In vitro characterization of elementary osmotic tablet containing celecoxib

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Abstract: Oral dosage form has limited control over the release of drug from dosage form, hence effective plasma level concentration do not achieve at site of action. Such unusual pattern of dosing results in inappropriate or erratic blood plasma concentrations. The absorption of drug from conventional dosage form depends on factors such as-Physio-chemical properties of the drug, presence of excipient, physiological factors such as presence or absence of food, PH of the gastrointestinal tract etc. Present study highlights osmotically driven oral drug delivery system (tablet) containing celecoxib as an active ingredient. Patients with long term treatment of NSAID (e.g. Arthritis) and suffering from various gastrointestinal side effect will be benefited from such a dosage form. Majority of controlled release dosage forms available in market are generally matrix-based, their principal drug release mechanism was based on drug diffusion through the matrix. Such mechanism is changed by-the pH, presence of food, in the gastrointestinal tract. Body's physiological factors (G.I. motility) also contribute their role in unpredictable absorption. All these factors also affect the release of celecoxib from conventional oral dosage form. Osmotic systems utilize the principle of osmosis as delivery force to release the drug from the dosage form, and the release rate has no effect of the body's pH and other physiological factors, also the various side effects due to long term therapy of NSAIDs are reduced. Batch 6 coated with semipermeable membrane give the maximum of 90.28% release from elementary osmotic tablet in control manner up to 8 hours and following zero order release, other batches e.g. 4and 8 coated with microporous membrane follow first order release.

Keywords: Osmotic tablet, celecoxib, NSAID's, oral osmotic tablet.

INTRODUCTION

Osmotic systems use the principle of osmosis as delivery force for delivering the drug from the system, and the release rate is unaffected by the body's pH and other physiological factors. There are several methods of oral osmotic drug delivery system apart from it elementary osmotic pump method was used. Celecoxib, which is selective COX 2 inhibitor used widely for the treatment of Rheumatoid arthritis, osteoarthritis and in ankylosing spondylitis and other general painful conditions (dental and gynecological).

After oral administration, celecoxib is rapidly absorbed and bioavailability is almost 40%. Peak plasma concentrations are reached approximately 11 hours following ingestion. Apart from this, it has been found that conventional oral administration of celecoxib often leads to various side effects such as irritation, ulceration or perforation of intestinal wall, mucosal damage, and gastroenteritis, Presence of food also decreases the absorption of celecoxib. Hence there is need of formulation that can extend the action of celecoxib with controlled slow release from dosage form over a predetermined time period and it will be very good for patients with long term therapy of arthritis and other painful conditions.

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The objective of the present study was to develop elementry osmotic tablet of celecoxib to be taken once daily and to evaluate effect of food and other factors on its release rate. Sodium chloride, potassium chloride & sodium bicarbonate were used as an osmogen. Core tablet of drug was formulated using wet granulation method. The tablets were coated with cellulose acetate as the semi permeable membrane containing castor oil as a plasticizer. Batch 4 and 8 are formulated by utilizing polyethelene glycol (PEG-400) as a plasticizer for formation of microporus membrane and to evaluate comparative drug release with semipermeable membrane.

MATERIALS AND METHODS

Preparation of core tablet

Core tablet of celecoxib was prepared by wet granulation method. The different batches prepared and their composition formula is mentioned in table 1.

Finely powdered and accurately weighed quantities of all ingredients mentioned in formula were passed through sieve No.85 (aperture size 180 micron, British standard). The whole ingredients, except lubricant (magnesium stearate, glidant talc and binder polyvinylpyrrolidone (PVP), were manually mixed homogeneously in a mortar and pastel following geometric dilution. Thereafter mixture was moistened with aqueous solution of 10% (m/v) PVP, and granulated through sieve No.18 (aperture

Table 1: Formulation of elementary osmotic tablet of celecoxib

S. No.	Ingredient (mg/tablet)	Batch Code									
		01	02	03	04	05	06	07	08	09	10
01	Celecoxib	100	100	100	100	100	100	100	100	100	100
02	MCC	177	177	177	177	147	137	127	147	137	112
03	Nacl	----	----	----	----	30	40	50	----	----	40
04	Kcl	----	----	----	----	----	----	----	30	40	----
05	$NaHCO_3$	----	----	----	----	----	----	-----	----	----	25
06	SLS	12	12	12	12	12	12	12	12	12	12
07	Talc	03	03	03	03	03	03	03	03	03	03
08	Mg Stearate	03	03	03	03	03	03	03	03	03	03
09	PVP	05	05	05	05	05	05	05	05	05	05

MCC-Microcrystalline cellulose, Nacl-Sodium chloride, Kcl-Potassium chloride
NaHCo3-Sodium bicarbonate, SLS-Sodium lauryl sulphate, PVP-Polyvinyl pyrrolidine

size 1003 micron, US standard) and dried in a hot air oven at 60ºC for sufficient time period (generally 3 to 4 hr) so moisture content of the respective granules reached 2-4% approximately. Later the dried granules were passed through sieve No.25 aperture size710 micron, US standard) and mixed with talc and magnesium stearate. The homogeneous mixture was then compressed into tablets (100/mg) using 10/mm diameter, deep concave punch. The compression force of tablet was adjusted to give approximately 7-8kg/cm^2 hardness on a Monsanto tablet hardness tester.

Table 2: Coating formula

Coating Formulation	
Ingredient	Concentration
Cellulose acetate (39.8 -acetyl substitution)	2% w/v
Castor oil or Polyethyleneglycol (400)	20% of total solid polymer 10% v/v
Isopropyl alcohol	10% v/v
Acetone	q.s. to 100% v/v

The coating of tablets was performed on conventional laboratory model coating pan in a batch of 40 in stainless steel, 20 cm diameter pear shaped, baffled coating pan. Baffles were three in number to allow free tumbling of tablets in the pan. The speed of pan was adjusted 30 rpm and the coating solution was sprayed on revolving bed of tablets with the help of spray gun manually. The inlet air temperature was maintained 40-45ºC and the coating procedure used was manual alternate spraying and drying technique. The coat weight and thickness of coating was controlled by the consumption of coating solution in the coating process. Coated tablets were allowed to dry completely in a hot air oven at 60ºC and finishing of tablets was done by using standard polishing procedure. An approximate pore was drilled in the center on one face of the tablet through the membrane by using mechanical microdrill.

Evaluation of tablet

In-vitro release

Celecoxib in saline phosphate buffer are shown in table 4.

In vitro release study of celecoxib from various elementary osmotic tablet were performed using the standard USP dissolution apparatus II at 50rpm. One tablet was placed in 900ml of dissolution media equilibrated to 37±0.1ºC. Then 5-ml sample were withdrawn, from middle of the surface of the dissolution medium and the top of the paddle, using pipette at every hour, on the contrary replacing with same volume of pre-warmed (37±0.1ºC) fresh dissolution medium and analyzed spectrophotometrically at 254nm after suitable dilution. Each sampling was performed in triplicate and the average values were calculated and reported.

Drug release as a function of agitation intensity

To analyze the effect of agitation intensity on drug release, studies were performed at a relatively high (100 rpm) and low (50 rpm) agitation intensity and maintaining static condition using the USP dissolution apparatus II in pH 1.2, similarly as mentioned above. Under static conditions, samples at different time intervals were taken after uniform mixing of the medium to avoid any possible sampling error.

Effect of pH of the dissolution medium on release rate:

Release rates of celecoxib from elementary osmotic tablet in phosphate buffer of pH 1.2 and 7.4 were compared using USP dissolution apparatus at 50 rpm, similarly as mentioned above.

Calibration curve for celecoxib

Drug release kinetics

To explain the kinetics of drug release more clearly, release data were fitted to the Korsmeyer equation which describe the general behavior of solute release from controlled release polymeric tablets.

Q =Ktn, Where, Q - is the percent of drug released
t-is the release time
K-is the constant that incorporated structure and geometric Characteristics of the release device and n-is

the release exponent that indicates the mechanism of release

When n - is equal to 1, the release mechanism approaches zero order.

Drug and Excipient interaction

To detect any incompatibility of drug with excipient the IR spectroscopic analysis was carried out; the potassium bromide disc-containing drug and physical mixture of drug and excipient was prepared to record the spectrum in the range of 400 to 4000 cm^{-1} by using FTIR Spectrophotometer

RESULTS

Drug release

In-vitro cumulative percent drug release of different EOP's batches of celecoxib in 1.2 and 7.2 PH were shown in table.

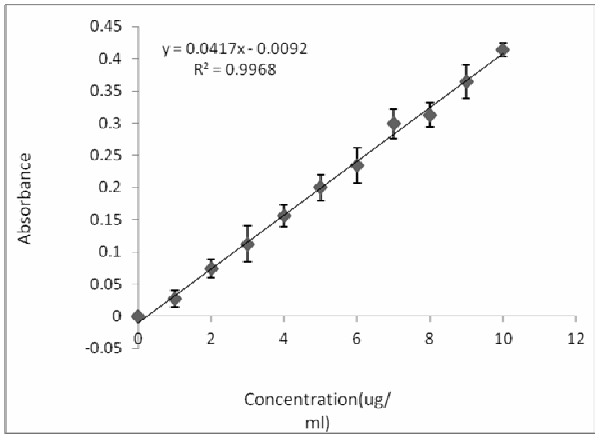

Fig. 1: Standard calibration curve for Celecoxib in 0.1 N HCL having PH-1.2, Bars indicates SD (n=3).

Kinetics of drug release

For comparison of *in vitro* drug release profile of celecoxib from osmotic tablets of different membrane type i.e. semipermeable and microporous are shown in fig. 2.

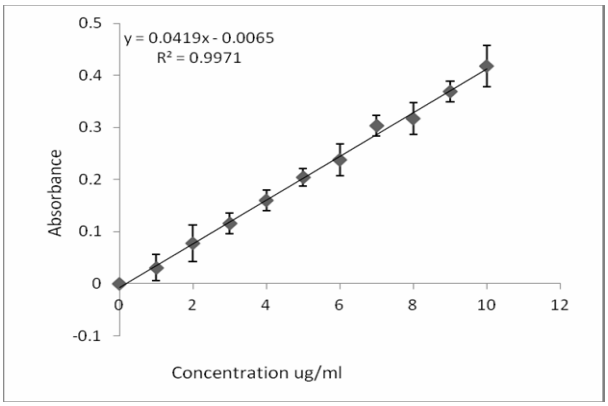

Fig. 2: Calibration curve of Celecoxib in

To explain the kinetics of drug release, release data were fitted to the modified Korsmeyer equation $Q(t)=Kt_n$, 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 percent 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 CPR at 7hr, for various batches of EOPs are listed in table 4 for comparison. The category of batches for which the release kinetics was compared is semipermeable and microporous membrane coated batches. The semipermeable membrane was formed by

Table 3: Percentage release per hour of different EOP batches of celecoxib (S.D n=3)

Hr	Batch Code									
	01	02	03	04	05	06	07	08	09	10
1	2.06± (0.95)	2.61± (0.90)	2.89± (0.90)	6.49± (0.99)	9.87± (2.00)	9.32± (1.70)	4.43± (0.67)	9.19± (1.19)	8.24± (1.23)	5.25± (3.21)
2	4.62± (0.90)	5.57± (1.20)	7.55± (0.99)	14.14± (1.00)	20.96± (1.89)	19.84± (2.00)	11.48± (1.80)	19.28± (2.21)	16.74± (3.10)	11.26± (3.00)
3	7.73± (1.45)	8.79± (1.56)	12.74± (2.23)	21.87± (1.34)	32.08± (2.60)	30.96± (3.70)	19.91± (2.60)	29.78± (2.31)	25.76± (2.50)	17.70± (2.31)
4	11.12± (1.99)	12.29± (1.34)	18.13± (1.09)	31.44± (1.46)	44.04± (3.00)	42.10± (1.61)	30.35± (2.32)	40.67± (1.98)	34.84± (3.00)	24.21± (3.00)
5	14.85± (2.00)	16.19± (1.21)	23.60± (1.97)	39.15± (1.99)	55.72± (1.50)	53.85± (2.00)	42.37± (2.23)	51.75± (2.00)	44.11± (1.60)	1.06± (3.50)
6	18.70± (1.30)	20.71± (2.03)	28.93± (1.70)	47.89± (2.00)	67.79± (2.47)	65.84± (2.50)	55.49± (1.45)	63.28± (1.21)	53.51± (2.50)	38.18± (2.41)
7	22.78± (1.30)	26.30± (3.00)	34.44± (1.99)	57.10± (2.78)	80.31± (1.89)	77.95± (1.50)	69.13± (2.91)	74.97± (2.46)	63.11± (2.60)	45.94± (3.60)
8	27.74± (1.46)	32.17± (3.05)	40.00± (1.67)	66.94± (0.88)	93.01± (1.99)	90.28± (1.10)	83.06± (3.00)	86.70± (3.00)	72.79± (1.52)	53.78± (2.50)

Table 4: Percentage release per hour of clecoxib EOP (S.D) (n=3)

Hr	Batch Code									
	01	02	03	04	05	06	07	08	09	10
1	2.06 ± (0.95)	2.61± (0.90)	2.89± (0.90)	6.49± (0.99)	9.87± (2.00)	9.32± (1.70)	4.43± (0.67)	9.19± (1.19)	8.24± (1.23)	5.25± (3.21)
2	4.62± (0.90)	5.57± (1.20)	7.55± (0.99)	14.14± (1.00)	20.96± (1.89)	19.84± (2.00)	11.48± (1.80)	19.28± (2.21)	16.74± (3.10)	11.26± (3.00)
3	7.73± (1.45)	8.79± (1.56)	12.74± (2.23)	21.87± (1.34)	32.08± (2.60)	30.96± (3.70)	19.91± (2.60)	29.78± (2.31)	25.76± (2.50)	17.70± (2.31)
4	11.12± (1.99)	12.29± (1.34)	18.13± (1.09)	31.44± (1.46)	44.04± (3.00)	42.10± (1.61)	30.35± (2.32)	40.67± (1.98)	34.84± (3.00)	24.21± (3.00)
5	14.85± (2.00)	16.19± (1.21)	23.60± (1.97)	39.15± (1.99)	55.72± (1.50)	53.85± (2.00)	42.37± (2.23)	51.75± (2.00)	44.11± (1.60)	31.06± (3.50)
6	18.70± (1.30)	20.71± (2.03)	28.93± (1.70)	47.89± (2.00)	67.79± (2.47)	65.84± (2.50)	55.49± (1.45)	63.28± (1.21)	53.51± (2.50)	38.18± (2.41)
7	22.78± (1.30)	26.30± (3.00)	34.44± (1.99)	57.10± (2.78)	80.31± (1.89)	77.95± (1.50)	69.13± (2.91)	74.97± (2.46)	63.11± (2.60)	45.94± (3.60)
8	27.74± (1.46)	32.17± (3.05)	40.00± (1.67)	66.94± (0.88)	93.01± (1.99)	90.28± (1.10)	83.06± (3.00)	86.70± (3.00)	72.79± (1.52)	53.78± (2.50)

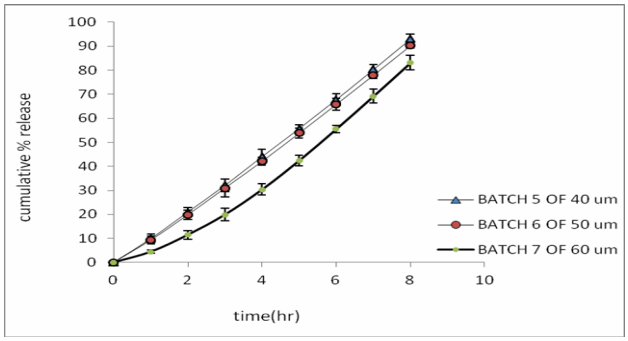

Fig. 3: Release profile of celecoxib from EOPs coated with different membranes in 7.2 pH. (Bars indicates S.D. n=3).

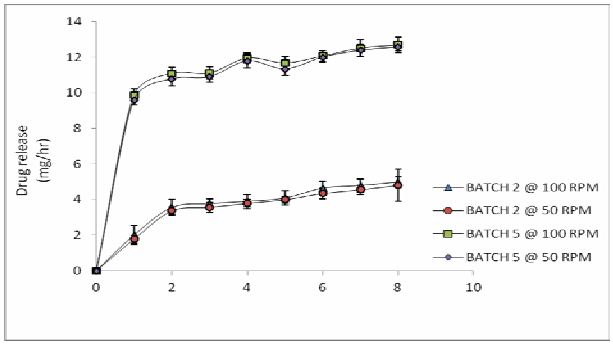

Fig. 4: Effect of agitation intensity on celecoxib tablet.

Table 5: Comparison of release characteristics and time exponents of EOPs

Batch Code	Average lag time (n=3)	Average Release rate (Mg/Hr)	Mean CPR at 8 Hrs.	Time Exponent (n)	Coeffi. of correlation
01	1.02	3.64	22.74	1.2	0.999
02	1.01	4.02	32.17	1.1	0.996
03	1.01	5.1	40.00	1.3	0.998
04	Zero	8.36	66.94	1.1	0.999
05	1.00	11.62	93.01	1.0	0.999
06	1.00	11.28	90.28	1.0	0.999
07	1.01	10.83	83.06	1.3	0.999
08	Zero	10.38	86.70	1.0	0.999
09	1.00	9.09	72.93	1.0	0.993
10	1.02	6.72	53.78	1.1	0.999

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 was formed by water soluble plasticizer. As it gets in contact with water get solublize and forms porous, sponge like membrane, which is evident from the release profile of 4 and 8 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 nonsignificant zero lag time is attributed to the same reason of nature of membrane i.e. microporous. On the other hand, the semipermeable membrane coated EOP batches such as 6 and 7 formed by using castor oil as a plastcizer 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 semipermeable 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:

$(dM/dt)z = S/h\ K\ pCs$

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

S- is the semipermiable membrane area; h is the membrane thickness;

K- is a permeability coefficient and p is the osmotic pressure of the formulation under zero-order condition.

The increase in osmotic pressure can be obtained by incorporating additional osmotic agent in core tablet.

DISCUSSION

Effect of agitation intensity

Osmotic pump drug delivery system is such a delivery system which is unaffected by environmental condition as agitation intensity. To characterize this feature of osmotic pump the batches coded with 2 and 5 were stirred at 50 and 100 rpm and their release profile was followed. The release profile has not shown any significant changes even on increase of stirring rate, which can be observed from the graph plotted (fig. 3).

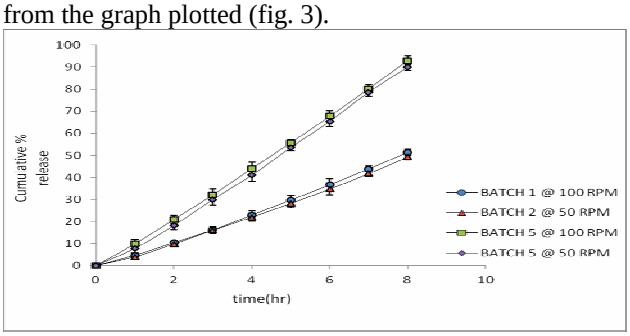

Fig. 5: Effect of agitation intensity on release of Celecoxib from EOPs in Saline phosphate buffer. Mean ± SD (n=3).

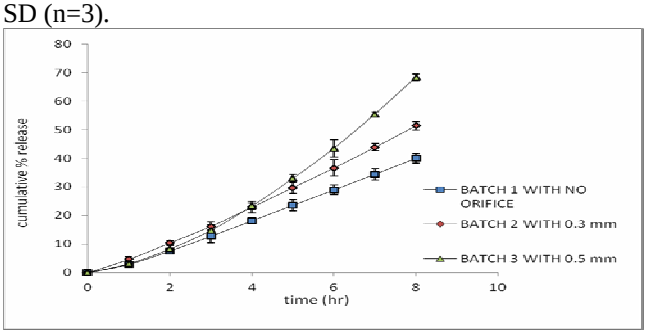

Fig. 6: Effect of orifice diameter on release of celecoxib from EOPs in 7.2 PH (Bars indicates S.D n=3)

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 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 semipermeable membrane was truly ion selective, ions are do not allow to diffuse through the membrane while solvent molecules are allowed to pass through it. The release profiles are plotted in fig 8 of the batches whose release profile was tested in different pH of dissolution medium. The average release rate in different pH media was tested for a statistically significant difference and has resulted in no significant difference.

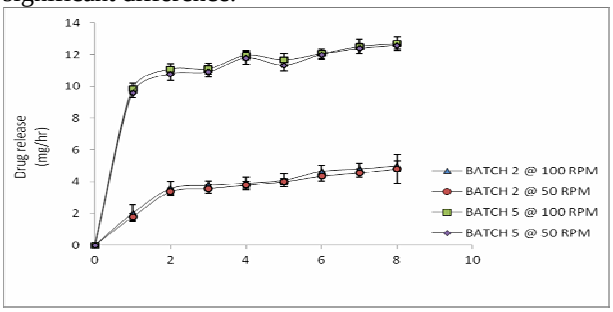

Fig. 7: Effect of agitation intensity on release of celecoxib from EOPs in 7.2 pH. Bars represent Mean S.D. (n=3)

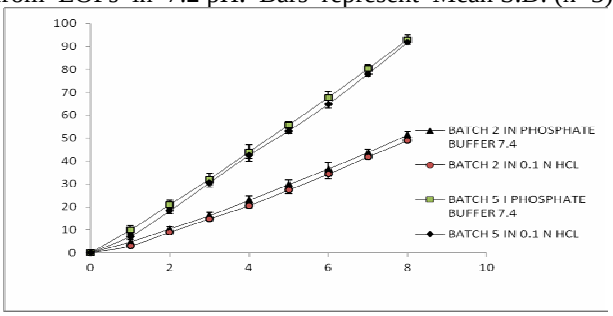

Fig. 8: Effect of pH of the dissolution medium on release rate of celecoxib.

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 coating damaged during the dissolution studies. Empty polymeric shell maintained their original shape and floated on the dissolution medium after drug exhaust or release. Release rate of semipermeable membrane coated osmotic pump was unaffected by hydrodynamic condition as well by the pH of dissolution medium, which confirmed the nature of membrane was a semipermeable which in addition confirmed by release rate as it was inversely proportional to the membrane thickness. The semipermeable membrane coated batches as 2, 3, 5 and as well as 6 behaved as a true semipermeable. The semipermeable nature of the membrane was 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 was insoluble. The kinetics of drug

release was linear as long as the transport mechanism was uniform and single direction.

CONCLUSION

Above study reveal that celecoxib 100mg tablet is able to maintain the therapeutic value as well as almost all characterization of elementary osmotic tablet.

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