

**A REVIEW: FIXED DOSE COMBINATIONS OF PENICILLINS****Mohini S. Jogdande\* and Sachin A. Nitave**

Dr. J. J. Magdum Trust's

Anil Alias Pintu Magdum Memorial Pharmacy College, Dharangutti. Tal: Shirol, Dist:  
Kolhapur, Maharashtra, India.

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**\*Corresponding Author****Mohini S. Jogdande**Dr. J. J. Magdum Trust's  
Anil Alias Pintu Magdum  
Memorial Pharmacy  
College, Dharangutti. Tal:  
Shirol, Dist: Kolhapur,  
Maharashtra, India.**ABSTRACT**

A combination drug is a fixed dose combination (FDC) that includes two or more active pharmaceutical ingredients (APIs) combined in a single dosage form, which is manufactured and distributed in fixed doses. Antibiotics also called antibacterials are a type of antimicrobial drug used in the treatment and prevention of bacterial infections. They may either kill or inhibit the growth of bacteria. In the management of adverse drug reaction and to control the side effects of the drug fixed dose combination formulations have their usefulness. Fixed dose combinations can also deal with pill burden in long term treatment. fixed dose combinations of penicillins can apply to fulfill the patient compliance, provide high therapeutic index and to provide cheaper medicines to the patient.

**KEYWORDS:** FDC, antibacterial, antibiotics, penicillins, patient compliance, therapeutic index.

**INTRODUCTION TO BETA LACTAM ANTIBIOTICS**

Beta-lactam antibiotics (beta lactum antibiotics) are a class of broad-spectrum antibiotics, consisting of all antibiotic agents that contain a beta-lactam ring in their molecular structures. This includes penicillin derivatives (penams), cephalosporin (cephems), monobactams, and carbapenams. Most beta lactum antibiotics work by inhibiting cell wall biosynthesis in the bacterial organism and are the most widely used group of antibiotics.<sup>[1]</sup>

Bacteria often develop resistance to beta -lactam antibiotics by synthesizing a beta-lactamase, an enzyme that attacks the beta- lactum ring. To overcome this resistance, beta-lactam antibiotics are often given with beta-lactamase inhibitors such as clavulanic acid.<sup>[1]</sup>

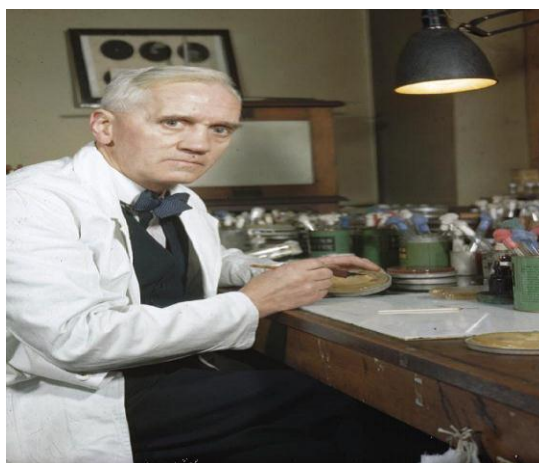
Antimicrobial agents are among the most dramatic examples of the advances of modern medicines. Many infectious diseases once considered incurable and lethal now can be treated. The remarkably powerful and specific activity of antimicrobial drugs is due to their selective toxicity for targets that are either unique to microorganisms or much more important in them than in humans.<sup>[1]</sup>

### Introduction to Penicillin

Penicillin is a group of antibiotics that are commonly used to treat different types of gram positive and gram negative bacterial infections. In their structures, Beta –lactum ring is located due to this reason these drugs are also called as beta-lactum antibiotics.

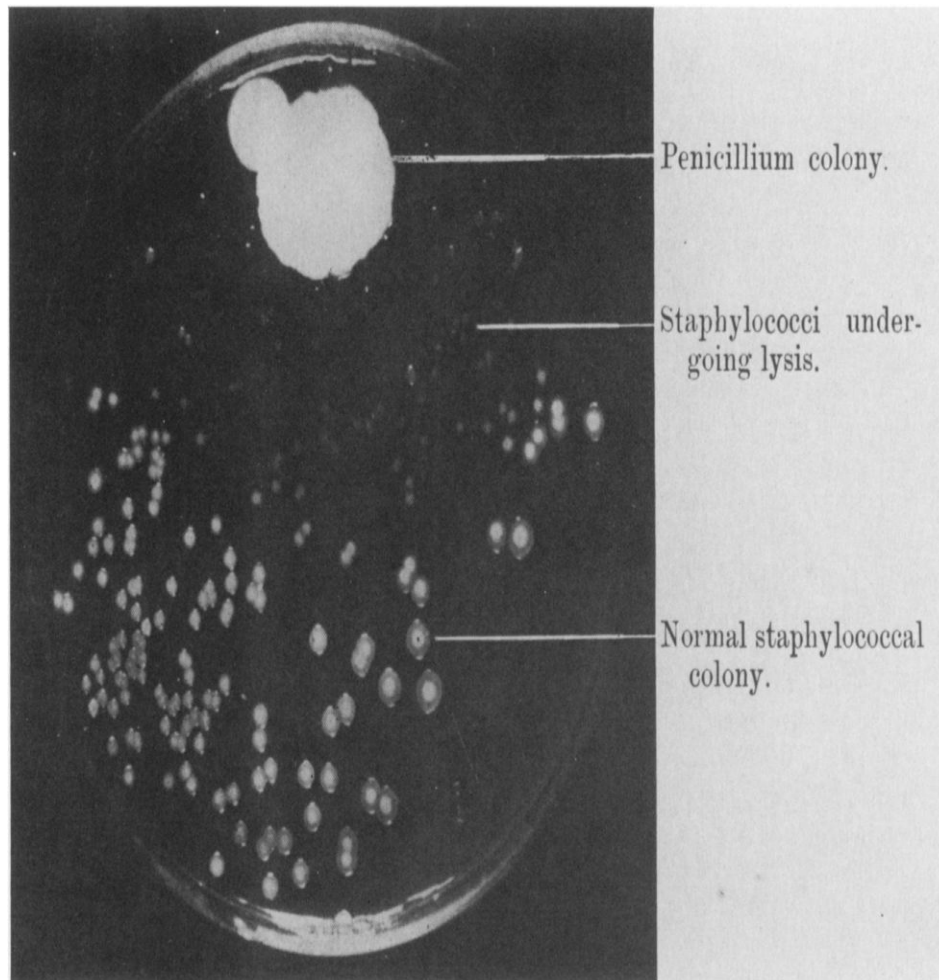
- Penicillin is derived from the penicillium mould.
- It destroys bacteria by inhibiting the enzyme responsible for the formation of the cell wall in the bacterial cells.<sup>[2,3,4]</sup>

### History



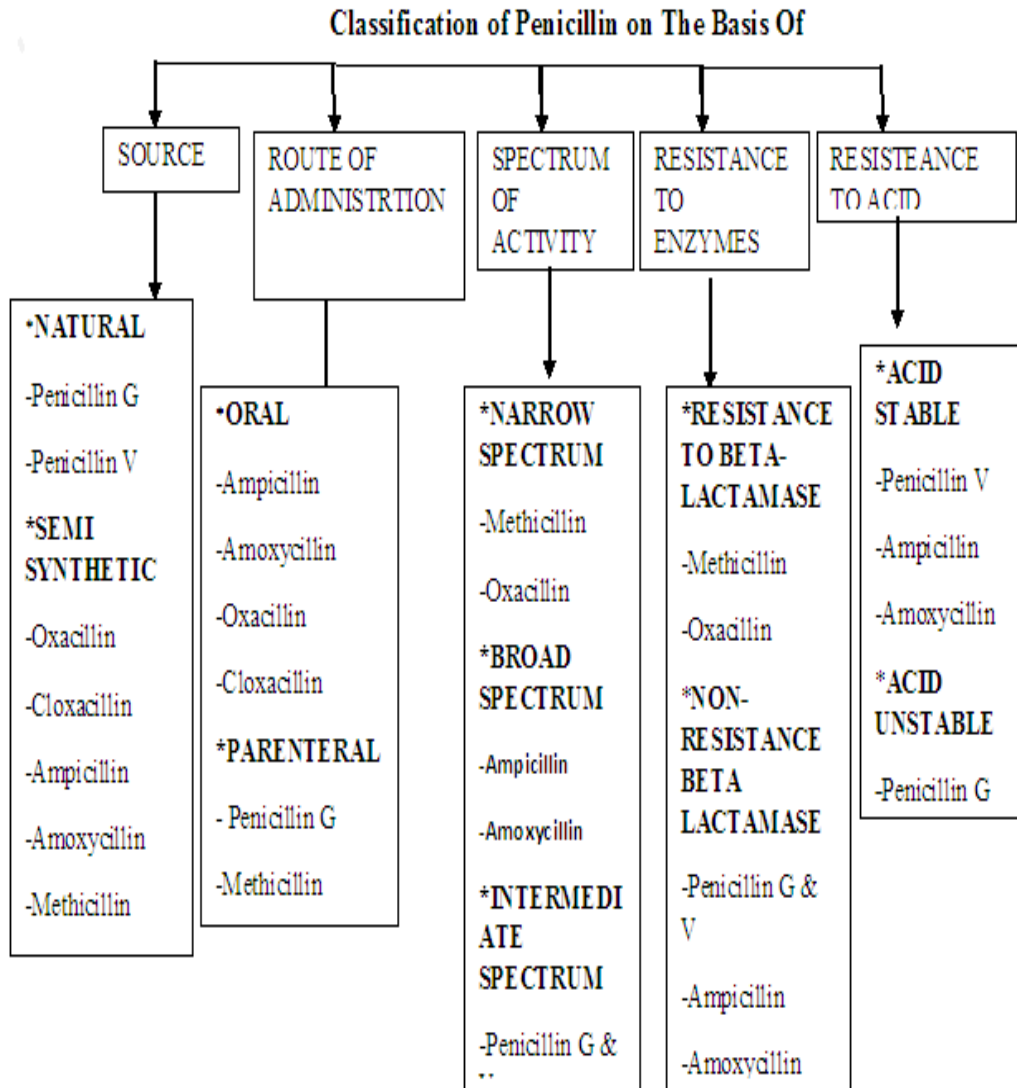
The scientist's name was Alexander Fleming. He became immortal on that fateful day in 1928. Even today, many (especially in the medical community) know his name. Who was the man behind the legend? Alexander Fleming was born in Darvel, Scotland (about 25 miles south of Glasgow) on August 6, 1881 to a farming family.<sup>[2,3,4,5,6,7,8]</sup>

This method is still used this day, making the discovery of penicillin not his only claim to fame. From here, he returned to St. Mary's, where he would make his incredible discovery.



**Figure: A picture of Fleming's original discovery**

- Penicillin, the world's first antibiotic, was discovered by British scientist Alexander Fleming in 1928 on accident.
- In 1928 Alexander Fleming discovered the compound produced by the fungus.
- The fungus was called *Penicillium notatum*.
- The isolated compound he is called penicillin.
- Fleming noted a fungus growing on his bacterial plates had killed off the surrounding bacteria.
- Fleming, Flory and Chain received a Nobel prize in 1945 for medicine for their work on penicillin.<sup>[2,3,4,5,6,7,8]</sup>



**Drug Profile for Penicillin Antibiotics**

**1. Ampicillin**



**Ampicillin** is an antibiotic used to prevent and treat a number of bacterial infections, such as respiratory tract infections, urinary tract infections, meningitis, salmonellosis, and endocarditis. It may also be used to prevent group B streptococcal infection in newborns. It is used by mouth, by injection into a muscle, or intravenously. Like all antibiotics, it is not useful for the treatment of viral infections.<sup>[9]</sup>

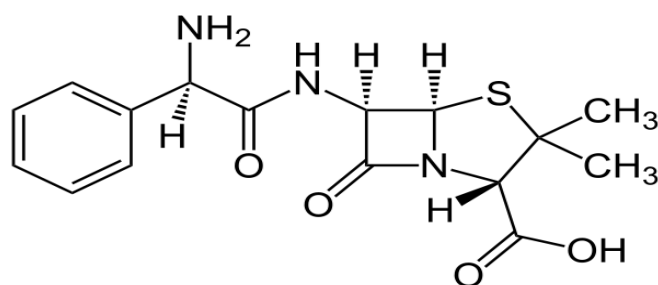
#### \* History

Ampicillin has been used extensively to treat bacterial infections since 1961. Until the introduction of ampicillin by the British company Beecham, penicillin therapies had only been effective against Gram-positive organisms such as staphylococci and streptococci. Ampicillin (originally branded *H. influenzae*, coliforms, and *Proteus* spp. as "Penbritin:") also demonstrated activity against Gram-negative organisms such as *H. influenzae*, coliforms, and *Proteus* spp.<sup>[9]</sup>

#### \* Mechanism of Action

Ampicillin acts as an irreversible inhibitor of the enzyme transpeptidase, which is needed by bacteria to make the cell wall. It inhibits the third and final stage of bacterial cell wall synthesis in binary fission, which ultimately leads to cell lysis; therefore, ampicillin is usually bacteriolytic.<sup>[9]</sup>

#### \* Structure



(2*S*,5*R*,6*R*)-6-([(2*R*)-2-amino-2-phenylacetyl]amino)-3,3-dimethyl-7-oxo-4-thia-1 azabicyclo [3.2.0]heptane-2- carboxylic acid

#### \* Pharmacokinetics

- Ampicillin is well-absorbed from the GI tract (though food reduces its absorption), and reaches peak concentrations in one to two hours
- The bioavailability is around 62% for parenteral routes. Unlike other penicillins, which usually have bind 60–90% to plasmaproteins, ampicillin binds to only 15–20%

- Ampicillin is distributed through most tissues, though it is concentrated in the liver and kidneys.
- Some ampicillin is metabolized by hydrolyzing the beta-lactam ring to penicilloic acid, though most of it is excreted unchanged.<sup>[9]</sup>

#### \* Dosage

-Usual dosage range

Oral: 250-500 mg every 6 hours

I.M., I.V.: 1-2 g every 4-6 hours or 50-250 mg/kg/day in divided doses (maximum: 12 g/day)

-Cholangitis (acute): I.V.: 2 g every 4 hours with gentamicin.

-*Infective*: I.V.: 12 g/day via continuous infusion or divided every 4 hours.

-*Prophylaxis in total joint replacement patient*: I.M., I.V.: 2 g 1 hour prior to the procedure

-Mild-to-moderate infections: Oral: 250-500 mg every 6 hours.

#### \* Indications

Treatment of susceptible bacterial infections (nonbeta-lactamase-producing organisms); treatment or prophylaxis of infective endocarditis; susceptible bacterial infections caused by streptococci, pneumococci, nonpenicillinase-producing staphylococci, *Listeria*, meningococci; some strains of *H. influenzae*, *Salmonella*, *Shigella*, *E. coli*, *Enterobacter*, and *Klebsiella*.<sup>[9]</sup>

#### \* Contraindications

Ampicillin is contraindicated in those with a hypersensitivity to penicillins, as they can cause fatal anaphylactic reactions. Hypersensitivity reactions can include frequent skin rashes and hives, exfoliative dermatitis, erythema multiforme, and a temporary decrease in both red and white blood cells. Ampicillin is not recommended in people with concurrent mononucleosis, as over 40% of patients develop a skin rashes.<sup>[9]</sup>

#### \* Interactions

-Ampicillin reacts with probenecid and methotrexate to decrease renal excretion. Large doses of ampicillin can increase the risk of bleeding with concurrent use of warfarin and other oral anticoagulants, possibly by inhibiting platelet aggregation.

- Ampicillin has been said to make oral contraceptives less effective, but this has been disputed.

-It can be made less effective by other antibiotic, such as chloramphenicol, erythromycin, cephalosporins, and tetracyclines. For example, tetracyclines inhibit protein synthesis in bacteria, reducing the target against which ampicillin acts.

-Ampicillin causes skin rashes more often when given with allopurinol. Both the liver cholera vaccine and live typhoid vaccine can be made ineffective if given with ampicillin.<sup>[9]</sup>

#### \*Side Effects

1. Ampicillin is comparatively less toxic than other antibiotics, and side effects are more likely in those who are sensitive to penicillin and those with a history of asthma or allergies.
2. Serious adverse effects also include seizures and serum sickness. Less common side effects can be nausea, vomiting, itching, and blood dyscrasias.<sup>[9]</sup>

## 2. Amoxicillin



**Amoxicillin**, also spelled **amoxycillin**, is an antibiotic useful for the treatment of a number of bacterial infections. It is the first line treatment for middle ear infections. It may also be used for strep throat, pneumonia, skin infections, and urinary tract infections among others. It is taken by mouth, or less commonly by injection.<sup>[10]</sup>

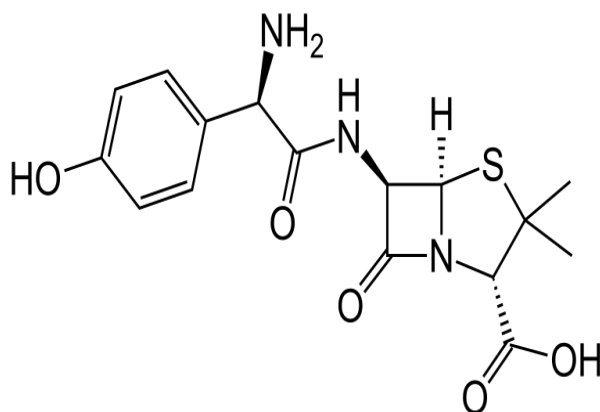
\* **Category:** Antimicrobial

#### \* History

Amoxicillin was one of several semisynthetic derivatives of 6-aminopenicillanic acid (6-APA) developed at Beecham, England in the 1960s. It became available in 1972 and was the second aminopenicillin to reach the market (after ampicillin in 1961). Coamoxiclav became available in 1981.<sup>[10]</sup>

**\* Action**

Amoxicillin is bacterial by virtue of its ability to inhibit synthesis of the bacterial cell wall. The benzyl ring in the side chain extends the antimicrobial action to gram negative bacteria. Bacteria susceptible to amoxicillin includes alpha and beta haemolytic streptococci strep pneumonia strep faecalis, bacillus anthracis, staphylococci, B. pertussis, E. coli Pseudomonas Enterobacter, Mycobacteria and viruses are not susceptible to amoxicillin. Among fungi actinomycetes are sensitive.<sup>[10]</sup>

**\*Structure**

2*S*,5*R*,6*R*)-6-[[*(2R)*]-2-Amino-2-(4-hydroxyphenyl)acetyl]amino}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

**\* Indication**

Susceptible infections including ear/nose/throat (ENT), lower respiratory tract, skin, and skin structures, genitourinary tract, acute uncomplicated gonorrhoea.

**\* Contraindications**

AMOXIL is contraindicated in patients who have experienced a serious hypersensitivity reaction {e.g., anaphylaxis or Steven-Johnson's syndrome} to AMOXIL or to other beta-lactam antibiotics {e.g., penicillins and cephalosporins}.<sup>[10]</sup>

**\* Interactions**

Amoxicillin may interact with these

1. Dabigatran.
2. Cancer treatment (methotrexate).
3. Uricosuric drugs.
4. Typhoid vaccine



5. Warfarin action is increased
6. Allopurinol (gout treatment).
7. Oral contraceptives may become less effective.

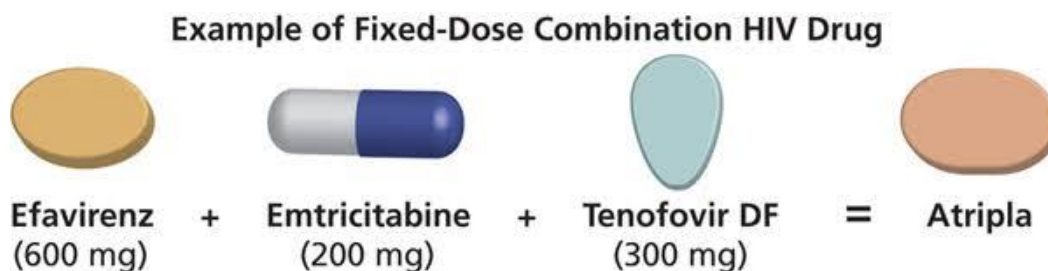
**\* Adverse Effects**

1. Side effects are similar to those for other  $\beta$ -lactam antibiotics, including nausea, vomiting, rashes, diarrhea and antibiotic-associated colitis
2. Rarer side effects include mental changes, lightheadedness, insomnia, confusion, anxiety sensitivity to light and lights and sounds, and unclear thinking.
3. The onset of an allergic reaction to amoxicillin can be very sudden and intense; emergency medical attention must be sought as quickly as possible.
4. Use of the amoxicillin/clavulanic acid combination for more than one week has caused mild hepatitis in some patients.<sup>[10]</sup>

**Review Study of Fixed Dose Combinations**



### Case Study for Fixed dose combinations



A combination drug is a fixed dose combination (FDC) that includes two or more active pharmaceutical ingredients (APIs) combined in a single dosage form, which is manufactured and distributed in fixed doses. Terms like “combination drug” or “combination drug product” can be common shorthand for a FDC product, although the latter is more precise if in fact referring to a mass –produced product having a predetermined combination of drugs and respective dosages. And it should also distinguished from the term “combination product” in medical contexts, which without further specification can refer to products- such as device/drug combinations as opposed to drug / drug combinations.<sup>[11]</sup>

### Advantages

In addition to simply being a means of facilitating the general advantage of combination therapy, specific advantage of fixed- dose combination (FDC)drug product includes:

- Improved medication compliance by reducing the pill burden of patients. Note that pill burden is not only the number of pills needing to be taken, but also the associated burdens such as keeping track of several medications, understanding their various instructions, etc.
- Ability to compose combined profiles of for example pharmacokinetics , effects and adverse effects that may be specific for the relative dosages in a given FDC products, providing a simpler overview compared to when looking at the profiles of each single drug individually,
- FDC drug product may be developed by a pharmaceutical company as a way to in effects extend proprietary rights and marketability of a drug product.
- Better blood pressure control.
- Lesser incidence of individual drug’s side effect.
- Neutralization of side effects.
- Increased patient compliance.
- Modification of risk factors.
- Lesser cost of therapy.<sup>[12]</sup>

### Disadvantages

- There may not be an FDC available with the appropriate drugs and in the most appropriate respective strengths for a given patient, which can lead to some patients getting too much of an ingredients and others getting too little, as the AAO notes that FDCs “limit clinicians’ ability to customize dosing regimen”
- If an adverse drug reactions occurs from using an FDC, it may be difficult to identify the active ingredients responsible for causing the reaction.<sup>[12]</sup>

### Review for the Drugs

#### Review for (A): Ampicillin

| Sr. No. | ‘A’ Drug   | ‘A1’ Drug   | Company         | Dose (A+A1) mg | Cost (RS/TAB) | Route Of Administration |
|---------|------------|-------------|-----------------|----------------|---------------|-------------------------|
| 1.      | Ampicillin | Cloxacillin | Walter bushnell | 250+250        | 5.20/cap      | Oral                    |
| 2.      | Ampicillin | Sulbactam   | FDC             | 01+0.5         | 89.00/inj     | Injectable              |

Ampicillin and cloxacillin are  $\beta$ -lactum antibiotics which are available in fixed dose combinations in the market. Both of these  $\beta$ -lactum antibiotics are antibacterial agents & they gives synergistic effect for each other after oral administration. It is a product of WalterBushnell company. Its dose is total 500 mg (250 mg each respectively) and cost is 5.20Rs/cap. Both of these drugs when compounded in single dose formulations then cost is become high along with the low therapeutic index. Ampicillin and cloxacillin when available in a fixed dose combination then along with the cost, efficacy patient compliance for the drugs have fulfill results.<sup>[13,14,15]</sup>

Ampicillin and sulbactam are also gives synergistic effect by after injecting it. Both are also antibacterial agents and gives synergistic effect after oral administration. Its dose is total 1.5 ml and cost is 89.00 Rs/inj The price of this product is less as compared to single dose formulation.<sup>[13,14,15]</sup>

#### Review For (B): Amoxycillin

| Sr. No. | ‘B’ Drug    | ‘B1’ Drug         | Company | Dose (B+B1) | Cost (RS/TAB) | Route of Administration |
|---------|-------------|-------------------|---------|-------------|---------------|-------------------------|
| 1.      | Amoxycillin | Clavunalanic acid | Cipla   | 500+125     | 18.00         | Oral                    |
| 2.      | Amoxycillin | Cloxacillin       | Alembic | 250+250     | 5.71          | Oral                    |

Amoxycillin is a antibacterial agent and clavunalanic acid is a beta- lactamase inhibitor. Which are available in fixed dose combinations in the market.. Bacteria produces  $\beta$ -lactuamase enzyme which is having ability to restrict the action of amoxicillin, so by using

clavunalanic acid or potassium clavulanate  $\beta$ -lactamase enzyme is breakdown. Because of this effect antibiotic will have a great pharmaceutical importance.<sup>[14,15,16]</sup>

Its dose is total 625mg (500mg and 125 mg respectively) and cost is 18.00 RS/tab. Both of these drugs when compounded in single dose formulation then cost is become high along with low therapeutic index. Amoxycillin and clavunalanic when available in a fixed dose combination then along with the cost, efficacy, patient compliance for the drugs have fulfill result.<sup>[14,15,16]</sup>

## CONCLUSION

Antibiotics also called antibacterials are a type of antimicrobial drug used in the treatment and prevention of bacterial infections. They may either kill or inhibit the growth of bacteria. A combination drug is a fixed-dose combination (FDC) that includes two or more active pharmaceutical ingredients (APIs) combined in a single dosage form, which is manufactured and distributed in fixed doses.

To deal with the pathogenic microorganism like gram positive and gram negative bacteria fixed dose combinations can play vital role. Fixed dose combinations kind of dosage form having their key usefulness in the treatment and illness along with patient compliance, patient acceptance, cost, synergism, microbial resistance, efficacy etc.

In the management of adverse drug reaction and to control the side effects of the drug fixed dose combination formulations have their usefulness. Fixed dose combinations can also deal with pill burden in long term treatment.

With this kind of project one can reveal the importance of fixed dose combinations of penicillins for the betterment of health of human beings and also to control the infections of known and unknown kind of pathogens.

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