

**FORMULATION AND EVALUATION OF GABAPENTIN SUSTAINED RELEASE MATRIX
TABLET USING *HIBISCUS ROSA SINENSIS* LEAVES MUCILAGE AS RELEASE
RETARDANT**

Abstract

The major goal of this study was to develop and evaluate Sustained release matrix tablets of Gabapentin with *Hibiscus rosa - sinensis* leaves mucilage prepared by using wet granulation technique with microcrystalline cellulose as a diluents and magnesium stearate as a lubricant. Pre-compression and post-compression evaluation of physicochemical parameters were carried out and to be within acceptable limits. Drug and polymer compatibility were validated by FTIR measurements. Further, tablets were evaluated for *in vitro* release study. To get the sustained release of Gabapentin, the concentration of *Hibiscus rosa- sinensis* mucilage was tuned with a gas-generating agent. The % drug release of all formulation from F1 to F5 showed 91.24%, 80.24%, 70.53%, 62.12% and 49.83% respectively. All the dosage form release kinetics was computed using zero order, first order, Higuchi, and Korsmeyer–Peppas methods. From the above results, it is concluded that the n value of formulation F5 showed 0.78 suggesting anomalous (non-fickian) behavior of the drug. *Hibiscus rosa-sinensis* leaf mucilage has an excellent retarding effect on drug release from the sustained release tablets.

Introduction

The oral route of administration is still the most preferred due to its various advantages, such as ease of administration, accurate dose, self-medication, variety, and pain avoidance, all of which contribute to a high level of patient compliance [1, 2]. However, the fundamental issue with oral dosage form design is drug bioavailability, which is primarily driven by low solubility and inadequate permeability [3]. Hence, one of the major issues for pharmaceutical industry is developing in attempt of improving the water solubility of drugs generally for oral-drug delivery system. Modified release drug delivery systems are categorized as sustained-release tablets, delayed-release tablets, or pulsatile-release tablets. A dosage form that slows the release rate of a drug is known as a sustained-release or extended-release dosage form [4, 5,6].

Natural gums are polysaccharides that naturally occur in plants and are made up of several sugar units joined together to form large molecules. These gums are pathological substances formed by cell breakdown after a plant damage (extracellular formation: gummosis). Natural gums, on the other hand, offer a wide range of applications in the pharmaceutical and food industries and are regarded safe for human consumption. [7,8].

The red flowered variety of *Hibiscus rosa - sinensis* Linn is used in medicine because its leaves and flowers have been proved to increase hair growth and improve wound healing. The leaves of hibiscus species contain a lot of water soluble mucilage, which when combined with water produces an aqueous colloidal suspension [9]. This mucilage can be employed as an excipient in a formulation when poorly soluble pharmaceuticals are included because it allows them to come into touch with water more quickly, enhancing drug solubility[7]

Gabapentin is an anti-epileptic drug that is now being used in the treatment of neuropathic pain. Gabapentin is started with a dose of 300 mg, 600 mg, or 1800 mg per day because it is easily absorbed from the gastrointestinal tract. [8]. Because of the high dose, the plasma half-life is around 5-7 hours and its short biological half-life and once-daily administration of a conventional tablet made it difficult to maintain a steady state of concentration. To overcome this problem, the present study proposed a Gabapentin sustained-release dosage form [9]. The rate and mechanism of drug release from the formulated tablets were examined.

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Materials and methods

The fresh leaves of *Hibiscus Rosa-Sinensis* were collected from the institution's botanical garden. Gabapentin was a free sample provided by Aurobindo Parma Ltd. in Hyderabad. All other chemicals, including acetone, were purchased in analytical grade.

Extraction of leaves of *Hibiscus Rosa-Sinensis*

To remove dirt and debris, the fresh *Hibiscus Rosa-Sinensis* leaves were properly rinsed with water. The leaves were crushed and soaked in water for 5-6 hours to allow total mucilage release into the water, then boiled for 30 minutes and set aside for 1 hour. The mucilage was extracted from the solution with a multi-layer muslin cotton bag to remove the marc. The mucilage was precipitated using acetone (three times the volume of the filtrate). Later, the mucilage was separated, dried at 400 degrees Celsius, collected, crushed, sieved # 80, and stored in desiccators at 300 ° C and 45 percent relative humidity until use [13]. The percentage yield, particle size, swelling index, angle of repose, and other physicochemical parameters of dried powdered mucilage were studied.

Method of Preparation of Matrix Tablet

Preparation of granules

Sustained release matrix tablets of Gabapentin with *Hibiscus Rosa - Sinensis* leaves mucilage were prepared by using wet granulation technique [14]. Weighed quantity of the powdered drug was blended with *Hibiscus rosa-sinensis* mucilage as superdisintegrants and used as matrix forming material while microcrystalline cellulose as a diluents and magnesium stearate as a lubricant. All ingredients used were passed through a #100 sieve, weight and blended. The granules were prepared by wet granulation technique and compressed by using 16/32 Flat punch as per the composition given in the **table 1**. Each tablet weighed 500mg.

Table 1
Composition of sustained release matrix tablet formulation

Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)
Gabapentin	200mg	200mg	200mg	200mg	200mg
<i>Hibiscus Rosa- Sinensis</i> leaves mucilage	20	40	60	80	100
Micro crystalline cellulose	275	255	235	215	195
Magnesium stearate	5	5	5	5	5
Total weight of tablet	500	500	500	500	500

Preformulation Study

Fourier Transform Infra- Red Spectroscopy

The compatibility of Gabapentin with selected polymers was investigated using FT-IR spectrophotometer. The FT-IR analysis was carried out on the pure drug, drug-polymer combinations, and formulations. The sample was prepared in KBr discs (2 mg sample in 200 mg KBr discs) and analyzed with a shimadzu Fourier transform infrared spectrometer. The Gabapentin and formulations were scanned over a frequency range 4000-400 cm⁻¹

Evaluation of pre formulation study

Formulation blends were assessed for all pre compression parameters like angle of repose, bulk density, tapped density, hausner's ratio and compressibility index Carr's index. All procedures described in pharmacopoeias were used to determine the flow characteristics of granules. [15]

Post compression parameters

Weight variation

The weight variation of all prepared tablets was assessed according to the USP XXIV monograph. The weight variations among tablets were measured using twenty tablets from each batch, and the mean and standard deviation were computed.

Friability

The USP XXIV monograph was utilized to assess the friability of tablets from all batches. The Roche Friabilator was used to perform the friability testing. Twenty tablets from each batch were placed in Roche Friabilator which rotates at a speed of 25 rpm for 4 min. The tablets were taken out, de-dusted and reweighed. Weight loss of less than 1% is generally considered as acceptable. The loss of friability of the tablets in percentage was calculated by using the formula mentioned below

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Hardness

The hardness of tablet of each batch was measured by Monsanto hardness tester. For all batches, the test was performed in triplicate according to the USP XXIV monograph.

Thickness

The matrix tablets thickness was measured with a digital vernier caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan).It was calculated by measuring the thickness of ten tablets from each

formulation. The extent to which thickness of each tablet deviated from $\pm 5\%$ of the standard value was calculated.

In - Vitro Release Studies

In-vitro drug release studies of Gabapentin from the designed tablets were performed using USP dissolution apparatus type II (Electro lab, Mumbai, India) at 50 rpm. The dissolution medium consists of 900ml of phosphate buffer (pH 6.8) kept at 37 ± 0.5 °C for 12 hrs (720 min). At regular intervals, 5 ml samples were taken from the dissolution medium and replaced immediately with freshly prepared medium to maintain the sink conditions. After filtration and suitable diluted samples were analyzed by UV spectrophotometer (UV-1800, Shimadzu, Japan) at the 217nm, the study was performed. The data presented here is for triplicate assessment (n=3)

Release kinetics

There are various kinetic models that describe the overall drug release from dosage forms. To elucidate the release rate and its mechanism, model dependent methods such as zero, first order, Higuchi, and Peppas were investigated [16]. The *in-vitro* release profiles obtained for all formulations were plotted in the following data treatment modes

Zero-order

Cumulative percentage drugs releases versus Time. If the release follows zero order release kinetics, a plot of the fraction of drug released versus time will be linear.

$$Q = K_0 t$$

Where,

Q = Fraction of drug released at time 't',

K_0 = Zero order release rate constant

First order release kinetics

Log cumulative percent drug remaining versus Time if the plot is linear, the data obeys zero order kinetics)

$$\ln(1 - Q) = -K_1 t$$

Where,

Q = represents the fraction of drug released at time 't',

K_1 = First order release rate constant

Higuchi's (cumulative percentage of drug released versus square root of time, if the plot is linear then data obeys diffusion mechanism)

C-H Stretching (3000-2850)	2929.67	2860.24	2860.24- 2966.31	2860.24- 2927.24	2860.24- 2966.31	2860.24- 2966.27
N-H Stretching (910-665)	889.12- 707.83	891.05- 669.25	891.12- 669.25	889.12- 669.25	891.05- 669.25	891.05- 669.25
C-O Stretching (1320-1000)	1238.21- 1020.27	1299.93- 033.77	1299.99- 1020.27	1299.92- 1033.77	1299.93- 1033.77	1299.93- 1259.43

Table 2: Pre Compression Studies on Evaluation of Granule

Angle of repose, bulk density, tapped density compressibility index, and Hausner ratio were determined in granules from various proposed formulations (F1 to F5) (**Table 3**). The bulk density ranged from 0.35 ± 0.07 – 0.51 ± 0.05 gm/ml and tapped density range from 0.42 ± 0.02 – 0.58 ± 0.09 g/cm³ indicating free flowing. The angle of repose results shows good flow in the range of 25.3 ± 0.76 – 32.80 ± 0.51 . The compressibility index (%) ranged from 12.51 ± 0.12 – 13.58 ± 0.10 . Compressibility index values of up to 15% result in good flow properties.

Evaluation of Tablet

The tablets' hardness, friability, thickness, weight variation, and content homogeneity were evaluated (**Table 4**). All formulations' weight variations were found to be within the acceptable pharmacopoeia limit of 5%. The thickness of the tablet was measured to be between 4.15 ± 0.04 and 4.93 ± 0.06 mm. The hardness of the tablets was determined to be range from 6.32 0.22 and 7.39 0.36 Kg/cm², which is sufficient to withstand mechanical shocks during manufacturing. The results showed that increasing polymer concentration has no effect on the hardness of the tablets. The friability value of a tablet specifies its resistance to surface abrasion. The tablet's friability was found to be in the range of 0.12 ± 0.14 – 0.35 ± 0.22 percent. For better resistance, the value of friability must be less than 1%.

In-Vitro Drug Release

In *in-vitro* release study, the cumulative percentage of drug release from Gabapentin sustained release matrix tablet of all formulation F1-F5 shows 91.24%, 80.24%, 70.53%, 62.12% and 49.83% respectively, The dissolution studies of matrix tablet formulation F1 have shown 91.24% of drug release at the end of 12 hours. But the *in-vitro* release of formulation F1 shows only within 12 hours in phosphate buffer pH (6.8). This indicated that *in-vitro* release pattern of the formulations prepared happened to be sustained in comparison to that of the other formulations. The release of the formulation F5 was prolonged than the other formulations. There are numerous approaches for creating sustained-release tablets such as erosion, permeation, and gradual dissolution with several designs [17].

The release of drug from matrices reduced as the concentration of matrix material increased in this investigation. This could be because the dissolution media takes a long time to penetrate the matrices. As a result, the initial drug release might be attributed to the drug's "burst" release on the tablet surface due to the drug particles present on the matrix system's surface. The *In-vitro* release profile for all developed matrix tablet formulations is represented in **Figure 3**.

***In-Vitro* Drug Release Kinetic Model Profile**

The data from all five formulations was fitted into several kinetic models to analyse the drug release mechanism. **Table 5** shows the findings of the kinetic models. The F5 formulation has a maximum sustained drug release of 49.83 percent at the end of 12 hours, as evidenced by the results. The regression coefficient (R²) values for Zero order, First order, Higuchi's, and Peppas plots for formulation F5 were found to be 0.9855, 0.9855, 0.8822, and 0.9761, respectively, indicating that drug release was mostly controlled by diffusion.

The Korsmeyer–Peppas equation was used to calculate the mechanism of drug release. The n value of optimized formulation F5 was found to be more than 0.5. The formulation F5 indicates that the drug release depends on swelling, diffusion, and erosion, approximates the result of the data non-fickian or anomalous type of diffusion.

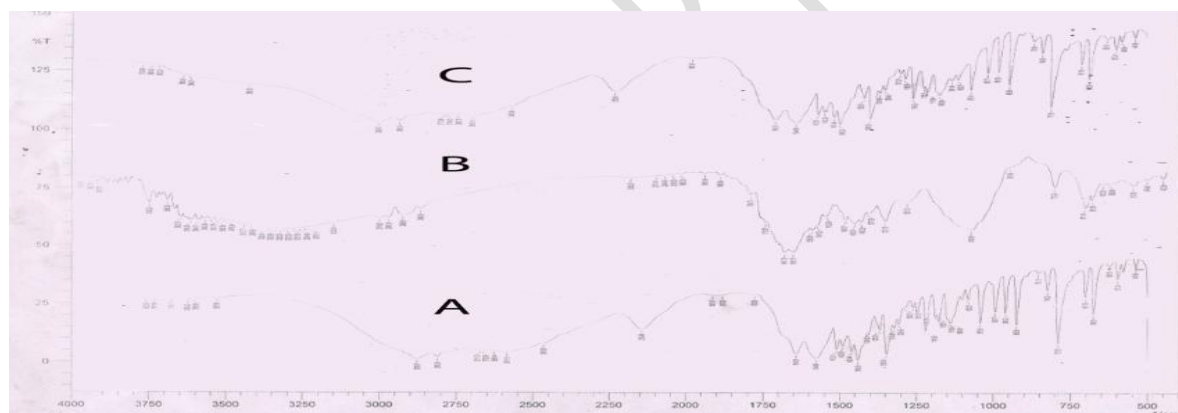


Figure -1 FT-IR Spectroscopy of Gabapentin A, Polymer B and Gabapentin+ Polymer C

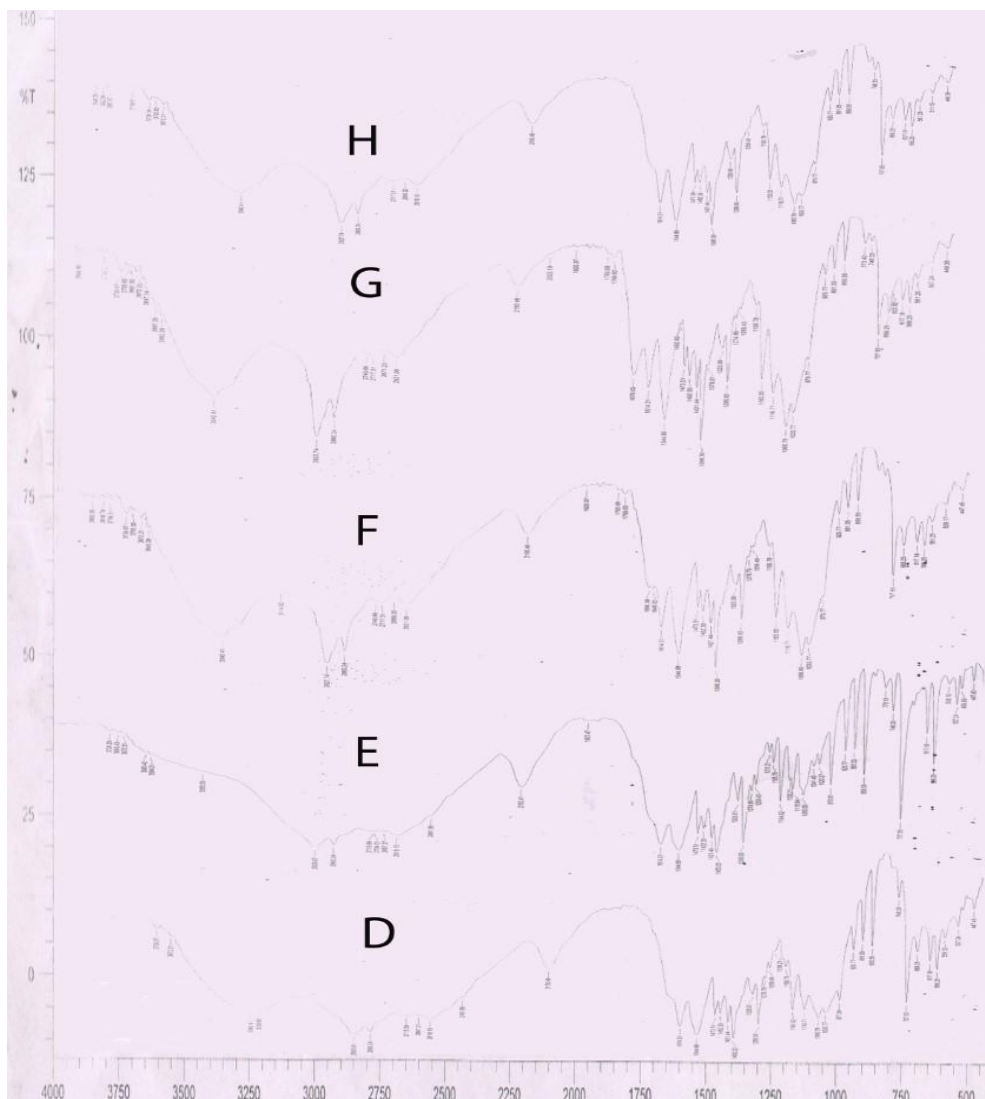


Figure:2 FT-IR Spectroscopy of formulation F1- F5.(D- F1, E- F2, F- F3, G-F4 and H -F5

Table.3: Pre-compression evaluation on granules.

Formulation	Bulk density (Gm/cm ³)	Tapped density Gm/ml	Compressibility Index*	Hausner Ratio*	Angle of Repose(Θ)
F1	0.45±0.09	0.52±0.08	12.50±0.12	1.13±0.04	32.8±0.51
F2	0.50±0.07	0.58±0.09	13.36±0.09	1.10±0.05	30.1±0.42
F3	0.51±0.05	0.57±0.06	13.46±0.07	1.16±0.07	31.4±0.71
F4	0.40±0.03	0.46±0.07	13.58±0.10	1.14±0.09	28.9±0.69
F5	0.355±0.07	0.42±0.02	13.26±0.12	1.18±0.05	25.3±0.76

Table.4: Post compression evaluation on formulated matrix tablet.

Formulation	Weight variation (gm [*])	Hardness (kg/cm ^{2*})	Thickness(mm ^{*)})	Friability (% [*])
F1	500 ± 0.06	7.39 ± 0.36	4.42 ± 0.06	0.12 ± 0.14
F2	501 ± 0.04	7.10 ± 0.58	4.15 ± 0.04	0.28 ± 0.11
F3	500 ± 0.07	7.55 ± 0.63	4.59 ± 0.07	0.29 ± 0.12
F4	500 ± 0.03	6.32 ± 0.22	4.64 ± 0.03	0.25 ± 0.17
F5	500 ± 0.06	6.44 ± 0.12	4.93 ± 0.06	0.35 ± 0.22

*Mean ± S .D. (n=3)

Figure.3: *In-vitro* release of Gabapentin and all formulation F1-F5

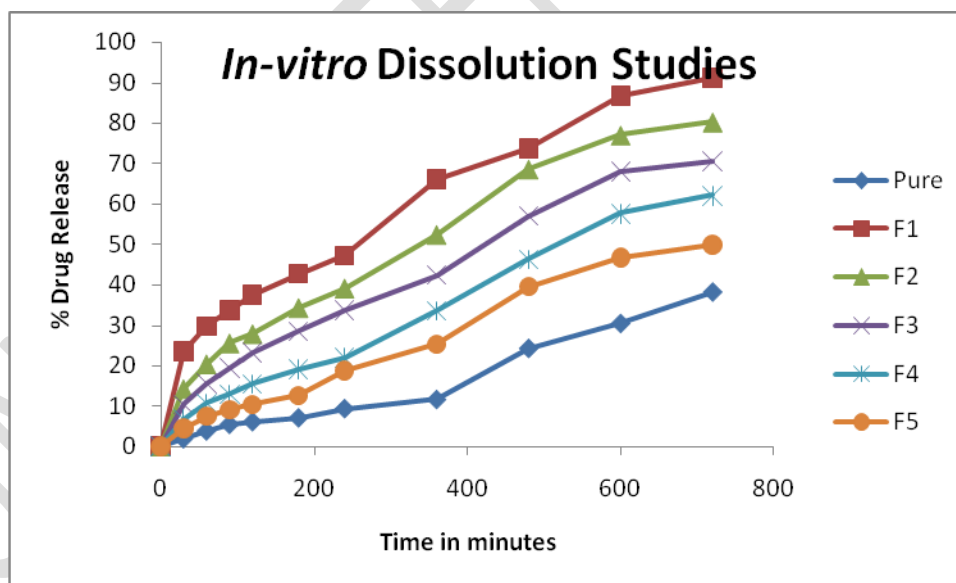


Table.5: *In-vitro* drug release kinetic profile of Gabapentin formulations.

S.No	Formulation	Zero order reaction(r^2)	First order reaction(r^2)	Higuchi diffusion (r^2)	Korsemeyer peppas	
					(r^2)	n Values
1	F1	0.9846	0.9846	0.9318	0.9753	0.441
2	F2	0.9807	0.9807	0.9341	0.9897	0.558
3	F3	0.9855	0.9855	0.9312	0.9741	0.613
4	F4	0.9922	0.9922	0.8931	0.9805	0.706
5	F5	0.9855	0.9855	0.8822	0.9761	0.781

Conclusion

The present investigation formulated Gabapentin sustained release matrix tablet by wet granulation technique using *Hibiscus rosa-sinensis* leaves mucilage. Pre and post compression studies were compared. It was observed that all the formulations were as per I.P. specification limits. FTIR is used to assess drug-excipient interactions. Gabapentin was confirmed to be compatible with all excipients included in the formulation during the drug-polymer interaction study. Based on the above results and discussion, it is concluded that this study was achieved by enhanced solubility of Gabapentin and maintain the drug therapeutic level for prolonged period by the formulated sustained release matrix tablet using natural mucilage polymer extracted from *Hibiscus rosa-sinensis* leaves as a release retardant. The study has successfully shown that the natural gum may be potential polymer for the preparation of matrix tablets for achieving desired drug release pattern.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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