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# DEVELOPMENT OF A PROLONGED-RELEASE SYSTEM FOR THE ASSOCIATION OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

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## ABSTRACT

Pain is a response to cellular injury caused by accidental or intentional tissue damage. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most prescribed medications worldwide for pain management, including postoperative pain. However, due to the high frequency of doses required during therapy, gastric injuries can develop. Tromethamine ketorolac and sodium diclofenac are two widely used NSAIDs for pain relief as anti-inflammatory and antipyretic agents (especially sodium diclofenac), but there are no formulations combining both drugs that provide sustained release. This drug release model is extremely useful in reducing the number of doses, increasing the dosing interval, and ensuring long-term effects. Microencapsulated systems are extensively used to better protect the drug from climatic conditions, gastric fluids, and to ensure greater stability, as well as being a great tool for modulating drug release according to the desired action and intended pharmacotherapy. Thus, in this study, using the most modern rational approach for the design of new drugs and evaluation of critical quality attributes, multivariate studies, in silico and in vitro prediction, a controlled release system for the combination of tromethamine ketorolac and sodium diclofenac was developed through microencapsulation in a lipid blend with beeswax and ethyl oleate using a cooling-induced emulsification method for the dispersed phase. Different concentrations of beeswax, ethyl oleate, and drugs were tested, and in experiments with lower percentages of ethyl oleate (wax-to-drug ratio of 6:1), it was possible to obtain matrix lipid solid system, with higher efficiency in modulating the release of both drugs for up to 12 hours. The drug content was quantified, ranging from 4 to 13 mg/mg for KT and 12 to 39 mg/mg for DS, and the release profile was analyzed using phosphate buffer pH 6.8 in USP apparatus 2. The formulations demonstrated a controlled release profile compared to free drug, indicating that drug release occurred through modulation of the lipid matrix system.

**Keywords:** microencapsulation, ketorolac trometamol, sodium diclofenac, lipidic blend and extended-release system

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## INTRODUCTION

Pain is a sensory and emotional response caused by cellular injury, as part of the inflammatory response of the immune system, which is a natural defense mechanism of the body in cases of accidental or intentional injury, such as in surgeries. According to the classifications and guidelines of the World Health Organization (WHO), pain is considered detrimental to health broadly, and over time, scientists have sought effective treatments to combat it. The immune response occurs when cells of the immune system are activated in response to foreign organisms or antigenic substances released during acute or chronic inflammation. This chronic inflammation involves the action of multiple cytokines and chemokines, which can lead to autoimmune diseases and inflammatory conditions. The goal of treatment in inflamed patients is to relieve symptoms and slow down or halt the process of tissue damage. Medical studies indicate that in patients undergoing surgical procedures and in the immediate postoperative period, pain may occur after the end of anesthesia and last for 2 to 3 hours, with potential to extend up to 24 hours after the procedure [1,5].

A pharmacological option for pain control is the use of non-steroidal anti- inflammatory drugs (NSAIDs) and analgesics. Among analgesics, opioids are widely used but are known for their potential to cause chemical dependence and, in extreme cases, even lead to death. To minimize the adverse effects of opioids, the administration of NSAIDs in combination with these medications has been used, especially in postoperative patients, with the aim of reducing the intensity of pain after surgical procedures [1,6].

Non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the biosynthesis of prostaglandins, which confers anti-inflammatory action, and may have other mechanisms of action, such as inhibition of chemotaxis and production of free radicals. The selectivity of these drugs for COX-1 and COX-2 varies, and selective COX-2 inhibitors may have an improved gastrointestinal safety profile but may increase the incidence of edema, hypertension, and possibly myocardial infarction. All NSAIDs have analgesic, anti-inflammatory, and antipyretic effects, except for selective COX-2 agents and non-acetylated salicylates. However, newer NSAIDs tend to cause less gastrointestinal irritation compared to acetylsalicylic acid [3,7].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed worldwide due to their effectiveness as anti-inflammatory, antithrombotic, antipyretic, and analgesic medications. In the context of postoperative pain management, the most used NSAIDs are ketorolac tromethamine (KT, DCB: 01964) and diclofenac sodium (DS, DCB: 2930). However, due to the need for prolonged use of these medications in this indication, the dosing regimen involves frequent administration of doses, which can result in adverse effects such as gastric lesions and other side effects associated with NSAID exposure 6,8,10.

Pharmaceutical formulations with different drug delivery systems are developed based on characteristics such as rapid metabolism or the need for long-term therapy (with repeated administration or prolonged effect) [11,13]. These systems include appropriate adjuvant or auxiliary processes and substances for the development of pharmaceutical formulations, ensuring stability, bioavailability, and therapeutic efficacy of the final product [14].

Ketorolac tromethamine (KT), marketed as a tromethamine salt, is a non- steroidal anti-inflammatory drug (NSAID) commonly prescribed as an analgesic, although it also exhibits significant anti-inflammatory activity. This makes it an important option as a substitute for morphine in some cases of mild to moderate post-operative pain [3,6,9,15,16]. ). Available formulations of ketorolac tromethamine (KT) in Brazil include injectable solution, ophthalmic solution, sublingual tablets, and oral solution. No combination products or prolonged-release formulations of the drug were found. This same situation is repeated in the United States of America [3,17,18].

Diclofenac sodium (DS) is another NSAID indicated for the treatment of mild to moderate pain, as well as for its antipyretic properties. Its solubility is pH- dependent, decreasing in acidic environments such as gastric juice compared to the pH of enteric juice [14,19,20]. The available formulations with DS in Brazil include oral suspension, extended-release coated tablets, and soft capsules. No formulations combining KT and DS with the aim of enhancing therapeutic efficacy were identified. This same situation is repeated in the United States, with the exception of the presence of injectable solution in the market. Furthermore, no formulations with extended-release systems were found for the combination of KT and DS [17,18].

Modification of the drug release can result in the reduction of dosing frequency of medication. To achieve prolonged-release pharmaceutical forms, increase stability, and reduce adverse effects due to high dosing frequency, microencapsulation technology has been utilized. In this process, active components are encapsulated by carrier material, forming micrometer-sized particles or capsules. Microencapsulation can be performed using natural or synthetic polymers, as well as lipids, and aims to: (I) protect the drug from gastric fluids; (II) increase the stability of the final product; (III) mask the taste; and (IV) improve drug absorption by the body. The mechanism of drug release from encapsulated particles involves diffusion and/or enzymatic degradation processes. The versatility of techniques used in this technology allows its application in a wide range of medications, with optimization of factors such as the physicochemical characteristics of the polymer and drug used, as well as parameters related to the preparation technique, which influence the properties of the final product [11,14,21].

Thus, the aim of this study is to develop a prolonged-release system through microencapsulation for the combination of the NSAIDs KT and DS. This combination seeks to promote better patient adherence to drug therapy, improve treatment efficacy, reduce the frequency of regular dosing, and consequently decrease adverse effects, resulting in increased patient safety.

## MATERIALS AND METHODS

### Materiais e reagentes

It is necessary to highlight that for the accomplishment of the

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present work, which aimed at the development of a matrix lipid solid system, the following materials were used for the elaboration of the matrix systems: Tromethamine ketorolac (MSN Laboratories); sodium diclofenac (Merck); carnauba wax, beeswax, Cetiol V (decyl oleate) (Bianquímica), HPMC capsule No. 01 (ACG), and Tween 80 (Merck).

**Proposed formulation**

The formulation described in Table 1 was determined with the objective of meeting the requirements intended for the product, as well as the proposed process.

**Tabela 1** - Final formulation for univariate experiments.

| **Lipid phase** | **Quantities** |
|---|---|
| Beeswax | 50 – 100% |
| Decyl oleate | 0 - 10% |
| Carnauba Wax | 0 – 50% |
| KT | 60 mg |
| DS | 100 mg |
| **Step 1 – Dispersion** | **Quantities** |
| 2M phosphate buffer pH 2.0 | 10 mL |
| Tween 80 | 0,6 % |
| **Step 2 - Dilution** | **Quantities** |
| 2M phosphate buffer pH 2.0 | 90 mL |
| Tween 80 | 0,6% |

**Process: Emulsification with dispersed phase cooling**

The microencapsulation process involves the following steps, according Vilivalam e Adeyeye (1994):

1. Emulsion preparation: An emulsion is prepared using a blend of beeswax, carnauba wax, and ethyl oleate, heated to 10°C above the melting temperature of the waxes, along with DS and KT. The emulsion is obtained by vigorous agitation at 600 rpm of these components added to an aqueous phase, with sodium phosphate buffer at pH 2.0 and Tween 80 (pre-dispersion step).

2. Dilution step: The pre-dispersion emulsion is then diluted with a new amount of aqueous phase under mechanical agitation ranging from 400 to 1200 rpm.

3. Emulsion cooling: The emulsion is then cooled to a temperature below the melting point of the waxes, usually using a refrigerant solution. The cooling causes the waxes to solidify, encapsulating the AINEs in a matrix system.

4. Separation of encapsulated systems: The formed matrix systems are separated from the non-encapsulated emulsion through filtration.

5. Washing of matrix systems: The isolated matrix systems are then washed with purified water to remove residues.

6. Drying of matrix systems: The purified matrix systems are dried to remove residual water and obtain solid lipid matrix systems.

Solid lipid matrix systems without the addition of drugs were also obtained for use in the validation of analytical methodology and are referred to as placebos.

**Univariate analysis:**

a. Blend proportion: from 0 to 50% of carnauba wax and 0 to 10% of ethyl oleate;

b. Cooling method: natural or controlled;

**Multivariate analysis:**

a. Range of mechanical impeller rotation;

b. Core-coating ratio;

c. Blend (if applicable);

**Statistical evaluations**

Multivariate experiments were planned and evaluated using Minitab® 16 software. The multifactorial model was defined according to the Plackett-Burman design. Statistical evaluations of the results were performed using GraphPad Prism® software. Quantitative experiments were conducted in triplicate to obtain means, standard deviations, and relative standard deviations. Statistical evaluations were conducted with a 95% confidence level, where p-value < 0.05.

## RESULTS AND DISCUSSIONS

**Physical and physicochemical characterization of raw materials**

**Drug characterization**

**Physical and physicochemical properties of drugs**

The physical and physicochemical characteristics of the drugs tromethamine ketorolac and sodium diclofenac were evaluated. Both drugs, according table 2, showed purity levels of 100%, impurities below the maximum control ranges of the specification, and particles with 90% of the population below 40 µm. Pharmacopeial monographs showed that both drugs have melting points higher than 100°C, compatible with the microencapsulation process temperature, and sodium diclofenac is less soluble in water than tromethamine ketorolac. In silico evaluation showed that both drugs have higher lipophilicity at pH values below 2, with sodium diclofenac being approximately 2 units more lipophilic than

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tromethamine ketorolac in this pH range. Additionally, the LogD values of the drugs were compared, and it was noted that DS had low solubility but high absorption, which could reduce the encapsulation efficiency of KT These characteristics may affect the encapsulation efficiency and kinetic release of tromethamine ketorolac from the lipid matrix.

**Table 2 -** Summary of physicochemical properties.

| **Characterization according to data from the analysis certificates of drug manufacturers** | | |
|---|---|---|
| **Teste** | **Especification** | **Result** |
| Assay KT | 98,5 - 101,5% | 100,0% |
| Assay DS | 99,0 - 101,0% | 100,5% |
| Particule size distribution d90 KT | < 40 µm | 34,8 µm |
| Particule size distribution < 25 µm DS | > 75% | > 75% |
| **Characterization according to data from the Chemicalize® prediction software** | | |
| **Characterization** | **pKa** | **LogP** |
| KT | 3,84 | 2,283 |
| DS | 4 | 4,259 |
| **Characterization according to data from USP-NF®** | | |
| **Physical proprieties** | **KT** | **DS** |
| Melting point | 165°C and 170°C | ~ 284°C |
| Water solubility | Freely soluble | Very slightly soluble |
| Methanol solubility | Freely soluble | Freely soluble |
| Ethanol solubility | Slightly soluble | Soluble in ethanol |

**Characterization of lipid matrix candidates**

Regarding the raw materials that will compose the lipid matrix, the properties of beeswax and carnauba wax are noteworthy. They are widely used in various pharmaceutical formulations such as capsule coatings and microemulsions. Beeswax is a white to yellowish solid, moderately soluble in cold alcohol and insoluble in water, composed of 70 to 75% of a mixture of esters of monohydric alcohols and esterified chains with acids, which gives it stabilizing and hardening properties. Carnauba wax, on the other hand, is a chemically classified substance as a simple, saturated lipid that is easy to handle. It is practically insoluble in water and has a melting point around 80 to 85°C, mainly used as a coating agent in various formulations, as well as having broad application in microencapsulation and microemulsions.

Additionally, it is worth highlighting that there are reports of polymorphic transition in lipid matrix particles of the waxes. These transitions occur due to the reduced size of the particles and the cooling rate of the system after the fusion of the waxes. There is also a discussion about decyl oleate, a wax ester used as a mixture in solid-state waxes to reduce the melting point of the mixture and facilitate handling after fusion, which is widely used in cosmetic formulations as an emollient.

**Evaluation of desired quality parameters for the microencapsulated product - Impact assessment by critical quality attributes of raw materials and process on the finished product**

A critical evaluation of critical attributes of raw materials as well as process characteristics was proactively performed to verify if: (a) the process could be viable to be carried out and (b) the target characteristics for the matrix lipid solid system could be achieved, as shown in Table 3, ensuring safety, quality, and possible efficacy of a potential product.

The drugs and the lipid matrix used in the process were characterized, making it possible to use the tool provided in ICH Q9 with the definition of Critical Quality Attributes (CQAs) for the matrix lipid solid system. The intention of proactively evaluating the raw material characterization data and prior knowledge of the intended process is to, according to ICH Q9, direct the development of the new product by understanding the process variables, ensuring product quality in accordance with the Quality Target Product Profile (QTPP) of the product.

It can be noted that for both drugs, logP and solubility characteristics have the potential impact associated with the CQAs of the intended product. Regarding the components of the lipid matrix,

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carnauba wax, due to its high melting point and rapid solidification, has the greatest impact on yield, as polymorphic transitions may affect encapsulation efficiency and release mechanism. Regarding process variables, the possibility of polymorphic transition during heating and cooling curve presents a possibility of interference in the intended QTPP. For the release mechanism and profile of related substances, modification of the aqueous phase may facilitate mechanisms of hydrolysis of drugs and lipid matrix.

**Tabela 3** - Quality target product profile (QTPP).

| QTPP | Target | Justification |
|---|---|---|
| Route of Administration | Oral Route | Route of Administration intended |
| Unit dose concentration | 60 mg for KT<br>100 mg for DS | Highest daily registered in the Brazil. |
| Controlled release system | Control release within 24-hour | Reduction of successive administrations of drugs already available on the market Adjusted by release mechanism and particle size. |
| Unit dose content | 60 mg to KT 100 mg to DS | Requirement for adequate therapeutic effect, according to the package insert of drugs available with KT and DS and for adequate dose delivery.<br>Consequence of yield and encapsulation efficiency |
| Unknown related substances | < 0,1% | Estimated value based on the maximum daily doses of each drug, calculated according to ICH Q3B, attributed to unknown impurities. |
| Knowed related substances | < 0,33% to KT<br>< 0,20% to DS | Estimated value based on the maximum daily doses of each drug, calculated according to ICH Q3B, attributed to known impurities |

**Experiments design**

**Univariate**

For the univariate experiments, beeswax was used as a carrier agent, carnauba wax as a hardening agent, and decyl oleate as a melting point decreasing agent to reduce the possibility of polymorphic differentiation. Additionally, Tween 80 was used as an emulsifying agent aiming for particles with an average size of 200 µm. The prepared suspensions were characterized by their shape by optical microscopy at 4 times magnification.

A third experiment was performed with a new ratio justified by the low incorporation of carnauba wax and the high polymorphic differentiation attributed to the high amount of decyl oleate. To initially mitigate polymorphic differentiation, a cooling curve was practiced in step II. Thus, experiment 3 was repeated, and after the start of step 2, two minutes were waited at the end of the pre-dispersion addition, and then a gradual cooling with water at room temperature and ice was started, simulating a reactor jacket.

For the minimum speed of step II, the same process as the univariate experiments was used, with only the homogenization speed being varied, which was carried out at 1200 rpm. The result indicated that the minimum speed for the formation of matrix lipid solid system in step II is 1200 rpm.

**Multivariate**

The continuation of this study was based on multivariate evaluation, aiming to elucidate how the independent variables: rotation (rpm), core:wax ratio (C:W), and blend percentage (% blend) interacted with each other during the preparation of the matrix lipid solid system in order to modulate the release of KT and DS, if it occurred, and to verify how each variable interacting with each other affected the modulation of drug release, according table 4.

The Minitab 16 software was used to design the experiment (DoE) based on a multivariate matrix constructed with the Plackett-Burman model, according to the determination specified, generated 12 experiments. The results of the multivariate analysis by DoE will be presented together with the topics of characterization of the matrix lipid solid system, to demonstrate the influential and relevant variables to each specific topic.

**Efficiency process**

The evaluation of matrix lipid solid system yield after oven drying showed the results of triplicates of the 12 experiments, through mean and RSD%, showing that 6 out of 12 experiments had a yield equal to or above 80%, but experiments 10 and

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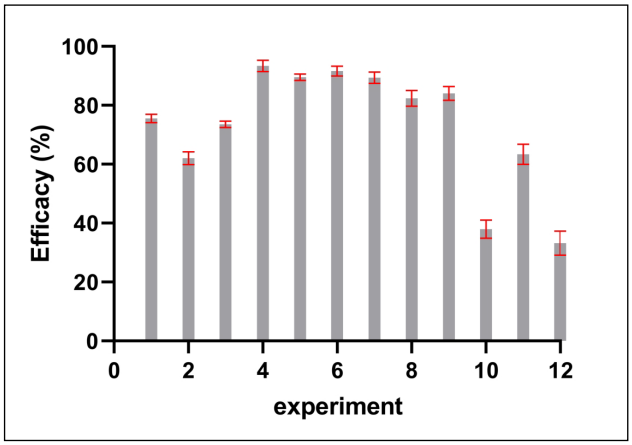
12 had a yield below 40%. An evaluation of the experiments was performed using the main effect technique, and Figure 1 showed that rotation was the variable that most contributed to the effect on yield. High rotations caused rapid consolidation of particles, generating particles below 40 µm that were not retained in the metal filter, contributing to the low recovery of matrix lipid solid system. These particles were not considered in the experiment.

**Table 4 -** Matrix of independent variables and levels for the multivariate study, based on risk mitigation justifications.

| Independent variable Level | Level (-) | Level (+) | Rationale |
|---|---|---|---|
| Rotation (rpm) | 400 | 1200 | Impact on PSD. |
| C:W ratio | 2 | 6 | Impact on encapsulation efficiency, yield and release modulation. |
| % blend | 0 | 10 | Impact on polymorphic differentiations, encapsulation |

**Figure 1 -** Efficiency process to 12 experiments, the data meaning the results of 12 experiments with median and bar error about triplicate test.



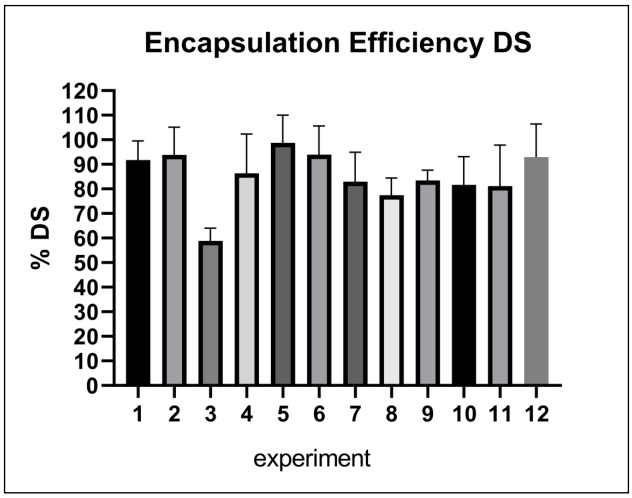

**Encapsulation yield**

Quantifications of drugs in matrix lipid solid system were performed in triplicate, and the results shown in Figure 2 and 3 indicated an average encapsulation efficiency of 60% for KT and 80% for DS. The Pareto chart indicated that none of the variables studied had a significant influence on KT, due to its hydrophilic nature. For DS, however, the C:C ratio and % blend were the factors that most influenced encapsulation efficiency. The results are consistent with the characteristics of each drug and with the mass balance experiments conducted in the univariate phase of the study.

**In sílico and in vitro compability**

Through the application of the Zeneth software, an in-silico evaluation and prediction of related substances that could be generated during the matrix lipid solid system production process, as well as the interaction between drugs and excipients, was performed. The compounds evaluated were DS, KT, free base ketorolac, tromethamine, decyl oleate, palmitic acid, and myristyl palmitate. Several probable reaction pathways were calculated for each compound, such as lactamization, epimerization, and decarboxylation. After evaluating the results generated by the software, it was possible to identify some possible impurities for the proposed formulation, such as impurity EP F for DS, impurity USP C for KT, and impurity EP C for both.

**Figure 2 -** Encapsulation yield to KT in 12 experiments, the data meaning the results of 12 experiments with median and bar error about triplicate test.




**Process reactivity and drug-excipient compatibility - in vitro prediction**

An in vitro analytical study was carried out to assess the possibility of related substance formation and compatibility of the formulation components. The substances investigated with greater emphasis were those that presented a higher probability of formation. Chromatographic peaks with areas below the limit of quantification were not considered. The in-silico analysis indicated that all peaks of interaction with the lipid matrix eluted in a specific region. In the case of DS, the USP F impurity was found

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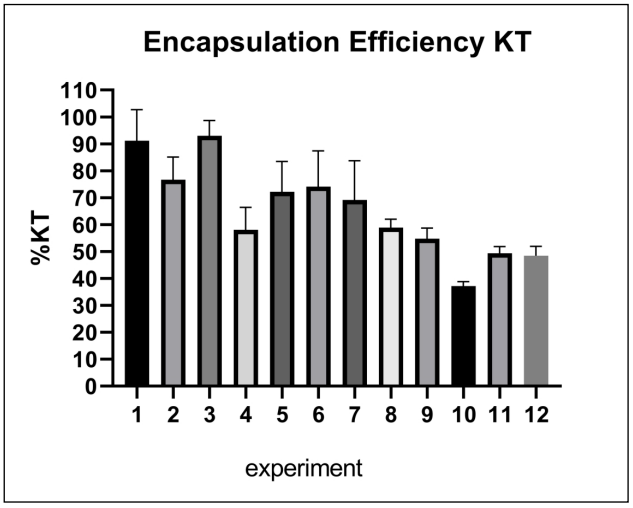
in all experiments, while for KT, the EP C impurity and four other unknown compounds were found.

**Figure 3 -** Encapsulation yield to KT in 12 experiments, the data meaning the results of 12 experiments with median and bar error about triplicate test.

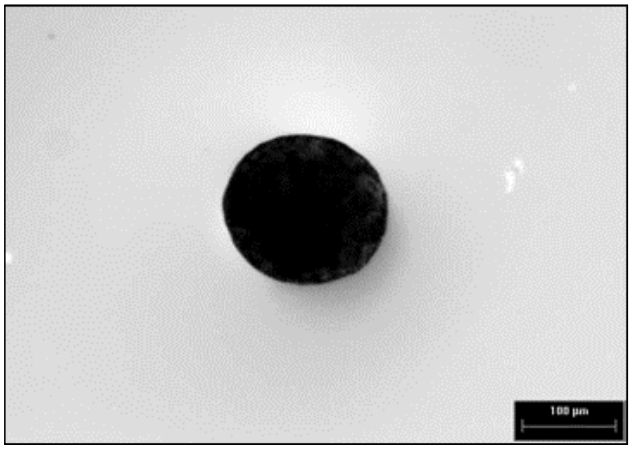



**Lipidic matrix system caracterization**

**Morfology**

The results of optical microscopy, obtained with a 4-fold magnification objective (Figure 4), showed spherical particles with regular shape, without the presence of possible polymorphic variations as observed in univariate studies. In this sense, the study demonstrated that the lipidic matrix system elaboration process was reproducible.

**Figure 4** - Photomicrograph with a 40x objective illustrating the *matrix lipid solid system* with a regular appearance and without optical evidence of polymorphic transition.




**Particle size distribution (PSD)**

Particle size distribution, shown in table 5, tests were performed in triplicate considering the d90 value. This evaluation is important for the pharmaceutical industry, as particle size affects drug release. The Pareto chart (figure 5) and interaction diagram (figure 6) were used to evaluate the effects of variables on PSD, and it was found that rotation is the variable that most affects the results, and its interaction with the N:N ratio and % blend can also have an impact.

**Tabela 5 -** Summarized results of experiments performed in triplicate with triplicate readings, with d90 results for PSD and percent coefficient of variation (VC%).

| Experiment | d90 (µm) | VC (%) |
|---|---|---|
| 1 | 1171,0 | 3,56 |
| 2 | 137,0 | 2,25 |
| 3 | 1391,0 | 1,75 |
| 4 | 1845,0 | 2,68 |
| 5 | 1008,0 | 3,37 |
| 6 | 156,2 | 2,87 |
| 7 | 1305,0 | 2,78 |
| 8 | 106,5 | 4,68 |
| 9 | 185,1 | 3,54 |
| 10 | 131,0 | 1,28 |
| 11 | 2275,0 | 2,34 |
| 12 | 74,03 | 5,69 |

**Figure 5** - Pareto chart show influence variable in PSD.

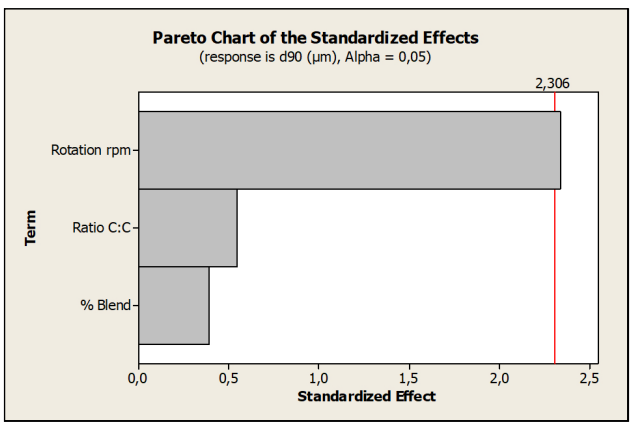



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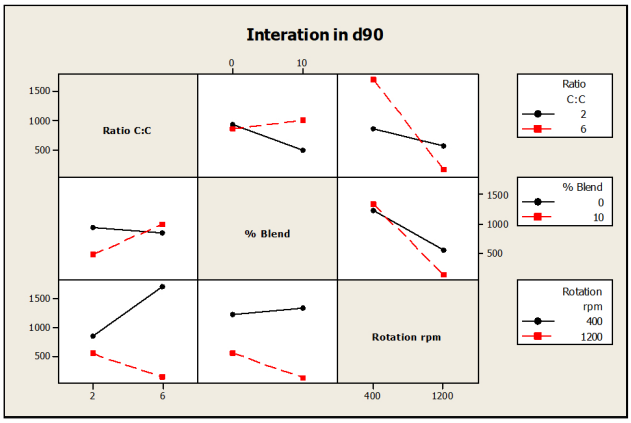
**Figure 6** - Interaction diagram.



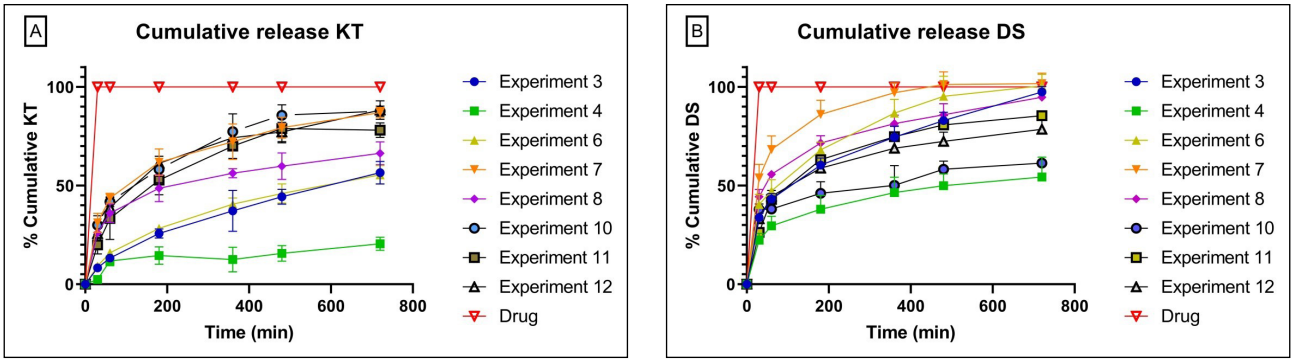

**In vitro release profile**

**In vitro release kinetics and characterization of the release model**

**Cumulative release (%)**

Dissolution experiments were carried out to evaluate the kinetics of in vitro release and to characterize the drug release model in matrix lipid solid system. The apparatus speed was increased to 100 rpm to evaluate the cumulative release of DS and KT. The results showed that the solid lipidic matrix systems exhibited a modulation in drug release compared to free drugs, with release values of 80% for both drugs after 6 hours. Free drugs were quantified at 100% after 30 minutes, according to figure 7 A to KT and B to DS.

**Figure 7** - Cumulative release profiles for KT (A) and DS (B) performed in triplicate, the results presented consider the condensed DoE experiment for better visualization.




**Characterization of the release kinetic model**

The study evaluated several drug release models, such as zero order, first order, Higuichi, Hixson-Crowell, Hopfenberg, Weibull, and Korsmeyer-Peppas, to determine which one best fits the release profile of KT and DS drugs. The results indicated that zero-order, first-order, Higuichi, Hixson-Crowell, and Hopfenberg models were rejected due to low correlation, while Weibull and Korsmeyer- Peppas models showed higher correlation, according to figure 8 to KT and 9 to DS.

**Figure 8** - Release mathematical model adjustment to KT.

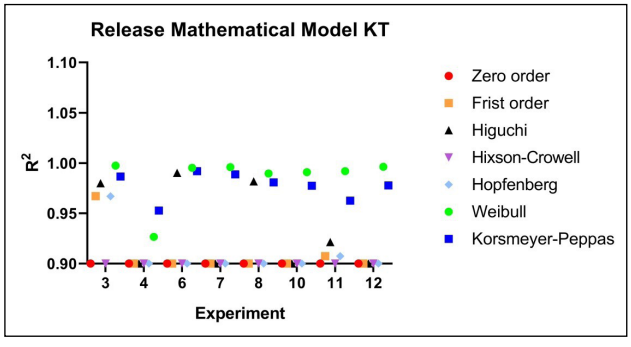
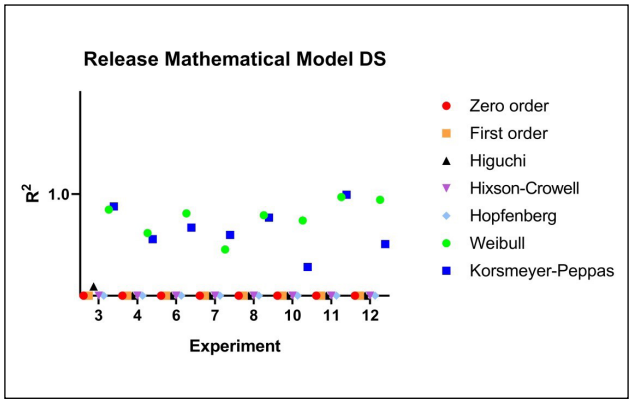



**Figure 9** - Release mathematical model adjustment to DS.




The Weibull model was chosen to be used in DoE evaluation since it had a high correlation in values of $\beta > 0.89$, indicating an exponential release profile predominantly related to the lipidic matrix system, according to figure 10. This model is an important tool in describing drug release patterns, due to its flexible mathematical equation, which considers changes in release rate and uses the parameter $\beta$ as a predictive and modeling element of release, with the aim of optimizing in vivo release conditions.

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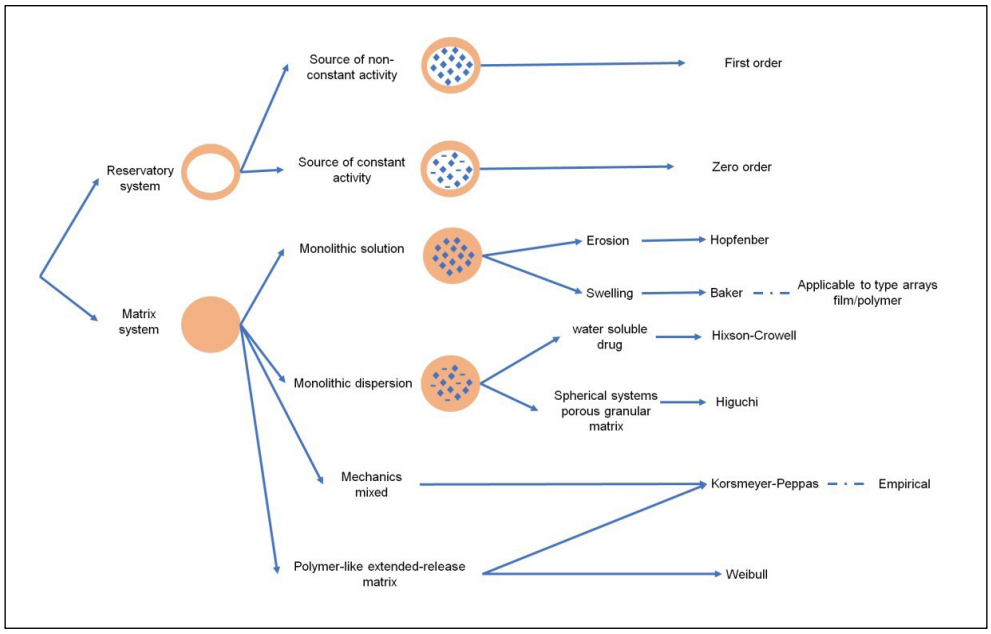
**Figure 10 -** Summary of adjustments of mathematical models applied to systems elaborated by microencapsulation and in which model the matrix lipid solid system best fits.




The rotation is the variable with the greatest impact on the PSD of the matrix lipid solid system, and the core:wax ratio indicated that the ratio 2 was the one that best satisfied the fitting model to ensure a prolonged release profile for both drugs. Regarding the Weibull model fitting, the core:wax ratio variables indicate that the ratio 2 was the one that best satisfied the fitting model to ensure a prolonged release profile for both drugs. Regarding the lipid blend, the same correlation was observed for the Weibull release model with a 10% blend. However, it is worth noting that due to the characteristics of KT, a lower lipid percentage generated higher encapsulation efficiency. For the rotation variable, the best fit obtained for the Weibull model was a rotation of 1200 rpm, which also obtained the smallest PSD, with magnitude ranges around 150 µm.

**Conclusion and future studies**

Finally, this work demonstrated the formulation of microparticles for the encapsulation of KT and DS in combination, to be employed as a prolonged release system applied in pain control therapy. It was possible to prepare a lipid matrix system through a dispersed phase cooling method, containing the combination of KT and DS for prolonged release through a lipid blend, with better results compared to the proposed modulation of drug release with a composition of beeswax (90%) and ethyl oleate (10%) at a ratio of 1:2 wax: nucleus. All raw materials that compose the formulation were characterized, indicating the role of each one in the structuring of the system, such as beeswax as a release vehicle and hardener and ethyl oleate as a softening agent for the wax.

Process parameters were also studied, defining a 7-step flowchart, including preparation of the oil and water phase, pre-dispersion, dilution, cooling, separation, washing, and drying.

The obtained microparticles showed modulation in the release kinetics for both drugs, and the most suitable mathematical model for the formulation profile was the Weibull model, which presented exponential release for 12 hours, confirming the modulation of in vitro release of the combined drugs and composing a prolonged release kinetics.

The Weibull model is important for the description of drug release patterns, being used to adjust different release profiles. It is flexible due to its mathematical equation, which takes into account changes in the release rate by calculating the natural logarithm. In addition, the β parameter can be used to predict and optimize drug release conditions, resulting in a more desirable and predictable release profile in vivo. It is important to note that the drug release phenomenon, confirmed by the Weibull model, in lipid matrix systems was predominantly dependent on the encapsulating agents.

It is concluded that the emulsification technique, with dispersed phase cooling and maintenance of pH 2.0 with a saline buffer modifier employed, was suitable for the study focus, being reproducible with a statistical data foundation. Furthermore, with the absence of a patent on this prolonged release system, future benefits for the employment of the technique are projected.

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