ORIGINAL ARTICLE

Design and Evaluation of Osmotic Drug Delivery System of Efonidipine

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Abstract

Introduction: The aim of the present research work was to design an elementary osmotic pump (EOP) of efonidipine hydrochloride (EFH), a biopharmaceutical classification system class II drug. **Materials and Methods**: To enhance the solubility of EFH by novel co-amorphous solid dispersion technique, drug-loaded solid dispersion composed of efonidipine/co-former at a weight ratio of 1:1, 1:2, 1: 4, 1:8, and 1:12 was prepared by fusion method. Based on the drug release profiles, efonidipine/pimelic acid dispersions were optimized. To formulate the core tablets, sodium chloride and mannitol were used as osmotic agents. Four distinct core compositions, labeled as EF1 through EF4, were prepared following a 2^2 full factorial design approach to systematically optimize the drug's release profile, and four different coating compositions (a, b, c, and d) were applied to four distinct formulations (EF1 to EF4) resulting in a total of 16 formulations. EOP tablets were prepared by applying a semipermeable membrane, cellulose acetate with an orifice on the surface. **Results and Discussion:** Evaluation of the prepared EOP tablets showed satisfactory results, with all 16 formulations exhibiting complete release of efonidipine over approximately 24 h. The steepest ascent method was employed to determine the appropriate quantities, and optimized formulation was designed to release the drug in a controlled manner over a 24-h period. The study demonstrated that the main factor affecting drug release was osmosis alone, and factors such as agitation and stagnant conditions had no significant impact on drug release. As a result, a successful controlled drug delivery system for efonidipine over a 24-h duration was developed using an optimized technique based on a 2^4 factorial design. *In vivo* study was performed in New Zealand white rabbits and various parameters such as Cmax, tmax, AUC, AUMC, and MRT were calculated and compared with that of marketed tablet. **Conclusion:** In summary, efonidipine osmotic pump tablets presented controlled release *in vitro,* high bioavailability *in vivo* and a good *in vitro-in vivo* correlation.

Key words: 2^4 factorial design, efonidipine, osmogens, zero-order release

INTRODUCTION

The administration of conventional preparations typically occurs twice or 3 times a day, resulting in significant fluctuations in drug plasma concentration and adverse effects on the human body. For numerous drugs, maintaining constant plasma levels can be beneficial in terms of therapy efficacy and patient tolerance.[1] Formulations with a once-daily controlled release are frequently preferred. One of the most popular controlled-release devices is the osmotic pump tablet, which offers a number of benefits including a lower chance of side effects, better patient compliance, and comparable *in vitro/in vivo* drug release. Over the past 20 years, there has been a growing interest in the development of osmotic devices because osmotic pressure can administer pharmaceutical substances in a regulated pattern over an extended period of time. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form.[2] The elementary osmotic pump (EOP) consists of an osmotic core, with the drug surrounded by a semipermeable membrane with a delivery orifice. In operation, the osmotic core acts by

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imbibing water from the surrounding medium through the semipermeable membrane. Subsequently, drug solution is generated within the device and delivered out of the device through the orifice.[3] Various attempts to increase the permeability of the semipermeable coating have been reported, such as incorporating water soluble pore-forming additives in the coating. The release rate from these types of systems is dependent on the coating thickness, level of leachable components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane but is independent of the pH and agitation of the release media. It was observed that predominantly the drug was released through the pores at a constant rate. It was also observed that most of the core content released through pores at a constant rate, where the mechanism was primarily governed by osmosis with simple diffusion playing a minor role.[4-6]

Efonidipine is chemically 2-(phenyl-(phenylmethyl) amino) ethyl 5-(5,5-dimethyl-2-oxo-1,3-dioxa-2λ5-phosphacyclohex-2-yl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4 dihydropyridine-3 carboxylate with empirical formula of $C_{34}H_{38}N_3O_7P$. Diastolic and systolic blood pressure can be efficiently lowered with efonidipine, a dihydropyridine calcium channel blocker that is frequently used alone to treat hypertension. Commercial efonidipine is in the form of a conventional tablet. Efonidipine is a biopharmaceutical classification system (BCS) class II drug.[7] The conventional tablet Landel 10 mg that is available in the market is taken twice a day, which causes a significant variation in the drug's plasma concentration and adverse effects in the human body. Efonidipine is studied for controlled drug delivery. The present report described osmotic drug delivery, another form of controlled delivery. The properties of efonidipine that supports the present proposal (desired properties in parenthesis) are molecular weight 631.7 g/mol (<1000 g/mol), log P 5.35 (>0.1), and melting point 169–170°C (<200°C). The plasma elimination half-life is 4.0 h (0.5–8 h). It is effectively absorbed by GIT. Based on its suitability from the above aspects, efonidipine was attempted for osmotic drug delivery, using the EOP delivery.[8]

MATERIALS AND METHODS

Materials

Efonidipine was obtained from Zuventus Healthcare Ltd., Mumbai. Pimelic acid, adipic acid, and suberic acid were purchased from Sigma Aldrich, Bengaluru. Sodium chloride, mannitol, talc, magnesium stearate, dibutyl phthalate (DBP), polyethylene glycol (PEG-400), and polyvinyl pyrrolidone (PVP-K 30) obtained from S.D. Fine Chem Limited, Mumbai. Avicel was purchased from Saraswathi Chemicals, Hyderabad. All the remaining chemicals were of analytical grade.

Formulation development and optimization

Drug-excipients interactions

Fourier (FTIR) analysis

The physicochemical compatibilities of the drug and excipients were tested by FT-IR spectrometry. FT-IR spectra of the drug alone and drug-excipients physical mixtures (1:1 w/w) were derived from an IR Affinity-1, FT-IR, Bruker, Japan. The FT-IR spectra of pure efonidipine showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.[9]

Differential scanning calorimetry (DSC)

Efonidipine pure drug alone, efonidipine along with excipients pimelic acid, suberic acid, adipic acid, mannitol, avicel, and PVPK-30 were characterized by DSC. Samples 5 mg were sealed in aluminum hermetic pans and thermograms were recorded at a heating rate of 10°C/min from 25 to 300°C. Indium was used for calibrating the equipment. Thermograms were analyzed for possible drug-excipient interactions. Thermal analysis of the drug using DSC showed a sharp endothermic peak at 160°C corresponding to its melting and indicating its crystalline nature and purity of the sample. The DSC thermogram is shown in Figures 1-4 which correspond to the functional groups present in the structure of the drug and there was no change in the endothermic peaks of physical mixtures indicating no interaction.[10]

PreparaWtion of Efonidipine Solid Dispersions

As efonidipine is a BCS class II drug, an attempt was made to increase its solubility by solid dispersion technique. The solid dispersions of efonidipine were prepared by the fusion method with pimelic acid, adipic acid, and suberic acid as co-formers. The ratios of efonidipine hydrochloride (EFH) to co-formers were 1:1, 1:2, 1:4, 1:8, 1:12 (w/w). The physical mixtures of the EFH and co-formers are melted in a heated vessel under agitation and the melt is rapidly cooled on a plate

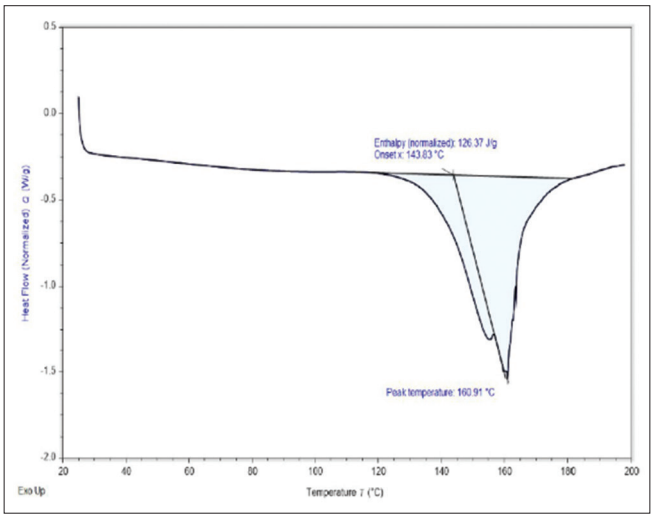

Figure 1: DSC scan of efonidipine

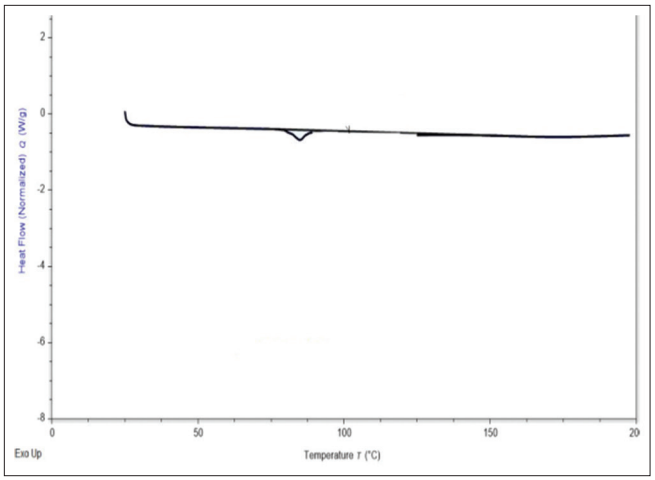

Figure 2: DSC of optimized solid dispersion

over ice. About 80% of the resultant solid dispersion was scraped out with a spatula. Solid dispersions were pulverized in a mortar and pestle and passed through 420 µm and 250 µm sieves before packing in an airtight container and stored in desiccators for further investigations such as powder X-ray diffraction, *in vitro* drug release studies, and drug content.[11]

Preparation of core tablets

The formulation of an EOP is developed in two phases: Core formulation and coat formulation, in the same sequence. In both phases, 2^2 design is applied for core formulation and separately another 2^2 design for coat formulation as shown in the Table 1. A 2^4 factorial design is applied sequentially for optimization. Thus, 16 formulation runs are attempted. Two osmogens are chosen, namely sodium chloride (strong electrolyte or high osmotic pressure), in two levels, 30 and 50 mg, and mannitol (non-electrolyte, low osmotic pressure), in two levels 60 and 100 mg. During granulation, osmogens sodium chloride, mannitol, and half the amount of binder are added in the proper amounts. The granular material is dried in an oven with an air stream at 40–50°C. The dried mass is put through a #20 sieve after drying. After the mixture has been put through a #40 sieve, the necessary amounts of talc, magnesium stearate, and PVP K30 (half) are added and blended. The efonidipine granules' pre-compression characteristics are assessed. A rotating tablet press is used to compress the powder mixture into tablets at a pressure of 5 kg/cm^2. The tablets with compressed core have been evaluated.[12,13] The physical parameters such as hardness, friability, and weight variation were evaluated for the core tablets.

Cellulose acetate (CA) polymer is selected for the semipermeable membrane during the coating step. DBP, an oil-soluble plasticizer, and PEG 400, a water-soluble plasticizer, are the two plasticizers (independent variables) that are selected at two levels.[13]

Process of coating

As the factorial design, the coating dispersion was prepared as shown in the Table 2. The coating dispersion of the CA along with the plasticizers is loaded into the glass reservoir tank attached to the spray gun. The pan rotation is allowed to rotate; the tablet bed is sprayed uniformly with the coating dispersion. Spraying at high rates could end up in sticky and damp films because the material does not dry quickly. The tablet bed is periodically paused when the dry air is passed across it. It needs to be coated layer by layer. Each batch was divided into 25 core tablets, which were coated. 25 coated tablets were weighed upon coating. This computed the percentage of weight gain. Using a hand-driven, mechanical drill bit measuring 0.8 mm, a hole is drilled. The hardness, diameter, and thickness of the coated tablets were measured.[13]

Characterization

PXRD of solid dispersion

X-ray diffraction patterns of the samples were obtained with Bruker D8 advance diffractometer based on a two-circle goniometer, enclosed in radiation safety enclosure. Samples were placed at an angle of 0 in the sample chamber. The X-ray beam allowed to fall over the sample. The slide was moved at an angle of theta degree, a proportional to an angle of 2 theta degrees[14] [Figure 5].

Drug content of coated tablets

Twenty coated osmotic pumps were selected at random to determine the average weight. Fifty milliliters of water were mixed with the equivalent of 10 mg of efonidipine, and the mixture was shaken for 10 min. The approximate volume is 80 mL in total. After filtering, the solution was made up to 100 mL with water and measured at 330 nm. The limitations of content uniformity are 90% and 110% of the labeled amount.

In vitro efonidipine release and analysis

Using the dissolution test apparatus 2 USP (paddle type), the *in vitro* efonidipine release of the osmotic pump was examined. After 2 h of dissolution in a 0.1N hydrochloric acid solution, the media was changed to phosphate buffer pH 6.8 using a replacement technique. The temperature is ± 37 0.5°C and the speed is 50 rpm. Five-milliliter samples were taken out in an aliquot at different times (0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h). Each time, the vessel was filled with the same volume (5 mL) of fresh medium at 37°C.[14]

The samples that were obtained were analyzed at 330 nm using corresponding blank solutions. A cumulative percentage of the release of efonidipine was computed. The experimental data were subjected to regression analysis utilizing MS Statistical Excel tools.

Effect of pH

To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release

studies of the optimized formulations were conducted in media of different pH simulated gastric fluid, pH 1.2, and simulated intestinal fluid pH 6.8. Dissolution apparatus used was rotating basket type (USP-I) at 100 rpm. The samples (5 mL) were withdrawn at predetermined intervals and analyzed after filtration through 0.45-m nylon membrane filters.[15]

Effect of osmotic pressure of dissolution medium

The release of the efonidipine was influenced by the differences in the osmotic pressure of the solutions on each side of the semipermeable membrane. As a result, release experiments were conducted using dissolution media that had different osmotic pressures. Drug release tests for the improved targeted formulation (TF) using the previously described protocol were conducted.[16]

Effect of agitation

Dissolution tests were conducted to investigate how agitational intensity affected the release of efonidipine. The drug release experiments of the target formulation were conducted as previously described methods but with continuous stirring in the first set. The dissolution in the second set was periodically stopped and stirred (during the same run).[17]

High-performance liquid chromatography (HPLC) analysis

Efonidipine was determined by HPLC analysis utilizing an automated sample injector and a Waters HPLC Alliance 2695 with a 996 PDA detector. The output signal was monitored and integrated using Empower 3 software. The chromatographic analysis was carried out in an isocratic mode using Waters Symmetry C18 reverse phase column (150 mm × 4.6 mm, 5.0 µm). The detection of the compounds was monitored at 330 nm. The optimized mobile phase composition was acetonitrile: KH_2PO_4 (65:35,v/v) at a flow rate of 1.0 mL/min. Detection was performed at 330 nm using a PDA detector.

Scanning electron microscopy (SEM) studies

The surface of coated tablets, both before and after dissolution studies, was studied using SEM. The samples were placed on a spherical brass stub (12 mm diameter) with a double-backed adhesive tape. The tablets (coated tablets before dissolution studies) were mounted as such on the specimen stub. On the other hand, small sample of the coating membrane was carefully cut from the exhausted shells (after 24 h of dissolution studies) and dried at 50°C for 12 h. The mounted samples were sputter coated for 5–10 min with gold using fine coat ion sputter (JFC-1100, Jeol, Japan) and examined under SEM (JSM-6100, Jeol, Japan).[15-17]

Drug release kinetics

The target formulation followed zero-order kinetics with an R^2 value of 0.9821.[18]

Prediction of *in vivo* performance

This project is approved by the Institutional Animal Ethics Committee (IAEC), India, under registration number 177/PO/RcBi/S/2000/CPCSEA/TBPL/SAPD/001/24 at Teena bio labs, Pvt., Ltd. Bachupally, Hyderabad.

In vivo study was performed to estimate various pharmacokinetic parameters and comparison was made between conventional marketed tablet (Efnocar) and formulated EOP tablet of efonidipine in rabbit plasma using RP HPLC method.

Animals

The study was carried out using adult male Newzealand white rabbits (weight 1.5–2 kg) in four groups of six animals each (n = 6). The animals were housed under standard condition with a 12 h light/dark cycle with free access to water before study.[19]

Recovery study

Efonidipine stock solution (100 µg/mL) was prepared by dissolving 10 mg of efonidipine in acetonitrile, and then, volume was made up to 100 mL with a further quantity of diluent. The stock solution was sonicated for 5 min, and the concentration obtained was 100 µg/mL. Internal standard solution (100 µg/mL) was prepared by dissolving 10 mg of nimodipine in acetonitrile, and then, volume was made up to 100 mL with a further quantity of diluent. The stock solution was sonicated for 5 min, and the concentration obtained was 100 µg/mL.

Then, working solutions were prepared by diluting the stock solution; 100 µL of these serial dilutions were transferred into 1.5 mL Eppendorf tubes and the solvent was evaporated to dryness. 250 µL of plasma, 250 µL of efonidipine, and 250 µL of nimodipine from the spiked solutions were transferred to a set of pre-labeled polypropylene tubes containing 1.5 mL of acetonitrile. The tubes were vortexed for 2 min and finally centrifuged for 5 min at 3200 rpm speed. After the centrifugation, the organic layer was collected and 10 µL was directly injected into HPLC. The concentrations of efonidipine between 50 and 2000 ng/mL were prepared from stock solution and subjected to chromatography to earmark the linearity range, having regression coefficient 0.998.

Administration of tablets and collection of plasma

The rabbits were fasted with water access for 12 h before initiation of study. Group 1 was control group on normal diet for 21 days. Group 2 with oral administration of oral suspension of

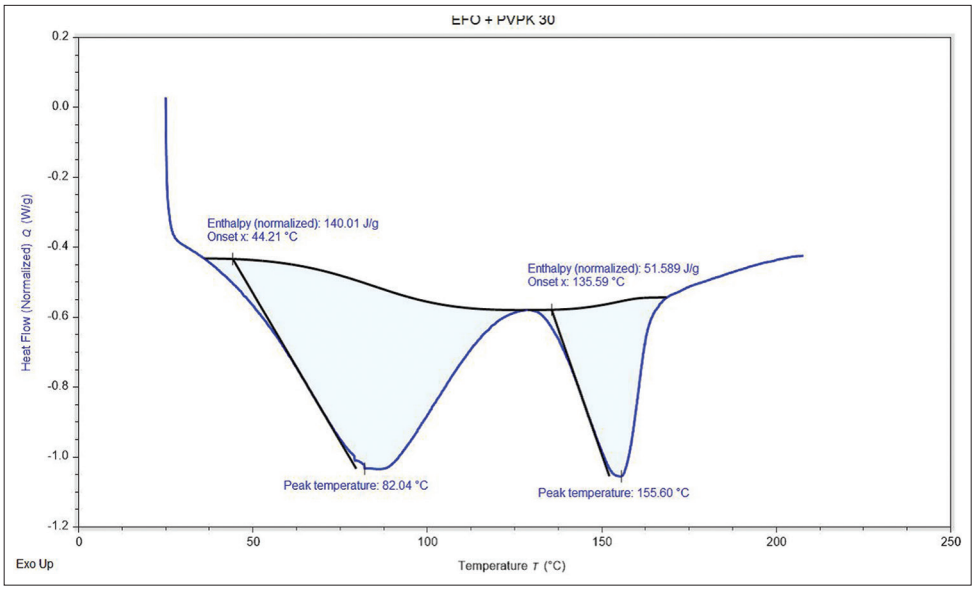

Figure 3: DSC scan of efonidipine+PVPk-30

Table 1: Composition of core tablets of efonidipine

S. No	Ingredients	EF1	EF2	EF3	EF4
	Efonidipine+Pimelic Acid (SD) (mg)	**100**	**100**	**100**	**100**
1	Sodium chloride (mg)	30	50	30	50
2	Mannitol (mg)	60	60	100	100
3	MCC (mg)	263	243	223	203
4	Magnesium chloride (mg)	8	8	8	8
5	Talc (mg)	10	10	10	10
6	SLS (mg)	25	25	25	25
7	PVP K – 30 (isopropyl alcohol)	4	4	4	4
8	Total weight (mg)	500	500	500	500

SLS: Sodium lauryl sulfate, PVP: Polyvinyl pyrrolidone

Table 2: Compositions of coating solution (for EF1 to EF4)

S. No	Coating dispersion ingredients	*a*	*b*	*c*	*d*
1.	Cellulose acetate, g	2.0	2.0	2.0	2.0
2.	PEG 400, mL	0.40	0.60	0.40	0.60
3.	DBP, mL	0.4	0.4	0.6	0.6
4.	Acetone, mL	50	50	50	50

pure drug. Group 3 with oral administration of Efnocar marketed tablet and group 4 with optimized EOP of efonidipine.

The blood samples were withdrawn from marginal ear vein of rabbit through a syringe with 24 gauge needle just before and at 0, 1, 2, 4, 6, 8, 10, and 12, 24, 36 h after dosing. Each time 1 mL of blood was withdrawn.[20,21]

Sample extraction and analytical procedure

The samples were subjected to centrifugation by adding 100 µL of acetonitrile cyclo mix at 8000 rpm for 30 min and the supernatant was collected by using micropipette.

After filtration 20 µL sample was injected into the HPLC system. Non-compartmental method was used for the estimation of pharmacokinetic parameters of Efonidipine Marketed tablet, and Efondipine optimized Formulation, Concentration versus time data. PK parameters were estimated by Thermo Scientific KINETICA 5.2 software.

Statistical Analysis was done with the help of Graph Pad Prism software data was statistically analyzed. For the comparison of PK parameters of test and control samples, paired t-test was used and a value of $P < 0.05$ was considered to be significant. ANOVA was used to determine any differences PK parameters obtained in a group (in six animals).[19]

Table 3: FTIR peaks corresponding to characteristics of the drug alone and excipients alone

S. No.	Functional group	Bands (cm^{-1}) obtained for Efonidipine	Bands (cm^{-1}) obtained in Pimelic acid	Bands (cm^{-1}) obtained in Adipic acid	Bands (cm^{-1}) obtained in Suberic acid
1	CH_2 (aliphatic)	2964	2900	2950	2934
2	Aromatic-NH stretching medium	3180	-	-	-
3	Aromatic CH_3	3070	-	-	-
4	C-N	1219.5	-	-	-
5	NO_2	1456	2900-3000(-OH) bond broadening	-	2530-2867(-OH) bond broadening
6	-C-O-	1347	-	-	-
7	C=O*	1702	1684	1684.2	1689

Table 4: FTIR characteristics peaks of efonidipine with excipients

S. No	Functional group	Bands (cm^{-1}) obtained for Efonidipine	Bands (cm^{-1}) in mixture, Efonidipine+ Pimelic acid	Bands (cm^{-1}) in mixture, Efonidipine +Avicel	Bands (cm^{-1}) in mixture, Efonidipine +Mannitol	Bands (cm^{-1}) in mixture, Efonidipine +Adipic acid	Bands (cm^{-1}) in mixture, Efonidipine+ Suberic acid
1	CH_2 (aliphatic)	2964	2872	2982	2968	2960.7	2932
2	Aromatic-NH	3180	-	3261	3281	3179	3180
3	Aromatic CH_3	3070	-	2982	-	3068	3068
4	C-N	1219.5	1222	1000.2	1219	1219	1291
5	NO_2	1456	1406	1347.1	1419	1419	1406
6	-C-O-	1347	1347	1342	-	-	-
7	C=O*	1702	1654	-	1078	1702.1	1643
Excipient	-	-	2938 (Ar CH)	3273 (OH broad)	3391 (OH)	-	-
	-	-		2932 (ArCH)	2901 (CH)	-	-

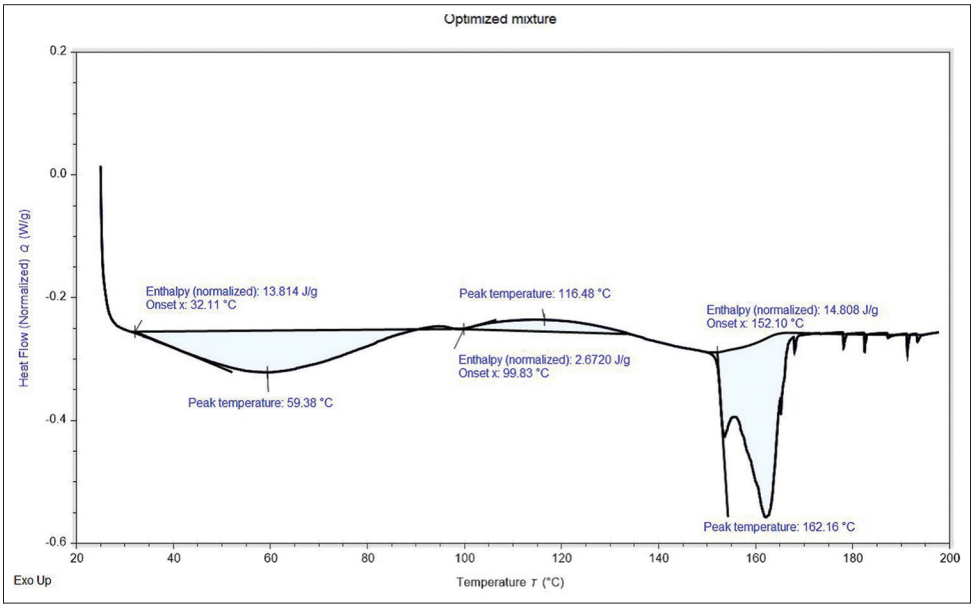

Figure 4: DSC scan of optimized mixture of target formulation

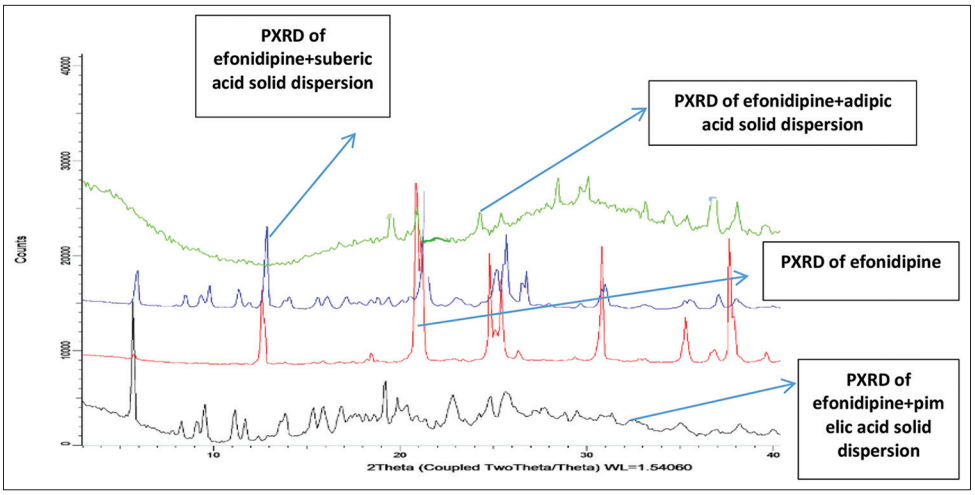

Figure 5: PXRD patterns of pure drug efonidipine and its solid dispersion with co-formers

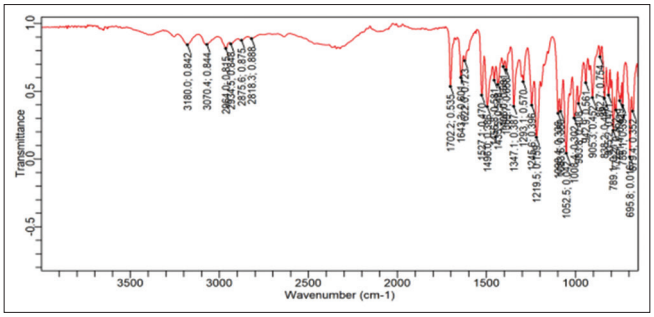

Figure 6: FTIR spectrum efonidipine

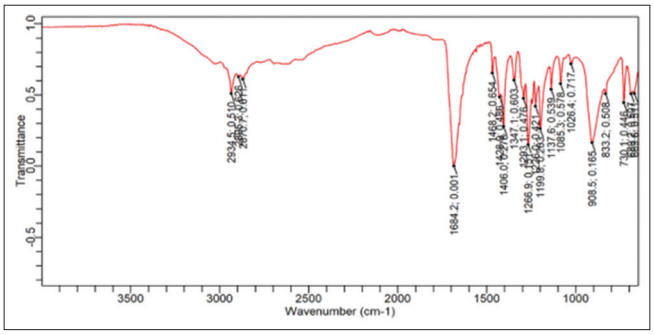

Figure 7: FTIR spectrum pimelic acid

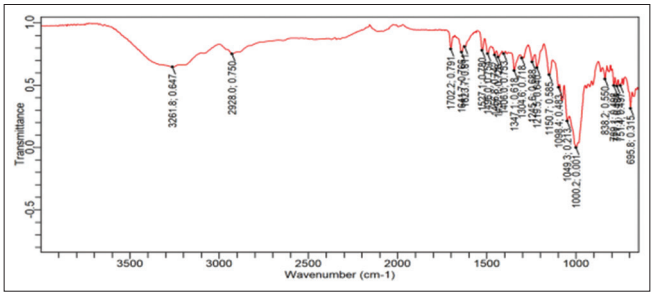

Figure 8: FTIR spectrum efonidipine and pimelic acid

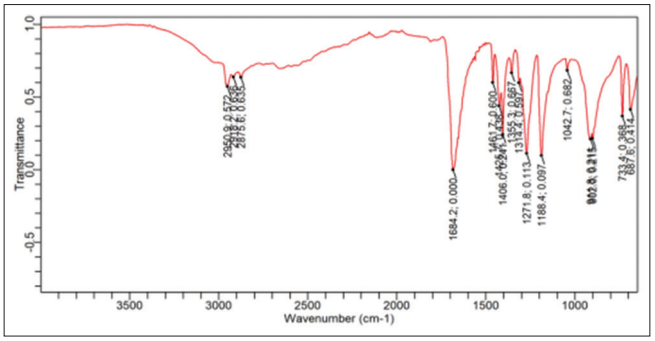

Figure 9: FTIR spectrum of adipic acid

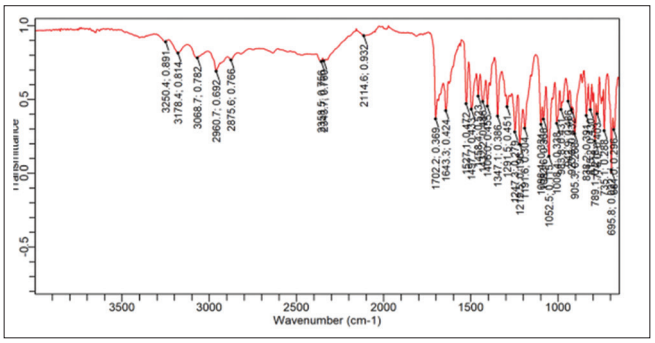

Figure 10: FTIR spectrum of efonidipine and adipic acid

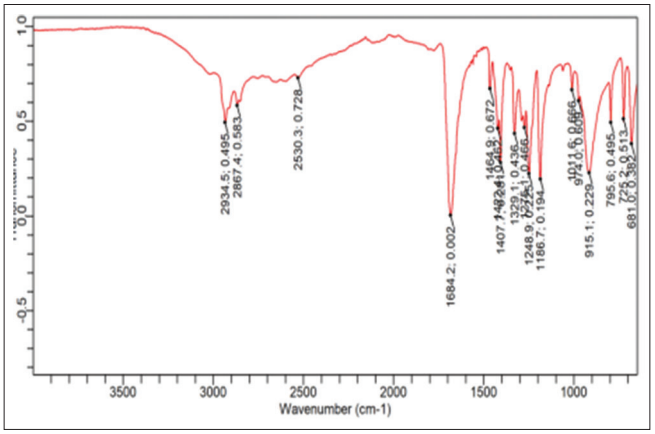

Figure 11: FTIR spectrum of subericacid

Table 5: Characterization of peaks of efonidipine and solid dispersion

2θ value (0)	Peak intensities				
	Efonidipine	SD (Pimelic acid)	SD (adipic acid)	SD (suberic acid)	Inference
21.21	Sharp single peak	The peak is lost	The peak is lost	The intensity was reduced	PXRD lacking peaks demonstrates amorphous nature (might be solid dispersion formed)
30.25	Sharp single peak	Peak is lost	The peak is lost	peak is lost	
38.1	Sharp single peak	peak is lost	The peak is lost	less intense peak	

Table 6: Drug content of efonidipine solid dispersion with co-formers

Formulation code	Drug content (%) AM*±SD		
	Pimelic acid	Adipic acid	Suberic acid
SD1 (1:1)	99.76±0.0927	99.45±0.6571	99.87±0.7781
SD2 (1:2)	100.34±0.067	100.378±0.451	100.21±0.0453
SD3 (1:4)	101.2±0.0934	101.1±0.4322	101.2±0.7681
SD4 (1:8)	102.63±0.087	102.45±0.4891	103.27±0.0466
SD5 (1:12)	103.93±0.458	103.27±0.712	103.63±0.0784

*Each value is an average of three determinations

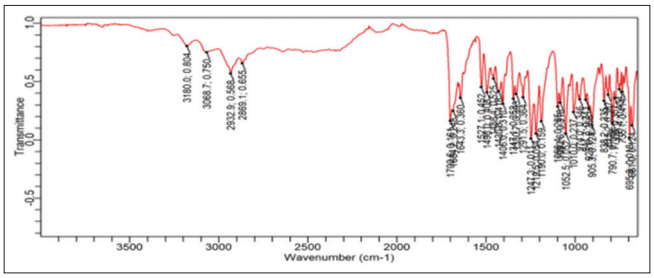

Figure 12: FTIR spectrum efonidipine and suberic acid

RESULTS AND DISCUSSION

Drug-excipient compatibilities

FTIR

The FTIR of efonidipine exhibited the characteristic bands pyridine-, CH_2 (aliphatic), C=O, aromatic NH, and aromatic CH_2, NO_2, etc., are verified for authentication as shown in Table 3 and Figure 6.

FTIR studies indicated that there is compatibility between the drug and substances such as pimelic acid, mannitol, and avicel. The characteristics peaks of major functional groups of the drug efonidipine CH_2 aliphatic (2964 cm^{-1}), CH_3 aromatic (3070 cm^{-1}), CN of amines (1219 cm^{-1}), NO_2 (1456 cm^{-1}) were retained in the physical mixture of drug and excipient with the evidence that the peaks obtained for major functional groups at the same wavenumbers as that of the drug alone as shown in the Table 4 and Figures 7-16.[22]

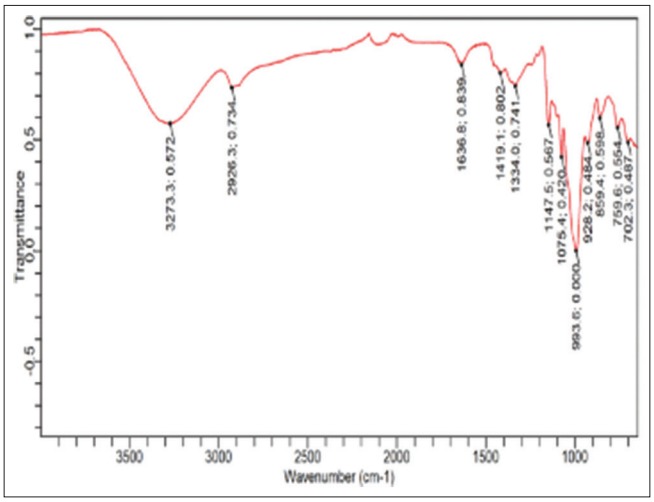

Figure 13: FTIR spectrum of MCC

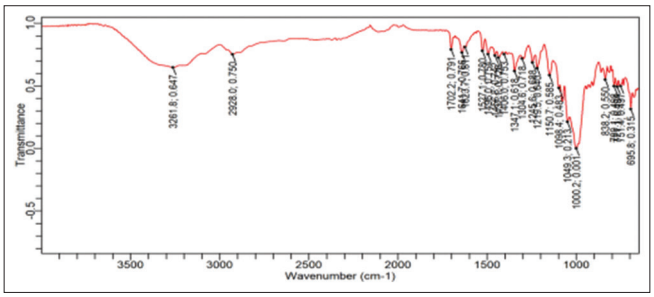

Figure 14: FTIR spectrum of efonidipine with MCC

DSC

Efonidipine pure drug has peak onset: 86.13°C, fusion endotherm: 160°C, NEARER to literature review 156°C.

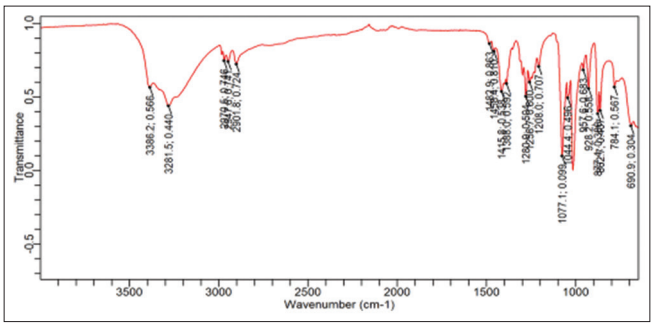

Figure 15: FTIR spectrum of mannitol

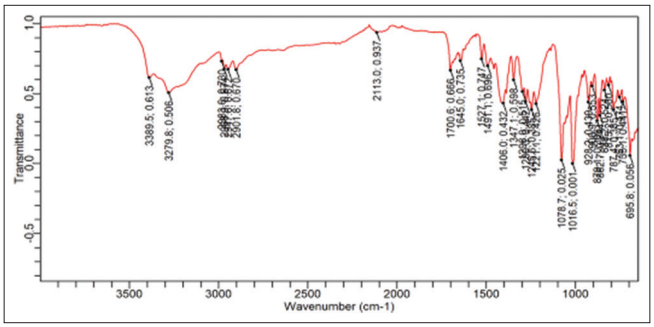

Figure 16: FTIR spectrum of efonidipine and mannitol

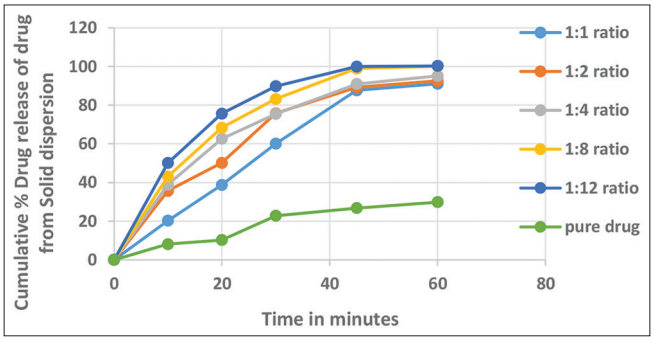

Figure 17: Dissolution graph of efonidipine SD with pimelic acid. *Each value is an average of three determinations

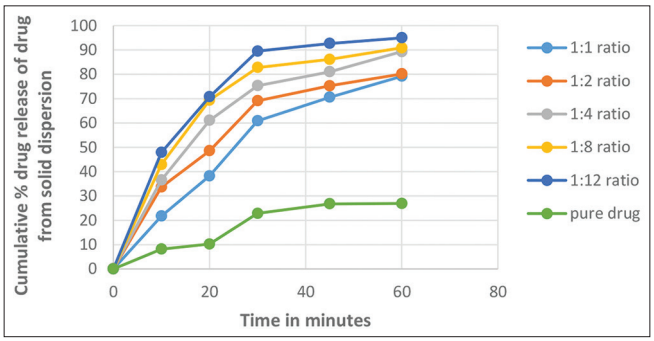

Figure 18: Dissolution graph of efonidipine SD with adipic acid. *Each value is an average of three determinations

Efonidipine and PVPK-30 physical mixture has two peaks, one peak onset is 135.5°C, fusion endotherm is 155.6°C, and the second one has fusion endotherm: 82°C (peak onset 44°C) indicating slight lowering of fusion temperature therefore no interaction between them. Efonidipine and mannitol physical mixture have peak onset at 164.91°C, fusion endotherm: 166.85°C as shown in the Figures 1-4. No lowering of fusion temperature indicates no interaction between them. Efonidipine optimized mixture has peak onset at 152, 32, 99°C and fusion endotherm at 162.16°C, 59°C, 116°C. No lowering of fusion temperature therefore no interaction.[22]

DSC of optimized solid dispersion shows that the endothermic melting peak corresponding to the drug was lost indicating the amorphous nature of the solid dispersion.

PXRD

Efonidipine presents a high crystallinity degree, showing diffraction peaks at following 2θ angles: 12.72; 21.21; 22.45; 23.47; 25.6; 26.61; 30.25; 29.41, 38.1 as shown in Figure 5. In Table 5, the main diffraction peaks observed for efonidipine were absent, indicating amorphous nature of the solid dispersion.[22]

Characterization

Drug content of solid dispersions

The solid dispersions of efonidipine with co-formers were analyzed for efonidipine using methanol. The drug content was within labeled amounts as shown in the Table 6.

In vitro dissolution of solid dispersion

For all the solid dispersions, 80% of drug release in 45 min was chosen and ratio of pure drug release: solid dispersion is calculated for 5 different ratios of solid dispersions. Based on the drug release studies, pimelic acid 1:4 ratio was chosen as the optimized formulation as it has 90.98% drug release at 45 min as shown in the Figures 17-19.

In vitro drug release study of the core tablets

Dissolution profiles of EF1 to EF4 and the release profiles are recorded.

From above Figure 20, EF-1 (A, B, C, D), the release of efonidipine from osmotic pump is not complete (92–94%) with 24 h. No change in drug release as osmogen concentration and plasticizer concentration are increased. It may be due to the solubility problem of efonidipine. No lag time is noticed. In initial 1 h, burst effect (up to 20%) is seen in all cases. Change in the trend is observed at 2 h, which may be due to the changeover of buffer from 0.1 N HCl to phosphate buffer. The efonidipine release is nearly uniform in 0.1 N HCl and in phosphate buffer EF-1 to EF4. Sodium chloride and mannitol are low levels.

From Figure 21, EF2 (A, B, C, D), the release of efonidipine is enhanced marginally from 94% to 97% in 24 h. No lag time is

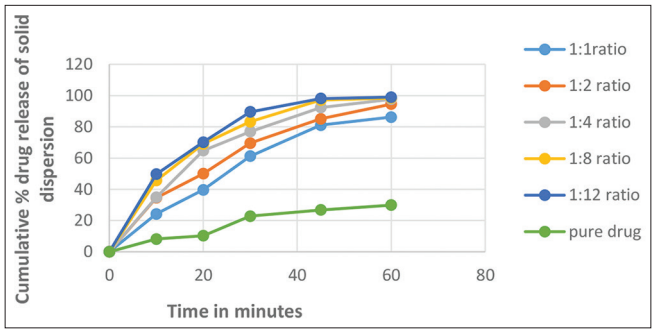

Figure 19: Dissolution graph of efonidipine SD with suberic acid. *Each value is an average of three determinations

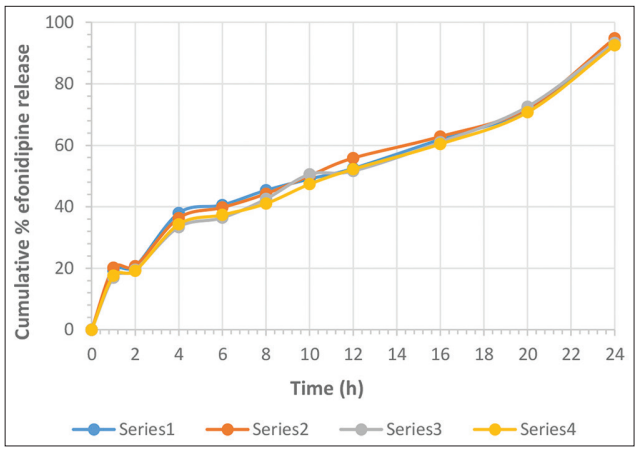

Figure 20: *In vitro* dissolution profile obtained for Efonidipine formulations EF1 A to EF1 D. *Each value is the average of three determinations

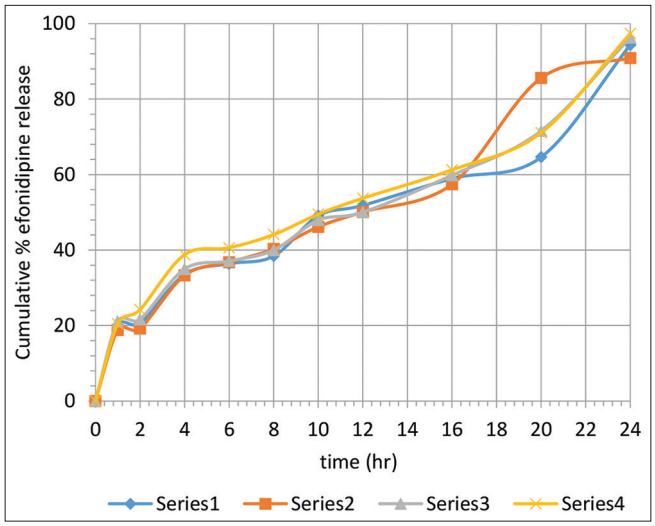

Figure 21: *In vitro* dissolution profile obtained for Efonidipine formulations EF2 A to EF 2 D. *Each value is the average of three determinations

noticed. In initial 1 h, burst effect (up to 20%) is seen in all cases. As plasticizer concentration increased EF2-D, the efonidipine release increased marginally. In the above ABCD formulations, the sodium chloride concentration is high. This must be responsible along with plasticizers to the marginal increase.

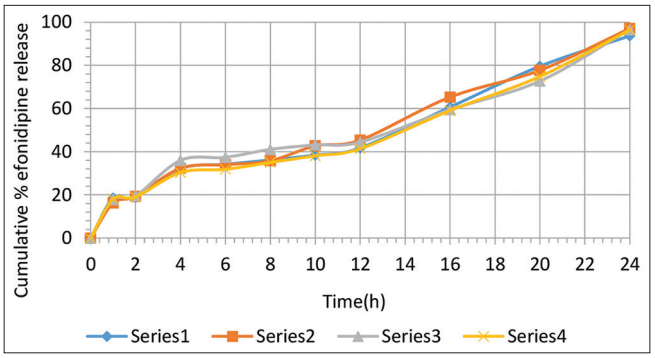

Figure 22: *In vitro* dissolution profile obtained for efonidipine formulations EF3 A to EF3 D. *Each value is the average of three determinations

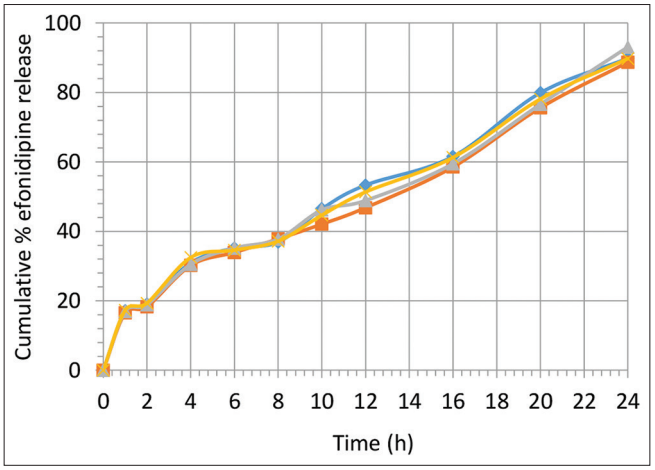

Figure 23: *In vitro* dissolution profile obtained for efonidipine formulations EF4 A to EF 4 D. *Each value is the average of three determinations

From Figure 22, for EF3 (A, B, C, D), the release of efonidipine is enhanced from 93% to 96% in 24 h. EF 3- B is better than others. No lag time, in the initial 1 h, explode effect (up to 18%) is seen in all cases. PEG 400 plasticizer exhibited higher release of efonidipine. There is not that much release because of solubility issue in efonidipine.

From Figure 23, for EF4C (A, B, C, D), the release of efonidipine is enhanced from 93% in 24 h. There is no lag time. In initial 1 h, explode effect (up to 17%) is seen in all cases. PEG 400 plasticizer exhibited higher release of efonidipine. Although osmogen is high in concentration, the release has been decreased.

Optimization

Efonidipine release at 1 h analysis by factorial design

The analysis involved examining the cumulative percentage of efonidipine released after 1 h, and the findings were recorded and coefficients were then recorded using conventional formatting, and Equation (1) was formulated based on the collected data.

Sl No..	sodium chlo...	mannitol	PEG 400	DBP	Estimated Response	Cost	Cost/unit
	30.0	60.0	0.4	0.4			
	50.0	100.0	0.6	0.6			
1	48 ...	40	0.5	0.5	21.3586	0.0	0.0
2							

Figure 24: A random simulation applied to the steepest ascent method for the analysis of drug release at the 1-h mark

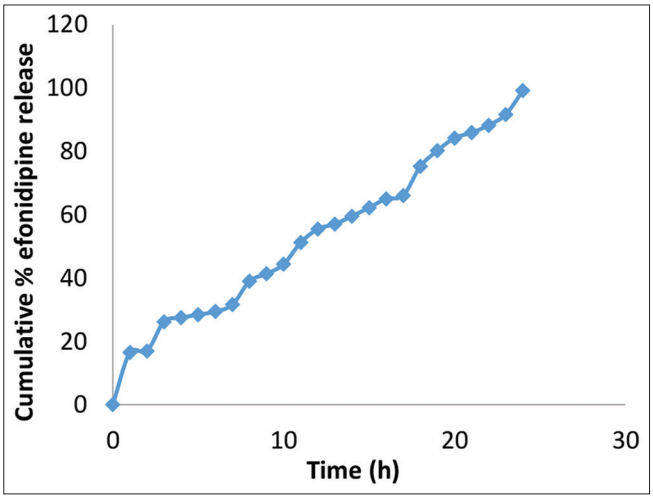

Figure 25: The target formulation's *in vitro* release profile

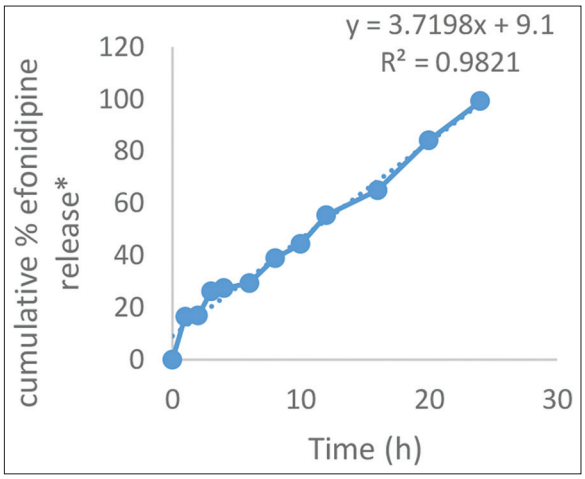

Figure 26: Kinetics at zero order of target formulation dissolution *in vitro* in phosphate buffer at pH 6.8

Efonidipine release equation at 1 h time

From the software analysis, the following polynomial equation was obtained at 1 h. $Y=18.29+0.2262X_1-0.9862X_2-0.5710X_1X_2-0.1662X_3-0.0934X_1X_3-0.1288X_2X_3+0.3238X_1X_2X_3-0.0212X_4+0.4337X_1X_4+0.2462X_2X_4-0.5137X_1X_4+0.2287X_3X_4-0.0387X_1X_3X_4+0.1912X_2X_3X_4-0.1513X_1X_2X_3X_4$

The analysis of the data from Table 7 to the conclusion that an increased SS ratio results in a greater contribution.

The primary factor, Mannitol (b_2), had the most significant impact with a high value of % ss ratio at 45.57%. Notably,

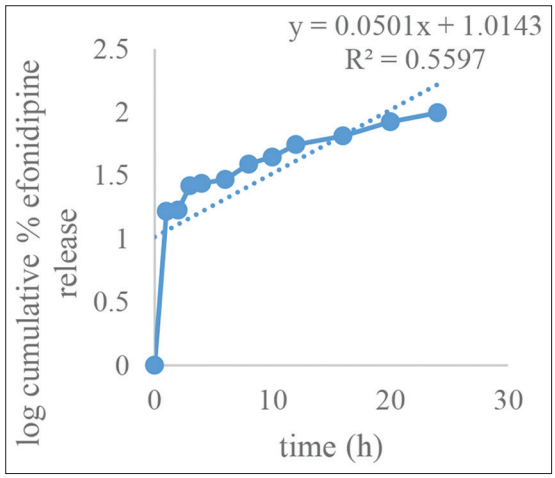

Figure 27: Kinetics at first order of target formulation dissolution *in vitro* in phosphate buffer at pH 6.8

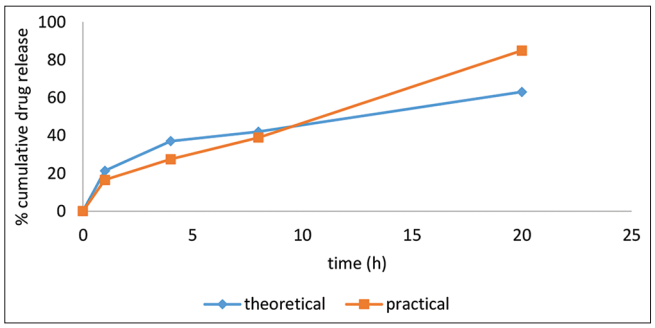

Figure 28: Comparing the *in vitro* dissolving profiles of drugs released theoretically and in practical

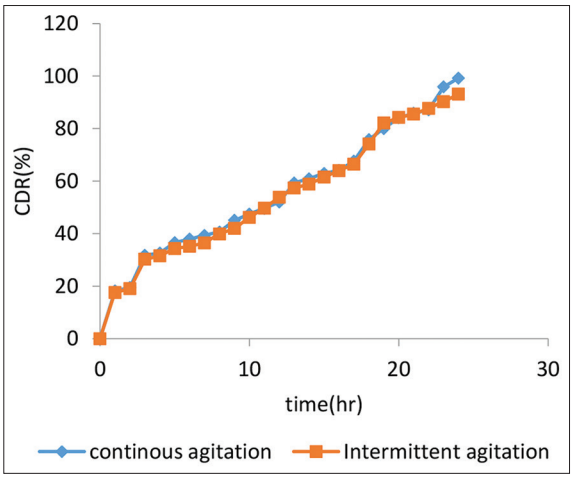

Figure 29: Comparing the *in vitro* dissolving profiles of drugs released with continuous agitation and intermittent agitation

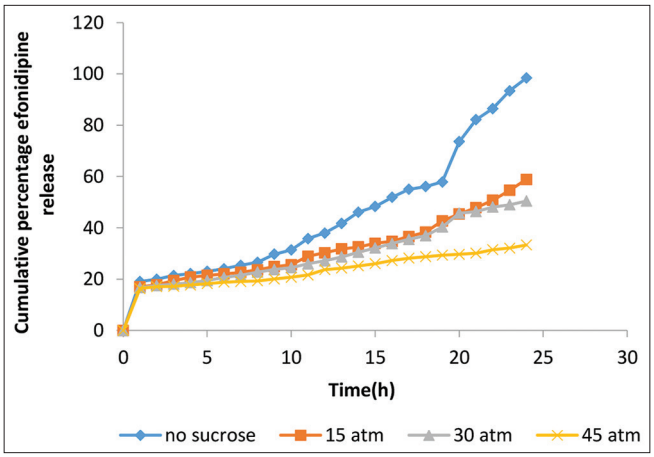

Figure 30: Comparing the *in vitro* dissolving profiles of drugs released in dissolution media having different osmotic pressures

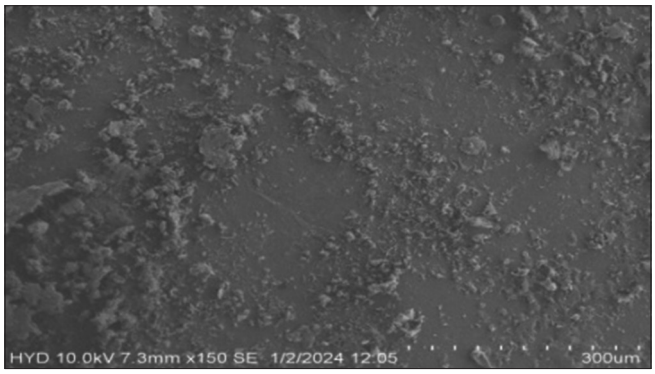

Figure 31: Coating membrane before dissolution

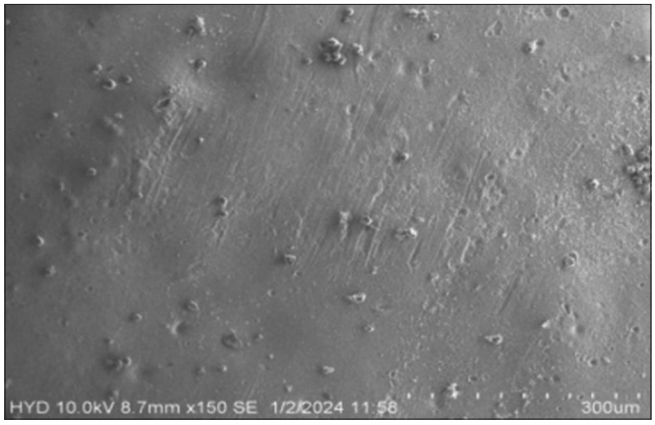

Figure 32: Coating membrane after dissolution

the efonidipine release decreased as the amount of X2 (b2) increased according to the factor's coefficient, which had a negative sign. Regarding the interaction term (b_{12}), it had a % ss ratio of 15.28%, and the coefficient also displayed a negative sign. This suggests that when both factors b_1 and b_2 were increased, the efonidipine release was reduced. Similarly, for the interaction term (b_{124}), the % ss ratio was 12.36%. Once again, the coefficient exhibited a negative sign, implying that higher amounts of factors b_1, b_2, and b_4 collectively led to a decrease in efonidipine release.

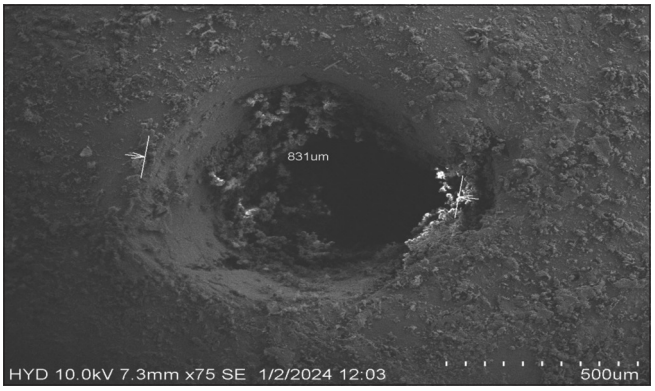

Figure 33: Drilled orifice on the coating membrane (0.83 mm)

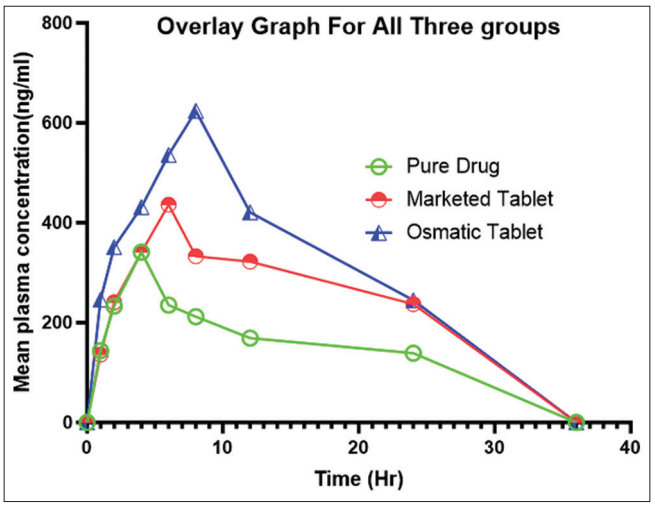

Figure 34: Plasma concentration versus time profile of all three groups. Given data AM±SD (n = 6)

In addition, the analysis involved the observation of simulation and search methods. It was noted that the primary factor, b_2, had a much more significant impact, accounting for approximately 50% of the influence compared to the combined effects of b_1, b_2, and b_4. As a result, the curvature effect was deemed negligible. The steepest ascent approach was used to simulate and optimize the conditions of the theoretical formulation.[23-25]

Method of calculation – simulation

The steepest ascent method was employed with random simulation, and subsequently, with systematic simulation, involving an increase in mannitol concentration by 5 mg while keeping other concentrations constant. The responses were then calculated using the equation, and resulting data are presented in Figure 24.

A decision was reached regarding the ingredient concentrations, resulting in the following finalized amounts: 48 mg of sodium chloride, 40 mg of mannitol, 0.5 mL of PEG 400, and 0.5 mg of DBP. These concentrations were determined to achieve the desired cumulative percentage release of 21.3%. Similarly, for 4 h, 8 h, 20 h, it is being done.

Table 7: Analysis of cumulative %drug release, coefficients, SS ratios

S. No.	Combination	Coefficient	SS ratio(%)
1	b0	18.2913	-
2	b1	0.2262	2.3975
3	b2	−0.9862	**45.5725**
4	b12	−0.5712	**15.2879**
5	b3	−0.1662	1.2943
6	b13	−0.0937	0.4114
7	b23	−0.1288	0.7773
8	b123	0.3238	4.9128
9	b4	−0.0212	0.0211
10	b14	0.4337	8.8136
11	b24	0.2462	2.8402
12	b124	−0.5137	**12.3649**
13	b34	0.2287	2.4508
14	b134	−0.0387	0.0702
15	b234	0.1912	1.713
16	b1234	−0.1513	1.0726

Bold values in the % SS ratio indicates more significant impact on the drug release when compared with that of the other factors.

Table 8: The optimized target efonidipine TF formula

S. No.	Ingredients	Amount per tablet in mg
1.	Efonidipine+Pimelic acid (SD)	100
2.	Sodium chloride	48
3.	Mannitol	40
4.	Avicel pH 101	265
5.	Talc	10
6.	Sodium lauryl sulfate	25
7.	Magnesium stearate	8
8.	PVP K – 30	4
9.	Total	500

Table 9: Coating composition for the target formulations

S. No	Ingredients	Composition
1	Cellulose acetate	2 g
2	PEG 400	0.50 mL
3	Dibutyl phthalate	0.50 mL
4	Acetone	80 mL
5	% weight gain	100%

Target formulation

For the purpose of achieving the desired formulation, the steepest ascent techniques were examined to determine the proper ratios of sodium chloride, mannitol, PEG-400, and DBP. The responses selected for goal formulation are listed in Tables 8 and 9.

Osmotic core tablets were successfully made after that. The criteria for both pre- and post-compression were acceptable.

Post-compression properties of the coated TF were all acceptable.

Efonidipine TF in vitro release study

In vitro drug release studies were carried out in accordance with the procedure described in the materials and methods chapter. Results of the target formulation's TF dissolving investigations are presented in the Figure 25 shows the release profile.

Release kinetics of efonidipine ORS

As shown in the Figures 26 and 27, the results of the kinetic analysis revealed a zero-order release pattern, demonstrated by an R-squared value of 0.9821. This outcome affirms that the current Osmotic Drug Delivery System (ORS) formulation aligns with the principles of controlled drug delivery.

Comparing the *in vitro* dissolving profiles of drugs released theoretical vs practical

From the Figure 28, in vitro dissolution studies were carried out, the theoretical as well as practical values of the percent drug released from the optimised osmotic tabletsdissolution were compared. The similarity factor was calculated, and f2 was found to be 50.

Effect of agitation on efonidipine release

From the Figure 29, it is inferred that continuous agitation was having more efonidipine release when compared to that of intermittent agitation. There was no significant difference observed on the drug release.[23-25]

Effect of osmotic pressure on drug release

From the Figure 30, it is inferred that the results of release studies of optimized formulation in media of different osmotic pressure indicated that the drug release is highly dependent on the osmotic pressure of the release media. The release was inversely related to the osmotic pressure of release media. This finding confirms that the mechanism of drug release is by osmotic pressure. The drug release of efonidipine target formulation was found to be 58.830% drug release at 15 atm, 50.437% for 30 atm, 33.311% for 45 atm and 98.379% for no sucrose or 0 atm, respectively. It is shown in Figure 9.[23-25]

SEM

Figures 31 and 32 depicts the SEM images of the film-coated optimized tablet formulation before and after dissolution. In all the images, the film was found to be intact with the presence of same and uniform morphological structure.

Table 10: Comparative bioavailability parameters of marketed and optimized efonidipine osmotic tablet (Test formulations) and pure drug

PK parameter	Pure drug	Marketed formulation	Optimized formulation	"*t*" test at 0.05
Cmax (ng/mL)	341±17.81	435.67±14.45	645±15.74	Significant
Tmax (Hours)	4.07±0.13	6.21±0.20	8.36±0.22	Significant
t1/2 (h)	4.13±0.30	5.24±0.30	6.5±0.39	Significant
MRT (h)	4.60±0.04	6.52±0.06	7.62±0.19	Significant
Total AUC (ng-h/mL)	237.13±15.61	263.42±15.3	445.86±17.98	Significant
Total AUMC (ng-h/mL)	2798.31±185	4233.96±159	6871.57±215	Significant
Cl (mL/min)	3.59±0.23	2.37±0.09	1.55±0.05	Significant
Kel (h^{-1})	0.26±0.02	0.34±0.02	0.42±0.03	Significant

Furthermore, the tablets obtained after dissolution revealed that the film was found to be intact without any cracks.

The orifice drilled was 831 μm [Figure 33].

Pharmacokinetic study

All the reported pharmacokinetic parameters obtained for both formulations were found. Figure depicts the *in vivo* pharmacokinetic profile of the optimized osmotic pump tablet formulation, marketed formulation (Efnocar), and pure drug. The peak plasma concentration (Cmax) of pure drug efonidipine was 341 ± 17.81 ng/mL and the marketed tablet was found to be 435.67 ± 14.45 ng/mL and 624 ± 15.7 ng/mL for optimized formulation, whereas the time required to reach Cmax (i.e. tmax) was 4.07 ± 0.13h, 6.21 ± 0.20 h, 8.36 ± 0.22 h. The AUC0-t was observed to be 445.86 ± 17.98 ng/mL for optimized and for marketed 263.42 ± 15.3 ng/mL, 237.13 ± 15.61 for pure drug to be statistically significantly ($P < 0.05$). Furthermore, the remarkably higher values of AUC revealed that increase in oral bioavailability of the drug owing to enhanced gastroretention and absorption vis-a`-vis the conventional marketed formulation. The relative bioavailability was 173% when compared with the marketed efnocar tablet as shown in the Table 10 and Figure 34.[19]

CONCLUSION

The results revealed that the prepared EOP is able to deliver more than 95% of EFH at zero-order kinetics up to 24 h. The release of the drug from developed EOP was found to be independent of physiological conditions of gastric lumen and agitational effect. The *in vivo* studies showed a significant increase in the MRT and AUC compared to the marketed tablet indicating a successful development of once-a-day formulation of EFH with enhanced bioavailability.

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REFERENCES

1. Adepu S, Ramakrishna S. Controlled drug delivery systems: Current status and future directions. Molecules 2021;26:5905.
2. Arafat M. Approaches to achieve an oral controlled release drug delivery system using polymers. A recent review. Int J Pharm Pharm Sci 2015;7:16-21.
3. Kunal NP, Tejal AM. A review on oral osmotically driven systems. Int J Pharm Pharm Sci 2013;5:1005-13.
4. Shireen F, Ajitha M, Roshan S. Development of nateglinide modified release dosage form using elementary osmotic pump and push pull osmotic pump methods. Int J Pharm Sci Res 2022;13:891.
5. Mehta TA, Kunal P. Development and optimization of elementary osmotic pump tablet of nicardipine hydrochloride using central composite experimental Design. Int J Drug Dev Res 2013;5:382-95.
6. Theeuwes F. Elementary osmotic pump. J Pharm Sci 1975;64:1987-91.
7. Otsuka M, Maeno Y, Fukami T, Inoue M, Tagami T, Ozeki T. Solid dispersions of efonidipine hydrochloride ethanolate with improved physicochemical and pharmacokinetic properties prepared with microwave treatment. Eur J Pharm Biopharm 2016;108:25-31.
8. Otsuka M, Maeno Y, Fukami T, Inoue M, Tagami T, Ozeki T. Developmental considerations for ethanolates with regard to stability and physicochemical characterization of efonidipine hydrochloride ethanolate. CrystEngComm 2015;17:7430-6.
9. Baman V, Ninama H, Gajre R, Dalwadi M, Upadhyay U. Development and validation of analytical method for estimation of efonidipine, telmisartan and chlorthalidone in synthetic mixture. Int J Creat Res Thoughts 2022;10:379-405.
10. Rajput AS, Jha DK, Gurram S, Devanshi S, Poornima D. RP-HPLC method development and validation for the quantification of Efonidipine hydrochloride in

HME processed solid dispersions. Futur J Pharm Sci 2020;6:1-9.
11. Otsuka M, Maeno Y, Fukami T, Inoue M, Tagami T, Ozeki T. Solid dispersions of efonidipine hydrochloride ethanolate with improved physicochemical and pharmacokinetic properties prepared with microwave treatment. Eur J Pharm Biopharm 2016;108:25-31.
12. Khandagale PM, Bhairav B, Saudagar R. Osmotically controlled drug delivery system-A novel approach. Asian J Res Pharm Sci 2017;7:68-76.
13. Kishan Pavani J, Pavani S, Shravan Kumar Y, Venkatesh A, Madhusudhan Rao Y. Formulation and evaluation of oral elementary osmotic pump tablets of Sumatriptan succinate. Br J Pharm Res 2014;4:1163-73.
14. Cheng X, Gao J, Li J, Cheng G, Zou M, Piao H. *In vitro-in vivo* correlation for solid dispersion of a poorly water-soluble drug efonidipine hydrochloride. AAPS PharmSciTech 2020;21:160.
15. Kumaravelrajan R. Development and evaluation of elementary osmotic pump for the simultaneous delivery of nifedipine and metoprolol tartrate. AJP 2016;10:583-94.
16. Verma RK, Garg S. Development and evaluation of osmotically controlled oral drug delivery system of glipizide. Eur J Pharm Biopharm 2004;57:513-25.
17. Ouyang D, Nie S, Li W, Guo H, Liu H, Pan W. Design and evaluation of compound metformin/glipizide elementary osmotic pump tablets. J Pharm Pharmacol 2005;57:817-20.
18. Sahoo CK, Rao SR, Sudhakar M, Formulation and evaluation of controlled porosity osmotic pump tablets for Zidovudine and Lamivudine combination using fructose as osmogen. J Drug Deliv Ther 2017;7:41-50.
19. Mohamed MI, Al-Mahallawi AM, Awadalla SM. Development and optimization of osmotically controlled drug delivery system for poorly aqueous soluble diacerein to improve its bioavailability. Drug Dev Ind Pharm 2020;46:814-25.
20. Thakkar HP, Pancholi N, Patel CV. Development and evaluation of a once-daily controlled porosity osmotic pump of tapentadol hydrochloride. AAPS PharmSciTech 2016;17:1248-60.
21. Alam N, Beg S, Rizwan M, Ahmad A, Ahmad FJ, Ali A, *et al*. Mucoadhesive elementary osmotic pump tablets of trimetazidine for controlled drug delivery and reduced variability in oral bioavailability. Drug Dev Ind Pharm 2015;41:692-702.
22. Pethappachetty P, Chandira RM, Rajandhran M, Samy DA. Formulation and evaluation for solid lipid microparticles of efonidipine. Asian J Biol Life Sci 2022;11:404-9.
23. Sharma F, Jain H, Kanzariya V, Upadhyay U. Formulation and evaluation of controlled release osmotic tablet of metoprolol succinate. Asian J Pharm Clin Res 2014;7:38-43.
24. Khan ZA, Tripathi R, Mishra B. Design and evaluation of enteric coated microporous osmotic pump tablet (ECMOPT) of quetiapine fumarate for the treatment of psychosis. Acta Pol Pharm 2012;69:1125-36.
25. Kanagale P, Lohray BB, Misra A, Davadra P, Kini R. Formulation and optimization of porous osmotic pump-based controlled release system of oxybutynin. AAPS PharmSciTech 2007;8:E53.

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