UNIVERSITI TEKNIKAL MALAYSIA MELAKA

INVESTIGATION OF EFFECTIVENESS AND CLEANLINESS OF AUTOMATED BLOW FILL SEAL PROCESS IN PHARMAUCEUTICAL INDUSTRY

Thesis submitted in accordance with the partial requirements of the
Universiti Teknikal Malaysia Melaka for the
Bachelor of Manufacturing Engineering (Robotic and Automation)

By

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UNIVERSITI TEKNIKAL MALAYSIA MELAKA

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This thesis submitted to the senate of UTeM and has been accepted as partial fulfillment of the requirements for the degree of Bachelor of Manufacturing Engineering (Robotic and Automation). The members of the supervisory committee are as follow:

…….

Supervisor

Muhammad Hafidz Fazli b Md Fauadi

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DECLARATION

I hereby, declare this thesis entitled “Investigation Of Effectiveness And Cleanliness Of Blow Fill Seal Automated Process In Pharmaceutical Industry
” is the results of my own research except as cited in the reference.

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ABSTRACT

This thesis describes the inspection process and requirement for Blow Fill Seal Automated for the Pharmaceutical Industry. This thesis describes the cleaning process which consists Clean In Place (CIP) and Sterilization In Place (SIP). The processes are Clean In Place (CIP) and Sterilization In Place (SIP). Both the cleaning process is to flush the all particle in Piping, inlet and of the machine. For the inspection process it is very critical for the pharmaceutical products this to be inspected effective and in short time before being delivered. Eye inspection by human is prone error. Therefore this thesis propose the use of machine vision to carry out the inspection tasks. The digital camera is use to capture image of product to be analyze using vision system. Automated inspection would reduce human error in executing inspection task.

DEDICATION

1 dedicate this PSM thesis to my beloved parents, Khadijah Mohd Yusoff and Yaacob Awang,my beloved young brother Muhamad Khusyairie Yaacob

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INTRODUCTION

1.0 Introduction

In the modern medical treatment, pharmaceutical solutions were the packed usually in plastic bottle. It very safe compares with former time them usually using glass as a packaging container or the empty plastic by using conventional filing process. Such process required extensive precaution for manufacturing pharmaceutical sterile product due to the difference local positioning the individual manufacturing steps, which usually in relatively high production costs.

In the current technology, the Blow Fill Seal Process (BFS) is characterized by the fact that the sterile plastic container production as well as the sterile filling and closing of the container of the performed at the same place.

This technology was developed by the Germany Company called Rommelag group since 1960s and it was already at the end of the 1960s. On 1970s when the bottle pack Blow Fill Seal (BFS) machine were applied for pharmaceutical solution. Start from early day, the solution used were mostly large volume products like post-sterilized influence. However today, the Blow Fill Seal machine can produce many type of volume, such small volume unit-dose for injection, contact lens cleaning solution, food industry, eye drop solution and other solution.

The plastic materials for manufacturing the container offer a considerable higher flexibility in the design of packaging compare to the glass packaging. When using plastic as a bottle pack material, every thing is possible to containers with

round, oval, angular cross section or bellow bottle design. The flexibility also allows mould closure design which can meet the requirement of a special product application.

For the course time, diversification of blow fill seal machine program took place in order to cover difference capacity needs. At the same time, the individual components were developed further in the order to meet the increasing requirement of the clients and authorities of the pharmaceutical sector.

The Blow Fill Seal machines normally operate after water preparation, product preparation and sterile filtration. The filling product is fed in sterile condition to the bottle pack blow fill seal machine. The plastic granulate is transported from the resin material storage to the blow fill seal machine. This processed there to plastic packaging, filled with the filling product and sealed immediately.

The essential components of the blow fill seal machines themselves are a resin-extrusion equipment and container molding system with the integrated dosing process as well as separated cabinet modules where motors, pump, ventilator, valves, and electrical installation to control the machine.

The blow fill seal process start with the forming of the plastic container. Usually they use the low, medium and high density polyethylene as well as melted, homogenized and extruded as plasticized parisons. In the blow process, the extruder parisons are molded as container in the mold. After that, they are filled immediately at the same position by dosing needles with the requested filling quantity. After completion of dosing, the filling mandrels rise vertically to their upper rest position and special closing tools weld the container hermetically, where the requested closure is welded by vacuum. After that the entire mold opens and the container is discharged the cycle begins again. The duration time to complete this process is depending on the container design and the filling quantity between 10sec until 18sec.

In the pharmaceutical industry, the Blow Fill Seal product called Intravenous Solution (IV Drips). The IV Drips function is to supply of nutrition with or without medicine direct into the blood stream of the patient. This solution must be clean from any contamination, sterile from any microorganism and non-pyrogenic substance and temper bottle. The nutrition content can be one or a mixture of carbohydrate, mineral salts, protein, fats and vitamins which are needed daily for patient's survival. The nutrition in IV drips is in the simplest form and can be absorbed by the human body direct without with other process. This solution administered intravenously cannot be removed from the patient by any mechanical or other means. In medical field, IV drips is very importance because patients need nutrition daily to survive, recover and recuperate their body. They also cannot and drink by usual means. They must used this IV Drips to produce energy to survive. The IV Drips is a vehicle for antibiotic and medicine treatment to treat the patient ailment.

The manufacturer must have relevant license certificate from National Pharmaceutical Control Biro (NPCB) from Malaysia Ministry of Health. The issued must issue by Malaysia Ministry of Health Director. Their certificate must renew for annually. Manufacturer must conform to the requirement for good practice in the manufacture and quality control as recommended by World Health Organization (WHO) and the Malaysian guideline on Good Manufacturing Practice. If any manufacturer not fulfills the Malaysian guideline or their product fails such as not sterile, pyrogenic, wrong labeling, wrong concentration and Good Manufacturing Practice by NPCB, the line process can be close.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

When we look at the plastic bottle, can we think how to produce that bottle? What the material they used? For this project we want to describe how to make it?, what the machine they used? What the automation element at the machine?. Basically, the plastic bottle produce by lower density plastic (LDPE). The main industry used this bottle is the pharmaceutical industry and food industry.

For this thesis we want to describe effectiveness and cleanliness of blow fill seal (BFS) technology in pharmaceutical industry. In pharmaceutical industry the cleanliness is very important to use it because it must sterile process to avoid any contaminations and sterile from microorganisms in the product.

The automation element also we discuss in this thesis. We can research about the automation to support the product produce. This thesis also can discuss about the down time for machining process.

2.2 Bottle Producing Process

2.2.1 Water Production

The bottle pack line process beginning with water treatment process. In this process it involves their water producing for mixing with raw material at line mixing room. The flow chart process shown in figure 2.1:-

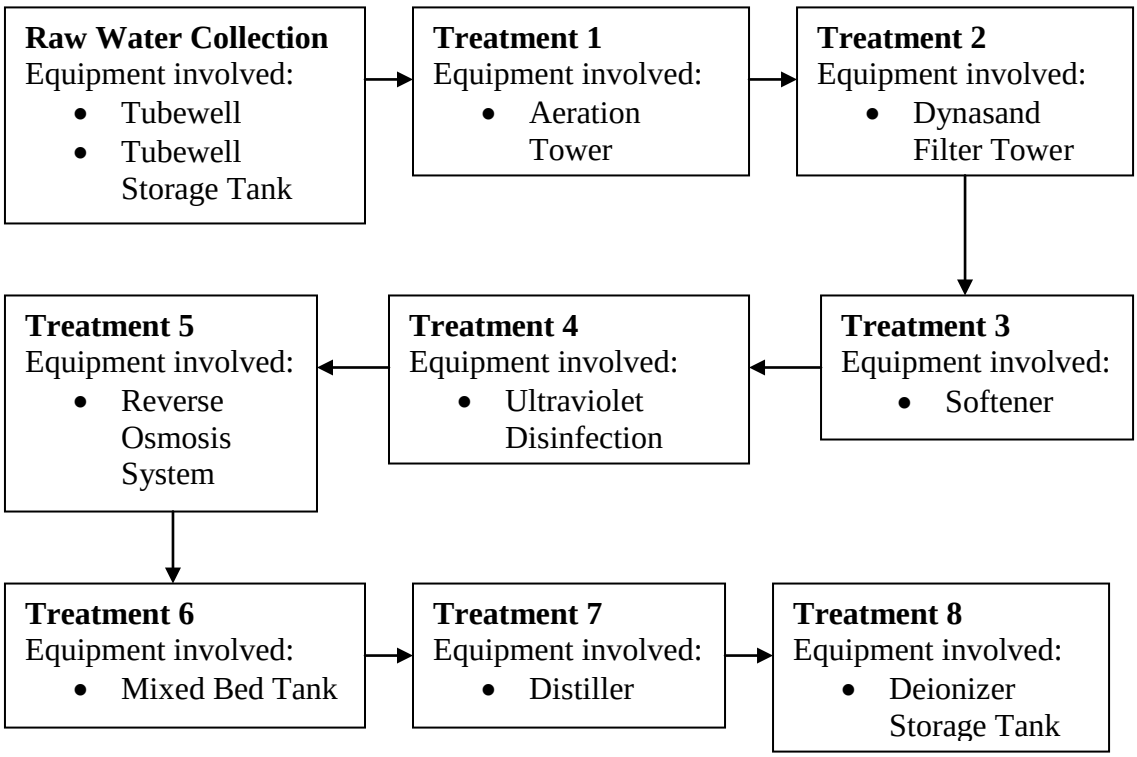


Figure 2.1: Water Treatment Flow Chart Process

2.2.1.1 Raw Water Collection

It function is sucking up water from the ground (ground water) to the Tubewell tank. It used one pump to operate this process. All water after sucking keeping in storage tank to avoid for any contaminations and chemical reaction. The tubewell capable to suck water 30m^3/hour or 720m3/day. The capacity of is 3500L/ period. Equipment involved are Tubewells and Tubewell Storage Tank.

2.2.1.2 Treatment 1

The process of this treatment is to carry the water and air combining to remove Ferum (Fe) and Mangan (Mn). In this process, Ferum (Fe^{3+}) curve to produce ferum Hidrokside [$Fe(OH)^3$] at packing tower. This process very importance because to increase the O_2 dissolved. For remove Hydrogen Sulfur (H^2S) gas and carbon Monoxide (C_2). Equipment involved is Aeration Tower. The tower capacities are:-

- Input = $30m^3$/hour
- Output = $30m^3$/hour
- Total supply = $720m^3$/day

2.2.1.3 Treatment 2

Dyanasand Filter function is to filter and remove Suspended Particle in raw water. This process is very important because to avoid their water from microorganisms contaminations. Equipment involved is Dynasand Filter .The Dynasand Filter capacities are:-

- Input = $30m_3$/hour
- Output = $27m^3$/hour
- Total supply = $648m^3$/day

2.2.1.4 Treatment 3

After raw water filter at the Dynasand Filter, the function of softener is to mixing with raw water they move to the softener to softening process with ion changing in the raw water with Natrium (Na^+) supply by softener tank. The main function of softener is to remove the bad particle from the raw water. Equipment involved is Softener. The capacities of Softener are:

- Input = $4m^3$/hour
- Output = $4m^3$/hour

2.2.1.5 Treatment 4

To make sure a microorganism free, UV Disinfection using UV radiation to activate the microorganism in the water the free the water from bad microorganism. It can supply 12 000 l/day. Equipment involved is Ultra Violet (UV) Disinfection.

2.2.1.6 Treatment 5

In this part were using membrane separation processes. This process is removing impurities with semi permeable membrane to produce Reverse Osmosis (RO) water. This water also call mineral water and properly to drink. The equipment involved is Reverse Osmosis System.

2.2.1.7 Treatment 6

In the Mixing Bed Deionizer, the processes operate to change positive ions and negative ions in the RO water with hydrogen supply by resin. The water in this system called Purified Water. Equipment involved Mixing Bed Deionizer

2.2.1.8 Treatment 7

The distiller function is to deionizer the water with heating process for deionizer water in Evaporator Column with raw steam supplying from Boiler House to produce distillate water. Equipment involved is Distiller.

2.2.1.8 Treatment 8

The function of this tank is to store the distillate water before mixing process with their raw material. The capacity of this tank is 20000L/tank in 80^0C. Equipment involved is Deionizer Storage tank.

2.2.2 Line Process

After water treatment process complete, Water in Deionizer Storage Tank must flow to the mixing tank before mix with raw material. The block diagram following figure 2.2:-

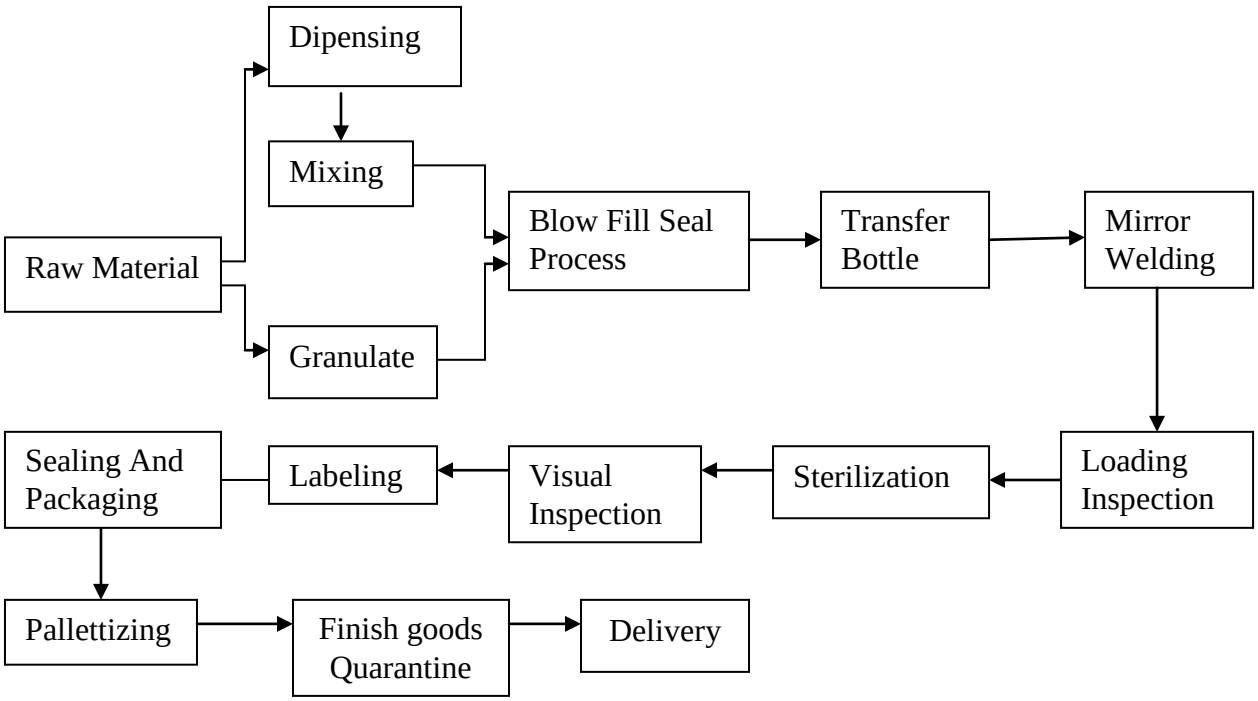


Figure 2.2: The whole process for bottle pack line

2.2.2.1 Raw Material

Raw Material can categories for the two types, first category is bottle pack material. The material using is LDPE for producing bottle. Second category is water solution raw material. The raw material will be mix with deionizer water in mixing tank. All raw materials coming from raw material warehouse.

2.2.2.2 Dispensing

Figure 2.3 shown the Dispensing Process to produce the water solution. Dispensing mean weighing process. The weighing process is to weight their raw material for the water solution. [European Pharmacopoeia Commission 2005]

Figure 2.3: Dispensing Raw Material

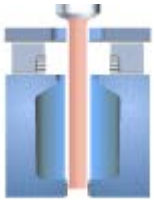
2.2.2.3 Granulate Tank

The granulate tank which is a storage for bottlepack material. This tank connected with BFS machine. When the BFS machine operate, the machine suck with in a one tube to the material hope at the machine. [European Pharmacopoeia Commission 2005]

2.2.2.4 Blow Fill Seal Process

BFS machine is the main part for the bottlepack process. It is place where the raw material for water solution and bottle producing will be combining. Table 2.1 show the processes executed by BFS machines. [Dr. R. Oschman, Dr. Willmar Schwabe Gmbh, D-Karlsruhe, Germany, Dr. O.E. Schubert, Hoffmann, CH Basel (1999)]

Table 2.1: The processes executed by BFS machines

Figure For Step	Process Description
Step 1 	**Extrusion** • The transparent polyethylene containers of medium density allow a post a post-sterilization of up to approximately 110^0C. • In the extrusion system, the resin is heated up to 170^0C-230^0C, whereas pressure of up to 350 bar exist. The container result in the sterility of the resin which is discharged as parisons. In various challenge tests in which bacterial inoculated resin contamination with the endotoxines were used, no growth of germs was discovered after evaluation and no endotoxines was proven to be in the plastic granulate are surrounded by the plastic melt and therefore cannot migrate from the packing into the product
Step 2 	**Molding** • When the parison is taken over by the mold, it is separated by an incandescent cutting knife below the extrusion die and within a second the mold with the parison move to the filling position. Sterile air with which the parison was kept under pressure escape at the upper opening of the parison and avoids the surrounding air entering into the parison and the sterility within the parison is kept. • The mold has reached the blowing/filling position, the combined blowing/filling mandrel moves from the upper rest position into the open parison. The parison is then blown up with sterile air and is pressed against the mold wall. The machine preparation, the blowing and filling mandrel are sterilized. Except during the blowing and filling. The combined blowing and filling mandrel are the upper rest position in a special sterile chamber where they are flushed.