**Formulation and Evaluation of Enteric Coated Elementary Osmotic Tablets of Aceclofenac**

**Aseklofenak Enterik Kaplı Elementer Ozmotik Tabletlerin Formülasyonu ve Değerlendirilmesi**

**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 $88.60\pm0.02\%$ 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

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**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 geliştirilmesi 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 $3^2$ faktörli tasarım kullanılarak tasarlanmış ve optimize edilmiştir. Formülasyonların fiziksel parametrelerini değerlendirerek 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 kullanılıldığı göstermiştir. Optimize edilmiş formülasyon, 9 saate kadar ilacın $88,60\pm0,02\%$ salınılmıştır. Hızlandırılmış stabilite çalışması, optimize edilmiş formülasyonun stabil olduğunu doğrulamıştır.

**Sonuç:** Aseklofenakın formülinde edilmiş ozmotik tabletlerini terapötik olarak güvenli ve etkili bulunan ve önceden belirlenmiş bir süre boyunca simül edilmiş gastrik ortamda herhangi bir ilac içeriği salmamıştır.

**Anahtar kelimeler:** Deneyin istatistiksel tasarımı, $3^2$ faktör tasarım, 3D grafik analizi, ozmotik tablet
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. Novel drug delivery systems can diminish the related difficulties by improving the efficacy, safety, product shelf life, and patient compliance. 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. The osmotic drug delivery systems utilized for controlled delivery of drugs are now well recognized in human and veterinary medication. Osmotically controlled oral drug delivery systems apply osmotic pressure, which is developed in the system for the controlled delivery of drugs. 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. 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.

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). Aceclofenac inhibits the enzyme cyclo-oxygenase in the body. This enzyme is engaged in the production of prostaglandins, which results in inflammation and pain. Aceclofenac can be used as an antirheumatic, anti-inflammatory, and analgesic (effective pain killer for the lower backache and dental). This compound is also engaged in the production of prostaglandins, which results in inhibition of the enzyme cyclo-oxygenase in the body. This enzyme is engaged in the production of prostaglandins, which results in inflammation and pain.

Aceclofenac possesses higher antipyretic, antirheumatic, anti-inflammatory, and analgesic (effective pain killer for the lower backache and dental). This compound is also engaged in the production of prostaglandins, which results in inhibition of the enzyme cyclo-oxygenase in the body. This enzyme is engaged in the production of prostaglandins, which results in inflammation and pain.

The long-term use of NSAIDs associated with different treatments causes heart burn, vertigo, hepatic toxicity, epigastric discomfort, dyspepsia, and abdominal pain. However, aceclofenac offers enhanced gastric tolerance compared with indomethacin, naproxen, and diclofenac, which is required for chronic treatment. 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. Aceclofenac meets all the criteria for being an ideal drug candidate for designing osmotic drug delivery systems.

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.

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 (KCI) was acquired from Merck Specialities 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. 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 KCI (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. 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. 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                                  |
| F2               | 150                  | 50                 | 0                                   |
| F3               | 250                  | 50                 | +1                                  |
| F4               | 50                   | 150                | -1                                  |
| F5               | 150                  | 150                | 0                                   |
| F6               | 250                  | 150                | +1                                  |
| F7               | 50                   | 250                | -1                                  |
| F8               | 150                  | 250                | 0                                   |
| F9               | 250                  | 250                | +1                                  |

MANN: Mannitol, KCl: Potassium chloride

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
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.

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
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 an ultraviolet-visible spectrophotometer at a wavelength 273.0 nm. 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.

**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. 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](image-url)

FT-IR: Fourier transform infrared spectroscopy
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.\textsuperscript{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.
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. 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.

| Sample                | Bulk density (g/cm$^3$) | Tapped density (g/cm$^3$) | Carr’s index (%) | Hausner’s ratio | Angle of repose (θ) |
|-----------------------|-------------------------|---------------------------|------------------|-----------------|---------------------|
| Aceclofenac           |                         |                           |                  |                 |                     |
| 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            | 1.17            | 35.80               |

**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) |
|--------|-------------------------|---------------------------|------------------|-----------------|---------------------|
| 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               |

**Powder blends**

| Sample | Bulk density (g/cm$^3$) | Tapped density (g/cm$^3$) | Carr’s index (%) | Hausner’s ratio | Angle of repose (θ) |
|--------|-------------------------|---------------------------|------------------|-----------------|---------------------|
| F1     | 0.479                   | 0.534                     | 10.29            | 1.11            | 25.43               |
| F2     | 0.468                   | 0.522                     | 10.34            | 1.15            | 25.48               |
| F3     | 0.457                   | 0.519                     | 11.94            | 1.13            | 27.40               |
| F4     | 0.449                   | 0.508                     | 11.61            | 1.12            | 26.92               |
| F5     | 0.458                   | 0.520                     | 11.92            | 1.13            | 22.65               |
| F6     | 0.464                   | 0.531                     | 12.61            | 1.14            | 28.54               |
| F7     | 0.476                   | 0.530                     | 10.18            | 1.11            | 29.45               |
| F8     | 0.482                   | 0.541                     | 10.90            | 1.12            | 27.65               |
| F9     | 0.467                   | 0.532                     | 12.21            | 1.13            | 27.96               |

**Granules**

| Sample | Bulk density (g/cm$^3$) | Tapped density (g/cm$^3$) | Carr’s index (%) | Hausner’s ratio | Angle of repose (θ) |
|--------|-------------------------|---------------------------|------------------|-----------------|---------------------|
| F1     | 0.489                   | 0.508                     | 11.61            | 1.12            | 26.92               |
| F2     | 0.468                   | 0.522                     | 10.34            | 1.15            | 25.48               |
| F3     | 0.457                   | 0.519                     | 11.94            | 1.13            | 27.40               |
| F4     | 0.449                   | 0.508                     | 11.61            | 1.12            | 26.92               |
| F5     | 0.458                   | 0.520                     | 11.92            | 1.13            | 22.65               |
| F6     | 0.464                   | 0.531                     | 12.61            | 1.14            | 28.54               |
| F7     | 0.476                   | 0.530                     | 10.18            | 1.11            | 29.45               |
| F8     | 0.482                   | 0.541                     | 10.90            | 1.12            | 27.65               |
| F9     | 0.467                   | 0.532                     | 12.21            | 1.13            | 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)**
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 (T80%) 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

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**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

**Table 11. Post-compressive parameters of formulations**

| Formulation code | Average weight (mg)± SD | Diameter (mm)± SD | Thickness (mm)± SD | Hardness (kg/cm²)± SD | Friability (% w/w)± SD | Drug content (% w/w)± 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, "n=10,"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). 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 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

| Dissolution media | Time (min) | Cumulative drug release (%)* ± SD |
|-------------------|-----------|---------------------------------|
| 0.1 N HCl (pH 1.2) | 0         | 0.0 ± 0.00                     |
|                   | 30        | 0.0 ± 0.00                     |
|                   | 60        | 0.0 ± 0.00                     |
|                   | 90        | 0.0 ± 0.00                     |
|                   | 120       | 0.0 ± 0.00                     |
| Phosphate buffer (pH 6.8) | 150      | 4.84 ± 0.04                    |
|                   | 180       | 7.74 ± 0.03                    |
|                   | 210       | 12.79 ± 0.04                   |
|                   | 240       | 19.90 ± 0.02                   |
|                   | 270       | 20.35 ± 0.04                   |
|                   | 300       | 23.86 ± 0.04                   |
|                   | 330       | 24.47 ± 0.05                   |
|                   | 360       | 30.95 ± 0.01                   |
|                   | 390       | 44.92 ± 0.02                   |
|                   | 420       | 53.79 ± 0.05                   |
|                   | 450       | 62.62 ± 0.01                   |
|                   | 480       | 72.71 ± 0.02                   |
|                   | 540       | 81.40 ± 0.04                   |

All values are expressed as mean SD, *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 (%) ± 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        |
|                   | 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        | 96.05±0.08                       | 86.80±0.07 | -          | -          |
|                   | 480        | -                                 | 93.25±0.08 | -          | -          |
|                   | 540        | -                                 | 99.94±0.02 | -          | -          |

All values are expressed as mean SD, *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|

**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                   |

**Figure 10.** Comparison of drug release between optimized and marketed formulation
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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Table 16. Tabulation of % cumulative drug release from the optimized and marketed formulation

| Dissolution media | Time (min) | Cumulative drug release (%) ± SD |
|-------------------|------------|---------------------------------|
| 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                      |
|                    | 180 | 3.99±0.04                      |
|                    | 210 | 8.24±0.27                      |
|                    | 240 | 16.35±0.09                     |
|                    | 270 | 23.40±0.025                    |
|                    | 300 | 30.97±0.47                     |
|                    | 330 | 39.76±0.05                     |
|                    | 360 | 47.93±0.007                    |
|                    | 390 | 58.28±0.02                     |
|                    | 420 | 66.17±0.03                     |
|                    | 450 | 71.19±0.07                     |
|                    | 480 | 78.80±0.07                     |
|                    | 540 | 88.60±0.02                     |

All values are expressed as mean SD, 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) ± 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) ± SD | 670±0.03 | 670±0.03 | 670±0.02 |
| 5      | Diameter (mg) ± SD | 12.10±0.09 | 12.10±0.09 | 12.10±0.09 |
| 6      | Thickness (mg) ± SD | 3.30±0.04 | 3.30±0.04 | 3.30±0.04 |
| 7      | Hardness (kg/cm²) ± SD | 6.0±0.12 | 6.0±0.12 | 6.0±0.10 |
| 8      | Friability (% w/w) ± SD | 0.65±0.05 | 0.65±0.05 | 0.65±0.05 |
| 9      | Drug content (% w/w) ± SD | 97.55±0.711 | 97.55±0.711 | 97.55±0.711 |
| 10     | In vitro drug release (%) ± SD, up to 9 h | 88.60±0.02 | 88.60±0.02 | 88.60±0.03 |

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