RESEARCH ARTICLE

Formulation and Evaluation of Pulsatile Drug Delivery System by Press Coating Method for Treatment of COPD (Asthma)

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ABSTRACT
The press coating approach has been employed in the current study; this system involves compressing directly of both core as well as the coat. The procedure is the same: first, we make the core tablet containing drug, diluent, binder, Crospovidone as superdisintegrant for burst release after lag time, glidant, and lubricant in an 8mm die. After that, we get the Eudragit S 100 as polymer in different ratios and divide it into two equal parts, subsequently the lower half is inserted in a cavity in 10mm die followed by core tablet has been placed in the middle, and the other half portion that comprises the coat is filled in the die cavity. Powder's assessment parameters were judged to be within an appropriate range. Overall, the evaluation results for the core and press-coated tablets passed within acceptable parameters. Optimized batch F7 shows 99.07% drug release. Optimized batches are further evaluated for tests like FTIR, DSC, and Stability study as per standard ICH guidelines. From all result conclude that as per concentration of superdisintegrant increases % drug release also increases after the lag time. Eudragit S 100 acts good lag time polymer release drug only at after pH 7 means colon target was done hence successfully pulsatile drug delivery was performed**.**

Keywords: Pulsatile drug delivery, asthma, Circadian rhythm, Lag time, Ph, Press coat etc
Keywords: Nanocrystals, Spray drying, Solubility, Manidipine.
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INTRODUCTION

The mechanism of drug delivery allows the medication's active component to be administered, delivering the intended therapeutic outcome.[1,2] Common medication delivery methods (tablets, capsules, syrups, creams and lotions etc.) show inadequate bioavailability alongside varies bloodstream concentrations of drugs, providing them inefficient for long-term use. A wide range of orally drug administration methods follow a predetermined medication-release pattern, maintaining medication concentrations within therapeutic range.[3,4] Additionally, in order to provide maximum safety and effectiveness, the medication must be carefully provided at a controlled rate and in the appropriate area.[5,6] Pulsatile drugs were designed to solve the challenges connected with conventional drug administration, which is additionally recognised as targeted drug administration, which takes action at a specific moment or whenever certain period of time is over with increased patient compliance.[7,8] It controls the condition's circadian rhythm and reduces the medication's adverse effects. Major purpose of the Pulsatile Drug Delivery System (PDDS) provide medicine at the ideal moment, place, its target, particularly amount.[9] As a result, it increases therapeutic effectiveness along with compliance among patients while lowering dosage repetition.[10] PDDS have been growing in acceptance due to its capacity to administer medicine to the proper location, at the precise moment, and in an appropriate amounts offering time-specific, spatial, and adaptive distribution in addition enhancing compliance among patients.[11] PDDS demonstrates several types of medication distribution mechanisms. (A) sigmoidal delivery shortly after lag time, (B) delayed onset after having lag time, (C) sustained release soon after lag time, as well as (D) prolonged release without properly lag time. Asthma is a chronic, broad inflammatory illness characterised by a history of respiratory symptoms that vary in intensity and duration, as well as fluctuating expiratory airflow limitation.[12,13] Smooth muscle contraction, airway swelling, bronchospasm, and enhanced mucus secretion all contribute to airway narrowing, as does bronchial wall thickening from edoema, smooth muscle hypertrophy, and subepithelial fibrosis.[14,15] Asthma remains the most prominent chronic disorders, and its prevalence has been rapidly boosting in the past several years.[16,17] It has a significant impact on patients, their families, the

Table 3: Analytical method (calibration curve

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Table 1: Formulation of core tablet of theophylline.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Theophylline	200	200	200	200	200	200	200	200	200
Avicel 102	35.5	29.5	29.5	35.5	32.5	35.5	29.5	32.5	32.5
PVP K30	9	9	9	9	9	9	9	9	9
Crospovidone	3	9	9	3	6	3	9	6	6
Mg. Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Aerosil 200	3	3	3	3	3	3	3	3	3
Coating of Polymer									
Eudragit S 100	242	363	242	120	363	363	120	120	242
Talc	13	20	13	7	20	20	7	7	13

* note all values in mg per tablet.

Table 2: Optimisation with Design Expert 12 Software's assistance.

Factor	Name	Units	Type	Minimum	Maximum	Coded Low	Coded High	Mean	Std. Dev.
A	Crospovidone	%	Numeric	1.0000	3.00	-1 ↔ 1.00	+1 ↔ 3.00	2.00	0.8660
B	Eudragit S100	%	Numeric	50.00	150.00	-1 ↔ 50.00	+1 ↔ 150.00	100.00	43.30

absorbance).

Concentration (µg/ml)	Absorbance (270nm)
0	0
10	0.161
20	0.311
30	0.472
40	0.646
50	0.765

healthcare system, and the community at large, resulting in lost employment and educational hours, inadequate standards of life, repeated visits to the emergency room in hospitals, hospitalisations, even deaths.[18,19] Asthma is considered one of the most prominent chronic noncommunicable diseases, impacting about 260 million people. globally and accounting for over 450000 deaths annually worldwide, the majority of which can be preventable.[20] For more than 80 years, theophylline (dimethylxanthine) became widely utilised as an effective bronchodilator for the treatment of respiratory difficulties, but the exceedingly high doses necessary resulted in frequent side effects.[21] Theophylline recently demonstrated to exhibit anti-inflammatory properties in bronchial asthma as well as chronic obstructive pulmonary disease or COPD, at low doses.[22,23] Theophylline is frequently employing third-line add-on prescription in patients with poorly managed disease due to its low cost, greater efficacy as bronchodilators, and superior anti-inflammatory activity.[24,25] Eudragit S 100 is typically used to administer medications towards the colon to treat for conditions which include bowel dysfunction, Crohn's disorder, and ulcerated colitis. This phenomenon is only recently developed during the time polymers with pH-sensitive properties have dissolved beyond to a neutral pH (greater than pH 7).[26,27]

MATERIAL AND METHODS

Material

Theophylline gift sample was obtained from Kores Pharmaceuticals India Ltd. Analytical grade excipients like Avicel 102, polyvinyl pyrrolidone K-30, Crospovidone, Magnesium Stearate, Aerosil ®-200 were procured from market.

Method

Preparation of core tablet

The formulation is prepared as shown in Table 1. Press-coated PDDS is suitable for protecting light-sensitive, acid-labile, oxygen-labile, and hygroscopic pharmaceuticals.[28] Press-covered PDDS can contain both hydrophobic and hydrophilic compounds.[29] Press-coated PDDSs are quite easy to use and affordable. This approach may include compression directly on both the inner core along with the outermost layer coat.[30] The innermost layer core tablet have been produced utilising the technique known as direct compression. Theophylline, Avicel 102, poly vinyl pyrrolidine (PVP), and Crospovidone powders comprised dried homogenised for 20 minutes before adding the ingredients magnesium stearate along with aerosil. These combinations were continuously mixed for 10 minutes. 255 mg of the resulting powder blend compacted employing an 8 mm punch to form a core tablets.[31,32] After completion, divide the Eudragit S-100 polymer into two equal parts, then insert the divided half portion into the die cavity. 10mm die after taking the inner core tablet is inserted in the centre and the other half of the coating has been filled into the inside of the cavity.

Optimization

Optimization of present investigation was done by Using Design- Expert -12 (DOE) Software (Table 2). Response surface study was done using 2^2 factorial randomized design. Following factors are consider for the optimization. Total 9 runs performed as per shown in above formulation table. Factor consider are Crospovidone used as Superdisintegrant play important role in burst release after lag time. Eudragit S 100 used as polymer coating agent for core tablet. All performed bathes are

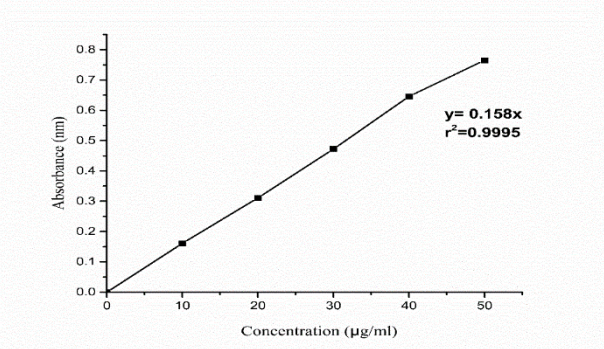

Figure 1: Calibration curve of theophylline.

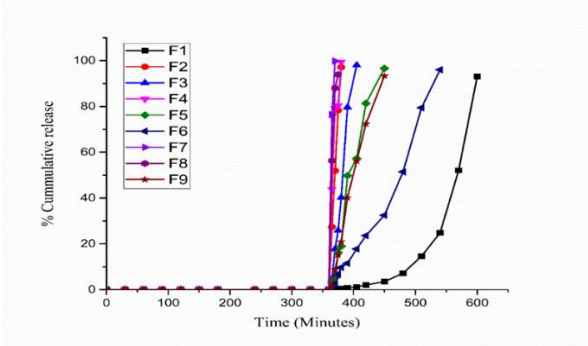

Figure 2: % Cumulative release of press coted tablets batch F1 to F9.

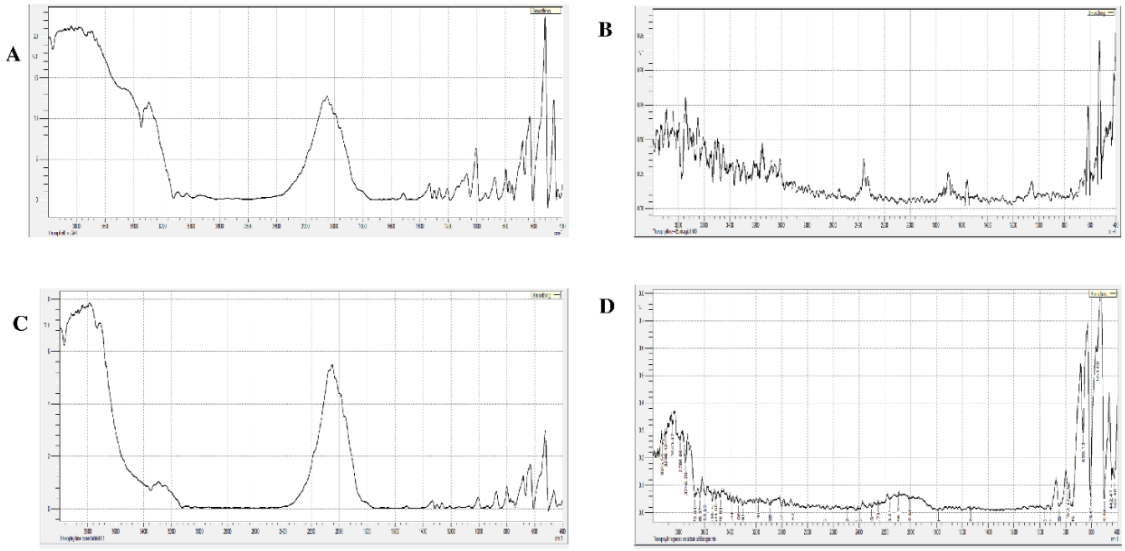

Figure 3: FTIR of (A) Theophylline (B) Theophylline with Eudragit S 100 (C) Core tablet (D) Press Coated tablet.

optimized on the basis of three response like disintegration of core tablet, Lag Time, T 100% drug release.

Calibration curve

Theophylline standardised solution has been produced by dissolve 100 mg in 100 millilitres of O.1N HCl to get 1000 µg/ml concentration by sonication for 5 minutes. After sonication, 1ml of previously prepared solution taken and diluted with 0.1 N HCl to obtained 100 µg/ml concentration solution. This solution was further used to prepare the serial dilution with .01 N HCL to obtained 10, 20, 30, 40 and 50 µg/ml concentration solutions. All the samples were analysed by UV Spectrometer (SHIMADZU-1780). The peak spectrum was found to be (λ max = 270 nm).[33] Absorption for various prepared concentration was summarized in Table 3. (Figure 1)

Evaluation of Core and press Coated Tables

Precompression study

Numerous development factors are involved in the mixing stage, and each one has the potential to affect how well the blended product turns out. Powder properties, are used to characterise mixed blends.[34] (Table 4)

Bulk Density

By passing 15 g of powder via funnel and into cylinder having a capacity of 50 ml, the bulk density was determined.[35,36]

Bulk density= mass /Bulk volume

Tapped Density

An Electro Lab density tester, including a graded cylinder fixed on an electronic tapping mechanism, was utilised to measure the taped density. A carefully weighed sample of powder was introduced to the cylinder using a funnel. The sample is typically tapped 100 times after the original volume is recorded, or until there is no more volume loss and the variation percentage is less than 2%. To guarantee that an appropriate number of taps should be used.[37]

Tapped density = mass / Tapped volume

Angle of Repose

The forces generated by attrition in loose particles are defined by angle of repose. It described as the angle that develops in a powder pile that exists between its base and its upward slope. Utilising Newman's funnel method angle of repose were computed. A vertically elevable funnel was used to pour the mixture until a sufficient cone the height was attained.[38]

Tan θ = (h/r)

Car's index

Table 4: Preformulation study results.

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (^{0})	Hausner's ratio	Car's index
F1	0.511±0.02	0.567±0.03	29.6±0.03	1.12±0.002	14±0.3
F2	0.491±0.02	0.534±0.02	26.4±0.002	1.16±0.0015	16.3±0.001
F3	0.479±0.05	0.481±0.04	25.2±0.003	1.07±0.20	15.1±0.7
F4	0.478±0.01	0.498±0.003	27.2±0.006	1.07±0.032	15.8±0.8
F5	0.521±0.04	0.564±0.015	26.3±0.002	1.08±0.011	13.9±0.5
F6	0.508±0.6	0.524±0.072	28.4±0.9	1.03±0.056	15.2±0.4
F7	0.507±0.04	0.518±0.026	24.7±0.009	1.07±0.041	12.65±0.033
F8	0.481±0.013	0.497±0.022	27.5±0.8	1.14±0.5	13.8±0.064
F9	0.478±0.54	0.488±0.03	28.8±0.002	1.12±0.2	16±0.067

All values are shown as mean ± SD (n=3).

Table 5: Post-compression evaluation of core tablet results.

Formulations	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time (minutes)	Drug Content (%)
F1	249± 3.4	6±0.6	4.1±0.4	0.34	8.2	98.4±0.5
F2	253± 1.2	5±0.3	3.9±0.02	0.14	0.55	99±0.02
F3	255±2.9	5±0.8	3.8±0.48	0.17	1.55	99±0.07
F4	252±2.1	7±0.42	3.7±0.51	0.56	7.45	96.5±0.5
F5	247±6.7	7±0.55	4.1±0.45	0.38	4.9	98±0.3
F6	254±1.9	7±0.69	4±0.61	0.28	7.05	97.9±0.45
F7	249±5.6	6±0.5	3.7±0.6	0.23	2.35	98.6±0.36
F8	250±4.7	5±0.47	3.8±0.53	0.46	4.3	94.8±0.62
F9	245± 8.8	6±0.66	4.2±0.72	0.41	5.55	95.2±0.55

All values are shown as mean ± SD (n=3).

Table 6: Evaluation of press coated tablet results.

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	508±2.6	6±0.5	6.2±0.2	0.34
F2	631±1.6	6.2 ±0.2	7.9±0.01	0.14
F3	507±1.9	5±0.1	6±0.6	0.17
F4	373±0.02	7.2±0.01	3.8±0.03	0.56
F5	632±0.2	7±0.8	8±0.4	0.38
F6	634±2.8	7±0.02	8.1±0.39	0.28
F7	379±5.3	6±0.4	3.9±0.03	0.23
F8	377±3.8	5±0.5	4±0.3	0.46
F9	504±6.3	6±0.3	5.9±0.4	0.41

All values are shown as mean ± SD (n=3).

It measures ability to compress of a powder. The following method is used to calculate Carr's index: where is the powder's bulk density while it is freely settled and what is its tapped bulk density after "tapping down".[39]

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

Hausner's ratio

The ability to flow of a granular or powdered material is estimated by Hausner's ratio.[40]

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

Core and Press- coated tablet post-compression characteristics

The generated tablets were assessed using various kinds of established standards. (Table 5, Table 6).

Weight variation

The mean weight of twenty randomly chosen pills was determined. Weighing each tablet separately allowed us to determine the percentage deviation from the average.[41]

Weight Variation = (Individual weigh - Average weight) / Average weight x 100

Hardness

Monsanto hardness tester tablet has been employed to measure its level of hardness. A random test was carried out on three separate tablets from all formulations batch, and the mean reading is recorded.[42]

Thickness.

Using a micro-screw gauge and a vernier calliper, the dimension on each tablet has been determined. Every formulation batch is triple-checked.[43]

Friability

The current test friability has been investigated using the Roche Friabilator. This gadget comprises circular device that drops the tablets six inches every time it rotates for four minutes at a pace of roughly twenty-five rotations per minute. Twenty pills that had been pre-weighed 100 times were spun in a friabilator. After dusting the tablets with a small muslin towel, they were weighed again (W).[44] it describes a compressed tablet's resistance to breaking and shattering while being transported. Less than 1% is anticipated as the result.

$$\% \text{ Friability} = \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \times 100$$

Disintegration

A disintegration test instrument (Electrolab, USP model, Mumbai) was used to measure the disintegrating time of six tablets of each batch. at 37.0±0.5°C in distilled water. The duration of time it takes for the tablet to dissolve

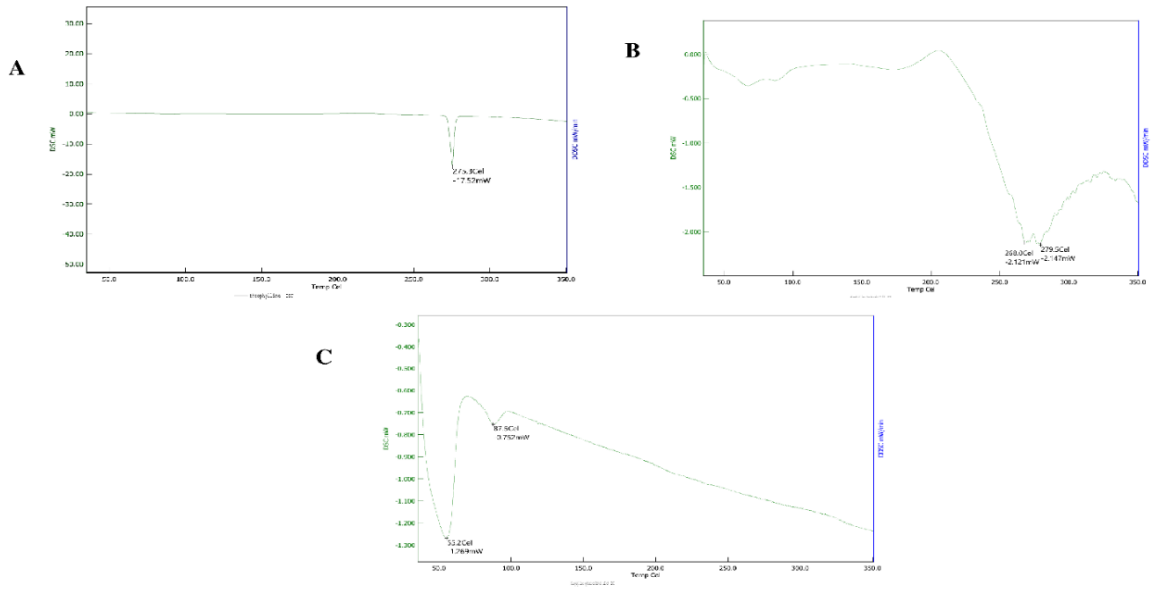

Figure 4: DSC of (A) Theophylline (B) Theophylline with Eudragit S 100 (C) Press Coated tablet.

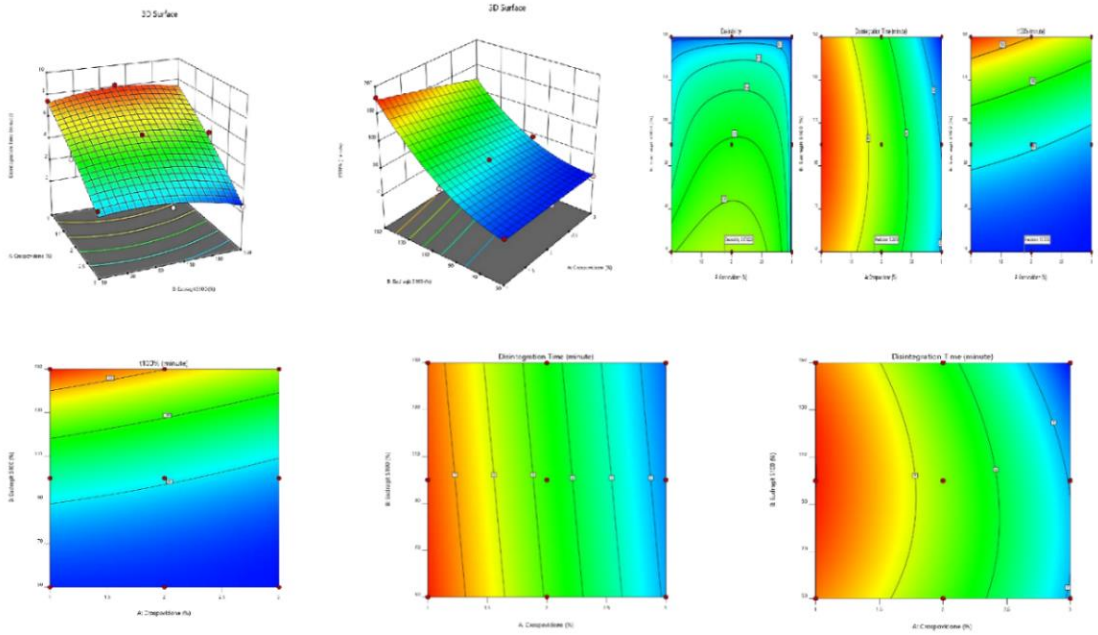

Figure 5: Factor consideration and its responses through Graphical presentation by Design of expert 12.

completely and no longer have any apparent bulk inside the device was tracked using a digital timer.[45] The test was performed in triplicate times.

Dissolution study (*In-vitro* study)

Theophylline release rate measured utilizing the USP Apparatus-2 (paddle method). Dissolving media were 0.1N HCl and a 6.8 pH phosphate buffer solution. Core pills, 900 millilitres of 6.8 pH phosphate buffer were used as a dissolution media. The coated tablets dissolved in the dissolution equipment for 120 minutes using 900 millilitres of 0.1N HCl dissolving media. The test was run for the next six hours after the 0.1 N HCl dissolution medium was swapped out for a 6.8 pH phosphate buffer. After that the dissolution medium phosphate buffer 6.8 was replace d with phosphate buffer pH 7.2 test were conducted for next 2 hours. Following that, phosphate buffer pH 8.5 was added in place of pH 7.2, and testing was carried out until the full release of the medication. Aliquoted was withdrawn at the time interval of 30 min and proceed for further UV analysis and drug released was calculated.[46,47] (Figure 2)

Drug content

A motor pestle was used to smash the tablets, and the resulting 200 mg of powdery form was collected then dispersed using 1N HCl. A appropriate amount was extracted and diluted before the solution was examined at the concentration of 20µg/ml using the UV Spectrometer (SHIMADZU-1780). The same amount of pure medication was also examined.[48] Using the formula, the percentage medication content was computed, and each formulation batch was tested in triplicate.

FTIR Study

Table 7: Accelerated stability data.

Physical Parameters	Storage conditions			
	40 °c ±2° c/75% RH±5% RH			
	Initial	1st month	2nd month	3rd month
Physical appearance	White, Round shape	No Change	No Change	No Change
Avg. weight (mg)	249±0.9	249±0.4	248.3±0.6	248±0.8
Hardness (kg/cm^2)		6±0.23	6±0.01	5.9±0.4
Thickness (mm)	3.74±0.07	3.74±0.02	3.74±0.07	3.73±0.07
Lag time(min)	310	310	311	310
Drug content (%)	98±0.4		97±0.7	97±0.9.

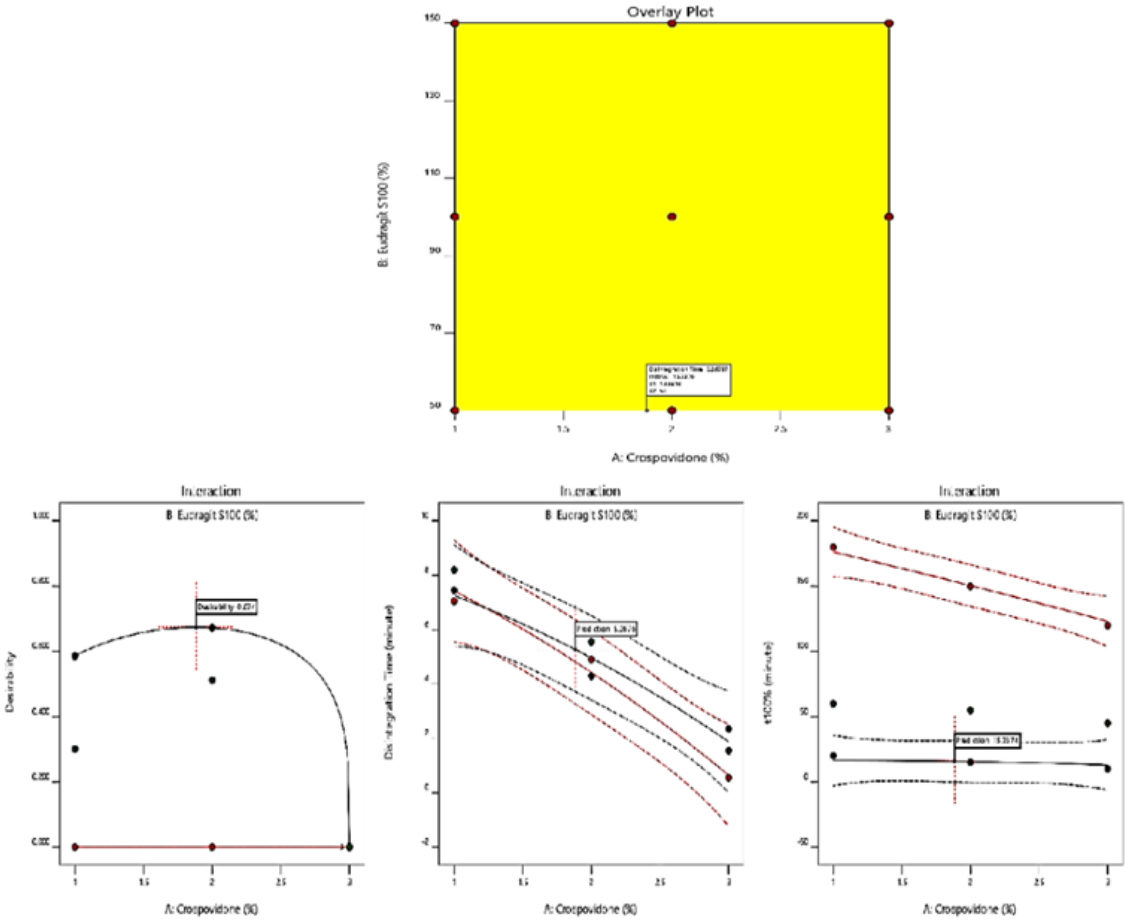

Figure 6: Optimization and its responses through Design of expert 12.

FTIR technology was employed determine physical and chemical interactions between the medicine and excipient. The FTIR-1700 Shimadzu FT-IR was used to obtain the FT-IR spectra of the drug, theophylline with polymer alongwith all tablet excipients using KBr mixing procedure.[49] (Figure 3)

DSC Study

The Theophylline physical as well as chemical interactions with its excipients were investigated using DSC40. The DSC spectra of pure drugs and drug composite mixes were recorded using the DSC-60 equipment. (DSC-60, Shimadzu).[50] (Figure 4)

RESULT AND DISCUSSION

Stability study

As per ICH Q1A (R2), stability testing is mandatory for products. The goals of rule stability testing are to establish a retest duration, recommended storage conditions, and the expected life span of a drug product.[51] Additionally, it demonstrates how several environmental elements, including temperature, humidity, along with light, can impact the long-term performance of a pharmaceutical or therapeutic substance.

Short-term stability testing of the optimised F7 batch was carried out at 40°C in a humidity container with 75% relative humidity (RH) to determine any changes in the in vitro dissolution profile and during storage. Batch F7 that was optimised was chosen for an expedited stability assessment. (Table 7)

CONCLUSION

Theophylline pulsatile tablet by press coating method for treatment of COPD (asthma) was successfully formulated. From % cumulative drug release conclude that Eudragit S 100 shows great retention of core tablet up to pH 7 means first 360 min is lag time for all batches no drug release in pH 1.2 (2 hours) and pH 6.8 (4 hours) only after pH 7 in colon region the polymer coat is getting dissolve hence, we get release of drug in colon. Crospovidone sodium used as superdisintegrant shows good disintegration as concentration of Crospovidone increase disintegration time of core tablet is decrease hence 3% shows burst release of the core tablet. F7 batch found to be optimized after all evaluation parameter was done successfully. Hence, we take medicine at night time and at time between 4-6 am drug was release in body at time which most chances of get asthma attack with this better patient compliance was done successfully.

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