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DEVELOPMENT AND EVALUATION OF PUSH-PULL BASED OSMOTIC DELIVERY SYSTEM FOR ROPINIROLE

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ABSTRACT

Ropinirole hydrochloride is indicated in Parkinson's disease and Restless leg syndrome. In advanced Parkinson's disease the usual dose of Ropinirole hydrochloride is 0.25 to 5 mg three to four times a day. Hence, an attempt was made to develop a once-a-day controlled release Osmotic drug delivery system. This may offer significant patient benefits by providing enhanced efficacy and reduced side effects and may also reduce the number of daily doses compared to conventional therapies. An oral push-pull system that can deliver Ropinirole hydrochloride for extended period of time has been developed and characterized. A bilayer osmotic drug delivery system was developed using drilling technique. The push layer swells releasing the drug at a controlled rate. An optimized system was selected to study the effect of pH of dissolution medium and the effect of agitation intensity. The drug release was found to follow zero order kinetics. The developed push-pull osmotic system showed the desired once-a-day release kinetic.

INTRODUCTION: The development of oral osmotic pumps has been the subject of increasing interest and in the past 20 years various types of oral osmotic delivery systems have been developed and studied for drug possessing differing aqueous solubilities. Oral osmotic pumps can deliver drugs in a controlled manner over a prolonged period of time, and various types of osmotic pumps have been described [1-4].

Push-pull osmotic drug delivery features a semi-permeable, rate-controlling membrane surrounding an osmotic core, which contains a push layer and a drug layer. The rate-controlling membrane consists of cellulose acetate with various hydrophilic-hydrophobic plasticizers. The push layer swells releasing the drug at a controlled rate. This may offer significant patient benefits by providing enhanced efficacy and reduced side effects and may also reduce the number of necessary daily doses compared to conventional therapies [5-7].

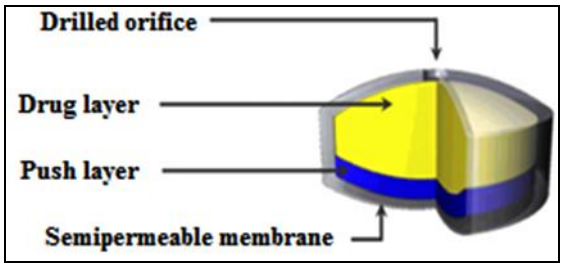

FIGURE 1: PUSH-PULL OSMOTIC PUMP

Parkinson's disease (PD) is a neurodegenerative disorder. It has worldwide incidence of 20 in 100,000 and is estimated to cost £ 700 million per year in drug treatment [8-11].

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In advanced parkinson's disease the usual dose of Ropinirole hydrochloride is as high as 4mg three to four times a day. Ropinirole hydrochloride has been associated with episodes of somnolence during the daytime (referred to as sleep attacks) and other adverse effects such as drowsiness, dizziness, fainting, hallucinations and many more [12].

The objective of the present study is to develop bilayered osmotic tablets of Ropinirole hydrochloride for once-a-day administration. This reduction in dose frequency is expected to improve patient compliance and maintain the therapeutic level of Ropinirole hydrochloride over a prolonged period of time. This may result in reduced severity of motor fluctuations and other side effects caused by ropinirole hydrochloride.

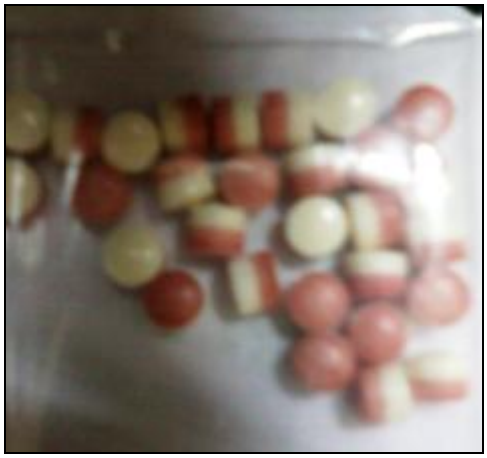
MATERIAL AND METHODS:

Materials: Ropinirole hydrochloride was obtained as a gift sample from Alembic Research Centre, Vadodara (India). Sodium chloride (Nacl) was used as osmogen and was obtained from Merck, Germany. Lactose was obtained from Meggle. Different grades of Polyethylene Oxide(PEO) were obtained as gift samples from Colorcon Asia Pvt. Ltd. Cellulose Acetate witha 39.8 % acetyl content was obtained from Sigma Chemicals (Bangalore, India). Propyleneglycol(PG) and Triethyl citrate (TEC) obtained from S.D. Fine-Chem Ltd, were employed as plasicizers. All the chemicals used were of analytical grade.

Formulation development: Bilayered osmotic tablets of Ropinirole hydrochloride were prepared using conventional wet granulation technology. Drug and excipients were mixed together to produce 500 tablets. The alcohol(Isopropyl alcohol) solution of PVP K 30 was added to produce a damp mass , which was passed through a # 16 sieve and dried in a hot air oven at 45̊ C for 30 minutes. The dried granules were then passed through a # 30 sieve and mixed with lubricants. Granules for the push compartment were prepared in a similar fashion and for identification a coloring agent (Iron oxide) was added to the push layer. The tablets were compressed at an average weight of 95 mg. The weight of the push compartment was adjusted to 45mg and the pull compartment weight was adjusted to 50 mg.

Prepared granules were compressed as bilayer tablets using 5mm concave punches on rotary compression machine.

Coating of Bilayer Tablets: The tablets were coated with cellulose acetate (5% w/v in Dichloromethane:Ethanol(90:10) along with a suitable plasticizer. The coating process parameters were optimized as follows : Pan diameter -6 inch; spray gun (pilot scale); baffles- 4; speed of pan -30-35rpm; spraying rate 10-15 ml/min; temperature-20-25̊ C. The coated tablets had smooth, uniform surfaces without any defects [13-14].



Before Coating

After Coating

FIGURE 2: UNCOATED AND COATED TABLETS

Drilling of Bilayer Tablets: The bilayer coated tablets were drilled by Cameron microdrillpress [15].

TABLE 1: FORMULATION TABLE (F1-F7)

Ingredients	F1	F2	F3	F4	F5	F6	F7
Drug Layer:							
Drug	13.68	13.68	13.68	13.68	13.68	13.68	13.68
Lactose	27.43	27.43	27.43	20.59	20.59	20.59	20.59
PEO 200K	6.84	6.84	6.84	13.68	13.68	13.68	13.68
Nacl	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PVP K30	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Mg. stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Push Layer:							
PEO 7000K	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Nacl	0.00	0.00	0.00	0.00	0.00	4.50	9.00
Lactose	38.18	38.18	38.18	38.18	38.18	33.18	29.18
PVP K30	1.35	1.35	1.35	1.35	1.35	1.35	1.35
Iron Oxide (red)	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Mg. stearate	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Coating:							
Cellulose acetate	8.55	8.55	17.10	8.55	17.1	8.55	8.55
Propylene Glycol	0.95	0.00	0.00	0.00	0.00	0.00	0.00
TEC	0.00	0.95	1.9	0.95	1.9	0.95	0.95
Wt. Gain	10%	10%	20%	10%	20%	10%	10%

TABLE 2: FORMULATION TABLE (F8-F14)

Ingredients	F8	F9	F10	F11	F12	F13	F14
Drug Layer:							
Drug	13.68	13.68	13.68	13.68	13.68	13.68	13.68
Lactose	20.59	18.09	18.09	18.09	15.59	15.59	15.59
PEO 200K	13.68	13.68	13.68	13.68	13.68	13.68	13.68
Nacl	0.00	2.50	2.50	2.50	5.00	5.00	5.00
PVP K30	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Mg. stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Push Layer:							
PEO 7000K	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Nacl	13.5	4.50	9.00	13.50	4.50	9.00	13.50
Lactose	24.65	33.18	29.18	24.65	33.18	29.18	24.65
PVP K30	1.35	1.35	1.35	1.35	1.35	1.35	1.35
Iron Oxide (red)	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Mg. stearate	0.45	0.45	0.45	0.45	0.45	0.45	0.45
Coating:							
Cellulose acetate	8.55	8.55	8.55	8.55	8.55	8.55	8.55
Propylene Glycol	0.00	0.00	0.00	0.00	0.00	0.00	0.00
TEC	0.95	0.95	0.95	0.95	0.95	0.95	0.95
Wt. Gain	10%	10%	10%	10%	10%	10%	10%

Evaluation:

Pre-compression Parameters:

Drug was evaluated for following parameters:

- Flow property of Drug: Bulk Density, Tapped Density , Carr's index and Hausner's Ratio
- Solubility
- UV Analysis of drug
- Interaction Study- It was carried out by Differential Scanning calorimeter(DSC).

Granules were evaluated for following parameters:

- Flow property of Drug: Bulk Density, Tapped Density , Carr's index and Hausner's Ratio
- Weight variation Hardness
- Friability
- Thickness of tablet and coat

- Drug Content- For determining the drug content, 20 tablets were crushed and powdered in a mortar. The powder equivalent 12mg of the drug was accurately weighed and transferred to a 50ml volumetric flask. The powder was dissolved in water and sonicated for 30 min. The solution was filtered through a 0.45µm nylon filter after dilution. This solution was analyzed by UV.
- *In vitro* Release- *In vitro* drug release studies were carried out using the USP type II dissolution test apparatus. Operating conditions were maintained at 37^{o}C±0.5^{o}C, paddle speed was 100 rpm, and the dissolution medium was water with a volume of 500ml. Aliquots of 5ml were withdrawn at 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours and the same amount of dissolution medium was replenished. Samples were filtered and analyzed. The experiments were performed in triplicate.

Effect of plasticizer on Drug Release: In osmotic drug delivery system coating of semipermeable polymer is given in order to control water entry in to the system. The water in flow can be modulated by different plasticizers. So formulations were made using water soluble (PG) and water insoluble (TEC) plasticizers to determine their effect on drug release.

Effect of pH of dissolution medium on Drug Release [16]: An osmotically controlled release system delivers its contents independent of external variables. Hence to assess the effect of pH on the in vitro release profile, dissolution studies were carried out in 0.1N HCL, pH 4.5 acetate buffer and pH 6.8 phosphate buffer.

Effect of Agitation Intensity [16, 17]: In order to assess the effect of the agitational intensity of the release media, the release studies of the optimized formulation were carried out in a dissolution rate test apparatus II at various rotational speeds. The paddle rotation speed was adjusted at rates of 50, 75and 100 rpm. The samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45µm nylon membrane filters.

Stability Studies [18]: The optimized formulation that gave the desired zero order release profile over a period of 24h was selected, strip-packed and subjected to stability studies as per ICH guidelines 40^{o}C/75%RH. Samples were withdrawn at time intervals of 0, 2, 4, 6, 8, 10 and 12th weeks. The samples were evaluated for appearance, drug content and in vitro-release.

RESULTS AND DISCUSSION: The push-pull bilayered osmotic tablet was designed to have a tablet core consisting of drug along with osmagen, low viscosity hydrophilic polymer and other conventional excipients. The push compartment consists of swellable polymer and osmagen. The compressed bilayer tablet was surrounded by a membrane consisting of a semipermeable membrane-forming polymer and a plasticizer capable of improving the film-forming properties of the polymers. The semipermeable membrane-forming polymer was selected in regard to its permeability to aqueous fluids but substantially impermeable to the components of the core.

In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane. The drug is released through the hole present in the membrane. Cellulose acetate was used as water-insoluble polymer and Propylene glycol/Triethylcitrate were used as water-soluble and water-insoluble plasticizers, respectively. Formulation development involved trials using different ratios of types of polymers and osmotic agents in both layers.

UV Scan of Drug to find λ_{max}:

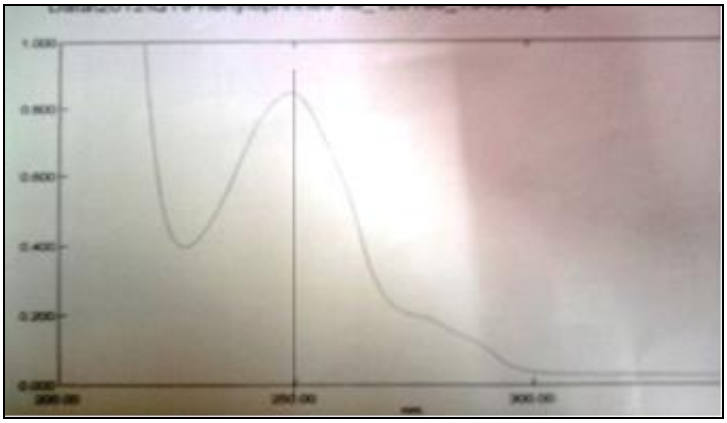


FIGURE 3: UV SCAN OF DRUG

The figure shows that the drug is having λmax of 250nm. And that was used for the analysis purpose.

Interaction Study: DSC thermograms of drug and formulation F14 were compared. In both thermograms drug peak appears between 240̊ C-250̊ C. It proves that there is no interaction between drug and other excipients.

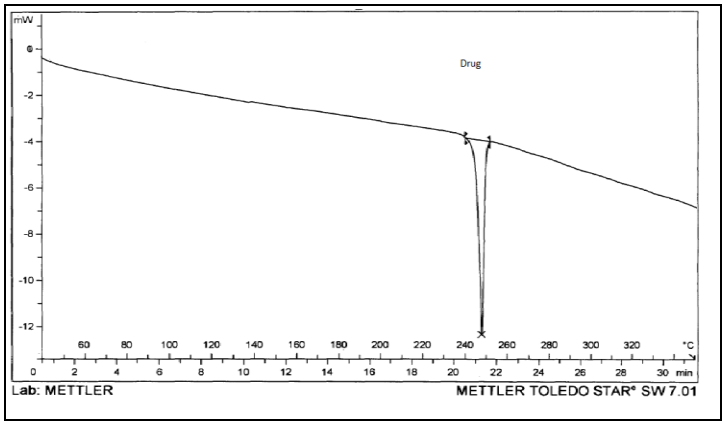


FIGURE 4: DSC THERMOGRAM OF DRUG

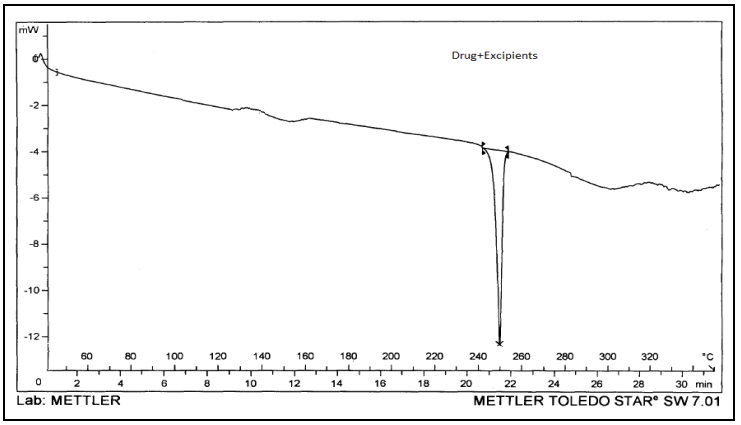


FIGURE 5: DSC THERMOGRAM OF DRUG AND EXCIPIENTS

Pre-compression parameters (Push layer):

TABLE 5: PRE-COMPRESSION PARAMETERS (PUSH LAYER) (F1-F7)

Parameters	F1	F2	F3	F4	F5	F6	F7
Bulk Density (g/ml)	0.481	0.471	0.470	0.437	0.452	0.487	0.479
Tapped Density (g/ml)	0.599	0.645	0.638	0.544	0.588	0.638	0.591
Carr's index (%)	19.608	26.923	26.415	19.608	23.077	23.636	18.868
Hausner's ratio	1.244	1.368	1.359	1.244	1.300	1.310	1.233

TABLE 6: PRE-COMPRESSION PARAMETERS (PUSH LAYER) (F8-F14)

Parameters	F8	F9	F10	F11	F12	F13	F14
Bulk Density(g/ml)	0.443	0.384	0.442	0.480	0.470	0.384	0.437
Tapped Density(g/ml)	0.560	0.551	0.575	0.600	0.638	0.551	0.544
Carr's index (%)	20.755	30.357	23.077	20.000	26.415	30.357	19.608
Hausner's ratio	1.262	1.436	1.300	1.250	1.359	1.436	1.244

Post-compression parameters:

TABLE 7: POST-COMPRESSION PARAMETERS (F1-F7)

Parameters	F1	F2	F3	F4	F5	F6	F7
Wt. variation	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Thickness (mm)	4.21±0.3	4.20±0.2	4.35±0.3	4.14±0.5	4.33±0.3	4.14±0.4	4.13±0.3
Hardness (Kp)	6.3±0.5	7.1±0.3	6.5±0.8	6.7±0.4	7±0.5	6.3±0.3	6.2±0.3
Friability (%)	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Assay (%)	99.8	100.3	100.3	100.9	99.1	100	101.3
Tickness of coat(µ)	170-210	150-210	270-340	160-200	260-320	180-240	160-210

TABLE 8 POST-COMPRESSION PARAMETERS (F8-F14)

Parameters	F8	F9	F10	F11	F12	F13	F14
Wt. variation	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Tickness (mm)	4.21±0.2	4.12±0.3	4.18±0.3	4.19±0.4	4.14±0.5	4.21±0.2	4.20±0.2
Hardness (Kp)	6.8±0.4	6.8± 0.5	6.3± 0.6	6.6± 0.5	6.7±0.2	6.8± 0.7	7.1±0.6
Friability (%)	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Assay (%)	99.7	100.6	99.8	101.2	100.9	99.7	101.1
Tickness of coat (µ)	160-210	180-240	160-210	150-210	160-200	160-210	160-200

Effect of type of plasticizer on Drug Release: Initial batches (F1 and F2) were prepared using different plasticizers. The core tablet formulation was kept constant and the plasticizer was optimized to provide zero-order drug release kinetics for extended period of time. The formulation containing PG released drug quickly and more than 80% of drug was released in 16 hours. In case of TEC drug release was consistent and it was able to prolong drug release up to 24 hours.

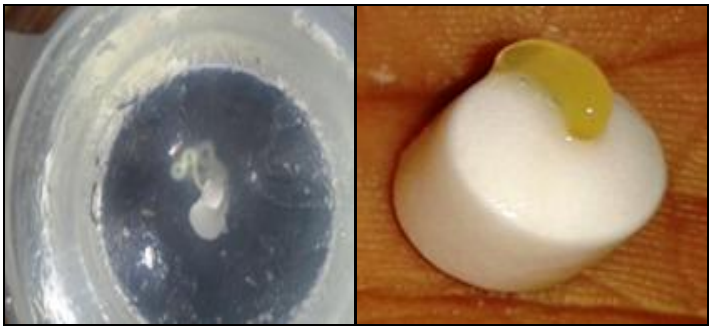


FIGURE 6: TABLETS AFTER DISSOLUTION TEST

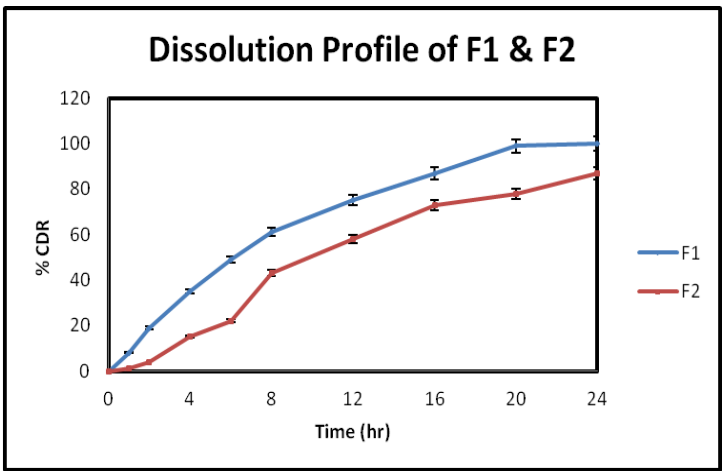


FIGURE 7: DISSOLUTION PROFILES OF F1 AND F2

Effect of Drug layer Polymer and coating wt. gain on Drug Release: Formulations F2, F3, F4 and F5 were formulated with different ratios of Drug:PEO WSR N80 (1:0.5 and 1:1) and coating wt. gain (10% and 20%). The formulations with 20% wt. gain were unable to release more than 50% of drug in 24 hours.

Formulation F4 (10% wt. gain and 1:1 ratio of Drug: PEO WSR N80) released more than 80% of drug in 24 hours with regression coefficient (zero order) of 0.98. So it was used for further optimization.

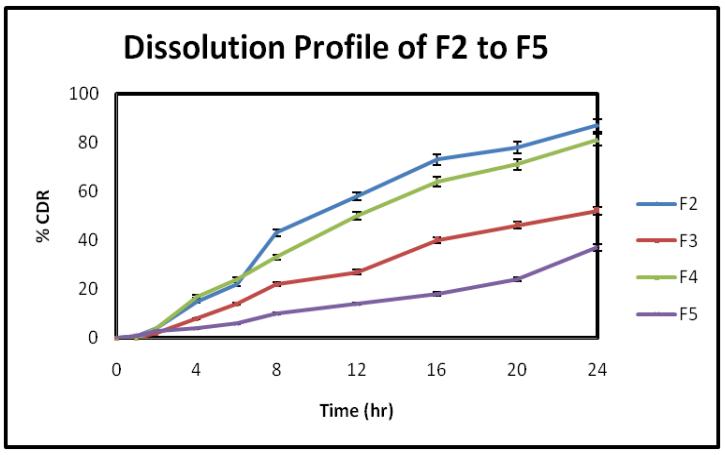


FIGURE 8: DISSOLUTION PROFILE OF F2 TO F5

Effect of Osmogen on drug release: Formulations F6 to F14 were formulated with different ratios of Sodium chloride in both layers. Formulations F6, F7 and F8 contains osmogen only in push layer at the level of 10%, 20% and 30% weight of push layer respectively. In formulations F9-F14 Sodium chloride is present in both layers in different ratios. From all batches formulations F10, F11, F13 and F14 were able to control the drug release for up to 24 hours. Formulation F14 was optimized because its granules were having better flow property with regression coefficient (zero order) of 0.99.

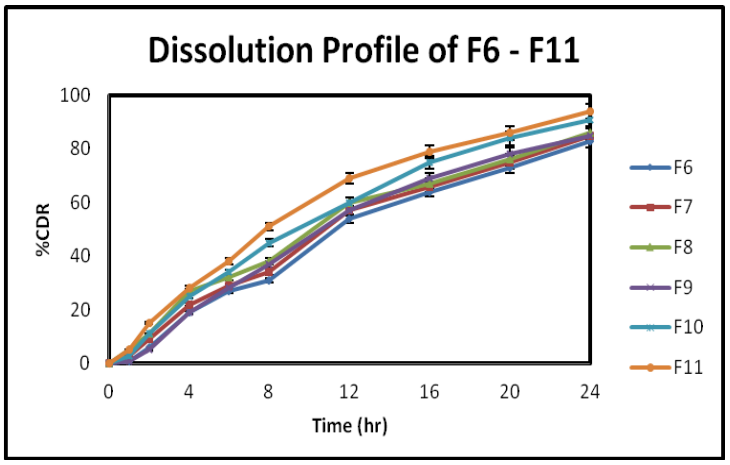


FIGURE 9: DISSOLUTION PROFILE OF F6 TO F11

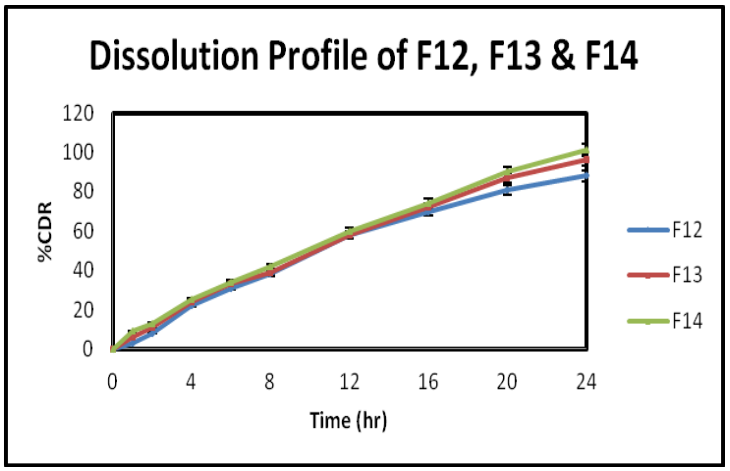


FIGURE 10: DISSOLUTION PROFILE OF F12 TO F14

Effect of pH: When formulation F14 was subjected to in vitro release studies in buffers of differing pH and in distilled water, no significant difference in release profiles was observed. In other words

The developed push-pull osmotic tablet was found to exhibit pH independent release kinetics.

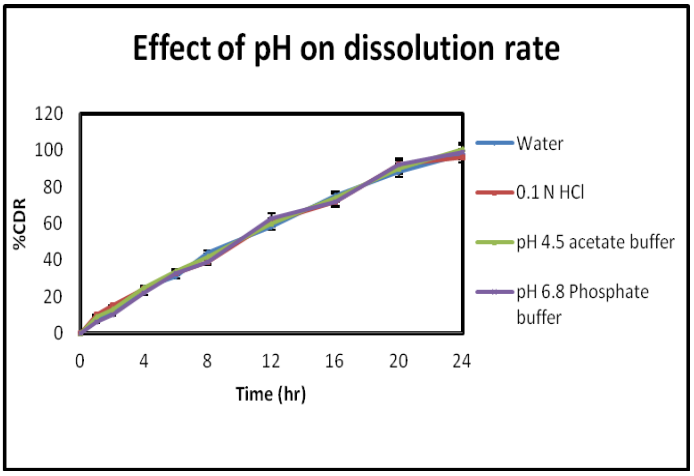


FIGURE 11: EFFECT OF pH ON DISSOLUTION PROFILE OF F14

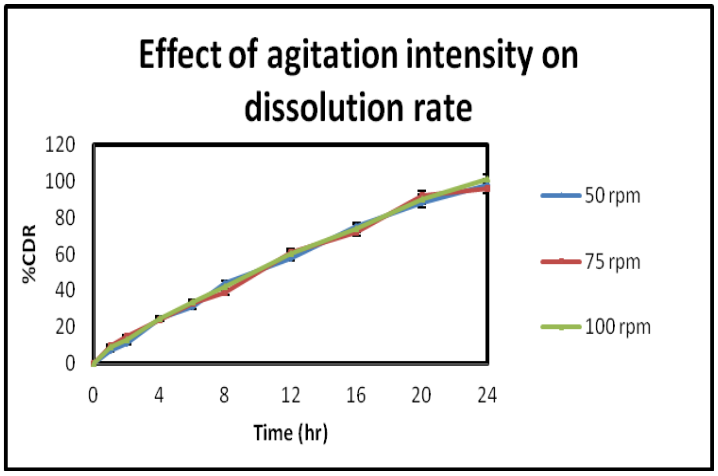


FIGURE 12: EFFECT OF AGITATION INTENSITY ON DISSOLUTION PROFILE OF F14

Effect of Agitation Intensity: The effect of different agitation rate on formulation F14 was also studied at 50, 75 and 100 rpm. There was no significant change in the drug release rate was observed. Hence, it can be concluded that the release rate of push-pull osmotic tablet was independent of agitational intensity.

Stability Studies: The formulations subjected to stability studies at each of the three temperature and humidity conditions were evaluated in terms of appearance, drug content and in vitro drug release. No significant changes were seen in the physicochemical parameters of the formulations over a period of 3 months. Stability data regarding appearance, drug content and texture are given in **Table 9**.

TABLE 9: STABILITY DATA OF FORMULATION F14 AS PER ICH GUIDELINES

Temperature Conditions	40°C/75% RH		
	Appearance Texture	Texture	Drug Content (%)
0	yellow & pink layer	Smooth	99.91
2nd week	NC*	NC*	99.86
4th week	NC*	NC*	99.84
6th week	NC*	NC*	99.80
8th week	NC*	NC*	99.77
10th week	NC*	NC*	99.74
12th week	NC*	NC*	99.71

NC* – No Change

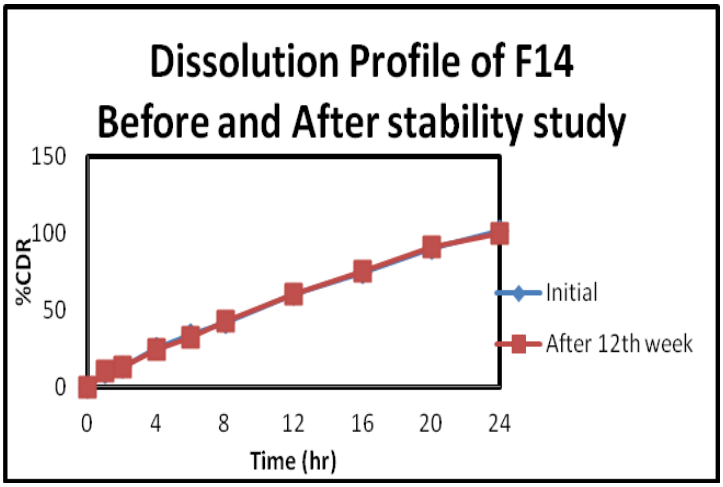


FIGURE 13: DISSOLUTION PROFILE COMPARISON OF F14 INITIAL AND AFTER 12TH WEEK

CONCLUSION: A push-pull osmotic tablet was developed for Ropinirole hydrochloride. The desired zero-order release profile was obtained by optimizing the concentrations of Osmogen and polymer in both the layers. From the results it was observed that the drug release increases with the amount of osmogen due to the increased water uptake and increased driving force for drug release. The drug release was further retarded using a proper concentration of PEO to achieve the desired zero-order release profile. The developed stable system was found to deliver Ropinirole hydrochloride at zero-order rate kinetics for an extended period of time independent of pH and agitational intensity. The system was easy to formulate and cost effective.

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