Design, Fabrication and Optimization of Fast Dissolving Solid Oral Formulations of Etodolac using Solvent Free Technology by 3^2 Factorial Design

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ABSTRACT:
The objective of the present study was to formulate and evaluate fast dissolving solid oral formulations of Etodolac using solvent free technology. Etodolac, BCS class II drug, with t1/2 approx. 7 hrs and absolute oral bioavailability about 80-85%, indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. In present study, solvent free technique is used in order to improve the dissolution and oral bioavailability of the model drug with poor solubility and high permeability. Solid oral formulations (F1 – F9) were prepared by lyophilization technique using solvent free technology with Kyron t 314 and Musa paradisiaca L as a super disintegrants in different ratios and analyse the usefulness of DOE in the development and optimization of a tablet of a model drug employing 3^2 full factorial statistical design. The drug-polymer compatibility study was carried out to determine the interactions, if any between the drug and the polymers used in the study. The FTIR, XRD and DSC study revealed that, polymers and excipients used were compatible with drug. The prepared tablets were subjected to various evaluation such as hardness (2.80–4.10 kg/cm2), friability (0.34–0.72%), disintegration time (26–35 s), drug content (95.15–99.20%), water absorption ratio (45–62%), wetting time (45–65 s) and in-vitro drug release shown in 5 min (96.40–99.80%). Optimized batch(F5) when subjected to stability at 40± 2^0C temperature with relative humidity 75±5% for six months, showed no degradation and change in tablet and showed rapid dissolution and effective in achieving patient compliance.

KEYWORDS: Etodolac, Solid oral tablet, Kyron t 314, Musa paradisiaca L, FTIR, XRD, DSC, 3^2 Factorial Design.
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INTRODUCTION:

The conventional dosage forms (tablet and capsule) have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self administration ,compact in nature, easy to manufacture and it can be deliver in accurate dose. One important drawback of solid dosage forms is the difficulty in swallowing (Dysphagia) or chewing in some patients particularly pediatric and geriatric patients. The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance. The most important vulnerable factors affecting the betterment of therapeutic outcomes irrespective of the age groups are swallowing and chewing difficulty[1]. Difficulties in swallowing of tablet and capsule are also occur when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection[2]. Approximately one-third of the population (mainly pediatric and geriatric) has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention[2].

Fast dissolving tablets are dosage form, which disintegrate in patient's mouth within a few seconds without the need of water, or chewing, providing best remedy for the patient suffering from dysphasia[3].

Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet[4]. Fast dissolving tablets dissolve or disintegrate in the oral cavity without the need of water. Most fast dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. It has been concluded that faster the dissolution, faster the absorption (only the unionized form of drug) and onset of action. Some drugs are absorbed from the oral cavity, pharynx and esophagus as the saliva passes down into the stomach. Thus the bioavailability of drug is significantly more than those observed from conventional tablets dosage form[5]**.** The time for disintegration of fast disintegrating tablets is generally considered to be less than one minute[6-9].

The fast dissolving solid dosage form turns into a soft paste or liquid form for easy swallowing, and thus it is free of risk of choking.[10-11] In recent years, a variety of improved methods for delivering drugs have been developed with the aim of improving bioavailability, convenience and patient compliance[11,12]. Some tablets are designed to dissolve in saliva within a few seconds, and so called true fast-dissolving tablets. Fast dissolving technology offers following advantages[13-16].

- Improved compliance/added convenience
- No water needed
- No chewing needed
- Better taste
- Improved stability
- Suitable for controlled as well as fast release actives
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.

The objective of the present study was to formulate and evaluate fast dissolving solid oral formulations of Etodolac using solvent free technology. Etodolac, BCS class II drug, with t1/2 approx. 7 hrs and absolute oral bioavailability about 80-85%, indicated for relief of signs and symptoms of rheumatoid arthritis and osteoarthritis. In present study, solvent free technique is used in order to improve the dissolution and oral bioavailability of the model drug with poor solubility and high permeability.

MATERIALS AND METHODS:

Materials

Etodolac was procured as a gift sample from

A. R. Life sciences Pvt Ltd., Hyderabad; Kyron t314(Polacrilin Potassium) was purchased from Aura Pharmaceuticals Pvt. Ltd., Mumbai; Musa paradisiaca L, purchased from Standard commercial supplies; Pearlitol SD200 purchased from Roquette India Private Limited, Mumbai. All chemicals used were of analytical reagent grade and double distilled water was used throughout the experiments.

Identification test for Etodolac[17,18].

Identification of Etodolac was performed by various parameters like colour, odour, solubility, Melting point range and FT Infrared spectrophotometer etc. In Ultra-violet Spectrum, electronic excitation occurs in the range from 200-800 nm and involves the promotion of electron to the higher energy molecular orbital.

Drug Excipient Compatibility Study using Fourier Transform Infrared Spectroscopy[19,20].

The samples were crushed with KBr to make pellets under hydraulicpressure of 10 tons, and then the FTIR spectra were recorded between 400 and 4000 cm^{-1}. It was used to study the interactions between the drug and polymer. IR spectral analysis of pure Etodolac (physical mixture of Etodolac with gelatin, glycine, Kyron t 314 and Musa paradisiaca L, optimized lyophilized Etodolac tablet were carried out.

Preparation of fast dissolving oral solid tablets of Etodolac by lyophilization method[21,22].

Fast dissolving oral solid tablets of Etodolac were prepared by lyophilization method using Kyron t 314 and Musa paradisiaca L as superdisintegrants in different concentration, gelatin in certain concentration as a matrix former, a sugar alcohol (Pearlitol SD200) and a collapse protectant (glycine) as shown in Table1.

Table 1. Formulation of Etodolac fast dissolving oral solidtablets

Sr. No	Batch	ETO (mg)	Kyron t 314 (mg)	Musa paradisiaca L. (mg)	Gelatin (mg)	Glycine (mg)	Pearlitol SD200 (mg)	Aspartame (mg)	Avicel pH 102 (mg)
1	F1	200	20	60	5	4	20	3	88
2	F2	200	20	20	10	4	20	3	123
3	F3	200	20	40	5	4	20	3	108
4	F4	200	40	20	5	4	20	3	108
5	F5	200	40	40	10	4	20	3	83
6	F6	200	60	20	10	4	20	3	83
7	F7	200	60	60	10	4	20	3	43
8	F8	200	60	40	5	4	20	3	68
9	F9	200	60	40	15	4	20	3	58

Total weight of Tablet = 400 mg

Optimization of formulation for Etodolac fast dissolving oral solid tablets by Taguchi design[23]

In this study, an experimental design matrix was formed with 2 factors,3 level, and 9 runs to optimized the influence of variable by using Minitab Statistical Software Ink. In this matrix design independent variable such as (A) Concentration of Kyron t 314 and (B) Concentration of Musa paradisiaca L. were selected and their impact on formulation was predicted. All these dependent variables are summarized in Table 2. On the behalf of this design set goals, nine Fast dissolving tablet formulation were prepared and characterized for in-vitro drug release

(R1), disintegration time (R2), water absorption ratio (R3), and wetting time (R4) which were taken as a dependent variable (response parameters).

Table 2. Variables and constraints in the experimental design

Variables	Constraints	
	Lower limit	Upper limit
	ETO	ETO
Independent variables		
A. Concentration of Kyron t 314	20	60
B. Concentration of Musa paradisiaca L.	20	60
Dependent variables	**Goals**	
R1. = In-vitro drug release	Maximize	
R2. = Disintegration time	Minimize	
R3. = Water absorption ratio	Optimize	
R4. = Wetting Time	Minimize	

ETO = Etodolac

Evaluation of Etodolac fast dissolving oral solid tablets[24]

Prepared fast dissolving oral solid Etodolac tablet batches (F1 - F9) were evaluated for thickness, shape, hardness, friability, weight variation, wetting time, water absorption ratio, In- vitro disintegration study, drug content and in vitro drug release study were carried out. Shape and thickness was measured using sliding Caliper scale. hardness was measured using Monsanto hardness tester . Tablets were tested for friability using Roche Friabilator.

Drug Content

Etodolac Tablets were selected randomly, and the average weight was calculated. Tablets were crushed in a mortar and accurately weighed the amount of tablet powder was taken from the crushed blend. Then the samples were transferred to 100 ml volumetric flask and diluted with phosphate buffer pH 6.8. The contents were shaken periodically and kept for 2 h for solvation of drug completely. The mixture was filtered in Whatmann filter paper and absorbance was measured at 278 nm for Etodolac using phosphate buffer pH 6.8.

In-Vitro Dissolution Study (In vitro drug release study)[25]

Dissolution was carried out using USP apparatus II taking 900 ml of Phosphate buffer pH 6.8. The rotational speed of the paddle was set at 50 rpm. One ml of aliquots was withdrawn at predetermined time interval several minutes and was being replaced by same volume of fresh medium. The sample were analyzed for drug content using double beam UV spectrophotometer at 278 nm for Etodolac against blank using Phosphate buffer pH 6.8. The dissolution was carried out in triplicate for each formulated batch. The cumulative % drug release was calculated using the equation generated from the standard calibration curve. Cumulative % drug release Vs time graph was plotted.

X-Ray Diffraction (X-RD)[26]

For the structural, crystal and physical state characterization of Etodolac, X-Ray diffraction studies were performed for pure drugs, Physical mixture of drug with excipients, and optimized lyophilized tablets. The study was carried out using X-ray powder diffraction system, Model No. XPERT-

PRO Diffractometer System. By using copper target, a voltage of 45 Kv and a current of 40 mA. The scanning was done over 2θ range of 5º to 100º.

Differential Scanning Calorimeter (DSC)[27]

For the structural, crystal and physical state characterization of Etodolac, DSC studies were performed for pure drugs, and optimized lyophilized tablets. The DSC study was carried out using Model No. METTLER DSC 30S. By using crucible Al 40µL, at of 10^0C /min heating rate, under nitrogen environment. The temperature range used was 25^0C – 300^0C.

Scanning Electron Microscopy (SEM)[28]

Optimized lyophilized Etodolac tablet were coated with platinum and visualized under Analytical Scanning Electron Microscope (SEM), using Model No. JSM-6380A. The SEM Photomicrographs showing surface morphology.

Stability Studies[29]

The optimized lyophilized Etodolac tablet batches were selected and wrapped in aluminum foil of thickness 0.04 mm and stored at stored at 40±2^0C temperature with relative humidity of 75±5%. The sampling was done after every two months for total 6 months and evaluation was done for appearance, thickness, hardness, friability, drug content and cumulative % drug release.

RESULT AND DISCUSSION:

Etodolac, (NSAIDs) fast dissolving solid oral formulations (tablet) has been made in order to improve bioavailability and patient compliance. Organoleptic property such as colour, taste, odour and melting point of procured Etodolac sample wascomplies as per IP.

Solubility study of Etodolac in different solvents like water, pH 6.8 Phosphate buffer and ethanol was carried out and found to be 0.490 mg/ml, 20.55 mg/ml, 22.05 mg/ml for Etodolac as shown in Table 3.

Table 3. Solubility study of Etodolac in differentsolvents

Sr. No	Solvents	Solubilit (mg/ml)
1.	Water	0.490
2.	pH 6.8 Phosphate Buffer	20.55
3.	Ethanol	22.05

Retention of basic characteristics peaks in FTIR of physical mixture of Etodolac with excipients at 3310 cm^{-1}, 1750 cm^{-1}, 2980 cm^{-1} & 2960 cm^{-1}, 2625 cm^{-1}, 1640 cm^{-1}, 1450 cm^{-1}, 1400 cm^{-1} for N-H stretch, -C=C stretch, =C-H (alkene aromatic), C-H (alkane stretching), O-H (carboxylic acid), C=O Stretch (ester), C-N Stretch and C-C stretch respectively, suggesting no incompatibility between dug and polymers as shown in figure 1.

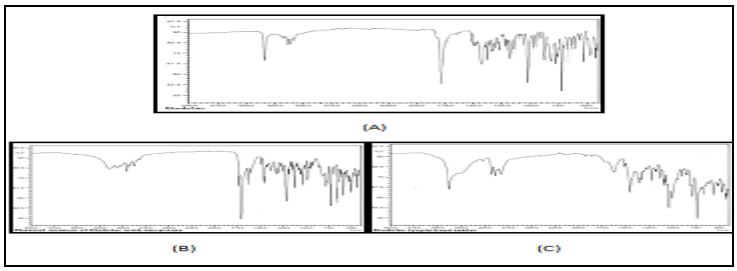


Figure 1.FTIR Spectra of (A) Etodolac (B) Physical mixture of Etodolac withexcipients (C) optimized lyophilized Etodolac tablet

Fast dissolving oral solid tablets of Etodolac were prepared by lyophilization method using Kyron t 314 and Musa paradisiaca L as superdisintegrants in different concentration, gelatin in certain concentration as a matrix former, a sugar alcohol (Pearlitol SD200) and a collapse protectant (glycine), an experimental design matrix was formed with 2 factors, 3 level, and 9 runs to optimized the influence of variable with Taguchi design by using Minitab Statistical Software Ink and characterized for in-vitro drug release (R1), disintegration time (R2), water absorption ratio (R3), and wetting time (R4) which were taken as a dependent variable (response parameters).

Prepared fast dissolving oral solid Etodolac tablet batches (F1 - F9) were evaluated for thickness, shape, hardness, friability, weight variation, wetting time, water absorption ratio, In- vitro disintegration study, drug content and in vitro drug release study and found to be complies as per specification given in I.P.

Etodolac lyophilized tablet with thickness was in the range of 5.62±0.12 to 7.24±0.11mm, hardness was in the range of 2.80±0.04 to 4.10±0.10 kg/cm^2, friability was in the range of 0.30±0.16 to 0.76±0.15%, weight variation ranges from 395±0.10 to 402±0.32 mg, wetting time ranges from 40 to 65 seconds, water absorption ratio ranges from 45.18±0.10 to 68.82±0.24 % whereas in-vitro disintegration was in the range of 26 to 38 seconds and drug content was in the range of 95.15±0.20 % to 99.20±0.22 %, was maximum in F5 batch and results were summarized in Table 4.

Table 4. Post-compression Evaluation of Etodolac tablets (Mean±SD)

Batches / Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)±SD	6.43±0.10	5.62±0.12	6.55±0.22	6.25±0.18	5.88±0.14	7.24±0.11	7.05±0.26	6.20±0.28	6.30±0.30
Hardness (kg/cm^2)±SD	4.10±0.10	3.10±0.18	4.00±0.22	3.40±0.16	3.55±0.20	3.60±0.26	3.40±0.12	2.80±0.04	3.80±0.06
Friability (%) ±SD	0.72±0.15	0.64±0.22	0.50±0.06	0.76±0.15	0.34±0.12	0.30±0.16	0.40±0.11	0.38±0.08	0.44±0.02
Weight Variation (mg) ±SD	402±0.32	399±0.10	400±1.00	395±0.22	397±0.14	398±0.20	399±0.20	398±0.84	395±0.10
Wetting time(Sec)	65	64	44	46	52	40	54	58	45
Water absorption ratio %	45.18±0.10	68.82±0.24	49.22±0.12	55.55±0.14	66.40±0.18	52.66±0.12	48.80±0.32	48.40±0.22	62.44 20.12
In-vitro	35	26	32	35	32	26	38	28	30

disintegration(Sec)									
Drug Content (%) ±SD	98.50 ±0.27	97.00 ±0.18	97.60 ±0.19	95.20 ±0.25	99.20 ±0.22	98.22 ±0.24	96.25 ±0.12	98.30 ±0.30	95.15 ±0.20

In vitro dissolution of Etodolac tablet batches F1 to F9 at different time interval is reported Figure 2. Formulations F5 showed maximum drug release 99.80±0.08 % with 40 mg Kyron t314 and Musa paradisiaca L 40 mg as superdisintegrant and 10 mg concentration of matrix former Gelatin as compared to other batches.

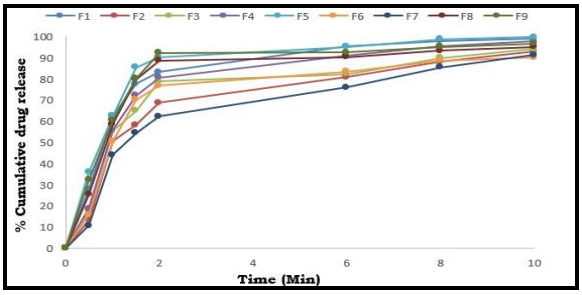


Figure 2. In-Vitro dissolution Profile of Etodolac F-1 to F-9

The X-Ray diffraction pattern of Etodolac exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. The X-Ray diffraction pattern of physical mixture of drug with excipients were simply a superimposition of each component with peaks of both drug and excipients however with lower intensity whereas optimized lyophilized Etodolac tablet showed less intense and highly diffused peaks of drug which was very poor in reflections which testified to a reduced ordering of crystal lattice indicating formation of amorphous state and molecular dispersion of drug and this amorphous, less crystalline and metastable form as compared to pure drug dissolvesat a faster rate as shown in Figure 3.

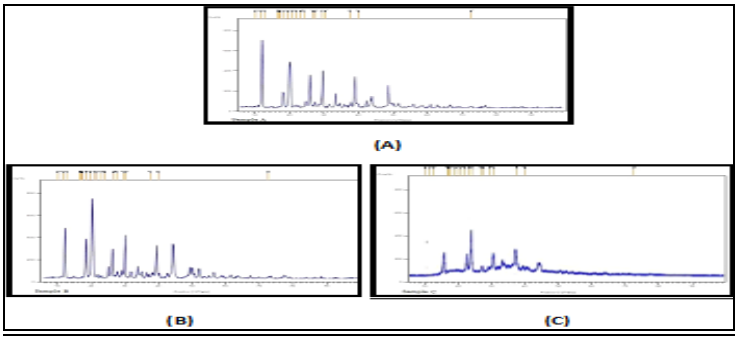
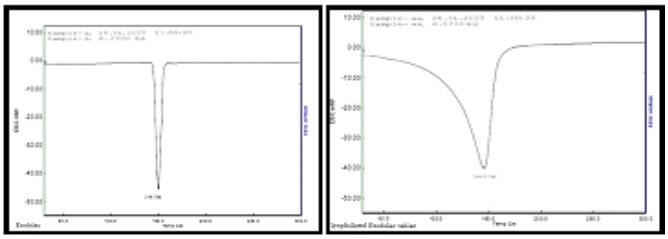


Figure 3. XRD Spectra of (A)Etodolac(B) Physical mixture of Etodolac with excipients(C) optimized lyophilized Etodolac tablet

DSC curve of pure components and of the various drug-polymers binary system are shown in Figure 4. The thermal curve of Etodolac (T_{peak} =146^{0}C) indicated its crystalline anhydrous state. Thermal curves of binary system of optimized lyophilized Etodolac tablet showed typical drug melting endotherm which progressively reduced its area and shifted to lower temperature (T_{peak} =144.5^{0}C) as consequence of gradually increasing interaction between components.



(A) (B)

Figure 4. DSC Spectra of (A) Etodolac(B) optimized lyophilized Etodolac tablet

Surface photomicrographs of optimized lyophilized Etodolac tablet as shown in Figure 5 indicate that homogenious or heterogeneous conditions during the preparation of tablet.

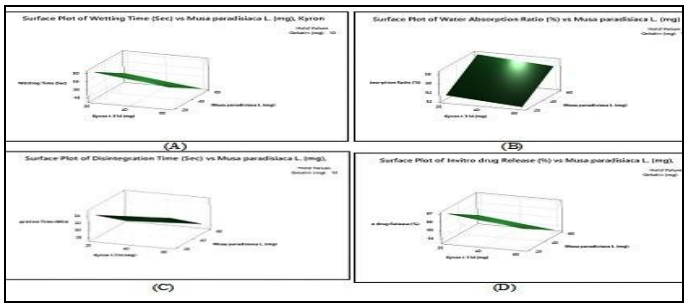
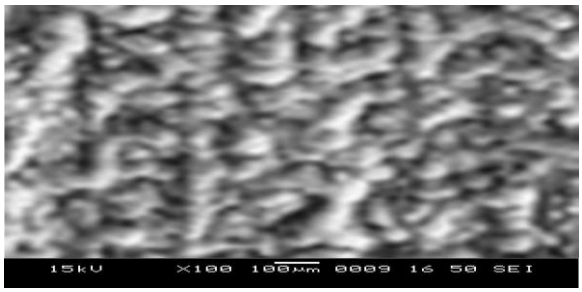


Figure 5. Surface plots for Etodolac showing effect of concentration of Musa Paradisiaca L. and Kyron t 314 on measured responses (A) Wetting time (sec), (B) Water absorption ratio (%), (C) Disintegration time (sec), (D) In-vitro drug release (%) keeping hold values of



gelatin 10 mg.

Figure 6. SEM of optimized lyophilized Etodolac tablet

The optimized formulation F5 batches of Etodolac were subjected to stability study when stored at 40□2^{0}C temperaturewith relative humidity of 75□5% for a period of six months. No significant change in physiochemical properties, drug release profile as well as drug content indicating there was no degradation andchange in the matrix system and shown in Table 5 and Figure 7 and for lyophilized Etodolac tablet.

Table 5. Evaluation of formulation F5 lyophilized Etodolac tabletkept for stability at 40^{0}C /75% RH

Parameters	0 Month	2 Months	4 Months	6 Months
Appearance/Colour	White	White	White	White
Thickness(mm)	5.88	5.88	5.85	5.88
Hardness	3.55	3.50	3.55	3.55

(Kg/cm^2)				
Friability (%)	0.34	0.34	0.30	0.40
Drug content (%)	99.20	99.00	99.40	99.30

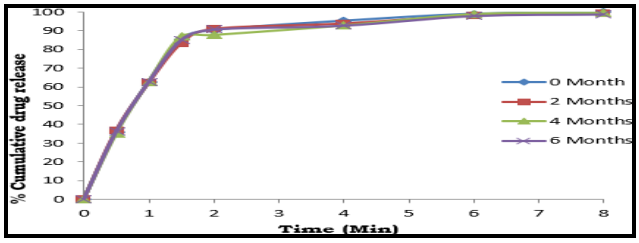


Figure 7. *In-vitro* release profiles of formulation F5 lyophilized Etodolac tablet kept for stability at $40^0 \pm 2^0$C and 75 ± 5% RH for 6 months

CONCLUSION

In present study, fast dissolving solid oral formulations for NSAIDs (Etodolac) was prepared using different types and concentrations of superdisintegrant by lyophilization method which was confirmed by various characterization and evaluation studies. Kyron t 314 and Musa paradisiaca L as superdisintegrant with certain concentration of matrix former Gelatine gives better result when design and optimized from surface plots by Taguchi design. Prepared optimized lyophilized tablets of Etodolac disintegrate within 32 seconds in mouth having better mouth feel.

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