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EXTENDED RELEASE OF NEVIRAPINE USING ELEMENTARY OSMOTIC PUMP TABLETS

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ABSTRACT

Nevirapine is currently administered twice daily in combination with lamivudine and stavudine for the treatment of HIV infection. Previous study suggests that once daily regimen of nevirapine provides a higher peak and lower trough levels compared with twice daily regimen of the same drug and has proved to be equally efficient. Presently extended release formulation of nevirapine is used for HIV infection in clinical practice; however it lacks zero-order characteristics. The present study aimed to design elementary osmotic pump tablet of nevirapine as once daily preparation to achieve zero-order characteristics. The elementary osmotic pump tablets were developed using variable concentration of poly ethylene oxide (polymer) and potassium chloride (osmogen) with variable orifice diameter and evaluated for physico-chemical and release characteristics. The elementary osmotic pump tablets released the drug at a zero-order rate over a period of 24 hours and the release rate of the drug was found to be influenced by the variables employed. The amount of poly ethylene oxide had a significant effect on the release rate and a direct correlation was observed between the concentration of potassium chloride and the drug release rate. It was seen that the formulations showed no remarkable changes in the physico-chemical and release characteristics as well as drug content after the stability studies. The results demonstrate that elementary osmotic pump tablet of nevirapine is beneficial as once daily preparation for effective control of HIV infection.

Keywords: Elementary osmotic tablet, Nevirapine, Extended release, PEO, Potassium chloride.

INTRODUCTION

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1). Anti retroviral therapy with nevirapine has demonstrated significant activity in HIV infected patients in combination drug with highly active anti retroviral therapy. Generally nevirapine immediate release 200 mg tablets are taken twice daily, in combination with other antiretroviral agents. A nevirapine once daily tablet formulation could be used to maintain optimum peak plasma concentration for effective viral suppression.[1] Nevirapine is readily absorbed (greater than 90 %) after oral administration in healthy volunteers and in adults with HIV-1 infection. To achieve durable virological suppression, adherence to the therapy is an important factor. The once daily regimen of nevirapine provides a higher peak and lower trough levels compared with twice daily regimen of the same drug and had proved to be equally efficient.[2] Many patients prefer once-daily dosed regimens of low pill count and without dietary restrictions.[3] This dosing strategy may improve adherence and treatment outcomes. Once-daily nevirapine dosing results in lower C_{min} levels of the drug when compared with twice-daily treatment.[4] NVP dosed once daily in clinical practice is at least as effective in suppressing HIV-1 replication as NVP prescribed twice daily.[5] Developments in the usage of oral controlled release delivery systems are fast emerging due to their independence from the different physiological factors. Oral osmotic systems are distinguished by their ability to release drugs independently of the medium composition and hydrodynamics.[6] Besides, these systems offer potential clinical benefits such as ability to mitigate the food effect, increase patient compliance and treatment tolerance.[7] Furthermore, these systems are used to deliver both poorly soluble and freely soluble drugs. And therefore, the present study aimed to design elementary osmotic tablet of poorly soluble nevirapine and evaluate the systems suitability for HIV therapy.

MATERIALS AND METHODS

Nevirapine was received from Hetero Life Sciences Ltd., Hyderabad, India as gift sample. Polyethylene oxide (6, 00, 000 g/mol) was purchased from Sigma Aldrich, Bangalore, India. Potassium chloride and starch was supplied by S.D. Fine chemicals, Mumbai, India. Microcrystalline cellulose, magnesium stearate, cellulose acetate phthalate, sodium lauryl sulphate and polyethylene glycol-400 were purchased from Loba chemie, Mumbai, India. All other solvents and chemicals used were of the analytical grade.

Enhancement of solubility of Nevirapine by micellar solubilzation method

The solubility of nevirapine in pH-6.8 buffer was determined in the presence of the surfactant, sodium lauryl sulphate (SLS) in varying concentrations. An excess of nevirapine was added to 10 ml each of the surfactant solution taken in 25 ml of stoppered flasks and were shaken for 10 h at 25 ± 1ºC in a mechanical shaker (Orbitrek). These solutions were allowed to equilibrate for the next 24 h to ensure saturation and then centrifuged for 15 minutes at 1500 rpm. Equilibrium samples were withdrawn and properly diluted and filtered through whatmann filter paper No.14 and finally analyzed for concentration of nevirapine using UV-spectrophotometer at 314 nm.

FTIR – Spectrophotometry

IR absorption spectrum of the drug was recorded by potassium bromide dispersion technique in which dry sample of drug and potassium bromide was mixed uniformly and the mixed powder blend was placed in sample holder and an IR spectrum was recorded using FTIR spectrophotometer (Shimadzu-4100 Type A). The same procedure was repeated for drug along with the polymer.

Differential Scanning Calorimetry (DSC)

The DSC thermo grams of pure drug and mixture of drug and polymer were recorded. The samples were separately sealed in aluminum cells and set in Perkin Elmer (Pyris 1) DSC (Waltham, MA). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C.

Development of Elementary osmotic pump tablets (EOPT; monolayer osmotic tablets)

Elementary osmotic pump tablets of nevirapine were developed using different variables like concentration of polyethylene oxide (PEO, mol.wt. 6,00,000 g/mol), concentration of potassium chloride (KCl) and variable orifice diameter (0.4 mm, 0.6 mm and 0.8 mm) as shown in Table 1. Drug was mixed with PEO, KCl, microcrystalline cellulose (MCC) and the powder blend was passed through sieve 120 before granulation. This mixture was moistened with 10 % starch paste and granulated by passing the wet mass through sieve 14. The granules were dried at 40°C for 2 h. Mixture was again passed through sieve 18. Finally talc and magnesium stearate were added to the mixture and compacted using 16/32 inch deep concave punches using rotary tablet compression machine with 8 stations (Cadmach, India) fitted with 16/32 in. (12.7 mm) punches. Tablets were coated by using a pan coater using coating solution of cellulose acetate phthalate (CAP) in acetone containing known level of polyethylene glycol (PEG) as plasticizer (Table 2). After coating, the tablets were dried over night at 60°C to remove residual solvent. Orifice with various diameter sizes of 0.4 mm, 0.6 mm and 0.8 mm were drilled on one side of the surface of the coated tablets using a mechanical drill.

Physico-chemical evaluations

The powder blend of the formulations were evaluated for various pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio before compression and the prepared elementary osmotic pump tablets were evaluated for their post-compression parameters like hardness, thickness, friability and % drug content by standard methods.

***In-vitro* drug release**

The *in- vitro* release of the elementary osmotic pump tablets was carried out using 900 ml of pH 6.8 phosphate buffer as the medium in USP II dissolution apparatus at 37°C ± 0.5°C and 50 rpm. Five-milliliter samples were withdrawn at 0, 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 h and filtered through 0.45 mm cellulose nitrate filter and analyzed at 314 nm by UV- spectrophotometric method. Fresh dissolution medium (5 ml) was replaced after each sampling. Each study was done in triplicate and the mean values utilized for evaluation.

***In-vitro* release models and Kinetics**

In order to describe the kinetics of drug release from the elementary osmotic pump tablets, various mathematical equations like zero order,[8] first order[9] and Higuchi model[10] were utilized and the suitable model was chosen according to the best correlation coefficient (r^2) values and the mechanism of release is confined with the n values of the Korsemeyer Peppa equation.

Effect of formulation variables

The drug release from an elementary osmotic tablet is basically dependent upon the variables like concentration of polyethylene oxide (PEO, mol. wt. 6, 00, 000 g/mol), concentration of potassium chloride (KCl) and orifice diameter which either directly or indirectly affects it. The effect of the variables on the drug release was studied by formulating the tablets with different concentrations of the polymer (10 mg, 20 mg and 30 mg) and osmogen (10 mg, 20 mg and 30 mg) and different orifice diameter (0.4 mm, 0.6 mm, 0.8 mm).

Effect of Coating thickness

The tablet cores were prepared and coated with coating solution having different levels of PEG-400 (10, 20 and 30 % w/w) with different levels of CAP (70, 80 and 90 % w/w) as shown in Table 3. The physico-chemical properties and drug release characteristics of the coated tablets were compared.

Effect of pH of release medium

The effect of pH on the drug release from the EOPTs was studied by conducting the release studies in three different media such as pH 1.2, pH 6.8 and pH change method (pH 1.2 for first 2 h followed by pH 6.8). 5 ml samples were withdrawn at pre-determined intervals, filtered through 0.45 mm cellulose nitrate filter and analyzed at 314 nm by UV-spectrophotometer. The cumulative percentage drug release of the formulations at different pH was plotted and compared.

Effect of Agitation speed

In order to study the effect of agitational intensity of the release media upon drug release, the study was conducted in dissolution apparatus USP II at 50, 100 and 150 rpm. Samples were withdrawn at pre-determined intervals and analyzed after filtration through 0.45 mm cellulose nitrate membrane filters. The cumulative percentage drug release of the formulations at different agitational intensity was plotted and compared.

Multivariable linear regression analysis

In order to study the influence of the variables upon drug release of EOPT, the drug release data were analyzed using multivariable linear regression analysis and the linearity of the correlation co-efficient was noted.

Stability studies on EOPT

The optimized formulation was subjected to stability study at 40°C ± 2°C and 75 % RH for a period of 90 days in the stability chamber (HTC-3003, In lab equipments, India) as per the criterion mentioned in the ICH guidelines and evaluated for physico-chemical properties and drug content.

RESULTS AND DISCUSSION

Enhancement of Nevirapine solubility

Among the approaches for extended release dosage forms, the EOPT was selected for delivery of nevirapine in the present study. EOPT is preferred as it releases the drugs independent of the environmental conditions such as pH and motility of gastro intestinal tract. Osmotic system is normally suitable for soluble drugs as they can ensure hydrodynamic pressure for delivery of the drugs. Osmotic systems act by imbibing water and generating hydrodynamic pressure which is basically dependent on the solubility of the drug present in the system. As nevirapine has a poor solubility character, it is important to enhance the solubility of nevirapine. Among the several approaches available for improving the solubility, micellar solubilisation technique is the easiest and effective method.[11] Therefore and attempt was made to improve its solubility in pH-6.8 using sodium lauryl sulphate (0.4 % w/v). The solubility of nevirapine increased as the concentration of sodium lauryl sulphate (SLS) improved and reached saturation solubility (184.52 µg / ml) with 0.4 % w/v of SLS. (Table 4)

Table 1: Basic formula of nevirapine elementary osmotic tablets

Ingredients	F1	F2	F3	F4	F5	F6
Nevirapine (mg)	400	400	400	400	400	400
Polyethylene oxide (mg)	10	20	30	20	20	20
Potassium chloride (mg)	10	10	10	20	30	30
MCC (mg)	5	5	5	5	5	10
Magnesium stearate (mg)	Trace	Trace	Trace	Trace	Trace	Trace
Orifice diameter* (mm)	0.4, 0.6, 0.8	0.4, 0.6, 0.8	0.4, 0.6, 0.8	0.4, 0.6, 0.8	0.4, 0.6, 0.8	0.4, 0.6, 0.8

*Each formulation was drilled with three different orifice diameters- 0.4 mm, 0.6 mm and 0.8 mm after coating and utilized for the study

Table 2: Formula for coating solution

Ingredients	
Cellulose Acetate Pthalate (% w/v)	80
PEG -400 (% w/w)	20
Glycerin (% v/v)	2
Acetone : Ethanol (% v/v)	40 : 60

Table 3: Variables of coating solution

Ingredients	weight gain 8 %			weight gain 12 %			weight gain 16 %		
	C1-A	C1-B	C1-C	C2-A	C2-B	C2-C	C3-A	C3-B	C3-C
Cellulose Acetate Pthalate (% w/v)	70	80	90	70	80	90	70	80	90
PEG -400 (% w/w)	30	20	10	30	20	10	30	20	10
Glycerin (% v/v)	2	2	2	2	2	2	2	2	2
Acetone : Ethanol (% v/v)	40:60	40:60	40:60	40:60	40:60	40:60	40:60	40:60	40:60

Table 4: Nevirapine solubility in different media

Ingredients	Water (µg/ml)	pH-1.2 (µg/ml)	pH-6.8 (µg/ml)
Nevirapine	104.01 ± 0.99	142.08 ± 0.51	122.6 ± 0.45
NVP + 0.1 % w/v SLS	107.04 ± 0.73	158.01 ± 0.22	148.31 ± 0.23
NVP + 0.2 % w/v SLS	109.27 ± 0.18	163.76 ± 0.81	161.78 ± 0.05
NVP + 0.4 % w/v SLS	114.11 ± 0.82	174.57 ± 0.06	184.52 ± 0.66
NVP + 0.6 % w/v SLS	108.84 ± 0.37	166.53 ± 0.23	179.56 ± 0.09

Table 5: FT-IR Spectral Analysis

Functional group	Characteristic peaks of Drug	Characteristic peaks of Drug / Polymer
- NH	3294	3419.90
C=O	1647	1685.84
C=C	1491	1496.81
Aromatic groups	461, 574, 621	488.01, 576.74, 642.32

Table 6A: Pre-compression parameters of EOPT

Formulation Code	Angle of Repose (θ)	Bulk Density (g/cc)	Tapped density (g/cc)	Carr's Index	Hausner ratio
F1	26.32 ± 0.010	0.223 ± 0.050	0.127 ± 0.006	15.54 ± 0.057	0.87± 0.005
F2	25.45 ± 0.016	0.143± 0.058	0.136 ± 0.152	16.23 ± 0.058	1.24 ± 0.507
F3	25.26 ± 0.108	0.245 ± 0.080	0.141 ± 0.115	11.22 ± 0.021	1.96 ± 0.015
F4	24.52 ± 0.105	0.137 ± 0.006	0.154 ± 0.112	16.61 ± 0.005	0.85 ± 0.017
F5	26.67 ± 0.058	0.445 ± 0.115	0.477 ± 0.002	17.94 ± 0. 115	1.45 ± 0.011
F6	26.48 ± 0.006	0.381 ± 0.026	0.428 ± 0.158	16.52 ± 0.005	1.58 ± 0.016

Table 6B: Post-compression parameters of EOPT

Formulation Code	Thickness	Hardness	Friability	Drug content	Wt. Variation
F1	4.47 ± 0.057	4.13 ± 0.057	0.427 ± 0.001	97.73 ± 0.153	1.043 ± 1.418
F2	4.81 ± 0.010	4.43 ± 0.011	0.488 ± 0.058	97.87 ± 0.057	1.044 ± 1.072
F3	4.22 ± 0.015	4.63 ± 0.054	0.451 ± 0.050	98.07 ± 0.115	1.042 ± 1.326
F4	4.85 ± 0.077	4.47 ± 0.077	0.386 ± 0.001	98.53 ± 0.057	1.042 ± 1.426
F5	4.37 ± 0.017	4.17 ± 0.115	0.481 ± 0.001	97.17 ± 0.054	1.043 ± 1.154
F6	4.54 ± 0.028	3.77 ± 0.104	0.514 ± 0.105	98.16 ± 0.058	1.043 ± 1.541

Table 7: Effect of variables on nevirapine release from elementary osmotic pump tablets

EOPT Code	Independent Variables			Dependent Variable
				*Cumulative % drug release
	PEO (mg)	KCl (mg)	Orifice diameter (mm)	Nevirapine
F1	10	10	0.6	65.86 ± 0.483
F2	20	10	0.6	56.79 ± 0.275
F3	30	10	0.6	53.42 ± 0.764
F4	20	20	0.6	89.07 ± 0.029
F5	20	30	0.6	74.00 ± 0.182
F6	20	30	0.6	77.50 ± 0.651

*Mean ± SD, n = 3

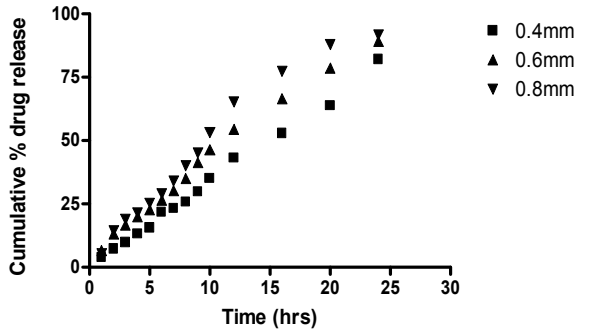

Figure 1: Comparative release of nevirapine from F4 with different orifice diameters

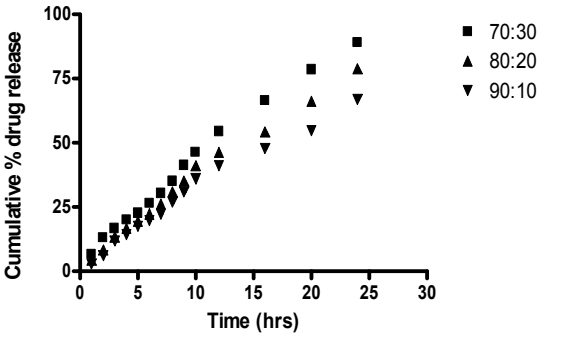

Figure 2: Nevirapine release from EOPT with different coating thickness (wt. gain 8 %)

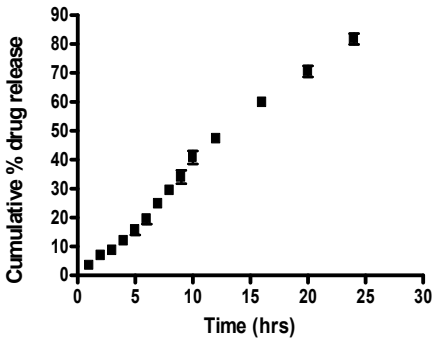

Figure 3: Nevirapine release from F4 at different pH

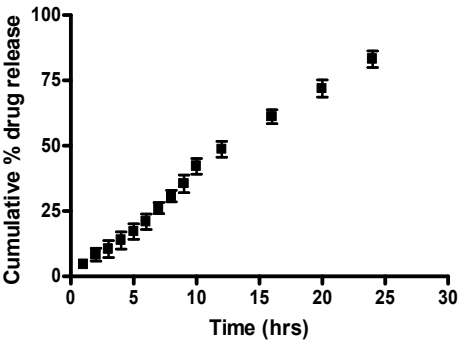

Figure 4: Nevirapine release from F4 at different agitation speeds

FT-IR studies

The FT-IR spectral analysis is used to examine the interaction if any between the drug and the polymer. The FT-IR absorption spectra of the drug showed specific peaks at 3294 for – NH group; 1647 for C=O group; 1491 for C=C group; and 461, 574, 621 for the aromatic groups which were also seen in the spectra of the mixture of the drug along with the polymer at 3419.90 for – NH group; 1685.84 for C=O group; 1496.81 for C=C group; 488.01, 576.74, 642.32 for the aromatic groups. The characteristic peaks of the drug were also seen in the mixture of drug and the polymer indicating no chemical interaction between the drug and polymer. (Table 5)

DSC studies

The DSC thermo gram of pure nevirapine was observed with sharp endothermic peak at 244.80°C which was well retained in the thermo gram of the physical mixture of the drug and the polymer.

Physico chemical evaluations

The results of the pre and post – compression parameters are shown in Table 6A and 6B.

Pre-compression studies

The granules of all the EOPT formulations were found to possess good flow property as the values of angle of repose, bulk density, tapped density, compressibility index, and hausner ratio were in the acceptable range.

Post-compression studies

EOPT was developed with variable concentration of poly ethylene oxide (PEO; mol. wt: 6, 00, 000 g/mol) and potassium chloride and different orifice diameter. Based on the previous report the coating thickness of all the formulations (F1-F6) was limited to 80:20 ratio of CAP: PEG. Hardness of the formulations ranged from 3.77 ± 0.11 to 4.63 ± 0.05 kg/cm^3. Thickness of the tablets was found to be between 4.37 ± 0.06 and 4.81 ± 0.01. Friability of all the formulations was less than 1 % (0.386 ± 0.01 and 0.488 ± 0.06) and weight variation was seen to be within the acceptable limits (1.042 ± 1.33 % to 1.044 ± 1.07 %) as per I.P. standards. The drug content of the elementary osmotic tablets was found to be between 97.17 ± 0.05 and 98.53 ± 0.07 % which ensured the uniform distribution of drug in the formulations. The percentage weight increase due to coating was found to be between 4.87 and 5.67 %. All the values were found to be within the USP limits (± 10 %). The orifice diameter was measured using optical microscope. The tablets having orifice diameter of specified value ± 0.01 % (Average ± SEM) were selected for further studies.

Scanning electron microscopy

Scanning electron microscope was used for analyzing the surface morphology of the coating membrane before and after dissolution studies and no significant difference in the membrane structure and orifice diameter was found before and after dissolution studies. Also, there were no pores in the membrane. There was no significant change in the surface morphology of the membrane which confirms that there was no blockade of delivery orifice during drug delivery. No rupture of the coating occurred during dissolution and the membrane was intact throughout the studies.

***In-vitro* release studies**

The *in-vitro* release data are shown in Table 7. The results showed that the release profiles of different formulations varied according to the orifice diameter, concentration of polymer and the concentration of osmogen used. All the formulations had a lag time of at least 1 hour. This may be attributed to the fact that the drug release is mainly based upon the osmotic pressure generated internally which is the result of water imbibing of the core that may be varied depending upon the concentration of the polymer, osmogen and the orifice diameter.

Effect of polymer concentration

PEO (20 mg) was found to yield the osmotic system with desired slow drug release. PEO concentration negatively correlated with release rate of the drug which was evident from multi-variable linear regression analysis (-0.14; R^2- 0.992). PEO control the drug release by producing high viscosity within the core which may restrict, delay the solvent contact of the drug molecules and increases the diffusion path length of solvents resulting in zero-order release of the EOPT.[12,13] The drug release profiles of the developed formulations (Table 7) indicate that the amount of PEO had a significant effect on the release rate. With increasing PEO, the release rate clearly slowed down. EOPT formulations showed the higher percentage drug release in case of 10 mg polyethylene oxide and the release rate lowered when the concentration was increased to 20 mg and 30 mg. The results also showed that the drug release from the system was inversely influenced by the concentration of the polymer.

Effect of osmogen concentration

Although the solubility of nevirapine was improved by using SLS it could not effectively develop hydrodynamic pressure for the release of the drug and therefore, KCl (osmogen) was used in concentrations of 10, 20, 30 mg. KCl (20 mg) was found to be suitable to yield EOPT with desired slow release characteristics. Osmogen increases the hydrodynamic pressure within the osmotic system by imbibing water from the environment that facilitates the drug release and thus osmogen concentration is critical in the design of osmotic systems with slow and extended release characteristics.[14] The multi-variable linear regression analysis shows that KCl concentration positively correlated (0.53; R^2- 0.992) with the release rate of the drug; as the concentration of KCl increased, the drug release rate also increased. A direct correlation was observed between the concentration of KCl and the drug release rate (Table 7). With an increasing amount of KCl, the release rate was accelerated, because the increasing osmotic pressure made more drug release from the core. EOPT formulations showed that percentage drug release of the drugs increased significantly when KCl concentration was increased from 10 to 20 mg or 30 mg, thus playing a direct role upon the drug release.

Effect of orifice diameter

Delivery orifice diameter is yet another factor, influencing the drug release for the osmotic systems influencing the drug release from the osmotic systems and therefore plays a critical role in achieving the desired release characteristics of the drug. It was found that a significant difference existed between the release profiles of the drug through the different orifice diameters of 0.4 mm, 0.6 mm and 0.8 mm as shown in Figure 1. Among the three different orifice diameters (0.4, 0.6, 0.8 mm) employed in the study, we observed the drug release faster through the larger orifice diameter (0.8 mm) and slower through smaller orifice diameter (0.4 mm). The EOPT with orifice diameter 0.6 mm showed a controlled release of the drug when compared to the formulations with other orifice sizes. It has been reported that the drug particles when presented in viscous suspension may occlude the smaller orifice and therefore reduce the drug release possibly due to increased viscosity generated by PEO as a result of swelling of the polymer. [15] Besides, the hydrostatic pressure inside the core increases which hinders the drug release.[16] The rapid drug release from larger orifice diameter (0.8 mm) may be the result of more diffusion from bigger orifice.[17] At highest value of 4.31(R^2 – 0.990) was obtained for orifice diameter indicating that among the independent variables, orifice diameter appears playing predominant role in influencing the drug release. Mean dissolution time (MDT) at various polymer and osmogen concentration and orifice diameters of different formulations was found to be statistically significant ($p < 0.0001$). While all the formulations (F1 – F6) showed slow and extended release of nevirapine, the formulation F4 was found to fit in FDA guidelines for slow and extended release.

Effect of coating thickness

Coating membrane thickness of the osmotic system plays an important role on the drug release[18,19], however limited to 8 % weight gain. And therefore, the formulation, F4 was subjected to further studies with varying proportions of CAP: PEG at (70:30; 80:20 and 90:10).[20] The ratio of 70:30 of CAP: PEG was found to be optimum to yield the desirable slow and extended release of nevirapine. The effect of different coating thickness (weight gain 8 %, 12 % and 16 %) on the same core tablets is shown in Figure 2 and the results showed that the release rate slowed following the increase of the coating membrane thickness. When the coating thickness increased, the weight of the membrane increased which in turn reduced the drug release. MDT between the different formulations at various coating thickness was found to be statistically significant ($p < 0.05$).

***In-vitro* release models and Kinetics**

The *in-vitro* kinetic analysis of the EOPT formulations showed that all the formulations followed the zero-order kinetics (r^2= 0.970 – 0.997) along with non-fickian transport mechanism ($1 < n > 0.5$).

Estimation of Burst Strength

In order to check the integrity of the EOPT in the gastro intestinal tract, the exhausted shells of the formulations were subjected to their burst strength analysis after dissolution. The burst strength of the exhausted shells was found to be directly proportional to the weight gain of the coating membrane. The burst strength increased when there is increase in the coating weight. No bursting was observed throughout the dissolution study. The burst strength of the formulations with highest weight gain was found to be satisfactory (> 320 g).

Effect of pH of release medium and agitation intensity

An ideal osmotic system should be independent of the pH or agitation intensity of the environment. And considering this, the formulation F4 was subjected to different pH conditions as well as agitation speed and compared. The f1 (difference factor) and f2 (similarity factor) values of the release behavior of the formulation F4 were determined. The effect of pH on the drug release from the EOPT was studied from the *in-vitro* release studies performed in buffers with different pH (pH 1.2, pH 6.8 and pH change method). There was no significant difference in the release profile, demonstrating that the developed formulation show pH-independent release.[21] The release profile of the drug was found to be similar in all the media demonstrating that the developed formulations show pH independent release (Figure 3). The f1 and f2 values were found to be 13 and 60 for pH-1.2 and pH-6.8; 6 and 73 for pH-1.2 and pH change method; 12 and 62 for pH-6.8 and pH change method, respectively which are within the acceptable range (< 15 and > 50 respectively) and they were statistically significant. Dissolution studies were conducted at three different rpm (50, 100 and 150) for

studying the effect of agitation intensity on the drug release from EOPT. The release of the drug was found to be independent of the agitational intensity. The f1 and f2 values were found to be 8 and 60 for 50 rpm and 100 rpm; 6 and 73 for 50 rpm and 150 rpm; 13 and 60 for 100 rpm and 150 rpm, respectively which are within the acceptable range. It was observed that the agitation intensity of 50, 100, 150 rpm of dissolution medium had no significant effect ($P > 0.05$) on the release rate of the drug from the osmotic formulations (Figure 4). The f1 and f2 values of F4 in different pH conditions and agitation speeds were < 15 and > 50 respectively indicating the developed EOPT (F4) meets the requirements of osmotic systems for extended release of the drug.[22]

Effect of Osmotic Pressure

The effect of osmotic pressure on the optimized formulation (F4) was studied in the media of different osmotic pressures such as 7.81 atm, 13.84 atm, and 21.28 atm. Drug release from the formulations decreased as the osmotic pressure of the media increased which confirm the inverse relation of the osmotic pressure to that of the release of the drug.

Multivariable linear regression analysis

The effect of the different independent variables such as concentration of PEO (X1), concentration of KCl (X2) and orifice diameter (X3) on the dependent variable (Y) i.e. the drug release rate of the EOPT were analyzed using the multivariable linear regression analysis. The regression equation for nevirapine drug release from EOPT was obtained as follows:

$$Y = 58.18 - 0.14\ X1 + 0.53\ X2 + 4.31\ X3$$

The correlation coefficient was 0.992

It was found that the independent variables (X1, X2, X3) had a significant influence upon the dependent variable. The concentration of PEO had a negative influence whereas the concentration of KCl and orifice diameter had a positive influence upon the drug release.

Stability studies

EOPT should ensure their stability over storage without affecting their physico-chemical properties, drug content and release characteristics. To examine this, we carried out stability study on the developed EOPT by storing them at 40°C ± 2°C / 75 % RH for 90 days as per ICH guidelines. Samples were withdrawn at regular intervals of time and tested for changes in their characteristics. We observed no significant changes in the physico-chemical properties, drug content and release rate of the drug and therefore, the developed formulation was found to be stable.

CONCLUSION

EOPT of nevirapine was developed as an alternative to conventional twice daily dosage forms for treatment of HIV infection. EOPT was developed using variable concentration of PEO, KCl, variable delivery orifice diameter and coating thickness. PEO (20 mg), KCl (20 mg), delivery orifice diameter (0.6 mm) and coating thickness (70:30 / CAP: PEG) were found to be optimum in the formulation F4 that release the drug with zero-order kinetics for 24 hours. The developed EOPT released the drug independent of the environmental pH and mobility of the gastro intestinal tract. EOPT can be considered ideal for slow and extended release of nevirapine for better control of HIV infection.

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