WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 11, 2146-2163. Research Article ISSN 2277– 7105

THE RESEARCH ON NOVEL TECHNIQUE OF PROCESS SCALE UP

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Article Received on
18 Sept 2015,

Revised on 10 Oct 2015,
Accepted on 1 Nov 2015,

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ABSTRACT

The aim of researcher in this research work is only to, the old technique of process scale up is to minimise by creating novel technique of process scale up. The scale up is the process as define to increasing the batch size or increasing the output of volumes. The old process scales up technique have many steps. It has trial batches, exhibit batch for approval by regulatory authority and validation batches for compile data and stability measurement, the validation batch complete in three steps, batch-1, batch-2 and batch-3 or first three batches after the approval of regulatory authority is called validation batches. This technique is the part of process development laboratories in Indian pharmaceutical industries. It is the counter part of Research and Development department. After the technology transfer by R&D the next step is process scale up by process development laboratory for approval of regulatory authority, validation, stability measurement and also compile the best possible parameters for technology transfer to production department for preparation of marketed batch.

KEYWORDS: Scale Up, Batch Size, Trials, Validation, Exhibit.

INTRODUCTION

Scale-up is defined as the process of increasing batch size. Scale-up of a process viewed as a procedure for applying the same process to different output volumes. There is a subtle difference between these two definitions: batch size enlargement does not always translate into a size increase of the processing volume (1).

METHOD

The Current Scenario of process scale up depends up to country to country and followed various steps. Like

In European Countries[2]

a) Lab Scale Batches

b) Lab Scale Trials

c) Process Optimization Batches/Trial Batches

d) Pivotal Batches/Exhibit Batches/Submission Batches (Divided into two batches)

e) Process Validation Batches (Divided into three batches)

In United State/Indian Pharmaceutical Industry[3]

a) Lab Scale Batches

b) Lab Scale Trials

c) Process Optimization Batches/Trial Batches

d) Pivotal Batches/Exhibit Batches/Submission Batches

e) Process Validation Batches (Divided into three batches)

The Indian Pharmaceutical Industries & United States Pharmaceutical Industries followed same steps in process scale up. The Researcher Focus in this research works for Indian pharmaceutical industries in process development laboratory.

Process Development Laboratory

In India the process development laboratory is the counter part of research & development department. The Research & Development have two counter parts one Formulation & development & the second process development laboratory.

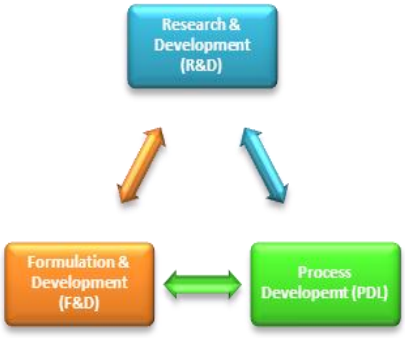


Figure-1 Flow chart shown counter parts of Research & Development

Process Scale Up Steps in Indian Pharmaceutical Industries

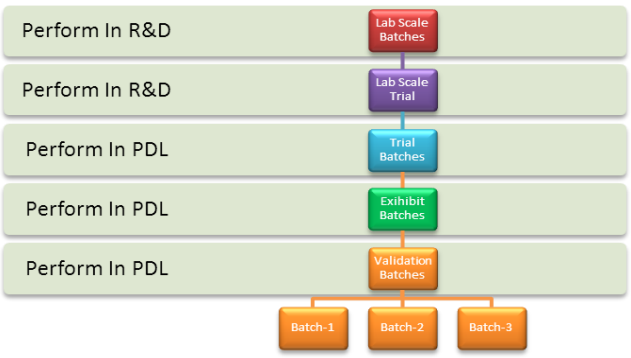


Figure-2 Description the steps of process scale up in Indian Pharmaceutical Industries

Lab Scale Batches.

The Lab Scale batches are performing in research & development laboratory.

Lab Scale Trials

The Lab scale trials batches performing just after lab scale batches in research & development laboratory & after the lab scale trials batches the technology transfer in process development laboratory.

Trials Batches[4]

Trial Batches are small batches or quantity in size; these batches are getting after R&D (Research & Development) division and performed in process development laboratory. The quantities of this trial batch are near about One thousand to ten thousand. This is initial batch of process scale up technique.

The aim of trials batch to perform all the ingredients, process, and parameters adapted by the research & development division and also prepare the small size of batch which is initiation of the minimum to maximum as per the definition of scale up.

Exhibit Batches[4]

The Exhibit batch is also called Submission batches. The main aim of exhibit batch is to get approval by regulatory authority. The exhibit batches shall submit to regulatory authority shall be charged for both accelerated & long term stability testing and the biological study shall be done on the same. The exhibit batches performed in process development laboratory. The batches size of the exhibit batches is not less than one lack or ten percent of proposed marketed batches. The example of some regulatory bodies

Table-1 Examples of Regulatory Authority

Country	Regulatory Authority
India	Food & Drug Administration
United State	United State Food & Drug Administration
United Kingdom	Medicine & Health Products Regulatory Agency
Brazil	National Health Surveillance Agency
Tanazinia	Tanazinia Food & Drug Administration
Uganda	National Drug Authority
Kenya	Pharmacy & Poison Board

Validation Batches

Once the regulatory authorities are approved the sample then we are started the validation batches. These batches are divided in to the three parts Batch-1, Batch-2 and Batch-3 or the first three commercial batches shall be validated. The same shall be charged for long term stability. These batches also performed in process development laboratory. In these three batches we performed different parameter of drug preparation like tablet punching, air pressure etc. the batch size of solid oral dosages form validation batch is more than one lack unit.

Novel/Adapted Technique of Process Scale Up

The aim of this Novel technique is to reduce the steps of process scales up, save time & cost of the industries. This technique will minimise the steps of process scale up. The new steps are

a) Novel Lab Scale
b) Novel Lab Scale Trials
c) Novel Trial Batches
d) Novel Exhibit Batches
e) Novel Validation Batches

In these steps it is not divided to validation batches in three parts but the data of trials batches, Exhibit Batches and Validation batches are use and compile for production and used for validation.

It also increases the batch size of the trial, exhibit batches. The new size of trials batches is not less than fifty Thousand, the exhibit batches increase up to two lack and the validation batches up to five lack. After preparing the batches all their data & drugs use for stability &

maintain the validation record and compile data for the technology transfer in production department for preparing the marketed size batches.

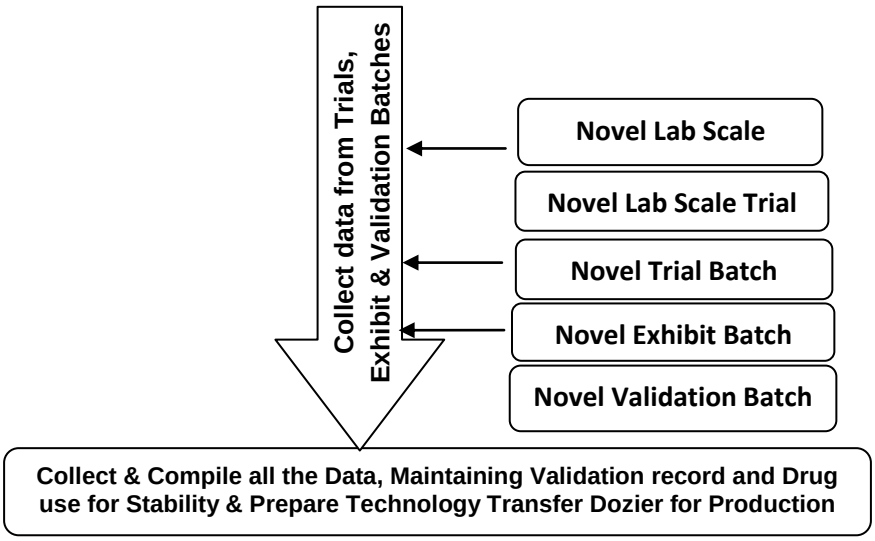


Figure-3 Flow Chart of the novel technique of process scale up

Novel Lab Scale Batches

The Lab Scale batches are performed in research & development laboratory as same as previous techniques.

Novel Lab Scale Trials

The Lab scale trials batches performed just after lab scale batches in research & development laboratory & after the lab scale trials batches the technology transfer in process development laboratory. This step also same as previous techniques.

Novel Trials Batches

The old size of trials batches for oral solid dosage form up to ten thousand but in novel trials batches it has increased the batch size, the prepare of new trials batch not less than fifty thousand of solid oral dosages form. The novel trials batches prepare in process development department as previous.

Novel Exhibit Batches

In the Novel Exhibit Batches it has increased the batch size of exhibit batch. The new size of batches increased up to two lacks or fifteen percent of marketed batch. This process also performed in process development department. The approval of regulatory authority same as old exhibit batches.

Novel Validation Batches

The Validation Batches has done in three steps, batch-1, batch-2 and batch-3 but in novel validation batch it can reduce two batches, therefore the new or novel validation batch has done only in one batch. But in novel validation batches it has increased batch size, so the new batch size of novel validation batches increased up to five lacks.

New Work Assign for PDL Department/Data Compile & Stability Management

The aim of this Section collected all the data from novel trials batches, novel exhibit batches and Novel validation batches with increased batch size. The collected data compile for technology transfer for production department.

The Increased Batch Size of Novel trial, exhibit and validation batches of units/solid oral dosage collects and manages for stability issue and put in stability chamber. In this section validate all the compiled records. it also analyse and compare to the best process in all batches.

Selection of Drug

The selected drug is Paracetamol tablet and the base of drug selection is currently running drug in pharmaceutical industry.

Paracetamol

Paracetamol is also known as Acetaminophen or APAP (5) (6). Paracetamol an international name used in European countries and all over world (7) and the Acetaminophen international name used in united State of America, canada, japan, Venezuela and colombia (8). Paracetamol / acetaminophen is one of the most popular and most commonly used analgesic and antipyretic drugs around the world, available without a prescription, both in mono- and multi-component preparations.

Paracetamol is classified as a mild analgesic (9). It is commonly used for the relief of headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies. In combination with opioid analgesics, paracetamol can also be used in the management of more severe pain such as post-surgical and cancer pain (10).

Preparation of Paracetamol IP Tablet 500 mg

The preparation of paracetamol tablet as per Indian Pharmacopoeia guideline by wet granulation technique.

Most Probably Excipients to be Use of Paracetamol Tablets

Paracetamol used as active pharmaceutical ingredient (API). The Excipients use for paracetamol tablet like disintegrates for disintegration, diluents for dilution, lubricant for lubrication.

Various Stages of Paracetamol Tablet preparation

In Indian Pharmaceutical Industries, the solid dosages form of tablet prepare in many stages.

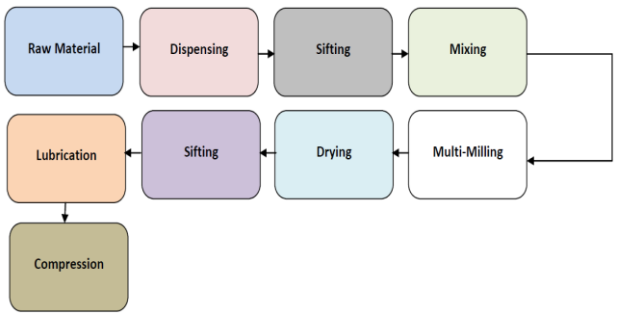


Figure-4 Flow Chart of Paracetamol tablet Preparation

RAW MATERIAL

The raw material is basic material which a paracetamol tablet is made. It export form other company and depend upon the grade & quality.

Dispensing

In this section the raw material of paracetamol & excipients is dispense to preparation of tablet. The quantity of dispense product depend upto batch size.

Sifting

In sifting the dispense product put in the sieve, so as to remove lumps or large particles. The sieve used to paracetamol 18 to 20 numbers.

Mixing

Mixing is the part of mixed to all the ingredients, additives with active pharmaceutical ingredients. The instrument used in mixing is planetary mixer. The speed of planetary mixer is 10 to 20 rpm for 10 minute.

Multi Milling

After mixing we received product in lumps or paste form. Then we use the multi mill for break the lumps of product. The hole diameter of multi mill for paracetamol is up to 8 mm for 5 minute.

Drying

The dryer used for paracetamol is fluid bed dryer (FBD). FBD is widely used granules dryer in Indian pharmaceutical industries. The temperature is maintained for paracetamol is 80 to 100 ^{o}c and used to esteem pressure 5 to 6 kg for 5 minute.

Sifting

After the drying by fluid bed dryer the granules passed form sieve number 18 to 20 for paracetamol 500mg tablet & size of tablet 12 to 14 mm. the sieve number of sifiter is depends up to the size of tablet.

Lubrication

The lubrication of granulation is done by octagonal blender for 20 minute. The cadmach octagonal blender used for this research.

Compression

The 27 station cadmach punching machine ready for the compression of granules with 50 to 60 rpm speed. After the lubrication we compress the granules for tablet form.

Evaluation Parameters of Paracetamol tablet for Novel Process Scale Up Which is done in Process Development Laboratory.

a) Weight Variation
b) Thickness
c) Hardness
d) Friability

Weight Variation

Random selection of tablet in all novel batches for weight variation. The prepared weight of paracetamol tablet is 625 to 650mg. Variation of 5mg is acceptable.

Thickness

Random selection of tablet in all novel batches for thickness testing. The thickness of prepared paracetamol tablet is 12 mm to 14mm. Digital Vernier Caliper used for thickness measurement.

Hardness

The hardness of paracetamol tablet is measured by Dr. Schleuniger hardness tester by selecting random process in all novel batches. Applying the cursing strength of paracetamol tablet is kg/cm^2 and1 kilogram equal to 10 Newton.

Friability

The Randomly selected tablet weighed and placed in Roche type fribilator and rotates up to 100rpm. Friability allowed upto 2% only.

RESULT AND DISCUSSION

The aim of researcher is about to reduce the steps of process scale up which is performs in process development laboratory. The Novel lab scale & novel lab trials are the part of research & development department. So our target is novel trials batches, novel exhibit batches and novel validation batches. They all performed in process development laboratory department in small scale pharmaceutical industry.

Table-2 Excipients Used in Paracetamol Tablet

Raw Material	Ingredients
Paracetamol	Paracetamol API
Diluents	Lactose
Binder	Gelatine, Starch
Lubricant	Talc, Sodium Lauryl Sulfate, Sodium benzote
Super Disintegrates	Sodium Starch Glycolate (SSG)
Glidants	Talc

Novel Trials Batches

The batch size of Novel Trials Batches is 30 kilogram or 45 thousand tablets. The shape of paracetamol tablet is round and get individual average weight of tablet is 630 mg of novel trial batches (500 mg API & 130 mg Excipients). For the preparation of granules started with dispensing, so the 30 kilogram raw materials dispensed including excipients and sift by 18 mm sieve. Then mixed by planetary mixer in 10 rpm for 20 minutes after mixer the products received in lumps form the next step is milling for 5 minutes by 8 mm hole size. Then the

granules insert in fluid bed dryer for drying in 5 minutes with 5.5 kilogram esteem air pressure at 80 ^{0}c. After drying the lubricant mixed in granules by octagonal blender for 18 minutes and then compresses the tablet by 50 rpm speed. The compressed tablet moved for next step i.e. evaluation parameters. The hardness of randomly selected tablet measured by Dr. Schleuniger hardness tester and the pressure is 7.5 kilogram this is equal to 75 newton. The next parameter is friability measured by Roche type fribilator rotate upto 100 rpm. The result of friability loss is 1.2% (maximum acceptable 2%). The tablet taken time for disintegration is 10 minutes and the thickness of tablet is 12 mm measured by Digital Vernier Caliper.

The Novel trials batch is acceptable & successful with minor changes, the changes is optional but for the betterment of product it needful.

Novel Exhibit Batches

The batch size of Novel Exhibit Batches is 100 kilogram or 1,50000 tablets. The shape of paracetamol tablet is round and get individual average weight of tablet is 640 mg of novel exhibit batches (500 mg API & 140 mg Excipients). For the preparation of granules started with dispensing, so the 100 kilogram raw materials dispensed including excipients and sift by 18 mm sieve. Then mixed by planetary mixer in 15 rpm for 20 minutes after mixer the products received in lumps form the next step is milling for 7 minutes by 8 mm hole size. Then the granules insert in fluid bed dryer for drying in 6 minutes with 6 kilogram esteem air pressure at 90 ^{0}c. After drying the lubricant mixed in granules by octa gonal blender for 20 minutes and then compresses the tablet by 55 rpm speed. The compressed tablet moved for next step i.e. evaluation parameters. The hardness of randomly selected tablet measured by Dr. Schleuniger hardness tester and the pressure is 8 kilogram this is equal to 80 newton. The next parameter is friability measured by Roche type fribilator rotate upto 100 rpm. The result of friability loss is 0.80 % (maximum acceptable 2%). The tablet taken time for disintegration is 9 minutes 24 second and the thickness of tablet is 13 mm measured by Digital Vernier Caliper.

The Novel Exhibit Batch is Prepared successfully and sent for regulatory authority for market approval.

Novel Validation Batches

After getting the approval by regulatory authority, ready for the preparation of novel validation batch. The batch size of Novel Validation Batches is 300 kilogram or 450000 tablets. The shape of paracetamol tablet is round and get individual average weight of tablet is 650 mg of novel validation batch (500 mg API & 150 mg Excipients). For the preparation of granules started with dispensing, so the 30 kilogram raw materials dispensed including excipients and sift by 20 mm sieve. Then mixed by planetary mixer in 20 rpm for 20 minutes after mixer the products received in lumps form the next step is milling for 8 minutes by 8 mm hole size. Then the granules insert in fluid bed dryer for drying in 5 minutes with 6 kilogram esteem air pressure at 100 ^{0}c. After drying the lubricant mixed in granules by octagonal blender for 25 minutes and then compresses the tablet by 60 rpm speed. The compressed tablet moved for next step i.e. evaluation parameters. The hardness of randomly selected tablet measured by Dr. Schleuniger hardness tester and the pressure is 9 kilogram this is equal to 90 newton. The next parameter is friability measured by Roche type fribilator rotate upto 100 rpm. The result of friability loss is 1.01% (maximum acceptable 2%). The tablet taken time for disintegration is 8 minutes 18 second and the thickness of tablet is 14 mm measured by Digital Vernier Caliper.

The Novel Validation batch is run successfully and collects all the increased amount of tablet from novel trials batch, novel exhibit batch and novel validation batch for validation and check stability by putting stability chamber. The stability measure helpful for the preparation of next market need with same formulation.

Compiled Data for Technology Transfer Dozier

In This Section the compare and compile all the data received from various batches and prepare the technology transfer Dozier for production department.

The best possible parameters for the production for preparing marketed batch are to depend of batch size but maximum 25, 00,000 tablets. The best parameter for sifting sieve number is 20 mm and rotate planetary mixer for 20 minutes in 20 rpm. Then milling the lumps for 5 minutes with 8 mm hole size. After milling of the lumps the best parameter of dryer esteem pressure is 6 kilogram for 5 minutes at 90^{0}c temperature. The time of lubricator rotation is 23 minutes and then the tablet prepared for punching, so the best rpm is 50 rpm.

The average weight of individual tablet is 650 mg (500 mg API and 150 mg Excipients) with the best thickness of 14 mm and for the friability test the instrument rotate upto 100rpm.

The compiled data or technology transfer Dozier is ready for the transfer to production department and prepare the marketed batch.

Tablet-3 Compiled Data for Technology Transfer Dozier

Scale Up Parameters	NTB	NEB	NVB	Best Possible Parameters
Batch Size (Maximum)	45000 Tablets	150000 Tablets	450000 Tablets	2500000 Tablets Maximum
Dispensing Weight (Maximum)	30 Kilogram	100 Kilogram	300 Kilogram	1500 kilo gram
Sifting (Sieve)	18 mm	18 mm	20 mm	20 mm
Mixing Time of Planetary Mixer	20 minutes	20 minutes	20 minutes	20 minutes
Mixed by Planetary Mixer	10 rpm	15 rpm	20 rpm	20 rpm
Milling Time	5 Minutes	7 Minutes	8 Minutes	5 Minutes
Milling Hole Size	8 Mili Meter	8 Mili Meter	8 Mili Meter	8 Mili Meter
Drying Time	5 Minutes	6 Minutes	5 Minutes	5 Minutes
Drying Pressure (Esteem Pressure)	5.5 Kilogram	6 Kilogram	6 Kilogram	6 Kilogram
Drying Temperature	80 ^{o}c	90 ^{o}c	100 ^{o}c	90 ^{o}c
Lubrication Time (Octa Gonal Blender Rotation)	18 Minutes	20 Minutes	25 Minutes	23 Minutes
Tablet Punching Machine Station	27 Station	27 Station	27 Station	27 Station
Compression (Tablet Punching rpm)	50 rpm	55 rpm	60 rpm	50 rpm
Shape	Round Shape	Round Shape	Round Shape	Round Shape
Individual Tablet Weight (Average)	630 Mili Gram	640 Mili Gram	650 Mili Gram	650 Mili Gram
Thickness	12 mm	13 mm	14 mm	14 mm
Friability Rotator Speed & Loss	100 rpm	100 rpm	100rpm	100 rpm

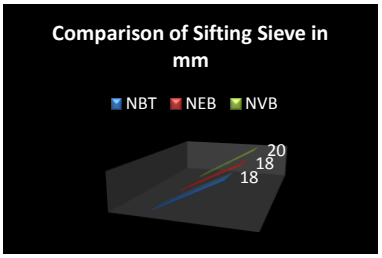
*NTB: Novel Trial Batches

NEB: Novel Exhibit Batches

NVB: Novel Validation Batches

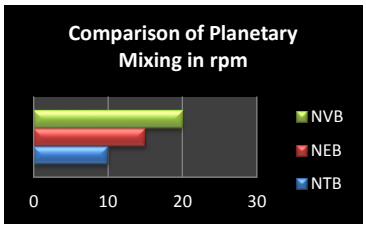
Comparison Graphs of Various Batches

1) Comparison Graph of Sifting



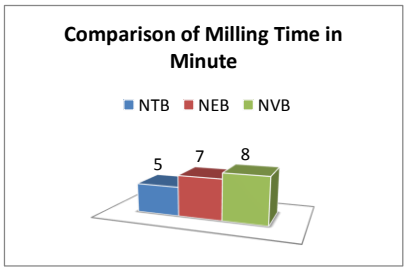
Graph of Sifting Comparison by various sieve in mm

2) Comparison Graph of Mixing



Comparison of the Planetary Mixer in rpm

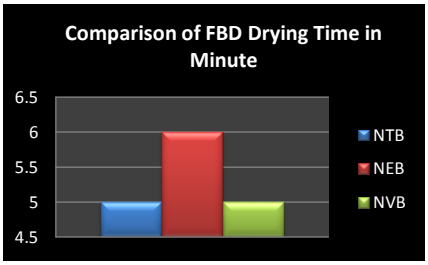
3) Comparison Graph of Milling



Graph of Milling Time Comparison in Minute

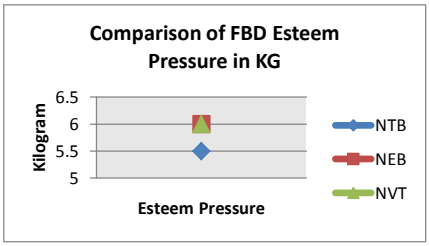
***NTB= Novel Trials Batches, NEB= Novel Exhibit Batches, NVB= Novel Validation Batches**

4) Comparison Graph of Drying Time



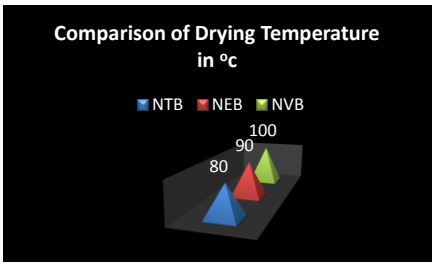
Comparison of FBD Drying Time in Minutes

5) Comparison Graph of Drying Pressure



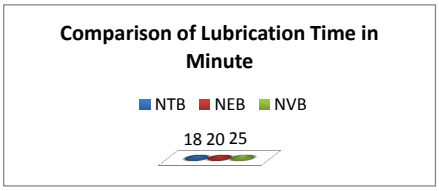
Comparison of FBD Esteem Pressure in Kilogram

6) Comparison Graph of Drying Temperature



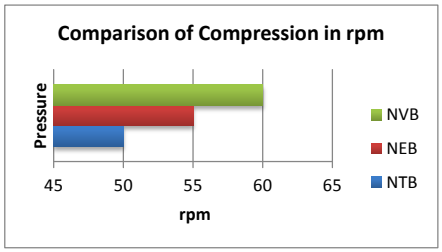
Comparison of Drying Temperature in ^{o}c

7) Comparison Graph of Lubrication Time (Octa gonal Blender Rotation)



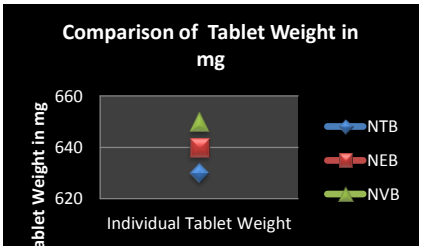
Comparison of Lubrication Time in Minute

8) Comparison Graph of Tablet Compression (Tablet Punching)



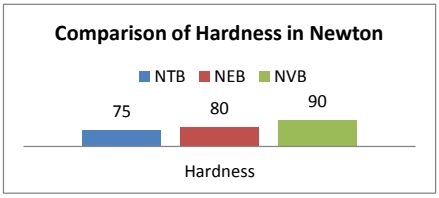
Comparison of Tablet Comparison in rpm

9) Comparison Graph of Individual Tablet Weight



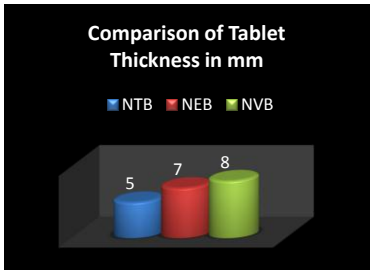
Comparison of Individual Tablet Weight in Miligram

10) Comparison Graph of Hardness



Comparison of Tablet Hardness in Newton (10 Newton equal to 1 kilogram)

11) Comparison Graph of Thickness



Comparison of Tablet Thickness in mm

CONCLUSION

In this research the researcher is to reduce the technique of the process scale up by using novel technique of process scale up for solid dosages form.

Using of this novel technique the industry has reduce their time for marketed batch preparation, cost of tablets because to reduce the steps so the expanse of labour cost or engage their manpower used in other works will reduce and it will affected the cost of drug which is beneficial for industries and our society. This technique will also helpful for our society because to save the manufacturing time and the drug is delivery previously and easily in the market, so the people get advantage of drug earlier for the treatment of their disease. It may also helpful for academician to conduct research on various dosages forms.

This Technique has some limitations which are, this Technique helpful only for small scale batch size which is maximum 1500 kilogram only because of if industry will prepare large scale of batches so; the risk factor is in compile of data of technology transfer. Due to this reason may be the batch of drug is waste or have a problem in preparing of standard drug as per IP, BP, USP or any other pharmacopoeia. This will affected to the cost and time of preparation and this technique will work only generic drugs or re-produce the same formulation drugs only, it will not applicable for new drugs because the nature of new drug is unknown.

ACKNOWLEDGEMENT

The author would like to thank all his mentors. The research compiled here is collected over a period of time and may have been reproduced verbatim. Apologize to all researchers if in-advertently failed to acknowledge them in the references.

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