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Quantitative estimation of film forming polymer–plasticizer interactions by the Lorentz–Lorenz Law

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Abstract

Molar refraction as well as refractive index has many uses. Beyond confirming the identity and purity of a compound, determination of molecular structure and molecular weight, molar refraction is also used in other estimation schemes, such as in critical properties, surface tension, solubility parameter, molecular polarizability, dipole moment, etc.

In the present study molar refraction values of polymer dispersions were determined for the quantitative estimation of film forming polymer–plasticizer interactions.

Information can be obtained concerning the extent of interaction between the polymer and the plasticizer from the calculation of molar refraction values of film forming polymer dispersions containing plasticizer.

Keywords: Molar refraction; Polymer–plasticizer interaction; Film coating

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1. Introduction

Determination of molar refraction and refractive index are often required to confirm the identity and purity of a compound. Determination of molecular structure and weight is frequently aided by these parameters (Shriner et al., 1980; Vakili-Nezhaad and Modarress, 2002). Molar refraction (R) is also used in other estimation schemes, such as in critical properties, surface tension, and the solubility parameter, which is a measure of intermolecular forces. The refractive index (n) is affected by changes in temperature, pressure, and wavelength of radiation. R remains nearly constant with changes of temperature and pressure by virtue of the density factor, which is a function of temperature and pressure, and thus offsets these effects (Padrón et al., 2002).

Molar refraction is useful in measure of intermolecular forces: van der Waals, London dispersion forces (Caner et al., 1996), indicates such interactions as: critical molecular association concentration (CAC), critical micellar concentration (CMC) and in the coating process the film–plasticizer interaction. The last one has a definite influence on the drug release.

Linearity between the refractive index changes and the concentration follows directly from the Lorentz–Lorenz equation, and therefore gives the same variation for the index changes. With that the development of the refractive index profile during in- and out-diffusion is well described by the diffusion theory, and consequently the dynamic response of the optical sensor can be modelled by a suitable theory (Podgorsek, 1999).

The alloy film densities can also be predicted from the measured refractive indexes using Lorentz–Lorenz analysis. The Lorentz–Lorenz analysis evaluates the refractive index of a compound film from the individual molar refractivities, of the components (Elam et al., 2003).

A close connection occurs between the molar refraction and molecular polarizability, dipole moment and reactivity (Wijers and De Boeio, 2001; McPhedran et al., 1997).

R_m is a value influenced by concentration and molecular mass. Any divergence in the measured (experimental values) R_m from the calculated R_c indicates intermolecular interaction, e.g. hydrogen bonding, network formation (Sinha and Lugujjo, 1978; Gapochenko and Belozertseva, 2001). The presence of

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polar functionality is especially beneficial when working with waterborne coatings. Not only does water tend to wet out more readily due to surface tension forces, but polar groups will promote adhesion through potential hydrogen bonding of suitable functionality of the coating polymer composition.

The converse situation is also important to recognize, where polar functionality present in the chemistry of the coating composition, thus influencing the performance of the final coated product. The higher the polar functionality of the plastic surface or substrate and/or the coating composition, the greater the probability of good interfacial stability (Brandrup and Immergut, 1989).

The Lorentz–Lorenz law is applied to the kinetics of formation of self-assembled monolayers, films (Sastry, 2000).

Precipitation of asphaltene particles was studied from crude oil using refractive index measurement. Before the onset of precipitation, the refractive index obeyed the Lorentz–Lorenz equation. However, as asphaltene particles began to precipitate from the mixture, the refractive index no longer followed the rule. The deviation from the Lorentz–Lorenz rule caused by the change in the amount of asphaltene particles dispersed in the crude oil. The refractive index data were used to predict the amount of asphaltene particles precipitated and the stability of the asphaltene particles in the crude oil (Wattana and Fogler, 2003).

Lorentz–Lorenz rule is applied by wide range of engineering territory, e.g. optics (Elam et al., 2003), light-induced polymerization (Pruner, 1998) characterisation of liquid crystals (Horn, 1978).

In the course of formulation of coated pharmaceutical dosage forms, selection of the suitable composition of the coating system is essential as regards dosage form (Musko et al., 2002). Since the systems applied for coating are multicomponent, it is highly important to quantitatively evaluate the possible interactions between the components. These interactions determine the physico-chemical stability of the formulated dosage form, the drug release process and the formulation parameters, as well.

Molar refraction values of polymer dispersions were determined for the quantitative estimation of polymer–plasticizer interactions. Among the additives that are incorporated into aqueous polymeric dispersions, the plasticizer is the most critical component that dictates proper film formation and quality of the resulting film (Hild et al., 2002; Fukumori et al., 1988). The prerequisite of the plasticizer effect is to diffuse into and interact with the polymer, and have minimal or no tendency for migration or exudation from the polymer. If a plasticizer does not remain in the film, then changes in the chemical and/or physical–mechanical properties of the polymeric material could occur.

Film layers are made up of molecules that have exactly they self intermolecular cohesive attractions (Laing, 2001). The interactions eventuate between film forming polymer and plasticizer result deviation in molar refraction measured and calculated, and this phenomenon can be applied as an indicator to detect the interactions. As a consequence of these interactions, several modifications in the drug release behaviour could occur. Incorporation of a plasticizer is recommended for polymer coating formulations due to the high glass transition temperatures of polymers. The plasticizer effect could generally be described using simplified forms of the Gordon-Taylor/Kelley-Bueche relationships derived from the free volume theory of polymers. The role of the free volume is explained by an increasing need for space caused by chain segment mobility which develops above the T_g, positron lifetime spectroscopy is frequently used to determine the size distribution of free volume holes in polymers. The measurements are based on the interaction of the free volume holes and the so-called ortho-positronium atom. This ‘atom’ is a bound state of an electron and a positron and reacts to the changes of the free volume very sensitively. Along with the free volume changes the occupied volume also changed which can be easily tracked by the determination of molar refraction values (Zelkó et al., 2002).

The shape of guest molecules has a significantly greater influence on the free energy of supramolecular effect in the formation of solid complexes (Gorbatchuk et al., 1999).

The optimization of drug release enables applying different types of plasticizers (Peppas et al., 2000). The importance of nonionizable but soluble excipients on solute transport through non-soluble coat is to control the rate of drug release. Because these additives are hydrophilic, they reduce dissolution time, thereby accelerating drug release.

Upon contact with the gastrointestinal fluid, the pores facilitate erosion of the coat and the subsequent release of the active ingredient. This erosion is often non-linear and is rarely capable of controlling drug release a near-linear fashion.

The aim of the present study was to introduce a simple indicative method for the prediction of these interactions.

2. Materials and methods

2.1. Materials

Eudragit L100-55 30 D, Eudragit RL 30 D (Rohm Pharma, Germany), hydroxypropil methylcellulose (mw: 86.000), methylcellulose (mw: 41.000), triacetin (Sigma), sebacic acid dibutyl ester (dibutyl sebacate (DBS), Sigma), sebacic acid dimethyl ester (dimethyl sebacate (DMS), Sigma), polyethylene glycols average molecular weight of 400, 1540, 4000 (PEG 400, 1540, 4000, 6000, Ph. Eur.4).

2.2. Sample preparation

Eudragit aqueous dispersions of 30% (w/w) polymer content were diluted with purified water under continuous stirring onto 10% (w/w) concentration. After 30-min homogenisation, plasticizer were added in different amounts to the samples and stirring was continued for 20 min. In the case of cellulose derivative film forming materials (hydroxypropil methylcellulose and methylcellulose), the film forming polymers were dispersed in purified water to get homogeneous dispersion with stirring for 20 min. The hydroxypropil methylcellulose concentration applied was 0.5% (w/w) and Pharmacoat 606 concentration was 2% (w/w), respectively. After homogenisation, plasticizers were mixed into the dispersion in different concentrations (5–20 and

5–25%, w/w). 24 ± 1 °C temperature was applied for sample preparation.

2.3. Determination of the refractive index of polymer dispersions

The refractive indices were determined at the sodium D line ($\lambda = 589.3$ nm), 24 ± 1 °C by an Abbé Refractometer. Preceding the measurements each sample was thoroughly stirred. In spite of the fact that the Eudragit samples were polymer latex dispersions, the sample preparation and the determination of the refractive index were reproducible without any problem.

2.4. Determination of density

The density of all the liquid samples were determined at 24 ± 1 °C using a DMA 35 (Anton Paar k.g., Austria) density meter.

2.5. Calculation of the molar refraction by the Lorentz–Lorenz equation

The following equation was used for the determination of molar refraction values (R):

$$R = V_m - \frac{n^2 - 1}{n^2 + 2} \qquad (1)$$

where n is the determined refractive index and V_m the molar volume ($m^3\,mol^{-1}$).

$$V_m = \frac{M}{\rho} \qquad (2)$$

where M is the molecular weight and ρ the density of the examined material (Neumüller, 1977). The molar refraction is an additive property. Due to the additive characteristics of molar refraction, the molar refraction of polymer solutions and latex dispersions containing different plasticizers can be calculated by adding up the molar refraction values of each component of the system. The difference between the measured and the calculated molar refraction values of the examined polymer–plasticizer systems refer to the nature and extent of polymer–plasticizer interaction (Orbán et al., 2000; Dredán et al., 2004a).

The space-filling factor (r) which is the fraction of the molar volume actually occupied by the molecules is calculated (Varada Rajulu and Mabu Sab, 1998) using Eq. (3):

$$r = \frac{n^2 - 1}{n^2 + 2} \qquad (3)$$

3. Results and discussion

Macromolecules of different concentration ranges, depending on their molecular masses, e.g. degree of polymerization, followed the Lorentz–Lorenz law with good correlation. Above the CAC, deviation occurred in the slope of linear regression (Fig. 1 and Table 1). Calculation the fraction of the molar volume refers on the actual occupied volume (Eq. (3)). Alteration of the linear regression slope of the fraction of molar volumes as a function of plasticizer concentration at a given concentration value signs the changes in molecular motility, thus referring to the possible formation of molecule-associates (Dredán et al., 2004b). Further studies on surface tension determination and osmolality justified these calculations results (Orbán et al., 2000) on determination of CAC.

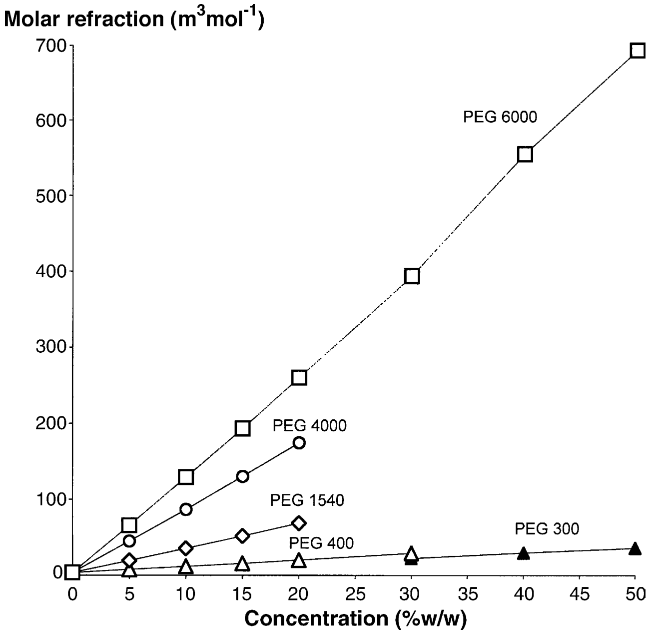


Fig. 1. Molar refraction values of PEGs vs. concentration.

As it was reported earlier (Orbán et al., 2001) along with the concentration of the plasticizer, the measured and calculated R values continuously increased. This phenomenon indicates that the molecules exist as individuals in the system, and there is no intermolecular interaction between the substituted cellulose and the PEG molecules in the examined concentration range (Table 2).

The increase in the occupied volume refers to the improved molecular mobility. It is assumed that as the dibutyl sebacate concentration increases there is an increase in the free volume of the polymer; thus, the total volume occupied by a given number of molecules will increase (Zelkó et al., 2002). It enables more movement of molecular groups and side chains (Table 3). Table 4 summarizes the measured (R_m) and the calculated (R_c)

Table 1
Slope and linear regression accuracy values of PEGs R calculations

Molecular weight	Concentration range (%, w/w)	Linear regression slope	R^2
300	30–70	0.73	0.992
400	0–30	1.01	0.991
1540	0–20	3.48	0.993
4000	0–20	8.73	0.999
6000	0–30	12.97	0.999
	30–50	*13.73*	*0.987*

Table 2
Changes of the deviations of the calculated R_c values from the measured R_m and space-filling factor (r) in HPMC (94 cPs, 0.5%, w/w) aqueous solutions containing different amounts of PEG 1540

PEG 1540 (%, w/w)	R_m ($m^3\ mol^{-1}$)	R_c ($m^3\ mol^{-1}$)	r	S.D.	Rel. S.E.
0	31.13	31.13	0.2063	0.00	0.0
5	47.35	50.72	0.2085	2.38	4.7
10	63.82	66.76	0.2130	2.08	3.1
15	80.56	83.20	0.2168[a]	1.87	2.2
20	97.71	99.94	0.2212	1.58	1.6
25	115.13	118.01	0.2237	2.04	1.7

[a] Linear regression slope-changing concentration, below this the slope 0.01144, above 0.00924, showing the change in occupied volume.

Table 3
The Lorentz–Lorenz plot $(R_m - R_c)/R_m$ values (%) of free films of Pharmacoat 606 containing different plasticizers

Plasticizer concentration (%, w/w)	PEG 400	DBS
5	0.63	11.70
10	0.20	12.48
20	1.09	12.74

Table 4
Measured (R_m) and calculated (R_c) molar refraction values of different Eudragit RL30D—dibutyl sebacate systems (average values, $n = 6$, R.S.D. < 5%)

Dibutyl sebacate concentration (%, w/w)	R_m	R_c	$(R_m - R_c)/R_m$ (%)
0	6547.87	6547.87	0
5	6554.61	6551.09	0.01
10	6599.05	6560.43	0.60
20	6860.70	6568.23	4.30

Table 5
Lorentz–Lorenz plot values (%) of Eudragit RL 30D samples in the presence of different plasticizers

Plasticizer content (%, w/w)	PEG 6000	PEG 400	DBS	Triacetin
0	0	0	0	0
5	0.34	0.99	0.01	−0.04
10	*1.26*	0.85	0.59	−0.04
20	*2.34*	*4.45*	*4.45*	−0.04

molar refraction values of Eudragit RL 30D dispersions containing dibutyl sebacate of different concentrations. Since the molar refraction is an additive property, the molar refraction of Eudragit RL 30D coating dispersions were obtained by adding the molar refraction values of Eudragit RL 30D and those of the various plasticizers. The obtained results show (Tables 4 and 5) that along with the increase of plasticizer concentrations, differences between the measured and calculated molar refraction values also increased. In the case of 20% (w/w) DBS concentration, the calculated molar refraction difference is higher with a magnitude than that of the difference calculated at 10% (w/w) plasticizer concentration. The reason of this phenomenon could be the immiscibility of dibutyl sebacate with Eudragit RL 30D at higher than 10% (w/w) concentrations. The latter is in good compliance with our earlier published results (Orbán et al., 2000) determined by differential scanning calorimetry and positron lifetime spectroscopy measurements (Orbán, 2002). Interaction was observed between Eudragit L 30D and dibutyl sebacate, and it was confirmed by the enthalpy relaxation values measured at the glass transition temperature of cast Eudragit films commonly applied for film coating procedures. The enhanced molecular mobility of the coating polymer along with the immiscibility of the plasticizer at 20% (w/w) dibutyl sebacate concentration, confirmed by DSC, could be an underlying factor in chemical and physical instability of the examined Eudragit film coatings. Along with the increase of dibutyl sebacate concentration of the free films, the free volume of the polymer was also increased. With increasing free volume, the molecular mobility of the polymer was also increased.

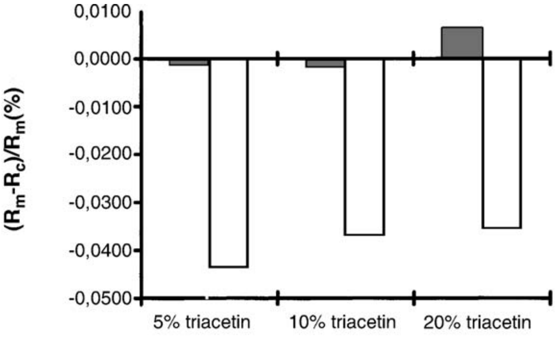
The effect of molecular weight and concentration of water-soluble PEGs on the molality of Eudragit dispersions was studied (Orbán et al., 2001). The results indicate that along with the increase of the concentration of PEGs, the molality of Eudragit dispersions also increased. In the case of PEG 400, the molality increased linearly with good correlation as a function of plasticizer concentration, while in the case of PEGs of higher molecular weights, the molality values more differed from the linear at higher concentration values. The latter refers to the possible interaction between the polymer and the plasticizer in dispersion, and it was confirmed by the molar refraction calculations based on the Lorentz–Lorenz equation.

Increase in the measured R_m values to that of the calculated, refers to the presence of larger molecules in the polymer mixture (e.g. molecular associates) or swelling of the plasticizer in the film forming material (Table 5).

Decrease of the measured R_m values was detected in the examined range of PEG molecular masses at the given concentration (10 %, w/w). A possible explanation of the phenomena could be the formation of hydrogen bridges between PEG molecules and the free –COOH groups of Eudragit chains (Table 6). By this process, the structure of Eudragit would be more ordered and these presumed hydrogen bridges could fix the distance between the polymeric chains, causing the subsequent decrease of the size of occupied and free volume holes of the film coating polymer. The latter was observed and interpreted by several authors (Gapochenko and Belozertseva, 2001; Horn, 1978; Mergel et al., 2000). This effect is more dominant in the case of PEGs of higher molecular mass. A magnitude difference

Table 6
Deviation of measured R_m from the calculated R_c values of Eudragit L 100-55 samples at 10% (w/w) PEG plasticizer content

Molecular weight of PEG	R_m ($m^3\ mol^{-1}$)	R_c ($m^3\ mol^{-1}$)	|S.D.|
Without PEG	3253.29	3253.29	0
400	*3182.35*	3264.96	17.39
1540	*3184.83*	3288.92	104.09
6000	*3280.70*	3382.76	102.06



	5% triacetin	10% triacetin	20% triacetin
▨ Eudr.L100-55	-0,0012	-0,0017	0,0064
☐ Eudragit RL 30D	-0,0436	-0,0368	-0,0352

Fig. 2. Lorentz–Lorenz plot values of Eudragit RL 30D and LI 00-55 film samples in the presence of triacetin plasticizer.

was obtained in the deviations of the measured and calculated R values depending on the molecular mass of the PEG. In the case of solid PEGs of higher molecular mass (PEG 1540 and 6000) the absolute STD was a magnitude higher than in the case of liquid PEG (PEG 400).

Negative Lorentz–Lorenz plot values were checked by monitoring different cast films of Eudragits containing triacetin (Fig. 2). Similar results were obtained in the case of Eudragit-PEG systems.

Information can be obtained concerning the extent of interaction between the polymer and the plasticizer from the calculation of molar refraction values of film forming polymer dispersions containing plasticizer. Theoretical results based on the calculation of molar refraction values of the selected polymer–plasticizer system were in good compliance with the results of applied physicochemical methods that characterize the film forming behaviour of polymers.

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