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PHYSICOMECHANICAL PROPERTIES AND RELEASE CHARACTERISTICS OF KETOROLAC TROMETHAMINE FROM CHITOSAN FILMS: EFFECT OF INCLUSION OF DIFFERENT POLYOLS PLASTICIZERS

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تم في هذه الدراسة تقييم تحضير أغشية بوليميرية من الكيتوزان والمحملة بعقار كيتورولاك تروميثامين باستخدام طريقة تبخير المذيب من المحلول المائي المحتوي على الملدنات وغير المحتوي عليها. وقد تم استخدام الجليسرول، السوربيتول و ١، ٤ اريثريتول كملدنات عديدة الهيدروكسيل. كما تم في هذه البحث أيضا دراسة الخواص الفيزيوميكانيكية للاغشية عن طريق دراسة حيود الأشعة السينية والمسح السعري التفاضلي. شملت الدراسة أيضا تقييم كفاءة تلدين الاغشية وذلك بقياس معامل المطاطية وقوة الشد ونسبة الاطالة. وقد دلت النتائج المستقاة من البحث أن الاغشية البوليميرية المحملة بالعقار الملدنة والغير ملدنة كانت عديمة اللون، وقد كان تركيز ٢٠% من المواد الملدنة كافيا للحصول على أغشية مرنة. وقد برهنت دراسات حيود الأشعة السينية والمسح الحراري التفاضلي على وجود العقار في الشكل اللابلوري في الأغشية دون الاعتماد على نوع الملدن المستخدم. أشارت النتائج كذلك الى أن اضافة الملدنات عديدة الهيدروكسيل سالفة الذكر قد حسن من قوام الأغشية وكذا الخواص الفيزيوميكانيكية لها. وقد بينت النتائج أن تأثير تلك الملدنات كان متوقفا على التركيب الكيميائي والميل للوسط المائي لكل من الملدنات والكيتوزان. أخيرا أشارت الدراسة أن معدل الانطلاق المعملي للعقار قد زاد زيادة ملحوظة باضافة الملدنات عديدة الهيدروكسيل، كما وجد أن الانطلاق المعملي للعقار قد تبع معادلة هــيجوشي للانتشار.

The film-forming ability of chitosan polymer loaded with ketorolac tromethamine (KT) was evaluated. Films were prepared by a casting/solvent evaporation technique from plasticizer - free

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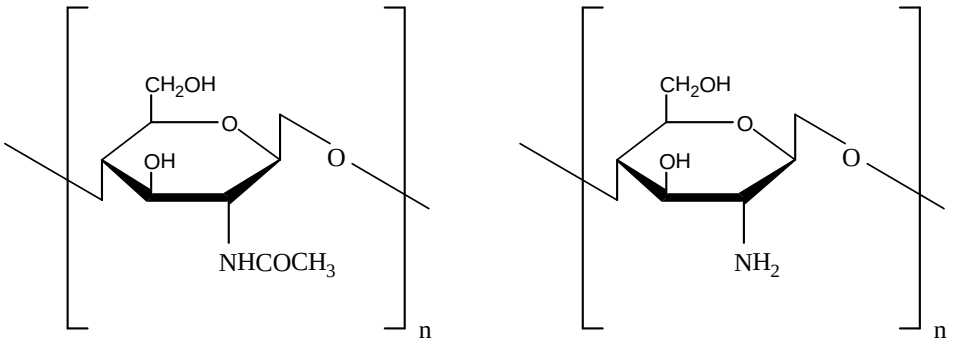
and plasticizer containing aqueous solutions. Glycerol, sorbitol, and 1-erythritol were used as plasticizers. Solid state of the films was studied by powder X-ray diffractometry (PXRD), and differential scanning calorimetry (DSC). The plasticizing efficiency was evaluated by measuring the physicomechanical properties as modulus of elasticity, tensile strength, percent of elongation and swelling ratio. The medicated films - plasticized or free - were clear and colorless. A plasticizer concentration of 20% (w/w of polymer weight) was sufficient to obtain flexible films with all tested samples. X-ray diffration patterns and DSC thermograms indicated an amorphous state of the films independent on the type of the plasticizer used. The results have showed that, incorporation of different polyols as plasticizers improves the consistency and the physicomechanical properties of the films. The plasticizers effect was dependant on the hydrophilicity and chemical structure of both plasticizer and polymer. The release profile of the drug was also significantly increased by addition of polyols as plasticizers. Moreover, the drug release pattern was found to follow Higuchi-diffusion model.

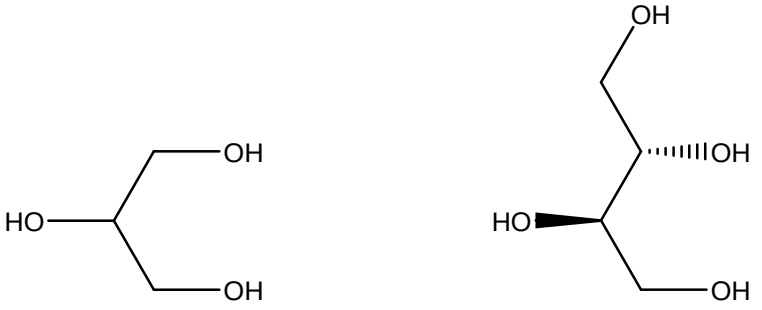
INTRODUCTION

Chitosan (Fig. 1A) is a cationic natural polysaccharide generally considered as a safe, biocompatible and biodegradable material[1]. During the last 20 years, chitosan has been evaluated for numerous pharmaceutical applications (e.g. direct compressible vehicle, wet granulation excipient, wetting agent, gel forming material, emulsifying agent and recently as a film coating agent). Commercially available chitosan is not well characterized regarding molecular weight as well as degree of deacetylation, therefore, it must be necessary to continue investigation the physico-mechanical characteristics of chitosan films for the *in-vitro* as well as *in-vivo* performance. Higher molecular weight chitosan has been reported to have good film forming properties as a result of intra- and intermolecular hydrogen bond[2]. The chitosan film characteristics, however, varied from one study to another. Difference in the sources of chitin used to produce chitosan, chitosan material properties, solvents used methods of film preparation, types and amounts of copolymers and plasticizers used may affect the physicochemical characters of the obtained polymeric films[3].

Chitosan has also been assessed for its potentiality in the development of controlled release systems and for targeting drugs to specific sites[4]. Various drug delivery systems based on chitosan have been described in the literature[5]. The potentiality of



Chemical structure of N-acetyl glucosamine (**A**) and glucosamine (**B**)

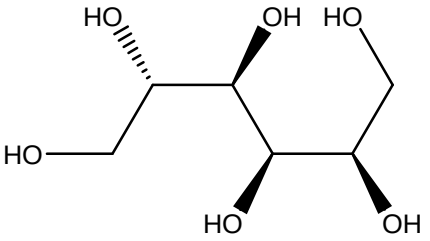


glycerol

C

erythritol

D



sorbitol

E

Fig. 1

chitosan in sustained release system has been assigned to its polymer character, including gel - as well as film-forming properties. The incorporation of a plasticizer is necessary to obtain a proper film with optimum physicomechanical properties defects such as hardness, brittleness, and splitting. Plasticizers are added to polymeric films to increase the flexibility or distenibilty of polymeric materials. For a plasticizer to be effective, it must be able to diffuse and interact with the polymer chain and must be able to have a minimal or no tendency for migration, exudation or volatility[6]. Physicomechanical testing can be used as a useful guide in predicting not only film integrity performance[7] but also in comparing the effect of plasticizers in film samples as a function of formulation, compatibility, type and concentration[8]. The mechanical parameters may be used for comparing film samples as a function of formulation factors, surfactant added and solvent system or polymer combination[9].

In the present study, chitosan films prepared by solvent evaporation technique were evaluated. The morphology, solid-state properties and the effect of different plasticizers on the physicomechanical properties of chitosan films were investigated. Furthermore, the mechanical parameters and swelling ratio were correlated with the chemical structure of both plasticizer and chitosan polymer. Ketorolac tromethamine was selected as a model drug. It is a potent nonsteroidal anti-inflammatory drug, used practically for the treatment of pain. However, it has side effects including GI irritation when administered orally[10]. One promising method is to administer the drug via skin.

The main aim of this work was to develop medicated chitosan films to study the effect of polyol plasticizers on both physicomechanical properties and the release profile of the drug.

EXPERIMENTAL

Materials

- Chitosan grades HV* (highly viscous), degree of deacetylation (%DD) 75%, MW 800.000-1000,000) Sigma-Aldrich chemical Company Inc., (Milwaukee, Wi, U.S.A).
- Ketorolac tromethamin (KT) was a gift sample from Al Ameria company, Alex., Egypt.
- Acetic acid, potassium dihydrogen orthophosphate, sodium hydroxide, anhydrous calcium chloride, ammonium chloride and Glycerol were obtained from [El-Nasr pharmaceutical chemicals Co., Egypt].
- Sorbitol (Ph Eur) and 1-erythritol were obtained from (Sigma-Aldrich Chemical Company, Steinheim, Germany).
- Silicon adhesive [super Automotive and consumer products Co., U.S.A.].

- All other chemicals used were of analytical grade and used as received.

Equipment

- Double beam spectrophotometer (Shimadzu, UV-150-02).
- Dissolution-test apparatus, SR11 6-flask (Hanson research, USA)
- Electronic digital balance (Metler–Toledo, Ag, CH–8606, Greifensce, Swizerland)
- Electronic digital Micrometer 0.25 mm [MIME technology Europe, Moastricht,Netherlands].
- Digital pH meter [Ama Co., Germany].
- DSC–50 Differential scanning Calorimeter (Schimadza) from [Shimadzu, Seisakusho Ltd., Kyoto, Japan].
- JEOL, scanning electron micro-scope [JSM–5200, Japan].
- X-ray diffractameter [Phillips Co., NetherLands].
- Teflon plates used as a casting substrate (8 cm in diameter) and glass funnels (diameter of the stem aperture was 0.6 cm).

Methods

Film preparation

The films were prepared by a casting solvent evaporation technique as follows: a weighed amount of chitosan (2.5 g) was dissolved in an aqueous acetic acid solution (25 ml) with a constant stirring for 48 hours to give chitosan solution (10% w/v). For the preparation of medicated films, 0.01 g of ketorolac trometamine (KT) [4% w/w of polymer] was dissolved in 10% w/v chitosan polymer with or without different types of plasticizers at 20% w/w of polymer (Glycerol, sorbitol and 1-erythritol). The resultant solution was left to stand until all air bubbles disappeared, then 8.5 ml of the bubble free liquid was poured into circular teflon mold (8 cm in diameter) on dust–free–leveled surface, and left to dry at room temperature (25±0.5°C) for 24 hours. The dried films were evaluated within one week after their preparation[11].

Drug content uniformity of the films

To ensure uniform distribution of KT in the prepared films, a content uniformity test was performed. Samples representing different regions of the film were cut and weighed, and KT was extracted with 1:1 solvent of acetonitrile and ethyl alcohol (V/V) twice for 12 hours at room temperature. The extracts were kept and the absorbance was measured spectrophotometrically at 324nm, and the drug concentration was calculated.

Film thickness

The film thickness was determined at ten points of the film, using digital micrometer, and the film thickness was evaluated and found to be 27±0.2 μm.

Viscosity determination of plasticized chitosan solution

The viscosity of chitosan solutions in aqueous acetic acid was determined using Ul-Adaptor of

speed of 0.3 RPM at 37°C. After a specified time of 5 minutes a constant reading was taken.

Scanning electron microscopic studies of the prepared films

The cross sections of the chitosan films were examined by electron microscopy (SEM). The test sample was attached to the metal stubs with double pressure sensitive adhesive tape and coated with a thin layer of platinum to improve the conductivity. Scanning electron photomicrographs were taken at 15000 x magnification.

X-ray diffraction

The X-ray diffraction patterns on powder and medicated films (free or plasticizers) were obtained using a Philips 1700 series diffractometer. The apparatus is equipped with a curved graphite crystal mono-chromater, automatic divergence slite and automatic controller PW/1710. The target used was CuK α radiation operating at 40 Kv and 30 mA (λ Ka= 1.54 18 A). The system was calibrated using silicon disc and/or powder (d_{111}= 3.1355 a) as an external standard. The diffraction pattern was achieved using continuous scan mode with 2θ° ranging from 40° to 60°.

Differential scanning calorimetry (DSC) of the prepared samples

DSC was carried out on chitosan powder as well as their corresponding films (free or plasticizers). The procedure involved heating the accurately weighed sample (5 mg) encapsulated in an aluminum pan at a predetermined scanning rate (10°C/min) and over a predetermined temperature range 30°C to 400°C in the presence of nitrogen flow rate of 40 ml/min. A similar empty pan was used as a reference under the same conditions. The temperature difference between the sample and the reference was represented graphically in relation to differential heat flow.

Mechanical strength measurements of the prepared films

A tensile testing instrument (Instron Model 1128-USA), was used to determine the mechanical properties of chitosan films. The films were cut into 2.5×6 cm and placed into the grips of the testing machine. The gripes are evenly and firmly tighten to a degree, which is necessary to prevent slippage of the specimen during the test, but not to the point where the specimen would be crushed.

Elongation as a function of loads added was recorded at the moment of rupture. Both film breaking and the percent of elongation at break were determined.

Tensile strength

Tensile strength can be computed from the applied load at rupture and the cross sectional area of fractured film as described in the following equation[12].

$$\text{Tensile strength} = \frac{\text{Breaking load (Kg)}}{\text{Cross-sectional area of the film (cm}^2\text{)}}$$

Cross-sectional area of the film equals to the width of the film (cm) multiplied by film thickness.

Elongation

Elongation is usually measured at the moment of the film rupture (percent of elongation at break) and can be computed from this equation:

$$\text{Percent of elongation} = (L_s - L_o / L_o) \times 100$$

Where: L_o = original film length, and L_s = film length after elongation.

The modulus of elasticity of the film was calculated from the slope of the linear parts of the stress- strain curve. Each experiment was performed in duplicate and the mean value was taken.

Determination of swelling ratio of the prepared films

A known weight of the dried films was placed in a phosphate buffer (pH= 6.8) for the required period of time. The swollen film was removed and blotted between filter paper to remove adsorbed buffer then immediately weighed. The weight of the swollen film was recorded at time intervals of 0.5, 1.0, 4.0, 6.0 and 24 hours[11]. Each experiment was repeated three times, and the average was calculated. The swelling ratio Q, of the film was represented by[13]:

$$Q = \frac{\text{Weight of the swollen sample}}{\text{Weight of dry sample}}$$

Drug release from the prepared chitosan films

The release experiments were performed according to paddle method (JP x II) at a rotational speed of 50 rpm, which was the optimum speed to prevent film rupture. The release medium was 400 ml of phosphate buffer (pH= 6.8) equilibrated at (37°C±0.5°C). It was taken into consideration that the used buffer volume offered sink conditions. To avoid water evaporation, the vessels were covered with an aluminum foil during the experiments. The film was carefully pressed into the bottom of the glass vessel by the aid of silicon adhesive. At time intervals 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0 and 6.0 hours, 5 ml sample was withdrawn and replaced by an equal volume of fresh release medium previously equilibrated at 37°C.The amount of drug released (mg) was measured spectrophotometrically at λ_{max} 324 nm, and plotted as a function of time.

A cumulative correction was made for the previously removed samples in determining the total amount of KT released according to the following formula:

$$C_n = C_n \text{ meas} + 5/400 \, \Sigma \, C_s^{n-1} \text{ meas}$$

Where:

C_n meas = spectrophotmetrically measured concentration.

C_n = concentration of the n^{th} sampling expected in the receiving medium if previous samples had not been removed.

n-1 = total volume of all samples removed prior to a sample being measured.
Cs = total of all spectrophotmetrically measured concentrations at n-1 samples[14].

Statistical analysis

Analysis of variance on SPSS software package (version 9) (SYSTAT statistical program) was used to test the obtained data. Probability value ≤ 0.05 were defined as significant throughout the present study; however the value > 0.05 was defined as non-significant. Probability value between 0.05 and 0.01 (both are included) were evaluated as significant, whereas that less than 0.01 were defined as highly significant.

RESULTS AND DISCUSSION

Drug content uniformity

Ketorolac tromethamine (KT) was extracted from different regions of chitosan film using acetonitrile: Ethanol (1:1) solvent system. After normalization of the amount of Ketorolac tromethamine on weight basis of film, the results show that the variation in the distribution of Ketorolac in different regions of the film was < 5%.

Scanning electron micrographs (SEM)

SEM of cross-sections of free films is presented in Figure 2. This figure showed that the structure of the films is homogenous without any micro-phase separation. Thus the films were suitable for further evaluation.

X- ray diffraction study

To get further evidence on the solid state change, X-ray diffraction spectra were carried out on chitosan powder and their corresponding medicated films either free or plasticized. X-ray diffraction patterns of chitosan powder show diffraction peaks at approximately 10° (2θ) &20 (2θ). The diffraction patterns of KT also show numerous diffraction peaks at 7.81, 14.70, 22.29 and 24.57 degree, indicating its crystalline nature (Fig. 3).

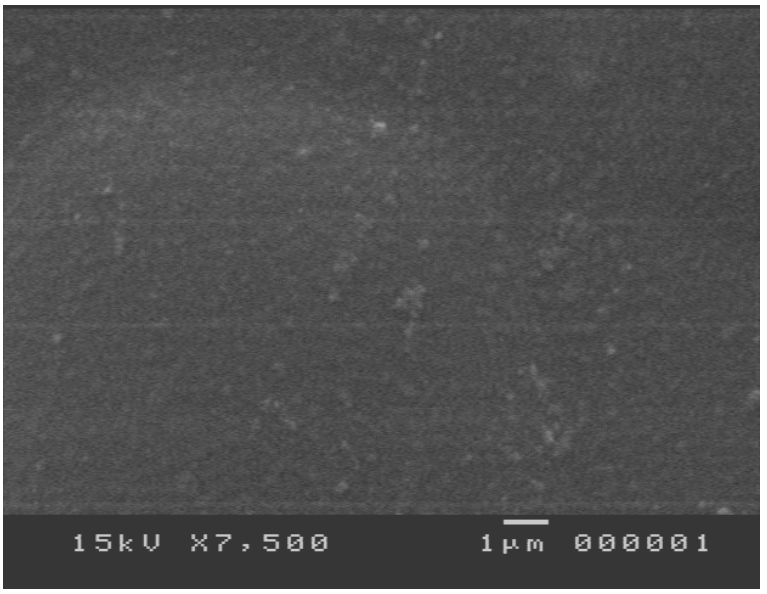
When processing chitosan powder into films, an amorphous state of the films is formed independent on the type of plasticizer used. These results are in agreement with Nunthanid *et al.*[3] who have reported that all chitosan films were in the amorphous state or in a partially crystalline state.

Differential scanning calorimetry (DSC)

The DSC thermograms of chitosan powder and their corresponding medicated films (free or plasticized) were performed to investigate the effect of different plasticizers on the structure of chitosan in the obtained films.

DSC thermograms of chitosan powder exhibited broad endothermic peaks due to water loss at 75-90°C and exothermic decomposition peaks at 309-312°C (Fig. 4). The DSC thermograms of untreated KT show two endothermic peaks, the first peak

A



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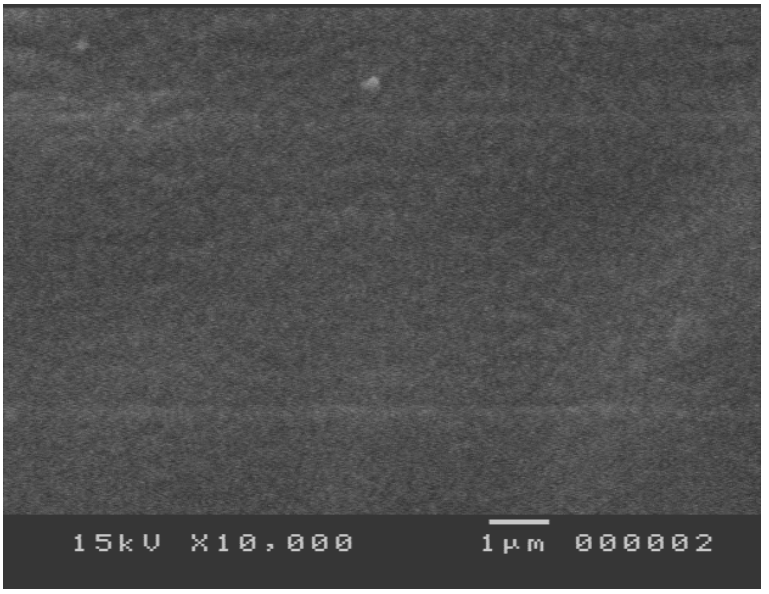

Fig. 2: Scanning electron photomicrographs of medicated chitosan films.
(**A**) Plasticized (**B**) Non plasticized

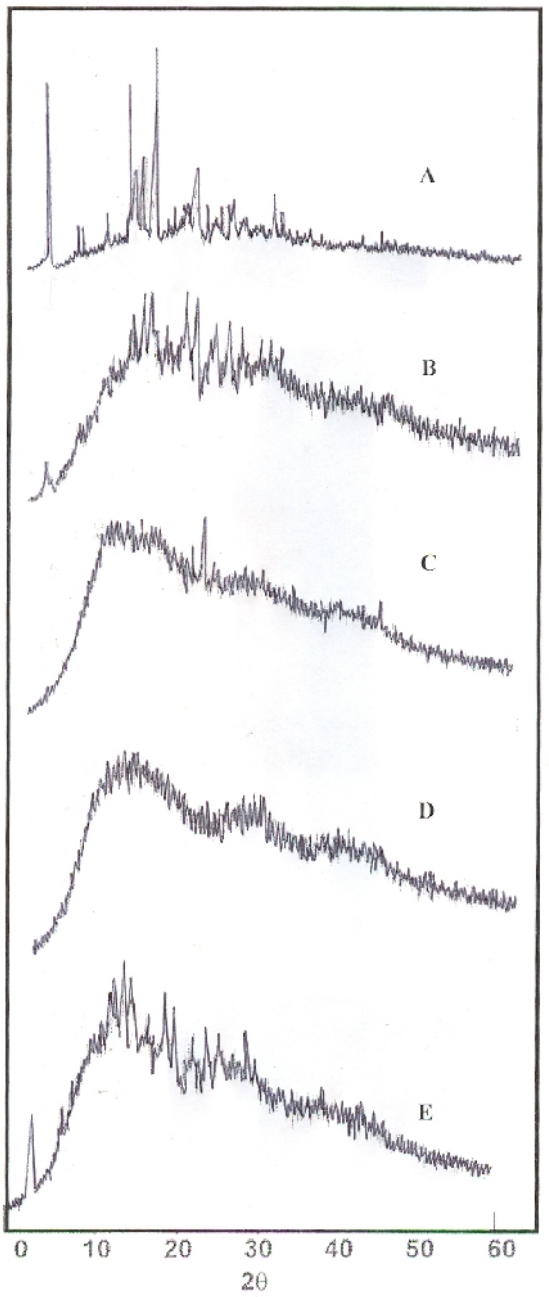

Fig. 3: X-ray Diffraction pattern of A. Ketorolac tromethamine (KT) B. chitosan (chit). C. KT + chit + glycerol D. KT + chit + erythritol, E. KT + chit + soribtol.

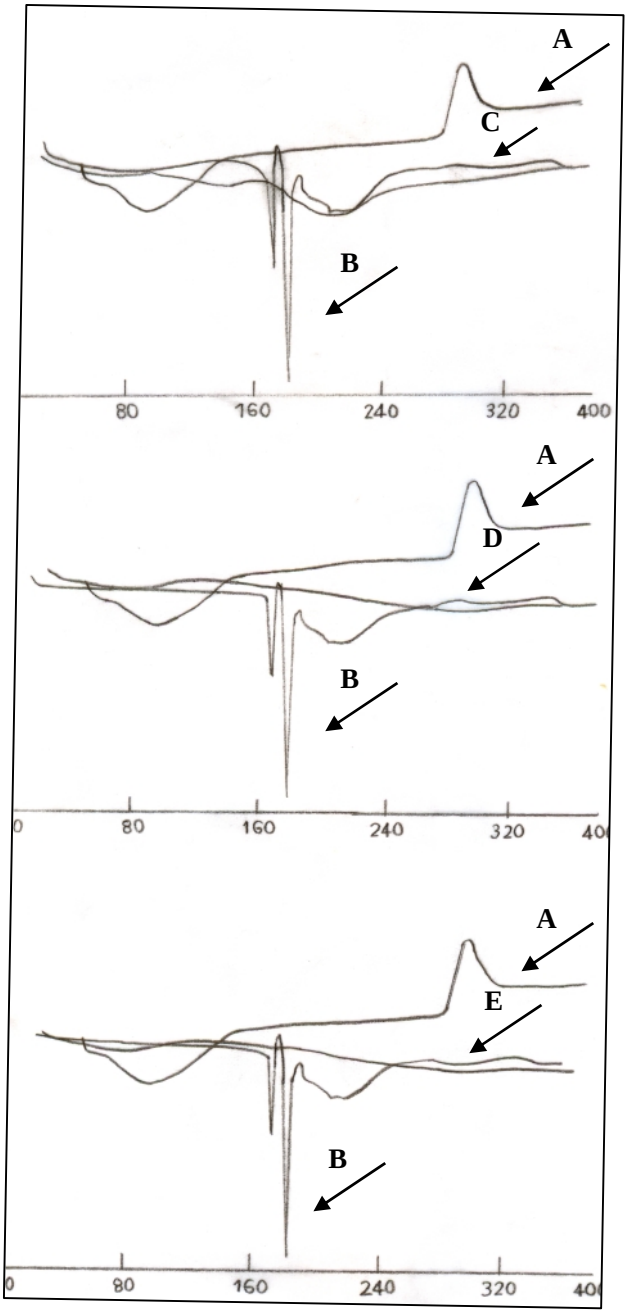

Fig. 4: DSC thermograms of A. Ketorolac tromethamine (KT) B. chitosan (chit) C. KT + chit + glycerol, D. KT + chit + erythritol, E. KT + chit + soribtol.

point at 158.54°C and ΔH= -29.64 Kcal/Kg, and the second peak point at 64°C and ΔH= -32.45 Kcal/Kg (Fig. 4a). The DSC thermograms of the corresponding medicated films (free or plasticized) show the absences of other endotherms in the DSC thermograms beside the broad endotherm at 100°C (Fig. 4b,c,d). The same results were obtained by Lim and Wan[15], also, by Nunthanid *et al.*[3] who have proven that chitosan films were in amorphous to partial crystalline forms. These results were also confirmed by the X-ray diffraction results.

Effect of inclusion of different polyols plasticizers on the mechanical properties of medicated chitosan films

The modulus of elasticity is an important factor in determining the degree of hardness, flexibility and stiffness of polymeric film. The values of modulus of elasticity for all chitosan films under investigation were shown in Table (1). The modulus of elasticity of non-plasticized film was found to be (0.261). This value is relatively high and indicative of brittleness and hardness of the obtained films. The inclusion of plasticizer in the film reduced the modulus of elasticity. This may be attributed to weakening of the intermolecular attractions between the chitosan molecules allowing the polymer molecules to move more freely resulting in an increase in the flexibility of the medicated films.

Table (1) and Figure (5) show that the addition of plasticizers had a considerable effect on the modulus of elasticity of chitosan films. From the obtained results, glycerol show the greatest effect on reducing tensile strength, modulus of elasticity and increasing the percent of elongation, whereas soribtol had the lowest effect. The effect of polyols

Table 1: The physico-mechanical properties of medicated chitosan films plasticized with different polyols at room temperature.

Plasticizer	Tensile strength (N/mm^2)*	Modulus of Elasticity	Percent of Elongation*	Viscosity of solution (CP)	Mechanical observations
None	56.81±2.01	0.261	2.21±1.01	642	Hard & brittle
glycerol	22.26±3.46	0.012	18.18±0.22	308	Soft & tough
erythritol	43.09±2.98	0.023	13.12±0.32	433	Soft & weak
soribtol	71.31±1.70	0.147	6.15±0.51	501	Hard & strong

* All values were the mean ± SD of three evaluations.

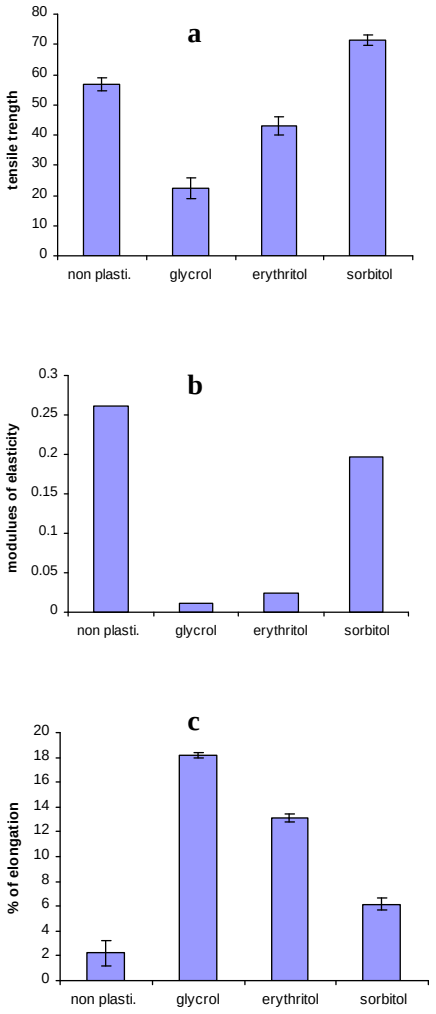

Fig. 5: Comparison of (a) tensile strength, (b) modulus of elasticity and (c) percent of elongation, of medicated chitosan films plasticized with different polyols (20% w/w) at room temperature.

plasticizers on reducing the modulus of elasticity of medicated chitosan films can be arranged according to the following order: Glycerol > erythritol> sorbitol. This may be explained by the probability of hydrogen bonding between the free hydroxyl groups of the glycerol and carbonyl oxygen of amide group. The probability of hydrogen bonding, in addition to the smaller molecular weight of glycerol rendered glycerol occupying the first sequence. Eythritol had four hydroxyl groups which also can form hydrogen bonds with carbonyl oxygen of amide group. It could be expected that the probability of hydrogen was decreased; therefore, erythritol had a moderate ability to break the polymer intermolecular attractions and hence had a lower effect than glycerol. Sorbitol had the lowest ability to increase the flexibility of chitosan films. This is may be attributed to the high molecular weight of Soribtol as compared to the other investigated polyols plasticizers used in this investigation, thus hindering its ability to diffuse and interact with the active groups in the polymer molecule.

These results are in agreement with Qun Wang *et al.*[16] who have investigated the effect of different Polyols of plasticizers on the mechanical properties of chitosan films. The authors have found that, glycerol blend films showed decrease in the tensile strength in comparison with films plasticized with sorbitol and erythriyol. In another study,

Srinivasa *et al.*[17] investigated the effect of inclusion of different plasticizers on the mechanical properties of chitosan films. The authors have found that the tensile strength of the chitosan films decreased with the addition of polyols and fatty acids, whereas the percent of elongation was increased in polyols blend films, but fatty acid blend films showed no significant differences.

Effect of inclusion of different polyols on swelling ratios of medicated chitosan films

Chitosan films were prepared from 10% w/v chitosan in aqueous acetic acid (1% v/v) and then were evaluated for their swelling characteristics in phosphate buffer of pH= 6.8. At the end of swelling time (24 hrs), the films became denser with subsequent change in color from colorless to white (Fig. 6).

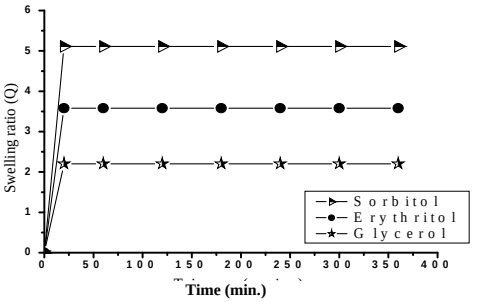

Fig. 6: Effect of inclusion of different plasticizers on the swelling ratios of medicated chitosan films in phosphate buffer pH= 6.8 at room temperature.

The swelling behavior of chitosan is represented by the relation between the swelling ratio Q of the swollen films and time. It is obvious that, the equilibrium swelling occurred in the first 20 min and no weight increase was recorded thereafter up to 24 hrs. these results could be explained by the cross-linking between cationic amino groups of chitosan and phosphate anions of the buffer, first, the films absorbed water, began to swell, and the amino groups of chitosan were simultaneously protonated. Phosphate anions from the medium penetrated the swollen film to cross-link with quaternary ammonium groups of chitosan molecules. These explanations are in agreement with those reported by Kanke *et al.*[18]. The authors have reported that the equilibrium swelling of chitosan film in phosphate buffer of pH= 7.4 was reached within the first 30 minutes and no weight increase thereafter up to 24 hrs has been observed. On the other hand, Nunthanid *et al.*[3] determined the swelling of chitosan films as a volume increase and found that the films swollen greatly in phosphate buffer (pH= 7.4) at an initial period of 15 minutes and then decreased in volume by time.

Incorporation of different polyols with medicated chitosan films can modify its hydrophilicity. The presence of plasticizer molecules in a chitosan system tends to disrupt crystallinity of chitosan in the blend. Disruption of crystallinity would increase the amorphous content and

therefore increase the swelling of the blend[19]. These plasticizers can be arranged according to their magnitude in increasing the swelling ratio in the following order:

Sorbitol > erythritol > glycerol

The highest swelling ratio of medicated chitosan films containing polyols may be due to the hydrophilic/ hydrophobic nature of these plasticizers. The hydrophilic nature of sorbitol may be explained on the basis of the probability of hydrogen honding between six hydroxyl groups of sorbitol and water molecules. Due to this consideration, sorbitol, the first member of the polyols, had the highest effect on swelling ratio. The relative ability of erythritol (four hydroxyl groups) to form hydrogen bonds with water molecules in the prepared film increases its swelling characteristics.

The hydrophilic nature of glycerol may be also attributed to the formation of hydrogen bonding between the three hydroxyl groups of glycerol and water molecules. According to this consideration, glycerol had the lowest effect on swelling ratio.

The obtained results are in good agreement with those obtained by Nakaisuka and Andrady[13] and that of Blair *et al.*[19] who have studied the effect of blending PVA on the swelling ratio of chitosan films and reported that by increasing the amount of PVA there is an increase in the swelling ratio Q.

Effect of inclusion of different polyols on drugs release pattern

The effect of the nature of different types of plasticizers on the release of Ketorolac tromethamine from chitosan films was studied.. The concentration of each plasticizer was 20% w/w of dry film and each film contained 100 mg ketorolac tromethamine. The obtained results are depicted in Tables (2&3) and in Figure (7).

Table 2: Effect of different polyols on KT release rate constant (k), half-life (t½) of medicated chitosan L* films containing 100 mg KT according to Higuchi-diffusion model.

Plasticizer concentration (% w/w of polymer)	Release rate constant (k) ($mg/cm^2/min^{1/2}$)	Correlation coefficient (r)	$t_{½}$ (min.)
0	2.54	0.999	372.68
soribtol	6.44	0.999	135.54
erythritol	5.99	0.998	156.77
glycerol	5.46	0.999	188.27

Table 3: Kinetic data of drug released from medicated chitosan films plasticized with different polyols.

Mechanism of Release		plasticizers			
		0	soribtol	erythritol	glycerol
First order	r	0.995	0.995	0.997	0.997
	K_1 (min^{-1})	0.0009	0.002	0.001	0.006
Zero order	r	0.989	0.990	0.990	0.998
	K_0 (mg/min.)	0.0867	0.095	0.091	0.075
Higuchi diffusion	r	0.999	0.999	0.998	0.995
	K_h ($mg/cm^2/min^{1/2}$)	2.59	2.583	2.468	2.213
Log Q vs log t	r	0.999	0.999	0.999	0.994
	Slope	0.547	0.512	0.533	0.489
Best fit model		Higuchi	Higuchi	Higuchi	Higuchi

r : Correlation coefficient
K_1 : First order release rate constant
K_0 :Zero order release rate constant
K_h : Diffusion release rate constan

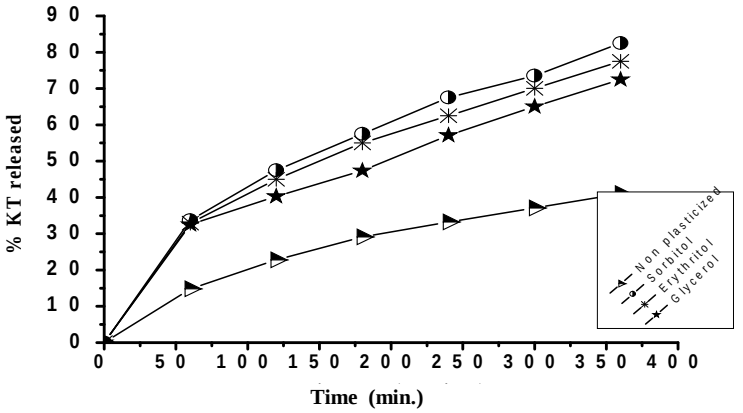

Fig. 7: Percent of drug released (mg/cm^2) from chitosan films each containing 100 mg ketorolac tromethamine with different polyols (20% w/w of polymer).

When the medicated plasticized chitosan films were immersed in phosphate buffer, two factors would be taken into consideration to explain the effect of plasticizer content on drug release profile. The first is the solubility of the plasticizer in water (i.e. the probability of hydrogen bonding between the plasticizer and water molecules), while the second

was the extent of forming channels or pathways through the plasticizer which could be leached from the polymeric matrix.

The mechanical properties of chitosan L* films for the investigated plasticizers could decrease the degree of compactness of polymeric matrix due to their binding with polymer molecules and consequently forming pores in the polymeric matrix.

Figure (7) shows the effect of different plasticizers on the release of the drug from chitosan films. This effect can be arranged in the following order:

Sorbitol > erythritol > glycerol

Soribtol is the most hygroscopic, and water soluble one (i.e. most hydrophilic) with respect to other investigated plasticizers. It facilitates the hydration of the film upon exposure to the release medium and consequently more channels would be created in the film. The hydration of sorbitol will enhance its leaching from the film through a hydrated network of channels connecting the upper and lower surfaces of the film. This assumption of soribtol leaching throughout the film may explain the spongy wetted appearance of the film at the end of experiment[20].

It could be also concluded that erythritol and glycerol would also be leached through a continuous hydrated capillary network of channels, which is a major characteristic for all tested plasticizers. The wetted spongy feature of the film at the end of experiment confirmed this assumption.

Statistical analysis

Table (4) shows the statistical analysis of SPSS software package (version 9) (SYSTAT statistical program), which indicates that significant results of the studied *in-vitro* release of the drug from

Table 4: Statistical analysis (correlation bivariate two tailed analysis) of *in-vitro* % released of ketorolac tromethamine from plasticized chitosan films, at room temperature.

Factors	Medicated non plasticized		Sorbitol		Erythritol		Glycerol	
	(r)	Sig.	(r)	Sig.	(r)	Sig.	(r)	Sig.
Time(min)	0.963	**	0.955	**	0.951	**	0.954	**
Medicated non plasticized			0.998	**	0.998	**	0.993	**
Sorbitol					0.999	**	0.997	**
Erythritol							0.997	**

plasticized films, in a medium of dissolution phosphate buffer (pH 6.8), prepared at different types of polyols. Correlation is significant at the 0.01 level (2-tailed).

Conclusion

Drug loaded films based on chitosan and three different polyols as plasticizers were produced by a casting/solvent evaporation method. With Ketorolac tromethamine as a model drug, we studied the physicochemical characteristics of the prepared films as well as the release of the drug from the prepared films. The tensile strength was decreased while the percent of elongation was increased. Glycerol films were more flexible compared with other plasticizers, on the other hand, the swelling ratio and the *in-vitro* release increased with soribtol films. The chemical structure of plasticizers affect both the physcomechanical properties as well as the *in-vitro* release. Thus, in the future work, we can prepare films which lead to successful application for local as well as systemic drug delivery.

REFERENCES

1- J. J. Karlsen, Manuf Chemist., 62, 18 (1991).
2- R. A. A. Muzzarelli and M. G. Peter (Eds.), Chitin Handbook, Bermen, Germany: European Chitin Society, 1997, p. 437.
3- J.Nunthanid, S.Puttipipatkhachorn, K. Yamamoto and G.E. Peck, Drug Dev. Ind. Pharm., 27, 143 (2001).
4- W. Paul and C. P. Sharma, S.T.P. Pharm. Sci., 10, 5 (2000).
5- G. C. Ritthidej, T. Phaechamud and T. Koizumi, ibid., 10, 112 (2000).
6- P. Jang Woo, W. Scott Whiteside and C. Seung Yong, Food Sci. and Tech., 41, 692 (2008).
7- A. T. Riku, H. Harry, H. Yrjo and J. Kirisi, Carbo. Poly., 24, 269 (2008).
8- B. Janos, F. Mate and P. Klara, Applied Sur. Sci., 253, 7303 (2007).
9- B. Giulia, M. Piera Di, P. Martina, C. Angela, R. Francesco and F. Giovanni, Int. J. Pharm., 313, 72 (2006).
10- H. B. Robert, N. Sara, N. R. Marcand A. Howard, J Emerg. Med., 26, 407 (2004).
11- D. Thacharodi and K. Panduranga Rao, Int. J. Pharm., 96, 33 (1993).
12- N. H. Parikh, S. C. Porter and B. D. Rohera, Pharm. Res., 10, 810 (1993).
13- S. Nakatsuka and L. A. Andrady, J. Appl. Polym. Sci., 44, 17 (1992).
14- D. Kerridge, Adv. Microbiol. Physiol., 27, 1 (1986).
15- L. Y. Lim and L. S. Wan, Drug Dev. Ind. Pharm., 21, 839 (1995).
16- W. Qun, D. Zhanfeng, D. Yumin, and F. John, Carb. Poly., 69, 336 (2007).
17- P. C. Srinivasa, M. N. Ramesh and R. N. Tharanathan, Food Hydro., 21, 1113 (2007).

18- M. Kanke, H. Katayama and H. Kuramoto, Chem. Pharm. Bull., 37, 523 (1989).
19- H. S. Blair, J. Guthrie, T. Law and P. Turkington, J. Appl. Polym. Sci., 33, 641 (1987).
20- A. Ismail, Ph.D. Thesis, Zagazig University, Zagazig, Egypt (1996).