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Original Article

OSMOTIC DRUG DELIVERY SYSTEM OF NICORANDIL: DESIGN AND EVALUATION

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ABSTRACT

Objective: The purpose of the current research was to design a nicorandil formulation with controlled drug release using the principles of osmotic pump technology. Nicorandil is a biopharmaceutical classification system (BCS) class 3 drug, having a shorter plasma elimination half-life and bioavailability of 75 to 80%.

M**ethods**: The elementary osmotic pump (EOP) was prepared by coating a cellulose acetate polymer on the prepared core tablet. A 2^4-factorial design was applied to optimize the parameters for the osmotic tablet. A surface orifice was drilled.

Results: Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD) results showed that there was no interaction between drugs and excipients. A 2^4-factorial design was applied to optimize the parameters for the elementary osmotic pump. The optimized batch was characterized for *in vitro* drug release studies, and the effects of pH, osmotic pressure, and agitation intensity were analyzed. All the batches showed a drug release ranging from 90.48% to 98.78% after 12 h. There was no change in the drug release pattern at different pHs and agitation intensities. The drug release was found to decrease with the increasing osmotic pressure of the dissolution medium. The results showed that the amounts of sodium chloride and mannitol were positively affecting the drug release, while the plasticizers PEG400 and DBP were not critical. Scanning electron microscopic studies (SEM) showed the integrity and surface morphology of the coating membrane before and after dissolution. The prepared EOP was found to deliver nicorandil at zero-order for up to 12 h.

Conclusion: Nicorandil was developed successfully as a controlled drug delivery during a 12-hour period, with variables optimized by the use of a 2^4-factorial design.

Keywords: Elementary osmotic pump tablet, Osmogens, Zero-order release, 2^4factorial design, Controlled drug delivery

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INTRODUCTION

A majority of oral controlled drug delivery systems are matrix-type, reservoir-type, or osmotic systems [1, 2]. Osmotic devices use the principle of osmotic pressure and are activated by water permeation through a semipermeable membrane [3, 4]. Several advantages include zero release and avoiding blood drug level fluctuation. The unique advantage is that the drug release doesn't depend on the factors influencing the GIT anatomy and physiology [5]. Several elementary osmotic pumps are demonstrated commercially. The technology of an elementary osmotic pump is easy to fabricate and develop [6]. Different design variations of the drug release of osmotic systems are available, namely push-pull, controlled porosity, burst type, asymmetric membrane, etc. The plasticizers help to modulate the film characteristics and achieve the desired release rate [7, 8].

It was successful to create a 12 h controlled drug delivery system for Nicorandil EOP. A drug containing the appropriate osmogens is compressed into the core tablet to create an EOP. After that, a semi-permeable membrane is applied by coating the core, and a micro-drill hole is created in the membrane. Such a tablet creates a saturated aqueous solution inside of it when it is placed in water because the semi-permeable covering allows water from the surrounding area to be sucked in. As a result, the tablet will have increased volume and hydrostatic pressure. Through the orifice, the saturated drug solution exits the osmotic pump. This process keeps going until the drug is completely released or the difference in osmotic pressure between the interior and outside of the tablet is equal [9].

In order to treat coronary heart disease, a new line of medications includes Nicorandil. By activating potassium channels, producing hyperpolarization, and upregulating the enzyme guanyl cyclase [10], nicotinic acid relaxes the muscles of the coronary arteries. Nicorandil is studied for controlled drug delivery [11–13]. The present report describes osmotic drug delivery, another form of controlled delivery. The properties of Nicorandil that support the present proposal (desired properties in parenthesis) are: molecular weight is 211.177 g/mol (<1000 g/mol); log P 0.49 (>0.1); melting point is 93 to 940 °C (<2000 °C) [14]. The plasma elimination half-life is 1.0 h (low) and has a bioavailability of 75 to 80% [15]. It is effectively absorbed by the GIT. It belongs to class 3 of BCS [16]. Further, the dose is low (10 to 20 mg) twice daily. Based on its suitability from the above aspects, Nicorandil was attempted for osmotic drug delivery using the EOP method.

MATERIALS AND METHODS

Materials

The materials and chemicals utilized in this experiment were all of AR or LR grade. Nicorandil was supplied by Aditya Chemicals, Ahmedabad. SD Fine Chem Limited, Mumbai, supplied sodium chloride, mannitol, polyvinyl pyrrolidone K-30 (PVP K-30), PEG 400, DBP, acetone, potassium dihydrogen phosphate, and isopropyl alcohol. Microcrystalline cellulose (MCC) and cellulose acetate were purchased from the suppliers Saraswathi Chemicals, Hyderabad.

Methods

Drug-excipients interactions

FTIR

The physicochemical compatibilities of the drug and its excipients were tested by FTIR spectrometry. FTIR spectra of the drug alone and drug-excipient physical mixtures (1:1 w/w) were derived from an IR Affinity-1, FTIR, Bruker, Japan [17]. The FTIR spectra of pure nicorandil showed peaks at wave numbers (cm-1), which correspond to the functional groups present in the structure of the drug [18].

DSC

Nicorandil pure drug, nicorandil and mannitol, nicorandil and avicel, nicorandil and PVPK-30 were characterized by DSC. Samples of 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 93.06 °C, corresponding to its melting and indicating the crystalline nature and purity of the sample. The DSC thermogram is shown in fig. 4-7, 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.

PXRD

PXRD patterns of the samples were obtained with a Bruker D8 advanced diffractometer based on a two-circle goniometer enclosed in a radiation safety enclosure. The x-ray beam is allowed to fall over the sample. The slide was moved at an angle of theta degrees, proportional to an angle of 2 theta degrees.

Formulation, development, and optimization

The formulation of an elementary osmotic pump is developed in two phases: core formulation and coat formulation, in the same sequence. In both phases, a design is applied for the core formulation and, separately, another 2^2 designs for the coat formulation. A 2^4-factorial design is applied sequentially for optimization. Thus, 16 formulation runs are attempted [19].

Manufacturing of core tablets

In the core phase, 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 (50 and 100 mg) [20]. The other ingredients and their quantities are mentioned, with low variability in MCC (directly compressible vehicles). A total of 4 formulations (FT1 to FT4) are attempted for core tablets. For the study, cumulative percentage drug release is the dependent variable, which is evaluated after coating the core tablets. 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 air stream at 40–50 °C (Remi, Mumbai). 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. 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 cores have been evaluated.

Table 1: Compositions of four core formulations of EOP

S. No.	Ingredients (mg)	FT1	FT2	FT3	FT4
1	Drug	20	20	20	20
2	NaCl	30	50	30	50
3	Mannitol	50	50	100	100
4	MCC	186	166	136	116
5	Magnesium stearate	6	6	6	6
6	Talc	6	6	6	6
7	PVP K–30 (isopropyl alcohol)	2	2	2	2
8	Total weight (mg)	300	300	300	300

Evaluation of core tablets

The physical parameters like hardness, friability, and weight variation were evaluated for the core tablets, which are described in the results and discussion [18].

Formulation of a coating solution

Cellulose acetate polymer is selected for the semipermeable membrane during the coating step [21]. DBP, an oil-soluble plasticizer, and PEG 400, a water-soluble plasticizer, are the two plasticizers (independent variables) that are selected at two levels. Consequently, an optimization attempt was made using a 2^2-factorial design. For every formulation of FT1 through FT4, a total of 4 formulations (A, B, C, and D) were finalized. As a result, 16 batches of tablets were produced.

Process of coating

The initial weight of twenty-five uncoated tablets was recorded. Coating has been done using a mini coating bowl. As part of the factorial design, the coating dispersion was prepared. The coating dispersion of the cellulose acetate, 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 result in sticky and damp films because the material does not dry quickly. The tablet bed is periodically paused when dry air (from the hair dryer) 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 computes the percentage 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 and reported in the results and discussion [21].

***In vitro* nicorandil release and analysis**

Using the dissolution test apparatus 2 USP (paddle type), the *in vitro* nicorandil release of the osmotic pump was examined [22]. After two hours of dissolution in a 0.1N hydrochloric acid solution, the media was changed to phosphate buffer pH 6.8 using a replacement technique. The data and graph cover twelve hours, while the original trials lasted for twenty-four hours. The temperature is±37 0.5 °C, and the speed is 50 rpm. Five-milliliter samples were taken out of an aliquot at different times (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h). Each time, the vessel was filled with the same volume (5 ml) of fresh medium at 37 °C. The samples that were obtained were analyzed at 262 nm using corresponding blank solutions. A cumulative percentage of the release of nicorandil was computed. The experimental data was subjected to regression analysis utilizing MS Statistical Excel tools.

Table 2: Composition of coating solution (For FT1 to FT4 cores)

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)	0.40	0.40	0.60	0.60
4	Acetone (ml)	50.0	50.0	50.0	50.0

Effect of osmotic pressure on the dissolution medium

The release of nicorandil was influenced by the differences in the osmotic pressure of the solutions on each side of the semipermeable membrane [23, 24]. As a result, release experiments were conducted using dissolution media that had different osmotic pressures.

Effects of agitation

The drug release experiments with the target formulation were conducted as previously described, but with continuous stirring in the first set. The dissolution in the second set was periodically stopped and stirred (during the same run) [24].

Release kinetics

Regression analysis of experimental data was performed using MS statistical EXCEL's tools. The description of fitting the equation for zero order is discussed in results and discussion.

RESULTS AND DISCUSSION

Drug-excipient interactions

The melting point of the Nicorandil sample was analyzed using a capillary tube and recorded between 93 and 94 °C (from 92 to 93 °C) [17].

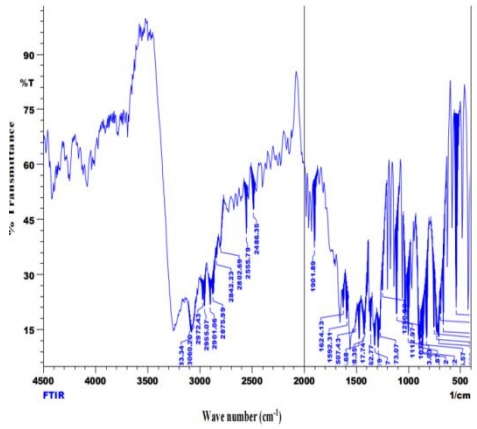

Fig. 1: FTIR spectra of nicorandil

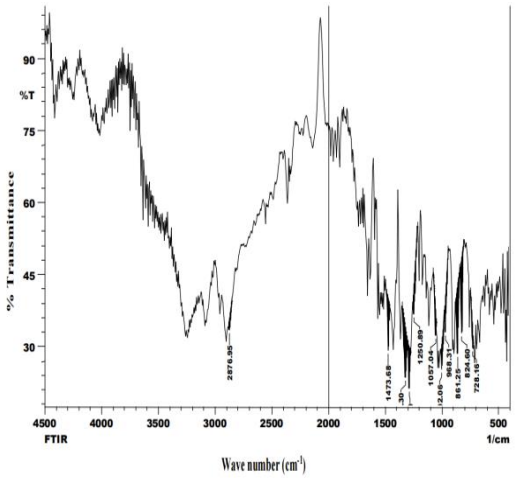

Fig. 2: FTIR spectra of nicorandil, Avicel mixture

FTIR

The FTIR of Nicorandil exhibited the characteristic bands (pyridine-, CH_2(aliphatic), C=O, aromatic NH, aromatic CH_2, etc.) are verified for authentication. The FTIR scans for pure drug and drug-excipient blends are recorded. The spectra have indicated that the characteristic bands are retained, suggesting that excipients are compatible with nicorandil.

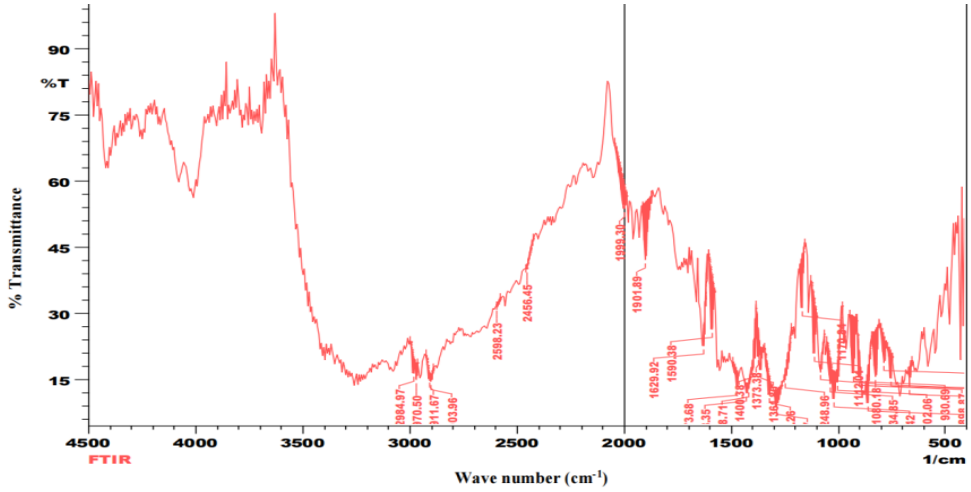

Fig. 3: FTIR spectra of nicorandil and mannitol mixture

Table 3: Characteristics peaks of nicorandil in FT-IR spectrum

S. No.	Functional group	Bands obtained for nicorandil (cm^{-1}	Bands (cm^{-1}) obtained in mixture of drug+mannitol	Bands (cm^{-1}) obtained in mixture of drug+ avicel
1	Pyridine	1592.31	1600	1530
2	CH (aliphatic)2	1362.77	1180	1290
3	C=O (CONH)	1624	1720	1610
4	Aromatic-NH	3500	3650	3450
5	Aromatic-CH2	3072	3000	3020

From table, it was observed that there were no changes in the bands of drug-excipient mixtures as against pure nicorandil, suggesting that there was no incompatibility of excipients with nicorandil [18].

DSC

From the DSC data compiled in the fig. and reported in the table, it was observed that nicorandil showed a sharp characteristic endothermic peak at approximately 93.060 °C, corresponding to its melting transition and indicated crystallinity. Thermograms for all nicorandil excipient physical mixtures indicate that there was no appreciable shift in the melting peak of nicorandil, indicating no possible interaction between the drug and the excipients (fig. 4–7).

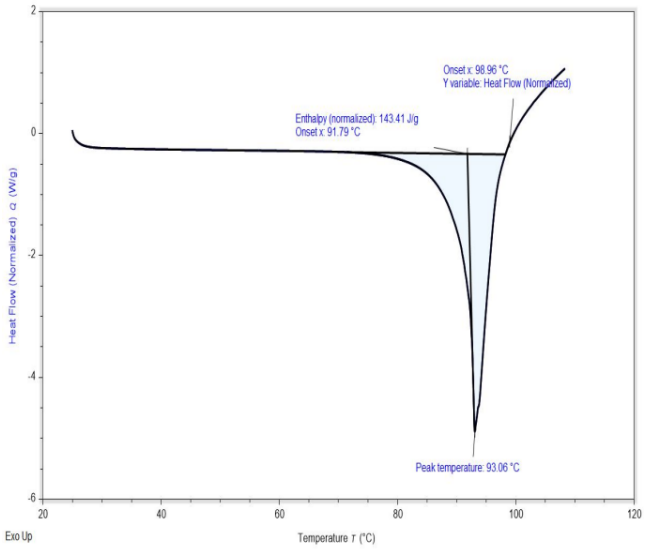

Fig. 4: DSC of pure nicorandil drug

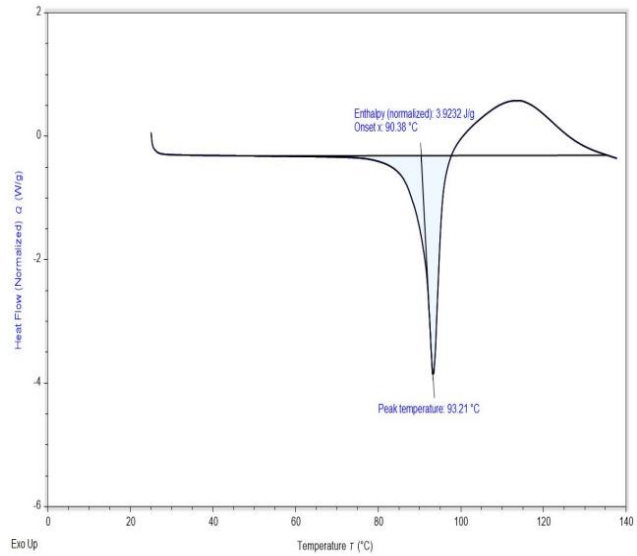

Fig. 5: DSC of nicorandil+mannitol

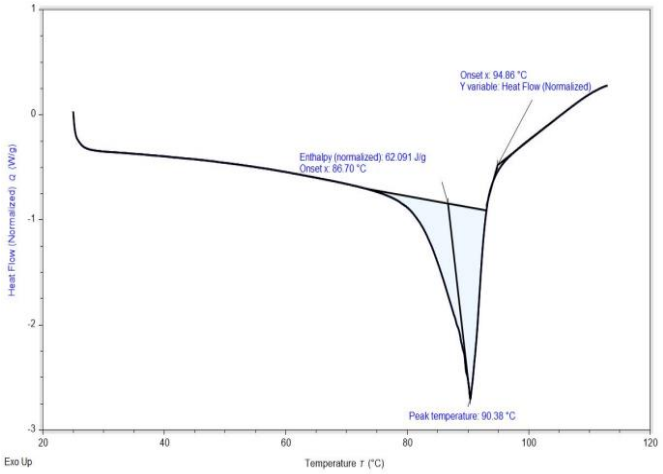

Fig. 6: DSC of nicorandil+Avicel

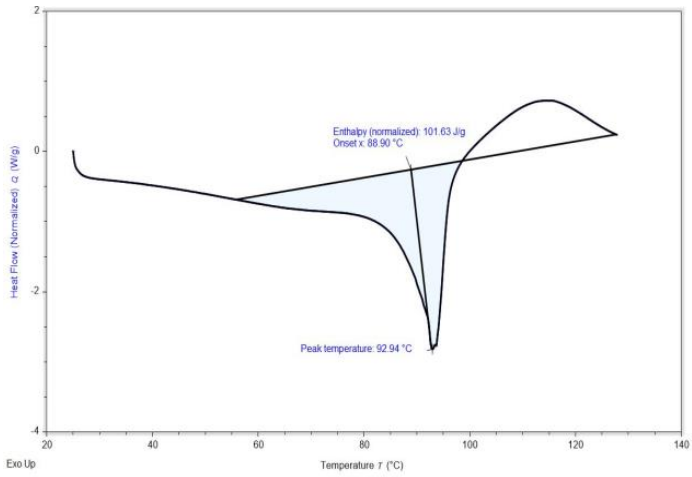

Fig. 7: DSC of nicorandil+PVPK-30

Table 4: DSC comptibility studies of drug nicorandil with excipients

Drug/physical mixture	Peak temperature, °C	Inference
Nicorandil	93.06	Nearer to literature melting point (92-93 °C)
Nicorandil+Mannitol	93.21	No interaction between drug and excipient. Decomposition temperature not observed.
Nicorandil+Avicel	90.38	No interaction between drug and excipient.
Nicorandil+PVPK-30	92.94	No interaction between drug and excipient.

PXRD

Using Cu Kα radiation (λ = 0.15418 nm), diffractograms were produced with a Bruker D8 focus X-ray powder diffractometer. For the test, a 2θ (theta) range of 10° to 80° was used. The distinctive responses of each unique pure component were reflected in the powder X-ray diffraction patterns of the other physical combinations. Additionally, the drug-excipient mixture diffraction patterns (fig. 8-11) revealed essential peaks exhibited by both the API and the excipients alone. Of particular note are the distinctive reflexes at diffraction angles of 2θ = 4.38, 16.27, 25.15, and 29.69° (nicorandil) that confirm the identity of the respective components and show that the excipients are compatible with the drug.

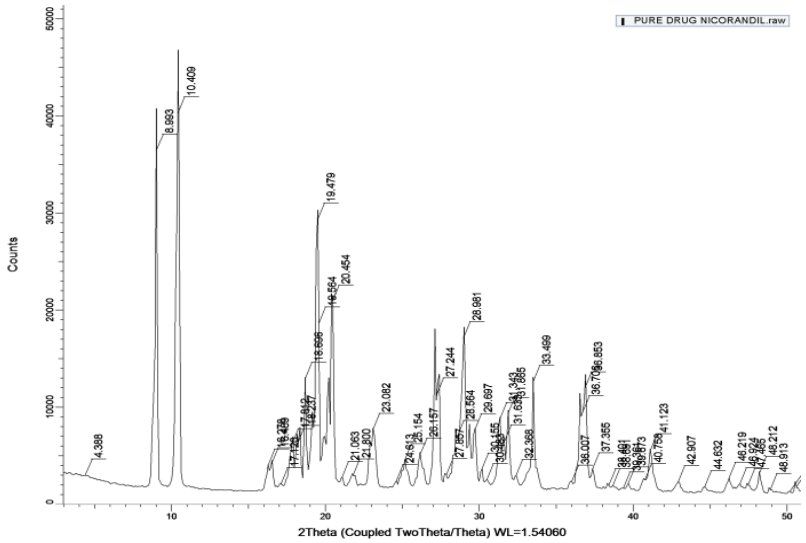

Fig. 8: PXRD patterns of nicorandil

Table 5: Post-compression properties of the core tablets of nicorandil formulations FT1 to FT4

Formulation code	Uniformity of weight (mg)*	Thickness (mm)*	Diameter(mm)*	Hardness (kg/cm)*	Friability (%)	Content uniformity* (%)
FT 1	299±0.19	2.85±0.05	7.13±0.09	5±0.37	0.64	85.2±0.82
FT2	298±0.06	2.84±0.03	7.10±0.02	6±0.22	0.52	90.1±0.53
FT3	302±0.61	2.88±0.02	7.21±0.013	5±0.08	0.6	89.1±0.16
FT4	298±0.54	2.84±0.07	7.10±0.05	4±0.63	0.68	96.7±0.57

*Data given is mean±SD (n=3)

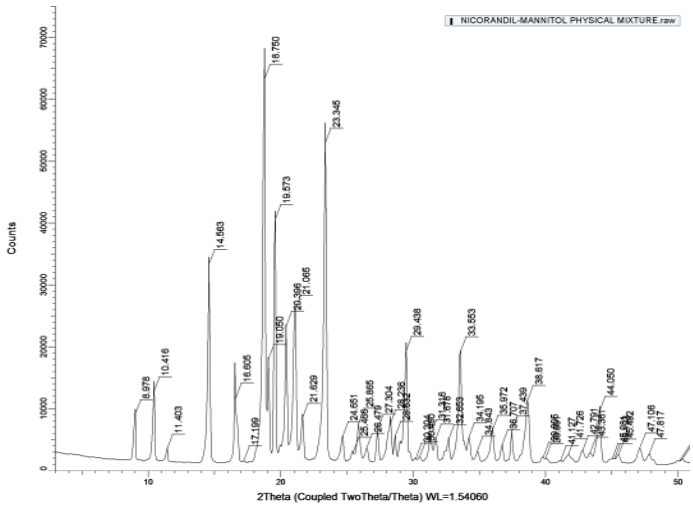

Fig. 9: PXRD patterns of nicorandil+mannitol

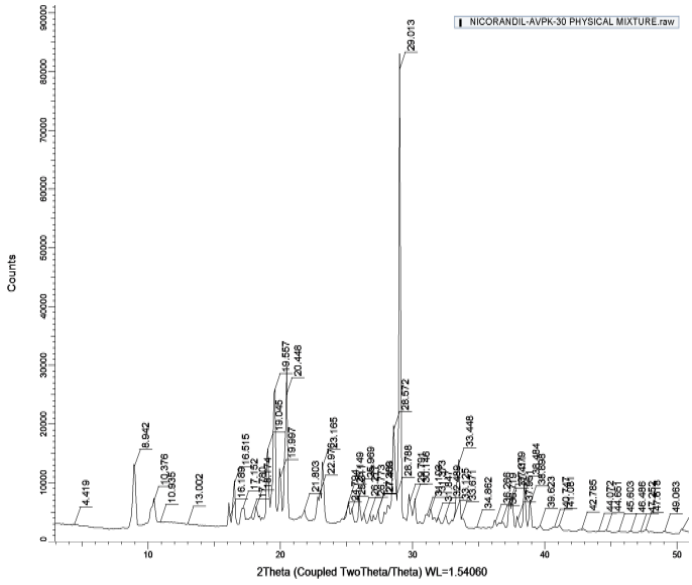

Fig. 10: PXRD patterns of nicorandi+PVPK-30

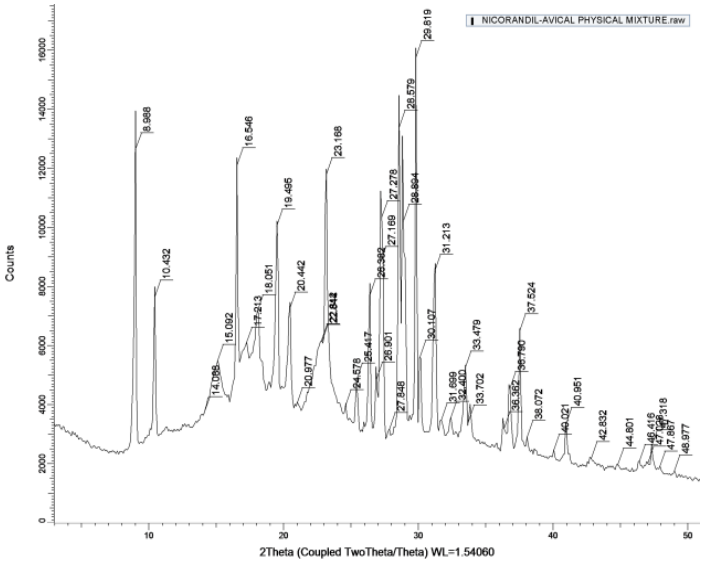

Fig. 10: PXRD patterns of nicorandi+avicel

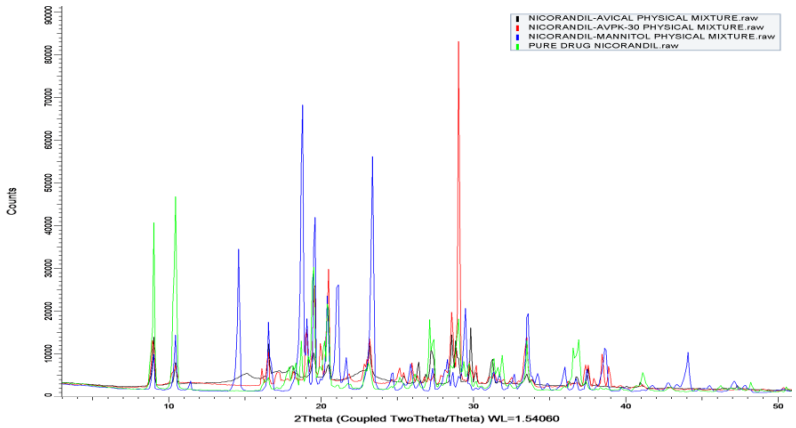

Fig. 12: X-ray powder diffraction patterns of pure components of the present study, namely pure drug nicorandil and mannitol, avicel, PVPK-30 (1:1 *w/w* physical mixtures with nicorandil)

PXRD

For formulations FT1 through FT4, the granules' flow characteristics (pre-compression) were assessed. The Hausner ratio and compressibility index [18] support the observations that the formulations' angle of repose is appreciable, indicating excellent flow. Post-compression characteristics, weight variation, hardness, friability, and content uniformity have been evaluated and documented for the core tablets.

Tablets of similar sizes are consistently produced in terms of thickness and diameter. An extremely low standard deviation has been observed. Less than 5% weight variation has been estimated for a 300-mg tablet. A variation in hardness was observed in the range of 4 to 6 kg/cm2, which indicates good mechanical strength for the tablets. Less than 1% friability for the tablets indicates the test is acceptable and within the limits specified in IP. Based on the above satisfactory results the tablets can proceed further with coating. The variation in the drug content is from 85% to 95%. At this stage of analysis, this is considered satisfactory [18-21].

Coating composition for the above formulations

Four different coating solution compositions (A, B, C, and D) were applied to the core tablets (FT1 to FT4). Coating is kept up until a weight gain of between 6% and 10% occurs. The coating causes a 0.19 mm increase in thickness, a 0.36 mm rise in diameter, and a roughly 26 mg increase in weight; the drug content and hardness remain unchanged.

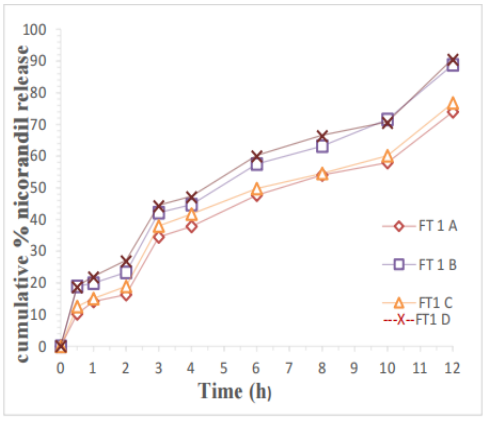

Fig. 13: FT1 Formulations *in vitro* nicorandil release profiles

***In vitro* nicorandil release studies**

The *in vitro* Nicorandil release experiments were first carried out in 0.1N hydrochloric acid for two hours and then, for the remaining time, in pH 6.8 phosphate buffer. Fig. 13 through 16 show the cumulative percentage of the nicorandil release and dissolution-time profiles, respectively, from FT1 to FT4. Nicorandil was almost completely released from all 16 osmotic pump formulations at 12 h, even though the delivery mechanism was designed for 24 h. Examining fig. revealed the absence of lag time, which is often seen in osmotic drug delivery solutions. This is a positive outcome. The zero-order release is anticipated since the trends are linear [23, 24].

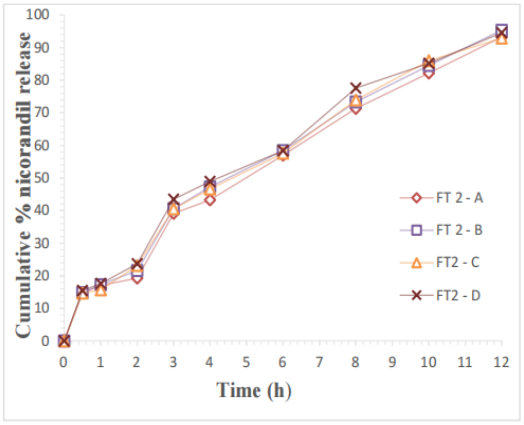

Fig. 14: FT2 formulations *in vitro* nicorandil release profile

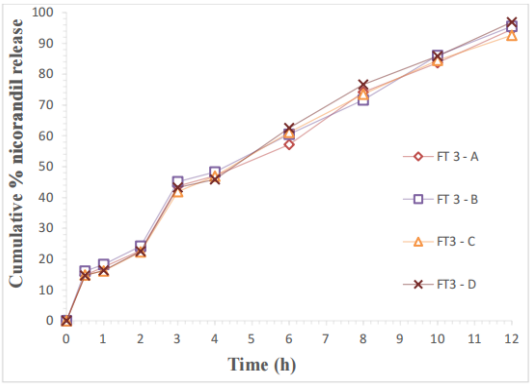

Fig. 15: FT3 formulations *in vitro* nicorandil release profiles

When we consider FT1 formulations (i.e., A to D, wherein osmogens are at low concentrations), differences in the release pattern were observed. Similar differences are visible in FT4 (i.e., A to D, wherein osmogens are at high concentrations). The levels in between them

exhibited nearly the same trends. This suggests that a blend of these osmogens may provide robustness for the release.

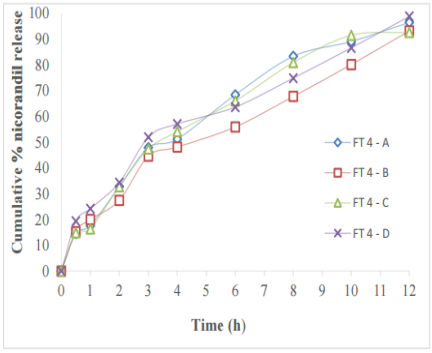

Fig. 16: FT4 formulations *in vitro* nicorandil release profiles

Optimization of formulation for EOP tablets

In this optimization analysis, the response is a single-point cumulative percentage of drug release. But several data points are reported. USP prescribed a 4-point time analysis for metoprolol succinate-controlled delivery for drug release for 24 h. For analytical purposes, four-time study points (30 min, 2 h, 4 h, and 10 h) were identified based on the dissolution-time profiles of Nicorandil (12 h). Consequently, for each of the sixteen formulations, the cumulative percentage of Nicorandil dissolution data was determined and documented. According to SigmaTech's factorial analysis, each response's data set was examined individually [24, 25]. The results are recorded for all time points for 16 formulations.

At 0.5 h analysis, the term X_2 (mannitol) is the main factor (%SS ratio = 26.21), and the second important factor is X_1 (sodium chloride), with a %SS ratio of 24.14. Both are nearly the same. The interaction term X_1X_2 is also important because of the high SS ratio of 36.67. This interaction term is less than the total of individual terms X_1 and X_2 (26.21+24.14 = 50.35). The remaining terms, including X_3 and *X4,* are not significant.

At 2-h analysis, the term X_2 (mannitol) is the main factor (%SS ratio = 35.58), and the second important factor is X_1 (sodium chloride), with a %SS ratio of 22.30. The interaction term X_1X_2 is also relevant because of the high SS ratio of 17.59. This interaction term is less significant. The remaining terms, including X_3 and *X4,* are not significant.

At 4-h analysis, the term X_2 (mannitol) is the main factor (%SS ratio = 34.63), and the second important factor is X_1 (sodium chloride), with a %SS ratio of 28. Both are nearly the same. The interaction term X_1X_2 is less significant because of the low SS ratio of 1.25. The remaining terms, including X_3 and *X4,* are not significant.

At 10-h of analysis, the term X_2 (mannitol) is the main factor (%SS ratio = 33.41), and the second important factor is X_1 (sodium chloride), with a %SS ratio of 30.17. Both are nearly the same. The interaction term X_1X_2 is also relevant because of the high SS ratio of 20.98. This interaction term is less than the total of individual terms X_1 and X_2 (33.41+30.17 = 63.58). The remaining terms, including X_3 and *X4,* are not significant.

The analysis permitted the trends at 4-point analysis, suggesting that the nicorandil release is consistent throughout 12 h. Secondly, the osmogens (e. g., sodium chloride and mannitol) are equally important, and individually, the responses may not be precise. Thirdly, no other factors, X_3 and X_4 (plasticizers, PEG 400, and dibutyl phthalate), are important for the nicorandil release. Plasticizers have a definite role in imparting flexibility to the semipermeable membrane, and these have nothing to do with nicorandil release. The %SS ratio of X_3 (PEG 400) and X_4 (DBP) was influenced to the same extent, confirming that both are required. The combined effect of individual factors is higher than the combined effect of interaction terms. This suggests that there is no curvature effect and that the steepest ascent method can be used for optimization simulation. The present analysis confirmed the release mechanism as osmotic-activated drug release [26].

Target formulation: steepest ascent method

A two-milligram jump in sodium chloride is used in a systematic simulation. It automatically fixes the concentrations of mannitol and other ingredients. Next, using the appropriate equations, responses are calculated. In order to determine the proper concentrations of sodium chloride, mannitol, PEG-400, and dibutyl phthalate for the target formulation at each time point, the steepest ascent method was used. For four timepoints, four formulations are thus analyzed. Sodium chloride (45 mg), mannitol (90 mg), PEG 400 (0.5 ml), and DBP (0.5 ml) form the target formulation. For the above composition, at 0.5 h, the theoretical cumulative % drug release of 22.7%, at 2.0 h, the theoretical cumulative % drug release of 28.05%, at 4.0 h, the theoretical cumulative % drug release of 50.1%, and at 10.0 h, the theoretical cumulative % drug release of 85.01% were analyzed. Each formulation is traded against others, and a final formulation that satisfies all time points is evolved, as the target formulation was given.

Table 6: EOP of optimized formulation

S. No.	Ingredients used in TF	Amount per tablet in mg
1	Nicorandil drug	20.0
2	Sodium chloride	45.0
3	Mannitol	90.0
4	Microcrystalline cellulose (avicel)	131.0
5	Talc	6.0
6	Magnesium stearate	6.0
7	Polyvinylpyrollidone (PVP K–30)	2.0
8	Total	300.0

Table 7: Optimized formulation coating dispersion

S. No.	Coating dispersion ingredients	Composition
1	Cellulose Acetate	2.0 (g)
2	PEG 400	0.50 (ml)
3	DBP	0.50 (ml)
4	Acetone	50.0 (ml)
5	Percent weight gain	6.0–7.50 (%)

Target formulations

The coating of the drug target formulation (TF) core tablets was done using a dispersion as per the composition given. There was a 5% increase in the weight of the tablets after coating the core osmotic pumps. A targeted formulation is evaluated for precompression and post-compression and found satisfactory. The *in vitro* Nicorandil release data are given. The nicorandil release kinetics suggested zero order (R^2 = 0.96). The four decimal places and similarity factor for theoretical and practical values are f2 = 75.

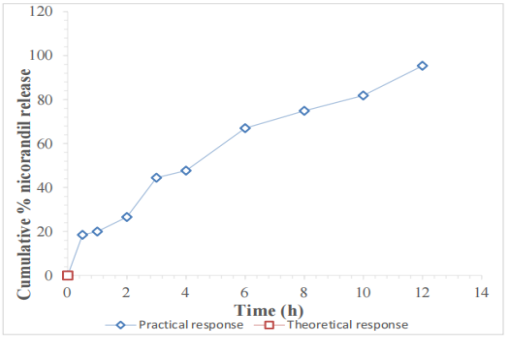

Fig. 17: *In vitro* release profile obtained for target formulation

Effect of the osmotic pressure of the dissolution medium on the nicorandil release

The drug release from the osmotic drug delivery system is controlled by the osmotic pressure. The main driving force behind the Nicorandil release is osmotic pressure differences on either side of the semipermeable membrane. The *in vitro* release studies of Nicorandil are investigated in four dissolution media with four different osmotic pressures. (0 atm) no sucrose, (15 atm) 201.78 g/l of sucrose, (30 atm) 402.6 g/l of sucrose, and (45 atm) 605.34 g/l of sucrose. For formulation, FT3A, dug release studies were conducted using the above media [26]. It can be suggested from the fig. that nicorandil release decreased with an increase in the osmotic pressure of the dissolution medium. According to the osmotic pressure changes, the decrease in drug release is accurate and proportionate (R^2 = 0.975). The findings showed that nothing else is impacting the release of Nicorandil; rather, it is solely caused by osmotic pressure (exerted by osmogens).

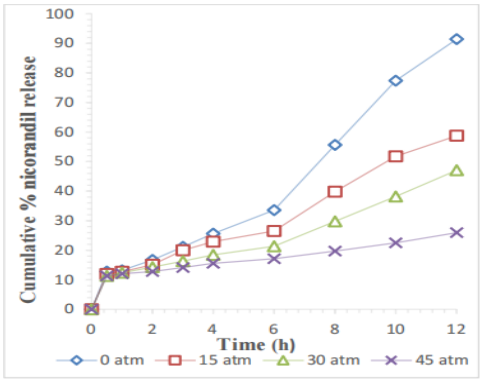

Fig. 18: Drug release profiles Vs. Nicorandil release dissolution media

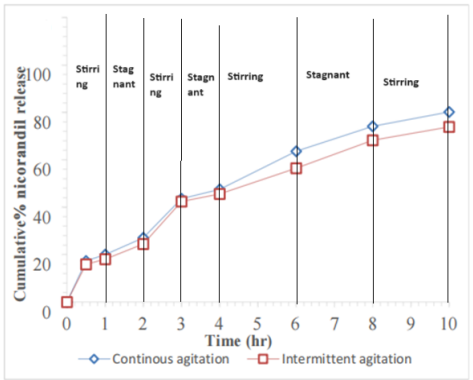

Fig. 19: Effect of mode of agitation on *in vitro* with different osmotic pressure (atm)

Effect of agitation and unstirred dissolution medium on Nicorandil release

Two tests were conducted in order to verify the effect of agitation. In the first experiment, target formulation release studies were conducted continuously at 50 rpm in the USP-II dissolution test apparatus. In the second experiment, the same formulation release studies were done by using intermittent stirring and stopping the stirring. From fig. 19, it was suggested that the nicorandil release was not affected by the agitation and stagnant (unstirred layers) of the dissolution medium [24–26].

Release kinetics

The nicorandil release kinetics of ODDS were determined in a 6.8-pH phosphate buffer. The kinetic analysis suggested zero-order release (R^2 = 0.96). Therefore, the present EOP formulation is in accordance with the principles of controlled drug delivery systems.

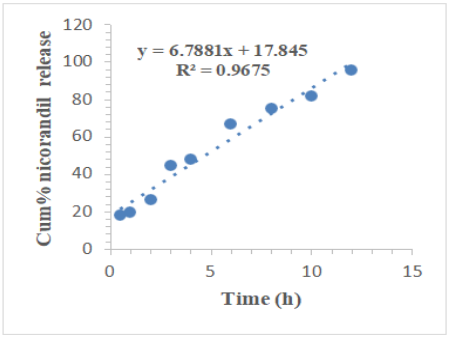

Fig. 20: Zero order kinetics dissolution of TF in phosphate buffer, pH 6.8, data given is mean±SD(n=3)

Surface morphology study

The SEM was used on the surfaces of the target formulation before and after dissolution to analyze the surface morphology of the coated membrane. The integrity of the membrane was the same before and after dissolution.

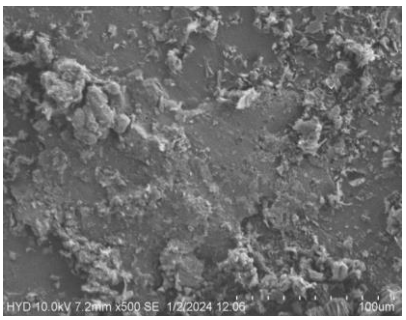

Fig. 21: SEM image of coating membrane membrane before dissolution

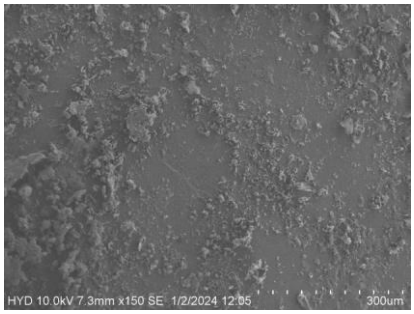

Fig. 22: SEM image of coating after dissolution

CONCLUSION

An elementary osmotic pump comprising a tablet coated with cellulose acetate as a semipermeable membrane containing different levels of plasticizers has been developed for nicorandil by 2^4 factorial design. The release mechanism from the optimized formulation was based on osmotic pressure alone, since the release rate was significantly affected by the osmotic strength of the dissolution medium, directly proportional to the osmogen concentration, but had no significant effect related to the plasticizer concentration. Drug release from the target formulation was found to be independent of pH. Results from a 12 h *in vitro* study on nicorandil dissolution in phosphate buffer with and without agitation support the idea that agitation has no effect on nicorandil release. It may be concluded that the nicorandil elementary osmotic pump may serve as an effective osmotic drug delivery system.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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