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PROCESS CONTROL AND MEDIUM FORMULATION FOR INDUSTRIAL FERMENTATION

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ABSTRACT

Fermenter control and media formulation has been a dynamic area of research and it captivated the attention of world. All this is because of the new advances in other interrelated areas which may be utilized to overcome the inherent complications in control of fermenter. Organization with conventional dictatorial control of variables such as pH, temperature and dissolved oxygen concentration, research in control of fermenter has undergone important changes including the current neural network based methods. At industrial scale fermentation, media are required for growth of specific microbes in a fermenter. Thus fermenter control, nutrients availability and fermentation efficiency, all are important factors in medium formulation process. The microorganisms used for process of fermentation grow in specially designed medium having appropriate supply of nutrients such as sources of nitrogen and carbon, energy sources, certain mineral elements, and water and perhaps vitamins plus oxygen in case of aerobic nature of microbes. Trace nutrients and growth factors are also important for microbes which are incapable of fulfilling their nutrient requirements. Trace elements including copper, zinc, cobalt, molybdenum, iron and manganese are added to medium when purified nitrogen and carbon sources are used. Phosphates and carbonates are used as mineral buffering salts to stabilize pH and antifoaming agents are used to prevent foam formation during fermentation process. Chelating agents are also used at higher concentrations of metal ions. There should be perfection in organism selection and correctness in medium formulation for large scale production of particular product. Although complete analysis is necessary to develop a suitable medium for fermentation process.

KEY WORDS: *fermenter, fermentation, media, nutrients, microbes, aerobic, variables, trace elements, growth factors, chelating agents, antifoaming agents.*

1. INTRODUCTION

The capability of microorganisms to change low cost substrates or raw materials into economically important organic compounds is called as industrial microbiology. Establishing the cost effectively viable processes by enhancing product yield and decrease operating cost is a primary objective in industrial fermentation development and research. By strain improvement, growth medium, using multiple techniques and improvement in nutrient feeding are the most important means to achieve primary objectives. This review deals with manipulation, control of those microorganisms able to produce desirable and economic products. Several means of reactor operation batch are present, continuous and fed batch each of them presenting different problems to control the structure of system. The control and modeling of fermentation should recognize however in fermentation the techniques that developed and used are promptly applicable, such as to the treatment of waste water and other biological processes. The software based methods are becoming of spatial interest such as state estimation and inferential and adaptive control methods, because they require conventional instrumentation in order to support them.

2. FERMENTATION

The procedure of utilizing microbes to convert solid or liquid substrates into additional different products is known as fermentation. The fermentation word is derivative of Latin verb **fervere** means **to boil** (Stanbury, Hall & Whitaker, 2000).Fermentation is a metabolic process carried out by some microorganisms in which sugar is consumed in the absence of oxygen and economically important by products are given out (Pumphrey, 1996). Consumable products obtained from process of fermentation are glutamic acid, soy sauce, pickled vegetables, cheese, bread, wine beer, and cocoa. (Ho, 2015).

2.1 Factors affecting Fermentation process

Factors affecting process of fermentation process are

pH

Nature of medium

Temperature
Composition of the medium
Outfitted schemes such as batch, fed-batch, continuous culture
Dissolved carbon dioxide, oxygen (Schaechter, 2009).

3. CONSTRUCTION OF FERMENTER

The apparatus fermenter maintains the optimal growth conditions of microbes, used in production of antibiotics and hormones at commercial level and in large scale fermentation. Selection of material is important in construction of a fermenter. Material which used should able to withstand repeated stem sterilization condition.

The design of fermenter vessel is established in that way it requires minimal maintenance and labor operation. The internal surface is smooth and geometry is similar. For industrial scale fermentation stainless steel vessels used and for the small scale glass vessels used. To improve aeration capacity and to prevent vortex all sizes baffles are assimilated in the agitated vessels. Number of mixing objectives is achieved by impeller like gas phase, solid particle suspension and bulk fluid etc. they are classified in disc turbines and variable pitch open turbine. In fermenter the air is introduced in liquid by sparger.

- Three types of sparPorous sparger
  Nozzle sparger
  Combined sparger-agitor.

- There are five types of valves which are used to control the flow of gases;
  Globe valves
  Butterfly valves
  Ball valves
  Diaphragm valves
  Safety valves. As shown in figure 1.

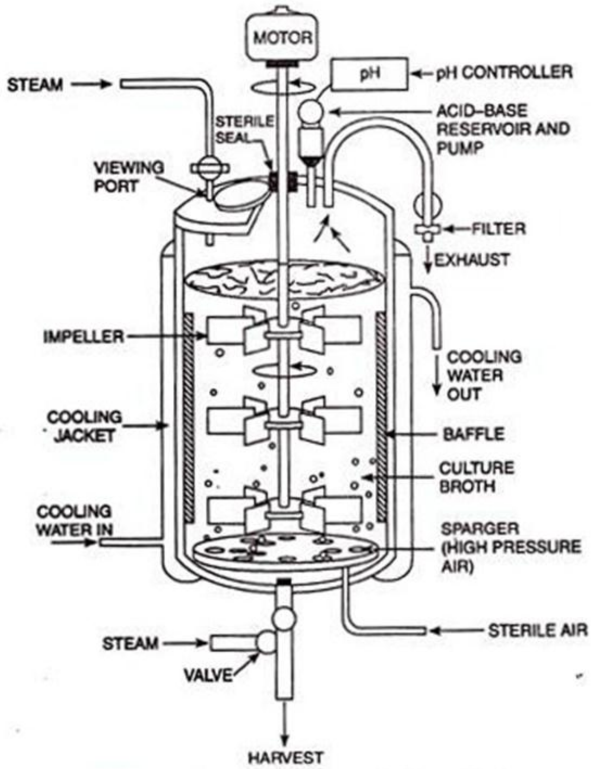

Figure 1: Components of fermenter.

3.1 Sensors

Sensors are available to measure and control the different variables in fermenter.

For process control it is also possible in relation to its application characterize a sensor

- **Online sensor:** The measured values cannot be use promptly for control, sensor play role as integral part of fermentation equipment. In process control if the data is to be use operator should enter the measured values in process control.

  For on line biosensors sensitivity and specificity require which indicate substantial potential (Cleland *et al*., 1983).
- **Offline sensor:** For process control measured value cannot be used straightforwardly. Sensor is actually not a part of equipment of fermentation. For actual measurement an operator is needed and for process control enrolling the measured values in control system with high stability and sterilization.
- **In line sensor:** This type of sensor is most complex part of the fermenter and values measured by them are precise.

4. MEASUREMENTS FOR CONTROL OF FERMENTATION PROCESS

The readiness of measurements at industrial level fermentation is greatly influenced by robustness, ease of use and reliability. From high output electrical resistant transducers and sensors, fermentation provides suitable environment for stable, reliable and noise free measurements (Clarke *et al*., 1982). The sensors which greatly used in chemical process are least reliable to the important sensors which used in fermentation e.g. pH probes (Flynn *et al.*, 1982).Metabolic rate indication provides by the control action of pH which taken in regulation (Cooney*et al.*, 1977). The mostly available online growth control measurements may be based on enabling CO2 production, gas analysis and theses can be calculated from inlet gases and fermenter exhaust (Meyer*et al.*, 1985). These measurements are comparatively fast for control purposes and lead to discrete data. Many other choices are examined for example an extensive range of measurement techniques are being applied in field of biomass (Ramsay *et al.*, 1985).

5. CONTROL OF PROCESS VARIABLES:

5.1. Temperature control

It may better in some cases at steady rate run the cooling water continuously and only connect the heating element to control unit. In large fermenters when heating is not required a monitoring valve placed at a cooling water inlet should be sufficent to control the temperature. If excessive cooling is required there might delivery for circulation of refrigerated brine.

5.2. Gases control

Flow control of gases is important in process management. Such valves as ‘flowstat’ available at small scale. In gas ‘flowstat’ when the gas stream is at controlled pressure the orifice should be upstream and the downstream when the back pressure is constant and supply pressure fluctuates. On base of the gas analysis (Spriet*et al*., 1982) precision and accuracy of calculations commented by Flynn (1982), demonstrating that care should take in their use.

5.3. Pressure control

In different part of fermentation plant various working pressures are compulsory to support in maintenance of conditions during normal operation of fermenter. During steam sterilization cycle this pressure raises. By regulation of valves pressure is controlled by connecting pressure gauges.

5.4. Foam control

To control foams a control unit and foam sensing is used. In fermenter from the top plate a probe is inserted. Above the surface of broth at defined level it is set. Through the circuit of probe a current is passed when foam rise and touch to the probe tip. Pump is actuates by current and then antifoams released in seconds.

6. ADAPTIVE CONTROL TECHNIQUES IN FERMENTATION

Number of researchers considered the adaptive control schemes controllers whose parameters can be discovered and wide ranging online as fermentation proceeds. Principles planned to categorize control techniques.

1. To reduce a cost function a control action can be approximated, for example pole-placement type of algorithm (Wellstead *et al.*, 1981) or generalized minimum variance (GMV) algorithm type (Clarke *et al*., 1979).
2. To evaluate the controller parameters straight forwardly an implied algorithm named as generalized minimum variance control (GMVC) or to assess the parameters of the system by which the controller parameters are examined, an understandable algorithm for example generalized predictive control (Clarke *et al*., 1985), by them parameter for estimation of routine can be operated.
3. A state space model (Warwick, 1981) ora time series model (GMVC. GPC) are the system models which used to calculate the control actions.

7. ARTIFICIAL NEURAL NETWORK

The model which used to deliver a mathematical alternate to quadratic polynomial for indicating data resulting from statistically planned experiments and calculate new data point is artificial neural network. The strong points of artificial neural networks are that they can handle simply out requiring no mechanistic category of system andthey work suitably with huge amount of data, to medium improvement this make actually artificial neural network more suitable (Kennedy *et al.*, 1999).By directing sequences of experiments first data produced and constructed a network and becoming the network to understand these data set, once trained the output of microbial product formation is calculated and new data points given to the network i.e., fermentation processconditionor media composition.(Patnaik, 2005).

7.1 NEAR-INFRARED TECHNOLOGY

Optical sensors present considerable advantages as they can detect multiple compounds instantaneously, they are non-invasive and it is not necessary to remove the sample from process (Höpfner*et al.*, 2010). During the last about twenty years in bioprocess exploration research, those sensors which are based on near infrared wavelength gained more implication. There are many applications reported which deal with near infrared technology useful for bioprocess monitoring, in international literature. During enzymatic starch hydrolysis online control of glucose concentration explained (Nishinari *et al.*, 1989), to manage the process of alcoholic fermentation use of an exterior optical fiber in near infrared wave instrument (Cavinato*et al.*, 1990) and the most recent is for protein production apply NIR to censoring solid state fermentation (Jiang *et al.*, 2013). On the assimilation of the radiation in front of infrared zone of electromagnetic spectrum ranges from 700-2500 nm, in sample all the molecules are present. (Siesler*et* *al.*, 2008) the functioning principle of NIR is based as shown in figure.

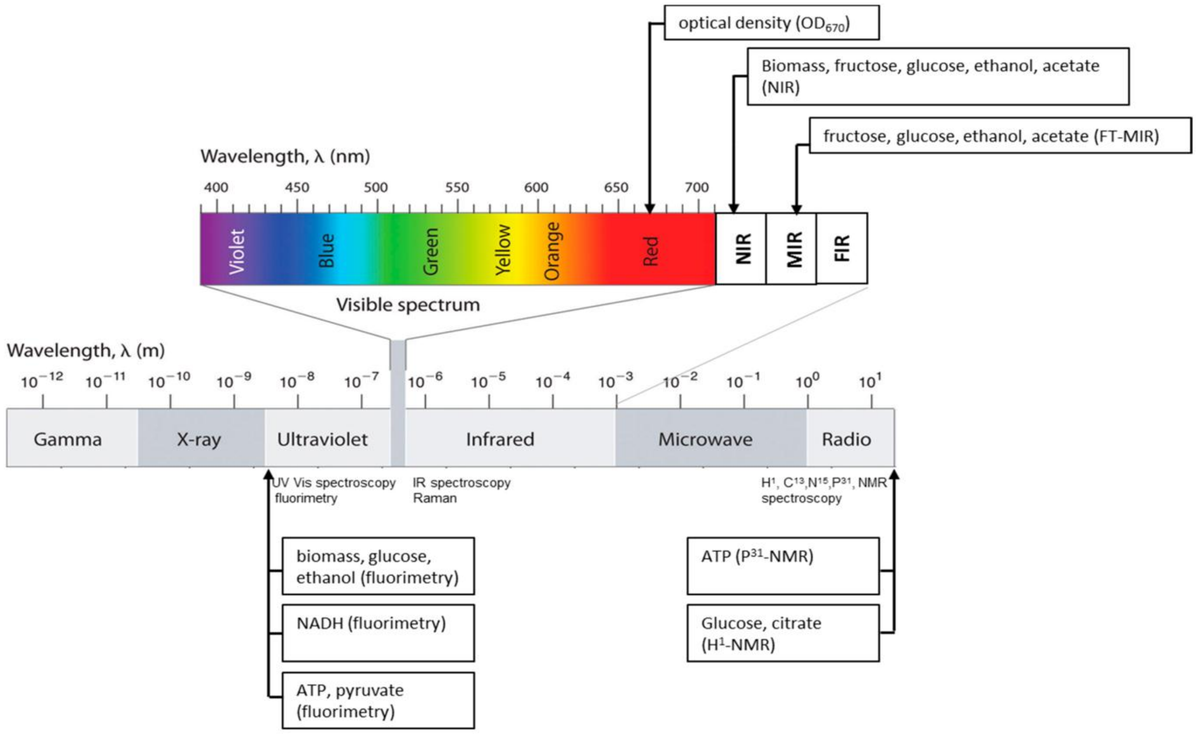

Figure 7.1: Methods of spectroscopy and principals of analytical application.

8. MEDIUM FORMULATION

Medium should offer the necessary amounts of carbon, nitrogen, micronutrients such as vitamins and trace elements (Schaechter, 2009). Variations in concentrations of specific nutrients during fermentation is important to get desired results. We should avoid few trace elements for example, little amount of iron causes lowering production of citric acid by Niger.

8.1. Complex Media

Numerous complex media consists of peptones which are hydrolysates of protein prepared by acidic incorporation of various types of raw resources and these peptones are considered as a source of nitrogen. In complex media, plant and meat extracts are utilized as a source of ingredients and consist of mixtures of carbohydrates, trace elements, amino acids, and minerals. A main constituent of complex media is yeast extracts which are synthesized from brewer's or baker's yeast by autolysis (Zhang *et al.*, 2003).

8.2. Chemically structured media

These media are used to ensure reproducible conditions of culture and learning specific bioprocess factors along with their properties. These media comprises of pure chemicals with all the basic requirements together with trace elements like ammonia, glucose and minerals such as Mg, Cl, K, and PO_4SO_4. But defined media becomes expensive if its requirements includes amino acids or other specific growth factors (Zhang *et al.*, 1999). Formulation of medium is an vital phase in pilot-scale expansion, laboratory experiments and developmental processes. Few are some measures important to consider while manipulating a medium for the purpose of huge range of production.

- It should produce maximum product.
- It should give minimum yield of undesired product.
- It should be cheap.
- It should cause minimal problems in aeration, medium formation, sterilization, agitation, extraction, purification and waste treatment.
- It should produce maximum concentration of biomass and must be available throughout the year.
- Media must satisfy all nutritional requirements of the organism and fulfil the objectives of the process(Rodgers, 1986).

9. COMPONENTS OF MEDIA

Fermentation medium consists of macronutrients, micronutrients, trace elements, dissolved oxygen, vitamins, enzymes, other dissolved gases, and inhibitors. The components of the medium should accomplish the elemental necessities for metabolite construction and biomass production with sufficient provision of energy for biosynthesis (Springham & Moses, 1999).

Carbon + Nitrogen + Oxygen + Other requirements -------› Biomass + Product + Carbon dioxide + Water + Heat

9.1 Water

Chief constituent of every fermentation medium is water and it is required in rinsing, cooling, and heating. It is significant to consider the dissolved salts, contamination, effluents, and pH, while evaluating the water supply. Water's mineral contents play an important function in brewing and are critical in squashing. Mineral contents of water historically influence the types of beer produced and the positioning of breweries (Hough, Briggs, and Stevens, 1971).

9.2. Energy Sources

Light or medium components of oxidation are main source of energy which is required for growth. As industrial microbes are chemoorganotrophs, so their source of energy is carbon source in form of lipids, proteins, and carbohydrates. While, in some cases, methanol or hydrocarbons may be used by some microorganisms as a source of energy or carbon (Bauchop and Elsden, 1960).

9.3Carbon Source

Carbon is considered as a main product of a fermentation process. If 60-70% of production cost is raw materials during single-cell protein or ethanol production, then the product's selling price will be indicated by expense of the carbon supply (Whitaker, 1973 and Moo-Young, 1977).

9.3.1. Examples of Carbon Sources

I. Carbohydrates

Starch obtained from cereals, potatoes, and maize, is easily available as a source of carbohydrates and are extensively used in fermentation of alcohol. Grains (maize etc) are used in the form of powder and also as a source of carbohydrates (Atkinson and Mavituna, 1991). Cheapest source of carbohydrates is molasses, and used in organic acid, amino acid, single-cell protein, and alcohol fermentations (Bawa*et al.*, 2010).

II. Fats and Oils

Oils were firstly used as antifoaming agents in antibiotic processes (Solomons, 1969). Oils provide maximum energy per weight than sugars. Oils posses anti-foaming qualities but are used as additives. These may also be used for their high content of the fatty acids. (Boekeloo, Bader, Graham, and Cagle, 1984).

9.4 Nitrogen Sources

Industrially used microorganisms have ability to use organic as well as inorganic means of nitrogen. Inorganic source of nitrogen is supplied as ammonium salts, ammonia gas and nitrates (Hutner, 1972). Inorganic substrates which can be used as a source of nitrogen includes urea, ammonium salts, and ammonia. Ammonia is used to control pH during fermentation process.

9.5 Minerals

Essential minerals which are used in all media formulation include potassium, sulphur, chlorine, phosphorous, magnesium, and calcium (Dahod*et al.*, 2010). We require a minute amounts other minerals such as cobalt, manganese, zinc, iron, copper and molybdenum and they exist as impurities. The specific concentration of these all elements depends on the micro-organism.

9.6 Chelators

Metal precipitation is avoided by addition of chelating agents. In large scale fermentation chelating agents are not necessary. Some other ingredients (yeast extract) will play role of formation of metal ion complexes. As EDTA is capable of forming bonds with magnesium and calcium ions thus they are widely used in soaps and detergents. (Hughes & Poole, 1991).

9.7 Growth Factors

Few of the microbes cannot produce complete complement of components of the cell and consequently requisite some of the preformed components known as growth factors. Growth factors includes amino acids, vitamins, sterols and fatty acids. Some natural sources such as nitrogen and carbon are used in growth medium formulations having required growth factors (Atkinson &Mavituna, 1991). Cautious mixing of materials can be used to eliminate the vitamin deficiency (Rhodes & Fletcher, 1966).

9.8 Buffers

pH has great influence on microbial growth. pH of the growth media can be maintained by addition of buffers that would resist pH changes. Many microorganisms have optimum pH range 7.0. Some of the examples of buffers that are commonly used include; ammonia sodium hydroxide and calcium carbonate.

10. ADDITION OF METABOLIC REGULATORS

10.1. Precursors

Many precursor molecules are used as metabolic regulators that improves product yield. Some of the chemicals are used as precursors and induced to cultivation processes that incorporate into the product formed by fermentation process. Improvement of penicillin yield is the earliest example of this phenomenon (Moyer &Coghill, 1946, 1947).

10.2. Inhibitors

A specific product or metabolic intermediate is formed by the addition of specific inhibitors to the fermentation. Earliest substrate includes glycerol, which is produced due to the microorganisms. Glycerol production is possible after modification of ethanol by removing acetaldehyde. Acetaldehyde is formed as sodium bisulfite is added to broth. As acetaldehyde is replaced by dihydroacetone phosphate as it is no longer available for the reoxidation of $NADH_2$, which is produced in glycolysis process. Product of this reaction(Glycerol-3-phosphate) is teansformed into glycerol. (Linder, Eoff and Beyer, 1919).

10.3. Inducers
Inducible enzymes are of interest in industry. Inducers are substrates which include pectin for pectinases, maltose for pullulanase, and starch or dextrin for amylases (Nagasawa, Kobayashi and Yamada, 1992). If substrate analogs are not attacked by enzymes, they may be used as inducers of enzyme. For example, fatty acids make lipase and maltodextrins will induce amylase. However, the use of inducers in commercial processes can be inhibited due to their cost (Demain, 1990).

11. REQUIREMENTS OF OXYGEN
Availability of oxygen is of huge importance in controlling the production of metabolites and growth rate of microbes. The medium can affect availability of oxygen in variety of ways as follows:

11.1. Fast Metabolism
Oxygen demand of the culture can be altered by different nutritional factors. Glucose is highly utilized by Penicillium chrysogenum as compared to lactose and sucrose, glucose has extremely precise uptake of oxygen when it is used as chief source of carbon. So, when limitation of oxygen is going on due to the rapid metabolism, at that time it may be minimized by reducing concentration of primary substrates and by the addition of these substrates into the medium as a semi-continuous or continuous feeding throughout process of fermentation (Johnson, 1946).

11.2. Rheology
The viscosity of a final medium can be affected by a single component. In a solution starch and other polysaccharides may imaprt rheological behavior to fermentation broth (Tuffile&Pinho, 1970). Degradation in polysaccharide will change their rheological properties.

11.3. Antifoaming
Antifoams act as surface active agents and lower down the transfer rate of oxygen. Large volume of foam is produced by microorganisms in the fermentation vessel(Vardar-Sukan, 1992). Reduced rate of heat transfer, reduction in working volume of fermentation vessel and deposition of cells on the upper side of fermenter is the result of foam formation. The growth of contaminating microbes occurs as air filter exits become wet. Antifoaming agents are named as surfactants too due their ability to disrupt the foam producing proteins and lower down the surface tension in the foam.

12. CONCLUSION
Various factors of fermenters should control to obtain the improved control. To obtain the desired product fermenter's main function is to grant controlled environment to grow the defined mixture of microbes or pure culture or animal cell. Material which used to construct the fermenter, should able to withstand repeated stem sterilization conditions. By modern techniques numerous parameters can be controlled. In operation the process become much computerized in order to control parameters. In bioprocess it is proved that the direct inline and online NIR spectroscopy can use to control and monitor the key biochemical parameters. A number of various fermentation strategies to be applied effectively allowed by appropriate bioreactor control system. In fermentation process the formulation of media is tiresome and never-ending process and never completed by using only one method. An elemental mass balance for ensuring sufficient components in order to get desired product is useful because too high concentration of minerals could be toxic. Corrosion of equipment may add toxicity to minerals if copper pipes are used. Although oxygen is of vital importance during medium formulation but carbon dioxide can act as inhibitor. Poor oxygen transfer during medium formulation and appearance of wall growth may lead to poor results at laboratory level. It is important to characterize a sterilized medium as organism of interest is to be grown over it. The process of formulation will stop only when no changings are seemed to improve the best medium or when resources run out. Medium formulation is both a logical science and an art form which makes it a challenge.

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