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Analysis on Flow of Materials for Pharmaceutical Syrup Manufacturing Process

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ABSTRACT

The present study offers a thorough exposition of medicinal syrups, emphasizing their classifications, manufacturing processes, and principal uses. The study commences with an in-depth investigation of the distinct classifications of pharmaceutical syrups, emphasizing their particular use in medical interventions. The many steps involved in the formulation of these syrups as well as the quality control procedures required to guarantee product efficacy and safety are then examined in relation to the production techniques for these syrups. Developing a process flow diagram, which illustrates the steps involved in making cough syrup from the first ingredient mixing to the last packaging, is a crucial component of this task. This figure is crucial for maximizing production efficiency as it provides guidance for comprehending the complex processes associated with manufacturing. The complete cough syrup production process is calculated using the material balance method, which comes after the process flow diagram. Making sure that every input material is accounted for, cutting waste, and increasing yield all depend on this computation. Through precise evaluation of the material balance, the research offers valuable insights into the productivity of the manufacturing process and pinpoints possible

avenues for enhancement. Overall, this study provides comprehensive insights into the procedures and computations that support the creation of cough syrups and other comparable products, making it an invaluable resource for comprehending the complexities of pharmaceutical syrup production.

INTRODUCTION

Pharmaceuticals are substances that are used to identify, treat or prevent disease, as well as to repair or restore organic functioning. Syrups are concentrated aqueous formulations containing 85 percent sugar or sugar replacement, flavouring agents, and therapeutic ingredients, with or without flavouring agents. Medical syrups are almost saturated solutions of 85 percent sugar in water for medications are dissolved, according to medical nomenclature. There are various medicinal syrups like as iron syrups, cough syrup, anti-allergy syrup, calcium syrups and so on. Several of the most common medicinal syrups are Ambroxol, Amoxicillin and Bromhexine [1].

The two types of syrups are aromatic or adjuvant and medicinal syrups. Aromatic syrups are primarily employed to make salty, bitter combinations taste better [1]. Medicinal syrups have medicinal properties. There are two kinds of them - Extractive medications are used to make this product. The syrup is combined with the fluid extract of the different drugs. Chemicals medications are used to make this product: Either a simple solution or a chemical reaction too solution. The flavour of the therapeutic substances is substantially altered in this process.

In addition to the distilled water and some pharmaceutical compounds, most syrup contains the following ingredients: Sweetening Agent that adds sweetness and viscosity to a mixture ,flavourings, colorants, viscosity modifier, antimicrobial preservatives, solubilizing agents, special solvents, stabilizers, and thickeners are found in many varieties of syrups, particularly those manufactured commercially. [2]

Desai et al., (2012) explored the Halal compliance of pharmaceuticals, a significant issue given that consuming Halal food and treatments is crucial for many in the Arab community. Some companies in Muslim-majority countries still have reservations about the use of medical products, especially those labelled as life-saving drugs. This study seeks to examine the perspectives of individuals affected by

hacks on the Halal compliance of hack medicines and their views on medications containing alcohol. A survey was used to collect data. The results indicated that most patients preferred Halal medications without alcohol. The data showed that 68 percent of patients received cough medicine containing alcohol in concentrations ranging from 2.5% to 10%. [3]

Dafale et al., (2014) examined the susceptibility of pharmaceutical preparations with high water content to microbial degradation, which can compromise consumer safety. To mitigate these risks, specialized preservatives are often added to these medicinal formulations. However, despite the use of preservatives, physical changes and clinical hazards can still occur. This study conducted a microbiological challenge test to assess and compare the effectiveness of preservatives in market samples of antacids, cough syrups, and ophthalmic solutions. The standard microbiological dilution pour plate method was employed to count the surviving bacteria. The preservatives Sorbitol, Sodium Citrate, and Benzalkonium Chloride, found in antacids, cough syrups, and eye treatments, were effective against all tested microorganisms. The analysis concluded that the preservatives in all liquid medical preparations tested are effective in preventing product contamination during use and storage. [4]

Al Mamun et al., (2014) investigated the production of substandard pharmaceuticals and the use of improper practices in the manufacturing of medical products by pharmaceutical companies, which could lead to non-therapeutic effects in patients, particularly children. This study was conducted to evaluate the microbiological standards of various brands of cough syrups and multivitamins available in local pharmacies in Dhaka. The findings revealed that 91% of the multivitamins and 50% of the cough syrups met official microbiological quality standards, as there was no microbial growth or their microbial count was below the USP permissible level (102 CFU/ml). Staphylococcus aureus (75%) was the most common contaminant in cough syrups, while Escherichia coli (17%) and total coliforms (42%) were the most prevalent contaminants in multivitamin syrups. [5]

Ramdhani et al., (2019) conducted a study using gas chromatography/mass spectrometry (GC-MS) to perform a qualitative assessment of chemical compounds that may migrate from plastic bottles used for cough medicine into the syrup itself. The study examined the migration process of compounds from plastic bottle materials into the medicine syrup, which could adversely affect the safety and quality of the product. The research included purposive sampling, cough syrup extraction, sample preparation, and testing using the GC-MS method. The tests identified several chemical compounds that migrated from

the plastic packaging into the liquid syrup, including diisooctyl phthalate (DIOP), phthalic acid, 3-nitrophthalic acid, bis-(2-ethylhexyl) phthalate, and benzene dicarboxylic acid. [6]

Ramadhani et al., (2022) examined the introduction of new cough medicine products by PT XYZ at the end of 2017, which received an unexpectedly positive response from consumers. The advantages of this cough medicine include the absence of drowsiness and the inclusion of herbal ingredients like anise oil, which can alleviate stomach issues caused by cough medicine. However, due to increased market demand, the company struggled to adapt to challenges such as unstable raw material supplies for cough medicine production. To determine material requirements, the study used the economic order quantity method, the period order quantity method, and the company's method. The most effective approach for planning and scheduling inventory needs for cough medicine production, as calculated using MRP and lot-sizing techniques, was the Period Order Quantity method, which resulted in a total cost of Rp. 61,193,700. This approach reduced material control costs compared to other lot-sizing methods. [7]

The aim of this work to understand the manufacturing process of pharmaceutical syrup and to perform material balance for the pharmaceutical syrup manufacturing process.

PROCESS FLOW DIAGRAM AND DESCRIPTION FOR COUGH SYRUP PRODUCTION PROCESS

Process flow diagram:

Pure water, sugars, active ingredients (API), fragrances, flavours, and other substances are combined to make pharmaceutical syrups. The components are added to one primary blending tank using metering or dosing equipment such as flow meters, with the sequence and quantity of ingredients stated in the method. [8]

Figure 1 is showing the preparation of cough syrup in full depth, including all of the equipment involved, such as mixers and tanks. As a result, studying cough syrup manufacture becomes simpler and clearer, and this diagram can be used to follow the process description.

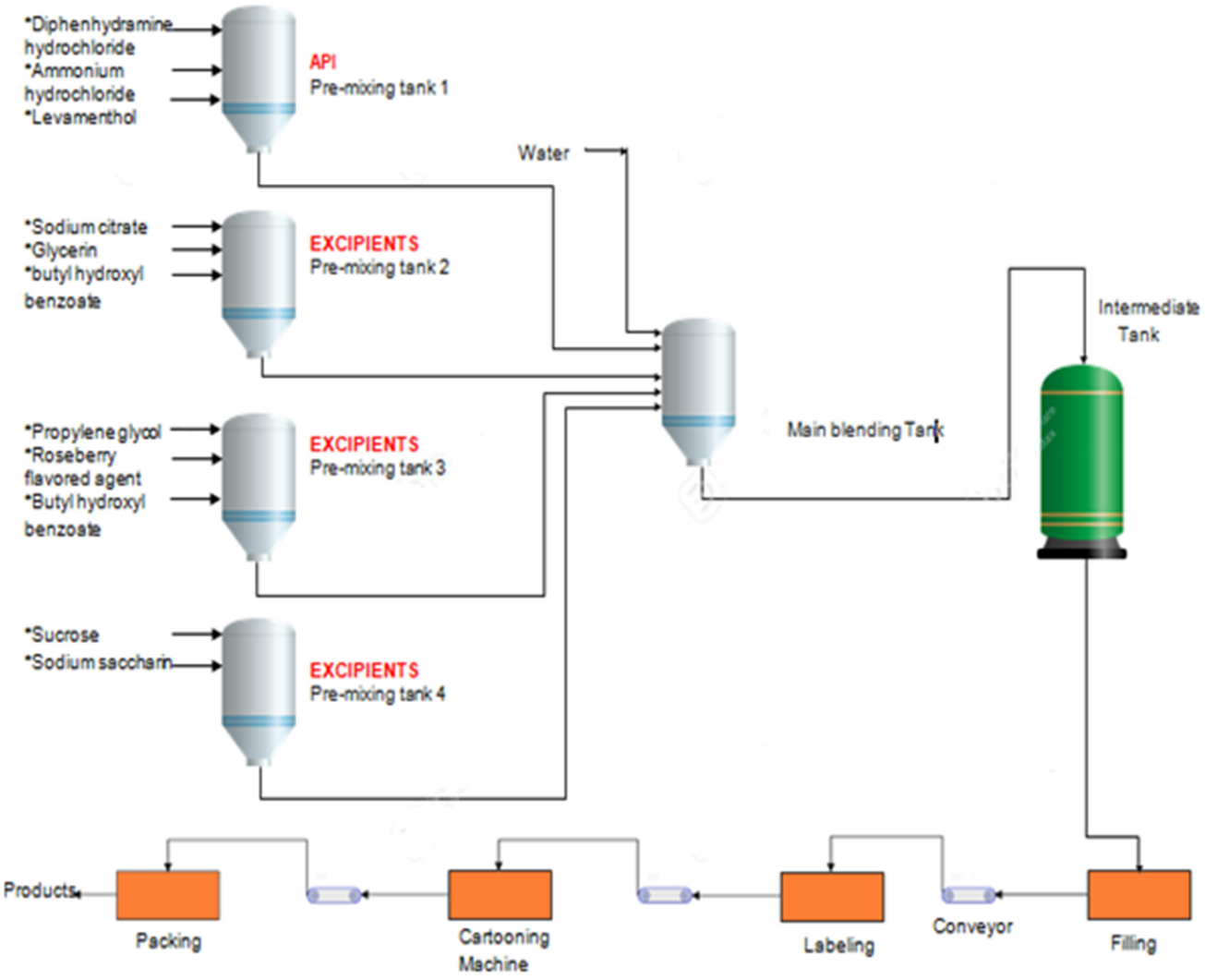

Figure 1 Process flow diagram of cough syrup production

Pure water, sugars, active ingredients (API), fragrances, flavors, and other substances are combined to make pharmaceutical syrups. The components are added to one primary blending tank using metering or dosing equipment such as flow meters, with the sequence and quantity of ingredients stated in the method. [9]. This figure is showing the preparation of cough syrup in full depth, including all of the equipment involved, such as mixers and tanks. As a result, studying cough syrup manufacture becomes simpler and clearer, and this diagram can be used to follow the process description.

API: API stands for Active Pharmaceutical Ingredient and it specifies the active ingredients in the drug. It is the main drug which treatments the disease.

Excipients: are substances formulated alongside with active pharmaceuticals ingredients. The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g.

stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient.

Intermediate*:* is where the ready product is store.

Filling: bottles are sent through the conveyor to filling machines where the bottles are filled with liquid through a nozzle. [10]

Labelling: *The Food and Drug Administration* need the following information to appear in the medicines labelling: [11]

- Dosage Form and Strength.
- Formulation/Composition
- Product Name
- Pharmacologic Category.
- Indication(s)
- Dosage and Mode of Administration.

Cartooning machine: Cartons containing the pharmaceuticals syrup bottles are closed tightly with the machines to avoided any breaking though packing.

Process description:

Cough syrup production is the process at which cough syrup is produced without a chemical reaction. The first step involved in the production process is the mixing of various ingredients:

•***API:*** Pre-mixing tank 1

Diphenhydramine hydrochloride

Ammonium hydrochloride

Levamenthol

•***Excipients:*** Pre-mixing tank 2

Sodium citrate

Glycerin

Water

•***Excipients:*** Pre-mixing tank 3

Propylene glycol

Roseberry flavored agent

Butyl hydroxyl benzoate

•***Excipients*****:** Pre-mixing tank 4

Sucrose

Sodium saccharin

The four tanks as we can see from the above information it is containing different ingredients for different purposes. The first tank API is having the main drugs for curing the disease, the second third and fourth excipients premixing tanks contain different ingredients for a specific purpose. After that, a total of four tanks are sent into the main blending tanks and added amount of water. The materials are mixed and stirred for about (8hr) hours. The next step is the mixed syrup is sent to intermediate tank for storage aim, here the syrup is ready for filling in bottles then labeling, cartooning machines and packing through conveyor finally the cough syrup products are ready to distribute it to pharmacies.

ANALYSIS ON FLOW OF MATERIALS FOR PHARMACEUTICAL SYRUP MANUFACTURING PROCESS

A quantitative depiction of all substances entering, exiting, and accumulating within a system is known as mass balance (material balance). Substance equilibrium is driven by conservation laws. The control volume selected determines the fundamental material balance expression [12].

Material balance is having two procedures - steady-state and unsteady-state. The most important condition between them is the steady state system is having a constant temperature, while unsteady-state the temperature is changing with time. There are two types of material balance: (i) Steady state: Those operations in which the conditions of the system like temperature, pressure, volume is not varying with time. All continues processes are steady state operations. (ii) Unsteady state: Those operations (batch) in which the conditions of the system like temperature, pressure, volume is varying with time. All batch processes are unsteady state operations.

According to the law of conversion of mass, we have general material balance equation:

Input +generation-consumption- output = Accumulation

where:

Input= (feed)

Output= (products)

Accumulation= (the changing of the amount of the system)

Generation= (reactants disappears in chemical reaction)

Consumption= (products formed in chemical reaction)

Material balance for pharmaceuticals syrup manufacture process:

Basis: 75L of cough syrup [batch process] as shown in Table 1.

100ml per bottle

Number of bottles required [75000/100] =750 bottle

Density of butyl hydroxyl benzoate=1.05g/ml

$$\text{Density} = \frac{\text{Mass of}}{\text{Volume of}}$$

$$\text{Volume of syrup} = \frac{\text{Mass of syrup}}{\text{Density of butyl hydroxyl benzoate}}$$

$$= \frac{52044}{05.1}$$

=49565.71ml of syrup and the remaining is water

=75000 ml - 49565.71 ml

Volume of water =25434.28ml

Mass of component required for 75000ml of syrup:

API Pre-mixing tank 1

1-diphenhydramine hydrochloride

$$5\ ml \rightarrow 14\ mg$$

$$75000\ ml \rightarrow x$$

$$x = 210000\ mg$$

$$x = 210\ g$$

2-Ammonium hydrochloride

$$5\ ml \rightarrow 135\ mg$$

$$75000\ ml \rightarrow x$$

$$x = 202500\ mg$$

$$x = 202.5\ g$$

3-Levomethol

$$5\ ml \rightarrow 1.1\ mg$$
$$75000\ ml \rightarrow x$$
$$x = 16500\ mg$$
$$x = 16.5\ g$$

Excipients Pre-mixing tank 2

Sodium citrate

$$5\ ml \rightarrow 3.5\ mg$$
$$75000\ ml \rightarrow x$$
$$x = 52500\ mg$$
$$x = 52.5\ g$$

Glycerin

$$5\ ml \rightarrow 125\ mg$$
$$75000\ ml \rightarrow x$$
$$x = 1875000\ mg$$
$$x = 1875\ g$$

Water

$$5\ ml \rightarrow 1000\ mg$$
$$75000\ ml \rightarrow x$$
$$x = 1500\ 000\ mg$$
$$x = 1500\ g$$

Excipients Pre-mixing tank 3

Propylene glycol

$$5\ ml \rightarrow 500\ mg$$
$$75000\ ml \rightarrow x$$
$$x = 7500\ 000\ mg$$
$$x = 7500\ g$$

Roseberry flavored agent

$$5\ ml \rightarrow 12.5\ mg$$
$$75000\ ml \rightarrow x$$

$$x = 187500\ mg$$

$$x = 187.5\ g$$

Butyl hydroxyl benzoate

$$5\ ml \rightarrow 7.5\ mg$$

$$75000\ ml \rightarrow x$$

$$x = 112500\ mg$$

$$x = 112.5\ g$$

Excipients Pre-mixing tank 4

Sucrose

$$5\ ml \rightarrow 1660\ mg$$

$$75000\ ml \rightarrow x$$

$$x = 24\ 900\ 000\ mg$$

$$x = 24900\ g$$

Sodium saccharin

$$5\ ml \rightarrow 11\ mg$$

$$75000\ ml \rightarrow x$$

$$x = 165000\ mg$$

$$x = 165\ g$$

Table 1 Mass of ingredients in 75L of syrup

Tank Name	Mass of component present in 5ml of syrup	Mass of component required for 75000ml of syrup
API Pre-mixing tank 1	-14mg of Diphenhydramine hydrochloride -135mg of Ammonium hydrochloride -1.1mg of Levamenthol	-210g of Diphenhydramine hydrochloride -202.5g of Ammonium hydrochloride -16.5g of Levamenthol
Excipients Pre-mixing tank 2	-3.5mg of Sodium citrate -125mg of Glycerin -1000mg of water	-52.5g of Sodium citrate -1875g of Glycerin -1500g of water

Excipients Pre-mixing tank 3	- 500mg of Propylene glycol - 12.5mg of Roseberry flavored agent -7.5mg of Butyl hydroxyl benzoate	- 7500g of Propylene glycol - 187.5g of Roseberry flavored agent -112.5g of Butyl hydroxyl benzoate
Excipients Pre-mixing tank 4	-1660mg of Sucrose -11mg Sodium saccharin	-24900g of Sucrose -165g Sodium saccharin
	Total	52044g

CONCLUSION

The process flow diagram and description of manufacture cough syrup was studied in this work. The material balance for the blending tank has been determined. It was designed to have two batch processes per day (16h). This study looked closely at the cough syrup manufacturing process, focusing in particular on creating a process flow diagram and providing a complete explanation of each step of the production process. The process flow diagram offered a concise, pictorial depiction of the sequential actions necessary to make cough syrup, from the first active ingredient and excipient production and mixing to the last product packing. This diagram was a useful tool for determining possible areas for optimization in addition to aiding in the comprehension of the intricacy of the production process. In addition, a thorough material balancing for the whole cough syrup production process was carried out. In order to ensure that all input materials were used effectively and that there was as little waste produced during manufacturing, the material balance was essential. This study was able to shed light on the effectiveness of the manufacturing process by precisely estimating the amounts of raw materials, intermediates, and finished products. The results of this study highlight how important material balance computations and process flow analysis are to the pharmaceutical sector. The study's methodology can also be used for other pharmaceutical items, which will help to enhance production procedures generally and guarantee that patients consistently receive safe and efficient treatments.

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