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Review Article

Development and Evaluation of Etodolac Osmotic Capsule

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Abstract:

controlled release formulations have been developed based on their significant advantages over conventional immediate release dosage forms, such as the decrease of dosing frequency, the increase of patient compliance, better dosing patterns, the reduction of side effects, or the maintenance of the drug concentration within a desired range, i.e., an overall improved therapeutic benefit. However, oral controlled release formulations are exposed to changing environment during transit through the GI-tract which may affect their performances e.g. physiological factors such as patient age or food-intake. Reported as releasing drug independently of these factors, oral osmotically-driven systems (OODS) have taken an integral place in the pharmaceutical field. The dissolution profile of orally delivered drugs can be controlled through the use of osmotically controlled drug delivery devices. The most commonly used device is the osmotic tablet/Capsule, which is essentially a tablet/Capsule core that is coated with a rate-limiting semipermiable membrane. Using osmotic pressure as driving force, various OCODDS design and compositions have been developed. Numerous products are launched based on these systems. In present investigation attempts are taken to formulate, optimize and develop an economic osmotically controlled Capsule containing drugs belonging to non steroidal anti-inflammatory category to release the drug in controlled manner. Such formulations are most beneficial for the patients shifted on long term pain management therapy(e.g. in arthritis) in view to reduce the associated side effects of these drugs.

Keywords: osmotic; elementary osmotic capsule; controlled release capsule; etc

Introduction:

"Osmosis" can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the *osmotic pressure*.

In 1748, Abbe Nollet first reported the osmotic process. In 1877, Pfeffer separated a sugar solution from water using a sugar-impermeable membrane and quantified the water transport. In1884, Hugo de Vries invoked osmotic concepts to understand the contraction of the contents of plant cells placed in solutions of high osmotic pressure, where the cell membrane acts as a semipermeable membrane. The osmotic pressure difference between inside and outside environments causes osmotic water loss and results in plasmolysis. In 1886, Van't Hoff identified an underlying proportionality between osmotic pressure, concentration, and temperature in Pfeffer's experiment. Later, he revealed a relationship between osmotic pressure and solute concentration and temperature that was similar to the ideal gas equation, where pressure is proportional to concentration and temperature. According to Van't Hoff 's equation, the osmotic pressure in a dilute solution is equal to the pressure that the solute would exert if it were a gas occupying the same volume. Osmotic pressure, a colligative property, depends on the concentration of solute (neutral molecule or ionic species) that contributes to the osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water, can be achieved by an osmotic delivery system that results in a constant release rate of drug. Therefore, zero-order release, which is important for a controlled release delivery system when indicated, is possible to achieve using these platforms. In 1974, Theeuwes and Higuchi applied the principle of osmotic pressure to a new generation of controlled drug delivery devices with many advantages over other existing controlled drug delivery systems. The first of these devices, the elementary osmotic pump, is considered a typical delivery system that operates on osmotic principles [6].

Advantages Of Osmotically Controlled Oral Drug Delivery System [7-8]

- They typically give a zero order release profile after an initial lag time.

- Deliveries may be delayed or pulsed if desired.
- Drug release is independent of gastric pH and hydrodynamic condition.
- Increase safety margin of high potency drug due to better control of plasma level.
- Maximum utilization of drug enabling reduction in amount of dose administration.
- The release mechanisms are not dependent on drug.
- A high degree of in-vitro and in vivo correlation.
- Improved patient compliance due to less frequent drug administration
- The rationale for this approach that the presence of water in g.i.t. is relatively constant, At least in terms of the amount required for activation and controlling osmotically base technologies.

Limitations of preparation: [9-10]

The preparation of controlled-release dosage forms is subject to several variables of considerable importance. The oral administration route remains the most popular, in spite of a number of problems. This include

The potential for chemical degradation under various pH conditions in the gastrointestinal tract.

- The influence of gastric emptying and its dependence on food.
- If the coating process is not well controlled there is a risk of film defects, which results in dose dumping.
- Size of hole is critical and expensive as compare to conventional tablets.

Arthritis [16]

(from Greek *arthro-*, joint + *-itis*, inflammation; plural: arthritides) is a form of joint disorder that involves inflammation of one or more joints. There are over 100 different forms of arthritis. The most common form, osteoarthritis (degenerative joint disease), is a result of trauma to the joint, infection of the joint, or age. Other arthritis forms are rheumatoid arthritis, psoriatic arthritis, and related autoimmune diseases. Septic arthritis is caused by joint infection. The major complaint by individuals who have arthritis is joint pain. Pain is often a constant and may be localized to the joint affected. The pain from arthritis is due to inflammation that occurs around the joint, damage to the joint from disease, daily wear and tear of joint, muscle strains caused by forceful movements against stiff painful joints and fatigue.

Classification

There are several diseases where joint pain is primary, and is considered the main feature. Generally when a Arthritis person has "arthritis" it means that they have one of these diseases, which include:

a) Osteoarthritis
b) Rheumatoid arthritis
c) Gout and pseudo-gout
d) Septic arthritis
e) Ankylosing spondylitis
f) Juvenile idiopathic arthritis
g) Still's disease

Joint pain can also be a symptom of other diseases. In this case, the arthritis is considered to be secondary to the main disease; these include: Psoriasis (Psoriatic arthritis), Reactive arthritis, Ehlers-Danlos Syndrome, Haemochromatosis, Hepatitis

Signs and symptoms

Regardless of the type of arthritis, the common symptoms for all arthritis disorders include varied levels of pain, swelling, joint stiffness, and sometimes a constant ache around the joint(s). Arthritic disorders like lupus and rheumatoid can also affect other organs in the body with a variety of symptoms. Inability to use the hand or walk Malaise and a feeling of tiredness Weight loss Poor sleep Muscle aches and pains Tenderness Difficulty moving the joint It is common in advanced arthritis for significant secondary changes to occur. For example, in someone who has limited their physical activity: Muscle weakness, Loss of flexibility, Decreased aerobic fitness

Material & Methods:

Etodolac: A.R. Lifesciences, Hyderabad, Telangana, Sodium Chloride, Potassium Chloride, Sodium bicarbonate, Cellulose acetate (D.S. 39.8), Microcrystalline Cellulose, acetone, iso propyl alcohol, castor oil, Polyethelene glycol 400: supplied by Vishal Chem, Thane.

Experimantal:

Formulation Of Core Capsule

The core Capsule was prepared by manual method. The different batches prepared and their composition formulae are mentioned in the table 1.

Table 1: *Designed composition details of different Etodolac EOP Capsule batches.*

Sr. No.	INGREDIENTS (Mg/Capsule)	BATCH CODE									
		01	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**

01	Etodolac	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
02	MCC	**88**	**88**	**88**	**88**	**58**	**48**	**38**	**58**	**48**	**23**
03	Nacl	**----**	**----**	**----**	**----**	**30**	**40**	**50**	**----**	**----**	**40**
04	Kcl	**----**	**----**	**----**	**----**	**----**	**----**	**----**	**30**	**40**	**----**
05	NaHCO3	**----**	**-----**	**-----**	**-----**	**-----**	**-----**	**-----**	**-----**	**-----**	**25**
06	SLS	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**

MCC-Microcrystalline cellulose, Nacl-Sodium chloride, Kcl-Potassium chloride, NaHCo3-Sodium bicarbonate, SLS-Sodium lauryl sulphate.

Preformulation Study of Powder Blend

Preformulation studies are the first step in the development of dosage form of a drug substance. Preformulation investigations are designed to identify those physicochemical properties and excipient that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. Followings are the test performed for the preformulation study.

1) Identification of drug by UV
2) Drug-Excipients interaction study
3) Bulk density
4) Tapped density
5) Flow property (Angle of Repose)
6) Carr's index & Hausner's ratio

Preapration of Elementry Osmatic Pump Capsule

Formulation of core Capsule

Accurately weighed quantities of ingredients mentioned in table 1 were passed through sieve No. 85 (aperture size 180 micron, British standard). The entire ingredients, were manually blended homogeneously in a mortar by way of geometric dilution. The homogeneous blend was then filled manually in Hard Gelatine Capsules (400 mg).

Coating of core Capsule:

Table 2: *Formula used for coating purpose*

Sr. No.	**COATING FORMULATION**	
01.	**Cellulose acetate**	**2% w/v**
02.	**Castor oil or Polyethyleneglycol(400)**	**20% of total solid polymer 10%v/v**
03.	**Isopropyl alcohol**	**10% v/v**
04.	**Acetone**	**q.s.to 100% v/v**

The coating operation was performed on 40-Capsule batch in a conventional laboratory model of stainless steel, 20 cm diameter pear shaped, baffled coating pan. Baffled were three in number to allow free tumbling of Capsules. The pan speed was 30 rpm and the coating solution was sprayed on tumbling bed of Capsule with the help of spray gun manually. The inlet air temperature was 30 and the manually coating procedure used was intermittent spraying and drying technique. The coat weight and thus was coating thickness was controlled by the volume of coating solution consumed in the coating process. Coated capsule were allowed to dry completely. An appropriate orifice was drilled on one face of the capsule through the membrane by mechanical micro drill.

Evolution of Uncoated Capsule

Weight Variation

Twenty Capsules were randomly selected from each batch and individually weigh. The average weight and standard deviation of 20 capsules was calculated. The batch passes the test for weight variation. If not more than 2 of the individual Capsule weight deviates from the average weight. Weight variation of uncoated capsule was performed by taking random sample of 20 capsules. All the capsules were individually weigh to calculate average weight and to verify the weight of the same.

Evaluation 0f Coated Capsule

Uniformity of Coating

The uniformity of coating among the tablet was estimated by determining the weight, thickness, and diameter of tablet before and after coating using 20 individual tablets, and the corresponding average values, standard deviation (SD) and coefficient of variation (CV) were calculated.

Coat weight and Thickness

The coat weight and thickness were determined (n=20) using a standard analytical balance and screw gauge, respectively, and their corresponding S.D. values were calculated.

Orifice Diameter

The average orifice diameter of the coated capsule was determined microscopically (n=20) using a recalibrated ocular microscope.

***In-vitro* release**

In vitro releases of Etodolac from various OPCs were investigated using the standard USP dissolution apparatus II at 100rpm. One capsule was placed in 900mL of dissolution media equilibrated to 37 ± 0.1 ^{0}C. Then 5mL sample were withdrawn, from the point halfway between the surface of the dissolution medium and the top of the paddle, with pipette at different time interval, replacing with an equal volume of pre-warmed (37±0.1^{0}C.) fresh dissolution medium and analyzed spectrophotometerically at 254nm after suitable dilution. Each study was done in triplicate and the mean values are reported.

Drug Release as a Function of Agitation Intensity

To study the effect of agitation intensity, drug release studies were performed at a relatively high (100 rpm) and low (50 rpm) agitation intensity and at static condition using the USP dissolution apparatus in saline phosphate buffer pH-7.4, similarity as described above. Under static conditions, samples at different times were taken after uniform mixing of the medium to preclude any possible sampling error.

Effect of pH of the Dissolution medium on Release rate

Release rates of Etodolac from OPTs in saline phosphate buffer of pH 7.4 and in 0.1 N HCl of pH 1.2 were compared using USP dissolution apparatus at 100rpm, similarly as described above.

Kinetic Model Fitting Study

Kinetics release studies

For determination of drug release kinetics from osmotic capsule , *in-vitro* release data were analyzed by zero order , first order, Higuchi, and Korsmeyer and Peppas model

Drilling of Orifice in Eop Capsule

The drilling of different sizes of orifice was done by with the help of mechanical microdrill as shown in figure 1 & 2.

Figure 1: *Mechanical microdrill & different size of rods*

Figure 2: *Drilling of orifice in EOP Capsule with mechanical microdrill*

Result & discussion:

Preformulation Studies of Powder Blend

The Preformulation study was carried out. The result obtain is presented in table 3.

Table 3: *Precompression parameter of powder blend of Etodolac, (Mean, (SD), (n=3))*

Batch Code	Angle of Repose(θ)	Tapped Density(g/cc)	Bulk Density(g/cc)	Carr's Index(%)	Hausner's Ratio
1a	**36.28±** (1.07)	**0.44±** (0.07)	**0.36±** (0.007**)**	**19.61±** (0.91)	**1.21±** (0.09)
2a	**37.49±** (1.06)	**0.45±** (0.013)	**0.38±** (0.011)	**16.18±** (0.93)	**1.17±** (0.08)
3a	**39.63±** (1.13)	**0.47±** (0.013)	**0.39±** (0.013)	**18.37±** (1.05)	**1.20±** (0.07)
4a	**35.40±** (1.12)	**0.48±** (0.017)	**0.40±** (0.012)	**18.04±** (1.11)	**1.21±** (0.06)

5a	**38.75±** (1.17)	**0.43±** (0.009)	**0.34±** (0.012)	**18.55±** (1.15)	**1.23±** (0.018)
6a	**39.31±** (1.13)	**0.49±** (0.015)	**0.40±** (0.013)	**19.77±** (1.07)	**1.22±** (0.014)
7a	**38.81±** (1.12)	**0.43±** (0.017)	**0.36±** (0.017)	**17.63±** (1.11)	**1.21±** (0.011)
8a	**36.47±** (1.09)	**0.48±** (0.013)	**0.40±** (0.07)	**18.05±** (1.13)	**1.21±** (0.004)
9a	**36.57±** (1.25)	**0.47±** (0.019)	**0.39±** (0.013)	**18.37±** (1.02)	**1.22±** (0.08)
10a	**37.25±** (1.17)	**0.51±** (0.014)	**0.36±** (0.014)	**17.63±** (1.17)	**1.43±** (0.06)

Evaluation of Core Capsule

Weight Variation

The weight variation test was carried out and the mean average weights of the batches found are given in the table 4. As the Indian pharmacopoeia limit prescribed is of ± 7.5 % of the average weights, all the batches are well within the limit, hence all the batches pass the weight variation test.

Table 4: *Evaluation details of uncoated core capsule of Etodolac, (Mean, (SD), (n=20))*

Sr No	Name of test	Batch Code									
		1a	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**
01	**Avg. wt. of uncoated Capsule (mg)**	**397±** (1.91)	**398±** (2.01)	**400±** (2.37)	**402±** (1.81)	**399±** (2.10)	**400±** (2.01)	**396±** (1.83)	**401±** (2.20)	**400±** (2.17)	**398±** (1.92)
02	**Thickness in(mm)**	**4.13±** (0.095)	**4.03±** (0.071)	**4.15±** (0.083)	**3.97±** (0.091)	**4.03±** (0.085)	**3.89±** (0.081)	**4.17±** (0.091)	**4.18±** (0.093)	**4.05±** (0.081)	**4.13±** (0.083)
03	**Diameter in(mm)**	**10.12±** (0.073)	**10.16±** (0.074)	**10.12±** (0.081)	**10.10±** (0.085)	**10.14±** (0.061)	**10.11±** (0.075)	**10.18±** (0.081)	**10.15±** (0.076)	**10.14±** (0.081)	**10.12±** (0.083)

In-Vitro Release Study Of Coated Capsule Batches

The aim of present study is to develop, evaluate and do the *in-vitro* characterization of osmotic pump capsule of Etodolac. The core capsule was fabricated by using microcrystalline cellulose as a diluent. Different batches of osmotic pump capsule were fabricated by using different type and concentration of osmogen. The batches with different membrane thickness, delivery orifice size, and plasticizer were developed to evaluate their effect. The Elementary osmotic pump developed was also evaluated and tested for its proven character of unaffected release of agitation intensity, pH of dissolution fluid.

The core capsule developed was coated with cellulose acetate polymer because of its high water vapor transmission rate and mechanical strength than other polymer. Two different category polymer of water soluble (polyethylene glycol-400)) and water insoluble (castor oil) type was used.

The core capsule were coated by using dilute polymer solution as it has advantage of resulting in more uniform coating and less sticking during coating operation. A plasticizer was included in the coating formulation in order to improve the stability of the film by increasing the flexibility of the membrane.

The plasticizer improve the membrane forming properties of polymer by improving its physical properties such as flexibility, hardness, tensile strength, and elasticity. The membrane characteristics and specifications of various elementary osmotic capsule designed shown in table 5 and 6 respectively.

Table 5: *Membrane characteristic of various EOP Etodolac capsule designed, (Mean, (SD), (n=20))*

Sr. no.	Parameter	Batch Code									
		1a	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**
01	**Coat Nature**	**SP**	**SP**	**SP**	**MP**	**SP**	**SP**	**SP**	**MP**	**SP**	**SP**
02	**Coat weight (mg)**	**4.4±** (0.21)	**4.6±** (0.25)	**4.5±** (0.13)	**6.4±** (0.21)	**4.6±** (0.23)	**6.9±** (0.5)	**8±** (0.17)	**6.4±** (0.27)	**4.6±** (0.24)	**4.5±** (0.12)

03	**Coat Thickness (µm)**	**40±** (1.12)	**40±** (1.56)	**40±** (2.03)	**75±** (1.51)	**40±** (1.14)	**50±** (2.7)	**60±** (1.52)	**75±** (1.51)	**40±** (1.27)	**40±** (1.21)
04	**Orifice Diameter (mm)**	---	**0.3±** (0.013)	**0.5±** (0.05)	----	**0.3±** (0.011)	**0.3±** (0.027)	**0.3±** (0.014)	-----	**0.3±** (0.012)	**0.3±** (0.019)

MP- *Microporous cellulose acetate coat with propylene glycol plasticizer,*
[1]Calculated from geometry of the capsule, SP- *semipermeable membrane with castor oil as plasticizer*

Table 6: *Specification for different batches of EOP Etodolac Capsule designed (Mean, (SD), (n=20))*

Sr no	**Para-meter**	**Batch Code**									
		1a	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**
01	**EOPs Weight (mg)**	**397±** (2.321)	**401±** (2.47)	**404±** (2.31)	**405±** (2.18)	**400±** (2.35)	**403±** (2.17)	**400±** (2.31)	**397±** (2.31)	**401±** (2.47)	**400±** (2.31)
02	**Thick ness (mm)**	**4.47±** (0.063)	**4.43±** (0.065)	**4.39±** (0.045)	**4.21±** (0.065)	**4.23±** (0.067)	**4.24±** (0.057)	**4.61±** (0.035)	**4.67±** (0.046)	**4.36±** (0.065)	**4.39±** (0.064)
03	**Dimeter (mm)**	**10.54±** (0.031)	**10.37±** (0.018)	**10.54±** (0.028)	**10.63±** (0.032)	**10.51±** (0.025)	**10.37±** (0.029)	**10.63±** (0.037)	**10.53±** (0.032)	**10.48±** (0.034)	**10.45±** (0.033)
04	**Surface area[1] (cm^2)**	**376.36±** (0.023)	**431.73±** (0.022)	**445.27±** (0.032)	**423.54±** (0.031)	**456.21±** (0.034)	**437.43±** (0.036)	**439.29±** (0.024)	**432.23±** (0.036)	**426.26±** (0.019)	**441.43±** (0.027)
05	**Volume[1] (cm^3)**	**599.91±** (0.029)	**69.36±** (0.022)	**599.53±** (0.019)	**597.67±** (0.019)	**579.87±** (0.023)	**607.39±** (0.029)	**596.34±** (0.012)	**603.33±** (0.012)	**578.32±** (0.017)	**598.29±** (0.021)

Uniformity of coating

The uniformity within batch before and after coating and also the comparing CVs of them is shown in table 16. Comparison within batch of tablets before and after coating of Coefficient of variances(CV) will say about the uniformity of the coating operation. Consistent CVs before and after coating guaranty about coating uniformity. Comparison of CVs between batches says about the uniformity between batches of tablet before and after coating as shown in table 7.

Table 7: *Determination of Uniformity of Coating*

Sr No	**Parameter**		**Batch code**								
			1a	2a	3a	4a	5a	6a	7a	8a	9a	10a
01.	Coefficient of weight Variation	Before coating After Coating	5.68 5.69	5.85 5.86	5.81 5.80	5.70 5.69	5.70 5.75	5.84 5.85	5.95 5.97	5.90 5.93	5.80 5.81	5.89 5.91
02.	Coefficient of Thickness Variation	Before coating After Coating	0.005 0.003	0.004 0.002	0.004 0.002	0.009 0.007	0.005 0.005	0.008 0.004	0.006 0.004	0.006 0.004	0.006 0.004	0.006 0.003
03.	Coefficient of Diameter	Before coating	0.928 0.931	0.936 	0.941 0.943	0.925 0.927	0.944 0.945	0.957 0.959	0.963 0.965	0.943 0.946	0.922 0.923	0.919 0.921

	t Variation	After Coating		0.937								
04.	Coefficient of coat weight Variation	0.238	0.549	0.541	0.460	0.529	0.322	0.14	0.559	0.448	0.468	0.238
05.	Coefficient of coat thickness Variation	0.40	0.30	0.35	0.35	0.31	0.44	0.07	0.35	0.35	0.05	0.40

Drug release

In-vitro cumulative percentage drug release of different EOP Capsule batches of Etodolac in saline phosphate buffer are shown in table 8

Table 8.: *Percentage release per hour of Etodolac, (Mean, (SD), (n=3))*

Hours	Batch code									
	1a	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**
01	**1.05±** (0.78)	**1.18±** (1.34)	**1.21±** (1.46)	**5.03±** (1.56)	**7.31±** (1.54)	**6.07±** (2.54)	**5.25±** (1.54)	**6.67±** (1.65)	**4.88±** (1.67)	**5.14±** (1.45)
02	**2.13±** (0.79)	**2.87±** (1.37)	**3.3±** (1.67)	**10.09±** (1.51)	**15.33±** (1.56)	**12.47±** (2.43)	**10.7±** (1.22)	**15.49±** (1.67)	**9.81±** (1.56)	**11.47±** (1.47)
04	**3.24±** (0.78)	**4.73±** (1.43)	**5.26±** (1.61)	**15.16±** (1.61)	**23.45±** (1.56)	**18.95±** (2.45)	**16.34±** (1.54)	**24.39±** (1.67)	**14.85±** (1.63)	**16.83±** (1.47)
06	**4.37±** (1.08)	**6.58±** (1.45)	**7.43±** (1.43)	**20.25±** (1.36)	**31.63±** (1.46)	**25.75±** (1.56)	**21.07±** (1.45)	**34.36±** (1.67)	**19.97±** (1.34)	**22.32±** (1.34)
08	**5.52±** (1.23)	**8.53±** (1.43)	**9.64±** (1.32)	**25.48±** (1.54)	**39.85±** (1.49)	**32.63±** (1.61)	**27.7±** (1.49)	**43.45±** (1.56)	**26.15±** (1.81)	**27.86±** (1.39)
10	**6.64±** (1.61)	**10.47±** (1.41)	**11.96±** (1.64)	**30.74±** (1.43)	**48.19±** (1.45)	**39.34±** (1.45)	**33.77±** (1.56)	**52.7±** (1.48)	**31.5±** (1.45)	**33.51±** (1.45)
12	**7.82±** (1.91)	**12.45±** (1.46)	**14.31±** (2.01)	**37.3±** (1.34)	**56.59±** (1.34)	**46.83±** (1.45)	**39.7±** (1.71)	**61.71±** (1.34)	**36.45±** (1.43)	**39.5±** (1.43)
14	**8.98±** (0.97)	**14.49±** (1.65)	**16.76±** (2.31)	**42.5±** (1.47)	**66.01±** (1.34)	**54.11±** (1.37)	**45.49±** (1.43)	**71.06±** (1.45)	**42.07±** (1.45)	**45.33±** (1.34)

Kinetics of drug release

For comparison of In-vitro drug release profile of Etodolac from osmotic pump tablets of different membrane type i.e. semipermiable and microporous are shown in figure 3.

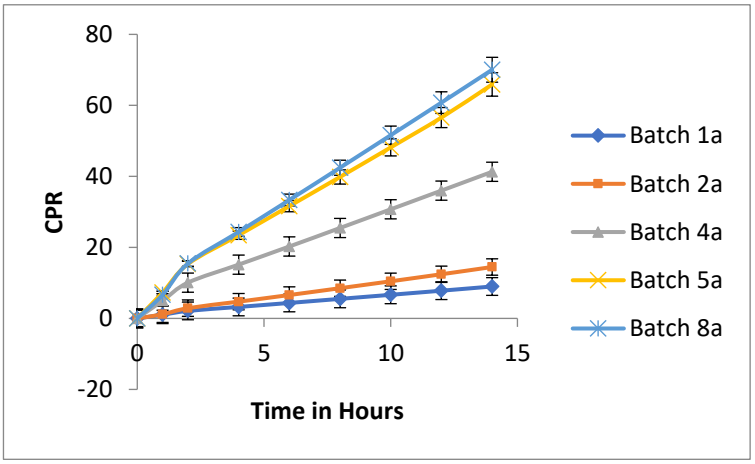

Figure 3: *Release profile of Etodolac from EOPs coated with different membrane thickness in Saline phosphate buffer 7.4, (Mean, (SD), (n=3))*

To explain the kinetics of drug release, release data were fitted to the modified Korsmeyer equation

$$Q(t) = Kt^n \quad \text{------} \quad (8.1)$$

Where,
Q(t) - is the fraction of the drug released after time t,
K - is a constant and,
n - is the time exponent that characterizes the drug transport mechanism. When the logarithm of the cumulative percentage released(CPR) is plotted against the logarithm of the time in minutes, the slope of the graph will give the value of the time exponent n. Calculated values of n, along with other release characteristics such as lag time, average release rate, and cumulative percent release released(CPR) at 14 hours, for various batches of Elementary osmotic pumps(EOP) are listed in table 8.7 for comparison.

Table 9: *Comparison of release characteristic and time exponents of EOP Capsule of Etodolac.*

Batch Code	Average lag time (n=3)	Average release rate(Mg/Hr)	Mean CPR at 8 Hrs.	Time Exponent (n)	Coefficient of Correlation
1a	1.01	1.01	8.98	0.775	0.995
2a	1.03	1.63	14.49	0.921	0.992
3a	0.99	1.88	16.76	0.964	0.989
4a	Zero	4.64	42.5	0.755	0.994
5a	1.02	7.32	66.01	0.780	0.995
6a	1.01	6.08	54.11	0.789	0.994
7a	1.01	5.11	45.49	0.783	0.994
8a	Zero	7.88	71.06	0.859	0.922
9a	1.03	4.61	42.07	0.763	0.995
10a	0.98	4.98	45.33	0.770	0.994

The category of batches for which the release kinetics was compared is semipermiable and microporous membrane coated batches. The semipermiable membrane was formed by using water in soluble plasticizer, castor oil, and microporous membrane was formed when the water soluble plasticizer, polyethylene glycol (400) was used.

The microporous membrane is formed by water soluble plasticizer as it gets in contact with water get soluble and form porous, sponge like membrane. This is evident from the release profile of 4a and 8a coded batches. The drug release is almost diffusion controlled as can be observed by following their curve and can also be confirmed by the value of time exponent. The observance of non-significant zero lag time is attributed to the same reason of nature of membrane i.e. microporous.

On the other hand, the semipermiable membrane coated EOP batches such as 2a and 5a formed by using castor oil as a plasticizer exhibited zero order release pattern. The release was mainly through the delivery orifice and has shown a lag time of short duration. Thus the drug release from the microporous coated EOPs is diffusion controlled while drug release from semipermiable coated EOPs is controlled by convection resulting in consistent linear release.

The release rate of drug from oral osmotic pump depends on factors which can summarize from formula as below

$$\left(\frac{dM}{dt}\right) z = \frac{S}{h} K \pi Cs \quad \text{-----} \quad \textbf{(8.2)}$$

Where,

(dM/dt)z - is the rate of delivery of the solute (drug) under zero-order condition,

S - is the semipermeable membrane area,

h - s the membrane thickness,

K - is a permeability coefficient and,

πCs - is the osmotic pressure of the formulation under zero-order condition.

Kinetic Model Fitting Study:

To explain the kinetics of drug release, release data were fitted to the various models like zero order, first order, Higuchi model, Hixon-Crowell, Korsmeyer–Peppas model. There values of coefficient correlation and time exponent in Peppas model shown in table 8.8.

Table 10: *Coefficient of correlation and release exponent from different models*

Batch	Zero order	Higuchi	First order	Hixon-crowell	Korsemeyer-peppas	
	R^2	R^2	R^2	R^2	R^2	N
6a	0.983	0.967	0.995	0.992	0.999	1.02

For non-fickian release , the value of n falls between 0.5-1.0, while in case of Fickian diffusion, n=0.5; for zero order release (case II transport), n=1; for supercase II transport , n> 1.2.Release exponent (n) value of optimized batch i.e. 6a is equal to 1 in Korsmeyer peppas model. So it follows zero order release

Effect of membrane thickness

Membrane thickness has a profound effect over the release rate of drug from osmotic pump. To evaluate and quantify the effect of membrane thickness, batches of different membrane thickness was fabricated and their release profile is compared in figure 4.

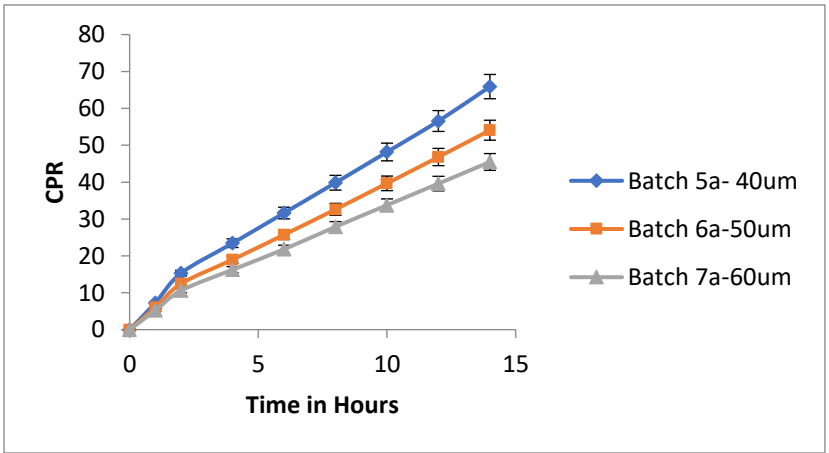

Figure 4: *Effect of membrane thickness on release profile of Etodolac from EOPs in saline phosphate buffer, (Mean, (SD), (n=3))*

The membrane thickness is inversely proportional to the release rate and eventually with the overall release profile which can expressed by following equation[136]

$$\frac{dm}{dt} = \left(\frac{As}{h}\right)L \quad \text{-------} \quad (8.3)$$

Where,

$\frac{dm}{dt}$ - is the zero-order release rate of the drug,

A - is the surface area of the film coated membrane,

h - is the membrane thickness,

Δπ - is the osmotic pressure difference across the membrane at saturation,

S - is the solubility,

Lp - is the hydraulic permeability of the membrane and,

σ - is the reflection coefficient having the value of one for an ideal semipermiable membrane like cellulose acetate and zero for a non-selective membrane.

The weight of the membrane (W) was shown to be related with the membrane thickness as follows in equation 8.4

$$W = \rho m A h \quad \text{------} \quad (8.4)$$

Where,

ρm - is the membrane density.

Consequently, the release rate can be expressed as a function of the membrane weight (W) by substituting equation 8.4 into equation 8.3.

$$\frac{dm}{dt} = \frac{(A_2)s}{w\rho mLp\sigma\Delta\pi} \quad \text{--------} \quad (8.5)$$

Effect of Delivery orifice size

Delivery orifice serves as a port through which the drug gets released as a result of build-up of osmotic pressure inside the osmotic pump. The delivery orifice should be sufficiently large enough to release the drug and should not allow the build-up of any hydrostatic pressure as hydrostatic pressure may hinder the zero-order release rate. At the same time it should not be larger so that it will allow release of drug by diffusion and not merely by convection for required zero-order rate.

Hence the delivery orifice size should be within upper and lower limit in order to affect zero-order release rate without any hindrance. To observe and get assured the size of delivery orifice of being within limit, batches of different orifice diameter was fabricated and their release rate is plotted in figure 8.7 and 8.8.

The delivery orifice size of 0.3mm and 0.5mm batches i.e. 2a and 3a, has not shown any significant difference in release rate ($p>0.01$) as can be inferred from the graph plotted comparing the release rate of this two batches in figure 5. Therefore it can inferred that the delivery size of range 0.3 to 0.5mm has exhibited perfect zero order release rate and has not allowed the diffusion to play a role in release and has also not allowed to build-up the hydrostatic pressure. The pump has maintained its shape during the operating period of 14 hours. Hence it can be inferred that the range of size of delivery orifice is well within limit as described by Theeuwes[138] and Ramadan and Tawashi.

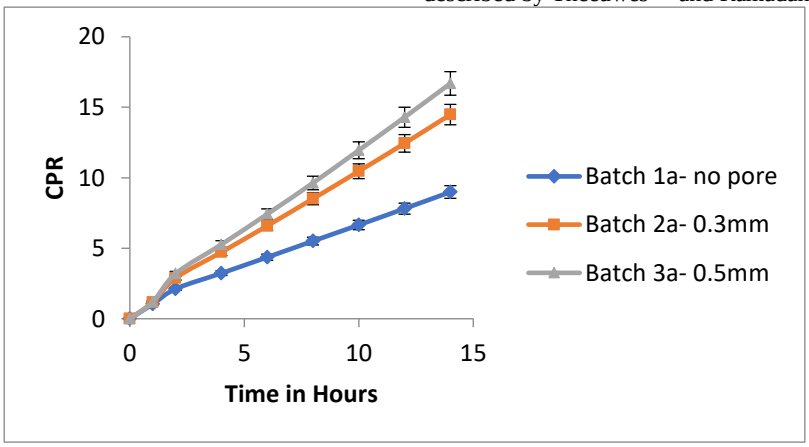

Figure 5: *Effect of orifice diameter on release profile of Etodolac from EOPs in saline phosphate buffer. (Mean, (SD), (n=3))*

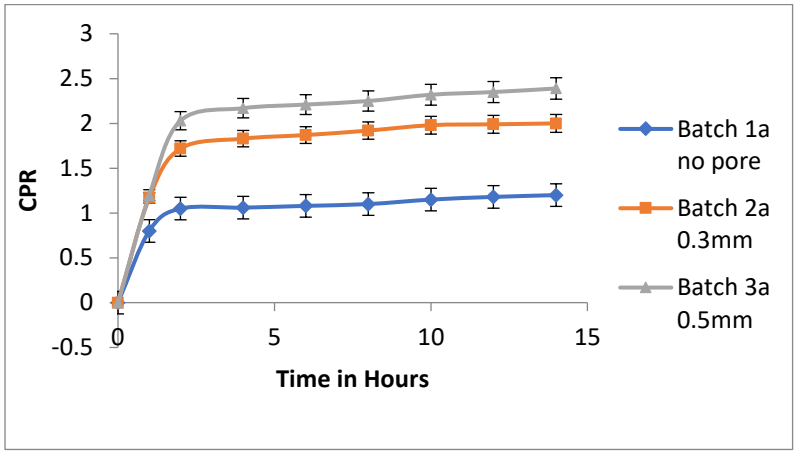

Figure 6: *Effect of Orifice diameter on release profile of Etodolac from EOPs in saline phosphate buffer. (Mean, (SD), (n=3))*

Effect of agitation intensity

Osmotic pump drug delivery system is such a delivery system which is un-affected by environmental condition as agitation intensity. To characterize this feature of osmotic pump the batches coded with 2a and 5a were stirred at 50 and 100rpm and their release profile was evaluated. The release profile has not shown any significant changes even on increase in stirring rate, which can be observed from the graph plotted in figure 7 and 8 respectively. ($p>0.01$)

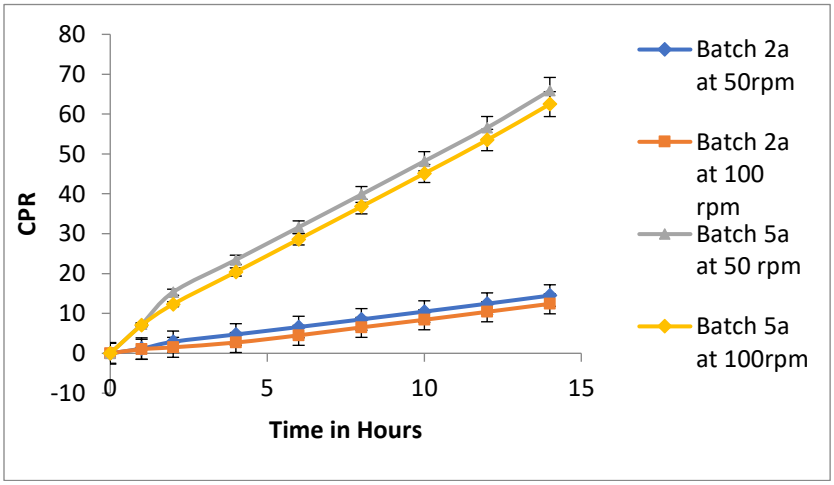

Figure 7: *Effect of agitation intensity on release of Etodolac from EOPs in saline phosphate buffer., (Mean, (SD), (n=3))*

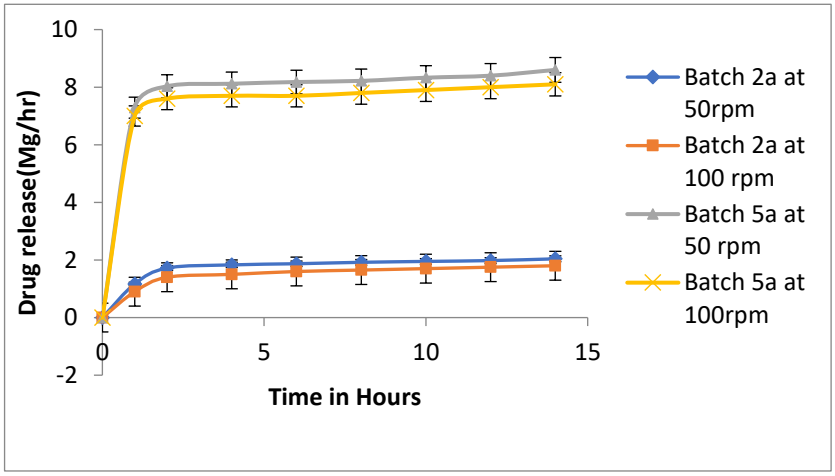

Figure 8: *Effect of agitation intensity on release of Etodolac from EOPs in saline phosphate buffer., (Mean, (SD), (n=3)).*

Effect of pH of the dissolution medium

To verify that the drug delivery profile from osmotically driven delivery system is independent of the other environmental factor as pH of dissolution medium, the dissolution test was carried out in pH 1.2 and also in pH 7.4. This is one of the important test to mark the distinguishing characteristic of osmotic pump and advantage over other delivery system. The semipermiable membranes truly ion selective, ions are not allowed to diffuse through the membrane while solvent molecule

is allowed to pass through it. The release profiles are plotted and there release rates were tested in different pH dissolution medium. The average release rate in different pH media were tested for a statistically significant difference and has resulted in no significant difference ($p>0.05$) as shown in figure 9 and 10.

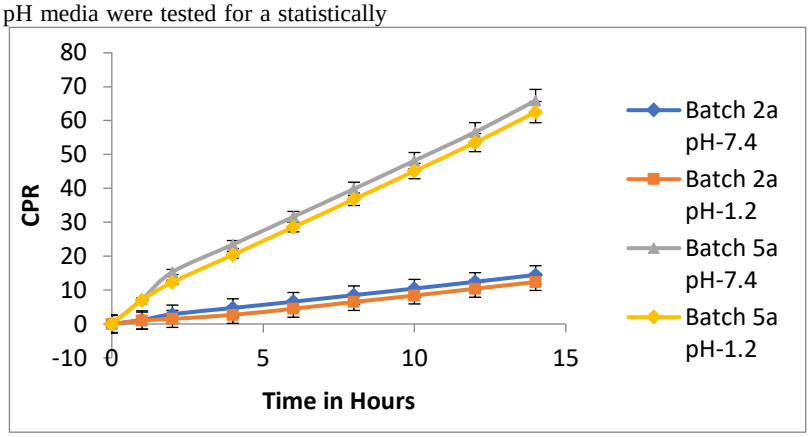

Figure 9: *Effect of pH on release of Etodolac from EOPs in saline phosphate buffer., (Mean, SD, (n=3))*

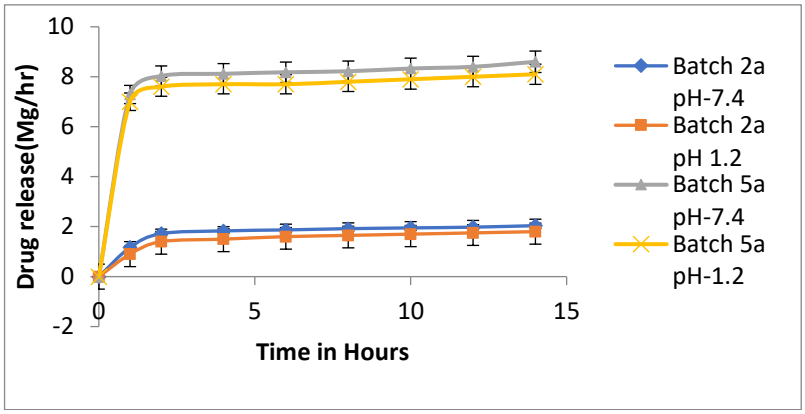

Figure 10: *Effect of pH on release of Etodolac from EOPs in saline phosphate buffer., (Mean, SD, (n=3))*

An important feature of any osmotic drug delivery system is that to maintain its mechanical stability and resistance of the film coating to rupture during passage through the gastrointestinal tract.

None of the tablet ruptured during the dissolution studies. Empty polymeric shell retained their original shape and floated on the dissolution medium after completion of drug release.

Release rate of semipermiable membrane coated osmotic pump were unaffected by hydrodynamic condition and as well by the pH of dissolution medium, confirms the nature of membrane as a semipermiable which is in addition confirmed by release rate which is inversely proportional to the membrane thickness. The semipermiable membrane coated batches as 5a, 6a, 7a and as well 9a behaved as a true semipermiable. The semipermiable nature of the membrane believed to involve the passage of solvent through the membrane by a diffusion process or by dissolving the material of the membrane in which the solute is insoluble. The kinetics of drug release remain linear as long as the transport mechanism is unidirectional.

Conclusion:

Etodolac can be developed as a once a day dosage form.(O.D.) Zero-order release rate can be obtained by using cellulose acetate as a polymer and castor oil as a plasticizer. In osmotic delivery systems, osmotic pressure provides the driving force for drug release. Increasing pressure inside the dosage form from water incursion causes the drug to release from the system. The major advantages include precise control of zero-order or other patterned release over an extended time period consistent release rates can be achieved irrespective of the environmental factors at the delivery site. Controlled delivery via osmotic systems also may reduce the side-effect profile by moderating the blood plasma peaks typical of conventional (e.g., instant release) dosage forms.

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