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Formulation And Evaluation Of Paracetamol Pellets

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Abstract

Pellets are small, spherical or semi-spherical particles that flow freely and are created by combining active substances with excipients. The particle size ranges from 500 to 1500 µm. This study aimed to formulate and assess Paracetamol Pellets using the Extrusion-Spheronization Method. Extrusion-Spheronization is preferred for pellet production because it is a straightforward and time-efficient method. Various formulations were created using Paracetamol as the active pharmaceutical ingredient, Microcrystalline cellulose (MCC) as the adsorbent, Polyvinylpyrrolidone as the binding agent, and distilled water as the solvent. The primary goal is to determine the concentration of impact factors, including PVP K-30 concentration, MCC concentration, and standing time. The quantities of pellet batch ingredients were prepared following a Box-Behnken design.

The final section involves assessing the pellets, where we conducted tests to measure % yield, bulk density, tapped density, angle of repose, particle size distribution, drug content, and drug release. Subsequently, we determined the overall results using Design of Experiments software. Usually, water is used as a granulation fluid to wet the drug-MCC powder blend before the extrusion process. MCC can absorb high amounts of water, due to the large surface area and high internal porosity.

Keywords: Spheronization, Pellets, Box Behnken design, Pelletization method

Introduction

The market for "fast disintegrating pellets," a pellet dosage form domain, has grown steadily over the past ten years and is now a quickly expanding sector in the pharmaceutical business (1). Pellets, which for pharmaceutical applications are defined as small (between 0.5 and 2.0 mm) (2).

One of the novel pharmaceutical dosage forms that has definite advantages over other traditional solid dosage forms is the pellet, which is a spherical or semi-spherical mixture of fine powder excipients and active substances. Their superiority is primarily attributable to their improved drug release profile, which includes less dose dumping and more steady plasma levels. They are therefore even less likely to have adverse local effects. The technical advantages of pellets, such as their enhanced flow characteristics and perfect coating shape, have also been taken into consideration (3).

These days A lot of attention is being paid to the pelletization process as an oral medication delivery method. They create tiny, free-flowing, spherical or semi-spherical solid units that range in size from 0.5 to 1.5 mm. Due to their technological and clinical advantages over single unit dose forms, pellets are frequently used as multiparticulate systems. Pellets are primarily intended for oral administration, while they can also be prepared into a variety of different dosage forms, including tablets and capsules, or they can be taken only that way. Nowadays, oral administration is the most adaptable, practical, and widely used method of medication delivery, with a primary focus on patient compliance.
Each formulation was subjected to a variety of drying methods, including microwave, freeze, and hot air drying. Physical characteristics like moisture content and particle size distribution
Each formulation was subjected to a variety of drying methods, including microwave, freeze, and hot air drying. Physical characteristics were assessed, including pellet shape, apparent density, moisture content, and particle size distribution.

MCC is the most important excipient in the pellets prepared by extrusion–spheronization. The efficacy of MCC–water combinations as fillers in extrusion spheronization has been explained by two qualitative microstructural models: the "crystallite-gel" (Kleinebudde, 1997) and the "sponge" (Fielden et al., 1988, Ek and Newton, 1998, Soh et al., 2008) (4).
Because of its rheological and binding qualities, microcrystalline cellulose (MCC) is regarded as the gold standard excipient for the extrusion/spheronization process (5).

Prior to the extrusion procedure, the drug-MCC powder blend is typically wetted with water as a granulation fluid. MCC's huge surface area and great internal porosity allow it to absorb large volumes of water. A high capacity for water absorption and retention is a crucial characteristic for excipients used in the extrusion-spheronization process to create pellets. MCC's great water-holding capacity is one of the factors that make it a popular excipient in extrusion and spheronization formulations (6). Through the use of a liquid binder and powders like microcrystalline cellulose (MCC), a viscoplastic paste—a highly-filled suspension—is created. This paste is then extruded to create cylindrical extrudates, which are then broken up and rounded on a revolving friction plate. The free (not well absorbed) liquid is then removed from the pellets by drying them. Using this method, cellulosic or starchy materials could be turned into bioadsorbent pellets. Paste processing research has shown that physical characteristics like as die geometry, liquid content, density, porosity, and particle size and shape all affect how well the extrusion and spheronization process's function (7). The most popular excipient for pellet manufacture through extrusion-spheronization is microcrystalline cellulose (MCC), which is a great base excipient for the process because of its distinctive wet mass cohesiveness and plasticity. It does, however, have some drawbacks, such as the delayed release rate of medications with low water solubility because the MCC pellets do not disintegrate (8).

PVP K30, also known as poly(vinylpyrrolidone) K30 or povidone K30, is a water-soluble polymer. Polyvinylpyrrolidone K-30 polymer is a hygroscopic, amporhous polymer. PVP K-30 are linear nonionic polymer that are soluble in water and organic solvents and are PH stable. It is hard glossy transparent films and have adhesive, cohesive and dispersive properties and appears as a white to slightly off – white powder it is used as binder in many pharmaceutical pellets. pvp-k30 is used in the production of pellets used in relieve the common cold and fever. PVP K30 can help to disperse and dissolve poorly soluble drugs, improving their bioavailability and absorption. It can form complexes with certain drugs, which can affect their solubility, stability, and release rate. PVP K30 showed the slowest release rate.

The aim of this study was to present formulation and evaluation of paracetamol pellets which were prepared to determine the impact factor of concentration MCC, Concertation PVP K-30 and Standing time.

Extrusion spheronization

Nowadays, extrusion/spheronization is regarded as one of the crucial processes for producing pharmaceutical pellets. By keeping an eye on the pellet composition and the extrusion/spheronization settings, pellets with certain characteristics could be produced. Because of its benefits over other traditional pellet manufacturing processes, the creation of sphere-shaped pellets or granules by extrusion/spheronization processes has gained recognition more recently (9),. For palletizations, extrusion-spheronization is the preferred technique because it is simple and quick. It is quite similar to wet granulation; the plastic wet mass is extruded into fine rods, and spheronization shapes it into narrow, spherical pellets. Higher concentrations of active substances can be used thanks to this approach without running the danger of creating very big particles (10). In the pharmaceutical industry and other fields, extrusion-spheronization (E-S) is frequently employed to create dense granules with regulated, high sphericity. A liquid (the binder) is mixed with the particle materials to create a thick paste or suspension, which is then extruded through dies or screens to produce cylindrical extrudates. After that, these extrudates are spheronized (11).

The quality of the spheres is significantly impacted by the spheronizer's speed. The extrudate did not significantly alter shape at very low speeds, while the particles shrank in size at extremely high speeds. A modification in the spheronization speed also affected the pellets' surface structure, friability flow velocity, hardness, roundness, porosity, and bulk and tapped densities. the main variables affecting pellet aspect ratio are spheronization speed, spheronization time, the number of holes in the extrusion screen, and the water content of the extrudate. Using a lot of holes during extrusion, a high spheronizer speed, and a longer spheronization period results in the most spherical pellets. It is possible to create spheroids with a modal fraction in the size range of 0.7–1.0 mm at speeds between 1000 and 2000 rpm and residence periods between 5 and 15 minutes.

Drug and excipient profile

1. **Drug profile-Paracetamol**

Sr. no	Use	Concentration (%)
1	Antipyretic	20–90
2	Analgesic	5–20
3	Non-steroidal anti-inflammatory drug	20–90

2. **Excipient profile –**

- **Micro crystalline cellulose (Avicel)**

Sr.no	Use	Concentration (%)
1	Adsorbent	20–90
2	Anti adherent	5–20
3	Capsule binder/diluent	20–90
4	Tablet disintegrant	5–15
5	Tablet binder/diluent	20–90

- **Poly vinyl pyrrolidone (PVP)**

Sr.no	Use	Concentration (%)
1	Carrier for drugs	10–25
2	Dispersing agent	Up to 5
3	Eye drops	2–10

4	Suspending agent	Up to 5
5	Tablet binder, Tablet diluent, or coating agent	0.5–5

Materials

Paracetamol, PVP K-30(Polyvinylpyrrolidone K-30), 0.1 N HCl, microcrystalline cellulose (Avicel® PH-101, FMC Bio Polymers, Philadelphia, PA, USA); and water were used…...

1.1. Drug/Excipients/Chemicals/Material

Sr no	Name	Grade	Company
1	PVP K-30	-	Central Drug House Ltd. Daryaganj, New Delhi
2	Paracetamol	-	Research Lab Fine ChemIndustries Mumbai
3	Distilled water	-	-
4	Microcrystalline cellulose	pH 101	Maple Biotech Private limited, Pune

1.2. Equipment

Sr. No	Name of the equipment	Model & make
1	Spheronizer sp	`
2	UV/Visible spectrophotometer	Shimadzu UV-1900i
3	pH meter	Equip-Tronics
4	Bulk density apparatus	Bulk density apparatus 951
5	Electronic Weighing Balance	SF400C
6	Perforated plate sieve	2mm
7	Sonicator	-
8	Tapped density apparatus	Tapped density apparatus

Method

A) Trial batches:

Procedure:

Firstly, Formulation of trial batches to find out the concentration of MCC, PVP K-30 and Standing time of extrudate

↓

In trial batches take a MCC in different in Conc. PVP K-30 also in varying conc. are well mixed in mortar and pestle & add water as binding liquid to formulate the dough by mixing it well

↓

Then by using sieve no. #10, extrudates are formed then standing time of extrudates are varied to find optimum standing time.

↓

By using extrusion spheronizer at the speed 900-1000 rpm, put extrudates in the up to 5min from uniform spherical shape pellets. and dried at room temperature

↓

The maximum and minimum conc. Of MCC and PVP k-30 and also maximum & minimum standing time fixed in 6 trial batches.

B). Paracetamol loaded batches:

Following 13 batches of pellets are formulated by using Box Behnken Design.

Box Behnken Design.					
Std	**Run**	**Block**	**Factor 1 A MCC gm**	**Factor 2 B PVP K-30**	**Factor 3 C Standing time Min**
1	14	Block 1	5.00	0.30	5.00
2	10	Block 1	10.00	0.30	5.00
3	17	Block 1	5.00	0.90	5.00
4	4	Block 1	10.00	0.90	5.00
5	7	Block 1	5.00	0.60	2.50
6	15	Block 1	10.00	0.60	2.50
7	8	Block 1	5.00	0.60	7.50
8	9	Block 1	10.00	0.60	7.50
9	5	Block 1	7.50	0.30	2.50
10	1	Block 1	7.50	0.90	2.50
11	13	Block 1	7.50	0.30	7.50
12	12	Block 1	7.50	0.90	7.50
13	16	Block 1	7.50	0.60	5.00

Table 1: Box Behnken Design.

Procedure:

Weigh the MCC and PVP K-30 according to the Box Behnken table

↓

Then add 1 gm of paracetamol for each batch.

↓

Then add powder of MCC, PVP K-30 and paracetamol in mortar and pastel. Well mixed it.

↓

Then add binding liquid water into the mortar and pestle and by using pestle mix it well to form a dough.

↓

Rest the dough for 5 minutes.

↓

Extrudates are formed by using sieve no. #10.

↓

Standing time of every batch varies according to the Box Behnken table.

↓

Put the pellets into extrusion Spheronizer (speed of the spheronizer is 900-1000 at the starting and reduce the speed of spheronizer up to 800 rpm. Plate no. used in spheronizer is 2mm).

↓

Rotate it for 5 minutes into spheronizer to break extrudates and convert it into spherical pellets.

↓

Remove the pellets and dry it at room temperature.

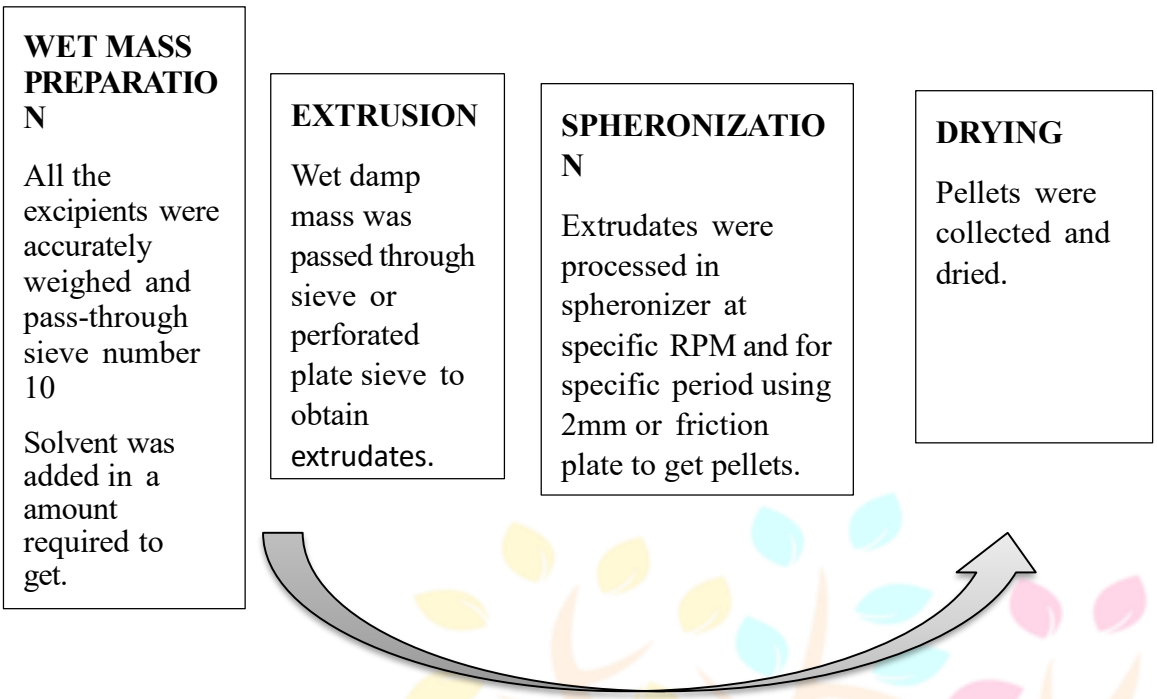


Figure 1: Formulation of pellets

Evaluation

1. **Percentage yield =**

The percentage yield is a used to measure the efficiency of a chemical reaction. It compares the actual yield (the amount of product obtained) to the theoretical yield (the maximum amount of product that could be formed based on basis of reactant).

Procedure to calculate % yield

- Write a Balanced Chemical Equation

Ensure that the chemical equation for the reaction is balanced, and note the molar ratio of reactants and products.

- Determine the Theoretical Yield
- Determine the Actual Yield
- Calculate the Percentage Yield

Use the following formula to calculate the percentage yield

$$\text{percentage yield} = (\text{Actual yield}/\text{Theortical yield} \times 100)$$

2. **Bulk Density =**

The inverse of bulk density is referred to as 'bulkiness' or 'bulk'. Bulk density.

Procedure

- Prepare the Sample: The sample should be free from moisture and impurities slowly mix the material to break up the clumps to get uniformity.
- Weigh the Container:
- Fill the Container: Gently tap the container on the table to help settle the material
- Measure the Volume of the Sample: This is known as bulk volume which includes the void spaces.
- Weigh the container with sample
- Calculate the Bulk Density:

$$\text{bulk density} = \text{Mass of powder}/\text{Bulk of volume}$$

The bulk density is usually expressed in g/mL or g/cm³.

3. **Tapped Density =**

Tapped density is bulk density after tapping or shaking.

Tapping compacts the material and reduces the void spaces between the practical.

Procedure

- Prepare the Sample:
- Weigh the Empty Graduated Cylinder:
- Fill the Graduated Cylinder with the Sample: Place the cylinder containing sample in bulk density apparatus.
- Tap the Cylinder: Adjust apparatus for 100tapping and operate.
- Measure the Tapped Volume: After tapping volume of the powder is knows as tapped volume.
- Weigh the Sample Again: Subtract the weight of the empty cylinder to determine the mass of the powder sample.

$$\text{Tapped Density} = \text{Mass of sample/tapped volume}$$

4. **Carr's Index =**

The Carr's index is used to indicate the compressibility of powder. It is measure of a powder's flowability and is calculated based on the bulk density and tapped density of a powder (12).

A Carr's index greater than 25 is considered to be an indication of poor flowablity.

Using the values of the bulk density and tapped density, Carr's Index is calculated using the formula:

$$\text{Carr's index} = \text{tapped density} - \text{bulk density/tapped density} \times 100$$

Carr's Index (%)	**Type of flow**
5-5	Excellent
12- 16	Good
18- 21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

5. **Hausner's ratio =**

The Hausner ratio is a value that is associated with the flow properties of pellets (13).

Procedure

- Determine the bulk density:
- Determine the tapped density:
- Calculate the Hausner ratio:

$$\text{Hausner's ratio} = \text{tapped density/bulk density}$$

Flow character	**Compressibility index (%)**	**Hausner's Ratio**
Excellent	<10	1.00-1.11
Good	11-15	1.12- 1.18
Fair	16-20	1. 19- 1.25
Passable	21-25	1.26-1.34

poor	26-31	1.35-1.45
Very poor	32-37	1.46-1.59
Very, very, poor	>38	>1.60

6. Angle of Repose =

The fixed funnel method can be used to measure the static angle of repose. Attach the funnel's 1 to 2 cm tip to a fixed stand. Gently pour the pellet through the funnel until the cone's peak just touches the funnel's lower tip. (14).
Determine the mean diameter of the base of the pile of pellet and calculate the angle of repose in degree using the following equation

$$\text{Angle of Repose } \theta = \tan^{-1} h/r$$

Where, h is the height of pile and r is the radius of pile.

Angle of repose (degree)	**Type of flow**
<20	Excellent
20-30	Good
30-40	Passable
>40	Very poor

7. Disintegration Test (0.1 N HCL) =

Disintegration of the pellet means the breakdown of the pellet into small particles after the administration time required to disintegrate the pellet is called "disintegration time " (15).

Procedure

- Place one pellet in each of the 6 tubes of the basket.
- Add a disc to each tube and operate the apparatus, maintain the water at 37± 2℃ as the immersion liquid.
- At the end of 15 mts or after the time specified in the individual monograph lift the basket from the liquid and observe the pellet.
- The pellet passes the test if all the size pellet has disintegrated. In case one or two pellet fail to disintegrate repeat the test on 12 additional pellets.
- The pellet passes the test if not less than 16 of the totals of 18 pellets tested have disintegrated.

8. Drug content uniformity = (16)

Procedure

- 100 mg pellets are weighed.
- Crush the pellets in mortar and pestle.
- 50 mg powder weighed.
- In 50 ml of 0.1 N HCl dissolve the powder by sonication.
- 1 ml in 10 ml 0.1 N HCl.
- 1 ml in 10 ml 0.1 N HCl.
- Check the absorbance by using UV.

9. **Determination of size** = (17)**,** (18), (19).

procedure

- Take a black card sheet.
- Make 1 cm line on it.
- Spread approximately 100 or above pellets on it and pellets should be placed separate from each other.
- By using software IMAGE J we will average size of pellets of a particular batch.

10. **Drug release** =

Procedure (20)**,** (21)

- Preparation of Dissolution Apparatus: Fill the dissolution vessel with an appropriate dissolution medium 0.1 N HCl.
- Weigh the pellets according to results of content of uniformity.
    - Transfer Pellets to the Apparatus: Place the weighed pellets into the dissolution vessel.
    - Initiate the Test: Start the test and ensure the dissolution medium is maintained at the required temperature.
    - Take 100 ml 0.1 N HCl and add weighed pellets into it.
- Sampling: Take a 10 ml sample of the dissolving media at pre-arranged intervals (e.g., 10, 20, 30 ,40 ,50 ,60 minutes) and add 10 ml fresh 0.1 N HCl solution into dissolution apparatus after each interval time.
    - Be careful not to disturb the pellets during the sampling process.
    - Filter the sample (if necessary) to remove any particulate matter.
- Analyze the Samples: Measure the concentration of the drug in the withdrawn samples using an appropriate method, such as:
    - UV-V is spectrophotometry (measuring absorbance at a specific wavelength corresponding to the drug).

Make sure to compare the sample's concentration with a calibration curve for accurate results

- Calculate the Drug Release:

$$\% \text{ of Drug Release} = (\text{Amount of Drug sample}/\text{total Amount of Drug In Pellets}) \times 100$$

Results and discussion

1. λmax and calibration curve

Solvent System	ʎmax	Equestion of straight line (y= mx+c)	Coefficient of regression
Phosphate buffer pH 5.8	246 nm	y = 0.0738x + 0.0209	R^2 = 0.9986

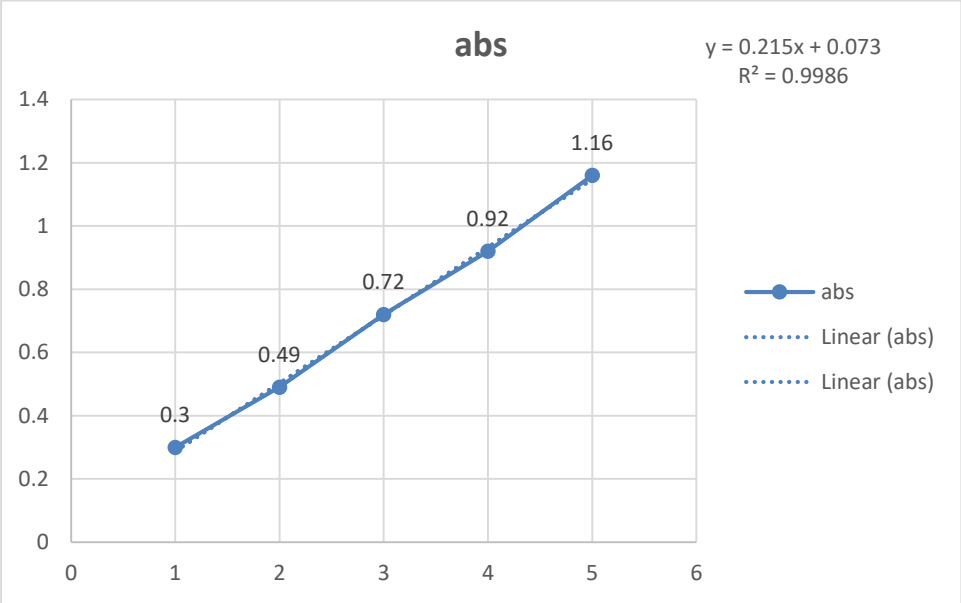


Figure 2: calibration curve of paracetamol

ʎmax of paracetamol is 246 nm and equation of straight line is y=0.0738x+0.0209 And coefficient of regression is R^2= 0.998

Evaluation of trial batch

Batch	Yield (%)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner ratio	Carr's Index (%)	Angle of response (Degree)
1	94	0.19	0.20	1.07	7.15	14.09
2	92	0.22	0.25	1.15	13.61	18.12
3	90	0.20	0.22	1.09	8.70	9.75
4	89	0.22	0.26	1.16	14.27	-
5	83	0.17	0.20	1.13	11.96	21.14
6	97	0.14	0.15	1.09	8.33	31.71

Table 2: Evaluation of trial batch

Evaluation of Paracetamol loaded batches

Batch	Yield (%)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner ratio	Carr's Index (%)	Angle of response (Degree)
PARA 1	83	0.18	0.21	1.15	10.74	12.68
PARA 2	77	0.17	0.21	1.21	17.09	11.32
PARA 3	82	0.16	0.17	1.06	5.72	13.79
PARA 4	75	0.17	0.20	1.16	13.17	9.75
PARA 5	71	0.16	0.18	1.11	10.00	18.12
PARA 6	90	0.20	0.24	1.19	15.99	9.75
PARA 7	73	0.18	0.20	1.09	6.89	14.09
PARA 8	90	0.20	0.21	1.04	3.98	21.14
PARA 9	58	0.20	0.24	1.19	15.79	25.37
PARA 10	75	0.32	0.35	1.10	9.11	18.12
PARA 11	62	0.15	0.17	1.08	7.97	18.12
PARA 12	75	0.32	0.35	1.10	9.101	31.71
PARA 13	82	0.14	0.17	1.13	11.98	15.85

Table 3: Evaluation of Paracetamol loaded batches

Carr's index all almost all batches is approximately 15 or less than 15, therefore it follows good type of flow.

Hausner's ratio of almost all batches is approximately 1.19 or less than 1.19 therefore it has good flow character.

1. Particle size

Batch	Practical Size % (mm)
PARA 1	1.86
PARA 2	2.44
PARA 3	2.87
PARA 4	2.87
PARA 5	4.64
PARA 6	3.50
PARA 7	2.18
PARA 8	2.56
PARA 9	3.00
PARA 10	2.38
PARA 11	2.33
PARA 12	1.96
PARA 13	1.91

Table 4: particle size

1. Particle size distribution

Particle size distribution							
		B1	B2	B3	B4	B5	B6
N	Valid	325	519	475	518	484	473
	Missing	323	129	173	130	164	175
Mean		1.8622	2.4426	2.8677	2.8743	4.6431	3.5043
Median		1.9200	2.6900	3.0700	3.0900	4.7400	3.5000
Mode		1.82	2.60	2.79[a]	0.15	0.50	3.59
Std. Deviation		0.51586	0.94912	0.99268	1.08657	1.21541	0.58299
Range		2.93	4.10	4.57	4.68	7.70	5.96
Minimum		0.36	0.15	0.14	0.15	0.50	0.36
Maximum		3.29	4.25	4.71	4.83	8.20	6.32

a. Multiple modes exist. The smallest value is shown

Particle size distribution								
		B7	B8	B9	B10	B11	B12	B13
N	Valid	648	383	438	212	307	327	352
	Missing	0	265	210	436	341	321	296
Mean		2.1816	2.5619	3.0039	2.3775	2.3261	1.9644	1.9134
Median		2.2000	2.7400	2.9900	2.4700	2.3900	2.2000	2.0200
Mode		2.42	2.52	2.81	2.52	2.23	.50[a]	2.08
Std. Deviation		0.48070	0.86979	0.36933	0.73024	0.51163	0.76704	0.57378
Range		3.02	3.86	4.30	3.77	3.03	3.22	2.85
Minimum		0.50	0.16	0.28	0.14	0.36	0.13	0.14
Maximum		3.52	4.02	4.58	3.91	3.39	3.35	2.99

a. Multiple modes exist. The smallest value is shown

Table 5: Particle size Distributions

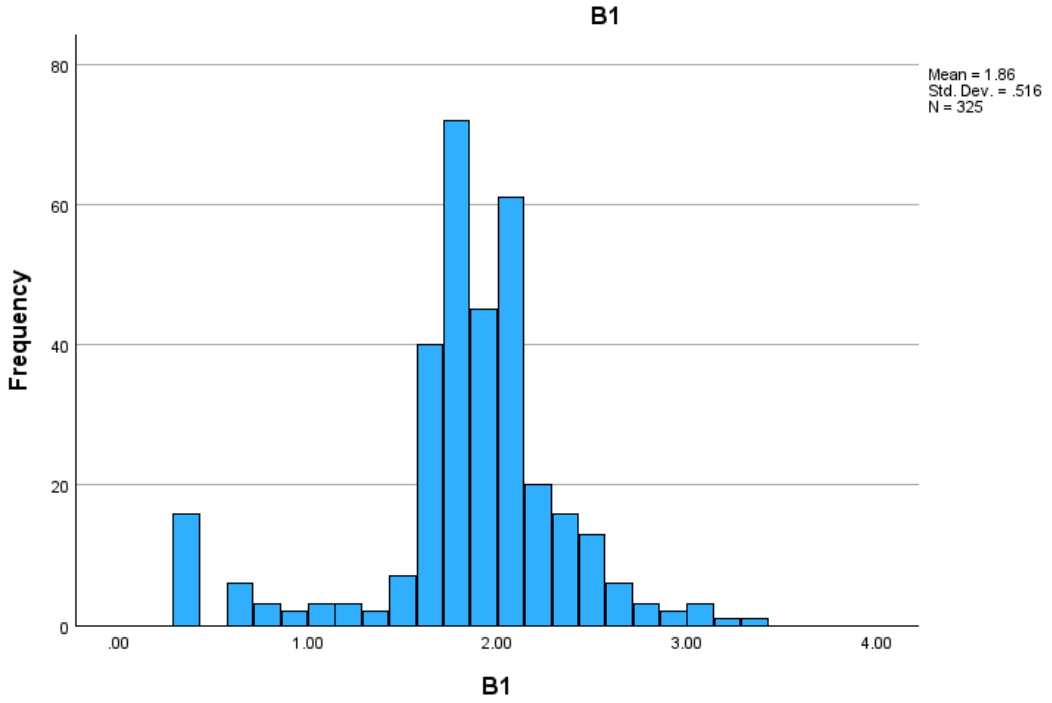


Figure 2: Particle size distribution Batch no. 1

The particle size of pellets between the range 1.6 to 2.3 Increases in graph.

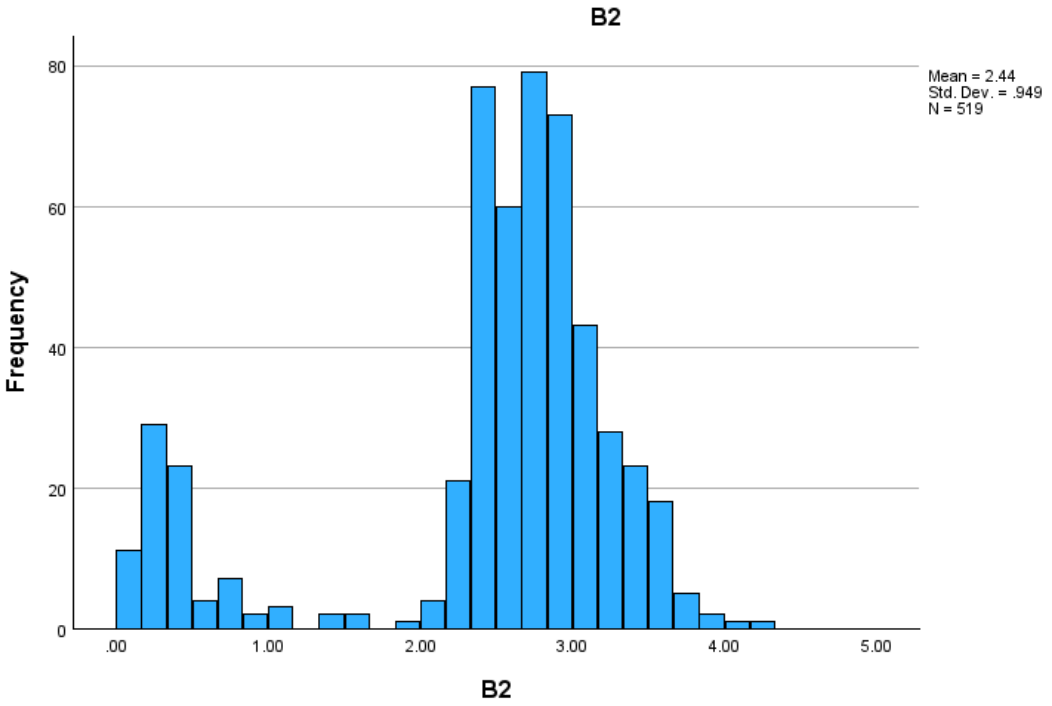


Figure 3: Particle size distribution Batch no. 2

The particle size of pellets is within the range of 2.4 to 3.3 shows increase in the graph.

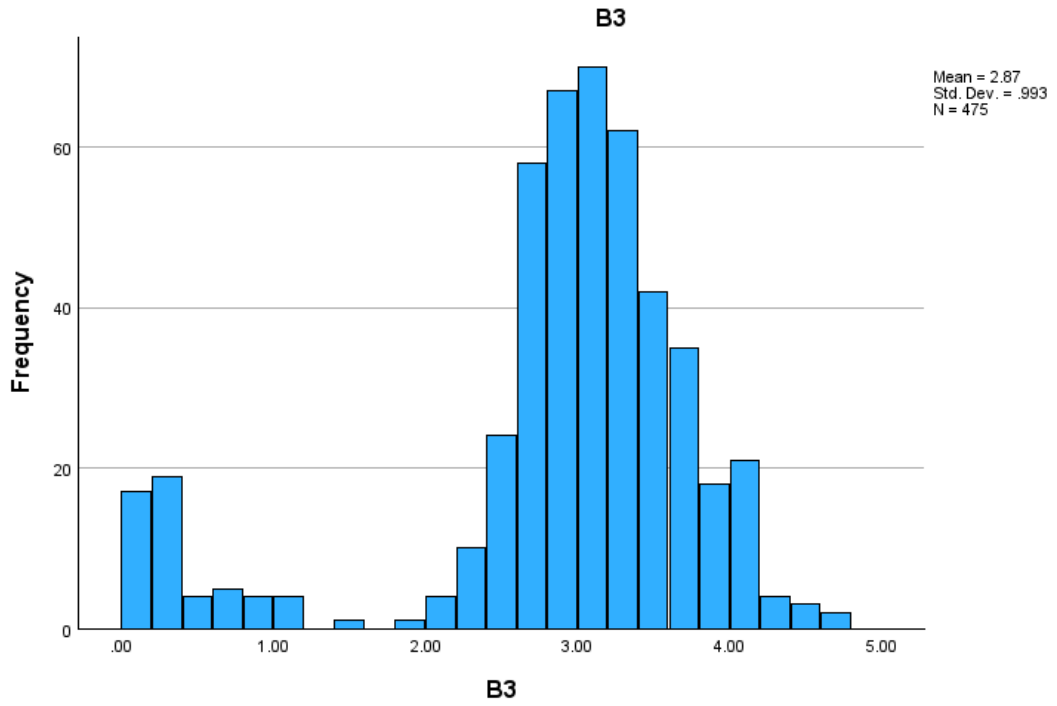


Figure 4: Particle size distribution Batch no. 3

Particle size of the pellets is large in the range of 2.6 to 3.6.

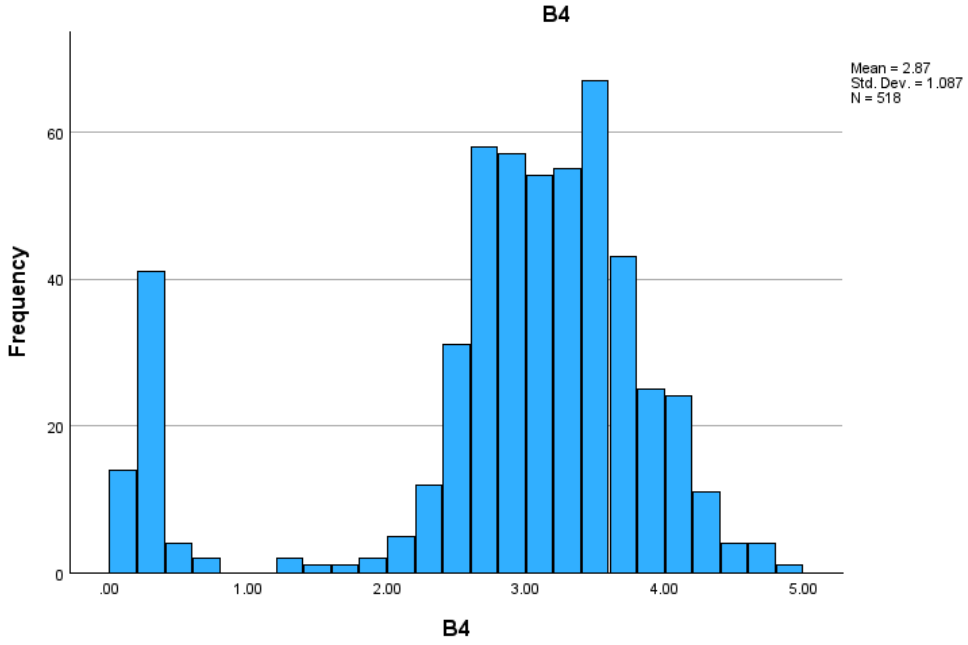


Figure 5: Particle size distribution Batch no. 4

The pellets particle size is large ranging from 2.7 to 3.8.

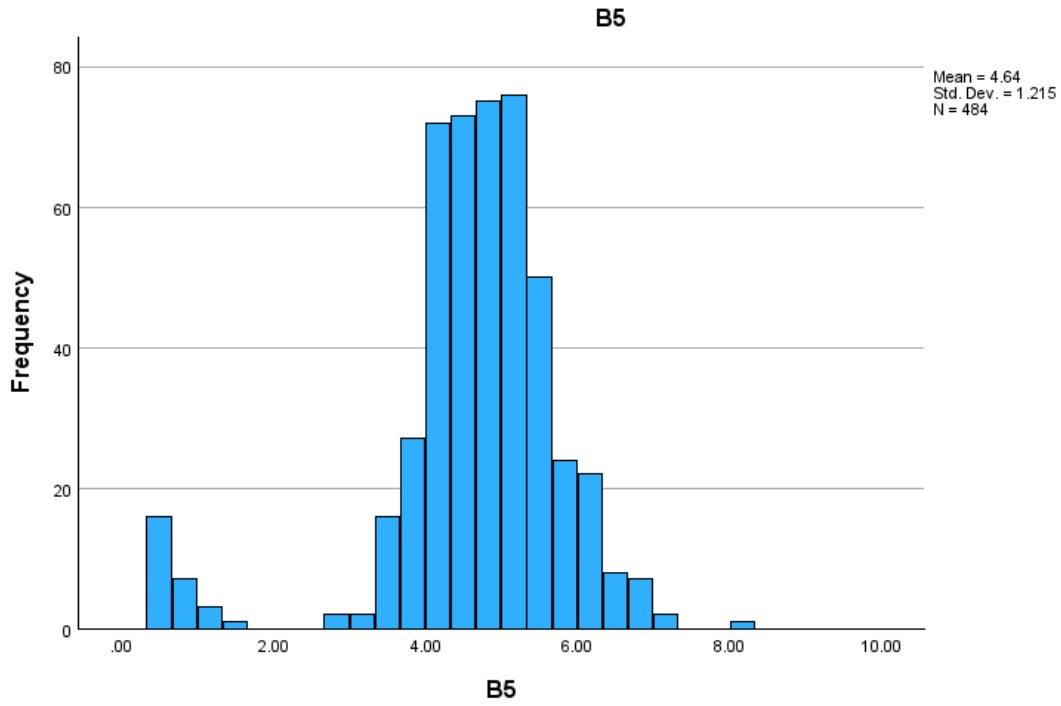


Figure 6: Particle size distribution Batch no. 5

The particle sizes of the pellets are increase varying from 4 to 4.8.

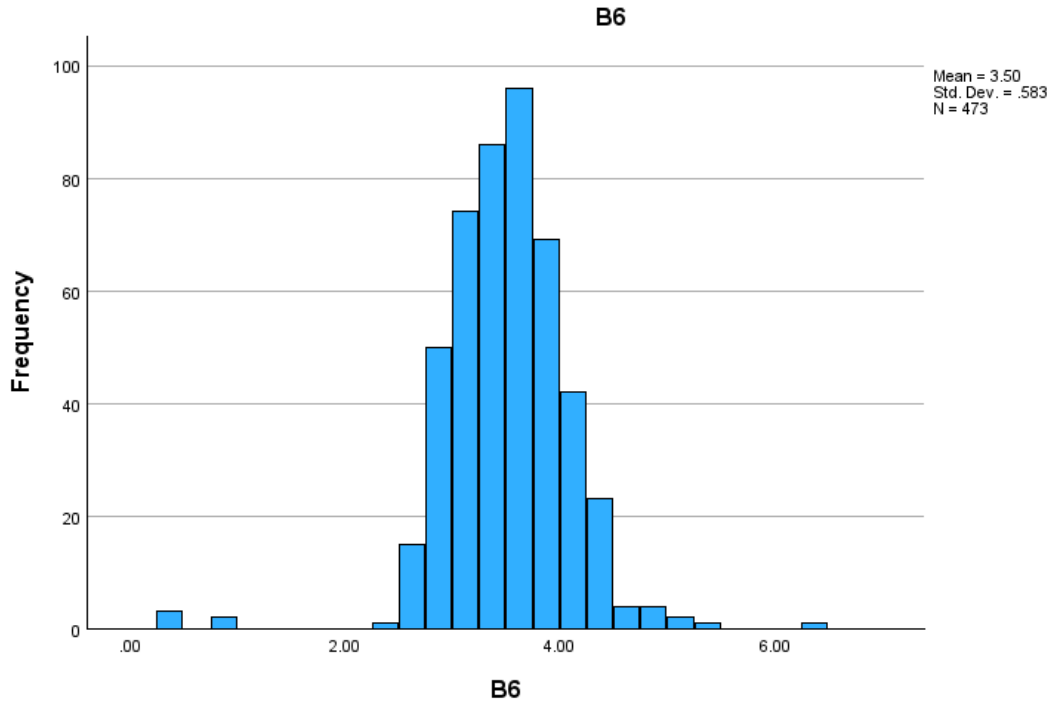


Figure 7: Particle size distribution Batch no. 6

Pellets have particle size ranging from 2.5 to 4

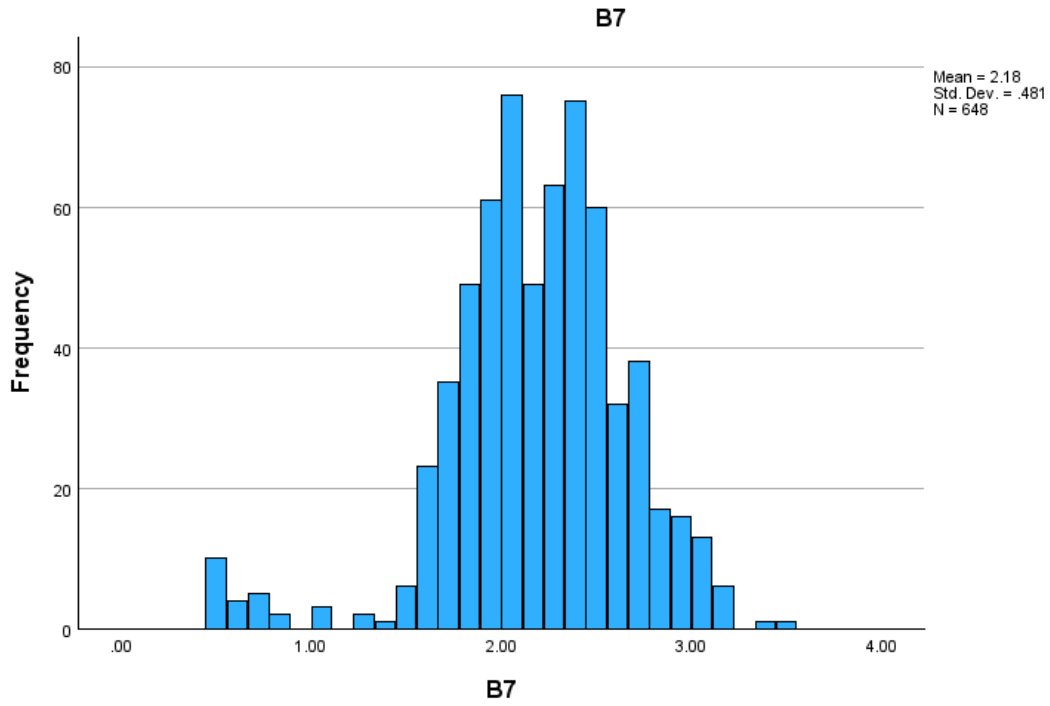


Figure 8: Particle size distribution Batch no. 7

Particle size of the pellets increases and it ranges from 1.8 to 2.7

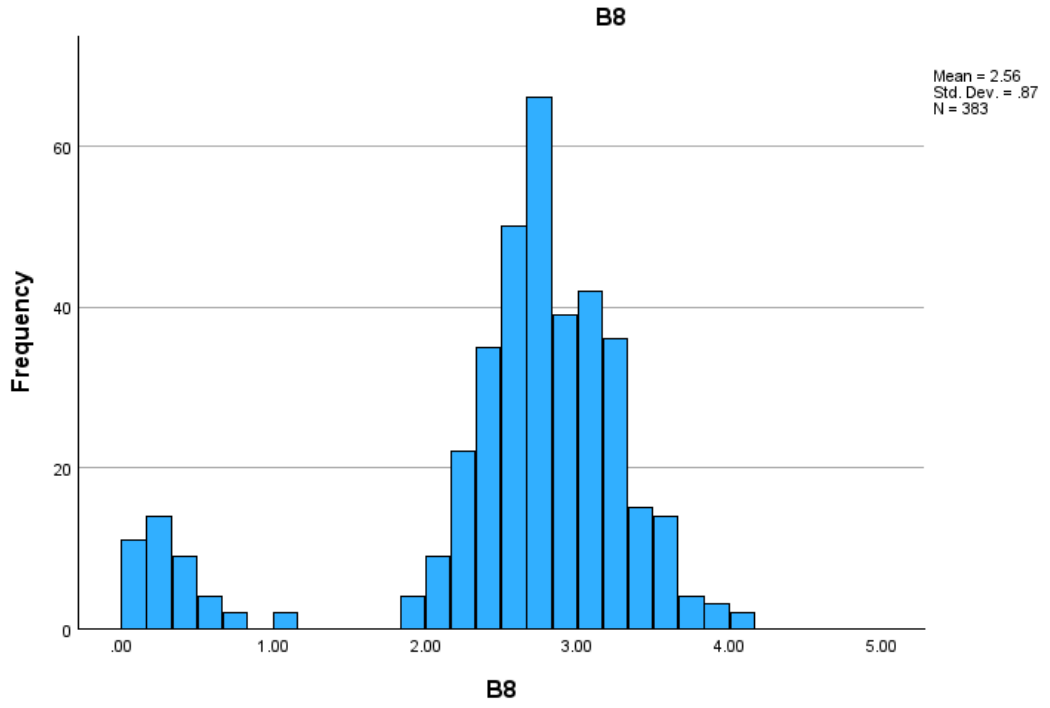


Figure 9: Particle size distribution Batch no. 8

Pellets with particle size which ranges from 2.4 to 3.2 is large.

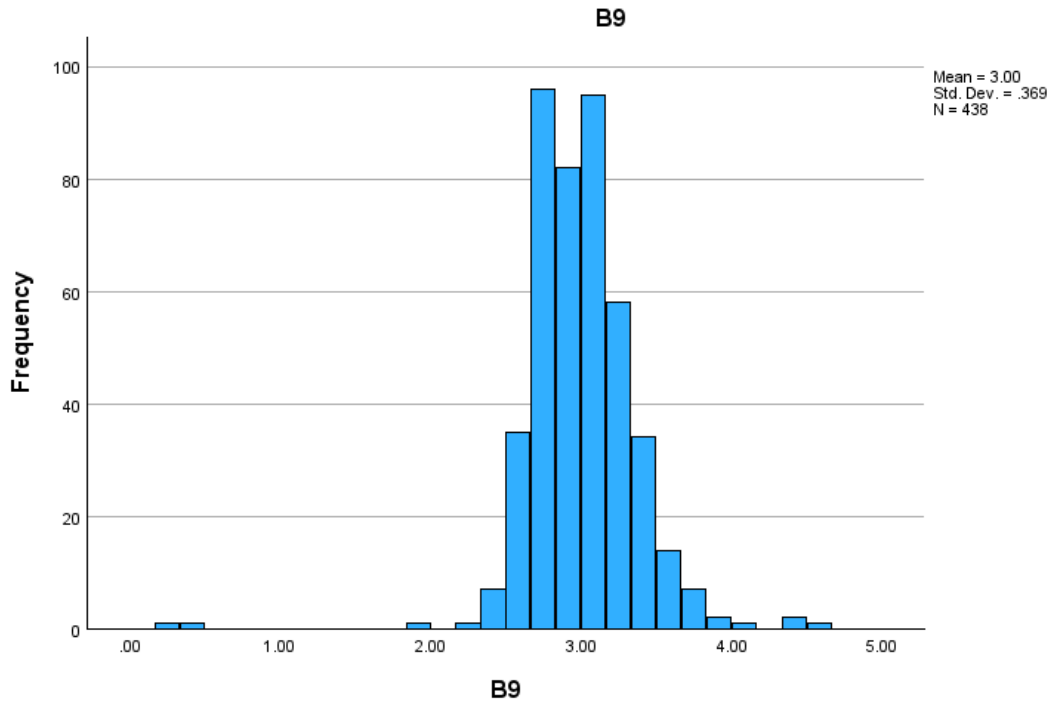


Figure 10: Particle size distribution Batch no. 9

Particle size of the pellets is large in the range of 2.7 to 3.2

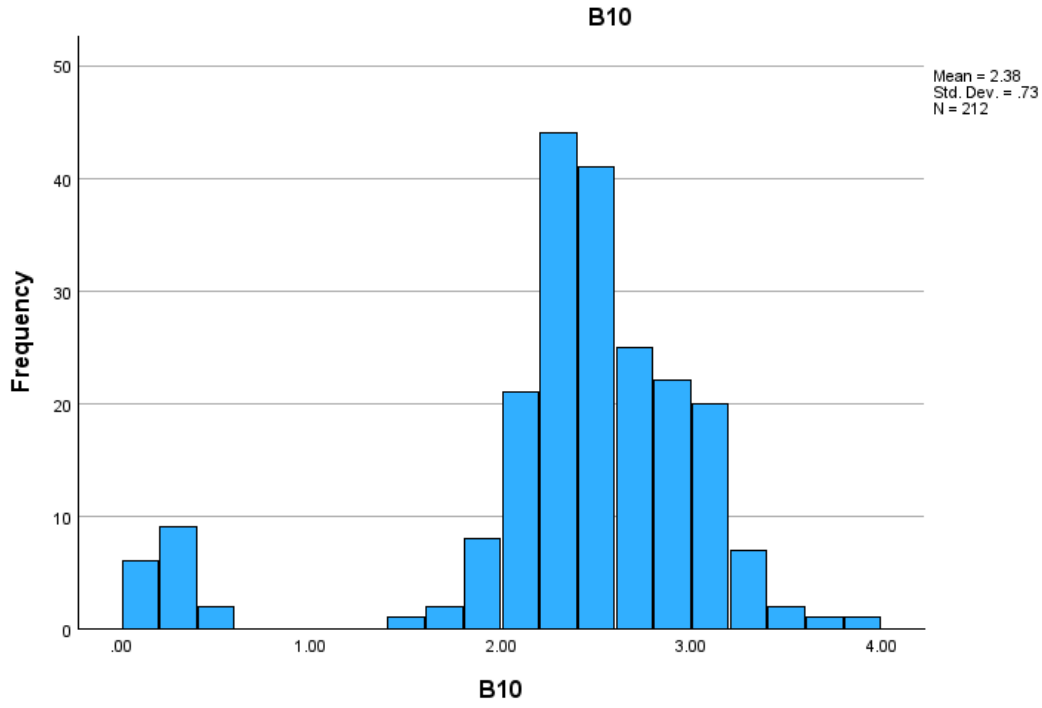


Figure 11: Particle size distribution Batch no. 10

The pellets particle size is large ranging from 2.2 to 2.6

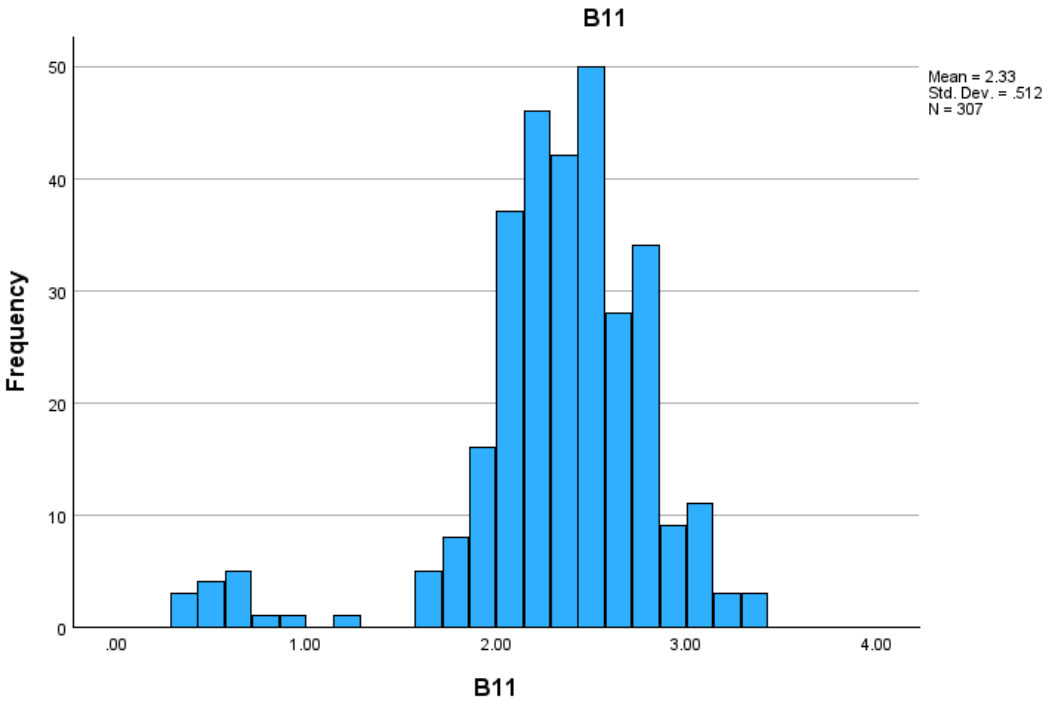


Figure 12: Particle size distribution Batch no. 11

The size of pellets particles is high between 2 and 2.6

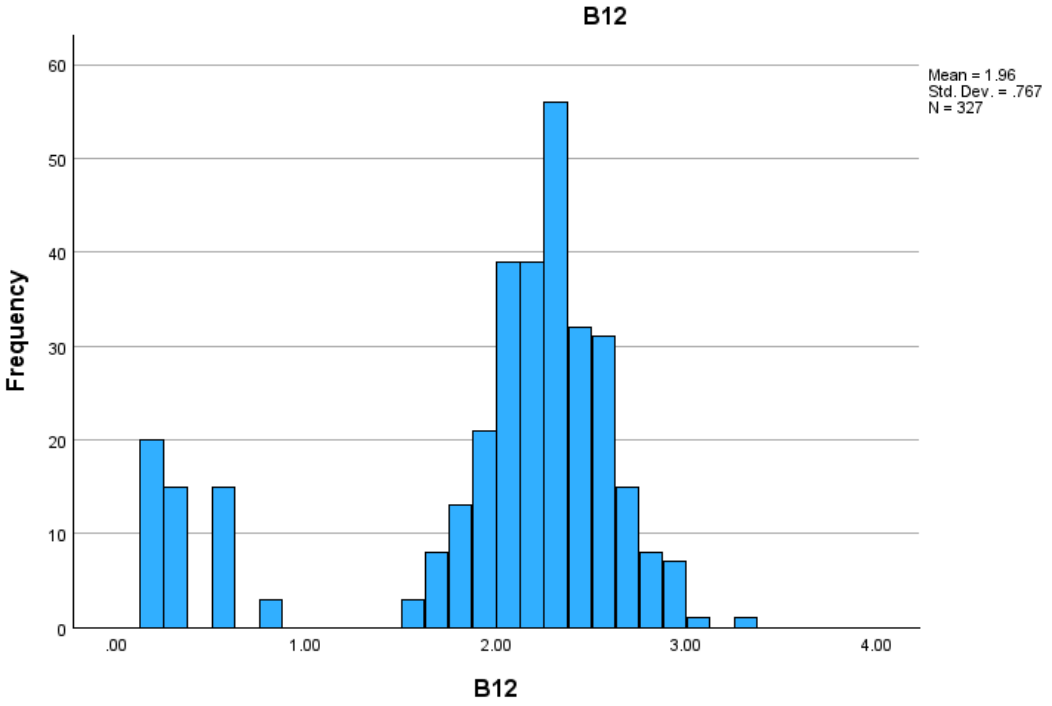


Figure 13: Particle size distribution Batch no. 12

Particle size of the pellets increases and it ranges from 2 to 2.7

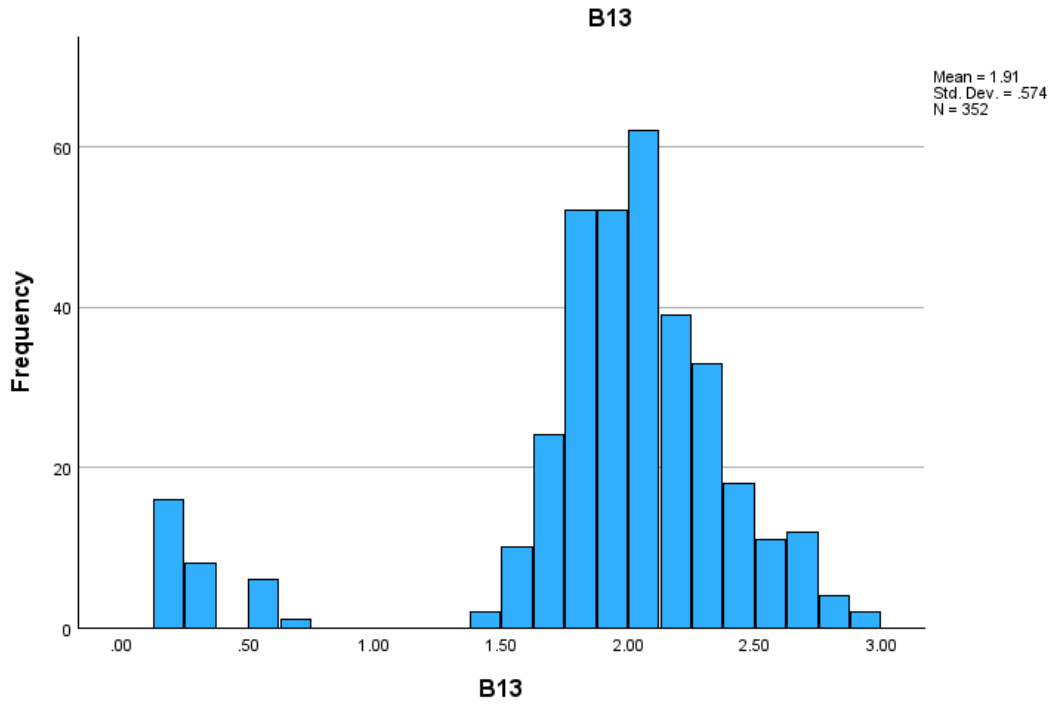


Figure 14: Particle size distribution Batch no. 13

Pellets with particle size which ranges from 1.8 to 2.4 is large.

1. Drug content and Drug release of Paracetamol pellets from formulation optimization

1.1 Absorbance of drug content

Drug Content Absorbance	
Batch 1	0.383
Batch 2	0.368
Batch 3	0.59
Batch 4	0.11
Batch 5	0.214
Batch 6	0.14
Batch 7	0.165
Batch 8	0.127
Batch 9	0.169
Batch 10	0.159
Batch 11	0.095
Batch 12	0.87
Batch 13	0.109

Table 6: Drug Content Absorbance

6.2 Absorbance of drug release

Time	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5	Batch 6	Batch 7	Batch 8	Batch 9	Batch 10	Batch 11	Batch 12	Batch 13

10min	0.828	0.56	1.104	0.963	3.022	3.213	1.838	1.107	1.631	1.107	1.177	0.792	0.56
20min	1.263	2.423	2.393	2.118	3.024	3.304	2.127	1.264	2.118	1.156	1.264	1	1.981
30min	2.917	2.942	2.589	2.194	3.27	3.564	2.721	2.365	2.399	2.264	2.365	2.969	2.941
40min	3.213	3.397	2.788	2.946	3.492	4	2.893	2.764	2.577	3.276	2.264	3.492	3.27
50min	3.304	3.492	3.145	3.209	3.683	4	3.211	3.398	3.27	4	3.398	4	4
60min	4	4	4	3.676	4	4	3.397	4	4	4	4	4	4

Table 7: Absorbance of drug release

Batch	Drug Content %	Drug Release %
PARA 1	76.26	63.15
PARA 2	34.62	68.55
PARA 3	22.84	65.22
PARA 4	15.37	61.40
PARA 5	44.15	83.94
PARA 6	32.66	90.60
PARA 7	29.25	65.93
PARA 8	26.30	60.53
PARA 9	17.21	65.12
PARA 10	28.44	64.32
PARA 11	22.45	58.73
PARA 12	70.87	87.00
PARA 13	12.55	68.29

Response 1 % Yield

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	pvalue Prob > F
Model	728.78	9	80.98	1.30	0.3737not significant
A-Standing Time	4.50	1	4.50	0.072	0.7960
B-PVP K30	91.13	1	91.13	1.46	0.2661
C-MCC	66.13	1	66.13	1.06	0.3375
AB4.00	1	4.00	0.064	0.8074	
AC1.00	1	1.00	0.016	0.9028	
BC0.25	1	0.25	4.007E-003	0.9513	
A2171.12	1	171.12	2.74	0.1417	
B2277.96	1	277.96	4.46	0.0727	
C2121.64	1	121.64	1.95	0.2053	
Residual	436.75	7	62.39		
Lack of Fit	436.75	3	145.58		
Pure Error	0.000	4	0.000		
Cor Total	1165.53	16			

Final Equation in Terms of Actual Factors:

$$
\begin{aligned}
\%\ \text{Yield} = {} & +47.00000 \\
& +11.90000 * \text{Standing Time} \\
& +128.75000 * \text{PVP K30} \\
& -11.15000 * \text{MCC} \\
& -1.33333 * \text{Standing Time} * \text{PVP K30} \\
& -0.080000 * \text{Standing Time} * \text{MCC} \\
& -0.33333 * \text{PVP K30} * \text{MCC} \\
& -1.02000 * \text{Standing Time}^2 \\
& -90.27778 * \text{PVP K30}^2 \\
& +0.86000 * \text{MCC}^2
\end{aligned}
$$

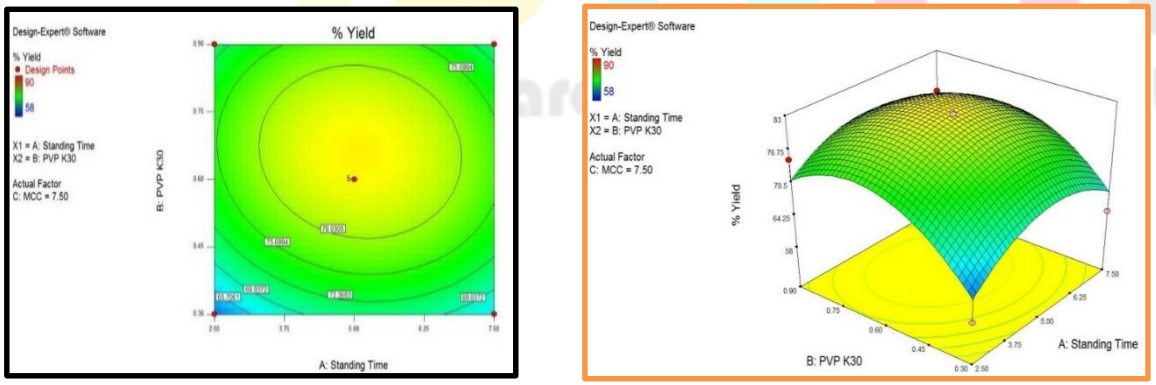


Figure 15: Design of experiment of % yield

As standing time increases upto 5 minutes the percentage yield also increases and after 5 minutes percentage yield decreases. Concentration of binder increases then percentage yield increases upto 5 gram of binder. If the concentration of binder is more than 5 gram then percentage yield decreases.

Response 2 Bulk Density

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	0.037	9	4.120E-003	2.21	0.1548 not significant
A-Standing Time	1.125E-004	1	1.125E-004	0.060	0.8132
B-PVP K30	9.112E-003	1	9.112E-003	4.88	0.0629
C-MCC	4.500E-004	1	4.500E-004	0.24	0.6386

AB6.250E-004	1	6.250E-004	0.33	0.5811
AC1.000E-004	1	1.000E-004	0.054	0.8236
BC1.000E-004	1	1.000E-004	0.054	0.8236
A20.016	1	0.016	8.46	0.0227
B29.007E-003	1	9.007E-003	4.82	0.0641
C21.112E-003	1	1.112E-003	0.60	0.4656
Residual	0.013	7	1.868E-003	
Lack of Fit	0.013	3	4.358E-003	
Pure Error	0.000	4	0.000	
Cor Total	0.050	16		

Final Equation in Terms of Actual Factors:

Buld Density =
+0.39125
-0.10350 * Standing Time
-0.63750 * PVP K30
+0.042000 * MCC
+0.016667 * Standing Time * PVP K30
-8.00000E-004 * Standing Time * MCC
+6.66667E-003 * PVP K30 * MCC
+9.80000E-003 * Standing $Time^2$
+0.51389 * PVP $K30^2$
-2.60000E-003 * MCC^2

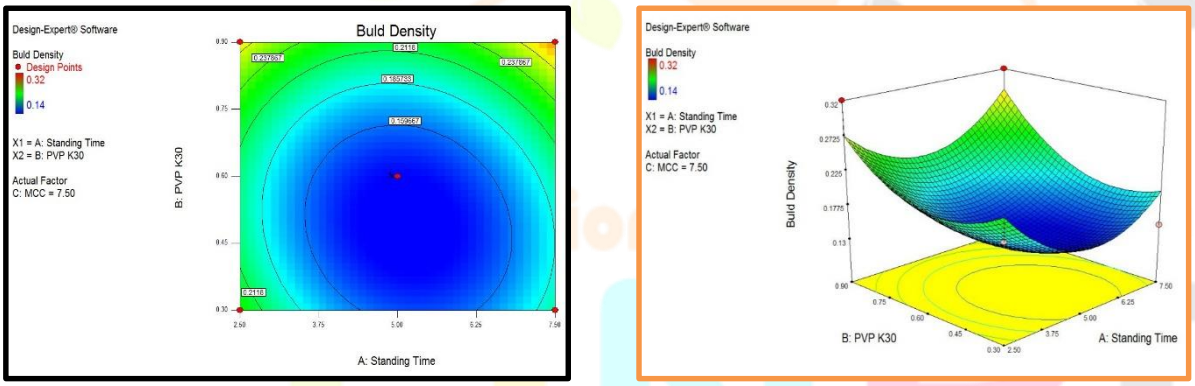


Figure 16: Design of experiment of Bulk Density

As the standing time increases then bulk density decreases upto 5 minutes of standing time but after that as standing time increases then bulk density also increases. As the concentration of PVP K30 increases then bulk density decreases.

Response 3 Tapped Density

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	0.038	9	4.244E-003	1.97	0.1922 not significant
A-Standing Time	8.000E-004	1	8.000E-004	0.37	0.5618
B-PVP K30	7.200E-003	1	7.200E-003	3.34	0.1104
C-MCC	1.250E-003	1	1.250E-003	0.58	0.4714
AB1.225E-003	1	1.225E-003	0.57	0.4757	
AC6.250E-004	1	6.250E-004	0.29	0.6071	
BC2.250E-004	1	2.250E-004	0.10	0.7562	
$A^2$0.015	1	0.015	6.74	0.0357	
$B^2$0.010	1	0.010	4.64	0.0682	
$C^2$1.901E-003	1	1.901E-003	0.88	0.3791	
Residual	0.015	7	2.157E-003		
Lack of Fit	0.015	3	5.033E-003		
Pure Error	0.000	4	0.000		
Cor Total	0.053	16			

Final Equation in Terms of Actual Factors:

Tapped Density =
+0.37125
-0.097000 * Standing Time
-0.74167 * PVP K30
+0.060000 * MCC
+0.023333 * Standing Time * PVP K30
-2.00000E-003 * Standing Time * MCC
+0.010000 * PVP K30 * MCC
+9.40000E-003 * Standing Time^2
+0.54167 * PVP K30^2
-3.40000E-003 * MCC^2

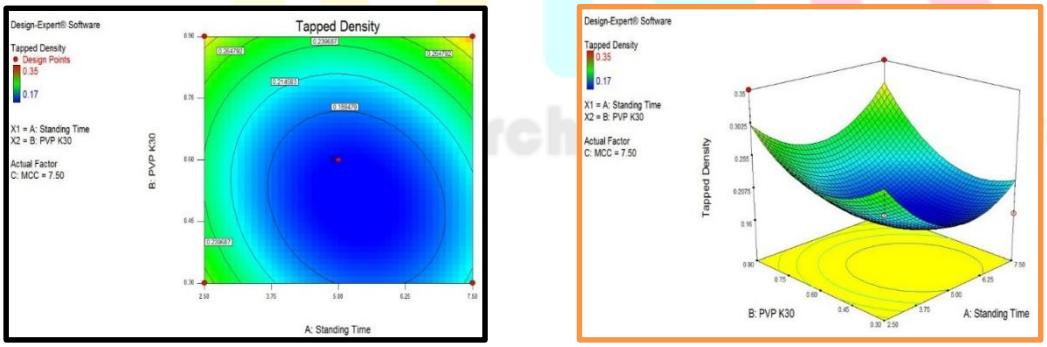


Figure 17: Design of experiment of Tapped Density

As the standing time increases then tapped density decreases upto 5 minutes of standing time but after that as standing time increases then tapped density also increases. As the concentration of PVP K30 increases then tapped density decreases.

Response 4 Angle of Repose

ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	478.82	9	53.20	46.60<		0.0001
significant						
A-Standing Time	23.46	1	23.46	20.55	0.0027	
B-PVP K30	4.32	1	4.32	3.79	0.0927	
C-MCC	5.64	1	5.64	4.94	0.0615	
AB108.58	1	108.58	95.11	< 0.0001		
AC59.44	1	59.44	52.07	0.0002		
BC1.80	1	1.80	1.57	0.2500		
$A^2$136.08	1	136.08	119.21	< 0.0001		
$B^2$13.57	1	13.57	11.88	0.0107		
$C^2$139.70	1	139.70	122.37	< 0.0001		
Residual	7.99	7	1.14			
Lack of Fit	7.99	3	2.66			
Pure Error	0.000	4	0.000			
Cor Total	486.81	16				

Final Equation in Terms of Actual Factors:

Angle of Repose =

+31.50500

-17.20500 * Standing Time

-49.51667 * PVP K30

+10.94000 * MCC

+6.94667 * Standing Time * PVP K30

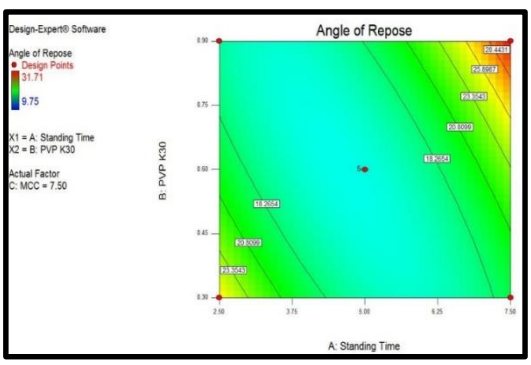
+0.61680 * Standing Time * MCC

-0.89333 * PVP K30 * MCC

+0.90960 * Standing Time^2

+19.94444 * PVP K30^2

-0.92160 * MCC^2



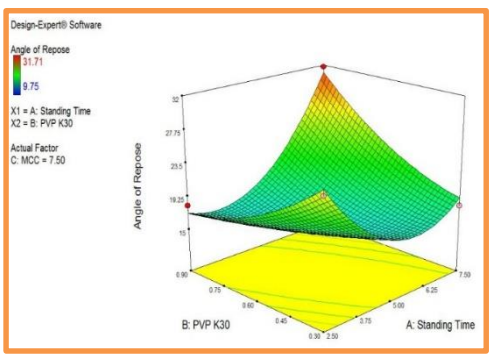


Figure 18: Design of experiment of Angle of Response

At the start when standing time is 2.5 minutes then angle of repose is high but as the standing time increases angle of repose decreases upto 6.25 minutes. Again angle of repose increase above 6.25 minutes of standing time.

Concentration of PVP K30 at 0.30 gram then angle of repose increases but as the concentration of PVP K30 increases then angle of repose decreases.

Response 5 Particle Size

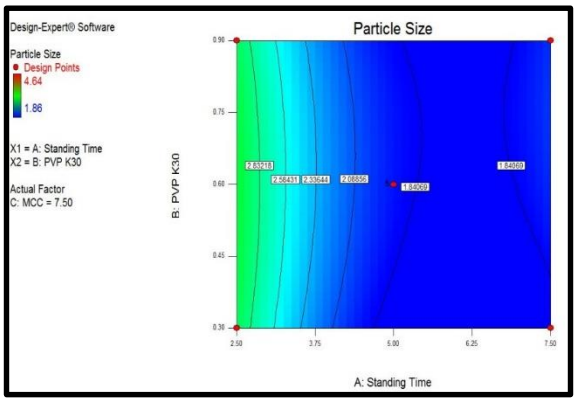
ANOVA for Response Surface Quadratic Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	7.06	9	0.78	3.37	0.0617not significant
A-Standing Time	2.52	1	2.52	10.82	0.0133
B-PVP K30	0.025	1	0.025	0.11	0.7512
C-MCC	4.050E-003	1	4.050E-003	0.017	0.8988
AB	0.016	1	0.016	0.067	0.8030
AC	0.58	1	0.58	2.48	0.1592
BC	0.084	1	0.084	0.36	0.5668
A^2	1.56	1	1.56	6.70	0.0360
B^2	0.043	1	0.043	0.19	0.6797
C^2	2.07	1	2.07	8.89	0.0204
Residual	1.63	7	0.23		
Lack of Fit	1.63	3	0.54		
Pure Error	0.000	4	0.000		
Cor Total	8.69	16			

Final Equation in Terms of Actual Factors:

Particle Size =
+12.98875
-1.70450 * Standing Time
+2.57083 * PVP K30
-1.88000 * MCC
+0.083333 * Standing Time * PVP K30
+0.060800 * Standing Time * MCC
-0.19333 * PVP K30 * MCC
+0.097400 * Standing $Time^2$
-1.12500 * PVP $K30^2$
+0.11220 * MCC^2



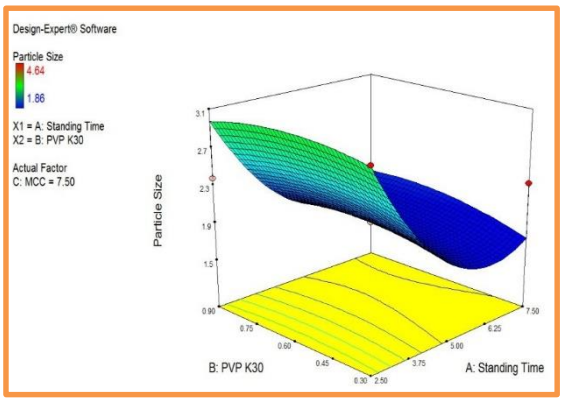


Figure 19: Design of Experiment of Particle Size

At the starting at standing time i.e 2.50 the particle size increases due to high moisture content and causes agglomeration of pellets.
At the standing time 5 minutes the particle size of the pellets is optimum i.e uniform spherical pellets are formed.
As the standing time increases then the particle size decreases.
As the concentration of PVP K30 increases then size of particle is constant but pellets becomes harder and harder as concentration of binder increases.

Response 6 % Drug Content

ANOVA for Response Surface Linear Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	613.20	3	204.40	0.49	0.6944not significant
A-Standing Time	87.19	1	87.19	0.21	0.6547
B-PVP K30	21.19	1	21.19	0.051	0.8250
C-MCC	504.83	1	504.83	1.21	0.2906
Residual	5408.53	13	416.04		
Lack of Fit	5408.53	9	600.95		
Pure Error	0.000	4	0.000		
Cor Total	6021.73	16			

Final Equation in Terms of Actual Factors:

% Drug Content =
+48.90551
+1.32050 * Standing Time
-5.42500 * PVP K30
-3.17750 * MCC

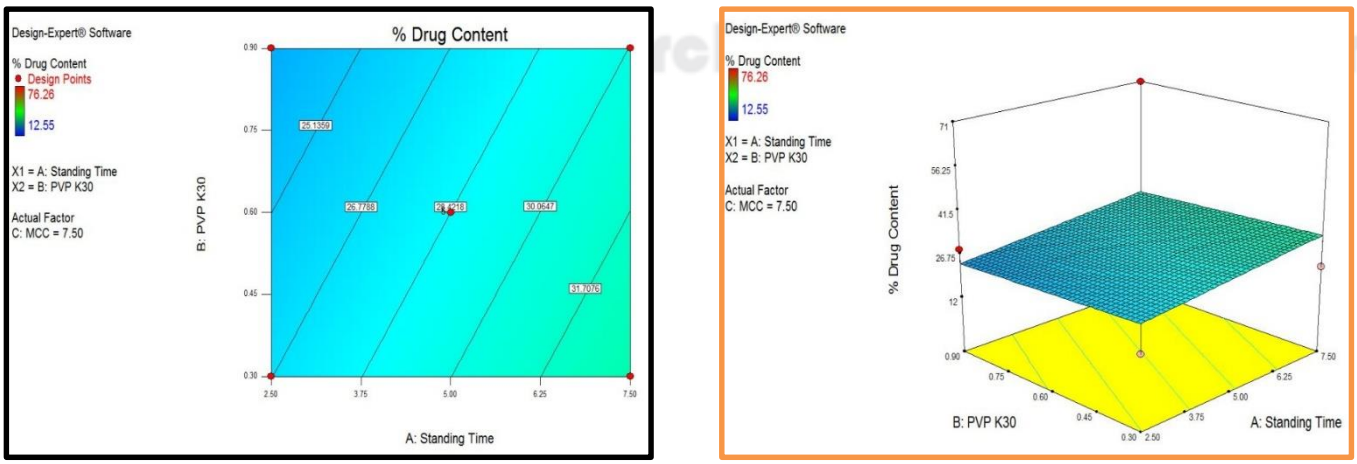


Figure 20: Design of experiment of % Drug Content

As the standing time increases then % drug release slightly increases. There is slight in % drug content as the concentration of PVP K30 increases.

Response 7 Drug Release

ANOVA for Response Surface Linear Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F
Model	190.00	3	63.33	0.71	0.5618not significant
A-Standing Time	126.33	1	126.33	1.42	0.2546
B-PVP K30	62.66	1	62.66	0.70	0.4164
C-MCC	1.01	1	1.01	0.011	0.9168
Residual	1155.85	13	88.91		
Lack of Fit	1155.85	9	128.43		
Pure Error	0.000	4	0.000		
Cor Total	1345.84	16			

Final Equation in Terms of Actual Factors:

Drug Release =
+70.45794
-1.58950 * Standing Time
+9.32917 * PVP K30
+0.14200 * MCC

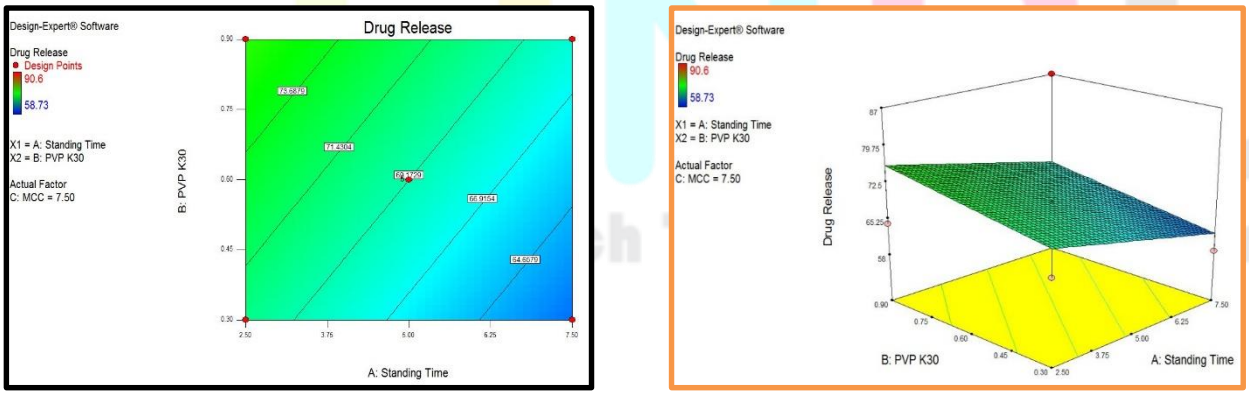


Figure 21: Design of experiment of % Drug Content

There is decrease in drug release if the standing time increases.

If the concentration of PVP K30 increases then Drug release also increases slightly.

Pellet wet mass is one of the most crucial parameters that should be optimized before pellet manufacturing. The impact of different concentrations of the binder solution PVP K and the pellet excipient MCC on pellet wet mass) is shown in Table 3. It was found that MCC significantly affected the we and the PVP solution. This is illustrated using ANOVA as shown in Table 3. As indicated from the main effect data Fig 15, 16, 17, 18, 19, 20, 21 the effect on the pellet wet mass was agonistic. Thus, increasing PVP concentration in the binder solution results in an increase.

Summary and conclusion

The drug paracetamol avaible in different dosage from in tablets, capsule it treats the fever but formulation of pellets in a small spherical size with high degree of flexibility due to free-flowing characteristics so they easily oral swallowing without any difficulty and give fast action of body.

Paracetamol drug is used as model drug and impact of various factors such as concentration of binder PVP K-30, concentration of spheronizing agent Microcrystalline cellulose, standing time of extrudate are studied.

Ideal standing time of extrudates 2.5-5min. if we take the conc. Of MCC 5gm then ideal conc. Of PVP K-30 is 0.3 gm

Conclusion – In extrusion Spheronization, firstly the powder of paracetamol and excipients are mixed with binding liquid. Extrudates are formed and by using spheronizer we get uniform spherical shaped pellets. Mostly Concentration of binder PVP K-30, standing time of extrudates, speed of spheronizer affect the results of pellets.

From the 13 batches it was observed that if the concentration of binder increases then pellets become hard, if concentration of binder decrease than optimum level then pellets become brittle. If standing time of pellets increases above then pellet size get decreased, if standing time is less then pellet size get increases and it causes agglomeration due to presence of moisture.

Ideal standing time of extrudates 2.5-5min.

If we take the conc. Of MCC 5gm then ideal conc. Of PVP K-30 is 0.3 gm.

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