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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**.**

Table 1 Solubility values of drug in different media

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* l. 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	0
1	5	0.296167	0.368767	0.358667	0.468967	0.389867

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	

Table 3: Regression parameters

Regression parameters	**Values**				
	0.1N HCl	**0.1N NaOH**	**Distilled water**	**40% ethanol**	**6.8 phosphate buffer**
Correlation co efficient	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 λ 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 size 3000 capsules				
Batch	**DS 1**	**DS 2**	**DS 3**	**DS 4**	**DS 5**

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	50	150	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 1was 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.

Table 5: Effect of concentration of binder

Batch	DS 1		DS 2		DS 3		DS 4		DS 5	
Binder	mg	gm	mg	gm	mg	gm	mg	gm	mg	gm
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	DS 1		DS 2		DS 3		DS 4		DS 5	
Binder	mg	gm	mg	gm	mg	gm	mg	gm	mg	gm

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

Flow rate of binder solution by peristaltic pump:

Table 8: Effect of Peristaltic pump in trail batches

Flow rate	1 ml /min	1ml/min	3 ml/min	1 ml/min	1ml/min

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)

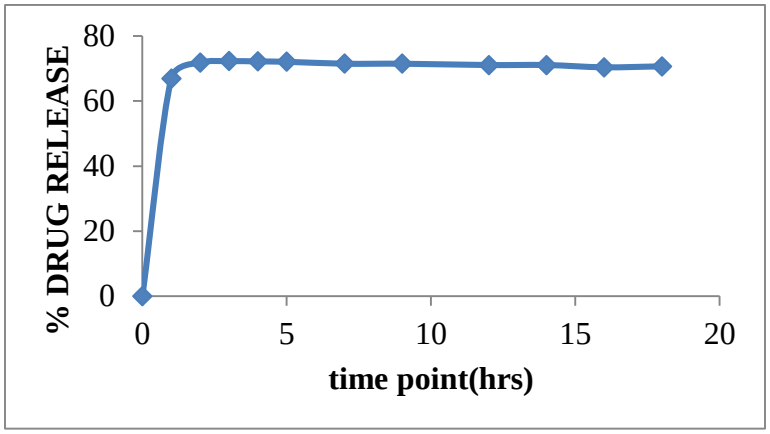


Figure 1: Graphical representation of dissolution data of batch DS 1

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:

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

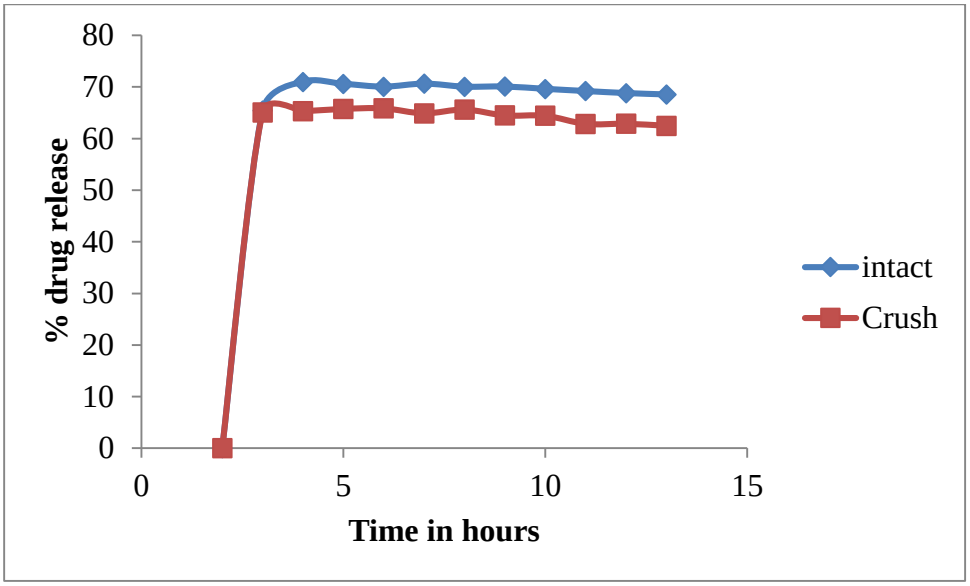


Figure 2: Graphical representation of dissolution data of batch DS 2 in 0.1N HCl

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 dose not retard the release rate.

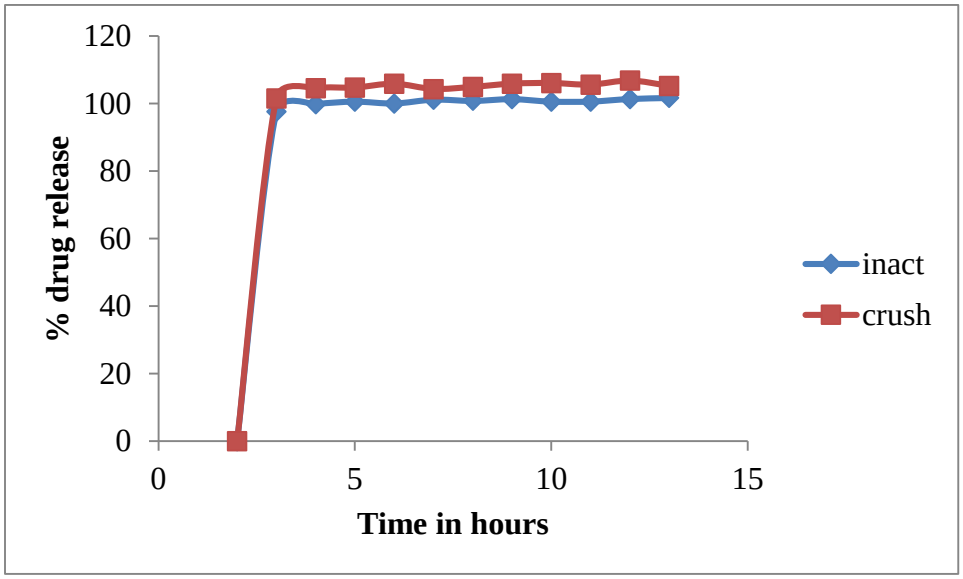


Figure 3: Graphical representation of drug release study of DS2 batch in 6.8 phosphate buffer

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 release within 1 hrs. So, they dose not retard the release rate. Therefore, further studies in different time points were not preformed.

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 release within 3 hrs. So, they dose not retard the release rate. Therefore, further studies in different time points were not be performed.

Drug release study of trial batch DS 5:

A drug release study was performed in 0.1N HCl.

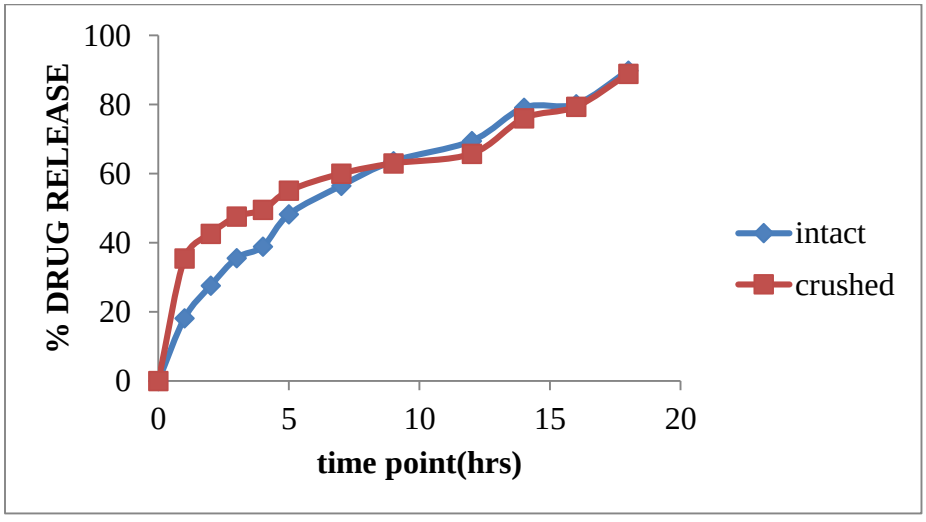


Figure 4: Graphical representation of batch DS 5:

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

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

Drug release study of ER coated tablet in 0.1N HCl.

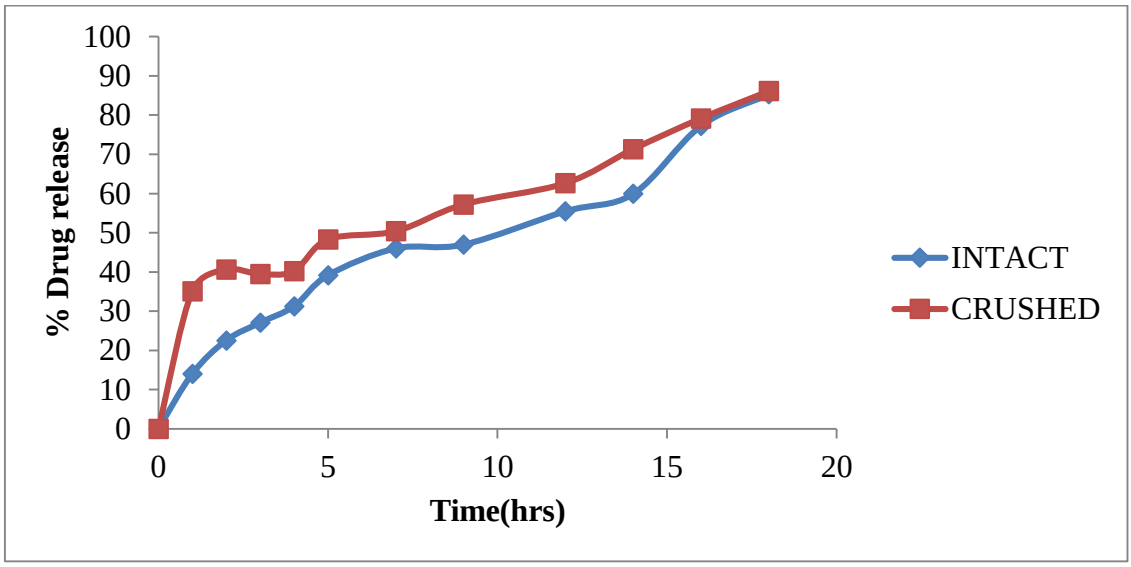


Figure 5: Graphical representation of drug release study of trial batch DS 5

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

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

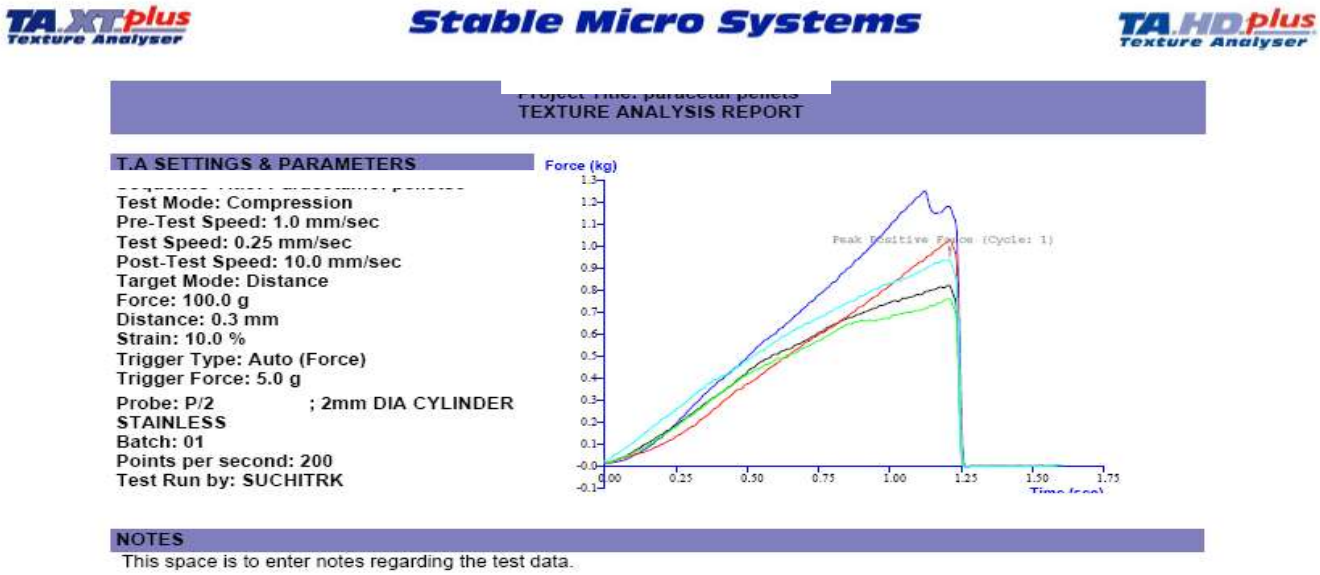
PC 2	40	20	3
PC3	40	8	10
PC 4	70	8	3
PC 5	70	20	10
PC 6	70	20	3
PC 7	40	8	3
PC 8	55	14	6.5
PC 9	55	12	4.5

Response of design batches.

Table 14: Responses of these design batches

Crusibility		**Loss on drying**	**LOD after drying**	**% Assay**	
Average of 5 pellets	**Standard deviation**	**105°C for 10 min**	**40°C for 24 hrs**	N=1	N=3
0.96	0.193	4.40%	3.40%	95.27%	93.52%
0.992	0.25	4.61%	2.61%	96.66%	94.63%
0.781	0.235	6.40%	5.54%	91.52%	94.77%
0.58	0.065	8.55%	5.67%	96.38%	95.37%
0.841	0.085	6.70%	4.81%	101.95%	98.94%
1.143	0.117	3.12%	2.12%	96.11%	93.27%
0.845	0.223	0.97%	0.88%	96.94%	92.44%
1.26	0.138	9.83%	5.66%	103.33%	98.56%
0.99	0.101	2.21%	4.01%	98%	98.30%

Crushing strength of design batch PC 1



TA.XT.plus Texture Analyser — Stable Micro Systems — TA.HD.plus Texture Analyser

RESULTS

Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 01	01		
End Batch 01	01		
Average:	01 (F)	AVERAGE("BATCH")	0.960
S.D.	01 (F)	STDEV("BATCH")	0.193
Coef. of Variation	01 (F)	STDEV("BATCH") / AVERAGE("BATCH") * 100	20.085
End of Test Data			

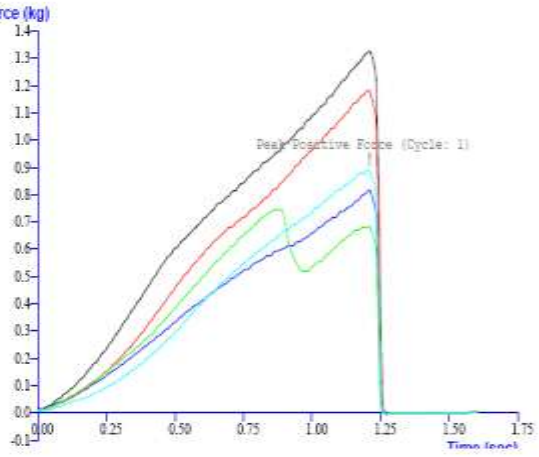
Crushing strength of design batch PC 2

TA.XT.plus Texture Analyser — Stable Micro Systems — TA.HD.plus Texture Analyser

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: 100.0 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



NOTES

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TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

RESULTS

Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 02	02		
pellets1	02		1.326
pellets2	02		0.818
pellets3	02		1.182
pellets4	02		0.746
pellets5	02		0.890
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	25.153
End of Test Data			

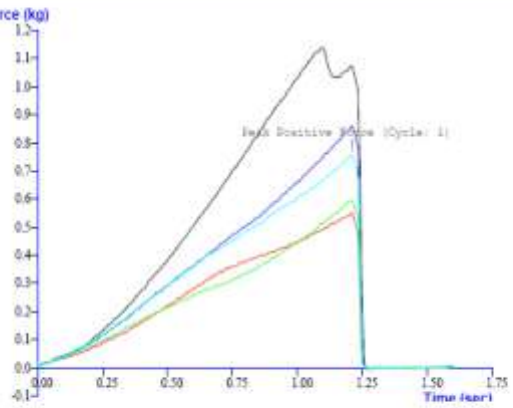
Crushability studies of design batch PC 3

TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

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: 100.0 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: 03
Points per second: 200
Test Run by: SUCHITRK



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TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

RESULTS

Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 03	03		
pellets031	03		1.138
pellets032	03		0.861
pellets033	03		0.552
pellets034	03		0.596
pellets035	03		0.756
End Batch 03	03		
Average:	03 (F)	AVERAGE("BATCH")	0.781
S.D.	03 (F)	STDEV("BATCH")	0.235
Coef. of Variation	03 (F)	STDEV("BATCH") / AVERAGE("BATCH") * 100	30.130
End of Test Data			

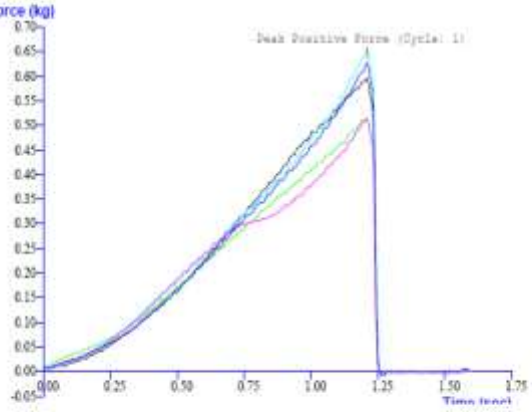
Crushability of design batch PC 4

TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

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: 100.0 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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TA.XT.plus Texture Analyser — Stable Micro Systems — TA.HD.plus Texture Analyser

RESULTS

Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 04	04		
pellets0	04		0.595
pellets1	04		0.627
pellets3	04		0.511
pellets4	04		0.654
pellets5	04		0.514
End Batch 04	04		
Average:	04 (F)	AVERAGE("BATCH")	0.580
S.D.	04 (F)	STDEV("BATCH")	0.065
Coef. of Variation	04 (F)	STDEV("BATCH") / AVERAGE("BATCH") * 100	11.253
End of Test Data			

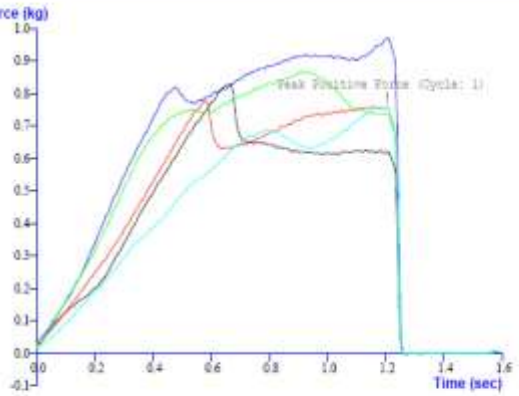
Crushability of design batch PC 5

TA.XT.plus Texture Analyser — Stable Micro Systems — TA.HD.plus Texture Analyser

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: 100.0 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: 05
Points per second: 200
Test Run by: SUCHITRK



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TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

RESULTS

Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 05	05		
pellets1	05		0.828
pellets2	05		0.971
pellets3	05		0.778
pellets4	05		0.870
pellets5	05		0.758
End Batch 05	05		
Average:	05 (F)	AVERAGE("BATCH")	0.841
S.D.	05 (F)	STDEV("BATCH")	0.085
Coef. of Variation	05 (F)	STDEV("BATCH") / AVERAGE("BATCH") * 100	10.114
End of Test Data			

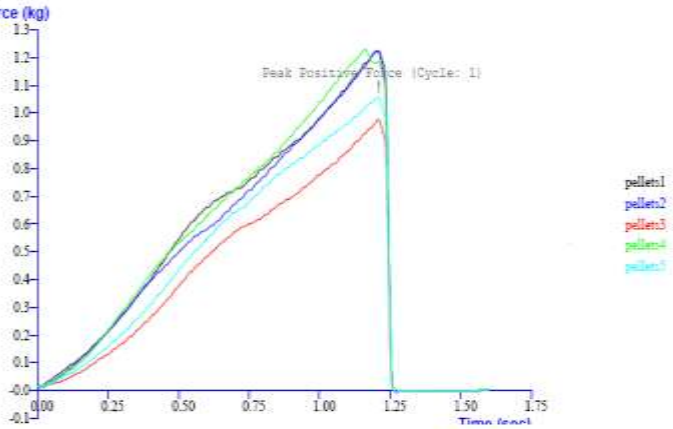
Credibility study of design batch PC 6

TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

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: 100.0 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: 06
Points per second: 200
Test Run by: SUCHITRK



NOTES

This space is to enter notes regarding the test data.

TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

RESULTS

Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 06	06		
pellets	06		1.223
pellets	06		1.226
pellets	06		0.979
pellets	06		1.231
pellets	06		1.058
End Batch 06	06		
Average:	06 (F)	AVERAGE("BATCH")	1.143
S.D.	06 (F)	STDEV("BATCH")	0.117
Coef. of Variation	06 (F)	STDEV("BATCH") / AVERAGE("BATCH") * 100	10.275
End of Test Data			

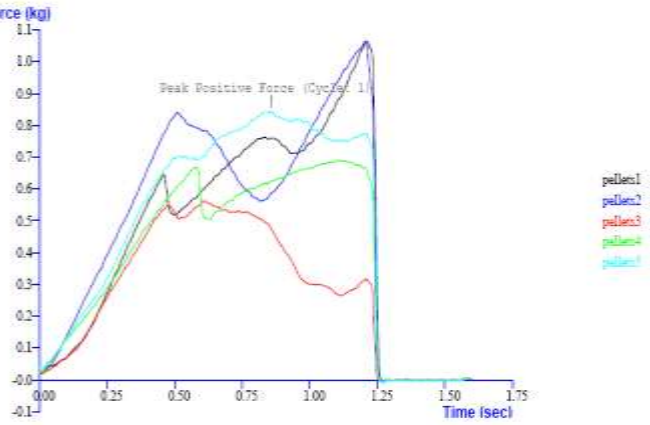
Crushability of design batch PC 7

TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

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: 100.0 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: 07
Points per second: 200
Test Run by: SUCHITRK



NOTES

This space is to enter notes regarding the test data.

TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

RESULTS

Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 07	07		
pellets1	07		1.065
pellets2	07		1.063
pellets3	07		0.563
pellets4	07		0.691
pellets5	07		0.843
End Batch 07	07		
Average:	07 (F)	AVERAGE("BATCH")	0.845
S.D.	07 (F)	STDEV("BATCH")	0.223
Coef. of Variation	07 (F)	STDEV("BATCH") / AVERAGE("BATCH") * 100	26.416
End of Test Data			

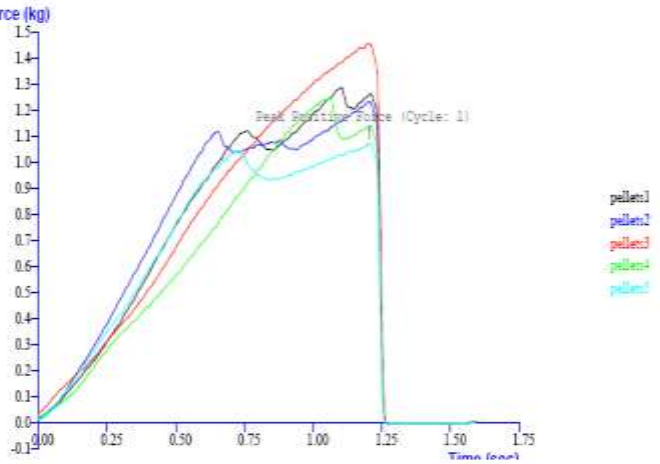
Crushability study of design batch PC 8

TA.XT plus Texture Analyser — Stable Micro Systems — TA.HD plus Texture Analyser

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: 100.0 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.

TA.XT.plus Texture Analyser **Stable Micro Systems** TA.HD.plus Texture Analyser

RESULTS

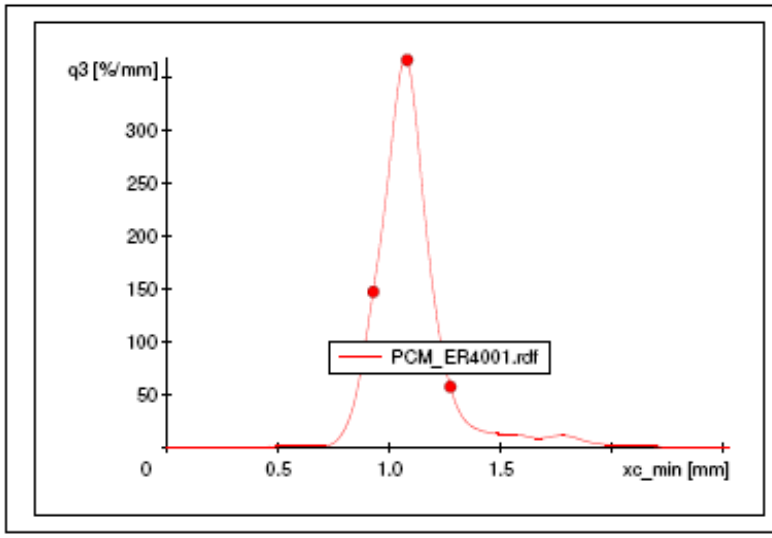
Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 08	08		
pellets	08		1.288
pellets	08		1.233
pellets	08		1.458
pellets	08		1.247
pellets	08		1.072
End Batch 08	08		
Average:	08 (F)	AVERAGE("BATCH")	1.260
S.D.	08 (F)	STDEV("BATCH")	0.138
Coef. of Variation	08 (F)	STDEV("BATCH") / AVERAGE("BATCH") * 100	10.942
End of 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.

CAMSIZER® Retsch® TECHNOLOGY

Company:	Retsch Technology
User:	formulation2
Result file:	C:\Solution11\CAMDAT\PCM\PCM_ER4001.rdf
Task file:	C:\Solution11\CAMSYS\PCM.afg
Time:	11/22/2017 , 17:15 , duration 0 min 17 s at 1.0 % covered area, image rate 1:1 and 60 mm feeder
Particle model:	xc_min
No. of particles:	CCD-B = 5523 , CCD-Z = 721
Fitting:	no
Material:	

Size class	[mm]	p3 [%]	Q3 [%]	SPHT3	Symm3	b/l3	PDN
	< 0.160	0.00	0.00	0.854	0.859	0.793	612
0.160	0.250	0.00	0.00	0.940	0.914	0.827	8
0.250	0.400	0.01	0.01	0.945	0.956	0.726	11
0.400	0.630	0.30	0.31	0.914	0.929	0.789	132
0.630	1.000	23.96	24.27	0.958	0.937	0.904	1832
1.000	1.600	72.15	96.42	0.896	0.905	0.812	3245
1.600	2.500	3.58	100.00	0.729	0.756	0.804	40
2.500	4.000	0.00	100.00				0
4.000	6.300	0.00	100.00				0
6.300	10.000	0.00	100.00				0
> 10.000		0.00	100.00				0



Characteristics

Q3 [%]	x [mm]
10.0	0.930
50.0	1.075
90.0	1.270

x [mm]	Q3 [%]
1.000	24.3
2.000	99.6
4.000	100.0

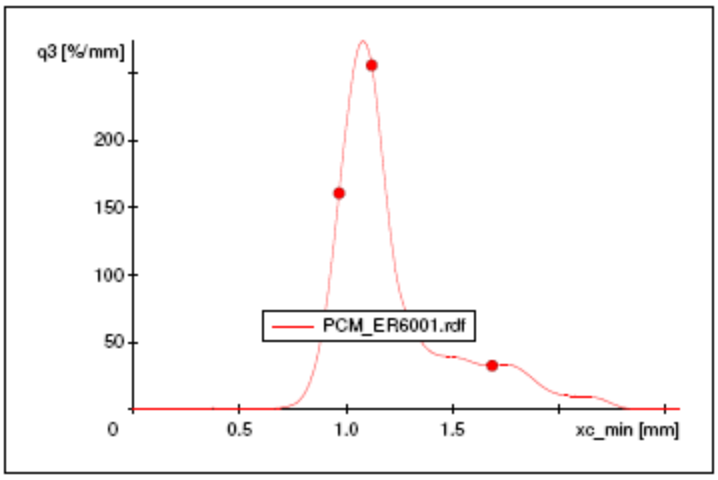
SPAN3 = 0.316
U3 = 1.185

Particle size of Design batch PC 6

CAMSIZER® Retsch® TECHNOLOGY

Company:	Retsch Technology
User:	formulation2
Result file:	CASolution11\CAMDAT\PCM\PCM_ER6001.rdf
Task file:	CASolution11\CAMSYS\PCM.afg
Time:	11/22/2017 , 17:18 , duration 0 min 17 s at 1.0 % covered area, image rate 1:1 and 60 mm feeder
Particle model:	xc_min
No. of particles:	CCD-B = 2671 , CCD-Z = 262
Fitting:	no
Material:	

Size class	[mm]	p3 [%]	Q3 [%]	SPHT3	Symm3	b/l3	PDN
	< 0.160	0.00	0.00	0.859	0.827	0.753	144
0.160	0.250	0.01	0.01	0.909	0.880	0.768	19
0.250	0.400	0.09	0.10	0.910	0.913	0.770	96
0.400	0.630	0.03	0.13	0.918	0.947	0.731	10
0.630	1.000	15.84	15.97	0.949	0.935	0.892	665
1.000	1.600	71.15	87.12	0.818	0.856	0.711	1632
1.600	2.500	12.88	100.00	0.661	0.726	0.723	82
2.500	4.000	0.00	100.00				0
4.000	6.300	0.00	100.00				0
6.300	10.000	0.00	100.00				0
> 10.000		0.00	100.00				0



Characteristics

Q3 [%]	x [mm]
10.0	0.969
50.0	1.123
90.0	1.690

x [mm]	Q3 [%]
1.000	16.0
2.000	97.7
4.000	100.0

SPAN3 = 0.642
U3 = 1.198

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

210	35	0.11	549	19.7	4.2	3	-0.2

Batch PC 2

Table 16: Process parameter of design batch PC 2 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	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	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	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	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	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

90	35	0.11	460	21.7	6	1	-0.4
120	35	0.11	460	20.9	7.5	5	-0.4
150	35	0.11	544	20.6	8.5	7	-0.4
180	35	0.11	544	20.5	9	10	-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	gm	mg	gm	mg	gm
PC 1	20	60	10	30	QS	2160	285	855	1.43	4.28
PC 2	20	60	3	9	QS	1656	278	834	1.39	4.17
PC 3	8	24	10	30	QS	1296	273	819	1.37	4.1
PC 4	8	24	3	9	QS	729	296	888	1.48	4.44
PC 5	20	60	10	30	QS	1512	315	945	1.58	4.73
PC 6	20	60	3	9	QS	1656	308	924	1.54	4.62
PC 7	8	24	3	9	QS	1584	266	798	1.33	3.99
PC 8	14	42	6.5	19.5	QS	1476	290.5	871.5	1.45	4.36
PC 9	8	24	10	30	QS	1296	303	909	1.52	4.55

Above batches were evaluated for dissolution studies and extractability studies.

Drug release studies for design batch PC 1 to PC 8

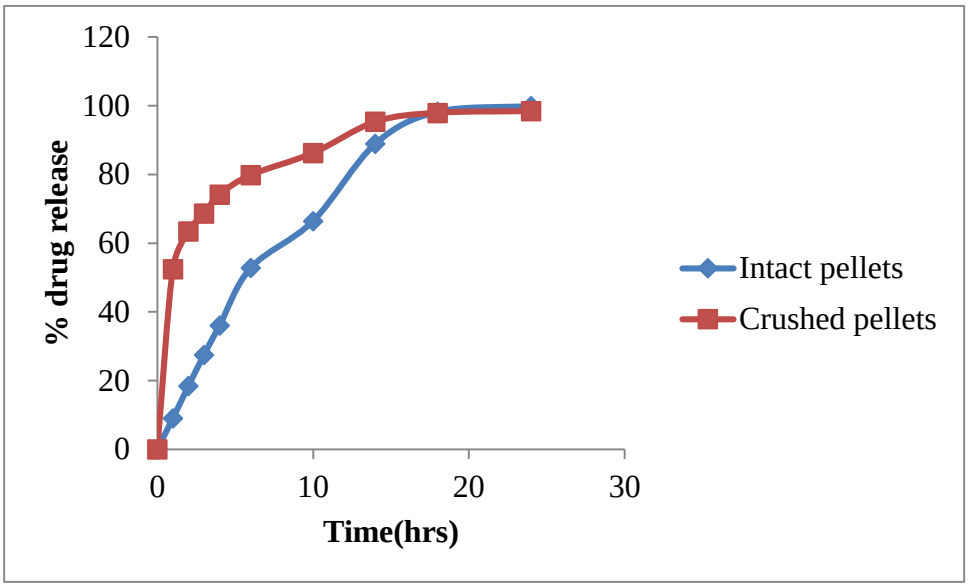


Figure 6: Graphical representation of Design batch PC 1

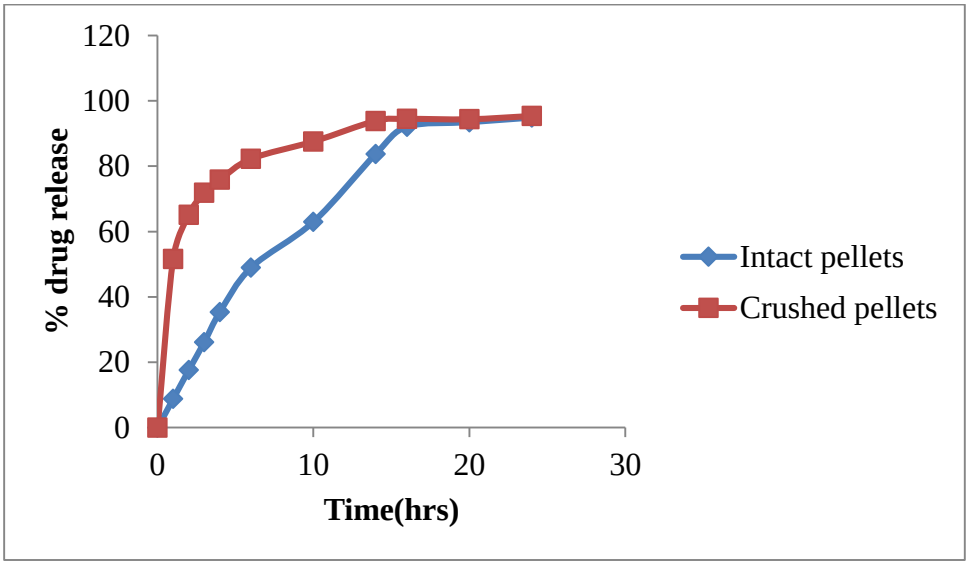


Figure 7: Graphical representation of design batch PC 2

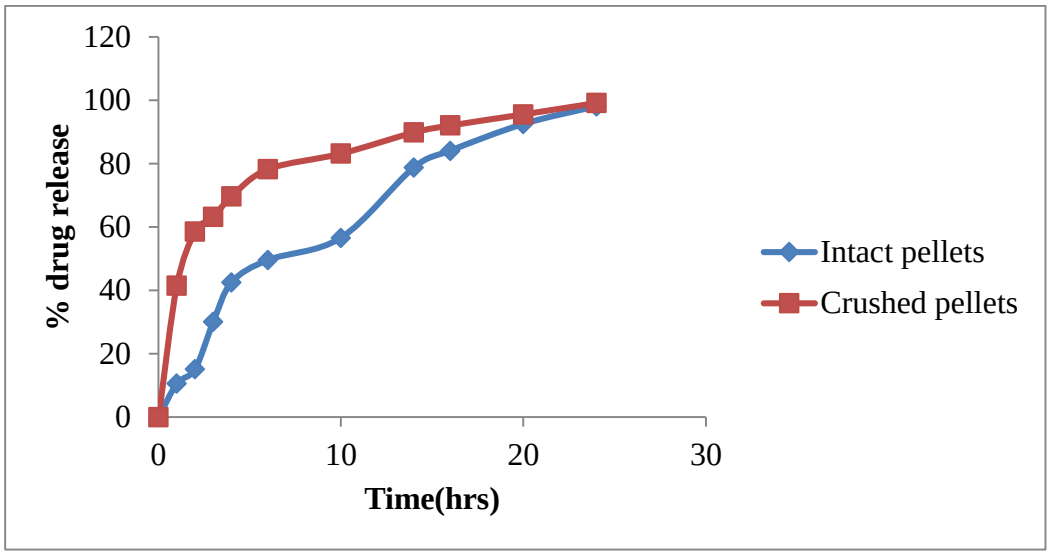


Figure 8: Graphical representation of design batch PC 3

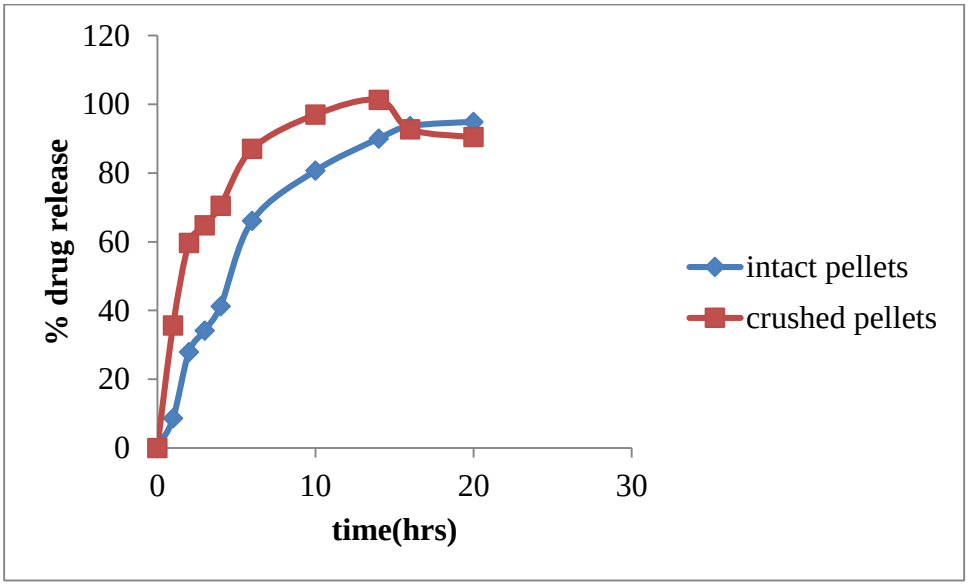


Figure 9: Graphical representation of design batch PC 4

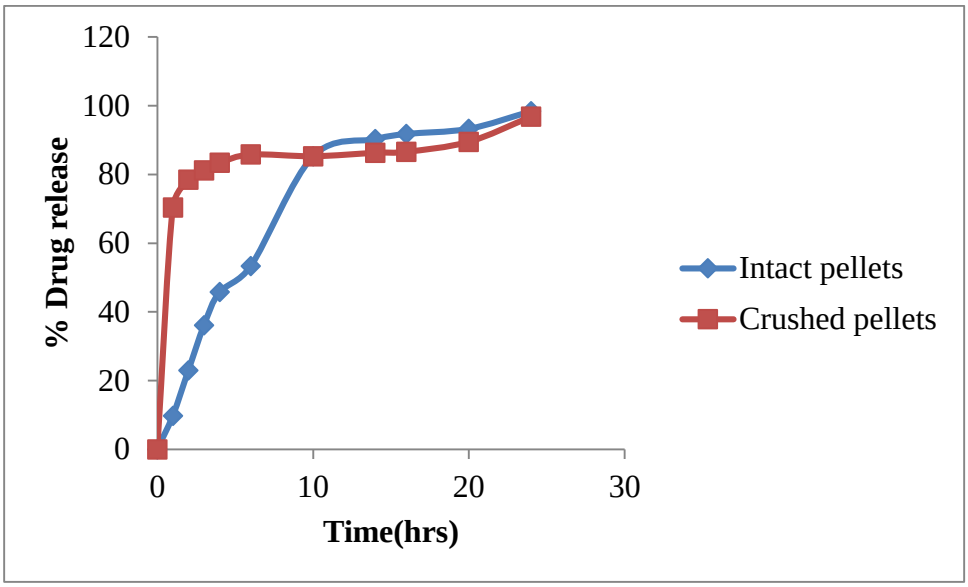


Figure 10: Graphical representation of design batch PC 5

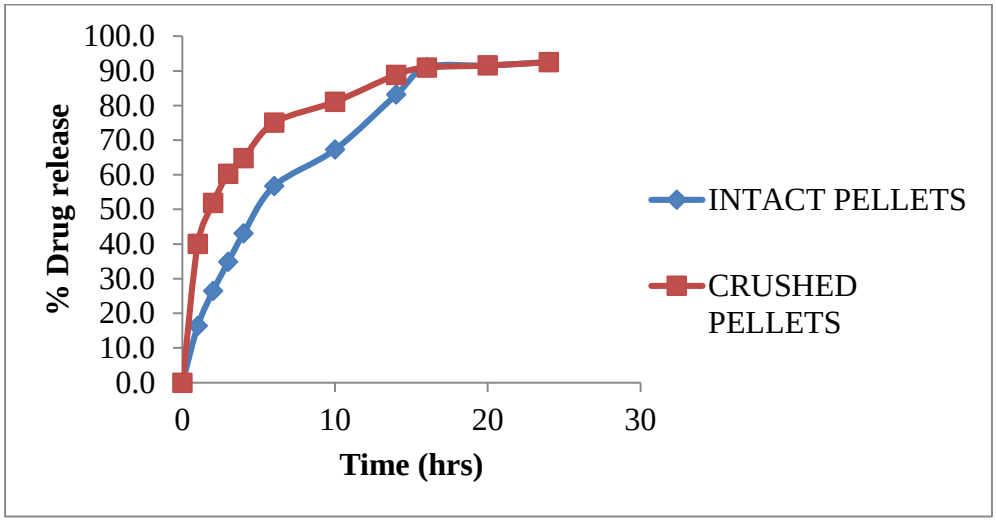


Figure 11: Graphical representation of batch PC 6

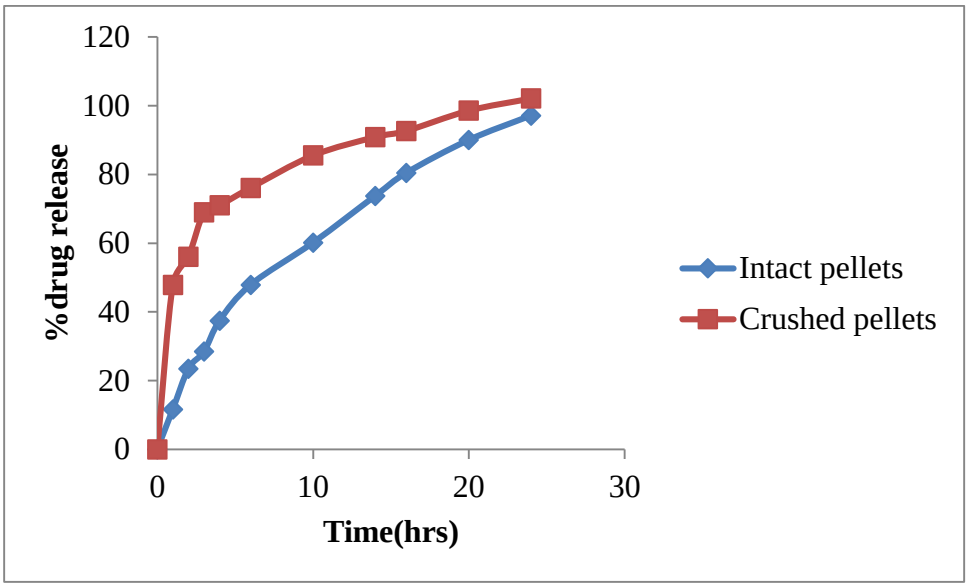


Figure 12: Graphical representation of batch PC 7

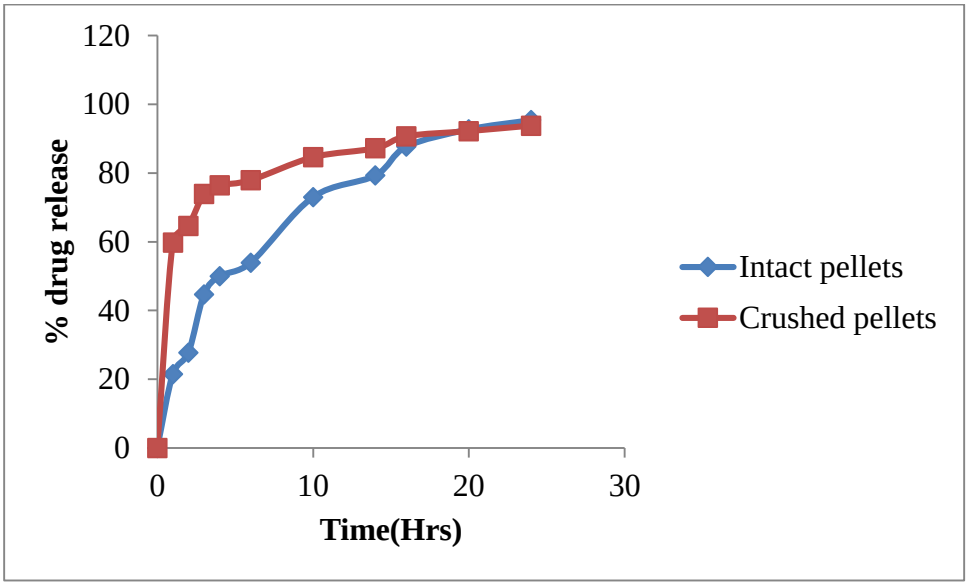


Figure 13: Graphical representation of batch PC 8

Extraction study

Table 24 Extraction study design batch PC 1

		% Extraction		
	Stage	1 h		
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		
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	0.1912	0.3152	36.2	56.14
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	0.593	0.8074	42.46	57.83
level 3 solvent(0.1N HCl)	condition- media volume-300 ml(0.1N HCl)			
	RPM-50			
	Absorbance		**% drug release**	
Time point(hr)	**Intact**	**Crushed**	**ntact**	**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		
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	0.0384	0.2469	11.63	42.16
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	0.6741	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)	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	0.6636	0.6965	47.55	49.89
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	0.132	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

	Crushed	23.95	0.115
40% Ethanol(level 2 solvent)	Intact	40.48	0.599
	Crushed	54.5	0.7135
0.1N HCl(level 3 solvent)	Intact	21.42	0.1052
	Crushed	35.6	0.2311

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-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	0.132	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)	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	0.155	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	0.1655	0.2999	25.48	44.48

Table 31: Extraction study of design batch PC 8

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-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	0.112	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	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	Air flow	Inlet air temp(°C)	Column height	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	Air flow	Inlet air temp(°C)	Column height	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	Air flow	Inlet air temp(°C)	Column height	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	Air	Inlet air	Column	Spray	Product	Exhaust air temp(°C)

	flow	temp(°C)	height	rate	temp(°C)	
0	0	0	0	0	0	0
20	99	40	19	30	29.1	28
40	97	40.1	19	30	30	29.1
60	97	40.4	20	30	30.2	30
90	93	40.2	20	30	30.3	29.2
120	97	40	20	30.8	31	30.1

Batch PC 6

Table 37: Process parameter for extended release coating of design batch PC 6

Time	Air flow	Inlet air temp(°C)	Column height	Spray rate	Product temp(°C)	Exhaust air temp(°C)
0	0	0	0	0	0	0
20	90	30	19	15.79	24.9	25.3
40	95	30	19	14.32	25	25.5
60	92	29.8	20	15.63	27	27
80	97	30.2	20	14.93	27.2	27.2
100	96	35.6	20	15	31.3	30.2
120	95	37.8	20	15	32	31
140	93	37.5	20	13	32	31.3

Batch PC 7

Table 38: Process parameter for extended release coating of design batch PC 7

Time	Air flow	Inlet air temp(°C)	Column height	Spray rate	Product temp(°C)	Exhaust air temp(°C)
0	0	0	0	0	0	0
10	98	40.3	19	18	35.2	33.1
30	100	40.1	18	18	35	32.5
50	100	41	19	19	34.1	32.9
70	92	40.3	19	20	34.9	33
90	95	43.2	19.2	20	35	33.1

Batch PC 8

Table 39: Process parameter for extended release coating of design batch 8

Time	Air flow	Inlet air temp(°C)	Column height	Spray rate	Product temp(°C)	Exhaust air temp(°C)
0	0	0	0	0	0	0
20	98	40.3	19	35	30.6	30.2
40	99	40	19	30	31	30.4
60	95	40.5	20	30	31.1	31.7
90	94	35.23	20	28	33	31.3

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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