

## **Novel Poly (glycerol-adipate) Polymers Used for Nanoparticle Making: A Study of Surface Free Energy**

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### **Abstract**

Nanoparticles made of biodegradable polymers has become the best approach for nanoparticle making due to their compatibility with the human body.

New glycerol adipate polymers with hydroxyl group substituted with different percent of acyl group, sited as figures within the abbreviated name in the text, and triptophan were synthesized and proposed to be used in the preparation of dexamethason phosphate loaded nanoparticles, using the evaporation-deposition technique. The particle forming ability, size and distribution of the nanoparticles might be related to more important physicochemical characteristics, such as the surface properties of the polymers.

In this study surface free energies of five derivatives (0%, 20%, 40%, 100% and triptophan 5%) were determined by means of contact angle measurement carried out on films formed on the glass slides KSC Cam 100 instrument. The results were then incorporated into the Fowkes equation, to obtain the surface energy of the polymers. Also, different concentrations of methanol were used to obtain contact angles, which in turn were used to give the critical surface tension ( $\gamma_c$ ) of the polymers, using the Zisman's method.

The results of surface characteristics indicated that the 40% C<sub>8</sub> polymer was probably the most consistent, compared to the others during the preparation stage, in order to form smaller sized particles with a narrower distribution, correlating with the other works carried out on the loaded particles.

In conclusion, it seems that this method could be used to predict characteristics of polymers used for the selection of the best polymer in this series and probably other polymers for nanoparticle making, particularly for the loading of ionized drugs.

**Keywords:** Nanoparticle; Contact angle; Surface energy; Critical surface tension.

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### **Introduction**

Today, nanotechnology has become one of the major aspects in the human life and sciences.

As a pharmaceutical vehicle, polymers are more reliable both in the technology of preparing nanoparticles and drug targeting. Many polymers have been introduced in this regard and shown interesting properties.

Microparticle and nanoparticle drug delivery systems have been widely studied over the past

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20 years (1). For parenteral delivery systems, it has been shown that nanosized particles and liposomes have great potential in cancer therapy due to their ability to extravasate from the leaky vasculature of tumors (2). However, only a few such delivery systems have progressed far toward clinical use (3). For liposomal systems, their stability, in vivo, is low (4). A number of polymeric systems have been investigated, with PLGA [poly (D, L-lactide-*co*-glycolide)] and PLA-PEG [poly (D, L-lactic acid)-poly-(ethylene glycol)] being the most widely studied since they are biodegradable, have low antigenicity, and have been approved for drug delivery. Unfortunately, the reported drug incorporation levels have been generally quite low (5-7), thus making it difficult to encapsulate sufficient amounts of drug for therapeutic efficacy. Improved drug incorporation has been observed using cyanoacrylate polymers, but these systems show some toxicity (8, 9). Another disadvantage for many of the nanoparticles produced using the nanoprecipitation/solvent extraction technique is the need for a surfactant during nanoparticle formation (10-12). Sufficient removal of the surfactant is also always a problem. We favored the use of polymeric nanoparticles for the advantages of stability, cost, and ease of formulation. Further more, it seems that drug incorporation and control of drug release, could be altered by the introduction of moieties into the polymers. This could increase the level of interaction with the drug. This strategy would require biodegradable polymers to enable in vivo biodegradation and subsequent removal from the body. A few functionalized polymers have previously been reported for use in drug delivery, including polysaccharides (13), poly (amino acids) (14) and poly(L-lysine citramide) (15). However, these polymers are variously not readily degraded, have significant toxicity, or are difficult to produce.

The chemical synthesis of functional polymers, particularly readily hydrolyzable polymers such as polyesters, is difficult due to the need for the synthesis of a suitable monomer, with a protected functional group, as well as the post-polymerization deprotection of the functional group (16). Frequently, the deprotection steps lead to the partial hydrolysis

of the polymer, which is wasteful and leads to poorly characterized products (17). To overcome these problems, enzymes can be used to facilitate the polymerization procedure (18, 19). An exceptional enzyme catalyzed process for the synthesis of functional polyesters has been reported (20). These polyesters have pendant hydroxyl groups that could be substituted to provide the basis to investigate the hypothesis. To illustrate this concept, the potent water soluble anti-inflammatory steroidal drug dexamethasone phosphate, has been chosen. This drug has potential in cancer therapy for the relief of inflammation and swelling in brain tumors. However, when used chronically, this drug has a range of undesirable side effects, which would benefit from reduction by a suitable delivery system, and so is particularly appropriate. Steroids are known to interact with the acyl groups of phospholipids in membranes. Hence, introduction of acyl groups into polymers seems to be an ideal way to increase interaction between drugs, as well as reaching an appropriate drug release profile nanoparticle core. Identification of polymers to predict potential incorporation of specific drug and release is a major key for formulation and designing of drug delivery systems.

Poly(glycerol-adipate) polymers are newly developed polymers which could be considered for this purpose synthesis and characterization of acyl substituted functional polymers and their application in enhancing the incorporation of dexamethasone phosphate into a nanoparticle delivery system (21) has been described in this work. Their energy characterization could play a very important role in nanoparticle making and stability (22).

In this article, we characterized surface free energy and the relevant parameters of the proposed polymers in terms of measuring contact angle of known liquid particulate-containing systems, using appropriate equations.

### *Theory*

The potential of a material to react physically with the others mainly depends on their mutual affinity. This reflected from many parameters, mainly their surface energy ( $\gamma$ ).

Contact angle ( $\theta$ ), which is the major

indication of this affinity is usually measured and solved in desired equations to calculate their surface free energy ( $\gamma$ ). In fact this angle is the tangent of a proposed line drawn on the drop of a liquid resting on another material surface.

Since it is rare to get an absolutely symmetrical drop profile, the advanced  $\theta$ , which is the biggest possible  $\theta$ , is often taken into the account for this purpose.

While the value of this angle is the definition of wettability of a particular system, it is rarely used for calculation of other parameters. Rather its cosine is usually undertaken.

Calculation of  $\gamma$  of polymers enables prediction of their potential affinity to attach to other materials, which is reflected in adhesion and cohesion sciences. On the other hand this value is an indication of polymer ability to spread, coil, dissolve etc. in a particular medium. This could also be used to calculate the solubility parameter ( $\delta$ ) of the material, which indicates a mutually possible solubility in another phase(s).

Surface free energy ( $\gamma$ ) is the sum of some parameters, including, mainly the London dispersion forces ( $\gamma^d$ ) and the Keesom polar forces ( $\gamma^p$ ) for nonionized molecules. This means that two materials with identical surface free energy but different ratio of dispersion and polar components might react completely different. In other words each component reflects its property of the material in question, this means that the higher the  $\gamma^d$  the more likely would be the chance of the material to react with non- polar systems and vice versa.

For these reasons it is very important to define these parameters for the polymer entitled to be used for nanoparticle technology, especially for their use as drug delivery systems, in order to predict their loading/ releasing, making, sizing, stability performance and so on.

To define these parameters accurately and more relevant, it is important to use liquids with the highest possible difference in their surface free energy components (23). Hence, di-iodomethane, the completely nonpolar symmetrical molecule and water as the highly polar liquids are often used for this purpose.

There is another energetic parameter that may be defined and used for a specific system, which is called the critical surface tension ( $\gamma_c$ ). This is

defined as the surface tension of a liquid that just wets the solid. It means that no liquid can wet the solid unless has an equal or lower surface tension value than the solid. The first pioneer of this aspect was Zisman and coworkers (24), who used a homologous series of liquids and measured their contact angle against a particular solid. The graph of  $\cos \theta$  on the y-axis and surface tension of the liquid on the x-axis could be drawn, followed by its extrapolation, in order to cross the  $\cos \theta = 1$  line, which gives the value of  $\gamma_c$  of that particular solid.

## Experimental

### Materials

Poly (glycerol-adipate) (PGA) polymers and a range of substituted ones, 0% PGA [SH-L1102], 20% C<sub>8</sub> PGA [SH-L1115], 40% C<sub>8</sub> PGA [SH-L1114], 100% C<sub>8</sub> PGA [SH-L1111] were synthesized at Liverpool John Moores University. 5% Trp PGA was modified using 0% PGA [SH-L2006 $\alpha$ ] by Sanyogita Puri, University of Nottingham in collaboration with Chen, University of Nottingham. Di-iodomethane was purchased from Sigma. Acetone and methanol were of analytical grades.

### Methods

#### *Thin layer preparation*

The polymers used in this study were substituted with either C<sub>8</sub> acyl group (0%, 20%, 40% and 100%) or Tryptophan (Trp) (5%). Microscopic glass slides were coated with polymers (100 mg/ml or 20 mg/ml for 40% C<sub>8</sub>-PGA) as a thin film by mean of dropping sufficient drops of acetone solution of the polymers which were spread by tilt- leaving a thin layer of the polymers. For non- spreadable polymer, more drops were used for slide- coating. The coated glass slides were made at the same day of surface free energy measurements.

#### *Contact angle ( $\theta$ ) measurements*

These were conducted using a KSV Cam 200 (Instruments Ltd., Helsinki, Finland) equipped with an appropriate software follows:

a small drop of the test liquid was placed on the polymer coated glass slide. Then the slide was mounted horizontally on the stand of the

instrument and drops of either pure distilled water or di-iodomethane were placed on it using a syringe with a flattened tip needle. The camera was switched on and the tangent of the line was executed to record each of them, each being taken per second. Ten measurements were recorded for each polymer. All measurements were carried out at room temperature ( $25 \pm 1.5$  °C).

#### Surface tension measurements

The instrument was first calibrated with a stainless steel 4 mm diameter ball. A drop of the solution was pendant from the edge of the syringe needle and enlarged for each sample until it reached the point just before detachment from the needle tip (Figure 1). The shape of pendant drops was analyzed for surface tension by using an available software (KSV instrument). All experiments were carried out at  $25 \pm 1.5$  °C.

#### Surface free energy calculations

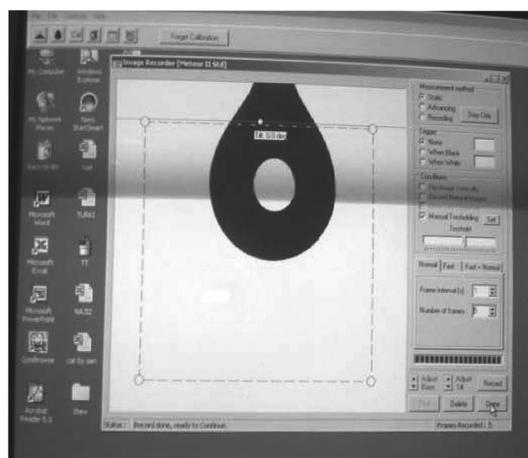
*Geometric Mean (Fowkes):* The method was adopted. This approach divides the surface energy into two components, dispersive and polar, and uses a geometric mean approach to combine their contributions. The resulting equation when combined with Young's equation yields:

$$\gamma_L (1 + \cos \theta) = 2(\gamma_s^d \gamma_L^d)^{\frac{1}{2}} + 2(\gamma_s^p \gamma_L^p)^{\frac{1}{2}}$$

where,  $\gamma_L^d$ ,  $\gamma_s^d$ ,  $\gamma_L^p$  and  $\gamma_s^p$  are London dispersion forces components ( $\text{mJ m}^{-1}$ ) of the liquids and the polymers and the, polar forces components ( $\text{mJ m}^{-1}$ ) of the liquids and the polymers used, respectively.

This was determined using two liquids, water and diiodomethane, for contact angle measurements incorporated in geometrical Fowkes equation (23), using by the instrument software.

Surface free energy of the polymers ( $\gamma_s$ ) is the sum of London dispersion forces and polar forces. The calculation was conducted by the instrument software on the basis of construction and solving two equations by inserting  $\cos \theta$  of two liquids. The unknown parameters [London dispersion forces and Keeson polar forces (23)] of polymers in the equation could be easily



**Figure 1.** An example picture of pendant drop on the monitor screen, used for surface tension determination by the aid of software.

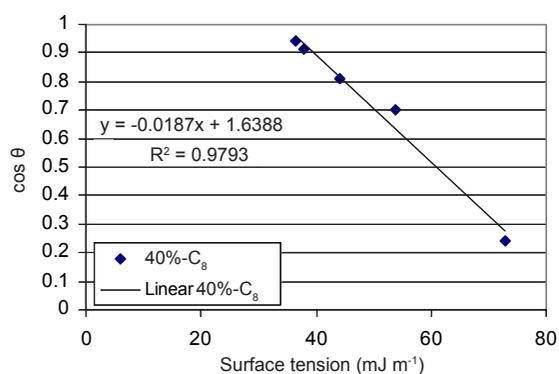
equated.

#### Determination of critical surface tension of the polymers

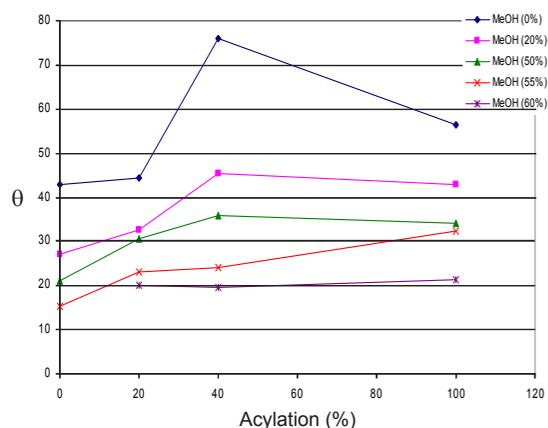
Using a series of homologous nonpolar liquids with different surface tensions and plotting the  $\cos \theta$  vs.  $\gamma$  graph a line is constructed which approaches  $\cos \theta = 1$  at a given value of  $\gamma$  (24). This value, called the *critical surface tension*, can be used to characterize solid surfaces. It is often presented as the highest value of surface tension of a liquid which will completely wet the solid surface. This approach is most appropriate for low energy surfaces which are being wetted by nonpolar liquids.

Due to the lack of available non-polar series of liquids that do not dissolve the polymers, different concentrations of methanol were tested. The results showed an excellent correlation between surface tension and concentration, in the range tested. That is, all concentrations up to 60% did not show any sign of solubility. Hence, this range was used for all the experiments.

In order to determine the *critical surface tension*, different concentrations of methanol were prepared and their contact angles against the polymers, as described in the previous section, were measured. Cosine of the resultant values of contact angle ( $\theta$ ) were plotted against the surface tension of the different concentrations of methanol used (Figure 2). Extrapolation of the best line of this value to line crossing the  $\cos \theta = 1$  line would give the value of *critical surface*



**Figure 2.** Correlation between Cos  $\theta$  and surface tension of different concentrations of MeOH used for critical surface tension of 40%  $C_8$  polymer under study (Cos  $\theta$  is cosine of contact angles).



**Figure 3.** Illustration of the relationship between contact angle of different concentrations of MeOH and acylation number of the polymers.

tension of individual polymers under study (24).

## Results and Discussion

Poly (glycerol adipate) (PGA) is a newly synthesized polymer backbone, mainly used in drug delivery systems. The polymer backbone is substituted by various functional groups like acyl groups ( $C_8$ ,  $C_{18}$ ) and aminoacids (Trp, Tyr). As it has been reported elsewhere (21), these polymers are self-assembled into nanoparticles in the absence of surfactant, while addition of the latter, did not offer any more advantages to the system. Therefore, the investigation of energy (dispersive, polar properties, surface tension and so on) and mechanical parameters would be very useful to explain the behavior of these polymers, and could probably predict their further potential applications.

At first, a range of methanol (MeOH) concentrations should be established for the estimation of surface tension and critical surface tension. Table 1 shows the surface tension and contact angle values of different concentrations of MeOH used against the polymers studied for determination of critical surface tension. As expected, the surface tension decreased as the MeOH concentration increased, and reached the point of 60% where, either the polymer was dissolved or no more surface tension changes occurred. This is clearly showed in Figure 3, where the contact angle of various MeOH concentrations against the % of polymer acylation is illustrated, indicating that at a concentration of 60%, a flat line was obtained, suggesting the polymer dissolution. Therefore, a range of 0-55% of MeOH solution was chosen for determination of the critical surface tension,

**Table 1.** Surface tension and contact angle of different concentrations of methanol used against the polymers for critical surface tension determination.

Methanol concentration	Surface tension ( $\text{mJ m}^{-1}$ )	Contact angle ( $\theta$ )				
		0%- $C_8$	20%- $C_8$	40%- $C_8$	100%- $C_8$	5% Triptophan
0%	72.94	42.85	44.47	75.88	56.42	104.1
1%	70.11	-	-	-	48.05	88.19
5%	69.96	-	-	43.03	47.13	90.85
20%	53.92	27.00	32.56	45.56	42.85	63.72
30%	46.72	25.29	35.32	-	-	-
50%	44.23	21.08	30.67	35.81	34.19	45.27
55%	37.73	15.21	23.04	24.04	32.44	-
60%	36.51	-	20.17	19.66	21.44	24.76

**Table 2.** Contact angle of water and diiodomethane against the polymers and the relevant calculated surface parameters. ( $\theta$  is the contact angle).

Polymer	Water		Diiodomethane		Surface free energy ( $\gamma$ )			$\gamma_c$	$W_c$
	$\theta$	Cos $\theta$	$\theta$	Cos $\theta$	$\gamma$ (mJ m <sup>-2</sup> )	$\gamma^d$ (mJ m <sup>-2</sup> )	$\gamma^p$ (mJ m <sup>-2</sup> )	(mJ m <sup>-1</sup> )	Julé
C <sub>8</sub> 0%	37.97(2.6)	0.788	49.05(2.6)	0.655	62.41	34.76	27.66	33.36	124.8
C <sub>8</sub> 20%	44.47 (1.17)	0.714	35.65(0.03)	0.813	60.70	41.67	19.13	22.04	121.4
C <sub>8</sub> 40%	69.43(4.38)	0.351	75.88(4.38)	0.224	31.38	20.76	10.62	33.45	62.8
C <sub>8</sub> 100%	56.42(1.80)	0.530	28.72(1.60)	0.877	57.26	44.71	12.56	23.00	114.5
5% Tryptophan	104.84(4.31)	0.249	61.25(1.52)	0.481	29.19	28.71	0.48	34.11	58.4

instead of using a homologous series of liquids usually applied (27).

Figure 3 also shows that for the first three polymer concentrations, (0%, 20%, 40% C<sub>8</sub>) there was an increase in contact angle as the % of acylation increased. This could be attributed to the higher polymer hydrophobicity, due to a higher percentage of acylation. Although, when the percentage of acylation increased from 40% to 100%, there was no significant increase in contact angle, which probably occurred because of the higher London dispersion forces,  $\gamma^d$ .

Table 2 summarizes the properties of the PGA polymers substituted with either C<sub>8</sub> or Trp from the energy point of view. We saw that the 40% C<sub>8</sub> PGA-12kDa polymer exhibited the lowest total surface free energy and it seems well balanced in terms of the nonpolar to polar components, which have quite close values. The latter could indicate that the particular polymer has the ability to blend/combine with materials of both low or high free surface energy. 0% PGA and 20% C<sub>8</sub> PGA polymers showed almost an identical total free surface energy, but the non-polar component value was higher than the polar one for the 20% C<sub>8</sub> PGA comparing to 0% PGA. This was expected, as the introduction of acyl groups would make the 20% C<sub>8</sub> PGA polymer more hydrophobic. The 20% acylation of the polymer might change the hydrophobicity of the polymer, but not necessarily the total free surface energy. The total surface free energy of 0% PGA and 20% C<sub>8</sub> PGA was almost twice higher than that obtained for the 40% C<sub>8</sub> PGA. The same is observed for the 100% C<sub>8</sub> PGA, which again showed an almost the same total free surface energy to that obtained for 0% and 20% C<sub>8</sub> PGA polymers. Thus, it appears to be

more hydrophobic, since it can be deduced from the non-polar and polar component values. As the percentage of acylation increases, the polar component value decreases.

The 5% Trp showed a very similar total free surface energy to the 40% C<sub>8</sub> PGA polymer, but its hydrophobicity is much more prominent than that of the latter. This suggests that materials of lower total free surface energy and high hydrophobicity would be more compatible with that polymer. From the same table, it is obvious that the critical surface tension of all the polymers studied is low, so these polymers can self-assemble into nanoparticles without the need for the addition of surfactant. This comes into agreement with the findings of Kallinteri et al. (21), where the presence of polysorbate-80 in the preparation medium did not make any difference in the particle preparation, compared to that in the absence of the surfactant.

Overall, it could be suggested that the 40% C<sub>8</sub> PGA solution might be a more appropriate/suitable candidate for nanoparticle technology than the others due to the properties described earlier.

The results obtained very well indicate that the molecules need a balance of acylation to meet a better performance of nanoparticles in their sizing, loading and stability properties.

From the last column of Table 2, it is clearly seen that the 40% C<sub>8</sub> system has the weakest strength amongst all the systems, except for the 5% Trp. This was observed during thin layer formation. While the 40% C<sub>8</sub> polymer gave the easiest and more complete film forming, the others failed to do so. 5% Trp failed to give a good film on a glass slide due to its hydrophobicity. This could also affect stability of its dispersion system

**Table 3.** Surface tension and the related concentrations of nanoparticle dispersions of the two polymers.

Surface tension (mJ m <sup>-1</sup> ) of 40% C <sub>8</sub> solution	Surface tension (mJ m <sup>-1</sup> ) of 20% C <sub>8</sub> solution	Concentration (mg/ml)
73.5	73.5	0
60.9	57.1	1.25
55.7	55.9	2.5
52.3	55.9	5
53.9	46.8	10
46.5	4.1	20

to hindrance collision and thereby prolonging its shelf-life.

The mechanical strength of polymers, beside other factors, is highly related to the molecular weight of the entire polymer. Since the polymers used have very similar molecular weights (polymer backbone M.W. 12kDa), we assume that the mechanical strength is highly depended upon the cohesive strength ( $W_c$ ).

Table 2 shows the values of contact angle of water and di-iodomethane against polymers of different specifications. These liquids have extreme differences in polarity and they are the most common liquids used to carry out surface free energy experiments. The significant difference in contact angle for the two liquids on each polymer tested reflects the resultant polymer properties relevant to hydrophobic/hydrophilic components. This is the result of acyl substitution group included within the polymer molecules. The low standard deviation indicates the accuracy of the procedures employed.

The total surface free energy is the sum of the  $\gamma^d$  (dispersive forces) and  $\gamma^p$  (polar forces). We noticed that as the acylation percentage of the polymer increases from 0% to 40%, there is a decrease in the total surface energy, while the 100% C<sub>8</sub> demonstrates a higher one. The total surface free energy of 5%Trp PGA polymer is quite similar to that of the 40% C<sub>8</sub> PGA polymer. Also, the dispersive force values for 0%, 20% and 100% PGA were very close, while the one for 40% exhibits an almost 2-folds decrease, comparing to the others. Again, 40% C<sub>8</sub> and 5% Trp PGA demonstrated similar  $\gamma^d$  values.

On the other hand, it is anticipated that the 40% acyl substituted polymer could have greater affinity for methanol than the others. Particularly

at lower, concentrations, the higher water content, which can be attributed to the greater balance in its hydrophilicity/hydrophobicity, is observed. This could be also noted from its very low surface energy and excellent film forming, even for a low concentration in acetone compared to the other polymers, when preparing film on the glass slides to achieve a proper film for this study.

Moreover, the increased acylation or the type of substitution has a more prominent effect on the polarity of the polymer, as clearly seen from the  $\gamma^p$  values. More specifically, as the acylation percentage increases, the polarity as expected decreases. The 40% C<sub>8</sub> PGA shows an almost 2.5-folds decrease. By replacing the acyl group with Trp, even to a lesser extent (5% instead of 40%), the polarity of the polymer drops massively, approximately 10-folds. Hence, the 5% Trp PGA is classified as a non-polar material.

However, regardless of the huge differences in the polymers in terms of surface energy component values and hydrophobicity, their critical surface tension is quite low and of similar values (Table 3).

In addition, the last column of Table 2 shows the work of cohesion ( $W_c$ ), which is double that of surface tension ( $W_c=2\gamma$ ), indicating the strength of the material. The results show that among the polymers of the same acylation evaluated, 40% C<sub>8</sub> PGA polymer is less cohesive and so potentially easier to work with (i.e. making particles, spread on surfaces, mixing etc.).

By replacing C<sub>8</sub> groups with Trp, the work of cohesion does not change, but due to the different nature of the two polymers, no direct comparison could be made.

Figure 2 represents the surface tension of

various concentrations of MeOH against  $\cos\theta$  for each one of the polymers examined. The extrapolation of the best fit line, as represented in those graphs for  $\cos\theta=1$ , gives the critical surface tension of the polymers, respectively. These values are sited in Table 2.

Table 2 shows the values of contact angle of water and diiodomethane against polymers of different specifications. These are the extremely high and low polarity liquids against cast layer polymers, that could be used for surface free energy calculation. As shown in this table, there is a difference in contact angles for the two liquids with high differences in polarity, reflecting on the other more important properties relating to the hydrophobicity/hydrophilicity relationship. This is the result of acyl substitution group included within the polymer molecules. The low standard deviation indicates the accuracy of the procedure used.

To show the effect of percentage of acyl substitution on the surface properties of the polymer, a graph was drawn, as shown in Figure 3. As could be seen, the trend for all methanol concentrations seems to be the same for all the polymers, indicating an excellent choice of the liquid, (i.e. methanol) for this purpose.

### Conclusion

In conclusion, it could be stated that the selection of a suitable polymer from different substituted derivatives could be carried out for optimized preparation of nano particles, based on surface energy determinations. Furthermore, 40%  $C_8$  seems to be the best amongst this series of polymers used for preparing nanoparticles.

### References

- (1) Allemann E, Gurny R and Doelker E. Drug-loaded nanoparticles- preparation methods and drug targeting issues. *Eur. J. Pharm. Biopharm.* (1993) 39: 173-91
- (2) Nagayasu A, Uchiyama K and Kiwada H. The way that PEG-DSPC liposomal doxorubicin particles penetrate in to areas of tumors and other ischemic tissues. *Adv. Drug Delivery Rev.* (1999) 104: 2224-34
- (3) Moses MA, Brem H and Langer R. Advancing the field of drug delivery: Taking aim at cancer. *Cancer Cell* (2003) 4: 337-341
- (4) Barratt G. Developing nanoparticle drug carriers, the development of cell. *Mol. Life Sci.* (2004) 60: 21-37
- (5) Leo E, Brina B, Forni F and Vandelli MA. *In vitro* evaluation of PLA nanoparticles containing a lipophilic drug in water-soluble or insoluble form. *Int. J. Pharm.* (2004) 278: 133-41
- (6) Govender T, Stolnik S, Garnett MC, Illum L and Davis SSJ. PLGA nanoparticles prepared by nanoprecipitation: drug loading and release studies of a water soluble drug. *J. Controlled Release* (1999) 57: 171-185
- (7) Vauthier C, Dubernet C, Fattal E, Pinto-Alphandary H and Couvreur P. Poly (alkylcyanoacrylates) as biodegradable materials for biomedical applications. *Ad Drug Delivery Rev.* (2003) 55: 519-48
- (8) Gelperina SE, Khalansky AS, Skidan IN, Smirnova ZS, Bobruskin AI, Severin SE, Turowski B, Zanella FE and Kreuter J. Nanomaterial toxicity core. *Toxicol. Let.* (2002) 126: 131-141
- (9) Lamprecht A, Ubrich N, Yamamoto H, Schafer U, Takeuchi H, Lehr CM, Maincent P and Kawashima Y. Nanomaterial toxicity. *J. Controlled Release* (2001) 71: 297-306
- (10) Cauchetier E, Deniau M, Fessi H, Astier A and Paul M. Atovaquone-loaded nanocapsules: influence of the nature of the polymer on their *in vitro* characteristics. *Int. J. Pharm.* (2003) 250: 273-81
- (11) Jung T, Breitenbach T and Kissel T. Sulfobutylated poly (vinyl alcohol)-graft-poly (lactide-co-glycolide)s facilitate the preparation of small negatively charged biodegradable nanospheres. *J. Controlled Release* (2000) 67: 157-169
- (12) Akiyoshi K, Deguchi S, Moriguchi N, Yamaguchi S and Sunamoto J and *J. Macromolecules* (1993) 26: 3062-3068
- (13) Brown MD, Schaetzlein A, Brownlie A, Jack V, Wang W, Tetley L, Gray AI and Uchegbu IF. The effects of hydrophobic helix length and side chain chemistry on the biomimetic behavior of peptoid. *Bioconjugate Chem.* (2000) 11: 880-891
- (14) Gautier S, Boustta M and Vert M. Complexity of the hydrolytic degradation of aliphatic polyesters. *J. Bioact. Compat. Polym.* (1997) 12: 77-98
- (15) Tian D, Dubois P, Grandfils C and Jérôme R. Ring-opening polymerisation of 1, 4, 8-Trioxaspiro [4, 6]-9-undecanone: a new route to aliphatic polyesters bearing functional pendent groups. *J. Macromolecules* (1997) 30: 406-409
- (16) Barrera DA, Zylstra E, Lansbury PT and Langer R. Synthesis and RGD peptide modification of a new biodegradable copolymer system: Poly(lactic acid-co-lysine). *J. Am. Chem. Soc.* (1993) 115: 11010-11011
- (17) Wang YF, Lalonde JJ, Momongan M, Bergbreiter DE and Wong CH. Lipase-catalyzed irreversible transesterifications using enol esters as acylating agents-Preparative enantioselective and regioselective syntheses of organometallics. *J. Am. Chem. Soc.* (1988) 110: 7200-7205
- (18) Uyama H, Wada S and Fukui T. Lipase-catalyzed synthesis of polyesters from anhydride derivatives involving dehydration, Lipase-catalyzed polymerization

- of divinyl adipate with glycols to polyesters. *Chem. Lett.* (1994) 1687-1690
- (19) Kline BJ, Beckman EJ and Russell AJJ. One-step biocatalytic synthesis of linear polyesters with pendant hydroxyl groups. *J. Am. Chem. Soc.* (1998) 37: 9475-9480
- (20) Kallinteri P, Higgins S, Hutcheon GA, St. Pourcain CB and Garnett MC. Novel functionalized biodegradable polymers for nanoparticle, drug delivery systems. *Biomacromolecules* (2005) 6: 1885-1894
- (21) Qi WH, Wang MP, Xu GY, Zhi Z and Che JY. Size Effect on the cohesive energy and the lattice parameter of nanoparticle. *J. Mat. Sci. Tech.* vol 18 (2002) 86-92
- (22) Longtana-anan M and Fell JT. Surface free energy determination on powders. *Powder Technology* (1987) 52: 215-218
- (23) Zisman WZ, Review the physical-chemical aspect on Adhesion, *Ind. Eng. Chem.* (1963) 55: 19-38
- (24) Kim D and Lee S. Comparison of surface properties of random, block, and graft copolymers having perfluoroalkyl and silicone-containing side chains. *J. Colloid Interface Sci.* (2002) 247: 490-93
- (25) Orafi H. and Honary S. Effect of core surface tension on roughness of film-coated tablets. *Iranian J. Pharm. Res.* (2003) 2: 66-7
- (26) Fowkes FM, Kaczinski MB and Dwight DW. Characterization of polymer surface sites with contact angles of test solutions. 1. Phenol and iodine adsorption from CH<sub>2</sub>I<sub>2</sub> onto PMMA Films. *Langmuir* (1991) 7: 2464-2470
- (27) Van Oss CJ and Goods RJ. Prediction of the solubility of polar polymers by means of interfacial tension combining rules. *Langmuir* (1992) 8: 2877-2879

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