

INDOMETHACIN-LOADED PELLETS PREPARED BY EXTRUSION/SPHERONIZATION. EFFECT OF COSOLVENTS

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Abstract

Indomethacin is a non-steroidal anti-inflammatory drug used in the treatment of rheumatoid arthritis, osteoarthritis, spondylitis and other disorders. The objective of this study was to enhance the dissolution rate of the drug by the formulation of microcrystalline cellulose (Avicel PH 101) pellets using extrusion/spheronization technique. Different cosolvents were incorporated in the pellet forming liquid (water), PEG 400, propylene glycol and ethanol. Mix torque rheometer was used to quantitatively determine the suitable moisture content in the pastes before the extrusion process. The produced pellets were characterized for their Indomethacin content, particle size, shape and dissolution profile. In addition, differential scanning calorimetry studies were carried out on indomethacin-avicel-cosolvent (1:1:1) physical mixtures and the individual components. The studies on the effect of additives on Avicel rheological properties revealed that the magnitude of torque for the system was not as high as that determined where water alone was used as the wet-massing liquid. It was found that pellets manufactured by adding different concentrations of PEG 400 (20, 40 and 60% w/w of water) released the drug faster than those containing the corresponding concentrations of other cosolvents. The relative dissolution rate of indomethacin at 30 minutes (RDR_{30}) using 60 % concentrations of PEG, propylene glycol and ethanol was enhanced to be 8.44, 4.46 and 3.22, respectively.

In conclusion, the addition of cosolvents to the manufactured pellets enhanced drug dissolution rates which might be beneficial in lowering the risk of side effects as an advantage of the pellets as drug delivery system.

Rezumat

Lucrarea prezintă rezultatele unor cercetări de tehnologie farmaceutică efectuate asupra unor pelete cu indometacin. A fost modificată formularea acestor preparate, utilizând excipienți noi, în scopul îmbunătățirii profilului de dizolvare al acestor forme farmaceutice. Pentru caracterizarea noilor pelete cu indometacin obținute, au fost analizați parametrii fizici specifici (mărime, circularitate, densitate) și, de asemenea, au fost efectuate studii reologice și teste de dizolvare.

Keywords: Indomethacin, Pellets, Mix Torque Rheometer, Dissolution, Cosolvents

Introduction

Multiple-unit dosage forms have several advantages compared with single-unit dosage forms including more stable plasma profiles and

decreased risk of local side effects [1]. Among the various types of multiple-unit dosage forms, pellets have attracted more attention due to their unique clinical and technical advantages. Pellets are defined as spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 μm for pharmaceutical applications [2]. The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously. Pellets as a drug delivery system offer therapeutic advantages such as less irritation of the gastro-intestinal tract and a lowered risk of side effects due to dose dumping [3]. In addition there are technological advantages, for example, better flow properties less friable dosage form, narrow particle size distribution, ease of coating and uniform packing. The reproducibility of the drug blood levels [4] is an additional advantage to the use of a pellet formulation. The *in vitro* release rate of hydrochlorothiazide from Avicel PH 101 pellets was enhanced by the incorporation of polyethylene glycol 400 (PEG-400) and PEG-40 hydrogenated castor oil [5].

Extrusion and spheronization is currently one of the techniques used to produce pharmaceutical pellets. With each production technique, pellets with specific characteristics are obtained. The preparation of spherical granules or pellets by extrusion and spheronization is now a more established method because of its advantages over the other techniques [2, 6].

Indomethacin (IM) is a non-steroidal anti-inflammatory drug used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and other disorders. The oral administration of conventional dosage forms of indomethacin can cause serious systemic side effects and gastric irritation [7]. Therefore, the pellets in the form of spherical granules with a diameter of 0.1–2 mm as a ‘multiple unit’ form of the drug are easier to assess than ‘single unit’ form tablets. As a drug delivery system the pellets ensure less irritation of the gastro-intestinal tract and a lower risk of side effects [8].

The use of the mixer torque rheometer (MTR) as an upfront analytical tool can greatly reduce the number of development batches. This equipment has been shown to be an excellent tool for the evaluation of wet granulated systems and as a scale-up tool for high shear granulations [9].

The objective of this study was to formulate indomethacin-loaded pellets using extrusion/spheronization technique. The prepared pellets were characterized for their particle sizes and morphology, indomethacin content and the *in vitro* drug release as well. In addition, the effect of cosolvents type and concentrations on the pellets properties were studied. The binder

ratio required for the preparation of wet mass prior to the pelletization process was measured by the mix torque rheometer.

Materials and methods

Indomethacin was purchased from Avocado Research Chemicals Ltd. (Heysham, Lancs, England). Propylene glycol (PG) was purchased from Winlab Co. (Bucks, England), Polyethylene glycol, PEG 400 was purchased from Fluka chemica (Buch, Switzerland). Absolute ethanol (Et) 99% was purchased from BDH (Poole, England). Microcrystalline cellulose (Avicel PH101) was purchased from Serva Feinbiochemica (Heidelberg, Germany). All other materials and solvents used were of reagent or analytical grade and were used without further purification.

Wet massing studies using a mixer torque rheometer

The mixer torque rheometer (MTR) used in the present study consisted of a 135mL capacity stainless steel bowl equipped with two mixing blades with rotational speed ranging between 20–150 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 was 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 following equipment settings were used for all the studies: mixer speed, 50 rpm; sampling rate at which data were captured during the logging periods. The data acquisition and analyses were carried out by a computer using data acquisition system and software package supplied by the equipment manufacturer.

Drug substance and excipients were mixed in turbula mixer (type S27, Erweka, Apparatebau, Germany). A 15g sample of this dry blend was used in these studies. Five milliliters of granulating fluid (deionized water with or without cosolvent) were added in multiply additions over 7 wet massing intervals. Each wet massing interval consisted of a one minute mixing period and a 20 seconds data logging (collection) period with the MTR operating at 50 rpm. Mean line torque was monitored during the granulation process.

Preparation of IM-loaded pellets

Pellets were prepared from those wet masses showing the highest mean torque. Avicel and IM were mixed in turbula mixer at 9.5: 0.5 weight ratio (type S27, Erweka, Apparatebau, Germany). The powder mixture was wetted with the granulation fluid (water containing different concentrations

of the tested cosolvents) depending on the composition of the formulation. Next the resulting wet mass was extruded at a speed of 90 rpm (Mini Screw Extruder, Model MSE1014, Caleva, Dorset, England), through 1 mm diameter die. 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 5min. Pellets were then dried on a tray in a hot oven at 50-60 °C for 6 hours.

Determination of IM content in the prepared pellets

Indomethacin (IM) content of the prepared pellets was determined spectrophotometrically (UV-9100 Spectrophotometer, Beijing Rayleigh Analytical Instruments Corp., China) at 320 nm in triplicate. Pellets were crushed in a porcelain mortar and about 25 mg of IM-loaded were dispersed in 20 mL phosphate buffer (pH=6.8) under sonication. The solution was filtered and IM was quantified.

Particle size analysis of the prepared pellets

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

Morphological analysis of the prepared pellets

The morphological characteristics of the prepared pellets were observed by scanning electron microscopy (SEM). The samples were sputter-coated with a 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).

Thermal analysis

The samples (3-5 mg) were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 25 °C to 250 °C. Thermograms of the samples were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software

programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. nitrogen was used as purging gas at a rate of 30 mL/min.

Fourier Transform Infrared Spectroscopy(FT-IR)

IR spectra of IM-avicel-cosolvents (1: 1: 1) physical mixtures as well as the untreated drug were determined in the range 4000-400 cm^{-1} using the KBr disk method (FT-IR-Spectrophotometer, spectrum BX, Perkin Elmer, USA).

***In vitro* release studies of the prepared pellets**

The release measurements were performed using an USP dissolution apparatus 1 (Caleva Ltd., Model 85T), at 100 rpm using a continuous automated monitoring system which consists of an IBM computer PK8620 series and PU 8605/60 dissolution test software, Philips VIS/UV/NIR single beam eight cell spectrophotometer Model PU 8620, Epson FX 850 printer, and Watson-Marlow peristaltic pump using in each flask 0.75 L phosphate buffer pH 6.8. The temperature was maintained at 37 ± 0.5 °C. An accurately weighed amount of the prepared formulation was added to each flask. For each formula, the experiment was run in triplicate and the absorbance was recorded automatically at 320 nm up to 2 hr. The percentage of drug released was determined as a function of time.

Kinetic assessment of the *in vitro* release of IM from the prepared pellets

In order to determine the release model which best describes the pattern of drug release, the *in vitro* release data were fitted to zero order, first order and diffusion controlled release mechanisms according to the simplified Higuchi model.

a) Zero-order Kinetic model: $C = C_0 - K_0 t$

b) First order Kinetic model: $\log C = \log C_0 - Kt/2.303$

c) Higuchi diffusion model: $Q = 2 C_0 (Dt/\pi)^{1/2}$

Where:

C_0 = initial drug concentration

C = drug concentration (released) at time t .

t = time of release

Q = amount of drug released/unit area

K_0 = zero order rate constant, K = first order rate constant

D = diffusion coefficient that was calculated according to the following equation: $D = (\text{Slope}/2C_0)^2 \pi$

The preference of a certain mechanism was based on the correlation coefficient (r) for the parameters studied, where the highest correlation coefficient is preferred for the selection of mechanism of release.

Successive evidence of the relative validity of diffusion first and zero order models obtained by analyzing the data using the following equation [10]:

$$M_t / M_{\infty} = K \cdot t^n$$

Where M_t/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 non swellable spheres, when $n=0.43$ Fick diffusion phenomenon is observed and the release rate depending on t , while $0.43 < n < 1.0$ indicates abnormal (non Fickian) transport and when $n=1$ (the release is zero order).

Solubility studies

IM aqueous solubility in the presence of different concentrations of excipients (propylene glycol - PG, polyethylene glycol - PEG 400 and Ethanol) was studied. An excess amount of IM powder was added to 10 mL of each solution in screw-capped bottle. The bottles were firmly closed and placed into the mechanical shaking water bath previously adjusted at $37^{\circ}\text{C} \pm 0.1^{\circ}\text{C}$. After equilibration has been attained (3 days), one mL aliquot sample was withdrawn and diluted to an appropriate volume with distilled water. The absorbance was measured at 320 nm and the drug concentration was calculated.

Results and Discussion

Wet massing studies using a mixer torque rheometer

In order to establish the massing binder ratio needed to reach an equilibrium torque response, wet massing experiments were performed. Figures 1-3 show the rheological profiles for Avicel PH 101 when mixed with water containing different concentrations of the used cosolvents. For the Avicel systems, different stages are passed through water, with the maximum torque occurring at the capillary state. Avicel-water system (0% cosolvent) exhibited a typical progression of mix torque rheometer (MTR) phases (pendular, funicular and capillary, respectively) in which the mean torque value increases by increasing the binder ratio. The rheometric characteristics of Avicel systems with water containing different PEG 400 concentration is displayed in Figure 1. Incorporation of PEG 400 in water resulted in reducing the mean line torque of avicel as well as shifting to higher binder ratio required for wet massing, especially with 20 and 40%w/w PEG. For water containing 60% w/w PEG, there was a shift to

higher binder ratio, but the reported mean line torque value was found to be slightly lower than that of 0% cosolvent. However, Avicel systems with water containing PG showed different profiles in which increasing the weight ratio of PG was accompanied by a significant increase in the torque value and at the same time, shifting to higher binder ratio, Figure 2. Incorporation of ethonal (Et) in water resulted in different rheometric profiles of Avicel-water systems. Increasing the weight ratio of Et was found to reduce the torque value and cause a shift of the binder ratio to slightly higher ratio, Figure 3.

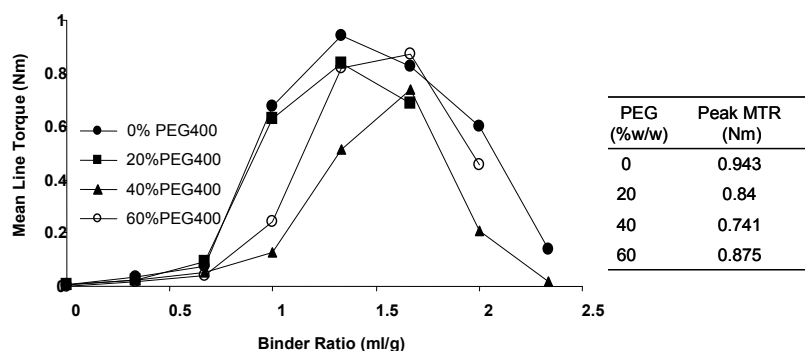


Figure 1

Effect of water containing different concentrations of PEG 400 on mean torque for Avicel® PH101 (The included table shows the effect of PEG 400 concentration on the peak torque; MTR – mix torque rheometer).

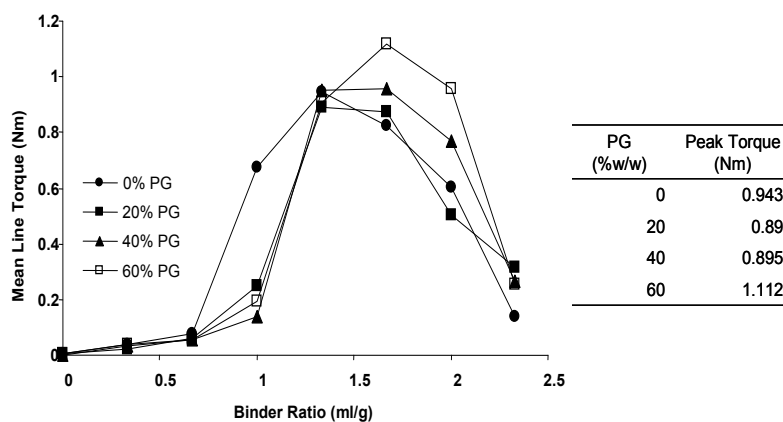


Figure 2

Effect of water containing different concentrations of PG on mean torque for Avicel® PH101 (The included table shows the effect of Propylene glycol concentration on the peak torque).

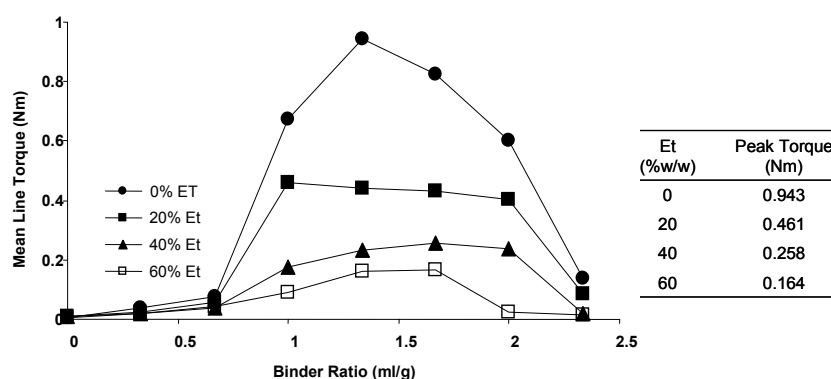


Figure 3

Effect of water containing different concentrations of ethanol on mean torque for Avicel® PH101 (The included table shows the effect of Ethanol concentration on the peak torque).

As the proportion of binder increases, the shearing forces required to drive the matrix blades through the damp mass change. In addition, by increasing the binder levels, the torque, at any particular moisture content, rises as the concentration of binder increases. In addition, it could be observed that there was an inverse relationship between the cosolvent concentration and the peak mean line torque of the wet mass. The peak torque was found to increase with increasing the concentrations of PEG and PG, while increasing Et concentration resulted in a pronounced decrease in the peak torque of the wet mass. For example, the maximum values of mean line torque recorded for 0, 20, 40 and 60% w/w Et concentrations were 0.943, 0.461, 0.258 and 0.164 Nm, respectively. Also, a good correlation was found between cosolvent concentration and the measured peak torque in the case of Et and PG ($r = 0.98$), while the relation is poorly correlated in case of PEG concentrations ($r = 0.251$), Figure 4. Any changes in the binder concentration are accompanied by corresponding changes in viscosity, and a large force is therefore necessary to drive the mixer blade through the wet mass [11]. The difference between binder concentrations on the mean line torque become obscured at very high moisture levels because of the lubrication effect of the excess binder.

According to Parker et al. [11], 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. An increase in the mean torque with the increase in the binder level at different concentrations either

a sharp or an extended peak followed by a drop in the torque as over-wetting of the powder mass occurred. Moreover, the magnitude of torque for the Avicel[®] system was not as high in the present studies as that reported where water alone was used as the wet-massing liquid (except 60% concentration of PG). This may possibly be due to better interaction of Avicel[®] with water which has been discussed thoroughly in the literature [12, 13]. Extensive hydrogen bonding, large surface area and mechanical interlocking of the irregular particles have been suggested to be the factors responsible for the excellent binding property of Avicel[®] [14]. The hydroxyl groups in the cellulose chains form intra- and intermolecular hydrogen bonds and are likely bonded with water molecules. However, PEG 400, PG and Et being less polar than water may not interact with microcrystalline cellulose (MCC) in the same way as water, i.e. they may not form hydrogen bonds to the same extent as water, and Avicel[®] may not behave like a molecular sponge for those cosolvents as it does for water alone. Instead those cosolvents, being organic solvents, may weaken or even disrupt the hydrogen bonds, replace the free bound water, and even make the surface of Avicel[®] relatively less polar [15].

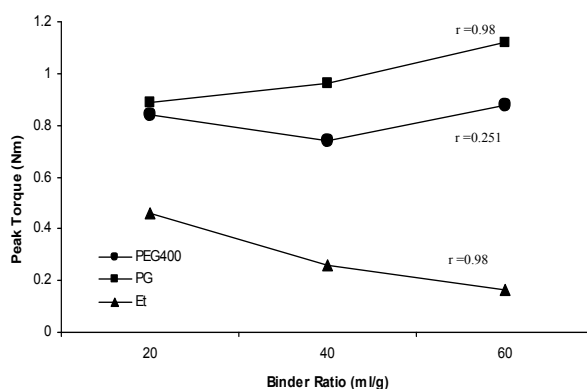


Figure 4

Effect of cosolvents concentrations on the peak torque of Avicel[®]

Size of the pellets

The mean particle size and the $d(0.1)$, $d(0.5)$ and $d(0.9)$ values of different pellet formulae loaded with IM (5%w/w as determined by laser diffractometry) are listed in Table I. Generally, the produced pellets have sizes in the range of 1000-1200 μm . The cosolvent concentration exhibited a pronounced effect on the pellets sizes. Increasing cosolvent concentration was accompanied by an increase in the sizes of the prepared pellets as in the case of PEG 400 and Et.

Table I

The mean particle size and the d(0.1), d(0.5) and d(0.9) values of different pellet formulae loaded with IM (5%w/w) as determined by laser diffractometry.

Pellets Formulae	Mean (μm)	d (0.1) μm	d (0.5) μm	d (0.9) μm
F#1 (no excipient)	989.14	746.06	1018.21	1391.29
F#2(20% PEG 400)	985.121	727.16	1021.66	1421.47
F#3(40% PEG 400)	1008.14	730.0	1053.37	1488.77
F#4(60% PEG 400)	1130.30	869.37	1162.46	1528.82
F#5(20% PG)	1150.35	833.40	1127.53	1504.37
F#6(40% PG)	1030.27	790.30	1090.16	1490.30
F#7(60% PG)	1054.28	670.39	1009.04	1509.08
F#8(20% Et)	1039.90	707.79	1006.09	1421.21
F#9(40% Et)	1146.75	834.62	1123.59	1494.33
F#10(60% Et)	1173.81	869.36	1150.78	1509.97

Drug content

The drug content data of 5% IM-loaded pellets are listed in Table II. It is clearly seen that the addition of cosolvents PEG and PG to water during pellet preparation lowered the drug content. This might be due to the fact that these two cosolvents did not evaporate during pellet drying. On the other hand, pellets formulated with water or water-Et exhibited a drug content similar to the theoretical value.

Table II

Indomethacin content, dissolution efficiency at 30 minutes ($DE_{30\%}$) and relative dissolution rate at 30 minutes (RDR_{30}) of Indomethacin from its- loaded Avicel PH101 pellets.

System	IM Content (%w/w)	$DE_{30\%}$	RDR_{30}
F#1 (no excipient)	5.29 $\pm$ 0.0	1.98	—
F#2(20% PEG 400)	4.59 $\pm$ 0.37	9.26	4.67
F#3(40% PEG 400)	3.24 $\pm$ 0.31	15.52	7.82
F#4(60% PEG 400)	2.73 $\pm$ 0.10	16.73	8.44
F#5(20% PG)	5.00 $\pm$ 0.30	3.22	1.62
F#6(40% PG)	3.44 $\pm$ 0.07	8.23	4.15
F#7(60% PG)	2.86 $\pm$ 0.49	8.44	4.46
F#8(20% Et)	5.24 $\pm$ 0.138	5.356	2.69
F#9(40% Et)	5.21 $\pm$ 0.0	5.796	2.92
F#10(60% Et)	5.08 $\pm$ 0.31	6.382	3.22

Morphological analysis

Scanning electron micrographs of IM pellets containing 60% concentration of each cosolvent (compared to the formula without excipients) are displayed in figure 5. The resulting pellets were spherical

and intact in shape. The pellets showed slightly rough surfaces. The images of the interior of the pellets revealed similar textures except for the pellets prepared using PEG 400 in which the drug crystallinity was significantly inhibited. The inclusion of PEG 400 and PG improved the sphericity and smoothness of the pellet surfaces.

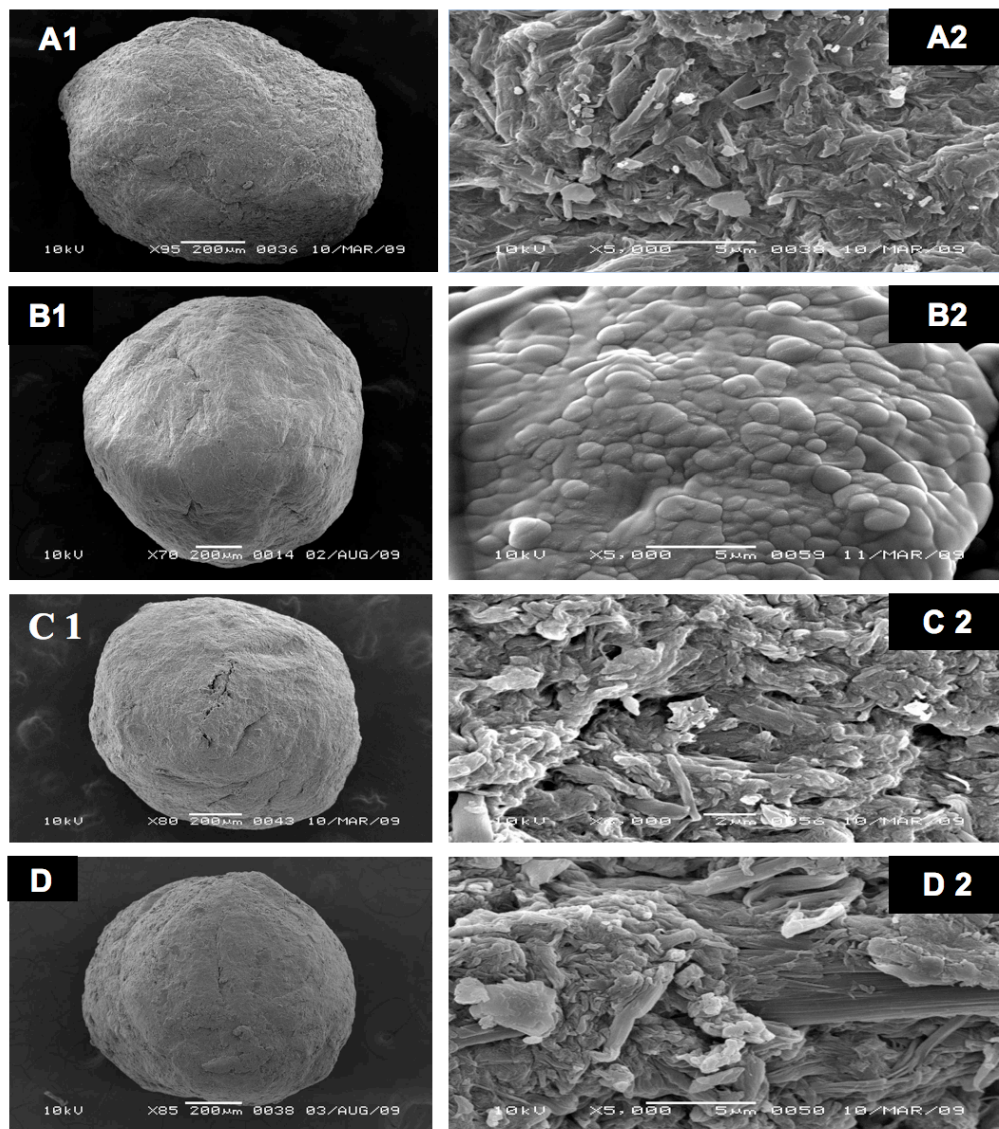


Figure 5

Scanning electron micrographs of the pellets and their surfaces prepared with: A; water only, B; 60% w/w PEG400, C; 60% w/w PG and D; 60% w/w Et, as low magnification, 1, and high magnification, 2.

Differential scanning calorimetry (DSC)

In order to shed a light on the possibility of solid state changes of IM with Avicel[®] and either PEG 400 or PG, DSC was performed on physical mixtures of 1:1:1 weight ratio as well as the individual components. IM displayed an endothermic peak at 160.26°C corresponding to its melting point with heat of fusion about -95.09 J/g, figure 6 A. On the other hand, Avicel[®], has no endothermic peak, figure 6 E. Thermal traces for the physical mixture of drug with Avicel[®] in 1:1 ratio showed a less intense peak at 159.9°C with heat of fusion about -49.2 J/g. Also the physical mixture of drug, Avicel and ethanol in 1:1:1 ratio appeared at 159.52°C with heat of fusion -48.2 J/g. This indicates, that ethanol has no effect and may be evaporated during mixing. On the other hand, for the mixture of drug, Avicel[®] and PEG 400 (1:1:1) the thermogram shows the disappearance of the characteristic peak of the drug. This may be due to the dissolving of the drug in PEG, figure 6 D.

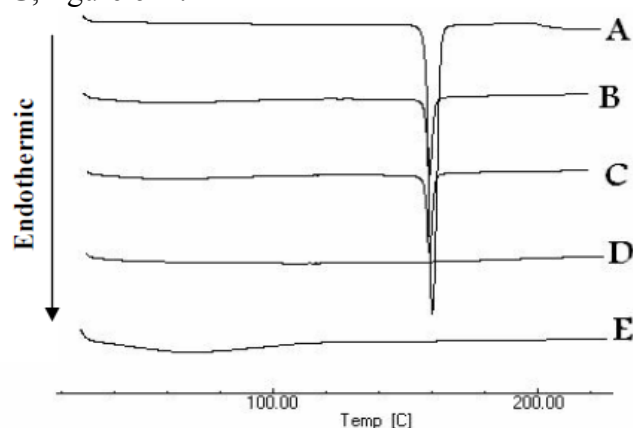


Figure 6

DSC curves of IM (A), IM: Avicel[®] 101 (1:1) physical mixture (B), IM: Avicel[®]: Ethanol (1: 1: 1) physical mixture (C), IM: Avicel[®]: PEG 400 (1:1:1) physical mixture (D) and Avicel[®] (E).

Some authors reported that drugs dissolve in PEG and the characteristic peaks of these drugs disappeared [16, 17]. These results suggested that IM was completely dissolved in PEG. On the other hand, IM-Avicel-PG (1: 1: 1) physical mixture showed an abnormal DSC pattern at the scanning region. This phenomenon might be related to the ability of PG to promote fragmentation of Avicel into small crystallites, which might result in retarding the drug release [18]. This finding is confirmed by the porous aggregates of microcrystals as shown in the electron micrograph of

Avicel[®] pellets formulated using 60% PG. This finding was also conformed by FT-IR studies on IM-Avicel-PG (1: 1: 1) physical mixture (data not shown). IM has two characteristic absorption bands at 1717 and 1692 cm⁻¹. The 1717 cm⁻¹ absorption band is assigned to the carbonyl stretch of the carboxylic acid dimer. The 1692 cm⁻¹ absorption band is assumed to be the carbonyl stretch of the non-protonated amide. These characteristic IM absorption bands were not changed in the previously mentioned physical mixture indicating the absence of chemical interactions among IM, PG and Avicel[®].

Drug release studies

The results of IM release in phosphate buffer pH 6.8 are presented in figures 7-9. It is clear that the incorporation of the used cosolvents has lead to an increase in the dissolution rate of IM. The relative dissolution rate of IM after 30 minutes (RDR₃₀) using 60% concentrations of PEG, PG and Et was enhanced at 8.44, 4.46 and 3.22, respectively. In addition the dissolution efficiency of IM after 30 minutes (DE_{30%}) showed a pronounced increase upon the incorporation of cosolvents during pellet manufacture. DE_{30%} values of IM were recorded to be 16.73, 8.44 and 6.38 for the pellets containing 60 % concentrations of PEG, PG and Et, respectively, compared to 1.98 for the pellets containing no excipient, table II. Also, the rate of IM release was increased by increasing the cosolvent concentration. This could be attributed to the increase in IM solubility as shown in table III, and DSC results in figure 6. The exception of that is ethanol, as it is volatile and expected to evaporate upon drying of pellets, which will lead to precipitation of IM again, so it shows the lowest enhancement in IM release with insignificant effect of its concentration. Obviously, the low solubility of IM will slow its release rate, since it should have the slowest dissolution rate as seen in table II and figures 7-9.

Table III

Indomethacin Solubility in different cosolvents concentrations at 37°C.

Cosolvent %w/w	Solubility (mg/mL)
Water	0.028
20% PEG 400	0.041
40% PEG 400	0.285
60% PEG 400	1.929
20% PG	0.036
40% PG	0.102
60% PG	0.563
20% Et	0.070
40% Et	0.802
60% Et	1.998

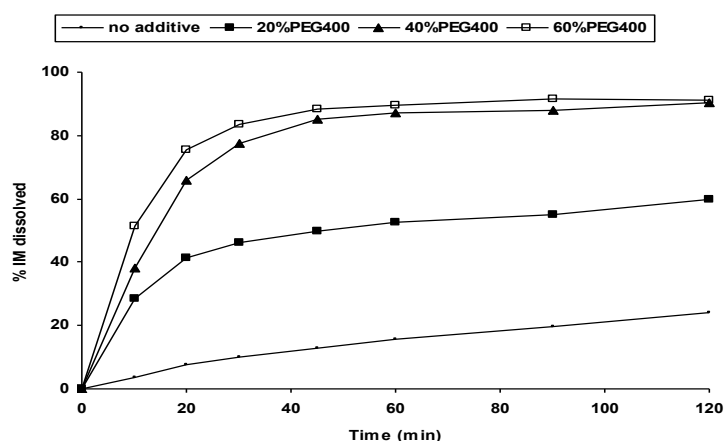


Figure 7

Effect of different concentrations of PEG 400 on the *in vitro* release profiles of Avicel[®] PH101 pellets containing 5% of Indomethacin.

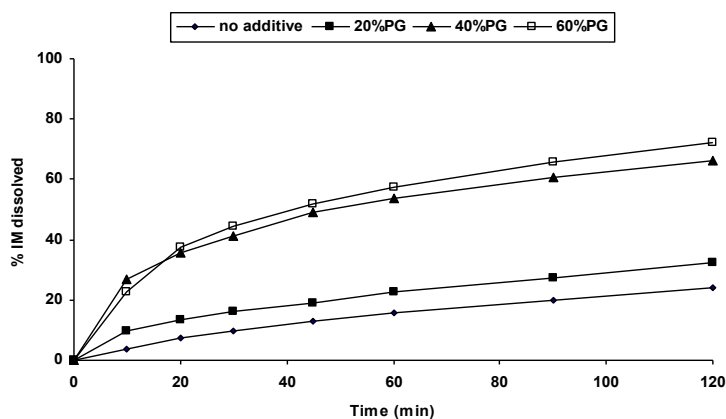


Figure 8

Effect of different concentrations of PG on the *in vitro* release profiles of Avicel[®] PH101 pellets containing 5% of Indomethacin.

It was observed that the pellets did not disintegrate in the dissolution medium even after 8 hours. Because neither swelling nor erosion of the pellet matrix was observed, the authors concluded that IM release was mainly a diffusion controlled process. In such systems, the diffusion and hence the drug release depends on the drug solubility in the pellets. Similar observations were previously reported by Debunne *et al.* [19], for piroxicam release from Avicel[®] pellets.

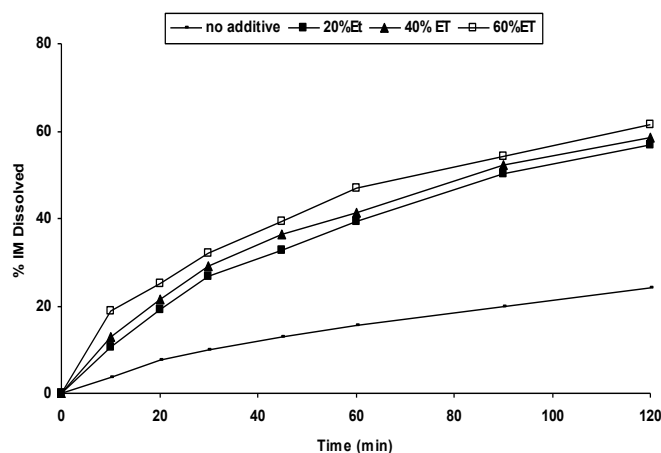


Figure 9

Effect of different concentrations of Et on the *in vitro* release profiles of Avicel® PH101 pellets containing 5% of Indomethacin.

Kinetic assessment of the *in vitro* release of IM from the pellets

The correlation coefficient (r), and the release exponent (n), of fitting the release data to zero, first, Higuchi diffusion and Peppas model for spheres are listed in Table 4. The higher correlation coefficient (r) values for Higuchi diffusion model obtained in most formulae indicate a diffusion mechanism for IM release. The diffusion rate increases with the increase in IM solubility as indicated by the increase in n values indicating an abnormal (non-Fickian) transport until it approaches the value of one in the case of formulae containing 40 and 60% PEG, which means a zero order model, i. e., the release becoming independent on time. The increase in diffusion and release rate with increase in IM solubility could be attributed to the formation of pores and channels in the pellets as a result of faster IM dissolution.

Table IV
Kinetic modeling for the prepared Indomethacin pellets.

Formula no.	Correlation coefficient			n value
	Zero order	First order	Higuchi model	
F# 1	0.9803	0.9876	0.9907	0.678
F# 2	0.7852	0.8567	0.9349	0.828
F# 3	0.9748	0.8786	0.9102	1.012
F# 4	0.9432	0.8316	0.8720	1.041
F# 5	0.9526	0.9702	0.9991	0.704
F# 6	0.8843	0.9520	0.9846	0.849
F# 7	0.9008	0.9685	0.9889	0.879
F# 8	0.9676	0.99131	0.9942	0.849
F# 9	0.9573	0.9867	0.9966	0.849
F# 10	0.9413	0.9804	0.9984	0.842

Conclusion

In conclusion, the addition of cosolvents to the manufactured indomethacin (IM) pellets caused enhanced drug dissolution rates which might be beneficial in lowering the risk of side effects as an advantage of the pellets as drug delivery system. In addition, the use of mix torque rheometer (MTR) enables the users to quickly, easily and in a repeatable way quantify the rheology of wet masses prior to granulation or spheronization.

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