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Development and Evaluation of Pulsatile Drug Delivery System Containing Etodolac

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ABSTRACT

In the current research work, Etodolac is taken as a model drug. Etodolac is nonsteroidal anti-inflammatory drug which is used in the treatment of rheumatoid arthritis in children. This research work deals with preparation of eroding or soluble barrier layer surrounding the core tablet and the drug release is time dependent. The system releases the drug after a predetermined lag time of 8h and thus the dosage form can be taken at bedtime so that the content will be released in the morning hours when the symptoms are prominent. It was observed that disintegration time of tablet decreases with increased in concentration of these super disintegrant. The thickness of press coated tablet was observed as 6.37(Kg/cm^3) whereas friability was less than 1% which indicated that tablet had good mechanical resistance. Drug content was found to be high and uniform in all tablet formulation and % drug release was found to be 98.58% after 12 h. On the basis of these evaluation parameter it was found that F9 formulation showed consistent release of drug after the predetermined lag time and therefore it was optimized as a promising approach of Etodolac as Pulsatile Drug Delivery System.

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1. INTRODUCTION:[1-8]

Rheumatoid arthritis is characterized by immunological abnormalities such as hypergammaglobulinemia, the presence of immune complexes and rheumatoid factors in the serum, and lymphocytic infiltration of the synovial membrane. The activity of certain immune processes varies with the time of day or night at which it is observed. Many symptoms and signs of active rheumatoid arthritis are worse at night or around the time of waking, and objective measurements have confirmed a diurnal variation in joint stiffness, hand volume, and grip strength, also a circadian rhythm in signs and symptoms was suggested. Kowanko *et al.* reported that there is a circadian rhythm of disease activity in rheumatoid arthritis, manifested by joint stiffness and grip strength, which is estimated to be maximal between 02:00 and 04:00.

Morning stiffness associated with pain at the time of awakening is a diagnostic criterion of rheumatoid arthritis and these clinical circadian symptoms are supposed to be outcome of altered functioning of hypothalamic–pituitary–adrenocortical axis. Chronopharmacotherapy for rheumatoid arthritis has been recommended to ensure that the highest blood levels of the drug coincide with peak pain and stiffness.

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects.

Etodolac is a Non-steroidal anti-inflammatory drug (NSAID'S) with anti-inflammatory, analgesic and antipyretic properties. The mode of action of Aceclofenac is largely based on the inhibition of prostaglandin synthesis. Etodolac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins.

The Drug inhibits synthesis of the inflammatory cytokines interleukin (IL)-1 and tumor necrosis factor and prostaglandin E2 (PGE2) production. Effects on cell adhesion molecular from neutrophils have also been noted. *In-vitro* data indicate inhibition of cyclooxygenase (Cox)-1 and 2 by Etodolac in whole blood assays, with selectivity for Cox-2 being evident. The half-life of Etodolac is around 7 h, protein binding of 99 % and the usual dose is patient

with body weight >60kg: a usual dose of 200to 400mg is administered every 6 to 8h with a maximum of 1200g daily. Patient <60 mg: maximum 20 mg/kg body weight daily.

A pulsatile drug delivery system that can be administered at night (before sleep) but that release drug in early morning would be a promising chrono pharmaceutic system.

1.2Merits and Demerits:[9,10,11]

Merits:

- Predictable, reproducible and short gastric residence time
- Less inter- and intra-subject variability
- Improve bioavailability
- Limited risk of local irritation
- No risk of dose dumping
- Flexibility in design
- Improve stability

Demerits:

- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Batch manufacturing process
- Higher cost of production
- Trained/skilled personnel needed for Manufacturing.

2. MATERIALS AND METHODS:

2.1 Materials:

Etodolac was received as a gift sample from the Lupin Pharma, Aurangabad, Maharashtra. India. Other chemicals and solvents of analytical grade were obtained from different commercial suppliers.

2.2 Preparation of Core tablet:

The inner core tablet was prepared by using direct compression method. As shown in Table 1 powder mixture of Etodolac, microcrystalline cellulose (MCC, Avicel PH 102), Cross-carmellose sodium, Crosspovidone ingredient was dry blended for 10 min. 180 m of resultant powder blend was manually compressed on 10 station pilot press using 8 mm flat faced punch. The machine was adjusted to produce an approximate weight of 400 mg tablet.

Table 1: Composition of formulation

Formulation code / Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Etodolac	200	200	200	200	200	200	200	200	200
Crospovidone	7.5	-	-	15	-	-	18.75	-	-
Croscarmelose sodium	-	7.5	-	-	15	-	-	18.75	-
Sodium starch glycolate	-	-	7.5	-	-	15	-	-	18.75
PVP	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Magnesium stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Microcrystaline Cellulose(Avicel) PH102	127.5	127.5	127.5	127.5	127.5	127.5	127.5	127.5	127.5
Lactose monohydrate	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5	57.5
Total	400	400	400	400	400	400	400	400	400

2.3 Coating of prepared core tablet of Etodolac:[12,13,14]

The core tablets of Etodolac were coated with 5% w/v Solution of cellulose acetate in acetone. Cellulose acetate was used as a semipermeable membrane provider. PEG 400 15% v/v was used as plasticizer. The tablets were warmed to 40±2°C before applying coating

solution. The composition of coating solution used for coating of core tablets is given in Table 2. Dip coating technique was used for the coating of tablet. Coating was continued until desired weight gain (10%) was obtained and tablets were dried at 50°C for 10 h. before further evaluation.

Table 2: Coating composition

Ingredients	Quantity for 100 ml
Cellulose Acetate	5 %
Polyethylene glycol 400	15 %
Acetone	100 ml

3. Evaluation and Characterization:

3.1 Melting Point:

Melting point of Etodolac was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate.

3.2 Solubility: [15]

The solubility of Etodolac was checked in different solvents like ethanol, methanol, water PBS pH 6.8 & PBS pH 7.4 etc.

3.3 IR interpretation of drug:[16]

The infra-red spectrum of drug and polymers was recorded with BRUKER OPUS 7.5 over wave number of 4000 to 400 cm^{-1} by using Infra-red spectroscopy.

3.4 DSC interpretation of drug:[17]

The study was carried out using a Mettler Toledo differential scanning calorimeter equipped with a computerized data station. The sample of drug and polymer was weighed individually and heated at a scanning rate of 10°C/min between 40 and 200°C and 40 ml/min of nitrogen flow.

3.5 Flow properties:

Flow properties and compressibility were determined by determining bulk density, tapped density angle of repose, compressibility index and Hausner ratio.

4. RESULT AND DISCUSSION

4.1 Melting point determination:

The melting point of compound was measured and reported as follows:

Table 3: Melting point

Drug	Observed value	Reported value
Etodolac	145^0C	145-148^0C

4.2 IR Spectroscopy:

A) IR of Etodolac:

The FTIR spectra of pure Etodolac showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.

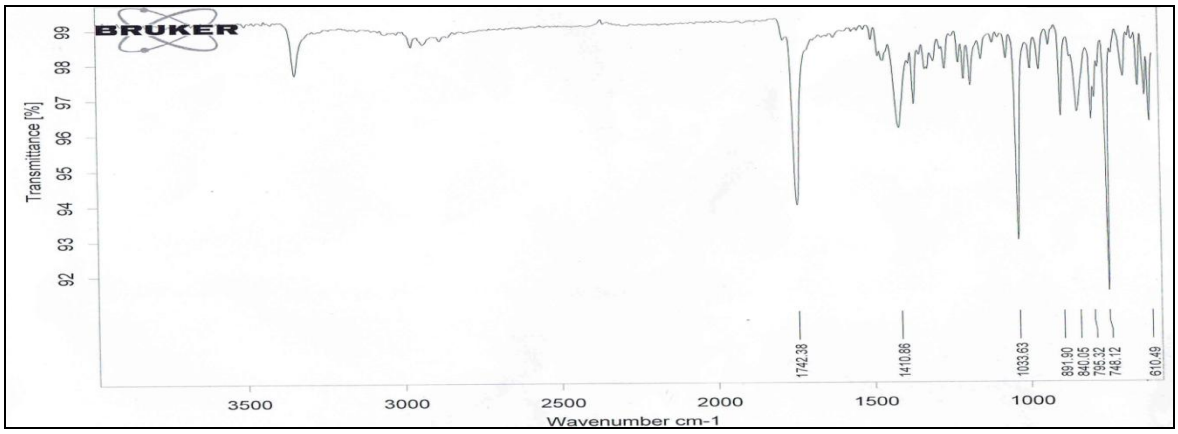

Figure 1: IR spectrum of Etodolac

B) IR of Etodolac + excipient mixture

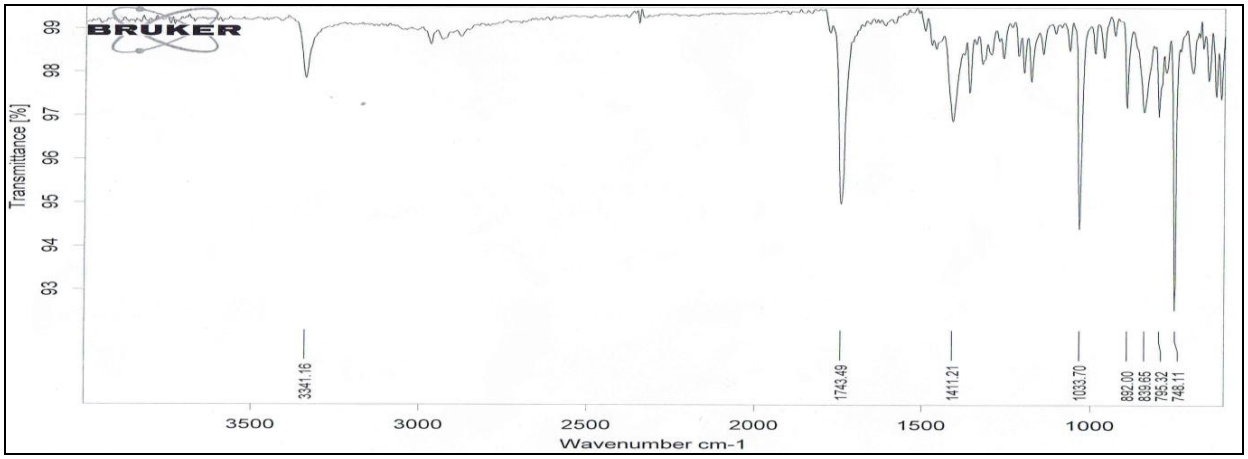

Figure 2: IR of spectra of Etodolac + excipient mixture

The presence of absorption bonds corresponding to the functional groups present in the structure of Etodolac and the absence of any well-defined unaccountable peak is a confirmation of the purity of the drug sample.

4.3 Differential Scanning Calorimetry (DSC):

A) DSC of Etodolac

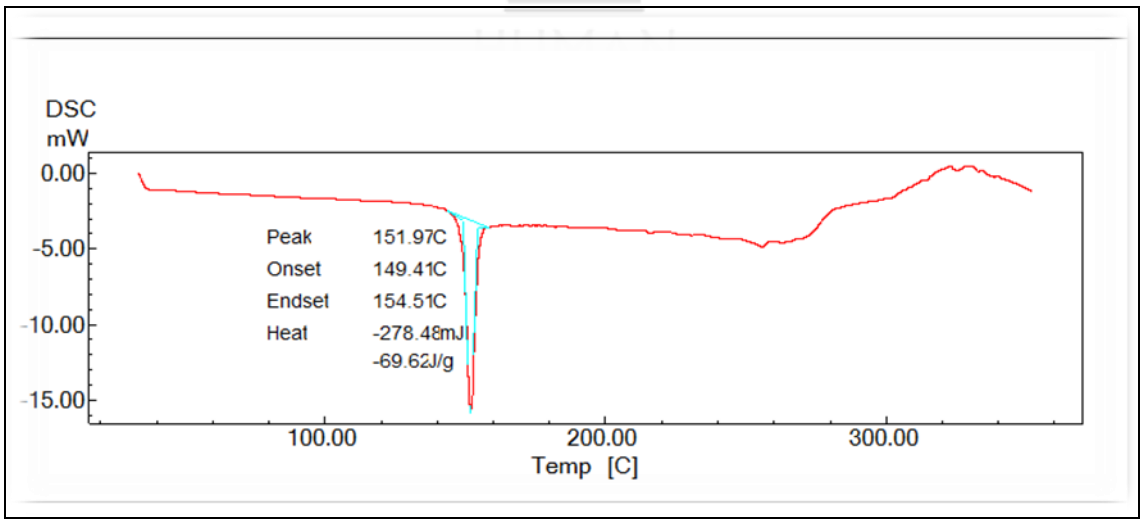

Figure 3: DSC of Etodolac

The thermal behavior of Etodolac was studied using DSC Thermogram. The DSC Thermogram of Etodolac exhibited an endothermic peak at 151.97^0c.

B) DSC of Etodolac + excipient mixture

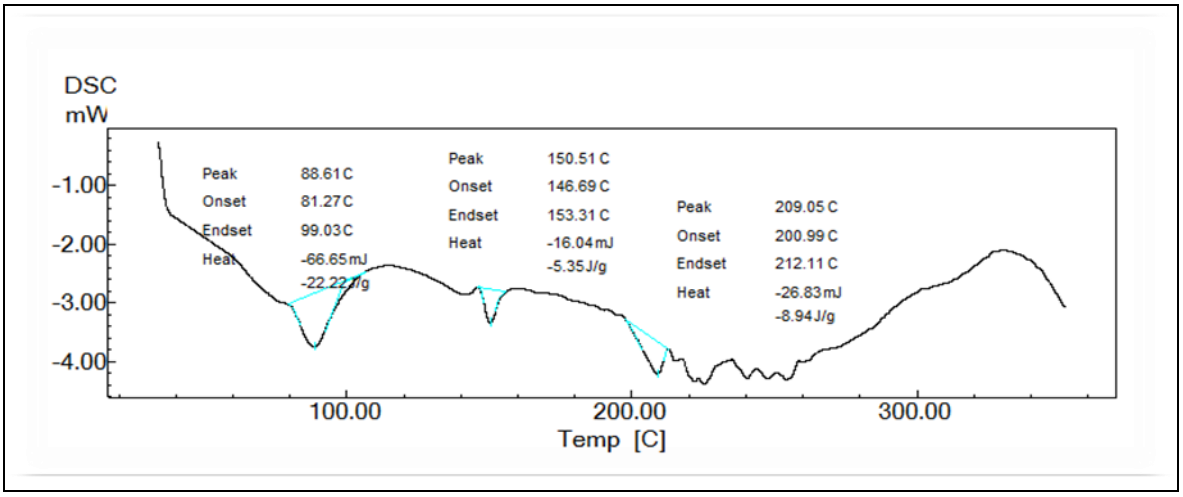

Figure 4: DSC of Etodolac + excipient mixture

The thermal behavior of drug and physical mixture of drug and polymer was studied by using DSC Thermogram. DSC thermogram of drug exhibited characteristic peak at 150.51^{0}c and physical mixture exhibited characteristic peak at 146.69°C.

4.4 Solubility:

Solubility of Etodolac was found to be as: insoluble in water & freely soluble in ethanol, methanol, alcohol, pH 6.8, pH 7.4

4.5 Evaluation of Powder Bulk for Tablets:

Table 4: Evaluation of Powder Bulk for Tablets

Formulation code	Angle of repose (θ) ± S.D.	Bulk density (gm/cm^3) ± S.D.	Tapped density (gm/cm^3) ± S.D.	Compressibility index (%) ± S.D.	Hausner's ratio ± S.D.
F1	27.99±0.766	0.3115±0.001	0.3428±0.001	9.12±0.3674	1.09±0.005
F2	27.69±0.527	0.3969±0.001	0.4328±0.001	8.32±0.3934	1.09±0.01
F3	28.37±0.505	0.3921±0.001	0.4524±0.002	13.32±0.632	1.11±0.046
F4	29.42±0.834	0.3968±0.001	0.4322±0.003	8.19±0.5815	1.08±0.0083
F5	26.43±0.477	0.3896±0.002	0.4538±0.001	14.14±0.415	1.15±0.0057
F6	28.32±0.160	0.3906±0.001	0.4444±0.002	11.9±0.5493	1.14±0.017
F7	27.50±0.437	0.3846±0.001	0.4650±0.003	17.29±0.705	1.20±0.01
F8	26.68±0.180	0.3947±0.003	0.4328±0.001	9.02±0.3439	1.08±0.001
F9	27.52±0.241	0.3973±0.004	0.4417±0.002	10.05±0.213	1.11±0.004

4.6 Pre-coating evaluation parameters of core tablets:

Table 5: Pre-coating evaluation parameters of core tablets

Formulation Code	Weight variation (mg)	Hardness (kg/cm^2) Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean± S.D	Drug content (%) Mean± S.D	Dis-integration Time MEAN±S.D
F1	394.8±0.54	5.59±0.16	5.43±0.03	0.87±0.01	91.80±0.614	3.25±0.5
F2	398.6±0.73	5.20±0.16	5.40±0.03	0.72±0.01	89.5±0.782	2.10±0.2
F3	397.2±0.65	5.55±0.16	5.70±0.02	0.66±0.01	94.7±0.974	3.00±0.8
F4	395.6±0.81	5.57±0.16	5.35±0.03	0.68±0.01	90.5±1.170	3.40±0.3
F5	394.6±0.45	5.56±0.16	5.58±0.03	0.51±0.02	87.2±0.538	2.20±0.5
F6	396.6±0.65	5.58±0.16	5.70±0.02	0.72±0.01	92.6±0.815	2.30±0.3
F7	395.1±0.23	5.23±0.16	5.65±0.01	0.76±0.01	93.1±0.678	3.10±0.4
F8	397.8±0.56	5.75±0.16	5.40±0.02	0.80±0.01	91.0±0.763	1.40±0.4
F9	398.7±0.15	5.45±0.16	5.23±0.02	0.67±0.08	95.8±0.517	1.30±0.5

4.7 Post coating evaluation:

All formulated coated osmotic tablet batches were evaluated for Weight variation, thickness and Film thickness. Due to uniform coating, weight variation and thickness of coated tablets were found within the range. Thickness of film was measured by taking the tablet after dissolution using digital vernier caliper. Evaluated data is shown in Table 6.

Table 6: Post coating evaluation

Formulation Code.	Weight Variation (mg)	Thickness of coated tablet Mean± S.D	Thickness of film(mm) Mean± S.D
F1	412±0.59	6.30±0.035	0.78±0.34
F2	410±0.61	6.61±0.032	0.62±0.25
F3	406±0.78	6.59±0.026	0.89±0.53
F4	409±0.68	6.28±0.033	0.31±0.42
F5	415±0.95	6.49±0.034	0.61±0.46
F6	415±0.2	6.59±0.023	0.70±0.20
F7	418±0.80	6.31±0.016	0.41±0.052
F8	412±0.52	6.57±0.027	0.91±0.46
F9	420±0.21	6.37±0.021	0.58±0.002

From above evaluated data of coated tablets, it was confirmed that weight variation and thickness of film was found within the range.

4.8 *In-vitro* Dissolution study of Formulations (F1-F9):

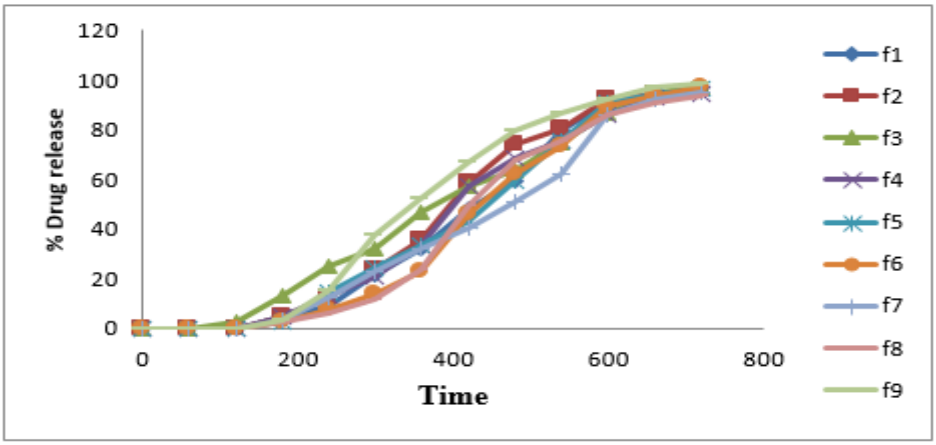

Figure 5: Dissolution profile of formulation batches (F1-F9)

4.9 Kinetic study of *in-vitro* dissolution:

Table 7: Kinetic Study of in-vitro dissolution

F9 Factors	Zero order	First order	Higuchi	Peppas
Slop	0.1727	0.0102	0.0276	0.0014
Intercept	-19.791	11.023	8.1041	1.9416
R^2	0.9797	0.9446	0.9765	0.8951

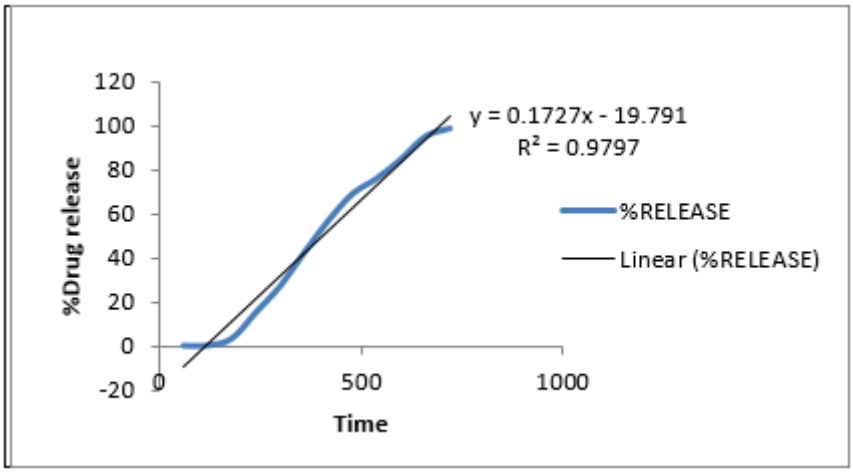

Figure 6: Zero order release kinetic graph of formulations F9

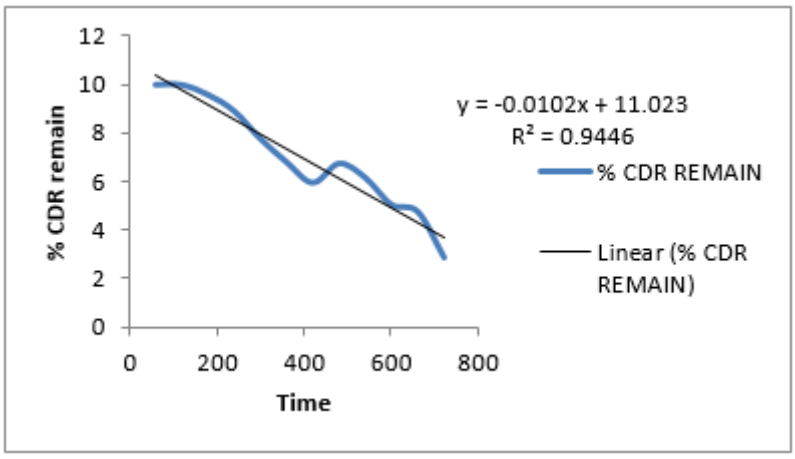

Figure 7: First order release kinetic graph of formulations F9

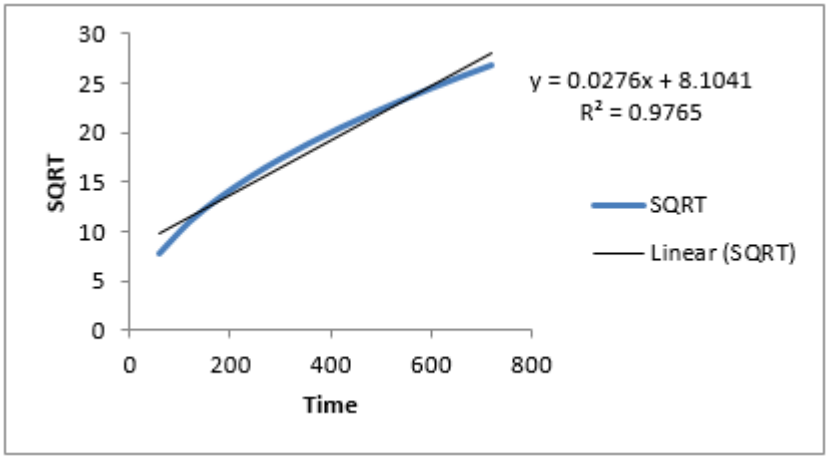

Figure 8: Evaluation of Higuchi model kinetic graph of formulations F9

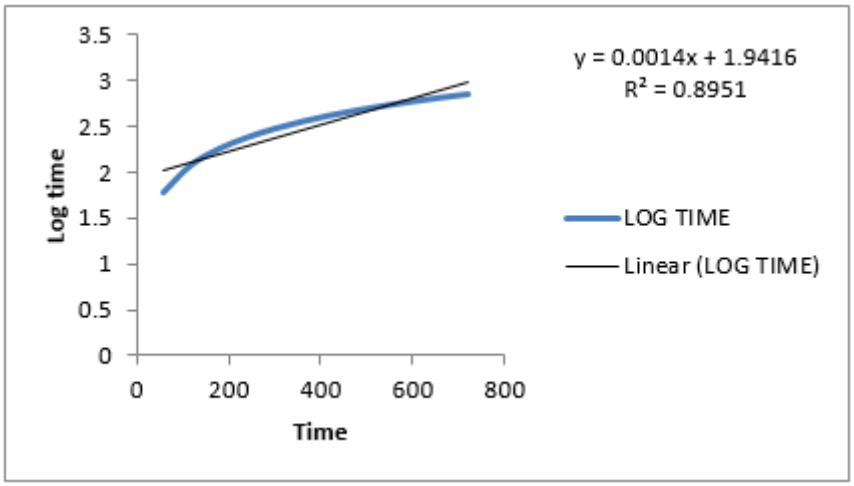

Figure 9: Korsemayer's Peppas kinetic graph of formulations F9

4.10 Stability study:

The effect of temperature and relative humidity was determined at 40°C±2°C, 75% ± 5% RH maintained in environmental stability chamber for six months. Evaluation was done after 180 days. Results are represented in Table 8.

Table 8: Effect of Temperature and relative humidity on optimized batch after stability

Parameter	Results obtained at 0 days	Result obtained after 6 months
Appearance	Yellow	Yellow
Hardness(Kg/cm$^{2)}$	5.45±0.164	5.30±0.571
Friability%	0.80±0.012	0.70± 0.016
Weight variation (mg)	420±0.21	412±0.31
Drug content(%)±SD	95.8±0.517	92.01±0.12
In-vitro drug release±SD	98.5840±0.854	96.59± 0.25

5. CONCLUSION

The formulation of pulsatile drug delivery system containing Etodolac was obtained by direct compression method successfully. The evaluation parameter including dissolution shows F9 as best formulation as its disintegration time was found to be very less for the core tablet. After this entire formulation test, F9 was selected as best formulation and therefore it is optimized as pulsatile tablet. The formulation may be a promising approach for the development of pulsatile drug delivery for rheumatoid arthritis with better patient compliance. This research work deals with the preparation of eroding or soluble barrier layer surrounding the core tablet and the drug release is time dependent. The system releases the drug after a predetermined lag time of 12hrs and thus the dosage form can be taken at bedtime so that the content will be released in the morning hours when the symptoms are more prominent.

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