

## Reciprocal Powered Time Model for Release Kinetic Analysis of Ibuprofen Solid Dispersions in Oleaster Powder, Microcrystalline Cellulose and Crospovidone

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**ABSTRACT- Purpose.** A physically sound derivation for reciprocal powered time (RPT) model for kinetic of drug release is given. In order to enhance ibuprofen dissolution, its solid dispersions (SDs) prepared by cogrinding technique using crospovidone (CP), microcrystalline cellulose (MC) and *Elaeagnus angostifolia* fruit powder, oleaster powder (OP) the vernacular name of which is senjed powder as a novel carrier and the model applied to the drug release data. **Methods.** The drug cogrounds with the carriers were prepared and subjected to the dissolution studies. For elucidation of observed in vitro differences, FT-IR spectroscopy, X-ray diffraction patterns, DSC thermograms and laser particle size measurement were conducted. **Results.** All drug release data fitted very well to newly derived RPT model. The efficiency of the carriers for dissolution enhancement was in the order of: CP>OP>MC. The corresponding release kinetic parameter derived from the model,  $t_{50\%}$  (time required for 50% dissolution) for the carrier to drug ratio 2:1 were 2.7, 10.2 and 12.6 min, respectively. The efficiency of novel carrier, OP, was between CP and MC. FT-IR showed no interaction between the carriers and drug. The DSC thermograms and X-ray diffraction patterns revealed a slight reduced crystallinity in the SDs. Also grinding reduced mean particle size of drug from 150.7 to 44.4  $\mu\text{m}$ . **Conclusion.** An improved derivation for RPT model was provided which the parameter of the model,  $t_{50\%}$ , unlike to previous derivations was related to the most important property of the drug i.e. its solubility. The model described very well drug release kinetics from the solid dispersions. Cogrinding was an effective technique in enhancing dissolution rate of ibuprofen. *Elaeagnus angostifolia* fruit powder was suggested as a novel potential hydrophilic carrier in preparing solid dispersion of ibuprofen.

## INTRODUCTION

The kinetic models are helpful in elucidating release mechanisms as well as factors affecting drug release. Other advantages of the kinetic models are to represent several release data with one or two parameters which can be of use in the *in vitro*- *in vivo* correlation and comparison of different delivery systems of a drug. Recently a novel kinetic model named as reciprocal powered time (RPT) model has been applied for describing drug release rate from solid dispersions (1) and nanoparticles (2). In the previous reports (1, 2) the most important property of drug, solubility, which

is directly related to release rate was canceled out in the process of derivation of the model. Thus the present work provides a physically sound derivation to establish the relation between  $t_{50\%}$  and the solubility. To this end, solid dispersions (SDs) of

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ibuprofen in *Elaeagnus angostifolia* fruit, oleaster powder (OP), microcrystalline cellulose (MC) and crospovidone (CP) were prepared for the purpose of enhancing its dissolution rate and new RPT model was applied to the drug release from the dispersions. A cogrinding technique has been employed to prepare the formulations. The method has some advantages over other techniques of SD formulations in that it does not require the use of toxic solvent therefore environmentally favorable and economically less expensive.

Ibuprofen is used widely in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, postoperative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis, peri-articular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains. It also possesses anti pyretic activity (3). Ibuprofen belongs to the class II biopharmaceutical classification system (BCS), the characteristics of which are low aqueous solubility, slow dissolution rate, high dose and high membrane permeability (4). Indeed, several studies demonstrated that the bioavailability of this drug was affected by its dissolution rate. The higher the dissolution rate the higher was the bioavailability (5, 6). Because of dissolution rate- limited bioavailability of ibuprofen many investigations were focused on enhancing its dissolution by variety of techniques. Adsorption (7), supercritical fluid (8), amorphous solid formation (9), solid lipid nanoparticle and nanosuspension formulations (10), microparticle preparation (11), melt sonocrystallization (12), melt granulation (13) and coprocessing with superdisintegrant (14) techniques were employed to enhance ibuprofen dissolution rate. In addition to mentioned methods, solid dispersion approach being relatively a simple technique attracted some attentions (15-17).

In order to clarify the drug release mechanisms as well as physicochemical properties, the formulations were subjected to powder X-ray diffraction, Fourier transform infra red, FT-IR, spectroscopy, differential scanning calorimetry and particle size measurement studies.

## MATERIALS AND METHODS

Ibuprofen (Biocause, China), crospovidone (BASF, Ludwigshafen, Germany), microcrystalline cellulose (Avicel RC-591, FMC, Brussels, Belgium) and *Elaeagnus angostifolia* fruit (vernacular name is senjed which is native to central and western Asia including Iran) powder (Tabriz produce, Iran) were used as received. All other materials were analytical grades.

### Preparation of SDs and Physical Mixtures

Solid dispersions (cogrounds) with 1:1 and 2:1 ratios of the carrier crospovidone, microcrystalline cellulose and oleaster powder to ibuprofen were prepared using the cogrinding method. The total weight of drug and carrier was 10 g. The cogrinding was carried out by means of a ball mill (Fritsch GmbH, Germany) containing balls of different diameters ranging from 8 to 20mm that occupied nearly 1/3 of the mill chamber. The rate of vibration was 360 rpm for 3 hrs. A sample of about 10g ground drug powder was prepared by a similar milling process used for the coground systems. The tumbling bottle method was employed to prepare the corresponding physical mixtures (PMs). Details of the formulations are seen in Table 1. The tumbling time was 15 min and the bottle volume was 100 ml. All the preparations were stored in screw-cap vials at room temperature until use.

### Drug Content

Three samples from each preparation, equivalent to 5 mg drug, were chosen randomly and their ibuprofen contents determined spectrophotometrically (Shimadzu UV-160 spectrophotometer, Kyoto, Japan) at a wavelength of 221.8 nm after dissolving in simulated gastric fluid without pepsin (SGFsp, pH= 1.2) and appropriate dilution with the fluid using the Beer's plot. Preliminary studies showed no interference of the carriers with the drug at the utilized wavelength.

### Dissolution Studies

Samples of the preparations equivalent to 5 mg of ibuprofen which assured the presence of sink conditions were added to 900 ml of SGFsp as the dissolution medium (10) in a USP 28 apparatus II.

**TABLE 1.** Release Parameters of Reciprocal Powerd Time Model and the Correlation Coefficient (R) for Different Formulations of Ibuprofen

No.	Formulation	m±sd	b±sd	<sup>3</sup> t <sub>50%</sub> <sup>4</sup> ±sd (min)	R
1	Unground drug powder (UD)	74.70±6.00	0.97±0.07	85.4±6.00	0.998
2	Ground drug powder (GD)	74.50±7.50	1.04±0.08	63.1±5.70	0.998
3	PM 1:1 Avicel <sup>1</sup> : ibuprofen	356.26±17.80	1.57±0.06	42.2±2.52	0.999
4	PM 2:1 Avicel: ibuprofen	24.66±2.25	0.90±0.06	35.2±2.80	0.987
5	SD 1:1 Avicel <sup>2</sup> : ibuprofen	29.65±3.60	1.07±0.08	23.7±2.45	0.997
6	SD 2:1 Avicel: ibuprofen	23.83±1.68	1.25±0.09	12.6±0.75	0.988
7	PM 1:1 crospovidone: ibuprofen	134.72±11.85	1.41±0.06	32.4±1.92	0.999
8	PM 2:1 crospovidone: ibuprofen	28.53±2.61	0.98±0.07	30.5±2.74	0.994
9	SD 1:1 crospovidone: ibuprofen	376.38±18.82	2.46±0.15	11.1±0.65	0.999
10	SD 2:1 crospovidone: ibuprofen	6.3±0.19	1.83±0.08	2.7±0.04	0.999
11	PM 1:1 oleaster powder: ibuprofen	115.59±10.44	1.31±0.09	37.6±4.18	0.999
12	PM 2:1 oleaster powder: ibuprofen	15.09±1.75	0.78±0.03	32.4±4.59	0.981
13	SD 1:1 oleaster powder: ibuprofen	41.41±2.52	1.33±0.07	16.4±0.90	0.999
14	SD 2:1 oleaster powder: ibuprofen	24.19±1.54	1.37±0.06	10.2±1	0.999

<sup>1</sup> PM means Physical Mixture and <sup>2</sup> SD stands for Solid Dispersion. <sup>3</sup> The value of t<sub>50%</sub>, time required for 50% dissolution is calculated by Equation. 2, <sup>4</sup>±sd represents standard deviation.

The temperature of the test medium was 37±0.2°C and the paddle speed was adjusted to 50 rpm. Five ml aliquots were withdrawn and filtered at predetermined time intervals of 5, 10, 15, 20, 30, 45, 60 and 90 min. The same volume of 37°C SGFsp solution was added to the medium to compensate for each sample taken. Samples were filtered and the dissolved drug was assayed spectrophotometrically at 221.8 nm. Three replicates of each dissolution test were carried out.

#### Drug Release Kinetic Analysis

The reciprocal powered time (RPT) model was applied to drug release data of the formulations:

$$\left(\frac{1}{F} - 1\right) = \frac{m}{t^b} \quad (1)$$

Where F is fraction of drug dissolved up to time t, b is a model parameter describing the shape of the dissolution curve and m is another parameter of the model related to the time required for 50% dissolution, t<sub>50%</sub>, which in turn inversely related to the dissolution rate. Nonlinear regression was used

to calculate the model parameters m and b and then t<sub>50%</sub> was determined by Eq. (2):

$$t_{50\%} = m^{(1/b)} \quad (2)$$

#### Differential Scanning Calorimetry (DSC)

Thermograms of the unground drug powder (UD), Ground drug powder (GD), PMs (1:1 ratio) and SDs (1:1 ratio) were recorded on a DSC-60 (Shimadzu, Kyoto, Japan). Samples (5mg weighed to a precision of 0.005 mg) were placed in aluminium pans and the lids were crimped using a Shimadzu crimper. Thermal behavior of the samples was investigated at scanning rate of 20°C/min, covering a temperature range of 25-100 °C. The instrument was calibrated with an indium standard.

#### Powder X-ray Diffraction

The powder X-ray diffraction, (PXRD), pattern of all ingredients, SDs and PMs were recorded using an automated X-ray diffractometer (Siemens D5000, Munich, Germany). Cross-section of the samples were taken and held in place on a quartz plate for exposure to Cu K α radiation of wavelength 1.5406 Å. The samples were then analyzed at room temperature over a 2θ range of 0-

40°, with sampling intervals of 0.02° 2θ and a scanning rate of 6°/min.

### Fourier Transform Infrared Spectroscopy

Fourier Transform Infrared, (FT-IR), spectroscopy (Bomem, Quebec, Canada) was performed using the KBr disk method. Samples were mixed with KBr powder and compressed into 10mm discs, using a hydraulic press at a pressure of 10 tons for 30 seconds. The scanning range was 450-4000  $\text{cm}^{-1}$  and the resolution was 4  $\text{cm}^{-1}$ .

### Particle Size Measurement

The size distribution of UD and GD powder was measured with a laser diffraction particle size analyzer (SALD-2101 Shimadzu, Kyoto, Japan). The particle size distribution and mean particle size diameter were automatically calculated using the software provided.

## RESULTS

### Drug content

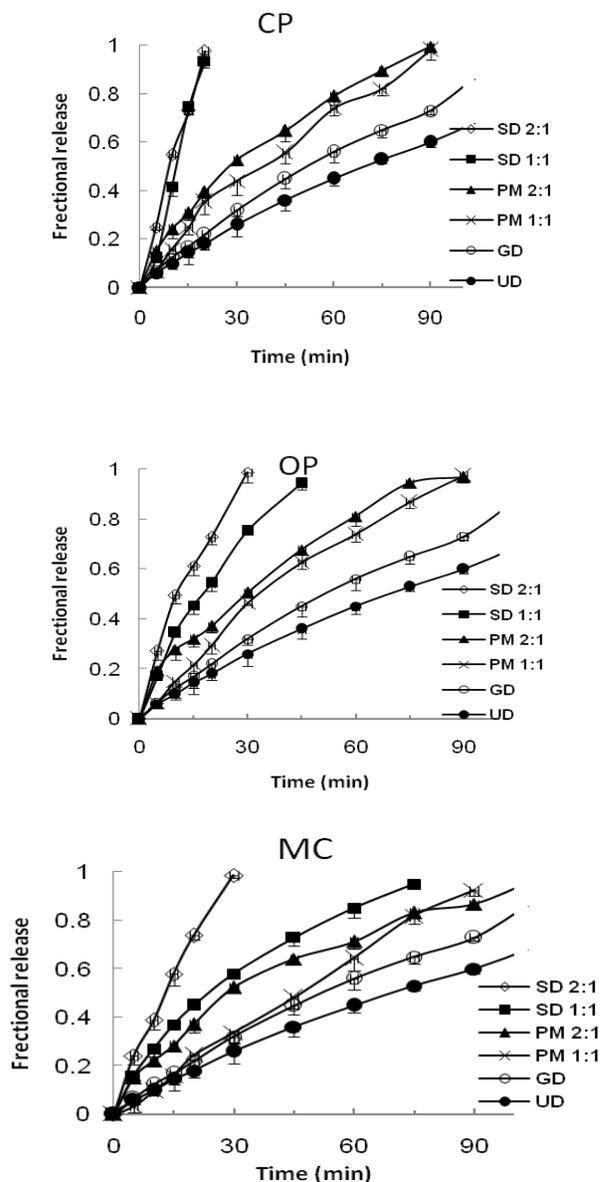
The drug contents were between 97.03 and 102.50% of the theoretical value.

### Dissolution Studies

The dissolution profiles of the preparations are shown in Figure 1. The time required for 50 percent of drug dissolved ( $t_{50\%}$ ) which is inversely related to the dissolution rate, for different formulations are given in Table 1. UD powder exhibited the longest  $t_{50\%}$  which was 85.4 min and the value of  $t_{50\%}$  for GD powder was 63.1 min. The values of  $t_{50\%}$  for PMs were between 30.5 and 42.4 min whereas those of SDs varied from 2.7 to 23.7 min. Therefore, SDs had the highest dissolution rates followed by PMs, GD and UD.

### Drug Release Kinetic Analysis

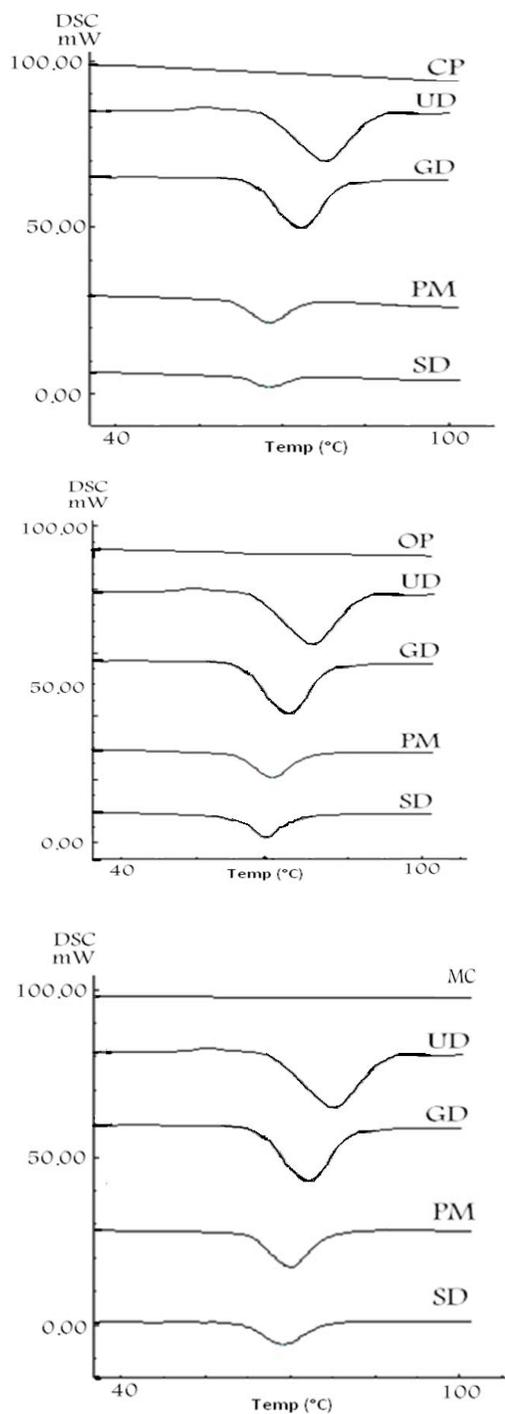
The parameters of RPT model for each formulation as well as the corresponding value of  $t_{50\%}$  calculated by the model parameters and the correlation coefficient (R) are seen in Table 1. The calculated  $t_{50\%}$  values were in excellent agreement with those obtained from the curves shown in Figure 1. The goodness of fitting the release data to the model was indicated by high R values and small errors.



**Figure 1.** Dissolution profiles of ibuprofen from unground drug, UD (●), ground drug, GD (○), different physical mixtures, PMs 1:1 (×), 2:1 (▲) and solid dispersions, SDs 1:1 (■), 2:1 (◇) with carrier: drug ratios containing crospovidone (CP), oleaster powder (OP) and microcrystalline cellulose (MC). The vertical lines represent standard deviation.

### Differential Scanning Calorimetry

DSC thermograms of the preparations are shown in Figure 2. The melting point of UD was 79 °C and upon grinding reduced to 76.5 °C. This reduction also reflected in the corresponding endotherms which represented relevant enthalpies of fusion.



**Figure 2.** DSC thermograms of the carriers crospovidone (CP), oleaster powder (OP) and microcrystalline cellulose (MC) together with those of unground drug (UD), ground drug (GD), physical mixtures (PMs) and solid dispersions (SDs) of the carrier: drug ratio of 2:1

Generally, there was slight decrease in melting point of PMs and SDs. But decrease of enthalpies of fusion in the cases of SDs Avicel and crospovidone was considerable as compared with those of PMs. However such a difference in enthalpy for SD and PM containing oleaster powder was negligible.

#### Powder X-ray Diffraction

In Figure 3, PXRD patterns of different formulations are seen. The patterns indicate slight alterations in the heights of peaks of SDs upon cogrinding the drug with the carriers.

#### Fourier Transform Infrared Spectroscopy

The FT-IR spectrum showed characteristic peaks for ibuprofen (18) i.e 1721, 1273, 1232, 1182, 870 and 779  $\text{cm}^{-1}$  in all the formulations (Figure 4).

#### Particle Size Measurement

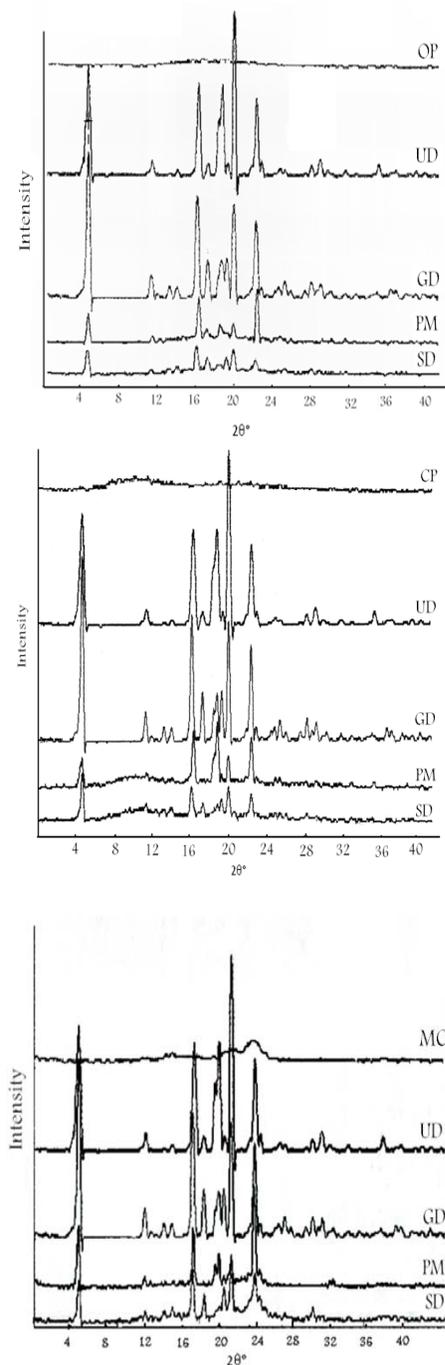
The mean particle size diameters for UD and GD were 150.7 and 44.4  $\mu\text{m}$ , respectively.

#### DISCUSSION

RPT model represented by equation 1 has been applied successfully for kinetic analysis of drug release from solid dispersions (1) as well as nanoparticles (2). The model for nanoparticles was justified theoretically via unification of the Fick's first law of diffusion and the Noyes-Whitney law of dissolution with introducing a time dependent variable into the unified law (2). The resultant differential equation is applicable for dissolution rate limited, diffusion rate limited and dissolution-diffusion rate limited release processes:

$$\frac{dw}{dt} = -\frac{dM}{dt} = \frac{D}{h} S C_s X \quad (3)$$

In which  $w$  and  $M$  are amounts of drug released and unreleased up to time  $t$ .  $dw/dt$  and  $-dM/dt$  are the rate of release in terms of  $w$  and  $M$ . The symbols  $D$ ,  $S$ ,  $C_s$ ,  $h$  and  $X$  are drug molecule diffusion coefficient, effective surface area of drug with release medium, drug solubility in the medium, the length of diffusion path and all time dependent variables involved in the release, respectively (2). Assuming all the parameters with the exception of  $C_s$  in the right hands of equation 3 are time dependent,



**Figure 3.** Powder X-ray diffraction pattern of the carriers crospovidone (CP), oleaster powder (OP) and microcrystalline cellulose (MC) together with those of unground drug (UD), ground drug (GD), physical mixtures (PMs) and solid dispersions (SDs) of the carrier: drug ratio of 2:1. its integration in terms of  $dw$  as well as  $dM$  between times 0 and  $t$  gives:

$$w = C_s \int_0^t \left( \frac{DSX}{h} \right) dt \quad (4)$$

$$M = M_0 - C_s \int_0^t \left( \frac{DSX}{h} \right) dt \quad (5)$$

As it is evident from equation 4 the amount of drug released,  $w$ , is directly proportional to  $C_s$ . Since the value of  $w$  increases with time thus assuming  $C_s$  remains constant the integral term in this equation should increase with time as well and  $w$  can be expressed by:

$$w = C_s \beta t^a \quad (6)$$

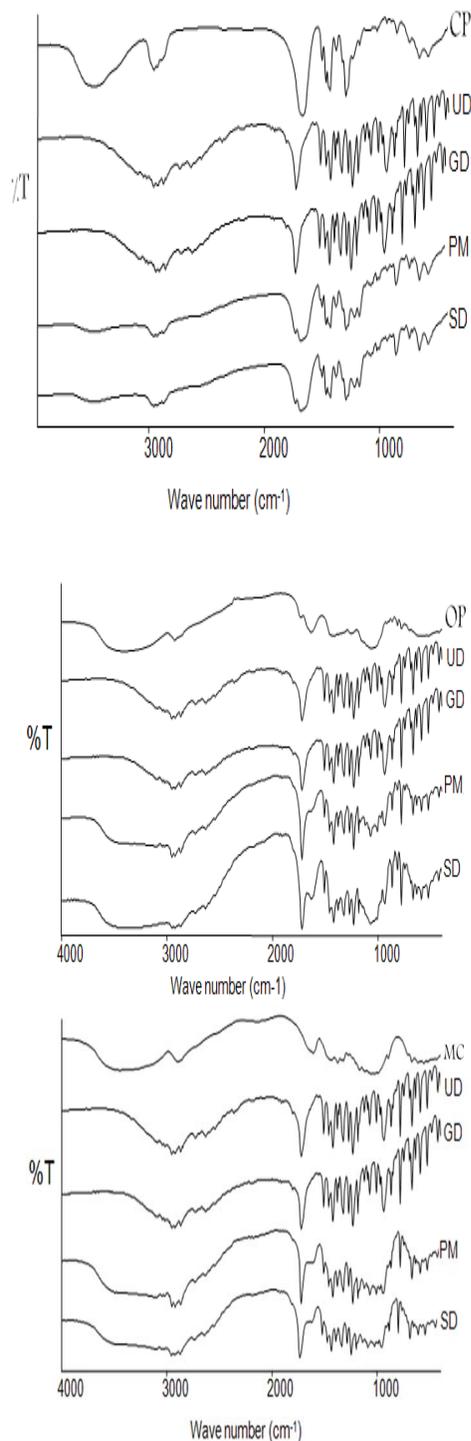
Where  $\beta$  and  $a$  are constants. In equation 5  $M_0$  is the amount of unreleased drug at time zero. The value of  $M_0$  equals  $W_\infty$  in previous reports (1, 2). The negative sign preceding the second term on the right hand side of equation 5 indicates that the amount of unreleased drug is inversely related to  $C_s$  and the integral term. In other words, the higher  $M$  the lower  $C_s$  and the integral and vice versa. In the previous work (2) the value of  $C_s$  was assumed to remain constant for a given drug from its various delivery systems as long as the release process was solely physical and no interaction occurred between the drug and excipients as well as ingredients of the release medium. The assumption of  $C_s$  constancy among various delivery systems resulted in the cancelation of  $C_s$  in the process of derivation leading to the equation 1. This meant the obvious direct relation between  $F$  and  $C_s$  was absent. However, the value of  $C_s$  for a given drug may vary in release medium because of different interactions of drug with ingredients of its delivery systems or the medium e.g. solubilisation, hydrotropism, ionization and complexation.

In order for  $C_s$  to be taken into account for the latter cases it is assumed that the right-hand side of equation 5 which is decreasing with time can be approximated by an inverse powered time relation in the form of:

$$M = \beta' t^{-a'} \quad (7)$$

$\beta'$  and  $a'$  are constants. Fraction of drug released,  $F$ , at any time is calculated by:

$$F = \frac{w}{w+M} \quad (8)$$



**Figure 4.** Fourier transform infra red spectra of the carriers crosppovidone (CP), oleaster powder (OP) and microcrystalline cellulose (MC) together with those of unground drug (UD), ground drug (GD), physical mixtures (PMs) and solid dispersions (SDs) of the carrier: drug ratio of 2:1.

Substitution of the power terms into the right side of equation 8 results in:

$$F = \frac{C_s \beta t^a}{C_s \beta t^a + \beta' t^{-a'}} = \frac{t^{a+a'}}{t^{a+a'} + \frac{\beta'}{C_s \beta}} = \frac{t^b}{t^{b+m}} \quad (9)$$

In which  $b = a + a'$  and  $m = \beta' / C_s \beta$ . Also the relationship between  $t_{50\%}$  and the parameters  $m$  and  $b$  is given by equation 2. Although the appearance of equation 9 is identical with the previously published equations (1, 2), it differs from those in that it shows explicitly the dependence of  $F$  to  $C_s$ . It is obvious that  $t_{50\%}$  (inversely related to the drug release rate as well as  $F$ ) is proportional to  $(1/C_s)^{1/b}$ . This is the relation between  $t_{50\%}$  and  $C_s$  which was not explicit in the previous publications (1, 2).

RPT model describes accurately the release data of ibuprofen formulations with higher correlation coefficients (Table 1). The overall error of the model for the fourteen formulations is 6.5% which was in agreement with the previously reported errors of 6.7% and 6.5% in the cases of solid dispersions (1) and nanoparticles (2), respectively. As it is evident from the process of derivation, the model holds for a dissolution of simple pure solid to more complex drug release from solid dispersion (1) as well as nanoparticles (2). Thus, it is applicable to release processes involving not only dissolution and diffusion or both but also other time dependent variables embedded in the model. In the case of UD powder the dominant mechanism would be such time dependent variables as wettability, deaggregation/aggregation and effective surface area of the particles. In addition, for GD powder an increased surface area is a factor affecting the release. Hydrophilicity accounts for enhanced wettability, deaggregation and surface area in PMs. In SDs further reduction in drug particle size causes faster drug release than PMs.

The values of  $t_{50\%}$  calculated from the model parameters differentiate the formulations very well. Drug release rate from UD due to its larger particle size diameter and higher crystallinity is lower than that of GD. The lower degree of crystallinity in GD is evident from decreased melting point in the DSC thermograms (Figure 2). Although such a reduced crystallinity is not clear in the PXRD (Figure 3)

possibly because of small particles orientation in GD which produces some higher peaks and masks the slight amorphicity. A similar pattern was reported for ibuprofen (19). The drug dissolution rate from PMs is greater than that of GD and depends on the nature as well as ratio of carrier to drug (Table 1 and Figure 1). The reason is possibly the adsorption of hydrophilic carriers on to the hydrophobic drug particles which in turn enhances wettability, deaggregation, dispersability and increased effective surface area of the particles (20-22). In addition, due to a high hydrophobicity of the relatively insoluble drug ibuprofen, its particles agglomerate in dissolution medium, might reduce effective surface area and hence decrease the dissolution of GD as compared with those of PMs. Such a phenomenon was demonstrated for the poorly water-soluble glioclazide ground and physical mixtures containing crospovidone and microcrystalline (23) the higher the carrier to drug ratio the greater is the dissolution rate. For a given ratio of carrier to drug, PMs containing crospovidone (CP) exhibits the highest dissolution followed by those of oleaster powder (OP) and microcrystalline cellulose (MC). The difference can be attributed to different hydrophilicity of the carriers. Apparently the influence of these factors on drug release from PMs is more effective than the reduced particle size and crystallinity in GD.

The drug dissolution from SDs, being dependent on the nature of the carrier as well as its ratio, is higher than those of UD, GD and PMs (Table 1 and Figure 2). In addition to the factors mentioned in the PMs, reduced drug particle size and decreased crystallinity accounts for the higher dissolution of SDs (22, 24). The DSC thermograms of SDs show shallow endotherms as well as slightly reduced melting points as compared to PMs indicating reduced crystallinity in the formers (Figure 2). Such a slight reduced crystallinity is evident in the corresponding PXRD patterns of SDs as compared with PMs. In all SDs the higher carrier to drug ratio yields faster dissolution than the corresponding PMs (Table 1 and Figure 1). Empirically, a general relationship exists between reciprocal of release half life and the ratio of carrier to drug (C/D):

$$\frac{1}{t_{50\%}} = \frac{1}{(t_{50\%})_0} + a(C/D)^p \quad (10)$$

In which  $(t_{50\%})_0$  is the release half life of GD in the absence of any carrier (63.1 min). The coefficient  $a$  is 0.074, 0.045 and 0.026 for solid dispersions containing CP, OP and MC, respectively. The power  $p$  is 2.256, 0.845 and 1.269 for the same SDs. It is seen from equation 10 that  $t_{50\%}$  (which is inversely related to the release rate) is directly related to the  $(t_{50\%})_0$  and inversely related to the parameters  $a$  and  $p$ . Thus, the efficiency of drug release from SDs is directly related to the product  $ap$ . The latter term ( $ap$ ) for the mentioned SDs is 0.167, 0.038 and 0.033. From these values the release enhancement efficiency of different carriers varies in the following descending order: CP > OP > MC. This may be attributed to differences in their hydrophilicity as well as drug particle size in their SDs (15, 21).

FT-IR spectrum of ibuprofen does not differ in GD, PMs and SDs reveals no appreciable interaction in the process of preparing the formulation.

As seen from the results the dissolution, augmentation power of oleaster powder is between those of crospovidone and microcrystalline cellulose. Thus, considering the abundance of *Elaeagnus angostifolia* in vast areas of central and western Asia including Iran, its fruit powder is suggested as a potential hydrophilic carrier for the NSAID drug ibuprofen solid dispersion formulation. Moreover, the fruit powder has been shown to possess anti nociceptive and anti inflammatory effects (25) which might potentiate the effects of ibuprofen. The major constituents of oleaster powder are glucose and fructose (more than 55% w/w) which confer a high degree of hydrophilicity to it. The powder is also contains some carbohydrates and other minor constituents (26).

The enhanced drug release from the solid dispersions suggest that the dose of ibuprofen can be reduced when used as a dosage form either alone or in the form of other solid delivery systems such as capsule and tablet forms. The reduction of drug dose is not only favorable economically but also is desirable in decreasing its side effects especially when administered in multiple dosage regimens.

## CONCLUSION

A physically sound derivation for reciprocal powered time model was given and applied to

ibuprofen release data from its solid dispersions in crospovidone (CP), microcrystalline cellulose (MC) and oleaster powder (OP) as a novel carrier. The drug release enhanced significantly from solid dispersions. The model parameter,  $t_{50\%}$ , indicated that the drug release rate from the carriers was in the descending order of: CP> OP> MC. Thus, OP is suggested as a potential hydrophilic carrier for increasing the drug release.

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