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ORIGINAL ARTICLE

Formulation and Evaluation of Enteric Coated Elementary Osmotic Tablets of Aceclofenac

Aseklofenak Enterik Kaplı Elementer Ozmotik Tabletlerin Formülasyonu ve Değerlendirilmesi

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ABSTRACT

Objectives: This study aimed to develop a controlled drug delivery device for aceclofenac, a non-steroidal anti-inflammatory drug. Therefore, the agent was projected to develop an osmotic pump with enteric coating. The strength of the semipermeable membrane was improved by optimizing the formulation of the device, which can control the drug release over a prolonged period of time.

Materials and Methods: The formulations were designed and optimized by using the statistical design of experiment followed by 3^2 factorial design to discover the best formulation. Several evaluation tests were performed to assess the physical parameters of the formulations. The percentage drug release of the formulations was observed for up to 9 h.

Results: The model 3D graph analysis indicated that as an osmogen, a higher percentage of potassium chloride was utilized more effectively than mannitol for the rapid dissolution of osmotic tablets. The optimized formulation can release 88.60±0.02% up to 9 h. The accelerated stability study confirmed that the optimized formulation was stable.

Conclusion: The formulated osmotic tablets of aceclofenac were therapeutically safe and effective and did not release any drug content in the simulated gastric medium for a predetermined time.

Key words: Statistical design of experiment, 3^2 factorial design, 3D graph analysis, osmotic tablet

ÖZ

Amaç: Bu çalışma, bir non-steroidal antienflamatuvar ilaç olan aseklofenakın kontrollü bir ilaç verme cihazını formüle etmeyi hedeflemiştir. Bu amaçla, enterik kaplamalı bir ozmotik pompa geliştirmesi öngörülmüştür. Yarı geçirgen zarın kuvveti ilacın uzun bir süre boyunca salımını kontrol edebilen cihazın formülasyonunu optimize ederek geliştirilmiştir.

Gereç ve Yöntemler: Formülasyonlar, en iyi formülasyonu bulmak için deneyin istatistiksel tasarımı ve ardından 3^2 faktörlü tasarım kullanılarak tasarlanmış ve optimize edilmiştir. Formülasyonların fiziksel parametrelerini değerlendirmek için çeşitli değerlendirme testleri yapılmıştır. Formülasyonların yüzde ilaç salımı 9 saate kadar gözlenmiştir.

Bulgular: Model 3D grafik analizi, ozmotik tabletlerin hızlı çözünmesi için bir ozmojen olarak mannitolden daha yüksek bir potasyum klorür yüzdesinin daha etkili bir şekilde kullanıldığını göstermiştir. Optimize edilmiş formülasyon, 9 saate kadar ilacın 88,60±%0,02'sini salabilmektedir. Hızlandırılmış stabilite çalışması, optimize edilmiş formülasyonun stabil olduğunu doğrulamıştır.

Sonuç: Aseklofenakın formüle edilmiş ozmotik tabletleri terapötik olarak güvenli ve etkili bulunmuş ve önceden belirlenmiş bir süre boyunca simüle edilmiş gastrik ortamda herhangi bir ilaç içeriği salmamıştır.

Anahtar kelimeler: Deneyin istatistiksel tasarımı, 3^2 faktör tasarımı, 3D grafik analizi, ozmotik tablet

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INTRODUCTION

Drug delivery refers to the methods, formulations, skills, and systems for carrying drug substances in the human body used to attain the desired therapeutic outcomes safely.[1] Novel drug delivery systems can diminish the related difficulties by improving the efficacy, safety, product shelf life, and patient compliance.[2] Ideal oral drug delivery systems uninterruptedly convey a measurable and duplicable amount of drugs over a prolonged period. Controlled release dosage form include systems that can furnish a drug for its absorption at zero-order magnitude.[3,4]

The osmotic drug delivery systems utilized for controlled delivery of drugs are now well recognized in human and veterinary medication.[5] Osmotically controlled oral drug delivery systems apply osmotic pressure, which is developed in the system for the controlled delivery of drugs.[6] These osmotic systems can deliver drugs in to a large extent, and the delivery is independent of the physiological factors of the gastrointestinal tract and drug concentration.[7] The drug release from these devices is dependent on the coating thickness of the device, drug's solubility in the core tablet, level of leachable constituents in the coating, and changes in the osmotic pressure across the semipermeable membrane.

Oral osmotic pump tablets became popular for their numerous advantages, such as simple operation, easy formulation, zero-order delivery rate, and reduced dosing frequency with improved patient compliance.[8,9]

Aceclofenac (2-[2-[2-(2,6-dichloroanilino)phenyl]acetyl]oxyacetic acid) is a phenylacetic acid derivative belonging to the category of non-steroidal anti-inflammatory drugs (NSAIDs).[10,11] Aceclofenac inhibits the enzyme cyclo-oxygenase in the body. This enzyme is engaged in the production of prostaglandins, which results in inflammation and pain.[12,13] Aceclofenac can be used as an antirheumatic, anti-inflammatory, and analgesic (effective pain killer for the lower backache and dental). This compound is also used in the treatment of osteoarthritis, rheumatoid arthritis, gynecological pain, and alkylosing spondylitis in an oral dose of 200 mg daily.[14,15] Reduced doses should be used in patients with hepatic impairment.[16,17] Aceclofenac possesses higher antipyretic, analgesic, and anti-inflammatory action than any other NSAIDs, thus achieving better patient compliance.[18]

The long-term use of NSAIDs associated with different treatments causes heart burn, vertigo, hepatic toxicity, epigastric discomfort, dyspepsia, and abdominal pain.[19] However, aceclofenac offers enhanced gastric tolerance compared with indomethacin, naproxen, and diclofenac, which is required for chronic treatment.[18] Aceclofenac is practically insoluble in water and has a molecular weight of 354.19 g/mol, pK_a value of 4.7, partition coefficient of 1.86, and biological half-life of 4 h.[18,20,21] Aceclofenac meets all the criteria for being an ideal drug candidate for designing osmotic drug delivery systems.[8]

Literature survey showed that the marketed products of osmotic tablets for any NSAIDs are unavailable, whereas such type of products are available for antihistamine, anti-hypertensive, anti-diabetic, and anticonvulsant drugs; however, none of these tablets are enteric coated.[8,22] Aceclo, Aceclo SR, Acenac SR, Hifenac, Hifenac SR tablets, etc., are the currently available marketed film-coated preparations of aceclofenac. Hence, this study aimed to formulate enteric coated elementary osmotic tablets of aceclofenac as a NSAID to explore its novel opportunities.

Given that the osmotic tablet was fabricated with enteric coating, any drug content was not released from the osmotic tablet in stomach. Hence, the most common adverse effects and contradictions related to aceclofenac for its gastric impairment can be prevented.

MATERIALS AND METHODS

Aceclofenac and cellulose acetate were purchased from Simson Pharma (Mumbai, India). Micro-crystalline cellulose, mannitol (MANN), polyvinyl pyrrolidone K30, sodium lauryl sulfate, magnesium stearate, talc, and ethyl cellulose were procured from Loba Chemie Pvt. Ltd. (Mumbai, India). Potassium chloride (KCl) was acquired from Merck Specialities Pvt. Ltd. (Mumbai, India). Cellulose acetate phthalate was obtained from Spectrochem Pvt. Ltd. (Mumbai, India). Changshu Hongsheng Fine Chemicals (Changshu City) provided the ethanol. Acetone and methanol were supplied by Qualigens Fine Chemicals (Mumbai, India). All the chemicals, reagents, and solvents used were of analytical grade. Hifenac Tablets (100 mg) were obtained from a retail pharmacy store.

Statistical analysis by design of experiment (DOE)

It can be only attained by a statistical approach that supports the optimization of the product within a defined range.[23] Using the Design-Expert software, enteric coated osmotic tablets were developed and optimized. The statistical design used for the formulation development and optimization was proceeded by 3^2 factorial design.

Two factors were selected considering three levels of concentration. Two osmogens, namely, MANN and KCl (Table 1), were mixed at different ratios in accordance with the design requirement to produce nine formulations (Table 2). The rationality for osmogen selection was aimed at the development of a composition comprising high and low osmotic pressures. Literature had reported sodium chloride, KCl, and MANN are the most commonly used osmogens.[22] Sodium chloride was avoided due to its capability to elevate cardiogenic problems.

Table 1. Factors and levels considered for analysis

Levels (mg/tablet)	Factors for osmogens	
	Mannitol	Potassium chloride
Lower (-1)	50 mg	50 mg
Middle (0)	150 mg	150 mg
Upper (+1)	250 mg	250 mg

Drug identification

The drug (aceclofenac) used for this work was identified through several monographic tests and fourier transform infrared spectroscopy (FT-IR) study.

Compatibility of drug with excipients

The compatibility between drug and excipients was checked using a FT-IR spectrophotometer. The spectrum was recorded in the wavelength region of 4000 cm^{-1} to 400 cm^{-1}.

Pre-compression studies

The angle of repose, Carr's index, and Hausner's ratio were determined to access the flow property of the mixed powder blends and granules formed.

Fabrication of core aceclofenac tablets

The core tablets were fabricated by the moist granulation technique. The drug and excipients, apart from talc and magnesium stearate, were separately weighed. The weighed ingredients were methodically triturated in a porcelain mortar. Then, the mixture was passed through a sieve no: 60. Polyvinyl pyrrolidone K30 in warm water as a binder solution was added to the resultant powder to form a coherent mass. Granules were formed by passing the cohesive mass through a 12-mesh screen. The wet granules were then dried at 60˚C-70˚C for about 3 h. The completely dried granules were sieved through a 22-mesh screen to break down the lumps, and uniform, fine particles of granules were obtained. Talc and magnesium stearate were passed through a sieve no: 40 and mixed with the dried granules. The lubricated granules were then compacted into round-shaped core tablets using a single-punch compression machine.[24] Altering the ratio of excipients nine batches (F1-F9) of aceclofenac core tablets were prepared (Table 3).

Table 2. Interaction of the factor levels for formulation development

Formulation code	A: MANN (mg/tablet)	B: KCl (mg/tablet)	Interaction of levels	
			A: MANN	B: KCl
F1	50	50	-1	-1
F2	150	50	0	-1
F3	250	50	+1	-1
F4	50	150	-1	0
F5	150	150	0	0
F6	250	150	+1	0
F7	50	250	-1	+1
F8	150	250	0	+1
F9	250	250	+1	+1

MANN: Mannitol, KCl: Potassium chloride

Designing the coating composition for osmotic tablets

The maximal rupturing time of the coating membrane was determined by combining ethyl cellulose and cellulose acetate in three different ratios. Glycerol was employed as a plasticizer, and ethanol was used as the solvent. The coating solutions were applied to dummy tablet batches.

Optimization of the plasticizer for osmotic tablets

Glycerol was added as a plasticizer to the designated coating solution in various proportions to enhance the flexibility of osmotic device.

Coating of the core aceclofenac tablets

The compressed core tablets were coated using an optimized coating composition (Table 4) with the aid of dip coating technology. After coating, the tablets were dried for about 1-2 h at temperature of 40˚C-50˚C to eliminate the residual solvent.[24]

Designing an orifice

Using an insulin syringe needle (gauge 31 or 0.226 mm or 226 µm), an orifice was fashioned on the surface of each coated tablet.

Enteric coating of the tablets

Using a suitable enteric coating solution of cellulose acetate phthalate (Table 5), the tablets were finally prepared as enteric

Table 3. Composition of core aceclofenac tablets

S. no.	Ingredients	Amount (mg/tablet) present in core formulation								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Aceclofenac	100	100	100	100	100	100	100	100	100
2	Micro-crystalline cellulose	357	257	157	257	157	57	157	57	7
3	Mannitol	50	150	250	50	150	250	50	150	250
4	Potassium chloride	50	50	50	150	150	150	250	250	250
5	Polyvinyl pyrrolidone K30	25	25	25	25	25	25	25	25	25
6	Sodium lauryl sulfate	10	10	10	10	10	10	10	10	10
7	Magnesium stearate	5	5.5	5	4.5	5	5	5	4.5	5
8	Talc	3	2.5	3	3.5	3	3	3	3.5	3
9	Warm water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight (mg)		600	600	600	600	600	600	600	600	650

coated. After the enteric coating of the tablets, they were dried for about 1-1.5 h at a temperature of 50˚C-60˚C to eliminate the residual solvent.

Evaluation of enteric coated elementary osmotic tablets

The formulated tablets were evaluated by performing several tests, such as uniformity of weight, diameter and thickness, hardness, friability, percentage drug content, etc.

In vitro dissolution studies

In vitro dissolution studies of the formulated enteric coated osmotic tablets were carried out using USP type II dissolution apparatus (paddle type). The tablets were placed in the dissolution medium, and the dissolution process was started. Then, 5 mL samples were withdrawn at 0, 30, 60, 90, and 120 min from the dissolution medium containing 0.1 N HCl (pH 1.2), and after completion of 120 min, the tablets were immediately transferred to alkaline medium from the acidic medium. 5 mL samples were withdrawn at 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, and 540 min from the dissolution medium containing phosphate buffer (pH 6.8). After sampling, an equal volume of fresh dissolution medium was replaced each time in the dissolution vessel to maintain the sink condition. The samples were diluted with the respective dissolution medium and filtered through a Whatman filter paper. Small aliquots of the filtrate were obtained in a cuvette, and the absorbance was measured by a ultraviolet-visible spectrophotometer at a wavelength 273.0 nm.[25,26] The percentage cumulative drug release was calculated.

Study of drug release kinetics

To explain the drug release kinetics, we fitted the *in vitro* drug release data of the optimized formulation to different mathematical models, such as zero-order, first order, Korsmeyer-Peppas, Higuchi, and Hixson-Crowell release kinetics.[27-29]

Comparative analysis of drug release with a marketed formulation

This study was performed to compare the drug release profile of the optimized formulation with a controlled release marketed formulation (Hifenac Tablet 100 mg).

Table 4. Composition of coating solution

S. no.	Ingredients	Quantity
1	Ethyl cellulose	3.45 g
2	Cellulose acetate	1.15 g
3	Glycerol	0.75 mL
4	Ethanol	q.s. to 50 mL

Table 5. Composition of the enteric coating solution

S. no.	Ingredients	Quantity
1	Cellulose acetate phthalate	10 g
2	Ethanol:acetone (1:3)	q.s. to 50 mL

Accelerated stability study

Stability studies were performed only for osmotic tablets from the best optimized batch. The osmotic tablets were quarantined and stored at a temperature 40˚C±2˚C and RH 75%±5% for a period of one month. Upon completion of the specific time period, the samples were withdrawn from the storage condition and evaluated for numerous parameters, such as loss on drying, visual appearance, and *in vitro* dissolution study.[30]

Given the limited time, a stability study was employed for a period of one month only. However, future work is projected to carry out 6 months of accelerated and 6 months of long-term analysis for this current study.

This study did not require any approval from the ethics committee nor any other patient informed consent because it did not focus on any clinical parameter nor utilize any human volunteer and animals for research development.

RESULTS AND DISCUSSION

Identification of aceclofenac

A number of monographic tests were performed (Table 6) to assess the identity of aceclofenac. The results obtained from particular tests were compared with the specifications required. All the results matched with their corresponding specifications, thus confirming the identity of aceclofenac.

FT-IR

The identification of aceclofenac and the compatibility study between the drug and excipients were performed using a FT-IR spectrophotometer. Physical compatibility was also checked visually. The results showed that the drug and excipients were physically compatible with each other.

The FT-IR characteristics of aceclofenac are almost identical to the spectra of genuine sample of aceclofenac (Figure 1). By scrutinizing the FT-IR spectra, the physical mixtures of aceclofenac with the different excipients exhibited the existence of aceclofenac characteristics bands at their similar wavenumbers (Figure 2, Table 7). This result specified that the drug was pure, and no chemical interaction occurred between the drug and excipients.

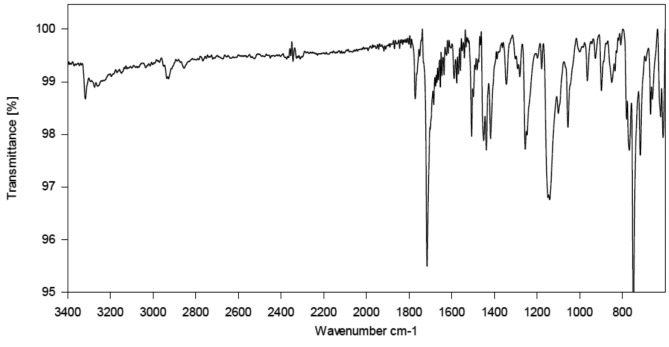

Figure 1. FT-IR spectrum of aceclofenac

FT-IR: Fourier transform infrared spectroscopy

Table 6. Identification of aceclofenac by performing numerous monographic tests

Tests	Expected result	Obtained result
About 10 mg aceclofenac was dissolved in 10 mL ethanol. To 1.0 mL of the solution, 0.2 mL mixture of equal volumes of a 0.6% (w/v) solution of potassium ferricyanide and a 0.9% (w/v) solution of ferric chloride (both were freshly prepared) were added. The resultant solution was allowed to stand and was protected from light for about 5 min. Then, 3.0 mL 1.0% (v/v) solution of hydrochloric acid was added	A blue color will develop, and a precipitate will be formed.	Blue color was developed and a precipitate was formed
Appearance of solution: A 5.0% (w/v) solution of aceclofenac in methanol	Clear	Clear
pH of 1.0% (w/v) solution of aceclofenac	6.5-8.5	7.25
Loss on drying: A total of 1.0 g aceclofenac was dried in a hot-air oven at 105°C for 3 h	Not more than 0.5%	0.4%
Assay: About 0.3 g aceclofenac was weighed accurately and dissolved in 40 mL methanol. The solution was titrated with 0.1 M sodium hydroxide. The end point was determined by the indicator method. A blank titration was also carried out (1 mL 0.1 M sodium hydroxide is equivalent to 0.03542 g aceclofenac)	-	95.21%

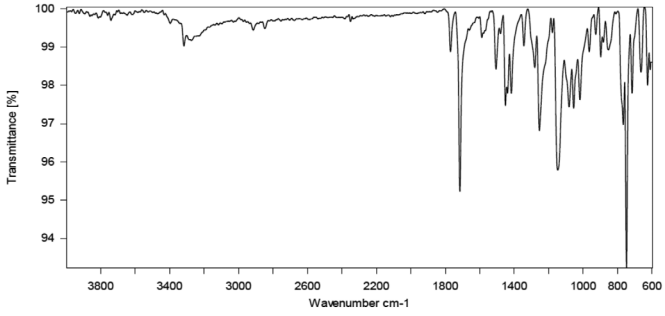

Figure 2. FT-IR spectrum of aceclofenac along with all excipients used
FT-IR: Fourier transform infrared spectroscopy

Table 7. Interpretation of FT-IR spectrum

Wave number of aceclofenac (cm^{-1})	Wave number of aceclofenac along with excipients (cm^{-1})	Interpretation
3317.60	3316.83	O-H stretching
1715.88	1715.49	C=O stretching (aromatic)
1619.84	1588.30	N-H bending
1456.27	1451.05	C-C stretching
1241.26	1253.97	C=C stretching
939.06	923.92	O-H bending

FT-IR: Fourier transform infrared spectroscopy

Pre-compression studies

Pre-compression studies were performed to check the parameters for aceclofenac, mixed powder blends, and granules formed. The results showed that value of all the pre-compression parameters, i.e., Carr's index, Hausner's ratio, and angle of repose were relatively less for granules compared with aceclofenac and powder blends formed (Table 8). Hence, as per the flow property of powders, aceclofenac and mixed powder blends exhibited a good flow property, whereas the formulated granules manifested an excellent flow property.[31,32]

Designing the coating composition of osmotic tablets

Compared with other coating compositions, ethyl cellulose:cellulose acetate (3:1) in solvent ethanol (100 mL) displayed the highest rupturing time of 4.5 h and can tolerate an osmotic pressure for a prolonged period (Table 9). Thus, the C3 coating solution was used in the coating of core aceclofenac tablets.

Optimization of the plasticizer amount for osmotic tablets

The maximum rupturing time of 4 h was determined when 0.75 mL glycerol was used as a plasticizer in the C3 coating solution (Table 10). Glycerol can provide elasticity for expansion and the maximum mechanical strength of the membrane. Thus, 0.75 mL glycerol was added to the optimized coating composition.

Evaluation of enteric coated elementary osmotic tablets

Post-compression parameters

Table 11 shows that the formulated tablets (F1-F8) were almost uniform in their weight, diameter, and thickness. The weight of the core tablets for batch F9 was higher (Table 3) compared with those of F1-F8 batches. Hence, batch F9 was not compared with other batches for these parameters.

The tablets from each batch exhibited adequate hardness and strength to withstand sufficient mechanical shocks during handling in manufacture, packaging, shipping, transport, etc. All the batches contained a satisfactory percentage of drug content in the formulated osmotic tablets (Table 11).

In vitro dissolution studies

The data obtained from *in vitro* dissolution studies (Table 12, 13) showed that any drug content was not released from the osmotic tablets in acidic medium (Figure 3-5). This finding proved the successful demonstration of enteric coating. It helped the device to control its drug release over a prolonged period of time and prevented gastric degradation by aceclofenac.

Table 8. Pre-compression studies of aceclofenac, mixed powder blends, and granules formed

Sample		Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
Aceclofenac		0.625	0.733	14.73	1.16	31.32
Powder blends	F1	0.622	0.730	14.79	1.17	35.44
	F2	0.610	0.718	13.15	1.17	35.10
	F3	0.618	0.722	14.95	1.16	34.21
	F4	0.640	0.731	15.18	1.14	34.08
	F5	0.605	0.711	14.90	1.175	35.80
	F6	0.621	0.742	14.95	1.19	37.21
	F7	0.635	0.750	15.23	1.18	37.01
	F8	0.627	0.734	14.57	1.14	33.90
	F9	0.621	0.755	17.74	1.21	40.09
Granules	F1	0.479	0.534	10.29	1.11	25.43
	F2	0.468	0.522	10.34	1.115	25.48
	F3	0.457	0.519	11.94	1.13	27.40
	F4	0.449	0.508	11.61	1.129	26.92
	F5	0.458	0.520	11.92	1.135	22.65
	F6	0.464	0.531	12.61	1.14	28.54
	F7	0.476	0.530	10.18	1.113	29.45
	F8	0.482	0.541	10.90	1.12	27.65
	F9	0.467	0.532	12.21	1.139	27.96

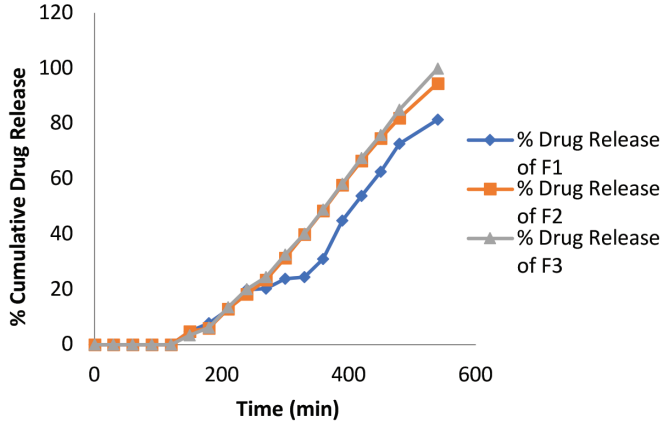

Figure 3. *In vitro* drug release study of osmotic tablets (F1-F3)

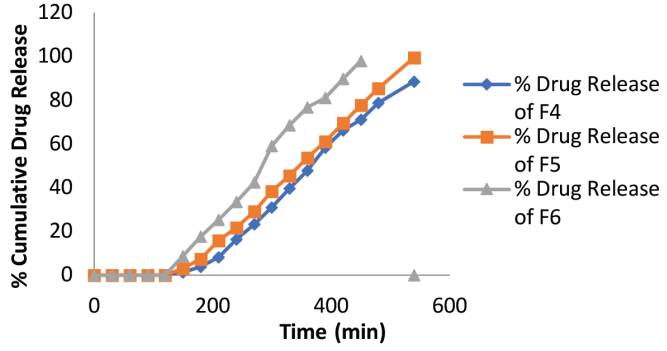

Figure 4. *In vitro* drug release study of osmotic tablets (F4-F6)

Statistical analysis

Statistical analysis by DOE using Design-Expert software

By analyzing the multiple regression analysis equation, dissolution times were reported to be linear type, thus proving that the factors did not interact. The equation obtained is demonstrated below:

Percentage drug release ($T_{80\%}$)= +440.92-46.00×MANN-63.00×KCl.

In the above case of percentage drug release (Table 14), KCl had a more negative effect than MANN. Thus, the increase in the concentration of KCl resulted in the increased time of drug release. On the other hand, MANN had a lesser effect because KCl has a greater osmotic pressure compared with MANN.[22] The drug was forced out of the orifice at a high release rate, reducing the time for 80% drug release ($T_{80\%}$). In this study, the drug release rate was controlled by optimizing the concentration of both osmogens.

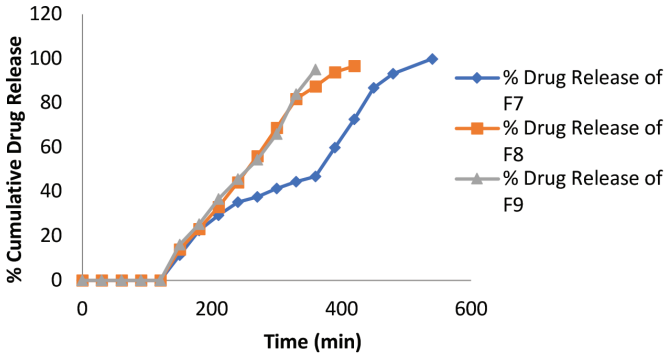

Figure 5. *In vitro* drug release study of osmotic tablets (F7-F9)

Table 9. Optimization of the coating composition

S. no.	Code	Coating materials	Rupturing time
1	C1	Ethyl cellulose:cellulose acetate (1:1) in ethanol	3.5 h
2	C2	Ethyl cellulose:cellulose acetate (1:3) in ethanol	2.0 h
3	C3	Ethyl cellulose:cellulose acetate (3:1) in ethanol	4.5 h

h: Hour

Table 10. Optimization of plasticizer amount

S. no.	Code	Amount of glycerol	Rupturing time
1	P1	0.35 mL	3.0 h
2	P2	0.50 mL	3.5 h
3	P3	0.60 mL	3.5 h
4	P4	0.75 mL	4.0 h
5	P5	0.90 mL	3.5 h

h: Hour

The model 3D graph analysis and contour plot analysis demonstrated that KCl had a greater effect on the dissolution time than MANN (Figure 6, 7). The dissolution time ($T_{80\%}$) was more diminished when the concentration of KCl increased compared with that of MANN. This result proved that the above consideration stated.

During the optimization study, the dissolution time was considered as a reference criterion within the range limits of the maximum and minimum values of dissolution time. The optimized ratio for using osmotic agents (MANN:KCl) was 81.91:111.65 (Figure 8). Among the various formulations, F4 had the ratio nearest to the desirability.

Drug release kinetics study

The drug release kinetics study for the optimized formulation (F4) showed that drug release from the device was independent of the drug concentration, following zero-order kinetics because it had the highest regression value (Figure 9, Table 15). Therefore, the drug release did not depend on the amount

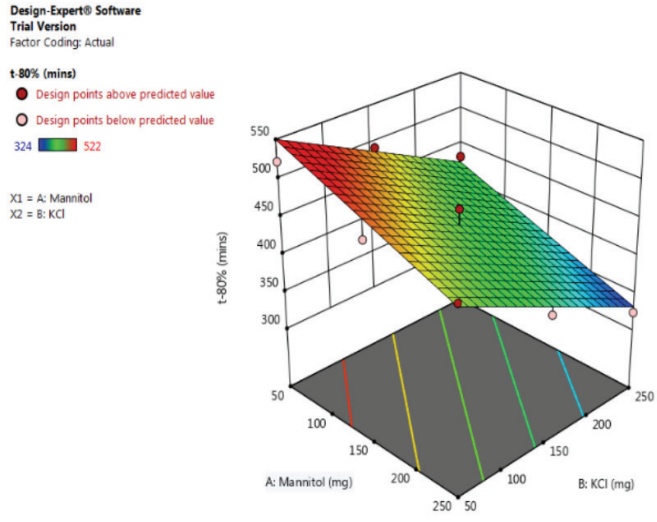

Figure 6. Model 3D graph analysis

Table 11. Post-compressive parameters of formulations

Formulation code	Average weight (mg)[b] ± SD	Diameter (mm)[a] ± SD	Thickness (mm)[a] ± SD	Hardness (kg/cm²)[a] ± SD	Friability (% w/w)[a] ± SD	Drug content (%)[a] ± SD
F1	672±0.05	12.04±0.05	3.11±0.12	5.8±0.14	0.75±0.04	98.58±0.627
F2	675±0.04	12.06±0.04	3.14±0.15	6.0±0.11	0.68±0.07	96.03±0.372
F3	671±0.01	12.00±0.06	3.19±0.11	6.5±0.14	0.52±0.01	99.86±0.672
F4	670±0.03	12.10±0.09	3.30±0.04	6.0±0.12	0.65±0.05	97.55±0.711
F5	671±0.06	12.10±0.03	3.58±0.12	5.9±0.13	0.71±0.06	100.12±0.12
F6	676±0.04	12.01±0.02	3.47±0.06	6.1±0.11	0.64±0.07	94.06±0.185
F7	675±0.10	12.05±0.02	3.28±0.04	6.5±0.13	0.50±0.04	95.16±0.188
F8	673±0.05	12.04±0.04	3.15±0.04	7.0±0.16	0.38±0.01	99.49±0.281
F9	706±0.09	12.07±0.03	3.48±0.02	6.0±0.15	0.65±0.06	98.20±0.418

All values are expressed as mean SD, [a]n=10, [b]n=20, SD: Standard deviation

present in the system, but it was completely dependent on the nature of the delivery device.

Comparative analysis of drug release with a marketed product

Given that the marketed product was film-coated, the drug was also released in an acidic medium (Table 16) which can often cause gastric impairment. The rate of drug release from the optimized formulation (F4) followed a constant linear trend compared with the marketed formulation in which the drug release was initially slow. However, it was superimposed at the later stage (Figure 10). The *in vitro* drug release data of optimized formulation (F4) was more closely fitted to the zero-order release kinetics model compared with the same of the marketed product (Figure 10).

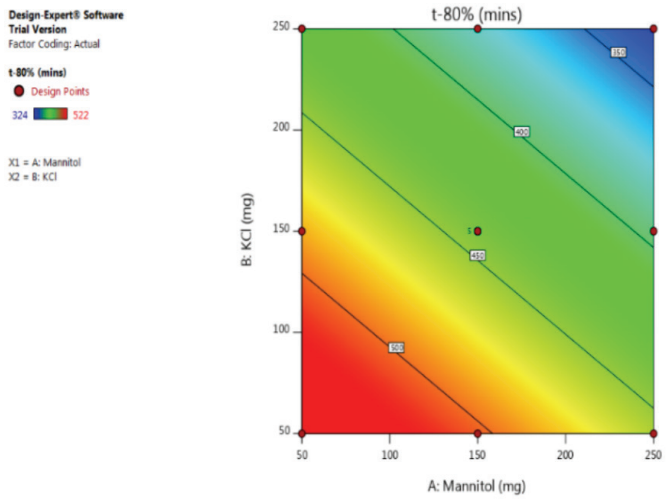

Figure 7. Contour plot analysis

Therefore, the optimized formulation (F4) was comparatively suited for controlled release of drug over a prolonged period of time and better patient compliance.

Accelerated stability study

Any significant degradation was not observed within the specified period in the accelerated stability study employed for the optimized batch (F4) of formulated osmotic tablets (Table 17). The study confirmed about the stability of optimized formulation (F4).

CONCLUSION

The *in vitro* drug release rate from the optimized batch (F4) of formulated osmotic tablets was 88.60%±0.02% in 9 h, and no evidence of drug release the from the device in acidic medium was observed, which justified the primary aim of the present study. The semipermeable membrane developed was extremely flexible and proficient to withstand satisfactory osmotic pressure. Thus, the formulated device

Table 12. Tabulation of % cumulative drug release from *in vitro* dissolution studies (F1-F5)

Dissolution media	Time (min)	Cumulative drug release (%)[a] ± SD				
		F1	F2	F3	F4	F5
0.1 N HCl (pH 1.2)	0	0	0	0	0	0
	30	0	0	0	0	0
	60	0	0	0	0	0
	90	0	0	0	0	0
	120	0	0	0	0	0
Phosphate buffer (pH 6.8)	150	4.84±0.04	4.69±0.05	3.32±0.02	1.19±0.04	3.19±0.01
	180	7.74±0.03	5.96±0.012	6.249±0.02	3.99±0.04	7.55±0.58
	210	12.79±0.04	12.85±0.25	13.56±0.58	8.24±0.27	15.86±0.24
	240	19.90±0.02	18.25±0.02	20.14±0.04	16.35±0.09	21.84±0.08
	270	20.35±0.04	23.40±0.38	24.47±0.04	23.40±0.025	29.17±0.02
	300	23.88±0.04	31.47±0.04	32.50±0.05	30.97±0.47	38.50±0.03
	330	24.47±0.05	39.87±0.05	40.21±0.08	39.76±0.05	45.61±0.01
	360	30.95±0.01	48.53±0.04	48.83±0.07	47.93±0.007	53.83±0.05
	390	44.92±0.02	57.88±0.47	58.12±0.01	58.28±0.02	61.12±0.02
	420	53.79±0.05	66.57±0.02	67.44±0.25	66.17±0.03	69.47±0.04
	450	62.62±0.01	74.69±0.04	75.80±0.03	71.19±0.07	77.86±0.05
	480	72.71±0.02	82.05±0.05	84.91±0.07	78.80±0.07	85.31±0.34
	540	81.40±0.04	94.59±0.25	99.89±0.09	88.60±0.02	99.51±0.14

All values are expressed as mean SD, [a]n=3, SD: Standard deviation

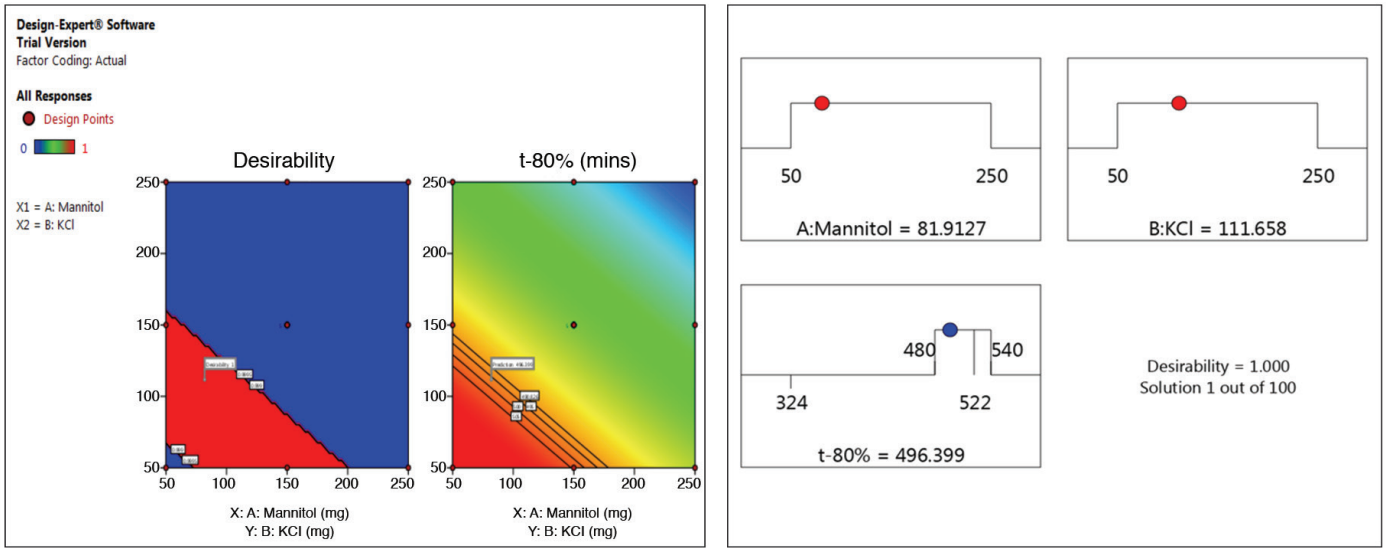

Figure 8. Optimized formulation with maximum desirability and design points

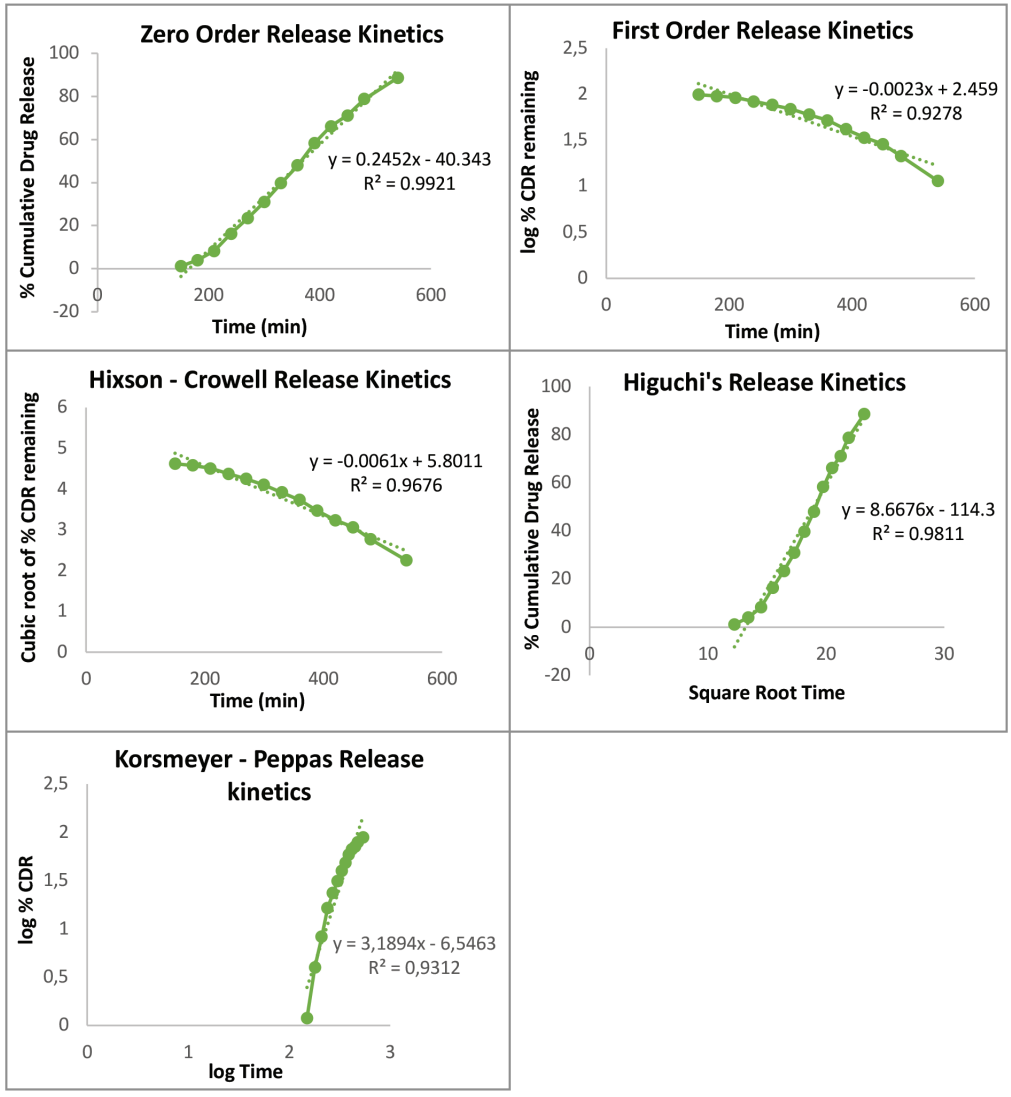

Figure 9. Fitting *in vitro* drug release data of optimized formulation (F4) in different release kinetics models

Table 13. Tabulation of % cumulative drug release from *in vitro* dissolution studies (F6-F9)

Dissolution media	Time (min)	Cumulative drug release (%)[a] ± SD			
		F6	F7	F8	F9
0.1 N HCl (pH 1.2)	0	0	0	0	0
	30	0	0	0	0
	60	0	0	0	0
	90	0	0	0	0
	120	0	0	0	0
Phosphate buffer (pH 6.8)	150	8.65±0.025	11.42±0.25	13.94±0.05	16.08±0.02
	180	17.66±0.07	22.55±0.025	23.28±0.02	25.34±0.27
	210	25.27±0.71	29.32±0.05	33.17±0.04	36.66±0.03
	240	33.53±0.07	35.20±0.05	44.30±0.17	45.75±0.14
	270	42.44±0.07	37.70±0.04	56.21±0.04	54.47±0.05
	300	59.13±0.07	41.33±0.08	68.81±0.02	66.02±0.07
	330	68.57±0.02	44.51±0.87	81.90±0.82	84.05±0.18
	360	76.62±0.02	46.78±0.14	87.47±0.05	95.10±0.24
	390	81.04±0.025	59.89±0.02	94.04±0.002	-
	420	89.77±0.05	72.59±0.58	96.67±0.05	-
	450	98.05±0.08	86.80±0.07	-	-
	480	-	93.25±0.08	-	-
	540	-	99.94±0.02	-	-

All values are expressed as mean SD, [a]n=3, SD: Standard deviation

Table 14. Time required to release a minimum of 80% drug from the formulations

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
$T_{80\%}$ (min)	522	478	462	492	462	384	432	328	324

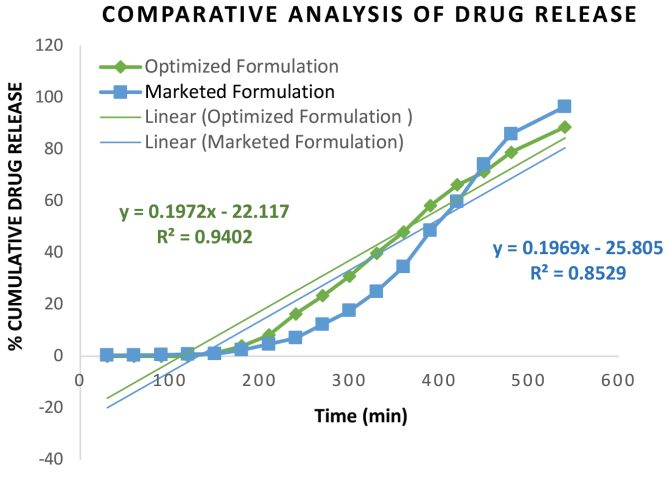

Figure 10. Comparison of drug release between optimized and marketed formulation

Table 15. Drug release kinetics study for optimized formulation (F4)

S. no.	Release kinetics	Regression equation	Regression value (R^2)
1	Zero order	y=0.2452x-40.343	0.9921
2	First order	y=-0.0023x+2.459	0.9278
3	Higuchi	y=8.6676x-114.3	0.9811
4	Korsmeyer-Peppas	y=3.1894x-6.5463	0.9312
5	Hixson-Crowell	y=-0.0061x+5.8011	0.9676

Table 16. Tabulation of % cumulative drug release from the optimized and marketed formulation

Dissolution media	Time (min)	Cumulative drug release (%)[a] ± SD	
		Optimized formulation (F4)	Marketed formulation (Hifenac tablet 100 mg)
0.1 N HCl (pH 1.2)	30	0	0.329±0.06
	60	0	0.397±0.01
	90	0	0.481±0.63
	120	0	0.763±0.72
Phosphate buffer (pH 6.8)	150	1.19±0.04	0.921±0.05
	180	3.99±0.04	2.43±0.07
	210	8.24±0.27	4.60±0.021
	240	16.35±0.09	7.06±0.58
	270	23.40±0.025	12.28±0.84
	300	30.97±0.47	17.61±0.01
	330	39.76±0.05	25.03±0.06
	360	47.93±0.007	34.53±0.05
	390	58.28±0.02	48.51±0.01
	420	66.17±0.03	59.64±0.14
	450	71.19±0.07	74.08±0.08
	480	78.80±0.07	85.88±0.04
	540	88.60±0.02	96.45±0.77

All values are expressed as mean SD, [a]n=3, SD: Standard deviation

Table 17. Accelerated stability study for optimized formulation (F4)

S. no.	Parameters	On 1st day	On 15th day	On 30th day
1	Visual appearance	White round-shaped tablets with smooth surface	White round-shaped tablets with smooth surface	White round-shaped tablets with smooth surface
2	Loss on drying (% w/w)[a] ± SD	0.51±0.04	0.51±0.04	0.52±0.03
3	Microbial or fungal growth	Absent	Absent	Absent
4	Average weight (mg)[b] ± SD	670±0.03	670±0.03	670±0.02
5	Diameter (mg)[b] ± SD	12.10±0.09	12.10±0.09	12.10±0.09
6	Thickness (mg)[b] ± SD	3.30±0.04	3.30±0.04	3.30±0.04
7	Hardness (kg/cm^2)[b] ± SD	6.0±0.12	6.0±0.12	6.0±0.10
8	Friability (% w/w)[b] ± SD	0.65±0.05	0.65±0.05	0.65±0.05
9	Drug content (%)[b] ± SD	97.55±0.711	97.55±0.711	97.55±0.711
10	*In vitro* drug release (%)[a] ± SD up to 9 h	88.60±0.02	88.60±0.02	88.60±0.03

All values are expressed as mean SD, [a]n=3, [b]n=10, SD: Standard deviation, h: Hour

can drug control the release over a prolonged period of time. The model 3D graph analysis engaged for the optimized device proved the greater effectiveness of KCl than MANN as an osmogen.

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