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Development of Controlled Release Osmotic Drug Formulation by Using Proponolol Hydrochloride to Improve Bioavailability

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Keywords: Osmotic drug, proponolol, Hydrochloride

Abstract

Controlled-release systems also offer a sustained-release profile but, in contrast to sustained-release forms, controlled-release systems are designed to lead to predictably constant plasma concentrations, independently of the biological environment of the application site. This means that they are actually controlling the drug concentration in the body, not just the release of the drug from the dosage form, as is the case in a sustained-release system. The main objective of this formulation development was to design an osmotic drug delivery system acting as a controlled release drug delivery system. In this formulation osmogen and release retardant were used to obtain suitable formulation. In the present study, attempts were made to formulate and evaluate API in extended release dosage form using osmotic drug delivery.

1. Introduction

Controlled-release drug delivery systems

Controlled-release systems also offer a sustained-release profile but, in contrast to sustained-release forms, controlled-release systems are designed to lead to predictably constant plasma concentrations, independently of the biological environment of the application site. This means that they are actually controlling the drug concentration in the body, not just the release of the drug from the dosage form, as is the case in a sustained-release system. Another difference between sustained- and controlled-release dosage forms is that the former are basically restricted to oral dosage forms whilst controlled-release systems are used in a variety of administration routes, including transdermal, oral and vaginal administration.

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2. Material And Methods

Design of trials:

The main objective of this formulation development was to design an osmotic drug delivery system acting as a controlled release drug delivery system. In this formulation osmogen and release retardant were used to obtain suitable formulation. The drug should be released for a prolonged period of time in order to achieve a zero-order release. Prepared osmotic tablet combination of gives drug release for up to 12hrs by combination of matrix and osmotic mechanism.

Design:

F1,F2,F3,F4,F5andF6 were designed to optimize the concentrations of sodium acetate, potassium chloride ,mannitol and to study the effect of sodium acetate , potassium chloride, mannitol can be shown in Table-1

Table no: 1

SNO	Ingredients	F1	F2	F3	F4	F5	F6
	Core of the tablet						
1.	Proponolol	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg
2.	Sodium acetate	80 mg	120 mg	-	-	-	-
3.	Potassium chloride	-	-	80 mg	120 mg	-	-
4.	Mannitol	-	-	-	-	80 mg	120 mg
5.	Micro crystalline cellulose	210 mg	170 mg	210 mg	170 mg	210 mg	170 mg
6.	Pvpk30	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
7.	Talc	4 mg	4 mg	4 mg	4 mg	4 mg	4 mg
8.	Magnesium striate	6 mg	6 mg	6 mg	6 mg	6 mg	6 mg
9.	Isopropylalcohol	q.s	q.s	q.s	q.s	q.s	q.s
	Total	400 mg	400 mg	400 mg	400 mg	400 mg	400mg
Coating solution							
10.	Cellulose acetate	400mg	400mg	400mg	400mg	400mg	400mg
11.	PEG400	20ml	20ml	20ml	20ml	20ml	20ml
12.	Castor oil	10ml	10ml	10ml	10ml	10ml	10ml
13.	Acetone	40ml	40ml	40ml	40ml	40ml	40ml
14.	Water	30ml	30ml	30ml	30ml	30ml	30ml
	Total	420mg	420mg	420mg	420mg	420mg	420mg

Preparation of core tablets:

Osmotic tablets were prepared by wet granulation method according to composition given in table. All the ingredients and drug were accurately weighed and mixed in motar with a pestle for 10minutes to get uniform mix. The drug blend was granulated with sufficient quantity of pvpk30 which was dissolved in isopropyl alcohol. The powder mass was dried at 60c in hot air oven for 6hrs and pass-through sieve no:20. The dried granules were mixed with magnesium stearate and talc for 3min. the blended powder was then compressed by single station rotary tablet compression machine. [1-10]

Coating of core tablets:

Coating solution (4%w/v) were prepared by mixing required quantity of cellulose acetate (semi-permeable membrane forming agent),PEG400(pore forming agent)and castor oil(20%v/w of total solid CA) (plasticizer) in acetone as specified in table and

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stirred on magnetic stirrer to get homogenous coating solution. Then the tablets were coated using small size coating pan made up of stainless steel with rotation speed of 25rpm and 55C temperature of hot air then the tablets were kept in oven at 40Cfor about 24hrs and weight to calculate the percentage gain. These tablets were coated repeatedly until the required weight gain was achieved. [11-18]

Evaluation Parameters

Pre-compression parameters:

As per standard procedures, the pre-formulation studies including compressibility index, hausner's ratio and angle of repose was performed for the powder.

I. Bulk density:

Loose bulk density and Taped bulk density was calculated by the following formulae

(a)LBD = Weight of the powder /Volume of the packing

(b)TBD = Weight of the powder/Tapped volume of the packing

(c) Carr's Compressibility Index:

% Carr's Index can be calculated by using the following formula

Carr's Index (%) = ×100

(d) Hausner's ratio:

Hausner ratio is an indirect index of ease of measuring the powder flow. It is calculated by the following formula

Hausner's ratio = (Tapped density)/(Bulk density)

(e) Angle of repose:

Angle of repose (θ) can be calculated from the following formula

Where tanθ=h/r

h=height of pile and r=radius of the base of pile

Post compression parameters

1. Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method for both uncoated and coated tablets.

2. Hardness

For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester.

3. Thickness

The thickness of the tablets was determined using a Screw guage for uncoated and coated tablets.

4. Friability

A sample of 6 tablets was taken and was carefully dedusted prior to testing. The tablets were accurately weighed and placed in the drum of the Roche Friabilator. The drum was rotated for 100 times at 25 rpm and the tablets were removed, dedusted and accurately weighed. Friability of tablets was calculated by using following equation.

f = (1- W0 / W) × 100

Wo = initial weight, W = final weight.

5. Drug content

Ten tablets were powdered in a mortar. An accurately weighed quantity of powdered tablets (80 mg) was extracted with pH 6.8 buffer and the solution was filtered through 0.45 µ membranes. Each extract was suitably diluted and analyzed spectrophotometrically at 289 nm.

***6. In-vitro* drug release studies**

The release rate of drug from osmotically controlled tablets was determined using USP type II apparatus. The dissolution test was performed in triplicate, using 900ml of ph6.8buffer, at 37± 0.5˚C at 50 rpm for 12 hrs. A 5ml sample was withdrawn from the dissolution apparatus at specified time points and the samples were replaced with fresh dissolution medium.The samples were filtered through a 0.45-µm membrane filter and diluted if necessary. Absorbances of these solutions were measured at 289nm using U.V Visible Spectrophotometer. Cumulative drug release was calculated using the equation (y = 0.0238x + 0.000246) generated from Beer Lambert's calibration curve in the linearity range of 5-50µg/ml.

7. Curve fitting analysis

To study the drug release kinetics, the data obtained from in vitro drug release studies were plotted in various kinetic models such as a zero-order, first order, Higuchi and peppas equations.

a. zero order kinetics

To study the zero order release kinetics the release data was fitted into the following equation.

$$DQ/dt=K0$$

Where Q is amount of drug release

K0 is zero order release rate constant

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t is release time
the graph is plotted percentage cumulative release v/s time

b. first order kinetics
To study the first order release kinetics the release data was fitted into the following equation.

$$DQ/dt=K1Q$$

Where Q is amount of drug release
K1 is zero order release rate constant
t is release time
the graph is plotted percentage log% cumulative release v/s time

c. higuchi release model
To study of higuchi release model the release kinetics the release data was fitted into the following equation.

$$Q=KHt1/2$$

Where Q is fraction of drug release
KH is release rate constant
t is release time
the graph is plotted percentage cumulative release v/s square root of time

d. krosmeyer peppas release
To study krosmeyer peppas release kinetics the release data was fitted into the following equation.

$$Mt/Minfi=kHp\ tn$$

Where Mt/Minfi is amount of drug release
KHP is release rate constant
t is release time
n is the diffusion exponent related to mechanism of drug release
the graph is plotted percentage cumulative release v/s log time

3. Result

Stability studies

The optimized formulation was subjected to stability studies at 40±20C and 75±5% RH for a period of three months [Table-2,3]. After each month, tablet was analyzed for drug content and *In-vitro* drug release along with other physical parameters.

Table-2

SNO	CHEMICALS	MANUFACTURER
1	Propanolol hydrochloride	Yarrow chem products, mumbai
2	Mannitol	Qualigens fine chemicals, mumbai
3	Sodium acetate	Qualigens fine chemicals, mumbai
4	Potassium chloride	Fisher scientific india pvt Ltd, mumbai
5	Micro crystalline cellulose	Lobal chemime, mumbai
6	Poly vinyl pyrollindine k30	Hi media Laboratories pvt Ltd, mumbai
7	Iso propyl alcohol	Merck specialited pvt Ltd, mumbai
8	Talc	Karnataka fine chemicals, mumbai
9	Magnesium striate	Karnataka fine chemicals, mumbai
10	Cellulose acetate	Oxford Laboratory, mumbai
11	Poly ethylene gycol 4000	Lobal chemime, mumbai
12	Acetone	Fisher scientific india pvt Ltd, mumbai
13	Castor oil	
14	Distilled water	

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Table-3

SNO	EQUIPMENT	MANUFACTURER
1	Electronic balance	Eagle
2	Mechanical sieve shaker	Jayant scientific IND
3	Rotary compression machine	Rimek, karnavathi
4	Tap density tester	Kshitij innovations
5	Disintegration tester	Kshitij innovations
6	Vernier caliper	Mansanto
7	Hardness tester	Mansanto
8	Friabilator	campbell
9	Dissolution apparatus USP2	LABINDIA
10	Conventional coating pan	Kshitij innovations
11	Hot air oven	fortune
12	Stability testing equipment	Remi elektrotechnic limited
13	Magnetic stirrer	Kshitij innovations
15	U.V spectrophotometer	Labindia model-uv3092

Pre compression parameters:

a. Solubility:

Solubility of propanolol hydrochloride is slightly soluble in water and can easily soluble in 0.1N Hydrochloride, ph 6.8 phosphate buffer, ph 7.4 phosphate buffer [Table-4].

b. Drug excipient compatibility studies:

c. **Standard curve of proponolol hydrochloride**:

Table-4

SNO	Concentration(µg/ml)	Absorbance
1.	0	0
2.	2	0.052
3.	4	0.093
4	6	0.146
5.	8	0.176
6.	10	0.213
7.	12	0.26
8.	14	0.303
9.	16	0.345
10	18	0.389
11.	20	0.432
12.	22	0.493
13.	24	0.544

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14.	26	0.585
15.	28	0.635
16.	30	0.682
17.	32	0.742
18.	34	0.771
19.	36	0.807
20.	38	0.854
21.	40	0.91

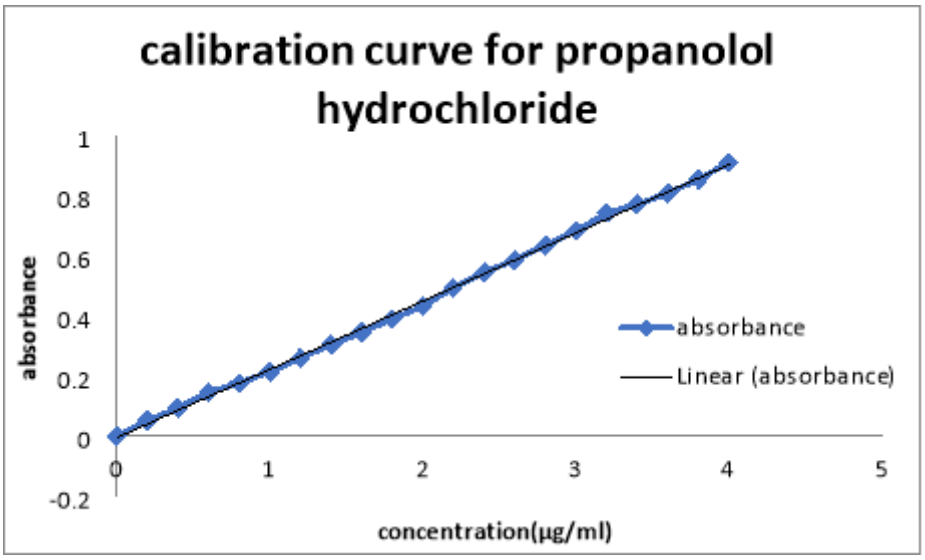

Figure no: 1

Discussion: based on above results, it has been inferred that API shows linearity in concentration range of 2-40µg/ml. the regression coefficient of calibration curve was found to be 0.998 shown in Figure-1.

Physical characterization of blends of different formulations: [Table-5]

Table no: 5

SNO	property	F1	F2	F3	F4	F5	F6
1.	Angle of repose(0)	15.90	20.65	16.3	17.38	18.15	17.01
2.	Bulk density(g/mL)	0.261	0.233	0.387	0.34	0.330	0.357
3.	Tapped density(g/mL)	0.392	0.327	0.516	0.48	0.455	0.50
4.	Carr's index(%)	50.19	40.3	33	41.17	37.8	30
5.	Hausner's ratio	1.50	1.40	1.33	1.41	1.37	1.40

Discussion: based on above results all the formulations show good flow properties and compression parameters were found to comply with in specified limits.

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Post compression parameters of different formulations:

Table no: 6

a. Weight variation test(g):

SNO	Tablet type	F1	F2	F3	F4	F5	F6
1.	Uncoated	With in limits	With in limits	With in limits	With in limits	With in limits	With in limits
2.	Coated	With in limits	With in limits	With in limits	With in limits	With in limits	With in limits

The propanolol hydrochloride osmotic tablets were uniform in weight (uncoated-0.390 to 0.400g, coated- 0.408 to 0.418g) and weight variation was less than 1, which is acceptable and within limits. [Table-6]

Table no: 7

a. Thickness (mm):

SNO	Tablet type	F1	F2	F3	F4	F5	F6
1.	Uncoated	4.7	4.8	4.04	3.35	3.3	4.04
2.	Coated	5.0	5.8	5.8	4.04	4.3	4.3

Discussion: thickness of the tablets was between 4.0mm to 5.0mm for uncoated and 5.0mm to 6.0mm for coated tablets and was maintained constant for all batches, which is acceptable. [Table: 7-12]

Table no: 8

b. Weight variation test(g):

SNO	Tablet type	F1	F2	F3	F4	F5	F6
1.	Uncoated	Within limits	Within limits	Within limits	Within limits	Within limits	Within limits
2.	Coated	Within limits	Within limits	Within limits	Within limits	Within limits	Within limits

The propanolol hydrochloride osmotic tablets were uniform in weight (uncoated-0.390 to 0.400g, coated- 0.408 to 0.418g) and weight variation was less than 1, which is acceptable and within limits.

Table no: 9

c. Hardness test (KP):

SNO	Tablet type	F1	F2	F3	F4	F5	F6
2.	Coated	5 .2	5. 6	5. 6	5.4	5. 8	5. 6

Hardness of the tablet was between 5 to 6 kp was maintained for all batches

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Table no: 10

d. Friability:

SNO	Tablet type	F1	F2	F3	F4	F5	F6
1.	Coated	0.60	0.58	0.58	0.69	0.53	0.66

Table no: 11

e. Drug content(%):

SNO	Tablet type	F1	F2	F3	F4	F5	F6
1.	Coated	98	92.5	95	100	92.5	100

All the formulations exhibited uniformity of drug content

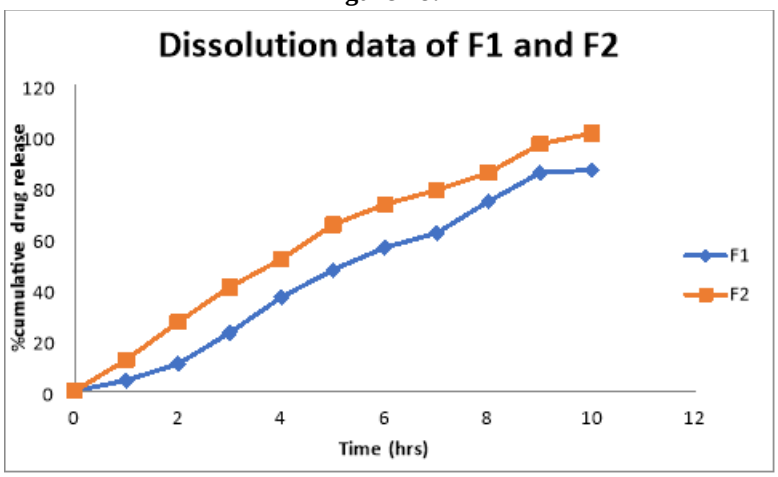
In vitro dissolution

Table no: 12

Dissolution data for F1 and F2

SNO	Time(hrs)	%CDR	%CDR
1.	0	0	0
2.	1	4.2	12.3
3.	2	10.6	27
4.	3	22.87	40.7
5.	4	36.80	51.7
6.	5	47.5	65.25
7.	6	56.25	73.13
8.	7	61.88	78.75
9.	8	74.28	85.50
10.	9	85.50	96.75
11.	10	86.63	101.26

Figure no: 2



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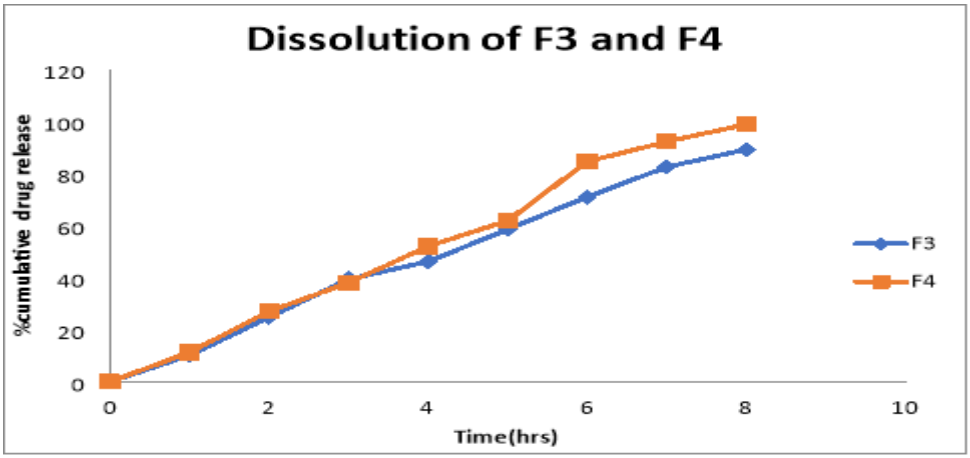
Discussion: increase in concentration of osmogens such as the sodium acetate increased in drug release [Figure-2]. Higher the amount of osmogen, greater is the driving force to release the drug. This is because increase in osmogen concentration increased osmotic pressure inside tablet thus release is increased.

Table no: 13

Dissolution data for F3 and F4:

SNO	Time(hrs)	F3%CDR	F4%CDR
1.	0	0	0
2.	1	10.1	11.25
3.	2	24.75	27
4.	3	39.37	38
5.	4	46.12	52
6.	5	58.5	61.88
7.	6	71	84.55
8.	7	82.5	92.25
9.	8	89.2	98.88
10.	9	-	-
11.	10	-	-

Figure no: 3



Discussion: increase in concentration of osmogen such as the potassium chloride increased in drug release [Figure-3]. Higher the amount of osmogen greater is the driving force to release the drug. This is because increase in osmogen concentration increased osmotic pressure inside tablet thus release is increased. [Table-13,14]

Table no: 14

Dissolution data for F5and F6

SNO	Time(hrs)	%CDR	%CDR
1.	0	0	0
2.	1	3.2	3.7
3.	2	6.75	9
4.	3	13.5	21.37
5.	4	29.5	38.5
6.	5	36	43.6
7.	6	47.25	51.3

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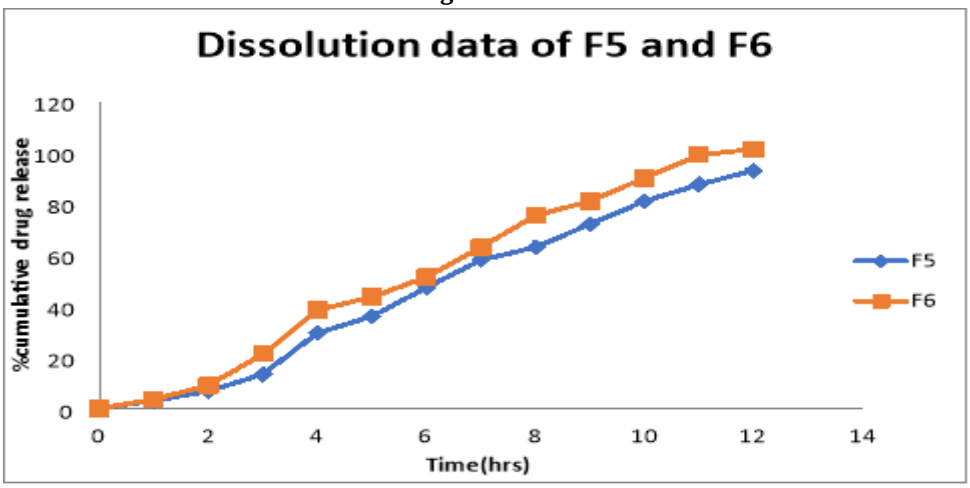
8.	7	58	63
9.	8	63	75.38
10.	9	72	81
11.	10	81	90
12.	11	87.42	99
13.	12	93	101.26

Figure no: 4



Discussion : increase in concentration of osmogen such as the mannitol, increased in drug release. Higher the amount of osmogen,greater is the driving force to release the drug. This is because increase in osmogen concentration increased osmotic pressure inside tablet thus release is increased.

Comparative study of all formulations:

Table no:15

SNO	Time	F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	1	4.2	12.3	10.1	11.25	3.2	3.7
3.	2	10.6	27	24.75	27	6.75	9
4.	3	22.87	40.7	39.37	38	13.5	21.37
5.	4	36.8	51.7	46.12	52	29.5	38.5
6.	5	47.5	65.25	58.5	61.88	36	43.6
7.	6	56.25	73.13	71	84.55	47.25	51.3
8.	7	61.88	78.75	82.5	92.25	58	63
9.	8	74.28	85.5	89.2	98.88	63	75.38
10.	9	85.5	96.75	-	-	72	81
11.	10	86.63	101	-	-	81	90
12.	11	-	-	-	-	87.42	99
13.	12	-	-	-	-	93	101.26

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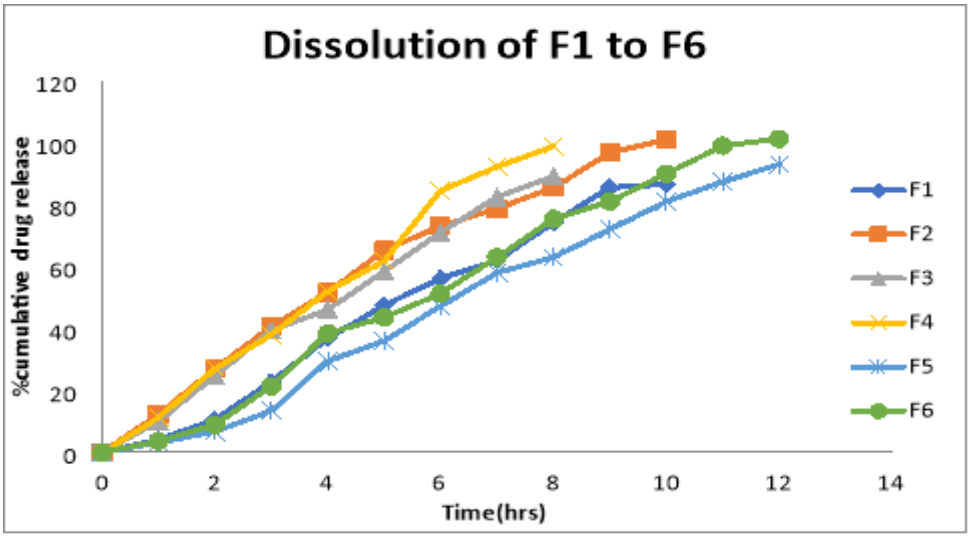
Figure no: 5



Discussion : increase in concentration of different osmogens such as the sodium acetate, potassium chloride, mannitol, increased in drug release [Figure-5]. Higher the amount of osmogen,greater is the driving force to release the drug. This is because increase in osmogen concentration increased osmotic pressure inside tablet thus release is increased. And from above results mannitol used formulation release up to 12hrs but others such as sodium aceate used osmogen stoped at 10hrs, potassium chloride used osmogen stoped at 8hrs and hence mannitol 120mg used is considered as optimized formulation. [Table-15]

KINETIC MODELLING

Figure no: 6

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Figure no: 7

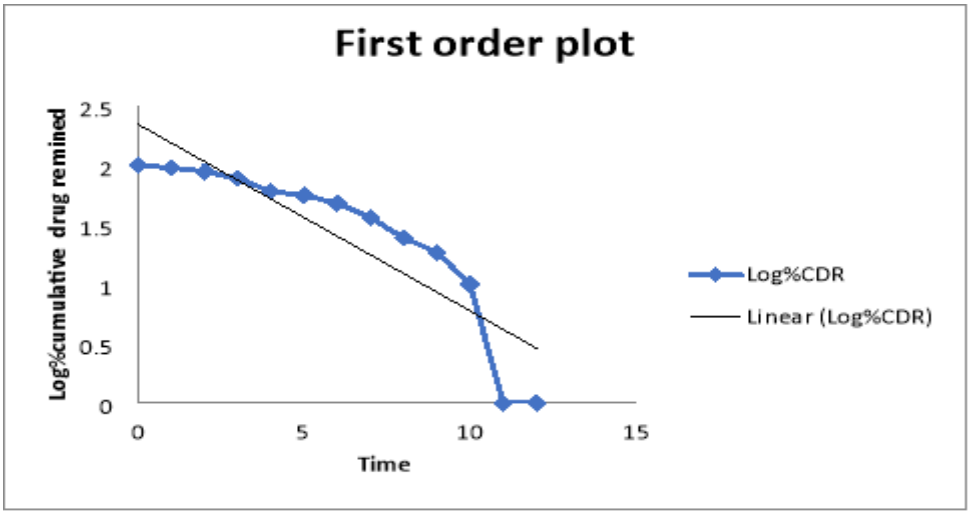

Figure no: 8

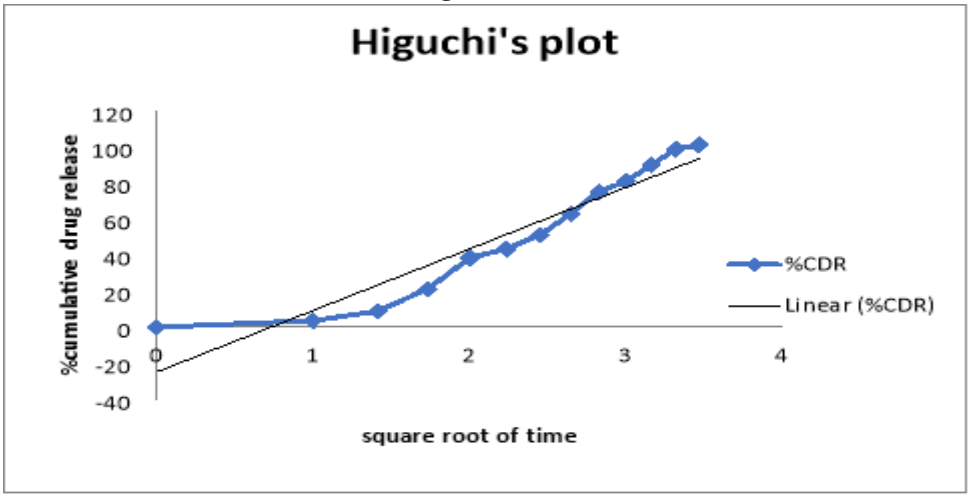

Figure no: 9

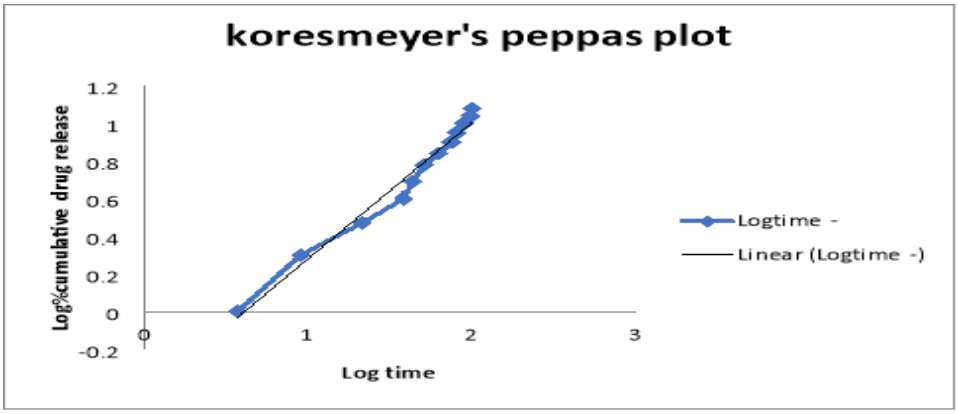

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Table no: 17

Kinetic data of optimized formula (F6) :

PLOT	Regression R2
Zero order plot	0.9907
First order plot	0.783
Higuchi plot	0.909
Korsemeyer-peppa's plot	0.976

From the regression valve closer to unity in case of zero order (R2=0.9907) the release is apparently zero order. As clearly indicated the release of the drug followed zero order release kinetics and regression valve indicates fair of linearity in the data.this shows that the release is independent of the concentration of drug.when plotted according to the first order equation, the data indicated poor linearity as represented by regession valvesR2=0.783. In our experiment, the invitro release profiles of the drug from the formulation could be expressed by higuchi's equation, as plot showed high linearity (R2=0.909) indicateing diffusion as one of mechanism of drug release. [Figure: 6-9]

To confirm the diffusion mechanism, the data were fit into korsemeyer-peooa's equation. The obtained regession valve(R2=0.976) indicate coupling of diffusion anmd erosion mechanism. The relative complexity of this formulation and its components may indicate that drug release is controlled by more than one process. [Table-17]

STABILITY STUDIES:

The optimized tablets from batch trial F6 were charged for stability studies at 40oc and 75%RH. There was no change in physical appearance, color. Formulations were analyzed for the period of 3months for general tablet properties like hardness, friability, and water by kf, drug content and dissolution studies. Tablets have shown no much deviation in hardness, friability valves. And average drug content of the tablets was found to be 95.5% of the labeled claim. In vitro dissolution profile showed that there was no significant change in the release rate of the drug from optimized tablets at for the period of 3months. [Table-18]

Table no: 18

SNO	Test	Initial	After 1st month	After 2nd month	After 3rd month
1.	Weight variation (mg)	Within limits	Within limits	Within limits	Within limits
2.	Hardness (kg/cm2)	5.6	5.5	5.5	5.5
3.	Friability (%w/w)	0.66	0.69	0.70	0.70
4.	Assay (%)	100	99	99	98
5.	Dissolution (drug release at 12th hrs)	101.26	99.5	99	98

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4. Conclusion & Summary

API belongs to the category of antihypertensives which is used for hypertensives. In the present study, attempts were made to formulate and evaluate API in extended-release dosage form using osmotic drug delivery. Preformulation studies were conducted using drug: excipients and the results showed that the excipient was compatible with drug. Formulation characteristics such as blend characteristics, tablet weight, hardness, and friability were found to be satisfactory. Formulations are evaluated for drug release in USP type 2 apparatus (paddle) with stationary baskets in ph6.8 buffer. Target zero order release was achieved with trial F6 in which 120mg mannitol was present as osmogens and coated with 80: 20SPM: PORE FORMER RATIO (15% TO 20% wt gain). Cellulose acetate tends to keep up the best suited reservoir coating material in controlling the release system. Finally, it was concluded that these trials will provide a novel approach for formulating proponolol hychloride.

The present investigation embodies the development of microporous osmotic pump of B.C.S class-1 molecule mainly with an objective to deliver a prolong time or to maintain controlled release of drug for an extended duration. Core of osmotic tablet was prepared by direct compression using drug, osmogen, release retardant, on rotary compression machine.core tablets were coated using cellulose acetate as semi permeable membrane and PEG 400 as pore former dissolved in 9:1acetone:watermixture.

Totally 6 formulations were prepared. All tablets were evaluated for physical parameters such as weight varation, hardness, friability, thickness and in-vitro drug release.

Trails F1, F2 were formulated by using sodium acetate as osmogen with 80mg, 120mg and these are coated as for procedure and the study the effect of osmogen concentration on drug release was studied and osmogen concentration was optimized . 120mg sodium acetate i.e 80mg per tablet showed controlled release for 10hrs and hence taken as optimized but it does not attain flow properties and assay valve. Trails F3, F4 were formulated by using potassium chloride as osmogen with 80mg, 120mg and these are coated as for procedure and the study the effect of osmogen concentration on drug release was studied and osmogen concentration was optimized . 120mg potassium chloride i.e 80mg per tablet showed controlled release for 8hrs and hence taken as optimized but it does not attain longer time. Trails F5, F6 were formulated by using mannitol as osmogen with 80mg, 120mg and these are coated as for procedure and the study the effect of osmogen concentration on drug release was studied and osmogen concentration was optimized. 120mg mannitol i.e 80mg per tablet showed controlled release for 12hrs and hence taken as optimized.

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