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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.

Sr	Drug	0.1N HCl	Phthalate	Phosphate	Phosphate
no			buffer pH 4.5	buffer pH 6.8	buffer pH 7.4
1	Oxycodone	0.0894gm/ml	0.0061 gm/ml	0.0056gm/ml	0.0049gm/ml
	hydrochloride	_	-	-	-
Esta	ablishment of stan	dard curve(Calil	oration curve) fo	or UV visible spect	roscopy method for
ana	lysis of Oxycodone	hydrochloride i	<u>n 0.1N HCl.</u>		

100mg Oxycodone hydrochloride was dissolved in 5 ml methanol and then diluted with 0.1N HClupto 100 ml to procedure stock solution $1000 \ \mu g/ml$. Preparation of stock solution 2:10 ml of stockwww.ajptr.com142

1 solution was taken and diluted with 0.1N HCl upto 100 ml to produce 100 μ g/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:

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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 μ g/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 μ g/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 μ g/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 μ g/ml stock solution concentrations.

	Concentratio	Average. A	bsorbance			
Sr	n			Distilled	40%	6.8 phosphate
no	(µg/ <i>ml</i>)	0.1N HCl	0.1N NaOH	water	ethanol	buffer
0	0	0	0	0	0	0
1	5	0.296167	0.368767	0.358667	0.468967	0.389867

Table 2: Values of Absorbance in different media

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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	

Regression	Values				
parameters	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

Table 3: Regression parameters

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 \rightarrow wt 0.15 g

Oxycodone hydrochloride \rightarrow 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 $\lambda \max = 257$ 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%.

Batch size 3000 capsules Batch **DS** 1 **DS 2 DS 3 DS 4 DS 5** www.ajptr.com

Table 4: Preliminary trial batches

II. J. I I	laimi	ech K	es. 20.	19; 9((J4)		15	SN: 2	249-:
mg	gm	mg	gm	mg	gm	mg	gm	mg	gm
100	300	100	300	100	300	100	300	100	300
100	300	100	300	50	150	100	300	100	300
10	30	60	180	80	240	50	150	60	180
10	30	10	30	10	30	10	30	10	30
5	15	5	15	5	15	5	15	5	15
	mg 100 100 10	mg gm 100 300 100 300 100 300 100 30 100 30 100 30	mggmmg100300100100300100103060103010	mggmmggm1003001003001003001003001003060180100301030	mggmmggmmg10030010030010010030010030050103060180801030103010	100 300 100 300 100 300 100 300 100 300 100 300 100 300 100 300 50 150 10 30 60 180 80 240 10 30 10 30 10 30	mggmmggmmggmmg100300100300100300100100300100300501501001003060180802405010301030103010	mggmmggmmggmmggm100300100300100300100300100300100300501501003001003006018080240501501030103010301030	mggmmggmmggmmggmmg1003001003001003001003001001003001003005015010030010010030060180802405015060103010301030103010

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.

				DS 3)	DS 4	ŀ	DS 5	•
ng	gm	mg	gm	mg	gm	mg	gm	mg	gm
0	30	10	30	20	60	10	30	10	30
j	15	5	15	15	45	5	15	5	15
IS	1080	qs	1080	qs	2520	qs	1080	qs	1080
5	0 s	0 30 15 s 1080	0 30 10 15 5 s 1080 qs	0 30 10 30 15 5 15 s 1080 qs 1080	0 30 10 30 20 15 5 15 15 s 1080 qs 1080 qs	0 30 10 30 20 60 15 5 15 15 45 s 1080 qs 1080 qs 2520	0 30 10 30 20 60 10 15 5 15 15 45 5	0 30 10 30 20 60 10 30 15 5 15 15 45 5 15 s 1080 qs 1080 qs 2520 qs 1080	0 30 10 30 20 60 10 30 10 15 5 15 15 45 5 15 5 s 1080 qs 1080 qs 2520 qs 1080 qs

 Table 5: Effect of concentration of binder

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

Nimesh	Am. J. PharmTech Res. 2019;9(04)								ISSI	N: 2249-3387	
	- FG 45	10	20	10	20	20	(0)	10	20	10	
	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 pu	np and flow	rate in shap	pe of the particles
	r r r			· · · · · · · · · · · · · · · · · · ·

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)

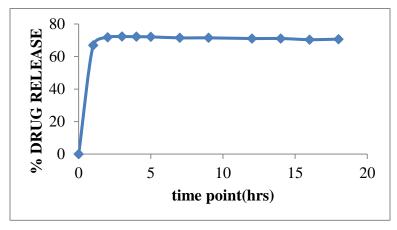
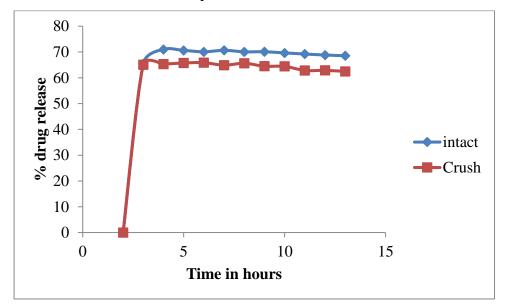


Figure 1: Graphical representation of dissolution data of batch DS 1

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





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.

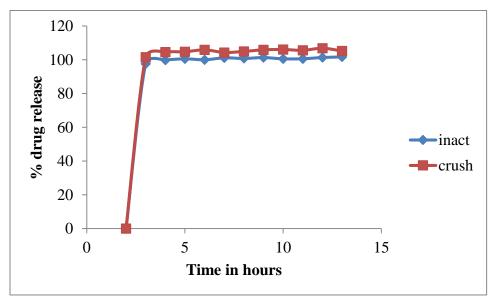


Figure 3: Graphical representation of drug release study of DS2 batch in 6.8 phosphate buffer

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:

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.

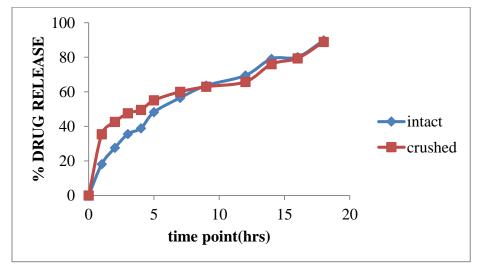


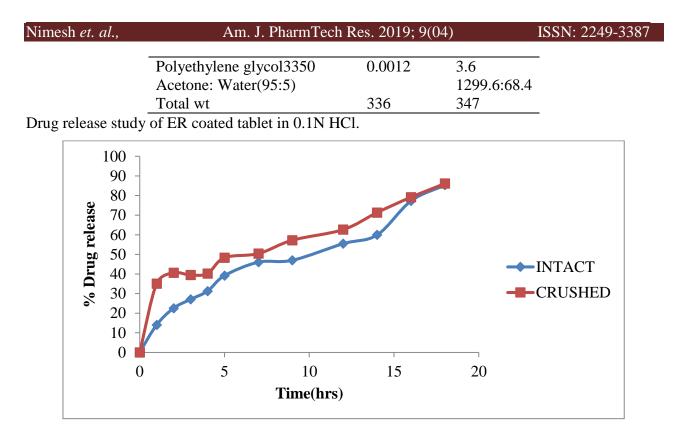
Figure 4: Graphical representation of batch DS 5:

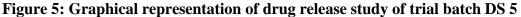
According to the data it was shows that there are steady increase in the drug release with respect to the time. No rapid release in drug in earlier time points. According to this data batch DS 5 was taken as center point in design of experiment studies.

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

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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

3² 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.

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

 Table 13: Full factorial design batches

Nimesh et. al.,	Am. J. Pha	rmTech Res. 2019	;9(04)	ISSN: 2249-3387
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.

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%

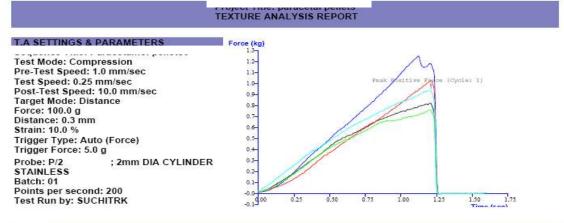
Table 14: Responses of these design batches

Crushing strength of design batch PC 1

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Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 01	01		2010, 2
End Batch 01	01		1
End Batch 01 Average:	01 01 (F)	AVERAGE("BATCH")	0.96
End Batch 01 Average: S.D.	01 01 (F) 01 (F)	AVERAGE("BATCH") STDEV("BATCH")	0.96
Average:	01 (F)	a second s	

Crushing strength of design batch PC 2



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T.A SETTINGS & PARAMETERS	Force (kg)	
Test Mode: Compression	13-	
Pre-Test Speed: 1.0 mm/sec	12-	
Test Speed: 0.25 mm/sec	11-	
Post-Test Speed: 10.0 mm/sec	10- Deal Postive Force (Dycle: 1)	
Target Mode: Distance	-09	
Force: 100.0 g	0.8-	
Distance: 0.3 mm	0.7-	
Strain: 10.0 %	0.5	
Trigger Type: Auto (Force)	0.5-	
Trigger Force: 5.0 g	04	
Probe: P/2 : 2mm DIA CYLINDE		
STAINLESS	02-	
Batch: 02	01-	
Points per second: 200		
Test Run by: SUCHITRK	00 025 0.50 0.75 1.00 1.25 1.50	1.75

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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



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T.A SETTINGS & PARAMETERS	Force (kg)
Test Mode: Compression Pre-Test Speed: 1.0 mm/sec	11-
Test Speed: 0.25 mm/sec Post-Test Speed: 10.0 mm/sec	10- 09- Feat Boartive Pfers (Dyris: 1)
Target Mode: Distance Force: 100.0 g	0.54
Distance: 0.3 mm	0.7-
Strain: 10.0 % Trigger Type: Auto (Force)	05
Trigger Force: 5.0 g	24
Probe: P/2 ; 2mm DIA CYLINDER STAINLESS	03-
Batch: 03 Points per second: 200	00

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Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 03	03		10.00
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")	0.78
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



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T.A SETTINGS 8	PARAMETERS	Force (kg)		
Test Mode: Com	pression	0.70	Deah Dournive Forme (Cy	tial il
Pre-Test Speed:		0.60-	1	
Test Speed: 0.26		0.55-	n	
Post-Test Speed		0.55-	1 1	
Target Mode: Di		0.45-	11 1	
Force: 100.0 g		0.40-	11/1	
Distance: 0.3 mr	n	0.35-	11/	
Strain: 10.0 %		0.30-		
Trigger Type: Au	to (Force)	0.25-		
Trigger Force: 5		0.20-		
Probe: P/2	: 2mm DIA CYLINDER	0.15-	/	
STAINLESS	, Linit Diri G TEMPER	0.10-		
Batch: 04		0.05		
Points per secon	nd: 200	0.00		
Test Run by: SU		0.000 0.25	0.50 0.75 1.00 1.25	1.50 2.75

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RESULTS			10
Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
1e			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("E	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



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T.A SETTINGS & PARAMETERS	Force (kg)
Test Mode: Compression	09-
Pre-Test Speed: 1.0 mm/sec	0.8- Teak Finiting Fords (Sprils: 1)
Test Speed: 0.25 mm/sec Post-Test Speed: 10.0 mm/sec	- All
Target Mode: Distance	8.74
Force: 100.0 g	0.6-
Distance: 0.3 mm	0.5
Strain: 10.0 %	44
Trigger Type: Auto (Force)	
Trigger Force: 5.0 g	03-
	0.2-
	0.2-
Probe: P/2 ; 2mm DIA CYLINDER STAINLESS	
Probe: P/2 ; 2mm DIA CYLINDER	02-01-02

NOTES





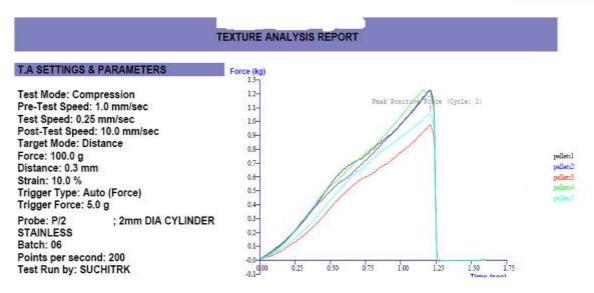
Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
		- T.	Peak Positive Force (Cycle: 1)
Start Batch 05	05		
pellets1	05		0.828
· pellets2	05		0.971
pellets3	05		0.778
pellets4	05		0.870
pellets5	05		0.758
End Batch 05	05		
Average:	05 (F)	AVERAGE("BATCH")	0.841
S.D.	05 (F)	STDEV("BATCH")	0.088
Coef. of Variation	05 (F)	STDEV("BATCH") / AVERAGE("BATCH") * 100	10.114
End of Test Data	1		

Credibility study of design batch PC 6



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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		10 10 10 10 10	

Crushability of design batch PC 7



Stable Micro Systems



T.A SETTINGS & PARAMETERS	Force (kg)	
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	11- 10- 09- 08- 07- 06- 05- 04- 03-	pellers pellers pellers pellers pellers
Probe: P/2 ; 2mm DIA CYLINDER STAINLESS Batch: 07	02- 01-	
Points per second: 200 Test Run by: SUCHITRK	0.0 0 0.25 0.50 0.75 100 1.25 1.50 1.75 0.1	

NOTES





Test ID	Batch		Peak Positive Force (Cycle: 1)
	CONTRACTOR INCOMENTS		kg
			Peak Positive Force (Cycle: 1)
Start Batch 07	07		
pellets 1	07		1.065
pellets2	07		1.063
pellets3	07		0.563
pellets4	07		0.563 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	10000		2,010,000

Crushability study of design batch PC 8



Stable Micro Systems



T.A. SETTINGS &	PARAMETERS	Force (kg)					
Test Mode: Comp	ression	1.4-			1		
Pre-Test Speed: 1	.0 mm/sec	13-			100		
Test Speed: 0.25	mm/sec	12-		P	a safety for	ce (Cycle: 1)	
Post-Test Speed:	10.0 mm/sec	11-		NX	LA		
Target Mode: Dis		1.0-		11/2			
Force: 100.0 g		-0.9-		1111			pellet
Distance: 0.3 mm		0.8-	/	111			pellet
Strain: 10.0 %		0.7- 0.6-	1	11			pellet
Trigger Type: Aut	n (Force)	0.5	11	1			pelle
Trigger Force: 5.0		0.5-					pille
		0.4- 0.3- 0.2-	11				
Probe: P/2	; 2mm DIA CYLINDER	0.3-					
STAINLESS		0.2-	11				
Batch: 08		0.1-					
Points per secon		0.0	115.55	122 2123	10 10	1	
Test Run by: SUC		-0.1900	0.25	0.50 0.75	1.00	125 150 1 Time (see)	75

NOTES





Test ID	Batch		Peak Positive Force (Cycle: 1)
			kg
			Peak Positive Force (Cycle: 1)
Start Batch 08	08		
pellets	08	11	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.

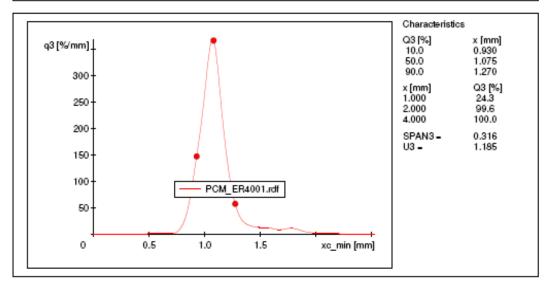
Am. J. PharmTech Res. 2019; 9(04)

CAMSIZER



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/13	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		

0.400	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	



Particle size of Design batch PC 6

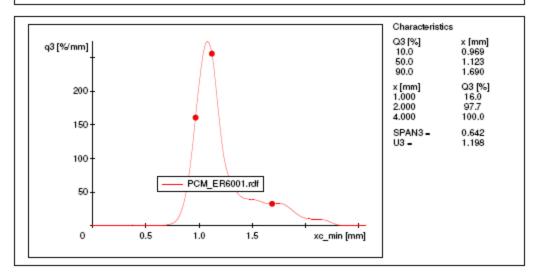
Nimesh et. al.,

Am. J. PharmTech Res. 2019;9(04)

CAMSIZER



b/13	PDN
0.753	144
0.768	19
0.770	96
	10
	665
	1632
0.723	82
	0
	0
	ő
	0.753 0.768



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		

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Nimes	sh <i>et. al.</i> ,	An	n. J. Pharr	nTech Res. 2	2019; 9(04)	ISSN	: 2249-3387
210	35	0.11	549	19.7	4.2	3	-0.2
Batch	PC 2						
	16: Process pa	rameter of	design ba	atch PC 2 in	granurex tech	nology	
Time	Slit air	Slit air	Disc	Product	Spray	Feed	Chamber
	Temp.°C	volume	RPM	temp	rate(RPM)	rate(rpm)	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	1	1				
Table	17: Process pa	rameter for	r design k	oatch PC 3 i	n granurex tec	hnology	
Time	Slit air	Slit air	Disc	Product	Spray	Feed	Chamber
	Temp.°C	volume	RPM	temp	rate(RPM)	rate(rpm)	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		1				
Table	18: Process pa	rameter for	r design b	oatch PC 4 i	n granurex tec	hnology	
Time	Slit air	Slit air	Disc	Product	Spray	Feed	Chamber
	Temp.°C	volume	RPM	temp	rate(RPM)	rate(rpm)	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	1	1				
Table	19: Process pa	rameter of	design ba	atch PC 5 in	granurex tech	nology	
Time	Slit air	Slit air	Disc	Product	Spray	Feed	Chamber
	Temp.°C	volume	RPM	temp	rate(RPM)	rate(rpm)	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
	35	0.1	490	22	7	2	-0.3
90	33	0.1	120				
90 120	35	0.1	512	20.7	9	7	-0.3
120 Batch	35 PC 6	0.1	512	1			-0.3
120 Batch Table	35 PC 6 20:Process par	0.1	512 lesign ba	tch PC 6 in	granurex tech	nology	
120 Batch	35 PC 6 20:Process par Slit air	0.1 rameter of of slit air	512	tch PC 6 in Product	granurex tech	nology Feed	-0.3 Chamber statics
120 Batch Table	35 PC 6 20:Process par	0.1	512 lesign ba Disc	tch PC 6 in	granurex tech	nology	Chamber
120 Batch Table Time	35 PC 6 20:Process par Slit air Temp.°C	0.1 rameter of o Slit air volume	512 lesign ba Disc RPM	tch PC 6 in Product temp	granurex tech Spray rate(RPM)	nology Feed rate(rpm)	Chamber statics

Nimes	sh <i>et. al.</i> ,	A	m. J. Phar	mTech Res.	2019;9(04)	ISSN	: 2249-3387
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						
			U		n granurex tec	hnology	1
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
	PC 8 22: process p	arameter o	f design b	oatch PC 8 i	n granurex tec	hnology	
Time	Slit air	Slit air	Disc	Product	Spray	Feed	Chamber
	Temp.°C	volume	RPM	temp	rate(RPM)	rate(rpm)	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 d	lesign batches	was prepa	red and	then evalua	ted after that	ER coating r	performed o

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 4	5 cps	Whit	te wax	Isoprop	oyl alcohol	Total	weight		alc 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

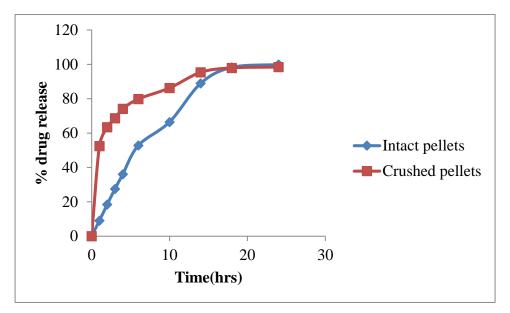


Figure 6: Graphical representation of Design batch PC 1

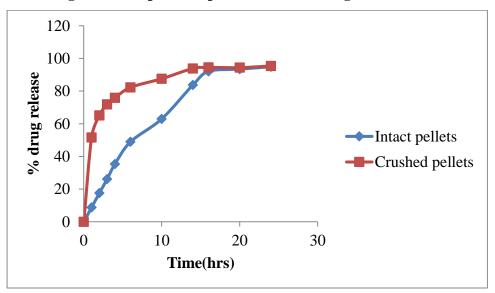
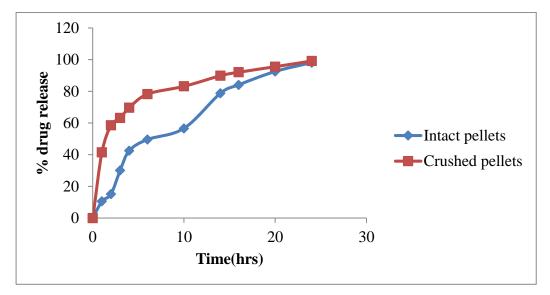


Figure 7: Graphical representation of design batch PC 2





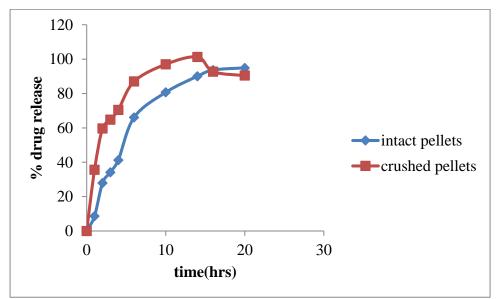


Figure 9: Graphical representation of design batch PC 4

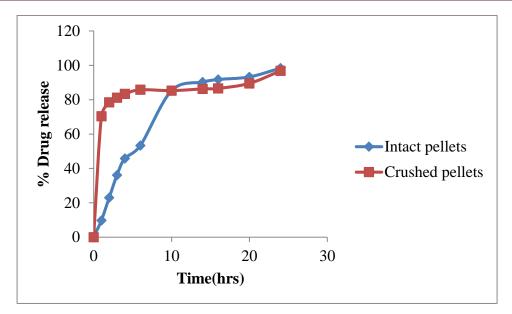


Figure 10: Graphical representation of design batch PC 5

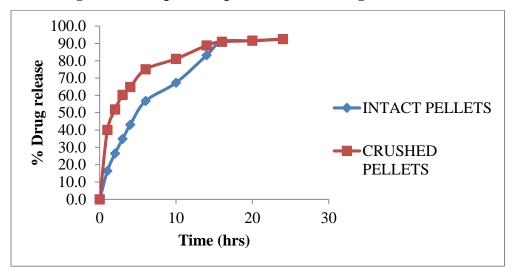


Figure 11: Graphical representation of batch PC 6

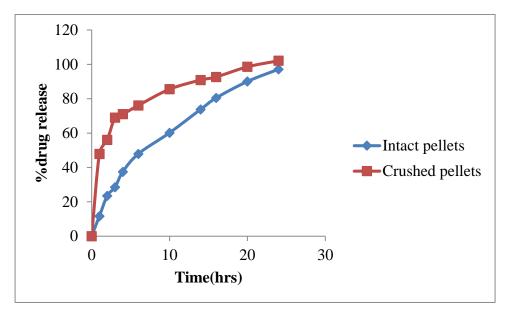


Figure 12: Graphical representation of batch PC 7

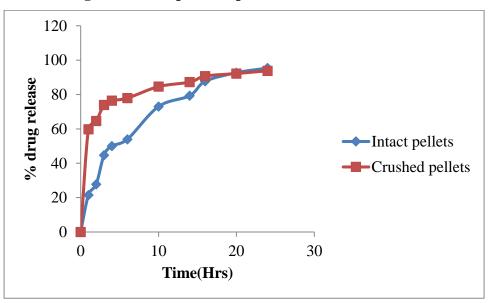


Figure 13: Graphical representation of batch PC 8

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 w							
	•						

Table 24 Extraction study design batch PC 1

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)	Absorbance Intact	Crushed	% drug Intact	release Crushed	
Time point(hr) 0		Crushed 0			
	Intact	_	Intact	Crushed	
0	Intact 0 0.593	0	Intact 0 42.46	Crushed 0 57.83	
0 1	Intact 0 0.593	0 0.8074	Intact 0 42.46	Crushed 0 57.83	
0 1	Intact 0 0.593 condition- med	0 0.8074	Intact 0 42.46	Crushed 0 57.83 HCl)	
0 1	Intact 0 0.593 condition- med RPM-50	0 0.8074	Intact 0 42.46 ml(0.1N	Crushed 0 57.83 HCl)	
0 1 level 3 solvent(0.1N HCl)	Intact 0 0.593 condition- med RPM-50 Absorbance	0 0.8074 dia volume-300	Intact 0 42.46 ml(0.1N) % drug	Crushed 0 57.83 HCl) release	

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-med	lia volume-300m	l(Distilled	water)
level 1 solvent(water)	RPM-50			
Stock solution	dilutions		lambda r	nax
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	0 / J	
	Absorbance	~	% drug	
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-med	dia volume-300	ml(Distill	ed water)
Level 1 solvent(water)	RPM-50			
Stock solution	dilutions		lambda i	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- me	dia 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)		dia volume-300	ml(0.1N	HCl)
	RPM-50			
			% drug	release
	Absorbance			
Time point(hr)	Absorbance Intact	Crushed	Intact	Crushed
Time point(hr) 0 1		Crushed 0 0.2996	-	Crushed 0

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

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	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(Di	stilled water)	
Level 1 solvent(water)	RPM-50			
Stock solution	Dilutions		lambda ma	ax
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		0/ dmig m	
	Absorbance		% drug r	
Time point(hr)	Intact	Crushed	Intact	Crushed
0	Intact 0	0	Intact0	Crushed 0
	Intact		Intact	Crushed
0	Intact 0	0	Intact0	Crushed 0
0	Intact 0 0.132 Condition- media	0 0.189	Intact 0 26.68	Crushed 0
0 1	Intact 0 0.132 Condition- media RPM-50	0 0.189	Intact 0 26.68 0% 0%	Crushed 0 35.85
0 1	Intact 0 0.132 Condition- media	0 0.189	Intact 0 26.68	Crushed 0 35.85
0 1 Level 2 solvent(40% ethanol) Time point(hr)	Intact 0 0.132 Condition- media RPM-50 Absorbance Intact	0 0.189 volume-300 ml(4 Crushed	Intact 0 26.68 00% ethanol) % drug regiment Intact	Crushed 0 35.85
0 1 Level 2 solvent(40% ethanol) Time point(hr) 0	Intact 0 0.132 Condition- media RPM-50 Absorbance Intact 0	0 0.189 volume-300 ml(4 Crushed 0	Intact 0 26.68 0% ethanol) % drug regiment Intact 0	Crushed 0 35.85
0 1 Level 2 solvent(40% ethanol) Time point(hr)	Intact 0 0.132 Condition- media RPM-50 Absorbance Intact	0 0.189 volume-300 ml(4 Crushed	Intact 0 26.68 00% ethanol) % drug regiment Intact	Crushed 0 35.85
0 1 Level 2 solvent(40% ethanol) Time point(hr) 0 1	Intact 0 0.132 Condition- media RPM-50 Absorbance Intact 0 0.8222	0 0.189 volume-300 ml(4 Crushed 0 1.1502	Intact 0 26.68 0% ethanol) % drug ro Intact 0 62.81	Crushed 0 35.85
0 1 Level 2 solvent(40% ethanol) Time point(hr) 0	Intact 0 0.132 Condition- media RPM-50 Absorbance Intact 0 0.8222 Condition- media	0 0.189 volume-300 ml(4 Crushed 0 1.1502	Intact 0 26.68 0% ethanol) % drug ro Intact 0 62.81	Crushed 0 35.85
0 1 Level 2 solvent(40% ethanol) Time point(hr) 0 1	Intact 0 0.132 Condition- media RPM-50 Absorbance Intact 0 0.8222 Condition- media RPM-50	0 0.189 volume-300 ml(4 Crushed 0 1.1502	Intact 0 26.68 0% ethanol) % drug ro Intact 0 62.81 .1N HCl)	Crushed 0 35.85 elease Crushed 0 87.86
0 1 Level 2 solvent(40% ethanol) Time point(hr) 0 1 Level 3 solvent(0.1N HCl)	Intact 0 0.132 Condition- media RPM-50 Absorbance Intact 0 0.8222 Condition- media RPM-50 Absorbance	0 0.189 volume-300 ml(4 Crushed 0 1.1502 volume-300 ml(0	Intact 0 26.68 0% ethanol) % drug ro Intact 0 62.81 .1N HCl) % drug ro	Crushed 0 35.85
0 1 Level 2 solvent(40% ethanol) Time point(hr) 0 1 Level 3 solvent(0.1N HCl) Time point(hr)	Intact 0 0.132 Condition- media RPM-50 Absorbance Intact 0 0.8222 Condition- media RPM-50 Absorbance Intact Intact	0 0.189 volume-300 ml(4 Crushed 0 1.1502 volume-300 ml(0 Crushed	Intact 0 26.68 0% ethanol) % drug regiment 0 62.81 .1N HCl) % drug regiment Intact 0 100 <t< td=""><td>Crushed 0 35.85 </td></t<>	Crushed 0 35.85
0 1 Level 2 solvent(40% ethanol) Time point(hr) 0 1 Level 3 solvent(0.1N HCl)	Intact 0 0.132 Condition- media RPM-50 Absorbance Intact 0 0.8222 Condition- media RPM-50 Absorbance	0 0.189 volume-300 ml(4 Crushed 0 1.1502 volume-300 ml(0	Intact 0 26.68 0% ethanol) % drug ro Intact 0 62.81 .1N HCl) % drug ro	Crushed 0 35.85 elease Crushed 0 87.86 elease

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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 29: Extraction study of design batch PC 6

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-med	lia volume-300		ed 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- me	dia 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- me	dia volume-300) ml(0.1N	HCl)
	RPM-50			
			0/ dmug	release
	Absorbance		70 urug	I CICASC

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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		dia volume-300r	nl(Distille	d water)
Level 1 solvent(water)	RPM-50			
Stock solution	Dilutions	1	lambda r	nax
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
-		0.21	23.47	+0.77
-		0.21	23.47	+0.77
Level 2 solvent(40%		0.21	23.47	+0.99
	Condition- me	edia volume-300		
Level 2 solvent(40%	Condition- me RPM-50			
Level 2 solvent(40%				thanol)
Level 2 solvent(40%	RPM-50		ml(40% et	thanol)
Level 2 solvent(40% ethanol)	RPM-50 Absorbance	edia volume-300	ml(40% et % drug	thanol) release
Level 2 solvent(40% ethanol) Time point(hr)	RPM-50 Absorbance Intact	edia volume-300 Crushed	ml(40% et % drug Intact	thanol) release Crushed
Level 2 solvent(40% ethanol) Time point(hr) 0	RPM-50AbsorbanceIntact0	edia volume-300 Crushed 0	ml(40% et % drug Intact 0	thanol) release Crushed 0
Level 2 solvent(40% ethanol) Time point(hr) 0	RPM-50AbsorbanceIntact00.556	edia volume-300 Crushed 0	ml(40% et % drug Intact 0 67.66	thanol) release Crushed 0 84.71
Level 2 solvent(40% ethanol) Time point(hr) 0 1	RPM-50AbsorbanceIntact00.556	cdia volume-300 Crushed 0 0.702	ml(40% et % drug Intact 0 67.66	thanol) release Crushed 0 84.71
Level 2 solvent(40% ethanol) Time point(hr) 0 1	RPM-50 Absorbance Intact 0 0.556 Condition- me	cdia volume-300 Crushed 0 0.702	ml(40% et % drug Intact 0 67.66	thanol) release Crushed 0 84.71 ICl)
Level 2 solvent(40% ethanol) Time point(hr) 0 1	RPM-50 Absorbance Intact 0 0.556 Condition- me RPM-50	cdia volume-300 Crushed 0 0.702	ml(40% et % drug Intact 0 67.66 ml(0.1N F	thanol) release Crushed 0 84.71 ICl)
Level 2 solvent(40% ethanol) Time point(hr) 0 1 Level 3 solvent(0.1N HCl)	RPM-50AbsorbanceIntact00.556Condition- meRPM-50Absorbance	cdia volume-300 Crushed 0 0.702 cdia volume-300	ml(40% et % drug Intact 0 67.66 ml(0.1N F % drug	thanol) release Crushed 0 84.71 HCl) release

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

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	1	cess paramete				0	<u> </u>		ch P	
Tim	Air	Inlet air	Colum		-	•	Pro			Exhaust air
e o	flow	temp(°C)	height(cm)	rat			p(°C)		temp(°C)
$\frac{0}{20}$	0	0	0		0		0			0
20	80	30	18		10.		25.9			25.5
40	80	30	18		10.		25.9			25.7
60	82	30.1	20		10.		27.2			27.3
80	79	30.5	20		12.		27.5			27.5
100	86	38.6	20		23.		32.3			30.3
120	90	38.3	20		30.		32.5			32.3
140	91	38	20		30.		32.1			31.9
160	90	38.2	20		30.	24	32.1			31.8
	h PC 2							_		
		cess paramete				<u> </u>	<u> </u>			
Time	e Ain flo		Column height	Spra	ay rate	Produ temp(°		Exh	aust	air temp(°C)
0	0	$\frac{1}{0}$	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		
<u>70</u>	92	40.9	19	20		33.1		32.9		
90	90	40.8	18	20		33.4		32.8		
	h PC 3	10.0	10	20		55.1		52.0		
		ocess paramete	er for extended	l rele	ase coati	ing of d	lesig	n bat	ch P	С 3
Time			Column		Spray	Produ				ust air temp(°C)
	flo	w temp(°C)	height		rate		$(\circ \mathbf{C})$			
	0					temp(
0	0	0	0		0	temp (()	
	98	0 40.1	0 18		0 30.82) 80	
20		-	-		-	0	<u>(()</u>	3		
20 40	98	40.1	18		30.82	0 30.1			30	
0 20 40 60 90	98 98	40.1 40.2	18 18		30.82 30.82	0 30.1 30			80 80.1	
20 40 60 90	98 98 95	40.1 40.2 40.4	18 18 19		30.82 30.82 30.8	0 30.1 30 31.2			80 80.1 81.1	
20 40 60 90 120	98 98 95 93	40.1 40.2 40.4 40.2	18 18 19 18		30.82 30.82 30.8 30.8	0 30.1 30 31.2 31.3			30 30.1 31.1 31.2	
20 40 60 90 120 Batch	98 98 95 93 97 h PC 4	40.1 40.2 40.4 40.2	18 18 19 18 18 18	l rele	30.82 30.82 30.8 30.8 30.8 30.8	0 30.1 30 31.2 31.3 31.2			30 30.1 31.1 31.2 30.1	C 4
20 40 60 90 120 Batcl Table	98 98 95 93 97 h PC 4 e 35: Pro	40.1 40.2 40.4 40.2 40 ocess paramete	18 18 19 18 18 18		30.82 30.82 30.8 30.8 30.8 30.8	0 30.1 30 31.2 31.3 31.2	lesig		30 30.1 31.1 31.2 30.1 ch P	C 4 xhaust air
20 40 60 90 120 Batcl Table	98 98 95 93 97 h PC 4 e 35: Pro	40.1 40.2 40.4 40.2 40 Cess paramete Inlet air	18 18 19 18 18 18 r for extended		30.82 30.82 30.8 30.8 30.8 30.8 30.8 ase coat	0 30.1 30 31.2 31.3 31.2 ing of d	lesig		80 80.1 81.1 81.2 80.1 ch P E	
20 40 60 90 120 Batch Table Time	98 98 95 93 97 h PC 4 e 35: Pro	40.1 40.2 40.4 40.2 40 ocess paramete Inlet air	18 18 19 18 18 18 er for extended Column		30.82 30.82 30.8 30.8 30.8 30.8 30.8 ase coati Spray	0 30.1 30 31.2 31.3 31.2 ing of d Produ	lesig		80 80.1 81.1 81.2 80.1 ch P E	xhaust air
20 40 60 90 120 Batch Table Time	98 98 95 93 97 h PC 4 e 35: Pro e Ain flo	40.1 40.2 40.4 40.2 40 ccess paramete Inlet air temp (°C)	18 18 19 18 18 18 Column height		30.82 30.82 30.8 30.8 30.8 30.8 30.8 ase coati Spray rate	0 30.1 30 31.2 31.3 31.2 ing of d Produ temp(lesig		30 30.1 31.2 30.1 ch P E te	xhaust air emp(°C)
20 40 60 90 120 Batcl Table Time 0 20	98 98 95 93 97 h PC 4 e 35: Pro e Ain flo 0	40.1 40.2 40.4 40.2 40 Cess paramete Inlet air temp (°C) 0	18 18 19 18 18 18 er for extended Column height 0		30.82 30.82 30.8 30.8 30.8 30.8 ase coati Spray rate 0	0 30.1 30 31.2 31.3 31.2 ing of d Produ temp(0	lesig		30 30.1 31.1 31.2 30.1 ch P E te 0 30	xhaust air emp(°C)
20 40 60 90 120 Batch Table Time 0 20 40	98 98 95 93 97 h PC 4 e 35: Pro e Ain flo 0 99	40.1 40.2 40.4 40.2 40 Cess paramete Inlet air w temp(°C) 0 40.1	18 18 19 18 18 er for extended Column height 0 18		30.82 30.82 30.8 30.8 30.8 30.8 ase coati Spray rate 0 30.86	0 30.1 30 31.2 31.3 31.2 ing of d Produ temp(0 30.1	lesig		30 30.1 31.1 31.2 30.1 ch P te 0 30 30 30	xhaust air emp(°C)
20 40 60 90 120 Batch	98 98 95 93 97 h PC 4 e 35: Pro e Ain flo 0 99 99	40.1 40.2 40.4 40.2 40 Decess paramete Inlet air w temp(°C) 0 40.1 40.2	18 18 19 18 18 er for extended Column height 0 18 18		30.82 30.82 30.8 30.8 30.8 30.8 ase coati Spray rate 0 30.86 30.86	0 30.1 30 31.2 31.3 31.2 ing of d Produ temp (0 30.1 30	lesig		30 30.1 31.1 31.2 30.1 ch P te 0 30 30 30 30 30 30 30 30 30	xhaust air emp(°C))).1
20 40 60 90 120 Batch Table Table 0 20 40 60 90	98 98 95 93 97 h PC 4 e 35: Pro e 35: Pro flo 0 99 99 99 95	40.1 40.2 40.4 40.2 40 Decess parameter Inlet air w temp(°C) 0 40.1 40.2 40.2	18 18 19 18 18 er for extended Column height 0 18 18		30.82 30.82 30.8 30.8 30.8 30.8 ase coati Spray rate 0 30.86 30.86 30.8	0 30.1 30 31.2 31.3 31.2 ing of d Produ temp(0 30.1 30 31.2	lesig		30 30.1 31.1 31.2 30.1 ch P te 0 30 30 30 30 30 30 30 30 30	xhaust air emp(°C))).1 1.1
20 40 60 90 120 Batch Table Time 0 20 40 60 90 Batch	98 98 95 93 97 h PC 4 e 35: Pro e 35: Pro flo 0 99 99 99 95 95 95 h PC 5	40.1 40.2 40.4 40.2 40 Decess parameter Inlet air w temp(°C) 0 40.1 40.2 40.2	18 18 19 18 18 er for extended Column height 0 18 19 18 19 18 19 18 18 18 18 18 18 18 18 18 18 18 18 18 18		30.82 30.82 30.8 30.8 30.8 30.8 ase coati Spray rate 0 30.86 30.86 30.86 30.8	0 30.1 30 31.2 31.3 31.2 ing of d Produ temp(0 30.1 30 31.2 31.3	lesig ıct (°C)	n bat	30 30.1 31.1 31.2 30.1 ch P te 0 30 30 30 30 30 30 30 30 30	xhaust air emp(°C))).1 1.1 1.2

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	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 P	PC 6		·		•	
Table 3			for extended re		<u> </u>	
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	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
		27.0	20	15	32	31
120	95	37.8	20	15	52	51
120 140	95 93	37.8	20 20	13	32	31.3
	93					
140 Batch P Table 3	93 PC 7 8: Proce	37.5 ss parameter 1	20 for extended re	13 elease coat	32	31.3 batch PC 7
140 Batch P	93 PC 7 8: Proce Air	37.5 ss parameter f	20 for extended ro Column	13 elease coat Spray	32 ing of design Product	31.3
140 Batch P Table 3 Time	93 PC 7 8: Proce Air flow	37.5 ss parameter f Inlet air temp(°C)	20 for extended ro Column height	13 elease coat Spray rate	32 ing of design Product temp(°C)	31.3 batch PC 7 Exhaust air temp(°C)
140 Batch F Table 3 Time	93 PC 7 8: Proce Air flow 0	37.5 ss parameter f Inlet air temp(°C) 0	20 for extended ro Column height 0	13 elease coat Spray rate 0	32 ing of design Product temp(°C) 0	31.3 batch PC 7 Exhaust air temp(°C) 0
140 Batch F Table 3 Time 0 10	93 PC 7 8: Proce Air flow 0 98	37.5 ss parameter f Inlet air temp(°C) 0 40.3	20 for extended ro Column height 0 19	13elease coatSprayrate018	32 ing of design Product temp(°C) 0 35.2	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1
140 Batch P Table 3 Time 0 10 30	93 PC 7 8: Proce Air flow 0 98 100	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1	20 for extended ro Column height 0 19 18	13elease coatSpray rate01818	32 ing of design Product temp(°C) 0 35.2 35	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5
140 Batch P Table 3 Time 0 10 30 50	93 PC 7 8: Proce Air flow 0 98 100 100	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41	20for extended restanded restand	13 elease coat Spray rate 0 18 18 19	32 ing of design Product temp(°C) 0 35.2 35 34.1	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9
140 Batch P Table 3 Time 0 10 30	93 PC 7 8: Proce Air flow 0 98 100	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1	20 for extended ro Column height 0 19 18	13elease coatSpray rate01818	32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5
140 Batch P Table 3 Time 0 10 30 50	93 PC 7 8: Proce Air flow 0 98 100 100	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41	20for extended restanded restand	13 elease coat Spray rate 0 18 18 19	32 ing of design Product temp(°C) 0 35.2 35 34.1	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9
140 Batch P Table 3 Time 0 10 30 50 70 90 Batch P	93 PC 7 8: Proce Air flow 0 98 100 100 92 95 95 PC 8	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41 40.3 43.2	20 for extended restanded resta	13 elease coat Spray rate 0 18 18 19 20 20 20	32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9 35	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9 33 33.1
140 Batch F Table 3 Time 0 10 30 50 70 90 Batch F Table 3	93 C 7 8: Proce Air flow 0 98 100 100 92 95 C 8 9: Proce	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41 40.3 43.2 ss parameter f	20 for extended ro Column height 0 19 18 19 19 19 19 19 19 19 19 19 19	13 elease coat Spray rate 0 18 19 20 20 20 20 elease coat	32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9 35 ing of design	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9 33 33.1 batch 8
140 Batch P Table 3 Time 0 10 30 50 70 90 Batch P	93 PC 7 8: Proce Air flow 0 98 100 98 100 100 92 95 C 8 9: Proce Air	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41 40.3 43.2 ss parameter f Inlet air	20 for extended registration Column height 0 19 18 19 <t< td=""><td>13 elease coat Spray rate 0 18 19 20 20 20 20 20 Spray elease coat Spray</td><td>32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9 35 ing of design Product</td><td>31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9 33 33.1 batch 8</td></t<>	13 elease coat Spray rate 0 18 19 20 20 20 20 20 Spray elease coat Spray	32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9 35 ing of design Product	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9 33 33.1 batch 8
140 Batch P Table 3 Time 0 10 30 50 70 90 Batch P Table 3 Time	93 C 7 8: Proce Air flow 0 98 100 98 100 92 95 C 8 9: Proce Air flow	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41 40.3 43.2 ss parameter f Inlet air temp(°C)	20for extended roColumnheight0191819191919for extended roColumnheight	13 elease coat Spray rate 0 18 19 20 20 20 20 Spray rate	32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9 35 ing of design Product temp(°C)	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9 33 33.1 batch 8 Exhaust air temp(°C)
140 Batch F Table 3 Time 0 10 30 50 70 90 Batch F Table 3 Time 0	93 PC 7 8: Proce Air flow 0 98 100 92 95 PC 8 9: Proce Air flow 0	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41 40.3 43.2 ss parameter f Inlet air temp(°C) 0	20 for extended restanded restanded restanded restanded 0 19 18 19 19 19 19 19 0 19 0 0 0 0 19 0 19 0 0	13 elease coat Spray rate 0 18 19 20 20 elease coat Spray rate 0 18 19 20 20 20 elease coat Spray rate 0	32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9 35 ing of design Product temp(°C) 0	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9 33 33.1 batch 8 Exhaust air temp(°C) 0
140 Batch P Table 3 Time 0 10 30 50 70 90 Batch P Table 3 Time 0 20	93 C 7 8: Proce Air flow 0 98 100 92 95 C 8 9: Proce Air flow 0 93	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41 40.3 43.2 ss parameter f Inlet air temp(°C) 0 40.3	20 for extended registration Column height 0 19 18 19 19 19 19 19 0 19 19 0 19 19 19 19 19 19 19 19 19 19 19 19 19 19 19 19 19 19	13 elease coat Spray rate 0 18 19 20 20 20 20 20 20 20 20 35	32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9 35 ing of design Product temp(°C) 0 35 36 9 30.6	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9 33 33.1 batch 8 Exhaust air temp(°C) 0 30.2
140 Batch F Table 3 Time 0 10 30 50 70 90 Batch F Table 3 Time 0 20 40	93 PC 7 8: Proce Air flow 0 98 100 92 95 C 8 9: Proce Air flow 0 95 Y 8 95 Y 8 95 Y 98 99	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41 40.3 43.2 ss parameter f Inlet air temp(°C) 0 40.3 40.3 40.1	20 for extended registration Column height 0 19 18 19	13 elease coat Spray rate 0 18 19 20 20 20 elease coat Spray rate 0 35 30	32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9 35 ing of design Product temp(°C) 0 30.6 31	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9 33 33.1 batch 8 Exhaust air temp(°C) 0 30.2 30.4
140 Batch P Table 3 Time 0 10 30 50 70 90 Batch P Table 3 Time 0 20	93 C 7 8: Proce Air flow 0 98 100 92 95 C 8 9: Proce Air flow 0 93	37.5 ss parameter f Inlet air temp(°C) 0 40.3 40.1 41 40.3 43.2 ss parameter f Inlet air temp(°C) 0 40.3	20 for extended registration Column height 0 19 18 19 19 19 19 19 0 19 19 0 19 19 19 19 19 19 19 19 19 19 19 19 19 19 19 19 19 19	13 elease coat Spray rate 0 18 19 20 20 20 20 20 20 20 20 35	32 ing of design Product temp(°C) 0 35.2 35 34.1 34.9 35 ing of design Product temp(°C) 0 35 36 9 30.6	31.3 batch PC 7 Exhaust air temp(°C) 0 33.1 32.5 32.9 33 33.1 batch 8 Exhaust air temp(°C) 0 30.2

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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