International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE
V-1, I-2, 2012

Formulation, Evaluation and Optimization of Osmotic Drug Delivery System for a Highly Insoluble Drug

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Manuscript No: IJPRS/V1/I2/00083, Received On: 12/05/2012, Accepted On: 16/05/2012

ABSTRACT

The present study focuses on the preparation of push pull osmotic drug delivery system for a highly insoluble drug, an antipsychotic category. The main aim is to improve the site specification and to provide the controlled release of drug for once-a-day drug delivery system with zero order drug release profile with applying drug release kinetic modelling. The push pull osmotic tablets were prepared by wet granulation method; the drug layer consists of the drug, osmotic agent, suspension agent and in push layer extender, osmotic agent and pigment to distinguish push layer form drug layer. The coating was carried out by cellulose acetate (CA) and plasticizer was used as propylene glycol. This study evaluates that regardless of the drug properties which do not significantly affect the drug delivery, the release kinetics is mainly controlled by some factors as, the plasticizer proportion in the membrane, the osmotic agent proportion and the drug layer polymer grade. The influence of each factor was investigated defining their acceptability range. Results shows that tablet made by PEO200K and diluents used in drug layer and PEO7000K and sodium chloride in push layer with 10% of CA coating, the plasticizer content was upto 20% to 30% and 0.8mm of orifice diameter. Results, shows that the use of suspension agent in drug layer affects the drug release. The formulation batch F13 was taken as ideal optimized batch and it follows the zero order drug release. On the basis of results the effect of orifice diameter, polymer concentration in drug layer, coating composition and plasticizer amount was tested and promising results were found. The drug release was independent of pH but dependent on the osmotic pressure of the dissolution medium. The release kinetics followed the Zero order model.

KEYWORDS

Push Pull Osmotic Drug Delivery System, Highly insoluble drug Osmotic pump, Antipsychotic agent, PEO and Cellulose acetate.

INTRODUCTION

The United States Pharmacopoeia definition of a control release or modified release system, as it is also called, that:

"*The drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience not offered by conventional dosage form*"

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The development of improved method of drug delivery has received a lot of attention in the last two decades.[2,3] Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed

due to imbibitions of fluids by osmogen. Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. Hence the release rate of drugs from osmotic dispensing devices is dependent on the solubility and molecular weight and activity coefficient of the solute (osmogent).

Push pull osmotic pump is a modified EOP through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (depict as the upper layer) contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and coloring agent, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semi-permeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet. When the system is placed in aqueous environment water is attracted into the tablet by an osmotic agent in both the layers. The osmotic attraction in the drug layer pulls water into the compartment to form in situ a suspension of drug. The osmotic agent in the nondrug layer simultaneously attract water into that compartment, causing it to expand volumetrically and the expansion of non drug layer pushes the drug suspension out of the delivery orifice.[4,5,6]

Schizophrenia[7,8,9] is a mental disorder characterized by a breakdown of thought processes and by poor emotional responsiveness. It most commonly manifests itself as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and it is accompanied by significant social or occupational dysfunction. The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of about 0.3–0.7%. Diagnosis is based on observed behavior and the patient's reported experiences.

MATERIALS AND METHODS

Materials

Quetiapine Fumarate and all excipients were obtained from Alembic, Research Center, Vadodara, Gujarat.

Methods

Determination of UV λmax of Drug

A standard stock solution of Quetiapine Fumarate was prepared by dissolving accurately weighed 50 mg of Quetiapine in 5ml methanol 100 ml volumetric flask. The volume was made up to 100 ml in phosphate buffer solution, to obtain a stock solution of 500µg/ml.

From the standard stock solution, 2 ml was pippetted into 100 ml volumetric flask. The volume was made up to 100 ml with above buffer solution. The resulting solution containing 10µg/ml was scanned between 200 and 400 nm. The λ_{max} was found to be 290 nm.

Confirmation of Complexation

FTIR Studies

IR spectra for Quetiapine Fumarate and complexation were recorded in a Fourier transform infrared spectrophotometer (FTIR 1615, Perkin Elmer, USA) with KBr pellets.

In-vitro Drug Release studies[8,9]

In vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml purified water, was placed into the dissolution flask maintaining the temperature of 37±0.5 ^{o}C and rpm of 50. One tablet was placed in each bucket of dissolution apparatus. The apparatus was allowed to run for 24 hours. Samples measuring 10 ml were withdrawn after every 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours using auto sampler. During sampling samples were filtered through 10µm filter which was in inline with auto sampler. The fresh dissolution medium (37 ^{o}C) was replaced every time with the same

quantity of the sample. Collected samples were suitably diluted with phosphate buffer (pH 6.8) and analyzed at 290 nm using phosphate buffer (pH 6.8) as blank. The cumulative percentage drug release was calculated.

Formulation Development of Push Pull Osmotic Tablet

Formulation of push pull osmotic tablet containing Quetiapine Fumarate was prepared by wet granulation technique. The composition of each tablet is shown in table.1The components of drug layer and push layer were separately mixed and granulated.

All components were passed through 40# size mesh and the granules were dried at 50^0c in tray drier. The dried granules were passed through 30# size mesh and lubricated with magnesium stearate. Compression of tablet was done on 12station (Rimek) using 12mm punches. The compressed tablets were subjected to functional coating by cellulose acetate with needed percentage of coating. After the coating the coated tablet were drilled by Cameron micro drill press with a selected orifice diameter of 0.8mm.

Table: 1 Formulation of preliminary trial F1-F6 Batches

SR.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
Drug layer							
1	Quetiapine fumarate	230	230	230	230.00	230.00	230.00
2	DCP	21.48	31.89	11.77	36.77	36.77	36.77
3	PEO 200K(WSR N80)	23.00	115.00	230.00	230.00	230.00	230.00
4	Sodium chloride	15.00	20.00	25.00	-	-	-
5	BHT	0.02	0.12	0.23	0.23	0.23	0.23
6	PVP K30	7.50	-	-	-	-	
7	IPA	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular							
8	Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00
Total weight of drug layer		300	400	500	500	500	500
Push layer							
1	PEO7000K(WSR N 303)	90	120.00	150.00	150.00	150.00	150.00
2	DCP	38.61	11.88	16.85	16.85	16.85	16.85
3	Sodium chloride	15.00	15.00	30.00	30.00	30.00	30.00
4	BHT	0.09	0.12	0.15	0.15	0.15	0.15
5	PVP K30	4.00	-	-	-	-	-
	IPA	q.s	q.s	q.s	q.s	q.s	q.s
Extra granular							
6	Iron oxide red	0.80	1.50	1.50	1.50	1.50	1.50
7	Magnesium stearate	1.50	1.50	1.50	1.50	1.50	1.50
Total weight of push layer		150	150	200	200	200	200
Total weight of un coated tablet		450	550	700	700	700	700
Functional coating							
1	Cellulose acetate 398-10	38	46	58	58	53	49
2	Propylene glycol	4	5	6	6	11	14
3	Tri ethyl citrate	4	5	6	6	7	7
Weight of coating		45.0	55.0	70.0	70.0	70.0	70.0

Evaluation of Push Pull Osmotic Tablet [10,11,12,13]

Weight variation

Weight variation was calculated as per method descried in Indian Pharmacopoeia (I.P. 1996). 20 tablets were weighed individually and the average weight is calculated.

Hardness

Five tablets from each batch were selected and hardness was measured using Monsanto hardness tester to find the average tablet hardness.

Thickness

Ten Tablets were selected at random from individual formulations and thickness was measured by using Vernier caliper scale, which permits accurate measurement.

Friability (%F)

Twenty tablets from each batch were selected randomly and weighed. These tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability:

%F =1-(loss in weight/ initial weight) 100*

Drug Content

The tablets were pulverized and then transferred into a 250-ml volumetric flask. The volume was adjusted with pH 6.8 phosphate buffer and kept on rotary shaker for 24 hrs in order to completely extract the drug. The mixture was filtered, and the drug was assayed spectrophotometrically at 290 nm (Shimadzu UV-1108).

***In Vitro* Drug Release studies** [14,15,16]

In vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml purified water, was placed into the dissolution flask maintaining the temperature of 37±0.5 ^{o}C and rpm of 50. One tablet was placed in each bucket of dissolution apparatus. The apparatus was allowed to run for 24 hours. Samples measuring 10 ml were withdrawn after every 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours using auto sampler. During sampling samples were filtered through 10µm filter which was in inline with auto sampler. The fresh dissolution medium (37^{o}C) was replaced every time with the same quantity of the sample. Collected samples were suitably diluted with phosphate buffer (pH 6.8) and analyzed at 290 nm using phosphate buffer (pH 6.8) as blank. The cumulative percentage drug release was calculated.

Coating Thickness

The tablet after the dissolution was taken of to the bowl and was washed with water. The part of tablet's coat was cutted and was thickness was measured by vernier calipers.

Kinetics of Drug Release[17,18,19]

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:

1) Cumulative percentage drug released Vs Time (In-Vitro drug release plots, Zero order plots)
2) Log cumulative percentage drug remaining Vs Time (First order plots)
3) Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
4) Log percentage drug released Vs Log time (Peppas plots)
5) Cube root of percentage drug remain Vs Time (Hixson-Crowell plots)

Stability Study of Optimized Batch

In the present work stability study was carried out for the optimized formulation for following condition and time period

40° C / 75% RH for 1 months and 15 days and samples were withdrawn at the end of 0, 2, 4 and 6 week and evaluated for active drug content, disintegration time and *in-vitro* drug release.

RESULTS AND DISCUSSION

Determination of UV Absorbance Maxima of Quetiapine Fumarate

Suitable analytical method was developed for Quetiapine Fumarate using UV spectroscopy and analytical wavelength of λ_{max} 290 nm was identified in phosphate buffer solution, pH 6.8, pH 4.5 and 0.1 N hydrochloric acid solution. Calibration curves were constructed in these media. The methods have shown reproducibility. The R^2 values were 0.9999, 0.9998, and 0.9998 for phosphate buffer, pH 6.8, pH 4.5, and 0.1 N HCl solutions, respectively. Beer Lambert law obeyed in the range of 5 to 45 µg/ml for corresponding buffer media.

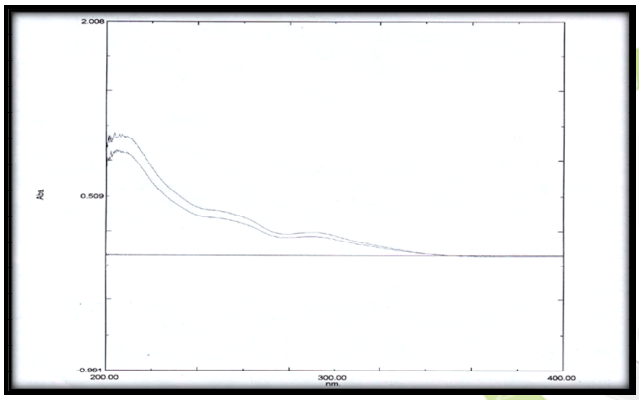

Figure: 1 UV absorbance maxima of the Quetiapine Fumarate

Standard Calibration Curve

Standard calibration curve was plotted in as absorbance Vs concentration in for HCl buffer pH 1.2, pH 4.5 and phosphate buffer pH 6.8. Absorbance value is plotted in Table no. 6.1. The beer's range of the Quetiapine Fumarate obeyed was 5 to 45 µg/ml.

FTIR Studies

IR spectrum of Quetiapine Fumarate (Figure 5) shows abroad peak at 3750 cm^{-1} may be due to O-H stretching,3080 cm-1 Ar-H stretching and 2880 cm^{-1} C-H stretching, 2380 cm^{-1} may be due to aromatic C=C stretching, 1600 cm^{-1} may be due to C-N, 1340 cm^{-1} maybe due to C-H bending. 1030 cm^{-1} may be due to –C-O-C group 791 cm^{-1} may be due to substituted benzene ring.

Table: 2 Standard calibration curve data for Quetiapine Fumarate in different media

Concentration in PPM	Absorbance		
	0.1N HCl	pH 6.8 buffer	pH 4.5 buffer
6	0.1003	0.111	0.1065
25	0.4167	0.4672	0.4329
30	0.5772	0.6311	0.6083
35	0.6606	0.7217	0.6863
40	0.7401	0.8194	0.7806
45	0.8223	0.9362	0.8588
50	0.9048	0.9952	0.9535

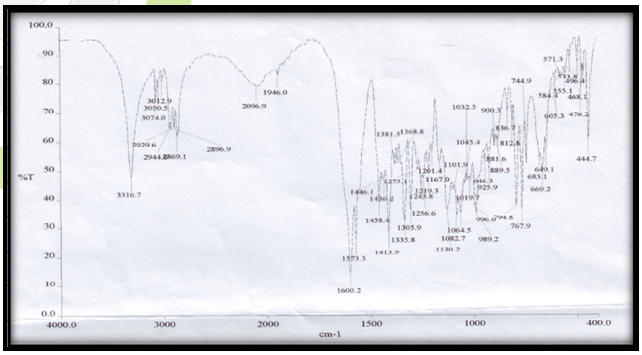

Figure: 2 Spectrum of Quetiapine Fumarate Drug Sample

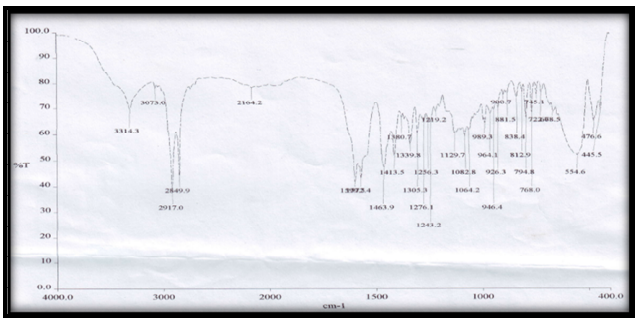

Figure: 3 FTIR of Drug and Excipients

Particle Size Analysis for Drug

Table: 3 Particle size for drug

Particle size	Drug
D(0.9)	8.663
D(0.5)	2.282
D(0.1)	0.537

Precompressional Parameters for Granules

Precompressional parameters of granules shows (Table 2), angle of repose (25.563 to 39.811), % compressibility (05.431 to 26.931%), and Hausner's ratio (1.057 to 1.369) are in the range given in official standards. Table 3 shows post compressional parameters i. e. hardness (5.06 to 6.52 kg/cm2), friability (0.317 to 1.497 %), weight variation (0.128 to 0.540) and thickness (5.30 to 5.42 mm). Drug content was (99.189 to 99.649%) within the acceptable official limits.

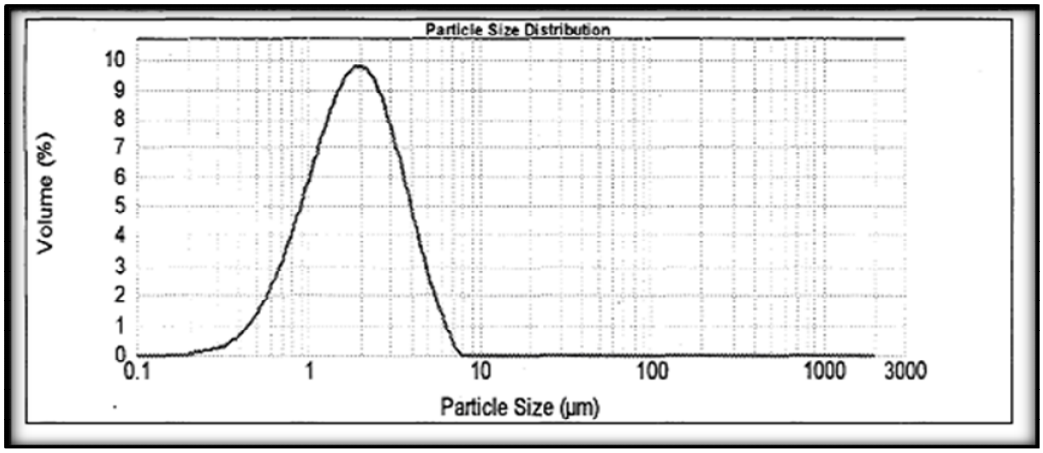

Figure: 5 Particle Size Distributions for Drug

Table: 4 Precompressional Parameters for Granules

Formulations	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's Ratio	Carr's Index (%)
F1	30.458±1.392	0.665±0.004	0.905±0.005	1.365±0.005	36.854±0.465
F2	28.315±1.624	0.612±0.003	0.712±0.014	1.185±0.027	18.908±2.654
F3	33.858±1.229	0.561±0.003	0.665±0.003	1.165±0.005	16.815±0.754
F4	25.498±0.812	0.575±0.004	0.639±0.002	1.081±0.007	08.835±0.652
F5	30.712±0.785	0.662±0.002	0.708±0.003	1.104±0.011	10.385±1.005
F6	32.113±1.375	0.619±0.002	0.572±0.013	1.095±0.023	09.367±2.316

Table: 5 Post Compressional Parameters

Formulation	Average Weight(mg)	Hardness (kg/cm^2)	Friability (%w/w)	Thickness (mm)	Weight Variation (%)	Coating Thickness(mm)	Drug content
	n=20	n=03	n=10	n=03	n=20	n=03	n=03
F1	495±2.842	10.12±1.02	0.547±0.054	5.82±0.031	0.194±0.176	0.23±0.021	99.66±0.910
F2	606± 1.154	10.14±1.04	0.581±0.023	6.12±0.048	0.223±0.289	0.25±0.023	98.75±0.852
F3	771 ± 2.955	12.65±2.06	0.562±0.045	7.12±0.028	0.256±0.313	0.26±0.021	96.74±0.765
F4	772±2.924	12.14±1.03	0.521±0.021	7.35±0.031	0.231±0.321	0.23±0.022	98.75±0.865
F5	773±2.856	12.06±1.06	0.568±0.054	7.34±0.036	0.265±0.341	0.24±0.025	99.92±0.779
F6	771±2.896	12.15±2.05	0.546±0.035	7.29±0.021	0.268±0.323	0.23±0.024	97.94±0.954

Table: 6 % Drug Release

Time(hr)	% Drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	2	0	2	2	3	2
2	3	2	5	4	9	3
4	6	6	9	7	14	7
6	12	12	12	11	20	14
8	17	21	16	14	41	26
12	22	35	34	33	59	42
16	26	45	54	53	67	53
20	29	54	73	71	81	74
24	32	59	98	96	94	94
R^2	0.957	0.984	0.967	0.964	0.982	0.990

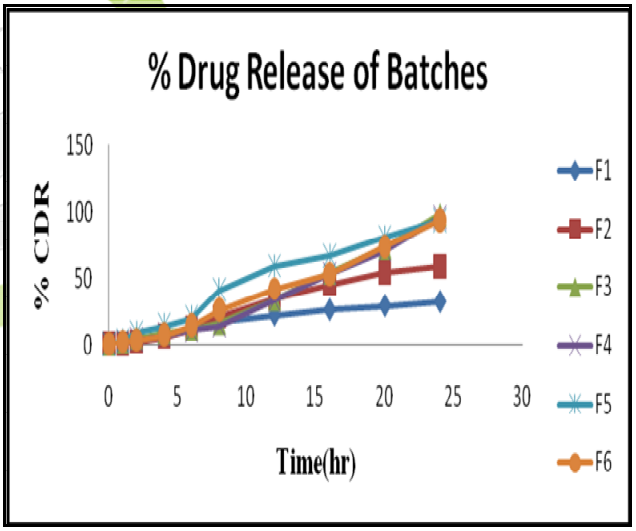

Figure: 6 % Drug Release of Formulation Batches

Dissolution Data Treatment

The dissolution of drug from prepared osmotic tablets product at different time periods was plotted as cumulative % drug release v/s time curve as shown in figure 7, 8, 9 and 10.

The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, Korsmeyer-Peppas models. Results were shown in table 5.

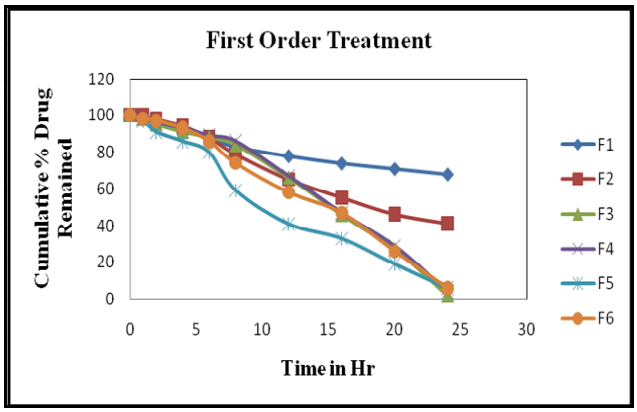

Figure: 7 First order treatment for PPOP tablet

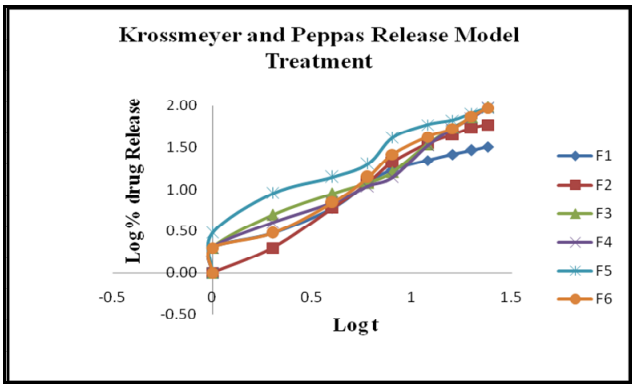

Figure: 9 Krosmeyer and Peppas release model treatment for PPOP tablets

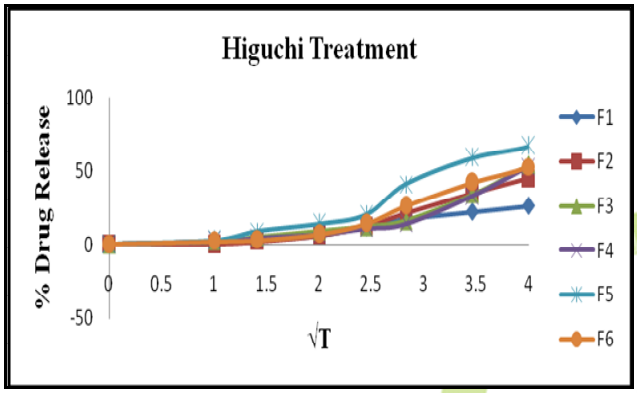

Figure: 8 Higuchi treatment for PPOP tablet

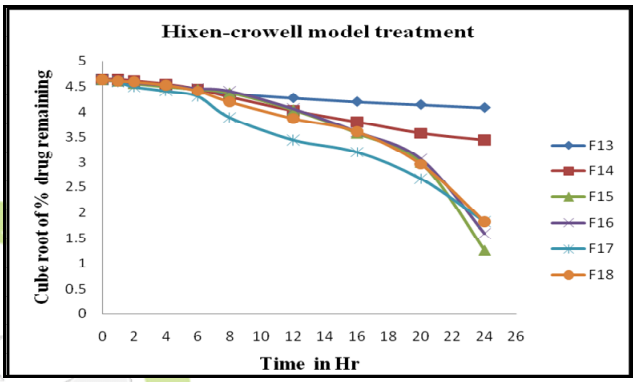

Figure: 10 Hixen Crowell model treatment for PPOP tablet

Table: 7 Different Kinetic Models Applied on PPOP Tablets

Batch Code	Zero Order Model			First Order Model			Higuchi Square Root Model			Korsmeyer-Peppas Model				Hixson-Crowell Model			Best Fit Model
	K_0	SSQ	R^2	K_1	SSQ	R^2	K_H	SSQ	R^2	n	K_{KP}	SSQ	R^2	K_{HC}	SSQ	R^2	
F1	1.51	70.91	0.97	0.01	35.78	0.97	6.04	106.12	0.91	0.75	3.03	27.010	0.97	0.06	45.386	0.96	Zero
F2	2.60	90.82	0.98	0.03	167.25	0.96	10.04	863.73	0.81	1.03	2.33	88.202	0.98	0.01	122.38	0.97	Zero
F3	3.56	523.53	0.94	0.05	1604.87	0.84	13.35	2926.55	0.90	1.51	0.80	24.187	0.99	0.05	1256.09	0.87	Zero
F4	3.46	589.19	0.94	0.04	1624.72	0.83	12.92	2996.72	0.90	1.56	0.67	23.655	0.99	0.01	1290.83	0.87	Zero
F5	4.12	213.11	0.98	0.06	542.67	0.94	16.17	1417.31	0.96	0.91	5.28	179.72	0.98	0.02	303.63	0.97	Zero
F6	3.61	224.44	0.99	0.05	1057.39	0.96	13.73	2284.03	0.93	1.27	1.63	39.131	0.99	0.01	762.66	0.97	Zero

*R^2-Correlation coefficients, SSQ-Sum of Square, K_0, K_1, K_H, $K_{HC,}$ K_{KP} Release rate constant for zero order, First order, Higuchi, and Hixson Crowell, Korsmeyer-Peppas release equation, respectively, n, diffusional exponent, indicative of release mechanism in Korsmeyer equation. All formulations F1 to F6, followed Non-Fickian (Anomalous) release.

CONCLUSION

Formulation of push pull osmotic tablets was selected as according to the percentage of the drug and the total weight of the drug layer and push layer. The ratio of percentage for PEO 200K was selected in different concentration according to the percentage of the drug. The formulation batch F1 was selected with 10% of suspending agent. The % drug release found was 32%. The further batches were selected with increase in percentage of the suspending agent and osmotic agent. The formulation batch F3 releases 98% of drug release. On the basis of increase of the suspending agent the other batches were made. The change in plasticizer content was made in F5 and F6. The F6 batch shows the 0.99 linearity of drug release as a zero order drug release. The orifice diameter was selected as 0.8mm and 10% of coating was suitable and found efficient for the formulation. From the kinetic modelling it is found that the best fit model for the formulation is zero order. The identification test and drug excipient compatibility studies were carried out as FTIR and DSC which shows no interaction in drug and polymer. Form the above study it is concluded that increasing the concentration of osmotic agent and suspending agent there is in increase in the amount of % dug release. The study of different kinetic modelling was carried out and the result shows the zero order release to be fit. The stability study of the optimized final batch was taken for 1 month and the desired results were achieved. The formulation, evaluation and optimization for a highly insoluble drug using push pull osmotic tablet system were successfully achieved.

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