Formulation and development of rosuvastatin calcium fast disintegrating tablet.

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ABSTRACT

The main aim of project work was to develop and formulate the fast disintegreting tablet of rosuvastatin calcium (FDTs) to enhance disintegration, solubility and overall bioavailability. The six formulations was prepared by using different concentrations of fenugreek mucilage as natural superdisintegrant with minimum side effects.

FDT's were evaluated for Flow properties, Disintegration time (DT), Dissolution studies, Solubility studies, Hardness, Thickness and Stability studies.

On the surface of FDT had fenugreek mucilage (Natural Superdisintigreting Agent) and pores that help's to swelling and penetration of water and hence rapid release of drug with highest solubility. There was maximum release of drug 97% from formulation F5 which contain *β-cyclodextrin* and *rosuvastatin calcium* at concentration 1:1 ratio which improve solubility and *fenugreek mucilage* as superdisintegration. This enhance dissolution rate of tablet and due to this property it can be used increase poor water solubility and drug bioavailability.

KEY WORDS: Fenugreek Seed Mucilage, Rosuvastatin, FDTs, B-Cyclodextrin, Rosuvastatin Calcium, Improved solubility.

INTRODUCTION:

In this modern generation need to the development of new and innovative dosage forms that is according to the needs of patients. For improve bioavailability, safety, efficacy with lower dose frequency and side effects for improve patient compliance (1). More than 41% of newly formulated drugs and dosage forms in pharmaceutical company are less water soluble under the BCS class 2 drugs (2,3). This affects the dissolution of drug in stomach and produce lower bioavailability. There are different methods and techniques used to solve this problem's and improve the bioavailability of poor soluble drugs. Which includes complexation, fast disintegration tablets (FDTs), microemulsion, hydrogel microemulsion etc. fined as a tablet's that disintegrate and dissolve rapidly in saliva within few seconds without need of drinking water or chewing (4).

In order to increase the surface area and facilitate a faster release of the pharmacological component, disintegrants are substances added to tablets and some encapsulated formulations that encourage the tablet and [capsule "slugs"] to break up into smaller pieces in an aqueous environment (5). types of superdisintegrants, including natural, synthetic, semi-synthetic, and co-processed mixes, among others Superdisintegrants are used as excipients in tablet formulations because they must fulfil certain requirements beyond their ability to swell. There should be a clear definition of the tablet disintegrant requirement. Most of these issues are resolved by a class of superdisintegrants that includes croscarmellose sodium (ac-di-sol), sodium starch glycolate (Primojel and Explotab), and crospovidone (6). Natural superdisintegrants due to their relative affordability, availability, non-irritating nature, and lack of toxicity, certain natural superdisintegrating agents are chosen over synthetic materials.

Because of their easy availability, affordability, environmental friendliness, emollient properties, non-irritating nature, non-toxicity, ability to undergo a variety of chemical modifications, potential for degradation, and compatibility due to their natural origin, natural materials like gums and mucilages have been widely used in the drug delivery industry (7). Plantago ovata seed mucilage (isphagula), Lepidium sativum mucilage, gum

karaya, *fenugreek seed mucilage*, locust seed gum, Cassia fistula gum, and guar gum are among the several gums and mucilages that shows superdisintegrating action. (8)

The risk of coronary heart disease (CHD), which includes heart attacks and strokes, is increased by cholesterol. High blood cholesterol levels can cause sticky deposits on the artery walls, which are known as plaque. Unavoidably, plaque can limit or stop blood flow to the heart, brain, and other organs. (9)

Lower water solubility and bioavailability of Rosuvastatin calcium's required the development of the FDTs tablet using superdisintegrants.

The research work was aimed to design and characterization of fast disintegrating tablet of rosuvastatin calcium cholesterol lowering tablet using the natural disintegrating agent; fenugreek seed mucilage.

MATERIALS AND METHODS

Rosuvastatin calcium was obtained as gift sample from DTDC Express Limited. Nagpur. Fenugreek seed was purchased from local market βcyclodextrin, Saccharine sodium, lactose, talc, was available in college. And vanilla flavour was obtained from local market.

METHODS

Mucilage extraction from fenugreek seeds

Fig 1: Fenugreek seed

A grinder was used to ground the seeds into a powder, and a Soxhlet apparatus was used to extract 50 g of the powder with n-hexane in order to eliminate lipophilic chemicals. The defatted powder was boiled in ethanol for 20 minutes in order to eliminate colours and deactivate the enzyme. After soaking this treated powder in five liters of water, 0.5 M hydrochloric acid was used to bring the pH down to 3.5. After 12 hours of stirring with a mechanical stirrer, the liquid was filtered via filtering paper. Following a 5000 g centrifugation of the filtrate, the supernatant was vacuum-concentrated to 50% of its original volume. The final solution was combined with an identical 96% volume. ethanol and kept for four hours in a refrigerator. Centrifugation (5000 g) was used to separate the precipitated mucilage. To get rid of chloride ions and other contaminants, the recovered mucilage was re-suspended in distilled water, shaken for 20 minutes, and then precipitated again. Ultimately, the residue was cleaned using acetone and diethyl ether and allowed to dry overnight at 45°C. to obtained white colour powder of fenugreek mucilage.

Fig 2: Wet mass of fenugreek seed fibres

PHYSICOCHEMICAL CHARACTERIZATION OF NATURAL SUPERDISINTEGRANTS (FENUGREEK MUCILAGE)

Fig 3: Fenugreek mucilage

Swelling ratio

The swelling ratio is the volume of liquid in ml occupied by 1 g of the drug; including any adhering mucilage after it has been swollen in an aqueous liquid for 4 hr. The swelling ratio was calculated from the mean of three determinations. One gram of powder was placed in a 25 mL ground glass stoppered cylinder that was graduated over a height of 120 to 130 mm in 0.5 divisions. 25 mL of water was added to this, and it was vigorously shaken every 10 m for one hour before being left to stand for 24 hours (10)

$$Swelling\ ratio = V2 - V1 / V1$$

where, V1 = initial volume of material before hydration; and V2 = volume of hydrated material.

Moisture content

Moisture content was carried out by using a hot air oven at 105˚ C for 2 hr (11)

$$\%\ Loss\ on\ drying = [(W1 - W2) / W1] \times 100$$

PROPERTIES OF DRUG AND EXCIPIENTS

Pre-formulation study on rosuvastatin calcium

Pre-formulation studies of rosuvastatin calcium focus on understanding the drug's physical and chemical properties to aid in formulation development. The pre formulation studies of rosuvastatin calcium is done like solubility, PH, Absorption maxima (λ max), stability, compatibility of drug substance alone and when combined with excipients. (12)

Solubility studies

Various aqueous and non-aqueous solvents were used to test Rosuvastatin's solubility. At room temperature, 10 mg of the medication was placed in 10 ml of each solvent in screw-capped test tubes, which were then agitated in a sonicator for 30 minutes at room tempreture. Show in table 3

Rosuvastatin's solubility into different pH range:

Equilibrium solubility is measure at different PH range. The compound rosuvastatin calcium show high solubility above PH range of 4 and highly soluble at PH 6.8 in phosphate buffer. Show in table 4. (12)

Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (Mettler Toledo) was used to examine the thermal behvior of pure drugs and polymers at a heating rate of 10°C/min. The observations were conducted in nitrogen atmospheres at temperatures ranging from 30 to 400°C. (13)

Compatibility Studies

One of the conditions for the selection of suitable excipients or carrier for the pharmaceutical formulation is its compatibility. The different excipients were combined with rosuvastatin in varying ratios. Additionally, it was kept in glass vials that were sealed and exposed to different humidity and temperature levels (25°C/60%RH, 30°C/65%RH, and 40°C/75%RH). Blends were examined for physical change, moisture content, and impurity profile after the allotted time had passed of 25-28 days. (13)

FORMULATION OF FAST DISINTEGRATING TABLETS (FDTS)

Direct compression method

The drug and excipients for fast disintegrating tablets were passed through mesh No. 60 separately. The ingredients were weighed, mixed geometrically, and compressed with 9 mm round, concave punch on a 10-station rotary tablet machine. To evaluate the effect of natural superdisintegrants and β-cyclodextrin on the solubility of rosuvastatin calcium 6 formulations were created at various doses see Table 1.

Ingredients in (mg)	F1	F2	F3	F4	F5	F6

Rosuvastatin	20	20	20	20	20	20
Mannitol	16	16	16	20	20	20
Fenugreek mucilage	-	8	16	24	32	30
β-cyclodextrin	65	50	20	20	20	20
Mg-stearate	4	4	5	5	4	4
Talk	4	4	4	5	5	4
Lactose	80	87	108	95	88	91
Vanilla Flavour	5	5	5	5	5	5
Saccharine sodium	6	6	6	6	6	6
Total weight	200					

Table 1. Composition of different formulations of rosuvastatin calcium

PRE-COMPRESSION PARAMETER OF THE POWDER

Powder Flow Properties:

The lubricated blend was examined for bulk density, tapped density, Hausner ratio, and compressibility index by vijay wakhare et al by using following method's outlined here. (14)

BULK DENSITY

It refers to how the particles are arranged. The quantity of drugs that occupies the volume, expressed in g/ml, was calculated using bulk density. A graduated cylinder was used to measure the components' bulk densities. It is the proportion of the powder's bulk volume to its overall mass. The volume was recorded after the weighed amount of powder was poured into a graduated measuring cylinder. The unit of measurement is g/ml. and calculated by using formula.

$$Bulk\ density = \frac{Mass\ of\ powder\ (W)}{ntapped\ volume\ of\ powder(V)g/ml)}$$

TAPPED DENSITY

It is the ratio of the powder's tapped volume to its overall mass. In accordance with USP, the powder was tapped 10, 100, and 500 times in measuring cylinder to determine the tapped volume. After 100 taps of the mix, the volume variation was calculated, and after another 500 taps, the variance percentage was also determined. By using formula.

$$Tapped\ density = \frac{weight\ of\ powder\ (W)}{tapped\ volume\ of\ powder(V)}$$

CARR'S INDEX

Also called as compressibility index. Compressibility index one of the important measurement that may be derived from the bulk and tapped densities. Theoretically, a material is more flowable the less compressible it is a substance is said to be free-flowing if its values are less than 20%. The relationship between % compressibility indexes and flowability can be measure by formula:

$$Compressibility\ Index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

HAUSNER'S RATIO

It indicates the flow properties of the granules. Measure by using formula:

$$Hausner's\ Ratio = \frac{Tappeddensity}{Bulk\ density}$$

ANGLE OF REPOSE

The friction forces between granule particles are indicated by the angle of repose. It is the greatest angle that can exist between the granule pile's surface and to the horizontal plane. By passing a fixed amount of powder from the funnel at a constant height till the top of the pile formed by the powder touching the funnel, the angle of repose was calculated. By using the fixed height method to calculate the angle of repose, the flowability of the granules was determined:

$$\theta = \tan^{-1}(h / r)$$

where, θ = angle of repose; h = height of pile; r = average radius of powder cone.

POST-COMPRESSION PARAMETER OF FAST DISINTE GRATING TABLET

Characterization

THICKNESS

The unit of measurement of thickness is mm. Tablet thickness was measured by using vernier calipers. 10 tablets were randomly taken and their thickness was measured by placing tablet between two arms of vernier Calipers (15).

HARDNESS

Hardness is a measure's the tablet's capacity to resist impact during handling. A Monsanto hardness tester was used to measure the tablet's hardness for each formulation. N is used to express it. The hardness of ten chosen tablet's was assessed.

Weight variation

A Shimadzu-AUX220 electronic balance was used to calculate the average weight of 20 randomly chosen tablets. Each tablet's weight was measured separately and compared to the average.

FRIABILITY TEST

The Roche Friabilator was used to assess the tablets' friability. The friabilator's drum was filled with twenty weighted tablets, and the speed was maintained at 25 rpm. For 4 minutes, the tablets were free to rotate and drop from a height of six inches. The tablets were then reweighed after being cleaned with a muslin cloth.

$$\% F = (W0 – W/ W0)] \times 100$$

Where, % F = friability in percentage; W = Weight of tablet after revolution; W0 = Initial weight of tablet.

DISINTEGRATION TEST OF TABLETS

Devices for dissolving tablets were employed. Each tube was filled with six tablets, which were then properly covered. The medium's temperature was kept at 37 ± 2 °C. The amount of time it took for the tablet to fully dissolve was recorded.

Fig 4: Tablet disintegrating apparatus (LABINDIA)

WETTING TIME

10 ml of the pH 6.8 buffer solution were collected in a Petri dish as saliva. In the petri dish was a circular piece of tissue paper with an 8 cm diameter that had been folded twice. On tissue paper, a single fast disintegrating tablet was placed and the duration of time required to achieve full wetness was recorded.

Fig 5: wetting of tablet

IN-VITRO DISSOLUTION STUDY

FDT dissolution tests were carried out using USP type-II equipment. The machine was set up to run at 50 rpm. 900 ml of phosphate buffer In each apparatus vessel, a phosphate buffer solution with a pH of 6.8 was used as the dissolving media. Each dissolution vessel had a single oral dissolving tablet, and the medium's temperature was maintained at 37 ± 0.5 °C. After a predetermined amount of time, the sample from each vessel was removed and replaced with the equal amount of freshly made buffer. The UV/Vis spectrophotometer was used to detect absorbance at 243 nm. (16)

IN VITRO DISPERSION TIME

In this test, the duration of time required for the tablet to completely disperse was measured. In a 10-ml beaker, six ml of phosphate buffer with a pH of 6.80 were added. After placing the tablet in the beaker, the dispersion time was measured. For every formulation, the experiment was conducted three times. (16)

STABILITY STUDY

According to the standards of the International Conference on Harmonization (ICH), stability studies of FDTs were carried out for a duration of three months. Tablets were reassessed for drug content and other previously listed characteristics after a three-month period. Research was done. at the following temperatures and relative humidity. 37 ± 1 °C, 40 ± 1 °C, and 50 ± 1 °C, with a relative humidity of 75 ± 5%. (16)

RESULTs AND DISCUSSION

six different FDT formulations were developed using different amounts of natural super disintegrating agents and β-cyclodextrin. FDTs were initially assessed. for the parameters of micromeritics. When compressing powder or particle matter into tablets, flow characteristics are important. It is difficult to compress materials with poor flow characteristics into tablets, which leads to weight variation. Powder was initially assessed for flow characteristics including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio in order to prevent such problems. Table 5 shows the results of these rheological parameters.
The results verified the concept that our material might be compressed into FDTs and that all of the elements were properly mixed before compression.

Physicochemical parameters of natural superdisintegrant's

Parameter	Result's
Colour	Cream yellow colour
Odour	Odour less
Taste	Test less
pH (1%)	5.9%
Swelling ratio (ml)	
HCl	7
Water	5.5
pH 6.8 buffer	6.7

Table 2. Physicochemical parameters of natural superdisintegrant's.

solvent	Amount	Result
Water	0.0886 g/l	Very Slightly Soluble
Ethanol	0.86 mg/ml	Very Slightly Soluble
Methanol	0.95 mg/ml	Slightly Soluble
0.1 M HCL	28 mg/ml	Soluble
0.1 M NaOH	1 mg /ml	Slightly Soluble

Table 3. Rosuvastatin's solubility profile in different solvents.

PH Buffer	Solubility in mg/ml

pH 1.2 HCL Acid (0.1N)	0.5±0.0
pH3.6 Acid phthalate Buffer	1.6±0.1
pH 4.6 Neutralized phthalate Buffer	3.7±0.2
pH6.0 Phosphate Buffer	10.7± 0.3
pH6.8 Phosphate Buffer	1.427 mg/mL
Deionised water	7.8± 0.1

Table 4. Rosuvastatin solubility into different pH range

PRE-COMPRESSION PARAMETERS

The bulk density, tapped density, compressibility index, and Hausner's ratio of the mix that was prepared for compression were assessed. The blend's compressibility index ranged from 5.63% to 5.90%, and Hausner's ratio between 1.05 and 1.06, indicating that the blend is prepared for compression. A blend of the aforesaid formulation was found to have excellent flow characteristics and compressibility index based on the values of Hausner's ratio and the compressibility index Table 5.

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Hausner's ratio	Carr's index %
F1	0.738	0.861	25.60	1.16	15.80
F2	0.742	0.860	24.80	1.15	16.20
F3	0.760	0.877	23.50	1.15	14.70
F4	0.745	0.877	25.50	1.17	15.90
F5	0.726	0.861	26.31	1.19	15.51
F6	0.743	0.871	25.68	1.15	16.85

5. Results of bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index.

POST-COMPRESSION PARAMETERS

A total of six FDT formulations were developed with different concentrations of β-*cyclodextrin*, sodium starch glycolate and fenugreek seed mucilage. A direct compression approach was used to prepare the different formulations of rosuvastatin calcium. due to the API's flow properties. Excipients like magnesium stearate, talc and mannitol, were included in the formulation of the tablets. Out of the six batches, the three best batches were screened based on factors such thickness, drug content, weight variation, hardness, friability, and disintegration time.

By increasing the hardness of tablet results in decrease the surface pours of tablet and it decrease the weatting time and disintegranting time of tablet so the addition of natural superdisintegrating agents in optimum concentration to increase the disintegration time

The tablet's DT had increased up. Overall, the hardness results show that they were present within the RDT's defined limit show in Table 6.

Formulations	Wt. variation (mg)	Hardness kg/cm2	Thickness (mm)	Friability (%)	Disintegration time (s)	Wetting* time (s)

F1	199.56	3.20	2.70	0.655 ± 0.02	77 ± 1.50	96 ± 1.50
F2	197.51	3.30	2.63	0564 ± 0.03	67 ± 1.73	88 ± 1.70
F3	198.87	3.40	2.76	0.564 ± 0.04	59 ± 1.15	76 ± 1.15
F4	199.67	3.10	2.66	0.345 ± 0.03	64 ± 1.70	83 ± 0.53
F5	199.45	3.40	2.69	0.476 ± 0.00	30 ± 1.50	43 ± 1.15
F6	195.58	3.50	2.94	0.602 ± 0.03	42 ± 1. 30	56 ± 1.70

TABLE 6. Result of post compression studies

In general, tablets with less than 1% friability are considered as good. All formulations showed friability below 0.8%, indicating that the tablets' mechanical strength was good. Tablets did not exhibit any needless particle breakdown when rotated in the friabilator's drum. Friability data were statistically assessed using a one-way ANOVA approach. The p-value for the ANOVA between the groups was 0.025, which was less than 0.05, according to the results see in table 6. And disintegration time graph show in Figure 6.

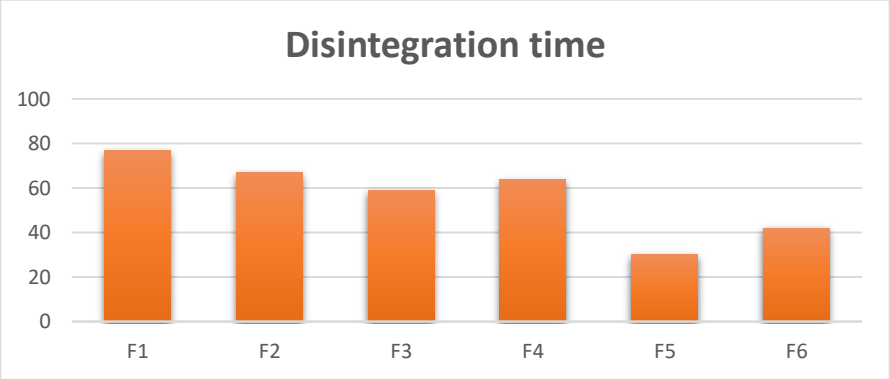

Fig 6: Disintegration time of different formulation

Wetting time is a measure of an ingredient's hydrophobicity. Disintegration will occur more quickly the shorter the soaking time. (17) As seen in Table 7, the wetting time for each of the 6 formulations was less than two minutes, ranging from 43 to 96 s. It was lowest for the drug-containing F5 formulation. with a 1:1 ratio of β-cyclodextrin and rosuvastatin.
By fenugreek mucilage acting as a natural superdisintegrant at 16%. The p-value for wetting time was 0.036, according to the findings. It shows that the type and amount of
β-cyclodextrin and natural superdisintegrants had an effect on tablet wetting and that the results were significant.

Formulation	**Wetting volume (ml)**	**Dispersion time (s)**	**Ph of solution**
F1	22 ± 1.50	57 ± 0.58	7.1

F2	20 ± 0.58	53 ± 1.15	6.8
F3	15 ± 1.73	45 ± 0.58	6.8
F4	23 ± 1.73	56 ± 1.15	7.2
F5	08 ± 0.53	29 ± 0.58	6.8
F6	12 ± 0.58	36 ± 1.15	6.8

Table 7. Results of wetting volume, dispersion time and pH of tablet solution.

Time in (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	06.12	08.13	5.25	8.8	16.32	12.75
10	33.12	34.50	31.25	35.44	54.33	39.67
15	52.33	54.32	50.56	54.25	77.19	64.55
20	61.89	63.21	71.35	74.88	85.01	82.43
25	72.31	74.12	88.87	90.56	97.50	93.12
30	87.5	88.40	87.43	87.65	97.62	94.15

Table 8. in vitro cumulative % drug release at PH 6.8 phosphate buffer

FDTs commonly disintegrate in less than a one minute, and patients may experience this for five to thirty seconds (Table 6). Tablet swelling may result from the medium's quick absorption of water.
finally rapid breakdown to produce a bursting effect. This causes the drug to diffuse from its medium into the surrounding environment quickly, improving the loaded drug's solubility. It was lowest for F5, similar to wetting time.
Every formulation passed an in vitro dispersion test. This test used a Petri plate to determine its dispersion time. Tablet dispersion was impacted by swelling brought on by superdisintegrants. Out of all the formulations, Formulation F5 had the shortest dispersion time. According to these findings, fenugreek mucilage was a natural superdisintegrant option over sodium starch glycolate and has no side effects. The amount of water that the tablets absorbed, which in turn affected how easily they disintegrated, was determined using the water absorption ratio. When more water comes in, then Disintegration will occur more quickly.

Dissolution study
To determine in vitro drug release, dissolution tests were conducted using a phosphate buffer with a pH of 6.8. The findings indicated that there was a significant variation in the release of rosuvastatin tablets made with *β-cyclodextrin* and other natural superdisintegrants (*fenugreek mucilage*) compared to those made commercially. For FDTs, the maximum drug release was seen in 1 minutes, while no discernible release was seen in the case of commercially available tablets. As seen in Table 8, the maximal drug release in formulation F5 was 97% in 25 minutes. Overall medication release values ranged from 91% to 97%. because result of more pores on the tablet's surface. That, demonstrated greater release and absorbed more water from the dissolving media than commercially available tablets.

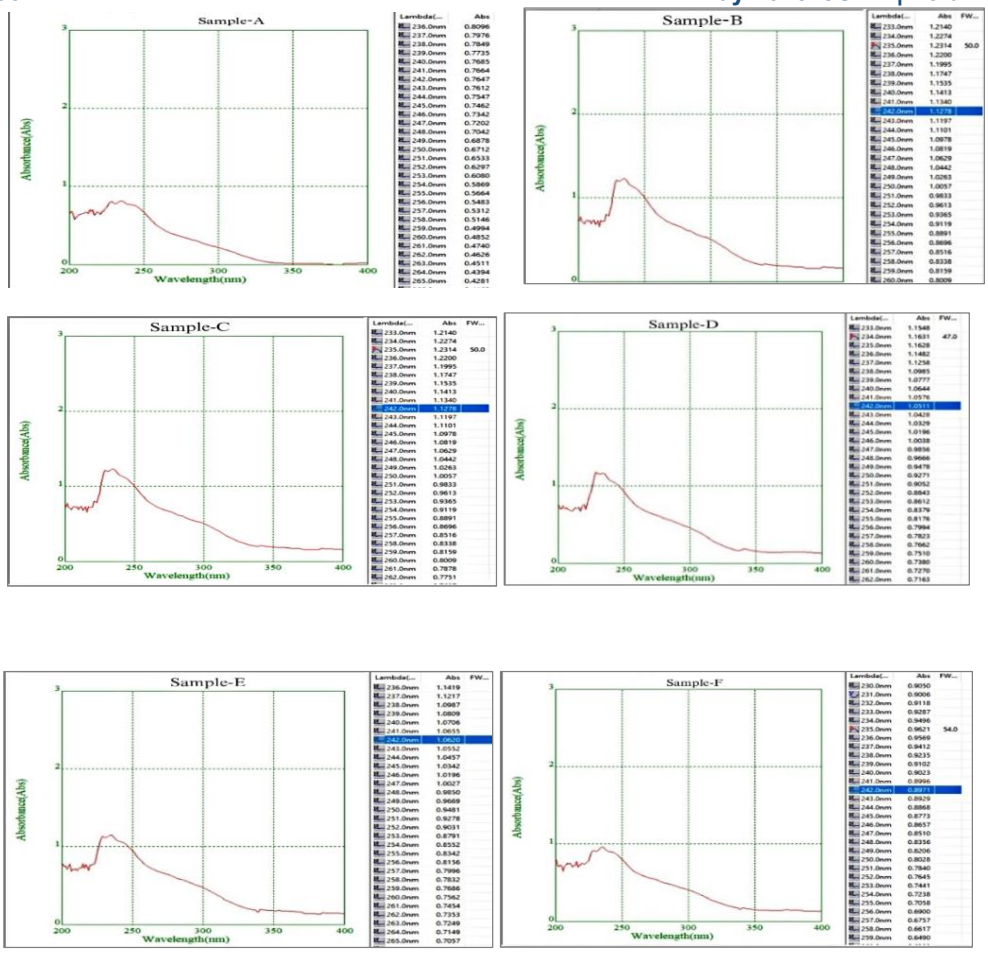

Figure 7. UV SPECTROSCOPY study of sample A, B, C, D, E and F

Stability study

Stability study the optimized batches conducted a three-month stability study at 40ºC and 75% relative humidity while covered in aluminum foil. When the stability samples were first examined and then again after one and three months, there was no change in their physical characteristics, assay, and medication release, demonstrating the stability of the tablet

CONCLUSION

This research successfully demonstrated that fenugreek seed mucilage can be effectively utilized as a natural superdisintegrant in the formulation of fast disintegrating tablets of Rosuvastatin calcium. Among the six formulations developed, F5 exhibited optimal pre-compression and post-compression characteristics, with the fastest disintegration time and highest in vitro drug release. The incorporation of β-cyclodextrin further enhanced the solubility and dissolution rate of the drug. Stability studies confirmed the formulation's durability under accelerated conditions. Overall, this study supports the use of natural disintegrants like fenugreek mucilage as a promising, biocompatible alternative to synthetic agents, contributing to safer and more effective oral drug delivery systems.

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