The aim of this study was to develop a new extended release capsules of indomethacin. The formulation has been prepared to enhance its dissolution which could provide better oral absorption of indomethacin (IND). Therefore, the effects of the component nature, their proportion in the release rate and the dissolution mechanism were investigated. Extended release capsules of IND were prepared by physical mixing using plasdone (PVP K-90) and compritol-HD5 ATO (Comp) at various drug-polymer ratios. Flow properties of the physical mixtures were evaluated by calculation of the Carr’s index, angle of repose and Hausner ratio. According to the United States Pharmacopeial (USP) drug release criteria of IND extend release capsules, the release results of formulations F2 and F3 were found to be similar to the USP (P < 0.05). Certain mathematical models were used for evaluation of release profiles and the results supported by multiple regression analysis. It was observed that the best-fit model to determine the mechanism of the formulation which has shown the highest release was Higuchi square-root of time model ($r^2 = 0.969$). According to the dissolution results, dissolution efficiency, relative dissolution rate and mean dissolution time were also evaluated. The results of the study indicated that new extended release hard gelatin capsules can be a promising alternative for the other oral formulations of IND.

Key words: Indomethacin, drug release, kinetic evaluation, hard gelatine capsule, stability, multiple regression analysis.

INTRODUCTION

Generally known as an analgesic and antipyretic drug, Indomethacin (IND) refers to the compound 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. It should be used attentively unlike any simple analgesic due to its potential adverse effects (Goodman and Gilman, 1980). Its areas of use could be listed as follows: Treating gout, rheumatoid arthritis, relieving pain, inhibiting cyclo-oxygenase with a diminishing effect on prostaglandia synthesis and also on body temperature of febric patients (Taha, 2009; Taha et al., 2009). Gastric output of prostaglandins and intestinal maintenance of mucoid secretion on gastrointestinal canal facing is inhibited by IND. Thus, as a result of its use, peptic ulcers are observed to occur, which is a common occasion with all other nonselective cyclo-oxygenase inhibitor drugs (Eis et al., 1998; Taha, 2009). Therefore it is thought that new delivery systems can be devised to overcome the side effects by controlling the drug release (Friend, 2005; Karasulu et al., 2003). Additionally, for poor soluble highly permeable (Class II) drugs, such as IND, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract (Nokhodchi et al., 2005). Moreover, solubility and dissolution behavior of a drug is one of the key determinants of its oral bioavability. Indomethacin
may show low and erratic oral bioavailability due to poor dissolution of the drug in the fluids of the gastrointestinal tract (Alsaidan et al., 1998; Elchidana and Deshpande, 1999). In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists (Dehghan and Jafar, 2006). Furthermore, Indomethacin is a drug possessing a safety risk during usage. Depending on this data, United States Pharmacopeial (USP) has some restrictions on extended release indomethacin preparations relating the in vitro drug release versus time. Apart from this, IND follows linear pharmacokinetics. These features allow the great development of a modified-release dosage form in which large variations in plasma concentration are reduced. The use of the sustained-release formulation is a more convenient way of prescribing indomethacin and is especially suited for patients who tend to be non compliant.

Solid dosage forms are important for oral administration because they have a high-metering accuracy, their application is easy and their stability is pretty good. Drug-polymer solid dispersion can improve the dissolution rate of drugs and lead to higher bioavailability (Lin and Huang, 2010). Thus, a capsule formulation often is in the industry in the first dosage form for early clinical studies. Moreover, capsules improve drug stability because the content is tightly enclosed by the capsule shell and thus protected from oxygen, humidity and light (Edgar et al., 2001).

The present study was designed to prepare a new extended release capsules of IND and to investigate the influence of plasdone (PVP K-90) as a hydrophilic polymer, compritol-HD5 ATO (Comp) as a lipophilic polymer on the in vitro dissolution of IND from hard gelatin capsules and to explore the mechanism of drug release through mathematical modeling of dissolution data for all formulations. Dissolution efficiency (DE), relative dissolution rate (RDR) and mean dissolution time (MDT) parameters were used to also evaluate the dissolution profiles of extended release IND capsules. In addition, multiple regression analyses have been performed to develop and evaluate a novel formulation of IND for oral delivery. Apart from this, the stability of all formulations in terms of drug content was analyzed during 3 months in order to have a suitable extended release IND formulation.

MATERIALS AND METHODS

Chemicals

Indomethacin was a gift from Deva Holding Inc. (Turkey). Plasdone (PVP K-90) was supplied by ISP, Tech. Inc. (USA), compritol-HD5 ATO was obtained from Gattefosse (France). Aerosil and avicel pH-101 were given kindly from Santafarma Pharmaceuticals (Turkey). All other chemicals and solvents were of analytical grade.

Preparation of extended release capsules

Physical mixture

A series of extended release capsules of IND were prepared in fixed concentration of IND (75 mg) and varying concentrations of plasdone (PVP K-90) and compritol-HD5 ATO (Comp). Each mixture were added 10% avicel pH 101 and 5% aerosil. Then all materials meant for mixing were taken into a cubic mixer at 10 min. The resultant physical mixtures were passed through 35-mesh sieve. The prepared mixtures were sealed and stored in desiccator until used for further studies. All samples which were used in dissolution studies, were analysed for drug content. Before the dissolution studies, these powders were hand filled into zero-size hard gelatin capsules using capsule filling apparatus. Hard gelatin capsule formulations are shown in Table 1.

Drug content estimation

An accurately weighed quantity of physical mixtures was transferred to a 100 ml volumetric flask containing 10 ml of ethanol and dissolved. The volume was made up to 100 ml with phosphate buffer pH 6.2. The solution was filtered and the absorbance was measured after suitable dilutions by using UV-Spectrophotometer at 320 nm (Lakshmi Narasaiah et al., 2011).

Determination of particle size distribution

Particle size analysis was carried out to determine mean particle size of the formulations by Master Sizer 3000 Aero S (Malvern Instruments Ltd. UK). Tests were performed in triplicate.

Determination of flow properties of the physical mixtures

Carr’s index

A pre-weighed quantity of dry powder was placed in a graduated 10 ml cylinder. The apparent volume occupied by the powder was then noted before and after the application of 1250 taps to the cylinder using a tap density tester (Varian, Inc. USA). Carr’s index formulas are calculated according to Equation (1) (Khan et al., 2012; Staniforth et al., 1996).

\[ \text{Carr's index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \] (1)

Angle of repose

The angle of repose can be defined as the constant three dimensional angle measured relatively to the horizontal base, assumed by a cone-like pile of material formed when the powder is passed through a funnel-like container (Khan et al., 2012; Rios, 2006; Abdullah and Geldart, 1999; Carr, 1965). Angle of repose of the powder material was calculated by using the formula Equation (2):

\[ \theta = \tan \left( \frac{h}{r} \right) \] (2)

Where \( h \) = height of the pile, \( r \) = radius.

Hausner ratio

The basic procedure is to measure the unsettled apparent
volume, $V_0$, and the final tap volume, $V_f$, of the powder tapping the material until no further volume changes occur. The Hausner ratio was calculated according to Equation (3) (Khan et al., 2012).

$$\text{Hausner ratio} = \frac{V_f}{V_0}$$  \hspace{1cm} (3)

Differential scanning calorimetry

Formulations F1-F5 were weighed and hermetically sealed in flat bottomed aluminum pan with crimped on lid. The pans were positioned on sample pan holder of a Perkin-Elmer DSC 8000. The samples were heated in an atmosphere of nitrogen at a flow rate of 20 m/min over a temperature range of 0 to 300°C with a constant heating rate of 10°C/min.

Drug release studies

The dissolution rates of the extended release capsules of indomethacin were measured by using USP XXIII apparatus I (rotating basket). The dissolution medium was 900 ml phosphate buffer with a pH 6.2 kept at 37 ± 1°C according to the USP drug release Test 2 criteria (Table 3). Samples of 5 ml were withdrawn at specified time intervals and analyzed spectrophotometrically at 320 nm using Shimadzu 160-A spectrometer. The samples withdrawn were replaced by fresh buffer solution. Each dissolution study was carried out twelve times and mean values were calculated.

Determination of mean dissolution time and dissolution efficiency

Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time $t$ and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (Equation 4) (Khan, 1975). Mean dissolution time (MDT) was employed for comparison of dissolution profiles (Polli et al., 1997), calculated according to Equation (5).

$$D.E. = \frac{\int_{0}^{\infty} \Delta y \, dt}{y_{100} \ast t} \times 100\%$$  \hspace{1cm} (4)

Where $y$ is the drug percent dissolved at time $t$.

$$MDT = \frac{\sum_{j=1}^{n} \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$$  \hspace{1cm} (5)

Where $j$ is the sample number, $n$ is the number of dissolution sample times, $t_j$ is the time at midpoint between $t_i$ and $t_{i+1}$ (easily calculated with the expression $(t_i + t_{i+1})/2$ and $\Delta M_j$ is the additional amount of drug dissolved between $t_i$ and $t_{i+1}$. Relative dissolution rate (RDR) is the ratio between amount of drug dissolved from optimized formulation and that dissolved from the conventional formulation (Gurrapu et al., 2012).

The analysis of release profiles

Kinetic evaluation

Kinetic evaluation of certain release from capsules were applied using a computer based kinetic programme. Three mathematical models (Zero order model, First order model, Higuchi square root of time model) were chosen to describe the release patterns of the indomethacin extended release capsules (Ege et al., 2001). The large value of the coefficient of determination ($r^2$) indicated a superiority of the dissolution profile fitting to mathematical models.

Determination of release mechanism

Determination of indomethacin release from capsules were estimated (Ozyazici et al., 2006; Ritger and Peppas, 1987) by the Korsemeyer-Peppas Equation (6):

$$Mt/M_{\infty} = k t^n$$  \hspace{1cm} (6)

$Mt/M_{\infty}$; the fraction of drug released, $t$; released time, $k$; release rate constant.

Dissolution stability studies of extend release IND capsules

For dissolution stability evaluation, extended release capsules of IND were investigated over 3 months under different temperature and relative humidity (RH) conditions at 25 ± 2°C, 65% RH and 40 ± 2°C, 75% RH. Samples were withdrawn at various time points and analyzed for dissolution using the methods described above.

Statistical analysis

Statistical analyses were conducted by one-way analysis of variance (ANOVA) using target significance levels of 0.05 ($P < 0.05$). Multiple regression analysis was undertaken using a computer program SPSS 10.0.

RESULTS AND DISCUSSION

Determination of flow properties of the physical mixtures

The drug content in physical mixtures were found to be in the range of 97.3 to 99.4%. The effect of formulation conditions on the flow properties of IND capsules are shown in Table 2 (Staniforth, 1996). The particle size affects flow rates and angle of repose. F4 presented higher particle size average than F2 and F3. Based on the obtained results, it can be suggested that the amount of the Comp in the formulations could be affected by the angle of repose. The flowability of IND powder was poorer than the flowability of pysical mixtures. Physical mixtures containing polyvinylpyrrollidone (PVP)
Table 2. Flow properties of extend release Indomethacin capsules.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose</td>
<td>75.37±6.74</td>
<td>62.97±2.79</td>
<td>49.34±2.71</td>
<td>35.82±3.19</td>
<td>66.70±7.45</td>
</tr>
<tr>
<td>Carr’s index</td>
<td>89.76±0.44</td>
<td>89.76±0.62</td>
<td>91.60±0.38</td>
<td>86.48±0.45</td>
<td>84.71±1.75</td>
</tr>
<tr>
<td>Hausner ratio</td>
<td>9.78±0.42</td>
<td>9.77±0.61</td>
<td>11.92±0.55</td>
<td>7.40±0.24</td>
<td>6.59±0.76</td>
</tr>
<tr>
<td>Particle size</td>
<td>3.61±0.01</td>
<td>5.71±0.13</td>
<td>7.34±0.50</td>
<td>9.00±0.51</td>
<td>5.62±0.41</td>
</tr>
</tbody>
</table>

Table 3. The percentages of indomethacin dissolved in a phosphate buffer of pH 6.2 and USP XXIII criteria of indomethacin extend release capsules according to time.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Formulations</th>
<th>USP XXIII criteria</th>
<th>Amount dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
<td>F2</td>
<td>F3</td>
</tr>
<tr>
<td>1</td>
<td>27.48±0.01</td>
<td>23.71±0.08</td>
<td>19.68±0.07</td>
</tr>
<tr>
<td>2</td>
<td>36.67±0.04</td>
<td>45.74±0.05</td>
<td>37.96±0.06</td>
</tr>
<tr>
<td>4</td>
<td>49.20±0.07</td>
<td>63.96±0.06</td>
<td>53.09±0.02</td>
</tr>
<tr>
<td>12</td>
<td>74.51±0.03</td>
<td>99.22±0.04</td>
<td>82.35±0.05</td>
</tr>
</tbody>
</table>

possessed slightly higher flow rate than formulations including only Comp. This may be responsible for the high bulk density obtained for IND including PVP. Also, the angle of repose is mostly affected by the presence of PVP. The values of Hauser ratio and Carr’s index obtained for the formulations were found to be in conformity with their flow rates. Both the Carr’s index and Hauser ratio indicated poor flow property in all formulations (Ozyazici et al., 1996). To sum up, as the particle size decreased, the cohesion of the particles increased and the inter-particulate forces between the powders became stronger. Therefore the high percentage of smaller particles displayed an influence on IND’s lack of flowability.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) studies have been conducted to understand the role of the physical interaction among PVP, Comp and IND. To explain more about the current studies, it is crucial to examine the DSC thermogram of IND, PVP, Comp, avicel, aerosil and all formulations which are exhibited in Figure 1. The DSC curve shows IND has an endothermic peak at 164.9°C corresponding to its melting and indicating its crystalline nature. Additionally, Comp showed a single endothermal peak at 64.8°C and PVP showed at 184.7°C. Melting of IND can be observed in physical mixtures of drug: PVP and Comp. The DSC thermogram of the physical mixtures showed a slight change in melting peak of the IND, suggesting the alteration in crystallinity of IND. Also, a peak intensity corresponding to the drug has decreased in all thermograms. It can be seen more conspicuous in those with higher proportions of PVP and Comp. In the study, the heat of fusion pertaining to IND has been higher (478.8 J/g) than to all other formulations. Should the results be mentioned, a decrease has been monitored in the crystallinity of IND in the presence of a higher amount of PVP and Comp (Wu et al., 2009).

Drug release studies

In vitro drug release was determined using the USP basket method. Release profiles of the extended release capsules containing IND were showed in Figure 2. The percentages of indomethacin dissolved in phosphate buffer of pH 6.2 according to USP XXIII criteria were given in Table 3.

When the dissolution results have been compared with USP XXIII criteria, it was observed that the release results of F2 and F3 capsule formulations were similar to the USP criteria (Table 3). The dissolution results indicate that the release of F5 formulation including large amount of PVP is faster than pure IND. This may be due to the presence of PVP, which appears to facilitate the dissolution of IND as it is more soluble and could hydrate in an easier manner and also possibly due to the increase in its wettability (Oliverira et al., 2013). An increase in the concentration of PVP may prevent drug aggregation or raise drug wettability resulting in a higher solubility (Oliveria et al., 2013). For this reason, it was observed that F5 formulation has shown faster release profiles in early stage of dissolution compared to F2, F3 and F4 formulations. Moreover, dissolution results showed that the formulations including Comp takes longer compared to formulations with PVP. Hydrophobic interaction between IND and Comp appears to possess a key function for a slower diffusion process in the capsule formulations (Roberts et al., 2012). Additionally, multiple regression analysis was applied to the results obtained...
The analysis of release profiles

Release profiles have been evaluated with the help of various mathematical models. According to the analysis of all mathematical models, it is clearly seen that Higuchi square-root of time model show obviously a better fit for IND extented release capsules (Orelli and Leuenberger, 2004) (Table 4). The Higuchi square root equation describes that the rate of drug release from systems is related to the rate of drug diffusion (Ertan et al., 2000; Iravani et al., 2011). This data confirms that the extended release of IND capsule formulations have been generated in a Higuchian diffusion fashion, which is statistically proven by the release curves in comparison with their correlation coefficients. To mention the formulations shortly, when F2 and F3 formulations are released in dissolution medium pH 6.2 phosphate buffer, the slope value arrives at its highest point. Formulations F4 and F5 as physical mixture of IND: PVP provided faster release than individual IND (F1) and physical mixture of IND: Comp (F2 and F3) in dissolution media.

Dissolution mechanism of the formulations has been shown to be significantly diffusion-controlled during which the high amount of PVP and Comp is the main factor to control the dissolution rate. Furthermore, dissolution release data were studied using Korsmeyer-Peppas release model. The release exponent (n) values from the power law Peppas equation have provided an insight to understand the release mechanism from the dosage form (Pritchard et al., 2010). Formulation F5 exhibited anomalous (non-Fickian transport) diffusion mechanism with "n" value 0.916 (Table 4). This suggests that some level of swelling must be operating within the system, causing deviation from the Fickian release because of higher amount of PVP. In the first 2 h, F4 and F5 formulations containing PVP showed higher release rate than the other formulations leading to a boost at the wettability and an acceleration of solvent penetration in the capsules to dissolve the drug thereby more rapidly, and they get diffused out (Mohana Raghava Srivalli et al., 2013). The "n" values of F2, F3 and F4 formulations have been found to be more than 1. This result indicates that the drug release from the polymer matrix formulations suggests super Case II transport, that is the mechanism of drug release has been administered by both diffusion and polymer relaxation (Apu et al., 2009).

As a foot-note to the above, the improvement in dissolution characteristics of a drug is described in terms of dissolution efficiency (DE) and RDR. In line with the outcome of the study, the RDR of 1 h have been acquired more slowly from F2, F3 and F4 formulations owing to the poor wettability of compounds compared to F5 formulation prepared with a high concentration level of PVP (Table 5). After 1 h, the wettability starts to become visible and within 2 to 6 h, RDRs of all formulations appear to be higher by comparison with F1 formulation. When RDR is greater than 1, this leads us to a dissolution enhancement. It is observed that all formulations were more than 1 values (Table 5) (Gurrapu et al., 2012). When formulations including Comp increase wettability, dissolution efficiency of formulations increased in the meantime. It is noticeable as given in Table 5 that the value of DE% 2 h was augmented for F2 and F3 formulations. Consequently, the percent dissolution efficiencies are noted considerably higher for F2, F3, F4
Table 4. Mathematical models of extended release capsules of indomethacin obtained after fitting the drug release data.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi</th>
<th>Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>r²</td>
<td>Slope</td>
<td>r²</td>
</tr>
<tr>
<td>F1</td>
<td>5.183</td>
<td>0.886</td>
<td>-0.104</td>
<td>0.973</td>
</tr>
<tr>
<td>F2</td>
<td>7.788</td>
<td>0.867</td>
<td>-0.351</td>
<td>0.951</td>
</tr>
<tr>
<td>F3</td>
<td>6.464</td>
<td>0.867</td>
<td>-0.146</td>
<td>0.976</td>
</tr>
<tr>
<td>F4</td>
<td>6.791</td>
<td>0.693</td>
<td>-0.209</td>
<td>0.866</td>
</tr>
<tr>
<td>F5</td>
<td>6.258</td>
<td>0.724</td>
<td>-0.153</td>
<td>0.891</td>
</tr>
</tbody>
</table>

Figure 2. Comparison of release profiles using PVP and Comp by physical mixtures with pure drug (F1) (n=12). Error bars smaller than the symbols are not shown.

Figure 3. Response surface plot of the effect of PVP concentration and time on drug release percentage (a), and PVP concentration and Comp concentration on drug release percentage (b), and Comp concentration and time on drug release percentage (c).
Table 5. Dissolution parameters of extended release capsules of indomethacin.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>31.45</td>
</tr>
<tr>
<td>DE (%)</td>
<td>13.08</td>
</tr>
<tr>
<td>RDR</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>46.12</td>
</tr>
<tr>
<td>DE (%)</td>
<td>22.58</td>
</tr>
<tr>
<td>RDR</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>79.39</td>
</tr>
<tr>
<td>DE (%)</td>
<td>32.92</td>
</tr>
<tr>
<td>RDR</td>
<td>1.00</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>115.21</td>
</tr>
<tr>
<td>DE (%)</td>
<td>39.85</td>
</tr>
<tr>
<td>RDR</td>
<td>1.00</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>MDT</td>
<td>140.14</td>
</tr>
<tr>
<td>DE (%)</td>
<td>45.25</td>
</tr>
<tr>
<td>RDR</td>
<td>1.00</td>
</tr>
</tbody>
</table>

and F5 formulations compared to F1 formulation after 6 h (P < 0.01) (Table 5).

At this point, it is necessary to state that MDT value is generally used to characterize the drug release rate from a dosage form and it indicates the drug release retarding efficiency of a polymer (Mohana Raghava Srivalli et al., 2013). MDT reflects the period of time for the drug to dissolve and is the first statistical data for the cumulative dissolution process that provides an accurate drug release rate (Elchidana and Deshpande, 1999). A higher MDT value indicates a greater drug retarding ability. In terms of the study, the MDT values of all formulations at 1 h were attested to be similar, which suggested a similar dissolution rate compared to F1 (IND powder). Furthermore, provided that dissolution release profiles of F4 and F5 formulations have come to a steady state after 8 h. Therefore, RDR, DE and MDT values incident to none of the formulation were taken under evaluation (Figure 1). Overall increase in the dissolution performance of the optimized formulations described in terms of dissolution parameters (MDT, DE, RDR) in comparison with F1 formulation could be due to increased wetting properties, solubility and enhanced surface area of drug particles (Kakran et al., 2012; Seedher and Kaur, 2003).

Stability of indomethacin capsules

The stability of new extended release Indomethacin capsules was investigated in terms of drug content in a time period of 3 months and the values were calculated to be at 25 ± 2°C, 65% RH and 40 ± 2°C, 75% RH. Dissolution data of stability studies on IND capsule formulations are presented at Table 6. No significant alteration was observed for the drug content values of the formulations (P > 0.05). The stability study has indicated that all formulations were stable at 25 ± 2°C, 65 ± 5% RH and 40 ± 2°C, 75 ± 5% RH. Herewith, the results showed that extended release IND capsule formulations could be employed as effective replacements for the conventional marketing products of IND which are currently used in the pharmaceutical area.

Conclusion

Taken together, in this study, the effect of component nature and the proportion at the release rate and the mechanism were investigated by virtue of IND extended release capsules. It was found that release results of formulations F2 and F3 were detected to be proper to the USP Drug Release Criteria. By this means, safety of the drug was improved by the usage of this new capsules. It would be an ideal formulation for 12 h release profile, they were considered to be suitable for prescribing the formulations for twice a day administration. It also indicates that these capsule formulations can be an effective dosage form for modified release formulations.
In conclusion, these findings suggest that the formulations F2 and F3 could be promising candidates for oral sustained drug delivery systems, especially for poorly soluble drugs such as IND.

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