Formulation of Dosage Forms with Amoxicillin: Challenges and Future Perspectives

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Abstract

Amoxicillin has been widely used as an antibiotic since its introduction in 1972 for the treatment of a variety of bacterial infections. However, there is still a strong need for a stable and effective dosage form of Amoxicillin that can be used in all age groups of patients, with the ability to easily adjust the dose according to the patient's needs. This review aims to discuss the discovery and development of Amoxicillin, the issues related to its formulation, and the possible solutions to these issues. It also presents different approaches involved in the development of new dosage forms of Amoxicillin, including Nanoparticles, Nanosuspension, Microparticles, Suppositories, etc. The review primarily focuses on the state of the art in the development of novel formulations with Amoxicillin, outlining the physicochemical properties of the drug. It anticipates the future possibilities in the formulation of new dosage forms of Amoxicillin, with the hope of developing a stable formulation that can be used effectively in all age groups of patients.

Key Words: *Amoxicillin, Amoxicillin trihydrate, Mucoadhesive, Transdermal, Nanoparticles, Microparticles, Suppositories.*

INTRODUCTION

Amoxicillin is a broad-spectrum penicillin antibiotic first marketed by Beecham Pharmaceuticals in 1972. In 1981 Beecham launched potassium clavulanate, a compound that broadened the range of antibacterial action to include organisms producing β-lactamase. Amoxicillin is listed in the list of essential drugs by the World Health Organization.[1]

Amoxicillin is usually an applied antibiotic that falls under the class known as penicillin drugs. It is mostly used to treat bacterial infections, among those of the respiratory and urinary tract, the skin, and the ear, among others. The way Amoxicillin works is by stopping the growth of the bacteria.[2,3]

Amoxicillin is a broad-spectrum antibiotic that is mainly used for a number of bacterial infections. The main indications include:[4]

1. **Respiratory Infections:** Widely used to treat pneumonia, bronchitis, sinusitis, and tonsillitis.
2. **Ear Infection:** The drug amoxicillin is commonly used in middle ear infections, especially among children who are affected by otitis media.
3. **UTI:** Amoxicillin is useful for UTIs caused by susceptible bacteria.
4. **Skin Infection:** Treatments that it is used for include skin infections such as cellulitis and impetigo.
5. **Gastrointestinal Infections:** Amoxicillin is used to treat gastrointestinal infections that are caused by bacteria, including Helicobacter pylori, which are associated with gastritis and peptic ulcers.
6. **Dental Infections:** Dentists use Amoxicillin to treat dental infections, including dental abscesses and periodontal infections.
7. **Sexually transmitted infections:** Amoxicillin, in some cases, may also be used to treat certain sexually transmitted infections.
8. **Lyme Disease:** Amoxicillin is used to treat early Lyme stage infections. This antibiotic may be used in toddlers and lactating mothers.

FORMULA [2]

Compound	Molecular Formula	Molecular Weight
Amoxicillin	$C_{16}H_{19}N_3O_5S$	365.41
Amoxicillin Trihydrate	$C_{16}H_{19}N_3O_5S.3H_2O$	419.45
Amoxicillin Sodium Salt	$C_{16}H_{18}N_3O_5SNa$	387.39

Table 1: Formula and Molecular Weight

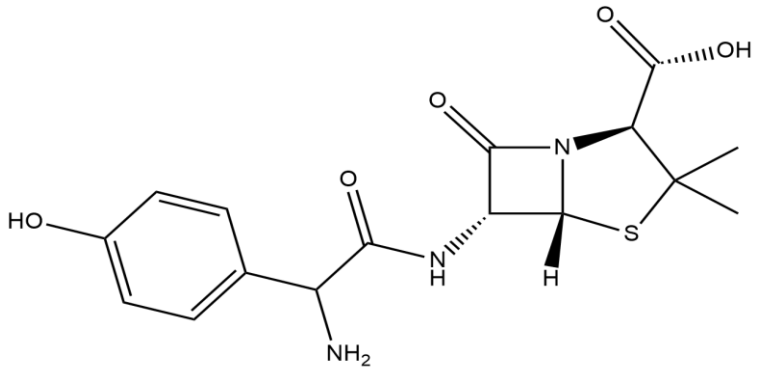

Figure 1: Amoxicillin

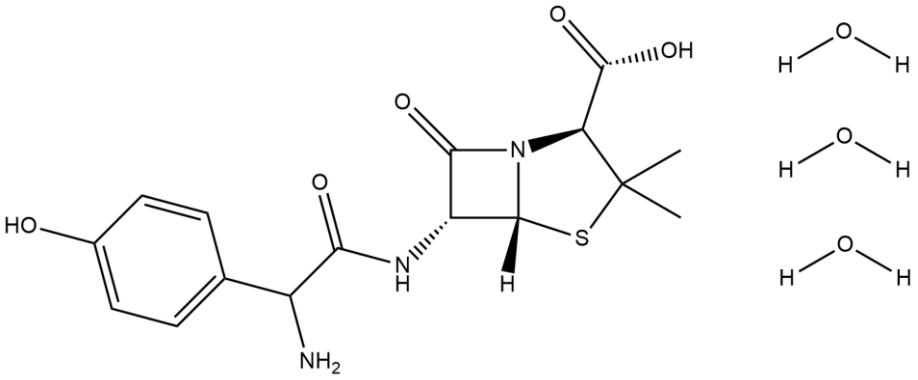

Figure 2: Amoxicillin Trihydrate

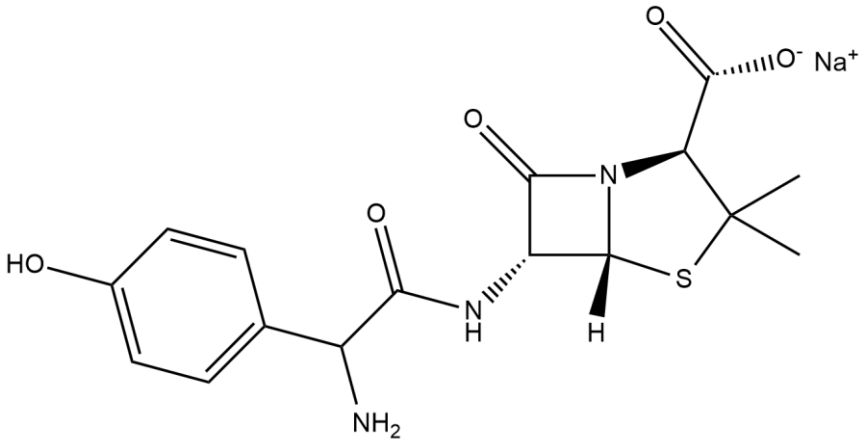

Figure 3: Amoxicillin Sodium Salt

PHARMACOKINETICS AND PHARMACODYNAMICS

Amoxicillin is easily absorbed orally with rapid and efficient absorption from the gastrointestinal tract. Food has no effect on absorption. It has extensive distribution in the body fluids and the tissues, including the lungs, liver, kidney, and middle ear. The major route of excretion is via the kidneys, with little metabolism. It is metabolized very poorly; most drugs are not degraded by hepatic metabolism. The mean half-life in adults is typically between 1 and 1.5 hours. This may vary depending on the renal function and age.[5]

Amoxicillin is bactericidal by inhibiting bacterial synthesis of cell walls. It does so by binding to penicillin-binding proteins that are involved in the final transpeptidase stage of peptidoglycan synthesis, which results in the formation of the intermolecular cross-linked structure of the bacterial cell wall. Its spectrum of activity includes a broad range of Gram-positive and Gram-negative bacteria, such as Streptococcus spp., Enterococcus spp., Haemophilus influenzae, Escherichia coli, and Proteus mirabilis, among others. The bactericidal effect of amoxicillin is primarily time dependent. Its efficiency is closely related to the duration of time that the concentration of the drug is above the MIC for the bacteria it is acting upon.

Resistance to amoxicillin is acquired through the production of β-lactamases, alterations in penicillin-binding proteins, and/or altered permeability of bacterial cell walls. When probenecid and amoxicillin are co administered, the renal excretion of penicillin can be significantly reduced. It has been observed through studies that about 10 to 25% of the drug is excreted as inactive penicilloic acid and the rest is excreted in its unchanged form.[6]

CLINICAL CONSIDERATIONS

1. **Dosing:** Amoxicillin is typically administered orally, with dosing adjusted based on the severity of the infection, patient age, and renal function.
2. **Adverse Effects:** Common adverse effects include gastrointestinal disturbances such as nausea, vomiting, and diarrhea. Allergic reactions, including skin rashes and anaphylaxis, can also occur.
3. **Drug Interactions:** Amoxicillin may interact with other medications, such as probenecid, which can decrease its renal excretion and increase its serum levels.[7]

FACTORS TO BE CONSIDERED WHILE FORMULATING DOSAGE FORM WITH AMOXICILLIN

The formulation of medicinal products that contain Amoxicillin, is a difficult process due to the low water solubility of Amoxicillin and stability problems. The main factors that affect the formulation of Amoxicillin are-

Physicochemical Properties:

Amoxicillin belongs to the penicillin class and subclass of aminopenicillins. It is usually available in the form of capsules containing its hydrate form. Its hydrate form is chemically known as (2S,5R,6R)-6-[(2R)-2-amino-2-(4 hydroxyphenyl)-acetylamino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2 carboxylic acid trihydrate. Its chemical formula is C16H19N3O5S, and its molecular mass is 365.404 g/mol.[8]

According to the Brazilian Pharmacopoeia in the year 2010, amoxicillin is poorly soluble in water, ethanol, and methanol. It is insoluble in benzene, ethyl acetate, chloroform, diethyl ether, and acetonitrile. However, it is very soluble in hydroxide alkali solution. Its melting point is 194°C, and its dissociation constants (pKa) are 2.4 for carboxylic acid, 7.4 for amine, and 9.6 for phenol.[9]

Stability:[6]

Stability of Rabeprazole and other Proton pump inhibitors are affected by some physical and chemical factors such as-

a) pH
b) Light
c) Temperature
d) Humidity
e) Formulation
f) Additives.
g) Interaction with another Drugs.

pH: The stability of amoxicillin is dependent on pH levels, Amoxicillin is most stable at acidic to neutral pH levels. On the other hand, at alkaline conditions of basic solutions or environments, amoxicillin tends to degrade, reducing potency and effectiveness.

Due to such conditions, at alkaline conditions, hydrolysis is likely to occur since chemical bonds in amoxicillin molecules are broken in the presence of water.

Light: Light, usually sunlight or fluorescent light, can degrade amoxicillin molecules; thus, the potency and effectiveness of the drug are reduced with time. In general, the degradation process involves the breaking of chemical bonds of the amoxicillin molecule, results in the formation of degradation products.
Such degradation products may be less effective or even inactive; hence reducing the therapeutic efficacy of the medication. Hence it is usually kept in opaque containers or glass container of amber colour

Temperature: Generally, amoxicillin is temperature-sensitive. It will be most stable if kept at controlled room temperature, which is usually defined as 20 to 25 degrees Celsius. Amoxicillin's stability may be compromised when exposed to extreme temperatures, which can be too high or too low.
High temperatures will easily attack the amoxicillin molecules through hydrolysis or oxidation processes, which accordingly will accelerate the degradation of amoxicillin. On the other hand, extreme coldness may equally affect stability of amoxicillin. Freezing temperatures may have physical changes such as crystallization, which may alter the effectiveness of the drug.

Humidity: Humidity can also affect the stability of amoxicillin; however, the effect is mostly less than many other factors, like light and pH. High humidity can result in the absorption of moisture by the solid dosage forms, such as tablets and capsules, containing amoxicillin. Besides the physical changes, high humidity can also speed up chemical degradation of amoxicillin, especially if water is available. This is because of a possible hydrolysis of the molecule of amoxicillin, hence producing degradation products and a possible loss of potency.

Formulation: Amoxicillin is available in tablets, capsules, and powder for oral suspension plus injectable forms. Different formulations of amoxicillin have different stability profiles, powders for suspension are more likely to degrade than solid dosage forms (such as tablets and capsules).

Additives: Additives may be included in certain formulations of amoxicillin to improve its stability and stabilize the formulation. These influences the self-life of medication.

Interaction With Another Drugs: Different studies were performed to understand the interaction of Amoxicillin with another drug. The studies shows that Amoxicillin interact significantly with several drugs like acetylsalicylic acid, clopidogrel, methotrexate etc.

CONVENTIONAL FORMULATION OF AMOXICILLIN AVAILABLE ON MARKET

There are a number of formulations of Amoxicillin that are available in market. The formulation presently available in market are mainly based on two basis and most important route of administration i.e. *Oral and Parenteral.*
The presently marketed products of Amoxicillin are based on conventional dosage forms. The major part of Amoxicillin market product includes-

1. Oral Tablets/Capsules [10,11,12,13]
2. Dispersible Tablets[14]
3. Effervescent Tablets [15]
4. Chewable Tablets
5. Oral Suspensions[16]
6. Lozenges[17]
7. Injectable Formulation (IM/IV**)**

DEVELOPMENT OF NOVEL FORMULATION WITH RABEPRAZOLE

In 1958 Amoxicillin was discovered but medical use of Amoxicillin was approved and started in 1972. Since then, a number of researches have been carried out on Amoxicillin and many formulations are proposed to enhance its stability, safety and efficacy. There is a lack of dosage form of the Amoxicillin that may suit all patient groups. There are a large number of conventional dosage forms of Amoxicillin but in recent years novel dosage forms like nanoparticles, microparticles etc have gained the interest of researchers.

Some Formulation which gains interest in recent years and could be a great area of interest as Amoxicillin formulation in future are-

Nanoparticles:

Ashraf N. at al 2023 had synthesized Amoxicillin loaded chitosan nanoparticle. The aim of the study was to develop and evaluate Amoxicillin nanoparticles. Nanoparticle were prepared using ionic gelation method and evaluated using different instrument like SEM and zetasizer.[18]

Guncum E. at al 2018 had formulated Amoxicillin nanoparticle with the aim of sustained drug delivery. The objective of the study was to develop a stable formulation for poultry use. The polymer used for nanoparticle preparation were sodium alginate and polyvinyl alcohol and different parameters of nanoparticles were characterized. The result reflects that the Amoxicillin nanoparticles have higher bioavailability and longer blood plasma life than free Amoxicillin.[19]

Nano Suspension:

Jadhav A. B. at al 2018 had formulated Amoxicillin nanosuspension. The aim of the study was to overcame the solubility issues related to amoxicillin drug and make dosage form cost effective. For the preparation of nanosuspension precipitation method was used and polymer used for preparation was PVP-K 30. Different parameters of nanosuspension were evaluated.[20]

Nano Emulsion:

Lin Yu-Hsin et al 2012 had prepared water in oil type nanoemulsion of amoxicillin. The aim of the study was to develop a carrier system for drug to increase its residence time of drug. Polymer used for preparation of amoxicillin nanoemulsion was chitosan. *In-vitro* and *In-vivo* test of nanoemulsions were performed.[21]

Nanocapsules:

Abdelghany A. et al 2021 had fabricated polymeric nanocapsule of amoxicillin for targeted delivery against *H.Pylori*. The aim of the study was to fabricate amoxicillin nanocapsule to enhance stability and activity against *H.Pylori.* Water-Oil-Water double emulsion was used to prepare spherical nanocapsule of Amoxicillin. Different parameters of nanocapsules like particle size, zetapotential, entrapment efficiency etc were evaluated.[22]

Nano Fibers:

Mirzaeei S. et al 2021 had developed Amoxicillin and Metronidazole containing Nanofiber system for the Periodontitis treatment. PLGA and PCL polymers were used for the fabrication of nanofibers. Different evaluation test like SEM and tensiometry were performed on the developed nanofibers. Results shows uniform morphology and Strong structure of nanofibers. *In-vivo* evaluation of nanofiber shows no sign of irritation on skin implant.[23]

Microparticles:

Earle R. R. et al 2020 had prepared Amoxicillin mucoadhesive microsphere for targeted delivery of drug to stomach. The aim of the study was to increase gastroretention time of drug. Glutaraldehyde was used as cross-linking polymer and chitosan was used as a mucoadhesive polymer. The result indicates no interaction between polymer and drug and microsphere had good flow property.[24]

Nayak D. et al 2020 had developed Amoxicillin trihydrate loaded microsphere for extended therapeutic effect against *H.Pylori* infection. Various parameters of Microsphere were evaluated. Two different quality of microsphere were prepared with floating and mucoadhesive properties.[25]

Liposomes:

Singh R. P. et al 2020 had formulated Liposomal gel of amoxicillin for the vaginal delivery of drug. The aim of the study was to develop a stable and effective vehicle for vaginal delivery of amoxicillin. Polyacrylate gel was used for the preparation of liposomes. Different parameters like pH, viscosity etc were evaluated and *in-vivo* study was performed.[26]

Transdermal Drug Delivery:

Erkus H. et al 2023 had prepared microneedle technology based transdermal drug delivery system of amoxicillin. Gelatine methacryloyl was used for preparation of microneedle using 3D printing technology. Microneedle were examined for different parameters like morphology, swelling, antimicrobial properties and drug release.[27]

Kandalkar A. et al 2023 had formulated Amoxicillin transdermal patches. Drug and polymer interaction was checked using FTIR. Different parameters of trans dermal patches like weight variation, thickness, moisture loss etc were evaluated.[28]

Suppositories:

Purohit T. J. et al 2023 had evaluate rectal bioavailability of Amoxicillin suppositories. The aim of the study was to evaluate the effect of two different chemical form of amoxicillin i.e. amoxicillin sodium and amoxicillin trihydrate.[29]

Hydrogel:

Almasri R. et al 2022 had prepared hydrogel beads of Amoxicillin for controlled delivery of drug. The aim of the study was to improve patient compliance. FTIR was used for compatibility study of drug and excipient. Drug released study of hydrogel was performed and in vitro swelling study was also performed on hydrogel.[30]

Khan Y. A. et al 2020 had prepared hydrogel system based on chitosan-alginate for sustained delivery of ciprofloxacin, amoxicillin and vancomycin. Hydrogel was prepared by complexation between chitosan and alginic acid and crosslinking with the help of $CaCl_2$. Prepared formulation was analysed with the help of SEM.[31]

Gholamali I. et al 2020 had prepared nanocomposite hydrogel of Amoxicillin for controlled release. An innovative drug delivery approach has been developed through the effective preparation of nanocomposite hydrogels in situ while CuO nanoparticles were being formed within swollen CMCS/starch hydrogels. This approach has shown great potential in enhancing drug delivery efficiency.[32]

Figueroa Ana V. T. et al 2020 had formulated an amoxicillin hydrogel system with the help of polyacrylamide and starch composite. The aim of the study was to develop a controlled release delivery system of amoxicillin. Different studies like FTIR, DSC, SEM etc were performed on hydrogel.[33]

Mucoadhesive Drug Delivery:

Villegas I. et al 2021 had developed a mucoadhesive system for delivery of Amoxicillin and Clarithromycin. The aim of the study was to develop a stable system for delivery of amoxicillin and clarithromycin for the treatment of *H.Pylori* infection. The characterization and pharmacokinetic studies were performed on mice.[34]

Goswami D. S. et al 2013 had formulated Amoxicillin mucoadhesive tablet. The objective of the research was to design mucoadhesive tablets of Amoxicillin trihydrate using moringa gum as a natural mucoadhesive polymer. Various characterizations, such as friability, content uniformity, surface pH, wash-off, and dissolution tests, were conducted for all formulations. The results of in vitro drug release and wash-off studies indicated that the formulation (F1) containing moringa gum exhibited better mucoadhesive properties.[35]

Gastroretentive Drug Delivery:

Patel M. S. et al 2021 had designed floating gel of amoxicillin for gastro retention of drug delivery system. The purpose of your work was to prepare a new intragastric flotation system that can help in the controlled administration of amoxicillin to treat peptic ulcers. This system can help in reducing the dosing frequency, improving patient compliance, enhancing the bioavailability of the drug, and minimizing side effects. It involves the preparation of controlled release floating in situ of amoxicillin.[36]

Jatav R. et al 2021 had formulated amoxicillin floating pellets for treatment of *H.Pylori*. The aim of your research work was to develop floating pellets of Amoxicillin Trihydrate that can remain in the stomach for a longer duration and eradicate H. Pylori. By creating such pellets, it is possible to enhance the effectiveness of the drug and improve patient compliance. The pellets will float on the gastric fluid and remain in the stomach for a longer period, increasing the contact time between the drug and the bacteria. This approach can help in reducing the frequency of dosing and minimizing side effects.[37]

Kamsali A. et al 2020 had developed a floating raft system of amoxicillin. The aim of your present study was to develop and characterize a floating raft system (FRS) of Amoxicillin that can enhance gastric residence time and drug release to effectively target Helicobacter pylori. Guar gum, glyceryl onostearate (GMS), and calcium carbonate were selected as factors in the development of this system. Gelation duration (h), floating lag time (min), and % Cumulative drug release (CDR) was selected as responses to measure the effectiveness of the FRS. To carry out the experimentation, a 2^3 factorial design with replicates was selected. By developing this system, it is possible to improve the therapeutic efficacy of Amoxicillin and reduce the frequency of dosing.[38]

CONCLUSION

It's interesting to note that Amoxicillin has been known for over 50 years as an effective treatment and prevention for a variety of infections, including respiratory infections, ear infections, UTIs, skin infections, gastrointestinal infections, dental infections, sexually transmitted infections, and Lyme disease. However, despite its efficacy, some issues still remain unsolved, such as stability and availability of a formulation suitable for children and all medical conditions. Researchers have proposed several approaches to address these issues, but there is still room for improvement.

Most research so far has focused on the oral route of administration, but recently, other novel routes of administration such as Mucoadhesive drug delivery, Transdermal drug delivery, and Buccal drug delivery have gained interest among researchers. The most commonly used polymers in the formulation of Amoxicillin dosage forms are Chitosan, Alginate, and Polyacrylate-based polymers.

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