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PHARMACEUTICAL TECHNOLOGY

EVALUATION OF DICLOFENAC SODIUM SUSTAINED RELEASE MATRIX PELLETS: IMPACT OF POLYETHYLENE GLYCOLS MOLECULAR WEIGHT

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Abstract: Sustained release matrix pellets loaded with 5% w/w diclofenac sodium (DS) were prepared using extrusion/spheronization technique. Different polyethylene glycols (PEGs) of different molecular weight, namely PEG 2000, PEG 4000 and PEG 6000 were mixed with avicel PH 101® in different weight ratios to manufacture the pellet formulations and water was used as a binder. Mix torque rheomter was used to characterize the pellets' wet mass. Also, the prepared pellets were characterized for their particle sizes, DS content, shape and morphology as well as the *in vitro* drug release. The results showed that increasing PEG weight ratio resulted in a reduction of wet mass torque as well as binder ratio, especially at PEG high weight ratios (30% and 50%) and the extent of lowering wet mass peak torque was inversely proportional to PEG molecular weight. The manufactured pellets exhibited size range of 993 to 1085 μm with small span values. The drug release from pellets was governed by the molecular weight of PEG used, since increasing PEG molecular weight resulted in slowing the drug release rate from pellets, but increasing its level resulted in enhancing release rate. This was attributed to increasing pellet wet mass peak torque by increasing PEG molecular weight and lowering it by increasing PEG level. The prepared pellets showed non-Fickian or anomalous drug release or the coupled diffusion/polymer relaxation.

Keywords: matrix pellets, diclofenac sodium, mix torque rheometry extrusion/spheronization, *in vitro* release.

Multiple-unit dosage forms have gained much attention, with single-unit dosage forms, regarding both therapeutic and formulation benefits. Among the various types of multiple-unit dosage forms, pellets have attracted more attention due to their unique clinical and technical advantages. Pellets or spherical granules are produced by agglomerating fine powders with a binder solution. Pellets are defined as spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 μm for pharmaceutical applications (1). The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously. Several therapeutic advantages could be achieved using pellets as drug delivery system, over the single-unit regimen, such as less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping (2). In addition, formulation advantages as the better flow properties, less friable dosage form, narrow particle size distribution, ease of coating and uniform packing can be gained with pellets. It was shown that multi-unit dosage forms have gained considerable popularity over conventional single units for controlled release technology. This is due to the rapid dispersion of pellets in the gastrointestinal tract; they maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without lowering drug bioavailability (3). Pellets also reduce variations in gastric emptying rates and overall transit times. Thus, intra and intersubject variability of plasma profiles, which are common with single-unit regimens, are minimized.

Different authors formulated matrix pellets for controlled drug delivery systems techniques, which avoid the use of organic solvents during coating procedures, due to stringent global requirements of

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product safety. Also, by formulating sustained release matrix pellets, time and money could be saved by omitting the coating operation. As the level of understanding regarding the toxic effects of these solvents is increasing, industrial hygiene rules and FDA regulations are being tightened world over, limiting the use of these solvents and exposure of workers to these solvents. Therefore, several reports have been published on alternative techniques such as melt granulation (4), melt extrusion (5, 6), melt dispersion (7), and melt solidification (8) for controlled drug delivery systems. In addition, several attempts have been made to modify drug release from multi-particulate oral dosage forms by incorporating various hydrophobic materials into a basic formulation for pellets (9). Such systems retard the penetration of aqueous fluids into the formulation and hence slow the rate of drug release.

The rheological properties of wet masses can be monitored successfully using a mixer torque rheometer (10, 11) so as to formulate pellets of tailored pharmaceutical characteristics. It was shown that the rheological properties of wet mass could affect the release patterns from pellet formulations. Ibrahim (12) showed that mefenamic acid matrix pellets could be successfully correlated with the wet mass characteristic using mixer rheometry. This will help to obtain a controlled release dosage form capable of lowering the risk of side effects and improving patient convenience as an advantage of pellets as a drug delivery system. Also, Mahrous et al. (13) observed that an inverse relationship exists between indomethacin release from the pellets and the peak torque values of the used polymer mixture.

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drug (NSAID) and belongs to the group of aryl acetic acid derivatives. It is widely used in treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis (14). Because of its short biological half-life (2 h), it is eliminated from plasma compartments of the body within few hours, so frequent administration is necessary to maintain its therapeutic concentration. Thus, DS is an ideal candidate for sustained release purposes (15, 16). Therefore, the formulation of DS as a sustained release dosage form matrix pellets could be an alternative approach to overcome the potential problems in the gastrointestinal tract, in addition to minimizing dosing frequency (17, 18).

The objectives of the present study were to formulate sustained release matrix pellets loaded with DS using extrusion/spheronization technique as an alternative method to coating technique. Different grades of polyethylene glycols (PEG 2000, PEG 4000 and PEG 6000) were used in combination with avicel. The effect of polyethylene glycol molecular weight on the wet mass peak torque, pellets' shapes and sizes will be characterized using mixer torque rheometry and the *in vitro* release rate of the drug loaded pellets will be assessed as well.

EXPERIMENTAL

Materials

DS was kindly supplied by Al-Jazeera Pharmaceutical Industries (Riyadh, KSA). Polyethylene glycols (PEG 6000, PEG 4000 and PEG 2000) were purchased from Koch-Light Laboratories Ltd. (Colnbrook, Bucks, U.K.). Microcrystalline cellulose (MCC) (Avicel® PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). All other materials and solvents used were of reagent or analytical grade and used without further purification.

Methodology

Characterization of pellets wet masses using a mixer torque rheometer

The mixer torque rheometer used in the present study consists of a 135-mL capacity stainless steel bowl equipped with two mixing blades with rotational speed ranging between 20 and 150 rpm (MTR-3, Caleva, Dorset, England). Depending on the bulk density, a sample of 15–30 g of dry powder material is sufficient to cover the mixer blades. The torque is measured directly on the mixer bowl with the help of a torque arm connected from the main body of the mixer to a calibrated load transducer. The used mixer speed for all the studies was 50 rpm. The data acquisition and analyses were carried out by a personal computer using data acquisition system and software package supplied by the equipment manufacturer.

Powders were mixed in turbula mixer (type S27, Erweka, Apparatebau, Germany) and 15 g sample of this dry blend was utilized in the wet massing studies. Two milliliters of granulating fluid were added in multiply additions over 10 wet massing intervals. Each wet massing interval consisted of a one minute mixing period and a 20-second torque data logging (collection) period with the MTR operating at 50 rpm. Mean torque was monitored during the granulation process.

Manufacture of pellets

Water was used as a granulating liquid in the manufacture of matrix pellets loaded with 5% w/w DS. The water volume required for wet massing was

selected according to the highest torque value measured by the rheometer. The compositions of the studied pellet formulations are shown in Table 1. DS and pellets excipients were mixed in turbula mixer at certain weight and the powder mixture was wetted with water. Next, the resulting wet mass was extruded at a speed of 90 rpm with a screen pore size of 1 mm ∅ (Mini Screw Extruder, Model MSE1014, Caleva, Dorset, England). Spheronization was performed in a spheronizer (Model 120, Caleva, Dorset, England) with a rotating plate of regular cross-hatch geometry, at a speed of 700 rpm, for 5 min. Pellets were then dried on a tray in a hot oven at 50-60°C for 6 h.

Drug content

DS content of the manufactured pellets was determined spectrophotometrically at 285 nm in triplicate. Pellets were crushed in a porcelain mortar and about 20 mg of the crushed pellets were dispersed in 250 mL phosphate buffer (pH 6.8) under sonication for 5 min. The supernatant was filtered through a cellulose nitrate filter with pores of 0.2 µm in diameter (Sartorius, Göttingen, Germany) and measured spectrophotometrically (UV-2800 spectrophotometer, Labomed Inc., USA), then MA content was calculated using a pre constructed calibration curve.

Morphological analysis

The morphological characteristics of particles were observed by scanning electron microscopy (SEM). The samples were sputter-coated with thin gold palladium layer under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then scanned and photomicrographs were taken with an SEM (Jeol JSM-1600, Tokyo, Japan).

Particle size analysis

The size distribution of the manufactured pellets was investigated using laser light diffraction (Mastersizer Scirocco 2000, Malvern Instruments, Grovewood Road, U.K.). For a typical experiment, about 300 mg of pellets were fed in the sample micro feeder. All samples were analyzed 5 times and average results were taken. The pellets 10th (d(0.1)), 50th (d(0.5)) and 90th (d(0.9)) percentiles were used to characterize the pellets size distribution. The approximate mean diameter was taken as the average of d(0.1), d(0.5), and d(0.9) values.

The span value was employed to characterize the pellet size distribution, since a small span value indicates a narrow particle size distribution. It was calculated from the following formula (19):

$$\text{Span} = \frac{D_{90}-D_{10}}{D_{50}}$$

In vitro dissolution studies

The dissolution measurements were performed using an automated dissolution tester (LOGAN Instrument Corp, Somerset, NJ, USA) coupled to an automated sample collector (SP-100 peristaltic pump, Somerset, NJ, USA). The USP dissolution basket method (apparatus 1) was used. MA loaded pellets equivalent to 20 mg DS were added to the 500 mL of dissolution medium (phosphate buffer, pH 7.4). The temperature was maintained at 37 ± 0.5°C. An accurately weighed amount of the pre-

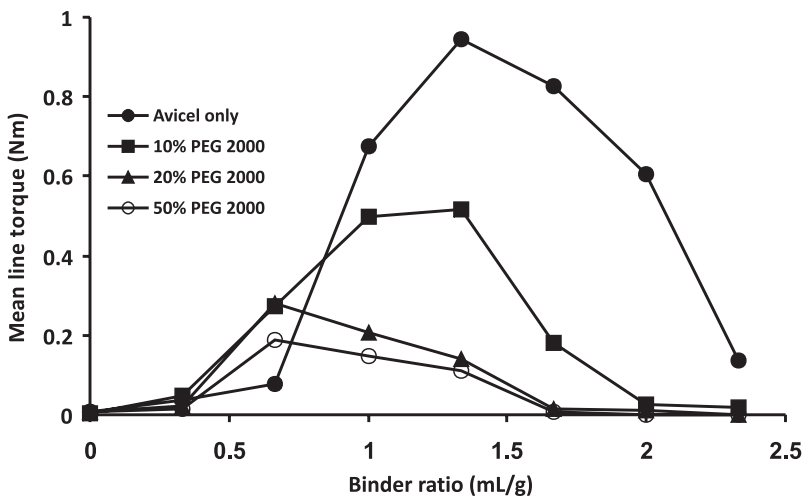

Figure 1. Effect of different concentrations of PEG 2000 on mean torque of Avicel PH101

pared pellets was added to each flask. For each sample formula, drug dissolution was run in triplicate and absorbance was recorded automatically at 285 nm up to 8 h. The percentage of drug dissolved was determined as a function of time.

Statistical analysis

The results were analyzed by using the software GraphPad Prism5 (GraphPad Software, La Jolla, USA) applying one-way ANOVA. Differences between formulations were considered to be significant at $p \leq 0.05$.

RESULTS AND DISCUSSION

Wet massing studies

The experiments of wet massing studies were conducted for avicel-PEGs systems in order to establish the water/powder ratio needed to reach a maximum torque response and the effect of PEG grade and level on the pellet wet mass characteristics. Regarding avicel-PEG 2000 systems (Fig. 1) different liquid saturation phases (pendular, funicular and capillary, respectively) were passed through by increasing binder level, with the maximum

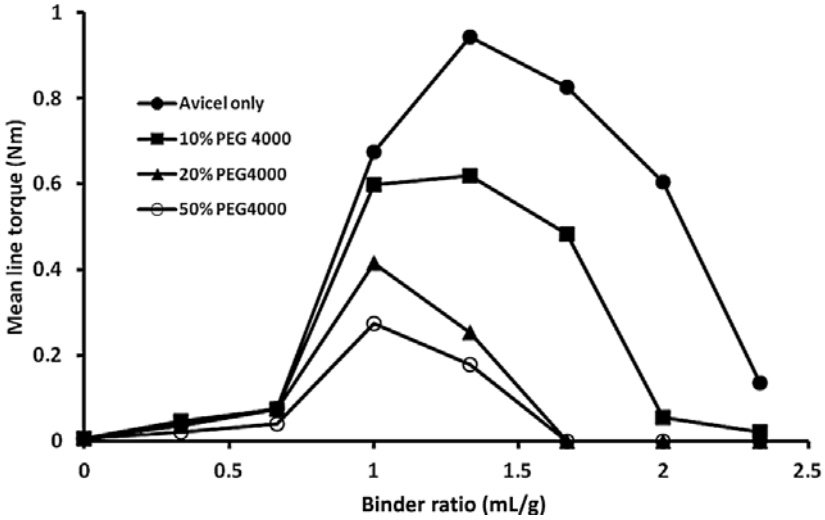

Figure 2. Effect of different concentrations of PEG 4000 on mean torque of Avicel PH101

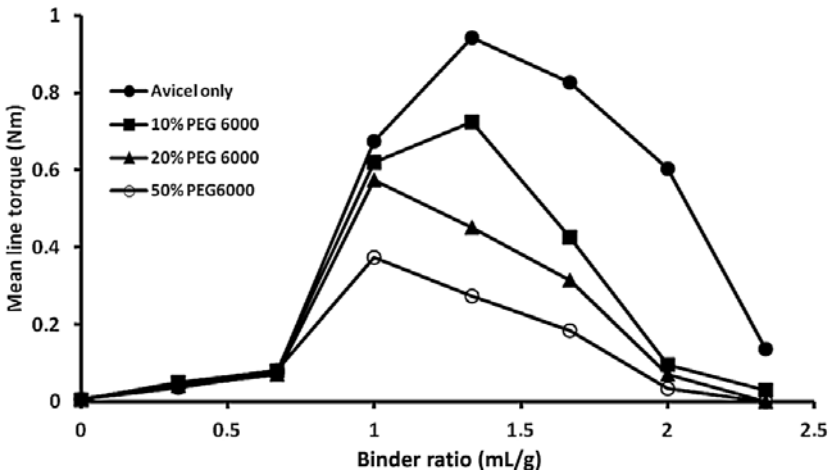

Figure 3. Effect of different concentrations of PEG 6000 on mean torque of Avicel PH101

Table 1. Composition of different pellets formulations loaded with diclofenac sodium.

Formula / Ingredients %	1	2	3	4	5	6	7	8	9	10
Avicel PH 101	85	75	45	43	85	75	45	85	75	45
PEG 2000	10	20	50	50	-	-	-	-	-	-
PEG 4000	-	-	-	2	10	20	50	-	-	-
PEG 6000	-	-	-	-	-	-	-	10	20	50
Diclofenac sodium	5%									
Water (binder)	Q. S.									

torque occurring at the capillary state. Avicel alone exhibited a typical progression of liquid saturation phases. The mean torque value was found to increase with the increase in the wet massing liquid (water) ratio. However, different profiles were detected regarding avicel-PEG 2000 systems, increasing PEG 2000 weight ratio resulted in a severe reduction of the area of MTR curve, i.e., progression of liquid saturation phases occurs at lower water/powder ratio. In addition, reductions of peak torque water/powder ratios (mL/g) and peak torque magnitudes were recorded, which reached the lowest value (0.208 Nm) at 50% w/w PEG 2000 level (Fig. 1). The rheological behaviors of avicel-PEG 4000 systems (Fig. 2) are quite the same as those recorded in case of avicel-PEG 2000. However, there is an increased peak torque in case of avicel-PEG 4000 levels compared to the use of corresponding levels of PEG 2000. For example, upon mixing 50% level of PEG 2000 and PEG 4000 with avicel, the recorded peak torque values were 0.189 Nm and 0.247 Nm, respectively. Similarly, mixing PEG 6000 with avicel for wet massing resulted in increasing the wet mass consistency higher than that measured in case of PEG 2000 or PEG 40000 (Fig. 3). On the other hand, pendular, funicular and capillary phases in case of avicel-PEG 6000 systems were reached at higher peak torque values than those observed in case of the other PEG polymer grades, and the peak torque values were found to decrease by increasing the PEG level. The impact of PEG molecular weight and concentration on the properties of DS pellets wet masses is displayed and summarized in Figure 4. It is clearly evident that high molecular weight grades showed an increase in the mean line torque of the wet mass at all the concentrations studied (10, 20 and 50%) and the mean torque value was found to be decreased by raising polymer level. According to Parker and Rowe (20), the degree of liquid spreading and wetting as well as the substrate binder interaction will determine the relative positions of the peak values of mean line torque. For each polymer concentration, an increase in the mean torque with the increase in the polymer molecular weight at different concentrations resulted in either a sharp or an extended peak followed by a drop in the torque as over-wetting of the powder mass occurred. In addition, the pendular and funicular states are characterized by a progressively increasing network of liquid bridges. Both of these stages will cause an increase in cohesiveness of the powder mass and hence an increased torque on the mixer (21). The capillary state which was reached when all the air spaces in the granular material were filled with liquid occurs at the maximum on the curve. With further addition of liquid the torque decreases as slurry of particles dispersed in liquid is formed.

Drug content

The obtained results showed DS content ranged from 90 to 110% of the theoretical content, which revealed a homogenous drug distribution in the prepared pellets.

Pellets sizes and shapes

The calculated values of volume weighted mean particle size and the d(0.1), d(0.5) and d(0.9) different pellet formulae loaded with DS as determined by laser diffractometry are tabulated in Table 2. One can observe that the volume weighted mean of the manufactured pellets was found to be in the range 993 to 1085 μm. Also, the particle size distribution of DS loaded matrix pellets was characterized by small span values, as these calculated values were found to be 0.64-0.72 indicating a narrow particle size distribution (22). Moreover, for each polymer grade, increasing the polymer concentration resulted in a decrease in the calculated volume weighted mean as well as the span value of particle

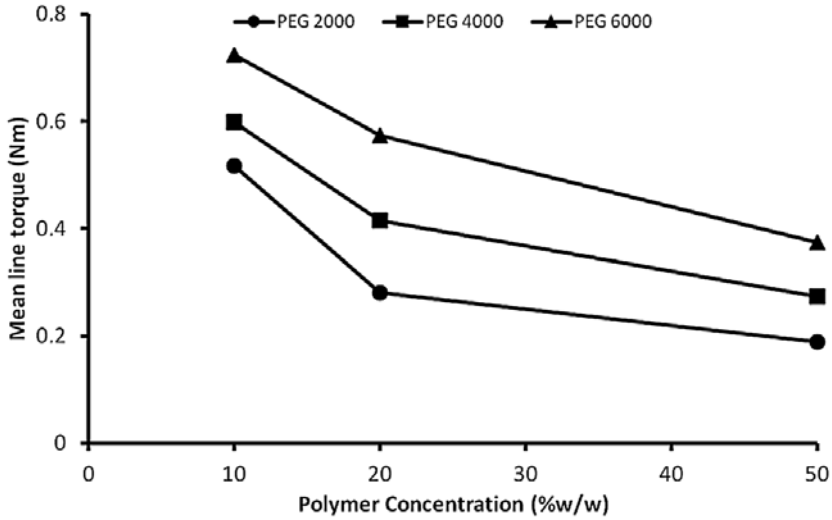

Figure 4. Effect of PEGs molecular weight and concentration of on mean line torque of Avicel PH101

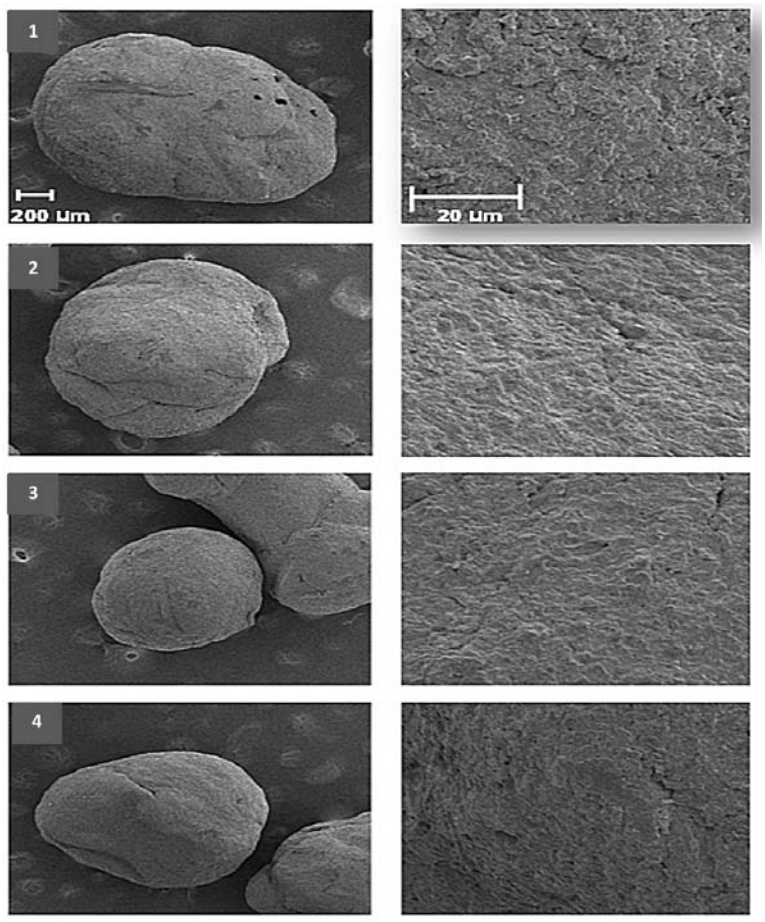

Figure 5. A column represents scanning electron micrographs of the pellets and B column represents scanning electron micrographs of the surface of pellets. Key: 1. Avicel only, 2. Avicel + 50% PEG 2000, 3. Avicel + 50% PEG 4000 and 4. Avicel + PEG 6000

size distribution. This is in accordance with the data obtained from wet massing studies; which showed a decrease in the wet mass by increasing polymer concentration, which in turn, reduced torque values. Kristensen and Schaefer (23) found a linear correlation between the torque value and pellet size for formulations containing 80% (w/w) of MCC.

Scanning electron micrographs of matrix pellets formulations containing 50% of each PEG grade mixed with avicel are compared with those prepared using avicel only and displayed in Figure 5. Most of the prepared pellets formulae were seen almost rounded and intact in shape, while pellets from avicel only (A) were not completely spherical. The higher torque value of this pellet wet mass formula (943) may be contributed to its irregular shape. Also, pellet formula prepared using 50% PEG 2000 (B) showed smooth surface compared to those prepared from 50% PEG 4000 (C) and PEG 6000 (D). Increasing PEG molecular weight caused increased roughness of the pellet surface, which might be due to increasing pellet wet mass mean torque as previously described. These results are in accordance with the data obtained by Mahrous et al. (13), who showed that the more hydrophilic polymer (PEG 4000), when mixed with MCC, produced a wet mass having the lowest mean torque value compared to that recorded with the same weight ratio of PVP and HPMC. This in turn, reflects on the easy extrusion of PEG wet mass resulting in pellets with smooth less rough surfaces. In addition, Law and Deasy (24) showed that the use of hydrophilic polymers with MCC favored more spherical and smooth pellets.

Table 2. Volume weighted mean particle size and the d(0.1), d(0.5), d(0.9) and span values of different pellet formulae loaded with 5% w/w diclofenac sodium (as determined by laser diffractometry).

Pellet formulations	Mean (µm)	d (0.1) µm	d (0.5) µm	d (0.9) µm	Span value
Avicel only	1065.74	741.52	1110.21	1541.87	0.72
Avicel + 10% PEG 2000	1030.24	734.21	1084.21	1498.21	0.71
Avicel +20% PEG 2000	1000.21	711.51	1051.21	1421.84	0.68
Avicel +50% PEG 2000	993.21	684.21	1000.10	1327.21	0.64
Avicel +10% PEG 4000	1075.11	721.45	1121.11	1524.32	0.72
Avicel +20% PEG 4000	1063.21	711.25	1101.01	1499.17	0.72
Avicel +50% PEG 4000	1033.45	700.14	1042.11	1418.71	0.69
Avicel +10% PEG 6000	1120.04	765.21	1132.10	1548.15	0.69
Avicel +20% PEG 6000	1086.21	751.78	1123.34	1513.01	0.68
Avicel +50% PEG 6000	1084.51	738.41	1108.91	1465.87	0.66

Table 3. Kinetic modeling of DS release from different sustained release matrix pellet formulations.

Formula	Zero order model	First order model	Higuchi diffusion model	Peppas model	n*
	r	r	r	r	
Avicel only	0.869	0.922	0.974	0.981	0.398
Avicel + 10% PEG 2000	0.957	0.970	0.999	0.999	0.50
Avicel +20% PEG 2000	0.869	0.981	0.974	0.981	0.398
Avicel +50% PEG 2000	0.819	-	0.948	0.960	0.366
Avicel +10% PEG 4000	0.869	0.938	0.975	0.981	0.398
Avicel +20% PEG 4000	0.879	0.965	0.978	0.984	0.41
Avicel +50% PEG 4000	0.872	0.967	0.976	0.982	0.399
Avicel +10% PEG 6000	0.869	0.930	0.974	0.981	0.398
Avicel +20% PEG 6000	0.870	0.952	0.973	0.978	0.41
Avicel +50% PEG 6000	0.855	0.948	0.966	0.972	0.394

r = correlation coefficient, and n is the release exponent. * obtained from Korsmeyer-Peppas equation.

***In vitro* release studies**

It was shown by Law and Deasy (24) that mixing various hydrophilic polymers with MCC had been reported previously to aid extrusion-spheronization and, at the same time, to enhance the dissolution of indomethacin. Therefore, the aim of studying DS *in vitro* release from matrix pellets is to investigate the effect of different PEGs on the drug release patterns. Incorporation of the drug in pellet formulations composed of MCC only resulted in slowing its release rate. Only 59% of the loaded DS was released from avicel matrix pellets after 8 h (Figs. 6-8). The effect of PEG 2000 concentration on the *in vitro* release profile of DS from matrix pellets is illustrated in Figure 6. The drug release rate was found to be enhanced by increasing PEG 2000 level in the pellets. For example, complete drug release was observed after 4 h in case of pellet formulation containing 50% PEG 2000, while only 66% and 79% of the loaded drug were released from the formulae containing 10 and 20% of such polymer at the same time, respectively. In case of pellet

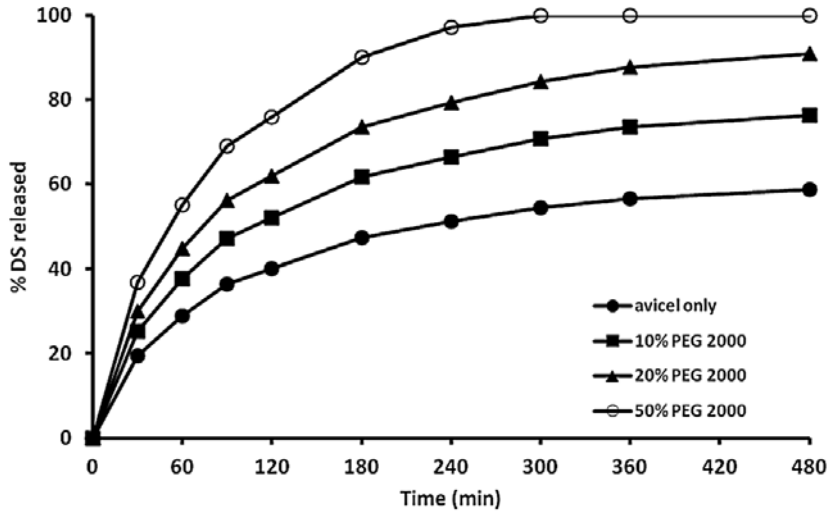

Figure 6. Effect of PEG 2000 concentration on the in vitro release profiles of DS from matrix pellets

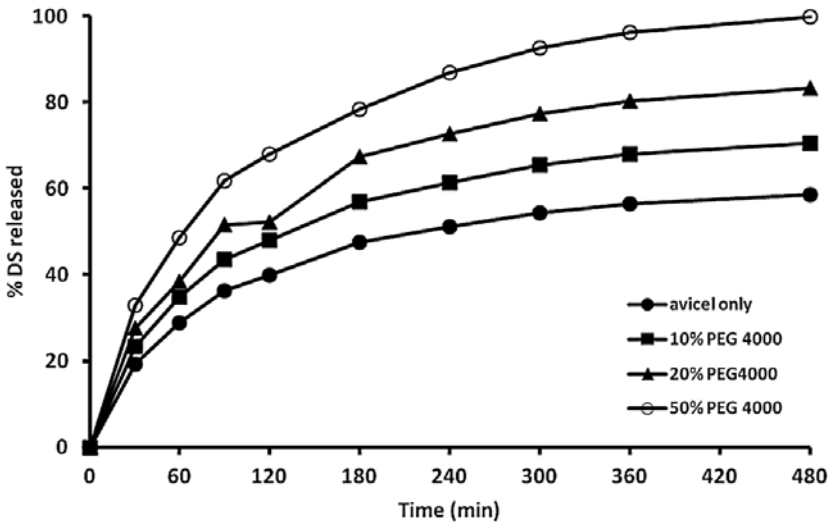

Figure 7. Effect of PEG 4000 concentration on the in vitro release profiles of DS from matrix pellets

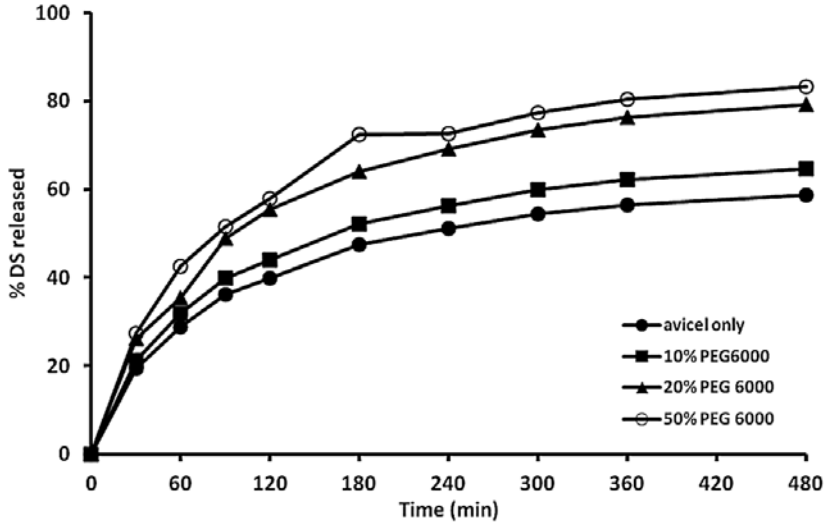

Figure 8. Effect of PEG 6000 concentration on the *in vitro* release profiles of DS from matrix pellets

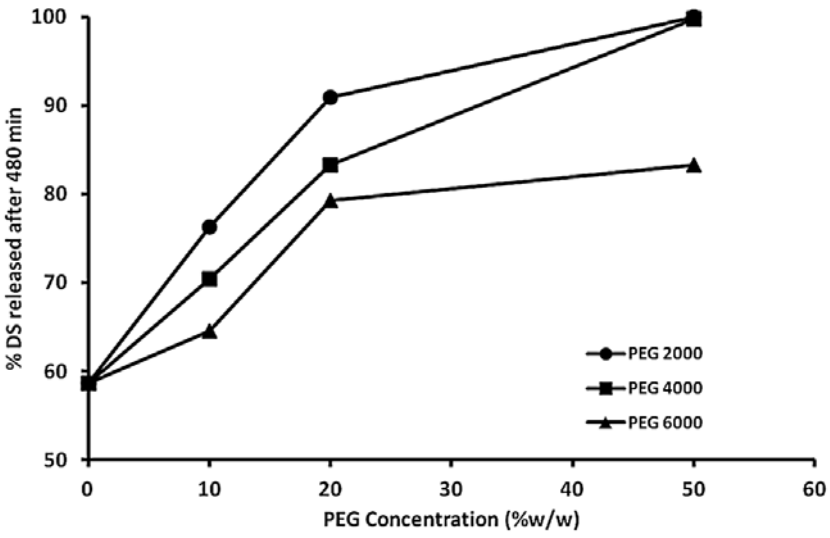

Figure 9. Effect of PEGs molecular weight and concentration on the release rate of DS from matrix pellets after 480 min

formulations containing PEG 4000 (Fig. 7) similar finding were recorded that by increasing PEG 4000 level in the pellet formulation, a pronounced rapid release rate was observed. However, the enhancement of DS release was in case of using different PEG 4000 concentrations lower that that exhibited by PEG 2000. Only 71, 83 and 99% of the loaded DS were released after 8 h from pellet formulations manufactured by using PEG 4000 concentrations of 10, 20 and 50% of the pellets' weight. Moreover, the addition of PEG 6000 in different levels caused an increase in the drug release rate by increasing PEG 6000 level (Fig. 8) but the enhancement is rather smaller than that seen in case of PEG 2000 and PEG 4000. For example, pellet formulations containing PEG 6000 concentrations of 10, 20 and 50% of the pellets' weight released 66, 79 and 83% of the loaded DS after 8 h.

Figure 9 correlates the effect of PEG molecular weight and level on the percentage of DS released

after 480 min. It is clearly evident that increasing PEG level in the pellet formula caused a decrease in the peak torque of wet mass, which in turn, enhanced DS release rate from pellet formulations. In addition, the effect of PEG 2000 and PEG 4000 on the drug release rate from pellet formulas is more noticeable than that exhibited by blending PEG 6000, especially at higher concentrations (20 and 50%).

In another study, Ibrahim (12) revealed that increasing lactose weight ratio was accompanied by enhancing the mefenamic acid release rate from matrix pellets by reducing pellet wet mass peak torque. He showed that lactose enhances the drug release rate by forming pores; it also promotes water penetration into the formulation core. In addition, increasing lactose concentration caused a pronounced lowering of the mean torque of pellet wet mass before extrusion/spheronization procedures. Also, Ibrahim et al. (25) found an inverse relationship between indomethacin release from its loaded pellets and the peak torque values of the polymer mixed with co-solvents.

Kinetic modeling of the *in vitro* release of MA from the matrix pellets

The *in vitro* release data of DS from different sustained release matrix pellets were fitted using zero order, first order and Higuchi diffusion models as well as Korsmeyer-Peppas equation to determine the best model that describes drug release from pellet formulations. Preference of the best release mechanism is based on the correlation coefficient value. The data revealed a good fit to Higuchi diffusion model. Successive evidence of the relative validity of diffusion model was obtained by analyzing the data using the equation of Korsmeyer et al., and the release exponent (n) was calculated from Korsmeyer equation: (26)

$$Mt/M_{\infty} = K. t^{n}$$

where Mt/M_{∞} is the fraction released by the drug at time t, K is a constant incorporating structural and geometric characteristic and n is the release exponent characteristic for the drug transport mechanism. For spherical samples, when n = 0.43 Fickian diffusion is observed and the release rate is dependent on t, while $0.43 < n < 1.0$ indicates anomalous (non Fickian) transport and when n = 1, the release is zero order.

The release kinetic parameters listed Table 3 indicated that the calculated n values were found mostly less than 0.45, indicating the so called non-Fickian or anomalous drug release or the coupled diffusion/polymer relaxation. Other investigators showed that when liquid diffusion rate and polymer relaxation rate (erosion) are of equal magnitude, anomalous or non-Fickian diffusion is observed (27, 28).

CONCLUSION

Diclofenac sodium was successfully prepared as sustained release matrix pellets using extrusion/spheronization technique. The results showed that the release of DS from matrix pellets can be tuned by controlling PEG molecular weight, which affects the rheological properties of pellets' wet masses. Mix torque rheometry was found to be a good tool for characterizing pellets' wet mass prior to extrusion/spheronization procedures. In addition, formulation of drug-loaded matrix pellets might be an alternative approach for pellet coating to avoid coating procedures drawbacks.

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