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FORMULATION DESIGN, PREPARATION AND EVALUATION OF ETODOLAC EXTENDED RELEASE TABLETS BY DIRECT COMPRESSION METHOD USING KOLLIDON®SR

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ABSTRACT

Background: Extended release formulations are becoming more popular day by day for the delivery of non-steroidal anti-inflammatory drugs (NSAIDs) because of their ability to maintain optimal and therapeutically effective drug levels for prolonged duration with reduction in dosing frequency and side effects associated with NSAIDs. **Aims:** The present study attempted to develop extended release tablets of a model NSAID drug, Etodolac using semi-synthetic polymer. **Materials and Methodology:** Etodolac matrix tablets were prepared by direct compression method using Kollidon® SR in different ratios as release rate controlling polymer. 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 with aid of greater stability.

KEYWORDS: $NSAID_S$, Etodolac, matrix tablet, direct compression, Kollidon®SR, rate controlling polymers.

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 develop an extended release tablet dosage form of Etodolac by direct compression method employing Kollidon® SR, as semi-synthetic polymer.

MATERIALS AND METHODOLOGY

Materials

Etodolac was obtained as gift sample from Platico Pharma (Indore, India). Polyvinyl acetate containing polyvinylpyrrolidone 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 direct compression technique by using semi-synthetic polymer, Kollidon® SR (denoted as F1 to F6) in 5, 6, 7, 8, 9 and 10 % w/w of total blend weight. Anhydrous lactose, talc (2 % w/w) and magnesium stearate (2 % w/w) were used as diluent, glidant and lubricant respectively. 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 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 1cm 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 ratio were calculated by formula:

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

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

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* drug 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 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 direct compression and 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 result are given in Table 2. The bulk density was found in the range of 0.331±0.0025 to 0.336±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 0.436±0.0007 to 0.440±0.0029 g/cc. The bulkiness was found between 2.976±0.0054 to 3.023±0.0225 cc/g, demonstrating good flow property. The granules of all tablet formulations had Hausner's ratio of 1.323±0.0085 or less (less than 1.5) indicating good flowability. The Carr's index was found between 23.48±0.4435 to 24.39±0.4861 %, demonstrating good flow property. The good flowability of the granules was also evidenced with angle of repose within range of 28.22±0.2783 to 29.85±0.9727º, suggesting that the flow property is good as angle of repose is less than 30º.

The diameter (12.52±0.0632 to 12.55±0.0527 mm) of all tablet formulations was almost same (Table 3). The hardness of all tablet formulations was ranges from 5.70±0.4807 to 6.04±0.3062 kg/cm^2. The maximum hardness was obtained with tablet formulation F6. 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 (598.10±8.0518 to 601.00±6.1044 mg). The friability of all tablet formulation was ranges from 0.7509±0.0879 to 0.8337±0.0718 %. All tablet formulations passed friability test as per Pharmacopoeial limits of USP-2002, as percentage loss on friability was less than 1%. All the batches of tablet exhibited good uniformity in drug content (97.8947±0.4217 to 99.2203±0.3573 %). The maximum drug content (99.2203±0.3573 %) was achieved with tablet formulation F6 using 10 % of Kollidon® SR as release rate controlling polymer. *In vitro* dissolution study showed (Table 4) that almost all Etodolac matrix tablet formulations were able to release the drug over extended period of time (Fig 1). The tablet formulation F6 showed minimum drug release profile. Better drug release profile was achieved from tablet formulations F3 to F6. Among all the tablet formulations, the tablet formulation F6 released drug (75.74±0.735 % 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) the release rate kinetic data for F1 to F6 formulations were plotted in different order of reactions, for zero order, the formulations showed linearity with regression co-efficient values (R^2) 0.9867 for optimized formula and it was observed that the drug release pattern For Hixon-Crowell, the formulations showed linearity with regression co-efficient values (R^2) 0.9837 which is closer to Higuchi's model. It showed that the drug release follows Korsmeyer-Peppas for the formulations F1 to F3 and for the formulations F4 to F6, it was Higuchi model. All the tablet formulations 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 F6 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 Korsmeyer-Peppas kinetic.

The stability study of optimized tablet formulation (F6) 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.

Table 1. Formulation design of Etodolac-Kollidon®SR extended release manufactured by direct compression method.

Ingredients (mg)	Concentration (in percent of tablet weight) of a functional polymer					
	5%	6%	7%	8%	9%	10%
	F1	F2	F3	F4	F5	F6
Etodolac	400	400	400	400	400	400

Kollidon SR	30	36	42	48	54	60
Lactose anhydrous	146	140	134	128	122	116
Talc	12	12	12	12	12	12
Magnesium Stearate	12	12	12	12	12	12
Total weight	600	600	600	600	600	600

Table 2. Pre compression parameters of extended release formulation of Etodolac prepared by direct compression method using Kollidon®SR.

Parameters	F1	F2	F3	F4	F5	F6
Bulk density (g/cc) (n=5)(X±SEM)	0.3308± 0.0025	0.3345± 0.0017	0.3336± 0.0014	0.3340± 0.0027	0.3344± 0.0015	0.3360± 0.0006
Tapped density (g/cc) (n=5)(X±SEM)	0.4376± 0.0008	0.4388± 0.0046	0.4360± 0.0007	0.4394± 0.0013	0.4375± 0.0013	0.4405± 0.0029
Bulkiness (cc/g) (n=5)(X±SEM)	3.0227± 0.0225	2.9892± 0.0152	2.9978± 0.0126	2.9946± 0.0243	2.9905± 0.0135	2.9759± 0.0054
Carr's index (%) (n=5)(X±SEM)	24.3999± 0.4861	23.7581 ± 0.6333	23.4820 ± 0.4435	24.0064± 0.3921	23.560± 0.4077	23.7171 ± 0.5367
Hausner ratio	1.3228± 0.0085	1.3117± 0.0109	1.3069± 0.0076	1.3159± 0.0068	1.3083± 0.0070	1.3110± 0.0092
Angle of repose(θ), (n = 3)(X±SEM)	29.8510± 0.9727	29.7849 ± 0.5353	28.7245 ± 0.5444	29.2860± 0.7858	28.934± 0.5607	28.2235 ± 0.2783

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 method.

Parameters	Formulations					
	F1	F2	F3	F4	F5	F6
Diameter[a] (mm)(X±SEM)	12.52± 0.0632	12.55± 0.0527	12.55± 0.0527	12.53± 0.0675	12.54± 0.0516	12.53± 0.0483
Hardness[a] (kg/cm^2)(X±SEM)	5.70± 0.4807	5.94± 0.3836	5.85± 0.3028	5.91± 0.3929	5.94± 0.4169	6.04± 0.3062
Weight[b] (mg)(X±SEM)	599.20± 7.7228	598.75± 6.8739	598.10± 8.0518	600.35± 6.8386	601.00± 6.1044	599.95± 6.7705
Friability[c] (%)(X±SEM)	0.7509± 0.0879	0.7729± 0.1329	0.8173± 0.0907	0.8012± 0.0151	0.7956± 0.0106	0.8337± 0.0718
Drug content[d] (%)(X±SEM)	97.8947± 0.4217	98.2456± 0.3509	98.0117± 0.5360	98.6355± 0.2435	98.5575± 0.4107	99.2203± 0.3573

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 method for Etodolac with Kollidon®SR.

Time (min)	F1	F2	F3	F4	F5	F6
30	5.40±0.237	3.91±0.421	3.06±0.325	3.04±0.355	2.52±0.302	1.73±0.158
90	19.66±0.42	16.47±0.466	12.00±0.351	10.28±0.366	8.48±0.371	7.88±0.227
150	33.53±0.33	25.60±0.355	20.67±0.394	16.79±0.329	15.48±0.38	13.29±0.221
210	47.68±0.12	34.94±0.491	30.06±0.507	24.94±0.360	22.34±0.42	20.12±0.398
270	54.68±0.27	41.05±0.210	37.76±0.442	31.37±0.360	29.01±0.38	25.45±0.246
330	59.54±0.26	48.71±0.330	45.25±0.290	40.11±0.375	35.91±0.39	29.84±0.539
390	64.29±0.15	53.79±0.210	49.52±0.447	46.23±0.601	40.25±0.92	36.58±0.510
450	70.54±0.23	63.47±0.436	55.56±0.406	51.60±0.576	47.59±0.46	44.11±0.485
840	97.50±0.58	92.38±0.420	88.37±0.395	85.14±0.366	78.81±0.66	75.74±0.735

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)
F1	0.8989	0.9174	0.9867	0.9837	0.9599	0.8688
F2	0.9598	0.9507	0.9942	0.9910	0.9769	0.9474
F3	0.9714	0.9592	0.9929	0.9928	0.9842	1.0283
F4	0.9872	0.9579	0.9793	0.9914	0.9959	1.0288
F5	0.9896	0.9731	0.9754	0.9947	0.9962	1.0602
F6	0.9954	0.9639	0.9617	0.9879	0.9927	1.1187

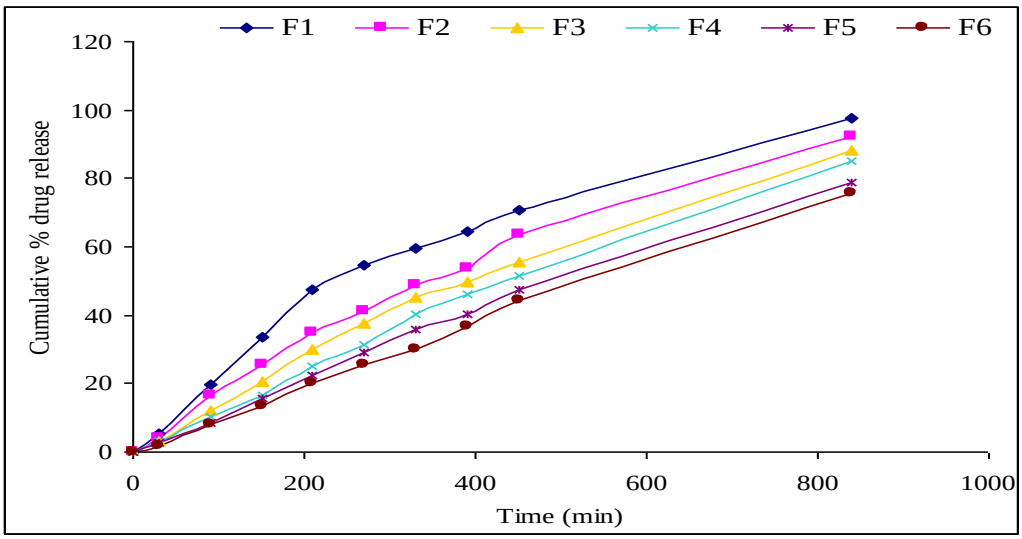
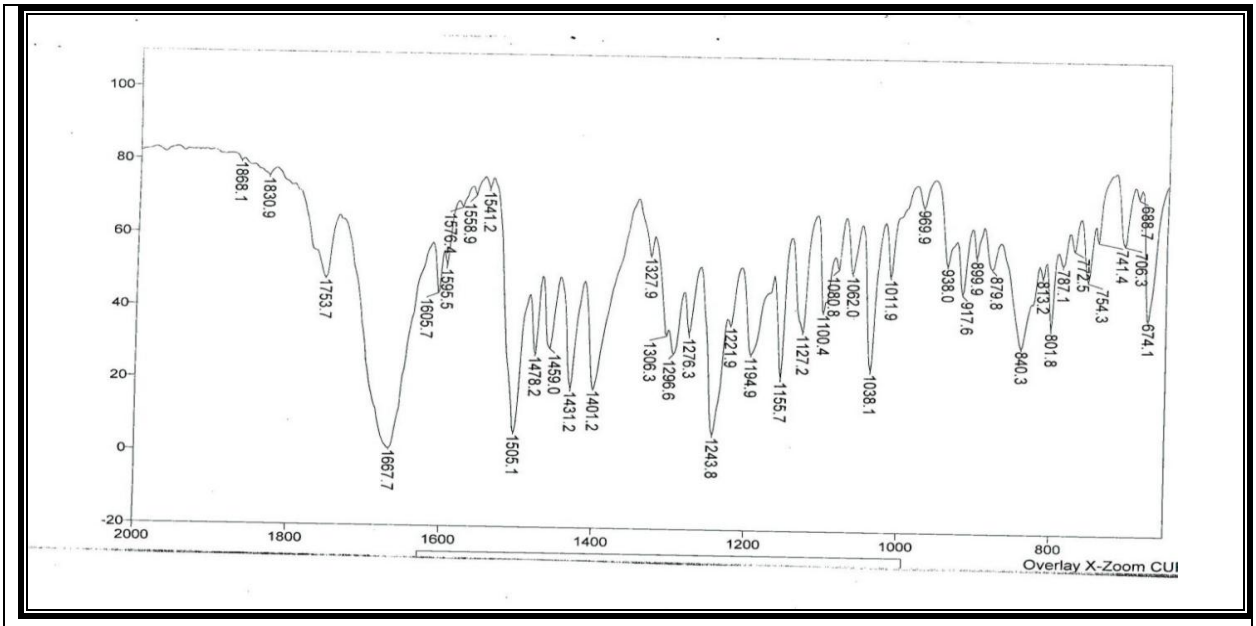
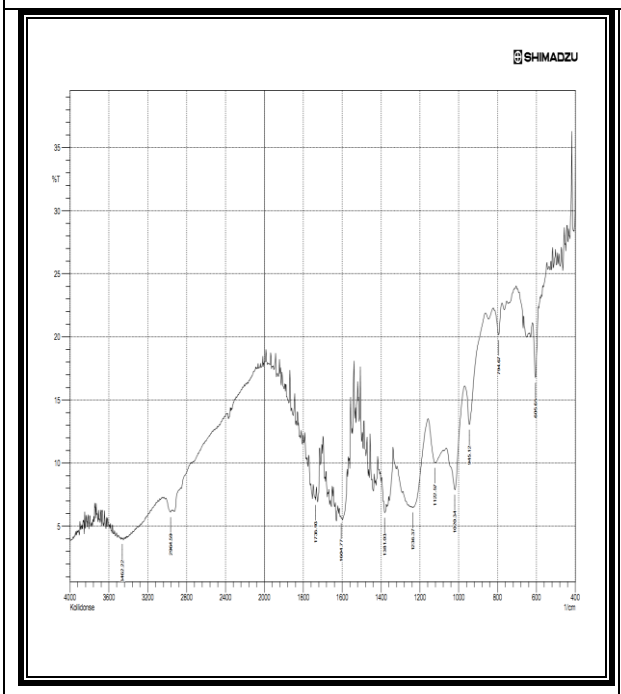


Fig 1. Drug release profile of Etodolac extended release tablet formulation prepared by direct compression method using Kollidon®SR as polymer.

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



(A)



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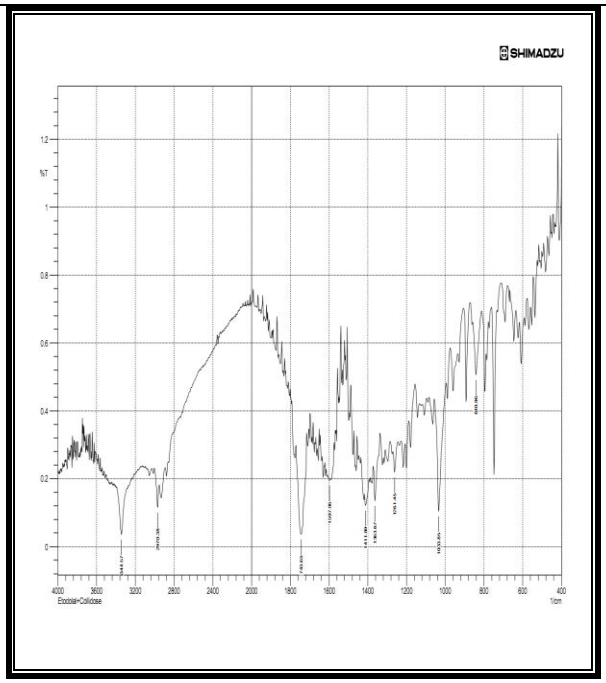

(C)

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}.

CONCLUSION

From the above experimental study it has been found that the tablet formulation F6 containing 10 % w/v of Kollidon®SR prepared by direct compression 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 Korsmeyer-Peppas drug release kinetic.

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