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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF RIOCIGUAT BY USING DIFFERENT POLYMERS

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Abstract:
The present study was aimed at the formulation and evaluation of sustained release (SR) matrix tablets of Riociguat using different polymers to prolong drug release and enhance therapeutic efficacy. Riociguat, a soluble guanylate cyclase stimulator indicated for pulmonary hypertension, requires controlled drug delivery to maintain steady plasma concentrations over an extended period. Sustained release matrix tablets were prepared by direct compression method employing various polymers such as Sodium alginate, Chitosan, and HPMC K15M in different ratios to modulate the drug release profile.
A total of nine formulations (F1–F9) were developed and evaluated for pre-compression and post-compression parameters. The pre-compression parameters including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio indicated good flow properties of the powder blend, all within Indian Pharmacopoeia (IP) limits. The post-compression parameters such as weight variation, hardness, thickness, friability, and drug content were found to be within acceptable IP limits, confirming the suitability of the formulation process.
In vitro dissolution studies were carried out for 12 hours to assess the drug release profile of all formulations. Among the nine formulations, F2 was considered the optimized formulation as it exhibited a sustained and controlled drug release of 99.58% over 12 hours. The release kinetics suggested that the drug release followed a diffusion-controlled mechanism with polymer matrix swelling contributing to sustained action.
The study concludes that sustained release matrix tablets of Riociguat can be successfully formulated using Sodium alginate, Chitosan, and HPMC K15M, and the optimized formulation (F2) demonstrated desirable physicochemical characteristics and extended drug release, making it a promising candidate for once-daily sustained release therapy.
Keywords: *Riociguat sustained Release Tablets, Sodium alginate, Chitosan, and HPMC K15M*

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INTRODUCTION:

A Sustained Release dosage form is engineered to release the active pharmaceutical ingredient (API) slowly and continuously over an extended period of time after a single administration.

This specialized release profile contrasts sharply with conventional dosage forms, which typically release the drug rapidly leading to quick, sharp peaks and troughs in the drug's concentration in the bloodstream.[1]

- The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes.
- The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[2]
- The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the pharmaceutical industry for some time.
- The desire to maintain a near constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.
- Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained or controlled release drug delivery systems.[3]
- Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. The goal of an extended release dosage form is to maintain therapeutic drug level in plasma for extended period of time.
- Sustained release systems are particularly beneficial for chronic diseases requiring long-term medication, such as hypertension, diabetes, arthritis, and psychiatric disorders. By reducing the frequency of administration, improving pharmacokinetic predictability, and minimizing adverse effects, these systems significantly enhance the therapeutic index of many drugs.
- The development of polymers, micro/nanocarriers, biodegradable matrices, and osmotic pumps has revolutionized the field, offering more precise control of drug release.[4]
- Sustained Release Drug Delivery Systems (SRDDS) represent an advanced approach in pharmaceutical technology aimed at controlling the release profile of therapeutic agents for extended periods. Conventional immediate-release dosage forms produce rapid drug absorption that often leads to fluctuations in plasma concentration, resulting in peaks (which may cause toxicity) and troughs (sub-therapeutic levels).
- Sustained release formulations are designed specifically to maintain a steady-state concentration within the therapeutic window for prolonged durations, thereby improving treatment efficacy and patient compliance.
- One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix.
- Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system is successful in maintaining constant drug levels in the blood or target tissue it is considered as controlled release system.
- If it is unsuccessful at this but nevertheless extends the duration of action over that achieved by conventional delivery, it is considered a prolonged release system. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design.[5]
- The design of oral sustained release delivery systems is subject to several inter related variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug.
- Sustained release dosage forms are made to release medicine at a given rate while keeping the drug level constant for a defined period of time with the minimal adverse effects possible. The fundamental concept behind sustained-release drug delivery systems is to improve the patient's compliance though increasing the bioavailability and effectiveness of the medicines.

- Sustained release with the introduction of extended release matrix tablet have proved to be an effective tool to control the release of drug without involving the complex production procedures. Through localising the drug to the site of action lowering the dosage needed, and ensuring uniform drug distribution, sustained or controlled delivery systems aim to boost drug effectiveness or decrease the frequency of dosing.
- Numerous sustain release oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed. Intense research has recently focused on the designation of SR systems for poorly water soluble drugs.
- However, designing such a system necessitates a number of factors, among which the half-life and pharmacological effect of the drug play an important role. Therefore, taking into account the shortcomings of the standard drug delivery system, the sustained release.

Concept of Sustained Release.[6]
Sustained release (SR) refers to a dosage form designed to release a drug slowly over an extended period. Unlike controlled release which implies precise, constant or zero-order kinetics sustained release mainly focuses on prolonging the release duration compared with conventional dosage forms.

In sustained release systems:

- The drug does not release immediately.
- A portion may release initially (loading dose), followed by slow release (maintenance dose).
- Release rate may be influenced by drug solubility, polymer characteristics, diffusion, erosion, and osmotic mechanisms.

The primary goal of sustained release tablets is to achieve prolonged therapeutic action while minimizing dose frequency.

The Primary Goals of SR Formulations.[7,8]
The rationale behind developing SR formulations is to improve the overall effectiveness, safety, and convenience of drug therapy. The main objectives are:

1. **Maintain Consistent Drug Levels:** To keep the drug concentration in the plasma (bloodstream) within the therapeutic window for a longer duration. This minimizes the risk of:
    - **Drug Toxicity:** Avoiding high peaks that exceed the Minimum Toxic Concentration (MTC).
    - **Therapeutic Failure:** Preventing low troughs that drop below the Minimum Effective Concentration (MEC).
2. **Reduce Dosing Frequency:** SR formulations often allow for once or twice-daily dosing, as opposed to multiple daily doses required by conventional forms.[9]
3. **Improve Patient Compliance:** Less frequent dosing makes it easier for patients, especially those with chronic conditions, to stick to their medication schedule.
4. **Enhance Safety and Efficacy:** By smoothing out fluctuations in drug levels, the drug works more consistently and may reduce the intensity of local or systemic side effects.[10]

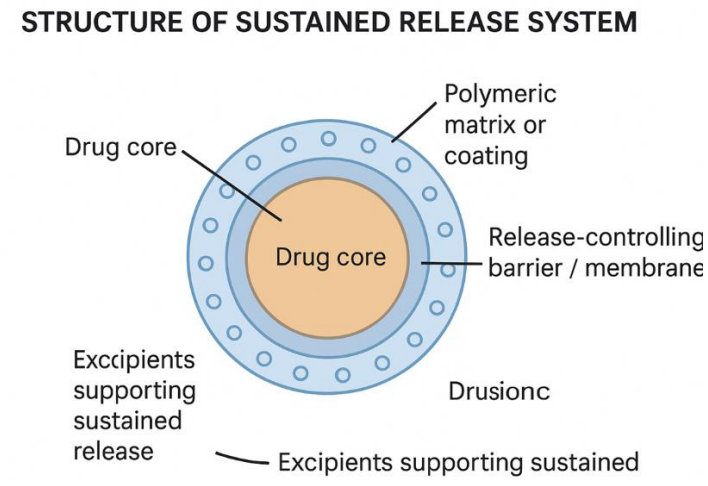


Figure No 1.1 : Structure of Sustained Release System

Structure and Mechanism.[11]
SR is achieved by modifying the physicochemical properties of the dosage form itself. The two primary structural approaches are:

Sustained release systems are designed with specific structural elements that control drug release over an extended period.

- **Matrix Systems:** The drug is embedded within a slowly dissolving or non-dissolving core material (a matrix, often a polymer or wax). The drug release is controlled by diffusion through the matrix or by the slow erosion of the matrix.[12]
- **Reservoir/Coated Systems:** The drug forms a core that is surrounded by a rate-controlling membrane or coating. The drug diffuses out of the core through this coating at a predetermined rate.

Sustained release formulations are a crucial tool in modern medicine, particularly for managing chronic diseases where a stable, long-lasting therapeutic effect is desired.

METHODOLOGY:

Analytical method development:

Determination of Wavelength:
10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve:
10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters
The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:
The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r$$

Tan θ = Angle of repose
h = Height of the cone ,
r = Radius of the cone base

Table 7.1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:
Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The

powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.
The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density:
After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where, Tap= Tapped Density
M = Weight of sample
V= Tapped volume of powder

Measures of powder compressibility:
The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticle interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density
Tap = Tapped Density

INGREDIENTS	FORMULATION CODE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Riociguat	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium alginate	10	20	30	-	-	-	-	-	-
Chitosan	-	-	-	10	20	30	-	-	-
HPMC K 15 M	-	-	-	-	-	-	10	20	30
PVP K 30	5	5	5	5	5	5	5	5	5
Lactose	78.5	68.5	58.5	78.5	68.5	58.5	78.5	68.5	58.5
Magnesium sterate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100

Table 7.2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Table 7. 3: Formulation composition for tablets

Formulation development of Tablets:
All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3. The tablets were prepared as per the procedure given below and aim is to prolong the release of Riociguat. Total weight of the tablet was considered as 100mg.

Procedure:

1) Riociguat and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

All the quantities were in mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets

were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table 7.4: Pharmacopoeial specifications for tablet weight variation

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness:
Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:
Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:
It is measured of mechanical strength of tablets. Roche Friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the Friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets
W2 = Weight of the three tablets after testing

Determination of drug content:
Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Dissolution parameters:

Apparatus -- USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl, p H 6.8 Phosphate buffer
RPM -- 50
Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,9,10,11,12
Temperature -- 37°c ± 0.5°c

Procedure:
900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl were removed and pH 6.8 phosphate buffer was added process was continued up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at required wavelength using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:
Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics:
To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log (100-F)} = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.
In Higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:
The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\ t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for super case II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$$(100\text{-}Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.
Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:
The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm^{-1} to 400cm^{-1}.

RESULTS AND DISCUSSION:

The present study was aimed to developing sustained release tablets of Riociguat using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method
Graphs of Riociguat were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 252 nm and 256 nm respectively.

Table 8.1: Observations for graph of Riociguat in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.122
10	0.231
15	0.342
20	0.456
25	0.573

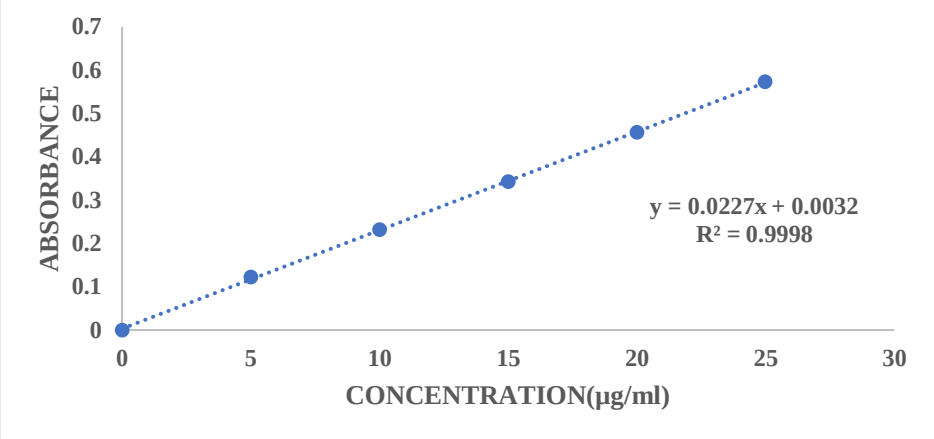


Fig 8.1: Standard curve of Riociguat

Table 8.2: Standard graph values of Riociguat at 256 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.141
10	0.281
15	0.418
20	0.553
25	0.682

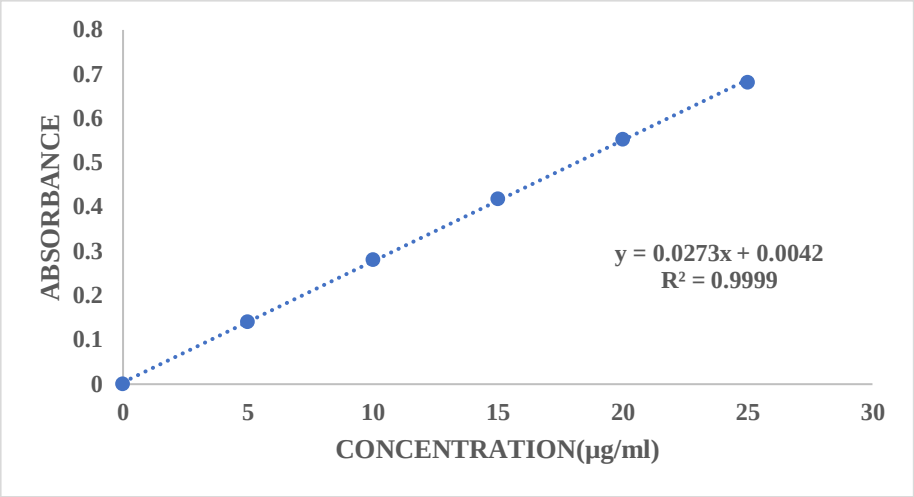


Fig 8.2: Standard curve of Riociguat

Preformulation parameters of powder blend

Table 8.3: Pre-formulation parameters of Core blend

Formulation code	Angle of repose (Θ)	Bulk density (gm/cm^3	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	26.45	0.54	0.65	16.92	1.2
F2	25.12	0.48	0.57	15.78	1.18
F3	27.08	0.58	0.69	15.94	1.18
F4	28.12	0.56	0.66	15.15	1.17
F5	25.24	0.53	0.65	18.46	1.22
F6	25.33	0.54	0.64	15.62	1.18
F7	27.7	0.52	0.64	18.75	1.23
F8	26.8	0.56	0.67	16.41	1.19
F9	25.01	0.49	0.57	14.03	1.16

All the values represent n=3

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range showing that the powder has good flow properties. The tapped density of all the formulations powders has good flow properties. The compressibility index of all the formulations was found to be below 10.30 which show that the powder has good flow properties. All the formulations have shown the Hausner ratio below 1.21 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression tablet.

Table 8.4: *In vitro* quality control parameters for tablets

Formulation codes	Average Weight (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	99.73	2.24	0.26	1.98	98.35
F2	100.62	2.19	0.12	1.86	99.46
F3	101.44	2.31	0.23	1.92	99.86
F4	98.26	2.28	0.19	1.95	97.51
F5	97.43	2.33	0.31	1.89	98.62
F6	99.88	2.26	0.28	1.92	98.88
F7	99.73	2.22	0.43	2.01	99.73
F8	98.49	2.25	0.29	1.98	97.29
F9	96.52	2.27	0.25	2.13	99.73

Weight variation test:
Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 97.43 to 101.44 mg, so the permissible limit is ±7.5% (>100 mg). The results of the test showed that, the tablet weights were within limit.

Hardness test:
Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 2.19 to 2.31 kg/cm^2, which was within IP limits.

Thickness:
Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 1.86 to 2.13 mm.

Friability:
Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content:
Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 97.29 -99.86%.
All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table 8.5: Dissolution Data of Riociguat Tablets

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	10.24	12.83	9.53	11.27	13.63	15.63	9.88	12.64	16.72
2	17.08	21.97	17.75	19.11	21.44	19.22	15.62	16.14	24.22
3	24.26	27.88	31.62	29.18	27.38	25.59	26.54	23.38	36.63
4	31.46	41.17	36.53	35.64	39.76	36.17	39.83	33.75	43.27
5	39.57	48.73	48.18	43.86	46.66	48.38	43.38	42.12	54.76
6	46.22	53.32	58.92	53.34	58.53	55.97	47.63	49.53	59.14
7	56.12	59.68	65.75	59.68	66.92	69.07	58.65	62.88	64.54
8	59.77	66.22	73.96	64.55	73.24	78.24	62.92	67.93	68.28
9	67.58	75.15	79.83	74.35	79.64	84.34	69.43	74.64	74.11
10	73.82	79.99	88.68	79.76	83.57	89.77	77.86	83.27	83.92
11	84.36	88.72	92.12	83.28	88.76	92.58	83.93	91.73	88.37
12	93.26	99.58	95.58	92.08	96.13	98.13	93.72	97.62	94.28

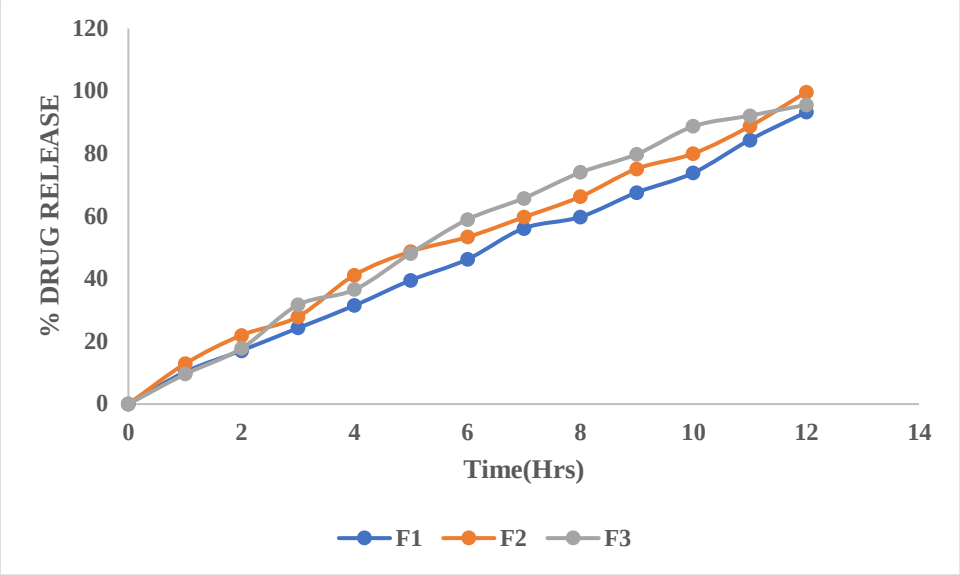


Fig: 8.3: Dissolution profile of Riociguat (F1, F2, F3 formulations)

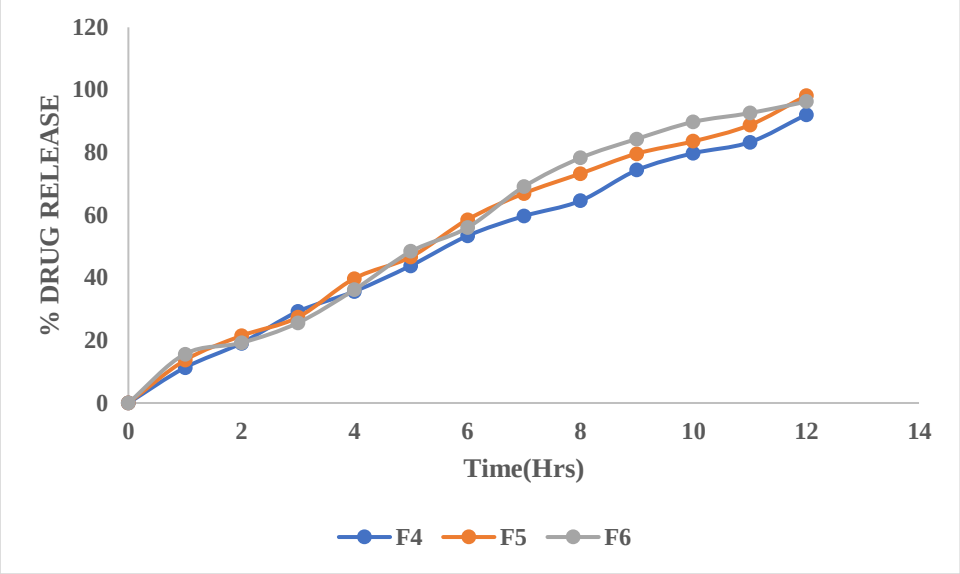


Fig: 8.4: Dissolution profile of Riociguat (F4, F5, F6 formulations)

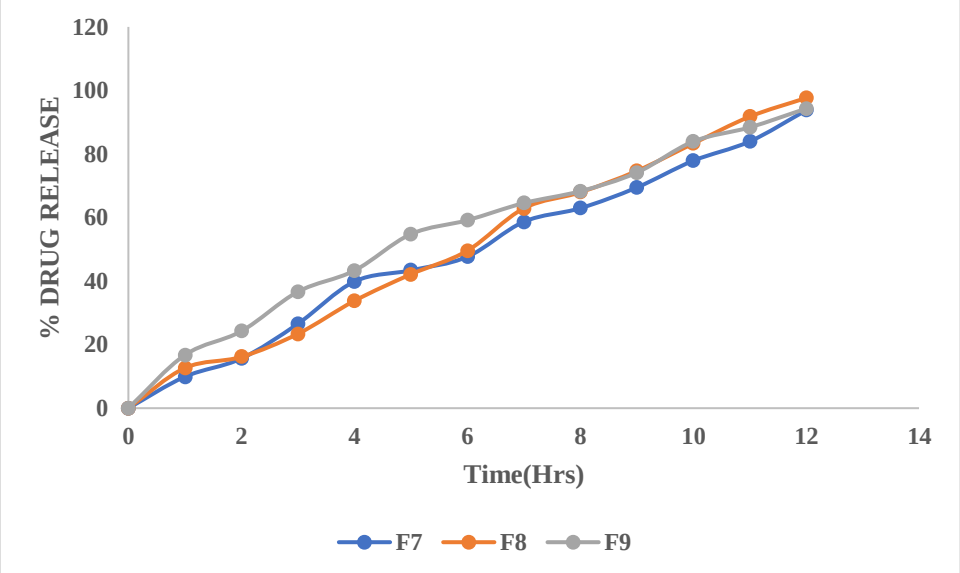


Fig 8.5: Dissolution profile of Riociguat (F7, F8, F9 formulations)

Formulations prepared with Sodium alginate retarded the drug release in the concentration of 20 mg (F2 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 99.58% in 12 hours with good retardation.

Formulations prepared with Chitosan retarded the drug release in the concentration of 12 mg (F6 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 98.13 % in 12 hours with good retardation.

Formulations prepared with HPMC K 15 M retarded the drug release in the concentration of 12 mg (F7Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 97.62 % in 12 hours with good retardation.

Finally Concluded that F2 formulation was considered as optimized formulation.

Table: 8.8: Release Kinetics:

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	%) REL	LOG (T	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0	0	0	0	0	0	0	0	0	0	0
12.83	1	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.000
21.97	2	1.414	1.342	0.301	1.892	10.985	0.0455	-0.658	78.03	4.642	4.273	0.368
27.88	3	1.732	1.445	0.477	1.858	9.293	0.0359	-0.555	72.12	4.642	4.162	0.479
41.17	4	2.000	1.615	0.602	1.770	10.293	0.0243	-0.385	58.83	4.642	3.889	0.752
48.73	5	2.236	1.688	0.699	1.710	9.746	0.0205	-0.312	51.27	4.642	3.715	0.927
53.32	6	2.449	1.727	0.778	1.669	8.887	0.0188	-0.273	46.68	4.642	3.601	1.041
59.68	7	2.646	1.776	0.845	0.423	8.526	0.0168	-0.224	40.32	4.642	3.429	1.213
66.22	8	2.828	1.821	0.903	0.452	8.278	0.0151	-0.179	33.78	4.642	3.233	1.409
75.15	9	3.000	1.876	0.954	0.477	8.350	0.0133	-0.124	24.85	4.642	2.918	1.723
79.99	10	3.162	1.903	1.000	0.500	7.999	0.0125	-0.097	20.01	4.642	2.715	1.927
88.72	11	3.317	1.948	1.041	0.521	8.065	0.0113	-0.052	11.28	4.642	2.243	2.399
99.58	12	3.464	1.998	1.079	0.540	8.298	0.0100	-0.002	0.42	4.642	0.749	3.893

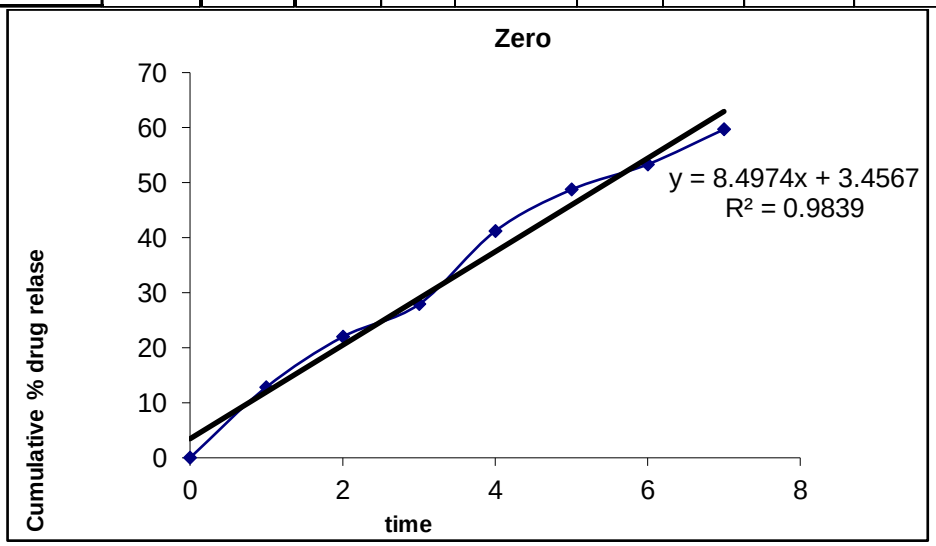


Figure :8.6: Zero order release kinetics graph

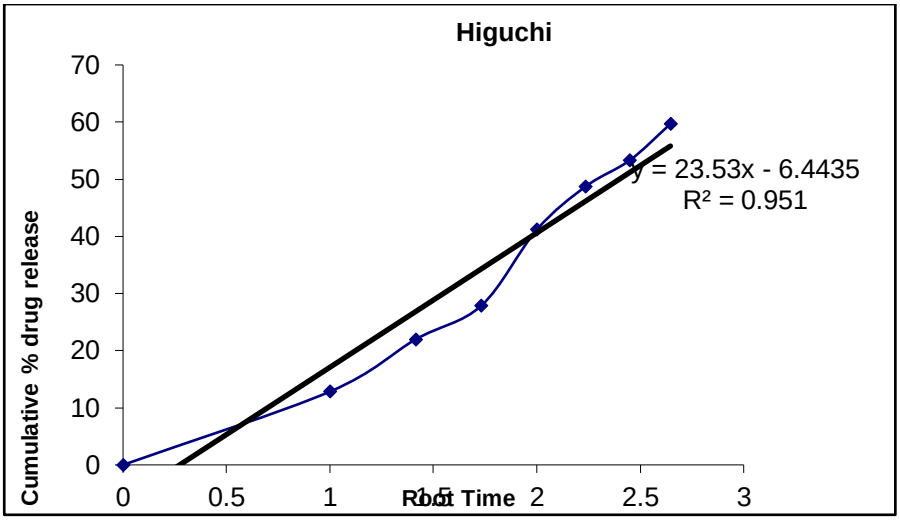


Figure :8.7: Higuchi release kinetics graph

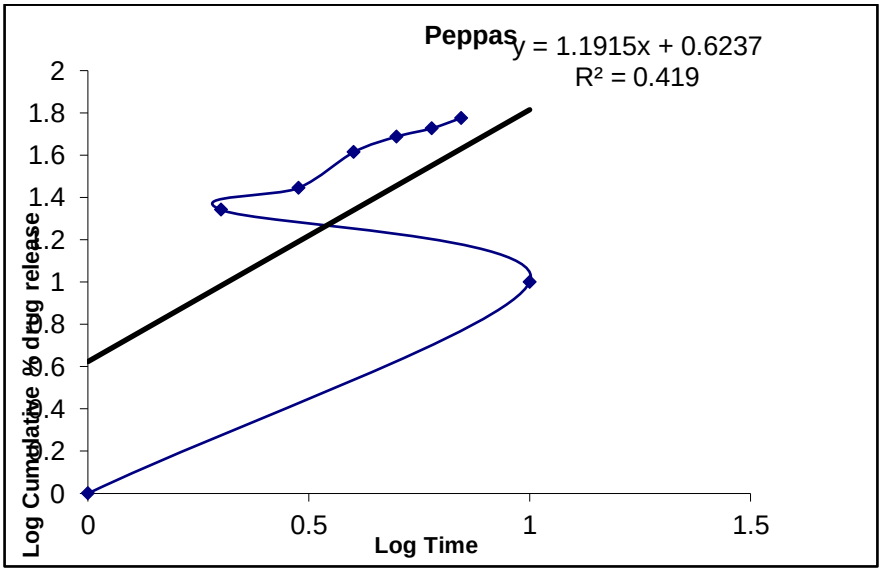


Figure :8.8: Peppas release kinetics graph

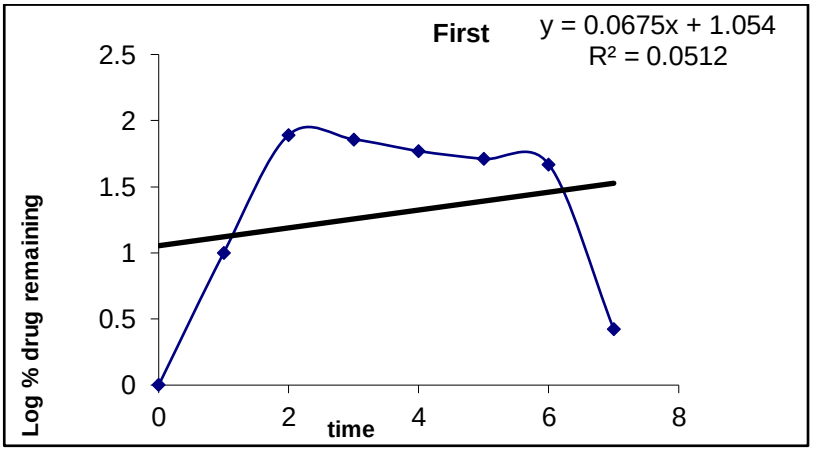


Figure 8.9: First order release kinetics graph

From the above graphs it was evident that the formulation F5 was followed Zero order release mechanism.

Drug – Excipient compatibility studies

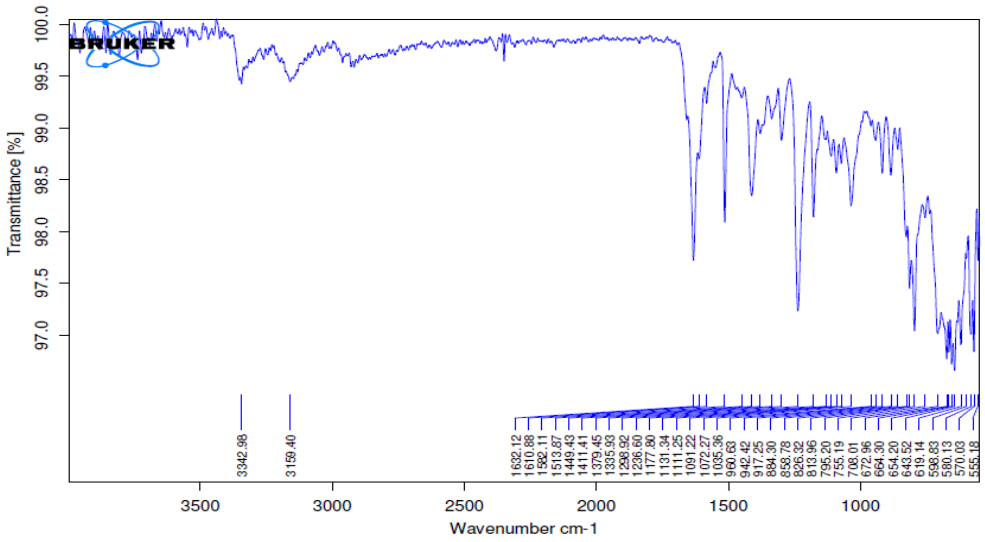


Figure: 8.10: FT-TR Spectrum of Riociguat pure drug

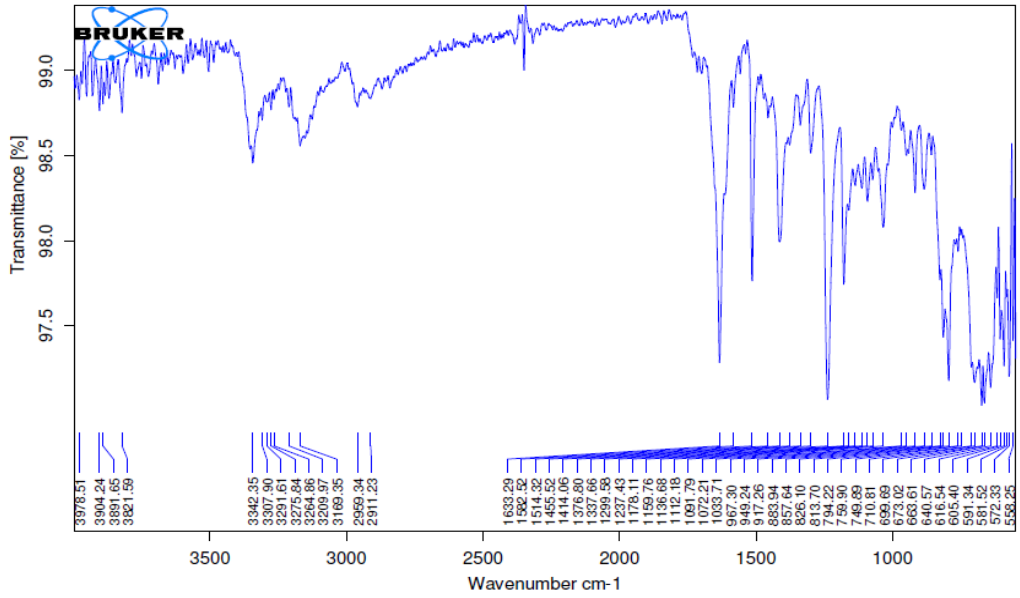


Figure: 8.11: FT-IR Spectrum of Optimized Formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Riociguat are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

CONCLUSION:

The present study on the formulation and evaluation of sustained-release matrix tablets of Riociguat demonstrated that the use of hydrophilic polymers such as sodium alginate, chitosan, and HPMC K15M is effective in developing controlled drug-delivery systems. Matrix tablets prepared by appropriate formulation techniques exhibited satisfactory physicochemical characteristics.

All pre-compression parameters (angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio) indicated good flow and compressibility of the powder blends, confirming suitability for tablet compression. Similarly, post-compression parameters including weight variation, hardness, friability, thickness, and drug content were found to be within Indian Pharmacopoeial (IP) limits, demonstrating acceptable tablet quality and mechanical integrity.

In vitro dissolution studies revealed that polymer type and concentration significantly influenced the drug-release profile. Among the polymers studied, HPMC K15M provided a more uniform and prolonged release, while sodium alginate and

chitosan contributed to controlled swelling and gel formation, collectively aiding sustained drug release over an extended period.

Overall, the optimized formulation successfully achieved sustained release of Riociguat with desirable tablet characteristics, indicating that a polymeric matrix approach using sodium alginate, chitosan, and HPMC K15M is a promising strategy for improving therapeutic efficacy, reducing dosing frequency, and enhancing patient compliance.

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