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作品名稱

Flavored Nanofiber Strips Loaded with
Amoxicillin as an Alternative Method for
Treating Bacterial Infections in
Children

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1 Introduction

Semisynthetic penicillin, Amoxicillin, is a broad-spectrum antibiotic that is widely used to treat bacterial infections in children suffering ear, nose, and throat infections, genitourinary tract infections, skin infections, and lower respiratory tract infections¹. This antibiotic works against both gram-positive and gram-negative bacteria, such as *Listeria monocytogenes*, *Haemophilus influenza*, *Streptococcus pneumonia*, *Streptococcus pyogenes* and *Escherichia coli*^{1,2}. It shows antibacterial activity by inhibiting dd-transpeptidase, which maintains the integrity of the bacterial cell wall which results in bacterial cell death due to a fragile cell wall³. Nonadherence to medication was associated with 50% of drug-related hospitalizations in children⁴. In order to improve adherence and influence clinical outcome, it is important to acknowledge the importance of drug palatability to children⁴⁻⁶.

The currently available liquid suspension form of this antibiotic is administered to patients through oral/GI routes. It is also available in capsules or tablets for adults⁷⁻⁹. In the gastrointestinal tract, the drug has to withstand variable pH conditions and enzymatic degradation, mucus and mucosal barriers to survive resulting in limiting drug bioavailability^{10,11}. In addition to conventional drug delivery formulations, nanofibers can be used to deliver drugs orally, topically, and through buccal or transdermal routes¹². Drug-loaded nanofibers offer many advantages as a delivery system, including their porous structure and their efficient delivery of various drugs and bioactive molecules including hydrophobic and hydrophilic drugs¹²⁻

14.

Considering that amoxicillin palatability can affect children patients' compliance and due to the advantages of both nanofiber drug delivery system and drug delivery through buccal routes, hence, this project aims to prepare flavored electrospun nanofibers loaded with amoxicillin to mask the unpleasant taste of the drug for treating children with bacterial infection. Nanofibers loaded with amoxicillin can be applied between the child's gum and cheek, allowing the fibers to dissolve in mucus and penetrate directly into the bloodstream.

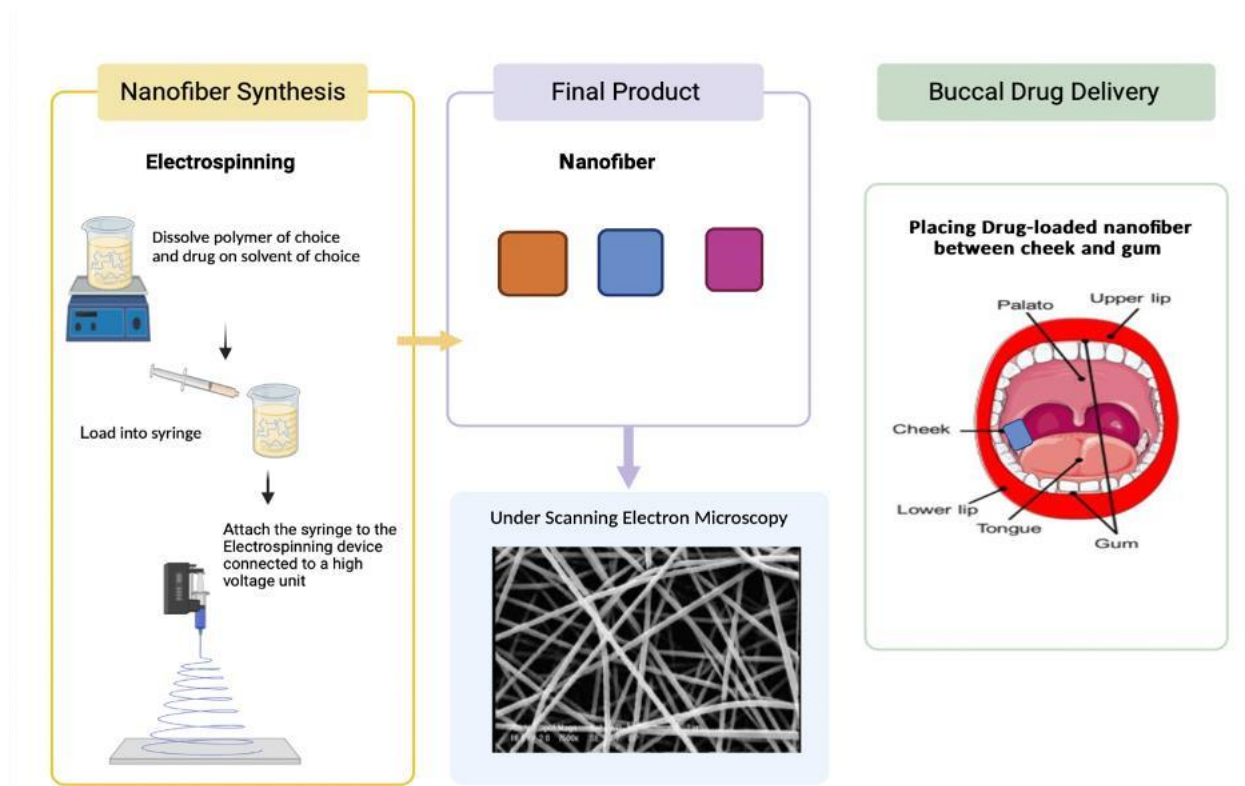


Figure 1: A schematic of the project's general workflow. We proposed to develop flavored nanofiber loaded with amoxicillin and to be delivered through a buccal drug delivery system

2. Problem statement

The poor taste of the antibiotic liquid formulation poses a significant problem, leading to low adherence and treatment failures among children. This lack of medication adherence has been linked to approximately 50% of drug-related hospitalizations in pediatric patients. Additionally, the oral/gastrointestinal (GI) route of drug delivery presents limitations such as reduced permeability across intestinal biological membranes, the need to withstand low pH conditions, and susceptibility to enzymatic degradation. These factors collectively contribute to limited drug bioavailability, further exacerbating the challenge of effective treatment in pediatric populations.

3. Hypothesis

Based on the literature review, we developed two main theoretical hypotheses:

Firstly, we propose the utilization of polyvinylpyrrolidone (PVP) to synthesize nanofibers. PVP is a well-established hydrophilic, biodegradable, and safe polymer. By loading the nanofibers with amoxicillin, we aim to deliver the drug through the buccal area, taking advantage of the mucus-dissolving properties of PVP.

Secondly, we hypothesize that incorporating a flavor component into the nanofiber formulation will enhance children's compliance with the drug. By introducing an appealing taste, we anticipate that children will be more willing to accept and adhere to the medication, thus improving treatment outcomes.

4. Objective

The objective of this project is to fabricate nanofibers loaded with amoxicillin and loaded with a flavor component. These nanofibers will be designed for delivery through the buccal area (inside the cheek). By incorporating the flavor and utilizing the buccal route of administration, the aim is to enhance the acceptability and compliance of children in taking the medication.

5. The novelty

Upon conducting a comprehensive literature review, it was found that no prior research has explored the utilization of flavored nanofibers loaded with amoxicillin using PVP nanofiber.

6. Variables

Not applicable

7. Materials

Chemicals

Ethanol, Ammonium hydroxide, Polyvinylpyrrolidone (PVP), Food flavor, Amoxicillin, Acetonitrile, Sodium Phosphate Dibasic Heptahydrate, Sodium Phosphate, Monobasic Monohydrate, HCl, Agar powder and Mueller Hinton broth.

Microorganisms

Staphylococcus aureus – (ATCC 29213) , E.coli – (ATCC 25922) reference bacteria were obtained from the American Type Culture Collection (ATCC) (Manassas, VA, USA). Tools

Laboratory devices

Balance, Magnetic stirrer, pH meter, Electrospinning device, High-Performance liquid chromatography (HPLC), X-ray diffraction (XRD), Biosafety cabinet

8. Experimental methodology

8.1 Preparation of Drug loaded nanofiber:

In this study, 10% (w/v) polyvinylpyrrolidone (PVP) was dissolved in 87.5 % ethanol and 12.5 % of 1 M ammonium hydroxide. Additionally, different ratios of either 1.25 % (v/v) or 2.5 % (v/v) of strawberry food flavor were added to the mixture and stirred at room temperature until a homogeneous polymer solution was formed. Subsequently, the polymer solution was then combined with 0.5 % (w/v) amoxicillin drug and stirred for an additional hour to ensure proper mixing.

To prepare the electrospun nanofibers, the Spraybase® electrospinning technique was employed. The electrospinning parameters, including the flow rate (0.8 ml/hr), voltage (blank: 8.27, drug-loaded: 10.12), and tip-to-collector distance (125), were optimized. These parameters are crucial in controlling the morphology, diameter, and uniformity of the resulting nanofibers. Additionally, 4 formulations were developed, 1: blank nanofiber, 2: drug-loaded nanofiber, 3 and 4: drug, pvp, and 2 different concentrations of flavor.

8.2 Materials characterization

Scanning electron microscopy (SEM): Scanning electron microscopy (SEM) is a powerful imaging technique commonly used to visualize the surface morphology and topography of samples at high resolution. In this project, the SEM is used to test the successfulness of each of the 4 nanofiber samples synthesis and to measure the size.

8.3 High-Performance liquid chromatography (HPLC): The analysis was conducted on Agilent 1260 Infinity II equipped with UV detector to determine the exact concentrations and purity of the drug within the nanofibers. The sample analysis data is processed by using Open lab software and drawing the calibration curve (CB). The mobile phase was prepared by mixing Phosphate buffer (0.01 mol/L) with acetonitrile. UV absorbance at 229 nm.

8.4 Determination of minimum inhibitory concentration of amoxicillin:

Media Preparation:

Mueller Hinton Agar and broth media is prepared as recommended by the manufacturer (Scharlau), The media was also sterilized by autoclaving at 121°C for 15 mins.

Minimal inhibitory concentration (MIC):

Broth microdilution was performed following CLSI reference method¹⁵ to test Amoxicillin against E.coli– ATCC 25922 and S. aureus– ATCC 29213.

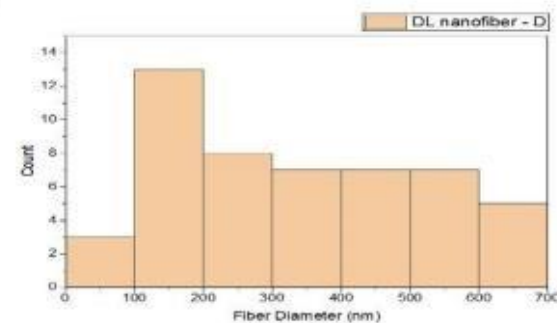
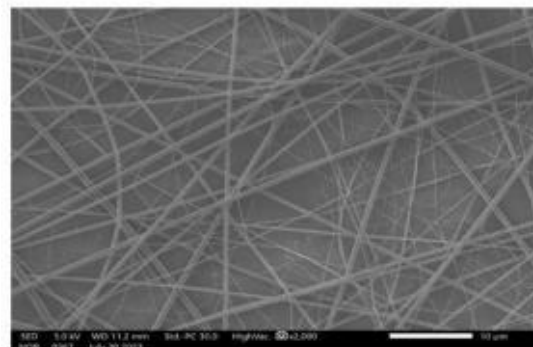
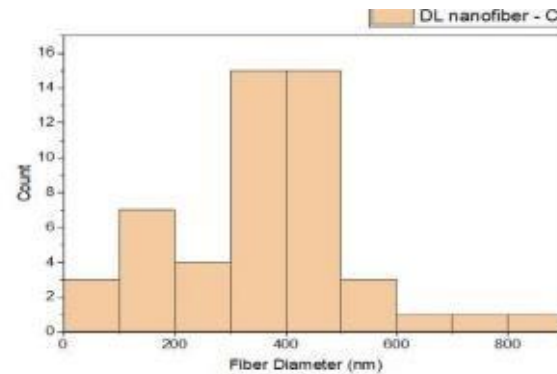
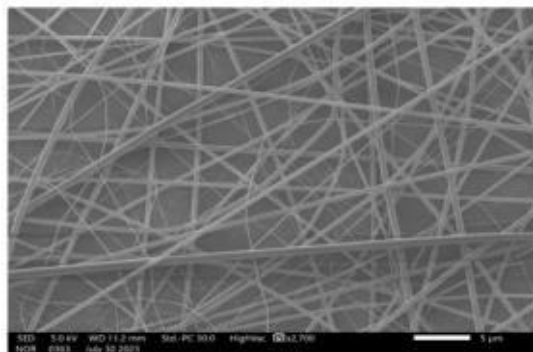
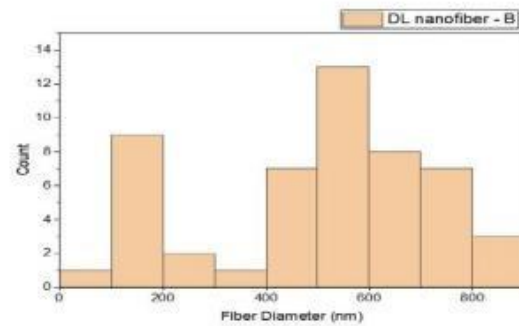
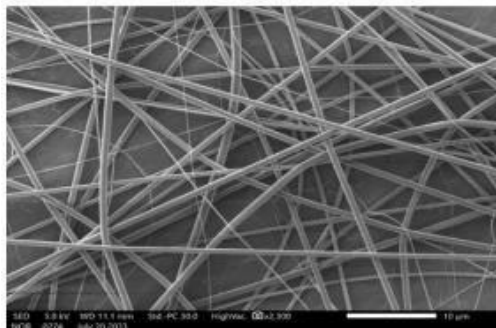
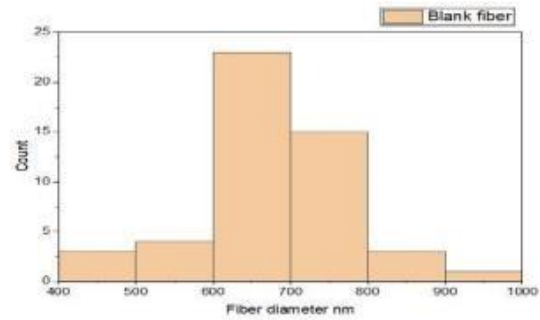
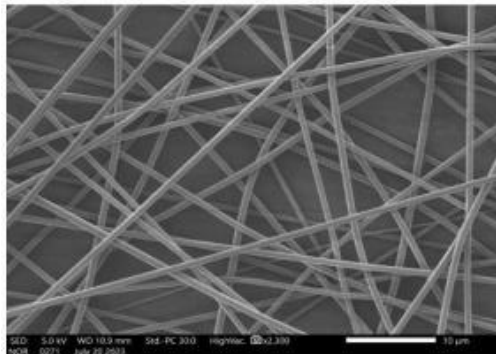
8.5 Antimicrobial activity of Fibers Loaded with Amoxicillin:

The antimicrobial activity of the fibers was evaluated for E.coli– ATCC 25922 and S. aureus– ATCC 29213 strains using the agar-diffusion method per modified of Wang et al¹⁶.

8.6 Disintegration Test of drug-loaded Nanofibers: This test was used to evaluate the dissolution or disintegration behavior of nanofiber formulations in a specific medium. It assesses the ability of the nanofibers to break down and release the drug effectively under simulated physiological conditions. The objective was to determine the time it takes for the nanofibers to completely disintegrate or release the drug from the nanofiber matrix. This was assessed visually.

9 Results

9.1 SEM



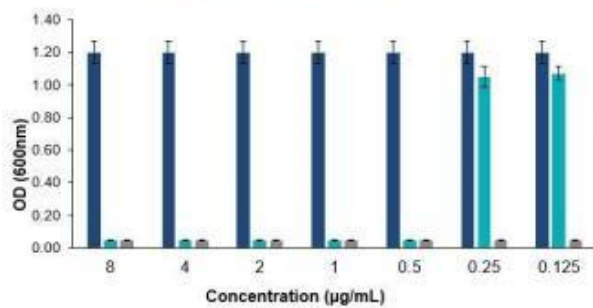
The overall results of the surface morphology of the nanofibers were highly promising. The nanofibers show a smooth surface without any noticeable beads or pores, revealing successful electrospinning. However, it was observed that the fibers with the drug and flavor sizes were different, and further investigation will be conducted in future research to determine the causes for this problem.

9.2 HPLC

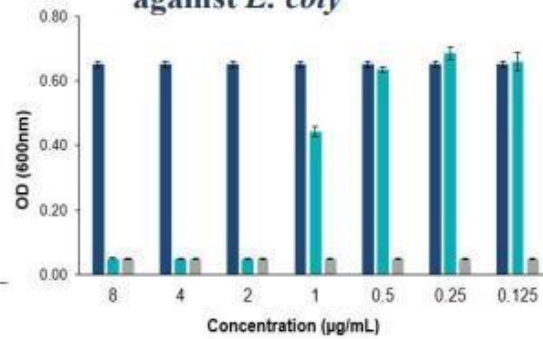
no.	Formulation components	Nanofiber Diameter (nm)	Drug loading ($\mu\text{g}/\text{mg}$)
(A)	Blank nanofibers: 10 % PVP	677 ± 100	0
(B)	DL nanofibers: 10% PVP, 0.5% amoxicillin	503 ± 219	29
(C)	1.25% DL nanofibers: 10% PVP, 0.5% Amox, 1.25% strawberry flavor	362 ± 167	23
(D)	2.5% DL nanofibers: 10% PVP, 0.5% Amox, 2.5% strawberry flavor	328 ± 184	13

9.3 Minimal Inhibitory Concentration test (MIC) and the Agar Diffusion

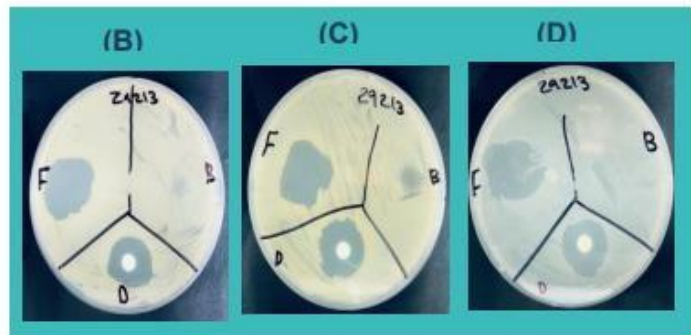
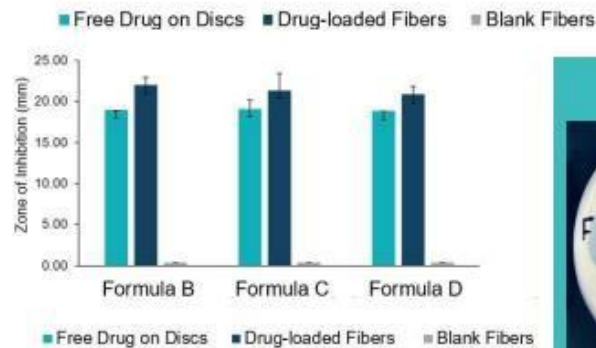
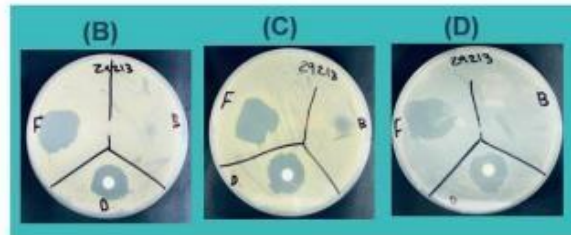
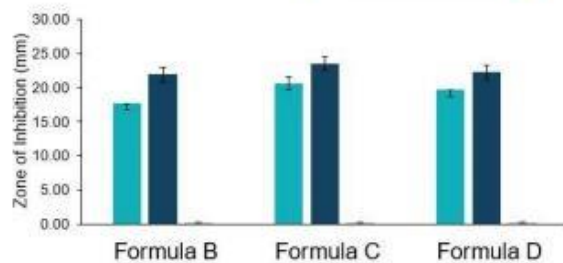
against *S. aureus*



against *E. coli*



■ Positive Control ■ Amoxicillin ■ Negative Control



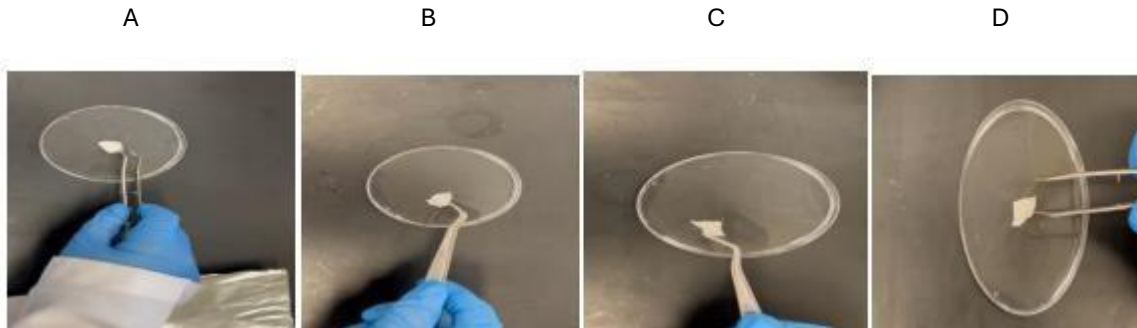
Nanofibers- Formula B: 10% PVP, 0.5%Amoxicillin, Formula C: 10% PVP, 0.5% Amox, 1.25% strawberry flavor, formula D: 10% PVP, 0.5% Amox, 2.5% strawberry flavor

The Minimal Inhibitory Concentration test (MIC) was conducted to determine the lowest concentration of the nanofibers capable of inhibiting bacterial growth. For *S. aureus*, the MIC was 0.5 µg/ml, while for *E. coli*, 2 µg/ml. Additionally, the agar diffusion test was made to assess the zone of inhibition demonstrated by the free drug, blank nanofibers, and amoxicillin-loaded nanofibers against pathogenic bacteria. This test aimed to evaluate whether the nanofibers showed similar or potentially improved effectiveness compared to the free drug in inhibiting bacterial growth.

The first figures show the Minimum Inhibitory Concentration (MIC) of amoxicillin against *S. aureus* (1) and *E. coli* (2). The figures below show the zone of inhibition of amoxicillin free drug, blank nanofibers and amoxicillin-loaded nanofibers formulations against pathogenic bacteria. These tests successfully demonstrated using flavored amoxicillin loaded nanofibers are more/as effective than the normal free drug.

9.4 Disintegration Test of drug-loaded Nanofibers

Complete detachment of nanofiber systems after ≤ 2 seconds



9.5 Conclusion

In conclusion, Amoxicillin-loaded nanofiber strips were successfully fabricated and showed antibacterial activity against pathogenic bacteria. These strips could serve as potential medicated strips for treating bacterial infections in children by applying it on the buccal area where it can dissolve in mucus and go directly into the bloodstream. A further study is required to determine the optimal dose of drug and flavor of these nanofiber strips.

10. Error Analysis

To ensure reliable results and minimize errors in the experimental process, several measures were taken. These include precise measurements, calibration of devices, and the use of clean and dry laboratory tools during sample preparation. Additionally, each experiment was conducted at least three times to enhance the statistical validity of the findings. By implementing these practices, the study aims to reduce potential sources of error and improve the accuracy and reproducibility of the experimental data.

11. Future work

11. 1. Short term future work

11. 1. 2. Fourier-transform infrared spectroscopy (FTIR): This test aims to determine whether any structural changes will occur due to the addition of the drug to hydrophilic polymer nanofibers, as well as to analyze the drug-polymer interaction.

11. 2. Long term future work

11. 2. 1. *In vitro* drug release study: This test will be conducted to evaluate the release profile of a drug from the nanofiber in vitro sink conditions. It involves simulating the conditions of the human body to understand how the drug is released over time.

11. 2. 2. Optimizing the concentration of flavor and test the taste in vivo or other tests.

11.2.3. Conduct comprehensive toxicity and safety studies to evaluate the potential adverse effects of the nanofibers.

11.2.4 Clinical Trials

12 Data analysis

Origin Lab, Open lab software , Excel from Microsoft were used

14. References

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【評語】 090032

1. Novelty and Significance:

This science project demonstrates significant novelty and potential impact in addressing a critical issue in pediatric medicine – the poor taste of antibiotic liquid formulations and its consequences on treatment adherence. The approach of using polyvinylpyrrolidone (PVP) nanofibers loaded with amoxicillin and a flavor component for buccal delivery is innovative and addresses multiple challenges simultaneously. By targeting the buccal route, the project aims to overcome limitations of oral/gastrointestinal drug delivery, such as reduced permeability, low pH conditions, and enzymatic degradation. The incorporation of a flavor component to enhance children's compliance is a thoughtful addition that could significantly improve treatment outcomes in pediatric populations.

2. Strengths:

The project's primary strength lies in its multifaceted approach to solving a complex problem in pediatric medicine. The use of PVP, a well-established hydrophilic, biodegradable, and safe polymer, for nanofiber synthesis demonstrates a

solid foundation in materials science. The design considers both the pharmacological aspects (drug delivery through the buccal area) and the practical challenges of pediatric medicine (improving taste for better compliance). The project also shows a clear understanding of the limitations of current antibiotic formulations and proposes a solution that could potentially improve drug bioavailability. The use of nanofibers for drug delivery is a cutting-edge approach that could offer controlled release properties, further enhancing the effectiveness of the treatment.

3. Weaknesses:

Despite its innovative approach, the project has several areas that require further development and clarification. The concentration of flavoring agents and their compatibility with the polymer and drug formulation are not fully optimized, which is crucial for the success of the taste-masking strategy. The antimicrobial activity assessment is limited to only two bacterial strains (*E. coli* and *S. aureus*), which may not provide a comprehensive picture of the formulation's effectiveness against a broader range of pathogenic bacteria. The project lacks detailed information on the kinetics of amoxicillin release from nanofibers in the buccal environment,

which is essential for understanding the drug's bioavailability and effectiveness. Additionally, the absence of an abstract in the project report suggests incomplete documentation, which could hinder a full evaluation of the research. These weaknesses indicate areas where further research and refinement are needed to fully realize the potential of this innovative approach to pediatric antibiotic delivery.