ORIGINAL ARTICLE
DOI: 10.4274/tjps.galenos.2020.03443

Formulation and Evaluation of Enteric Coated Elementary Osmotic Tablets of Aceclofenac

Aseklofenak Enterik Kaplı Elementer Ozmotik Tabletlerin Formülasyonu ve Değerlendirilmesi

Preparation of Osmotic pump

Ozmotik pompanın hazırlanması

Shankhadip Nandi[1*], Ayan Banerjee[2], Kh. Hussan Reza[2]
[1]Department of Pharmaceutics, Gitanjali College of Pharmacy, Lohapur - 731237, West Bengal, India
[2]Department Of Pharmaceutics, Bengal School Of Technology, Chinsurah - 712102, West Bengal, India

Corresponding Author Information
Shankhadip Nandi
shankhadipnandi@gmail.com
9804344736
https://orcid.org/0000-0002-7673-7645
25.05.2020
16.11.2020

ABSTRACT
Objectives: This study was aimed to formulate a controlled drug delivery device of Aceclofenac, an NSAID agent. Therefore, it was projected to develop an osmotic pump with enteric coating. It was planned to improve the strength of the semi-permeable membrane by optimizing the formulation of the device, which can control release of the drug over a prolonged period of time.
Materials and Methods: The formulations were designed and optimized by using Statistical Design of Experiment followed by using 3^2 Factorial Design to discover the best formulation. Several evaluation tests were performed to check physical parameters of the formulations. Percentage drug release of the formulations was observed up to 9 hour.
Results: Model 3D graph analysis directed that as a osmogen, higher percentage of Potassium chloride was utilized more effectively than Mannitol for rapid dissolution of the osmotic tablets. The optimized formulation was capable of releasing the drug up to 88.60±0.02% in 9 hour. Accelerated stability study confirmed that optimized formulation was stable.
Conclusion: The formulated osmotic tablets of Aceclofenac were found to be therapeutically safe and effective, which did not release any drug content in simulated gastric medium for a predetermined time.
Key words: Statistical Design of Experiment, 3^2 Factorial Design, FT-IR: Fourier transform infrared spectroscopy, Osmotic tablet.

ÖZ

Amaç: Bu çalışma, bir NSAID ajanı olan Aceclofenac'ın kontrollü bir ilaç verme cihazını formüle etmeyi amaçlamaktadır. Bu nedenle, enterik kaplamalı bir ozmotik pompa geliştirmesi öngörülmüştür. İlacın uzun bir süre boyunca salımını kontrol edebilen cihazın formülasyonunu optimize ederek yarı geçirgen zarın mukavemetinin iyileştirilmesi planlandı.
Materyaller ve Yöntemler: Formülasyonlar, en iyi formülasyonu keşfetmek için Deneyin İstatistiksel Tasarımı ve ardından 3^2 Faktör Tasarımı kullanılarak tasarlanmış ve optimize edilmiştir. Formülasyonların fiziksel parametrelerini kontrol etmek için birkaç değerlendirme testi yapıldı. Formülasyonların yüzde ilaç salımı 9 saate kadar gözlendi.
Sonuçlar: Model 3D grafik analizi, bir ozmojen olarak, ozmotik tabletlerin hızlı çözünmesi için daha yüksek Potasyum klorür yüzdesinin Mannitole göre daha etkili bir şekilde kullanıldığını yönlendirdi. Optimize edilmiş formülasyon, ilacı 9 saat içinde% 88.60 ± 0.02'ye kadar serbest bırakabildi. Hızlandırılmış stabilite çalışması, optimize edilmiş formülasyonun stabil olduğunu doğruladı.
Sonuç: Aseclofenac'ın formüle edilmiş ozmotik tabletlerinin terapötik açıdan güvenli ve etkili olduğu ve önceden belirlenmiş bir süre için simüle edilmiş mide ortamında herhangi bir ilaç içeriği salmadığı bulundu.
Anahtar kelimeler: Deneyin İstatistiksel Tasarımı, 3^2 Faktör Tasarımı, FT-IR: Fourier dönüşümü kızılötesi spektroskopi, Ozmotik tablet.

INRODUCTION

Drug delivery denotes to the methods, formulations, skills, and systems for transporting the drug compound in the human body as needed to safely attain its desired therapeutic effect.[1] Novel drug delivery system can minimize the difficulties by improving efficacy, safety, product shelf life and patient compliance.[2] Ideal oral drug delivery systems are those that uninterruptedly convey a measurable, duplicable amount of drug over an extended period. Controlled release dosage form are those systems, which are also capable to furnish a drug for its absorption at zero order.[3,4]

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

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

Aceclofenac, known as 2-[2-[2-(2,6-dichloroanilino)phenyl]acetyl]oxyacetic acid is a phenylacetic acid derivative belongs to the group of non-steroidal anti-inflammatory drug (NSAID).[10,11] Aceclofenac blocks the action of cyclo-oxygenase in body. COX is involved in the formation of prostaglandins which cause pain, inflammation.[12,13] Aceclofenac can be used as anti-rheumatic, anti-inflammatory, analgesic (effective pain killer in lower backache, dental). It is used in the treatment of osteoarthritis, rheumatoid arthritis, gynecological pain and alkylosing spondylitis in oral doses 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 to achieve better patient compliance.[18] Long-term use of NSAID drugs associated with different treatments causes heart burn, vertigo, hepatic toxicity, epigastric discomfort, dyspepsia, and abdominal pain.[19] But Aceclofenac offers enhanced gastric tolerance as compared to indomethacin, naproxen,

diclofenac required for chronic treatment.[18] Aceclofenac is practically insoluble in water with 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 hour.[18,20,21] Aceclofenac meets all the criteria for being an ideal drug candidate for designing an osmotic drug delivery system.[8]

From the literature survey it has been found that marketed products of osmotic tablets for any NSAIDs are not available whereas such type of products are available for antihistamine, anti-hypertensive, anti-diabetic, anticonvulsant drugs but none of these are enteric coated. [8,22] Aceclo, Aceclo SR, Acenac SR, Hifenac, Hifenac SR tablets etc are the currently available marketed preparations of Aceclofenac which are film-coated. Hence this study was aimed to formulate enteric coated elementary osmotic tablets of Aceclofenac as a NSAID for exploring its novel opportunities.

Being the osmotic tablet was fabricated as enteric-coated, the tablet didn't release any drug content in stomach environment. Hence the most common adverse effects and contradictions related to Aceclofenac for its gastric impairment could be prevented.

MATERIALS AND METHODS

Aceclofenac and Cellulose acetate was purchased from Simson Pharma (Mumbai, India). Micro-crystalline cellulose, Mannitol, Polyvinyl pyrrolidone K30, Sodium lauryl sulfate, Magnesium stearate, Talc and Ethyl cellulose were purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). Potassium chloride was purchased from Merck Specialities Pvt. Ltd. (Mumbai, India). Cellulose acetate phthalate was purchased from Spectrochem Pvt. Ltd. (Mumbai, India). Ethanol was purchased from Changshu Hongsheng Fine Chemicals (changshu City). Acetone and Methanol was purchased from 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.

Design of Experiment (DOE)

It can be only attained by a statistically or mathematical approach that supports in optimization of the product within the defined range.[23] Enteric coated osmotic coated were designed and optimized by using Design-Expert software. The design used for formulation development and optimization was proceeded by 3^2 Factorial Design.

According to this two factors were chosen considering 3 levels of concentration. Two osmogens namely mannitol (MANN) and potassium chloride (KCL) as shown in Table 1 were mixed at different ratios according to design requirement to produce nine formulations shown in Table 2. The rationality for the selection of osmogen was aimed to develop a composition comprising of a higher osmotic pressure and lower osmotic pressure. According to literature it had been reported sodium chloride, potassium chloride and mannitol are most commonly used as 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 (MANN)	Potassium chloride (KCL)
Lower (-1)	50 mg	50 mg
Middle (0)	150 mg	150 mg
Upper (+1)	250 mg	250 mg

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

Identification of Drug

The drug, Aceclofenac used for this work was identified through performing several monographic tests and FT-IR study.

Compatibility of Drug with Excipients

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

Pre-compression Studies

To access the flow property of the mixed powder blends and granules formed, angle of repose, carr's Index and hausner's ratio were determined.

Preparation of Core Aceclofenac Tablets

The core tablets were prepared by moist granulation technique. Drug and all the ingredients except talc and magnesium stearate were accurately weighed. The ingredients were mixed thoroughly in a porcelain mortar. Then the mixture was passed through sieve no. 60. To the resultant powder, polyvinyl pyrrolidone K30 in warm water as a binder solution was added to form a coherent mass. The coherent mass was passed through 12 mesh screen to form granules. The wet granules were then dried at 60-70□ for about 3 hour. After getting completely dried, the granules were passed through sieve no. 22 to break the lumps and get uniform and fine particle of granules. Talc and magnesium stearate were passed through sieve no. 40 and mixed with the dried granules. The lubricated granules were compressed into round-shaped tablets using standard single punch tablet compression machine.[24] Altering the ratio of excipients nine batches (F1-F9) of Aceclofenac core tablets were prepared (Table 3).

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

Designing the Coating Composition for Osmotic Tablets

Ethyl cellulose and Cellulose acetate were used together in three different ratios to find out the maximum rupturing time of the semi-permeable membrane. Ethanol was used as solvent, and Glycerol was served as a plasticizer. The coating solutions were applied to dummy tablet batches.

Optimization of the Plasticizer for Osmotic Tablets

To enhance the elasticity of the osmotic device, Glycerol, as a plasticizer was added at different amounts in the designated coating solution.

Coating of Core Aceclofenac Tablets

Compressed tablets were coated using appropriate coating solution (Table 4) by the aid of dip coating technology. After coating the tablets were dried at a temperature of 40-50□ for about 1-2 hour to remove residual solvent.[24]

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

Designing an Orifice

An orifice was designed on the surface of each coated tablets using a needle of an insulin syringe (gauge 31 or 0.226mm or 226 μm).

Enteric Coating of Tablets

The tablets are finally made enteric coated using appropriate coating solution (Table 5) of Cellulose acetate phthalate. After coating the tablets were dried at a temperature of 50-60□ for about 1-1.5 hour to remove residual solvent.

Table 5. Composition of enteric coating solution

S. No.	Ingredients	Quantity
1	Cellulose acetate phthalate	10 g
2	Ethanol : Acetone (1 : 3)	q.s. to 50 ml

Evaluation of Enteric Coated Elementary Osmotic Tablets

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 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. 5 ml of samples were withdrawn at 0, 30, 60, 90, 120 min from the dissolution medium containing 0.1N HCl (pH 1.2) and after completion of 120 min, tablets were immediately transferred to alkaline medium from the acidic medium. 5 ml of samples were withdrawn at 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 540 min from the dissolution medium containing Phosphate buffer (pH 6.8). After sampling performed, equal volume of fresh dissolution medium is replaced each time in the dissolution vessel to maintain sink condition. The samples were diluted with respective dissolution medium and then filtered through whatman filter paper. Small aliquots of the filtrate were

taken in a cuvette and the absorbance was measured by UV-visible Spectrophotometer at 273.0 nm.[25,26] The percentage cumulative drug release was calculated.

Drug Release Kinetics Study

In-vitro drug release data of the formulations were fitted to various mathematical models such as zero order, first order, Higuchi release kinetics, Korsmeyer – Peppas release kinetics, Hixson – Crowell release kinetics to describe the kinetics of drug release.[27,28,29]

Comparative Analysis of Drug Release with a Marketed Formulation

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

Accelerated Stability Study

Stability studies were carried out only for osmotic tablets from the best optimized formulation batch. The tablets were quarantined, and stored at 40 ± 2□ and 75 ± 5% RH for the duration of one month. After completion of specific time period, samples were withdrawn from the storage condition and tested for different parameters such as visual appearance, loss on drying, *in-vitro* dissolution study.[30]

Due to the limitation of time, stability study was employed for a period of one month only. But it is projected to carry out 6 months accelerated and 6 months long term analysis from this current study in recent future.

This study did not require any approval from ethics committee or any other patient informed consent because the present study did not focus on any clinical parameter or utilize any human volunteer and animals for development of the research work.

RESULTS AND DISCUSSION

Identification of drug

Several monographic tests were performed (Table 6) to check the identity of Aceclofenac. The results obtained from the particular tests were compared to the specifications required. All the results matched with their corresponding specification which confirmed the identity of Aceclofenac.

Table 6. Identification of drug by performing several monographic tests

Tests	Expected Result	Obtained Result
About 10 mg of Aceclofenac was dissolved in 10 ml of Ethanol. To 1.0 ml of the solution, 0.2 ml of a 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) was added. The resultant solution was allowed to stand and protected from light for about 5 minutes. 3.0 ml of 1.0% (v/v) solution of hydrochloric acid was added.	A blue colour develops and a precipitate will be formed.	Blue colour 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: 1.0 g Aceclofenac is dried in a hot air oven at 105□ for 3 h	Not more than 0.5%	0.4%
Assay: About 0.3 g of Aceclofenac was weighed accurately and dissolved in 40 ml of Methanol. It was titrated with 0.1 M Sodium hydroxide. The end point was determined by indicator method. A blank titration was also carried out. (1 ml of 0.1 M sodium hydroxide is equivalent to 0.03542 g of Aceclofenac)	-----	95.21%

Fourier Transform Infrared Spectroscopy (FT-IR)

The identification of the drug and compatibility between drug and excipients were carried out using FT-IR spectrophotometer. The physical compatibility was also checked visually. These results showed that the drug and the excipients were physically compatible with each other. The FT-IR characteristics of Aceclofenac resembled almost the same with the spectra of authentic sample of Aceclofenac (Figure 1). By scrutinizing the FT-IR spectra, it was evidently manifest that the physical mixtures of Aceclofenac with different excipients showed the presence of Aceclofenac characteristics bands at their same wavenumbers (Figure 2, Table 7). This specified that the drug was pure, chemical interaction between the drug and excipients was absent.

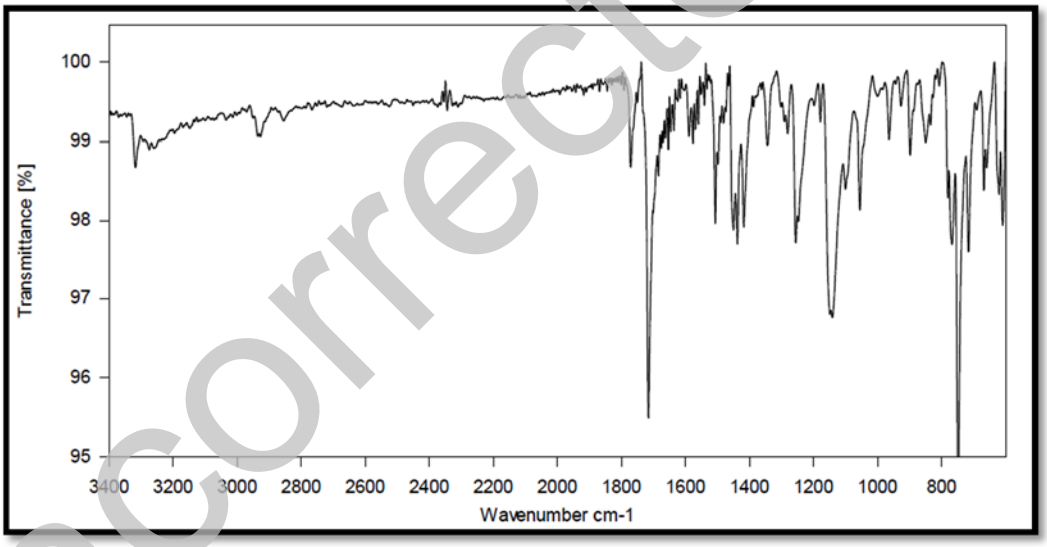

Figure 1. FT-IR spectrum of Aceclofenac

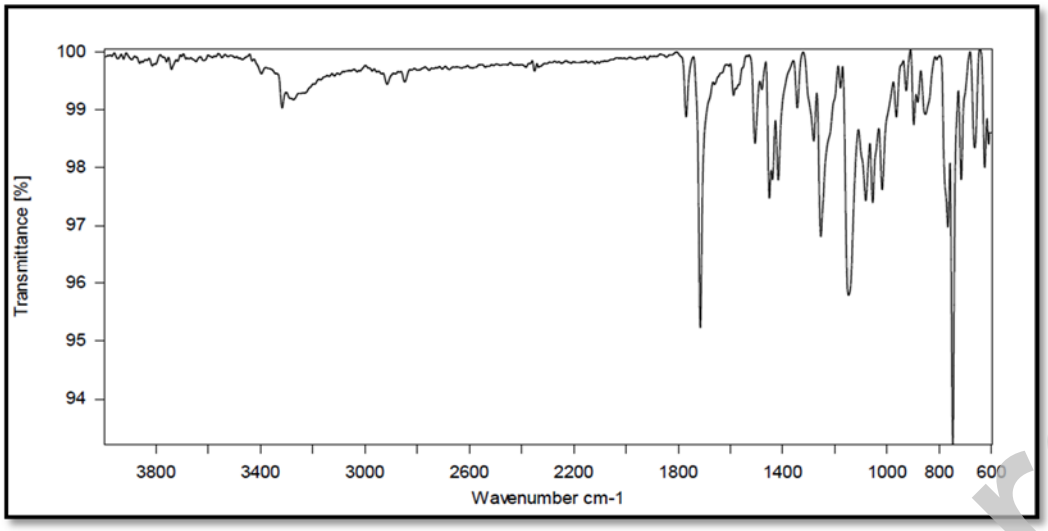

Figure 2. FT-IR spectrum of Aceclofenac along with all excipients used

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

Pre-compression Studies

Pre-compression studies were performed to check the parameters for drug, formulated powder blends, and granules. 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 as compared to Aceclofenac and powder blends formed (Table 8). Hence as per the flow property of powders, Aceclofenac and the formulated powder blends exhibited good flow property whereas, flow property of the granules was found excellent.[31,32]

Table 8. Pre-compression studies of the drug, powder blends, and granules

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

Designing the Coating Composition for Osmotic Tablets

Ethyl cellulose : Cellulose acetate (3 : 1) in Ethanol (100ml) – this coating composition provided the maximum rupturing time 4.5 hour and was capable to withstand the osmotic pressure for a longer time in comparison with other coating compositions (Table 9). So, this (C3) coating composition was used for coating of the core Aceclofenac tablets.

Table 9. Optimization of coating composition

S. No.	Code	Coating Materials	Rupturing Time
1	C1	Ethyl cellulose : Cellulose acetate (1 : 1) in Ethanol	3.5 hour
2	C2	Ethyl cellulose : Cellulose acetate (1 : 3) in Ethanol	2.0 hour
3	C3	Ethyl cellulose : Cellulose acetate (3 : 1) in Ethanol	4.5 hour

Optimization of the Plasticizer Amount for Osmotic Tablets

By using 0.75ml Glycerol as a plasticizer in the C3 coating solution, the maximum rupturing time 4 hour was found (Table 10). Glycerol is capable to provide the elasticity for expansion, and maximum mechanical strength of the membrane. So, 0.75 ml of glycerol was added to the optimized coating composition.

Table 10. Optimization of plasticizer amount

S. No.	Code	Amount of Glycerol	Rupturing time
1	P1	0.35 ml	3.0 hour
2	P2	0.50 ml	3.5 hour
3	P3	0.60 ml	3.5 hour
4	P4	0.75 ml	4.0 hour
5	P5	0.90 ml	3.5 hour

Evaluation of Enteric Coated Elementary Osmotic Tablets

Post-compression Parameters

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

parameters.

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

Table 11. Post-compressive parameters of formulations

Formulation Code	Average Weight (mg)[b] ± S.D	Diameter (mm)[a] ± S.D	Thickness (mm)[a] ± S.D	Hardness (kg/cm^2)[a] ± S.D	Friability (% w/w)[a] ± S.D	Drug Content (%)[a] ± S.D
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

N.B.- All values are expressed as mean S.D, [a] n = 10, [b] n = 20

In-vitro Dissolution Studies

The data obtained from in-vitro dissolution studies (Table 12, Table 13) showed that osmotic tablets did not release any drug content in acidic medium. It was the proper evidence for successful demonstration of enteric coating. It helped the device to control its drug release over a prolonged period of time and also prevent gastric degradation of Aceclofenac.

Table 12. Tabulation of %CDR from in-vitro dissolution studies (F1-F5)

Dissolution media	Time (min)	Cumulative drug release (%)[a] ± S.D				
		F1	F2	F3	F4	F5
0.1N 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

N.B.- All values are expressed as mean S.D, [a] n = 3

Table 13. Tabulation of %CDR from in-vitro dissolution studies (F6-F9)

Dissolution media	Time (min)	Cumulative drug release (%)[a] ± S.D			
		F6	F7	F8	F9
0.1N 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	-	-

N.B.- All values are expressed as mean S.D, [a] n = 3

Table 14. Time required to release minimum 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

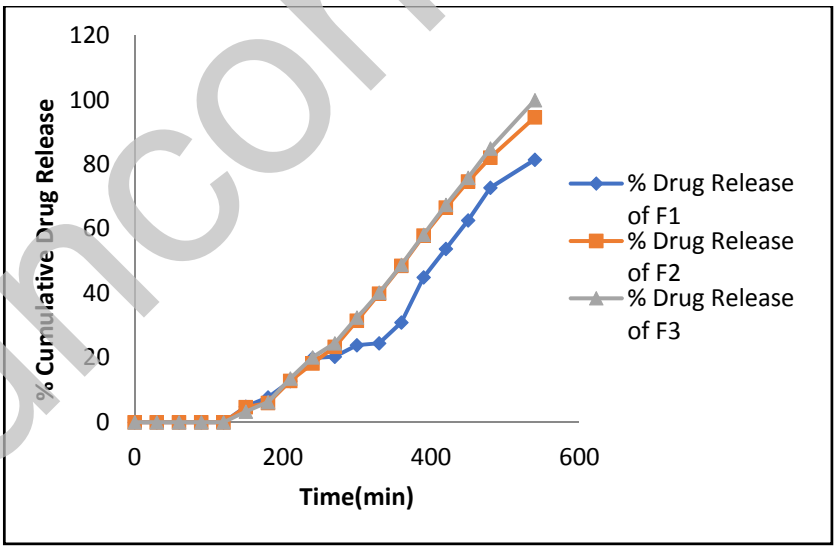

Figure 3. *In-vitro* drug release study of osmotic tablets (F1-F3)

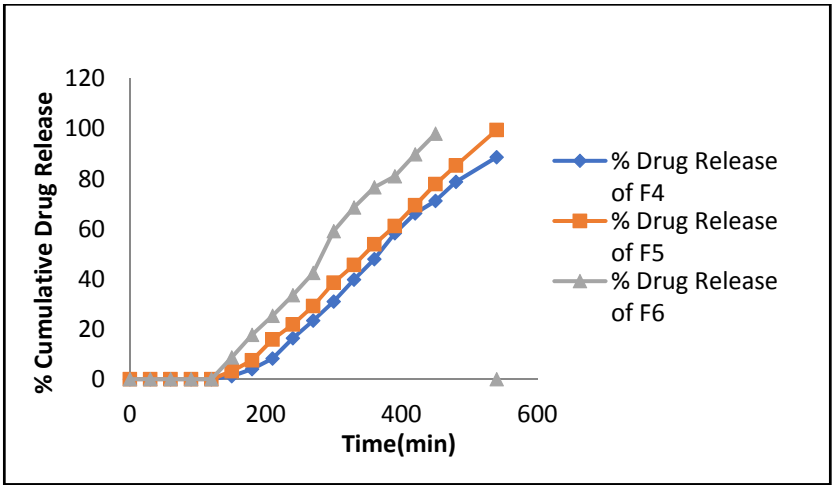

Figure 4. *In-vitro* drug release study of osmotic tablets (F4-F6)

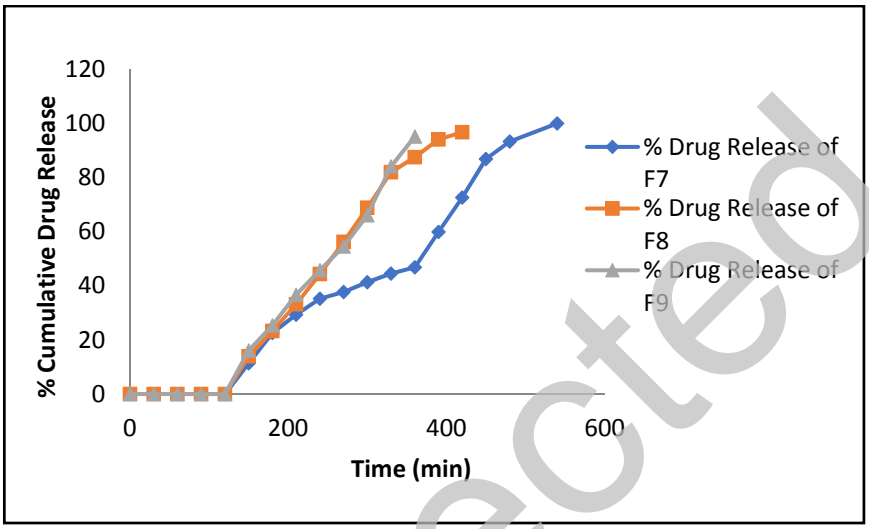

Figure 5. *In-vitro* drug release study of osmotic tablets (F7-F9)

Design of Experiment (DOE) using Design-Expert Software

By analyzing Multiple Regression Analysis (MRA) 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*Mannitol - 63.00*Potassium chloride

In the above case of percentage drug release, Potassium chloride was found to have negative effect than Mannitol. Thus increase in the concentration of Potassium chloride resulted increasing in the time of drug release. On the other side Mannitol had lesser effect since it has been reported that Potassium chloride has a greater osmotic pressure as compared to Mannitol.[22] The drug was forced out of the orifice at a higher release rate reducing the time for 80% drug release ($T_{80\%}$). In this study drug release rate was controlled by optimizing the concentration of both the osmogens.

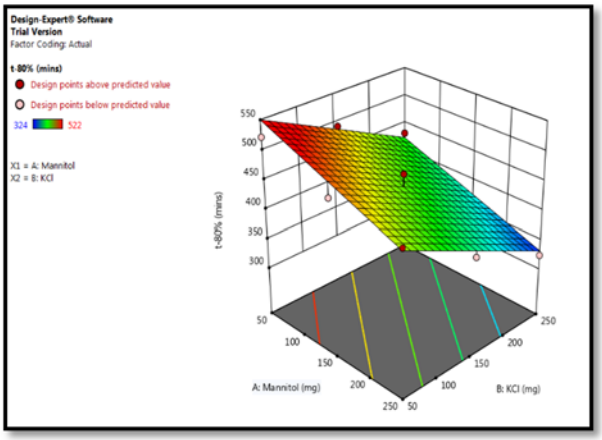

Figure 6. Model 3D graph analysis

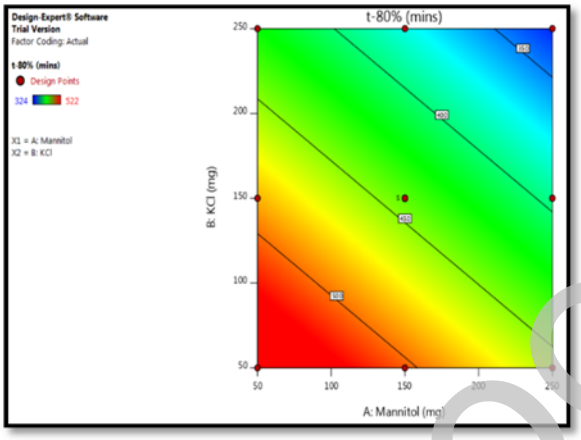

Figure 7. Contour plot analysis

From the Model 3D Graph Analysis and Contour Plot Analysis, it was demonstrated that Potassium chloride had greater effect on dissolution time than Mannitol (Figure 6, Figure 7). The dissolution time ($T_{80\%}$) was found more diminished when concentration of Potassium chloride was increased as compared to the same of Mannitol. This proved the above consideration stated.

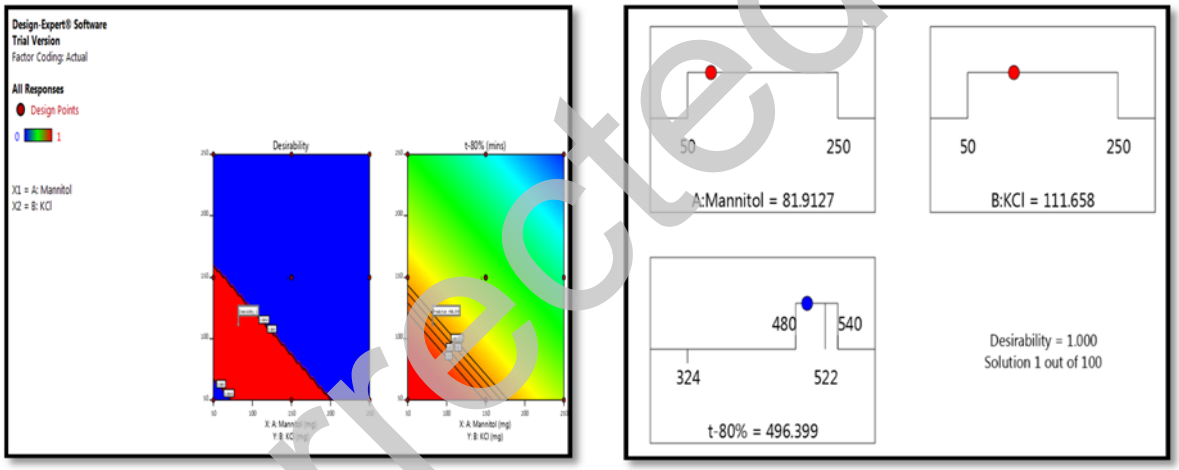

Figure 8. Optimized formulation with maximum desirability and design points

During optimization study, dissolution time was taken as reference criteria within the range limits of the maximum and minimum values of dissolution time. Optimized ratio for using osmotic agents (Mannitol:Potassium chloride) was determined to be 81.91:111.65 (Figure 8). Among the various formulations, F4 was found to have the ratio nearest to the desirability.

Drug Release Kinetics Study

From drug release kinetics study for the optimized formulation (F4), it was cleared that the drug release was independent of drug concentration, following zero order kinetics as it had a highest regression value (Figure 9, Table 15). Therefore, the release of the drug did not depend upon its amount present in the system rather it was completely dependent upon the nature of delivery device.

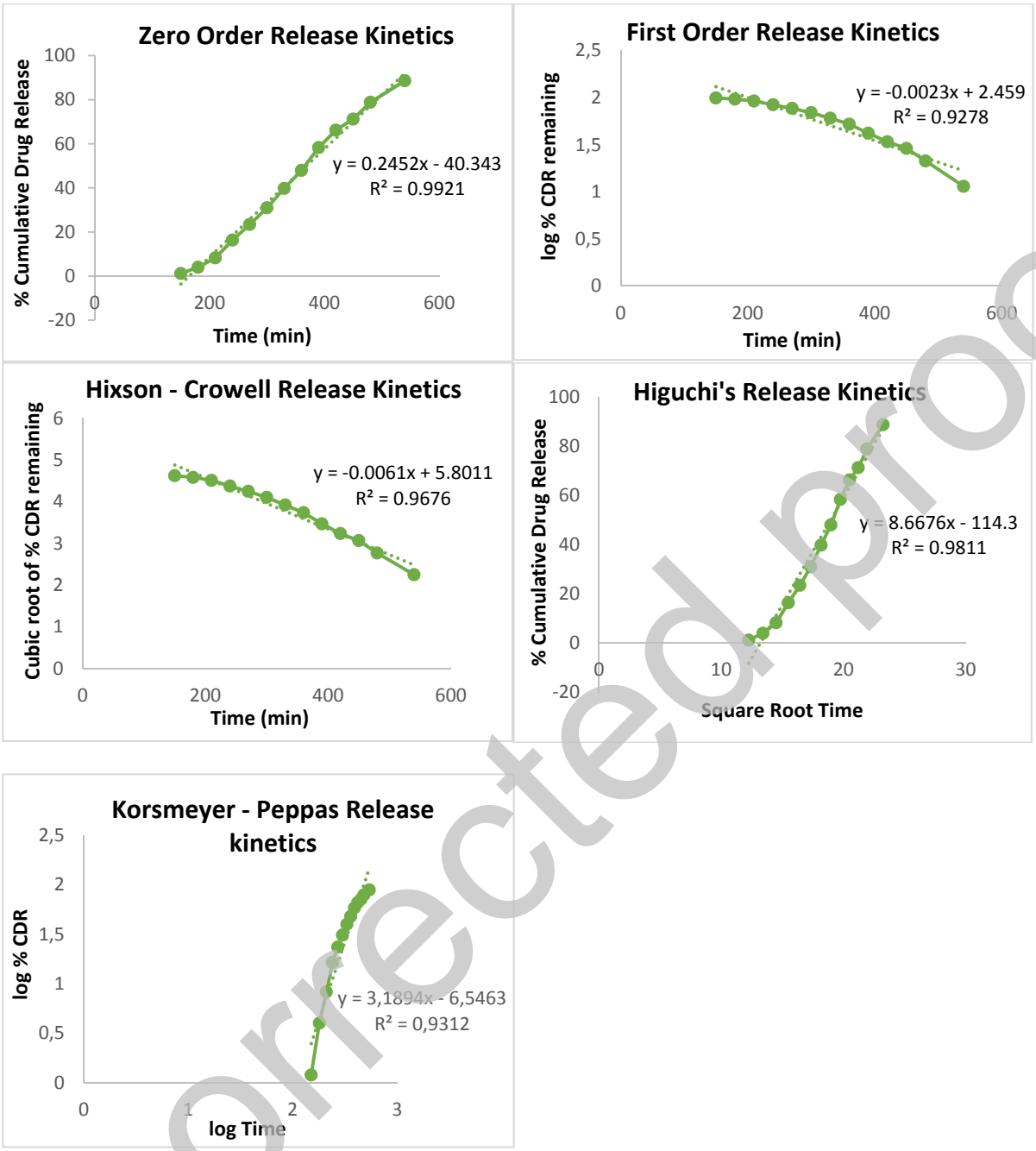

Figure 9. Fitting *in-vitro* drug release data of optimized formulation (F4) in different release kinetics models

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

Comparative Analysis of Drug Release with a Marketed Product

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

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

Table 16. Tabulation of %CDR from the optimized and marketed formulation

Dissolution media	**Time (min)**	**Cumulative drug release (%)[a] ± S.D**	
		Optimized Formulation (F4)	**Marketed Formulation (Hifenac Tablet 100 mg)**
0.1N 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

N.B.- All values are expressed as mean S.D, [a] n = 3

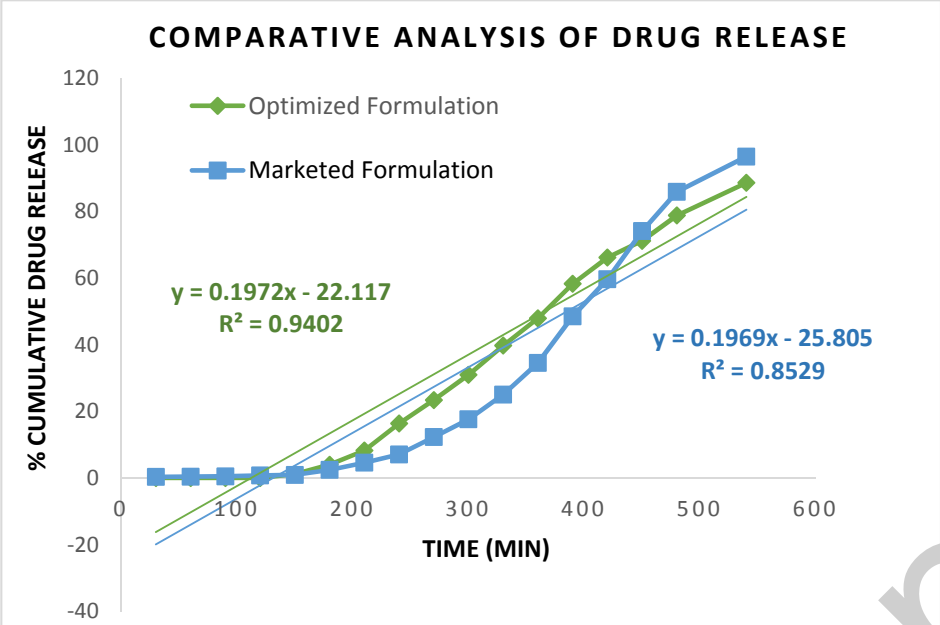

Figure 10. Comparison of drug release between optimized and marketed formulation

Accelerated Stability Study

The accelerated stability study employed for the optimized batch (F4) of formulated osmotic tablets showed that there was no significant degradation (Table 17) within the stipulated time. The study confirmed that the optimized formulation (F4) was stable.

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] ± S.D	0.51 ± 0.04	0.51 ± 0.04	0.52 ± 0.03
3	Micrbial or fungal growth	Absent	Absent	Absent
4	Average weight (mg)[b] ± S.D	670 ± 0.03	670 ± 0.03	670 ± 0.02
5	Diameter (mg)[b] ± S.D	12.10 ± 0.09	12.10 ± 0.09	12.10 ± 0.09
6	Thickness (mg)[b] ± S.D	3.30 ± 0.04	3.30 ± 0.04	3.30 ± 0.04
7	Hardness (kg/cm^2)[b] ± S.D	6.0 ± 0.12	6.0 ± 0.12	6.0 ± 0.10
8	Friability (% w/w)[b] ± S.D	0.65 ± 0.05	0.65 ± 0.05	0.65 ± 0.05
9	Drug content (%)[b] ± S.D	97.55 ± 0.711	97.55 ± 0.711	97.55 ± 0.711
10	*In-vitro* drug release (%)[a] ± S.D upto 9 hour	88.60 ± 0.02	88.60 ± 0.02	88.60 ± 0.03

N.B.- All values are expressed as mean S.D, [a] n = 3, [b] n = 10

CONCLUSION

In-vitro drug release rate from the optimized batch (F4) of formulated osmotic tablets was observed to be 88.60±0.02% in 9 hour and there was no evidence of releasing the drug from the device in acidic medium which justified the primary aim of the present study. The semi-permeable membrane developed was capable of withstanding satisfactory osmotic pressure and of producing extreme elasticity so as formulated device can control release of the drug over a prolonged period of time. Model 3D Graph Analysis engaged for the optimized device proved about the greater effectiveness of potassium chloride than mannitol as a osmogen.

ACKNOWLEDGEMENTS

The authors would like to thank the laboratory facility of Bengal School of Technology, West Bengal, for carrying out necessary research work and providing the compulsory requirements for successful completion of the research study.

CONFLICTS OF INTEREST

Authors have no conflict of interest regarding the publication of this article.

REFERENCES

1. Mothilal M, Swati PS, Nelofar S, Damodharan N, Manimaran V, Lakshmi KS. Formulation and evaluation of Aceclofenac compression coated tablets for colon drug delivery. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2012;3:1062-1071.
2. Roco MC, Bainbridge WS. Societal implications of nanoscience and nanotechnology: Maximizing human benefit. Journal of Nanoparticle Research. 2005;7:1-13.
3. Ahuja N, Kumar V, Rathee P. Osmotic-controlled release oral delivery system: An advanced oral delivery form. The Pharma Innovation. 2012;1:116-124.
4. Rathore GS, Gupta RN. Formulation development and evaluation of controlled porosity osmotic pump delivery system for oral delivery of atenolol. Asian Journal of Pharmaceutics. 2012;6:151-160.
5. Dasankoppa FS, Ningangowdar M, Sholapur H. Formulation and evaluation of controlled porosity osmotic pump for oral delivery of ketorolac. Journal of Basic and Clinical Pharmacy. 2013;4:2-9.
6. Venkateswarlu BS, Pasupathi C, Pasupathi A, Jaykar B, Chandira RM, Palanisamy P. Osmotic drug delivery system: A review. Journal of Drug Delivery and Therapeutics. 2019;9:611-616.
7. Rastogi V, Shukla S, Singh R, Lal N, Yadav P. Microspheres: A Promising Drug Carrier. Journal of Drug Delivery and Therapeutics. 2016;6:18-26.
8. Mathur M, Mishra R. A review on osmotic pump drug delivery system. International Journal of Pharmaceutical Sciences and Research. 2016;7:453-471.
9. Lachman L, Lieberman HA. The Theory and Practice of Industrial Pharmacy (4th ed). New Delhi; CBS Publishers and Distributors; 2013:872-876.
10. Tripathi KD. Essentials of Medical Pharmacology (7th ed). New Delhi; Jaypee Brothers Medical Publishers Pvt. Ltd; 2013:192-204.
11. Raza K, Kumar M, Kumar P, Malik R, Sharma G, Kaur M, Katare OP. Topical delivery of Aceclofenac: Challenges and promises of novel drug delivery systems. Biomed Research International. 2014;2014:1-11.
12. Ashok CH, Bhaskar NV, Prakash PR. Design and characterization of press coated tablets of Aceclofenac for pulsatile delivery. International Journal of Pharmaceutical Sciences and Research. 2015;6:2902-2912.
13. Shivkant S, Roshan I, Prakash NB. Evaluation of formulation parameters for

development of Aceclofenac nanosuspension using Doe statistical tool. International Journal of Drug Delivery Technology. 2016;6:142-150.
14. Ragidi A, Madhuri J, Anusha P, Venkateswara RT. Formulation and *in-vitro* evaluation of compression coated tablets of Aceclofenac for controlled release. World Journal of Pharmacy and Pharmaceutical Sciences. 2012;2:216-222.
15. Patel PB, Patel TK. Efficacy and safety of aceclofenac in osteoarthritis: A meta-analysis of randomized controlled trials. European Journal of Rheumatology. 2017; 4:11–18.
16. Vohra F, Raut A. Comparative efficacy, safety, and tolerability of diclofenac and aceclofenac in musculoskeletal pain management: A systematic review. Indian Journal of Pain. 2016;30:3-6.
17. Kamal AH, Malla SFE, Hammad SF. A review on uv spectrophotometric methods for simultaneous multicomponent analysis. European Journal of Pharmaceutical and Medical Research. 2016;3:348-360.
18. Dave V, Paliwal S. A novel approach to formulation factor of aceclofenac eye drops efficiency evaluation based on physicochemical characteristics of *in vitro* and *in vivo* permeation. Saudi Pharmaceutical Journal. 2014;22:240-245.
19. Shaikh AC, Nazim S, Siraj S, Khan T, Patel MS, Zameeruddin M, Shaikh A. Formulation and evaluation of sustained release tablets of Aceclofenac using hydrophilic matrix system. International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3:145-148.
20. Jayanthi B, Madhusudhan S, Mohanta GP, Manna PK. Preformulation characterisation, designing and formulation of aceclofenac loaded microparticles. International Journal of Drug Development and Research. 2012;4:186-196.
21. Kala S, Juyal D. Preformulation and characterization studies of aceclofenac active ingredient. The Pharma Innovation Journal. 2016;5:110-119.
22. Keraliya RA, Patel C, Patel P, Keraliya V, Soni TG, Patel RC, Patel MM. Osmotic drug delivery system as a part of modified release dosage form. ISRN Pharm. 2012;2012:528079.
23. Politis SN, Colombo P, Colombo G, Rekkas DM. Design of experiments (DoE) in pharmaceutical development. Drug Development and Industrial Pharmacy. 2017;43:889-901.
24. Reza KH, Vikram NS, Kumaravelrajan R. Formulation and optimization of aceclofenac monolithic osmotic pump. International Journal of Pharmaceutical Sciences Review and Research. 2011;6:42-47.
25. Attimarad M, Narayanswamy VK, Aldhubaib BE, SreeHarsha N, Nair AB. Development of UV spectrophotometry methods for concurrent quantification of amlodipine and celecoxib by manipulation of ratio spectra in pure and pharmaceutical formulation. Plos One. 2019;14:1-15.
26. Sultana T, Sohel D, Kawsar H, Banoo R. *In-vitro* dissolution study and assay of diclofenac sodium from marketed solid dosage form in Bangladesh. Journal of Bioanalysis & Biomedicine. 2017;9:118-122.
27. Zhan S, Wang J, Wang W, Cui L, Zhao Q. Preparation and *in vitro* release kinetics of nitrendipine-loaded PLLA–PEG–PLLA microparticles by supercritical solution impregnation process. Royal Society of Chemistry. 2019;9:16167-16175.
28. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;51:1145-1149.
29. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 1985;60:110-111.
30. Yasmeen A, Sofi G. A review of regulatory guidelines on stability studies. The Journal of Phytopharmacology. 2019;8:147-151.
31. Purushothaman M, Kalvimoorthi V. Formulation and evaluation of colon targeted

drug delivery system of flurbiprofen using HPMC and K4M sodium alginate as polymeric carrier. International Journal of ChemTech Research. 2017;10:156-168.
32. Bolmal UB, Subhod RP, Gadad AP, Patill AS. Formulation and evaluation of carbamazepine tablets using biosurfactant in ternary solid dispersion system. Indian Journal of Pharmaceutical Education and Research. 2020;54:302-309.