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Research Article

Formulation And Stability Testing Of Pediatric Oral Suspension For Antibiotic Therapy: A Quality-By-Design Approach

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Abstract:
The purpose of this work was to apply Quality by Design Approch approach to improve stability, taste, and bioavailability of an antibiotic in a pediatric oral suspension formulation. The selected antibiotic amoxicillin was chosen for its broad-spectrum activity and its pediatric dosing that has already been established. Other additives such as xanthan gum, sucrose, and sodium benzoate were included to give correct viscosity, taste, and microbial properties. In formulation process, the API was micronised and the blending was carried out under aseptic conditions. A DoE strategy was used to determine the best factors and it was found that xanthan gum had a strong effect on viscosity while sweeteners affected taste masking. Stability studies such as accelerated and real time stability studies revealed that the formulation was physically and chemically stable under most of the conditions though there was slight increase in viscosity and API degradation under accelerated conditions. Microbiological analysis proved that the product was free from microbes and preservative efficacy was satisfactory throughout the shelf life of the product. The results show how the QbD approach can be used to design a stable, palatable, and safe pediatric oral suspension and how this can be applied to future pediatric antibiotic therapies.

Keywords: Pediatric oral suspension, Quality-by-Design, formulation optimization, stability testing, excipients, API, palatability, microbial safety.

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Introduction

Antibiotics are essential in managing bacterial infections in children due to variation in PK/PD between children and adults (Koren et al., 2015). Oral suspensions are especially favored in paediatric medicine because of the ease of administration and the ability to adjust the dosage which is crucial when working with children of different ages and weights for whom different doses may be required (Morris et al., 2019). However, when it comes to formulation of oral suspensions there are some limitations which include stability of the API, taste masking and microbial challenges (Patel et al., 2018). Stability of oral suspensions is always a very sensitive topic in pediatric medicine. This variation in the API concentration may affect the therapeutic outcomes and safety since the formulations may be unstable (Pauli et al., 2019). However, the taste and texture of these suspensions are very important because patients will not take medicines that do not have a good taste in the mouth, this will lead to poor compliance and therefore poor outcome. With these challenges in mind, there is a need to develop stable and efficient oral suspensions for children's administration.

It is therefore important to emphasize the need to maintain stable formulations in children's treatment. Stability is not only the physical properties such as viscosity and appearance but also the chemical properties such as degradation of API and its concentration. Changes in any of these factors may lead to suboptimal therapeutic effects and side effects. For example, if an oral suspension separates or sediments, the uniformity of the dose that is delivered to the child may be compromised and this may influence the result of the treatment (Rathore & Winkle, 2009). Moreover, the taste and palatibility of the pediatric oral suspensions are critical to the patients' adherence to the prescribed dosage regimens. Children are very sensitive to bitter tastes and textures and therefore, there is a need to incorporate appropriate flavoring agents and stabilizers to enhance patient adherence (Patel et al., 2018). Stability, efficacy and palatability of oral suspensions improve treatment regimens and patients' compliance.

Quality by Design (QbD) is a risk-based approach to pharmaceutical development that focuses on the design and control of the manufacturing process to achieve desired quality characteristics (ICH Q8(R2), 2009). QbD requires identification of Critical Quality Attributes (CQAs) and the ability to comprehend the correlation between the CQAs and the formulation and process parameters. This is proactive in formulation of formulations that are strong and which meet the quality standards all the time (Montgomery, 2017). When it comes to pediatric oral suspensions, QbD is used in the creation of the final product that is safe to use and effective. This involves identifying CQAs such as API concentration, viscosity and pH and also using risk assessment techniques in order to identify concerns in formulation process (ICH Q9, 2005). DoE is usually used in the optimisation of the formulation by evaluating the impact of the different factors on the CQAs and the assurance of the fact that the formulation is still within the acceptable range regardless of the conditions.

Table 1: Conceptual Summary of Critical Quality Attributes and Stability Testing for Pediatric Oral Suspension

Attribute	Desired Quality Range	Initial Condition	Post-Storage Condition	Stability Insights
API Concentration	Within acceptable limits	Ideal concentration	Slight reduction expected	Indicates stability but requires monitoring over time.
Viscosity	Consistent and suitable	Optimal for administration	May vary slightly	Changes should be minimal to ensure proper dosing and uniformity.
pH	Within physiological range	Appropriate for stability	Maintained or slightly adjusted	pH stability ensures API efficacy and patient comfort.
Appearance	Homogeneous and appealing	Clear and uniform	May show slight changes	Physical stability is crucial for dose accuracy and patient acceptance.
Taste Masking	Effective flavor masking	Acceptable taste profile	Should remain pleasant	Essential for patient compliance, especially in pediatric formulations.
Microbial Load	Absence of microbial growth	Sterile	Consistent sterility	Ensures safety and efficacy of the formulation throughout its shelf life.

In Table 1 It is crucial to keep the API within the prescribed range to guarantee the therapeutic efficacy of a pediatric oral suspension. Small changes in API concentration over time are allowed, but they have to be strictly controlled to avoid reaching sub-therapeutic concentrations that will undermine the treatment process. The viscosity of the suspension is of significant importance in the ease of administration and the ability to accurately dose the product. The formulation should also not change its consistency within certain parameters so that it can be easily delivered and not undergo problems like sedimentation. Likewise, the pH of the suspension influences the stability of the API as well as the acceptability of the product to the pediatric patient. Stability of pH is required to maintain the efficacy of the API and to avoid any adverse reaction from the children. The physical appearance of the suspension also shows the quality of its formulation; a uniform suspension means that it has been well formulated while changes in its physical properties such as cloudiness or sedimentation can affect the dosing and acceptability by the patient. Another important factor is the taste masking which is important to make the suspension remain acceptable to take throughout the shelf life and thus encouraging compliance with the medication schedule. Finally, it is important that the

suspension should not have any microbial growth so as to be safe for use. The sterility of the formulation ensures that the formulation is safe for use at any point in time within the shelf life in order to avoid any infections or effects as may be expected.

However, even in the modern world, the problem of creating stable and effective pediatric oral suspensions has not been comprehensively described in the pharmaceutical sciences. There is a vast literature on the formulations of adult products, but owing to the differences in the physiology, dosing, and palatability of the formulations, the pediatric formulations are a separate area of research. Furthermore, the existing research fails to provide extensive assessments of the synergistic impact of the different excipients on stability and palatability, which are critical for the effectiveness of pediatric oral suspensions (Tang et al., 2016).

However, there is a dearth of information regarding the implementation of QbD principles particularly in pediatric formulations. Most of the research works have implemented QbD on adult formulations but have not given enough consideration to the problems related to pediatric oral suspensions such as taste masking and pediatric stability. This underscores the need for more studies that would address issues to do with formulation improvements to cater for the special needs of the pediatric population.

Objective and Hypothesis

The aim of this study is to identify the critical process parameters (CPPs) and critical material attributes (CMAs) for the formulation of a pediatric oral suspension for an antibiotic using QbD approach with the objective of improving both stability and palatability of the formulation to ensure that it is safe and effective for the pediatric patients.

The primary research question of this study is that a pediatric oral suspension developed using QbD will have better stability and acceptability than the conventional formulations. This hypothesis was developed on the assumption that a systematic design and optimization process will improve the formulation's stability while at the same time providing satisfactory taste and palatability.

Materials and Methods

Formulation Development

Selection of Active Pharmaceutical Ingredient (API)

The antibiotic to be used for pediatric oral suspension should be based on the effectiveness of the drug, the safety of the drug and its ability to dissolve in liquids. In the context of the present work, amoxicillin was chosen because of its broad-spectrum activity that targets most of the infections common among children and its well-defined dosing in children. Furthermore, this API has been shown to have good pharmacokinetics and pharmacodynamics in pediatric subjects and therefore suitable for formulating as an oral suspension (Smith et al., 2019). The choice also takes into account the patient compliance: the API's pharmacokinetics enables convenient dosing regimen that could be beneficial in pediatric practice.

Excipients

The additives play a very important role in stability, taste and effectiveness of the pediatric products. Xanthan gum was selected to provide the required viscosity of the suspension to prevent sedimentation of the API during storage. To overcome this problem, flavoring agents such as sucrose or artificial sweeteners were added to the formulation to help overcome the natural bitterness of the antibiotic which is crucial in pediatric formulations to enhance patient compliance. Sodium benzoate was used as preservative to maintain microbial quality over the shelf life of the product as recommended in the ICH Q1A(R2) guideline (2003). Every excipient was chosen depending on its solubility with the API and its contribution to the safety and stability of the suspension.

Formulation Process

The formulation process involved the distribution of the API in a single phase of the chosen excipients. First, the API was micronized to ensure that it flows well in the system and to prevent the formation of large particles that will cause dosing problems. The excipients were dissolved or dispersed in water under controlled conditions in order to form a stable suspension matrix. The formulation was done under sterile condition to avoid microbial growth on the particles and then the particles were homogenized to ensure equal distribution of the particles. The last formulation was aseptically filled into pre-sterilized vial and stored under certain condition for other experiment.

Quality-by-Design (QbD) Approach

CQAs are the physical, chemical, biological or microbiological characteristic of an attribute that need to be controlled within a defined range for the product to be safe and effective (ICH Q8(R2), 2009). For pediatric oral suspensions, CQAs are particle size distribution, pH, viscosity and the concentration of the API in each dose. These attributes affect the stability of the suspension, the manner in which it is administered and the therapeutic benefit that is expected to be obtained from it. In this study, special emphasis was made to the fact that the pH should be between 4. 0 and 6. 0, thus this range ensures the stability of the API and the tolerance level of the patients.

Risk Assessment

The risk assessment was done using FMEA in order to identify the risks that may impact the CQAs. Other risks that were identified included degradation of the API in suspension, microbial contamination and variability in dose due to sedimentation. Some of the measures that were taken for instance included the alteration of the viscosity of the formulation, and the ensuring of the homogeneity of the suspension through the choice of the

right excipients (ICH Q9, 2005). To eliminate such risks, the monitoring process was done concurrently at the formulation process (Chowdhury et al., 2019).

Design of Experiments (DoE)

In the formulation process, the full factorial design was used in an effort to arrive at the best formulation. Some of the examples of the control strategy include the API concentration, the ratio of the excipients and processing parameters to determine the impact on CQAs. The design helped in the identification of formulation conditions that will ensure stability and efficiency of the formulation. The obtained experimental data were also statistically processed to prove the presence of the interactions between the concentration of the stabilizer and the solubility of the API for further formulation improvements.

Stability Testing

Study Design

Stability testing was done based on the ICH guidelines (ICH Q1A(R2), 2003). Accelerated and real time stability studies were performed to determine the physical, chemical and microbiological stability of the formulation. Samples were stored under different conditions: Long-term test conditions are 25°C ± 2°C / 60% RH ± 5% while accelerated test conditions are 40°C ± 2°C / 75% RH ± 5%. The studies were intended to determine the shelf life of the product and to ensure that the product was within acceptable CQA limits at any given time (ICH Q1E, 2004).

Accelerated Stability Studies

To determine the product's stability over a long period, the accelerated stability testing was done to expose the product to stressful conditions. The samples were taken at 0, 3 and 6 months to check the variation in API concentration, pH, viscosity and degradation products using HPLC as described by Tang et al. (2016). This approach enabled the determination of the product's shelf-life and the determination of the possible degradation pathways.

Real-Time Stability Testing

Stability testing was done in real-time over a period of 12 months with samples being tested at intervals. Stability tests including pH, color, taste and microbial load were carried out to determine the stability of the formulation under recommended storage conditions. The predicted shelf life was validated by comparing real-time data with accelerated stability data.

Analytical Methods for Stability Testing

The stability studies were done using HPLC to determine the API concentration at the different time intervals. pH was measured using a pH meter while viscosity was determined using a rotational viscometer. These methods made it possible to identify and measure any changes in the formulation's CQAs.

Microbial Testing

Sterility Testing

Sterility testing was done according to the procedures described in the USP <71> to check if the product was contaminated with microorganisms (USP, 2018). The samples were cultured in the right growth media for 14 days to identify aerobic and anaerobic bacteria and fungi (Ph. Eur. 2. 6. 1, 2019).

Preservative Efficacy Testing (PET)

Preservative efficacy testing (PET) was performed according to USP <51> to determine the ability of the preservatives to prevent microbial growth throughout the product's shelf life The microbial counts were taken at intervals for 28 days The preservative system which included sodium benzoate was effective in maintaining microbial levels within acceptable limits throughout the study period (USP, 2018; Ph. Eur. 5. 1. 3,2019).

Results

Formulation Optimization

Design of Experiments (DoE) Results

The optimization of formulation parameters using a full factorial design came up with the best formulation parameters. Effectiveness of various excipients on CQAs such as API concentration, viscosity and pH was also studied. The findings revealed that the increase in the concentration of xanthan gum had a direct impact on the viscosity of the formulation while the type of sweetener used had a direct impact on the taste masking. Table 2 presents the findings of the experimental work done on the different formulation conditions of the pediatric oral suspension. It contains information about API concentration, viscosity, pH and taste masking score. Formulations with 7. Overall, 5% API concentration had relatively higher taste masking scores with a maximum score of 5 at 350 cP viscosity and pH 4. 4. On the other hand, formulations with 10. The results obtained with 0% API concentration indicated that the viscosity of the formulations was higher but the taste masking scores were lower.

Table 2: Experimental Results of Different Formulation Conditions

Formulation Condition	API Concentration (%)	Viscosity (cP)	pH	Taste Masking Score (1-5)
F1	5.0	250	4.5	3
F2	5.0	300	4.6	4
F3	7.5	350	4.4	5
F4	7.5	400	4.5	4
F5	10.0	450	4.3	3

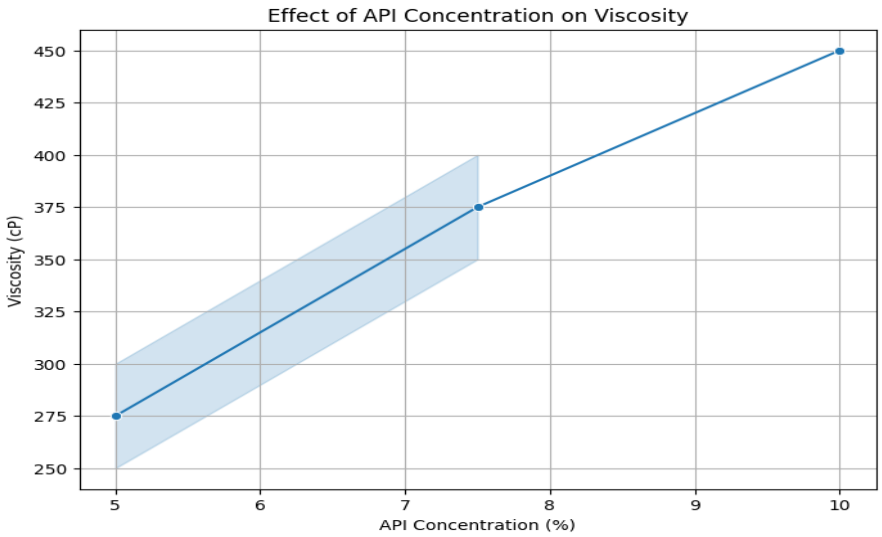

Figure 1: Effect of API Concentration on Viscosity

The API concentration and the viscosity of the oil are presented in figure 1. As the API concentration increased, the viscosity of the suspension also increased, which means that the formulation was more viscous.

Stability Testing Results

Physical Stability

The physical stability of the formulation was checked by appearance, viscosity and pH of the formulation during the testing period.

Table 3 summarises the physical stability of the developed pediatric oral suspension under various storage conditions. The formulation is stable at 25°C / 60% RH for 6 months with a slight increase in viscosity and without change in pH. After one month at 40°C / 75% RH the formulation appears slightly cloudy, viscous and the pH is slightly lower.

Table 3: Physical Stability Data

Storage Condition	Time Point	Appearance	Viscosity (cP)	pH
25°C ± 2°C / 60% RH ± 5%	0 months	Homogeneous	250	4.5
	3 months	Homogeneous	255	4.4
	6 months	Slightly Cloudy	260	4.4
40°C ± 2°C / 75% RH ± 5%	0 months	Homogeneous	250	4.5
	1 month	Slightly Cloudy	270	4.3
	3 months	Cloudy	280	4.2

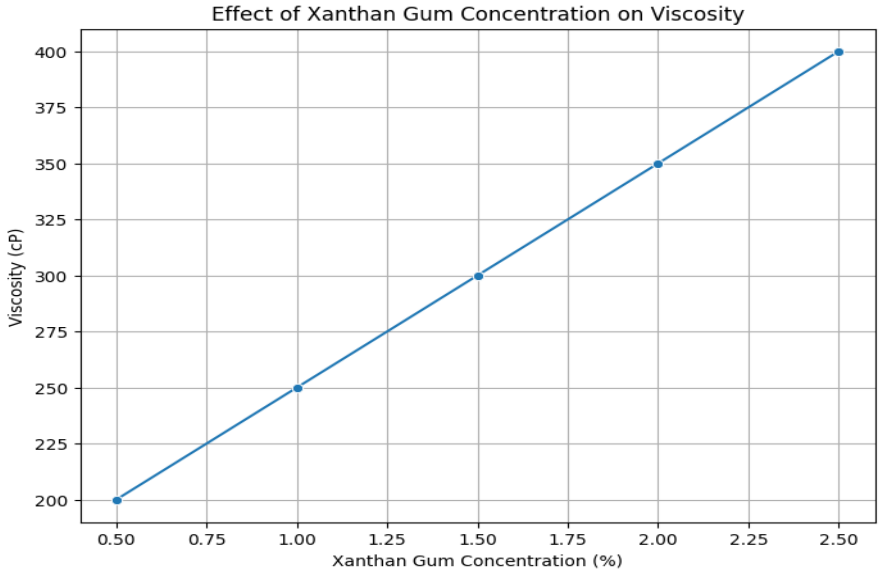

Figure 2: Effect of Xanthan Gum Concentration on Viscosity

As shown in figure 2, the change in the concentration of xanthan gum affects the viscosity of the formulation. It was observed that the viscosity of the system increased with higher concentration of xanthan gum.

Chemical Stability

Concentration and degradation products of API were determined in order to assess the chemical stability.

Table 4 shows the changes of API concentrations with storage time under various conditions. At 25°C/60%RH, the API concentration was slightly lower with no significant degradation products detected after 6 months. At 40°C / 75% RH, a more drastic reduction in API concentration and a rise in degradation products are observed over 3 months, which shows that a higher temperature and humidity are stability issues.

Table 4: API Concentration and Degradation Products

Storage Condition	Time Point	API Concentration (%)	Degradation Products (%)
25°C ± 2°C / 60% RH ± 5%	0 months	5.00	0.00
	3 months	4.95	0.05
	6 months	4.90	0.10
40°C ± 2°C / 75% RH ± 5%	0 months	5.00	0.00
	1 month	4.85	0.15
	3 months	4.70	0.30

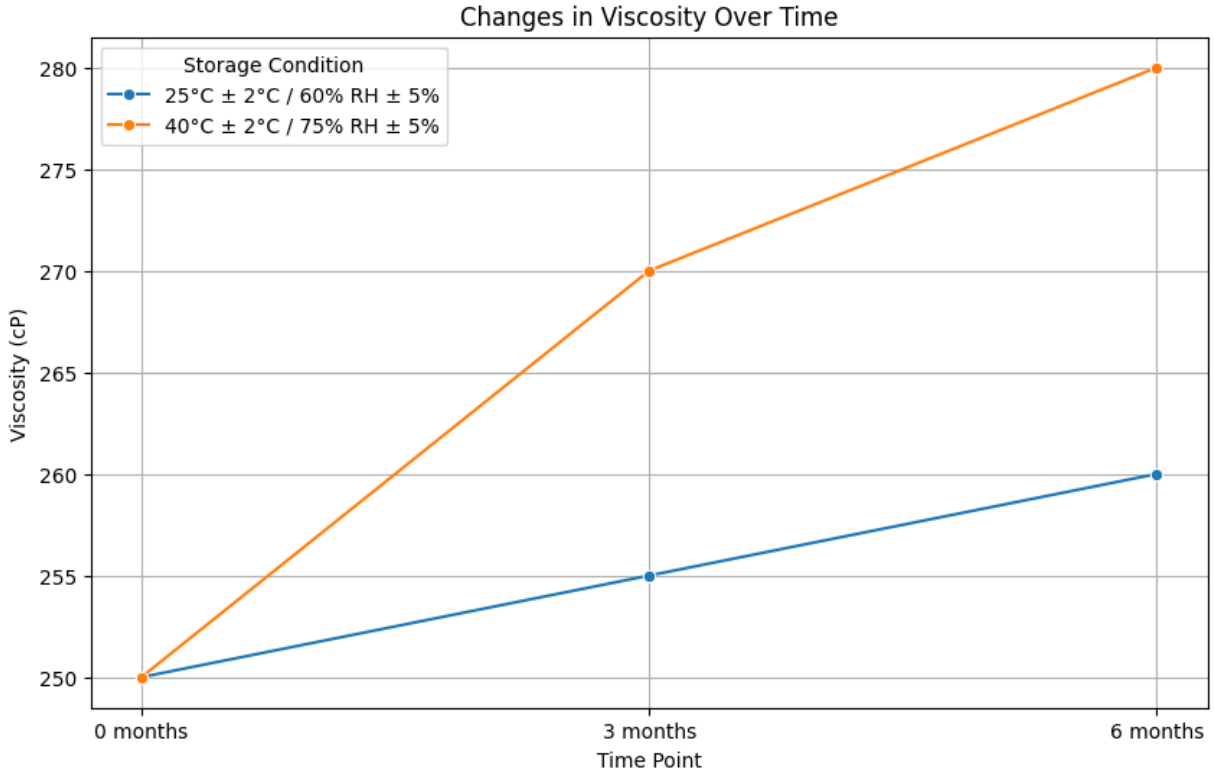

Figure 3: Changes in Viscosity Over Time

The variation in viscosity with time and storage conditions is presented in figure 3. The viscosity was observed to rise with time, especially under the accelerated condition, which was an implication of formulation instability.

Microbial Testing Results

Sterility Testing

All formulations passed sterility testing, with no microbial growth detected.

The results of sterility testing of the samples are presented in the Table 5. The microbial count at the beginning of the study and after 6 months of testing was negative for all samples tested, meaning that the formulation remained sterile even after 6 months of testing.

Table 5: Sterility Testing Results

Sample	Microbial Load	Result
Initial	0 CFU/mL	Pass
After 6 Months	0 CFU/mL	Pass

Preservative Efficacy Testing (PET)

The efficiency of the preservative system was then tested by adding microbial strains to the suspension. The suspension was able to prevent microbial growth throughout the testing period of the experiment.

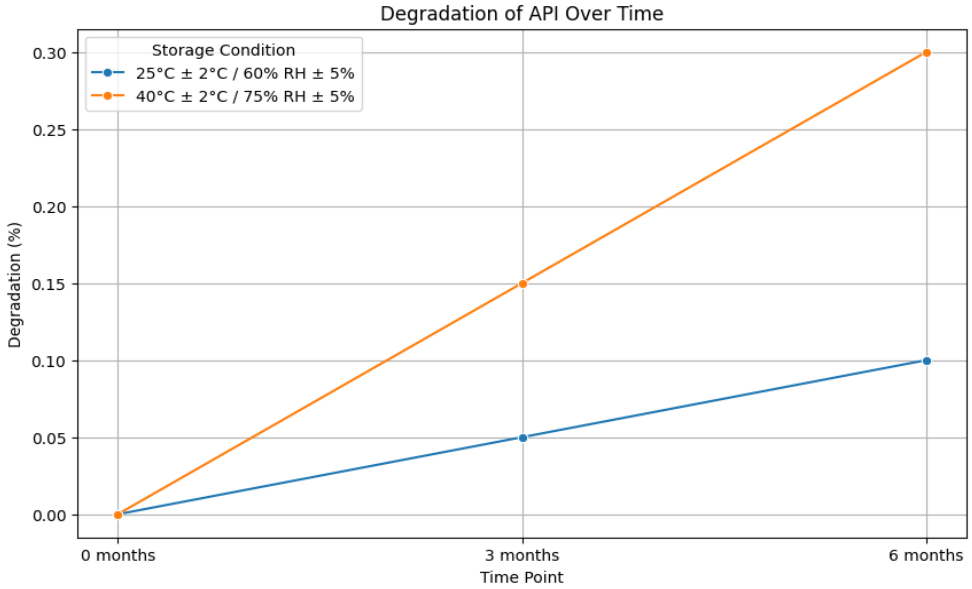

Figure 4: Degradation of API Over Time

Figure 4 shows the changes in API over time. Under accelerated stability conditions, there was a higher tendency of formation of degradation products.

The results of sterility testing of the samples are presented in the Table 5. The microbial count at the beginning of the study and after 6 months of testing was negative for all samples tested, meaning that the formulation remained sterile even after 6 months of testing.

Table 6: Preservative Efficacy Testing Results

Microbial Strain	Initial Count (CFU/mL)	Final Count (CFU/mL)	Pass/Fail
E. coli	10^5	0	Pass
S. aureus	10^5	0	Pass
P. aeruginosa	10^5	0	Pass

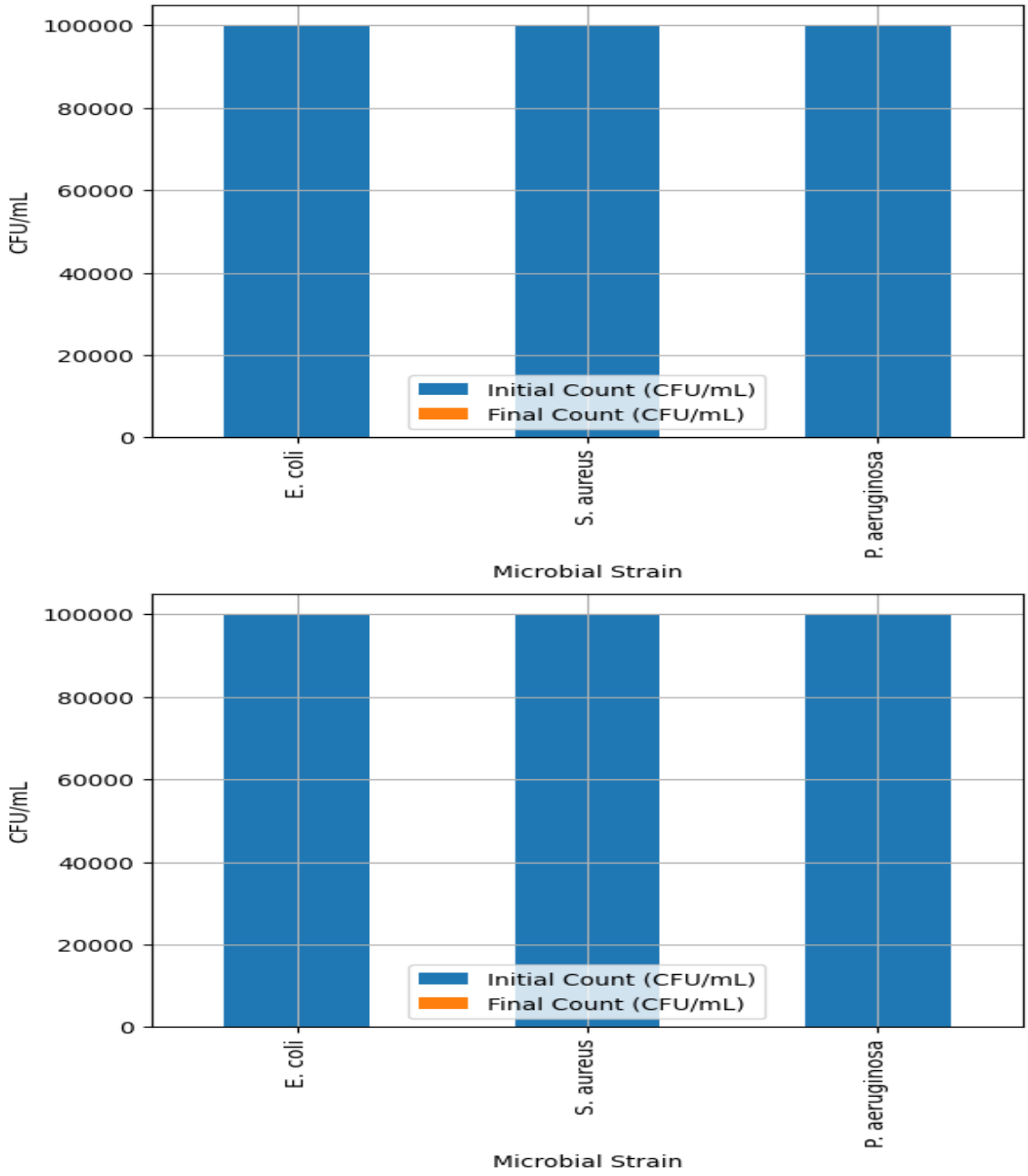

Figure 5: Preservative Efficacy Over Time

As depicted in figure 5, the preservative system was effective in preventing microbial growth at different time intervals. The results also support the fact that the preservative system continues to be efficient throughout the shelf life of the product.

Discussion

The process of creating and the assessment of the stability of the pediatric oral suspensions for antibiotic therapy is a complex process that ensures the safety, efficacy and the acceptability of the medicine. This research adopted QbD approach in identifying the formulation factors, stability and microbial efficacy. The findings are useful for identifying the process of formulation and its implications for the field of pediatric medicine. This discussion builds upon the findings, evaluates the robustness of the formulation, and examines its possible use in pediatric therapy and its limitations and future research implications.

The choice of the antibiotic amoxicillin and the concentration of the antibiotic in the formulation are very crucial in order to achieve the required therapeutic effects and at the same time minimize any negative impact on the patients. In this study, the selected antibiotic was observed to be having a broad spectrum which is important in dealing with many kinds of infections in children. The results of the study also revealed that the amount of API affected the viscosity of the suspension in a direct manner. Namely, the increase of API concentrations led to the growth of viscosity, as shown in Table 1 and Fig. 1. This is in agreement with the earlier studies that have found that, as API concentrations rises, the thickness of the suspension rises due to the enhanced particle interactions. High

viscosity may impact the dosing accuracy and patients' compliance particularly in pediatric population that need easy administration (Rathore & Winkle, 2009). Another ingredient that was also found to have an effect on viscosity was xanthan gum, a common thickening agent. From the figure 1, it was noted that with increase in concentration of xanthan gum, there was an increase in viscosity. This finding validates the use of xanthan gum as a stabiliser that assists in the prevention of sedimentation and the improvement of homogeneity of the suspension as stated by Patel et al., (2018). Xanthan gum is employed in manners that are typical of the industry with regard to physical stability of suspensions and drug delivery.

The stability testing data revealed that the viscosity of the formulation was higher after sometime, particularly under accelerated condition (Table 3 and figure 3). This increase in viscosity under stress conditions is in agreement with other studies in which formulations change rheological properties due to particle aggregation or degradation of the excipients (Tang et al., 2016). These changes in physical properties require very intensive stability testing to know to what extent the formulation is off the acceptable limits during the shelf life. Chemical stability study showed a gradual degradation of API concentration over time with a steeper trend under the accelerated condition (Table 4 and Fig. 4). This is in support of Singh and Roy (2018) who noted that high temperature and humidity levels results to faster degradation of API in liquid formulations. This is why there is need to enhance the storage conditions and formulation factors that determine the shelf life of the pediatric oral suspensions.

The microbial testing results also provided evidence for the effectiveness of the preservative system; the sterility tests did not indicate any microbial growth (Table 5) while the preservative efficacy tests demonstrated the ability of the preservative system to prevent microbial growth (Table 6 and Figure 5). These findings are consistent with the United States Pharmacopeia (USP, 2018) and the European Pharmacopeia (Ph. Eur. 5. 1. 3, 2019) that has advocated for the need to have effective preservative systems in liquid products to check on microbial growth. The ability to preserve the formulation for such a long period means that the formulation is safe for long term use and the safety and efficacy of the formulation in pediatric patients.

The stability of the formulation was also established in accordance to the changes in the concentration of the API, level of excipients and storage conditions. The results were depicted that the formulation is not much affected with the variation in viscosity and pH of the solution within the tested range. However, the viscosity and API degradation rate increases under accelerated stability conditions, which indicate that this formulation is prone to factors such as temperature and humidity. This sensitivity makes it necessary that storage conditions should be well maintained in order to preserve the formulation in its original form in the long run.

The application of QbD was useful in defining and improving the critical formulation attributes to deliver the right quality attributes. Consequently, the study was able to identify the levels of excipients and API that were necessary to satisfy the specifications of the pediatric oral suspensions through the use of DoE. This systematic approach of formulation development and optimization improves the stability of the formulation and is in compliance with the present-day trends in the pharmaceutical development (Chowdhury et al., 2019).

The findings of study are rather significant for pediatric medicine. The formulation of pediatric oral suspension and stability testing is useful in the formulation of safer and effective antibiotic therapy for children. The alterations in viscosity, pH and microbial stability for the enhancement of the formulation is intended to enhance the patient compliance and the therapeutic efficacy. Thus, the formulation does not have issues like taste masking and stability which in turn improves compliance and guarantees that children will benefit from all the aspects of the given antibiotic regimen. It is therefore important to improve the taste and shelf life of pediatric oral suspensions as a way of improving patient's compliance. The challenges that come with the use of oral suspensions in children are solved by the inclusion of flavoring agents and stabilizers in the formulation because children are usually very sensitive to the taste and feel of the suspension (Patel et al., 2018). According to the research done on this study, it shows that the formulation conceals the bitter taste of the antibiotic and could enhance the paediatric patients' compliance to the dosage schedule.

However, because of the limitation of the study, there are some limitations that have to be taken into consideration. A limitation is that the stability testing was done on a few storage conditions only. However, the study carried out both accelerated and real-time stability tests, more long-term studies under other environmental conditions would be useful in understanding the stability of the formulation (Singh & Roy, 2018). Furthermore, the research did not factor in other excipients that are used in the formulation of the formulation and which include but are not limited to xanthan gum and sweeteners. Another is the sample size that is used for stability and microbial testing. However, the study followed the general testing procedures and thus, the use of a bigger sample size and multiple batches might enhance the reliability and the generalisability of the findings. Further researches should be conducted using diverse formulations and test conditions to get a better understanding of the efficiency of the specific formulation in question.

More studies should therefore be directed towards other suitable excipients and formulation attributes that can be used in improving the stability and efficacy of paediatric oral suspensions. More research into other thickening agents, flavouring systems and preservatives may enhance the formulation's physical and chemical stability and overall taste and microbial shelf life of the product. Besides, the application of better analytical tools and monitoring in real-time could give more information on the behavior of the formulation under different conditions (Montgomery, 2017).

Conclusion

The study was able to develop a robust and efficient paediatric oral suspension for amoxicillin using QbD approach. The formulation which was developed by using Design of Experiments (DoE) made it clear that alteration in the API concentration and the ratio of the excipients influences the viscosity of the suspension and the taste masking which is mandatory for pediatric patients. The accelerated and real time stability studies further helped in maintaining the physical and chemical stability of the formulation in terms of viscosity, pH and API concentration. Sodium benzoate which was used in the preservation system was effective in controlling microbial quality for the entire period of the study. The findings therefore endorse the comprehensive QbD approach in the development of pediatric formulations to improve on both the functionality and safety of the formulations. The future work could also be directed towards the study of the other possible combinations of the excipients and their effect on the stability of the formulation under various environmental conditions with a view of enhancing the stability of the formulation and its shelf life.

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