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Effect Of Ether Derivative Cellulose Polymers On Hydration, Erosion And Release Kinetics Of Diclofenac Sodium Matrix Tablets

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Abstract

Objectives: The work aims to investigate the effect of hydrophilic and hydrophobic polymers swelling and erosion on the release behaviour of DCL-Na from controlled matrix tablets prepared by direct compression and wet-granulation techniques.

Materials and Methods: Powder preformulation studies were conducted. Tablets were prepared by direct compression technique and their physicochemical properties were evaluated. Drug-polymer interaction was analyzed by FTIR spectroscopy. The *in-vitro* drug release study was conducted using phosphte buffer pH 7.4 as dissolution medium and different kinetic parameters were applied.

Results and Discussion: F-1 and F-5 containing ethycellulose prepared by direct compression and wet granulation techniques released 94 % and 84 % drug after 24hrs, while F-2 and F-6 containing hydroxypropylmethylcellulose polymer prepared by direct compression and wet granulation released 98.46 % and 91.25 % drug after within 24 hrs respectively. Ethylcellulose and hydroxypropylmethylcellulose based matrix tablets showed the best anomalous drug release behaviour, with the release exponents " *n* " ranging from 0.685 to 0.809.

Conclusion: It has been concluded that ethylcellulose ether derivative polymer is used to prepare oral controlled release matrix tablet of diclofenac sodium. Fickian drug diffusion, polymer hydration and erosion mechanisms occurred simultaneously and were considered as the main drug release controlling factors.

Key words

Matrix Tablets, Dissolution, Hydration, Erosion, Kinetics, Controlled Release

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Introduction

The need to deliver a therapeutic moiety to the systemic circulation and to make it available for its desired therapeutic effects has prompted the pharmaceutical scientists to develop modified drug delivery systems. Controlled release drug delivery technologies have made quantum advances in the array of drug development for the last three decades. At the same time, advances in this area of biotechnology have brought many new challenges to the pharmaceutical scientists. The researchers working in this field have skilfully overcome many problems that encumber the clinical applications of a therapeutic entity [1]. A drug can now be made effectively bioavailable at zero-order for the periods ranging from days to years. Such technological advances have designed many clinically useful controlled release dosage forms and granted new lives to various existing drugs molecules. It can better afford a consistent bioavailability of a drug with lesser side effects to the desired site of action using different hydrophilic hydrophobic biocompatible polymers. These polymers provide several advantages in designing oral controlled release dosage forms, including good stability, safe applications, improved effectiveness, lesser side effects and reduced number of dosage administrations [2]. The oral matrix tablets containing controlled release polymers like prepared by direct compression and wet-granulation techniques could be simple and more predictable [3]. The most widely used polymers are derived from cellulose such as ethylcellulose, hydroxypropylmethylcellulose and sodium carboxymethylcellulose. It has been observed that the water uptake properties of these polymers and the physical properties of the gel layer formed by polymer hydration usually influence drug release from the matrices. The hydrated gel laye,r formed after the contact of polymer with the dissolution medium, might act as a barrier to allow the medium to penetrate into the matrix core and to release the drug out [4]. At the same time, matrix surface erodes and the drug diffuses out. It has also been observed that the erosion is the predictability of drug release, which is usually harder to achieve, if other mechanism has to be taken into account. Matrix swelling

and erosion behaviour has been investigated and evaluated for hydrophilic hydrophobic extended release matrix tablets, using various polymers [5]. Real-time swelling and erosion behaviour of Ethylcellulose-Chitosan matrix tablets were carried out by observation of the tablets immersed in the distilled water or dissolution media, and was found that the complex possess excellent swelling erosion characteristics, resulting in prolonged drug release from the matrix tablets. Swelling behaviour of hot-melt extruded ethylcellulose cylinders containing HPMC was investigated and a zero-order erosion-controlled drug release was found for the developed matrices [6]. Preparation and evaluation of sustained release directly compressed mini matrix tablets containing ibuprofen, EC and HPMC have been studied and the release data was evaluated up to 12 hrs. It could be observed that ethylcellulose ether derivative polymer is an inert, non-toxic and stable hydrophobic polymer that has been widely used in a number of dosage forms, as a binder [7, 8] and as a film forming and matrix forming material for different NSAIDs having shorter half lives like diclofenac sodium [9]. Diclofenac sodium is widely used NASID for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondilitis and gout [10]. No doubt, it effectively controls mild to moderate joint pain associated with osteoarthritis, but their use is accompanied by the risk of gastrointestinal toxicity, including gastrointestinal perforation, Ulceration and bleeding especially with large doses and long term therapy [11]. In order to lesser the side effects, associated with lager doses of diclofenac sodium and to increase the patient compliance due to higher dosage frequency during the treatment, a once-daily controlled release matrix tablet is desired. Although DCL-Na have been formulated into sustained and prolong drug release tablets having a release profile up to 12 hrs maximum. There is a need to design a controlled release matrix tablet with an intended release profile up to 24 hrs or maximum using simple and economic development approach. This study aims to design, formulate and evaluate controlled release matrix tablets of 100 mg DCL-Na by direct compression and wet-granulation techniques, using ethylcellulose, hydroxypropylmethylcellulose and sodium carboxymethylcellulose polymers and to investigate their swelling erosion behaviour. Such kind of approach can be very useful both for the interpretation of polymer hydrogel behaviour to release the drug from the matrices and to optimize the modified release matrix tablets.

Material and Methods

Material

Diclofenac sodium (DCL-Na) was received as a gift from Danas pharma, Pakistan, Monobasic potassium phosphate, CMC, Starch and NaOH (Merck, Germany) were received as gift from Wilshire Pharmaceutical, Lahore. Lactose, magnesium stearate (BDH Chemical Ltd, Pool England), were purchased from (Sohail chemical, Rawalpindi, Pakistan). Ethocel (ethylcellulose ether derivative polymer) and HPMC (Dow chemical Co., Midland USA). All the chemicals used were, of analytical grade.

Methods

Solubility

The solubility study of DCL-Na was conducted by equilibrium solubility method in seven different solvents of pH 2.1, 4.5, 6.8, 7. 7.2, 7.4 &10 at 25, 37 and 400° C in a shaking water bath for 24 hrs. Excess amounts of diclofenac sodium were added to the solvents taken in 100 ml conical flasks. After two days, the aliquots were withdrawn, filtered (0.22 µm) and diluted with their respective solvents. The samples were analyzed spectrophotometrically at 276 nm using concerned solvents as blank [12].

Physical characteristics of starting material and granules

Both bulk density and tapped density were determined by the method reported by Abdullah *et al*. [13], Hausner's ratio (HF), angle of repose and compressibility index were also calculated and evaluated for the starting material.

Fourier Transform Infra-Red Absorption Spectroscopy

DCL-Na and its all physical mixtures were analyzed using a computerized FTIR (iS10, Thermo Fischer Scientific, USA) in order to investigate any possible drug-polymer interaction among DCL-Na and EC or other excipients like HPMC, CMC and starch. Samples of approximately 10 mg dry powders were placed at the plate, enough pressure was applied and sharp peaks were obtained of each sample. FTIR spectroscopy for all samples were carried out in the range of 500-4000 cm^{-1} [14].

Preparation of matrix tablets

DCL-Na 100 mg tablets were prepared by direct compression and wet granulation methods, composition details are given in the Table 1. The powder was sieved through sieve # 30. The calculated amounts of DCL-Na and the excipients were mixed thoroughly. The formulations to be prepared by direct compression, were compressed directly [15], using single punch machine model AR 400 (Erweka GMBH, Germany), applying 450 kg force for about 2 seconds. Then, the formulations to be prepared by wet granulation were added with sufficient amount of the granulating agent slowly to obtain a cohesive mass which was sieved through a sieve of 1 mm. The prepared granules were dried at 40°C in a vacuum oven for 30 min and were kept at room temperature for 48 hours. The dried granules were then passed through a 650 µm sieve and magnesium stearate was added as lubricant. Finally the powder was weighed (200 mg) and compressed as mentioned earlier. The tablets compositions are given in table 1.

Physical properties of the matrix tablets

Physical properties containing thickness & diameter, hardness, weight variation, friability and content uniformity were also evaluated for each batch of the matrix tablets.

In-Vitro drug release study

Drug release study was performed according to USP method as mentioned previously in the section of polymer hydration. Each flask was filled up to 900 ml dissolution medium of 0.2 M phosphate buffer solution pH 7.4, kept at 37 ± 0.1° C and stirred at 100 rpm (Perfect sink conditions). Tablets were placed in different baskets and at predetermined time intervals of 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 hrs, a 5 ml sample was taken with syringe using 0.45 µm filter and was replaced with the

fresh medium. Samples were analyzed at 247 nm, using UV-visible spectrophotometer UV-1601 (Shimadzu, Japan). Mean of three tablets was used to evaluate the drug release for each of the formulations.

Drug Release Kinetics

To interpret the drug release rate from matrices, the data obtained from *in-vitro* drug release studies were plotted in various kinetics models: Zero-order, $W = k_1 t$ (Eq. 3). Where k_1 is the zero-order rate constant expressed in the units of concentration/time and "t" is the time on hours. First order, $\ln(100 - W) = \ln 100 - k_2 t$ (Eq. 4), Where k_2 is the first order constant and $\ln 100$ is the initial drug concentration. Hixson Crowell's Equation or Erosion Model, $(100 - W)^{1/3} = 100^{1/3} - k_3 t$ (Eq. 5), Where k_3 is the rate constant for Hixson Crowell's equation, $(100 - W)^{1/3}$ is the initial concentration while $100^{1/3}$ is the amount of drug released in time "t". Higuchi's model, $W = k_4 t^{1/2}$ (Eq. 6), Where k_4 reflects the design variable of the system and is the constant. "t" is the time in hours. Korsmeyer-Pappas equation, $M_t / M_\infty = k_5 t^n$ (Eq. 7), Where M_t / M_∞ is the fractional solute release, k_5 is power law constant of drug-polymer system and "n" is an exponent that indicates drug release mechanism from matrix.

Polymer hydration or water uptake

Polymer swelling studies were conducted by equilibrium weighed gain method as reported by [16], using USP apparatus 1, containing 8-station dissolution apparatus Pharma Test PTWS-11/P, TPT (Hamburg, Germany). The initial weight of selected formulations of DCL-Na matrix tablets, F-1, F-2, F-5 & F-6, was determined and were placed in dissolution flasks containing 900 ml phosphate buffer solution (pH 7.4) maintained at 37 ± 0.5° C. At predetermined regular intervals of 0.5, 1, 1.5, 2, 3, 4, 5 and 6 hours, the pre-weighed baskets were withdrawn from the dissolution apparatus, slightly blotted with tissue paper to remove the excess water from the baskets, and were re-weighed. The degree of swelling matrix, at each time point, was calculated using the following equation.

$$\%WaterUptake = \frac{W_1 - W_0}{W_0} * 100 \quad \text{(Eq. 1)}$$

Where W_1 is the weight of the swollen matrix at time't' and W_0 is the initial weight of the tablet. Mean of three tablets were used to evaluate the swelling behaviour of matrices.

Matrix Erosion

Erosion studies were performed using the method reported by [17]. The wet-tablets were taken out of the dissolution medium at specified time intervals of 0.5, 1, 1.5, 2, 3, 4, 5, & 6 hrs, dried carefully in oven at 60° C to a constant weight. The matrix erosion was calculated by the following equation.

$$\%MatrixErosion = \frac{W_i - W_t}{W_i} * 100 \quad \text{(Eq. 2)}$$

Where W_i is the initial weight of the matrix and W_t is the weight of the matrix subjected to erosion for specified time't'. Mean of three tablets were used to evaluate the erosion of matrices.

Effect of Aging on Release of DCL-Na

Selected DCL-Na matrix tablets were subjected to the aging studies, kept at room temperature in amber coloured bottles for six months. The DCL-Na dissolution studies were performed by the procedure previously mentioned.

Results and Discussion

Solubility Study

DCL-Na is a salt of week acidic with pKa value 3.99±0.01 [18]. Its solubility at different pH values 1.2, 4.5, 6.8, 7, 7.2, 7.4 & 10 ranged from 0.005 to 12.20 mg/ml at 25, 37 & 40° C. Solubility was found increasing beyond the pH 7, maximum at pH 10 12.20 at 40° C, as shown by graphical presentation below. Both the calculated solubility and pKa value of DCL-Na were found in good agreement. Because of acidic nature of DCL-Na the active part of the drug might be very slightly soluble at acidic pH 1.2, as the pH increased solubility also increased achieving its maximum value beyond pH 7 because of drug ionization at basic pH.

Physical characteristics of starting material and granules

Table 2. Preformulation factors, including Bulk density, tapped density, Hausner's ratio, angle of repose and compressibility index, were studies to evaluate the best flowability and compressibility of powder formulations. Bulk density and tapped density ranged from 0.299 to 0.381 and 0.308 to 0.921 respectively, indicating that there is no conclusive effect of physical mixing upon the particle size, but tapped density for DCL-Na powder drug was improved after the addition of excipients. After granulation both of the densities fell in the acceptable limit, which might be resulted in uniform granules with better flowability and compressibility. HF for DCL-Na powder was found to be 2.630 which might be contributed to the poor flow properties because of interparticular friction of powdered DCL-Na. While HF for physical mixtures and granules ranged from 1.017 to 1.046, indicating good flow properties of powder with reduced friction. Angle of repose was measured as 32.64° for DCL-Na powder. Angle of repose for physical mixtures was found ranging from 20° to 28° indicating the fair flow properties of the physical mixtures and solid dispersion. The frictional force between the particles in the loose powder was acceptable but the addition of polymer and excipients improved the powder flow properties and reduced the cohesive force among the particles up to negligible extent during compression [19]. Percent compressibility indicates the indirect measurement of flow property, bulk density, size and shape, moisture content surface area. Percent compressibility of DCL-Na

powder was calculated by equation 5 and was found to be 51.20 % which was in close agreement with angle repose. While % compressibility for physical mixtures ranged from 17.21-20.45 % indicating improved compressibility and flowability of physical mixtures and solid dispersion [20].

Fourier Transform Infra-Red Absorption Spectroscopy

FTIR studies of DCL-Na (A), EC (B), DCL-Na-EC (C), DCL-Na-EC-starch (D), DCL-Na-EC-CMC (E) and DCL-Na-EC-HPMC (F) are presented in Figure 2: was conducted to investigate the possible Drug-Polymer interaction. In case of pure drug and all physical mixtures, DCL-Na spectra showed principal peaks at 1572, 756 (C-Cl), 1504 (C=C), 775, 1586 (C=C, aromatic) and 1308 cm^{-1} which could be ascribed as simple addition of EC to DCL-Na [21]. DCL-Na peaks in case of all physical mixtures were present, but the intensity of the specific peaks were decreased in the absorbance pattern especially in the regions of 1000-1700 and 2500-3500 cm^{-1}. At the same time, the polymer specific peak at about 1000 cm^{-1} (C-H) disappeared in case of physical mixtures which could be due to minimum quantity of polymer. While the reduction in the intensity of DCL-Na principal peaks, in case of all physical mixtures, could be due to variations in the resonance structure, stretching and bending, rotation of a part of molecule or certain bonds or minor distortion of bond angles. The summary of characteristic bands are shown in the figure 2 [22].

Physical Characteristics of Tablets

Physical characteristics of the tablets are given in the table 3, including hardness, friability, weight variation, % drug content, thickness and diameter. Hardness of the tablets ranged from 6.4 ± 0.40 to 7.2 ± 0.44 kg/cm^3 , which is suitable to reduce the tendency to cap. Friability calculated was in the acceptable range of 0.31 ± 0.06 to 0.87 ± 0.05 w/w. Weight variation test showed that all of the tablet were in the acceptable range of 200 ± 0.8 mg to 203 ± 0.8 mg. Content uniformity test fell in the best suitable range of 98.30 ± 0.17 to 99.9 ± 0.10% for 100 mg DCL-Na tablets, whereas the drug content for DCL-Na pure drug showed 99.0±0.01% of drug purity. Thickness and diameter affect the internal stress of the tablet and are counted drug handling. Thickness and diameter ranged from 2.1 ± 0.02 mm to 2.3 ± 0.08 mm and 4.0 ± 0.05 mm to 4.4 ± 0.10 mm and were found to be in acceptable range.

Dissolution

Figures 3, 4 and 5 show the release of DCL-Na from matrix tablets designed with different EC, HPMC, and Na-CMC by direct compression and wet-granulation. F-1, formulated with ethycellulose polymer by direct compression method released 94% DCL-Na after 24hrs, whereas, F-5 containing the same ingredients, prepared by wet granulation method release the drug sustained the release of DCL-Na showing maximum release of 84% after 24hrs. EC is the most suitable agent widely used to design controlled release matrices. This effect might be ascribed to an increase in the extent of gel formation in the diffusion layer formed by the polymer [23], with more toutosity, compressibility, swellability and slow diffusion and erosion. Matrices formulated with ethylcellulose polymer might have formed uniform channels for water to diffuse into the matrix, to dissolve and to release the drug in controlled manner [24]. F-2 and F-6 containing hydroxypropylmethylcellulose prepared by direct compression and wet granulation released 98.46 % and 91.25 % DCL-Na after within 24 hrs respectively. HPMC is a release controlling polymer and is actively used in controlled release matrix tablets to deliver the desired amount of drug effectively. Swellability and polymer chain relaxation of HPMC plays a vital role to sustain the drug release rate [25]. F-2 and F-6 released 70 % and 60 % of drug after 10 hrs prepared by direct compression and wet granulation respectively. It could be observed that HPMC formed gel layer when it came in contact with water having a longer diffusional path. It was also suggested that in small quantities HPMC could act as channelling agent, and enhance the drug release rates from a matrix system [26, 27]. F-3 and F-7 CMC-based tablets released 99% of drug within 2 & 3 hrs prepared by direct compression and wet granulation methods, respectively. It has been observed when the concentration of CMC increased, the hydrophillicity of the network also increased, thereby resulting in enhanced water sorption by the matrix [28]. Starch-based tablets released 98.99% and 98.89% DCL-Na after 2 and 4 hrs for each directly compressed and wet-granulated tablet respectively. It might be due to the polyvalent cations of starch which could swell in water by about 5-10% at 37° C and because of this characteristic, it could break the polymeric membrane, hence released maximum amount of the drug from polymer matrices. It could be observed that diffusion, erosion and polymer swelling were the main release controlling factors involved in prolonging the drug release rate [25]. The above said observations could also be evaluated by applying different kinetic models to the drug release data.

Drug Release Kinetics

DCL-Na release data obtained was evaluated by zero-order, first-order and Higuchi models to study the release behavior of the drug from the matrix core. As the dissolution of controlled release matrices followed the anomalous release, coupled with combination of diffusion and erosion, so the Higuchi model failed to explain the release behavior. Therefore, Korsmeyer equation was applied to the release profile, which is always used to describe anomalous release behavior from the matrices [12]. Korsmeyer model describes the release of the drug from matrices while "n" is the release exponent that actually characterizes the release mechanism of the drug from the matrix core. If $n = 0.45$, then the release is Fickian and if $0.45 \leq n \leq 0.89$ then it is non-Fickian. While 0.98 value of "n" exponent indicates typical zero-order release [29]. Because of uniformity of mixing and significant improvement of the physical characteristics, all the tablets remained intact during the dissolution time and gave the highest release exponent with a good linearity and correlation coefficient ranging from $r^2 = 0.658$-0.992. Release exponent for F-5 prepared with EC by wet-granulation (D:P, 10:3), $n = 0.805$ followed by the linearity $r^2 = 0.984$ indicated the best

anomalous (non-Fickian, Case 1) release coupled by diffusion and erosion when the release data was fitted to equation 10. The exponent shows the ideal release which quite near to zero-order release. While F-1 prepared by direct compression gave the release exponent $n = 0.74$ with linearity of $r^2 = 0.981$. HPMC-based matrices F-2 and F-6 also gave the non-Fickian release with exponents $n =$ 0.68 and 0.75 for matrices prepared by direct compression and wet-granulation techniques respectively. CMC and starch-based matrices F-3, 4, 7 and 8, showed a burst release with release exponents ranging from 0.016-0.095 [30]. Summarizing the kinetic analysis it could be observed that a best linear relation was shown for F-1, 2, 5, and 6 when the release data was fitted to Eq. 6 & 7 as shown in table 4.

Polymer hydration or water uptake

Swelling of matrix depends upon the rate of penetration of dissolution medium into the polymer matrix. The result of water uptake test is given as the % weight change as shown in the figure 6. The swelling behaviour of selected formulations F-1, F-2, F-5 & F-6, formulated with EC and EC-HPMC matrices prepared by direct compression and wet-granulation techniques, with the release exponents ranging from 0.685 to 0.809, indicated the rate at which the matrices absorbed water from the external medium and swelled. The figure below characterizes out the study of the effect of EC, HPMC polymers and the formulation techniques on the matrix swelling. It could be observed that the water uptake by the polymer matrix started from the placement of the tablet into the dissolution medium [31] The surface layer swelled, formed a gel and as a result the tablet increased in size. This hydrated swelled layer, then, dissolved and eroded slowly and a new layer formed with the exposure of core material to the dissolution medium. This process continued until the matrix tablet dissolved and eroded completely, normally it took 6 hrs of the experiment. During the first 2 hrs a hysteresis mechanism was observed and the water rapidly entered the matrix through metastable pores to swell it up [32]. It could also be observed that, as EC is a hydrophobic polymer and the tendency for swellability declined with presence of a cross-linked polymer structure. Whereas, the matrices containing HPMC swelled more as compared to the matrices containing EC alone due to the hydrophilic nature of HPMC as shown in the figure 3. The morphological changes of the matrix tablets captured at various time points are also in good agreement with swelling behaviour of the polymer as shown in the figure 6.

Matrix erosion

The surface layer of the matrix tablets initially hydrated when came in contact with the dissolution medium to generate and outer viscous gel layer. Later matrix bulk hydration, swelling and erosion took place sequentially. It could be observed that the overall dissolution and release rate of DCL-Na was controlled by the rate of swelling, diffusion and erosion [4] of the matrix gel. The result of matrix erosion is shown in the figure: showing the amount of polymer eroded and dissolved in the dissolution medium. Both the selected matrix tablets F-1, F-2, F-5 and F-6 showed a linearity of weight loss and polymer erosion. It was observed that the matrices prepared by wet granulation eroded slowly losing about 50% of the weight as compared to the matrix prepared by direct compression technique losing about more than 60% of their weight after 6hrs, as presented in the figure 8.

Effect of Aging on Release of DCL-Na

The effect of six months storage at ambient conditions on the DCL-Na release was studied. It was observed that the selected tablets did not reveal any sort of degradation or reduction in the drug contents and these results suggested that DCL-Na release properties, under the above said storage conditions, were stable.

Conclusion

Cellulose derivative polymers like ethylcellulose and hydroxypropylmethylcellulose controlled the release of DCL-Na from prepared matrix tablets. Diffusion, polymer hydration and erosion were the main drug release determining factors. Polymer gel layer formed acted as a controlled release membrane to diffuse the drug out of the matrix over an extended period of time., While coexcipients like CMC and Starch showed a burst release and tablets disintegrated within 2 hrs.

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Table 1. Composition of DCL-Na controlled release matrix tablets

Formulation Components	Technique							
	Direct Compression			Wet Granulation				
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
DCL-Na	100	100	100	100	100	100	100	100
Ethycellulose	30	30	30	30	30	30	30	30
HPMC	---	20.7	---	---	---	20.7	---	---
CMC	---	---	20.07	---	---	---	20.07	---
Starch	---	---	---	20.7	---	---	---	20.7
Lactose	49.3	49.3	49.3	49.3	49.3	49.3	49.3	49.3
Mg. Stearate	1	1	1	1	1	1	1	1

Table 2. Physical characteristics of starting material and granules

Formulation	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Hausner Factor	Angle of repose (θ)	Compressibility (%)
Pure Drug	0.351	0.921	2.630	32.64	48.72
F-1	0.346	0.352	1.017	21	17.21
F-2	0.373	0.385	1.032	25	19.32
F-3	0.335	0.347	1.035	26	15.28
F-4	0.381	0.394	1.034	22	18.15
F-5	0.373	0.385	1.032	19	19.73
F-6	0.304	0.318	1.046	28	20.45
F-7	0.299	0.308	1.030	22	18.92
F-8	0.367	0.379	1.032	20	18.83

Table 3. Hardness, Friability, Weight variation, Drug content, Thickness and Diameter of the prepared tablets, Expressed as Mean ± SD

Batch	Hardness (kg)	Friability (%)	Weight variation (mg)	Drug content (%)	Thickness (mm)	Diameter (mm)
F-1	6.7 ± 0.25	0.72 ± 0.08	201 ± 0.7	99.10 ± 0.08	2.2 ± 0.3	4.4 ± 0.2
F-2	6.9 ± 0.42	0.32 ± 0.09	202 ± .0	99.10 ± 0.04	2.2 ± 0.5	4.4 ± 0.1
F-3	6.8 ± 0.38	0.87 ± 0.05	203 ± 0.8	99.70 ± 0.34	2.2 ± 0.4	4.2 ± 0.2
F-4	6.4 ± 0.40	0.77 ± 0.04	201 ± 1.2	99.90 ± 0.10	2.1 ± 0.5	4.3 ± 0.0
F-5	7.2 ± 0.44	0.31 ± 0.06	203 ± 0.5	99.12 ± 0.56	2.2 ± 0.3	4.2 ± 0.2
F-6	6.9 ± 0.34	0.40 ± 0.09	200 ± 1.1	99.00 ± 0.05	2.3 ± 0.8	4.1 ± 0.3
F-7	7.0 ± 0.38	0.52 ± 0.02	200 ± 0.8	98.30 ± 0.17	2.1 ± 0.6	4.0 ± 0.5
F-8	6.9 ± 0.42	0.37 ± 0.09	202 ± 1.0	98.77 ± 0.09	2.1 ± 0.2	4.2 ± 0.1

Table 4. Parameters of kinetics model applied to the release profiles of DCL-Na matrix

Kinetics	W =k_1t $k_{1\pm}$S D	r_1	(100-w) =ln100-k_2t k_2±SD	r_2	$(100-w)^{1/3}=100^{1/3}-k_3t$ $k_{3\pm SD}$	r_3	$W=k_4t^{1/2}$ k_4±SD	r_4	$M_t / M_\infty=k_5 t^n$ k_5 ± SD	r_5	n
Formulation					**Direct Compression Technique**						
F-1	6.846±0.488	0.965	0.165±0.060	0.733	1.194±0.036	0.849	6.953±0.413	0.965	0..053±0.112	0.981	0.740
F-2	7.164±0.264	0.954	0.204±0.032	0.782	0.234± 0.008	0.871	7.035±0.355	0.954	0.022±0.049	0.978	0.685
F-3	2.641±3.462	0.051	1.259±0.713	0.024	1.182± 0.661	0. 0005	1.741±4.099	0.051	0. 000±3.389	0.658	0.016
F-4	3.701±2.712	0.152	1.200±0.671	0.002	1.118±0.616	0.016	2.491±3.568	0.152	0. 000±1.323	0.749	0. 034
					Wet Granulation Technique						
F-5	4.782±1.948	0.964	0.075±0.123	0. 828	0.107±0.098	0. 886	5.235±1.628	0.964	0. 592±1.292	0. 984	0.809
F-6	5.116±01.711	0.949	0.090±0.012	0.781	0.126±0.085	0.852	5.623±1.353	0.949	0.229± 0.551	0.992	0.755
F-7	3.841±2.613	0.367	0.970±0.509	0.048	0.971±0.512	9.157	2.727±3.410	0.367	0.000± 6.280	0. 984	0.060
F-8	5.832±1.205	0.401	0.856±0.428	0.088	0.874±0.444	0.226	4.121±2.415	0.401	0.000±9.05	0. 957	0.095

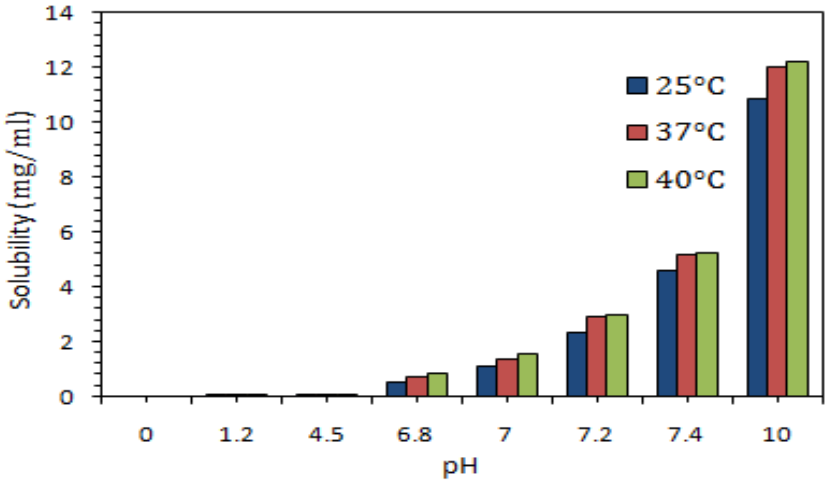

Figure 1. Solubility of DCL-Na in 7 different pH solvents at 25°, 37° & 40° C

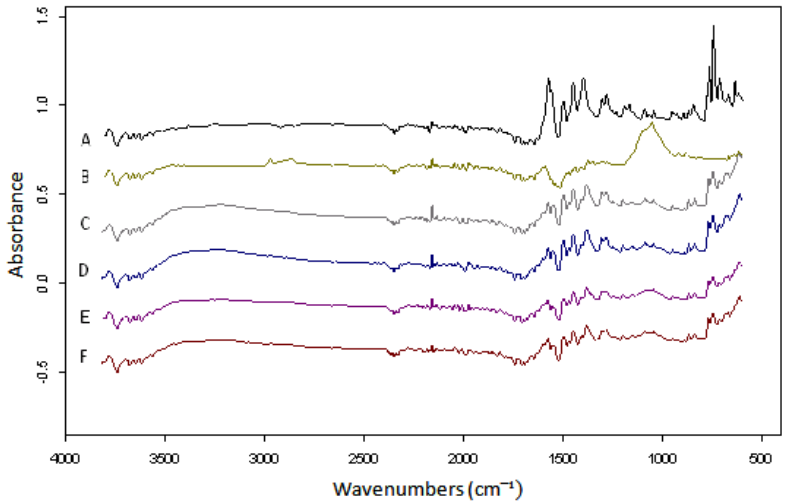

Figure 2. FTIR spectra of DCL (A), EC (B), DCL-EC (C), DCL-EC-Starch (D), DCL-EC-CMC (E), and DCL-EC-HPMC (F)

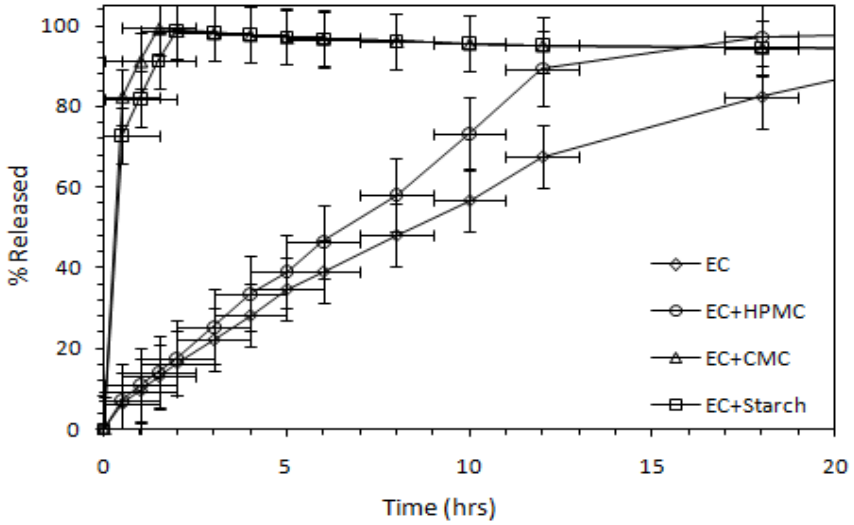

Figure 3. DCL-Na release profile from matrix tablets prepared by direct compression method

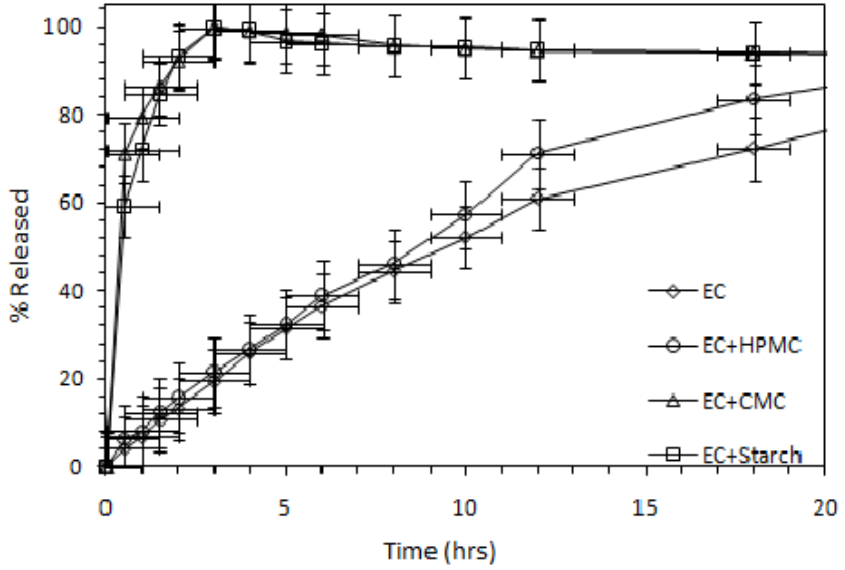

Figure 4. DCL-Na release profile from matrix tablets prepared by wet-granulation method

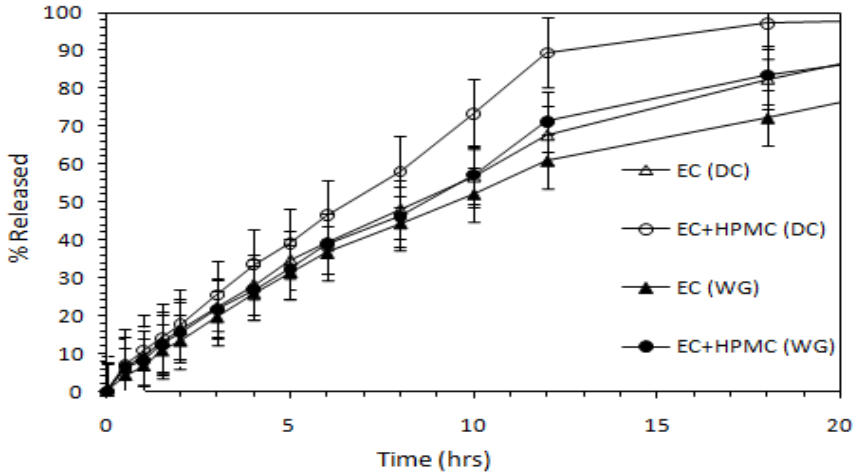

Figure 5. DCL-Na release profile, comparison of direct compression & wet-granulation methods

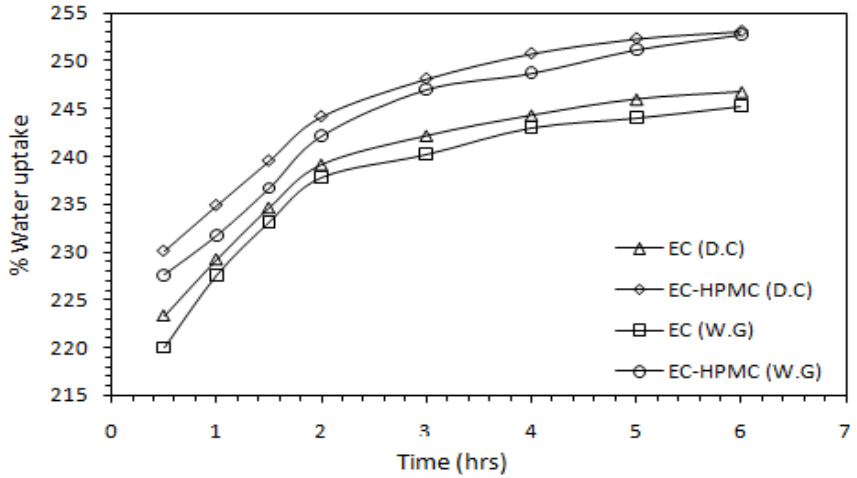

Figure 6. Plot of % swelling by DCL-Na controlled release tablets as a function of time

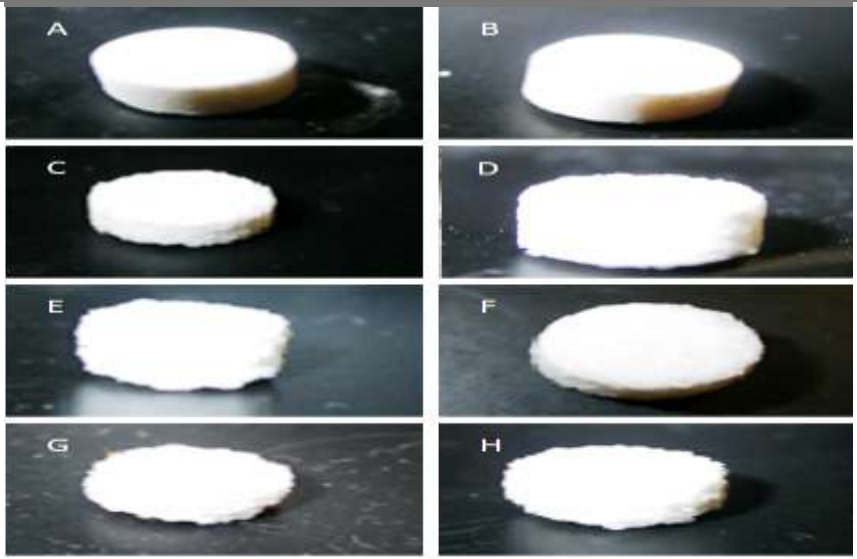

Figure 7. Morphology of matrix swelling prepared by direct compression (A, C, E, & G) and wet-granulation (B, D, F & E) at 0.5, 1, 2 and 3 hrs

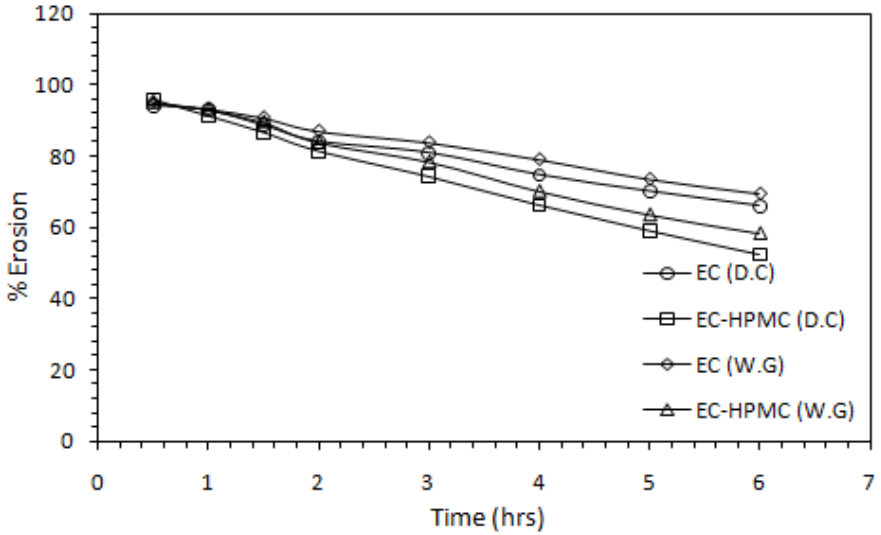

Figure 8. Plot of % weight loss of DCL-Na controlled release matrix tablets

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