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FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF OSMATIC CONTROLLED DRUG DELIVERY SYSTEM OF VERAPAMIL HYDROCHLORIDE

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ABSTRACT

It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semipermiable membrane in-situ releases from such a matrix system containing an osmogen could, therefore be modulated by the osmotic phenomenon. Osmat thus judiciously combines both matrix osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix system. Osmat produces controlled drug release with adequate delivery rates in an agitation in dependent manner. Thus osmat represents simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cot technology.

Keywords: Verapamil, Osmatic, Controlled drug delivery system.

INTRODUCTION

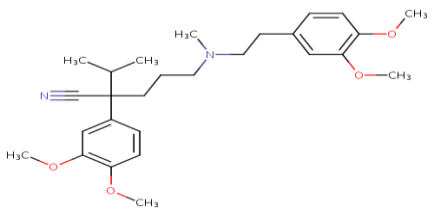
There are various types of polymers are used as semi permeable membrane .the selection of polymer is based on the solubility of drug as well as amount and rate of drug to be released from pump. Cellulose acetate is commonly used polymer for preparation of semi permeable for osmotic pump devices [1]. Different grades of cellulose acetate with different acetyl content usually 32% and 38% are mostly used. A part from cellulose derivative, some other polymers such as poly (vinyl methyl) ether copolymer, poly (orthoester), poly acetals and selectively permeable poly (glycolic acid) and poly(lactic acid) derivatives, Eudragit can be used as semi permeable film forming materials [2]. The permeability is the most important criteria for the selection of semi permeable membrane. Therefore, the polymeric membrane selection is important to osmotic delivery formulation [3].

Plasticizers have a crucial role to play in the formation of a film coating and its ultimate structure. Plasticizers increases the workability, flexibility and permeability of fluids .generally from 0.001 to 50 parts of plasticizer or a mixture of plasticizers are incorporated in to 100 part of wall forming material. They can change viscous-elastic behavior of polymers and these changes may affect the permeability of the polymeric films [4]. Plasticizers can have a marked effect both quantitatively and qualitatively on the release of active materials from modified release dosage forms where they are incorporated into the rate-controlling membrane36. Some of the plasticizers used are as below: Polyethylene glycols, Glycolate, Glycerolate, myristates, Ethylene glycol monoacetate; and diacetate- for low permeability, Tri ethyl citrate, Diethyl tartarate or Diacetin- for more permeable films [5].

VERAPAMIL

A calcium channel blocker that is a class IV anti-arrhythmia agent.

Structure



Systematic (IUPAC) name: 2-(3,4-dimethoxyphenyl)-5-{[2-(3,4-dimethoxyphenyl)ethyl](methyl)amino}-2-(propan-2-yl)pentanenitrile

Physiochemical Data:

Formula : $C_{27}H_{38}N_2O_4$

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Molecular weight : 491.06
Melting point : 140-144^{0}c
Solubility : Soluble in water; sparingly soluble in chloroform; soluble in ethanol, isopropyl alcohol, acetone, ethyl acetate; freely soluble in methanol, DMF, partially insoluble in ether.

Pharmacology: For the treatment of hypertension, angina, and cluster headache prophylaxis.

Pharmacodynamics: Verapamil is an L-type calcium channel blocker that also has antiarrythmic activity. The R-enantiomer is more effective at reducing blood pressure compared to the S-enantiomer. However, the S-enantiomer is 20 times more potent than the R-enantiomer at prolonging the PR interval in treating arrhythmias.

Mechanism of action: Verapamil inhibits voltage-dependent calcium channels. Specifically, its effect on L-type calcium channels in the heart causes a reduction in ionotropy and chronotropy, thuis reducing heart rate and blood pressure. Verapamil's mechanism of effect in cluster headache is thought to be linked to its calcium-channel blocker effect, but which channel subtypes are involved is presently not known.

Pharmacokinetic characters
Absorption: 90%
Protein binding: 90%
Half-life: 2.8-7.4 hours
Toxicity: LD_{50}=8 mg/kg (i.v. in mice)
Affected organisms: Humans and other mammals

MATERIALS AND METHODS

Preparation of 0.1 N Hydrochloric Acid (pH 1.2) with 0.5% SLS

8.5 ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000 ml. Then add and dissolve 5gm of sodium lauryl sulphate in same solution.

Determination of Verapamil λ_{max} in 0.1N HCL with 0.5% SLS

Procedure

Working standard: 100mg of Verapamil was weighed and dissolved in 10ml methanol and then make up to the volume with 0.1N HCL with 0.5% SLS, it give 1000µg/ml concentrated stock solution.
Dilution 1: From the working standard, 10ml solution was diluted to 100ml with 0.1NHCL with 0.5% SLS, it will give 100µg/ml concentrated solution.
Dilution 2: From the dilution1, 10ml solution was diluted to 100ml with 0.1NHCL with 0.5% SLS, it will give 10µg/ml concentrated solutions.

This solutions was scanned at range of 200-400nm wavelength light corresponding scan spectrum curve was noted .the corresponding wavelength having highest absorbance is noted as λ_{max}.

Construction of calibration curve of Verapamil in 0.1N HCL with 0.5% SLS

Procedure:

Working standard: 100mg of Verapamil was weighed and dissolved in 10ml methanol and then make up to the volume with 0.1NHCL with 0.5% SLS, it give 1000µg/ml concentrated stock solution.
Dilution 1: From the working standard, 10ml solution was diluted to 100ml with 0.1NHCL with 0.5% SLS, it will give 100 µg/ml concentrated solutions.
Dilution 2: From dilution 1, take 0.2, 0.4, 0.6, 0.8, and 1ml of solution was diluted up to the mark with 0.1NHCL with 0.5% SLS in 10ml volumetric flask to obtain 2, 4, 6, 8 and 10µg/ml concentrated solutions. This solutions absorbance was noted at 241nm.

II. Preparation of core tablets

Procedure

Accurately weighed quantities of ingredients mentioned in formula were passed through sieve no.80. The entire ingredients, except lubricant (magnesium stearate) were manually blended homogeneously in a motor by geometric dilution. Finally blended with magnesium stearate. The homogeneous blend was then compressed into tablets by using concave punches. The compression was adjusted to tablet with approximately 7-8 kg cm^2 hardness.

Coating of tablet

The tablet coatings were applied using dip coating process. The tablets were dip coated in polymer solution consisting of CAP (cellulose acetate phthalate) dissolved in solutions of acetone, water and PEG. In this, cores to be dipped into coating solution and then dried taking care to prevent adherence to one another. For obtaining more perfect or heavier coats the dipping and drying steps repeated several times one after another.

EVALUATION OF TABLETS

The formulated tablets were evaluated for the following Pre and Post compression quality control studies

A) Pre Compression studies:

1. **Angle of Repose:** It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation [6].

$$\theta = \tan^{-1} (h/r)$$

Where:

θ = angle of repose
h = height in cms
r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

2. Density:

a. Bulk density (BD): It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22#sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

Bulk density = weight of powder/ Bulk volume.

$$\mathbf{D_b} = \frac{M}{V_0}$$

M = mass of the powder

V_0 = bulk volume of the powder.

b. Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder. Weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula.

Tapped density = Weigh of powder / Tapped volume

Dt = *(M)* / (V_f).

M = mass of the powder,

V_f = tapped volume of the powder.

3. Carr's Index: Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below:

$$\textbf{Compressibility index} = 100 \times \frac{\text{Tappeddensity} - \text{Bulk density}}{\text{Tappeddensity}}$$

4. Hausner's Ratio:Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$\textbf{Hausner's Ratio} = \frac{\text{TappedDensity}}{\textit{Bulk Density}}$$

B. Post compression studies

1. General appearance: The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

2. Average weight/Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

3. **Thickness:** Thickness of the tablets (n=3) was determined using a Vernier callipers.

4. **Hardness test:** Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

5. **Friability test:**This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting.

Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min.

The difference in the weight is noted and expressed as percentage.

It should be preferably between 0.5 to 1.0%.

% Friability = $[(W_1-W_2)/W_1]$ X 100

Where, W_1= weight of tablets before test,

W_2 = weight of tablets after test

Content uniformity test: Ten tablets were weighed and powdered, a quantity of powder equivalent to 100 mg of Drug was transferred to a 100 ml volumetric flask and 10 ml methanol is added. The drug is dissolved in methanol by vigorously shaking the volumetric flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the solution is filtered. From prepared solution take 1ml solution in 100ml volumetric flask and make up to mark with distilled water. The Drug content was determined by measuring the absorbance at suitable wavelength after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations [7].

Calculate the quantity in mg of drug in the portion taken by the formula

$$Assay = \frac{TestAbsorbance}{StandardAbsorbance} * \frac{StandardConcentration}{SampleConcentration} * \frac{Averageweight}{Labelclaim} * \frac{\%\ Purityofdrug}{100} * 100$$

***In vitro* Dissolution Study** [8]

900 ml of 0.1N HCLwas placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of $37^0C \pm 0.5^0C$. A tablet was placed in the vessel and was

covered; the apparatus was operated up to 12hours at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} =241nm using a UV-spectrophotometer (Lab India).

C. In vitro Release Kinetics Studies: The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from ER was described by using zero order kinetics or first order kinetics. The mechanism of drug release from ER was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

1. Zero Order Release Kinetics:

It defines a linear relationship between the fractions of drug released versus time.

$$\mathbf{Q=k_0t.}$$

Where, Q is the fraction of drug released at time t and $k_o$is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

2. First Order Release Kinetics: Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\mathbf{Log\ C= Log\ C_o\text{-}kt/2.303}$$

Where C is the amount of drug dissolved at time t,
C_o is the amount of drug dissolved at t=0 and k is the first order rate constant.

A graph of log cumulative of log % drug remaining Vs time yields a straight line. Will be linear if the release obeys the first order release kinetics.

3. Higuchi equation: It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$\mathbf{Q=K_2t^{1/2}}$$

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

4. Peppa's-Korsemeyer equation (Power Law): In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa's-Korsemeyer equation (Power Law) [9].

$$\mathbf{Mt/\ M_\infty =K.t^n}$$

Where, Mt is the amount of drug released at time t
M_α is the amount released at time α,
M_t/M_α is the fraction of drug released at time t,
K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug release up to 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value. The kinetic data of the formulations were included. Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using MS EXCEL.

Table 1. List of equipments

S. No.	Name of the Equipment	Model
1	Electronic weighing balance	Scale-tec
2	Friabilator	Roche Friabilator Electrolab, Mumbai
3	Laboratory oven	Dtc-00r
4	Compression machine	Cmd(Cadmach)
5	Tablet hardness tester	Pfizer Hardness Tester, Mumbai
6	UV	Labindia Uv 3000+
7	Dissolution apparatus	Electrolab TDT-08L
8	Vernier calipers	Cd-6"Cs

Table 2. Formulation for Verapamil Osmotic pump tablets

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Verapamil	120	120	120	120	120	120	120	120	120
HPMC K4M	20	40	60	-	-	-	-	-	-
HPMC K15M	-	-	-	20	40	60	-	-	-
HPMC K100M	-	-	-	-	-	-	20	40	60
Mannitol	100	100	100	100	100	100	100	100	100

MCC	103	83	63	103	83	63	103	83	63
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Mg.stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total wt (mg)	350	350	350	350	350	350	350	350	350

Table 3. Preparation of Coating solution

Ingredients	Quantity
Cellulose acetate phthalate	4mg
PEG	0.5ml
Acetone	10ml
Water	1ml

Table 4. Angle of repose limits - Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Table 5. Compressibility index limits - Scale of Flow ability (USP29-NF34)

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

Table 6. Weight variation tolerance for uncoated tablets - Acceptance criteria for tablet weight variation (USP 29-NF 34)

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Table 7. Dissolution parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1 N HCL with 0.5% SLS
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
ime points	1, 2, 4, 8 and 12 hours
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	241nm

Range:

Time (Hours)	% Drug Release
1	12-35%
2	36-43%
4	44-67%
8	68-79%

12	NLT80%

Table 8. Drug release kinetics mechanism

Diffusion exponent(n)	Mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous(Non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

RESULTS AND DICUSSION

Table 9. Standard Calibration graph values of Verapamil in 0.1N HCL with 0.5% SLSat241 nm

Concentration (µg / ml)	Absorbance at 241 nm
0	0
2	0.153
4	0.310
6	0.457
8	0.609
10	0.790

Evaluation of Tablets

A) Pre Compression studies

Table 10. Pre compression studies for Verapamiltablets

Formulation Code	Bulk density	Tapped density	Cars index	Hausners ratio	Angle of repose
F1	0.54	0.61	11.47	1.12	31.26
F2	0.52	0.59	11.86	1.13	32.31
F3	0.45	0.50	10.00	1.11	30.42
F4	0.44	0.51	13.72	1.15	33.81
F5	0.4	0.45	11.11	1.12	32.14
F6	0.48	0.55	12.72	1.14	34.38
F7	0.50	0.56	10.71	1.12	31.75
F8	0.45	0.53	15.09	1.17	37.83
F9	0.46	0.51	09.80	1.10	29.32

B) Post compression studies:

Table 11. Post compression studies of Verapamil tablets

Formulation Code	% Weight Variation	Thickness (mm)	% Friability	% Drug Content	Hardness (Kg/cm^2)
F1	pass	4.92	0.120	101.2	7.69
F2	pass	5.12	0.312	101.5	7.43
F3	pass	5.02	0.13	99.2	7.69
F4	pass	5.02	0.123	99.9	7.48
F5	pass	4.93	0.110	100.2	7.7
F6	pass	5.10	0.133	100.5	7.53
F7	pass	5.03	0.132	99.6	7.63
F8	pass	5.03	0.143	98.9	7.5
F9	pass	5.03	0.62	100.1	7.85

*Test for Friability was performed on singlebatch of 20 tablets

Table 12. *In-vitro* Dissolution results of Formulation trails

Time (Hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	41	38	25	**21**	11	7	11	7	6
2	52	41	35	**32**	26	11	24	22	12
4	68	54	46	**53**	46	33	40	38	27
8	86	74	69	**74**	68	53	60	59	43
12	99	97	97	**98**	89	78	75	71	64

Table 13. R^2 value and n result table

Formulation code	R^2 value				N value
	Zero order	First order	Higuchi	Peppas	
F1	0.805	0.933	0.974	0.999	0.356
F2	0.882	0.901	0.981	0.948	0.381
F3	0.952	0.880	0.983	0.985	0.528
F4	0.952	0.896	0.990	0.996	0.616
F5	0.963	0.979	0.973	0.973	0.815
F6	0.989	0.972	0.924	0.979	1.008
F7	0.953	0.998	0.980	0.977	0.754
F8	0.946	0.993	0.966	0.941	0.895
F9	0.992	0.987	0.937	0.992	0.948

Figure 1. First order plot for F1, F2 and F3formulations

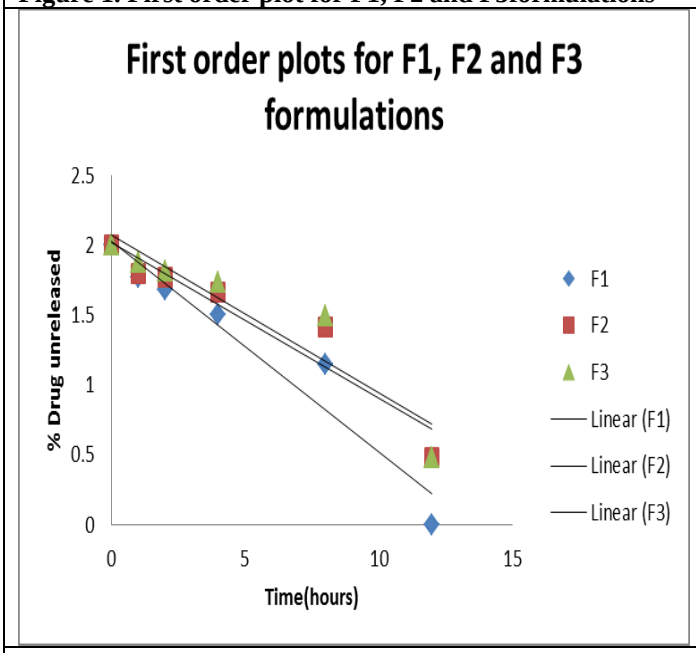


Figure 2. First order plot for F4, F5 and F6formulations

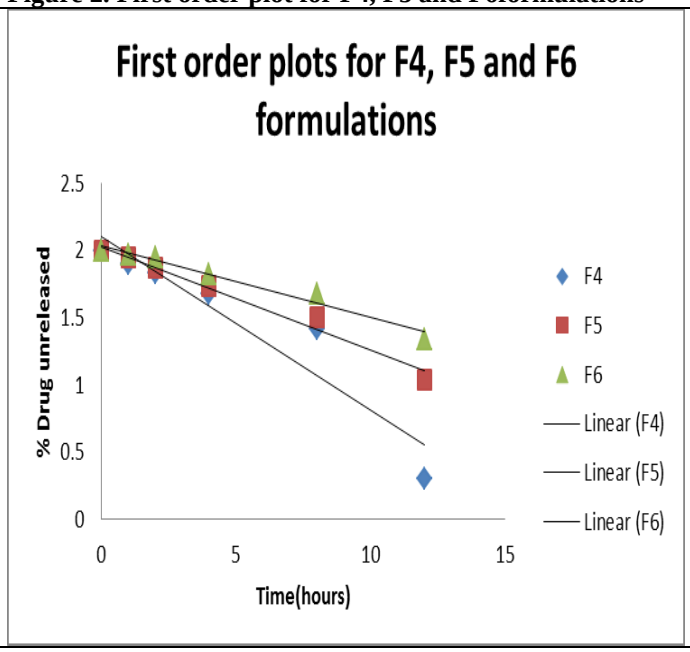


Figure 3. First order plot for F7, F8 and F9formulations

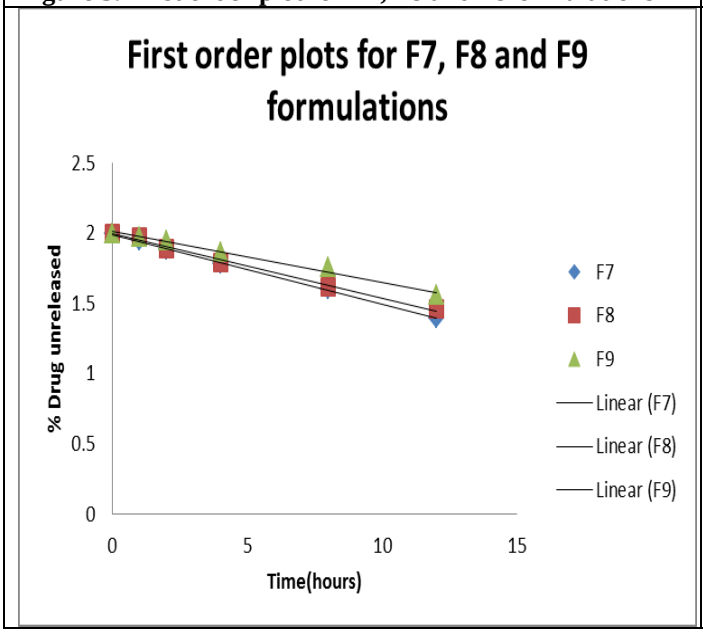


Figure 4. Higuchi plot for F1, F2 and F3 formulations

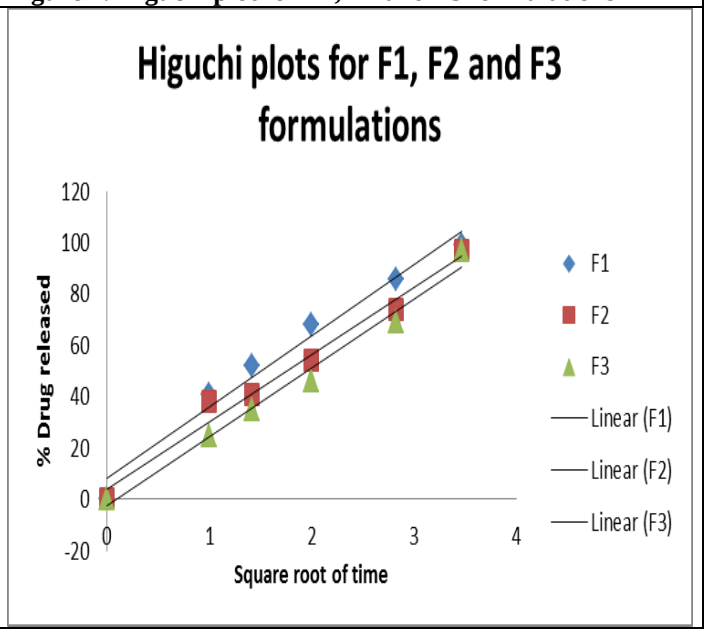


Figure 5. Higuchi plot for F4, F5 and F6 formulations

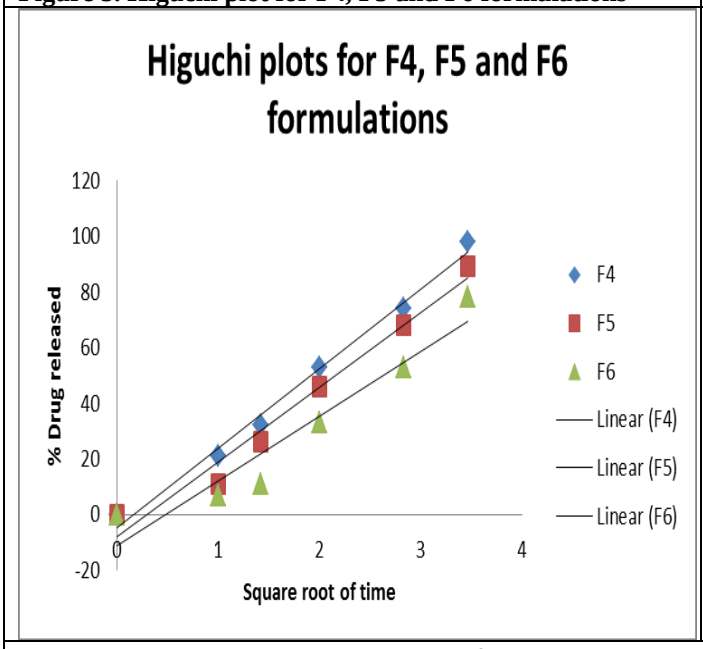


Figure 6. Higuchi plot for F7, F8 and F9 formulations

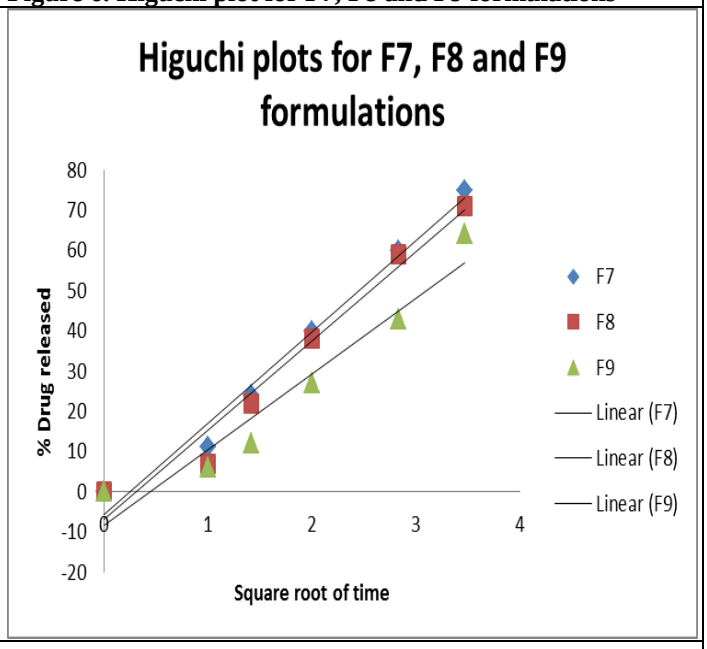
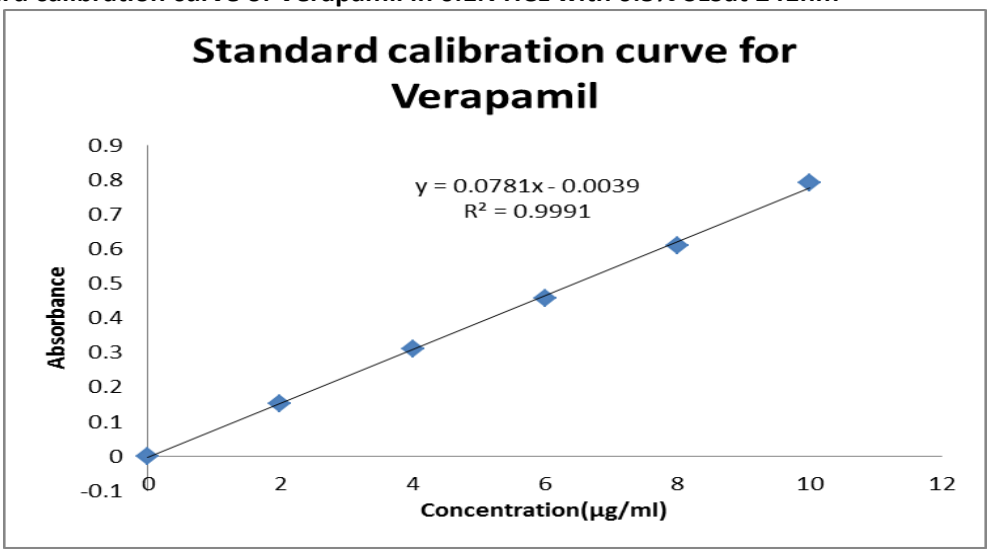


Figure 7. Standard calibration curve of Verapamil in 0.1N HCL with 0.5% SLSat 241nm



Construction of Standard calibration curve of Verapamil in 0.1N HCL with 0.5% SLS

The absorbance of the solution was measured at 241nm, using UV spectrometer with **0.1N HCL with 0.5% SLS**as blank. The values are shown in below table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml.

Standard calibration curve of Verapamil in 0.1N HCL with 0.5% SLSat 241nm

Inference: The standard calibration curve of Verapamil in 0.1N HCL with 0.5% SLSshowed good correlationwith regression value of 0.999

Evaluation of Tablets

A) Pre Compression studies

Pre compression studies for Verapamiltablets

Inference

- Verapamil tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.10 to 1.17 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 29.32-37.83˚ which indicating passable flow.

B) Post compression studies

Post compression studies of Verapamil tablets

Inference

- The variation in weight was within the limit**.**
- The thickness of tablets was found to be between 4.92 – 5.12 mm.
- The hardness for different formulations was found to be between 7.48 to 7.85 kg/cm^2, indicating satisfactory mechanical strength**.**
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 102 %.
- Among the different control release polymers Poly ethylene oxide, HPMC K15M and Ethyl cellulose were showing highest drug release retarding capacity
- F4were showing the satisfactory results.
- For the F4formulation diffusion exponent n value is in between 0.45 to 0.89 so they are following non fickiananmolous diffusion model.

CONCLUSION

The approach of the present study was to make a comparative evaluation among these polymers (Poly ethylene oxide, HPMC K15M and Ethyl cellulose) and to assess the effect of physico-chemical nature of the active ingredients on the drug release profile. The angle of repose, bulk density, tapped density and compressibility index results shown that the formulation is suitable for direct compression method. These dosage forms have the ability to reduce the dosing frequency. By increasing the polymer, release rate of the drug decreases. F4 gave better release when compared to all formulations. By the results we can confirm that order of drug release zero order.

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