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DEVELOPMENT OF ELEMENTARY OSMOTIC PUMP DOSE FORMULATION OF IMINOSTILBENE ANTICONVLSANT DRUG

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ABSTRACT

An oral dosage form faces a number of challenges concerned with Pharmacodynamic and Pharmacokinectic characteristics responsible for producing a desirable results in obtaining the optimal efficacy. Such challenges may be of wider to narrower magnitudes. An innovative approach to solve such problems focuses onto the enhancement of certain parameters i.e. disintegration and dissolution time, absorption from specific parts of GIT, bioavaibility of active medicament present in the dosage form, onset & duration of action, etc. It must accompanying reduction of toxic effects of variable nature. The present work was aimed at development of Elementary osmotic pump dose formulation (tablets) of Iminostilbene anticonvlsant drug (the name kept secret due to the ongoing patenting process) abbreviated as DABC. EOP dose formulation has been reported in literature to be effective in oral therapy with optimized Pharmacodynamic & Pharmacokinectic properties together with reduced toxic parameters. Solid dispersions of the drug were prepared using polymers i.e. PEG 6000 and Plasdone S-630. The dispersion with PEG 6000 was prepared by fusion method while with Plasdone S- 630 it was prepared by hot melt hot granulation. The dissolution studies were carried out with different formulation batches and the optimized formulation was selected for future studies i.e. the drug:PEG 6000(1:2) and drug:Plasdone S-630 in the same ratio. The latter also contained 33.33% of PEG 6000 as a plasticizer. The core tablets were formulated with the optimized batches. The comparative dissolution studies of these two batches carried out with produced core tablets in water revealed that former as solitarily optimized batch. Now the finally selected batch of tablets were seal coated (with 3% HPMCe5cps). Functional coating was done with the entire batch using 3% Cellulose acetate.

Keywords: Iminostilbene, Osmotic Pump, Development.

INTRODUCTION

An osmotic system releases a therapeutic agent at a predetermined zero order delivery rate based on the principle of Osmosis [1] which is movement of a solvent from lower concentration towards higher concentration of solute across a semi-permeable membrane**.** After administration of osmotic system, water is imbibed into the core osmotically through semi permeable membrane resulting in development of hydrostatic pressure that pumps drug containing solution or suspensions out of the core through one or more delivery ports [2]. The delivery from the system is controlled by the water influx through semipermeable membrane.

Drug Profile

IMINOSTILBENE

Physical and Chemical Properties

Melting Point	190.2°c
State	solid
Water solubility	17.7mg/ml
Log P	2.3
Mol. Weight	Average: 236.2686

Pharmacology

Indication: For the treatment of epilepsy and pain associated with true trigeminal neuralgia.

Protien binding: An anticonvulsant drug in blood is 76% bound to plasma protein.

Half-Life: 25-65 hours

Toxicity: mild ingestions cause vomiting, drowsiness, ataxia, slurred Speech, dystonic reactions and hallucinations.

Pharmacodynamics

Drug, an anticonvulsant structurally similar to tricyclic antidepressants is used to treat partial seizures, tonic-clonic seizers, pain of neurologic origin such as trigeminal neuralgia, and psychiatric disorders including manic-depressive illness and aggression to dementia.

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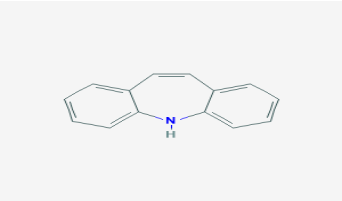
Structure



Mechanism of action

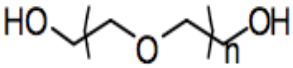
An anticonvulsant drug inhibits sustained repetitive firing by blocking use dependent sodium channels [3]. Pain relief is believed to be associated with blockade of synaptic transmission in the trigeminal nucleus and seizure control with reduction of post-tetanic potentiation of syenaptic transmission in the spinal cord.

Polymer Review

PEG 6000

Synonym: Macrogol 6000

Structural formula



Chemical name: α-hydroxyl-ω-hydroxypoly(oxy-1,2,-ethanediyl)

Empirical formula: $HOCH_2$ $(CH_2OCH_2)NCH_2OH$, where n is the average number of oxethylene group.

Molecular weight: 7300-9300 Dalton

Functional category: Ointment base, plasticizer, solvent, suppository base, tablet and capsule lubricant.

Solubility: Solubility in water and miscible in all Proportions with other polyethylene glycol

Melting point: 55-63 ˚C

Plasdone S-630

Chemical name: Acetic acid ethyl ester

Synonyms: Acetic acid Vinyl Ester, Copovidone

Functional Category: Film-former, granulating agent, tablet binder

Description: Copovidone is a white to yellowish-white amorphous Powder

Melting Point: 140°c

Denisity (bulk): 0.24-0.28g/cm³

Denisity (tapped): 0.35-0.45g/cm³

Glass Transition Temperature: 106°c

Solubility: Greater than 10% solublility in methanol, water, polyethylene Glycol, butanol, Glycerol and Chloroform

MATERIALS AND METHODS

Preformulation Study

Preparation of Reagents

a) pH 6.8 Phosphate buffer(PB)Solution

0.2(M) monobasic Potassium Phosphate:- An accurately weighed (27.218gm) of monobasic potassium phosphate was placed in an one litre volumetric flask and added with approximately 100ml distilled water with continuous shaking until the solid material dissolved completely. The clear homogenous solution thus obtained was added with sufficient distilled water to make-up the volume up to the mark (1000ml).

0.2(M) Sodium hydroxide:- 8.0g of sodium hydroxide (flakes) was weighed accurately and dissolved in about 200ml of distilled water until complete dissolution occurred. The obtained solution was added with sufficient distilled water up to the mark (1000ml).

50 ml of 0.2(M) monobasic potassium phosphate solution was placed in a 200ml volumetric flask and added with 22.4 ml of 0.2(M) NaOH solution. The contents were mixed thoroughly and later on sufficient distilled water was added to make up the volume up the mark.

b) 0.1N Hydrochloric acid (HCl) (pH=1.2)

0.2(M) Potassium chloride:- 14.911g of Potassium chloride was dissolved in a portion of distilled water and diluted up to 1000ml.

0.2(M) Hydrochloric acid:- 7.292g of HCl was taken and volume was made up to 1000ml with distilled water.

50 ml of 0.2(M) potassium chloride solution was taken in a volumetric flask and added 85 ml of 0.2(M) HCl solution. The contents were mixed thoroughly and added water to make up the volume up to the 200ml.

c) Standard (Stock) Solution:

200mg of drug was weighed and dissolved in 40 ml of ethanol and volume was made up to the mark with purified water. 10 ml from this solution was taken and diluted up to 100 ml in a volumetric flask. Further 10 ml of diluted solution was pipetted out and added with distilled water upto 100ml in a volumetric flask to give the desired stock solution.

Afterwards 1µg/ml, 2.5µg/ml, 5µg/ml, 7.5µg/ml and 10µg/ml solutions were prepared by diluting predetermined pipetted volume of the stock solution with pH 1.2 HCl, pH 4.5 acetate and pH 6.8 phosphate buffer solutions. Consequently all dilutions were made with individual buffers. Similarly all above mentioned sample solutions were also prepared by diluting the predetermined volume of the stock solution with water, 1%(w/v)SLS and 0.01 N HCl solutions.

Determination of absorbance maxima(ƛ max) in different media

A solution of selected drug (DABC) with concentration (100µg/ml) was prepared in pH 1.2 HCl, pH 4.5 acetate buffer, pH 6.8 Phosphate buffer, water, 0.01N HCL and 1% SLS solution. Each sample was scanned between the wavelength range 200- 400nm using shimadzu UV-2400 UV/Vis double beam spectrophotometer against the respective blanks. The wavelength corresponding to the sharp and steep peak was selected as the ƛ max.

Preparation of calibration curve:

Absorbance of all above prepared solutions of concentration 1-10µg/ml was measured at ƛ max 285nm

using shimadzu UV-2400 UV/Vis double beam spectrophotometer against the respective blanks. A graph was plotted with absorbance versus concentration values which gave straight line curve.

Determination of saturation solubility:

The Drug (DABC) in excess amount was added in to different media (5ml) so that the solution got saturated. The containers were kept in the shaker at 37°c for 24 hours. All saturated solutions were filtered with 0.45µm nylon filter and used for the determination of solubility. The absorbance of each solution was measured at 285 nm. The solubility of the drug was determined in different media (pH 1.2 HCl, pH 4.5 acetate buffer, pH 6.8 Phosphate buffer, water and 0.01 N HCl) using the absorbance data.

Solution state stability determination of the Drug in Different media:

Only those media in which maximum solubility was found were selected for further studies. 100µg/ml of drug solution was prepared using water, pH 4.5 acetate and pH 6.8 Phosphate buffer. The absorbance of the each prepared solution was measured at different time (T) intervals (T=0, 2, 4, 6, 24, and 48 hours) at 285 nm and the stability was assessed.

Filter Compatibility study:

100µg/ml solution was prepared using water, pH 4.5 acetate and pH 6.8 Phosphate buffer. Assays were conducted with all solutions spectrophotometrically at the 285 nm before filtration and after filtration.

Preparation of solid dispersion

Preparation of physical mixture of Drug: Plasdone-S-630(1:2)

15g of Drug was taken in mortar and 30 g of Plasdone S-630 was added and mixed with pestle for 5 min until a homogenous mixture was obtained.

Hot Melt Granulation Technique

Solid Dispersion of drug was prepared according to the proportions given in table below. Accurately weighed Quantity of physical mixture of drug:Plasdone S- 630 were taken in glass beaker. Now different proportions of PEG 6000 was added to it and heated to melt with vigorous stirring till granules were formed. The formed granules were taken out and air dried. These granules were then passed through sieve no. 40.

Solid Dispersion of Drug: PEG 6000

Solid Dispersion of drug was prepared according the proportion given in the table below. Accurately weighed quantity of PEG 6000 was taken in glass beaker and melted at 60°c. Drug was added slowly into the beaker with constant stirring. After complete dispersion of the drug, the obtained physical mixture was dried in hot air oven for 2-3 hours at 40°C. Finally the resulted mass was powdered in mortar & pestle and passed through sieve no. 60.

Drug Content Uniformity of solid dispersion

Solid dispersion equivalent to 100 mg of the drug was weighed and a solution containing 100µg/ml solution was prepared in water. The assay of the prepared solution was performed spectrophotometrically at 285nm. The drug content was determined and verified.

Characterization of Solid Dispersion

Differential Scanning Calorimetry

The samples were sealed in aluminium pans and analysed using a Perkin Elmer Thermal analyzer. In the DSC method, the sample & reference drug were kept and the heat required for maintaining the fixed temperature at which the phase transition occurred, was measured. The scanning range was between 25°c to 250°c.

Fourier Transform Infrared Spectroscopy (FTIR):

The infrared spectra were obtained using a FTIR (Shimadzu IR Affinity-1) Spectrophotometer.The sample of pure drug, physical mixture, carrier and solid dispersion were previously ground and mixed thoroughly with KBr. The KBr discs were prepared by compressing the Powder. The characteristic Peaks were recorded by scanning from 400 to 4000 cm^{-1}.

***In Vitro* Dissolution Profile of Solid Dispersion**

In-vitro dissolution of pure drug, solid dispersion and prepared formulations were carried out with the USP XXXIII Apparatus II at an agitation rate of 100 rpm in 900 ml of water. The temperature of medium was set at 37±5°C. A 5 ml of sample was withdrawn at regular time intervals and replaced with fresh dissolution media. The samples were filtered and the drug concentration was determined spectrophotometrically at 285 nm in triplicate.

Method of Preparation of Core Tablets

Direct Compression method: The core tablets were prepared by this method. The Solid dispersion equivalent to 100 mg of drug & other ingredients were accurately weighed, mixed properly and blended. The final blend thus obtained was further compressed using 11mm concave punches.

Drug: PEG6000 (1:2)

Wet Granulation method: The core tablets were also prepared by this method. The solid dispersion equivalent to 100 mg drug and other ingredients were accurately weighed, mixed properly and blended. The powder mass was moistened with water and kneaded properly till granules were formed, dried at 40°C in hot air oven & passed through the sieve no.44, and mixed properly. Afterwards magnesium stearate was added and mixed to produce the final blend which was further compressed using 11mm concave punches.

Control Tablet

The control tablets were prepared by wet granulation method. 100 mg of drug was weighed, mixed properly with other ingredients, moistened with water and kneaded properly till granules were formed, dried at 40°C in hot air oven & passed through the sieve no. 44 and mixed properly. Afterwards mag. stearate was added to produce the final blend which was further compressed using 8.5mm concave punches.

Formulation of Elementary osmotic Tablet

Coating of Core and Control Tablets

The core and control tablets were coated with 3% seal coating using HPMCe 5cps followed by 3% functional coating using cellulose acetate.

Procedure of coating the control tablet

1) 3% Seal coating using HPMCe5cps

Preparation of 6% HPMCe 5cps solution: 10.5 gm of HPMCe 5cps was weighed and stirred with 98.7gm isopropyl alcohol and 65.8gm methylene chloride for 45 minutes. Coating was done on Hicota machine. Inlet temperature was kept at 60°C and bed temperature was maintained at 42°C. In Coating Pan containing control and 300gm dummy tablet 6%HPMCe5cps solution was sprayed with a pump at 4-5 rpm till final weight consumed to the predetermined value.

2) 3% Functional Coating using Cellulose Acetate

Preparation of Cellulose Acetate Solution: 9.71gm of cellulose acetate was weighed and stirred with 164.5 gm of acetone and 0.79 gm of polyethylene glycol for 45 minutes. Product temperature was kept 18-22°c and cellulose acetate solution was sprayed with the spray pump at 4-5 rpm till final weight conformed to predetermined values.

Procedure of coating core tablet (without osmogen)

1) 3%seal coating using HPMCe5cps

Preparation of 6% HPMCe 5cps Solution: 15 gm of HPMCe5cps was weighed and stirred with 141gm isopropyl alcohol and 94 gm methylene chloride.

Coating methodology was similarly followed as it was in case of control tablets.

2) 3% Functional coating using Cellulose Acetate:

Preparation of Cellulose Acetate Solution: 13.88 gm of Cellulose acetate was weighed and stirred with 235 gm of acetone and 1.13gm of polyethylene glycol 4000 was added after melting.

Exactly similar methodology was adopted as it was practiced in the coating of control tablets.

Comparison of *In-vitro* dissolution of Control tablet and Elementary osmotic tablet (without osmogen)

In-vitro dissolution of EOP and control tablet was carried out in USP XXIII Apparatus II at an agitation speed of 100 rpm in 900 ml of water and pH 6.8 PB. The temperature of the medium was kept 37±0.5°C. EOP and control tablets were drilled with 0.97mm mechanical driller on one side & on both sides and thereafter started the dissolution. 5 ml of sample was taken at 0.5, 1, 2, 4, 6, 8, 10 and 12 hours intervals and 5 ml of fresh media was added to maintain the sink condition. The samples were filtered with 0.45µm nylon filter and assayed spectrophotometrically at 285 nm.

Formulation of Elementary Osmotic Tablet using NaCl as Osmogen

Wet Granulation Method: The another batch of core tablets (with osmogen) was prepared by this method. The solid dispersion equivalent to 100 mg drug and other ingredients were accurately weighed, mixed properly and blended. The obtained powder mass moistened with water and kneaded properly till granules were formed, dried at 40°c in hot air oven and passed through the sieve no.44. Afterwards mag. stearate was added to produce the final blend which was further compressed using 11mm concave punches.

Procedure of coating the core tablet (with osmogen)

3%seal coating using HPMCe 5cps

Preparation of 6% HPMCe5cps Solution: 15 gm of HPMCe5cps was weighed and stirred with 141gm isopropyl alcohol and 94 gm methylene chloride. Coating was performed in the similar fashion as described earlier. After seal coating approximately half of the tablets (core containing NaCl as osmogen) were coated with Cellulose acetate while and half was coated with Ethylcellulose.

3% Functional coating using Cellulose Acetate

Preparation of Cellulose acetate solution: 13.88 gm of Cellulose acetate was weighed and stirred with 235 gm of acetone and 1.13gm of Polyethylene glycol 3350 was added after melting. Similar process of coating was adopted as describe earlier.

5% Functional coating using Ethyl cellulose 10 cps

Preparation of Ethyl cellulose 10 cps solution: 21.25 gm of ethyl cellulose was weighed and stirred with 3.75 gm dibutyl sebecate, 235 gm isopropyl alcohol and 156 gm methylene chloride. Product temperature was kept at 35-40°C and coating was started with 5% Ethyl Cellulose 10 cps solution at 4-5 rpm with the spray pump till final weight conformed to the predetermined values.

***In-Vitro* release of Elementary Osmotic Tablet (using NaCl as Osmogen)**

In-vitro dissolution of elementary osmotic tablet was carried out in USP XXIII Apparatus II at an agitation speed of 100 rpm in 900 ml of water and pH 6.8 Phosphate buffer. The temperature of the medium was kept at 37±0.5°C. Osmotic tablet (coated with cellulose acetate) was drilled with 0.97mm mechanical driller on one side & both sides. 5 ml of sample was taken at 0.5, 1, 2, 4, 6, 8, 10,

12 and 24 hours intervals and 5 ml of fresh media was added to maintain the sink condition. The samples were filtered with 0.45µm nylon filter and assayed spectrophotometrically at 285 nm.

Comparative study of release kinetics of different formulation batches

The comparison of different formulations studies was done using five kinetic models as mentioned below:

(a) Zero-order release kinetics

$$Q(t)=k_0t$$

Where Q (t) is the percent of drug dissolved as a function of time t in minutes and k_o described the dissolution rate constant for zero order release. A plot of the percent of drug released against time was found linear which confirmed that the release obeyed zero-order kinectics. Values of release rate constant k_0 was obtained in each case from the slope of percent drug released versus time plots.

(b) First-order release kinectics

$$\text{Log } Q_1=\text{Log } Q_0 + k_1t/2.303$$

The first-order equation described the rate of release of a drug from a system was concentration dependent, where Q_0 was the initial amount of the drug, t time in minutes and k_1 described the dissolution rate constant for first- order release kinectics [4]. A plot of the logarithm of the percent of drug remained against time was found linear and this obeyed first-order release. Values of release rate constant k_t was obtained in each case from the slope of the graph.

(c) The simplified Higuchi model

$$Q(t)= k_H\, t^{1/2}$$

Where Q (t) was the percent of drug dissolved, time t in minutes and k_H corresponded the dissolution rate constant. A plot of the fraction of drug released against square root of time was linear and thus obeyed Higuchi equation [5]. Values of release of rate constant k_H was obtained in each case from the slope of the graph thus obtained.

(d) Korsmeyer-Peppas model

Korsmeyer et. al. (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data fitted in korsmeyer-peppas model [6].

$$M_t/M_Q= Kt^n$$

Where M_t/M_Q= A fraction of drug released at time t,
K= the release rate constant
n= the release exponent

The n value was used to characterize different release for cylindrical shaped matrices. In this model, the value of n characterized the release mechanism of drug.

(e) The Hixon- crowell cube root model

$$W_0^{1/3}- W_t^{1/3} = k_{HC}{}^t$$

Where W_0 is the initial amount of drug in the dosage form, W_t is the remaining amount of drug at time t. Hixon-crowell cube root law described the release from systems where there was a change in surface area and diameter of the Particles. K_{HC} called as the release rate constant for Hixon-crowell rate equation. Then a graph of the cubic root of the unreleased percent of drug versus time would be linear if the equilibrium conditions were not reached and if the geometrical shape of the dosage forms diminished proportionately over time. The release rate constant K_{HC} corresponded to the slope. This model had been used to describe the release profile from the diminishing surface of the drug particles during the dissolution [7].

Table 1. Design of drug: Plasdone S-630 solid dispersion

S. No.	Drug:Plasdone S-630 ratio	physical mixture	PEG 6000	Drug:plasdone S-630: PEG6000 ratio
1	01:02	3gm	1gm (33.33%)	1:2:1
2	01:02	3gm	1.5gm (50%)	1:2:1.5
3	01:02	3gm	1.98gm (66%)	1:2:1.98

Table 2. Design of Drug: PEG 6000 solid dispersion

S. No.	Drug	PEG 6000	Drug: PEG 6000 ratio
1	15gm	15gm	01:01
2	15gm	30gm	01:02
3	15gm	75gm	01:05

Table 3. Composition for Drug: Plasdone S-630 core tablet formulation

S. No.	Ingredients	mg/tablet
1	Drug DABC Equivalent to 100mg	400
2	PVP K-30	20
3	Avicel(PH102)	60
4	Polyplasdone(XL-10)	15
5	Mag.Stearate	5
6	**Tablet weight**	500

Table 4. Composition for Drug: PEG 6000 core tablet

S. No.	Ingredients	mg/tablet
1	Drug DABC Equivalent to 100mg	300
2	PVP K-30	15
3	Avicel(PH102)	100
4	Polyplasdone(XL-10)	15
5	Mag.Stearate	5
6	Lactose 200M	65
7	Tablet weight	500

Table 5. Composition for control tablet

S.No.	Ingredients	mg/tablet
1	Drug DABC	100
2	PVP K-30	12
3	Avicel(PH102)	82.5
4	Polyplasdone(XL-10)	12
5	Mag.Stearate	3.5
6	Lactose 200M	140
7	Tablet weighed	350

Table 6. Formula for EOP formulation using NaCl as osmogen

S.No.	Ingredients	mg/tab
1	Drug DABC equivalent to 100 mg	300
2	PVK-30	15
3	Avicel pH(101)	88
4	Polyplasdone(XL-10)	15
5	Mag.Stearate	15
6	Lactose 200 M	65
7	Sodium chloride	12
8	Tablet total weight	500

Table 7. 3% seal coating of core tablet (with osmogen)

	mg/tab
Core weight of Drug: PEG 6000(1:2)Tablet	**500**
3% seal coating using HPMCe5cps(6%Solids)	**15**
a)HPMCe5cpss	**15**
b) Isopropyl Alcohol	**141**
c) Methylene chloride	**94**

Table 8. 3% functional coating of core tablet (with osmogen)

	mg/tab
3% Functional coating	**15**
a) Cellulose Acetate 39810	**13.88**
b) Polyethylene Glycol 4000	**1.13**
c) Acetone	**235**
Final weight	**530**

Table 9. 5% functional coating of core tablet

	mg/tab
5% Functional Coating(6% solids)	**25**
a) Ethyl Cellulose 10 cps	**21.25**
b) Dibutyl Sebacate	**3.75**
c) Isopropyl Alcohol	**235**
d) Methylene Chloride	**156**
Final weight	**540**

RESULTS AND DISSCUSSION

Table 10. Standard calibration curve of drug DABC in water

S. No.	Concentration(µg/ml)	Absorbance
1	1	0.042
2	2.5	0.108
3	5	0.211
4	7.5	0.317
5	10	0.416

Table 11. Standard calibration curve of drug DABC in pH 4.5 AB

S.No.	Concentration(µg/ml)	Absorbance
2	1	0.037
3	2.5	0.099
4	5	0.209
5	7.5	0.309
6	10	0.409

Table 12. Standard Calibration curve of drug DABC in pH 6.8 PB

S. No.	Concentration(µg/ml)	Absorbance
1	1	0.033
2	2.5	0.096
3	5	0.199
4	7.5	0.315
5	10	0.404

Table 13. Standard calibration curve of drug DABC in 0.01 N HCL

S.No.	Concentration(µg/ml)	Absorbance
1	1	0.035
2	2.5	0.094
3	5	0.2
4	7.5	0.3
5	10	0.402

Table 14. Standard calibration curve of drug DABC in 1% SLS solution

S. No.	Concentration(µg/ml)	Absorbance
1	1	0.044
2	2.5	0.115
3	5	0.238
4	7.5	0.356
5	10	0.474

Table 15. Optical Characteristics of Calibration

S. No.	Media	curve Equation	Correlation Coefficient	ƛ max (nm)
1	water	y=0.0416x+0.0026	0.9998	285
2	pH 4.5	y=0.0415x-0.003	0.9996	285
3	pH 6.8	y=0.0479x-0.0035	0.9999	285
4	0.1N HCL	Y=0.047x-0.0082	0.9989	286
5	0.01NHCL	Y=0.0479x-0.0035	0.9999	285
6	1% SLS	Y=0.0479x-0.0035	0.9999	286

Table 16. Solubility of Drug DABC in different media

S. No.	Media	Saturation Solubility	Dose Solubility Volume
1	water	0.2311mg/ml	1730
2	pH 1.2 HCl	0.2167mg/ml	1904
3	pH 4.5 AB	0.261mg/ml	1697

4	pH 6.8 PB	0.2170mg/ml	1846
5	0.01 N HCL	0.2011mg/ml	1964

Table 17. Solution state stability of drug solution in various time points

Time(hrs)	Absorbance		
	water(285nm)	pH 4.5 AB(285nm)	pH 6.8 PB(285nm)
0	0.505	0.537	0.517
2	0.504	0.537	0.516
4	0.504	0.535	0.517
6	0.504	0.507	0.53
24	0.501	0.498	0.517
48	0.479	0.501	0.506

Table 18. Filter compatibility study of Drug DABC in various Filters

S. No.	Media	Absorbance			
		Before Filtration	After Filtration		
			Nylon filter	SY filter	PVD filter
1	water	0.556	0.551	0.553	0.552
2	pH 4.5	0.581	0.580	0.573	0.562
3	pH 6.8	0.574	0.571	0.565	0.556

Table 19. Drug content uniformity of solid dispersion of various batches in water

S.No.	Solid dispersion	Drug content(%w/w)
1	Drug:plasdone S-630(1:2)PEG6000 33.33%	98.23
2	Drug:plasdone S-630(1:2)PEG6000 50%	98.75
3	Drug:plasdone S-630(1:2)PEG6000 66%	97.65
4	Drug:PEG 6000(1:1)	98.50
5	Drug:PEG 6000(1:2)	99.15
6	Drug:PEG 6000(1:5)	99.15

Table 20. Solubility of solid dispersion in Different Media

S. No.	Solid Dispersion	Saturation Solubility		Dose solubility Volume	
		Media		Media	
		water	pH 6.8	water	pH 6.8
1	Drug:Plasdone S-630(1:2)				
	PEG 33.33%	0.47mg/ml	0.76mg/ml	851	526
	PEG 50%	0.66mg/ml	0.61mg/ml	606	655
2	Drug: PEG 6000 01:01	0.49mg/ml	0.63mg/ml	816	634
	01:02	0.55mg/ml	0.77mg/ml	727	519

Table 21. % Drug release of Drug:Plasdone S-630(1:2) PEG 6000

S. No.	Time (hours)	Pure Drug	PEG 33.33%	PEG 50%	PEG 66%
0	0	0	0	0	0
1	5	3	2	3	3
2	10	44	22	18	16
3	15	57	55	42	41
4	20	68	82	62	63
5	30	76	91	81	80
6	45	85	96	93	94
7	60	86	96	96	95
8	90	87	97	95	96
9	120	87	97	97	97

Table 22. Comparative release profile of solid dispersion of the drug with PEG 6000

S. No.	Time	pure drug	D:PEG(1:1)	D:PEG(1:2)	D:PEG(1:5)
1	0	0	0	0	0
2	5	3	5	18	35
3	10	44	45	44	54
4	15	57	58	54	76
5	20	68	74	76	92
6	30	76	78	92	95
7	45	85	86	95	97
8	60	86	87	98	98
9	90	87	88	98	98
10	120	87	88	98	98
11	150	88	90	99	99

Table 23. Comparative release profile of optimized formulations

S. No.	Time	formulation 1	formulation 2
1	0	0	0
2	5	8	35
3	10	21	56
4	15	34	70
5	20	45	77
6	30	63	95
7	45	82	102
8	60	100	102

Table 24. Dissolution profile of control and EOP tablet in water (drilled on one Side)

S. No.	Time (hrs)	Control	EOP Formulation (Without osmogen)
1	0.5	1	6
2	1	2	11
3	2	2	18
4	4	3	30
5	6	5	42
6	8	8	50
7	10	9	55
8	12	10	60
9	24	14	69

Table 25. Dissolution profile of control and EOP formulation in water drilled on both sides

S. No.	Time (hrs)	Control	Final formulation
1	0.5	2	3
2	1	4	8
3	2	6	19
4	4	7	32
5	6	9	43
6	8	10	54
7	10	11	62
8	12	11	68
9	24	17	83

Table 26. Dissolution profile of control and EOP Formulation in pH 6.8 PB Drilled on both sides

S. No.	Time (hrs)	Control	Final formulation
1	0.5	3	2
2	1	6	12
3	2	8	20
4	4	11	33

5	6	12	45
6	8	12	53
7	10	12	61
8	12	13	66
9	24	18	81

Table 27. Dissolution data of EOP coated with cellulose acetate drilled on both sides

S. No.	Time (hours)	Water	pH 6.8
1	0.5	3	3
2	1	9	14
3	2	21	23
4	4	37	39
5	6	51	50
6	8	60	60
7	10	66	65
8	12	72	70
9	24	89	88

Table 28. Comparative release profile of EOP coated with cellulose acetate (with & without osmogen)

S. No.	Time (hours)	With osmogen		Without osmogen	
		Water	pH 6.8	Water	pH 6.8
1	0.5	3	3	3	2
2	1	9	14	8	12
3	2	21	23	19	20
4	4	37	39	32	33
5	6	51	50	43	45
6	8	60	60	54	53
7	10	66	65	62	61
8	12	72	70	68	66
9	24	89	88	83	81

Table 29. Dissolution data of EOP coated with ethyl cellulose

S. No.	Time (hours)	Water	pH 6.8
1	0.5	1	1
2	1	8	7
3	2	16	15
4	4	30	27
5	6	41	40
6	8	50	48
7	10	57	54
8	12	63	62
9	24	76	73

Table 30. Statistical Kinetic values of the different batches

S. No.	Batches	Mathematical models for drug release kinetics									
		zero order		First order		Higuchi		Hixon- Crowell		Korsmeyer Peppas	
		slope	r^2	slope	r^2	slope	r^2	slope	r^2	Slope	r^2
1	**Pure Drug**	0.5029	0.4974	0.007	0.7254	7.7726	0.6649	-0.0008	0.6255	0.8064	0.6072
2	**PEG 33.33%**	0.633	0.4728	-0.011	0.709	9.8614	0.6421	-0.0021	0.4728	0.993	0.6502
3	**PEG 50%**	0.7153	0.6052	-0.014	0.8449	10.785	0.7699	-0.0024	0.6052	0.9564	0.7544
4	**PEG1:1**	0.4829	0.4665	-0.007	0.663	7.671	0.6498	-0.0016	0.4665	0.6834	0.6008
5	**PEG 1:2**	0.5542	0.5478	-0.015	0.777	8.4794	0.7175	-0.0018	0.5495	0.4633	0.7184
6	**Formulation 1**	1.6392	0.9746	-0.0178	0.9952	16.915	0.9991	-0.0055	0.9746	0.9957	0.9735

7	**Formulation 2**	1.5953	0.882	-0.0433	0.9531	18.192	0.9928	-0.0076	0.9568	1.7985	0.9795
8	**EOP formulaton**	3.4667	0.8353	-0.033	0.9653	20.73	**0.9676**	-0.0116	0.8353	0.8702	0.9548

Fig. 1. Scanning of drug DABC in water

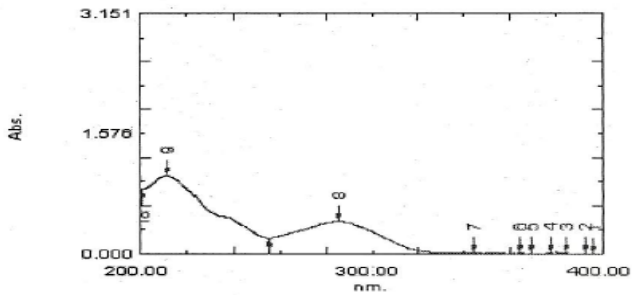


Fig. 2. Calibration curve of drug DABC in water at 285nm

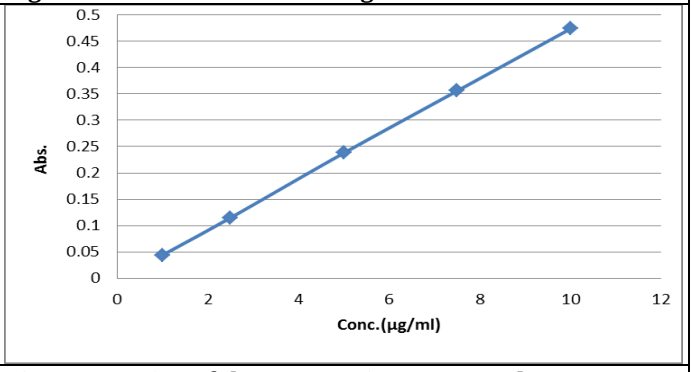


Fig. 3. Regression curve of drug DABC in water at 285nm

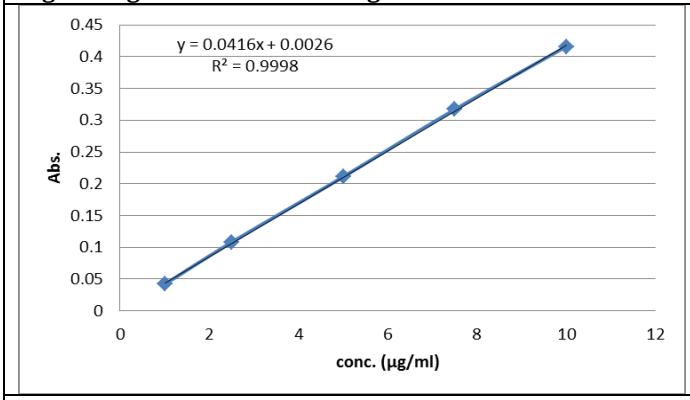


Fig. 4. Scanning of drug DABC in pH 1.2 HCl

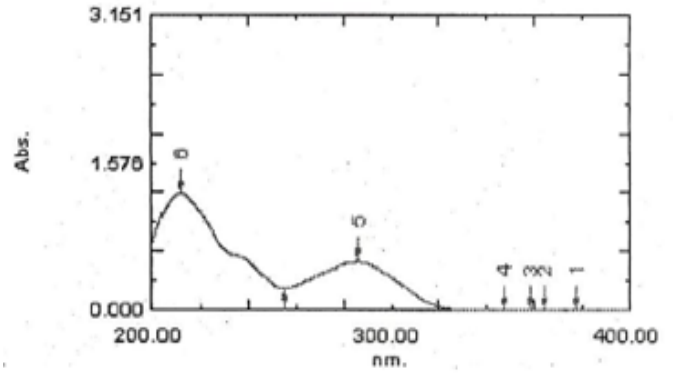


Fig. 5. FTIR Spectra of Pure Drug

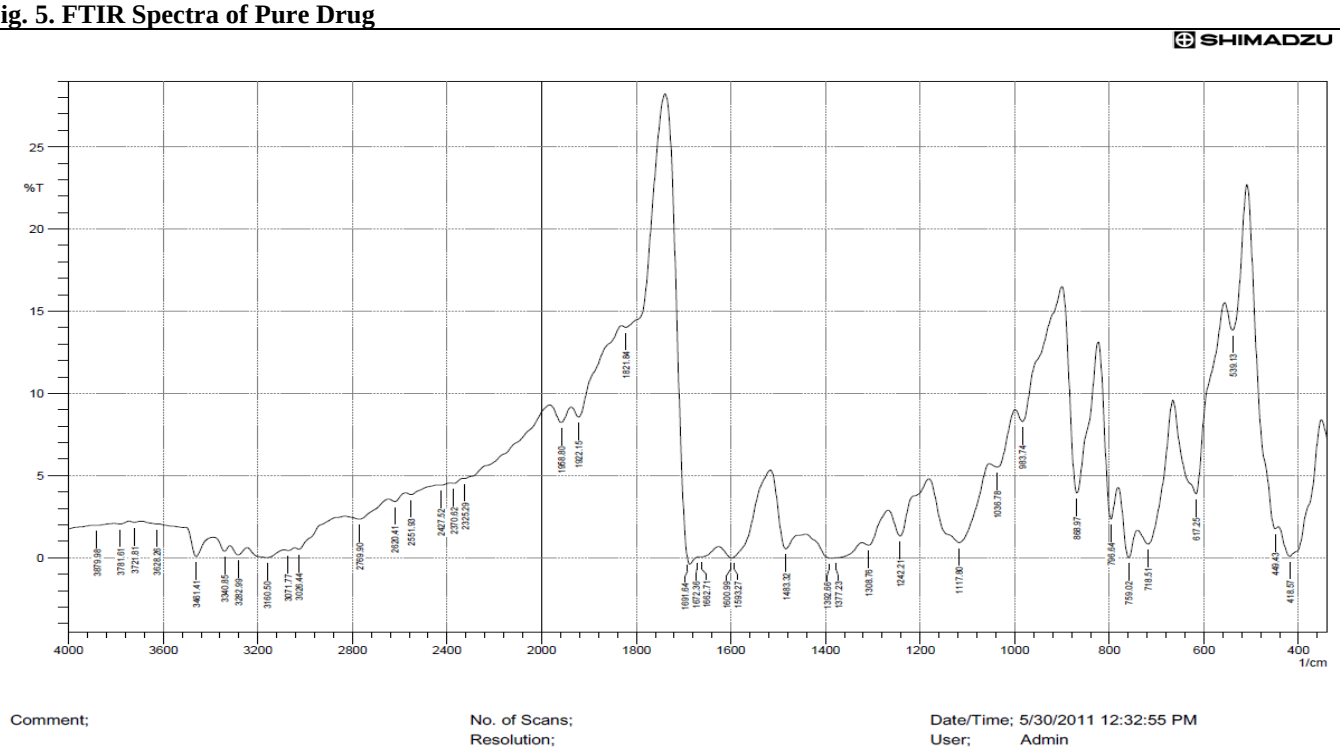


Fig. 6. FTIR Spectra of Physical Mixture of Drug:PlasdoneS-630

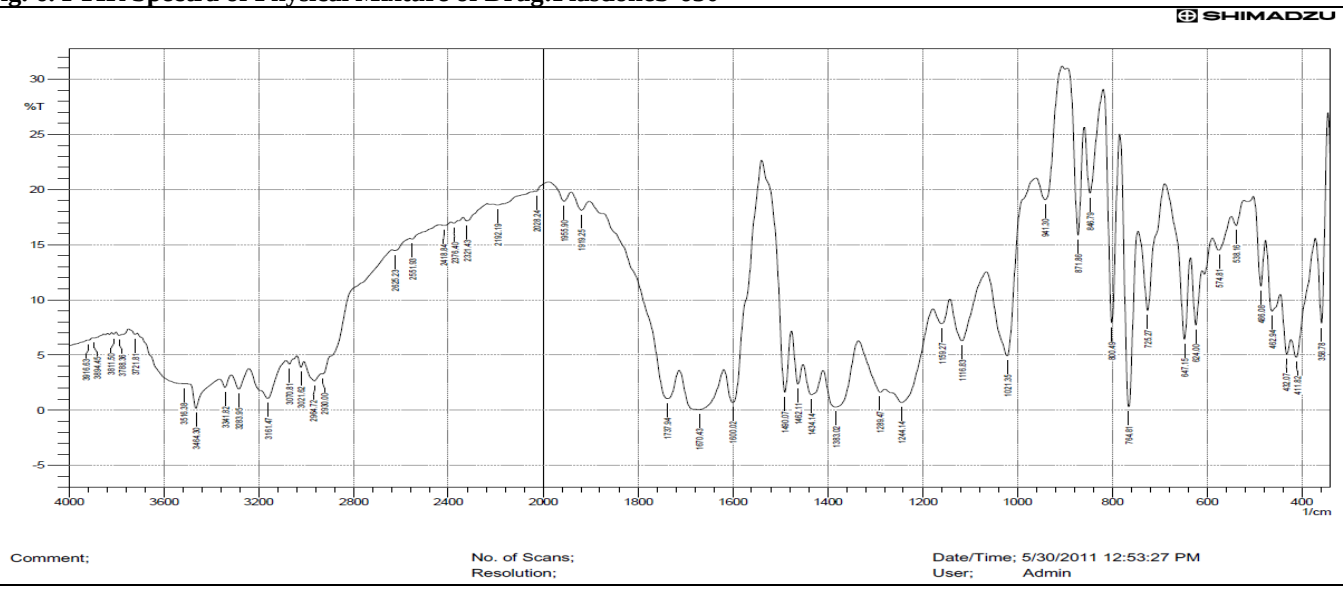
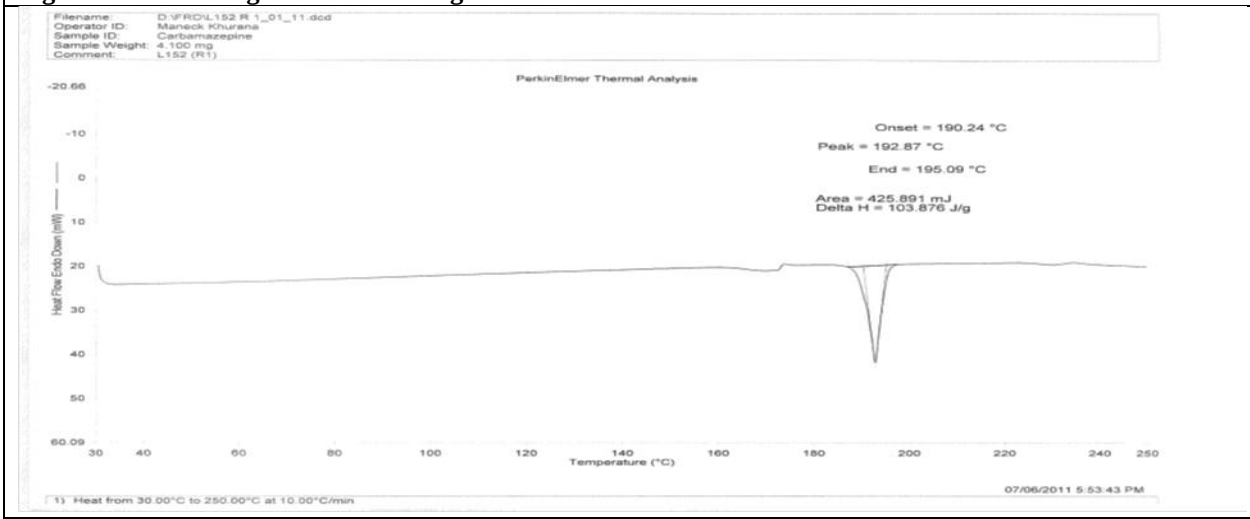


Fig. 7. DSC Thermogram of Pure Drug



Preformulation Studies

Determination of Absorbance Maxima of Drug in Different media (water, pH 1.2 HCl, pH 4.5 AB, pH 6.8 PB, 0.01N HCl and 1% SLS solution) was carried out by scanning the solution by UV/visible spectrophotometry between the wavelength of 200-400 nm. A distinct peak appeared at 285 nm in water, pH 4.5 AB, pH 6.8 PB and 0.01 N HCl and at 286 nm in pH 1.2 HCl & 1% SLS solution.

Preparation of Calibration Curve

Calibration curve in different media was prepared by plotting absorbance with respect to Concentration. The regression coefficient was calculated which showed good linearity. The absorbance values obtained for different concentrated solutions in water, pH 1.2 HCl, pH 4.5 AB, pH 6.8 PB, 0.01 N HCl and 1% SLS solution. The Calibration curves obtained with Water, pH 1.2 HCl, pH 4.5 AB, pH 6.8 PB, 0.01N HCl and 1% SLS solution.

Saturation solubility study of Drug DABC in Different media

The results of solubility study obtained with Iminostilbene Anticonvulsant drug in different media (water, pH 1.2 HCl, pH 4.5 AB, pH 6.8 PB, 0.01 N HCL and 1% SLS solution).

Dose solubility volume= Highest dose(mg)/solubility(mg/ml). Dose solubility volume should be < 250 for a highly soluble drug. Dose solubility volume indicated that drug was poorly soluble. The data showed maximum solubility in water, pH 4.5 AB & pH 6.8 PB. Consequently the following media were selected for further studies.

Solution state stability of Drug DABC in water, pH 4.5 and pH 6.8

Solution state stability of drug DABC solution determined over 48 hours at concentration of 50µg/ml. By comparing the absorbance values of the given concentrated solution in water, pH 4.5AB and pH 6.8 PB at different time points it was found that there was no significant variation in initial and followed time point reading. Thus the solution was stable up to 48 hours.

Filter Compatibility Study of Drug DABC in water, pH 4.5, pH 6.8

Filter compatibility study of Anticonvulsant drug at the concentration of 100µg/ml. By comparing the absorbance value of the given concentrated solution in water, pH 4.5 AB & pH 6.8 PB, before and after filtration, the results were inferred that there was no significant variation in absorbance. It showed drug and filter material compatibility.

Characterization of Solid Dispersion

Fourier Transform Infra-red (FTIRS) Spectroscopy

FTIR had been used to assess the interaction between carrier and guest molecule in the solid state. The FTIR Spectra of pure drug gave characteristics peaks at 3470 (-NH-Streching), 1691 (-C=O-Streching), 1600 (-C=C-Aromatic) which were consistent with all the binary system with the drug. The absence of major shift in the peak position of pure drug in all the binary systems (with the drug) showed absence of interaction between pure drug and polymers (PlasdoneS-630, PEG 6000).

Differential Scanning Calorimetry (DSC)

DSC Thermogram of Pure drug showed apparent endotherm peaks at 192.87°C corresponding to its melting point. Similiarly, endothermic Peak of PEG 6000 was observed at 61.58°c. In solid dispersion, the characteristics peak of drug was completely lost which indicated that crystallinity of pure drug was considerably reduced by the solid dispersion. In the presence of polymer the peak of pure drug was lost because the polymer melted down, dissolved the pure drug and solubilised. The reduction of peak of PEG 6000 in solid dispersion indicated dispersion of polymer.

Drug Content Uniformity of Solid dispersion:

Such studies were carried out as per the analytical procedures adopted in the industry (Ranbaxy Research & Development Centre, Gurgaon) and the results obtained were as summarized.

Saturation Solubility study of solid Dispersion in Different media

Water & pH 6.8 PB were selected for studies while pH 4.5 AB was skipped because the simulated area was duodenum & the contact time was very less.

The comparative release profile of trial batches containing Drug:plasdone S-630(1:2) with different concentration of PEG 6000 (33.33%, 50% and 66%) were taken. The formulations containing the same ratio of drug:plasdone but 33.33% PEG 6000 was selected as the best optimized batch because it showed better release profile than others

Dissolution Profile Optimized Formulations (Core Tablets)

The selected optimized formulations were:-

Formulation 1: Drug: PLASDONE S-630 (1:2) PEG 33.33%

Formulation 2: Drug: PEG 6000 (1:2)

The comparative release profile of the two optimized formulations was determined and the results inferred that formulation 2 had better profile than the other which was taken as the finally optimized formulation.

Formulation of Elementary Osmotic Tablet

In-Vitro release profile of control and EOP (without osmogen) formulation when drilled on one side. The study revealed that release profile of EOP was far much better (69%) than the control tablet in water when drilled on one side with a mechanical driller. The dissolution study of control and EOP formulation in pH 6.8 drilled on both side with a mechanical drill revealed that the dissolution profile of EOP formulation is far much better (81%) than the control one.

***In-Vitro* Release Profile of Elementary Osmotic formulation (using NaCl as osmogen)**

Dissolution Profile of EOP coated with cellulose acetate when drilled on both sides. The study revealed that dissolution profile of EOP using NaCl as osmogen increased as compared to EOP devoid of any osmogen.

From the release kinetics of different batches of core formulations slope and r^2 were calculated. In Formulation 1 and 2, r^2 was found to be 0.9991 and 0.9928 respectively (maximum in Higuchi release kinetics). In EOP Formulation r^2 was found to be maximum of 0.9676 (Closest to 1) in Higuchi release model so it followed the Higuchi release kinetic model.

SUMMARY

The present study was done to carry out preparation and characterization of elementary osmotic pump of poorly water soluble Iminostilbene anticonvulsant drug using solid dispersion Technique. Determination of absorbance maxima of pure drug was carried out in different media (water, pH 1.2 HCl buffer, pH 4.5 AB, pH 6.8 PB, 0.01 N HCl and 1% SLS solution) and ƛ max was reported at 285nm. Calibration curve was prepared in water, pH 1.2 HCl, pH 4.5 AB, pH 6.8 PB, 0.01N HCl and 1% SLS solution. Solution state stability study was carried out at time intervals of 0, 2, 4, 6, 24 ,48 hrs & absorbance was checked and it inferred that the solution is stable up to

48 hrs. Filter compatibility study was carried out in Nylon, Sy and PVD Filters. 100µg/ml solution was prepared and absorbances were checked before & after filtration. Conclusively solution was found compatible with different filter media. Saturation solubility study of pure drug and solid dispersion showed that there was 2 to 3 fold increase in solubility of drug in solid dispersion. Characterization of solid dispersion was done by FTIR and DSC study. FTIR spectra of pure drug gave characteristic peaks at 3470 (-NH-Streching), 1691 (-C=0-Sreching), 1600 (-C=C-Aromatic) which were consistent with all the binary system with the drug. The absence of major shift in the peak position of pure drug in all the binary system with the drug showed absence of interaction between Pure drug and Polymers (Plasdone S-630, PEG 6000). DSC Thermogram of Pure drug and all binary system with drug showed characteristic Peaks at 192.87°C. In solid dispersion, Characteristic peak of the drug was lost which indicated that crystallinity was considerabely reduced in solid dispersion. In-vitro drug release of trial batches of solid dispersion was carried out in 900ml water at an agitation speed of 100rpm. From the study it was considered that Drug:PEG 6000(1:2) and Drug:Plasdone S-630(1:2) with additional PEG 33.33% gave the Optimised batches for tablet formulation. Control Tablets were also formulated using Pure Drug. On the basis of results obtained from In-vitro studies on both the optimised formulations f_1 and f_2, the latter was taken as the core tablet to formulate the elementary osmotic pump. The core tablet was coated in coating pan with dummy tablet (having different diameters) with 3% seal coating using HPMCe5cps and 3% functional coating using Cellulose acetate. Control formulation was also coated with 3% seal and 3% functional coating using cellulose acetate. In-vitro drug release of EOP and control formulation was carried in 900ml water and pH 6.8PB at an agitation speed of 100 rpm at time intervals 0.5,1,2,4,6,10,12, and 24 hours and showed the constant release up to 24 hours. In-vitro drug release of EOP formulation was much better than the control formulation. Using NaCl as osmogen elementary osmotic tablets were prepared with 3% seal coating using HPMC e5cps and 3% functional coating using cellulose acetate and 5% Ethyl cellulose. In vitro drug release of EOP formulation was carried in water and pH 6.8PB at time intervals 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours &showed the constant release up to 24 hours and conclusively the drug release was independent to pH condition. Comparitive release kinetics study of different formulation batches was carried out (zero order, first order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas kinetics) & Slope and r^2 values of different kinetic models revealed that r^2 value of EOP formulation (with osmogen) was found to be maximum in Higuchi release Kinetic model (0.9676). Thus the EOP formulation (with osmogen) fullfills the objective of research.

CONCLUSION

The conclusion of the study was as follows: 285nm was considered the absorbance maxima of the drug DABC (under patenting process). In the solution state stability study it was found that drug DABC solution is stable up to 48 hours. Filter compatibility study revealed that nylon, sy and PVD filter medias were Compatible aids. The saturation solubility studies, it was found that solubility of drug DABC increased (2 or 3 fold) in solid dispersion. Characterization of solid dispersion was done by FTIR and DSC analysis and inferred that there was no interaction between the drug and the polymer. Dose solubility volume of solid dispersion indicated increase in solubility of drug after solid dispersion. Among the In-vitro drug Profile f_1 (Drug:plasdoneS-630(1:2) PEG6000(33.33%), f_2 (Drug:PEG 6000(1:2) was considered the optimized batch for the formulation because it has better release Profile among different batches of solid dispersion. Formulation f_2 was taken as core tablet for coating because it has better release profile than the f_1. EOP formulations were prepared by coating the core tablet by 3% seal coating using HPMCe5cps and 3% functional coating using cellulose acetate. Control tablet were also coated with 3% seal coating and 3% functional coating using HPMCe5cps and cellulose acetate. In-vitro drug release profile of EOP (without osmogen) formulation was much better than the control formulation. EOP formulation using NaCl as osmogen were prepared and coating was done with 3% seal coating using HPMCe 5cps and 3% functional coating using cellulose acetate and 5% Ethyl cellulose. In-vitro release profile of EOP formulation using NaCl as Osmogen coated with cellulose acetate, drilled on both side in water and pH 6.8PB showed constant release profile up to 24 hours and independent of pH condition. In-vitro release profile of EOP formulation using NaCl as osmogen coated with ethyl cellulose in water and pH 6.8PB showed constant release profile up to 24 hours and independent of pH condition. Under the study of kinetic models, five models have been studied namely Zero order first order, Higuchi, Hixon-crowell and Korsmeyer-Peppas model revealing that drug release of EOP formulation (with osmogens) followed Higuchi release kinetics (having maximum r^2 value 0.9676).

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