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Formulation, Development and *In-vitro* Evaluation of Osmotic Tablet of Nefopam Hydrochloride

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Abstract-The major objective of this study was to develop osmotic tablet of Nefopam Hydrochloride to be taken once daily. In this study,osmotic tablet consist of core surrounded by semipermeable membrane with an immediate-release drug overcoat, which provides reducing dosing Frequency. Unlike the elementary osmotic tablet drilled with a delivery orifice, controlled porosity osmotic tablet accomplished by the use of channeling agent in the coat. CCS and HPMC were used as superdisintegrant and binder respectively in immediate release layer. NaCl and HPMC K100M were used as an osmogent and release retardant respectively in core layer. Cellulose acetate was used as the semipermeable membrane and PEG 400 was used as pore forming agent. Optimization was done using 3^2 factorial design considering two independent variable at three levels. Optimized formulation exhibited zero order kinetics with a drug release of 98.35% in 24 hrs. Scanning electron microscope studies showed the formation of pores in membrane (Coat. It can be concluded that osmotic tablet of Nefopam HCl by using osmotic technology can be successfully applied for immediate release and controlled release of Nefopam HCl, and thus it is a promising tool in the drug delivery system.

Keywords: Osmotic, Porosity, Immediate Release, Controlled Release.

1. INTRODUCTION

The oral route for drug delivery is the most popular, desirable, and easy method for administrating therapeutically agents for systemic effects because it is a natural, convenient, and cost effective manufacturing process. An oral controlled release (CR) system has important area in novel drug delivery system because of pharmaceutical agents can be delivered in a controlled manner over a long period. Osmotic drug delivery is a most promising strategy based system for controlled drug delivery. Osmotic system utilizes the principles of osmotic pressure for controlled delivery of drug. Osmotic pressure is used as driving force for release the drug in controlled manner for long period. Drug release from these systems to a large extent is independent of pH and other physiological parameters and it is possible to modulate the release characteristics by optimizing the properties of drug and system. The system can be utilized for systemic as well as targeted delivery of drugs. The system is simple and easy to formulate improved patient compliance with reduced dosing frequency and prolong therapeutic effect.[1,2]

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In This study, osmotic tablet consist of core surrounded by semipermeable membrane with an immediate-release drug overcoat and core osmotic tablet is controlled layer which provides controlled release of drug. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing initial dose of drug. Water permeates through the membrane into the tablet core. As osmotically active polymer excipients expand, drug is released through the pores formed on semipermeable membrane. The membrane controls the rate at which water enters the tablet core, which in turn controls dug delivery. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components.[3]

Nefopam HCL is centrally acting non-opioid analgesic drug it is work in the brain and spinal cord to relive pain. It has been also useful for relief of dental, musculo-skeletal, acute traumatic, acute wound and cancer pain. Nefopam HCL produces fewer side effects and has much less abuse potential, and so is useful either as an alternative to opioids.[4,5]

2. MATERIALS AND METHOD

Materials: Nefopam Hydrochloride was purchased from Swapnrup Drug and Pharmaceutical, Auarangabad. Croscarmellose sodium, HPMC, Sodium chloride, Cellulose acetate, Lactose, PEG 400, and Acetone was procured from Research – Lab Fine chem. Industry, Mumbai. All other chemicals used in study were of analytical grade.

METHOD

Formulation of Core Osmotic tablet (CPOP):[6]

A core tablet of Nefopam HCl was prepared by wet granulation method. The composition of core tablets is given in table no.1. Nefopam HCl was mixed with Sodium chloride, Lactose and HPMC, this powder blend was kneaded in the mortar and pestle for 15-20 min .The blend was granulated using PVP K30 as a binder in water. Wet mass was formed; resulting wet mass was passed through sieve #22. Granules were dried in oven at 50°C for 2 hrs. Dried granules were lubricated with magnesium stearate and talc. Then desired amount of blend was compressed into the tablet using Rimek tablet punch machine equipped with 8 mm punch, Weight of the tablet was kept to 250 mg.

Table 1: Composition of Core Osmotic tablet (CPOP) as per Factorial Design:
(All values are expressed in mg)

Ingredients	**Formulation code**								
Quantity(mg)	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**
Nefopam HCl	30	30	30	30	30	30	30	30	30
Sodium chloride	5	10	15	5	10	15	5	10	15
HPMC	50	50	50	65	65	65	80	80	80
PVP K30	15	15	15	15	15	15	15	15	15
Lactose	145	140	135	130	125	120	115	110	105
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total weight (mg)	250	250	250	250	250	250	250	250	250

Formulation of Drug overcoat layer (IR layer):[7,8]

Core osmotic tablet (placebo) was firstly prepared by tablet compression machine. Then coating solution for semipermeable membrane was prepared, and core tablet (placebo) was coated by this solution by dip coating technique until desired weight gain (10%) was obtained and tablets were dried for 10 hr. Then ingredients for overcoat (IR layer) weighed and dissolved in water (q.s.) and overcoat solution was prepared. Core osmotic tablet (placebo) was coated with overcoat solution. Tablets were coated until they weigh 300mg and tablets were allowed to dry completely.

Table 2: Composition of Overcoat layer as per Factorial Design (IR Layer):
(All values are expressed in mg)

Ingredients	**Formulation code**								
Quantity(mg)	**I1**	**I2**	**I3**	**I4**	**I5**	**I6**	**I7**	**I8**	**I9**
Nefopam HCl	30	30	30	30	30	30	30	30	30
CCS	2	2	2	4.5	4.5	4.5	7	7	7
HPMC	2	4.5	7	2	4.5	7	2	4.5	7
PEG 400	1	1	1	1	1	1	1	1	1

Formulation of optimized Drug overcoat osmotic tablet:[7,8]

C6 batch from core tablet and I5 batch from overcoat core tablet (IR layer) were selected to form Optimized Drug overcoat controlled porosity osmotic tablet (C6I5).

Preparation: Core osmotic tablet C6 was firstly prepared by tablet compression machine. Then coating solution of semipermeable membrane was prepared, and core tablet was coated by this solution by dip coating technique until desired weight gain (10%) was obtained and tablets were dried for 10 hrs.

before further evaluation. Then ingredients for overcoat (IR layer) I5 weighed and dissolved in water (q.s.) and overcoat solution was prepared. Core osmotic tablet was coated with overcoat solution. Tablets were coated until they weigh 300mg and tablets were allowed to dry completely.

Table 3: Formulation of optimized Osmotic tablet of Nefopam HCl core osmotic tablet CR layer (C6) and overcoat on core tablet IR layer (I5).

Sr. No.	Ingredients	Quantity
	Formulation of Core osmotic tablet (C6)	
1	Nefopam HCl	30
2	Sodium Chloride	15
3	HPMC	65
4	PVP K30	15
5	Lactose	120
6	Magnesium Stearate	2
7	Talc	3
	Total	**250**
Sr. No.	**Composition of coating solution**	
1	Cellulose Acetate	5%
2	Polyethylene Glycol 400	1%
3	Acetone: alcohol (1:1)	50:50
	Total weight of tablet	**260**
Sr. No.	**Composition for overcoat on core tablet IR layer(I5)**	
1	Nefopam HCl	30
2	Cross Carmellose Sodium	4.5
3	HPMC	4.5
4	PEG 400	1
	Total	**40**
	Total tablet weight	**300mg**

3. CHARACTERIZATION:

Table 4: Evaluation of osmotic tablet

Pre compression studies	Post compression studies		
	Before coating:	**After coating:**	**After Drug overcoat:**
1. Bulk density.	1. Hardness	1. Thickness	1. Thickness
2. Tapped density.	2. Thickness	2. Thickness of film	2. Thickness of film
3. Carr's index.	3. Friability	3. Weight variation	3. weight variation
4. Angle of repose.	4. Weight variation		4. Friability
	5. Content uniformity		5. Content uniformity
			6. Disintegration Test

Evaluation of Granules:[9,10]
Flow properties of granules were evaluated by established methods. Angle of Repose was determined using funnel method. Bulk Density, Tapped Density, Compressibility index and Hausner's ratio were calculated.

Evaluation of Precoated Tablets:[9-12]
The formulated core tablets were evaluated for different parameters like hardness, thickness, weight Variation, friability and drug content uniformity of tablet.

Thickness: The uniformity of thickness was measured using digital vernier caliper. The average thickness of the tablet was calcutated.

Weight Variation Tests:[9] 20 tablets were weighed individually average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The percent deviation was calculated.

Hardness: The hardness of tablets was measured using Monsanto hardness tester. In this tablet was place between the plungers, and was tightened from one end, and pressure required to break tablet diametrically was measured.

Friability: In this test 20 tablet were weighed and placed in a roche friabilator test apparatus. After 100 revolutions the tablets were removed, de-dusted and

weighed again. The friability was determined as the percentage loss in weight of the tablets.

$$\% \text{ friability} = \frac{\text{Initial weight of tablet} - \text{Final weight of tablet}}{\text{Final weight of tablet}}$$

Uniformity of Content: Twenty tablet weighed individually and powdered in mortar; 30 mg of drug dissolved in the 100 ml of phosphate buffer 6.8. The solution was filtered and the content of Nefopam HCl in the solution was determined by measuring absorbance on double beam UV spectrophotometer (Shimadzu 1800) at 266.5nm.

Evaluation of Coated Tablet:[11,12]

Thickness of tablet: All tablets were initially subjected for thickness measurement by using digital vernier caliper after coating to assess thickness of coat.

Thickness of film: Thickness of film was calculated by considering difference between coated tablet and uncoated tablet.

$$\text{Thickness of coat} = \frac{\text{Thickness of coated tablet} - \text{Thickness of uncoated tablet}}{2}$$

Weight Variation Tests: 20 tablets were weighed individually average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The percent deviation was calculated.

Scanning Electron Microscopy: The surface morphology of the tablet coating layer before and after dissolution was examined by scanning electron microscope.

Evaluation of drug overcoated Tablet (IR layer):[10,12]

Thickness of tablet: All tablets were initially subjected for thickness measurement by using digital vernier caliper after coating to assess thickness of coat.

Thickness of film: Thickness of film was calculated by considering difference between coated tablet and uncoated tablet.

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Disintegration Test:

Disintegration test determines whether dosage forms such as tablets disintegrantes within prescribed time when placed in a liquid medium under prescribed experimental conditions.

In –vitro Release Studies:[13] In vitro drug release of the formulation was carried out in a USP dissolution apparatus (paddle type) set at a rotating speed of 50 rpm and temperature of 37±2C. The dissolution medium (900ml) was 0.1N HCl for the first 2 hrs and phosphate buffer (pH 6.8) there after upto 24 hrs samples (5ml) were withdrawn at specific time intervals and the medium was replenished with fresh dissolution fluid.

Dissolution Kinetics:[14]

In order to investigate the mode of release from the tablets the release data were analyzed with the zero order, first order, higuchi square root, korsmeyer plot.

Stability study:[15,16]

Stability study of optimized formulation was carried out to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of optimized Nefopam HCl formulation was assessed at 40 ± 2^0c/ 75±5% RH as per ICH Guidelines. Tablets were packed in aluminium foil and stored for 3 months. Sample was analyzed after 3 months for physical appearance, drug content and in vitro dissolution profile.

4. RESULT AND DISCUSSION

Evaluation of Granules

Results of precompression evaluations of formulation mixtures as shown in table no.34 From the results of Compressibility (Carr's) index and Hausner's ratio it can be clearly concluded that the Nefopam HCl tablet blend were having excellent flow properties, fair to good compressibility which allow these formulation mixtures to be directly compressed into tablets and

good flow of the mixture from hopper with good content uniformity in final tablets.

Table 5: Precompression evaluation of formulation mixture (core tablet)

Batch (n= 3)	Angle of repose(θ°)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (%)	Hausner's ratio
	Mean± S.D	Mean± S.D	Mean± S.D	Mean± S.D	Mean± S.D
C1	31.06±0.72	0.274±0.004	0.370±0.015	5.2±0.20	1.05±0.007
C2	29.06±0.46	0.252±0.003	0.30±0.010	6.5±0.93	1.07±0.03
C3	27.93±0.57	0.245±0.004	0.333±0.010	7.1±0.15	1.07±0.04
C4	30.26±0.25	0.306±0.005	0.319±0.015	6.32±0.30	1.06±0.07
C5	26.42±0.16	0.291±0.005	0.352±0.007	5.76±0.21	1.07±0.017
C6	28.55±0.35	0.228±0.002	0.307±0.013	6.84±0.34	1.08±0.010
C7	28.30±0.37	0.2893±0.006	0.331±0.010	4.48±0.19	1.06±0.017
C8	31.13±0.10	0.236±0.004	0.306±0.006	6.52±0.23	1.06±0.010
C9	29.08±0.33	0.223±0.003	0.320±0.008	7.33±0.15	1.08±0.011

Precoating Evaluation

All formulated uncoated osmotic tablet batches were evaluated for weight variation, Hardness, thickness, friability and drug content. Weight variation, hardness, thickness, friability, and drug content of uncoated tablets were found within the range.

Table 6: Precoating evaluation parameters of core osmotic tablets

Batch (n=3)	Average Weight (mg) Mean±S.D	Weight variation(%)	Hardness ($kg/cm^{2)}$ Mean±S.D	Thickness (mm) Mean±S.D	Friability (%) Mean±S.D	Drug content (%) Mean± S.D
C1	249.03±0.81	0.48	4.02±0.51	4.18±0.22	0.12±0.04	96.78±0.004
C2	249.00±1.34	0.55	4.5±0.30	4.25±0.03	0.014±0.021	96.51±0.0014
C3	248.77±1.55	0.65	4.7±0.25	4.26±0.028	0.012±0.024	96.38±0.0015
C4	249.20±1.21	0.66	4.3±0.47	4.17±0.025	0.10±0.023	98.08±0.0054
C5	250.15±0.48	0.43	4.9±0.15	4.15±0.03	0.09±0.023	97.93±0.003
C6	250.19±1.56	0.52	3.10±0.31	4.14±0.04	0.11±0.024	98.95±0.0052
C7	249.10±1.53	0.65	4.7±0.20	4.12±0.03	0.13±0.025	98.15±0.0022
C8	249.00±0.33	0.47	4.2±0.50	4.13±0.024	0.17±0.054	98.22±0.0043
C9	250.15±1.43	0.54	4.3±0.26	4.15±0.022	0.09±0.023	98.18±0.0032

Post coating evaluation

All formulated coated osmotic tablet batches were evaluated for Weight variation, thickness and film thickness. Due to uniform coating weight variation and thickness of coated tablets were found within the range. Thickness of film was measured by calculating the difference between thickness of coated tablet and uncoated tablet

Table 7: Post coating evaluation parameters of core osmotic tablets

Batch (n=3)	Average Weight (mg) Mean± S.D	Weight Variation %	Thickness of coated tablet Mean± S.D	Thickness of film(mm) Mean± S.D
C1	259.5±0.45	0.638	5.04±0.042	0.43±0.04

C2	261.3±0.49	0.534	5.07±0.060	0.410±0.05
C3	260.9±1.18	0.830	5.09±0.082	0.415±0.03
C4	263.5±0.54	0.768	5.08±0.044	0.455±0.02
C5	268.2±1.13	0.631	5.06±0.043	0.455±0.05
C6	262.1±1.54	0.674	5.10±0.038	0.48±0.02
C7	258.5±0.46	0.583	5.08±0.047	0.48±0.03
C8	259.9±0.79	0.481	5.09±0.052	0.481±0.02
C9	261.4±1.46	0.540	5.11±0.051	0.485±0.05

SEM of Coating (before and after dissolution)
Evaluation of coating layer before dissolution study and after dissolution study suggest that, aqueous pores were generated during testing through which the drug solution has passed across the Cellulose Acetate barrier after creation of osmotic pressure in the tablet core. This was confirmed by SEM Analysis of coating layer before and after dissolution testing.

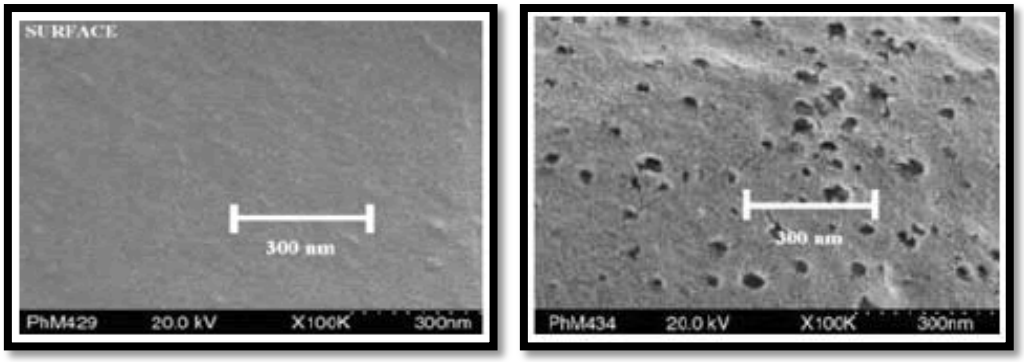

Fig 1: Scanning Electron Microscopy (SEM) of Semipermeable membrane coating layer
a) Before dissolution b) After dissolution

In *Vitro* Dissolution study of core osmotic tablet formulations (C1-C9):
The result shows that with increase in concentration of Sodium chloride (NaCl) and decreasing the concentration of HPMC the release rates gradually increases. The results showed that the osmotic tablet has the ability to extend the release of Nefopam HCl for the duration of about 23 hrs. On the basis of *In–vitro* drug release profile the optimum formulation C6 was selected as it releases 98.05% drug within 23 hrs.

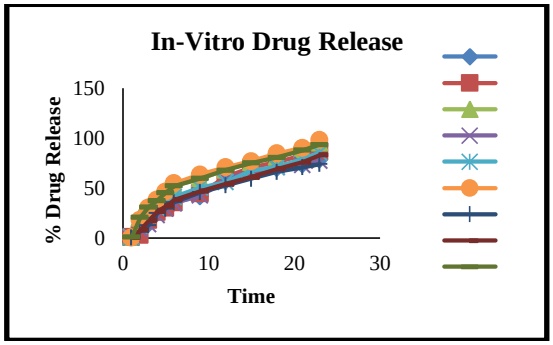

Fig 2: Dissolution Profile of Core osmotic tablet Batches (C1-C9)

Evaluation of Drug overcoat osmotic tablet (IR layer):
All formulated drug overcoated osmotic (placebo) tablet batches were evaluated for weight variation, friablility, Disintegration time, drug content, thickness and film thickness.

Table 8: Post drug coating evaluation parameters of osmotic tablets

Batch Code (n=3)	Average Weight (mg) Mean± S.D	Weight Variation %	Thickness of coated tablet Mean± S.D	Thickness of film(mm) Mean± S.D	Friability (%) Mean± S.D	Drug Content	DT (min)
I1	299.6±0.55	0.689	6.55±0.041	0.55±0.05	0.18±0.026	96.78±0.005	43.20
I2	300.3±0.48	0.626	6.64±0.050	0.53±0.04	0.016±0.021	96.51±0.0014	48.14
I3	302.9±1.16	0.542	6.89±0.091	0.50±0.03	0.012±0.024	96.48±0.0025	52.45
I4	298.4±0.53	0.761	6.63±0.044	0.52±0.04	0.10±0.024	97.08±0.0054	50.21
I5	303.2±1.23	0.632	6.58±0.043	0.51±0.02	0.09±0.023	98.93±0.0021	52.4
I6	310.3±1.34	0.667	6.52±0.048	0.56±0.03	0.13±0.024	98.95±0.0042	49.51
I7	299.5±0.86	0.691	6.61±0.048	0.51±0.01	0.14±0.026	98.15±0.0022	47.45
I8	298.9±0.64	0.441	6.74±0.050	0.52±0.03	0.17±0.054	98.12±0.0033	50.10
I9	312.4±1.42	0.553	6.69±0.055	0.50±0.04	0.10±0.022	98.28±0.0012	53.21

In *Vitro* Dissolution studies of Drug overcoat layer:

The result shows that with increase in concentration of Croscarmellose Sodium (CCS) and decreasing the concentration of HPMC the release rates gradually increases. Drug overcoat layer has the ability to release the drug for duration of one hour. On the basis of *In–vitro* drug release profile the optimum formulation I5 was selected as it releases 98.42% drug within one hr.

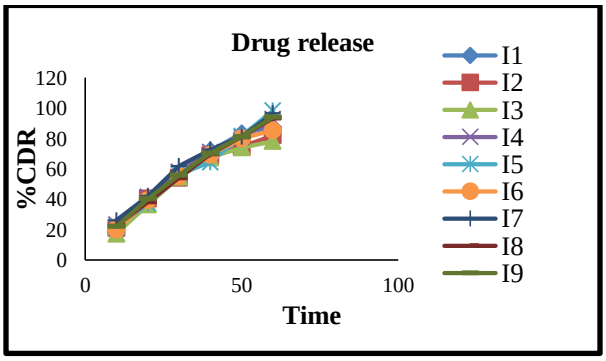

Fig 3: Dissolution Profile of IR layer of osmotic Tablet Batches (I1-I9)

Evaluation of optimized Osmotic Tablet of Nefopam HCl (C6I5):

C6 batch from core osmotic tablet and I5 batch from overcoat on core tablet (IR layer) were selected to form Optimized Osmotic tablet (C6I5) of Nefopam HCl. Tablet was subjected to in vitro drug release study to check the drug release.

Table 9: Evaluation of optimized batch of drug overcoat osmotic tablet

Sr no.	Parameter	Observation
1	Weight variation	0.632
2	Thickness	6.58
3	Thickness of overcoat	0.51
4	Friability	0.09
5	Drug content	97.93
6	Disintegration	52.4

In-vitro drug release of optimized drug overcoat osmotic tablet (C6I5):

The prepared tablet was subjected to dissolution test to asses' in vitro release of Nefopam HCl IR layer and CR layer from optimized tablet. Dissolution rate of drug overcoat osmotic tablet (C6I5) shown in table no.10

Table 10: In-vitro drug release of optimized formulation (C6I5)

Time (Hrs)	C6I5 Optimized Formulation % CDR (n=3)
1	98.04±0.23
2	98.96±0.77
3	13.66±0.64
4	21.09±0.39
5	28.29±0.61
6	33.65±0.74
7	39.41±0.65
8	44.17±0.32
9	50.27±0.62
12	61.06±0.42
15	70.25±0.56
18	79.55±0.58
21	88.21±0.45

24	98.35±0.73

Dissolution Kinetic:

Release kinetics studies

Different kinetic treatments (zero order, first order, Higuchi's square root equation and Korsmeyer treatment) were applied to interpret the release of Nefopam HCl from different matrices. All formulations follows zero order, first order, higuchi's model and korsmeyer model, But the best fitted model is zero order. C6 follow zero order kinectics with r^2=0.998. So the drug release is of fickian release

Table 11: Kinetic treatment of prepared Nefopam HCl osmotic tablet formulations

Formulation code	Coefficient of determination (R^2)			
	Zero order	First order	Higuchi square root	Korsmeyer plot
C1	0.994	0.877	0.960	0.91
C2	0.996	0.803	0.965	0.94
C3	0.987	0.920	0.973	0.90
C4	0.986	0.917	0.988	0.93
C5	0.991	0.851	0.985	0.90
C6	0.998	0.926	0.983	0.95
C7	0.992	0.886	0.972	0.92
C8	0.980	0.916	0.983	0.89
C9	0.994	0.685	0.968	0.92

Zero order study:

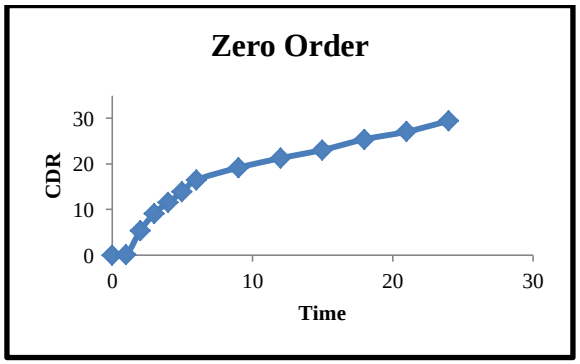

Figure 4: Model Graph for Evaluation of Zero Order Release Kinetics

Stability Study:

Table 12: Characteristics of optimized formulation C6I5 after 3 months storage

Parameter	Initial sample of optimized formulation	After storage at 40±2°C / 75±5% RH, for 3 months
	C6I5	C6I5
Color	White	White
Drug content	98.59%	98.50 %
% Drug Released (After 24 hrs.)	98.35%	98.52%

5. CONCLUSION

The present work of osmotic tablet of Nefopam HCl was successfully prepared on the basis of osmotic technology. A 3^2 full factorial design was performed, and the desired release of Nefopam HCl from the osmotic tablet was achieved through careful monitoring of the selected formulation variables. Wet granulation method was used for preparation of granules and prepared granules were evaluated for various parameters, all parameters were found within the limit Evaluation of osmotic tablet before coating was carried out for various parameters and these were found within the limits, coating of core tablet was done by dip coating method. After coating evaluation of osmotic tablets were evaluated for evaluation parameters and the results found were within limits. Evaluation of coating layer before and after dissolution was done by scanning electron microscope it was observed that aqueous pores were generated during dissolution test. In-vitro dissolution of osmotic tablet was performed for IR layer (I5) and

CR layer (C6), Drug release was found for optimized formulation 98.42% and 98.05% respectively. Dissolution kinetics was studied for all formulations and the best fitted model was found to be zero order dissolution kinetic models Optimized formulation was stable for period of 3 months as there was no significant variation in the physical appearance, drug content and drug release of formulation. It can be concluded that osmotic tablet of Nefopam HCl by using osmotic technology can be successfully applied for immediate release and controlled release of Nefopam HCl, and thus it is a promising tool in the drug delivery system.

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