Ritesh Kumre *et al*, International Journal of Pharmaceutical Sciences and Medicine (IJPSM), Vol.9 Issue. 8, August- 2024, pg. 1-14

ISSN: 2519-9889
Impact Factor: 5.958

Formulation and Evaluation of Antiplatelet Clopidogrel Tablet using β-cyclodextrin for Solubility Enhancement

Ritesh Kumre*; Nidhi Bais; Sachin Kumar Jain; Sudha Vengurlekar

Oriental College of Pharmacy and Research, Indore

DOI: 10.47760/ijpsm.2024.v09i08.001

Abstract:
Cardiovascular diseases (CVDs) are a major cause of global morbidity and mortality, necessitating effective therapeutic strategies. Clopidogrel, an antiplatelet drug, is crucial for preventing thrombotic events but suffers from poor aqueous solubility, affecting its bioavailability. This study investigates the enhancement of clopidogrel's solubility through its inclusion in β-cyclodextrin complexes prepared by the solvent evaporation method. Saturation solubility studies demonstrated that the complexes significantly improved solubility, with values of 4.5 µg/ml for formulation F1, 7.7 µg/ml for F5, and 6.2 µg/ml for F9. Tablet formulations incorporating these complexes were evaluated for physicochemical properties, including angle of repose (21.56° to 49.85°), bulk density (0.48 to 0.694 g/cm³), tapped density (0.625 to 0.834 g/cm³), Carr's Index (16.67% to 29.09%), and Hausner's ratio (1.2 to 1.44). Hardness ranged from 4.34 ± 0.26 kg/cm² to 6.75 ± 0.25 kg/cm², with friability between 0.2% and 0.5%. Disintegration times varied from 42 to 58 seconds. In-vitro drug release studies in 0.1 N HCl revealed that formulation F9 achieved a release of 44.89% at 2 minutes, 67.71% at 4 minutes, 84.13% at 6 minutes, and 93.21% at 8 minutes. These findings suggest that β-cyclodextrin significantly enhances clopidogrel's solubility and dissolution, potentially improving its clinical efficacy and patient outcomes.

Keywords: Clopidogrel, β-Cyclodextrin, Solubility Enhancement, Drug Formulation, Orodispersible Tablets, In-vitro Dissolution

***Correspondence Address:** riteshkumre7869@gmail.com
Ritesh kumre
Contact No.: 9340458325

ISSN: 2519-9889
Impact Factor: 5.958

Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality globally, necessitating the continuous development and improvement of therapeutic agents. Among these agents, clopidogrel, an antiplatelet medication, plays a critical role in the prevention of thrombotic cardiovascular events, such as myocardial infarction and stroke. Clopidogrel functions by inhibiting platelet aggregation, thereby reducing the risk of clot formation in at-risk individuals.

Despite its therapeutic efficacy, clopidogrel poses significant challenges in pharmaceutical formulation due to its poor aqueous solubility, which can lead to suboptimal bioavailability and variable therapeutic outcomes. Enhancing the solubility of clopidogrel is thus imperative to improve its clinical effectiveness and patient compliance.

β-cyclodextrin, a cyclic oligosaccharide, has garnered considerable attention in pharmaceutical sciences for its ability to form inclusion complexes with poorly soluble drugs. This complexation can enhance the solubility, stability, and bioavailability of drugs, making β-cyclodextrin a promising excipient for improving the delivery of clopidogrel. By encapsulating clopidogrel within the hydrophobic cavity of β-cyclodextrin, the solubility of clopidogrel can be significantly increased, potentially leading to enhanced absorption and therapeutic efficacy.

This study aims to formulate and evaluate clopidogrel tablets incorporating β-cyclodextrin to enhance the drug's solubility. The research focuses on the preparation of clopidogrel-β-cyclodextrin inclusion complexes, characterization of these complexes, and the subsequent formulation of tablets. Additionally, the study evaluates the physicochemical properties, dissolution profiles, and in vitro performance of the formulated tablets to determine their potential for improved bioavailability.

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Method and Material

Drug Clopidogrel was a gift sample provided by Cyano Pharmaceuticals, Indore and other excipients were procured from institute

Formulation of clopidogrel-β-Cyclodextrin inclusion complexes using solvent evaporation method

In the solvent evaporation method, clopidogrel-β-cyclodextrin are dissolved together in a solvent (Methanol) to form a uniform solution. This solution is then evaporated under reduced pressure or at an elevated temperature, causing the solvent to evaporate and leaving behind the Clopidogrel-β-cyclodextrin inclusion complex. The complex is then collected, dried, and processed further as needed.

Saturation solubility study of clopidogrel-β-cyclodextrin complexes

The solubility studies of clopidogrel-β-cyclodextrin inclusion complexes prepared by the solvent evaporation method were conducted to evaluate their solubility enhancement compared to the drug alone. The experimental procedure involved adding excess quantities of the complexes into glass vials containing 10 ml of 0.1 N HCl, followed by 24 hours of continuous shaking on a lab shaker for thorough mixing and equilibration. Filtration was then performed to remove any undissolved particles, and UV absorbance measurements were taken at 230 nm using a UV-visible spectrophotometer after appropriate dilutions. This systematic approach enabled the identification of the complex with superior solubility, aiding in the selection of an optimal complex for further in-vitro dissolution studies and formulation development.

Method of Preparation of Powder Blend

The formulation of clopidogrel tablets using β-cyclodextrin for solubility enhancement involves preparing a powder blend with the following excipients: β-cyclodextrin, microcrystalline cellulose (MCC), polyvinylpyrrolidone (PVP), croscarmellose sodium, magnesium stearate, and colloidal silicon dioxide. The formulation ensures that the total amount of clopidogrel in the tablets equals 75 mg.

In the initial stage, the active ingredient (clopidogrel) and β-cyclodextrin, along with other excipients, were accurately weighed according to the specific formulation requirements. These ingredients were then sifted through a 60-mesh sieve to ensure uniform particle size. The sifted β-cyclodextrin, with quantities

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varying by formulation (25 mg, 30 mg, or 35 mg), was blended with MCC (70 mg, 75 mg, or 80 mg), PVP (10 mg), croscarmellose sodium (6 mg), magnesium stearate (2 mg), and colloidal silicon dioxide (2 mg). The blend was mixed for 20 minutes to achieve a homogenous mixture. After blending, the resulting powder blend was passed through a 40-mesh sieve to further refine the particle size and improve flow characteristics. The prepared powder blend was then evaluated for its flow properties to ensure suitability for tablet compression.

Table no:1 Formulation table of Clopidogrel tablet

Ingredient(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Clopidogrel	75	75	75	75	75	75	75	75	75
β-Cyclodextrin	25	30	35	25	30	35	25	30	35
MCC	80	75	70	80	75	70	80	75	70
PVP	10	10	10	10	10	10	10	10	10
Croscarmellose Sodium	6	6	6	6	6	6	6	6	6
MagnesiumStearate	2	2	2	2	2	2	2	2	2
ColloidalSiliconDioxide	2	2	2	2	2	2	2	2	2
Total (mg)	200	200	200	200	200	200	200	200	200

Evaluations of Powder Blend for Flow Properties

A. **Angle of Repose:** The angle of repose is the maximum angle between a powder heap and a horizontal plane. It was determined using the fixed funnel method, adjusting the funnel height to touch the apex of the powder heap on paper. The angle (θ) was calculated from the diameter and height of the resulting cone using a formula.

$$\Theta = \tan -1(h/r)$$

B. **Bulk density:** Bulk density is a powder's mass (M) occupying a known volume (Vo), typically expressed in g/ml. In this test, accurately weighed granules were placed in a 50 ml measuring cylinder, and the unsettled apparent volume was measured. The bulk density was calculated using a specific formula.

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$$\rho bulk = m/Vo$$

C. **Tapped density:** Tapped density is determined by repeatedly tapping a measuring cylinder with a powder sample until volume changes become minimal. Initially, the granule-filled cylinder's volume is noted, and then it undergoes 500 taps using a tapped density tester (Electro Lab USP II).

$$\rho t = m/V_t$$

D. **Carr's Compressibility Index:** The compressibility index indicates arch formation and its likelihood to fail, influencing flowability. The formula calculates this index, revealing its relationship with flowability, as shown in the table.

$$CI = \rho t - \rho bulk / \rho t \times 100$$

E. **Hausner's ratio:** Hausner's ratio, calculated using a specific formula, is related to interparticle friction and predicts powder flow properties. Lower friction results in ratios around 1.2 for free-flowing powders like coarse spheres, while more cohesive powders, such as flakes, have higher values above 1.6, as indicated in the table.

$$\text{Hausner's Ratio} = \rho t / \rho bulk$$

Preparation of clopidogrel orodispersible tablets using direct compression technique

Following the evaluation of the powder blend, orodispersible tablets were produced using a direct compression technique on a 10-station rotary tablet compression machine equipped with flat-faced 6 mm punches. Before compression, the die and punch surfaces were lubricated with magnesium stearate. Nine different formulations, each containing varying amounts of superdisintegrant, were created and stored in airtight containers at room temperature for future analysis.

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Evaluation of Orodispersible Tablets of Clopidogrel

- **Thickness** Uniformity in tablet size was ensured by measuring the thickness of the tablets using a Vernier Caliper. Three tablets from each batch were assessed for this purpose.
- **Hardness** Hardness for each formulation was evaluated by testing three tablets with the Monsanto hardness tester.
- **Drug Content Uniformity Study** Five tablets were individually weighed and powdered. The powder equivalent to 10 mg of Clopidogrel was dissolved in methanol, and the volume was adjusted to 100 ml with methanol. A 10 µg/ml dilution was then prepared from this solution. The drug content was determined by measuring UV absorbance at 230 nm.
- **Weight Variation Test** Twenty tablets were weighed individually, and the average weight was calculated by summing all individual weights and dividing by the number of tablets. Individual weights were compared to the average, and the percentage deviation from the average was calculated using the formula:

  Weight Variation=Iw−AwAw×100%\text{Weight Variation} = \frac{Iw - Aw}{Aw} \times 100\%Weight Variation=AwIw−Aw×100%
- **Wetting Time** A piece of tissue paper was placed in a petri dish with 6 ml of water. The tablet was positioned on the paper, and the time for the tablet to fully wet was recorded. The water temperature was maintained at 37°C. Wetting time, which reflects the duration for the tablet to disintegrate on the tongue, was subsequently calculated.
- **Disintegration Time** In-vitro disintegration studies were performed using the Tablet Disintegration Test Apparatus. Each of the six tubes in the basket assembly held one tablet with an added disk, and the assembly was submerged in a one-liter beaker of distilled water at 37±2°C. The basket was moved vertically through 5 to 6 cm at a frequency of 28 to 32 cycles per minute. The time required for the complete disintegration of the tablet was recorded for all formulations (F1-F9).
- ***In-vitro* Drug Release Study** Drug release studies were conducted for 30 minutes on the nine formulations of orodispersible tablets using an eight-station USP type 2 apparatus at 50 rpm. The tablets were placed in 900 ml of 0.1 N HCL at 37 ± 0.5°C. At intervals of 5, 10, 15, 20, 25, and 30 minutes, 10 ml samples were withdrawn, filtered through Whatman No. 41 filter paper, and

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replaced with an equal volume of fresh dissolution medium. The filtered samples were analyzed spectrophotometrically at 230 nm, and the cumulative percentage of the labeled drug amount released was calculated.

Result and Discussion

a. FTIR Analysis

Fourier transformed infra-red (FTIR) spectra of Clopidogrel and the physical mixture of drug with excipient were taken by using an IR Spectrophotometer. The scanning range was 450 - 4000 cm⁻¹ and the resolution was 1 cm⁻¹. The IR spectrum of pure drug and physical mixture of drug and excipient were studied. The characteristic absorption peaks of Clopidogrel and absorption peaks of the physical mixture correlate with each other. This indicates that the drug was compatible with the excipient.

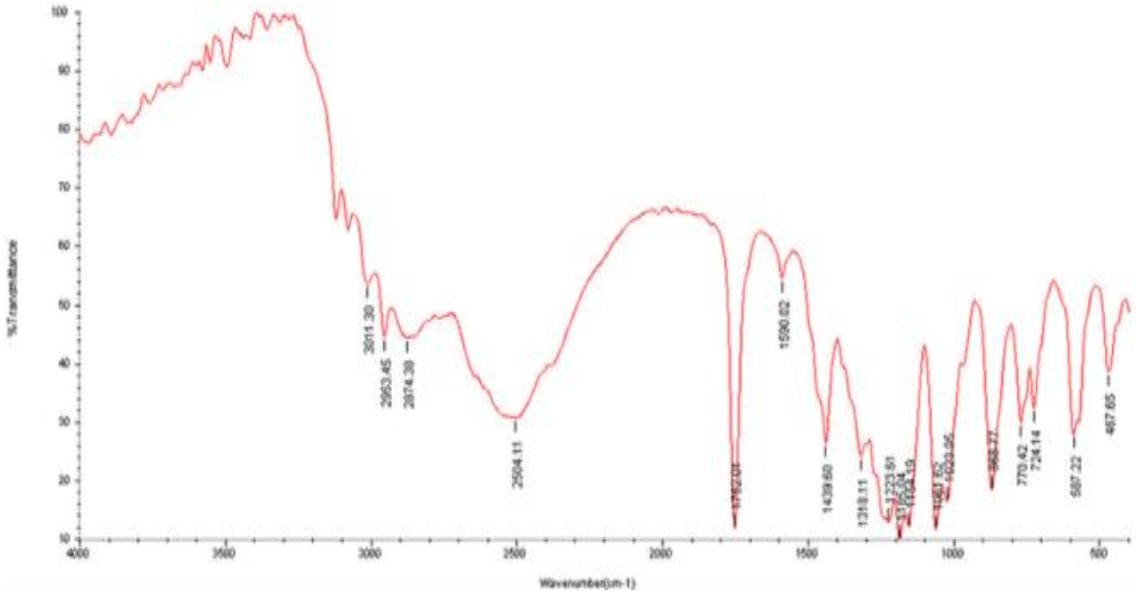

Figure:1 FTIR spectrum of clopidogrel pure drug

b. Saturation solubility studies data of clopidogrel-β-cyclodextrin inclusion complex

Prepare a saturated solution by mixing excess inclusion complex with solvent and stirring for 24-48 hours. Filter the mixture to remove undissolved particles. Create a calibration curve by measuring the absorbance of standard Clopidogrel solutions at the λ_{max} using a UV-Visible Spectrophotometer.

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Measure the absorbance of the diluted saturated solution, then determine its concentration using the calibration curve. Finally, calculate the saturation solubility of Clopidogrel in the inclusion complex, accounting for the dilution factor.

Table:2 Saturation solubility data of complexes

Sr. No	Ratio of clopi-β-CD Complexes	Saturated Solubility (µg/ml)	Drug Content (%)
1	Clopi-β-CD (f1)	4.5	96.80 ± 0.60
2	Clopi-β-CD (f5)	7.7	98.00 ± 0.50
3	Clopi-β-CD (f9)	6.2	97.50 ± 0.40

c. Evaluation of powder blend

Table:3 Evaluation data of powder blend

Formulation Code	Angle of Repose (°)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner's Ratio
F1	41.18	-	-	-	1.514
F2	26.85	0.581	0.714	18.6	1.22
F3	34.03	0.654	0.802	18.45	1.22
F4	43.47	0.694	0.834	16.67	1.2
F5	49.85	0.48	0.625	23.07	1.3
F6	33.62	0.519	0.732	29.09	1.44
F7	34.65	0.583	0.745	21.74	1.27
F8	26.99	0.582	0.714	18.6	1.22
F9	21.56	0.51	0.641	20.4	1.25

The table presents the flow properties and density measurements of different formulations labeled F1 to F9.

- **Angle of Repose** measures the flowability of the powder; lower values indicate better flow. Formulations F2, F8, and F9 exhibit good flow with angles around 26°, while F5 shows poor flow with an angle close to 50°.

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- **Bulk Density** and **Tapped Density** values are provided to assess the packing properties of the powders; higher values generally indicate better packing.
- **Carr's Index** and **Hausner's Ratio** are calculated from the bulk and tapped densities to evaluate compressibility and flow properties. Carr's Index values between 15-20% indicate fair flow and compressibility, seen in formulations F2, F3, F4, and F8. Higher values, like in F6 (29.09%), suggest poorer flow properties.
- **Hausner's Ratio** values around 1.2-1.3 are generally acceptable, indicating fair flow, with formulation F1 having a high ratio of 1.514, suggesting poor flow properties.

d. Formulation of Clopidogrel Tablet by Direct Compression Technique

Clopidogrel tablets were produced using the direct compression technique on a 10-station rotary tablet compression machine with flat-faced 6 mm punches. Magnesium stearate was used as a lubricant on the die and punch surfaces before compression. Nine formulations, each with different amounts of a superdisintegrant, were carefully prepared. All formulations were then stored in airtight containers at room temperature for further examination.

Table:4 Post- Compression evaluation data of clopidogrel tablet

S.no	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Content Uniformity (%)	Disinte.Time (sec)
F-1	4.38 ± 0.27	0.4	1.08 ± 0.55	84.6 ± 2.5	32
F-2	4.34 ± 0.26	0.24	868.00 ± 0.30	89.60 ± 3.10	33
F-3	4.75 ± 0.16	0.29	723.00 ± 0.30	86.00 ± 1.60	29
F-4	5.32 ± 0.16	0.22	981.00 ± 0.50	91.8 ± 2.20	30
F-5	5.88 ± 0.16	0.27	785.00 ± 0.60	91.10 ± 4.70	36
F-6	6.75 ± 0.25	0.43	654.00 ± 0.70	91.5 ± 3.90	34
F-7	6.42 ± 0.21	0.5	831.00 ± 0.45	94.20 ± 2.20	39
F-8	5.35 ± 0.26	0.2	664.50 ± 0.40	86.30 ± 1.30	29
F-9	6.32 ± 0.18	0.42	553.00 ± 0.25	91.8 ± 1.30	32

ISSN: 2519-9889
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The table presents the evaluation parameters for nine different formulations (F-1 to F-9) of orodispersible tablets. The parameters measured include hardness, friability, weight variation, content uniformity, and disintegration time.

- **Hardness (kg/cm²)**: This measures the tablet's strength. Formulations F-6 and F-7 show the highest hardness values (6.75 and 6.42 kg/cm²), indicating they are the most robust, while F-2 has the lowest hardness (4.34 kg/cm²).
- **Friability (%)**: This indicates the tablet's tendency to crumble. Lower friability values are better. F-8 has the lowest friability (0.2%), indicating good resistance to crumbling, while F-7 has the highest (0.5%).
- **Weight Variation (mg)**: This assesses the consistency of tablet weight. F-1 has the smallest variation (1.08 ± 0.55 mg), suggesting good uniformity, whereas F-9 has the largest variation (553.00 ± 0.25 mg), though this appears to be an anomaly since most formulations show a small range.
- **Content Uniformity (%)**: This measures how uniformly the active ingredient is distributed in the tablets. F-7 shows the highest content uniformity (94.20 ± 2.20%), while F-1 has the lowest (84.6 ± 2.5%).
- **Disintegration Time (sec)**: This measures how quickly the tablet disintegrates in a solution. The shortest disintegration time is seen in F-1 (42 seconds), making it the fastest to dissolve, while F-3 has the longest disintegration time (58 seconds).

e. Drug Release Percentage of Formulation of Clopidogrel FDTs in Phosphates Buffer pH 6.8

Formulation Code	Table: 5 Drug Release %			
	5 min	**10 min**	**15 min**	**20 min**
F1	46.45	53.33	69.3	73.93
F2	57.62	66.44	72.7	76.54
F3	55.16	61.3	73.36	79.3
F4	30.22	38.51	46.67	57.75
F5	33.74	42.96	48.22	53.87
F6	33.12	38.86	50.68	54.82
F7	27.34	32.85	41.72	48.2
F8	12.4	31.64	42.93	51.34
F9	68.69	74.54	83.66	91.31

ISSN: 2519-9889
Impact Factor: 5.958

The table displays the drug release percentages of Clopidogrel fast-dissolving tablets in a phosphate buffer at pH 6.8 over 5, 10, 15, and 20 minutes. Formulations F1, F2, and F3 show relatively high release rates, with F1 reaching 73.93% at 20 minutes. Formulation F9 achieves the highest release, reaching 91.31% by 20 minutes, indicating superior performance. In contrast, F4, F5, F6, and F8 exhibit slower release rates, with F4 only reaching 57.75% and F8 51.34% by 20 minutes. Thus, F9 is the most effective in rapidly delivering the drug, while the other formulations release the drug more slowly.

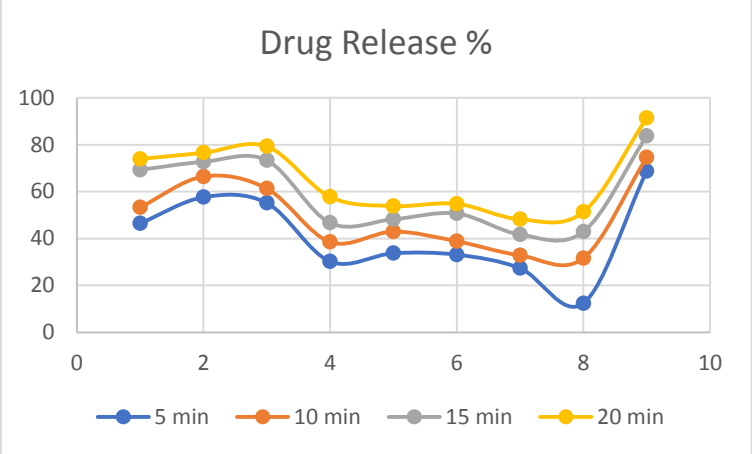

Figure: 2 Clopidogrel FDTs in Phosphates Buffer pH 6.8

a. Drug Release Percentage of Formulation of Clopidogrel FDTs in 0.1 N HCL

Formulation Code	Table: 6 Drug Release %			
	2 min	**4 min**	**6 min**	**8 min**
F1	83.62	88.01	87	90.13
F2	93.35	94.2	96.31	97.92
F3	90.79	93.78	95.36	98.08
F4	13.23	51.34	70.21	80.89
F5	23.59	46.22	80.92	93.9
F6	26.01	82.11	87.01	87.39
F7	18.47	68.59	80.12	85.11
F8	13.85	39.23	67.83	87.35
F9	44.89	67.71	84.13	93.21

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Impact Factor: 5.958

The table presents the drug release percentages of Clopidogrel fast-dissolving tablets in 0.1 N HCl at intervals of 2, 4, 6, and 8 minutes. Formulations F2 and F3 demonstrate the highest release rates, with F2 achieving 97.92% and F3 reaching 98.08% by 8 minutes, indicating rapid and complete drug release. Conversely, formulations F4 and F8 exhibit the slowest release profiles, with F4 only reaching 80.89% and F8 87.35% by 8 minutes. Formulation F5 also shows a notable increase in release, reaching 93.90% by 8 minutes, while F9 shows a steady release, achieving 93.21% by the same time point.

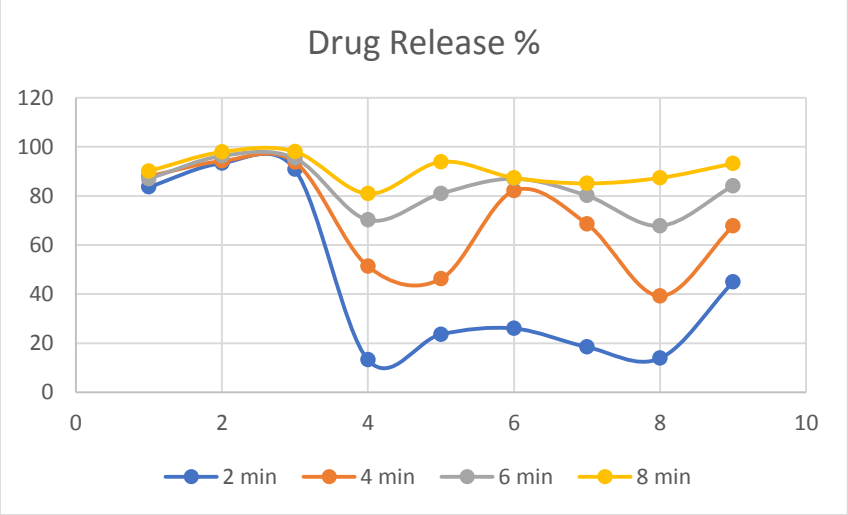

Figure: 3 Clopidogrel FDTs in 0.1 N HCL

Conclusion

Clopidogrel, a critical antiplatelet drug for preventing thrombotic events, suffers from poor aqueous solubility, impacting its therapeutic effectiveness. Inclusion of clopidogrel in β-cyclodextrin complexes, prepared via the solvent evaporation method, significantly improved its solubility. Saturation solubility studies confirmed this enhancement. The formulated tablets were assessed for physicochemical properties, disintegration times, and in-vitro drug release profiles. Notably, formulation F9 exhibited the highest drug release, achieving 93.21% within 8 minutes. These findings indicate that β-cyclodextrin is effective in enhancing the solubility and dissolution rate of clopidogrel, potentially leading to improved clinical efficacy and patient outcomes.

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Impact Factor: 5.958

Acknowledgement

I extend my sincere gratitude to Dr. Nidhi Bais, my guide, for her invaluable mentorship and unwavering support throughout this project. My heartfelt thanks also go to Dr. Sachin Kumar, my supervising guide, for his insightful advice and constructive feedback. I am equally grateful to Dr. Sudha Vengurlekar, Head of the Department, for her guidance and encouragement. Additionally, I appreciate the resources and facilities provided by Oriental College of Pharmacy and Research, Indore, which greatly contributed to the successful completion of this work.

Conflicts of interest

The authors have no conflicts of interest

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