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Formulation and Evaluation of Controlled Release Formulations of Anti-Hypertensive Drugs Clevidipine

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A B S T R A C T
The main objective of the Study was to develop the control release of the tablets of Clevidipine. A standard calibration curve was developed by measuring absorbance at 263 nm. Pre-formulation studies revealed similar bulk and tapped densities, with Carr's index, Hausner's ratio, and angle of repose (11.03° to 18.23°) confirming good flow properties. Post-formulation assessments demonstrated acceptable weight variation, tablet thickness (3.66 to 5.26 mm), hardness (5.89 to 6.98 kg/cm²), friability (<1.0%), and drug content (98% to 102%). In vitro dissolution studies showed significant drug release over 12 hours, with formulation F2 exhibiting the most favorable release profile. Kinetic analysis suggested non-Fickian diffusion mechanisms for formulation F2, with an "n" value between 0.45 and 0.89. FTIR spectroscopy confirmed no significant interactions between Clevidipine and the excipients, indicating successful molecular dispersion in the polymer matrix. This study established Clevidipine CR tablets with favorable physicochemical properties and release profiles, making them suitable for clinical use in blood pressure management.
Keywords: Clevidipine ,Carr's index, Hausner's ratio.

A R T I C L E I N F O

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1. Introduction

The management of hypertension, a prevalent cardiovascular condition, is critical for reducing the risk of adverse cardiovascular events such as stroke, heart attack, and renal failure. Anti-hypertensive drugs play a crucial role in the treatment regimen for hypertension, helping to control blood pressure and prevent complications. Among these, Clevidipine, an ultra-short-acting calcium channel blocker, has emerged as a potent therapeutic agent for the rapid control of blood pressure in acute settings. However, the need for frequent dosing due to its short half-life presents a significant challenge in chronic management. This underscores the importance of developing controlled release formulations that can provide sustained therapeutic effects, improve patient compliance, and minimize the risk of fluctuations in blood pressure levels. Controlled release drug delivery systems are designed to release the active pharmaceutical ingredient (API) at a predetermined rate, ensuring a consistent and prolonged therapeutic effect. This approach not only enhances the efficacy of the drug but also reduces the dosing frequency, thereby improving patient

adherence to the treatment regimen. The formulation and evaluation of controlled release formulations of Clevidipine are aimed at addressing the limitations associated with its conventional dosage forms, particularly the need for continuous intravenous administration in acute settings and frequent dosing in chronic management.

Significance and Rationale

Clevidipine's unique pharmacological profile makes it an ideal candidate for controlled release formulations. As a dihydropyridine calcium channel blocker, Clevidipine exerts its antihypertensive effect by inhibiting the influx of calcium ions into vascular smooth muscle cells, leading to vasodilation and a subsequent reduction in blood pressure. Its rapid onset of action and ultra-short duration of effect make it highly effective in acute settings; however, these characteristics necessitate continuous infusion for sustained control, posing practical challenges for long-term use.

The development of controlled release formulations of Clevidipine is driven by the need to extend its therapeutic action, thereby enabling its use in chronic hypertension management. By designing a formulation that releases Clevidipine gradually over an extended period, it is possible to maintain stable blood pressure control, reduce the risk of rebound hypertension, and enhance patient convenience. This approach can also mitigate the potential side effects associated with peak plasma concentrations, such as hypotension and reflex tachycardia.

Formulation Strategies

The formulation of Clevidipine into controlled release dosage forms involves the selection of suitable polymers and excipients that can modulate the drug release profile. Various formulation strategies can be employed, including matrix tablets, microencapsulation, and liposomal delivery systems. Each strategy offers distinct advantages and challenges, necessitating careful consideration of the drug's physicochemical properties and the desired release kinetics.

Matrix tablets are one of the most commonly used approaches for controlled release formulations. In this method, Clevidipine is embedded within a polymer matrix, which controls the release of the drug through diffusion and erosion mechanisms. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and hydrophobic polymers like ethylcellulose are often used to achieve the desired release rate. The ratio of drug to polymer, the type of polymer, and the manufacturing process all play a critical role in determining the release characteristics of the matrix tablets.

Microencapsulation is another promising strategy for controlled release drug delivery. In this approach, Clevidipine is encapsulated within biodegradable polymeric microspheres, which release the drug over time as the polymer degrades. Polymers such as poly(lactic-co-glycolic acid) (PLGA) are commonly used for microencapsulation due to their biocompatibility and controlled degradation properties. This technique can provide a high degree of control over the drug release rate and can be tailored to achieve specific therapeutic goals.

Liposomal delivery systems offer an advanced approach to controlled release formulations. Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate Clevidipine, protecting it from degradation and controlling its release. This method not only enhances the stability of Clevidipine but also allows for targeted delivery to specific tissues, reducing systemic exposure and potential side effects.

Evaluation and Assessment

The evaluation of controlled release formulations of Clevidipine involves rigorous in vitro and in vivo testing to ensure their efficacy and safety. In vitro dissolution studies are conducted to characterize the drug release profile under various conditions that simulate physiological environments. These studies provide critical insights into the release kinetics and help optimize the formulation parameters.

In vivo pharmacokinetic studies in animal models and clinical trials in human subjects are essential to validate the controlled release formulations. These studies assess the pharmacokinetic parameters such as peak plasma concentration (Cmax), time to reach peak concentration (Tmax), and area under the plasma concentration-time curve (AUC). The data obtained from these studies are used to determine the bioavailability and therapeutic efficacy of the formulations.

Stability studies are conducted to evaluate the robustness of the formulations under different storage conditions. Parameters such as hardness, friability, and uniformity of content are assessed to ensure the quality and consistency of the dosage forms. Advanced analytical techniques, including high-performance liquid chromatography (HPLC) and mass spectrometry, are employed to quantify drug levels and monitor the presence of degradation products.

2. Materials and methods

Chemicals used in Experiment

For the formulation of the drug, several high-quality materials were sourced from reputable manufacturers. Clevidipine was obtained from Qualychrome Research Labs, ensuring the active ingredient's purity. Excipients such as PEG 400, Tween 80, and Xanthum gum were all supplied by Colorcon, providing reliable consistency and quality in the formulation process. Tragacanth was sourced from FMC BioPolymer, known for its superior bio-polymer products. Additionally, MCC PH102, Magnesium Stearate, and Aerosil were procured from SD Fine, with the magnesium stearate specifically from their Mumbai branch, ensuring a robust and reliable composition for the sustained release formulation.

Equipments used in the Formulation:

For the formulation and evaluation process, several essential pieces of equipment were utilized, each from reputable manufacturers. The electronic weighing balance, a Scale-tech model, was used for precise measurement of ingredients. The laboratory oven, model Dtc-00r, provided controlled heating necessary for various experimental procedures. For the analysis of drug concentrations, the Labindia UV 3000 UV-Vis Spectroscopy was employed, ensuring accurate spectrophotometric measurements.

Additionally, the dissolution apparatus from Electro Lab was used to assess the drug release profile, facilitating comprehensive evaluation of the formulations.

Method for the analytical method

Kh_2PO_4 Preparation:

A stock solution of monobasic potassium phosphate was prepared by weighing 27.22g of the substance and diluting it to a final volume of 1000 ml. To prepare a 0.2M sodium hydroxide solution, 8g of sodium hydroxide was measured and diluted to a final volume of 1000ml. Fifty millilitres ofdiortho potassium solution and transferred to a 200 ml flask, followed by the addition of 22.4 ml of 0.2M sodium hydroxide solution from the stock solution. The volume was subsequently modified with water.

Calculating the λmax of the phosphate buffer Clevidipine 6.8:

Method: Standard operating procedure: After weighing and dissolving 50 mg of Clevidipine in 50 ml of 6.8 phosphate buffer, the volume was increased to 50 ml with 6.8 phosphate buffer, yielding a concentrated stock solution of 1000 µg/ml ppm.

Dilution 1: A concentrated solution containing 10µg/ml was obtained by diluting 10 ml of the working standard solution with 100 ml of 6.8 phosphate buffer.

Dilution 2: A concentrated solution containing 10µg/ml was obtained by diluting 10 ml of the working standard solution with 100 ml of 6.8 phosphate buffer.

Develop the Clevidipine 6.8 phosphate buffer calibration curve:

Operational standard: 50 mg of Clevidipine was measured and dissolved in 50 mL of 6.8 sodium phosphate buffer, subsequently adjusted to a final volume of 50 mL using the same buffer, resulting in a concentrated stock solution of 1000 µg/mL (ppm).

Dilution 1: A ten ml aliquot working standard diluted to 100 ml using 6.8 phosphate buffer, resulting in a concentration of 100 ppm.

A series of Dilution are prepared for the linearity curve to get a concentration range of 2,4,6,8 and 10 ppm by diluting the solution from stock.

III. Development Clevidipine SR Tablets via the Liquid Solid Compact model technique:

The Clevidipine SR Tablets were formulated according to the General Methodology outlined below:

- All materials and the medication were weighed precisely, except for Aerosil and magnesium stearate, which were co-sifted through a #60 sieve and mixed with the solvent.
- The aforementioned mixture passed through # fourty mesh Mg Sterateand Aerosil.

Tablets Evaluation:

1. Angle of Repose: The angle of repose refers to the maximum angle at which a pile of granular material can remain stable without collapsing. This angle is influenced by various factors, including the size, shape, and moisture content of the particles**.**

When granular material is poured onto a surface, it forms a conical shape, and the slope of this cone is the angle of repose. At this angle, the downward force of gravity is balanced by frictional forces between the particles. If the angle exceeds this critical point, the material will start to slide or collapse. The angle of repose is commonly used in engineering, geology, and materials science to understand the stability of slopes, design of silos and hoppers, and the handling of various bulk materials.

A) Density of tapped:

Weigh 25 g of the powder mix, which has been sieved through a 22# sieve, and transfer it to a 100millilitre cylinder designated for the tap density tester. Utilise the tester for a specified number of taps until the powder bed volume attains a minimum, calculated via a formula.18. Tapped density is calculated as the weight of the powder divided by the tapped volume. The formula is expressed as Dt = M / Vf, where M represents the mass of the powder.

V f represents the tapped volume of the powder.

Assay Methodology.

Weigh and finely grind a minimum of 20 tablets. Transfer a measured quantity of powder corresponding to approximately ten milligram of the sample into a 10 milliltres of VF. Introduce 6 ml of six point eight buffer, then agitate and sonicate for 10 minutes to ensure complete extraction. Prepare a diluted methanol solution by modifying the volume and ensuring thorough mixing. Transfer 1 ml of the aliquot into a 10 millilitre volumetric flask. Dilute to the mark with the diluent, mix thoroughly, and filter. Withdraw a 1 ml aliquot and dilute to the designated mark using buffer. Determine the quantity of the model drug in milligrammes within the specified portion utilising the provided formula**.**

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$$\%\ \boldsymbol{Assay} = \frac{Test\ absorbance}{Standard\ absorbance} * \frac{Weight\ of\ standard}{Dilution\ of\ standard} * \frac{Dilution\ of\ test}{Weight\ of\ test}$$

$$* \frac{Average\ weight}{lable\ claim} * \frac{\%\ purity\ of\ drug}{100} * 100$$

A dissolution study was performed in vitro utilising 900 ml of Phosphate Buffer in a paddle type apparatus configured per the paddle method. The Buffer solution was stabilise at a 37 degrees temperature. The formulation was inserted into bowl and sealed; The apparatus functioned for 12 hours at a rotation speed of 50 rpm. At specific time intervals, 5 ml of the dissolution medium was withdrawn, filtered, and replaced with 5 ml of fresh medium to ensure sink conditions were maintained. The resulting dilutions were prepared with the dissolution medium and analyzed spectrophotometrically at a wavelength of 263 nm using a UV spectrophotometer.

3. Results & Discussion

The creation of a normative Linearity Curve for Clevidipine in 6.8 Potassium buffer:

The scanned absorbance was recorded at 263 nm utilising a UV spectrometer, with a Phosphate buffer having pH-6.8 used as the reference as blank. The absorbance values are taken in the consideration and plot graph between the concentration and absorbance to get the correlation point.

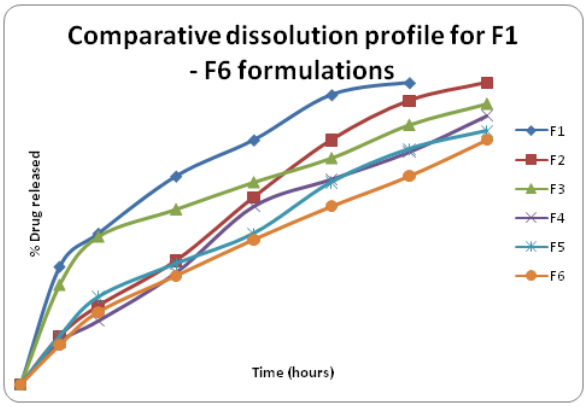

Figure 1.UVSpectroscopy

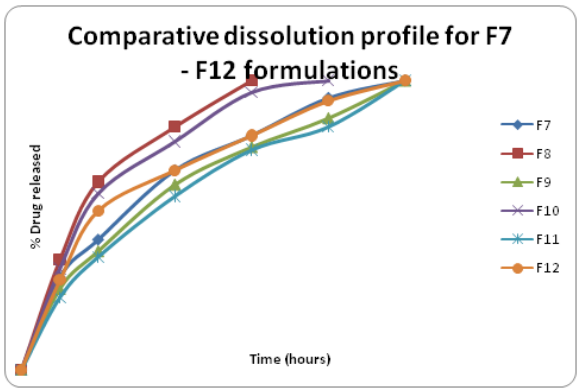

Figure 2: Com Drug release patterns of Formula 7 to 8.

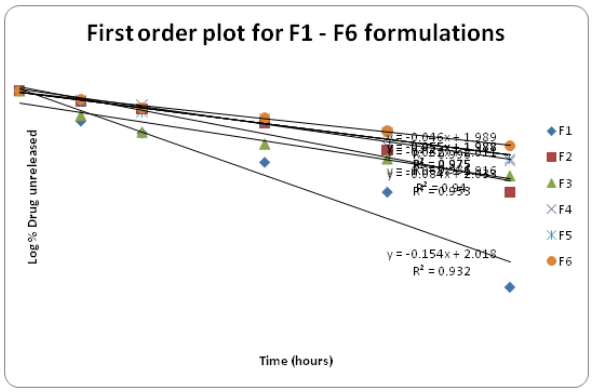

Figure 3: Formula 1 to 6 Kinetic Profile for Forst Order

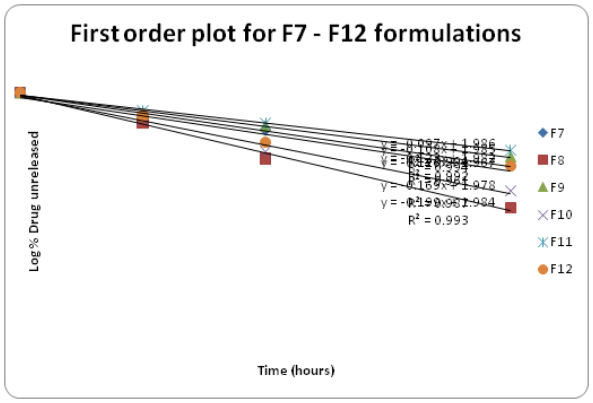

Figure 4: Formula 7 to 12 Kinetic Profile for Forst Order

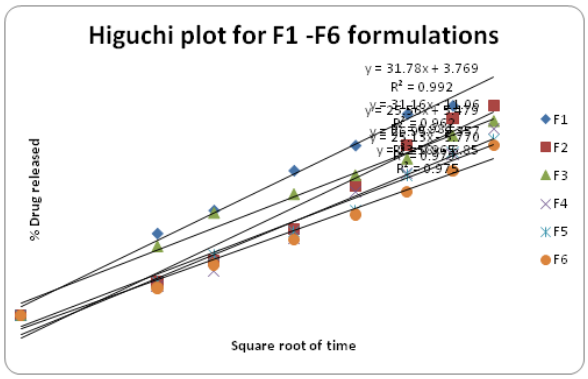

Figure 5: Formula 1 to 6 Kinetic Profile for higuchi

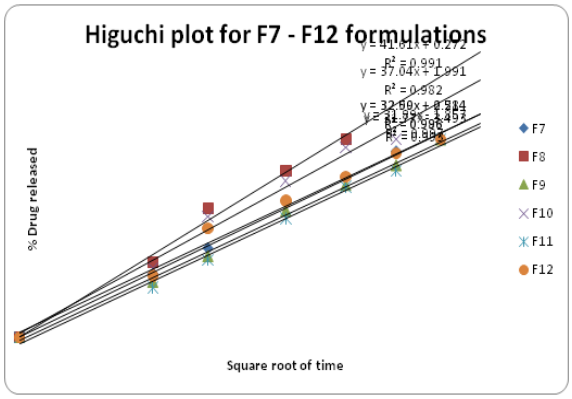

Figure 6: Formula 7 to 12 Kinetic Profile for Forst Order

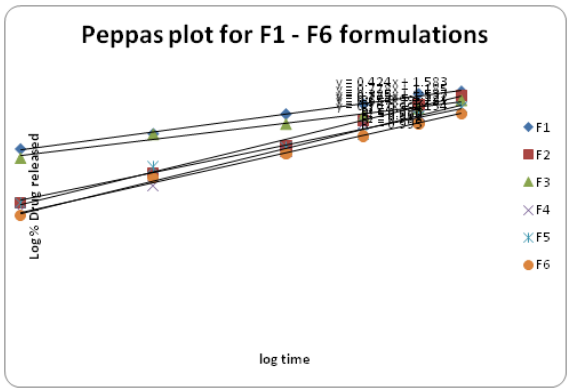

Figure 7: Formula 1 to 6 Kinetic Profile for Kross Mayerspeppas

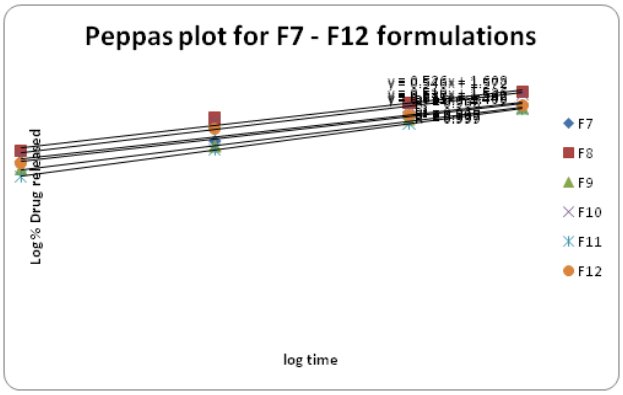

Figure 8: Formula 7 to 12 Kinetic Profile for Kross Mayerspeppas

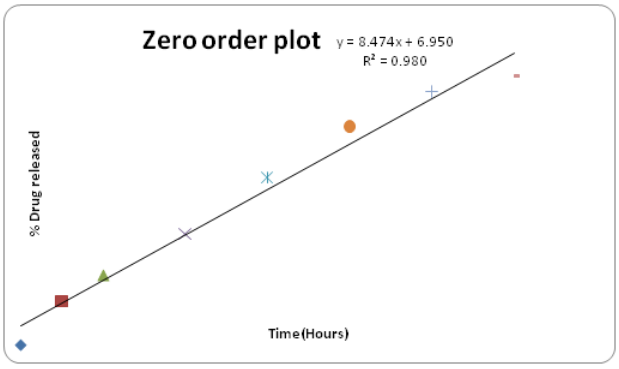

Figure 9: Formula 2 Kinetic Profile for Zero Order

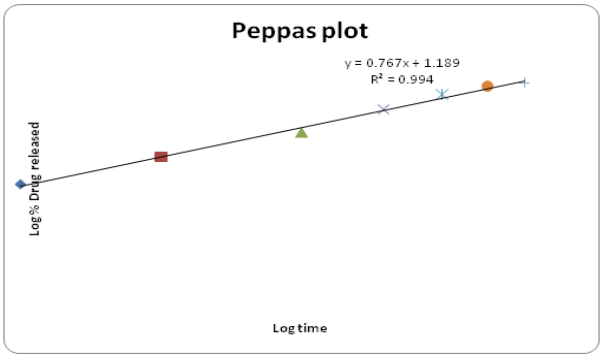

Figure 12: Formula 2 Kinetic Profile for Peppas

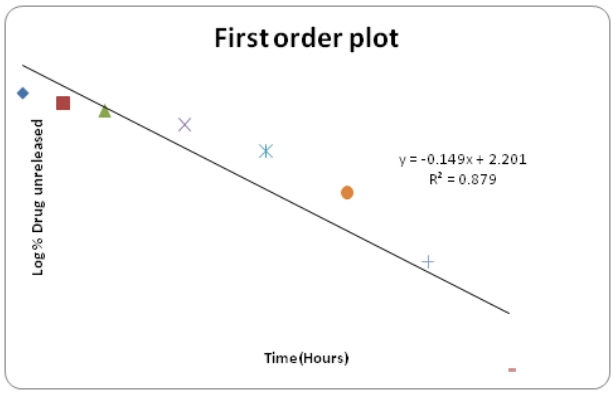

Figure 10: Formula 2 Kinetic Profile for First Order

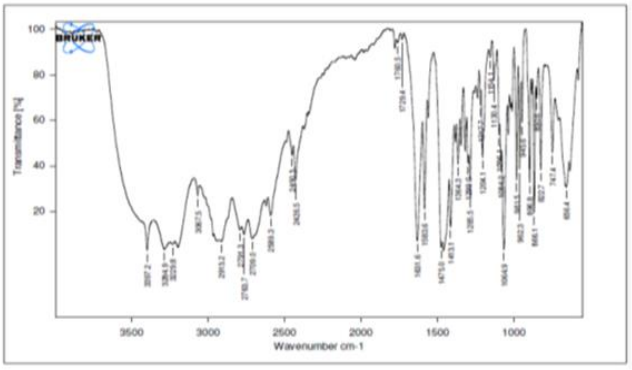

Figure:13 Showing the Infrared Spectrum of Clevidipine

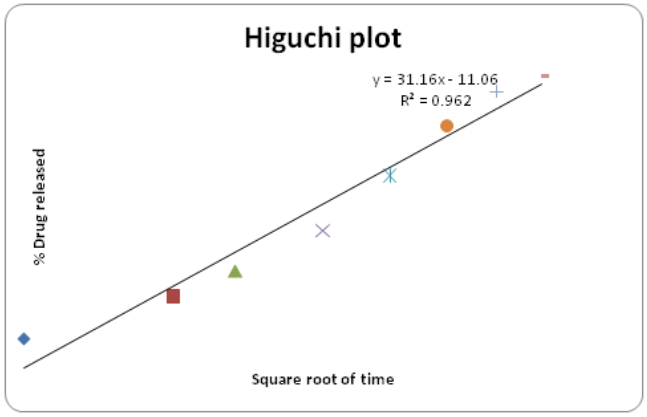

Figure 11: Formula 2 Kinetic Profile for Higuchi

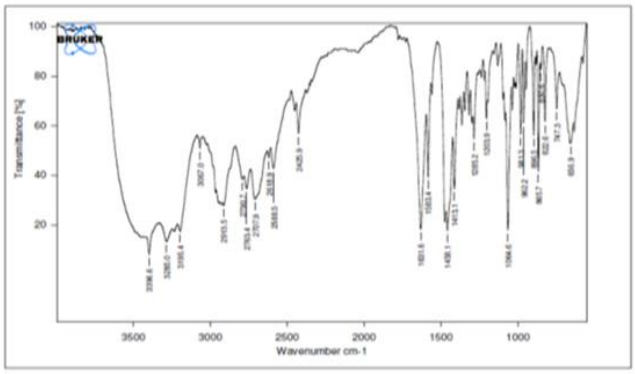

Figure :14 Infrared Spectrum Showing the Final Formulation

Table 1: Evaluation of Clevidipine CR Tablets – Pre-Formulation Studies

Code for The Formulation	Values for BD	TD Values	CI Values	Values of hansures	AR Values
Formulation-1	0.42	0.51	16.5	1.43	12.54
Formulation-2	0.41	0.42	12.8	1.48	12.35
Formulation-3	0.49	0.55	12.90	1.12	11.56
Formulation-4	0.45	0.52	113.65	1.23	9.15
Formulation-5	0.38	0.46	16.65	1.55	18.22
Formulation-6	0.43	0.51	18.90	1.44	13.12
Formulation-7	0.39	0.38	7.58	1.05	11.22
Formulation-8	0.38	0.48	18.10	1.48	17.4
Formulation-9	0.35	0.49	18.20	1.22	11.96
Formulation-10	0.35	0.51	19.6	1.58	12.26
Formulation-11	0.41	0.52	15.3	1.39	13.62
Formulation-12	0.43	0.45	8.8	1.02	11.85

Table 2: Post formulation studies of Clevidipine CR Tablets

Formulation Code	% weight vaiation	Thickness (millimeter)	% Friability	% Drug Content	Hardness (Kg/cm^2)
F1	passed	2.66±0.11	0.25	101.0 ±1.1	6.58 ±0.17
F2	passed	2.93±0.15	0.12	101.3 ±1.5	6.23 ±0.15
F3	passed	4.06±0.057	0.15	98.8±1.3	6148 ±0.13
F4	passed	4.81±0.1	0.22	102.7 ±0.8	6.58 ±0.04
F5	passed	4.03±0.05	0.28	99.6±1.2	6.23 ±0.05
F6	passed	3.83±0.15	0.13	97.9 ±2.1	6.2 ±0.02
F7	passed	4.93±0.05	0.19	98.2± 1.7	6.7 ±0.10
F8	passed	5.26±0.1	0.28	98.5± 1.4	6.93 ±0.05
F9	passed	4.02±0.2	0.18	98.2±1.3	6.39 ±0.02
F10	passed	4.48±0.14	0.21	100.3 ±1.4	6.86 ±0.03
F11	passed	4.91±0.18	0.32	101.2± 1.6	6.72 ±0.12
F12	passed	5.14±0.12	0.16	100.3 ±1.8	5.89 ±0.13

Table 3: Dissolution profile

Parameter	Details
Dissolution Instrument	Paddle type
Buffer	Potassium Buffer pH-6.8
Volume of Media	Nine hundred ml
Paddle Speed	Fifty rpm
Temp	37± 0.5 ºC
Sample taken	Five ml
Sample Withdrawal Time	1,2,4,6,8,10 and 12 hr
Method of Anlaysis	UV VIS Method
Wavelength	263 nm

Table 4: In-vitro dissolution results of formulation trials

TIME (hrs)	% Release of Drug											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	**0**	0	0	0	0	0	0	0	0	0	0
1	39	**16**	33	14	16	13	32	38	28	35	25	31
2	50	**26**	49	21	29	24	45	65	41	61	39	55
4	69	**41**	58	37	40	36	69	84	64	79	60	69
6	81	**62**	67	59	50	48	81	100	77	96	76	81
8	96	**81**	75	68	67	59	94		87	100	84	93
10	100	**94**	86	77	78	69	100		100		100	100
12		**100**	93	89	84	81						

Table 5: In-vitro dissolution results of formulation trials

TIME (hrs)	% Release of Drug											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	**0**	0	0	0	0	0	0	0	0	0	0
1	39	**16**	33	14	16	13	32	38	28	35	25	31
2	50	**26**	49	21	29	24	45	65	41	61	39	55
4	69	**41**	58	37	40	36	69	84	64	79	60	69
6	81	**62**	67	59	50	48	81	100	77	96	76	81
8	96	**81**	75	68	67	59	94		87	100	84	93
10	100	**94**	86	77	78	69	100		100		100	100
12		**100**	93	89	84	81						

Table 6: Kinetic values of Formulation

Formulation Code	R^2 value				n value
	"0" Order	"1st "order	Plot of Higuchi	Plot of Peppas	
Formulation-1	0.865	0.932	0.992	0.995	0.424
Formulation-2	0.985	0.879	0.962	0.994	0.767

Formulation-3	0.862	0.94	0.984	0.98	0.385
Formulation-4	0.974	0.986	0.965	0.99	0.778
Formulation-5	0.965	0.975	0.979	0.988	0.657
Formulation-6	0.982	0.996	0.975	0.995	0.707
Formulation-7	0.914	0.992	0.993	0.995	0.532
Formulation-8	0.885	0.993	0.991	0.967	0.526
Formulation-9	0.925	0.994	0.997	0.997	0.575
Formulation-10	0.885	0.987	0.982	0.968	0.546
Formulation-11	0.952	0.994	0.993	0.999	0.621
Formulation-12	0.863	0.961	0.988	0.949	0.519

4. Conclusion

This study aimed to compare two polymers Xanthan gum and Tragacanth and examine how the physicochemical characteristics of active ingredients affect drug release profiles using the liquid-solid compact method with PEG400 and Tween 80. Measurements, including all the parameters like angle of repose index of compressibility and sieve Analysis, confirmed and final optimized formulation suitability of the liquid-solid compaction method. The results indicated that Clevidipine could serve effectively in a controlled-release drug delivery system, providing extended therapeutic action within a safe concentration range, unlike conventional dosage forms. This type of formulation could also help reduce dosing frequency and improve patient adherence. Analysis of the drug release data revealed a first-order kinetic model, with the release mechanism consistent with the Higuchi model. Successful dissolution studies indicate that final formulation holds promise future development of the evaluation, potentially improving patient compliance.

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