Evaluation of Powder Drug Layering Technique as Possible means of Abuse Deterrent Formulation

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ABSTRACT

Abuse and misuse of prescription opioids is a significant public health concern. The strategies used to confer abuse-deterrent properties on opioid abuse deterrent formulations (ADFs). The objective of this study was to develop techniques for an abuse deterrent (AD) platform utilizing the Granurex process. For the preparation of abuse deterrent extended release formulation core material was layered with dry active pharmaceutical ingredient with the help of Granurex technology and after the drug layering suitable polymeric coat was applied to make formulation crushed resistance and resistance to dose dumping. Formulation optimization was accomplished by utilizing full factorial design of experiments to determine the effect of the three formulation factors: Ethyl cellulose 45 cps, white wax and carbopol 974P NF; each of which was studied at three levels on crushed resistance (CR) attributes of the produced extended release pellets. Suitable formulation ingredients were employed as carrier matrices and processing aids. All of the formulations were evaluated for the crushed resistance and dose dumping attributes, such as crushing strength, extraction studies of drug in different levels of solvents and particle size. All of the design of experiments formulations demonstrated sufficient hardness and elasticity, and could not be reduced into fine particles, which is a desirable feature to prevent snorting. In addition, all of the formulations exhibited good gelling tendency in water with minimal extraction of drug in the aqueous medium. Moreover, Carbopol 974P NF, in combination with white wax, could be utilized to produce pellets with crushed resistance potential. Granurex has been demonstrated to be a viable technique with a potential of develop novel AD formulations.

Keywords: Abuse deterrent formulations, Crushed resistance

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INTRODUCTION

The Aim and Objective of these work is to identify abuse deterrent properties of extended release pellets and differentiate of this properties of extended release pellets with reference products by several tests. To describes various type of studies like dose dumping studies with 40% alcohol, drug release studies in different media, hardness, Crushability of the pellets.

MATERIALS AND METHOD

Materials

Oxycodone hydrochloride was obtained as a gift sample from Sun Pharmaceutical Laboratories Limited, Gurgaon. Microcrystalline sphere was obtained from cellets, Aerosil and talc Powder obtained from Evonik and Brenntag specialties, White wax was Purchased from Bramble berry. Other excipients used were of standard pharmaceutical grade. Isopropyl alcohol was used throughout the experiment. Ethyl cellulose 45 cps was obtained from colorcon. Cellulose acetate CA-398-10NF/EP was obtained from EASTMAN. Name of equipment used for these are Granurex, Glatt(Bottom spray).

Identification of API

Oxycodone hydrochloride, is medicine mostly use in the treatment of pain management and for the persons who are in the stress. This drug was typically administered by the oral route(mouth). It is sometimes used to treat or reduce the pain after the big surgery or the surgery like cancer. Oxycodone hydrochloride is classified as a mu-receptor agonist or sometime mild analgesics.

Mode of action of Oxycodone hydrochloride It is weak inhibitor of prostaglandins receptors. Sometime it act as an inhibit COX receptor in the brain. Sometimes it acts as an COX-2 inhibitor.

Oxycodone hydrochloride solubility. Water Solubility=14000 mg/L (at 25 °C), 14 mg/mL at 25 °C. Very slightly soluble in cold water, soluble in boiling water. Freely soluble in alcohol. Soluble in methanol, ethanol, dimethyl formamide, ethylene dichloride, acetone, ethyl acetate; slightly soluble in ether. Practically insoluble in petroleum ether, pentane, benzene.

| Sr no | Drug                        | 0.1N HCl | Phthalate buffer pH 4.5 | Phosphate buffer pH 6.8 | Phosphate buffer pH 7.4 |
|-------|-----------------------------|----------|--------------------------|--------------------------|--------------------------|
| 1     | Oxycodone hydrochloride     | 0.0894gm/ml | 0.0061 gm/ml             | 0.0056gm/ml             | 0.0049gm/ml             |

Establishment of standard curve(Calibration curve) for UV visible spectroscopy method for analysis of Oxycodone hydrochloride in 0.1N HCl.

100mg Oxycodone hydrochloride was dissolved in 5 ml methanol and then diluted with 0.1N HCl upto 100 ml to procedure stock solution 1000 µg/ml. Preparation of stock solution 2:10 ml of stock
1 solution was taken and diluted with 0.1N HCl upto 100 ml to produce 100 µg/ml stock solution concentration.

**Establishment of standard curve (Calibration curve) for UV visible spectroscopy method for analysis of Oxycodone hydrochloride in 0.1N NaOH.**

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder containing about 0.15gm of Oxycodone hydrochloride add 50ml of 0.1M NaOH, dilute with 100ml of water, shake for 15 minutes and add sufficient water to produce 200 ml. Mix, filter and dilute 10 ml of the filtrate to 100ml with water. To 10 ml of the resulting solution add 10ml of 0.1M NaOH, dilute to 100ml with water and mix. Measure the absorbance of the resulting solution at the maximum at about 257nm. Calculate the content of Oxycodone hydrochloride taking 715 as the specific absorbance at 257nm.

**Establishment of standard curve (Calibration curve) for UV visible spectroscopy method for analysis of Oxycodone hydrochloride in distilled water.**

Preparation of stock solution 1:

100mg Oxycodone hydrochloride was dissolved in 5 ml methanol and then diluted with distilled water upto 100 ml to procedure stock solution 1000 mcg/ml. Preparation of stock solution 2: 10 ml of stock 1 solution was taken and diluted with distilled water upto 100 ml to produce 100 µg/ml stock solution concentration.

**Establishment of standard curve (Calibration curve) for UV visible spectroscopy method for analysis of Oxycodone hydrochloride in 6.8 phosphate buffers.**

100mg Oxycodone hydrochloride was dissolved in 6.8 phosphate buffer upto 100 ml to procedure stock solution. 1000 mcg/ml. 10 ml of stock 1 solution was taken and diluted with 6.8 phosphate buffer upto 100 ml to produce 100 µg/ml stock solution concentration.

**Establishment of standard curve (Calibration curve) for UV visible spectroscopy method for analysis of Oxycodone hydrochloride in 40% ethanol.**

100mg Oxycodone hydrochloride was dissolved in 40% ethanol upto 100 ml to procedure stock solution 1000 µg/ml. Preparation of stock solution 2: 10 ml of stock 1 solution was taken and diluted with 40% ethanol upto 100 ml to produce 100 µg/ml stock solution concentrations.

**Table 2: Values of Absorbance in different media**

| Sr no | Concentration (µg/ml) | Average. Absorbance |
|-------|-----------------------|---------------------|
|       | 0.1N HCl | 0.1N NaOH | Distilled water | 40% ethanol | 6.8 phosphate buffer |
| 0     | 0        | 0         | 0                | 0            | 0                     |
| 1     | 5        | 0.296167  | 0.368767         | 0.358667     | 0.468967              | 0.389867              |
Table 3: Regression parameters

| Regression parameters | Values          |
|-----------------------|-----------------|
|                       | 0.1N HCl | 0.1N NaOH | Distilled water | 40% ethanol | 6.8 phosphate buffer |
| Correlation coefficient | 0.9993    | 0.999     | 0.998          | 0.9992      | 0.9973              |
| Intercept             | -0.0145    | 0.0148    | 0.0136         | 0.0232      | 0.0214              |
| Slope                 | 0.0665     | 0.0705    | 0.0636         | 0.0856      | 0.0677              |

Assay

Weigh and powder 20 tablets. Take a quantity of the powder equivalent to 0.15 g of Oxycodone hydrochloride
20 tablets * 0.5g Oxycodone hydrochloride  wt 0.15 g
Oxycodone hydrochloride  X
Place in a volumetric flask (200ml) Add 50 ml 0.1 M NaOH (using a burette) .Dilute with 100 ml of water, shake for 15 minutes, and add sufficient water to produce 200 ml. Mix, and filter. Dilute 10 ml of the filtrate to 100 ml with water (in a volumetric flask 100ml). Add 10ml of the resulting solution to 10 ml of 0.1 M NaOH, dilute to 100 ml with water (in a volumetric flask 100ml) . Measure the absorbance of the resulting solution at \( \lambda_{\text{max}} = 257 \) nm taking 0.715 as the value of \( E_{1\%} \).
Blank: take 20 ml of 0.1 M NaOH and complete to 100 ml with water
Limit: Content: 95-105% of the prescribed (labeled)

Experimental Work:

Preliminary trials

The aim of the presented work was to develop extended release pellet formulation and release retardant formulation. For that multiple formulation and process parameter were studied. Drug concentration selected based upon the dose. The amount of MCC sphere was kept constant 300gm per batch based upon the capacity of Granurex machine. Amount of talc was kept constant usually it was used in the range of 1-10%.

Table 4: Preliminary trial batches

| Batch | Batch size 3000 capsules |
|-------|--------------------------|
|       | DS 1 | DS 2 | DS 3 | DS 4 | DS 5 |
| 2     | 10   | 0.649167 | 0.742867 | 0.639867 | 0.8994 | 0.702633 |
| 3     | 15   | 0.9936 | 1.082833 | 0.9596 | 1.309 | 1.024 |
| 4     | 20   | 1.314033 | 1.4061 | 1.289133 | 1.721733 |
Drug layered | mg | gm | mg | gm | mg | gm | mg | gm | mg | gm
---|---|---|---|---|---|---|---|---|---|---
MCC Sphere(30-35 mesh) | 100 | 300 | 100 | 300 | 100 | 300 | 100 | 300 | 100 | 300
Oxycodone hydrochloride | 100 | 300 | 100 | 300 | 100 | 300 | 100 | 300 | 100 | 300
Carbopol 974P NF | 10 | 30 | 60 | 180 | 80 | 240 | 50 | 150 | 60 | 180
Talc | 10 | 30 | 10 | 30 | 10 | 30 | 10 | 30 | 10 | 30
Aerosil | 5 | 15 | 5 | 15 | 5 | 15 | 5 | 15 | 5 | 15

Effect of amount of Carbopol 974P NF

Carbopol 974P NF was used to increase the viscosity of the pellets. At certain level they increase the hardness of the pellets. When we increase the level of carbopol to 240 mg, it shows uneven shaped particle. This was observed because viscosity was increased too high.

During formulation of batch 1 and batch 2, it was observed that pellets are formed by batch 1 was crushable and from batch 2 was harder than batch 1. In batch 3, it was observed that 240mg of carbopol 974P NF was enough to make hard pellets but uneven shape pellets were observed. It was observed that ethyl cellulose and white wax were factors which affect hardness of the pellets.

Effect of concentration of binder:

Ethyl cellulose taken as binder and different percentage of ethyl cellulose 45cps was studied. The viscosity of ethyl cellulose 45 cps was found to be 42-48 centipoises. It was observed that when we increase the concentration of ethyl cellulose 45 cps the shape of the pellets were changed.

| Batch Binder | DS 1 | DS 2 | DS 3 | DS 4 | DS 5 |
|---|---|---|---|---|---|
| EC 45 cps | 10 | 30 | 10 | 30 | 20 | 60 | 10 | 30 | 10 | 30 |
| White wax | 5 | 15 | 5 | 15 | 15 | 45 | 5 | 15 | 5 | 15 |
| Isopropyl alcohol | qs | 1080 | qs | 1080 | qs | 2520 | qs | 1080 | qs | 1080 |

Table 6: Evaluation of trial batches

| Batch number | Pellets strength | Shape of pellets |
|---|---|---|
| DS 1 | hard | Round |
| DS 2 | hard | Round |
| DS 3 | soft | Star Shape |
| DS 4 | hard | Round |
| DS 5 | hard | Round |

From above trial it was concluded that batch 3 with 60mg of ethyl cellulose 45cps concentration was not enough to make hard pellets. Batch 1, 2, 4, and 5 with 30mg of concentration were shows good strength to the pellets and shows a round shape pellets.

Effect of peristaltic pump and flow rate:

Table 7: Effect of ethyl cellulose and white wax in trial batches:

| Batch Binder | DS 1 | DS 2 | DS 3 | DS 4 | DS 5 |
|---|---|---|---|---|---|
| mg | gm | mg | gm | mg | gm | mg | gm | mg | gm
Flow rate of binder solution by peristaltic pump:

| Flow rate  | 1 ml/min | 1ml/min | 3 ml/min | 1 ml/min | 1ml/min |
|------------|----------|---------|----------|----------|---------|
| EC 45 cps  | 10       | 30      | 10       | 30       | 20      | 60      | 10      | 30      | 10      | 30      |
| White wax  | 5        | 15      | 5        | 15       | 15      | 45      | 5       | 15      | 5       | 15      |
| Isopropyl alcohol | qs | 1080 | qs | 1080 | qs | 2520 | qs | 1080 | Qs | 1080 |

Table 8: Effect of Peristaltic pump in trail batches

Evaluation of shape:

Table 9: Effect of peristaltic pump and flow rate in shape of the particles

| Batch number | Shape of the pellets |
|--------------|----------------------|
| 1            | Round                |
| 2            | Round                |
| 3            | Star                 |
| 4            | Round                |
| 5            | Round                |

As flow rate was increased from 1 ml/min to 3 ml/min shape of the pellets becomes change (star shaped) So, flow rate 1ml/min required for pellets formation.

Dissolution studies of trial batches:

Dissolution study data of trial Batches:

Drug release study of trial batch DS 1

A dissolution study of batch 1 was performed in 0.1N HCL. Dissolution of drug layered pellets.

Condition- Media -900ml volume of 0.1N HCL, RPM-100, Apparatus-USP type 2 (paddle)

![Graphical representation of dissolution data of batch DS 1](image)

According to graph and dissolution data we concluded that more than 60% of drug was released in around 2 hrs for intact drug layered pellets. According to data pellets does not show abuse deterrent or release retardant properties, So we did not performs drug release studies with crushed pellets.

Drug release study for trial batch DS 2:

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Drug release study of batch 2 was performed in 0.1N HCl and 6.8 phosphate buffer. Drug release study in 0.1N HCl for intact and crushed pellets

![Graphical representation of dissolution data of batch DS 2 in 0.1N HCl](image1)

**Figure 2: Graphical representation of dissolution data of batch DS 2 in 0.1N HCl**

According to the data, it was concluded that there are not large difference between the crushed pellets and intact pellets. Graph also shows that above 60% of drug was release within 3 hrs. So, they do not retard the release rate.

![Graphical representation of drug release study of DS2 batch in 6.8 phosphate buffer](image2)

**Figure 3: Graphical representation of drug release study of DS2 batch in 6.8 phosphate buffer**

According to the data, it was concluded that there are not large difference between the crushed pellets and intact pellets. Graph also shows that around 100% of drug was release within 3 hrs. So, they dose not retard the release rate.
Drug release study of trial batch DS 3:
Drug release study was performed in 0.1N HCl

**Table 10: Dissolution of intact pellets of trial batch DS 3 in 0.1 N HCl**

| Time (Hrs) | Intact pellets | Crushed pellets |
|------------|----------------|-----------------|
| 0          | 0              | 0               |
| 1          | 108.8          | 98.4            |

Data shows that around 100% of drug was released within 1 hrs. So, they do not retard the release rate. Therefore, further studies in different time points were not performed.

Drug release study of batch DS 4:

**Table 11: Dissolution of intact pellets of trial batch DS 4 in 0.1 N HCl**

| Time (Hrs) | Intact pellets | Crushed pellets |
|------------|----------------|-----------------|
| 0          | 0              | 0               |
| 1          | 91.8           | 96.1            |
| 2          | 94.3           | 95.4            |
| 3          | 95.1           | 96.4            |

Data shows that around 95% of drug was released within 3 hrs. So, they do not retard the release rate. Therefore, further studies in different time points were not performed.

Drug release study of trial batch DS 5:

A drug release study was performed in 0.1N HCl.

![Graphical representation of batch DS 5](image)

**Figure 4: Graphical representation of batch DS 5:**

According to the data it was shows that there are steady increase in the drug release with respect to the time. No rapid release in drug in earlier time points. According to this data batch DS 5 was taken as center point in design of experiment studies.

**Table 12: Formula for extended release coating of drug layered pellets**

| Extended release coating | Mg/capsule | Gm/batch |
|--------------------------|------------|----------|
| Cellulose acetate (CA-398-10) | 0.0228    | 68.4     |
Drug release study of ER coated tablet in 0.1N HCl.

According to the data it was shows that there is steady increase in the drug release with respect to the time. No rapid release in drug in earlier time points when ER coating

**3**² Full factorial design

A full factorial design is the one of the process in which we can determine the causes between the process and output of the process variable. We can measure the relationships between the dependent variable which can affect the independent variable. So, we sets input variables to gets optimize output results. From the preliminary trial was observed that concentration of carbopol has effect in % drug release.

Response factors include:

i. Crushability
ii. Loss on drying
iii. LOD after drying
iv. Percentage assay

**Design of experiment batches data with actual value and response.**

**Table 13: Full factorial design batches**

| Design batches | Changes(mg/units) | Carbopol(mg) | Ethyl cellulose 45 cPs (mg) | White Wax(mg) |
|----------------|-------------------|--------------|----------------------------|---------------|
| PC 1           | 40                | 20           | 10                         |               |

**Figure 5: Graphical representation of drug release study of trial batch DS 5**

Polyethylene glycol3350 | 0.0012 | 3.6
Acetone: Water(95:5)   | 1299.6:68.4
Total wt               | 336    | 347

**Figure 5: Graphical representation of drug release study of trial batch DS 5**

According to the data it was shows that there is steady increase in the drug release with respect to the time. No rapid release in drug in earlier time points when ER coating
Response of design batches.

Table 14: Responses of these design batches

| Average of 5 pellets | Standard deviation | % Assay | Experimental No. (N) |
|----------------------|--------------------|---------|---------------------|
|                      |                    | Lod     |                     |
|                      |                    | after   |                     |
|                      |                    | drying  |                     |
|                      |                    | %       |                     |
|                      |                    | LOD     |                     |
|                      |                    | drying  |                     |
|                      |                    | hrs     |                     |
|                      |                    |         |                     |
|                      |                    | 4.40%   | 95.27%              |
|                      |                    | 4.61%   | 96.66%              |
|                      |                    | 6.40%   | 91.52%              |
|                      |                    | 8.55%   | 96.38%              |
|                      |                    | 6.70%   | 101.95%             |
|                      |                    | 3.12%   | 96.11%              |
|                      |                    | 0.97%   | 96.94%              |
|                      |                    | 9.83%   | 103.33%             |
|                      |                    | 2.21%   | 98%                 |

Crushing strength of design batch PC 1
### RESULTS

| Test ID | Batch | Peak Positive Force (Cycle: 1) | kg |
|---------|-------|---------------------------------|----|
|         |       |                                 |    |

Start Batch 01 01

| End Batch 01 | 01 |
|--------------|----|
| Average:     | 01 (F) AVERAGE(BATCH^0) | 0.003 |
| S.D.:        | 01 (F) STDEV(BATCH^0)   | 0.123 |
| Coef. of Variation | 01 (F) STDEV(BATCH^0) / AVERAGE(BATCH^0) * 100 | 20.085 |

End of Test Data

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**Crushing strength of design batch PC 2**

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### TEXTURE ANALYSIS REPORT

**T A SETTINGS & PARAMETERS**

- Test Mode: Compression
- Pre-Test Speed: 1.0 mm/sec
- Test Speed: 0.25 mm/sec
- Pre-Test Speed: 10.0 mm/sec
- Target Mode: Distance
- Force: 100.0 g
- Distance: 0.3 mm
- Strain: 10.0 %
- Trigger Type: Auto (Force)
- Trigger Force: 5.0 g
- Probe: P/2; 2mm DIA CYLINDER
- STAINLESS
- Batch: 02
- Points per second: 200
- Test Run by: SUCHITRK

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**NOTES**

This space is to enter notes regarding the test data.
Crushability studies of design batch PC 3

**RESULTS**

| Test ID | Batch | Peak Positive Force (Cycle 1) kg |
|---------|-------|----------------------------------|
|         | Start Batch 02 | 02 |
|         | pellets1 | 02 | 1.12 |
|         | pellets2 | 02 | 0.818 |
|         | pellets3 | 02 | 1.182 |
|         | pellets4 | 02 | 0.748 |
|         | pellets5 | 02 | 0.896 |
|         | End Batch 02 | 02 |
| Average | 02 (F) AVERAGE("BATCH") | 0.992 |
| S.D.    | 02 (F) STDEV("BATCH") | 0.250 |
| Coef. of Variation | 02 (F) STDEV("BATCH") / AVERAGE("BATCH") * 100 | 26.15 |

**NOTES**

This space is to enter notes regarding the test data.
Crushability of design batch PC 4

### RESULTS

| Test ID  | Batch | Peak Positive Force (Cycle 1) kg |
|----------|-------|----------------------------------|
| Start Batch 03 | 03    |                                  |
|         | pellet031 03 | 1.138                            |
|         | pellet032 03 | 0.861                            |
|         | pellet033 03 | 0.562                            |
|         | pellet034 03 | 0.596                            |
|         | pellet035 03 | 0.756                            |
| End Batch 03 | 03    |                                  |
| Average: | 03 (F) | AVERAGE("BATCH")                 |
| S.D.    | 03 (F) | STDEV("BATCH")                   |
| Coef. of Variation | 03 (F) | STDEV("BATCH")/AVERAGE("BATCH") * 100 | 30.130 |
| End of Test Data |        |                                  |

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**T.A SETTINGS & PARAMETERS**

- Test Mode: Compression
- Pre-Test Speed: 1.0 mm/sec
- Test Speed: 0.25 mm/sec
- Post-Test Speed: 10.0 mm/sec
- Target Mode: Distance
- Force: 100.0 g
- Distance: 0.3 mm
- Strain: 10.0 %
- Trigger Type: Auto (Force)
- Trigger Force: 5.0 g
- Probe: P/2; 2mm DIA CYLINDER
- STAINLESS
- Batch: 04
- Points per second: 200
- Test Run by: SUCHITRK

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**NOTES**

This space is to enter notes regarding the test data.
Crushability of design batch PC 5

**Texture Analysis Report**

**T.A SETTINGS & PARAMETERS**

- Test Mode: Compression
- Pre-Test Speed: 1.0 mm/sec
- Test Speed: 0.25 mm/sec
- Post-Test Speed: 10.0 mm/sec
- Target Mode: Distance
- Force: 100.6 g
- Distance: 0.3 mm
- Strain: 10.0 %
- Trigger Type: Auto (Force)
- Trigger Force: 5.0 g
- Probe: P/2, 2mm DIA CYLINDER
- STAINLESS
- Batch: 05
- Points per second: 200
- Test Run by: SUCHITRK

**Notes**

This space is to enter notes regarding the test data.
Credibility study of design batch PC 6
Crushability of design batch PC 7

| Test ID | Batch | Peak Positive Force (Cycle 1) kg |
|---------|-------|----------------------------------|
|         |       | Peak Positive Force (Cycle 1) kg |
| Start Batch 06: | 06     | 1.223                            |
|         | pellets 06 | 1.223                            |
|         | pellets 06 | 0.979                            |
|         | pellets 06 | 1.231                            |
|         | pellets 06 | 1.068                            |
| End Batch 06: | 06     |                                  |
| Average: | 06 (F)  | AVERAGE("BATCH")                |
|         | S D     | STDEV("BATCH")                  |
|         | Conf. of Variation | STDEV("BATCH") / AVERAGE("BATCH") * 100 |
| End of Test Data |       |                                  |
### Crushability study of design batch PC 8

**Stable Micro Systems**

#### RESULTS

| Test ID | Batch | Peak Positive Force (Cycle: 1) kg |
|---------|-------|----------------------------------|
|         |       | Peak Positive Force (Cycle: 1)   |
| Start Batch 07 | 07 | 1.065 |
| pellets1 | 07 | 1.065 |
| pellets2 | 07 | 0.563 |
| pellets3 | 07 | 0.691 |
| pellets4 | 07 | 0.840 |
| pellets5 | 07 | 0.648 |
| End Batch 07 | 07 | 0.648 |
| Average | 07 | AVERAGE("BATCH") = 0.648 |
| S.D. | 07 | STDEV("BATCH") = 0.220 |
| Coef. of Variation | 07 | STDEV("BATCH") / AVERAGE("BATCH") * 100 = 26.416 |
| End of Test Data | | |

#### T.A SETTINGS & PARAMETERS

- **Test Mode:** Compression
- **Pre-Test Speed:** 1.0 mm/sec
- **Test Speed:** 0.25 mm/sec
- **Post-Test Speed:** 10.0 mm/sec
- **Target Mode:** Distance
- **Force:** 100.0 g
- **Distance:** 0.3 mm
- **Strain:** 10.0 %
- **Trigger Type:** Auto (Force)
- **Trigger Force:** 5.0 g
- **Probe:** P/2; 2mm DIA CYLINDER STAINLESS
- **Batch:** 08
- **Points per second:** 200
- **Test Run by:** SUCHITRK

#### NOTES

This space is to enter notes regarding the test data.
Particle size studies were performed for these design batches and we got precise D 90 values in batch PC 4 and batch PC 6.
Particle size of Design batch PC 6
Factors to be set on making drug layered pellet on Granurex of Design batch PC 1 to batch PC 8

**Batch PC 1**

**Table 15: Process parameter for design batch PC 1 in granurex technology**

| Time | Slit air Temp.(°C) | Slit air volume | Disc RPM | Product temp | Spray rate(RPM) | Feed rate(rpm) | Chamber statics |
|------|-------------------|-----------------|----------|--------------|----------------|----------------|-----------------|
| 10   | 35                | 0.11            | 377      | 20.9         | 3              | 1              | -0.1            |
| 30   | 35                | 0.11            | 377      | 19.3         | 3              | 2              | -0.2            |
| 50   | 35                | 0.11            | 448      | 19.2         | 2.6            | 2              | -0.3            |
| 70   | 35                | 0.11            | 448      | 19.1         | 2.8            | 2              | -0.2            |
| 90   | 35                | 0.11            | 448      | 19.2         | 2.3            | 2              | -0.2            |
| 120  | 35                | 0.11            | 497      | 20.3         | 4.2            | 1              | -0.2            |
| 150  | 35                | 0.11            | 497      | 19.8         | 4.2            | 2              | -0.3            |
| 180  | 35                | 0.11            | 549      | 19.7         | 4.2            | 2              | -0.2            |
### Batch PC 2
Table 16: Process parameter of design batch PC 2 in granurex technology

| Time (min) | Slit air Temp. °C | Slit air volume | Disc RPM | Product temp | Spray rate (RPM) | Feed rate (rpm) | Chamber statics |
|-----------|-------------------|-----------------|----------|--------------|-----------------|-----------------|----------------|
| 10        | 35                | 0.11            | 370      | 21           | 3.4             | 2               | -0.3           |
| 30        | 35                | 0.11            | 370      | 20.2         | 3               | 2               | -0.3           |
| 50        | 35                | 0.11            | 370      | 20.6         | 3.8             | 1               | -0.3           |
| 70        | 35                | 0.11            | 460      | 20.8         | 3.8             | 1               | -0.3           |
| 90        | 35                | 0.11            | 460      | 20.9         | 5               | 1               | -0.3           |
| 120       | 35                | 0.11            | 544      | 19.8         | 7               | 10              | -0.3           |

### Batch PC 3
Table 17: Process parameter for design batch PC 3 in granurex technology

| Time (min) | Slit air Temp. °C | Slit air volume | Disc RPM | Product temp | Spray rate (RPM) | Feed rate (rpm) | Chamber statics |
|-----------|-------------------|-----------------|----------|--------------|-----------------|-----------------|----------------|
| 20        | 35                | 0.11            | 480      | 21           | 4               | 3               | -0.3           |
| 40        | 35                | 0.11            | 480      | 20.6         | 4               | 5               | -0.2           |
| 60        | 35                | 0.11            | 480      | 19.8         | 4               | 3               | -0.3           |
| 80        | 35                | 0.11            | 507      | 20           | 4               | 3               | -0.4           |

### Batch PC 4
Table 18: Process parameter for design batch PC 4 in granurex technology

| Time (min) | Slit air Temp. °C | Slit air volume | Disc RPM | Product temp | Spray rate (RPM) | Feed rate (rpm) | Chamber statics |
|-----------|-------------------|-----------------|----------|--------------|-----------------|-----------------|----------------|
| 20        | 35                | 0.11            | 370      | 24           | 5               | 6               | -1             |
| 40        | 35                | 0.1             | 370      | 21.4         | 7               | 3               | -1             |
| 60        | 35                | 0.1             | 370      | 20.5         | 7               | 6               | -0.9           |
| 90        | 35                | 0.1             | 460      | 20.4         | 7               | 7               | -0.9           |
| 120       | 35                | 0.1             | 460      | 20           | 7               | 7               | -0.7           |
| 150       | 35                | 0.1             | 544      | 20           | 7               | 7               | -0.7           |

### Batch PC 5
Table 19: Process parameter of design batch PC 5 in granurex technology

| Time (min) | Slit air Temp. °C | Slit air volume | Disc RPM | Product temp | Spray rate (RPM) | Feed rate (rpm) | Chamber statics |
|-----------|-------------------|-----------------|----------|--------------|-----------------|-----------------|----------------|
| 20        | 35                | 0.1             | 377      | 20           | 5               | 2               | -0.1           |
| 40        | 35                | 0.1             | 400      | 21.5         | 6               | 2               | -0.3           |
| 60        | 35                | 0.1             | 451      | 21.9         | 6               | 2               | -0.3           |
| 90        | 35                | 0.1             | 490      | 22           | 7               | 2               | -0.3           |
| 120       | 35                | 0.1             | 512      | 20.7         | 9               | 7               | -0.3           |

### Batch PC 6
Table 20: Process parameter of design batch PC 6 in granurex technology

| Time (min) | Slit air Temp. °C | Slit air volume | Disc RPM | Product temp | Spray rate (RPM) | Feed rate (rpm) | Chamber statics |
|-----------|-------------------|-----------------|----------|--------------|-----------------|-----------------|----------------|
| 20        | 35                | 0.11            | 370      | 22.1         | 5               | 1               | -0.4           |
| 40        | 35                | 0.11            | 370      | 21.6         | 5               | 1               | -0.4           |
| 60        | 35                | 0.11            | 370      | 21.6         | 5               | 1               | -0.4           |
Batch PC 7
Table 21: process parameter of design batch PC 7 in granurex technology

| Time | Slit air Temp.°C | Slit air volume | Disc RPM | Product temp | Spray rate(RPM) | Feed rate(rpm) | Chamber statics |
|------|-----------------|----------------|----------|--------------|----------------|----------------|----------------|
| 20   | 35              | 0.11           | 388      | 19.8         | 5              | 5              | -0.4           |
| 40   | 35              | 0.11           | 436      | 20.4         | 5              | 5              | -0.4           |
| 60   | 35              | 0.11           | 436      | 20.3         | 5              | 5              | -0.4           |
| 90   | 35              | 0.11           | 518      | 20           | 5              | 5              | -0.4           |
| 120  | 35              | 0.11           | 518      | 19.9         | 5              | 5              | -0.4           |

Batch PC 8
Table 22: process parameter of design batch PC 8 in granurex technology

| Time | Slit air Temp.°C | Slit air volume | Disc RPM | Product temp | Spray rate(RPM) | Feed rate(rpm) | Chamber statics |
|------|-----------------|----------------|----------|--------------|----------------|----------------|----------------|
| 20   | 35              | 0.12           | 364      | 21           | 5.5            | 2              | -0.5           |
| 40   | 35              | 0.12           | 364      | 20.3         | 5.5            | 3              | -0.5           |
| 60   | 35              | 0.12           | 502      | 20.3         | 5.5            | 3              | -0.5           |
| 90   | 35              | 0.12           | 502      | 20.4         | 6.5            | 7              | -0.5           |
| 120  | 35              | 0.12           | 592      | 20.6         | 7              | 10             | -0.5           |

The design batches was prepared and then evaluated after that ER coating performed on those DoE batches.

Table 23: Composition used for ER coating

| Batches | EC 45 cps | White wax | Isopropyl alcohol | Total weight | Talc (0.5%) |
|---------|-----------|-----------|-------------------|--------------|------------|
|         | mg        | gm        | mg                | gm           | mg         |
| PC 1    | 20        | 60        | 10                | 30           | QS         |
| PC 2    | 20        | 60        | 3                 | 9            | QS         |
| PC 3    | 8         | 24        | 10                | 30           | QS         |
| PC 4    | 8         | 24        | 3                 | 9            | QS         |
| PC 5    | 20        | 60        | 10                | 30           | QS         |
| PC 6    | 20        | 60        | 3                 | 9            | QS         |
| PC 7    | 8         | 24        | 3                 | 9            | QS         |
| PC 8    | 14        | 42        | 6.5               | 19.5         | QS         |
| PC 9    | 8         | 24        | 10                | 30           | QS         |

Above batches were evaluated for dissolution studies and extractability studies.

Drug release studies for design batch PC 1 to PC 8
Figure 6: Graphical representation of Design batch PC 1

Figure 7: Graphical representation of design batch PC 2
Figure 8: Graphical representation of design batch PC 3

Figure 9: Graphical representation of design batch PC 4
Figure 10: Graphical representation of design batch PC 5

Figure 11: Graphical representation of batch PC 6
**Extraction study**

**Table 24 Extraction study design batch PC 1**

| Solvent Type                  | State   | % Extraction |
|-------------------------------|---------|--------------|
| Water (level 1 solvent)       | Intact  | 36.2         |
|                               | Crushed | 56.1         |
| 40% Ethanol (level 2 solvent) | Intact  | 79.9         |
|                               | Crushed | 84.4         |
| 0.1N HCl (level 3 solvent)    | Intact  | 29.5         |
|                               | Crushed | 38.4         |

**Figure 12: Graphical representation of batch PC 7**

**Figure 13: Graphical representation of batch PC 8**
| solvent (level 1) | RPM | stock solution | dilutions | lambda max |
|------------------|-----|----------------|-----------|------------|
| water            | 50  | 100 mg in 300 ml | 1 ml to 10 ml, 3 ml to 10 ml | 243 nm |
|                  |     | 333.33 mcg/ml    | 33.33 mcg/ml, 9.99 mcg/ml     |          |

| Time point (hr) | Intact  | Crushed  | Intact  | Crushed  |
|-----------------|---------|----------|---------|----------|
| 0               | 0       | 0        | 0       | 0        |
| 1               | 0.1912  | 0.3152   | 36.2    | 56.14    |

| solvent (level 2) | condition | media volume | RPM |
|-------------------|-----------|--------------|-----|
| 40% Ethanol       | 300 ml    | 50           |

| Time point (hr) | Intact  | Crushed  | Intact  | Crushed  |
|-----------------|---------|----------|---------|----------|
| 0               | 0       | 0        | 0       | 0        |
| 1               | 0.593   | 0.8074   | 42.46   | 57.83    |

| solvent (level 3) | condition | media volume | RPM |
|-------------------|-----------|--------------|-----|
| 0.1N HCl          | 300 ml    | 50           |

| Time point (hr) | Intact  | Crushed  | Intact  | Crushed  |
|-----------------|---------|----------|---------|----------|
| 0               | 0       | 0        | 0       | 0        |
| 1               | 0.1916  | 0.2489   | 29.52   | 38.35    |

**Table 25: Extraction study of design batch PC 2**

| Extraction studies | % Extraction |
|--------------------|--------------|
| Stage              | 1 h          |
| Water (level 1 solvent) | Intact 11.6  | Crushed 42.2 |
| 40% Ethanol (level 2 solvent) | Intact 58.1  | Crushed 77.6 |
| 0.1N HCl (level 3 solvent) | Intact 22.3  | Crushed 34.2 |

| solvent (level 1) | RPM | Stock solution | dilutions | lambda max |
|------------------|-----|----------------|-----------|------------|
| water            | 50  | 100 mg in 300 ml | 1 ml to 10 ml, 3 ml to 10 ml | 243 nm |
|                  |     | 333.33 mcg/ml    | 33.33 mcg/ml, 9.99 mcg/ml     |          |

| Time point (hr) | Intact  | Crushed  | Intact  | Crushed  |
|-----------------|---------|----------|---------|----------|
| 0               | 0       | 0        | 0       | 0        |
| 1               | 0.0384  | 0.2469   | 11.63   | 42.16    |

| solvent (level 2) | condition | media volume | RPM |
|-------------------|-----------|--------------|-----|
| 40% Ethanol       | 300 ml    | 50           |

| Time point (hr) | Intact  | Crushed  | Intact  | Crushed  |
|-----------------|---------|----------|---------|----------|
| 0               | 0       | 0        | 0       | 0        |
| 1               | 0.0384  | 0.2469   | 11.63   | 42.16    |
| RPM-50 | Absorbance | % drug release |
|--------|------------|----------------|
|        |            |                |

| Time point(hr) | Intact | Crushed | Intact | Crushed |
|----------------|--------|---------|--------|---------|
| 0              | 0      | 0       | 0      | 0       |
| 1              | 0.6741 | 0.902   | 48.26  | 64.61   |

Table 26: Extraction study of design batch PC 3

| Extraction studies | % Extraction |
|--------------------|--------------|
|                    | Stage 1 h    |
| Water (level 1 solvent) | Intact 19.5 | Crushed 41.0 |
| 40% Ethanol (level 2 solvent) | Intact 47.6 | Crushed 49.9 |
| 0.1N HCl (level 3 solvent) | Intact 19.5 | Crushed 46.2 |

| Extraction studies | Condition-media volume-300ml(Distilled water) |
|--------------------|-----------------------------------------------|
| Level 1 solvent (water) | RPM-50 |
| Stock solution dilutions | lambda max |
| 100 mg in 300 ml | 1 ml to 10 ml | 3ml to 10 ml | 243 nm |
| 333.33mcg/ml | 33.33mcg/ml | 9.99 mcg/ml |

| Absorbance | % drug release |
|------------|----------------|
|            |                |

| Time point(hr) | Intact | Crushed | Intact | Crushed |
|----------------|--------|---------|--------|---------|
| 0              | 0      | 0       | 0      | 0       |
| 1              | 0.087  | 0.221   | 19.45  | 40.99   |

Level 2 solvent (40% ethanol)

| Absorbance | % drug release |
|------------|----------------|
|            |                |

| Time point(hr) | Intact | Crushed | Intact | Crushed |
|----------------|--------|---------|--------|---------|
| 0              | 0      | 0       | 0      | 0       |
| 1              | 0.6636 | 0.6965  | 47.55  | 49.89   |

Level 3 solvent (0.1N HCl)

| Absorbance | % drug release |
|------------|----------------|
|            |                |

| Time point(hr) | Intact | Crushed | Intact | Crushed |
|----------------|--------|---------|--------|---------|
| 0              | 0      | 0       | 0      | 0       |
| 1              | 0.132  | 0.2996  | 19.45  | 46.16   |

Table 27: Extraction study of design batch PC 4

| Extraction studies | % Extraction | Absorbance |
|--------------------|--------------|------------|
|                    | Stage 1 h    |            |
| Water (level 1 solvent) | Intact 12.7 | 0.045      |
### Table 28: Extraction study of design batch PC 5

| Extraction studies                              | % Extraction |
|-------------------------------------------------|--------------|
| Stage                                           | 1 h          |
| Water (level 1 solvent)                         |              |
| Intact                                          | 26.7         |
| Crushed                                         | 35.9         |
| 40% Ethanol (level 2 solvent)                    |              |
| Intact                                          | 62.8         |
| Crushed                                         | 87.9         |
| 0.1N HCl (level 3 solvent)                       |              |
| Intact                                          | 32.7         |
| Crushed                                         | 48.2         |

Extraction studies Condition media volume-300 ml (Distilled water)  
**Level 1 solvent (water)**  
RPM-50  
Stock solution Dilutions lambda max  
100 mg in 300 ml 1 ml to 10 ml 3 ml to 10 ml 243 nm  
333.33 mcg/ml 3.33 mcg/ml 9.99 mcg/ml  
**Absorbance** % drug release  
| Time point(hr) | Intact | Crushed | Intact | Crushed |
|----------------|--------|---------|--------|---------|
| 0              | 0      | 0       | 0      | 0       |
| 1              | 0.132  | 0.189   | 26.68  | 35.85   |

**Level 2 solvent (40% ethanol)** Condition media volume-300 ml (40% ethanol)  
RPM-50  
Absorbance % drug release  
| Time point(hr) | Intact | Crushed | Intact | Crushed |
|----------------|--------|---------|--------|---------|
| 0              | 0      | 0       | 0      | 0       |
| 1              | 0.8222 | 1.1502  | 62.81  | 87.86   |

**Level 3 solvent (0.1N HCl)** Condition media volume-300 ml (0.1N HCl)  
RPM-50  
Absorbance % drug release  
| Time point(hr) | Intact | Crushed | Intact | Crushed |
|----------------|--------|---------|--------|---------|
| 0              | 0      | 0       | 0      | 0       |
| 1              | 0.212  | 0.313   | 32.66  | 48.22   |
### Table 29: Extraction study of design batch PC 6

| Extraction studies          | Absorbance | % Extraction |
|-----------------------------|------------|--------------|
| Stage                       | 1 h        |              |
| Water (level 1 solvent)     |            |              |
| Intact                      | 0.057      | 14.63        |
| Crushed                     | 0.199      | 37.45        |
| 40% Ethanol (level 2 solvent)|            |              |
| Intact                      | 0.5248     | 40.091       |
| Crushed                     | 0.4027     | 30.76        |
| 0.1N HCl (level 3 solvent)  |            |              |
| Intact                      | 0.223      | 34.35        |
| Crushed                     | 0.302      | 45.13        |

### Table 30: Extraction study of design batch PC 7

| Extraction studies          | % Extraction |
|-----------------------------|--------------|
| Stage                       | 1 h          |
| Water (level 1 solvent)     |              |
| Intact                      | 30.38        |
| Crushed                     | 58.68        |
| 40% Ethanol (level 2 solvent)|              |
| Intact                      | 79.94        |
| Crushed                     | 84.71        |
| 0.1N HCl (level 3 solvent)  |              |
| Intact                      | 25.48        |
| Crushed                     | 44.48        |

Extraction studies Condition-media volume-300ml (Distilled water)

#### Level 1 solvent (water)

| Stock solution | Dilutions | lambda max |
|----------------|-----------|------------|
| 100 mg in 300 ml | 1 ml to 10 ml | 3 ml to 10 ml | 243 nm |
| 333.33 mcg/ml    | 33.33 mcg/ml   | 9.99 mcg/ml   |

| Absorbance | % drug release |
|------------|---------------|
| Time point (hr) | Intact | Crushed | Intact | Crushed |
| 0           | 0       | 0       | 0       | 0       |
| 1           | 0.155   | 0.331   | 30.38   | 58.68   |

#### Level 2 solvent (40% ethanol)

| Condition- media volume-300 ml (40% ethanol) |
|---------------------------------------------|
| RPM-50                                      |

| Absorbance | % drug release |
|------------|---------------|
| Time point (hr) | Intact | Crushed | Intact | Crushed |
| 0           | 0       | 0       | 0       | 0       |
| 1           | 0.6611  | 0.7021  | 79.94   | 84.71   |

#### Level 3 solvent (0.1N HCl)

| Condition- media volume-300 ml (0.1N HCl) |
|------------------------------------------|
| RPM-50                                   |

| Absorbance | % drug release |
|------------|---------------|
| Time point (hr) | Intact | Crushed | Intact | Crushed |
| 0           | 0       | 0       | 0       | 0       |
| 1           | 0.6611  | 0.7021  | 79.94   | 84.71   |
| Extraction studies | % Extraction |
|--------------------|-------------|
| Stage | 1 h |
| Water (level 1 solvent) | Intact | 23.5 |
| Crushed | 41.0 |
| 40% Ethanol (level 2 solvent) | Intact | 67.7 |
| Crushed | 84.7 |
| 0.1N HCl (level 3 solvent) | Intact | 30.2 |
| Crushed | 34.2 |

| extraction studies | Condition | media volume | 300 ml (Distilled water) |
|--------------------|-----------|--------------|---------------------------|
| **Level 1 solvent (water)** | RPM-50 |
| Stock solution | Dilutions | lambda max |
| 100 mg in 300 ml | 1 ml to 10 ml | 3 ml to 10 ml | 243 nm |
| 333.33 mcg/ml | 33.33 mcg/ml | 9.99 mcg/ml |

| Absorbance | % drug release |
|-----------|----------------|
| Time point (hr) | Intact | Crushed | Intact | Crushed |
| 0 | 0 | 0 | 0 | 0 |
| 1 | 0.112 | 0.21 | 23.47 | 40.99 |

| **Level 2 solvent (40% ethanol)** | Condition | media volume | 300 ml (40% ethanol) |
|----------------------------------|-----------|--------------|-----------------------|
| RPM-50 |

| Absorbance | % drug release |
|-----------|----------------|
| Time point (hr) | Intact | Crushed | Intact | Crushed |
| 0 | 0 | 0 | 0 | 0 |
| 1 | 0.556 | 0.702 | 67.66 | 84.71 |

| **Level 3 solvent (0.1N HCl)** | Condition | media volume | 300 ml (0.1N HCl) |
|---------------------------------|-----------|--------------|-------------------|
| RPM-50 |

| Absorbance | % drug release |
|-----------|----------------|
| Time point (hr) | Intact | Crushed | Intact | Crushed |
| 0 | 0 | 0 | 0 | 0 |
| 1 | 0.196 | 0.212 | 30.18 | 32.65 |

Process parameter of which can be set on the preparation of design batches are as follows:
### Batch PC 1

#### Table 32: Process parameter for extended release coating of design batch PC 1

| Time (min) | Air flow | Inlet air temp(°C) | Column height(cm) | Spray rate | Product temp(°C) | Exhaust air temp(°C) |
|------------|----------|--------------------|-------------------|------------|-----------------|----------------------|
| 0          | 0        | 0                  | 0                 | 0          | 0               | 0                    |
| 20         | 80       | 30                 | 18                | 10.89      | 25.9            | 25.5                 |
| 40         | 80       | 30                 | 18                | 10.89      | 25.9            | 25.7                 |
| 60         | 82       | 30.1               | 20                | 10.89      | 27.2            | 27.3                 |
| 80         | 79       | 30.5               | 20                | 12.77      | 27.5            | 27.5                 |
| 100        | 86       | 38.6               | 20                | 23.61      | 32.3            | 30.3                 |
| 120        | 90       | 38.3               | 20                | 30.25      | 32.5            | 32.3                 |
| 140        | 91       | 38                 | 20                | 30.24      | 32.1            | 31.9                 |
| 160        | 90       | 38.2               | 20                | 30.24      | 32.1            | 31.8                 |

### Batch PC 2

#### Table 33: Process parameter for extended release coating of design batch PC 2

| Time (min) | Air flow | Inlet air temp(°C) | Column height(cm) | Spray rate | Product temp(°C) | Exhaust air temp(°C) |
|------------|----------|--------------------|-------------------|------------|-----------------|----------------------|
| 0          | 0        | 0                  | 0                 | 0          | 0               | 0                    |
| 10         | 96       | 40.5               | 18                | 15         | 33.3            | 33.3                 |
| 30         | 98       | 40                 | 18                | 15         | 33.2            | 32.8                 |
| 50         | 84       | 40.8               | 19                | 20         | 33.4            | 33                   |
| 70         | 92       | 40.9               | 18                | 20         | 33.1            | 32.9                 |
| 90         | 90       | 40.8               | 18                | 20         | 33.4            | 32.8                 |

### Batch PC 3

#### Table 34: Process parameter for extended release coating of design batch PC 3

| Time (min) | Air flow | Inlet air temp(°C) | Column height(cm) | Spray rate | Product temp(°C) | Exhaust air temp(°C) |
|------------|----------|--------------------|-------------------|------------|-----------------|----------------------|
| 0          | 0        | 0                  | 0                 | 0          | 0               | 0                    |
| 20         | 98       | 40.1               | 18                | 30.82      | 30.1            | 30                   |
| 40         | 98       | 40.2               | 18                | 30.82      | 30              | 30.1                 |
| 60         | 95       | 40.4               | 19                | 30.8        | 31.2            | 31.1                 |
| 90         | 93       | 40.2               | 18                | 30.8        | 31.3            | 31.2                 |
| 120        | 97       | 40                 | 18                | 30.8        | 31.2            | 30.1                 |

### Batch PC 4

#### Table 35: Process parameter for extended release coating of design batch PC 4

| Time (min) | Air flow | Inlet air temp(°C) | Column height(cm) | Spray rate | Product temp(°C) | Exhaust air temp(°C) |
|------------|----------|--------------------|-------------------|------------|-----------------|----------------------|
| 0          | 0        | 0                  | 0                 | 0          | 0               | 0                    |
| 20         | 99       | 40.1               | 18                | 30.86      | 30.1            | 30                   |
| 40         | 99       | 40.2               | 18                | 30.86      | 30              | 30.1                 |
| 60         | 95       | 40.2               | 19                | 30.8        | 31.2            | 31.1                 |
| 90         | 95       | 30.41              | 18                | 30.8        | 31.3            | 31.2                 |

### Batch PC 5

#### Table 36: Process parameter for extended release coating of design batch PC 5

| Time (min) | Air | Inlet air temp(°C) | Column | Spray | Product | Exhaust air temp(°C) |
|------------|-----|--------------------|--------|-------|---------|----------------------|
Dissolution data and extraction studies provide information regarding the drug release in presence of different media. It was observed that drug release profile of intact pellets and crushed pellets are nearly similar. Apart from this extraction studies provides significant drug release in different solvents. In extraction studies it was observed that dose dumping in 40% ethanol was prevented and significant release of drug.
SUMMARY AND CONCLUSION (Buhse, 2016)

The present study showed that drug containing carbopol 974P NF pellets were successfully prepared. Carbopol 974P NF matrix found effective to protect the drug in ethanol, while effectively releasing the drug up to 24 hrs. The % drug release was studied in appropriate medias simulating the conditions and maintaining the release at precise rate. The pellets were prepared using granurex technique. The optimization of the drug loaded carbopol 974P NF pellets was done using $2^3$ full factorial design with critical variables like Concentration of carbopol polymer and concentration of white wax and concentration of ethyl cellulose 45 cps was investigated. During formulation it was revealed that increasing the carbopol concentration up to certain level, hard pellets were observed. While ethyl cellulose 45 cps concentration affects % drug release of the pellets by forming the coat on the drug layered pellets. The present study shows the use of carbopol 974P NF as a tool to protect the drug entity and thereby helping to release the drug in the desired site. This type of approach can be used for retard the drug release. An in-vitro performance test revealed that the optimized batch shows less than 10% drug release in 1 hours and about 94.9% in 20 hours. Apart from this, it was observed that difference between the intact pellets and crushed pellets were less. Hence, we successfully formulated drug loaded carbopol 974P NF matrix based pellets which deter the abuse and has a potential of retard the drug release by using carbopol 974P NF.

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