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Formulation and Evaluation of Controled Release Tablets of Efonidipine

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A B S T R A C T
This study aimed to develop and evaluate controlled-release (CR) tablets of Efonidipine, focusing on calibration curve construction and tablet property assessment. Calibration curves were established in Acid media(0.1N hydrochloric acid) and Potassium Buffer having pH-6.8, with absorbance measured at 271 nm and 270 nm, respectively, showing excellent linearity ($R^2 = 0.999$) in the 2 to 10 µg/ml concentration range. Pre-compression studies indicated good flow properties, with Carr's index (≤ 18%) and Hausner's ratio (1.09-1.21) within acceptable limits, and an angle of repose between 22.17° and 31.11°. Post-compression evaluations confirmed consistent tablet weights, thickness (5.82-5.91 mm), hardness (5.9-6.3 kg/cm²), friability (<1%), and drug content within 98-102%. In vitro dissolution studies conducted in 0.1N HCl and 6.8 sodium phosphate buffer showed significant drug release over 12 hours, with varying profiles across formulations. Kinetic modeling using zero-order, first-order, Higuchi, and Korsmeyer-Peppas plots indicated diverse release mechanisms, with most formulations demonstrating anomalous transport. These results suggest that the Efonidipine CR tablets have potential for controlled drug delivery applications.

Keywords: Efonidipine, First order, Second order, Korsmeyer-Peppas, Hausner's ratio

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

The quest to enhance the therapeutic efficacy and patient compliance of pharmaceutical compounds has driven significant advancements in drug delivery systems. Controlled release formulations, specifically, have revolutionized the way medications are administered, ensuring a consistent release of the drug over an extended period, thereby maintaining therapeutic levels in the bloodstream. Efonidipine, a dihydropyridine calcium channel blocker, is a prime candidate for such formulations. Known for its dual action on both L-type and T-type calcium channels, Efonidipine effectively reduces hypertension by inducing vasodilation and decreasing peripheral resistance. However, its relatively short half-life necessitates frequent dosing, which can lead to patient non-compliance. Developing controlled release tablets of Efonidipine presents a promising approach to mitigate these limitations and improve its clinical outcomes.

Significance and Rationale

Efonidipine's mechanism of action involves the inhibition of calcium influx through voltage-dependent calcium

channels in the vascular smooth muscle and cardiac myocytes. This dual inhibition results in vasodilation and a subsequent reduction in blood pressure. Despite its efficacy, the conventional dosage form of Efonidipine requires multiple daily administrations to maintain therapeutic levels, which can be burdensome for patients, particularly those managing chronic conditions such as hypertension. Controlled release formulations can address this challenge by releasing the drug at a controlled rate, ensuring sustained therapeutic levels and reducing the frequency of administration. This not only enhances patient adherence but also stabilizes blood pressure control, minimizing the risk of hypertensive crises and related complications.

The rationale for developing controlled release tablets of Efonidipine is further supported by its pharmacokinetic profile. Efonidipine exhibits a relatively rapid absorption and clearance, necessitating frequent dosing to achieve effective plasma concentrations. By incorporating the drug into a controlled release matrix, it is possible to modulate the release kinetics, extending the duration of action and enhancing its overall therapeutic efficacy. This approach aligns with the principles of sustained drug delivery, aiming to optimize drug therapy and improve patient outcomes.

Formulation Strategies

The formulation of Efonidipine into controlled release tablets involves the selection of suitable polymers and excipients that can modulate the drug release profile. Various formulation strategies can be employed, including hydrophilic matrix systems, hydrophobic matrix systems, and multi-particulate systems. Each strategy offers distinct advantages and challenges, necessitating a thorough understanding of the drug's physicochemical properties and the desired release kinetics.

Hydrophilic Matrix Systems:

In this approach, Efonidipine is embedded within a hydrophilic polymer matrix, which controls the release of the drug through swelling and diffusion mechanisms. Polymers such as hydroxypropyl methylcellulose (HPMC) are commonly used due to their ability to form a gel-like barrier when exposed to gastrointestinal fluids. As the polymer hydrates and swells, the drug is released gradually through the gel matrix. The rate of drug release can be tailored by adjusting the polymer concentration and the degree of cross-linking.

Hydrophobic Matrix Systems:

Hydrophobic matrix systems involve the incorporation of Efonidipine into a matrix composed of hydrophobic polymers such as ethylcellulose. These polymers form a non-swelling barrier that controls drug release through a combination of diffusion and erosion mechanisms. The drug release rate can be modulated by varying the polymer content and the porosity of the matrix. This approach is particularly useful for drugs with poor water solubility, as it enhances their dissolution and bioavailability.

Multi-Particulate Systems:

Multi-particulate systems, such as pellets and microspheres, offer a flexible approach to controlled drug delivery. In this strategy, Efonidipine is encapsulated within small, discrete particles that can be coated with polymers to control the release rate. The multi-particulate nature of these systems allows for uniform distribution in the gastrointestinal tract, reducing the risk of dose dumping and ensuring a consistent release profile. Polymers such as poly(lactic-co-glycolic acid) (PLGA) are commonly used for encapsulation due to their biocompatibility and controlled degradation properties.

Evaluation and Assessment

The evaluation of controlled release tablets of Efonidipine 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. Dissolution testing involves the use of different media, such as simulated gastric and intestinal fluids, to assess the release behavior of the tablets.

In vivo pharmacokinetic studies in animal models and clinical trials in human subjects are essential to validate the controlled release formulations. These studies assess 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

Ingredients and Manfactures

The formulation of the drug involved the use of various high-quality ingredients, each sourced from reputable suppliers. Efonidipine was supplied by Qualychrome Lab, ensuring the purity of the active pharmaceutical ingredient. Several excipients were obtained from SRL Chemicals, including HPMC K 100m, Sodium Alginate, Guar Gum, Avicel PH102 (MCC), Aerosil, and Magnesium Stearate. These carefully selected components were essential for creating a reliable and effective drug formulation, providing the necessary properties for sustained release and stability.

Analysis Procedure for Creating the Standard Calibration Curve for Efonidipine:

Chemicals: 0.1N Buffer Solution of Hydrochloric Acid 6.8 Solution in Buffer. Procedure for making 6.8 buffer solutions and 0.1n HCL. The 0.1N Hcl solution is prepared as follows: 8.5 millilitres of strong hydrochloric acid were diluted with 1000 millilitres of distilled water to create 0.1N Hcl.

Making the 6.8 pH Potassium Buffer:

To prepare a stock solution of monobasic potassium phosphate, 27.22 grams of the compound were measured

and then diluted to a total volume of 1000 milliliters. For the 0.2M sodium hydroxide solution, 8 grams of sodium hydroxide were weighed and also diluted to 1000 milliliters. In a 200 mL volumetric flask, 50 milliliters potassium buffer was combined with 22.4 milliliters of the 0.2M sodium hydroxide solution, and then distilled water was added to reach the final volume.

The idea

a) Efonidipine standard solution with 0.1 N Hcl: 100 cc of methanol is used to dissolve 100 milligrammes of the medication. This is the first stock solution.100 millilitres of 0.1N hydrochloric acid buffer are used to dilute 10 millilitres of the first stock solution.

b) Efonidipine standard solution utilising 6.8 pH Potassium Buffer: 100 mg medication taken into 100 ml ofcarbinol. 100ml of 6.8 buffer is used to dilute 10ml of the first stock solution. The second stock solution is this one. Now, using the same 6.8 buffers, different concentrations of 2 ug/ml, 4 ug/ml, 6 ug/ml, 8 ug/ml, and 10 ug/ml were generated from the second stock. With the exception of the medication, blank was likewise made using the identical buffer composition. In comparison to the blank, all of the samples were examined at 270 lambda max.

III. Preparation of matrix tablets by non aqueous wet granulation method:

- Efonidipine+ polymers+ Diluent are cosifted through sieve no. 60# and mix in a bag for ten minutes.
- Blend after preparation was granulated by taking isopropyl alcohol.
- The above granules were lubricated with sieve no. 60#.Sifted colloidal silicon dioxide (Aerosil-200) and magnesium stearate mix in a poly bag for 5 min.
- Lubricated granules were compressed by rotary machine having round concave shaped punches with an average wt of 500 mg, & min hardness of 5-6 kg/cm^2.

Tablets Evaluation

Quality control, in vitro buoyancy, and dissolving investigations were conducted on the tablets following compression.

B) Post compression studies:

1.Description: The prepared tablets have to check description of the tablet

Uniformity of weight:

Twenty tablets were weighed both collectively and individually. The average weight was determined from the combined weight of all tablets. Each tablet's individual weight was then compared to this average to ensure it met the acceptable range. For tablets weighing 300 mg, no more than two individual weights could deviate from the average by over 7.5%, and no single tablet could exceed twice that percentage.

Thickness: The thickness of each tablet was measured using a Verniercaliper.

Hardness Test: Three tablets were tested for hardness euipment of hardness tester. Placing the tablet with the bottom plunger in contact allowed for the initial zero reading to be recorded. The plunger was pressed against a spring until the tablet broke, and this was accomplished by rotating a bolt that was threaded. A pointer moved along a gauge in the barrel to represent the applied force as the spring compressed.

Friability test:

To assess the tablet's resistance to abrasion during packing, handling, and transportation, 20 tablets were weighed and placed in a friabilator, which rotated at 25 rpm for 4 minutes. The weight difference before and after the test was recorded and calculated as a percentage to determine friability.

It should be preferably between 0.5 to 1.0%.

%Friability = [(W1-W2)/W1] X 100

Where, W1= Initial weight of tablets,

W2 = weight of tablets after friabialation

5. The Assay Method.

At least 20 pills should be weighed and coarsely powdered. Fill a 10 ml volumetric flask with a precisely weighed fraction of the powder, which is equal to around 10 mg of the model medicine. To finish the extraction, add around 6 ml of 0.1N Hydrochloric acid, mix, and sonicate for 10 minutes. Mix the methanol after diluting it to volume. One millilitre of the aliquot should be pipetted into a 10-milliliter volumetric flask, diluted with mobile phase to volume, mixed, and filtered. Take a 1 ml aliquot out of it and use buffer to label it. Determine the model drug's dosage in milligrammes. In the section extracted using the formula

assay = test absorbance/standard absorbance*standard concentration/sample concentration*drug purity/100* 100, hydrochloride

In-vitro Drug Release Studies:

In vitro Dissolution Studies At 100 rpm, the USP 24 dissolving equipment type II14 (paddle technique) was used to conduct the in vitro dissolution investigations. A 12-hour dissolve test was conducted using a 0.1N HCl (pH 1.2) solution (750 ml) as the hydrochloride, a pH 6.8 phosphate buffer solution (1000 ml), and a dissolution medium at 37 ± 0.5° for the first two hours. At regular intervals, ten millilitres of the sample were removed and replaced with the same volume of freshly heated (37 ± 0.5°) dissolving media. The extracted samples were filtered using a 0.45 µ membrane filter, and the drug concentration of each sample was measured using a UV-visible spectrophotometer at the appropriate λ max of each dissolving medium following the appropriate dilution.

In-vitro release kinetics studies:

studying how a pharmaceutical dosage form releases its contents is an important but difficult process that is easily observable in matrix systems. The drug release sequence from FDDS was characterised using either zero-order or first-order kinetics. Investigating how FDDS releases its pharmacological components was done using the Higuchi equation and the Peppa's-Korsemeyer equation.

3. Results and Discussion

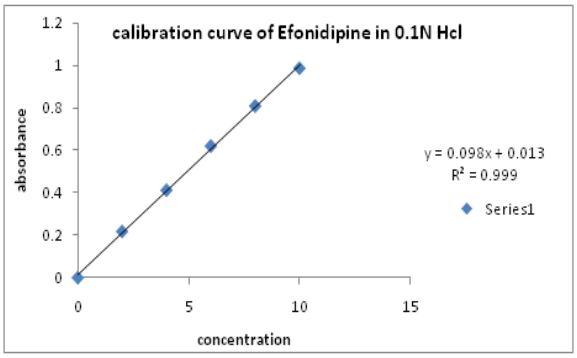

Figure 1: calibration curve of Efonidipine in 0.1N hydrochloric acid at λMax = 271 nm

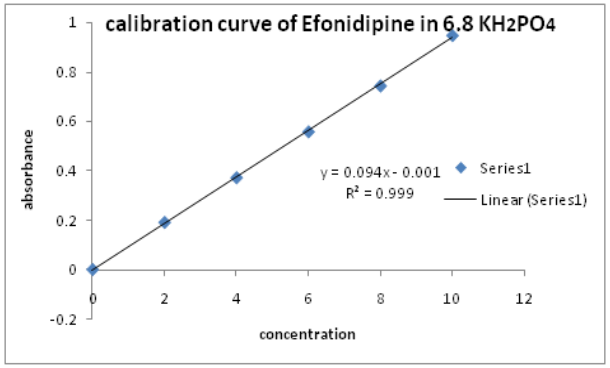

Figure 2: Standard calibration curve of Efonidipine in 6.8 phosphate buffer at λMax = 270nm

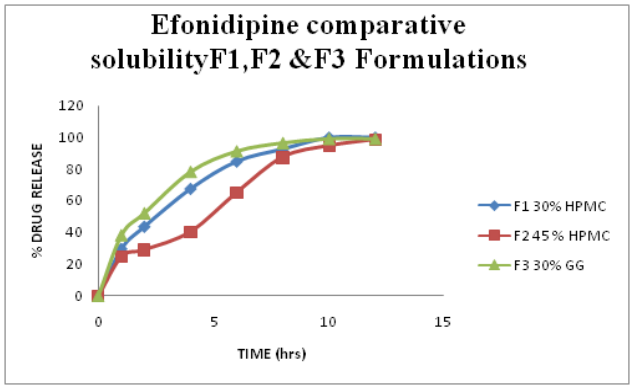

Figure 3: Efonidipine's comparative solubility F1, F2, and F3 formulations

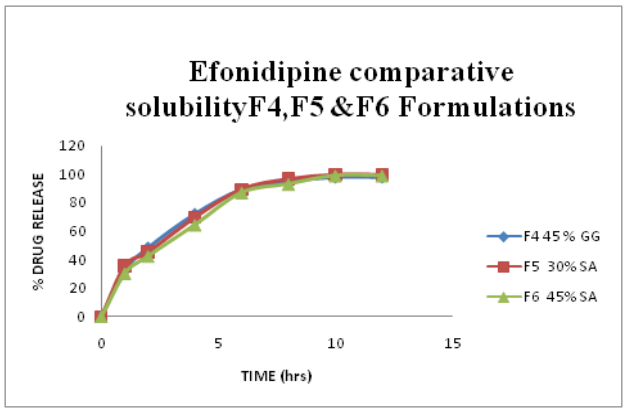

Figure 4: Efonidipine comparative solubilityF4,F5& F6 Formulations

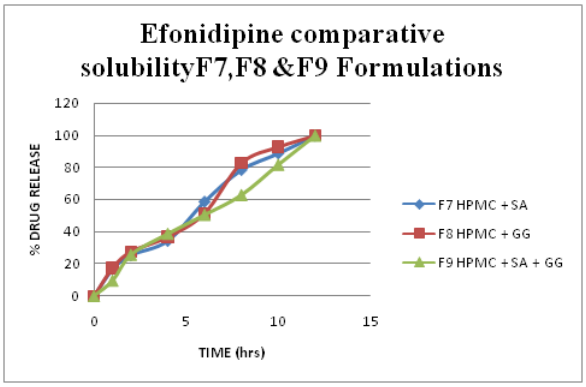

Figure 5: Efonidipine comparative solubilityF7,F8&F9 Formulations

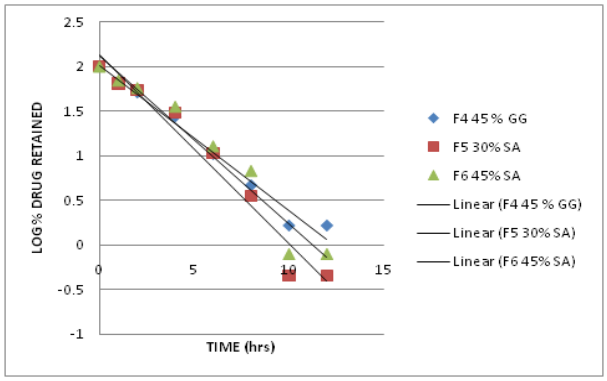

Figure 7: Formulation 4 to First order

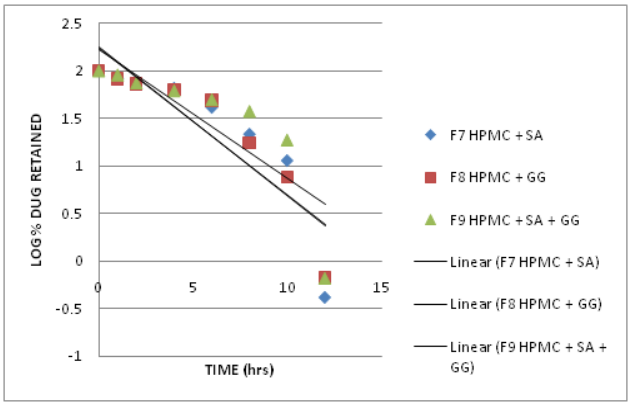

Figure 8: Formulation 7 to 9 First order

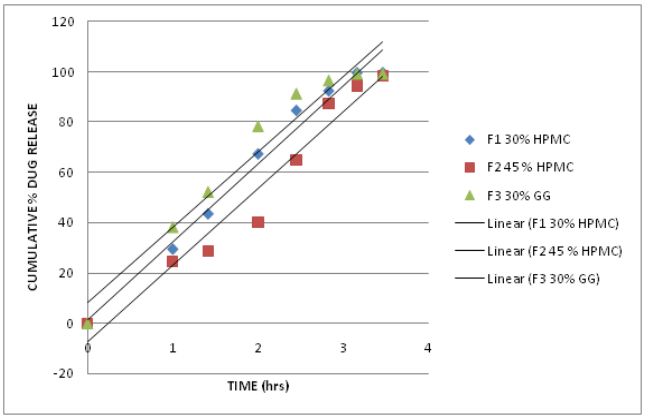

Figure 9: Figure 11: Formulation F1 to F3 Higuchi

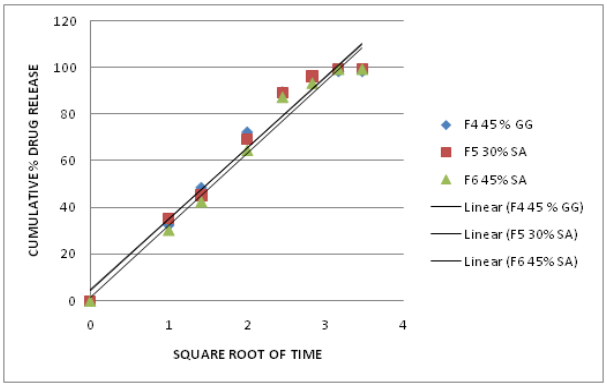

Figure 10: Formulation F4 to F6 Higuchi

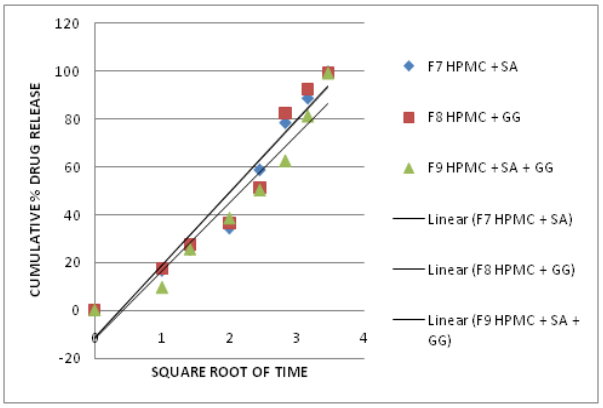

Figure 11: Formulation F7 to F9 Higuchi

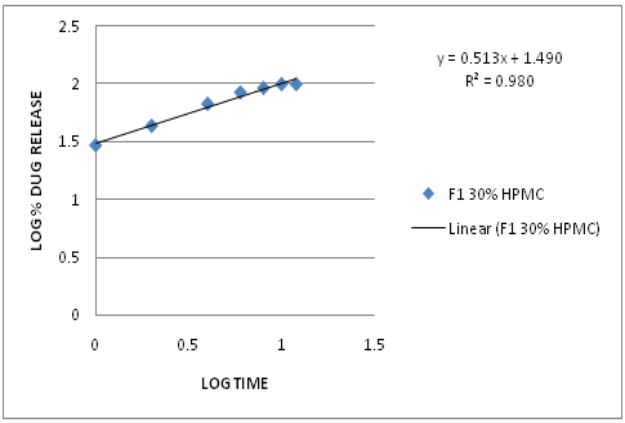

Figure12: korsmayerspepas plot for formulationF1

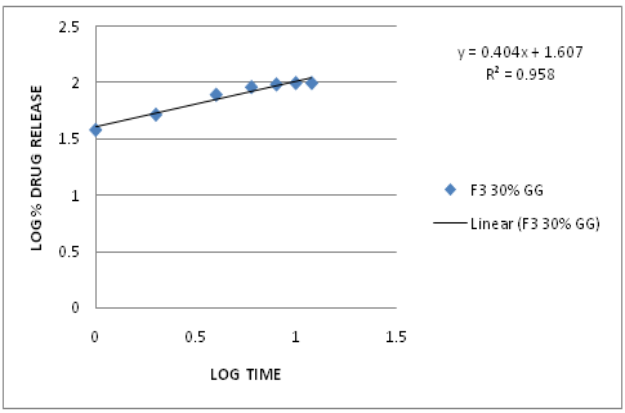

Figure 14: korsmayerspepas plot for formulationF3

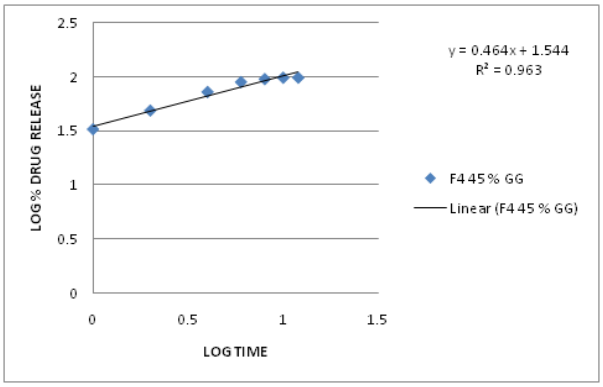

Figure15: korsmayerspepas plot for formulationF4

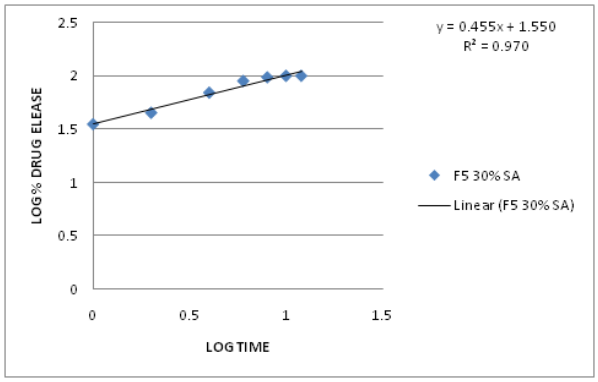

Figure16: korsmayerspepas plot for formulationF5

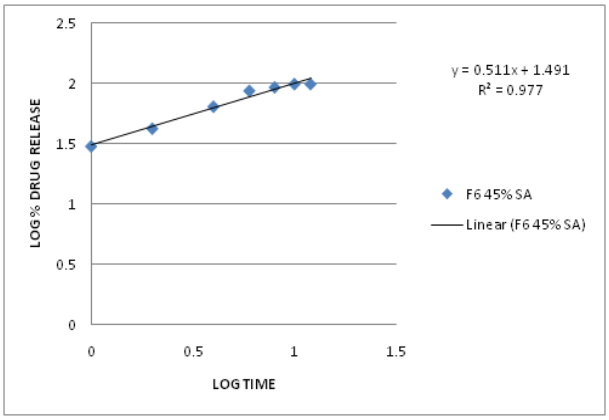

Figure16: korsmayerspepas plot for formulationF5

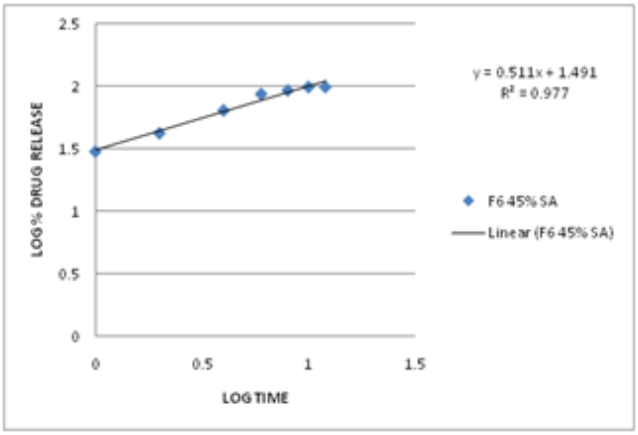

Figure 17: korsmayerspepas plot for formulation F6

Table 1: In-vitro Dissolution Studies

Dissolution Condition	**Types**
Apparatus Type	Paddle type
Medium taken	HCL (0.1N) and KH_2PO_4
Media	Nine hundred milliliter
Paddle rotation	Hundred rotations
Temp(^{0}C)	37.05± 0.5 ºC
Test Solution withdrawn	Five milliliter
Intervals	One, Two, Four,Six,Eight ,ten and twelve hours.
Analysed by	U V Spectrophotometer
λ_{max}	271 nm

Table 2: Efonidipine formulation table for f1 –f6 formulations

S.no	**Ingredients**	**F1 HPMC**	**F2 HPMC**	**F3 GG**	**F4 GG**	**F5 SA**	**F6 SA**
INTRAGRANULAR							
	Efonidipine	20	20	20	20	20	20
	HPMC K100M	10	20	--	--	--	--
	Sodium Alginate	--	--	--	--	10	20
	Guar gum	--	--	10	20	--	--
	Avicel PH 102	160	150	160	150	160	150
Extragranular							
	Aerosil	5	5	5	5	5	5
	Mg Stearate	5	5	5	5	5	5
	Total	200	200	200	200	200	200

Table 3: Efonidipine formulation table for f7 – f9 formulations

Sno	**Ingredients**	**Qty per Tablet (mg)**			**Purpose**
		F7 HPMC+SA	**F8 HPMC+GG**	**F9 HPMC+SA+GG**	
Intragranular					
1	Efonidipine	20	20	20	API
2	HPMC K100M	20	20	20	Synthetic CR Polymer
3	Sodium Alginate	50	--	25	Natural CR Polymer
4	Guar gum	--	50	25	Natural CR Polymer
5	Avicel PH 102	100	100	100	diluent
Extra granular					
6	Aerosil	5	5	5	glidant
7	Mg Stearate	5	5	5	lubricant
	Total	200	200	200	

Table 4: In-vitro Dissolution Studies

Dissolution Condition	**Types**
Apparatus Type	Paddle type
Medium taken	HCL (0.1N) and KH_2PO_4
Media	Nine hundred milliliter
Paddle rotation	Hundred rotations
Temp(^{0}C)	37.05± 0.5 ºC
Test Solution withdrawn	Five milliliter
Intervals	One, Two, Four,Six,Eight ,ten and twelve hours.
Analysed by	U V Spectrophotometer
λ_{max}	271 nm

Table 6: graph values of Efonidipine6.8 phosphate buffer at λ_{Max} = 270 nm

Conc	Absorbance at λ_{Max} = 270 nm
0	0
2.0	0.185
4.0	0.362
6.0	0.541
8.0	0.732
10	0.922

Table 7: Post compression studies of Efonidipine CR tablets

Formulation Code	Post compression studies				
	Avg. Wt (mg) (n=20)	Thickness (mm) (n=3)	Hardness (kp) (n=3)	*%Friability	%Drug content (n=3)
F1	200±0.6	5.82±0.34	5.9±0.26	0.59	99.98±0.18
F2	200±0.4	5.91±0.23	6.2±0.25	0.68	100.21±0.20
F3	200.6±0.4	5.84±0.1	6.3±0.21	0.58	99.67±0.12
F4	198.0±0.3	5.88±0.1	5.9±0.23	0.59	100.32±0.14
F5	199.6±0.4	5.84±0.1	6.3±0.21	0.58	99.67±0.12
F6	202.2±0.4	5.91±0.23	6.2±0.25	0.68	100.21±0.20
F7	200.4±0.6	5.82±0.34	5.9±0.26	0.59	99.98±0.18
F8	202.2±0.4	5.91±0.23	6.2±0.25	0.68	100.21±0.20
F9	199.6±0.4	5.84±0.1	6.3±0.21	0.58	99.67±0.12

Table 8: Dissolution profile

Dissolution Condition	Types
Apparatus Type	Paddle type
Medium taken	HCL (0.1N) and KH_2PO_4
Volume	900 ml
Speed	100 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1,2,4,6,8,10 and 12hr
Analytical method	U V Spectroscopy
λ_{max}	271 nm

4. Conclusion

As the conc. of CR polymer increases the order of CR is also increasing F2 >F1(HPMC), F4 > F3 (GG),F6 > F5 (SA). When the CR tablets with only natural CR polymers (SA & GG) were tried in both concs. (30% & 45%) no CR was obtained upto 12 hrs, hence there are not intended to use alone for CR. In all the CR polymers 45 % of HPMC (F2) is showing better CR, hence for further studies to know the effect of natural CR polymers (SA & GG) with HPMC, the 45% OF HPMC is kept constant.(F7,F8 & F9). Out of all formulations the 45% HPMC + 10%SA + 10% GG, (F9) is having better CR, due to combination of various release mechanism characters of all three polymers. The order of CR F9>f7>F8 From the dissolution data evident that the order of CR was It is evident that CR was better attained with combination of HPMC & the two natural polymers, than HPMC + single Natural polymer or HPMC alone.

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