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Materials Saving and Waste Minimization in Indian Pharmaceutical Industries

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Abstract

This paper presents different techniques suggested for cleaner production in three pharmaceutical plants. The main focus of this paper is towards evaluation of source reduction and waste minimization. This paper also finds the various other possibilities to reuse the waste produced in the above-mentioned unit. All input materials, starting from raw materials, potable water, purified water, and water for injection and polyethylene granules are so quantified as to fix limit for all raw materials as 2.5 EU/ gm determined through Bacterial Endotoxin Test (BET). An extensive literature review presents different approaches made by leading pharmaceutical industries to save materials and to minimize wastes generated. Attempts to replace organic solvents by aqueous media have been proved to be successful in all respects. It is successfully experimented that in large volume parenterals industry a measure of endotoxin test at raw material stage, intermediate stage and finished stage could save a huge loss of product rejection resulting in saving of materials and waste minimization. Existing formulation of raw materials should be audited time to time to find the scope for reduction of excipients for resource reduction and waste minimization..

Keywords: Techniques, cleaner production, pharmaceutical plants, source reduction, waste minimization

Introduction

Formulation industries are equipped with stringent infrastructure, machineries, utilities, resource, and manpower but completely dependent on input materials or raw materials for their formulation, generally used either as active or as inactive ingredients. With respect to life saving drugs, parenteral preparations are very crucial both for small volume parenterals and large volume parenterals. Among these, large volume parenterals are most sensitive because a large volume of 500 to 540 ml solution is going inside the blood through intravenous route. Endotoxin are toxic lipopolysaccharide material, originating from dead cell wall of Gram-negative pathogenic and non-pathogenic microorganisms contaminating on and often large volume parenterals during manufacturing as it is a heat stable organic material. The dead cell bacteria may come from any area, starting from potable water, equipment, purified water and water for injection and raw materials. Potable water, equipment, purified water, water for injection are likely to be controlled but it is very difficult to control the raw materials and hence basic drug industries are rarely producing parenteral grade endotoxin free materials. All materials need to undergo Bacterial Endotoxin Test (BET) to ensure compliance with EU limit prescribed to appraise their usage suitability. Reduction in input supplies and change in input materials and processes will invariably lead to manufacturing of above desired products. Hence extensive study is required to see whether there is any scope of saving some input materials to accomplish this objective. Saving of input materials may result in waste minimization in the existing pharmaceutical industries as well. The objective of the present paper is to study on saving of input materials and on waste minimization in a drug formulation plant producing tablets, capsules, oral liquids and injectables.

Many leading pharmaceutical industries are attempting to change their manufacturing processes or input materials to find out ways of saving and waste minimization.

Gujarat Themis Biosyn Limited producing Anti-Tuberculosis drug, reduce its overall environmental load by 33%, reduce fugitive loss of Chloroform from 936 TPA to 475 TPA, reduce fugitive loss of a chlorinated Solvent MDC by 26 TPA, and reduce loss of Isopropyl Alcohol by 25 TPA.

Themis Medicare Limited producing Anti-Tuberculosis drug Ethambutol hydrochloride reduced its solvent consumption from 168 kg per batch to 150 kg per batch.

Mangalam Drugs and Organics Ltd., unit-I, achieved a reduction in loss of benzene by 1500 litres / month, reduction in the consumption of caustic soda by 6000 kg/month and a reduction in wastewater discharge by over 100 cu.m./month.

Mangalam Drugs and Organics Ltd., unit-II, increased the yield of metanitroaniline by 9 kg / batch, achieved a reduction in water consumption by 150 cu.m./ month, reduction in TSS load from 2473 ppm to 593 ppm and a reduction in wastewater discharge by over 150 cu.m./month[1].

Table-1
Waste Minimization in Virchow Laboratories, a Bulk Drug Plant

Sr. No.	Recovery of Materials and Waste Minimisation	Savings (Rupees/ annum)	Payback
1	Recovery of Ammonia and Methanol from effluents and vents during Amidation stage	Rs.12,60,000	2 years
2	Recovery of Acetone and Methanol by providing vent condensers to storage tanks	Rs.54,000	1 year
3	Replacing glands of all process pumps with seals leading to reduction in emissions/leakage	Rs.1,44,000	1.2 years
4	Recovery of Sodium Sulphate and Ammonium Sulphate from the second stage of production process to reduce the TDS in effluents	Nil	–
5	Recovery of Sodium Acetate and Sodium Sulphate as useful by products from mother liquor of fifth stage	Rs.63,00,000	2 years

The production of Oxytetracycline was investigated by the fermentation of household kitchen waste cocoyam peels, an agricultural byproduct waste[2].

Virchow Laboratories, a bulk drug Sulphamethoxazole manufacturing unit achieved waste minimization in a remarkable manner as shown in table 1[3].

In Lupine Limited, Ankleswar, steam condensate recovery is achieved up to 75%[4].

GSK aims to produce tablets without excipients and by cutting the traditional route of making a tablet saves raw materials (inactive ingredients) at source, thereby eliminating waste generation at source and saving money[5].

Pharma companies are scouting for customers to sell the waste products including solvents and pigments, generated in their companies. These products are used as raw materials in other industries, which buy at reduced costs, sometimes as much as 50 %.

Dr.Reddy's Laboratories has six active pharmaceutical units in Andhra Pradesh. The waste streams from API units mostly contain potassium sulphate, caustic lye, potassium chloride and sodium sulphate salts. The streams are segregated and distilled to separate the salts in them. These are then sold to authorized agencies to be used as raw materials in fertilizer, paper and soap industries. DRL is currently selling paper and plastic waste and industrial packaging material to ITC for onward recycling. The green effort of DRL earns 40 lakh as revenues per year[6].

Paracetamol is produced from paranitrophenol using iron-acid for hydrogenation and as a result huge amount of hazardous waste is generated with high organic impurities, which is difficult to dispose. A catalytic hydrogenation is employed as cleaner options so that the effluent /emissions/ hazardous waste generation can be minimized. Such an attempt with respect to H-acid and vinyl sulphone provided us insight for production and waste minimization. Steps suggested are i. replacement of iron-acid reduction by catalytic hydrogenation to eliminate generation of iron-sludge. ii. stepwise catalytic hydrogenation and acetylation to eliminate generation of iron-sludge. iii. addition of borate in hydrolysis step to reduce undesirable products to reduce load on effluent treatment and to improve purity of product, iv. use of activated carbon pre-treated with sulphite solution. The objective of the above steps comprises the development of cleaner production process for manufacturing of paracetamol, improvement in the efficiency of production, cost reduction and waste minimization[7].

Virchow laboratories sell sodium sulphate, gypsum, solvents and fly-ash generated at the company's Hyderabad and Visakhapatnam bulk drug manufacturing units. White sodium sulphate is the raw material for the soap and detergent industry, gypsum finds use in the cement industry and solvents are the key raw materials for the paint industry. The fly-ash is used for making bricks. The industries produce antibacterial drug sulphamethoxazole, 6000 tonne per annum, utilizing the steam generated by 1.5Mw captive power plant at Hyderabad and 3Mw unit at Visakhapatnam, saving huge power. Jupiter Bioscience Limited, Hyderabad manufacturer and exporter of bulk drugs and intermediate, sell the recovered solvent to small scale paint industries through third party traders. The solvents are also used as fuel in furnaces[8].

Pfizer's Green chemistry implemented enzymatic synthesis of pregabalin to save more than 2, 00,000 metric tons of chemical waste between 2007 and 2020. They designed to save 25,000 tons of waste per year in the manufacture of Vfend an antifungal through a green chemistry modification in manufacturing[9].

The manufacturing process of diabetic drug sitagliptin previously done by a hazardous rhodium based hydrogenation catalyst is changed by an ecofriendly catalyst a transaminase enzymes[10].

In production of progabalin, neuroactive agent, API synthesis, 86kg waste/kg of product is changed by Pfizer using biocatalyst in green chemistry project, performing an enzymatic screen for a problematic cyanodiester, a lipase derived from Thermomyces lanuginosus, resulting marked reduction of useless byproduct[11].

In drug synthesis statin, rouvastatin wasteful chemical reaction is replaced by enzymatic step using deoxyribose phosphate aldolase (DERA)[12].

Alternate processes are based on E-factor (kg by product per kg product) and use of high-atom utilization, low-salt catalytic processes. Table 2 shows E factor[13].

Table 2
The E factor

Industry segment	Product tonnage	kg byproduct per kg product
Bulk chemicals	10^4 - 10^6	<1 - 5
Fine chemicals	10^2 - 10^4	5 – 50
pharmaceuticals	10 - 10^3	25- > 100

Material and Methods

The present study was conducted in three pharmaceutical formulation industries, one producing tablets, second one producing oral liquid and third one manufacturing injectables in the form of generic and patented finished drugs. The selected drug plants were studied in three subsequent years (2010, 2011 and 2012). In the first year, the in-plant processes were studied extensively. Thorough study of the in-plant processes revealed that there was enough scope of process changes to achieve waste minimization, material saving and accordingly some suggestions were put forward to the management of the industry by the present investigator. The suggestions were followed entirely. Then in next two years, similar observations were made regarding improvements in material savings and waste minimization. Some of the important recommendations were the following.

Tablet film coating are done for antibiotic Ofloxacin tablet, antitrichomonial Metronidazole tablet and antiprotozoal Tinidazole tablet by using organic solvent isopropyl alcohol and acetone. Investigator stops this operation by substituting coating operation by aqueous base coating solution. This is implemented and results of resource savings are shown in table 3 and table 4.

A suspension of paracetamol is a regular product. Reduction of inactive raw materials in paracetamol suspension formulation is suggested, implemented and final achievement is shown in table 5.

Main test of injectables are sterility test and endotoxin test. Dextrose injections are tested for bacterial endotoxin by Limulus Amebocyte Lysate (LAL) reagent purchased from Charls Liver Endosafe. As per Indian Pharmacopea, 2010 limit of BET is 0.5EU/ml. Fate of a 3500 litre batch comprising 7000 x 500 ml bottles depends on this test. Batch after batch are rejected as the limit of 0.5EU/ml is crossed. Then present investigator suggested conducting Bacterial Endotoxin Test (BET) for all input materials, starting from Raw materials, Potable water, Purified water, Water for injection and Polyethynene granules. For large volume parenterals (LVP) production, raw materials used are dextrose anhydrous, sodium chloride, sodium lactate, calcium chloride, potassium chloride, sodium acetate, sodium metabisulphate, sodium sulphite, dibasic potassium phosphate, magnesium chloride, ammonium chloride, metronidazole, ciprofloxacine monolactate, pefloxacin, mannitol, fructose, glycerin, tinidazole and the water for injection. Among these raw materials, pharmacopeia specifies only the limit of bacterial endotoxin for water for injection. Indian Pharmacopea, 2010 specifies the limit of 0.5 EU/ml bacterial endotoxin as for 5% dextrose injection, 10% dextrose injection 0.9% sodium chloride injection, 5% dextrose and 0.9% sodium chloride injection and for other injections.

Endotoxins are lipopolysaccharide complex part of outer membrane of the cell wall of Gram-negative bacteria, of *Escherichia coli, Salmonella, Shigella, Pseudomonas, Neisseria, Hemophillus influenzae, Bordetella pertussis and Vibrio cholera.*

Now in the said pharmaceutical factory, LVP finished products failed consecutively and water for injection also failed due to non-compliance of EU limit. Now present investigator developed an innovative idea to fix limit for all raw materials as 2.5 EU/ gm. i. 5% Dextrose = 5gm/100ml = 5000 mg/100ml.= 50 mg/1ml, Now, 1gm/2.5EU = 1000mg/2.5EU = 50 mg/0.125 EU, so endotoxin coming from dextrose raw material = 0.125 EU/ ml. ii. 0.9% sodium chloride = 0.9gm/100ml = 900mg/100ml = 9mg/ml., Now, 1gm/2.5EU = 1000mg/2.5EU = 9 mg/0.0225 EU, so endotoxin coming from sodium chloride raw material = 0.0225 EU/ ml. iii. Water for injection limit specifies in Indian Pharmacopea, 2010 is 0.25 EU/ml. iv. Polyethylene granules purchased as BASF medical grade contribute 0.0225 EU/m to the product. v. So, in a 5% dextrose Injection contribution of all ingredients towards endotoxin level is 0.125 + 0.25 + 0.0225 = 0.3975 EU/ml

After following this system of determination of individual EU level of each input material and knowing the total EU load before giving the batch charge, presently products are complying with the prescribed specifications.

A tablet formulation had been followed with a fixed formula for long period. As per present investigator's suggestion the quantities of filler and binder were reduced as shown in table 6, table 7 and table 8.

Results and Discussion

All drugs have their own characteristics, e.g. some drugs are bitter in taste, some have unpleasant odour, some are sensitive to light or oxides, and some are hygroscopic in nature. Coating is a barrier applied to oral medication like Metronidazole, Ofloxacin, Tinidazole tablets to prevent its release at acidic juice in stomach at pH 2-3, instead it will release in alkaline pH 7-9 at intestine[14]. Change of organic based coating solution to

aqueous based coating solution does not alter the situation, values of test parameters remain within specification (table 8) and effectiveness is ensured. On the other hand, hazardous chemicals, like organic solvents and raw materials are saved, as shown in table 3 and table 4.

Paracetamol suspensions are made for pediatric use. Sodium carboxy methyl cellulose, suspending agent and thickener, refined sugar or sucrose, sweetener and extra cleaning water are reduced in quantities as shown in table 5. After the change of formulation of paracetamol suspension, parameter like assay remains within specification as shown in table 9.
Paracetamol tablets are used for ailment of fever. Average weights of Starch filler, Guar gum and tragacanth binder are reduced as shown in table 6. Materials are saved and waste generation is minimized as shown in table 7.

After the change of formulation of paracetamol tablet, bioavailability of the products remains same. Dissolution test and assay test results show compliance with specifications as shown in table 10. The above process developments also reduce the wastewater load as shown in table 11.

In the above formulation, out of the above six ingredients, five are inactive ingredients and only one that is Paracetamol I.P. is active ingredient. So no reduction can be done in case of active ingredient, but attempts have been made to reduce bulk filler starch I.P. in the following altered / modified formulation.

Product name: Paracetamol tablets I.P. 500 mg, batch size: 2, 00,000 tablets, weight of dried granules: 115.56 kg average weight of each tablet: (115.56 x 1000 x 1000) mg / 2, 00,000 tablets = 577.80 mg

Table-3
Reduction in the Quantities of Organic Solvents due to Change from Organic Solvent based Coating to Aqueous Solvent based Coating

Raw material added per Batch for Organic Solvent based Coating	Category	Quatity per Batch for Organic solvent based Coating	Raw material added per Batch for aqueous coating	Category	Quantity
Cellulose acetate pthalate	Coater	1.00 kg	Insta Aqua	Coater	6.00 kg
Ethyl cellulose	Coater	0.3 kg	Water	Solvent	20 litre
Propylene glycol	Solvent	300 litres	-	-	-
Sorbitan monooleate	Emulsifier	0.18 litres	-	-	-

Metronidazole tablet, Batch size: 3, 00,000 tablets.

Table-4
Results Achieved after Change from Organic Solvent based Coating to Aqueous Solvent based Coating

Coating system	Solvent used	Safety issues	Environment	Savings	Raw material savings
Organic solvent Coating	Alcohol, Methylene Chloride, Acetone	safety issue are taken for Operators	Can not be released to atmosphere	None	None, five raw materials are used
Aqueous solvent Coating	Water	No safety issue	Can be released to atmosphere	12,000 litres of organic solvent per annum	80% saved as only one RM used

Table-5
Reduction of Inactive Raw Materials in Paracetamol Suspension Formulation

Raw material	Category	Quatity per Batch in previous formulation	Quatity per Batch in new formulation	Raw material savings per Batch	Raw material savings per annum
Sodium carboxy methyl cellulose	Suspending agent and Thickener	1.75 kg	1.00 kg	0.75 kg	600 kg
Refined Sugar Or Sucrose	Sweetener	120 kg	90 kg	30 kg	18,000 kg
Water	Cleaning	300 litres	200 litres	100 litres	60,000 litres
Electricity	Power	4.25 kWh	3.00 kWh	1.25 kWh	900 kWh

Waste Reduction and Minimization at Source in Manufacturing of Tablets, Product name: Paracetamol tablets I.P. 500 mg, Batch size: 2, 00,000 tablets, Charged quantity: 2, 00,000 tablets

In the previous formulation 20 kg starch I.P. per batch was given, so in three batch per day = 3 x 20 kg = 60 kg starch I.P was given, 25 days x 60 kg = 1500 kg was given per month, So annually 1500 kg x 12 = 18,000 kg or 18.0 tonne are used.

In the modified formulation the reduction is 4 kg starch I.P. per batch, so in three batch per day 3 x 4 = 12 kg starch I.P are saved, and 25 days x 12 kg = 300 kg/ month are saved. So annually 300 kg x 12 = 3600 kg is saved.

So annually net savings are 3600 kg /18,000 kg x 100 = 20 %, guar gum saved per annum = 0.2 kg x 3 batch/day x 25 days x 12 months = 180 kg, traganth saved per annum = 0.1 kg x 3 batch/day x 25 days x 12 months = 90 kg

Table-6
Quantity of Ingredients Used before and after Modifications

Name of active pharmaceutical ingredient and inactive ingredients	Quantity required before modifications	Quantity required after modifications	Quantity of savings per batch
Paracetamol I.P.	100 kg	100 kg	
Starch I.P.	20 kg	16 kg	4 kg
Guar gum I.P.	1 kg	0.8 kg	0.2 kg
Tragacanth I.P.	0.5 kg	0.4 kg	0.1 kg
Magnesium Stearate I.P.	1 kg	1 kg	
Talc I.P.	0.6 kg	0.6 kg	

Weight of dried granules: 120.37 kg, Average weight of each tablet: (120.37 x 1000 x 1000) mg / 2, 00,000 tablets, = 601.85 mg

Table-7
Net Savings of Raw Materials after Modification

Name of raw materials	Quantity added before modification kg/ annum	Quantity added after modification kg/annum	Quantity saved due to modification kg / annum
Starch	18,000 kg	16,400 kg	3600 kg
Guar gum	900 kg	720 kg	180 kg
Tragacanth	450 kg	360 kg	90 kg

Table-8
Test report of Metronidazole 200 MG Tablet I.P. after Change of Coating

Metronidazole tablet 200 mg	Specifications[15]	Organic solvent based coating	Aqueous solvent based coating
Assay	95% to 105% of the stated amount of metronidazole, $C_6H_9N_3O_3$	199 mg per average weight of tablet	198 mg per average weight of tablet
Dissolution	Not less than 85% of the stated amount of metronidazole, $C_6H_9N_3O_3$	90%	91%

Table-9
Test Report of Paracetamol Oral Suspension I.P. before and after Modifications

Paracetamol suspension 125 mg per 5 ml	Specification[16]	Before modification	After modification
Assay	Not less than 90% and not more than 110% of the stated amount of paracetamol, $C_8H_9NO_2$	124mg per 5 ml of suspension	125mg per 5 ml of suspension

Table-10
Test report of Paracetamol Tablet 500mg I.P. before and after Modifications

Paracetamol tablet 500 mg	Specifications[17]	Before modification	After modification
Assay	95% to 105% of the stated amount of paracetamol, $C_8H_9NO_2$	495mg per average weight of tablets	498mg per average weight of tablets
Dissolution	Not less than 80% of the stated amount of paracetamol, $C_8H_9NO_2$	86%	89%

Table-11
Characteristic Change in Effluent Generated from Pharmaceutical Industry due to Process Modifications

Parameters	Effluent Characteristics Before Modification	Effluent Characteristics After Modification
Volume (m^3/h)	05 – 10	03 - 07
pH	5 – 9	6.5 – 7.5
TSS (mg/l)	400-500	< 200
TDS (mg/l)	600-700	< 200
COD (mg/l)	400 – 500	< 100
BOD (mg/l)	200 – 250	< 30

Conclusion

It is revealed that savings of raw materials, reduction in use of hazardous solvents and minimization of waste is amply achieved by adopting certain measures. The following conclusion can be drawn from the above investigative research that preference has to be given to use aqueous solvents as far as possible replacing organic solvents. Tablet coating has to be done with aqueous solvents and not with organic solvents. Existing formulation of raw materials should be audited time to time to find the scope for reduction of excipients for resource reduction and waste minimization. Good results are achieved with regard to paracetamol suspension and paracetamol tablet formulation. Reduction of rejection in pharmaceutical industries should be judiciously contemplated in order to save resource, minimize wastes and prevent water pollution. It is successfully experimented that in large volume parenterals industry a measure of endotoxin test at raw material stage, intermediate stage and finished stage could save a huge loss of product rejection resulting in saving of materials and waste minimization.

References

1. Bhatti P.D., Roy S., Aggarwal R., Dash R., Sekhar M. and Kaliprasad V., Cleaner Production in Dye Manufacturing Clusture, *Waste Minimisation Circle News,* **4(1)**, 3-9, **(2003)**

2. Nodubuisi Ezejiofor Tobias I, Duru Carissa I., Asagbra Agnes E, Ezejiofor Anthonet N., Orisakwe Orish E., Afonne Johnson O. and Obi Ejeatuluchukwu, Waste to wealth: Production of oxytetracycline using streptomyces species from household kitchen wastes of agricultural produce, *African Journal of Biotechnology*, **11(43),** 10115-10124 **(2012)**

3. APPCB Information Bulletin, Opportunities for Waste Minimisation in Bulk Drug and dye intermediate Industries, Publication no.**105**, April **(1999)**

4. Energy Efficiency workshop, Approach and Case studies**,** presented by S.K. Lasod, Lupin Limited, Ankleshwar, Available at : ent-india.net/Presentation2010/26-Fertiliser /LupinPharma **(2010)**

5. Taylor Nick, GSK aims to cut time to clinic with excipient-free compression, 8th Febtuary, **(2012),** in-pharmatechnologist.com/Ingredients/GS

6. Mohan B. Krishna, Pharma firms look to profit from waste, *Business Standard* **(2009)**

7. Paribesh R. and D of Central Pollution Control Board, Annual report **(2003)**

8. Krishna Mohan B**.,** May15, Business Standard **(2009)**

9. Green Chemistry commitments and actions Pfizer : the world's largest research based pharmaceutical company, July4, **(2012)** available,on Pfizer.com /responsibility /protecting_environment/green_chemistry_commitments.jsp

10. Grate J., Huisman G., A greener biocatalytic manufacturing route to sitagliptin Paper presented at 13th annual Green Chemistry and Engineering Conference, June 23, College Park, Md. **(2009)**

11. Martinez C.A., Hu S. and Dumond Y., et.al. Development of a Chemoenzymatic manufacturing process for pregabalin, Organic Process Res. Dev. **(2008**)

12. Jennewein S., Schurmann M. and Wolberg M., et.al**.** Directed evolution of an industrial biocatalyst: 2- deoxy-D-ribose 5-phosphate aldolase, *Biotechnol. J.,* **1(5)** 537-548 **(2006)**

13. Roger A. Sheldon Catalyst: The Key to Waste Minimization, *J. Chem. Tech. Biotechnol*., **68** 381-388 **(1997)**

14. Enteric coating, available at Wikipedia.org /wiki /Enteric_coating **(2012)**

15. Indian Pharmacopoeia**,** Volume II, page 1686-1687, Government of India, Ministry of Health and Family welfare, Indian Pharmacopoeia Commission, Ghaziabad **(2010)**

16. Indian Pharmacopoeia **(2010),** Addendum, Government of India, Ministry of Health and Family welfare, Indian Pharmacopoeia Commission, Ghaziabad 2940-2941 **(2012)**

17. Indian Pharmacopoeia, Government of India, Ministry of Health and Family welfare, Indian Pharmacopoeia Commission, Ghaziabad, **III,** 1861-1862 **(2010)**