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Formulation and In-vitro Characterization of Clobazam Fast Dissolving Tablets by Solid Dispersion Technique

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ABSTRACT

Clobazam belongs to the 1, 5-benzodiazepine class of drugs and is expected to have a better side-effect profile compared to older 1,4-benzodiazepines. It is a BCS class II drug having higher half-life. To improve the biological performance of Clobazam solid dispersion with oral disintegrating tablet was formulated by using Povidone, Mannitol. Solid dispersions of Clobazam were prepared with different carriers in different ratios of drug and carrier (1:1, 1:2 and 1:3). Results of prepared solid dispersions of Clobazam by solvent evaporation method were discussed which includes solubility, melting point determination, drug content uniformity, and in vitro dissolution studies. Characterization in solid state was done by various analytical techniques such as FT-IR studies. Finally by comparing all the formulations, formulation (F3) containing Clobazam + Povidone (1:3) shows better results by solvent evaporation method at the end of 60 min with maximum drug release, hence it was selected as the best formulation. From the optimized formulation the Fast dissolving tablets were formulated using different disintegrants in different concentrations. The pre compression and post compression parameters were studied and the results were given. All the results are in the acceptable limit. The in vitro drug release of the formulated tablets were performed using 6.8pH buffer. F3C6 formulation containing Lycoat shows 98.02% drug release in 20mins. The optimized formulation follows First order release kinetics.

Keywords: Clobazam, povidone, lycoat, FTIR.

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CONTENTS:

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1. Introduction

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Methods available to improve dissolution include salt formation, micronization and addition of

solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.

Solid dispersions:

Solid dispersions (SDs) traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. Since 1961, many investigators have studied SDs of poorly water-soluble drugs with various pharmacologically inert carriers to increase the dissolution and oral absorption of poorly water-soluble drugs however, only a few systems are useful commercially.Fast or immediate drug dissolution from solid dispersions has been observed due to increased wettability, improved dispersibility of drug particles, existence of the drug in amorphous form with improved solubility and absence of aggregation of drug particles .Literature shows that the solvent evaporation method has been used for the preparation of solid dispersions for dissolution enhancement .Earlier studies show that solid dispersion systems increased the drug dissolution due to improved solubility, wettability and dispersibility using hydrophilic carriers In the present work, physical mixtures, co-grinding and co-precipitation or solvent evaporaration method was used to prepare solid dispersions of prednisolone. This method requires the minimal amount of solvent in dissolving the drug. We used various polymeric carriers in this study. Polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) were chosen as water-soluble polymers.

Fast Disintegrating Tablets:

The performance of FDTs depends on the technology used in their manufacture. The FAST disintegrating property of these tablets is attributable to the quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop FDTs include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation.

Clobazam belongs to the 1,5-benzodiazepine class of drugs and is expected to have a better side-effect profile compared to older 1,4-benzodiazepines. Clobazam is an BCS class II drug having absolute bioavailability of Clobazam is low. To improve the biological performance of Clobazam solid dispersion with fast dissolving tablet was formulated by using Mannitol, Povidone.

2. Materials and Methods

Chemicals used:

Table 1: List of Instruments

S. No.	Instrument used	Manufacturer
1.	Electronic weighing	Shimadzu 2000
2.	UV-Visible	Shimadzu-1700,
3.	Dissolution test apparatus USP23	Tab machines, Mumbai
4.	Hot air oven	Tapman, Mumbai
5.	Dessicator	Hindustan Apparatus

Table 2: List of Chemicals

S. No.	Material	Manufacturer
1	CLOBAZAM	B.M.R. Chemicals,
2	Mannitol	S.D Fine Chemicals
3	POVIDONE	S.D Fine Chemicals
4	Methanol	S.D Fine Chemicals
5	Plantago ovata	B.M.R.
6	Lycoat	B.M.R.
7	Micro crystalline	B.M.R.
8	Magnesium sterate	B.M.R.
9	Talc	B.M.R.

Preformulation studies:

Preformulation testing is the first step in the rational development of dosage forms of a drug substance.

Solubility studies:

Solubility of Clobazam was carried out in different buffers. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the shaker for 24 hrs at 25°C under constant vibration. Filtered samples (1ml) were diluted appropriately with suitable buffer and solubility of Clobazam was determined spectrophotometrically at 231 nm.

Drug–polymer compatibility studies

In the preparation of tablet formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Clobazam, and the selected polymers. The pure drug and drug with excipient were scanned separately.

Analytical method development by U.V. Spectroscopy:

UV-Visible spectrophotometry is one of the most frequently employed techniques in pharmaceutical analysis. It involves measuring the amount of ultraviolet or visible radiation absorbed by a substance in solution. Instrument which measure the ratio, or function of ratio, of the intensity of two beams of light in the U.V-Visible region are called Ultraviolet-Visible spectrophotometers.

Scanning of λmax of Clobazam:

Preparation of Stock Solution: 10 mg of Clobazam was taken in a 10 ml volumetric flask. To that 2 ml of methanol was added and shaken well to dissolve the drug. The solution was made up to the mark with 6.8pH buffer to give 1000 µg /ml concentration.From the above solution 1 ml is diluted to 10 ml with 6.8pH buffer to give 100 µg /ml concentration. From the above solution, take 1 ml, and diluted to 10 ml with 6.8pH buffer, to give 10 µg /ml concentration. The prepared solution i.e., 10 µg/ml concentration was scanned for λmax from 200-400 nm in UV/Visible spectrophotometer.

Preparation of Solid Dispersions of Clobazam:

There are several carriers, which have been reported for the preparation of solid dispersions by using Mannitol, Povidonevarious methods of preparation.

Solvent evaporation: In solvent evaporation method, the drug and carriers were mixed in 1:1, 1:2 and 1:3 ratios in

methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed through sieve # 60. And now the obtained product was collected.

Evaluation of Solid Dispersions:

Prepared polymer drug conjugates were evaluated by

1) **Estimation of drug content**
2) ***In- vitro* dissolution studies**

Estimation of Drug Content:

A quantity, which was equivalent to 5 mg of drug, was accurately weighed and transferred to 100ml volumetric flask. Then the volume was made up with, 6.8pH buffer buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. Same concentration of standard solution was prepared by dissolving 5 mg of standard drug in 6.8pH buffer. For both the sample and standard solutions absorbance was measured at 231 nm for Clobazam in UV-Visible spectrophotometer.

***In vitro* dissolution study:**

The prepared solid dispersions containing 5 mg weight equivalent of Clobazam was placed in a capsule and subjected to *in vitro* dissolution. Dissolution test was carried out using USP type 2 Paddle methods [apparatus II]. The stirring rate was 50 rpm, 6.8pH buffer was used as dissolution mediumand dissolution medium was maintained at 37±0.5oC. Samples of 5 ml were withdrawnat regular intervals of time, filtered and replace with 5 ml of fresh dissolutionmedium, dilutions were made wherever necessary and were analyzed for Clobazam at 231 nm by using UV-visible spectrophotometer.

Formulation of Clobazam Tablets:

Equivalent weight of Clobazam was added with suitable excipients and the tablets were formulated by direct compression according to the formulae given in the table.All the ingredients were passed through # 40 mesh sieve separately. The drug and MCC were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside.Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#40 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm^2 for all batches. The weight of the tablets was kept constant for all formulations F3C1 to F3C6.

Precompression Parameters:

All the materials were passed through sieve no. 80. Required quantity of each ingredient was taken for each specified formulation (Mentioned in Table) and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc). The powdered blend was evaluated for flow properties as angle of repose, bulk density, tapped density, compressability index and hansur's ratio.

Post compression parameters:

The formulated tablets are also evaluated by post compression parameters such as weight variation, hardness, friability, thickness, content uniformity, in vitro disintegration time and in vitro dissolution studies were performed.

In-Vitro Disintegration time:

Tablet disintegration is an important step in drug absorption. The test for disintegration was carried out in Electrolab USP disintegration test apparatus. It consists of 6 glass tubes which are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing pH 6.8 pH buffer buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

Dissolution studies:

In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. 6.8pH buffer 900 ml is used as dissolution medium which is maintained at 37±0.5°C. Aliquots of dissolution medium (5 ml) are withdrawn at specific time intervals and filter. An equal amount of fresh dissolution medium is replaced immediately following withdrawal of test sample. The percentage of drug released at various intervals is calculated using beer-lamberts law.

Kinetics of Drug Release:

The mechanism of drug release for the Clobazam solid dispersions was determined using zero order and first order.

3. Results and Discussion

Solubility:

Solubility of Clobazam was carried out at 25^{0}C using 0.1 N HCL, 6.8 phosphate buffer, 7.4 pH buffer, methanol and ethanol.From the conducted solubility studies in various buffers we can say that 6.8pH buffer solution has more solubility when compared to other buffer solutions.

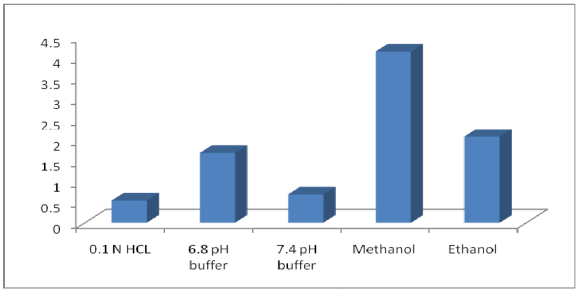

Fig 1: Graphical representation of Clobazam Solubility studies

Analyticalmethod development by U.V. Spectroscopy: Clobazam at 10µg/ml was found to be 231nm.

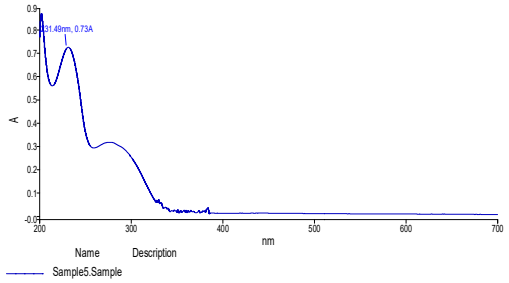

Fig 2: UV Scan Spectrum of Clobazam

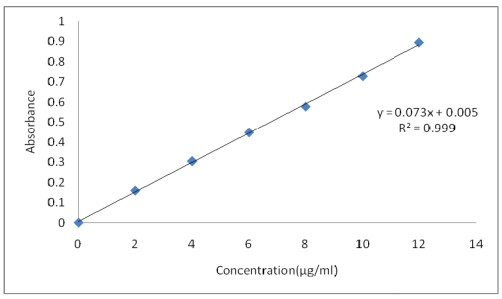

Fig 3: Calibration curve of Clobazam

Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.From the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Clobazam) and optimized formulation (Clobazam: excipients) which indicates there are no physical changes.

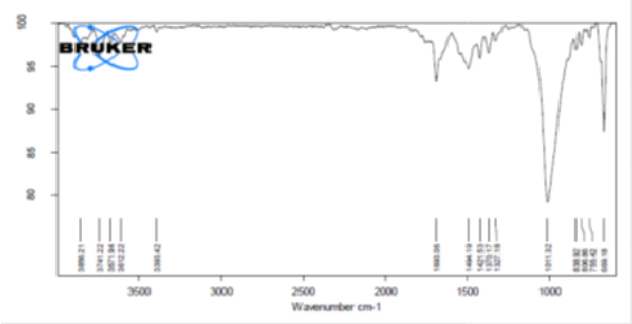

Fig 4: IR spectrum of Clobazam optimised Formulation

***In vitro* drug release studies of solid dispersions:**

In-vitro drug release of Clobazam solid dispersions with Povidone in various ratios were observed which shows at the end of 60 mins, the formulation F1 releases 83.26%, formulation F2 releases 90.42 %, F3 releases 96.12%, while Mannitol used as carrier shows formulation F4 releases 73.56%, formulation F5 releases 79.45%, and formulation F6 releases 88.02%. Among all formulation F6 formulation shows maximum drug release at the end of 60 minutes so it was chosen as optimized formulation.

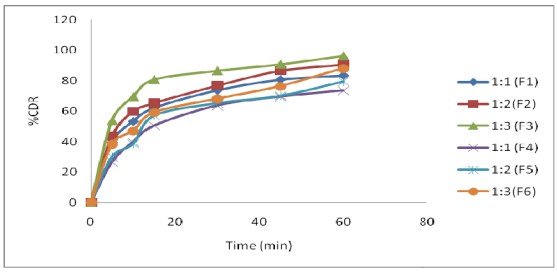

Fig 5: *Invitro* drug release profile for (F1-F6)

***In-vitro* drug release kinetics studies for best formulation F3:**

By comparing the release kinetics studies of best formulation with zero order and first order we can say that the best formulation follows first order release kinetics studies having R^2 value 0.919 were as zero order release kinetics studies having R^2 value 0.574, hence we can say that the best formulation follows first order release kinetics.

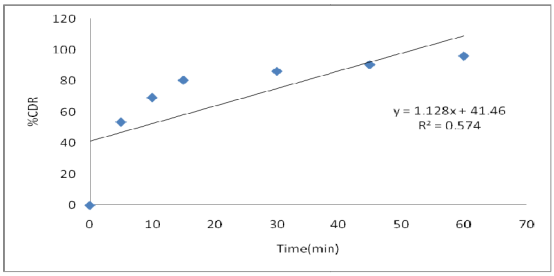

Fig 6: Zero order release profile for best formulation (F3)

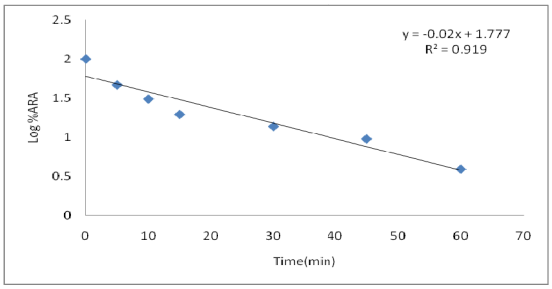

Fig 7: First order release profile for best formulation (F3)

Evaluation ofClobazam Fast disintegrating Tablets:

The angle of repose of different formulations was ≤ 30.12 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.312g/cm^3 to 0.334g/cm^3.Tapped density was found between 0.389g/cm^3 to 0.359g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.56-16.49 and Hausner's ratio from 1.13-1.20 which reveals that the blends have good flow character.

Post Compression parameters:

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table 8.Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3.1 – 3.6 kg/cm^2.All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F3C1 – F3C6 and considered to be satisfactory ensuring that all the formulations are mechanically stable.The drug content values for all the formulations (F3C1 – F3C6) was found to be in the range of 96.02-100.36%

Dissolution studies of the tablets:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release. From the in vitro drug release in studies it was observed that the formulations containing Plantago ovata as a super disintegrant in different concentrations like 3%, 6%, and 9%, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F3C3

formulation containing Plantago ovata 9% shows maximum amount of drug release (100.23%) at the end of 25mins. Whereas formulations containing Lycoat as a super disintegrant in different concentrations like 3%, 6%, and 9%, reveals that the increased in the super disintegrant concentration decreases the drug release time and the F3C6 formulation containing Lycoat 9% shows maximum amount of drug release (98.02%) at the end of 20 mins.

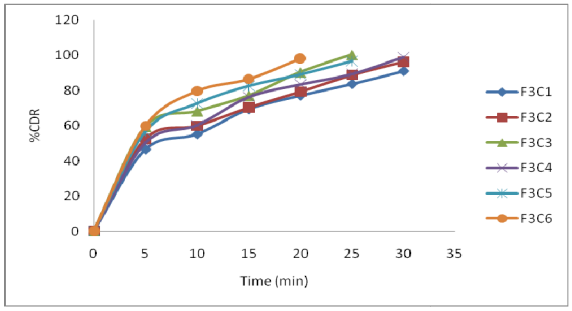

Fig 8: *In vitro* drug release of formulations F3C1-F3C6

Drug Release Kinetics:

The drug release from the tablets was explained by using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation F3C6 follows First order kinetics.

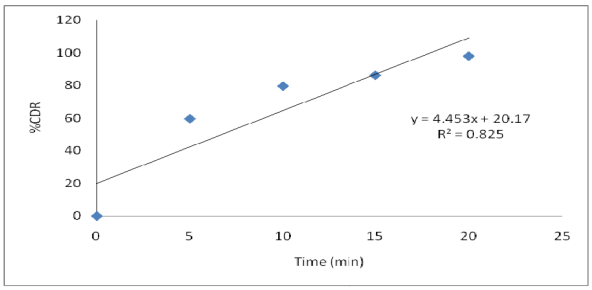

Fig 9: Zero order plot of (F3C6)

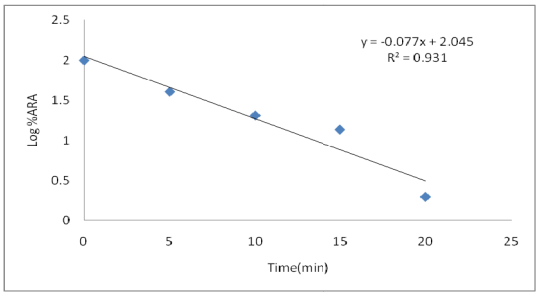

Fig 10: First order plot of (F3C6)

Table 3: Formulation of Clobazam Tablets

Ingredients (mg)	F3C1	F3C2	F3C3	F3C4	F3C5	F3C6
Clobazam (weight equivalent to 5mg)	18	18	18	18	18	18
Plantago ovata	3	6	9	--	--	--
Lycoat	--	--	--	3	6	9
MCC	76	73	70	76	73	70
Mg.st	2	2	2	2	2	2
Talc	1	1	1	1	1	1
Total	100	100	100	100	100	100

Table 4: Solubility studies data of Clobazam

Medium	Solubility (mg/ml)
0.1 N HCL	0.541
6.8 pH buffer	1.692
7.4 pH buffer	0.689
Methanol	4.152
Ethanol	2.084

Table 5: Calibration curve data of Clobazam

Concentration (µg/ml)	Absorbance
0	0
2	0.159
4	0.305
6	0.448
8	0.578
10	0.729
12	0.896

Table 6: *In vitro* drug release studies for formulations (F1-F6)

Time (Min)	Percentage drug release					
	Clobazam : Povidone			Clobazam :Mannitol		
	1:1 (F1)	1:2(F2)	1:3 (F3)	1:1 (F4)	1:2 (F5)	1:3(F6)
0	0	0	0	0	0	0
5	39.42	43.26	53.62	26.53	29.84	38.21
10	53.16	59.63	69.35	39.62	38.42	46.82
15	62.05	65.12	80.53	50.36	56.98	59.12
30	73.62	76.59	86.32	63.62	65.23	68.02
45	80.59	86.32	90.56	69.43	70.04	76.36
60	83.26	90.42	96.12	73.56	79.45	88.02

Table 7: Pre Compression parameters

Formulation Code	Derivedproperties		Flowproperties		
	Bulkdensity (mean±SD)	Tapped density (mean±SD)	Angleof repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F3C1	0.326	0.378	26.53	13.76	1.16
F3C2	0.329	0.372	29.54	11.56	1.13
F3C3	0.334	0.389	30.12	14.14	1.16
F3C4	0.312	0.359	28.64	13.09	1.15
F3C5	0.321	0.382	29.71	15.97	1.19
F3C6	0.319	0.382	26.35	16.49	1.20

Table 8: Characterization of Clobazam Fast disintegrating tablets

Formulation	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)	DrugContent(%)
F3C1	101.26	2.03	8.01	3.2	0.21	29	98.86
F3C2	100.54	2.08	8.06	3.1	0.53	20	96.32
F3C3	99.25	2.12	8.00	3.1	0.36	15	97.42
F3C4	101.45	2.04	8.15	3.2	0.41	26	96.02
F3C5	98.36	2.16	8.04	3.6	0.53	28	98.12
F3C6	100.45	2.06	8.02	3.5	0.69	20	100.36

Table 9:% Cumulative drug release of formulations F3C1 – F3C6

Time (Min)	F3C1	F3C2	F3C3	F3C4	F3C5	F3C6
0	0	0	0	0	0	0
5	46.38	52.36	59.21	50.23	56.57	59.68
10	55.06	59.87	68.12	60.23	72.65	79.53
15	69.24	70.23	76.92	76.23	82.63	86.32
20	76.95	79.26	90.23	83.42	89.15	98.02
25	83.54	88.74	100.23	89.35	96.74	
30	90.85	96.32		99.02		

Table 9: Order of kinetic values of Formulation F3C6

Order of kinetics	Zero Order	First Order
Regression values	0.825	0.931

4. Conclusion

Povidone and Mannitol was used in the preparation of solid dispersions by solvent evaporation method. By observing the dissolution studies the Clobazam with Povidone (1:3).shows better drug release. And all the prepared solid dispersions were evaluated and results was explained in above mentioned data.The following conclusions were drawn from the present investigations. From the Solubility studies in various buffers we can say that 6.8 pH buffer has more solubility when compared to other buffer solutions for Clobazam.Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which

indicates there are no physical changes.All the formulations of Clobazam were prepared solvent evaporation method. All the prepared solid dispersions were evaluated for drug content. The invitro dissolution studies of Clobazam was performed.From the optimized formulation of the solid dispersions(i.e.,F3) weight equivalent of Clobazam was used along with the superdisintegrants like Lycoat & Plantago ovata.Pre compession and Post compression evaluation studies were performed.The better drug release with 9% lycoat with 98.02% of drug release at the end of 20mins.Drug release kinetics of the optimized formulation shows First order drug release.

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