

DEVELOPMENT AND EVALUATION OF EXTENDED RELEASE ETHYLCELLULOSE BASED MATRIX TABLET OF DICLOFENAC SODIUM

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ABSTRACT

Objective: The present study involved the preparation of Diclofenac sodium extended release hydrophobic matrix tablets formulated from Ethylcellulose polymer following its different grades, Ethocel Standard Premium and Ethocel Standard FP Premium.

Methods: The matrix tablets were prepared with wet granulation method. Lubricated blends were characterized for physical properties like loose bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio; all blends showed satisfactory properties. Tablets were evaluated for uniformity of weight, thickness, hardness, percentage (%) friability and in vitro release studies. Effect of viscosity and particle size of ethylcellulose on drug release was determined.

Results: Lower viscosity grades of ethylcellulose were more compressible than higher viscosity grades, allowing production of harder tablets. Ethylcellulose grades with fine particle size showed better control on drug release rate. The release of diclofenac sodium was prolonged with increase in the concentration of ethylcellulose. Effect of diluent on drug release was also studied by comparing microcrystalline cellulose, dicalcium phosphate and lactose. Dicalcium phosphate had maximum retarding capacity followed by microcrystalline cellulose then lactose. The release kinetics of the final batch (K017) prepared using ethylcellulose followed Korsmeyer-Peppas kinetic model.

Conclusion: This study reveals that a combination of low viscosity and fine particle grade (Ethocel 7cps FP Premium) was the best grade for controlling the release rate. The optimized formulation has drug release profile up to 24 hours.

Keywords: Diclofenac sodium, Ethylcellulose, Matrix tablet, Extended release, Wet granulation.

INTRODUCTION

Modified release drug delivery systems are developed to modulate the apparent absorption or alter the site of release of drugs, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms. These systems cover a wide range of prolonged action formulation which provides continuous release of their active ingredients at a predetermined rate [1]. Extended release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time after administration of a single dose. Extended release dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate release dosage forms [2]. Extended release dosage forms would be most applicable for drugs having short elimination half lives [3]. Possible therapeutic benefits of a properly designed ER dosage form include low cost, simple processing, improved efficacy, reduced adverse events, flexibility in terms of the range of release profiles attainable, increased convenience and patient compliance [4,5]. Many innovative methods have been developed for obtaining modified drug release. Matrix systems fall into category of extended release oral solid products. In a matrix system, the drug substance is homogeneously mixed into the rate controlling materials and other inactive ingredients as a crystalline, amorphous dispersion. Drug release occurs either by drug diffusion or erosion of the matrix system. Matrix system is widely used due to easy to fabricate in a wide range of sizes and shapes, capability of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties and it is suitable for both non-degradable and degradable systems [6]. Matrix systems appear to be a very attractive approach from the economic as well as from the process development and scale-up points of view in controlled release systems [7]. From the practical view point, hydrophobic matrix tablet is one of the least-complicated approaches for developing a modified release dosage form.

ETHOCEL is a trademark of the Dow Chemical Company for its family of thermoplastic cellulose ethers. Ethyl cellulose polymers are derived from and have the polymeric backbone of cellulose, which is naturally occurring polymer, which contains a basic repeating structure of β -anhydroglucose units, joined together by acetal linkages. ETHOCEL polymers are produced and marketed in a number of different viscosities. Viscosity increases as the length of the polymer molecule increases [8].

Standard and Medium ethoxyl types are available in Premium grades, useful in regulated applications and industrial grades. Premium grades are designed to meet the requirements of pharmaceutical applications. ETHOCEL Std. 7, 10, and 100 Premium polymers are also available in a fine particle size. These products are designated ETHOCEL Std.7 FP, Std.10 Premium FP, and Std. 100 Premium FP [9]. Ethylcellulose is a potential release rate retardant in prolonged release formulations. Concentration of Ethyl cellulose polymer has great impact in the retardation of release rate, as its amount increases in formulation release rate decreases. As water insoluble excipients, ETHOCEL polymers can effectively control the release of an active ingredient by modifying the size and length of diffusion path. By varying the type and amount of the insoluble excipient ratio and the particle size, a wide variety of release rate profiles can be achieved [10].

Diclofenac sodium is nonsteroidal anti-inflammatory drug (NSAID); it is used in pain management associated with cancer, arthritis or acute injury. The most frequent side effects on long term administration are gastro intestinal disturbances, peptic ulceration and git bleeding. It is poorly soluble in water and it has acidic pH 1-3 but is rapidly soluble in alkaline pH 5-8 [11]. Thus an extended release formulation of diclofenac sodium is required for patient compliance and decreased signs of adverse effects. Presently, diclofenac sodium (Voveran SR) is available in commercial market and is based on hydrophilic matrix using hypromellose.

The aim is to formulate an extended release matrix tablet of diclofenac sodium based on hydrophobic matrix using ethyl cellulose polymer with wet granulation method because it leads to improved flow of blend, compressibility and consolidation are improved via the choice of correct binder and the moisture content of the granules. Also dissolution is modified with the choice of more insoluble binders, to obtain a modified release pattern. To achieve an extended release profile of diclofenac sodium different variables of the formulation were evaluated:- Effect of particle size and viscosity grade of ethyl cellulose, increasing binder concentration in formula, increasing hardness on release rate and effect of various diluents.

MATERIALS AND METHODS

Diclofenac sodium was obtained from AmoliOrganics; Ethylcellulose with different viscosity and particle size grades were received as a gift from Dow Chemical Company, USA; Microcrystalline cellulose was obtained from FMC Biopolymers; Lactose 200M was obtained from DMV fonsera excipients GmbH, Germany; Polyvinylpyrrolidone from ISP technology; Dicalcium phosphate by Signet chemicals; Magnesium stearate from Mallinckrodt, USA; and Talc from Barrents, USA.

Preparation of extended release matrix tablet

Tablets were prepared with wet granulation method in which intragranular and extragranular ingredients were dispensed according to formula. Intragranular ingredients were moistened with ethanol (q.s.) and kneaded continuously until the subjective end point of suitable consistency was attained. The wet granulations were dried in a hot air oven at 60°C until a moisture content of 0.5-2% was achieved. The dry granules were milled using BSS #30 and lubricated with magnesium stearate and talc sifted from BSS #44. The granulations were compressed into tablets using a 16 station compression machine equipped with round and standard concave tooling of 8.6mm diameter.

Evaluation of tablet blend

Bulk density

Apparent bulk density was determined by placing pre-sieved drug excipient blend in to a graduated cylinder and measuring the volume and weight as it is [12].

Tapped density

Tapped density was determined by USP method II tablet blend was filled in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula $D_t = M/V_b$, Where, M = Weight of powder taken; V_b = tapped volume [13].

Angle of Repose

Angle of repose was determined using funnel method. Tablet blend were poured from funnel, that can be raised vertically until a maximum cone height h was obtained diameter heap D, was measured. The angle of repose was calculated using formula $\tan \theta = 2h/D$.

Compressibility index and Hausner ratio

This was measured for the property of a powder to be compressed; as such they are measured for relative importance of interparticulate interactions [14].

Compressibility index was calculated by following equation

$$\text{Compressibility index} = \left| \frac{D_t - D_b}{D_t} \right| \times 100$$

Where, D_t = tapped density; D_b = bulk density;

Hausner ratio was calculated by following equation

$$\text{Hausner ratio} = D_t / D_b$$

Where, D_t = tapped density; D_b = bulk density

Evaluation of tablets

Thickness

The thickness of the tablet was measured by using digital vernier caliper, twenty tablets from each batch were randomly selected and thickness was measured [15].

Hardness

Hardness was measured using Pfizer hardness tester, for each batch three tablet were tested [16].

Weight Variation Test

Weight variation was determined using 20 tablets of each formulation, weighed using an electronic balance (Sartorius electronic balance: Model CP-2245, Labtronic), and the test was performed according to the official method [17].

Friability

The friability of the tablets was measured by Roche friabilator. Tablets of a known weight (W_0) or a sample of tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation (5), the weight loss should not be more than 1% w/w [17].

$$\% \text{ Friability} = (W_0 - W) / W_0 \times 100 \dots \dots \dots (5)$$

Drug content (Assay)

Drug content was determined by taking an accurately weight amount of powdered Diclofenac sodium with phosphate buffer pH 7.5 and solution was filtered through 0.45µm nylon filter. The absorbance was measured at 276 nm, using double beam UV visible spectrophotometer [18].

$$\text{Assay} = \text{Test Absorbance} / \text{Standard Absorbance} \times 100$$

In-Vitro Drug Release Study

Dissolution studies were conducted to determine the release pattern of the product. Dissolution test for Diclofenac sodium was carried out as per USP method for dissolution test for tablets using apparatus-II. Dissolution medium used was 900ml of pH 7.5 phosphate buffer rotating the paddle at 50 rpm with temperature $37^\circ\text{C} \pm 0.5^\circ\text{C}$. An aliquot of 5ml of samples were withdrawn at different time periods (1, 2, 4, 6, 8, 12, 16, 20, 24 hrs.). The samples were filtered through nylon filters, suitably diluted and analysed at 276nm using double beam UV/Visible spectrophotometer (Shimadzu Corporation, UV-1601). The content of drug was calculated using equation generated from standard calibration curve. The dissolution study was continued for 24 hours to get a stimulated picture if drug released *in vivo* condition. The drug release profiles obtained were fitted into several mathematical models and drug release mechanism was determined from the matrix tablet.

Zero order release equation: $Q = K^0 t$

Higuchi's square root of time equation: $Q = K H t_{1/2}$

Korsmeyer- Peppas equation: $F = (M_t/M) = K t_n$

RESULT AND DISCUSSION

Characterization of granules

Granules prepared for compression of tablets were evaluated for micromeritic properties and the results are given in table 1. The tapped density was in range of 0.566 to 0.731. Bulk density was found to be 0.447 to 0.555. Angle of repose was in between 26.5 to 37.9 indicating the good powder flow. Carr's index values were from 2.0 to 29.9. Hausner's ratio was found to be in range of 1.13 to 1.4. The results obtained for all blends showed satisfactory physical properties.

Physical evaluation of diclofenac sodium matrix tablets

The tablets of the proposed formulations were evaluated for thickness, hardness, weight variation, friability and drug content. Thickness of the tablets was found to be in the range of 5.0-5.7mm. The hardness and percentage friability of the tablets of all batches ranged from 7.0-20.0kp and 0.02-0.03 % respectively. The average weight percentage deviation of the 20 tablets of each formula was less than $\pm 5\%$. Drug content among different batches of tablets ranged from 98.92-100.9%. Thus, all the physical parameters of the matrices were practically within limits (Table 2).

Table 1: Micromeritic properties of powder blend of different formulations.

Batch no.	Tapped density (gm/cm ³)	Bulk density (gm/cm ³)	Angle of repose(θ)	Carr's index (%)	Hausner's ratio
K 003	0.697±0.03	0.535±0.06	35.8±1.32	23.2±0.75	1.3±0.01
K 004	0.566±0.02	0.454±0.03	28.4±1.26	19.7±0.80	1.2±0.02
K 005	0.612±0.01	0.483±0.02	26.5±1.15	21.0±0.91	1.2±0.02
K 006	0.600±0.00	0.500±0.02	33.1±1.41	16.6±1.14	1.2±0.02
K 007	0.576±0.05	0.461±0.01	35.2±1.19	19.9±1.25	1.2±0.03
K 008	0.567±0.03	0.458±0.05	30.0±1.26	19.2±1.13	1.2±0.01
K 010	0.625±0.02	0.500±0.04	34.7±1.18	2.0±1.30	1.2±0.01
K 012	0.566±0.06	0.500±0.03	26.7±1.25	11.6±1.45	1.13±0.03
K 013	0.576±0.04	0.491±0.07	36.1±1.17	14.7±1.49	1.17±0.06
K 014	0.714±0.02	0.555±0.06	37.9±1.11	22.2±1.23	1.28±0.04
K 017	0.731±0.03	0.600±0.02	36.8±1.21	17.9±1.39	1.21±0.05

Table 2: Evaluation parameters of tablets from different batches

Batch no.	Average weight (mg)	Thickness (mm)	Friability (%)	Hardness (kp)	Drug content (%)
K 003	305±0.02	5.4±0.10	0.03±0.01	7.0-8.0±0.8	98.95
K 004	300±0.06	5.1±0.13	0.03±0.02	7.0-8.0±0.9	98.98
K 005	299±0.03	5.0±0.15	0.02±0.01	7.0-8.0±1.1	99.00
K 006	307±0.01	5.3±0.08	0.02±0.01	7.0-8.0±1.6	100.1
K 007	304±0.08	5.2±0.16	0.03±0.01	7.0-8.0±1.2	98.92
K 008	302±0.06	5.4±0.14	0.02±0.01	10.0-11.0±0.5	99.31
K 010	305±0.04	5.2±0.19	0.03±0.02	11.0-12.0±0.8	100.9
K 012	402±0.08	5.4±0.11	0.02±0.01	19.0-20.0±1.2	99.48
K 013	305±0.07	5.2±0.16	0.03±0.02	11.0-12.0±1.9	99.67
K 014	307±0.02	5.1±0.17	0.02±0.01	9.5-10.0±1.7	100.5
K 015	604±0.09	5.7±0.09	0.03±0.02	11.0-12.0±0.9	100.2
K 016	602±0.05	5.6±0.14	0.02±0.01	19.0-20.0±1.3	99.70
K 017	503±0.02	5.5±0.11	0.02±0.01	11.0-12.0±1.5	100.4

Effect of different parameters on release pattern of Diclofenac sodium

Different matrix tablets containing diclofenac sodium as active ingredient having ethyl cellulose polymer were prepared to evaluate the effect of this polymer. After preparation their dissolution studies were carried out using paddle apparatus at 50 rpm in phosphate buffer with pH 7.5 medium at 37 °C. Six tablets from each formulation were used in dissolution study. The release profile of diclofenac sodium was monitored.

Effect of different viscosity grades

Formulation batches K003, K004, K005, K006 were prepared using various viscosity grades of Ethylcellulose (Ethocel 20cps, Ethocel 45cps, Ethocel 10cps, Ethocel 7cps respectively) using microcrystalline cellulose as diluent resulted in different release rate profiles. By comparing all the release profiles it is observed that with Ethocel 7cps the release rate is slowest and with 45cps release rate is fastest. This is explained by the fact that Ethocel of lower viscosity grades are more compressible and hence exhibit less porosity. Further particle size of Ethylcellulose was evaluated.

Effect of particle size

Formulation batches K007, K008, K010 with different fine particle grades of Ethylcellulose (Ethocel 100FP, Ethocel 10FP, and Ethocel 7FP respectively) were prepared and release profile was compared to the standard premium grades. It was observed that the release decreases with Ethylcellulose FP grades. Whereas Ethocel of higher viscosity grades (larger particle size and higher porosity) may not have produced a matrix containing pores sufficiently small to trap the drug and retard its release. Diclofenac sodium extended release tablets were formulated with both Ethylcellulose standard premium and Ethyl cellulose FP premium resulting in use of Ethylcellulose FP premium polymers extended the diclofenac sodium release rates more efficiently than the conventional granular form of the polymer. This is due to small particle size of the Ethocel FP polymers. Based on the result Ethocel 7cps FP was finalised as the rate controlling polymer and to be used in further formulations to extend the release of diclofenac sodium.

Effect of increasing polymer concentration

Formulation batch K012 was prepared with increased polymer concentration in the formula and the release rate was compared to formulation K010 containing less polymer concentration in the formula. The observation was that the release appeared to decrease with increasing polymer concentration because the matrices formed at higher ethyl cellulose concentration would be expected to be strong. Hence, it was decided to keep higher concentration of polymer to retard the drug release rate.

Effect of different diluents

Formulation batches K010, K013, K014 were prepared using different diluents in same concentrations (using microcrystalline cellulose, dicalcium phosphate and lactose 200M respectively) and release rate profiles were compared given in table. It was observed that dicalcium phosphate containing Ethyl cellulose formulation was the best diluent to retard the release rate as compared to microcrystalline cellulose and lactose. Granules containing dicalcium phosphate generally produced smaller particle size which helps to control the dissolution rate. Amount of Ethyl cellulose also influence the release of drug from drug- polymer matrices that on increasing the polymer in formula further decreased the dissolution rate because the matrices formed at higher ethyl cellulose concentration would be expected to be strong.

Evaluation of scale up formulations

Scale up formulations of batches K010, K013 was prepared by increasing the amount of each ingredient to twice in the formulation. From the release profile it was seen that scale up formulation with dicalcium phosphate retards release rate more in comparison to microcrystalline cellulose and it was decided to use dicalcium phosphate in further formulations. Further formulation batch K017 was prepared with scale up and scale down concentrations for polymer and binder concentrations to attain once a day profile of dosage form. From the resulted data of release profile by scale up and scale down the formula, K 017 batch formulation has drug release profile up to 24 hours which is now the final formulation.

Effect of increasing hardness

The formulations with different hardness were prepared to study the effect of hardness on release profile of diclofenac sodium. Drug release profile with different hardness was obtained and is given in table. It was observed that as the hardness increases the dissolution rate of diclofenac sodium extends. Ethyl cellulose is a good compressible excipient. The lower viscosity grades of ethyl cellulose are more compressible than the higher viscosity grades, resulting in harder tablets. Higher viscosity grades are less compressible and produce lower tablet hardness. Maximum hardness can be achieved by increasing the compression force. With microcrystalline cellulose maximum

hardness has been attained. By keeping maximum hardness the dissolution rate can be extended.

Study of Release Kinetics

The regression coefficient (R²) value of Zero order, First order, Higuchi's, Hixon-crowell and Peppas plots for formulation K017 were found to be 0.9496, 0.8443, 0.9881, 0.0707, 0.9911. Among the entire kinetic model studied for the final batch (K 017), it was found that the batch followed Korsmeyer-Peppas model because of having maximum R² value of 0.9911 (closest to 1.0). In semi-empiric model, diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time.

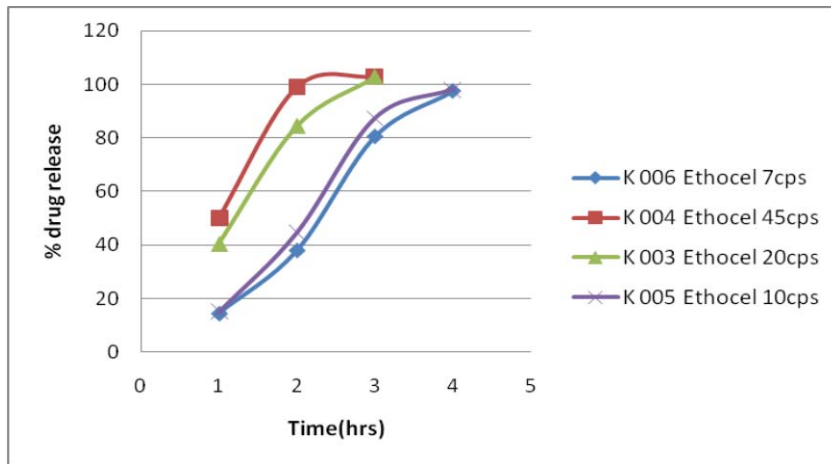


Fig. 1: Dissolution rate profile of formulations using different Ethyl cellulose grades

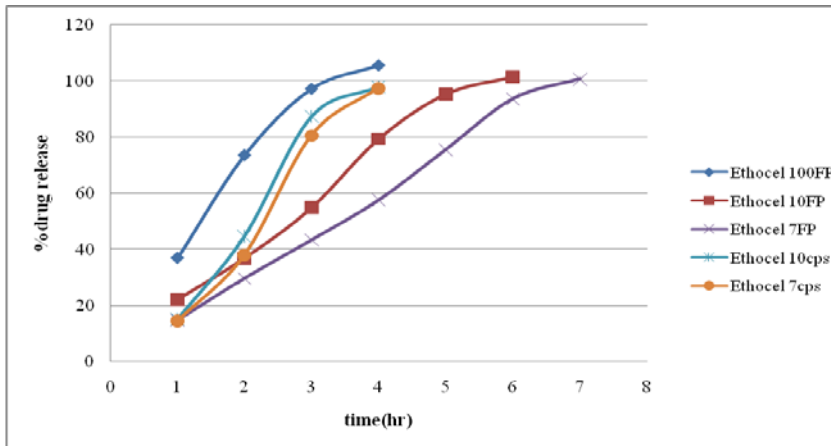


Fig. 2: Dissolution Rate Profile of formulations using various Ethylcellulose FP grades.

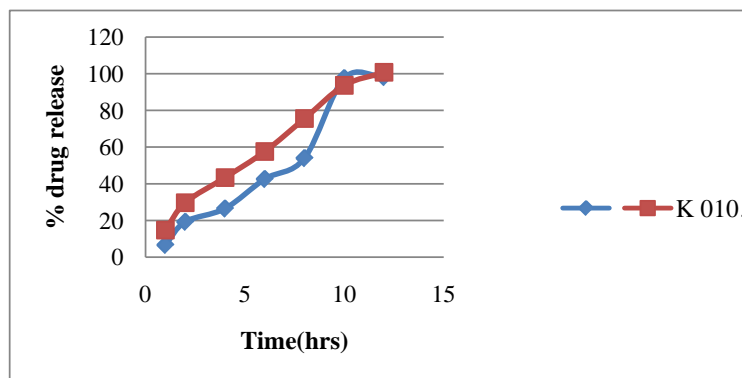


Fig. 3: Dissolution profiles of formulations containing polymer in different concentrations.

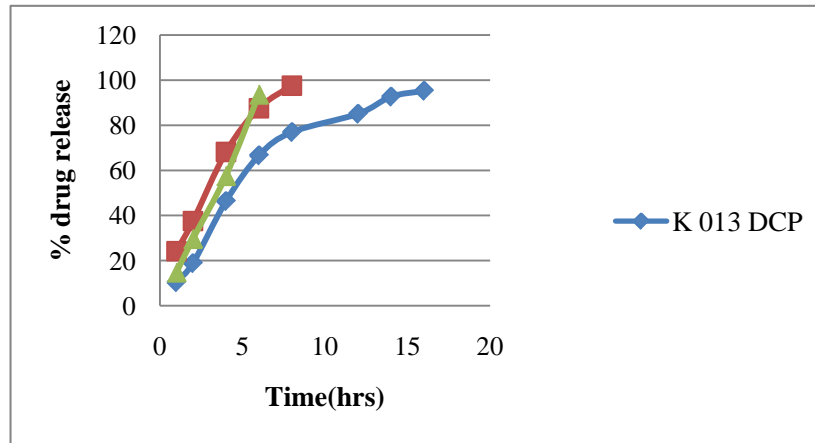


Fig. 4: Dissolution rate profile of formulations containing different diluents.

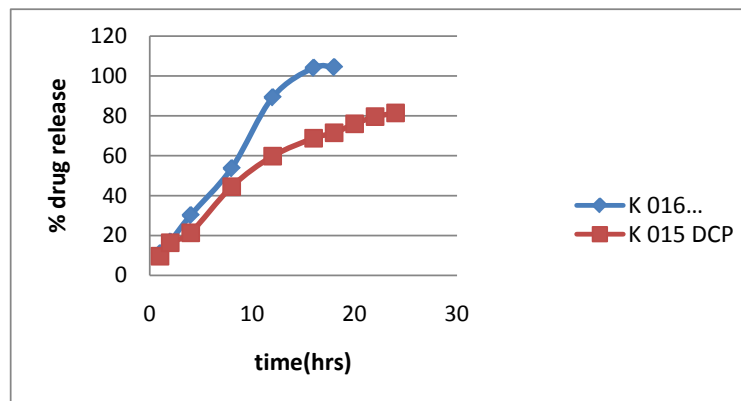


Fig. 5: Dissolution rate profile of scale up formulations with different diluents.

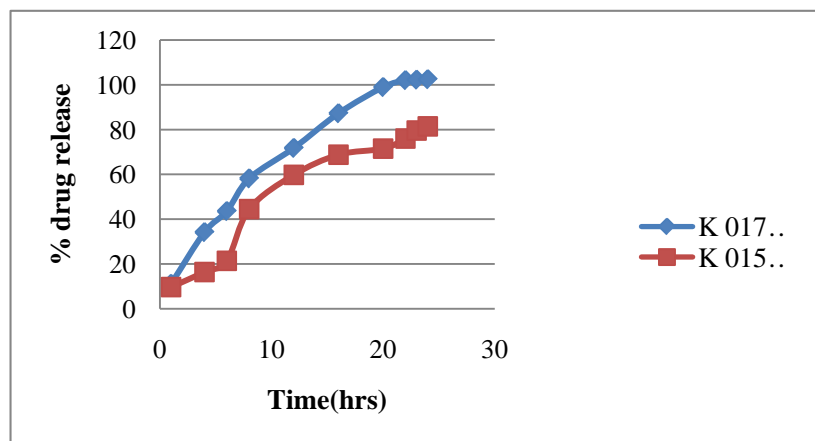


Fig. 6: Dissolution rate profile of formulation containing Ethocel 7FP and dicalcium phosphate in increased concentration.

CONCLUSION

It may be concluded from the present study that the hydrophobic matrix tablets of formulation K017 prepared using ethylcellulose showed drug release of 102.5% and can be employed as once a day oral extended release drug delivery system. Therefore, ethyl cellulose is suggested as an ideal polymer for production of extended release matrix tablets of diclofenac sodium with wet granulation technique.

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