



ISSN No: 0975-7384

J. Chem. Pharm. Res., 2010, 2(2): 136-146

Once a day osmotic drug delivery system for highly water soluble Pramipexole

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Abstract

An oral monolithic osmotic system for highly water-soluble pramipexole dihydrochloride monohydrate has been developed and characterized. Monolithic osmotic system was developed using controlled porosity membrane, this system delivers drug in controlled manner for prolonged period of time. Controlled porosity osmotic membrane consists of cellulose acetate as coating polymer and water-soluble pore formers, which forms an in-situ microporous membrane after imbibing water, hence no laser drilling is required. Pore formation was controlled by varying concentration of pore forming agents to get controlled release of pramipexole for period of 24 hrs. Scanning electron microscopy was carried out to confirm the microporous structure. An optimized system was selected to study the effect of different concentration of coating polymer, osmotic agents, pH of dissolution media and effect of agitation on the release of drug. From in vitro release studies it was evident that drug release was independent of pH and agitation but highly dependent on concentration of pore forming agents used. Increasing concentration of cellulose acetate from 2 % - 5 % w/v drastically retarded drug release. Osmotic pressure generated was determined using 3D3 Freezing point osmometer and was found to be linear with drug release. The developed formulation gave desired once a day release of pramipexole without using laser drilling technique making it more patient compliance and cost effective.

Key words: Osmotic drug delivery system, highly water soluble drugs, Pramipexole.

Introduction

There has been increasing interest in the development of oral osmotic pumps in the past twenty years and varying types of oral osmotic delivery systems have been developed and studied for drugs possessing different aqueous solubilities. Oral osmotic pumps can deliver the drugs in controlled manner over prolonged period of time [1]. Various types of osmotic pumps have been reviewed by Santus and Baker [2].

Monolithic osmotic drug delivery features a semi-permeable rate-controlling membrane surrounding tablet core consisting of drug, swelling polymers and osmotic agents [3,4]. The rate controlling membrane consists of cellulose acetate with various water-soluble additives. When such systems come in contact with water, the additives dissolve forming an in-situ microporous membrane [5-11]. Osmotic agents present in the core dissolve generating osmotic pressure, which releases drug from the system at controlled rate. 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.

Parkinson's disease (PD) is a neurodegenerative disorder. It has worldwide incidence of 20 in 100,000 and is estimated to cost £ 700 million in drug treatment. Pramipexole has been investigated as a monotherapy in the treatment of PD [12-15]. In advanced Parkinson's disease the usual dose of pramipexole is as high as 1.5 mg three to four times a day. Pramipexole has been associated with episodes of somnolence during the daytime called as sleep attacks, other adverse effects caused are abnormal behavior, drowsiness, dizziness, fainting, hallucinations and many more. It has molecular weight of 302.27, half life of 8 hrs and is highly water soluble with solubility of 200 mg/ml in water. The objective of the study was to develop monolithic osmotic tablets of pramipexole for once a day administration. Reduction in dose frequency will improve patient compliance and maintain therapeutic level of pramipexole over a prolonged period of time. This may result in reduced severity of motor fluctuations and other side effects caused due to pramipexole.

Material and Methods

Pramipexole dihydrochloride monohydrate was obtained as gift sample from Sekhsaria Chemicals Ltd. India. It is white crystalline powder with melting point of 290°C. The percent purity of the drug sample was found to be 99.92%. Sodium bicarbonate, sodium chloride, mannitol, magnesium stearate, (s.d fine Chem, India) were used as osmogents, Lactose, microcrystalline cellulose were gifted by Signet Chemicals. Hydroxypropyl methyl cellulose of various grades were obtained as gift samples from Colorcon Asia Pvt. Ltd. Cellulose Acetate with 39.8% acetyl content was purchased from Sigma Chemicals was used as semipermeable membrane. Polyethyleneglycol 400, dibutylphthalate (s.d fine Chemicals), were employed as pore formers. Titanium dioxide and talc was gifted by Sekhsaria Chemicals Ltd. Potassium dihydrogen orthophosphate, sodium hydroxide (s.d fine chemicals), acetonitrile HPLC grade (Ranbaxy). All the chemicals used were of analytical grade.

Formulation Development

Drug-excipient interaction studies were first carried out to see the compatibility of drug with other excipients used in the formulation. Differential scanning Calorimetry technique was used for the studies. The isotherms obtained showed that the excipients used in final formulation were compatible with Pramipexole.

Microporous membrane coated monolithic osmotic tablets of Pramipexole dihydrochloride monohydrate were prepared by conventional wet granulation technology. Drug, osmotic agents like sodium bicarbonate, sodium chloride and other excipients were blended together to produce 500 tablets. The alcoholic solution of PVP K 30 M was added to produce damp mass. The wet mass was passed through # 16 sieve and dried in hot air oven at 60°C for 2 hrs. The dried granules were then passed through # 22 and mixed with lubricants. The core tablets were compressed at an average weight of 250 mg using 8 mm deep concave punches in single punch tablet machine.

Coating of tablet core

The tablets were coated with cellulose acetate (2% w/v in acetone) along with suitable pore former i.e PEG 400 (20% w/w of total weight of polymer) [16]. Talc and titanium dioxide were used as antiadherent and opacifier respectively in concentration of 1%. The tablets were coated using pan 9 inch in diameter, spray gun (pilot scale), baffles 4, speed of pan, 25 rpm, nozzle diameter, 1mm, spray pressure, 40-50 lb/sq.in, drying temperature, 55°C. For comparison another batch of tablets was given dense coat of 2% CA without pore former and a delivery orifice was drilled by mechanical drilling using needle. After coating the tablets were dried overnight at 60°C to remove residual solvent. The residual solvent content was determined by headspace gas chromatography and was found within limits (2000 ppm for acetone). There was no change in membrane characteristics. The coated tablets had smooth and uniform surface without any defects. The tablets had smooth, uniform surface without any defects.

Drug content

For determining the drug content, 20 tablets were crushed and powdered in a mortar. The powder equivalent 4.5 mg of drug was accurately weighed and transferred to 50 ml volumetric flask. The drug was extracted into diluent (phosphate buffer pH 7.4:acetonitrile in ratio 40:60) by sonication for 30 min. The solution was filtered through 0.45 µm nylon filter after making up the volume. One ml of this solution was diluted to 10 ml with diluent and analyzed by HPLC [16].

***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± 0.5°C, paddle speed was 100 rev/min, the dissolution medium was phosphate buffer pH 7.4 volume being 900 ml. Since the solubility of drug is not pH sensitive pH change method was not used. Samples of 5 ml were withdrawn at every hour and same amount of dissolution medium was replenished. Aliquots were filtered using 0.45µm nylon membrane filter and analyzed by HPLC. The studies were done in triplicate.

HPLC analysis

HPLC was used as the method of determining drug content and *in-vitro* release profile. The HPLC system used was Tosho, Japan with UV-Visible detector and data management system.

The column used was C18 Hypersil gold (250cm x 4.6 mm, 5 μ). The mobile phase consisted of Phosphate buffer pH 7.4: Acetonitrile (40:60 v/v) at a flow rate 1 ml/min. Analysis was done at wavelength of 262 nm.

Effect of pH on drug release

An osmotically controlled release system delivers its contents independent of external variables. Hence to assess the effect of pH on *in-vitro* release profile, the dissolution studies were carried out in phosphate buffers of different pH, viz, pH 1.2 buffers, pH 6.8 buffer and pH 7.4 and in distilled water.

Effect of agitation intensity

In order to study the effect of agitational intensity of the release media, the release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. The effect of agitation intensity was studied on optimized formulation in dissolution rate test apparatus II at various rotational speeds. The paddle rotation speed was adjusted at rates of 50, 75 and 100 rev./min. The samples were withdrawn at predetermined intervals and analyzed by HPLC after filtration through 0.45 μ m nylon membrane filters.

Effect of different concentration of cellulose acetate

The effect of various concentration of cellulose acetate on *in-vitro* drug release was studied. The tablets were coated with cellulose acetate 2% w/v, 3% w/v, 4% w/v and 5% w/v, the concentration of pore forming agent i.e 20% w/w of total weight of cellulose acetate was kept constant. The weight gain by the tablets was 8 ± 0.5 %.

Determination of osmotic pressure

Drug release from osmotic systems depends upon osmotic pressure generated in the tablet. The effect of osmotic pressure on drug release was assessed by performing *in-vitro* release studies. Osmotic pressure generated within the tablet was determined using 3D3 Freezing point osmometer (Model 3D3 Advanced Instruments Osmometer)[15]. The readings obtained were in mosmol/kg. Before measurement osmometer was calibrated using standards of 100 mosm/kg and 1500 mosm/kg.

Scanning Electron microscopy

To evaluate the surface morphology of the coating membrane, surfaces of the coated tablets were examined using Scanning Electron microscopy both before and after dissolution. Samples of the coating membrane were cut from the exhausted shells (after 24hr dissolution studies) dried at 50°C for 12-16 hrs and mounted on the stub with double sided adhesive tape[16]. Whereas the coated tablet (before dissolution) was placed as such on specimen stub and examined under SEM Model FEI Quanta 200F.

Stability studies

The optimized formulation which gave desired zero order release for extended period of time was selected, strip packed and subjected to stability studies as per ICH guidelines, 25°C/60%RH, 30°C/65%RH and 40°C/75%RH. Samples were withdrawn at time intervals of 0, 2, 4, 6, 8, 10 and 12th week. The samples were evaluated for appearance, drug content, *in vitro* release profiles and osmotic pressure.

Results and Discussion

The monolithic osmotic tablets developed were designed as a tablet core consisting of drug along with osmogen, and other conventional excipients to form the core compartment. The concentrations of swelling polymer and osmogents are given in (Table 1). The compressed tablets were surrounded by a membrane consisting of a semi permeable membrane-forming polymer, water-soluble additives, and at least one plasticizer capable of improving film-forming properties of the polymers. The semi permeable membrane-forming polymer was permeable 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 pores created after leaching of water-soluble additives in the membrane. Cellulose acetate was used as water-insoluble polymer and PEG-400 and Dibutylphthalate were, used as water-soluble and water-insoluble plasticizers, respectively. Formulation development involved trials with different types of polymers, osmotic agents and water-soluble additives.

Table No.1 Formulations containing various concentration of osmotic agent

Ingredients Core	Core code				
	I	II	III	IV	V
Pramipexole	4.5	4.5	4.5	4.5	4.5
Microcrystalline cellulose	120	120	120	120	120
Lactose	90	90	90	90	90
HPMC K4 M	20	20	20	20	20
Sodium chloride	5	-	-	-	-
Sodium bicarbonate	-	5	-	-	-
Potassium chloride	-	-	5	-	-
Fructose	-	-	-	5	-
Mannitol	-	-	-	-	5
PVP	10	10	10	10	10
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5

*Total weight of tablet was 250 mg
The weights are given in milligrams.*

Table No.2. Various pore formers used in coatings on formulation (core II)

Ingredients	Coating code			
	C1	C2	C3	C4
Cellulose Acetate (% w/v)	2	2	2	2
PEG 400 (% w/w)	20	40	-	-
Dibutylphthalate (% w/w)	-	-	20	40

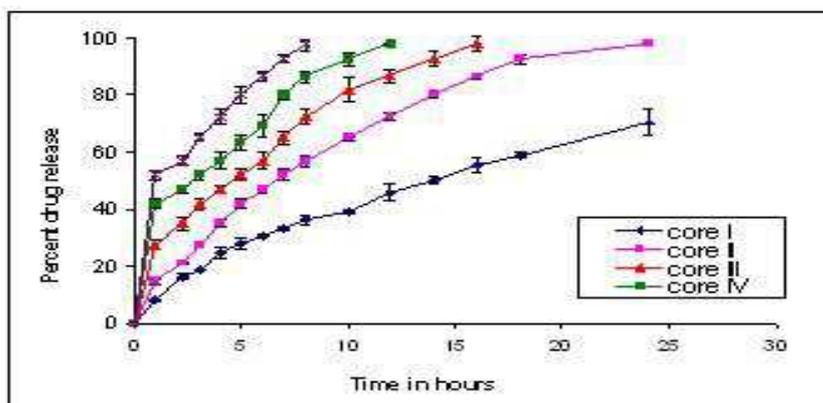
*Cellulose acetate (% w/v) in acetone, PEG 400 and
Dibutylphthalate (% w/w) of total solid contents of cellulose acetate).*

Effect of swelling polymer and osmotic agents on drug release

Initially several batches were prepared using different concentrations of swelling polymer and osmotic agents. Various formulations tried are given in (Table 1). The formulations core I- V showed that as the concentration of osmotic agent was increased the drug release also increased drastically as observed from the (Fig 1). When the concentration of polymer was increased beyond a certain point the integrity of coating was completely lost. This may be due to the presence of high concentration of hydrophilic polymer (above 20% w/w).

Table No.3 Different Types of coating solution tried on formulation (core II)

Ingredients	Coating code		
	Coating I	Coating II	Coating III
Cellulose Acetate (% w/v)	2	2	2
PEG 400 (% w/w)	20	-	20
Acetone (%)	100	100	-
Dichloromethane:Methanol:Water	-	-	70:20:10

Figure 1 : Effect of various concentrations of osmotic agents on drug release**Table No 4. Fitting of drug release data of the optimized formulation (core II) according to various mathematical models**

Models	Parameters used to assess the fit of model			
	R ²	r	Intercept	Slope
Zero order	0.9824	0.9915	1.3502	0.142
First order	0.9226	0.9625	1.5889	0.0182
Higuchi	0.8998	0.9455	- 0.3287	22.81

Influx of dissolution medium through the coating membrane caused the polymer to swell resulting in high hydrostatic pressure inside the tablet. This lead to cracking and bursting of coating membrane, as observed visually. The formulation (core II) gave desired release profile of the drug; almost 90% of drug was released in 16 hrs. Hence formulation (core II) was selected as an optimized batch and was chosen for further characterization. Dissolution data of the optimized

formulation (core II) was fitted to various mathematical models (zero order, first order and Higuchi).

Figure 2- Effect of various concentrations of pore-formers on in-vitro drug release carried on formulation (core II)

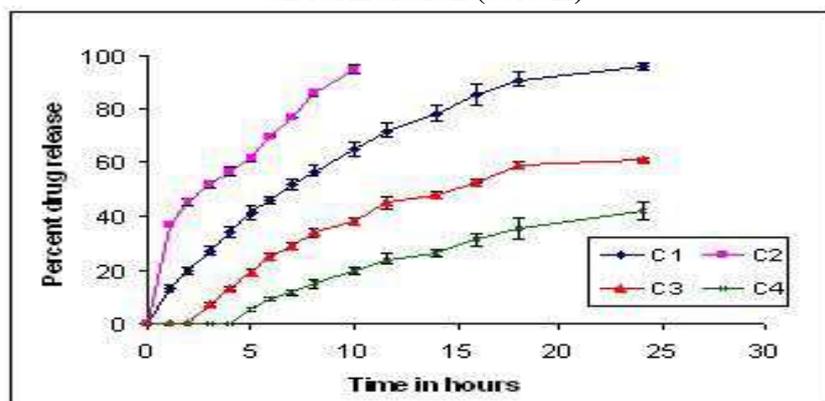


Figure 3- Effect of different coating solutions on in-vitro drug release carried on formulation (core II)

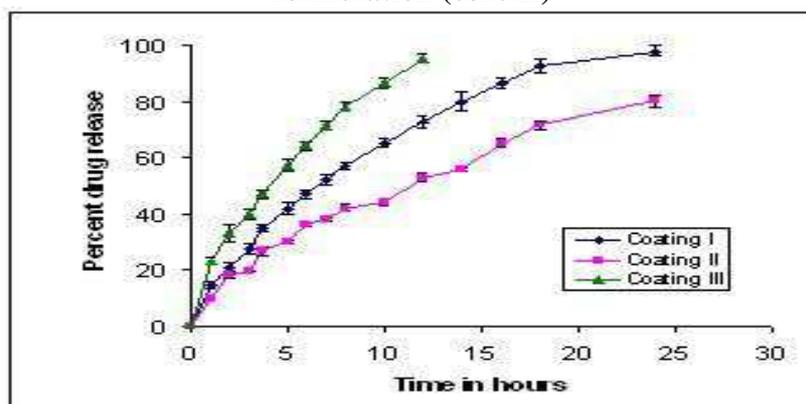
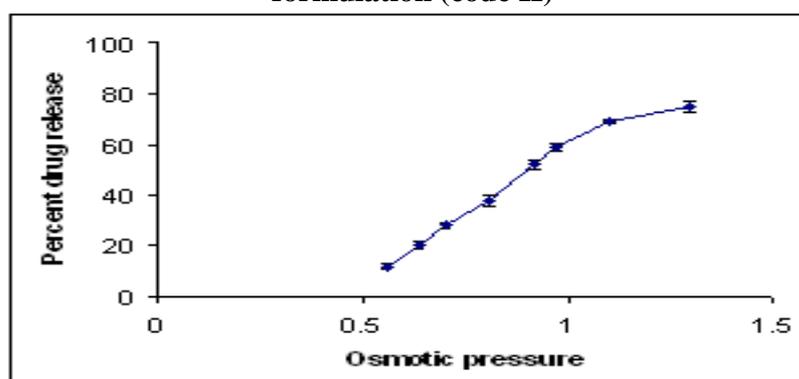


Figure 4: Effect of Osmotic pressure on in-vitro drug release studies performed on formulation (code II)



Drug release from formulation (core II) fitted well into zero order kinetics with r value of 0.9915, while the second best model describing the release was first order kinetics (20) (Table 4).

Figure 5: Effect of various concentration of cellulose acetate on in-vitro drug release studies performed on formulation (core II)

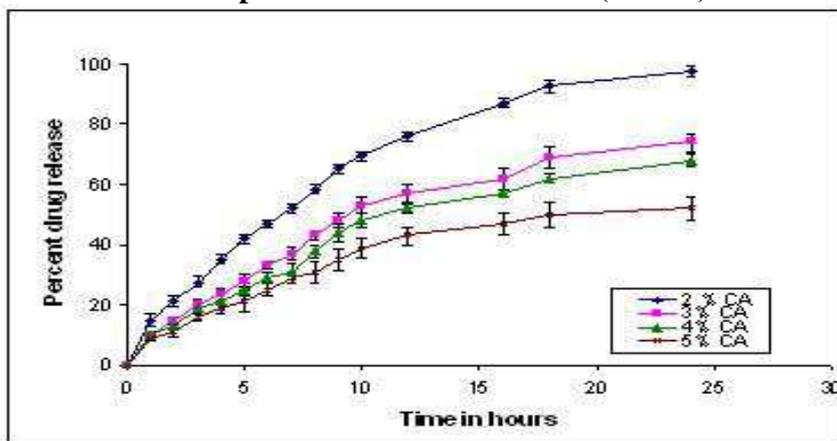


Figure 6 (a) SEM microphotograph (at 500X magnification) of monolithic osmotic tablet before dissolution

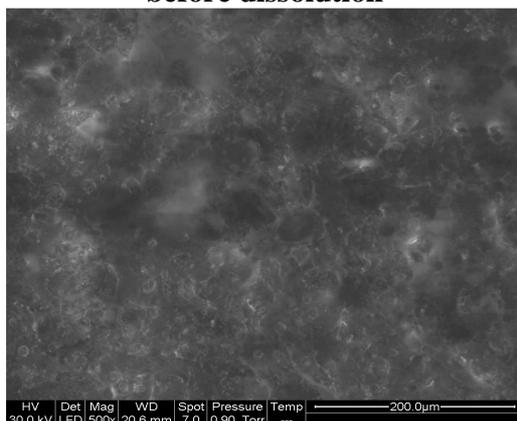


Figure 6 (b) SEM microphotograph (at 500 X magnifications) of monolithic osmotic tablet after dissolution, showing formation of pores

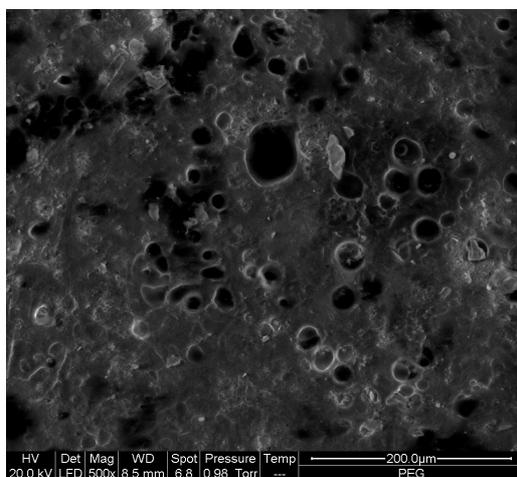


Figure 7, Photographs of monolithic osmotic tablet kept in dissolution medium taken at specified time intervals.



(a) Initially 0 hrs



(b) After 1 hr (This is close view (zoom) of the tablet)

Effect of pore-formers

The developed monolithic osmotic tablets (core II) were coated with different coating solutions and *in-vitro* release studies were performed. The weight gain by the tablets and membrane thickness were $8 \pm 0.5\%$ and 0.4 ± 0.05 mm respectively both were kept constant. The (Table 2) shows the concentration and contents of pore formers used. The effect of PEG 400 and dibutylphthalate in concentration range (20-40%) on drug release was studied. *In-vitro* release studies (Fig 2) indicated that as the concentration of PEG 400 in the polymeric coat was increased the drug release was increased. PEG 400 being water-soluble gets dissolved and thus increases the permeability of coating membrane. The desired release of drug was obtained with PEG 400 at 20 % concentration as observed from (Fig 2, C1), almost 90 % of drug released in 16 hrs. When the concentration of PEG 400 was increased up to 40%, about 90 % drug was released in just 6 hrs. Reverse was observed when dibutylphthalate was used as pore former at high concentration of 40 % (Fig 2, C4) lag time of 4 hrs was seen. When the concentration was reduced to 20%, lag time also reduced to 2 hrs. Hence it can be concluded that dibutylphthalate decreases the permeability of the coating membrane and can be used at low concentration. As the concentration of dibutylphthalate increases, hydrophobicity of the coating membrane also increases. This acts as a barrier for permeation of dissolution medium inside the tablet core.

Effect of coating solutions on drug release

The developed formulation (core II) was coated with different coating solutions given in (Table 3) and effect on drug release was studied. From the *in-vitro* release profile in Fig. 3 it was observed that coating (I) containing 2% w/v of cellulose acetate (in acetone) and 20 % w/w of PEG 400 as pore former gave a desired drug release of 97.23 % in 16 hrs. The release was found to follow zero order kinetics. The release rate was found to be slow in case of coating (II), consisting of 2% CA in acetone (without any pore former) with mechanically drilled orifice, only 80 % of drug was released in 24 hrs. Coating III also called as asymmetric membrane, consisted of dichloromethane, methanol and water, gave a drug release of 90 % in 12 hrs. This may be due to the fact that the membrane formed by this coating (III) was due to phase inversion process. The solvent gets evaporated during spray coating process and water which acts as a non-solvent for cellulose acetate gets precipitated. This results in formation of large pores which increased the water flux, thereby increasing the drug release from the tablets.

Effect of pH and agitation intensity

When formulation (core II) was subjected to in-vitro release studies in phosphate buffer, 0.1N HCL and in the distilled water, no significant difference in release profiles was observed. In other words the developed monolithic osmotic tablet was found to exhibit pH independent release kinetics.

The effect of different agitation rate was also investigated on formulation (core II) at 50, 75 and 100 rev./min. There was no significant change in drug release rate. Hence it can be concluded the release rate of monolithic osmotic tablet was independent of agitational intensity.

Effect of different concentrations of cellulose acetate

From figure 5, it can be concluded that as the concentration of cellulose acetate was increased from 2%- 5% w/v the in-vitro drug release was found to decrease. Increasing the concentration of cellulose acetate increases the density of the membrane which resulted in decreased drug release from the tablets.

Surface morphology

To investigate the change in the membrane structure, surface of coated tablets (both before and after dissolution studies) was studied using Scanning Electron microscopy microphotographs showed in (Fig.6a-b). Figure 6a shows membrane structure before dissolution, initially the surface of coated tablets was smooth before coming into contact with aqueous environment and coats appeared to be free of point defects. A microporous structure of the membrane after dissolution was observed from (Figure 6b), which shows SEM of membrane after dissolution. This significant porosity has resulted due to leaching of water-soluble additive i.e PEG 400 during dissolution through which drug release takes place.

The changes in the appearance of the monolithic osmotic tablets during the dissolution process are shown in (Fig 7). As soon as the tablet is suspended in the dissolution medium, the coating membrane imbibes water thereby forming pores by leaching the water-soluble pore formers. Initially at 0 hrs the tablet was intact, photograph taken at 0 hrs. Photograph taken after 30 min showed that the as tablet imbibes water, osmotic agents also dissolves thus creating osmotic gradient inside the tablet which releases its content through the pores formed in the membrane.

Effect of Osmotic Pressure

It was observed from the Fig. 4 that the drug release from the monolithic osmotic tablet was directly proportional to the osmotic pressure generated in the tablets. The drug release was increased with the osmotic pressure.

Stability studies

The formulations subjected to stability studies at different temperature and humidity conditions were evaluated for appearance, possible weight gain, drug content, in-vitro drug release and any changes in osmotic pressure. There was no change in the physicochemical parameters of the formulations during 3 months of stability.

Conclusion

Monolithic osmotic tablets coated with cellulose acetate as a semi permeable membrane containing different channeling agents have been developed for Pramipexole. The desired zero order release profile was obtained by optimizing concentration of osmogen, polymer and pore formers. Drug release increased with the amount of osmogents due to the increased water uptake and increased driving force for drug release. The drug release was further retarded using proper pore former to achieve desired zero order release profile.

The developed formulation was found to be stable. And the system delivered Pramipexole at zero order rate for a period of 24 hrs independent of pH and agitational intensity. This system is simple to prepare and is cost effective, alternative to conventional osmotic delivery pump as the sophisticated laser drilling technique is not required.

Acknowledgements

The authors are thankful to Sekhsaria Chemicals Ltd. (Now Watson Pharma Pvt.Ltd, India) for providing for financial assistance.

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