An Introduction to Antibiotic Production

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Summary

"Antibiotics" is an important group of medicines that is being used widely in normal medical practice. Antibiotics are prepared from micro-organisms by fermentation process. Genetic engineering has increased and improved quantity of antibiotic production.

Key Words: Antibiotics, Production

Introduction

Antibiotics are the substances derived from micro-organisms which inhibit the growth of other micro-organisms or kill them (1). Antibiotics that inhibit the growth of other micro-organisms are called bacteriostatic antibiotics. e.g. Tetracyclins. Antibiotics that kill the other micro-organisms are called bactericidal antibiotics. e.g. Penicillins.

SOURCES OF ANTIBIOTICS

About 85% of antibiotics are obtained from Actinontycetes, 11% from Fungi and 4% from Bacteria (2).

Table1: Sources of antibiotics

Antibiotic	**Source**
Streptomycin	*Streptomyces griseus*
Erythromycin	*Streptomyces erythreus*
Lincomycin	*Streptomyces lincolnensis*
Tetracyclin	*Streptomyces aureofaciens*
Chloramphenicol	*Streptomyces venezuelae*
Cephalosporins	*Cephalosporium* species
Penicillins	*Penicillium* species

FERMENTATION

Fermentation involves the cultivation of micro-organisms. First step in fermentation is the isolation of the micro-organism. It is possible to isolate different micro-organisms by enrichment technique (3, 4). Inoculation is done simply by scattering spores on the substrate on which the micro-organisms grow. The apparatus in which the growth of microorganisms is carried out is called fermentor. Several types of fermentor are available (5,6) e.g. tray fermentor, rotary drum fermenter.

GENETIC ENGINEERING

DNA portion of the micro-organism containing the antibiotic gene is cut by restriction enzyme. A plasmid DNA is also cut with the same enzyme. Now DNA fragment containing antibiotic gene is joined with the plasmid DNA by enzyme DNA lygase. Many copies of these recombinant plasmids are transformed into the micro-organism where the gene expresses and causes the production of the antibiotic (7, 8).

RELEASE OF INTRACELLULAR COMPONENTS

There are many ways to disrupt cells to liberate the product containing antibiotic (9).

Mechanical Methods

Bead Mill: A bead mill consists of a grinding cylinder. The cylinder is also filled with small beads made up of glass or zirconium oxide. (10)

Homogeniser: Homogeniser causes the cell disruption by pumping the cell suspension into its orifice with a high pressure.

Non-Mechanical Methods:

Heat Shock Method: Thermolysis can be used for heat stable products.

Chemical Cell Lysis: Detergents (such as cationic, anionic and non-ionic) and solvents (such as octanol and acetone) solubalise the cell wall.

Enzymatic Cell Lysis: Lysozyme has ability to hydrolyse peptidoglycane of cell wall of bacteria. Gluconase and mannase, often in combination with proteases, are used for degradation of yeast cell wall.

SOLID-LIQUID SEPARATION

The required antibiotic in liquid form may be separated from solid wastes by filtration.

Filtration:

Filtration is the separation of a solid-liquid suspension (e.g. fermentation broth) into a concentrate (cake) and a liquid (filtrate) by means of a porous medium that retain the solid but allow the liquid to pass (11, 12).

Broth Treatment (13):

1. Pre-treatment: Broth can be pre-treated to reduce the cake resistance.

   There are two ways:

   - Addition of filter aid: e.g. Diatomite, Perlite
   - Addition of flocculent: e.g. Al sulphate, Polyamine

2. Post treatment: After the filtration, the cake can be washed and dried.

CONCENTRATION OF PRODUCT

After separating the cake from whole broth, the filtrate contains upto 98% water. Thus water must be removed. This can be done in different ways (14):

Evaporation: Evaporation is the vaporization of the liquid from its surface by heat.

Precipitation: In precipitation, the solubility is reduced by addition of salts (salting out) or organic solvents. Then the insoluble solid is separated from the liquid. (15)

PURIFICATION

Next step for recovery of the product is purification. (16) Chromatography is usually used for purification of antibiotics.

Chromatography:

Chromatography is a separation process based upon the differential distribution of a mixture between two phases, one of which is percolated through the other. The fixed phase is called stationary phase and the moving phase is called mobile phase. Column chromatography is commonly used for the purification of antibiotics. During the process of chromatography, one of the following principles involves:

Adsorption: If stationary phase is solid, adsorption is the principle of chromatography.

Partition: If stationary phase is liquid, partition is the principle of chromatography.

Gel filtration: It is simple filtration that depends upon the molecular mass of components and pore size of the packed gel

Ion exchange: Here the exchange of ions occurs between the stationary phase and the sample.

Table 2: Clinical uses of common antibiotics

Antibiotic	**Clinical Uses**
Erythromycin	Whooping cough Diarrhoea
Tetracyclins	Cholera Urogenital infection
Chloramphenicol	Meningitis Gonorrhoea
Cephalosporins	UTI Tetanus Gangrene
Penicillins	Pneumonia Infection of wounds Meningitis Tetanus Gangrene

FORMULATION

It is necessary for the antibiotics, to be developed into a suitable dosage form (drug delivery system). For example as penicillin is unstable at low pH, it will be destroyed in stomach if not given in a suitable dosage form. Thus it is developed in injectable dosage form. The other antibiotics that are stable at stomach pH may be developed into oral dosage forms.

USES OF ANTIBIOTICS

With the help of antibiotics we have been able to treat a large number of infectious disease. Some clinical uses of common antibiotics are given here. (1)

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