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Effect of Manufacturing Process Variable on Designing of Extended Release Tablet of Etodolac Using Natural Polymer

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ABSTRACT

Background: The drug Etodolac, is a non-steroidal anti-inflammatory drugs (NSAIDs) prominently used for treatment of chronic rheumatism. **Aims:** The objective of the present study to evaluate the effect of manufacturing process variable on designing of extended release tablet of Etodolac using natural polymer. **Materials and Methodology:** Etodolac control release tablets were prepared by direct compression and wet granulation methods using xanthan gum (Natural polymer) in different ratios (8, 9, 10 and 11 %) as release rate controlling polymers. The granules were evaluated for flow properties by evaluating bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. The tablets were evaluated for drug polymer compatibility study by FTIR, diameter, weight variation test, hardness, friability, disintegration test, *in vitro* drug release, release kinetics and stability studies. **Results and Discussions:** The FTIR study revealed that no such interactions being taking place in between drug and polymers. The flow property of granules of all tablet batches was found to be good. All the tablet formulations had good tablet physiochemical properties. *In vitro* drug release data showed dependence of release kinetics on different percent of drug to polymer in cross-linked matrix systems. **Conclusion:** The results of *in vitro* study, it was concluded that Etodolac matrix tablet containing xanthan gum (11.0 %) prepared by wet granulation method, provided most controlled release of water-soluble Etodolac over extended period of time. Thus wet granulation method is the optimized method in designing of extended release tablet of Etodolac.

INTRODUCTION

Numerous techniques were reported previously for preparation of sustained release pharmaceutical formulations such as coating an osmotically active drug core with a semi-permeable membrane, encapsulation of beads, pellets or tablets with different levels and types of diffusion barriers. However use of sophisticated equipments in their formulation, number of critical manufacturing process variables, difficulties in scale-up and use of skilled manpower had limited their routine use in the industry. A common technique of preparation of sustained release tablets include the use of a matrix or carrier-based system, in which the active ingredient is dispersed uniformly throughout a controlled release functional polymer [1-3].

Etodolac, 2-(1,8-diethyl-4,9-dihydro-3H-pyrano[3,4-b]indole-1-il)acetic acid is an example of non-steroidal anti-inflammatory drugs (NSAIDs). It is especially beneficial in treatment of chronic conditions of arthritis, osteoarthritis and similar rheumatismal diseases. Etodolac is a medicine with a short elimination half life of 8 h and low and pH-dependent solubility between pH 3 to 7 [4-6]. Thus in order to maintain the effective plasma levels of the drug, its frequent administration are needed which would in turn lead to NSAID-related side effects on gastro-intestinal (GI) system. Also once-a-day sustained action medications for drug molecules with short half lives typically like Etodolac present formulation problems because of their relatively short residence time into GI tract before elimination [7-9].

Thus the present study aimed to evaluate the effect of manufacturing process variable on designing of extended release tablet of Etodolac using natural polymer.

MATERIALS AND METHODOLOGY

Materials

Etodolac was obtained as gift sample from Platico Pharma (Indore, India). Xanthan Gum USP/ NF was supplied as a gift sample by BASF Corporation (Washington, USA) as Xantural®. All other commonly used excipients with reported compatibility with Etodolac and chemicals were of analytical grade and procured from authorized supplier.

Formulation design and preparation of Etodolac matrix tablet

Etodolac extended release tablets 400 mg were prepared by both direct compression (Formulations F1, F2, F3 and F4) and wet granulation (Formulations F5, F6, F7 and F8)

techniques by using natural polymer, xanthan gum at concentrations of 8, 9, 10 and 11% w/w. Microcrystalline cellulose (Avicel pH 101), talc (2% w/w) and magnesium stearate (2% w/w) were used as diluent, glidant and lubricant respectively. The PVP K-30 and isopropyl alcohol used in wet granulation method were used as binder and co-solvent. The wet granulation was done by using sieve No. 16. The granules were dried in hot air oven at 45°C for 30 min and air dried granules were kept for two days. For all batches, the drugs were mixed with excipients in a Turbula apparatus (WA Bachofen, Basel, Switzerland) for 10 min at 30 rpm, and compressed between 7 mm round flat faced punches on a ten stations automatic punching machine (Cad Mack Ltd. Mumbai, India) [10].

Characterization

Evaluation of Etodolac and xanthan gum granules

Angle of repose, Carr's index, Bulk density and Hausner's ratio were determined to assess the flow ability of the prepared Etodolac granules [11-14].

Angle of repose

The angle of repose was determined by allowing the granules to fall freely through a fixed funnel at a distance of 1 cm above the horizontal surface with the apex of the conical pile just touching the tip of the funnel.

The angle of repose (θ) was calculated by the formula: $\theta = \tan^{-1} (h/r)$ …… (1)

Where, h is cone height in cm of granules and r is radius in cm of circular base formed by granules on the ground.

Bulk density

The product was tapped using bulk density apparatus (Terknik P-87, India) for 1000 taps in a cylinder and the change in volume were measured. The Carr's index and Hausner's ratio were calculated by formula:

$$\text{Carr's index (\%)} = [(D_f - D_o) / D_f] \times 100 \quad \text{..... (2)}$$

$$\text{Hausner's ratio} = D_f / D_o \quad \text{..... (3)}$$

Where, D_o is the poured density in g/cc and D_f is the tapped density in g/cc.

Quality control test on the Etodolac matrix tablets

Hardness

Hardness study was conducted by following the guidelines of the USP. Six tablets were taken and hardness of each tablet of each batch was measured by Pfizer type Hardness Tester (Campbell Electronics Company, Mumbai, India) [15].

Diameter

The study of the tablet thickness was conducted by the following USP guidelines [15]. Fifteen tablets of each batch were taken and thickness was measured by using Digimatic caliper, Mitutoyo Corporation, Japan.

Friability

Friability testing was done by using 6 tablets for each batch by using Friability Test Apparatus (Campbell Electronics, Mumbai, India) [15].

Weight variation

Weight variation study was conducted by following guidelines of USP. In short 20 tablets were taken and they were weighed together and individually in electronic digital balance. The individual weight variations were studied from the mean weight of each set [15].

Drug content

About 20 tablets were selected randomly from each formulation, weighed. The weighed tablets were powdered. The powder equivalent to 100 mg of Etodolac was accurately weighed and dissolved in phosphate buffer pH 6.8. After suitable dilution, the solution was analyzed for drug content by using UV-Visible spectrophotometer (Shimadzu UV 1700, Japan) at 276 nm [16].

***In vitro* release study**

Dissolution rate of Etodolac and its release from all the tablet formulations was performed, in triplicate using U.S.P. grade XXXII, Type II Dissolution Test Apparatus (Electrolab, Model: TDT-06P, India). Samples were placed in the dissolution vessels containing 900 mL of Phosphate buffer (pH 6.8) solutions maintained at 37.0±0.5°C and stirred at 50 r.p.m. +/- 4%. Selection of Phosphate buffer, pH 6.8 as dissolution medium signifies simulation of intestinal condition in terms of pH where the extended release formulation is expected to release the

drug. The aliquots of suitable volume (i.e. 5 mL) were collected at predetermined intervals of time and replaced immediately with equal volumes of fresh dissolution medium, maintained at the same temperature. After filtration, each of the collected aliquots was suitably diluted with methanol and analyzed spectrophotometrically at λ_{max} of 276 nm. The data was studied using PCP-Disso v2.08 software [16].

Drug release kinetics

In order to determine mechanism of drug release from the tablet formulations, the drug release data were outfitted into various drug releases mathematical kinetics equations such as zero order, first order models, Higuchi model, Hixon–Crowell Square root and Korsmeyer-Peppas model, which were based on equations that describe the drug release phenomenon [17-19].

Stability study

Stability study was conducted on optimized formulation of Etodolac matrix tablet at storage conditions like temperature 40±2°C and humidity 75±5% RH as per ICH guidelines, to assess the changes in their molecular interactions, assay and drug release during their storage in Alu-Alu blister packs over the period 6 months [20,21].

Drug-excipient compatibility study

Drug-excipient compatibility screening to identify drug – excipient interactions and to avoid potential stability problems was performed by preparing the physical mixtures of Etodolac with each of xanthan gum in a ratio of 1:10 and filled into the Glass-I amber colored vials of suitable size. The compatibility was assessed at the end of 1 month by observing the changes in color, appearance and confirmed with the help of Fourier Transform Infrared (FT-IR) spectroscopy using Tensor-27 Spectrometer (Bruker Optik GmbH, Germany) operated with Star^{e} software (version 9.01). In FT-IR, about 2–3 mg of the samples was finely ground with dry KBr and mounted on the sample cell. The spectra were scanned over wave number range of 4,000−450 cm^{-1} [22].

RESULTS AND DISCUSSION

The direct compression and wet granulation methods with formulation additive were found to be efficient for successful preparation of Etodolac tablets (Table 1). The prepared granules were evaluated flow properties by measurement of angle of repose and the results are given in Table 2. The bulk density was found in the range of 0.269±0.0004 to 0.31±0.005 g/cc. The

tapped density was found in the range of 0.354±0.0020 to 0.43±0.0056 g/cc. The bulkiness was found between 3.070±0.0256 to 3.713±0.0052 cc/g, demonstrating good flow property. The granules of all tablet formulations had Hausner's ratio of 1.334±0.0072 or less (less than 1.5) indicating good flowability. The Carr's index was found between 13.29±1.6053 to 24.8±0.546 %, demonstrating good flow property. The good flowability of the granules was also evidenced with angle of repose within range of 28.2±0.4574 to 29.94±0.6944º, which is below 30° indicating good flowability.

The diameter (12.50±0.0667 to 12.57±0.0483 mm) of all tablet formulations was almost same (Table 3). The hardness of all tablet formulations was ranges from 5.96±0.227 to 6.14±0.212 kg/cm^2. Hardness of tablet formulations increased with increase in concentration of xanthan gum. The hardness of all extended release tablet formulations was within Pharmacopeial limit. All the batches of tablet exhibited equal uniformity in weight (596.5±5.6111 to 601.2±7.3742 mg). The friability of all tablet formulation was ranges from 0.245±0.062 to 0.67±0.0456%. All tablet formulations passed friability test as per Pharmacopoeial limits of USP, as percentage loss on friability was less than 1%. All the batches of tablet exhibited good uniformity in drug content (97.69±0.4107 to 99.10±0.1787%). The maximum drug content (99.10±0.1787%) was achieved with tablet formulation F7 using 10% of xanthan gum as release rate controlling polymer. Almost all the tablet formulations were able to extend the drug release. Almost all the tablet formulations were able to suitably extend the drug release from their dosage form. *In vitro* dissolution study showed (Table 4) that drug released from the tablet formulations, prepared by using xanthan gum employing direct compression and wet granulation methods at four different concentrations was more than 90% in 840 min (Fig 1) except tablet formulations F4 and F8. The tablet formulation F1 showed lesser drug release profile that release drug up to lesser extended period of time (390 min). Among all the tablet formulations, the tablet formulation F8 (Containing 11% of xanthan gum prepared by wet granulation method) released drug (78.9±0.57% in 840 min) in more controlled manner over extended period of time. Model dependant methods were used to investigate the kinetics of drug release from the formulations. *In vitro* drug release kinetic study revealed that (Table 5) Etodolac tablet formulations F4 release drug with zero order kinetics, where as tablet formulations F2, F3, F6, F7 and F8 release drug following Hixon-Crowell model. The tablet formulation F1 and F5 release drug with Higuchi release kinetic. From the Korsmeyer-Peppas model, it is revealed that the drug release profile tablet formulations F1 to F6 follow Fickian transport mechanism but F7 and F8 follow non-Fickian transport mechanism.

Unchanged position of the characteristic absorption bands with respect to Etodolac, xanthan gum in the FT-IR spectrum of the blend of Etodolac and xanthan gum mixture suggested compatibility of the functional polymers with the drug (Fig 2). Also the absorption bands at 3342 cm^{-1} corresponding to secondary N-H stretching and at 1738 cm^{-1} corresponding to C=O stretching with respect to Etodolac was not found to be broadened or shifted to lower wave number, which indicated absence of intermolecular hydrogen bonding between the drug and the functional polymer molecules in the blend. The FTIR study revealed that no such physical and chemical interaction being taking place in between Etodolac and xanthan gum [23,24].

The tablet formulation F8 containing 11% w/v of xanthan gum prepared by wet granulation method, as drug release controlling polymer, was the optimized tablet formulation as it showed satisfactory hardness, drug content and drug release profile (in more controlled manner over extended period of time) with Hixon-Crowell release kinetic.

The stability study of optimized tablet formulation (F8) was carried out at temperature 40±2°C and humidity 75±5% RH as per ICH guidelines. The tablets were found to be stable at such conditions; other parameters were found to be unaffected and were under Pharmacopoeial limits of USP.

CONCLUSION

From the above experimental study it has been found that the tablet formulation F8 containing 11% w/v of xanthan gum, as drug release controlling polymer, was the optimized tablet formulation as it showed satisfactory drug release profile (in more controlled manner over extended period of time) with zero order release kinetic. Thus wet granulation method as process variable was found to more efficient than direct compression method for designing of extended release tablet formulation of NSAIDs drug that is Etodolac.

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Table 1. The matrix tablet formulations of Etodolac with xanthan gum manufactured by direct compression and wet granulation methods.

Ingredients (mg)	Concentration (in percent of tablet weight) of a functional polymer							
	8%	9%	10%	11%	8%	9%	10%	11%
	Direct compression				Wet granulation			
	F1	F2	F3	F4	F5	F6	F7	F8
Etodolac	400	400	400	400	400	400	400	400
Xanthan gum	48	54	60	66	48	54	60	66
Avicel	116	110	104	98	116	110	104	98
PVP K-30	-	-	-	-	12	12	12	12
Isopropyl alcohol	-	-	-	-	q.s	q.s	q.s	q.s.
Talc	12	12	12	12	12	12	12	12
Magnesium Stearate	12	12	12	12	12	12	12	12
Total weight	600	600	600	600	600	600	600	600

q.s. – Quantity sufficient

Table 2. Pre compression parameters of extended release formulation prepared by direct compression and wet granulation methods for Etodolac with xanthan gum.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Bulk density (g/cc)(n=5) (X±SEM)	0.31± 0.003	0.31± 0.005	0.31± 0.0036	0.325± 0.0027	0.269± 0.0005	0.271± 0.0018	0.269 ± 0.0004	0.272± 0.001
Tapped density (g/cc)(n=5) (X±SEM)	0.42± 0.006	0.41± 0.002	0.42± 0.0075	0.43 ± 0.0056	0.354± 0.0050	0.354± 0.0020	0.356 ± 0.0013	0.358± 0.002
Bulkiness (cc/g)(n=5) (X±SEM)	3.18± 0.028	3.22± 0.057	3.17± 0.0358	3.070± 0.0256	3.714± 0.0062	3.689± 0.0249	3.713 ± 0.0052	3.678± 0.011
Carr's index (%)(n=5) (X±SEM)	24.8± 0.546	24.28 ± 0.985	24.7± 0.5745	24.51± 0.4085	13.29± 1.6053	14.46± 0.3234	14.29 ± 0.3707	14.06± 0.463
Hausner ratio	1.33± 0.009	1.320 ± 0.017	1.32± 0.0102	1.334± 0.0072	1.153± 0.0211	1.169± 0.0044	1.166 ± 0.0051	1.163± 0.006
Angle of repose(θ)(n = 3) (X±SEM)	29.2± 0.735	29.13 ± 0.371	29.1± 0.383	29.11± 0.6769	29.42± 0.7538	29.94± 0.6944	28.6± 0.5980	28.2± 0.457

Each data represents mean ± standard error of mean (n = no. of observations).

Table 3. Quality control tests of various Etodolac extended release tablet formulations prepared by direct compression and wet granulation methods.

Parameters	Formulations							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Diameter[a] (mm)(X±SEM)	12.53± 0.0483	12.55± 0.0527	12.54± 0.0516	12.56± 0.0516	12.57± 0.0483	12.56± 0.0516	12.50± 0.0667	12.55± 0.0707
Hardness[a] (kg/cm^2)(X±SEM)	5.98± 0.1476	6.01± 0.5782	6.02± 0.1989	6.12± 0.5731	5.96± 0.227	6.14± 0.212	5.98± 0.147	6.02± 0.199
Weight[b] (mg)(X±SEM)	596.5± 9.1965	599.6± 8.1517	601.2± 7.3742	598.6± 8.2742	597.7± 5.6111	598.2± 5.2073	600.2± 5.077	600.1± 5.8802
Friability[c] (%)(X±SEM)	0.67± 0.0422	0.67± 0.0456	0.66± 0.0637	0.63± 0.0872	0.323± 0.101	0.305± 0.135	0.272± 0.099	0.245± 0.062
Drug content[d] (%)(X±SEM)	97.69± 0.4107	97.78± 0.3094	98.56± 0.3573	98.56± 0.2943	98.79± 0.2943	98.83± 0.3094	99.10± 0.1787	98.91± 0.1351

Each data represents mean ± standard error of mean. a – Test done with 10 tablets, b – Test done with 20 tablets, c – Test done with 10 tablets three times, d – Test done with 20 tablets three times

Table 4. Comparison of drug release profile from extended release formulation prepared by direct compression and wet granulation methods for Etodolac with xanthan gum.

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
30	36.8±0.3	25.5±0.6	19.5±0.3	12.8±0.4	32.7±0.2	22.8±0.2	16.8±0.1	8.1±0.3
90	55.1±0.3	34.3±0.3	30.9±0.3	20.5±0.5	53.8±0.3	31.7±0.1	25.9±0.3	15.8±0.2
150	70.2±0.4	42.1±0.3	36.8±0.3	26.9±0.4	67.4±0.3	39.9±0.2	32.4±0.3	21.7±0.4
210	78.1±0.2	49.2±0.3	42.6±0.4	33.1±0.6	76.9±0.2	47.8±0.1	41.7±0.3	27.5±0.2
270	87.3±0.4	57.5±0.6	50.4±0.4	40.5±0.5	84.7±0.2	56.8±0.2	48.1±0.3	30.6±0.2
330	93.6±0.4	66.1±0.5	56.4±0.4	45.5±0.5	89.2±0.1	63.0±0.4	54.3±0.2	40.3±0.5
390	99.2±0.3	73.1±0.3	64.9±0.5	50.8±0.6	94.2±0.3	71.6±0.2	63.1±0.2	45.8±0.4
450	-	80.0±0.3	73.5±0.4	57.7±0.5	99.1±0.1	77.5±0.3	72.0±0.3	49.8±0.5
840	-	99.2±0.4	96.9±0.8	89.7±0.8	-	97.3±0.1	94.9±0.2	78.9±0.6

Each data represents mean ± standard error of mean (n = 3).

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Table 5. *In vitro* drug release kinetic data of extended release tablet formulations of Etodolac

Formulations	Correlation Co-efficient (r^2) value				Korsmeyer-Peppas	
	Zero order	First order	Higuchi	Hixson-crowell	R^2	Slope (n)
F1	0.9573	0.8712	0.9962	0.9712	0.9979	0.3974
F2	0.9332	0.8838	0.9502	0.9882	0.9704	0.4541
F3	0.9602	0.9132	0.9122	0.9799	0.9757	0.4994
F4	0.9909	0.9324	0.8655	0.9801	0.9850	0.6001
F5	0.9245	0.9044	0.9857	0.9832	0.9939	0.4077
F6	0.9321	0.9485	0.9801	0.9957	0.9727	0.4791
F7	0.9560	0.9473	0.9807	0.9902	0.9815	0.5613
F8	0.9854	0.9723	0.9691	0.9895	0.9865	0.6456

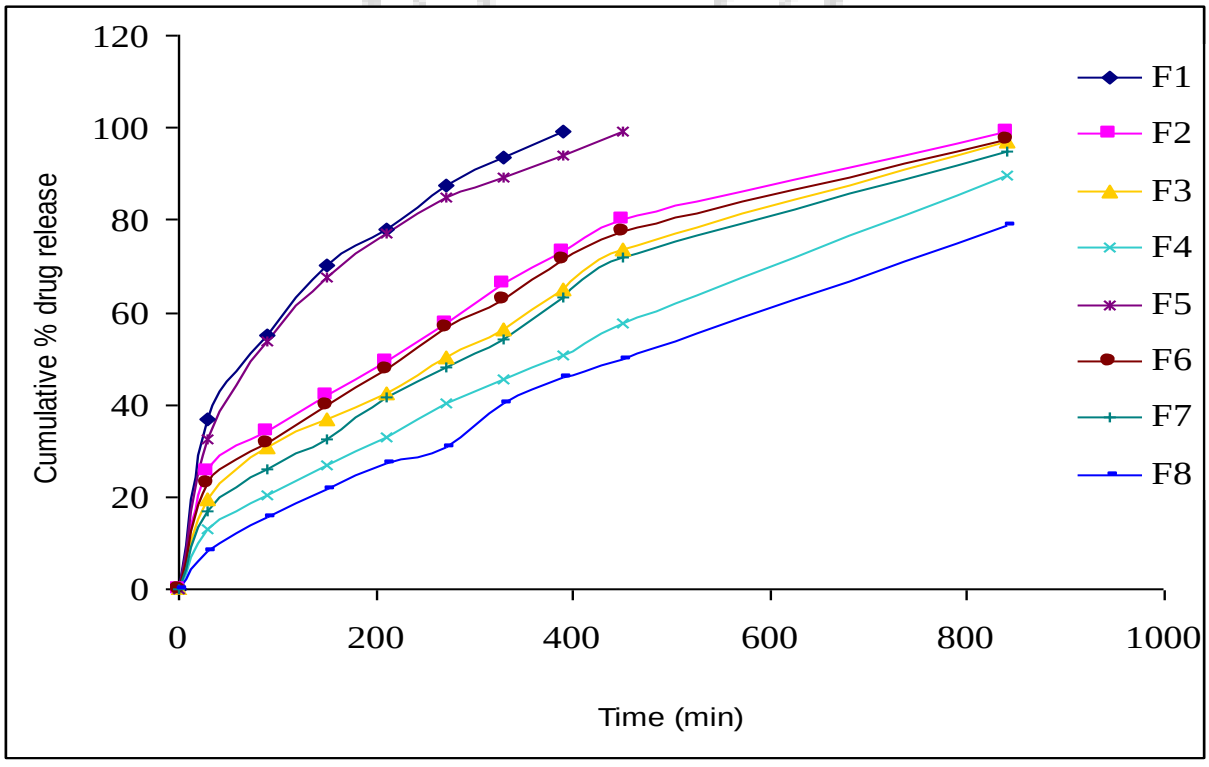

Figure 1. Drug release profile chart – Extended release formulation prepared by direct compression and wet granulation methods for Etodolac with xanthan gum. Each data represents mean ± standard error of mean (n = 3).

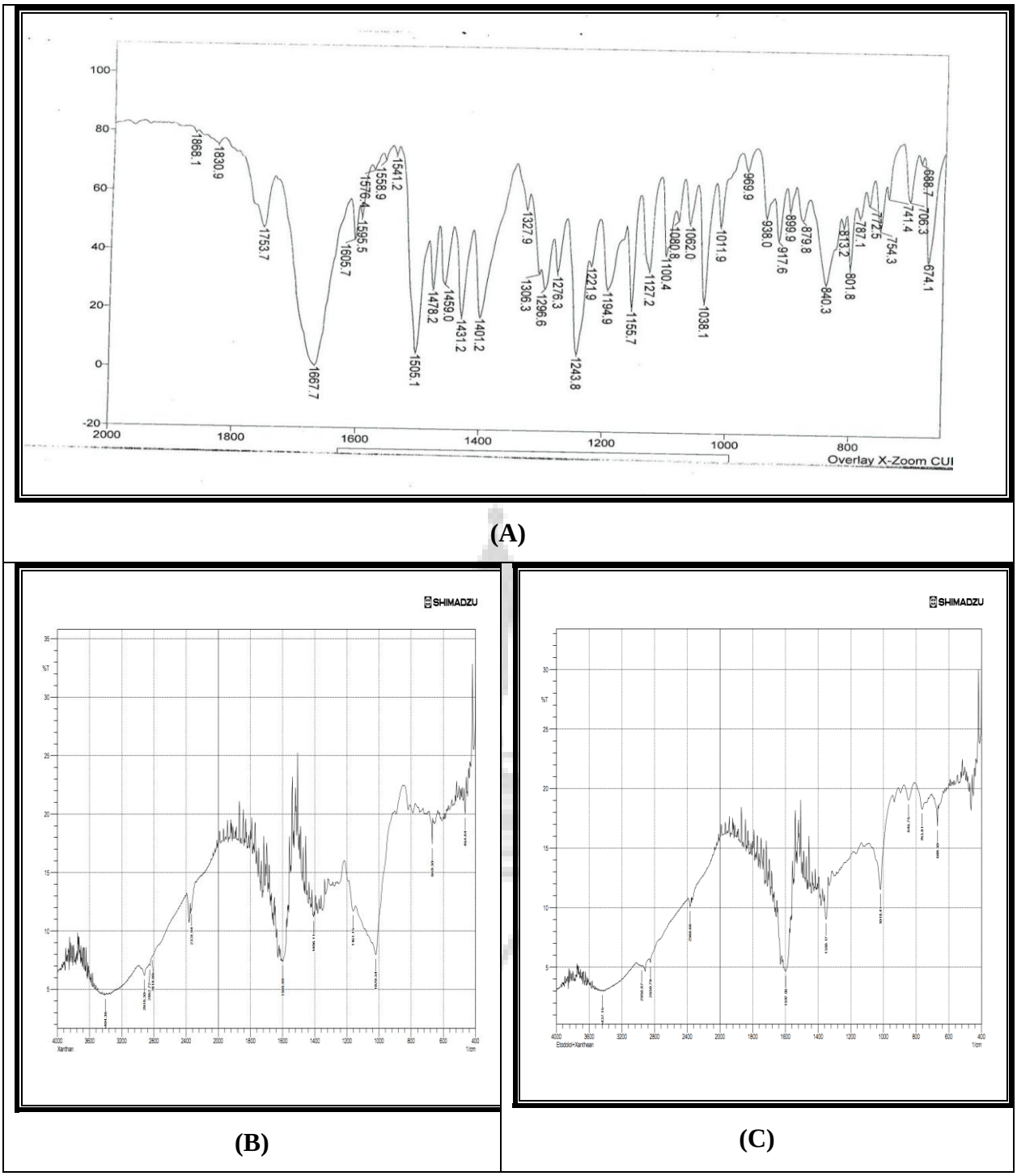

Figure 2. FTIR spectrum of Etodolac pure drug (A), xanthan gum (B) and physical mixture of drug and xanthan gum over wave number range of 4,000−450 cm^{-1}.