Formulation And In Vitro Evaluation of Daridorexant Sustained Release Tablet

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***Abstract*—The present study was aimed at the development and evaluation of sustained-release matrix tablets of Daridorexant using natural hydrophilic polymers, namely sodium alginate and tragacanth, by the direct compression method. Daridorexant, a dual orexin receptor antagonist used for the treatment of insomnia, possesses favourable pharmacokinetic properties that make it a suitable candidate for sustained-release drug delivery. FTIR studies confirmed the compatibility of Daridorexant with the selected excipients, indicating the absence of significant drug–excipient interactions. Eight formulations (F1–F8) were prepared using varying concentrations of sodium alginate and tragacanth. The compressed tablets were evaluated for post-compression parameters such as weight variation, thickness, hardness, friability, drug content, and disintegration time. All formulations complied with acceptable quality standards for tablet evaluation. In-vitro dissolution studies demonstrated sustained drug release over an 8-hour period. Among all formulations, F7 exhibited the most desirable release profile with 98.68% cumulative drug release at the end of 8 hours, along with satisfactory hardness (3.60 kg/cm²), drug content (95.58%), and the shortest disintegration time (13 minutes). Drug release kinetic analysis revealed that the optimized formulation followed Zero-order kinetics (R^2 = 0.978) and closely fitted the Higuchi diffusion model (R^2 = 0.975), indicating diffusion-controlled drug release from the hydrated polymer matrix. Stability studies conducted under long-term and accelerated storage conditions for three months showed no significant changes in the dissolution profile, confirming the stability of the optimized formulation. In conclusion, the study demonstrated that sustained-release matrix tablets of Daridorexant can be successfully formulated using sodium alginate and tragacanth. The optimized formulation F7 provided controlled drug release, satisfactory physicochemical characteristics, and excellent stability, suggesting its potential as a once-daily sustained-release dosage form for the effective management of insomnia.**

***Index Terms*—Daridorexant, Natural polymers, FTIR Studies, Direct compression method, In vitro drug release studies**

I. INTRODUCTION

Sustained release matrix tablets are among the most widely used controlled drug delivery systems because of their simplicity of formulation, cost-effectiveness, ease of manufacturing, and reproducible drug release characteristics. These systems generally employ hydrophilic or hydrophobic polymers that regulate drug diffusion and matrix erosion, thereby extending drug release over an extended period.[1] The successful development of sustained release formulations depends on careful optimization of formulation variables, including polymer type, polymer concentration, drug-to-polymer ratio, binder concentration, and compression characteristics.[2] Daridorexant is a novel dual orexin receptor antagonist (DORA) approved for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and sleep maintenance. It selectively blocks orexin receptor type 1 (OX1R) and orexin receptor type 2 (OX2R), thereby suppressing wake-promoting signaling pathways in the central nervous system without significantly altering the normal architecture of sleep.[3] The prepared formulations were evaluated for their physicochemical properties, including hardness, friability, weight variation, thickness, drug content, and in vitro dissolution profile.[4] Drug release data were further analyzed using various kinetic models to elucidate the mechanism of drug release.

The optimized formulation was identified based on its sustained drug release characteristics, satisfactory tablet quality attributes, and stability, with the ultimate objective of developing an effective once-daily oral dosage form capable of improving therapeutic efficacy, patient adherence, and long-term management of insomnia.[5]

II. MATERIALS

Daridorexant was procured from Hetero labs, HYD. Sodium alginate and Tragacanth were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

III. METHODOLOGY

Formulation Development

Table-1: Formulation of SR Tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
1	Daridorexant	25	25	25	25	25	25	25	25
2	Sodium alginate	25	50	75	100	-	-	-	-
3	Tragacanth	-	-	-	-	25	50	75	100
4	MCC	20	20	20	20	20	20	20	20
5	Lactose	125	100	75	50	125	100	75	50
6	Magnesium stearate	3	3	3	3	3	3	3	3
7	Talc	2	2	2	2	2	2	2	2
8	Total Wt.	200	200	200	200	200	200	200	200

Preparation method

Daridorexant sustained release tablets were prepared by direct compression method as per the formulae given in Table. All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were compressed into tablets on a tablet punching machine to a hardness of 6 kg/cm ^{2} using 8 mm concave punches.[6]

Characterization

Hardness

Hardness of all eight preliminary batches determined by Monsanto tester. From the six determinations, the average is considered as “hardness factor” [7]

Thickness

Thickness and diameter of tablets were accurately measured by using digital Vernier caliper for desired uniformity in size and shape. [8]

Uniformity of weight

All preliminary batches were evaluated for the weight variation test by individually weighing all the final twenty batches selected for the study. Weight obtained from the resolved tablet. Finally, individual and average weights were compared with each other. Differences in the case of percentage variation in weight ought to be between 7.5% of the acceptable limit. Finally determined the % deviation using the below formulae.[9]

Deviation (%) = Weight (individual) – Weight (average) x 100 Weight (average)

Friability test

Friability of batches (preliminary) was performed with Roche Fiabilator (Kumar Mfg. Ltd.). Combine weighed 10 tablets and placed inside the friability. Turned on the stabilator with the rate of 25 rpm. Tablets permitted rolling inside the friabilator, and coming about since free tablet falling inside the chamber. Following 100 revolutions per 4 minutes, samples were taken it out, and tablets intact were weighed again collectively. Allowed friability limit is 1.0 %. The friability in percent was resolved to utilize the below formulae. [10]

Friability = 100 X tablet weight (before weight) – tablet weight (after test) Tablet weight (before the test)

Drug content

Drug content of every single primer group is resolved to choose arbitrarily twenty tablets though effectively

determined normal of loads. Tablets crushed utilizing a mortar and exactly ordinary checked proportion of tablets, chose triturate for examination. Tests moved into different flagons though adequately weakened using pH 6.8 phosphate buffer. The substance was shaken well and put something aside for 30 minutes for dissolving the prescription completely. Mixes were isolated and weakenings were appropriately done. In each tablet, the substance of medication was assessed to 275 nm λmax close by looking at reference as a reference. [11]

In Vitro Disintegration Test

The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.**[12]**

In- Vitro Release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for remaining period of time. Temperature maintained at 37□1o C. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. The solution was filtered through Whattmann filter paper. The filtrate was analyzed by U.V. spectrophotometer (Labindia). The drug release was plotted against time to determine the release profile of various batches.[13]

Drug release kinetics[14]

To examine the release pattern from the tablets the release statistics were investigated using accompanying models of mathematics:

A. Kinetic (0 order)

$Q0 = Qt + k0t$

Whereas, the release of drug at the time (t) - Qt Constant for zero-order release - k0 Amount of drug present at t = 0 - Q0

B. Kinetics (1st order)

$\ln (100 – Q) = \ln Q0 – k1t$

Whereas, the release of drug at time t - Q Initially drug present - Q0 Constant of 1st order release - K1

C. Equation of Higuchi

$Q = kH\ t\ 1/2$

Whereas, drug release amount at t - Q, Dissolution constant of Higuchi - KH

D. Model of Korsmeyer - Peppas

$Q = kP\ i\ n$

Whereas,

KP is steady including geometric and structural attributes of the device of release. Mechanism of demonstrative release exponent 'n'.

Stability studies[15]

The success of an effective formulation can be evaluated only through stability studies. The prepared sustained release Matrix tablets of Daridorexant were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2oc and refrigerator 2-8oc for a period of 90 days.

IV. RESULTS AND DISCUSSION

Post compression parameters

Table-2: Evaluation parameters of Brivaracetam SR tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Disintegration time (min)
F1	200	4.10	3.26	0.75	88.93	29
F2	199	4.26	3.18	0.69	85.20	25
F3	201	4.13	3.50	0.63	86.39	22
F4	200	4.28	3.19	0.73	91.25	19
F5	199	4.40	3.20	0.71	89.81	16

F6	200	4.15	3.54	0.65	93.56	20
F7	200	4.42	3.60	0.78	95.58	13
F8	201	4.39	3.48	0.72	94.53	15

Discussion

Weight Variation

The weight variation test was performed to ensure uniformity of tablet weight and proper die filling during compression. The average tablet weight of all formulations (F1–F8) ranged from 199 to 201 mg, which was very close to the theoretical weight of 200 mg. The minimal variation observed among the formulations indicates good flow properties of the powder blend and uniform compression. All formulations complied with the acceptable pharmacopeial limits for weight variation, confirming the consistency of the manufacturing process.

Thickness

The thickness of the tablets ranged from 4.10 to 4.42 mm. Slight variations in thickness were observed due to differences in polymer concentration and compression behavior. Formulations containing higher concentrations of polymers, particularly F7 (4.42 mm) and F8 (4.39 mm), exhibited slightly greater thickness because of increased matrix formation during compression. However, all formulations showed acceptable dimensional uniformity, indicating proper die filling and consistent compression force.

Hardness

Tablet hardness ranged from 3.18 to 3.60 kg/cm², indicating adequate mechanical strength to withstand handling, packaging, and transportation. Formulation F7 exhibited the highest hardness (3.60 kg/cm²), whereas F2 showed the lowest hardness (3.18 kg/cm²). The increase in hardness observed in formulations containing higher polymer concentrations may be attributed to improved interparticle bonding and stronger matrix formation. Nevertheless, all formulations possessed sufficient hardness while maintaining acceptable disintegration characteristics.

Friability

The friability values varied between 0.63% and 0.78%, which are well below the pharmacopeial limit of 1%. This indicates that all formulations possessed adequate mechanical integrity and resistance to abrasion during handling. Formulation F3 exhibited the lowest friability (0.63%), indicating excellent resistance to mechanical stress, while F7 showed the highest friability (0.78%), although it remained within acceptable limits. These results demonstrate satisfactory tablet strength and durability.

Drug Content

The drug content of the formulations ranged from 85.20% to 95.58%. The highest drug content was observed in F7 (95.58%), followed by F8 (94.53%) and F6 (93.56%), indicating relatively better drug distribution within these formulations. The lower drug content observed in formulations F1–F5 may be attributed to non-uniform mixing, drug loss during processing, or analytical variations. Although F6–F8 approached the acceptable pharmacopeial range, the formulations with drug content below 90% would require further optimization to achieve complete dose uniformity.

Disintegration Time

The disintegration time of the tablets ranged from 13 to 29 minutes. Formulation F7 exhibited the shortest disintegration time (13 minutes), followed by F8 (15 minutes) and F5 (16 minutes), indicating faster tablet breakdown. In contrast, F1 showed the longest disintegration time (29 minutes).

Dissolution studies

Table-3: Drug release studies of all formulations

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	20.48	19.95	17.82	23.56	16.72	18.86	21.24	22.48
2	32.84	36.92	33.48	29.56	31.82	35.74	38.65	39.84
3	43.69	45.78	48.25	47.41	40.37	45.18	49.36	43.15
4	58.46	54.83	52.65	54.78	57.26	52.38	58.84	58.46
5	66.81	67.48	66.52	65.83	61.25	64.25	69.38	63.31
6	74.18	73.56	73.92	75.84	71.58	77.24	77.63	74.18
7	86.28	82.15	88.34	83.62	85.42	80.86	89.54	85.28
8	95.46	97.12	96.38	94.72	95.84	97.24	98.68	96.46

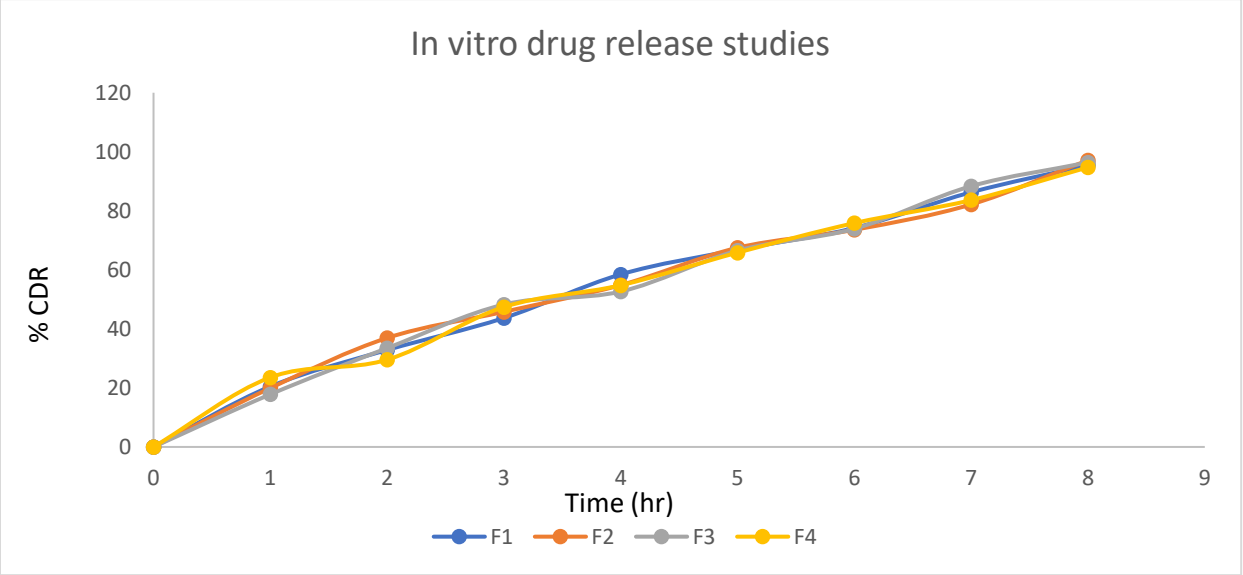

Fig-18: Dissolution Profile of F1 to F4 formulations

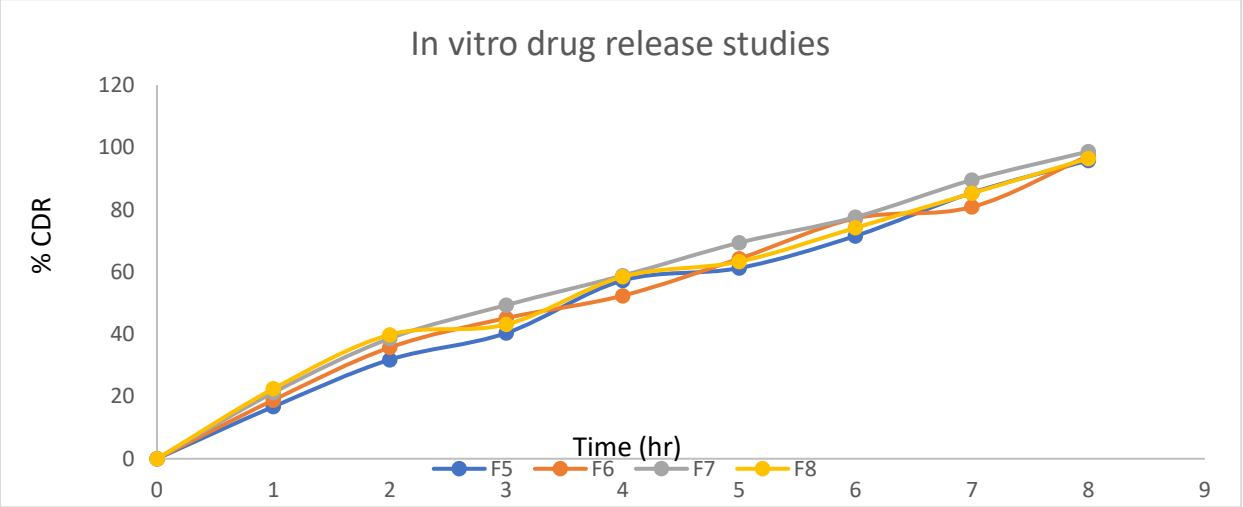

Fig-19: Dissolution Profile of F5 to F8 formulations

Discussion

The in-vitro dissolution study was carried out to evaluate the sustained-release behavior of Daridorexant tablets formulated with different concentrations of sodium alginate and tragacanth. The cumulative percentage drug release of formulations F1–F8 was determined over a period of 8 hours. The results demonstrated that the type and concentration of polymer significantly influenced the drug release profile. Overall, all formulations successfully sustained the release of Daridorexant over 8 hours, demonstrating the effectiveness of sodium alginate and tragacanth as hydrophilic matrix-forming polymers. Based on the dissolution profile, F7 showed the highest cumulative drug release (98.68%) with a uniform and controlled release pattern, suggesting that it may be considered the optimized formulation for sustained-release Daridorexant tablets.

Kinetic modelling of drug release

Zero order kinetics

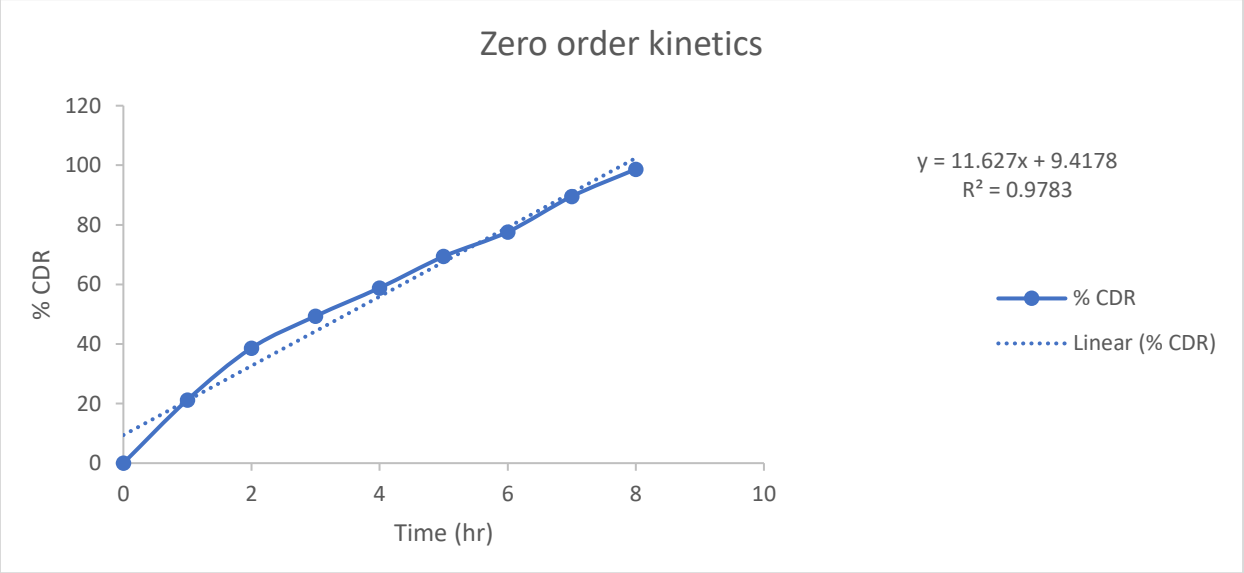

Fig-20: Zero order kinetics of optimized formulation

First order kinetics

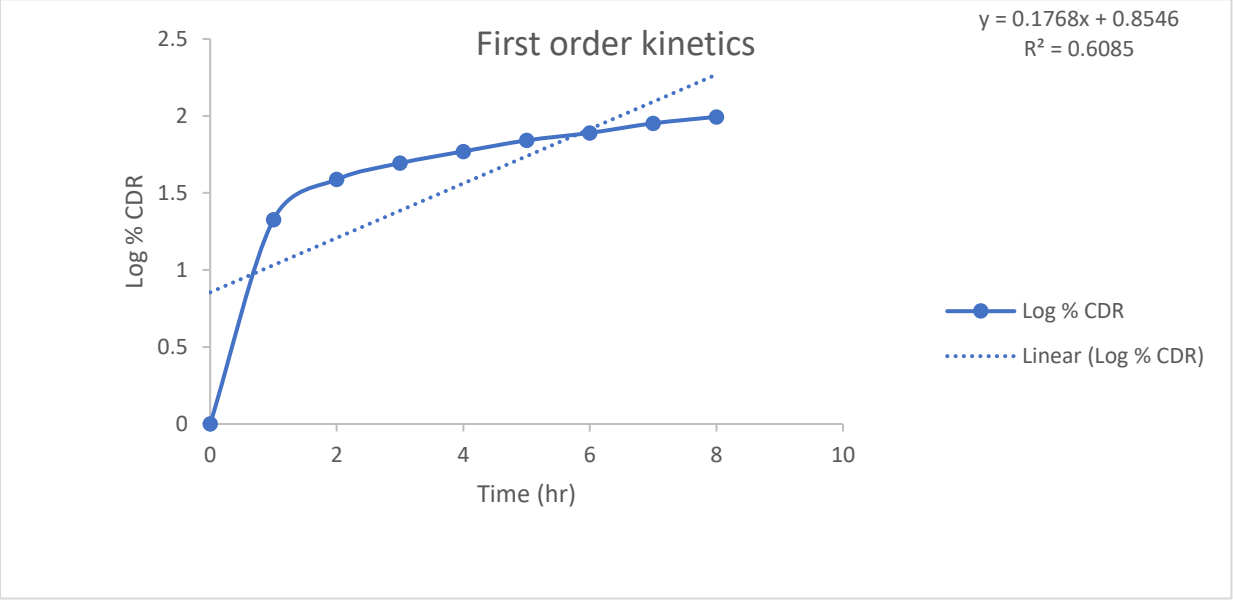

Fig-21: First order kinetics of optimized formulation

Higuchi model

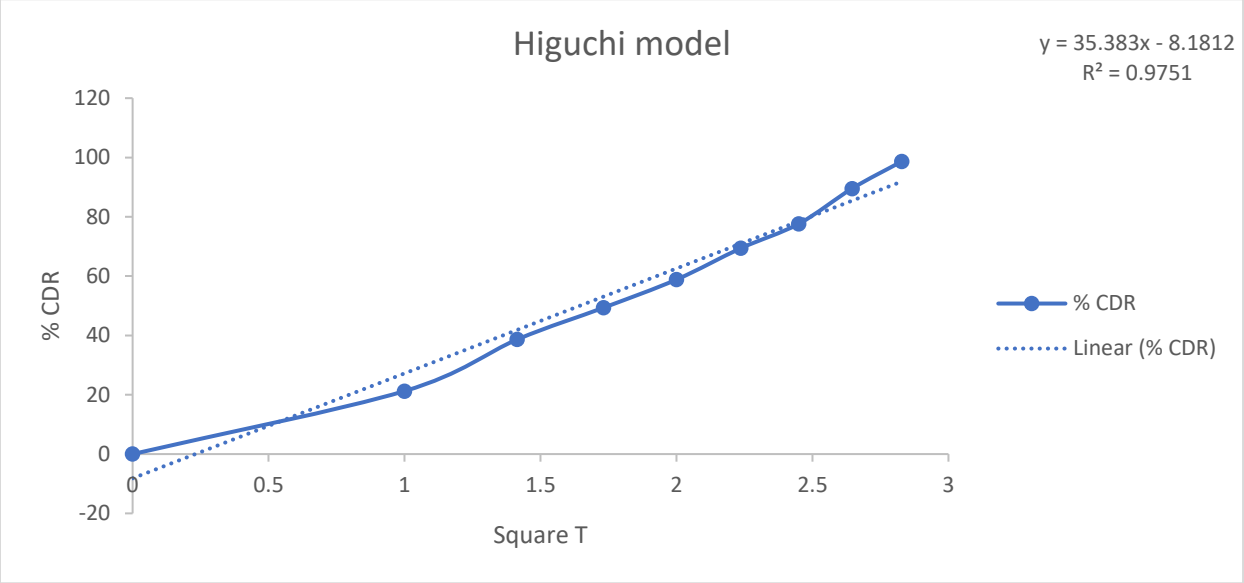

Fig-22: Higuchi model of optimized formulation

Korsmeyer peppas

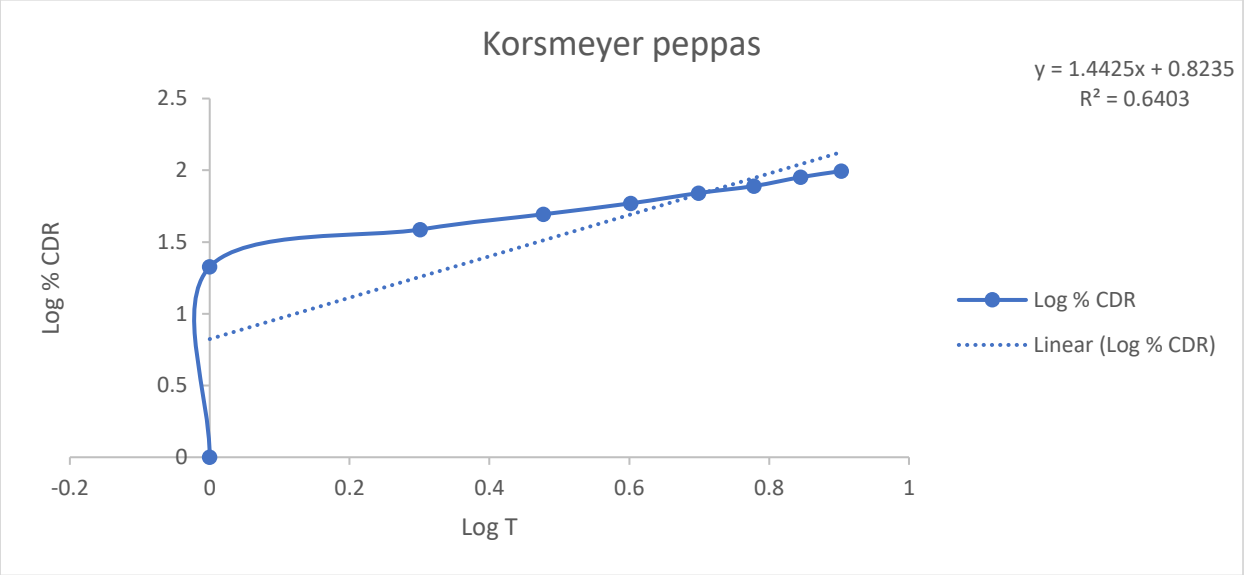

Fig-23: Korsmeyer peppas of optimized formulation

Discussion

Overall, comparison of the regression coefficients demonstrated that the Zero-order model (R^2 = 0.978) provided the best fit for the dissolution data, followed closely by the Higuchi model (R^2 = 0.975). These findings indicate that the optimized formulation F7 released Daridorexant in a nearly constant and controlled manner, with diffusion through the hydrated polymer matrix being the dominant mechanism of drug release. The lower correlation obtained with the First-order and Korsmeyer–Peppas models confirms that the release was not primarily concentration-dependent. Therefore, formulation F7 can be considered an effective sustained-release matrix tablet capable of providing prolonged and controlled drug delivery over the study period.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-7 after 90 days. Parameters quantified at various time intervals were shown.

Table-5: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-7	25^0C/60%RH % Release	98.68	97.52	96.37	95.81	Not less than 85 %
F-7	30^0C/75% RH % Release	98.68	97.50	96.32	95.20	Not less than 85 %
F-7	40^0C/75% RH % Release	98.68	97.48	96.349	95.18	Not less than 85 %

Discussion

Overall, the stability study confirms that the optimized formulation F7 possesses excellent physical and chemical stability under both long-term and accelerated storage conditions. Since the cumulative drug release remained above 95% throughout the study and exceeded the specified limit of not less than 85%, the formulation can be considered stable, with no significant changes in its sustained-release behavior during the three-month storage period.

V. CONCLUSION

The present investigation successfully developed Daridorexant sustained-release matrix tablets using sodium alginate and tragacanth by the direct compression technique. Preformulation and compatibility studies confirmed that the drug was compatible with the selected excipients and suitable for sustained-release formulation development. The prepared formulations exhibited satisfactory pre-compression and post-compression characteristics, indicating good manufacturability and tablet quality. Among the eight formulations, F7 was identified as the optimized formulation based on its superior physicochemical properties, highest drug content, desirable hardness, shortest disintegration time, and maximum cumulative drug release (98.68%) over 8 hours. Drug release kinetic analysis demonstrated that the optimized formulation followed Zero-order kinetics with a release mechanism predominantly governed by Higuchi diffusion, confirming effective controlled drug delivery. Furthermore, the optimized formulation remained stable during three months of storage under both long-term and accelerated conditions, with no significant reduction in drug release or tablet performance. Therefore, formulation F7 can be considered a promising sustained-release matrix tablet of Daridorexant capable of providing controlled drug release, improved patient compliance, and consistent therapeutic performance. .

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