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Efficacy and Patient-Centered Outcomes of Antiasthmatic Orodispersible Tablets in Acute Asthma Exacerbation

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ABSTRACT

Respiratory system is the system of gaseous exchange. If any part of the system affected then the respiratory diseases occur like asthma, COPD, bronchitis etc. for treating such respiratory diseases salbutamol sulphate was used. Salbutamol sulphate as a model β2 adrenergic agonist drug which under goes first pass metabolism in liver, which can decrease the bioavailability of drug. Thus, the aim of this study was to improve bioavailability, swift action and improved patient compliances. This work represents a new design of salbutamol sulphate Orodispersible tablets using box-Behnken design with the three independent variables: the two super disintegrants (jackfruit seed starch and Lepidium sativum seed mucilage) and a binder (polyvinyl pyrrolidone K-30) were selected to study their effect on the critical dependent variables. The natural ingredients are extracted and desirable evaluated. All the evaluation pre-compressional and post-compressional was observed. The responses variables were analysed and the optimised formulation was obtained using the box-Behnken design.

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Introduction

Respiratory system is the system of exchange of gases i.e., inhalation of oxygen and exhalation of carbon dioxide by the help of lungs, trachea, and alveoli. The gaseous exchange or any part of the respiratory system is affected mainly breathing difficulties which causes respiratory diseases. The respiratory diseases are the third leading cause of death. focusing on respiratory diseases is important because of their high prevalence, impact on quality of life, and economic burden. Respiratory disease like asthma, COPD, bronchitis etc [1].

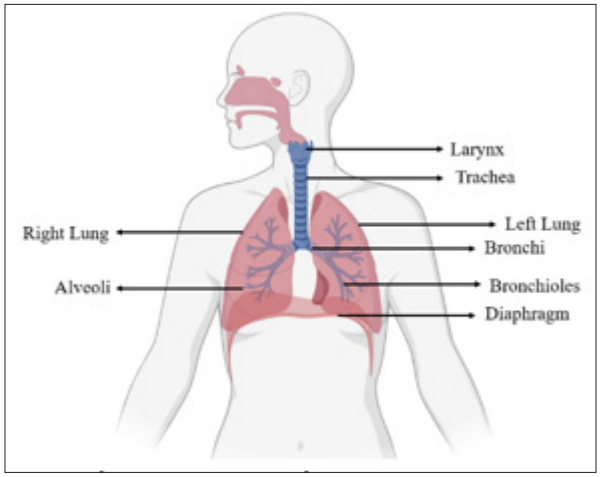


Figure 1: Respiratory System

Asthma is a chronic respiratory disease which causes inflammation in the airways marked by bronchial hyper responsive ness and reversible airflow obstruction which make it difficult to breathe, with symptoms including wheezing, shortness of breathing, chest tightness, and coughing [2]. A common respiratory disease that affects both adult and children. The severity of disease is influenced by genetic factors, environmental triggers and airway inflammation and remoulding. There are many types of medication to treat asthma like salbutamol sulphate [3].

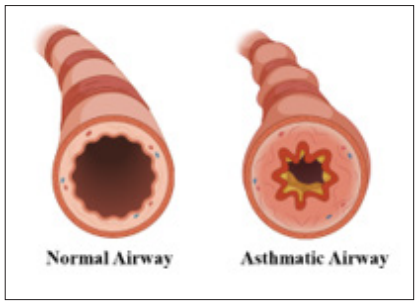


Figure 2: The Normal Airways and the Asthmatic Airways

To treat asthma, salbutamol sulphate is a short-acting beta-2 adrenergic agonist. It increases cyclic AMP via activating beta-2 receptors, which relaxes smooth muscles in the airways and inhibits the release of mast cell mediators. Novel drug delivery methods seek to increase its efficacy even while it is converted to an inactive form in the liver, decreasing bioavailability [4].

The ability of Orodispersible Tablets (ODTs) to dissolve rapidly in the mouth without the need for water improves patient adherence, especially for geriatric, pediatric, and dysphagic patients. When these tablets come into touch with saliva, they

dissolve quickly, allowing for quicker medication release [5]. Fast disintegration, high drug loading, stability, and the capacity to prevent the first-pass effect, which enhances bioavailability, are important features. Benefits include decreased adverse effects, enhanced safety because of less asphyxiation hazards, quicker medication absorption, enhanced bioavailability, and simplicity of administration for individuals who have trouble swallowing [6].

In order to improve patient adherence and treatment effectiveness for asthma, the project intends to create salbutamol sulphate orodispersible pills. For the advantage of both young and old patients, the pills will dissolve in the mouth without the need for water. The formulation aims to enhance bioavailability and prevent first-pass metabolism by using super disintegrants. Evaluation will involve testing for thickness, hardness, dissolution, and dispersion time both before and after compression [7].

Materials and Method

Salbutamol sulphate was gifted from Cipla Private Limited, other chemicals like polyvinyl pyrrolidone k-30, talc, magnesium stearate, etc are from Swarnaroop laboratories, and the natural ingredients like Jackfruit seed starch and Lepidium sativum are extracted in IPS Academy college of pharmacy Indore laboratories. All the chemicals are used of analytical grade.

Extraction of Jackfruit Seed Starch

The extraction of starch from the seeds of jackfruit

- The extraction of starch from jackfruit seeds can be done by using two different solvents which are aqueous (distilled water) and alkali (sodium hydroxide) medium.
- Extract the seeds from the jackfruit and make the powder of it.
- Weigh accurately about 5 g of jackfruit seed powder in two different beakers.
- Add the 100 ml of aqueous and alkali medium to the beakers separately.
- Put it at room temperature and constant stirring for 6-8 hrs.
- After 6-8 hrs the slurry was found and the slurry was pass through with the sieve number 212 and wash the sediment with the distilled water consequently for three times.
- The collected filtrate was precipitated over night with 10 ml acetone at 4°C.
- Then wash the obtained crude starch with water and the supernatant was discarded.
- The obtained starch cake was dried for 24 hrs at 40°C in the dryer.
- Then the obtained dry cake was grounded in the pestle and mortar and then packed it in air-tight container [8].

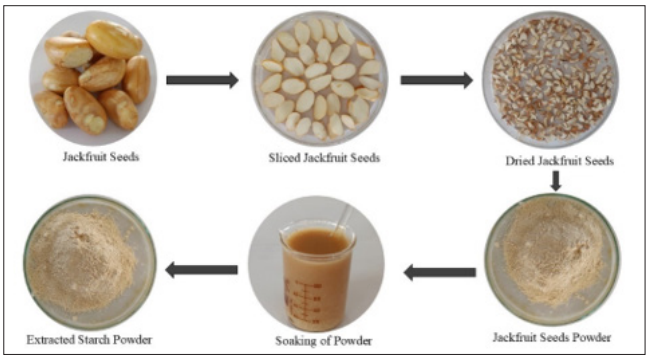


Figure 3: The Extraction Process of Jackfruit Seed Starch

Table 1: Organoleptic Properties of Jackfruit Seed Starch

S. No.	Evaluation Parameters	Results
1	Color	Slightly off-white
2	Odour	Neutral odour
3	Taste	Mildly starchy
4	Appearance	Fine
5	Nature	Hydrophilic
6	Melting point	69°C
7	pH	6.9
8	Swelling index	180 %
9	Water absorption ratio	2.2 ml/g

Extraction of Lepidium Sativum Seed Mucilage

The extraction of mucilage from the seeds of Lepidium sativum

- Weigh accurately about 50 g of Lepidium sativum seeds.
- Add the 400ml of distilled water to the seeds and soaked them for 12 hrs.
- Then the seed (soaked seeds) were blended at 2000 rpm for 15-20 min.
- Then the obtained mix was filtered through the 8 folds of muslin cloth.
- The again blend the seeds by adding 100 ml of distilled water.
- The refilter it.
- The precipitation of the filtrate was done using 400ml of acetone.
- Then filter out the precipitate which gives the coagulant mass using muslin cloth.
- Then the coagulant mass was dried in the dryer at 60°C for 16-18 hrs.
- Then spraying with the acetone to dried mucilage to obtained the mucilage flakes from the Petridish.
- Then the obtained flakes were dried in dryer at 60°C for 5 min.
- Then the obtained mass was grounded in the pestle mortar and passed through the sieve number 80 and then packed in air tight container [9].

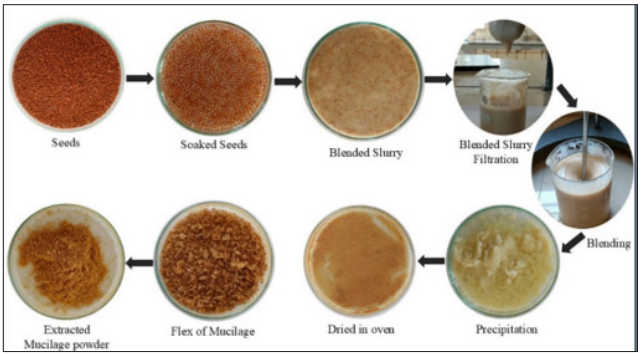


Figure 4: The extraction Process of Lepidium Sativum Seed Mucilage

Table 2: Organoleptic Properties of Lepidium Sativum Seed Mucilage

S. No.	Evaluation parameters	Results
1	Color	Brown
2	Odour	Odourless
3	Taste	Tasteless
4	Appearance	Lustrous amorphous

5	Nature	Hydrophilic
6	Melting point	69°C
7	pH	6.5
8	Swelling index	351.5
9	Water absorption ratio	10.5 ml/gm

Box-Behnken Design (BBD)

Box-Behnken design is the response surface methodology in which the three levels of a factor should be studied that is 1 (higher level), 0 (middle level), -1 (lower level). BBD was used to making polynomial model using design expert software by placing 3 dependent and 3 independent variables. The three independent variables X_1, X_2, X_3 that are concentration of jackfruit seed starch, concentration of Lepidium sativum seed mucilage, and concentration of polyvinyl pyrrolidone k-30 selected respectively as shown in table.

Table 3: The Table Showing the Independent Variable and the Levels that are Selected

S. No	Independent variable	Levels	
		1(higher level)	-1(lower level)
1	Concentration of jackfruit seed starch	5	15
2	Concentration of lepidium sativum seed mucilage	2	8
3	Concentration of polyvinyl pyrrolidone k-30	2	5

The response of the change of these three independent variables on three dependent variables Y_1, Y_2, Y_3 which are disintegration time, in-vitro drug release, and hardness of tablets are studied as shown in table.

Table 4: The Table Showing the Dependent Variable

S. No.	Dependent variables	Units
1	Disintegration time	Seconds
2	In-vitro drug release	percent
3	Hardness	Kg/cm2

By selecting the three independent and three dependent variable the design expert software gives the 15-formulation composition for these three independent variables which was shown in the table.

According to the design expert software the composition for the formulation is provided and according to this we can formulate the tablets by direct compression method.

Table 5: The Runs from the Box-Behnken Design

Runs	Concentration of Jackfruit Seed Starch	Concentration of Lepidium Sativum Seed Mucilage	Concentration of Polyvinyl Pyrrolidone k-30
1	10	8	5
2	5	8	3.5
3	15	5	2
4	10	5	3.5
5	10	8	2
6	5	5	5
7	5	2	3.5
8	10	2	2
9	10	5	3.5
10	15	5	5
11	10	5	3.5
12	10	2	5
13	15	2	3.5
14	15	8	3.5
15	5	5	2

Formulation of Tablets

The formulation of orodispersible tablets of salbutamol sulphate is formulated using direct compression method, the formula for making tablets is shown in the table. The procedure for formulating the orodispersible tablets of salbutamol sulphate by direct compression method is given below

- Weigh accurately the quantities of active pharmaceutical ingredient and the excipient according to the table.
- The weighed quantities of salbutamol sulphate, jackfruit seed starch, lepidium sativum seed mucilage, polyvinyl pyrrolidone k-30, and mannitol was grinded in dry and clean mortar.
- Then all the grinded ingredients are passed through sieve number 60.
- Then finally the talc and magnesium stearate were added and mixed for 5 minutes.
- Then the mixed ingredient of active pharmaceutical ingredient and excipients were compressed into tablets using 6.5 mm punch in Karnavati tablet compression machine
- Then the evaluation was done of tablets.

Table 6: Formulation Table for All the 15 Batches of Salbutamol Sulphate Orodispersible Tablets

Formulation	OT 1	OT 2	OT 3	OT 4	OT 5	OT6	OT 7	OT 8	OT 9	OT 10	OT 11	OT 12	OT 13	OT 14	OT 15
Salbutamol sulphate	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Jackfruit seed starch	10	5	15	10	10	5	5	10	10	15	10	10	15	15	5
Lepidium sativum seed mucilage	8	8	5	5	8	5	2	2	5	5	5	2	2	8	5
Polyvinyl pyrrolidone k-30	5	3.5	2	3.5	2	5	3.5	2	3.5	5	3.5	5	3.5	3.5	2
Mannitol	66	72	67	70.5	69	74	78.5	75	70.5	64	70.5	72	68.5	62.5	77
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Pre-Compressional Parameter

Organoleptic Properties

Firstly, the pre-compressional studies are very important parameter and the Preformulation was start with the description of the drug substances. In the description of the drug substance, we observe the parameters like color, odour, taste, and nature. The terminology that we have to use for describing the color, odour, taste, and nature was shown in table.

Table 7: Terminology Describing the Organoleptic Properties

Color	Odour	Taste	Nature
Off-white	Aromatic	Bitter	Acidic
Cream yellow	Odourless	Sweet	Basic
Tan	Fruity	Tasteless	Lipophilic
Shiny	Pungent		Hydrophilic

Particle Size Determination

The size determination is important parameter in which the size of the particle present in a drug is determined. For the determination of particle size of the drug there are different methods for determination for example microscopy, sieving, sedimentation technique, laser diffraction method, permeametry technique.

Table 8: Techniques and Particle Size

S. No.	Techniques	Particle size (mm)
1.	Microscopic	1-100
2.	Sieve	>5
3.	Sedimentation	>1
4.	Elutriation	1-50
5.	Centrifugal	<50
6.	Permeability	>1
7.	Light Scattering	0.5-50

Melting Point

Melting point of a compound is a physical constant which is defined as the temperature at which the compound can change its state from its solid state to its liquid state. Melting point can used to identify the compound. The melting point of salbutamol sulphate was determined using the melting point apparatus in which the capillary is used. Firstly, the one end of capillary was closed and then the salbutamol sulphate was filled in the capillary tubes. Then the capillary tubes were placed in the melting point apparatus with the thermometer. And the temperature at which the salbutamol sulphate changes its state from solid to liquid state was noted. For the accuracy in the melting point the three consecutive temperature was noted and the average value of the temperature was represented as the melting point of the salbutamol sulphate.

Solubility

Solubility is defined as the maximum amount of a solute that can be dissolve in the given amount of the solvent making a saturated solution. Solubility can be determined by shake flask method. According to this method, four different type of the solvent was taken and in four different veils and poured maximum amount of solvent in the veils individually making a solution. And place aside for 24 hrs. after 24 hrs if the solution was found to be in unsaturated form, then the heating was applied. After heating the solution was filtered and the solution was analysed in UV spectrophotometry and the solubility can be calculated.

Table 9: Description of Solubility

Descriptive Term	Parts of Solvent Required for 1 part of Solute	g/L in Water	M=400 mol/L in Water	M=40000 mol/L in Water
Very soluble	≤1	≥1000	≥2,5	≥0,025
Freely soluble	1 to 10	1000 to 100	2,5 to 0,25	0,025 to 0,0025
Soluble	10 to 30	100 to 33	0,25 to 0,08	0,0025 to 0,0008
Sparingly soluble	30 to 100	33 to 10	0,08 to 0,025	0,0008 to 0,00025
Slightly soluble	100 to 1000	10 to 1	0,025 to 0,0025	0,00025 to 0,0000025
Very slightly soluble	1000 to 10,000	1 to 0,1	0,0025 to 0,00025	0,000025 to 0,0000025
Practically insoluble	≥10,000	≤0,1	≤0,00025	≤0,0000025

Bulk Characterization

A wide variety of pharmaceutical ingredients exist in multiphase forms called powders, which can be liquids as well as solids. One of the most important aspects of powder's physical characteristics is its individuality. For instance, a powder can be analysed by its densities, flow properties, compressibility, etc.

Densities

Bulk Density

Bulk density of a powder or granules is the amount of powder weight that is present in a defined volume. The bulk density was determined by pouring the powder into the measuring cylinder and the volume was noted. The bulk density was calculated using the formula

$$\text{Bulk Density} = \frac{\text{Powder Weight}}{\text{Volume of Powder}}$$

Tapped Density

Tapped density of a powder or granules is the amount of powder weight that is present in a defined volume after tapping or avoiding the voids present in it. The tapped density was determined by pouring the powder in the measuring cylinder and the volume is noted after the 50 tapping of the measuring cylinder. The tapped density is calculated using the formula

$$\text{Tapped density} = \frac{\text{Weight of Powder}}{\text{Volume after 50 Tapping}}$$

Powder Flow Properties

Compressibility Index

The compressibility is the ability to decrease the volume under the pressure. the compressibility is also known as the Carr's index and is used to predict the flow property of powder and it is predicted using the bulk and tapped density. The carr's index is calculated using the formula

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100\%$$

Table 10: Carr's Index and Flowability

S. No.	Carr's Index	Flowability
1.	5-15	Excellent
2.	12-16	Good
3.	18-21	Fair possible
4.	23-35	Poor
5.	33-38	Very poor
6.	>40	Ver, very poor

Hausner's Ratio

Hausner's ratio is used to determine the flow property of the powder or granules by the compressibility and compactibility. The compressibility can be defined as the ability to decrease the volume of powder under the pressure and the compactibility can be defined as the ability of the powder to compressed to a specific tensile strength into tablet. The Hausner's ratio can be determined using the bulk and tapped density. The Hausner's ratio was calculated using formula

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table 11: Hausner's Ratio and Flowability

S. No.	Hausner' ratio	Flowability
1.	1.05 - 1.18	Excellent
2.	1.14 - 1.20	Good
3.	1.22 - 1.26	Fair possible
4.	1.30 – 1.54	Poor
5.	1.50 – 1.61	Very poor
6.	>1.67	Ver, very poor

Angle of Repose

Angle of repose measures the resistance between movement of particles i.e., frictional force within loose powder. The angle of repose (θ) was determine using the funeel method. Funnel was placed on the tripod stand at a fixed height above the graph paper. The funnel tip can be closed and the poured the powder and the stoper is removed and then height of the pile and the diameter can be noted. The angle of repose can be calculated using formula

$$\tan\theta = \frac{\text{Height of Pile}}{\text{Radius}}$$

Table 12: Angle of Repose and Flow Property

S. No.	Flow Property	Angle of Repose
1.	Excellent	25-30
2.	Good	31-35
3.	Fair	36-40
4.	Passable	41-45
5.	Poor	46-55
6.	Very poor	56-65
7.	Very, very poor	>66

Calibration Curve

Calibration curve was used to determine the unknown sample's concentration, to calculate the limit of detection and limit of quantitation. The standard curve was formulated using the set of standard samples at a range of concentration from the responses found from UV spectrophotometer. For preparing the calibration curve of salbutamol sulphate firstly, prepared the stock solution (1000 µg) of the salbutamol sulphate using the phosphate buffer pH 6.8. Then the sub stock (100 µg) was prepared and then the dilution was prepared using sub stock solution of 10 to 50 µg/ml. the absorbance of the all dilution were observed using UV-Visible spectrophotometer at maximum wavelength 272 nm [10-16].

Post-Compressional Parameter

Organoleptic Properties

The organoleptic properties are simply the general appearance of the tablets in which the colour, odour, and the taste of the tablets are studied. Usually for the organoleptic properties 10 tablets was studied.

Shape and Size

The shape and size are mainly the determination of the thickness and diameter of the tablets. The thickness and diameter are determined with the help of vernier calliper or by the micrometre screw gauge. There are many automated machines were there in market to measure the thickness and the diameter by only placing the tablets in the instrument and the instrument gives the thickness and diameter of the tablet.

Weight Variation

The weight variation is an important parameter in the weight of a tablets. According to the IP the weight variation is studied by taking the random 20 tablets from the formulation batch and then the weight of individual and collectively 20 tablets by using digital weighing balance. The average weight of one tablet was determine from the collective weight of the tablet. Then the both individual and average weight was compared.

Table 13: Weight Variation and Deviation

S. No.	USP	Max % difference allowed	IP / BP
1.	130mg > or less	±10%	80mg > or less
2.	130mg > 324 mg	±7.5%	80mg-250mg
3.	324 mg < or more	±5%	250mg < or more

Hardness
The hardness of the tablets was determined using Monsanto hardness tester. For the hardness of the tablets the three tablets from each formulation batch randomly selected and the individual tablet was placed in the Monsanto hardness tester and after it the pressure is applied to break the tablets and the average reading was noted. The hardness of the tablet was measured in Kg/cm2. For the orodispersible tablets the hardness was kept to be lower than the other tablets. The hardness for the orodispersible tablets should be in the range of 3-5 Kg/cm^2.

Friability
The friability test of tablets was determined to access the ability of the tablets to withstand in packaging, handling, and transportation of the tablets. Friability was the removal of the fine particle which are on the surface of the tablets in the container due to which the weight of the tablets was decreases. For testing the friability of the tablets, we use the Roche friabilator. Roche friabilator consist of a plastic chamber and revolves at 25 rpm in which we place the tablets of 6.5 mg tablets or nearer to it because the weight of the tablet is less than the 650 mg. the loss of the weight of tablets was measured and is expressed in percentage. The formulae for calculating the friability were

$$\%\text{Friability} = \frac{\text{Loss in weight}}{\text{Initial weight}} \times 100$$

Wetting Time
Wetting time is the important parameter in the formulation of orodispersible tablets. Wetting time is the time taken for the tablets to disintegrate. Wetting time can indicate the inner structure of the tablets and the nature of excipient i.e. hydrophilicity nature. The lower the value of the wetting time faster is the disintegration of tablets. The process to determine the wetting time was first place a double folded tissue paper in a small Petridish and the pour 6ml of phosphate buffer pH 6.8 into the Petridish. The place the tablet on the tissue paper and note the time taken to the tablet for complete wetting. Three tablets were randomly selected for each formulation and the average time was calculated.

Water Absorption Ratio
The water absorption ratio is the amount of water is absorbed by the complete tablet. The process to measure the water absorption was taking a clean and dry Petridish. Then place a twice or thrice folded tissue paper in Petridish and poured 6 ml of water in the Petridish. Then put the weighed tablet on the tissue paper and the time was measured to complete wetting. Then the wetted tablet was weighed. Three randomly selected tablets from each formulation were studied and the average weight was taken. The formulae for calculating the water absorption ratio were

Water absorption ratio (R) = $10 \times \frac{Wa}{Wb}$

Where,
Wa = the weight of tablet after water absorption
Wb = the weight of tablet before water absorption

In-Vitro Disintegration Time
The disintegration test indicates how faster and efficiently a tablet breaks down into smaller particles in the liquid medium. The disintegration test is used to established that the absorption of drug by the body on had envisioned. The procedure to determine the disintegration time of tablets. First, the disintegration apparatus was maintained at 37°C± 2°C and the apparatus filled with distilled water. Then randomly select the six tablets from each formulation and placed individually in the six cylinders of a disintegration test apparatus. Then the apparatus was operated, causing the up and down movement of basket in the apparatus. Then the time is noted for completely disintegration of each tablet. The average time was taken for the disintegration of the tablets.

In-Vitro Dissolution Test
The in vitro dissolution test is important test in the post compressional parameter. The in-vitro dissolution test is used to determine the drug release profile. Here is the procedure to perform in-vitro dissolution test for the orodispersible tablets. For the orodispersible tablets the in-vitro dissolution test was performed by USP type II apparatus that is paddle type. The temperature of the water bath is maintained at 37°C± 0.5°C and the speed of the paddle was set at 50 rpm. The 500 ml of phosphate buffer pH 6.8 is poured in the vessel which act as a dissolution medium. A randomly selected tablet is placed in the vessel of dissolution test apparatus. the 5 ml sample was withdrawn from the vessel at every 5 minutes interval upto 30 minutes and the sink condition should be maintained. The samples were filtered and then the sample was analyses in the UV-Visible spectrophotometer at 272 nm and the absorbance is noted and the percent drug release and the percent cumulative drug release is calculated.

Stability Studies
Stability studies is an important evaluation parameter which helps to determine the shelf life of a product or over the time how environmental conditions can affect the quality of finished product. All salbutamol sulphate tablet formulations were tested for stability for one month using ICH rapid study criteria. In sealed glass containers, each sample was safely wrapped in aluminium foil. We subjected these tablets to three distinct temperature conditions. During 10- 20 and 30-day intervals, tablets were taken out of storage to be examined, with an emphasis on physical characteristics, drug concentration, and segregation patterns [17-23].

Result and Discussion
Organoleptic Properties
All the organoleptic properties like color, odour, taste, etc are studied of the drug and that are mentioned in table 14.

Table 14: Organoleptic Properties of Salbutamol Sulphate

S. No.	Organoleptic parameters	Results
1	Color	A white to off-white
2	Odour	Odourless
3	Taste	Bitter taste
4	Crystallinity	Fine powder
5	Nature	Hydrophilic

Shape and Size
On the evaluation of the salbutamol sulphate formulated tablets have the circular in shape and the size of the tablets was found to be 0.65± 0.05 cm.

Melting Points
While studied done on the salbutamol sulphate, the melting point was determined using melting point apparatus was found to be 148.2 ±0.5°C.

Solubility
The solubility of the salbutamol sulphate was determined in Solubility in water, ethanol and dichloromethane and mentioned in table 15.

Table 15: Solubility of Salbutamol Sulphate

S. No.	Solvents	Solubility range
1	Water	From 1 to 10
2	Ethanol	From 100 to 1000
3	Dichloromethane	From 1000 to 10,000

Calibration Curve
The calibration curve of the salbutamol sulphate was studied using the standard sample and the prepared dilutions in the phosphate buffer pH 6.8 as a solvent at the 272 nm and the results are shown in table 16 and the graph is shown in figure 5.

Table 16: Calibration Curve of Salbutamol Sulphate in Phosphate Buffer pH 6.8

S. No.	Concentration (µg/ml)	Absorbance (272 nm)
1	5	0.1404
2	10	0.2824
3	15	0.4513
4	20	0.5914
5	25	0.717

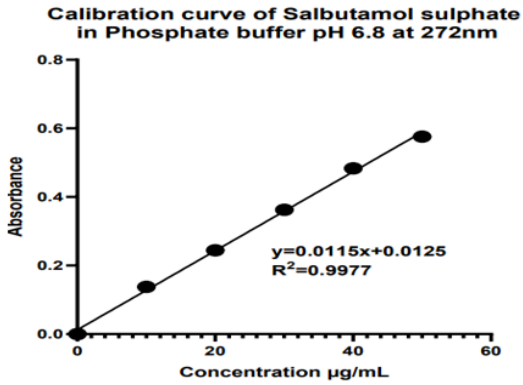


Figure 5: The Calibration Curve of Salbutamol Sulphate at 272nm

Table 17: Pre-Compressional Data of the Formulation Batches

Formulation Batch	Bulk Density (gm/ cm3)	Tapped Density (gm/ cm3)	Hausner's Ratio (HR)	Carr's Index (CI)	Angle of Repose(θ)
OT1	0.452	0.538	1.179	6.328	28
OT 2	0.458	0.532	1.161	6.832	27
OT 3	0.462	0.536	1.160	7.123	30
OT 4	0.448	0.539	1.123	9.758	33
OT 5	0.455	0.530	1.164	8.243	27
OT 6	0.464	0.537	1.157	8.695	32
OT 7	0.469	0.538	1.125	10.564	30
OT 8	0.454	0.531	1.169	6.983	29
OT 9	0.459	0.540	1.176	7.920	27
OT 10	0.461	0.537	1.164	6.795	31
OT 11	0.467	0.544	1.164	10.198	27
OT 12	0.460	0.542	1.178	5.978	29
OT 13	0.457	0.535	1.170	8.491	33
OT 14	0.463	0.529	1.142	9.762	30
OT 15	0.467	0.533	1.141	10.221	28

Post-Compressional Evaluation
All the post-compressional parameters like weight variation, thickness, hardness, wetting time, disintegration time, friability was studied for all the 15 batches and the results of all the 15 batches are shown in the table 18

Table 18: Post-Compressional Data of the Formulation Batches

Formulation Batch	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm2)	Wetting Time (Sec)	Disintegration Time (sec)	Friability (%)
OT 1	100	6.2	3.4	6	49	0.15
OT 2	101	6.2	4	4	51	0.17
OT 3	104	6.2	3.1	7	44	0.13
OT 4	101	6.2	3.8	5	42	0.25
OT 5	98	6.2	3	6	45	0.26
OT 6	97	6.2	4.2	4	47	0.12
OT 7	100	6.2	3.5	5	42	0.16
OT 8	100	6.2	2.9	3	44	0.19
OT 9	95	6.2	3.9	7	40	0.23
OT 10	100	6.2	4.3	6	48	0.24
OT 11	105	6.2	3.8	6	38	0.22
OT 12	100	6.2	4.4	7	37	0.13
OT 13	103	6.2	3.6	5	45	0.15
OT 14	100	6.2	3.2	5	50	0.21
OT 15	99	6.2	3.4	4	43	0.14

In-Vitro Dissolution Studies

The in-vitro dissolution studies are studied using electro lab dissolution apparatus in which we used the USP apparatus II (paddle type) at 50 rpm and the temperature maintained at 37°C ± 2°C and the absorbance was observed at every 5 min of interval of time and the sink condition was maintained. And the absorbance was observed using UV spectrophotometer at 272 nm for all the 15 batches and the results of all the 15 batches are shown in table 19 and the figure shows the dissolution graph for drug release at the specified interval of time.

Table 19: In Vitro Dissolution Test Data of the Salbutamol Sulphate Orodispersible Tablets

Formulation Batch	0 min	5 min	10 min	15 min	20 min	25 min	30 min
OT 1	0	23.412	39.216	47.412	58.53	81.942	95.425
OT 2	0	22.942	38.237	45.885	57.355	80.297	91.77
OT 3	0	23.377	38.962	46.755	58.442	81.819	93.501
OT 4	0	22.667	37.778	45.334	56.667	79.334	90.668
OT 5	0	21.889	36.214	42.977	54.723	76.661	85.955
OT 6	0	21.969	36.614	43.937	54.922	76.891	87.874
OT 7	0	21.224	35.373	42.447	53.06	74.284	84.894
OT 8	0	22.487	37.478	44.975	56.217	78.704	89.955
OT 9	0	21.585	35.974	43.169	53.962	75.547	86.339
OT 10	0	24.046	40.075	48.091	60.115	84.161	96.183
OT 11	0	22.249	37.082	44.499	55.623	77.872	88.998
OT 12	0	23.185	38.641	46.37	57.963	81.147	92.74
OT 13	0	23.733	39.555	47.467	59.332	83.065	94.934
OT 14	0	24.418	40.696	48.836	61.045	85.463	97.672
OT 15	0	22.118	36.863	44.236	55.295	77.413	88.473

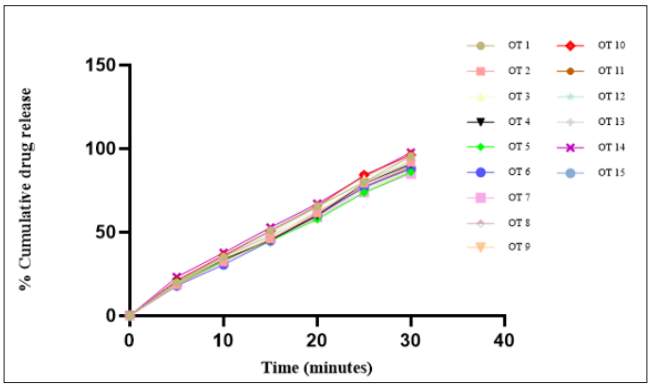


Figure 6: Percent Cumulative Drug Release of Salbutamol Sulphate of all the 15 Batches

Preparation of Salbutamol Sulphate Orodispersible Tablets with Responses

Table 20: The BBD Composition of Salbutamol Sulphate Orodispersible Tablets Formulations and their Measured Responses

	Independent Variables			Dependent Variables		
Formulation batch	**Jackfruit seed starch**	**Lepidium sativum seed mucilage**	**Polyvinyl pyrrolidone K-30**	**Disintegration time (Minute)**	**In-vitro dissolution time (%)**	**Hardness (kg/ cm2)**
OT 1	10	8	5	49	95.425	3.4
OT 2	5	8	3.5	51	91.77	4
OT 3	15	5	2	44	93.501	3.1
OT 4	10	5	3.5	42	90.668	3.8
OT 5	10	8	2	45	85.955	3
OT 6	5	5	5	47	87.874	4.2
OT 7	5	2	3.5	42	84.894	3.5
OT 8	10	2	2	44	89.955	2.9
OT 9	10	5	3.5	40	86.339	3.9
OT 10	15	5	5	48	96.183	4.3
OT 11	10	5	3.5	38	88.998	3.8
OT 12	10	2	5	37	92.74	4.4
OT 13	15	2	3.5	45	94.934	3.6
OT 14	15	8	3.5	50	97.672	3.2
OT 15	5	5	2	43	88.473	3.4

Response Data Analysed for all 15 Batches Using Box-Behnken Design

All the responses are analysed for all the 15-formulation batch using Box-Behnken Design by design expert software and the results of the analysis of all the three responses disintegration time, in-vitro dissolution test, and hardness are in ANOVA table and model graph provided below

Response 1: Disintegration Time

ANOVA for Quadratic Model

The suggested model of response 1 is quadratic model for which ANOVA was studied and in this model F-value of 5.31 implies the model is significant. There is only a 4.04% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case B, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

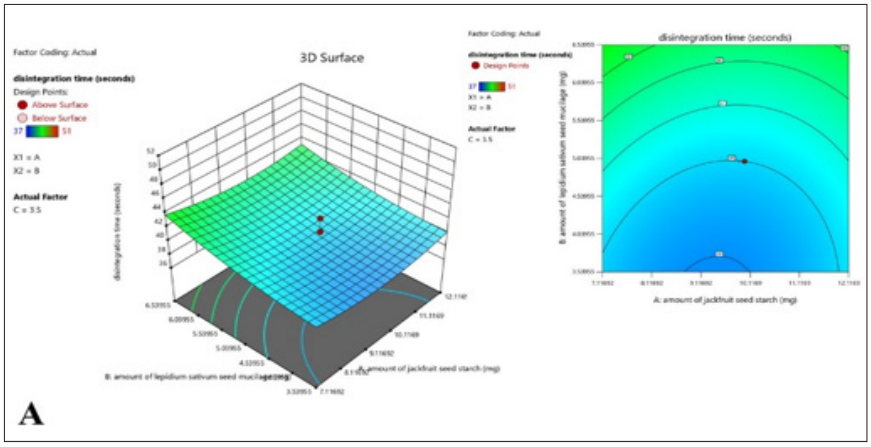
Citation: Krutika Mandloi, Kratika Khadsondni, Aman Kumar, Tushar Sonare, Akash Yadav, Dinesh Kumar Jain (2025) Efficacy and Patient-Centered Outcomes of Antiasthmatic Orodispersible Tablets in Acute Asthma Exacerbation. Journal of Pharmaceutical Research and Reports. SRC/JPRSR-192.
DOI : doi.org/10.47363/JPRSR/2025(6)168

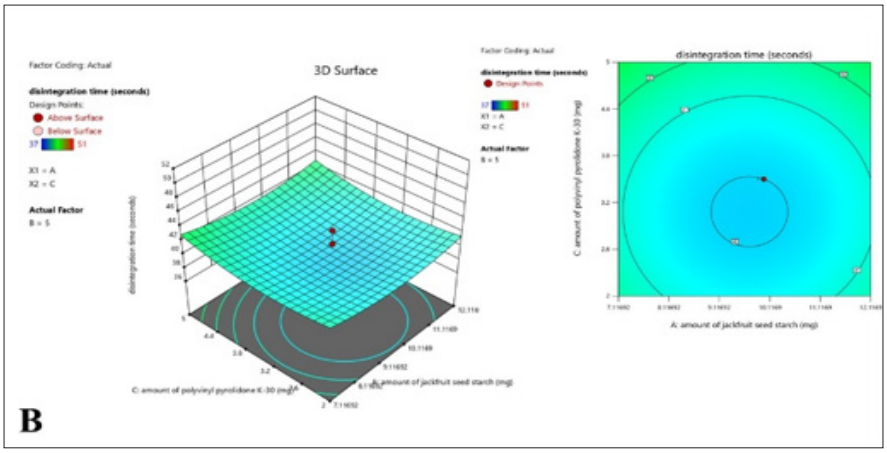
Table 21: The Analysis Table of ANOVA for Disintegration Time

Source	Sum of Squares	df	Mean Square	F-Value	p-Value	
Model	222.08	9	24.68	5.31	0.0404	significant
A-amount of jackfruit seed starch	2.00	1	2.00	0.4301	0.5409	
B-amount of lepidium sativum seed mucilage	91.12	1	91.12	19.60	0.0068	
C-amount of polyvinyl pyrolidone K-30	3.13	1	3.13	0.6720	0.4496	
AB	4.00	1	4.00	0.8602	0.3962	
AC	0.0000	1	0.0000	0.0000	1.0000	
BC	30.25	1	30.25	6.51	0.0512	
A^2	70.67	1	70.67	15.20	0.0114	
B^2	25.44	1	25.44	5.47	0.0665	
C^2	4.67	1	4.67	1.00	0.3621	
Residual	23.25	5	4.65			
Lack of Fit	15.25	3	5.08	1.27	0.4688	not significant
Pure Error	8.00	2	4.00			
Cor Total	245.33	14				

Model Graph for the Response 1

2D and 3D surface plot represent that factor B (amount of Lepidium sativum seed mucilage) significant effect on the response one of the formulations while the factor A (amount of jackfruit seed starch) has optimum effect on disintegration time. An increase or decrease in the factor B significantly affect the disintegration time here, optimum amount of factor B shows the desired disintegration time. While factor C has non-significant effect.





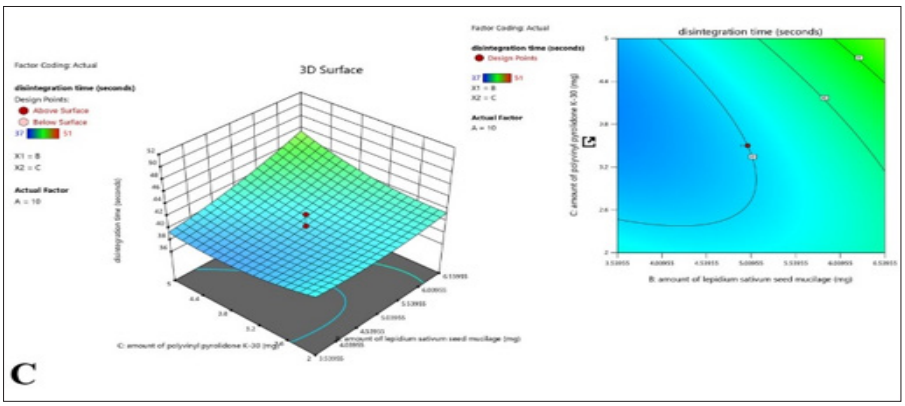


Figure 7: The 2-D Contour Map and 3D Surface Graph Shows How the Total Amount of Jackfruit Seed Starch (X1), Lepidium Sativum Seed Mucilage(X2) and Polyvinyl Pyrrolidone K-30 (X3) affects the Disintegration Time

Response 2: Percent Drug Release

ANOVA for Linear Model

The suggested model for response 2 is linear model for which ANOVA was studied. According to the model F-value of 6.43 implies the model is significant. There is only a 0.89% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case A is a significant model term. Values greater than 0.1000 indicate the model terms are not significant.

Table 22: The Analysis Table of ANOVA for Percent Drug Release

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	141.46	3	47.15	6.43	0.0089	significant
A-amount of jackfruit seed starch	107.16	1	107.16	14.61	0.0028	
B-amount of lepidium sativum seed mucilage	8.61	1	8.61	1.17	0.3018	
C-amount of polyvinyl pyrolidone K-30	25.70	1	25.70	3.50	0.0880	
Residual	80.67	11	7.33			
Lack of Fit	71.13	9	7.90	1.66	0.4322	not significant
Pure Error	9.53	2	4.77			
Cor Total	222.13	14				

Model Graph for Response 2

The represented 3D and 2D contour plot suggest that there is significant effect of factor A (amount of jackfruit seed starch) on the percent drug release while the factor B and factor C has no or negligible effect on the desired response. The green colour represent the optimum response while on increasing the factor A the response also increases shown in the reddish

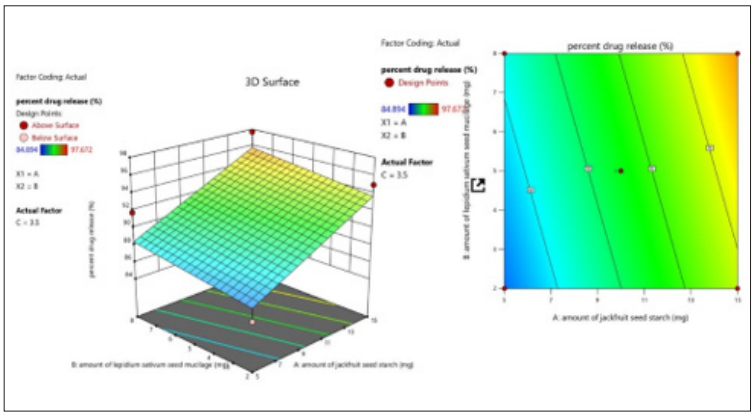


Figure 8: The 2-D Contour Map and 3D Surface Graph Shows How the Total Amount of Jackfruit Seed Starch (X1), Lepidium Sativum Seed Mucilage(X2) and Polyvinyl Pyrrolidone K-30 (X3) affects the Percent Drug Release

Citation: Krutika Mandloi, Kratika Khadsondni, Aman Kumar, Tushar Sonare, Akash Yadav, Dinesh Kumar Jain (2025) Efficacy and Patient-Centered Outcomes of Antiasthmatic Orodispersible Tablets in Acute Asthma Exacerbation. Journal of Pharmaceutical Research and Reports. SRC/JPRSR-192.

DOI : doi.org/10.47363/JPRSR/2025(6)168

Response 3: Hardness

ANOVA for Quadratic Model

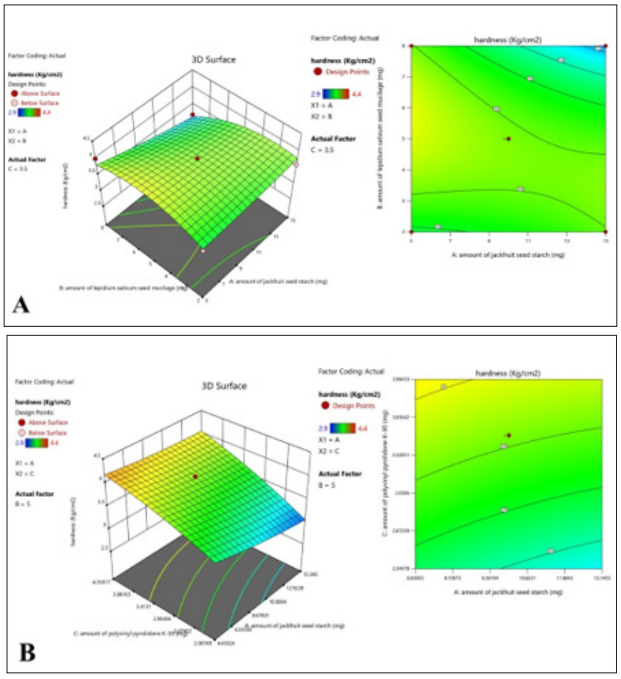
The suggested model for response 2 is quadratic model for which ANOVA was studied. According to the model F-value of 10.12 implies the model is significant. There is only a 1.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant. In this case C, BC, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant.

Table 23: The Analysis Table of ANOVA for Hardness

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2.99	9	0.3321	10.12	0.0101	significant
A-amount of jackfruit seed starch	0.1013	1	0.1013	3.08	0.1394	
B-amount of lepidium sativum seed mucilage	0.0800	1	0.0800	2.44	0.1793	
C-amount of polyvinyl pyrolidone K-30	1.90	1	1.90	57.91	0.0006	
AB	0.2025	1	0.2025	6.17	0.0556	
AC	0.0400	1	0.0400	1.22	0.3200	
BC	0.3025	1	0.3025	9.21	0.0289	
A^2	0.0041	1	0.0041	0.1250	0.7381	
B^2	0.3141	1	0.3141	9.57	0.0271	
C^2	0.0503	1	0.0503	1.53	0.2709	
Residual	0.1642	5	0.0328			
Lack of Fit	0.1575	3	0.0525	15.75	0.0603	not significant
Pure Error	0.0067	2	0.0033			
Cor Total	3.15	14				

Model Graph Response 3

The given contour plot represent that the Factor C (amount of polyvinyl pyrolidone K-30) has significant effect on the response three, an increase in the amount of factor C leads to increase in the hardness of tablet. The factor B (amount of lepidium sativum seed mucilage) also has significant effect on the hardness. The optimum interaction between factor C and factor B gives the desired response. The factor A has non-significant effect on this response.



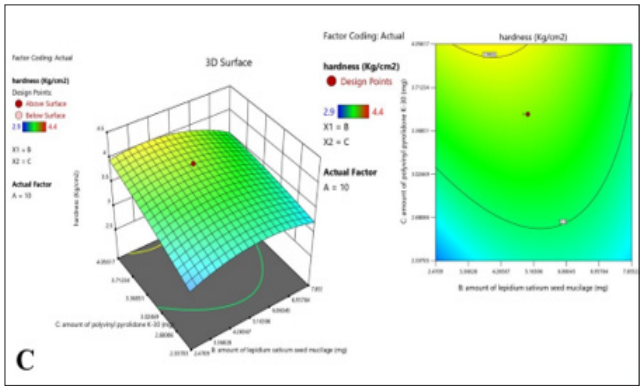


Figure 9: The 2-D Contour Map and 3D Surface Graph Shows How the Total Amount of Jackfruit Seed Starch (X1), Lepidium Sativum Seed Mucilage(X2) and Polyvinyl Pyrrolidone K-30 (X3) Affects the Hardness

Optimized Batch

As we studied the Box-Behnken design we put the responses that we analysed from the evaluation studies as shown in the table. then the Box-Behnken design optimized the responses and give the optimized batch of formulation and the optimized batch responses and the formulation are shown in table.

Table 24: Formulation of Optimized Batch from BBD

S. No.	Ingredient	Quantities (in mg)
1	Salbutamol sulphate	8
2	Jackfruit seed starch	10.838
3	Lepidium sativum seed mucilage	6.460
4	Polyvinyl pyrrolidone K-30	2.432
5	Mannitol	69.27
6	Magnesium stearate	2
7	Talc	1

Table 25: Pre- compressional Data of Optimized Batch

S. No.	Pre-compressional evaluation parameter	Results
1	Bulk density	0.469
2	Tapped density	0.538
3	Hausner's ratio	1.172
4	Carss index	6.875
5	Angle of repose	27

Table 26: Post-Compressional Data of Optimized Batch

S. No.	Post-compression evaluation parameter	Results
1	Weight variation	103
2	Thickness	6.2
3	Hardness	3.357
4	Wetting time	6±0.5 seconds
5	Disintegration time	41.562
6	Friability	0.16
7	% Drug release	90.868

Table 27: The Percent Drug Release of the Optimised Tablet

Formulation batch	0 min	5 min	10 min	15 min	20 min	25 min	30 min
Optimised Batch	0	22.717	34.075	45.434	58.53	81.942	90.868

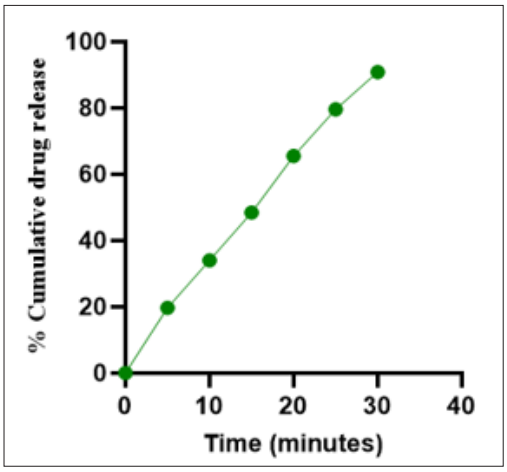


Figure 7: Percent Cumulative Drug Release of Salbutamol Sulphate of Optimised Batch

Conclusion

The orodispersible tablet for anti-asthmatic drug of salbutamol sulphate was prepared using the natural super disintegrants jackfruit seed starch and Lepidium sativum seed mucilage by using direct compression method. All the pre-compression parameters (organoleptic properties, melting point, solubility, bulk density, tapped density, carr's index, hausner's ratio, angle of repose, calibration) and post-compression parameters (organoleptic properties, shape and size, weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time, percent drug release) are evaluated. And by using Box-Behnken design the results were optimized.

Conflict of Interest: The authors declare that they do not have any financial and personal relationship with other people or any other organization that could inappropriately influence this research work.

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