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EFFECT OF PLASTICIZERS ON THE PHYSICOMECHANICAL PROPERTIES AND CHLORPHENESIN RELEASE FROM EUDRAGIT FILMS

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ABSTRACT

The effect of water soluble and insoluble plasticizers on the physicomechanical properties of Eudragit RS 100, RSPM and S 100 was investigated. The plasticizing efficiency was evaluated by measuring the mechanical properties e.g. modulus of elasticity, tensile strength and percent of elongation of the polymeric films. The results showed that the plasticizer effect was dependent on hydrophilicity and chemical structure of both the plasticizers and polymers. The interaction of plasticizers with the polymers was also concentration dependent. The efficiency of pasticizers could be arranged in the following order: glycerol triacetate > glycerol> propylene glycol > polyethylene glycol 400 > dimethylphthalate > diethylphathalate. Also, the moisture absorption capacity was considerably increased by plasticizers in the following order: glycerol> glycerol triactate> polyethylene glycol 400 > propylene glycol> dimethylphthalate > Diehtylphthatlate. The release profile of chlorphenesin was also significantly increased by the polyol plasticizers rather than the organic esters. Moreover, the drug release pattern was found to be following Higuchi diffusion model.

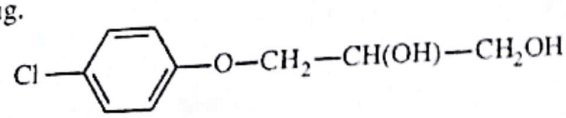
INTRODUCTION

The use of drugs dispersed in inert polymer matrices to formulate a dermal polymeric films has received considerable attention[1-4]. Many polymers used for topical film formulation exhibit brittle properties under normal ambient temperature and humidity conditions. The incorporation of a plasticizer is necessary to obtain a proper topical film without defects such as hardness, brittleness and splitting. Plasticizers are also added to polymeric films to increase the flexibility or distensibility of polymeric material.

The addition of plasticizer may affect the modulus of elasticity, the tensile strength and the percent of elongation[5,6]. For a plasticizer to be effective, it must be able to diffuse and interact with the polymer chain and to have a minimal or no tendency for migration, exudation or volatility[7-9]. Thus, physico-mechanical testing can be used as a useful guide in predicting not only the film integrity performance[10] but also in comparing the effect of plasticizers in film samples as a function of formulation, compatibility, type and concentration[11-13].

In addition, the incidence of hardness, brittleness or cracking as well as the effect of aging and storage conditions[14] can be predicted from physico-mechanical testing. Environmental factors may appreciably affect the mechanical properties and the stress-strain relationships of certain polymeric films. Flexible ethylcellulose films of maximum tensile strenth can be obtained when highly non-polar solvents are used such as toluene, xylene or methyl isobutyl ketone which have no affinity to water. Brittle films with relatively poor strength usually resulted when polar solvents such as acetone or alcohol are used[15]. The mechanical parameters may be used in comparing film samples as a function of formulation factors, surfactant added and solvent system or polymer combination.

This study was designed to examine the effect of different plasticizers on the physico-mechanical properties of Eudragit polymeric films. Furthermore the mechanical parameters and moisture absorption capacity were correlated with the chemical structure of both the plasticizer and Eudragit polymer. Chlorphenesin was incorporated in the films to study the effect of plasticizers on the release profile of the drug.



chlorphenesin

MATERIALS AND METHODS

Materials:

Chlorphenesin (BDH chemicals Ltd., Poole, England), Glycerol triacetate GTA, Dimethylphthalate DMPh and Diethylphthalate DEPh (Merck. Suhuchardt, Munchen, Germany), Eudragit RS100, RSPM, S100 (Rohm Pharma, GMBH Darmstadt, Germany), Polyethylene glycol PEG 400, Glycerol, Propylene glycol PG (El-Nasr Company, Egypt), Cathetometer, (W. George and Becker, Birmingham, London), Load deformation machine (W. Tester Amsler, Germany), Thickness micrometer (Cord type) Tesa Master, Tesa, Switzerland), Dissolution test apparatus (Pharmatest, Germany).

Methods:

Preparation of Eudragit films: A specified weight of Eudragit polymer and chlorphenesin were gradually

transfered to 100ml beaker containing 20 ml of the casting solvent (chloroform), gently stirred for 2 hrs and the final volume was adjusted to 25 ml using the casting solvent to give 4% w/v polymeric solution. The casting solution was transfered into previously cleaned and dried Teflon-coated plate (50.24 cm^2) and covered with inverted glass funnel of stem orifice 0.6 cm diameter.

The solvent was allowed to evaporate for 72 hrs and the film was removed and dried in open air for 48hrs. Rectangular films (2.5x6.0 cm), 20 mg drug content, were obtained by cutting the film with a razor blade using a rectangular piece of glass as a template. The films were wrapped in an aluminium foil, stored at room temperature and subjected to evaluation within one week.

Determination of the mechanical properties of films:

Dried film sample of 50±7 um thickness was cut to uniform size of 2.5 x 6 cm using a sharp razor blade. Two pieces of cardboard (1 x 2.5 cm) were attached to the upper and lower ends of the film using cyanoacrylate resin adhesive. The film (exposed area 4.00 x 2.5 cm) was clamped between the two jaws of the machine. The load automatically applied to the film was gradually increased and the corresponding magnitude of elongation was recorded by means of cathetometer microscope until the break point of the film was reached. The effect of different types and concentrations of the plasticizers on the physico mechanical properties of Eudragit polymeric films was studied. The concentration of each plasticizer used was 10 and 20% w/w of polymer. Three types of Eudragit polymers were used, Eudragit RS 100, RSPM and S100. All the Eudragit films contained the same concentration of chlorphenesin (20 mg/film).

Calculation of the mechanical parameters: Both film breaking load and percent of elongation were determined. The stress strain curves were drawn from the obtained data and the tensile strength of the film was calculated from the breaking load and the cross-sectional area of the film as represented by the following equation:

$$\textbf{Tensile strength} = \frac{\text{Breaking load (kg)}}{\text{cross-sectional area of film } (cm^2)}$$

The percent of elongation was calculated according to the following equation:

$$\textbf{Percent of elongation} = \frac{L_s - L_o}{L_o}$$

where:

Lo = original film length

Ls = Film length after elongation.

The modulus of elasticity was calculated from the slope of the linear parts of the stress- strain curve for each film.

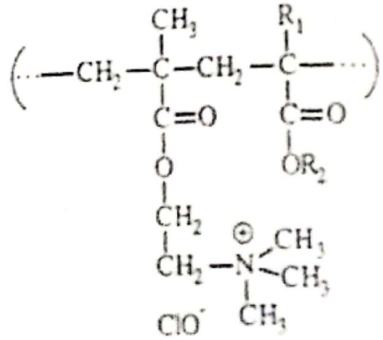
Determination of moisture absorption capacity of films:

A.S.T.M. test No DS 70 - S9T (Approved by American society for testing materials) was applied. Films (4.0 x 2.5 cm) were conditioned by placing them in a dessicator containing silica gel for 48 hrs before use. The conditioned films were then suspended by means of fine wire in a humidity chamber (Saturated aqueous solution of potassium sulfate RH 97% at 25°C in 100 ml glass bottle). The films were weighed every 24 hrs for fourteen days. The percentage of moisture asborption was then calculated by the following equation :

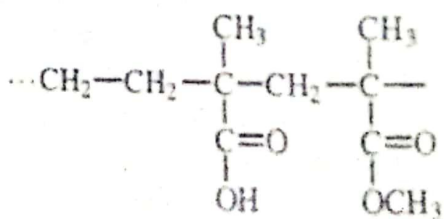
$$\% \text{ of moisture absorption} = \frac{\text{wt. of exposed film- wt. of dry film}}{\text{wt. of dry film}}$$

Drug release from films: The films was adhered onto a glass microscopic slide (2.5 x 7.5 cm) using silicone adhesive. 75 ml of citrate buffer pH 5.03 at 23 ±0.5°C was used as dissolution medium. The slide with the film was placed at the bottom of the dissolution medium vessel and the stirrer was allowed to rotate at 25 rpm (the optimum speed to avoid film rupture). Samples were withdrawn at time intervals for drug analysis spectrophotometrically at 280 nm.

Eudragit RS 100



R_1=H, CH_3 R_2=CH, C_2H_5



Eudragit S 100

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RESULTS

The modulus of elasticity and tensile strength values for non plasticized films were found to be high, which is indicative of the brittleness and hardness of those films. Fig. (1) shows that the addition of plasticizers had a considerable effect on both modulus of elasticity and tensile strength of the medicated Eudragit RS100, RSPM and S100 films, and the observed effect was dependent upon the plasticizer concentration. The addition of water soluble plasticizers e.g. glycerol, glycerol triacetate, propylene glycol and polyethylene glycol 400 resulted in a remarkable decrease in the values of the two parameters, and the reducing efficiency in Eduragit RS100 and RSPM could be arranged as follows: GTA > glycerol > PG > PEG 400 while in the case of Eudragit S100 the order was; glycerol > GTA > PG > PEG400.

On the other hand, the addition of water insoluble plasticizers e.g. Dimethylphthalate and diethylphthalate resulted in a very small changes, although DMPh was more efficient than DEPh.

The values of modulus of elasticity and tensile strenth of different polymers were observed to be in the following order: Eudragit S100 > RSPM > RS100.

Fig. (1) also shows that the addition of different plasticizers resulted in increasing the percent of elongation to varying extents. Again, the water soluble plasticizers showed a higher efficiency than water insoluble ones in affecting such parameter. Regarding the percent of elongation, the three polymers could be arranged as follows: Eudragit R S100 > RSPM > S100.

From the data listed in table (1), it is obvious that the capacity of medicated eudragit RS100 films to absorb moisture was slightly greater than that of Eudragit RSPM films. On the other hand, the amount of moisture absorbed by Eudragit S100 films was negligable within the time of the experiment. From the obtained results, the effect of different plasticizers on increasing the moisture absorption capacity of Eudragit films was concentration dependent and could be arranged in the following order:

Glycerol > GTA > PEG400 > PG > DMPh > DEPh.

Fig (2) shows the effect of different plasticizers on the release profile of chlorphenesin from different polymeric films. The effect of plasticizers could be arranged as follows:

Glycerol > GTA > PEG400 > PG > DMPh > DEPh.

Fig (2) shows the effect of different plasticizers on the release profile of chlorphenesin from different polymeric films. The effect of plasticizers could be arranged as fllows:

Glycerol > GTA > PEG400 > PG > PMPh > DEPh.

It could be noticed form fig. (3), where log release rate constant was plotted against the fraction of the plasticizer, that the effect of plasticizers was concentration dependent. Moreover, the linearity in the same figure proves that the release of chlorphenesin follows Higuchi pattern.

DISCUSSION

The modulus of elasticity is an important parameter in determining the degree of hardness, flexibility and stifness of the polymeric film. This parameter is calculated from the slope of the straigth line portion of stress - strain curve. The high values of both modulus of elasticity and tensile strenght for Eudragit S100 films than that of RS 100 and RSPM explaning the brittlness and hardness of such films. The inclusion of chlorphenesin in the three types of films reduced the modulus of elasticity and tensile strength which could be attributed to the weakening of the polymer intermolecular binding allowing the polymer molecules to move more freely resulting in an increase in the flexibility of the medicated films. For the same reason a considerable increase in the percent of elongation was noticed by the inclusion of the drug.

From the presented results, GTA had the greatest effect on reducing the tensile strength, modulus of elasticity and increasing the percent of elongation for Eudragit RS100 or RSPM. This may be attributed to the probability of electrostatic forces between the carbonyl oxygen of ester group in GTA molecule and the positively charged nitrogen (N+) of the quaternary ammonium group in the polymer molecule. Also, the electrophilicity of ester oxygen rendered the hydrogens attached to C1, C2 and C3 of GTA molecule more nucleophilic, therefore an additional probabiltiy of hydrogen bonding between those nucleophilic hydrogens and the carbonyl oxygen of ester group of the polymer. This would lead to weakening of the polymer intermolecular attractions and increasing the flexibility of the films.

Glycerol came after GTA in affecting the mechanical parameters due to the probability of hydrogen bonding between the three hydroxyl gorups of glycerol molecule and the carbonyl oxygen of the polymer which is weaker than the interaction of GTA. On the other hand, glycerol had the greatest effect in Eudragit S100 films. This could be explained by the probability of hydrogen bonding between the free hydroxyl groups of glycerol and either the carbonyl oxygen of the ester group or that of the carboxylic group. The two probabilities of hydrogen bonding, in

Table (1): Moisture absorption capacity (w/w %) of chlorphenesin polymeric films after fourteen days of conditioning and plasticized with different plasticizers.

Polymeric film type	Percentage of moisture absorption capacity (w/w) non-plasticized	glycerol	GTA	PEG400	PG	DMPh	DEPh
Eudragit RS100	35.62	62.48[a]	58.18	55.48	49.36	44.15	42.39
		68.35[b]	63.72	57.23	52.58	47.10	45.56
Eudragit RSPM	34.41	61.30[a]	57.92	51.44	46.22	41.73	39.66
		66.02[b]	60.78	53.36	48.13	44.22	41.29
Eudragit S 100	0.00	38.21[a]	33.39	24.86	26.52	21.33	16.11
		42.48[b]	38.10	28.86	34.86	27.04	23.63

a = 10% plasticizer b = 20% plasticizer

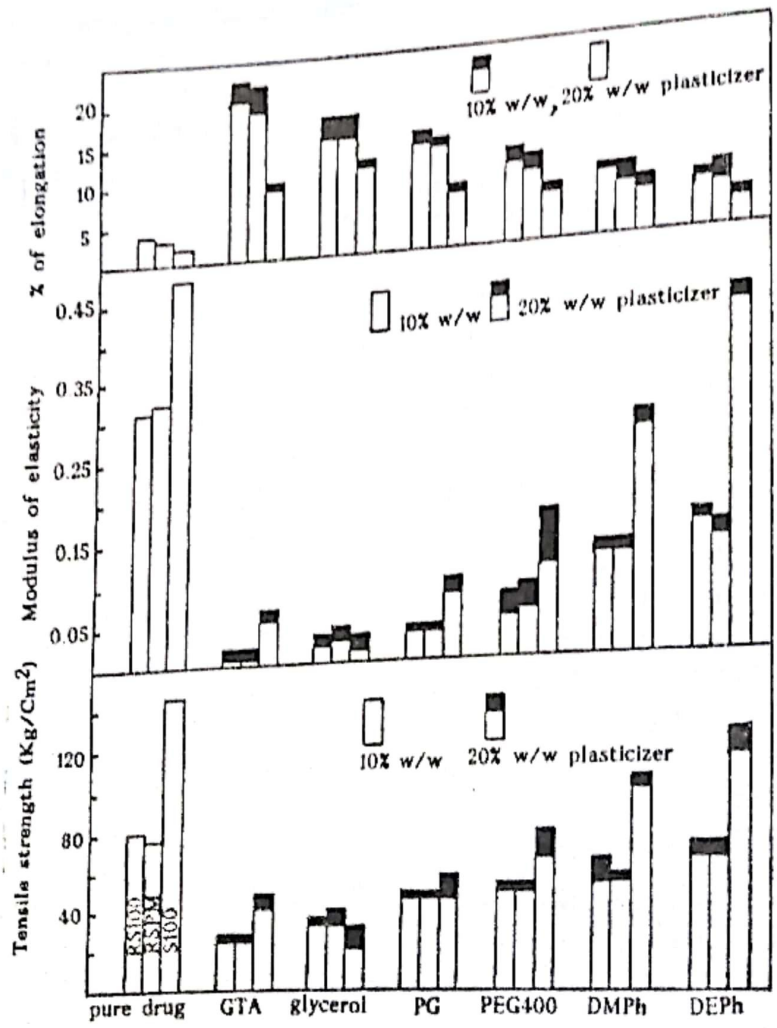

Fig (1): The effect of plasticiziers on physico-mechanical properties of eudragit, RS100, RSPM, and S100 films containing 20 mg chlorphenesin.

addition to the smaller molecular volume of glycerol rendered glycerol occupying the first sequence. GTA came after glycerol on the basis of probability of hydrogen bonding between the carbonyl oxygen of GTA and hydroxyl group of the polymer. The slightly nucleophilic hydrogen adjacent to C1, C2 and C3 in GTA molecule will tend to form a weak hydrogen bond with the carbonyl oxygen of both carboxylic group and ester group of the polymer.

Propylene glycol has two free hydroxyl groups which can form hydrogen bonds with carbonyl oxygen of both Eudragit RS100 and S100 molecules. It could be expected that the probability of hydrogen bonding by hydroxyl group No. 2 is hindered by the alkyl side chain (methyl group) resulting in a reduction of accessibility of this hydroxyl group to be bound with the carbonyl oxygen of the polymer. Therefore, propylene glycol had a moderate ability to break the polymer intermolecular attractions and hence had a lower effect than glycerol and GTA.

PEG 400, as a water soluble plasticizer had the lowest ability to increase the flexibility of both Eudragit RS 100 or S 100 for two possible reasons: first, PEG 400 has a higher molecular volume when compared to other water soluble plasticizers, thus hindering its ability to diffuse and interact with the active groups in the polymer molecules. Secondly the only probability of bonding was found to be between the electronegatively charged oxygen of ethylene oxide unit and the positively charged nitrogen of the quaternary ammonium group (in Eudragit RS100) or with the hydroxyl group of Eudragit S 100.

For water insoluble plasticizers DMPh and DEPh, it was found that DMPh was more efficient than DEPh in improving the mechanical properties of the films i.e. reduction of both modulus of elasticity and tensile strength and increasing the percent of elongation. This could be explained by considering the electrostatic forces between carbonyl oxygen of ester group in the plasticizer and the nitrogen of quaternary ammonium group (in Eudragit RS 100) or with the hydroxyl group of Eudragit S 100. DEPh had a lower ability to be bound with polymer molecules when compared to DMPh due mainly to the hinderance of the bulky ethyl group. The presence of aromatic moiety (benzene ring) may also weaken the electronegativity of the carbonyl oxygen in the plasticizer molecule leading to a lower accessibility for bonding.

The chemical structure, physical properties and other standard specifications for Eudragit RSPM are the same as for Eudragit RS 100 with the exception that Eudragit RSPM occurs as a powder of medium finess and contains 0.5% talc. The study proved that Eudragit RSPM has almost the same ability to be affected with all plasticizers as Eudragit RS 100 but to a lower extent due mainly to the presence of talc.

Moisture absorption capacity by polymeric films represents one of the physical properties of considerable significance in determining the degree of drug release from the polymeric films. There is a direct proportionality between the amount of moisture absorbed and the degree of drug release.

From the data listed in Table (1), it is obvious that the capacity of Eudragit RS100 films to absorb moisture was slightly greater than that of Eudragit RSPM. This could be explained by considering that the presence of talc in Eudragit RSPM may fill the interstices of the polymer or acting as a water repellant. However, in the case of Eudragit S100, there was a negligable amount of moisture absorbed within the time of experiment. This may be attributed to the strong polymeric compactness due to the intermolecular hydrogen bonding between carboxylic and ester groups. So, Eudragit S100 possesses a water proof character. From the obtained data, it can be seen that the effect of plasticizers on the moisture absorpton capacity could be arranged in the following order: Glycerol> PEG400> GTA > PEG 400 > PG > DMPh > DEPh.

This arrangement is in good agreement with the hydrophilic nature of the plasticizers.

Two proposed factors could be taken into consideration to explain the effect of plasticizer content on drug release profile. The first is that the plasticizer may decrease the degree of compactness of the polymeric matrix due to their bonding to the polymer molecules and forming pores through which the drug leaches out. Secondly is the solubility of the plasticizer in water through hydrogen bonding leading to an increase in the hydrophilic properties of the matrices and formation of hydrated channels.

This would explain the higher effect of water soluble plasticizers on drug release rate from the polymeric matrix. Glycerol which is the most hydrophilic water soluble plasticizer facilitates more hydration of the film on exposure to the dissolution medium and consequently more hydrated channels in the film would be created. This assumption of glycerol leaching throughout the film may explain the spongy wetted appearance of the film at the end of the dissolution experiment.

Therefore, the increase in the concentration of the plasticizer would result in increasing the amount of

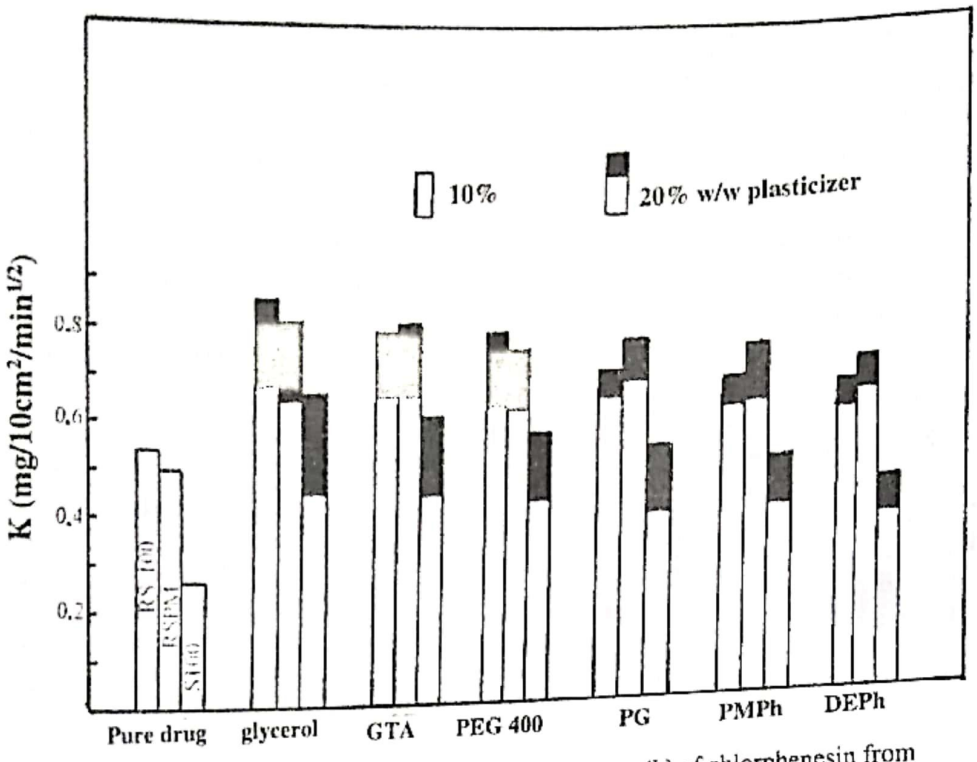

Fig (2): Effect of plasticizers on release rate constant (k) of chlorphenesin from Eudragit RS 100, RSPM and S100 films.

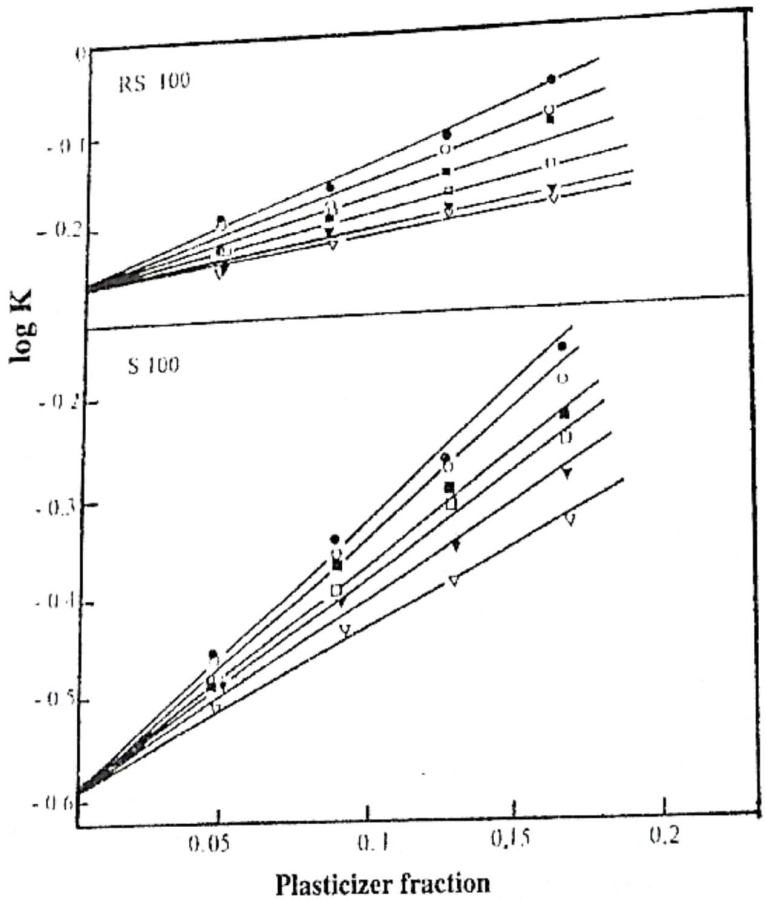

Fig (3): Relationship of plasticizer fraction to log K in Eudragit RS 100, S100 films containing 20 mg chlorphenesin per film. (● glycerol, ○ GTA, ■ PEG 400, □ PG, PMph, DEph).

drug release through: increasing the amount of leached plasticizer, increasing the probability of hydrated channels formation and increasing the degree of porosity. This may explain the smaller amount of drug released from films plasticized with the water insoluble plasticizers DMPh and DEPh where only limited hydrated voids may be created by these plasticizers. Moreover, the presence of bulky ethyl group attached to benzene ring in DEPh would markedly decrease the hydrophilic nature when compared to DMPh.

Plotting log K against the fraction of plasticizer used, fig. (3) linear relationship was obtained according to the following equation derived from Higuchi model (16).

$$\log K = K_D F_P + \log K_E$$

where K_D = constant specific for each drug

F_P = fraction of plasticizer in the film.

K_E = release rate constant of film composed of nonplasticized matrix.

This linear relationship is an indication parameter to explore the effect of plasticizer content on the release profile of the drug.

REFERENCES

(1) Sciarra, J.J. and Gidwani, R.N., **J. Soc. Cosmet. Chem.**, 21, 667 (1970).

(2) Sciarra, J.J. and Gidwani, R.N., **J. Pharm. Sci.**, 61, 754 (1972).

(3) Bodmeier, R. and paeratakul, O., Int. J. Pharm; 59, 197 (1990).

(4) Bodmeier, R. and Paeratarkal, O., J. Pharm. Sci.l., 79, 32 (1990).

(5) Nielsen, L.E., "Mechanical Properties of Polymers and Composites", Dekker, New York, Vol. 1, pp. 189 - 190 (1974).

(6) Gutierrez-Rocca, J.C. and McGinity, J.W., **Intl. J. Pharm.**, 103, 293 (1994).

(7) Sears, J.K. and Darby, J.R., "The Technology of Plasticizers". Wiley, New York, pp 480 - 577 (1982).

(8) Jenquin, M.R. and Mc Ginity, J. W., Int. J. Pharm., 101, 23 (1994).

(9) Bodmeier, R. and Paeratakul, O., ibid, 96, 129 (1993).

(10) Goohart, F.W., Harris, M.R., Murthy, K.S. and Nesbitt, R.M., **Pharm. Tech**., 8, 64 (1984).

(11) Bindschaedler, C., Gurny, R. and Doelker, E., **J. Pharm. Pharmacol**., 39, 335 (1987).

12- Kassem, m.A., Tayel, S. and osman, A.A., Egypt. j. Pharm. Sci., 33, 539 (1992).

13- Bodmeier, R. and paeratakul, O., Drug Dev. Ind. Pharm., 18, 1865 (1992).

(14) Row, R.C. and Forse,S.F., **ibid**., 33, 174 (1981).

(15) Munden, B.J., Dekay, H.G. and Banker, G.S., **J. Pharm. Sci**., 53, 395 (1964).

(16) Samuelov, Y., Donbrow, M. and Friedman, M., **ibid**., 68, 328 (1979).

تأثير الملدنات على الخواص الطبيعية الميكانيكية

وانطلاق عقار الكلورفينيزين من أغشية الإيدراجيت

محمد سلامه - فخر الدين غازى - أحمد بصيله - أحمد اسماعيل

قسم الصيدلانيات - كلية الصيدلة - جامعة الزقازيق

فى هذا البحث تم دراسة تأثير الملدنات الذائبة وغير الذائبة فى الماء على الخواص الطبيعية الميكانيكية للإيدراجيت S100, RSPM, RS 100. وقد تم تقييم القدرة على التلدين بقياس الخواص الميكانيكية مثل معامل مودلس وقوة الشد ونسبة الاستطالة للأغشية. وقد أوضحت النتائج أن تأثير الملدنات يعتمد على الميول المائى والتركيب الكيميائى لكل من الملدنات والبلمرات. كما أن التفاعل بين الملدنات والبلمرات يعتمد أيضا على التركيز.

ويمكن ترتيب كفاءة الملدنات كالآتى:

ثلاثى خلات الجلسرين > جلسرين > بروبيلين جليكول > عديد الإيثيلين جليكول ٤٠٠ > ثنائى ميثيل الفثالات > ثنائى ايثيل الفثالات.

وقد لوحظ أن القدرة على امتصاص الرطوبة زادت زيادة ملحوظة فى وجود الملدنات حسب الترتيب الآتى:

جلسرين > ثلاثى خلات الجلسرين > عديد الإيثيلين جليكول ٤٠٠ > بروبيلين جليكول > ثنائى ميثيل الفثالات > ثنائى ايثيل الفثالات وقد زاد معدل انطلاق عقار الكلورفينزين بصورة واضحة فى وجود الملدنات عديدة الهيدروكسيل أكثر من لدانات الاسترات العضوية بالاضافة الى ذلك وجد أن انطلاق العقار يتبع نموذج هيجوشى الإنتشارى.