CODEN: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

Available online at: http://www.iajps.com Research Article

PREPARATION AND *IN VITRO* EVALUATION OF ETODOLAC EXTENDED RELEASE TABLETS PREPARED BY WET GRANULATION METHOD EMPLOYING KOLLIDON® SR

Arun Kumar Arumugarajan[1*], G. Geetha[2], Bhabani Shankar Nayak[3]

[1]Department of Pharmaceutics, RVS College of Pharmaceutical Sciences, 242 B, Trichy road, Sulur, Coimbatore, Tamil Nadu - 641 402, India.

[2]Departments of Pharmaceutical Analysis, PSG College of Pharmacy, Coimbatore, Tamil Nadu – 641004, India.

[3]Department of Pharmaceutical Technology, Jeypore College of Pharmacy, Rondapalli, Jeypore – 754002, Koraput, Odisha, India.

Abstract:

Background: *The most prominent advantages of extended release formulations of non-steroidal anti-inflammatory drugs (NSAIDs) are their ability to maintain optimal and therapeutically effective drug levels for prolonged duration with reduction in dosing frequency and side effects associated with NSAIDs.* ***Aim:*** *The objective of the present study to develop diffusion controlled matrix tablets for extended release of a model NSAID drug, Etodolac.* ***Materials and Methodology:*** *Etodolac control release tablets were prepared by wet granulation method using Kollidon® SR in different ratios 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 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 Kollidon® SR (10.0 %) provided most controlled release of water-soluble Etodolac over extended period of time.*

Keywords: *Extended release, NSAIDS, Etodolac, matrix tablet, wet granulation.*

Address for correspondence:

Arun Kumar Arumugarajan,
RVS College of Pharmaceutical Sciences,
242 B, Trichy road, Sulur, Coimbatore,
Tamil Nadu - 641 402, India.
Mob. No. 09594099294
E. Mail I.D. - kumar.arunpharma@gmail.com

QR code

Please cite this article in press as Arun Kumar Arumugarajan *et al* , **Preparation and *In Vitro* Evaluation of Etodolac Extended Release Tablets Prepared By Wet Granulation Method Employing Kollidon® SR,** *Indo Am. J. Pharm. Sci, 2015;2(7).*

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 [1]. 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 [2]. 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 [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) [4]. It is especially beneficial in treatment of chronic conditions of arthritis, osteoarthritis and similar rheumatismal diseases [5]. Etodolac is a medicine with a short elimination half life of 8 h and low and pH-dependent solubility between pH 3 to 7 [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 [7]. 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 [8,9].

Thus the present study aimed to develop an extended release tablet dosage form of Etodolac by wet granulation method employing semi-synthetic polymer that is Kollidon® SR.

MATERIALS AND METHODOLOGY:

Materials:

Etodolac was obtained as gift sample from Platico Pharma (Indore, India). Polyvinyl acetate containing polyvinylpyrrolidone (denoted as KOL) was supplied as a gift sample by BASF Corporation (Washington, USA) as Kollidon®SR. 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 Tablets:

Etodolac extended release tablets 400 mg were prepared by wet granulation technique by using semi-synthetic, Kollidon® SR at concentrations of 5, 6, 7, 8, 9 and 10 % w/w (Formulations T1 to T6). Anhydrous lactose, talc (2 % w/w) and magnesium stearate (2 % w/w) were used as diluent, glidant and lubricant respectively. The PVP K-30 was used as binder. Isopropyl alcohol was used as 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 Kollidon® SR 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 by wet granulation method [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:

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

Hausner's ratio = D_f / D_o …… (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. For these fifteen tablets were taken for each batch and thickness were measured by using Digimatic caliper, Mitutoyo Corporation, Japan [15].

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 electronically 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 [17,18,19].

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 Kollidon® SR 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 DISCUSSIONS:

The wet granulation and formulation additive were found to be efficient for successful preparation of Etodolac tablets (Table 1) using Kollidon®SR as drug release rate controlling polymer. The prepared granules were evaluated flow properties by measurement of angle of repose and the result are given in Table 2. The bulk density was found in the range of 0.196± 0.0001 to 0.1981±0.0006 g/cc. Bulk densities of the prepared granules were found to increase slightly by increasing the concentration of polymer, Kollidon® SR. This result may be due to the formation of larger agglomerates and decrease in fines in the granules. The tapped density was found in the range of 0.225±0.0011 to 0.2294±0.0004 g/cc. The bulkiness was found between 5.0489±0.0160 to5.095±0.0037 cc/g, demonstrating good flow property. The granules of all tablet formulations had Hausner's ratio of 1.1618±0.0218 or less (less than 1.5) indicating good flowability. The Carr's index was found between 12.34±0.4145 to 13.895±0.5977, demonstrating good flow property. The good flowability of the granules was also evidenced with

angle of repose within range of 29.44±0.1793 to 32.286±0.7922º, which is close to 30° indicating good flowability.

The diameter (12.51±0.0568 to 12.56±0.0516 mm) of all tablet formulations was almost same (Table 3). The hardness of all tablet formulations was ranges from 5.49±0.3464 to 6.15±0.2635 kg/cm^2. Hardness of tablet formulations increased with increase in concentration of Kollidon® SR. The hardness of all extended release tablet formulations was within Pharmacopeial limit. All the batches of tablet exhibited equal uniformity in weight (599.05±4.7292 to 599.75±5.0874 mg). The friability of all tablet formulation was ranges from 0.2719± 0.0996 to 0.4167±0.1009 %. 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 (99.3372±0.2435 to 99.7271±0.0675 %). The maximum drug content (99.7271±0.0675 %) was achieved with tablet formulation T6 using 10 % of Kollidon® SR as release rate controlling polymer. Almost all the tablet formulations were able to extend the drug release more efficiently. *In vitro* dissolution study showed (Table 4) that drug released from the tablet formulations, prepared by using Kollidon® SR at six different concentrations was more than 70 % in 840 min (Fig 1). The tablet formulation T1 and T2 showed poor drug release profile in regards to extended drug release point of view. Among all the tablet formulations, the tablet formulation T6 released drug (71.67±0.567 % 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 reveled that (Table 5) Etodolac tablet formulations T1 and T5 release drug with Korsmeyer-Peppas release kinetics, where as tablet formulations T2, T3 and T5 release drug following Hixon-Crowell model. The tablet formulation T6 release drug with zero order release kinetic. From the Korsmeyer-Peppas model, it is reveled that the drug release profile tablet formulations T1 to T6, follow non-Fickian transport mechanism.

Unchanged position of the characteristic absorption bands with respect to Etodolac, Kollidon® SR in the FT-IR spectrum of the blend of Etodolac and Kollidon® SR 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 reveled that no such physical and chemical interaction being taking place in between Etodolac and Kollidon® SR [23, 24].

The tablet formulation T6 containing 10 % w/v of Kollidon® SR , 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 zero order release kinetics.

The stability study of optimized tablet formulation (T6) 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 T6 containing 10 % w/v of Kollidon® SR , 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 zero order release kinetic.

ACKNOWLEDGEMENT:

Author wish to thanks to thanks authority of RVS College of Pharmaceutical Sciences, for providing facility to carry out this research work.

REFERENCES:

1. Baylan S. 2002. Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker Inc.
2. Dey NS, Majumdar S, Rao MEB. Multiparticulate Drug Delivery Systems for Controlled Release. Trop J Pharm Res, 2008; 4(3): 134-9.
3. Jan S, Cheng XX. Oral dosage for the controlled release of analgesic. US Patent, US 6197347, 2001.
4. Benet LZ. Rheumatol, Pharmacokinetics of sustained release Etodolac. Int J Pharm, 1993; 13(2): S3-5.
5. Raghuvanshi RS, Rampal A, Sen H. Extended release formulation of Etodolac. US Patent, US 6586005, 2003.
6. Crum CP. 1999. Diabetes. In: Cotran RS, Kumar V, Collins T, ed. Robbins, Pathologic Basis of Disease. New Delhi: Published by Harcourt (India) Private Ltd. 934-46.
7. Rang and Dales Pharmacology. 2007. Analgesic drugs. Philadelphia: Churchill Living Stone Elsevier.

8. Tripathi KD. 2003. Analgesic drugs. In: Essentials of Medical Pharmacology. New Delhi: Jaypee Brothers Ltd. 345-52.
9. Madgulkar A, Kadam S, Pokharkar V. Studies on formulation development of mucoadhesive sustained release Itraconazole tablet using response surface methodology. AAPS PharmSciTech, 2008; 9(3): 998-1005.
10. Abd-Elbary A, Tadros MI, Alaa-Eldin AA. Sucrose stearate-enriched lipid matrix tablets of etodolac: modulation of drug release, diffusional modeling and structure elucidation studies. AAPS PharmSciTech, 2013; 14(2): 656-68
11. Lachman L, Liberman HA, Kanig JL. 1987. Tablets. In: The Theory and Practice of Industrial Pharmacy. Bombay: Varghese Publishing House 293-326.
12. Martin A, Bustamante P, Chun AHC. 1994. Powder Rheology. In: Martin Physical Pharmacy. New Delhi: B.I. Waverly Pvt. Ltd. 465-6.
13. Banker GS, Neil RA. 1987. Theory and Practices of Industrial Pharmacy. Mumbai: Varghese Publication 297-305.
14. Aulton ME. 2007. Powder flow. London, New York: Churchil Livingstone 176-183.
15. The United States Pharmacopoeia. 2002. USP/NF, 25/20. Rackville, MD: The U. S. Pharmacopoeial Convention.
16. Monographs and Appendix. 1996. In: Indian Pharmacopoeia. Govt. of India, Ministry of Health and Family Welfare. New Delhi: Published by the Controller of Publications 488-9 and A-147.
17. Higuchi T. Mechanism of rate of sustained-action medication. J Pharm Sci, 1963; 52(11): 1145-9.
18. Ritger PL, Peppas NA. Modelling of water transport solute release in physiologically sensitive gels. J Control. Release, 1987; 5: 34-7.
19. Munday DL, Cox PJ. Compressed xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. Int J Pharm, 2000; 203: 179–92
20. Carstensen JT. 1989. Drug Stability, Principles & Practices. New York: Marcel Dekker Inc. 17-58.
21. Stability Data Package for Registration Applications in Climatic Zones III and IV-Q1F [Internet]. 2003. ICH Harmonised Tripartite Guideline. [Cited 2013 Jul 3]. Available from: www.ich.org.
22. Guruswami S, Kumar V, Mishra DN. Characterization and *in vitro* dissolution studies of solid systems of valdecoxib with chitosan. Chem Pharm Bull, 2006; 54: 1102-6.
23. Kemp W. 2009. Infrared Spectroscopy. New York: Palgrave Houndmills 19-65.
24. Silverstein RM, Webster FX. 2005. Infrared Spectroscopy. New Delhi: Wiley India (P) Ltd. 71-100.

Table 1: The Matrix Tablet Formulations of Etodolac with Kollidon® SR Manufactured By Wet Granulation Method

Ingredients (mg)	**Concentration (in percent of tablet weight) of a functional polymer**					
	5%	6%	7%	8%	9%	10%
	T1	T2	T3	T4	T5	T6
Etodolac	400	400	400	400	400	400
Kollidon® SR	30	36	42	48	54	60
Lactose anhydrous	134	128	122	116	110	104
PVP K-30	12	12	12	12	12	12
Isopropyl alcohol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc	12	12	12	12	12	12
Magnesium Stearate	12	12	12	12	12	12
Total weight	600	600	600	600	600	600

q.s. – Quantity sufficient.

Table 2: Pre Compression Parameters of Extended Release Formulation Prepared By Wet Granulation Method for Etodolac with Kollidon® SR

Parameters	T1	T2	T3	T4	T5	T6
Bulk density (g/cc)(n=5)(X±SEM)	0.1971± 0.0008	0.1981± 0.0006	0.1971± 0.0008	0.196± 0.0001	0.196± 0.0001	0.197± 0.0006
Tapped density (g/cc)(n=5)(X±SEM)	0.2290± 0.0036	0.2294± 0.0004	0.2284± 0.0028	0.225± 0.0011	0.225± 0.0022	0.225± 0.0017
Bulkiness (cc/g)(n=5)(X±SEM)	5.0733± 0.0207	5.0489± 0.0160	5.0726± 0.0208	5.095± 0.0037	5.080± 0.0032	5.057± 0.0152
Carr's index (%)(n=5)(X±SEM)	13.895± 1.5977	13.652± 0.3469	13.682± 0.9236	13.14± 0.5023	12.66± 0.8044	12.34± 0.4145
Hausner's ratio	1.1618± 0.0218	1.1581± 0.0047	1.1586± 0.0124	1.151± 0.0067	1.145± 0.0105	1.140± 0.0054
Angle of repose(θ),(n = 3)(X±SEM)	32.286± 0.7922	31.883± 0.6350	31.903± 0.6211	30.98± 0.6799	30.74± 0.5049	29.44± 0.1793

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

Table 3: Quality Control Tests of Various Etodolac-Kollidon® SR Extended Release Tablet Formulations Prepared By Wet Granulation Method

Parameters	Formulations					
	T1	T2	T3	T4	T5	T6
Diameter[a] (mm)(X±SEM)	12.51±0.0568	12.53±0.0675	12.56±0.0516	12.52± 0.0632	12.53± 0.0675	12.53± 0.0675
Hardness[a] (kg/cm^2)(X±SEM)	6.07±0.2983	5.49±0.3464	6.12± 0.2781	6.15± 0.2635	6.11± 0.1792	6.02± 0.2781
Weight[b] (mg) (X±SEM)	599.10±5.5241	599.05±4.729	599.75±5.087	598.15±3.9772	599.5± 3.9270	599.55±4.211
Friability[c] (%)(X±SEM)	0.4167±0.1009	0.399±0.1299	0.355±0.1229	0.3235±0.1010	0.3055± 0.1348	0.2719±0.099
Drug content[d] (%)(X±SEM)	99.337±0.2435	99.454±0.135	99.532±0.117	99.337± 0.271	99.532± 0.309	99.727±0.067

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 from Extended Release Formulation Prepared By Wet Granulation Method for Etodolac with Kollidon® SR

Time (min)	T1	T2	T3	T4	T5	T6
30	4.98±0.2107	3.43±0.0917	3.09±0.2108	2.88±0.2425	2.16±0.2107	1.35±0.1510
90	15.36±0.180	12.12±0.183	10.91±0.210	9.64±0.2400	7.92±0.2350	7.34±0.1833
150	25.67±0.237	21.41±0.270	17.78±0.210	16.03±0.210	14.42±0.237	12.94±0.124
210	35.44±0.183	28.49±0.330	25.79±0.177	23.33±0.180	19.94±0.240	18.94±0.160
270	48.73±0.210	35.77±0.175	32.94±0.297	30.32±0.242	27.90±0.265	24.03±0.151
330	57.30±0.270	44.37±0.205	39.38±0.205	37.78±0.210	33.53±0.302	29.23±0.175
390	63.25±0.302	52.00±0.297	46.63±0.210	44.31±0.145	39.58±0.295	35.95±0.275
450	68.65±0.302	58.72±0.141	53.91±0.124	49.60±0.183	45.71±0.355	40.61±0.335
840	96.49±0.703	90.28±0.805	85.06±0.710	81.01±0.866	76.39±0.860	71.67±0.567

Each data represents mean ± standard error of mean (n = 3). Each value is expressed as cumulative percentage drug release.

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)
T1	0.9744	0.9511	0.9872	0.9934	0.9945	1.0062
T2	0.9759	0.9527	0.9864	0.9927	0.9923	1.0034
T3	0.9836	0.9650	0.9811	0.9940	0.9938	1.0213
T4	0.9860	0.9736	0.9790	0.9960	0.9954	1.0396
T5	0.9906	0.9767	0.9733	0.9958	0.9960	1.0925
T6	0.9959	0.9753	0.9675	0.9933	0.9876	1.1794

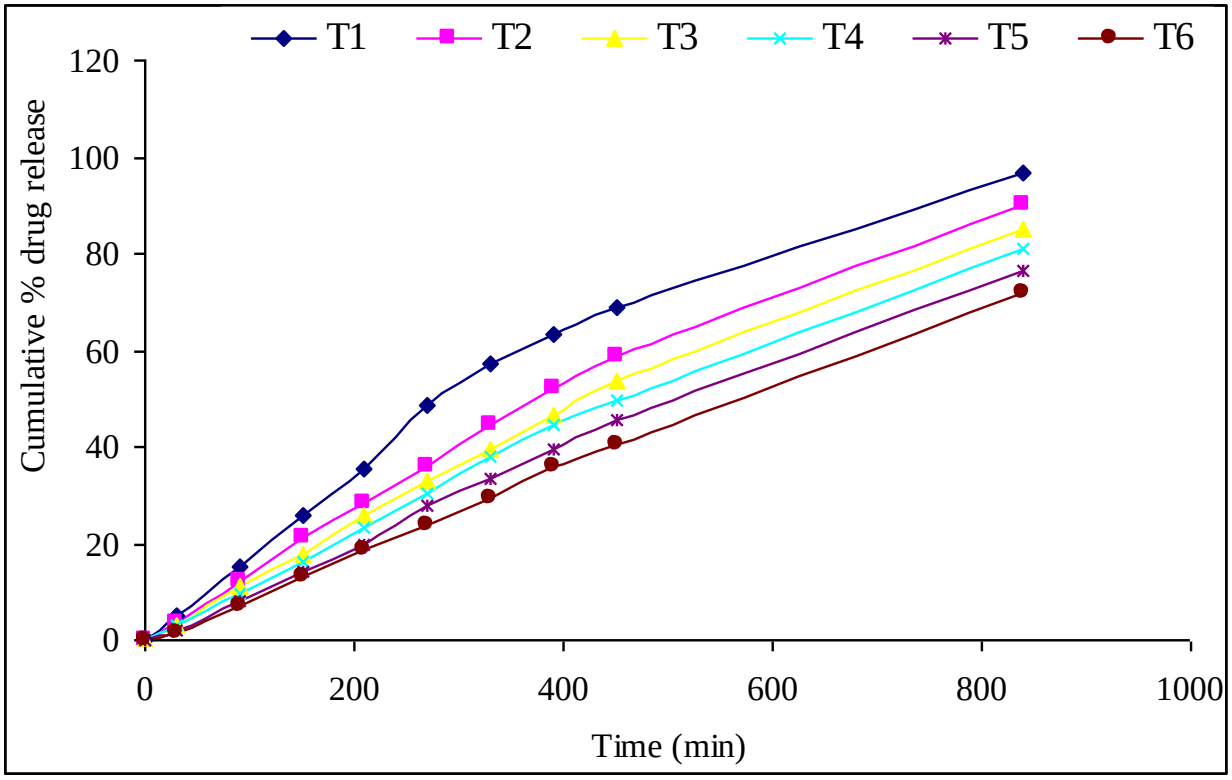

Fig 1: Drug Release Profile Chart – Extended Release Formulation Prepared By Wet Granulation Method for Etodolac with Kollidon® SR.
Each data represents mean ± standard error of mean (n = 3).

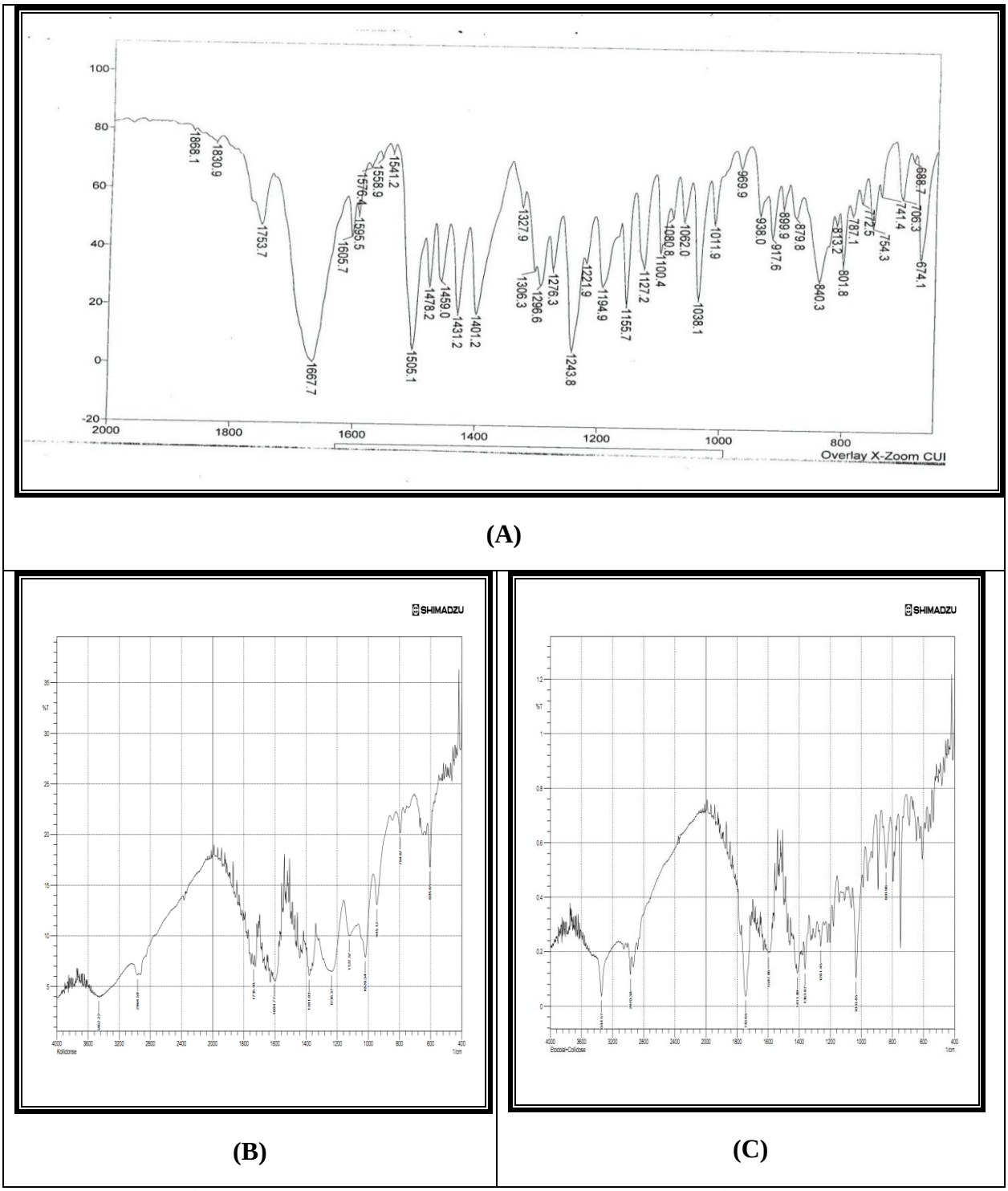

Fig 2: FTIR Spectrum of Etodolac pure drug (A), Kollidon® SR (B) and Physical Mixture Of Drug and Kollidon®SR Over Wave Number Range of 4,000−450 cm^{-1}.