space

In Figure 5 illustrates the obtained design space with the robust set point; which is demonstrated by the interception of arrows and the colour scale indicates the likelihood that the quality target product profile will not be met. The otherwise depiction of the design space when it comes to a multidimensional design space is to use a hypercube that details the edges of the design

space as high and low values for the set point. For the verification of the design space, formulations were prepared according to the test robust setpoint, and control tests were performed. All test results obtained were within intended QTPP limits.

DISCUSSION

The microscopic pictures at 20X and 40X magnifications show that Oxyclozanide has irregular crystalline particles that stick to each other. Also, a wide range of particle size distribution can be deduced from the microscopic image.

The compatibility and tiltability studies for the core material used in the formulation showed that the yield Pressure (Py) increased with a higher surface area which is indicated reflecting increase in plasticity with reduced granule size. This is consistent with past findings and is often explained by a greater counteraction to particle deformation brought on by a decrease in the frequency of crystal defects with a smaller granule size.[33]

An inverse correlation between tensile strength and porosity was also observed, with Oxy+Ludiflash having the lowest porosity and highest tensile strength at both compression forces, which is concurrent with the Ryshkewitch–Duckworth equation used to describe the compatibility of materials.[8,34]

As expected, the hardness of tablets increased and the friability decreased as the compaction force increased.[35,36] The significance of super-disintegrant concentration at different particle grades on the disintegration time of chewable tablets at 5 kN and 10 kN was observed. It was indicated that at 5 kN, the disintegration time increased slightly as the super-disintegrant concentration increased and this is concurrent with the existing literature.[37] However, at 10 kN, the disintegration time was not affected by increasing the super-disintegrant concentration.

The model fit (Table 4 and Figure 3); R^2 and Q^2 are high for hardness response, indicating that the function is a good fit of the data. For friability and disintegration time, the model's predictive power (Q^2) is higher than 0.1, indicating that a significant model was created for both responses as well. The differences between R^2 and Q^2 for hardness, friability, and disintegration responses were less than 0.3 which in agreement with previous studies suggests a good model was created.[24]

Modde (version 12.1) and PLS (partial least squares) models were used to create the design space using the process variables and formulations. With a failure rate of under 1%, green spaces are an element of the design space. The likelihood of failure is higher in the red and yellow areas.

CONCLUSION

The objective of the study was to obtain a robust oxyclozanide chewable tablet formulation through the application of QbD, by understanding the critical material attributes and critical process parameters that would significantly affect the quality attributes. The compactibility and tabletability study of the excipients provided sufficient knowledge of the powder's capacity to form compacts, which is advantageous for formulation development.

The theoretical and scientific background-based risk analysis supported by the laboratory-based QbD approach conveys a clear insight for predicting the tablet quality and designing risk avoidance strategies in advance before real loss of time and material in actual manufacturing formulation in an industrial set up.

In conclusion, the design space resulted in a range of formulations that satisfied the QTPP, and thus, it can be said that an optimum formulation was obtained with predictable and desired quality attributes. Furthermore, development of solid dosage form variations such as chewable tablets which have proven to be advantageous over conventional tablets in terms of acceptability and ease of administration; is needed in veterinary practice.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

QbD: Quality by Design; **ICH:** International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; **TPP:** Target Product Profile; **QTPP:** Quality Target Product Profile; **CQA:** Critical Quality Attributes; **CPP:** Critical Process Parameters; **CMA:** Critical Material Attributes; **PLS:** Partial least squares; **Py:** Yield Pressure; **MPa:** Megapascal; **kN:** Kilonewton; **rpm:** Rotations per minute; **mm:** Millimeter; **Oxy:** Oxyclozanide; **mg:** Milligram; **kg:** Kilogram; **mL:** Milliliter; **DoE:** Design of Experiments; **DS:** Design Space; **API:** Active Pharmaceutical Ingredient; **g:** Grams; **BET:** Brunauer-Emmett Teller; **USP:** United States Pharmacopoeia.

SUMMARY

The modern approach to formulation design and optimization essentially entails Quality by Design (QbD). QbD is a systemic method of pharmaceutical development, which comprises the design and development of formulations as well as manufacturing processes to meet the target product quality. The focus of this research was to identify undiscovered knowledge associated

with the production of oxycloznide tablets utilizing QbD in order to develop an ideal formulation that would guarantee constant product quality. Pre-formulation studies on excipient flow properties, compactibility and tabletability profiles, identification of Critical Process Parameters (CPP) and Critical Quality Attributes (CQA) were carried out. An experimental design was adopted to investigate the effect of formulation and process variables (compression force, super-disintegrant type and concentration) on the CQAs using Modde Pro 12.1. The obtained results were used to generate a Design Space (DS) based on the study data. At the end of the study, a new optimized formulation derived was tested and it was confirmed to be within the design space. The aim of this study was to implement preformulation studies to design a formulation containing Oxyclozanide (API) with a combination of excipients. Process parameters and formulation variables were studied within the framework of Quality by Design (QbD) to develop a robust chewable tablet formulation.

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