ORIGINAL ARTICLE

FORMULATION AND EVALUATION OF FLUVASTATIN SODIUM BILAYERED OSMOTIC TABLETS

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Abstract

The aim of this study was to design bi-layered osmotic tablets of fluvastatin sodium using osmogens in the upper layer and in the lower layer, PEO (polyethylene oxide) - Coagulants. The tablets were prepared by wet granulation method and evaluated for hardness, friability, drug content, and weight variation. All the parameters were found within the compendial limits. Osmogens (mannitol:lactose) in the upper layer were taken in different ratios of 1:1, 1:2 and 1:3. From the dissolution studies, 1:3 was considered as optimum for further studies. In the push layer, the osmogen (NaCl) was varied in concentrations of 50, 75 and 100 mg. To the best batch of the above (i.e. 75 mg NaCl), PEO-N-80 was added in different proportions. The resultant tablet was coated with cellulose acetate. A tablet weight gain of 7%, and an orifice size of 0.8 mm was set as optimum for all the batches. The formulations were subjected to different kinetic models and the regression coefficient was 0.995 indicating a zero order release and the "n" value was 0.902, indicating an anomalous transport mechanism. F1 and F2 values were 5 and 80 respectively indicating similarity to that of the innovator drug (Lescol® XL 80 mg, Novartis GMBH). The optimized batch was kept for accelerated stability study under ZONE III according to the International Conference on Harmonisation (ICH) guidelines and the formulation was found to be stable.

Rezumat

Scopul acestui studiu a fost de a proiecta tablete osmotice bistratificate de fluvastatin sodic utilizând osmogeni în stratul superior şi în stratul inferior, PEO (oxid de polietilenă) - Coagulanti. Tabletele au fost preparate prin procedeul granulării umede şi evaluate din punct de vedere al durităţii, friabilităţii, conţinutului în substanţă activă şi variaţiei greutăţii. Toţi parametrii au corespuns limitelor compendiale. Osmogeni (manitolul: lactoză) în stratul superior au fost folosiţi în proporţii diferite 1:1, 1:2 şi 1:3. Din studiile de dizolvare, formularea în care s-a folosit raportul 1:3 a fost considerată ca optimă pentru studii ulterioare. În stratul de împingere, cantitatea de osmogen (NaCl) a fost variată în concentraţii de 50, 75 şi 100 mg. Pentru cea mai bună formulare de mai sus (adică 75 mg NaCl) s-a adăugat PEO-N-80 în diferite proporţii. Tableta rezultată a fost acoperită cu acetat de celuloză. S-a constatat o creştere în greutate a tabletei de 7%, iar dimensiune orificiului de 0,8 mm a fost stabilită ca optimă pentru toate loturile. Formulările au fost supuse la diferite modele cinetice şi coeficientul de regresie a fost de 0,995 şi indică o eliberare de ordin zero şi valoarea "n" a fost 0,902, indicând un mecanism de transport anormal. Valorile F1 şi F2 au fost 5 şi respectiv 80 indicând similaritate cu medicamentul inovator (Lescol® XL 80 mg, Novartis GMBH). Şarja optimă a fost folosită într-un studiu de stabilitate accelerată în zona III, conform Conferinţei Internaţionale privind Armonizarea (CIA), ghidurile şi formularea dovedindu-se a fi compatibile.

Keywords: Fluvastatin sodium, Osmogen, Bilayered osmotic tablets

Introduction

Controlled release (CR) drug delivery systems provide the desired concentration of drug at the absorption site allowing maintenance of plasma concentrations within the therapeutic range and reducing the dosing frequency. These products provide significant benefits over immediate release formulations, with greater effectiveness in the treatment of chronic conditions with reduced side effects and greater patient compliance due to a simplified dosing schedule [2, 15]. A number of design options are available to control or modulate the drug release from a dosage form. Most of the oral CR dosage forms fall in the category of monolithic, reservoir or osmotic systems.

Osmotic systems are also known as Gastro Intestinal Therapeutic System (GITS). Different types of osmotic pumps are available to meet the variety of drug delivery demands. Osmotic systems use the principles of osmotic pressure for the delivery of drugs, independent of pH and other physiological parameters [4, 7, 11, 17]. Osmotic pumps can be used as experimental tools to determine important pharmacokinetic parameters of new or existing drugs and even utilized to deliver drugs at a controlled and predetermined rate.

Fluvastatin sodium used as hypolipemiant, which decreases levels of HDL-cholesterol (HDL-C) and its

transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Hence this drug must be released in a controlled manner over a period of time. In the present study fluvastatin sodium osmotic bilayered tablets were prepared by wet granulation method using PEO (polyethylene oxide) N-80 as release retardant polymer and HPC (hydroxypropyl cellulose) as a binder. Osmotic system release the drug at a predetermined rate, typically zero order delivery based on the principle of osmosis. These systems imbibe water from the body through a semi permeable membrane into an osmotic material, which swell resulting in slow and constant delivery of drug formulations.

Materials and Methods

Materials

Fluvastatin sodium was a gift from Hetero Labs Ltd., Hyderabad. Polyethylene oxides (PEO Coagulant and PEO-N-80) were purchased from Dow Chemicals, Mumbai. Sodium chloride was purchased from Merck, Mumbai. Ferric oxide was purchased from Rockwood pigments, China. Klucel LF was purchased from Ashland, Covington, USA. Isopropyl alcohol (IPA), Lactose Monohydrate and Mannitol were purchased from SD fine chemicals, Mumbai and Opadry® CA Clear was purchased from Colorcon, Goa. All other chemicals, reagents and solvents used were of analytical reagent (AR) grade.

Methods

Preformulation studies: Preformulation studies are the first step in the rational development of dosage forms of a drug substance. The dry powder blend was subjected for flow properties like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.

Dose calculation: The maximum amount of a daily dose of fluvastatin is 80 mg and it is equal to 84.24 mg fluvastatin sodium. If 10% overages are taken for osmotic tablets, the calculated drug dose for Fluvastatin sodium osmotic tablets is equal to 92.66 mg.

Preparation of Layer 1 (Drug Layer/Pull layer)

Fluvastatin sodium, lactose, PEO N-80 and mannitol were dry mixed in the required proportion, manually (Table I). Binder solution was prepared by dissolving HPC (Klucel LF) in IPA (isopropyl alcohol) under constant stirring. The dry mix blend was granulated with the prepared binder solution. The wet mass was then dried at 50ºC. The dried granules were passed through 20# sieve. The above blend was mixed with magnesium stearate.

Preparation of Layer 2 (Push layer)

PEO Coagulant, NaCl and ferric oxide were mixed manually. HPC (Klucel LF) was dissolved in IPA under stirring. The dry mix blend was granulated with the prepared binder solution in the fluidized bed processor. The dried granules were passed through 20# sieve. The above blend was mixed with magnesium stearate.

Preparation of tablets by double Compression: Lubricated granules were compressed using 12.1mm, round, standard concave punches, plain on both the sides in bilayered rotary compression machine [8]. Tablet formulations were prepared using drug, osmogens and PEOs coagulant in different ratios as given in Table I.

Coating process: Bilayered core tablets were coated with semi-permeable coating solution of 42 g of Opadry CA® Clear in a ratio of (95:5) acetone and water 1290 g : 67.9 g using a perforated Neocota/Gansons coating machine. The coating parameters are inlet air temperature 45°C, bed temperature 38°C, pan speed at 6 to 8 rpm and atomization air pressure of 1 psi. The coating process continued till achieving 7% weight gain of core tablet. The coated tablets were dried at 50ºC for 30 min in a coating pan at 1-2 rpm.

Drilling of orifice: An orifice with a diameter and depth of 0.8 mm was drilled on the drug layer side of coated tablet using a cobalt micro-drill [6].

Table I

Formulations of bilayered osmotic tablets

RATIO		**(1:1)**	**(1:2)**	**(1:3)**	**(1:3)**	**(1:3)**	**(1:3)**	**(1:3)**	**(1:3)**	**(1:3)**
Formulation code	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
DRUG / PULL LAYER										
Fluvastatin sodium (mg)	92.66	92.66	92.66	92.66	92.66	92.66	92.66	92.66	92.66	92.66
Lactose (mg)	387.34	193.67	129.113	290.505	290.505	290.505	265.505	96.835	253.005	234.255
Mannitol (mg)	-	193.67	258.226	96.835	96.835	96.835	96.835	253.005	84.335	78.005
PEO N-80 (mg)	-	-	-	-	-	-	25	37.5	50	75
HPC (Klucel® LF) (mg)	15	15	15	15	15	15	15	15	15	15
IPA (mL)	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Mg. stearate (mg)	5	5	5	5	5	5	5	5	5	5
Drug Layer Wt. (mg)	500	500	500	500	**500**	**500**	500	500	500	500

PUSH LAYER										
PEO Coagulant (mg)	187	187	187	187	162	137	162	162	162	162
NaCl (mg)	50	50	50	50	75	100	75	75	75	75
Ferric Oxide (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
HPC (Klucel® LF) (mg)	10	10	10	10	10	10	10	10	10	10
Mg. Stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
IPA (mL)	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Push Layer Wt. (mg)	250	250	250	250	**250**	**250**	250	250	250	250
TOTAL TABLET Wt. (mg)	750	750	750	750	**750**	**750**	750	750	750	750
COATING										
% Weight gain	7	7	7	7	7	7	7	7	7	7
Opadry® CA Clear (g)	42	42	42	42	42	42	42	42	42	42
Acetone (95%) (g)	1290	1290	1290	1290	1290	1290	1290	1290	1290	1290
Water (5%) (g)	67.9	67.9	67.9	67.9	67.9	67.9	67.9	67.9	67.9	67.9
COATED TABLET Wt. (mg)	**802.5**	**802.5**	**802.5**	**802.5**	**802.5**	**802.5**	**802.5**	**802.5**	**802.5**	**802.5**

Evaluation of prepared tablets

The prepared bilayer tablets were evaluated for varied parameters like weight variation, thickness, hardness, friability [10], drug content, content uniformity and *in vitro* dissolution studies [18].

Weight Variation: Twenty tablets of each formulation were weighed, average weights were calculated, and individual tablet weights were compared with the average weight.

$$PD= [(W_{avg}) – (W_{initial}) / (W_{avg})] \times 100$$

Where, PD is the percentage deviation, W_{avg} - average weight of tablet, $W_{initial}$ - individual weight of tablet.

Hardness test: The tablet crushing strength, which is the force required to break a tablet into pieces by compression is expressed as tensile strength (kg/cm^2). It was measured using a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation batch were tested randomly and the average readings were registered.

Friability test: The friability is the ability of tablets to withstand mechanical shocks during handling and transportations. 10 tablets were randomly picked from each batch, weighed and placed in the Roche friability test apparatus and operated at a rate of 25 rpm for 4 min, tablets were de-dusted and reweighed. The loss of tablet weight due to abrasion and fracture was measured in terms of % friability (a value of < 1% friability is acceptable).

$$F\ \% = (1\text{-}W0 / W) \times 100$$

Thickness: The thickness of tablets was measured for 10 tablets by Vernier Calipers in millimetres, and is related to the tablet hardness. Tablet thickness should be controlled within a ± 5% variation of a standard value.

$$Thickness = MSR + [VSR \times 0.01]$$

where, MSR - main scale reading, VSR - vernier scale reading.

Drug content: Twenty tablets were randomly selected and powdered in a glass mortar. Powder equivalent to individual tablet weight was weighed and dissolved in 100 mL of distilled water, filtered and analysed by an UV spectrophotometer at 303.2 nm.

Content uniformity: The content uniformity test is used to ensure that each tablet contains the same amount of drug substance within a batch. It was determined the amount of drug in each of the 10 tablets, using the analytical method as mentioned above, for the drug content [18].

In vitro dissolution studies: The *in vitro* drug release of fluvastatin sodium tablets was determined using the USP dissolution apparatus-I (basket type) (Electrolab TDT-08L). At 0.5, 2, 4, 6 and 8 hr intervals, 5 mL of sample was taken from 1000 mL of distilled water and replaced with 5 mL of fresh medium. Samples were analysed by an UV spectrophotometer (ELICO-164 double beam spectrophotometer) at a wavelength of 303.2 nm.

Effect of variables on the optimized formulation [4]: The optimized formulation was subjected to different rotational speeds (rpm) for the effect of agitation intensity (50, 100 and 150 rpm.), various pH media (0.1N HCl, pH = 6.8 and pH = 7.4) to study the pH effect on drug release. The study was conducted to prove that the osmotic pressure, only due to the concentration of osmogen is affecting the drug release, not the pH, agitation and orifice diameter.

Drug-excipient compatibility studies

Fourier Transform Infrared (FTIR): The spectrum analysis of pure drug and optimized formulation F8 were studied by FTIR. FTIR spectra were recorded from 4000 cm^{-1} to 500 cm^{-1} using potassium bromide (KBr) disks on a Shimadzu Corporation system (Koyto, Japan).

Differential Scanning Colorimetry study (DSC): Thermograms were recorded for pure drug and optimized formulation F8 individually using a Differential Scanning Calorimeter (DSC-8500 with Hyper DSC, Perkin Elmer, USA). 3 mg of sample were placed on aluminium plates sealed with aluminium seals and heated at constant temperature of 5°C / min over a temperature range of 0 - 400°C.

Model dependent kinetics [9, 12, 14]: For all the formulations regression coefficients (r^2) were calculated for order of release and 'n' value for the release mechanism.

Model independent kinetics: A model independent approach was used to estimate the difference factor (f1) and similarity factor (f2) to compare the dissolution profile of optimized formulation with the marketed formulation. The marketed formulation Lescol® XL (80 mg of fluvastatin sodium) was manufactured by Novartis (Mfg Lic.No.: KD-2070-A, Mfg. date: Nov 2011, Exp. date: Oct 2014). The following equations were used for calculating f1 and f2**,** **w**here, n = no of time points, Rt = dissolution value of the reference batch at time t, Tt=dissolution value of the test batch at same time point**.**

$$f1\ (Difference\ factor) = \{\left[\sum_{t=1} n|\ \mathrm{R\ t} - \mathrm{Tt}|\right]\ /\ \left[\sum_{t=1} n\ \mathrm{Rt}\right]\}\ \mathrm{x100}$$

$$f2\ (Similarity\ factor) = 50\ .\ log\{\left[1 + (1/n)\sum_{t=1} n(\ \mathrm{R\ t} - \mathrm{Tt})2\right] - 0.5\ \mathrm{x100}$$

Accelerated stability studies: The optimized formulation F8 was subjected to stability studies at 40ºC ± 2ºC / 75% ± 5% RH and room temperature analysed for its physical characteristics, drug content and dissolution every month for a period of three months.

Results and Discussion

The present study was undertaken in order to formulate and evaluate the bilayered osmotic tablets of fluvastatin sodium by wet granulation method using different osmogens namely lactose, mannitol, NaCl and water-swellable polymer PEO N-80.

Preformulation studies: The values of angle of repose were found to be between 31.9 ± 0.95 to 36.3 ± 0.05 (IP limits 31 - 35), the values for compressibility index were between 11.92 ± 0.23 to 33.82 ± 0.09 (IP limits 16 - 20), Hausner's ratio was within 1.13 ± 0.005 to 1.51 ± 0.004 (IP limits 1.19 to 1.25) as given in Table II.

Table II

Pre-compression parameters of powder blend

Formulation Code	Angle of repose (θ)	Bulk density (g/cm^3)*	Tapped Density (g/cm^3)*	Hausner's ratio*	Carr's Index (%)*
Fluvastatin sodium	35.6 ± 0.96	0.536 ± 0.05	0.81 ± 0.03	1.51 ± 0.004	33.82 ± 0.09
Fluvastatin sodium + PEO	36.3 ± 0.05	0.545 ± 0.03	0.79 ± 0.13	1.46 ± 0.005	31.64 ± 0.04
Fluvastatin sodium + Lactose + Mannitol +PEO	31.9 ± 0.95	0.598 ± 0.08	0.812 ± 0.12	1.35 ± 0.006	26.4 ± 0.06
NaCl + PEO	32.8 ± 0.85	0.644 ± 0.06	0.732 ± 0.01	1.13 ± 0.005	11.92 ± 0.23

Values are expressed as Mean ± SD, * n = 3

Table III

Pre-compression parameters of formulation granules

Formulation Code	Angle of repose (θ)*	Bulk density (g/cm^3)*	Tapped Density (g/cm^3)	Hausner's ratio*	Carr's Index (%)*
F1	25.7 ± 0.27	0.642 ± 0.01	0.735 ± 0.04	1.144 ± 0.09	12.6 ± 0.04
F2	25.8 ± 0.85	0.646 ± 0.06	0.735 ± 0.09	1.137 ± 0.03	12.1 ± 0.23
F3	26.9 ± 0.95	0.617 ± 0.04	0.722 ± 0.03	1.170 ± 0.13	14.5 ± 0.06
F4	26.1 ± 0.84	0.634 ± 0.05	0.720 ± 0.08	1.136 ± 0.22	11.8 ± 0.03
F5	27.6 ± 0.96	0.645 ± 0.05	0.742 ± 0.05	1.150 ± 0.01	13.1 ± 0.09
F6	25.9 ± 0.92	0.652 ± 0.12	0.740 ± 0.03	1.134 ± 0.21	11.8 ± 0.02
F7	25.6 ± 0.98	0.669 ± 0.24	0.757 ± 0.02	1.131 ± 0.19	11.6 ± 0.07
F8	26.7 ± 0.89	0.641 ± 0.04	0.727 ± 0.02	1.134 ± 0.04	11.8 ± 0.02
F9	25.4 ± 0.82	0.630 ± 0.05	0.710 ± 0.06	1.126 ± 0.19	11.2 ± 0.07
F10	25.4 ± 0.88	0.642 ± 0.05	0.712 ± 0.09	1.128 ± 0.07	9.83 ± 0.04
Push layer	27.54 ± 0.81	0.646 ± 0.05	0.728 ± 0.03	1.126 ± 0.04	11.2 ± 0.33

Values are expressed as Mean ± SD, * n = 3

The wet granulation method was chosen to improve the flow properties. For this study, the binder solution was prepared using HPC (Klucel LF) in isopropyl alcohol (IPA). The flow property parameter values are given in Table III, the angles of repose were found in the range of 25.4 ± 0.82 to 27.62 ± 0.96 (IP limits 25 - 30) showing that the blend of powder was freely flowing. The values for the Carr's index were between 11.2 ± 0.07 to 14.5 ± 0.06 (IP limits 11 - 15) indicating that all batches of powder blends were having good compressibility characteristics. The Hausner's ratio was within the limits 1.126 ± 0.19 to 1.170 ± 0.13 (IP limits 1.12 - 1.10). The results showed that all the formulations showed good flow properties.

Evaluation of prepared tablets: Evaluation of the prepared tablets was conducted and the results are given in Table IV. Weight variation was in the range of 747 ± 0.32 to 752 ± 0.25 (limits 10% deviation), hardness 7-8 kg/cm^2 (IP limits 4 - 8%), friability 0.1 ± 0.12 to 0.17 ± 0.45 (limits 0.5 - 1%), thickness 6.7 ± 0.26 to 6.9 ± 0.32 (limits ± 5% deviation), drug content 91.32 ± 0.51 to 98.44 ± 0.95 (limits 85 - 115%). This indicates that the evaluation parameters for all the formulations are within the limits.

Table IV

Evaluation of prepared tablets

Batch No	Weight variation[a] (mg)	Hardness[b] (kg/cm^2)	Thickness[c] (mm)	Friability[d] (%)	Drug content[e] (%)	Content Uniformity[f]
F1	748 ± 0.82	7 - 8	6.86 ± 0.02	0.17 ± 0.05	97.68 ± 0.01	98.43 ± 0.12
F2	752 ± 0.25	7 - 8	6.89 ± 0.01	0.15 ± 0.01	98.44 ± 0.05	97.36 ± 0.57
F3	751 ± 0.45	7 - 8	6.9 ± 0.04	0.13 ± 0.05	96.98 ± 0.05	98.17 ± 0.84
F4	750 ± 0.62	7 - 8	6.72 ± 0.05	0.15 ± 0.06	93.96 ± 0.08	97.84 ± 0.16
F5	749 ± 0.45	7 - 8	6.8 ± 0.04	0.12 ± 0.05	97.48 ± 0.04	96.75 ± 0.13
F6	747 ± 0.32	7 - 8	6.8 ± 0.01	0.1 ± 0.02	96.32 ± 0.02	98.39 ± 0.73
F7	748 ± 0.45	7 - 8	6.9 ± 0.06	0.19 ± 0.05	98.32 ± 0.06	98.36 ± 0.01
F8	749 ± 0.63	7 - 8	6.8 ± 0.02	0.17 ± 0.04	97.64 ± 0.05	98.97 ± 0.79
F9	748 ± 0.45	7 - 8	6.8 ± 0.04	0.15 ± 0.06	98.22 ± 0.05	98.79 ± 0.12
F10	751 ± 0.36	7 - 8	6.7 ± 0.06	0.12 ± 0.05	94.08 ± 0.05	97.19 ± 0.97

Values are expressed as Mean ± SD for a: n = 20, b & d: n = 5, c & e & f: n = 10

Evaluation of coated tablets: Evaluation of prepared coated osmotic tablets was carried out and the values for the initial weight, final weight, % weight gain, were checked and results are given in Table V. Initial weights of the tablets were found to be between 747 ± 0.12 to 752 ± 0.15. Final weights were in the range of 801 ± 0.16 to 804 ± 0.17. The weight gain of the tablets was between 6.91 ± 0.03 to 7.49 ± 0.07. The orifice diameter was maintained constant at 0.8 mm.

Table V

Evaluation of coated tablets

Batch No	Initial weight (mg)	Final weight (mg)	% weight gain	Orifice diameter (mm)
F1	748 ± 0.12	803 ± 0.05	7.35 ± 0.14	0.8
F2	751 ± 0.05	802 ± 0.05	6.7 ± 0.06	0.8
F3	752 ± 0.15	804 ± 0.12	6.91 ± 0.03	0.8
F4	750 ± 0.02	802 ± 0.15	6.93 ± 0.07	0.8
F5	749 ± 0.45	804 ± 0.5	7.34 ± 0.19	0.8
F6	747 ± 0.12	803 ± 0.13	7.49 ± 0.07	0.8
F7	748 ± 0.15	802 ± 0.01	7.21 ± 0.01	0.8
F8	749 ± 0.03	801 ± 0.16	6.94 ± 0.15	0.8
F9	748 ± 0.15	804 ± 0.13	7.48 ± 0.19	0.8
F10	751 ± 0.16	804 ± 0.17	7.05 ± 0.03	0.8

Values are expressed as Mean ± SD, *n = 3

In vitro dissolution study: Formulations F1 to F4 are with different compositions of osmogens (mannitol, lactose). It was observed that the drug release rate increased as the amount of osmogen (lactose) in the drug layer increased as shown in Figure 1**.** It is evident from the release profiles of drug that the combination of osmogens (mannitol: lactose) showed significant increases in drug release i.e. F2, F3, F4 showed 58.2 %, 68.8 % and 82.3 % respectively in the ratios (1:1, 1:2 and 1: 3) at 8 hr. F4 showed better results and were within limits. Hence F4 was optimized for further studies. This may be due to the osmotic pressure in the GIT (gastro intestinal tract) which remains relatively low; an osmogen that provides significantly higher osmotic pressure will affect a steady driving force for water imbibition through the tablet coating. The driving force of internal osmotic pressure caused by dissolving either the osmotic drug or osmogens or both acts radically outwards [5].

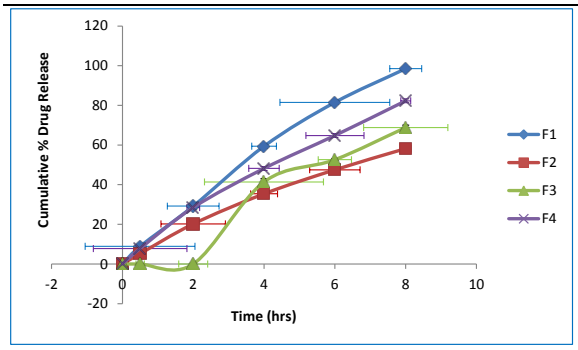

Figure 1.
Drug release profiles F1 - F4 for optimization of osmogen in drug layer

Osmogen concentrations were changed in the push layer to select the optimum concentration that provides sufficient pressure on the pull compartment for an extended period of time, which could mimic zero order drug release kinetics. Formulation F4 to F6 results show the influence of sodium chloride on drug release. A higher concentration of sodium chloride increased the release rate from the tablets because there was more pressure on the pull compartment as shown in Figure 2. Water uptake increased with the increase in the concentration of sodium chloride and resulted in the swelling to its maximum capacity to exert pressure on the pull compartment. A composition containing 75 mg of sodium chloride in the push compartment showed zero order release kinetics, while where with 100 mg integrity was lost due to excess pressure. The PEO coagulant produced a gel like matrix in the tablet push layer. This gel like matrix helped maintaining an integrated consistency in the push compartment without much loss of water-soluble constituents from the compartment due to its gel-forming properties [16].

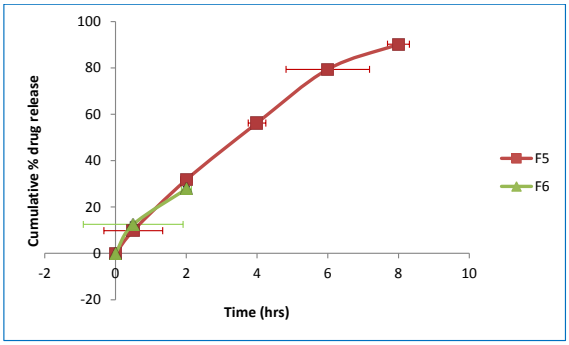

Figure 2.
Drug release profiles F5, F6 for optimization of osmogen in push layer

PEO N-80 (MW: 200000) in the drug layer and polyethylene oxide coagulant (MW: 5000000) in the push layer were incorporated in the tablet and studied for drug release rate. Based on the results polyethylene oxide have been proposed as an alternative to cellulose or other ethylene glycol derivatives in the production of controlled drug delivery system [1, 13].

Formulations F7 to F10 given in Figure 3 shows that Fluvastatin sodium release rate decreased from 65.3 % to 48.62 % as the polyethylene oxide concentration in the drug layer increased from 25 mg to 75 mg. This may be due to the control of the release by producing high viscosity within the core which may restrict and delay the solvent contact with drug molecules and increase the diffusional path length of solvent to get the desired zero order release rate.

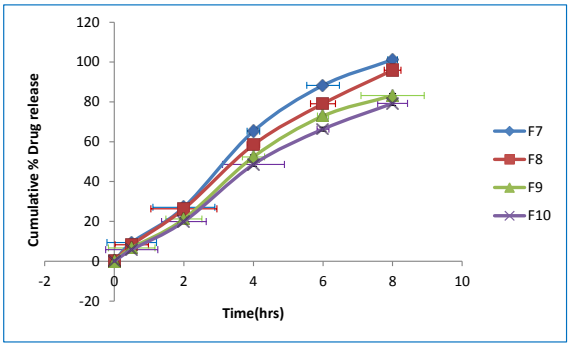

Figure 3.
Drug release profiles F7 - F10 for optimization of PEO N-80 in drug layer

Appearance of tablets: To discriminate the control release upper and lower layers they were coloured with Ferric oxide (Figure 4a, 4c). The drug layer was drilled with a 0.8 mm mechanical drill (Figure 4b) and a push layer (Figure 4d).

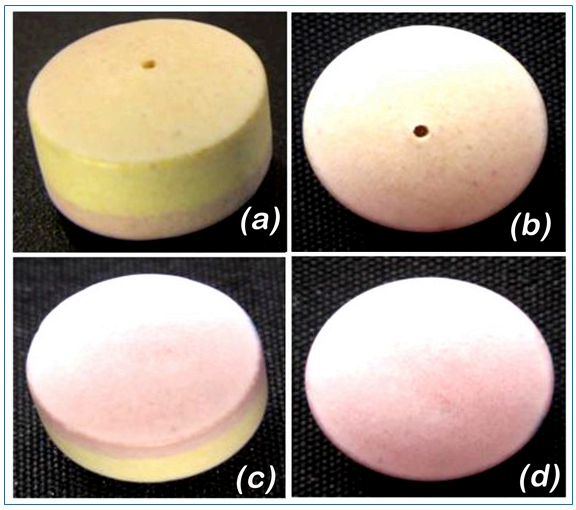

Figure 4.
Appearance of the bilayered tablets (a) Bilayered tablet with the drug layer facing upwards (b) Top view of drilled drug layer (c) Bilayered tablet with the push layer facing upwards (d) Top view of the push layer

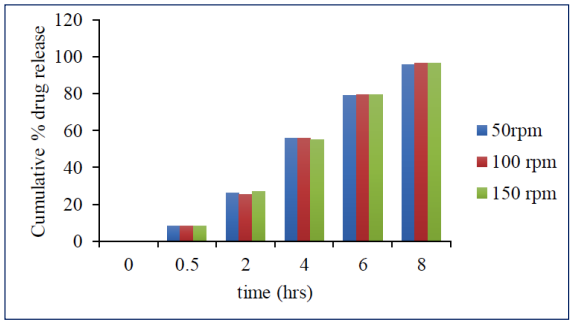

Figure 5.
The drug release of formulation F8 in order to study the effect of the agitation rate on drug release

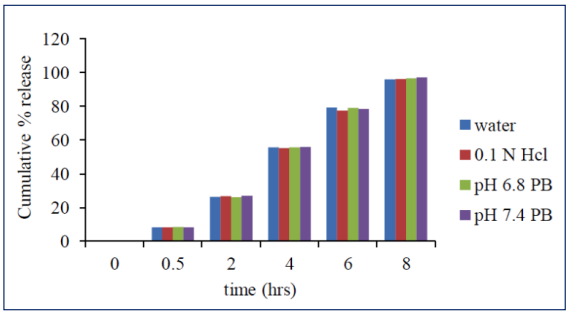

Figure 6.
The drug release of formulation F8 in order to study the effect of the pH on drug release

Effect of variables: There were no significant changes observed during the drug release study considering the agitation rate (Figure 5) and pH (Figure 6), which strongly indicates that the release of the drug from the system takes place mainly through the osmotic pressure generated within the system. Therefore, it might be predicted that the mobility and media with different pH values of the gastrointestinal tract hardly affected the drug release of the prepared osmotic tablet [3].

Drug-Excipients compatibility studies

1. Fourier transformer infrared spectroscopy analysis: The characteristic peaks observed for fluvastatin sodium (Figure 7a) a broad band at 3392 cm $^{-1}$, attributed to C=C stretch, a band at 3221.605 cm^{-1} representing aryl-H functional group, a band at 1560 cm^{-1} indicating C=0 stretch and another band at 968.5 cm^{-1} showing the presence of an aryl-functional group.

In the case of the optimized formulation F8 there was no change in the characteristic peaks of drug in the FTIR spectra, suggesting that there were no physical or chemical interactions and there was no functional alteration of drug as shown in Figure 7b.

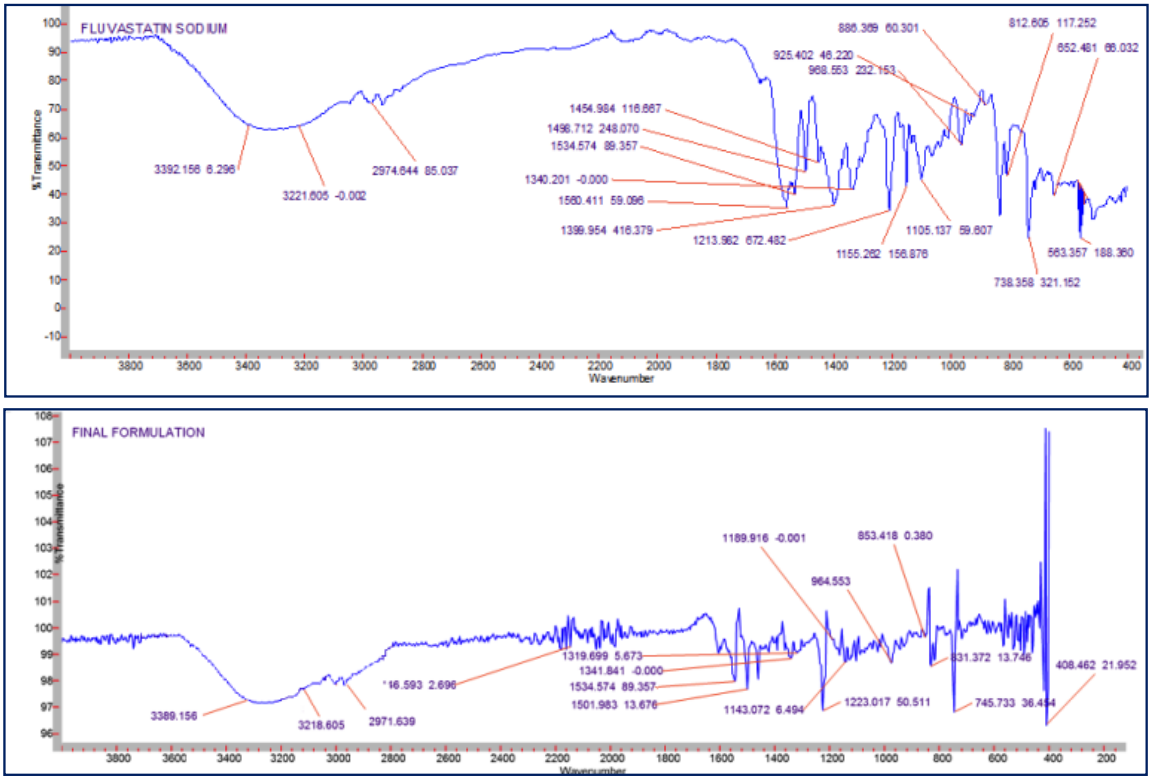

Figure 7.
FTIR spectra of (a) fluvastatin sodium (b) F8 formulation

2. Differential scanning calorimetry: DSC thermograms of fluvastatin sodium and optimized formulation F8 exhibited a sharp endothermic peak corresponding to its melting point are shown in Figure 8a, 8b

respectively. It indicates there is no interaction of the drug and excipient as it is evident from the unaltered thermogram of F8 (Figure 8b).

The DSC analysis of drug showed an endothermic peak at 149˚C corresponding to the melting point of fluvastatin sodium, thus it signifies the presence of the pure form of fluvastatin sodium. The thermogram of drug does not show profound shifts in peaks indicating compatibility as shown in the Figure 8b.

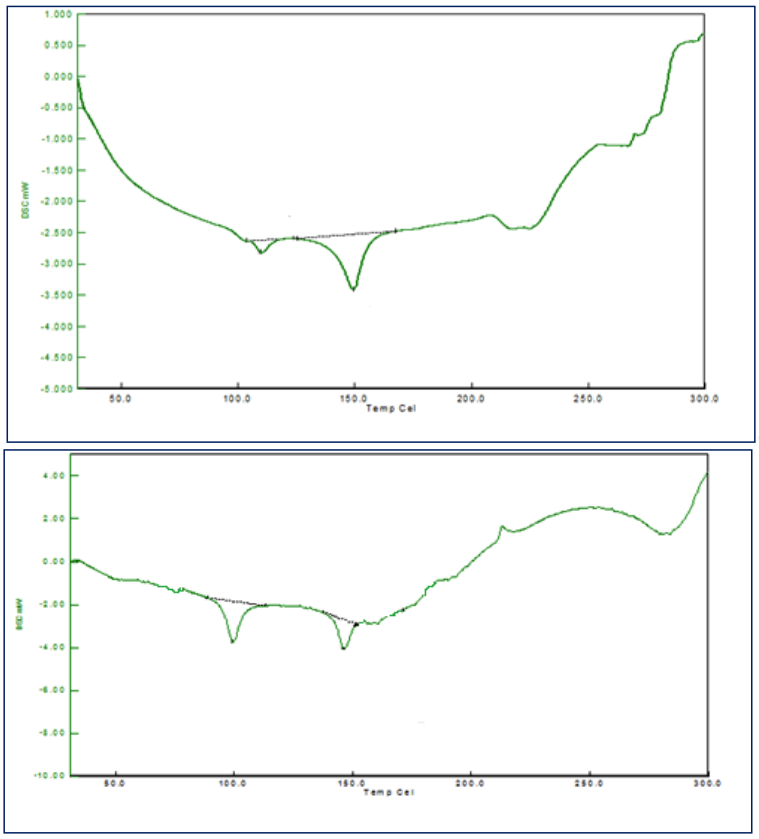

Figure 8.
DSC thermograms of (a) fluvastatin sodium (b) F8 formulation

Model dependent kinetics: The release kinetics for all 10 formulations were calculated using Microsoft Office Excel 2013 version. The release data was analysed by fitting the drug release profiles of all the formulations into zero order, first order, Higuchi and Korsmeyer-Peppas model. Regression coefficients (R^2) were calculated for all the formulations. The apparent dissolution rate constants K_0, K_1, K_H and n were calculated (Table VI)..

Table VI
Model dependent kinetics of all the formulations

Formulations	Zero order	First order	Higuchi	Peppas	
	R^2	R^2	R^2	R^2	n
F1	0.986	0.855	0.957	0.998	0.883
F2	0.981	0.998	0.968	0.995	0.874
F3	0.977	0.989	0.967	0.997	0.824
F4	0.978	0.974	0.967	0.997	0.845
F5	0.969	0.978	0.969	0.997	0.816
F6	0.924	0.968	0.996	1.000	0.574
F7	0.975	0.889	0.948	0.998	0.893
F8	**0.994**	**0.907**	**0.948**	**0.992**	**0.902**
F9	0.977	0.986	0.941	0.996	0.947
F10	0.985	0.984	0.942	0.996	0.973
Lescol® XL	0.999	0.916	0.964	0.992	0.842

Higher R^2 value of 0.994 indicates zero order drug release and slope of Korsmeyer–Peppas plot was 0.902 indicating that the formulation followed the non-Fickian diffusion kinetics (because n > 0.5)

shown in Table VI. Hence from the obtained results, F8 was considered as the optimized formulation.

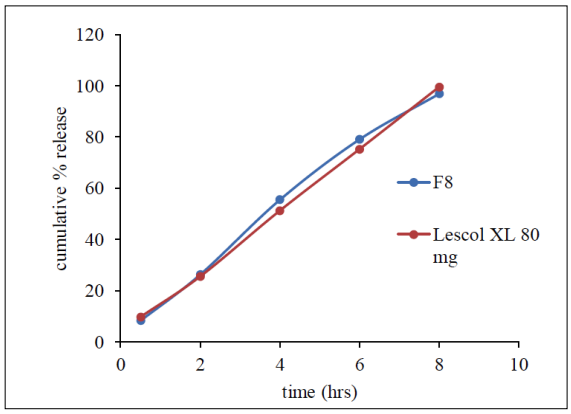

Figure 9.
Drug release comparison of formulation F8 with Lescol® XL

Model independent kinetics: The optimized formulation F8 was compared with the marketed Lescol® XL (80 mg) tablets. Results are shown in Figure 9 f1 was found to be 5 (0 - 15) and f2 was found to be 80 (50-100) which shows that the optimized formulation F8 is similar to the Lescol® XL marketed tablet considering the *in-vitro* release studies. No osmotic tablet was available on the market, so it was compared with extended release tablets. Both F8 and Lescol® XL formulations follow zero order kinetics and Korsemeyer Peppas release.

Accelerated stability studies: There was no significant change in the appearance and physico-chemical properties of the tablets of the optimized formulation F8 after 3 months. The parameters quantified at various time intervals were given in Table VII.

Table VII
Physico-chemical properties of F8 during accelerated stability studies

Parameters	Time in months			
	0 (Initial)	1st month	2nd month	3rd month
Appearance	Pale yellow and light pink	Pale yellow and light pink	Pale yellow and light pink	Pale yellow and light pink
Hardness (kg/cm^2)	7.6 ± 0.12	7.6 ± 0.54	7.5 ± 0.63	8.4 ± 0.89
Drug content (%)	98.63 ± 0.12	97.12 ± 0.45	96.91 ± 0.23	96.82 ± 0.13
Friability (%)	0.17 ± 0.21	0.16 ± 0.45	0.16 ± 0.95	0.15 ± 0.12

The optimized formulation F8 was found to be stable, with insignificant changes in the appearance, hardness, drug content, friability (Table VII) and *in vitro* drug release (Figure 10).

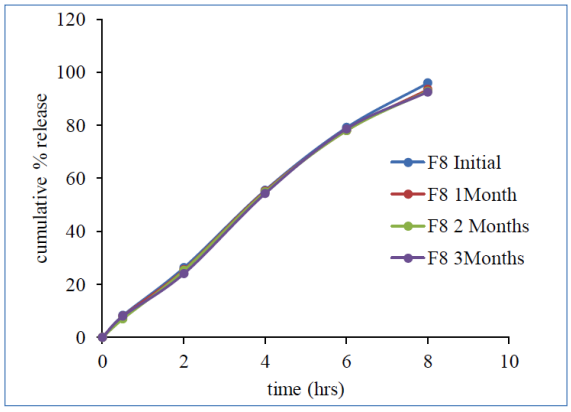

Figure 10.
Stability dissolution profile of formulation F8

Conclusions

Formulation F8 having mannitol: lactose (1:3), 162 mg of PEO coagulant and 50 mg of NaCl in the push layer was concluded to be the optimized formulation. It followed the zero order release with non-Fickian diffusion kinetics. From the results it can be inferred that the drug release is not affected by environmental conditions such as rpm, pH and orifice diameter, depending only on the concentration of osmogen, not even mechanical force.

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