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Synthesis of chitosan triethylene glycol phthalate and its evaluation as a binder in wet granulation procedures

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The naturally occurring polymer chitosan was linked to triethylene glycol phthalate (CH-Aph-Teg). The generated hydrophilic polymer was evaluated as a binder in wet granulation procedures. Granules containing 0.2 to 1.2% w/w chitosan triethylene glycol phthalate were prepared. Sodium salicylate and lactose were used as the model drug and the diluent, respectively. The prepared granules were tabletted on a single punch tabletting machine. The binding properties of CH-Aph-Teg were compared to those of maize starch. Tablet hardness, friability, disintegration time and dissolution rate were studied as functions of CH-Aph-Teg contents. At all investigated concentrations, tablets containing CH-Aph-Teg gave better hardness and friability values compared to those prepared using maize starch. The release rates of sodium salicylate from tablets containing CH-Aph-Teg were slower than those containing maize starch. The prolonged tablet disintegration times associated with CH-Aph-Teg suggest the suitability of the newly developed chitosan derivative as a binder in sustained-release tablet formulations.

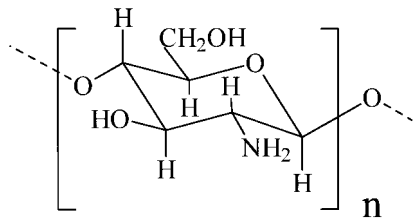
1. Introduction

The use of natural polymers in pharmaceutical technology has received considerable attention in the field of dosage form design. Chitosan, a partially deacetylated chitin (polyglucosamine) and its various synthetic derivatives have recently attracted interest because it is biocompatible and biodegradable, showing extremely low toxicity [1]. Much importance has been attached to chitosan derivatives with a defined degree of deacetylation and depolymerization. Such derivatives have significantly different physicochemical properties, in particular regarding water solubility [2]. Chitosan was reported to fulfill the general requirements for auxiliary substances in the process of direct tableting [3]. However, the same report mentioned that the addition of chitosan in the proportion of 50% of tablet mass, resulted in rapid tablet disintegration. In another report, chitosan was evaluated as a binder for chlorpheniramine maleate tablets in comparison with other cellulose binders. The authors concluded that the rank order correlation for binder efficiency was: hydroxypropylmethylcellulose > chitosan > methylcellulose > sodium carboxymethylcellulose [4].

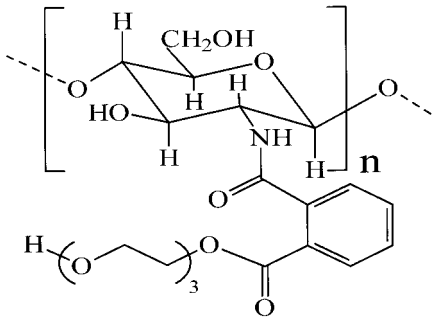
Chitosan's basic nature suggests that a minimum amount of acid is required to transform the glucosamine units into the positively charged, water soluble form. At neutral pH most chitosan molecules will lose their charge and precipitate from solution [5].

We envisaged the possibility of improving the binding properties of chitosan by increasing its hydrophilicity. Substituting triethylene glycol unites on the chitosan backbone is expected to generate a highly hydrophilic polymer, hence possessing improved binding properties.

Accordingly, the aim of the present work was to prepare and evaluate chitosan triethylene glycol phthalate (CH-Aph-Teg) as a binder in wet granulation procedures. In particular, this work focuses on evaluating the main physical properties for tablets prepared with CH-Aph-Teg, i.e. hardness, friability, disintegration and dissolution rates.



Chitosan



Chitosan triethylene glycol phthalate

2. Investigations, results and discussion

In this preliminary investigation, the binding properties of CH-Aph-Teg were compared with those of the readily available tablet binder maize starch. At equivalent binder concentrations, CH-Aph-Teg produced harder tablets than maize starch, as illustrated in Fig. 1. Tablets prepared with 0.2% w/w maize starch were too soft to be tested for hardness. It is evident from Fig. 1 that the mean tablet hardness increased with the increase in binder concentration. This observation agrees with the previously reported findings that higher binder content was associated with improved tablet hardness [7]. Fig. 2 shows the effect of binder type and concentration on tablet friability. With each binder, there is an observed decrease in friability with the increase in binder concentration. Higher binder levels have been reported to improve bonding capabilities during compaction, and therefore leading to minimal friability loss [8]. Friability has been used to evaluate binder efficiency [9]. Under equivalent provisions of binder content, the chitosan derivative, CH-Aph-Teg, produced tablets with lower friability values than those containing maize starch, as illustrated in Fig. 2.

The improved hardness and friability values for CH-Aph-Teg containing tablets compared to those containing maize starch, illustrate the excellent binding properties of the chitosan derivative. Such superior binding is probably due

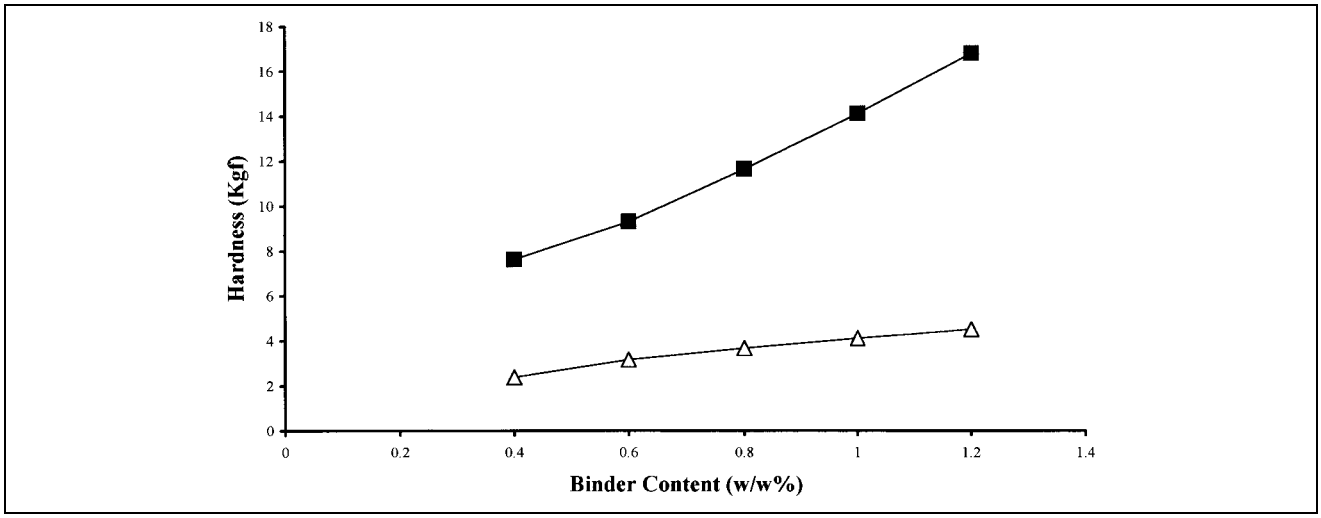


Fig. 1: Effect of binder type and concentration on tablet mean hardness: ■ CH-Aph-Teg, △ maize starch

to the enhanced hydrophilic nature of the CH-Aph-Teg. Undoubtedly, linkage to triethyleneglycol (Teg) is the reason behind the enhancement in hydrophilicity. The improved water solubility of the binding polymer is expected to increase the thickness and strength of the binder crystalline bridges formed between the granulated particles, thus enhancing its binding efficiency.

Although there are no official limits for the acceptance or rejection of tablet batches based on friability results, recent literature indicates that conventional tablets with a friability less than 0.5 to 1% in weight are generally considered acceptable [10]. According to this convention, tablet batches containing 0.4 to 1.2% w/w of either binder (CH-Aph-Teg or maize starch) are considered acceptable in terms of friability, as the corresponding percentage loss in weight falls within this range.

The binding capacity was also calculated for all tablet batches (whether containing CH-Aph-Teg or starch). Table 1 shows the binding capacity values and the corresponding binder ratios for the different tablet batches. Binding capacity is calculated by dividing tablet hardness by tablet thickness. This relationship is based on the following: at constant die fill during compaction, the break-

Table 1: Effect of binder type and content on binding capacity

	Binder content (w/w%)				
	0.4	0.6	0.8	1.0	1.2
Binder capacity for CH-Aph-Teg (Kgf)	3.06	3.17	3.58	3.72	3.96
Binder capacity for Maize starch (Kgf)	0.71	0.88	0.98	1.16	1.24

Table 2: The preparation formulas for sodium salicylate tablets

Ingredients	Content per tablet					
	1	2	3	4	5	6
Sod. sal. (mg)	100	100	100	100	100	100
Lactose (mg)	250	250	250	250	250	250
Stearic acid (w/w %)	1.0	1.0	1.0	1.0	1.0	1.0
Ac-Di-Sol (w/w %)	1.75	1.75	1.75	1.75	1.75	1.75
Binder (w/w %)	0.2	0.4	0.6	0.8	1.0	1.2

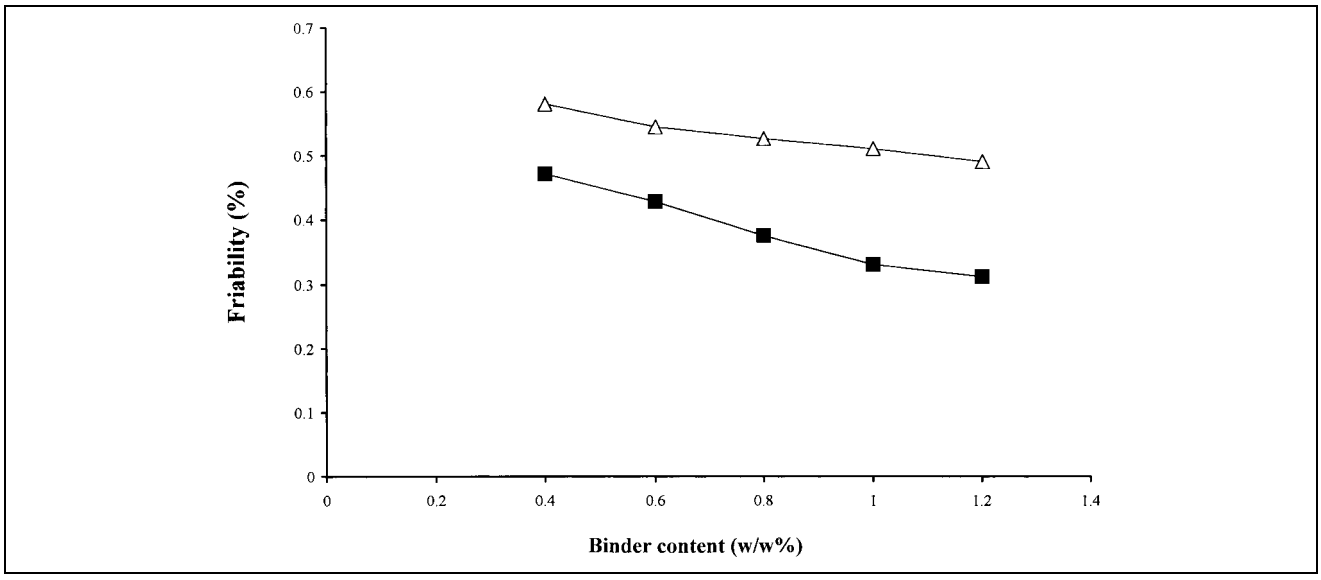


Fig. 2: Effect of binder type and concentration on tablet friability: ■ CH-Aph-Teg, △ maize starch

ing strength of tablets increases as the thickness decreases whilst additional compression force is applied [11]. However, under constant compression force, slight variation in tablet thickness may occur due to variations in die fill volume. This affects the breaking strength to a magnitude that may not be perfectly correlated with the type and concentration of binder used. The calculated value of binding capacity eliminates the thickness factor, and it has been suggested that this parameter is a better index for comparing the effects of various excipients on the mechanical properties of tablets [12]. At all employed concentrations, tablets containing CH-Aph-Teg exhibited higher binding capacity than those containing starch.

Fig. 3 shows the disintegration times for different tablet batches. The figure clearly illustrates the longer disintegration times for tablets containing CH-Aph-Teg compared to those containing maize starch. However, all tablet batches containing CH-Aph-Teg failed the BP 1988 disintegration time limit of 5 min for uncoated tablets. The prolonged tablet disintegration time is probably due to the formation of a highly viscous aqueous gel within the tablet matrix, resulting from the hydration of CH-Aph-Teg. Tablet disintegration is known to depend on the physical and chemical properties of the granulating agent as well as tablet hardness and porosity [13].

Figs. 4 and 5 report the release profiles of sodium salicylate from the different tablet formulations. From Fig. 4, the release half-life time (t_{50}) for tablets containing 0.4, 0.6 and 0.8% CH-Aph-Teg were 13, 24 and 32 min respectively, whilst the release t_{50} for those containing the equivalent concentrations of starch were 4,5 and 8 min, respectively. Fig. 5 shows that the release t_{50} tablets containing 1.0 and 1.2% CH-Aph-Teg were 50 and >100 min, respectively. The release t_{50}, for tablets containing the equivalent concentrations of starch, were 10 and 14 min, respectively.

It is evident from Figs. 3–5 that drug dissolution profiles for tablet batches containing CH-Aph-Teg correlate well to the corresponding disintegration times, suggesting the dependence of drug release on tablet disintegration. Madan

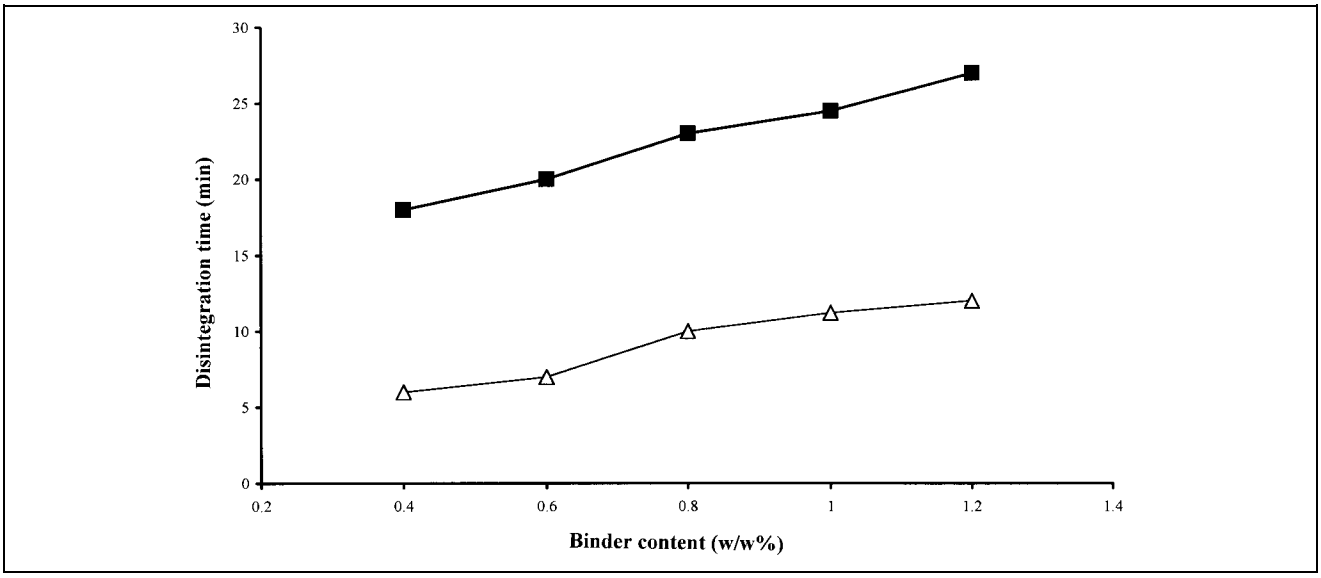


Fig. 3: Effect of binder type and concentration on disintegration time: ■ CH-Aph-Teg, △ maize starch

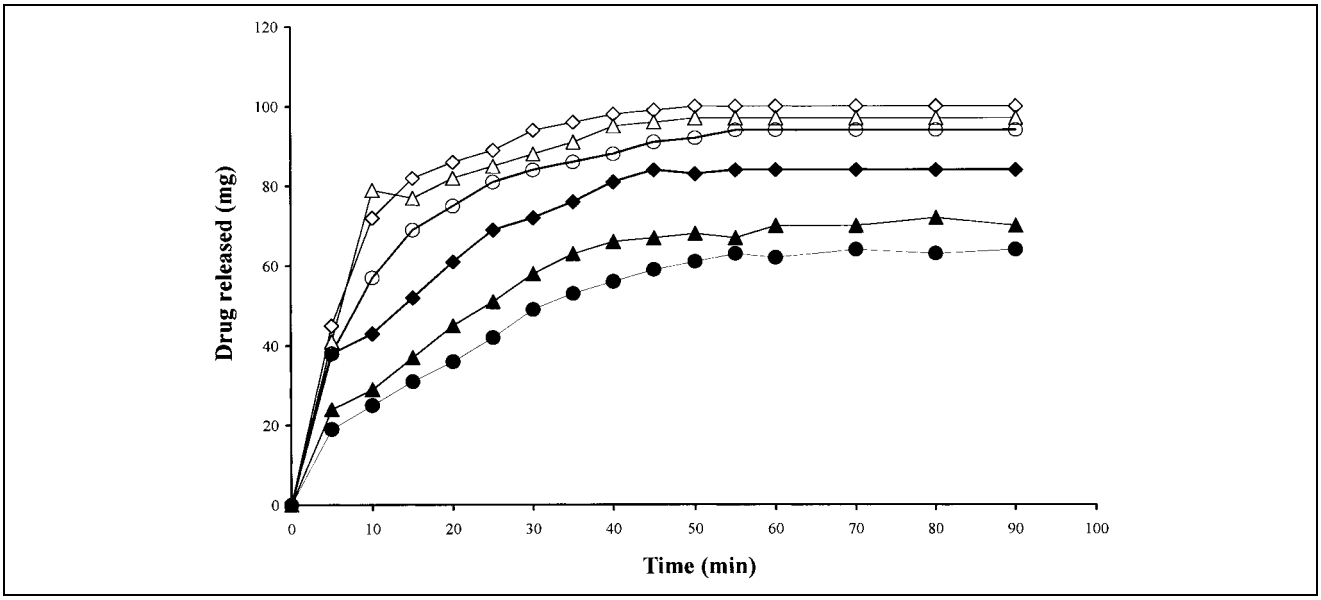


Fig. 4: Effect of binder type and concentration on drug dissolution: ◇ 0.4% maize starch, △ 0.6% maize starch, ○ 0.8% maize starch, ◆ 0.4% CH-Aph-Teg, ▲ 0.6% CH-Aph-Teg, ● 0.8% CH-Aph-Teg

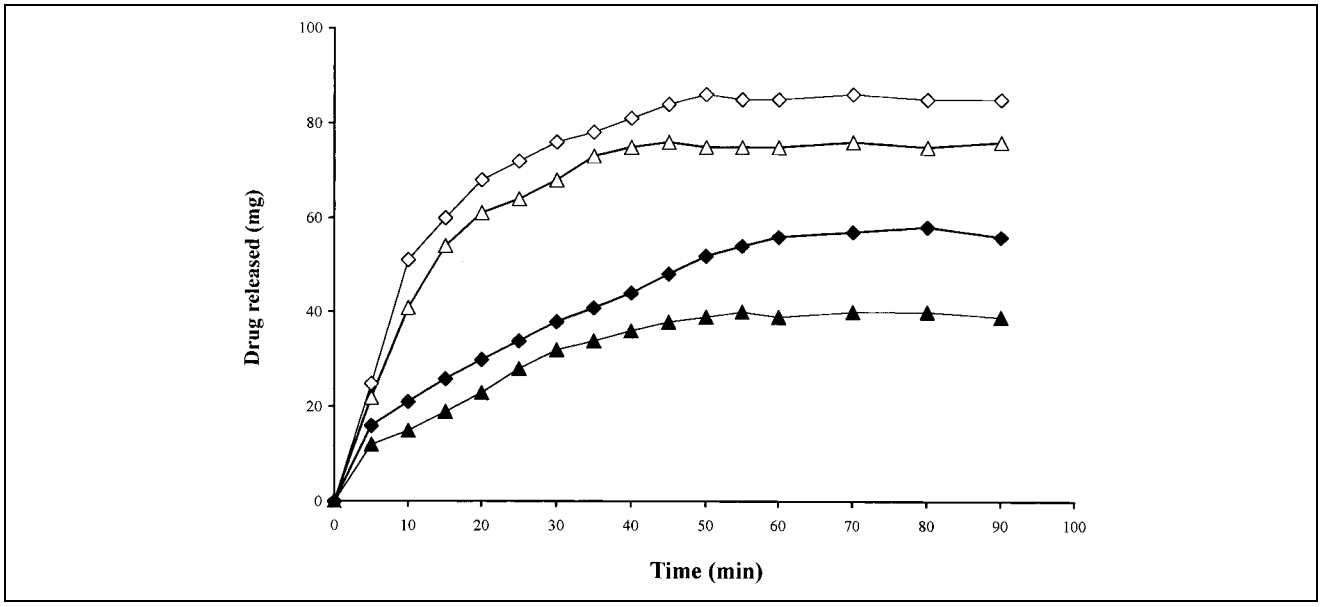


Fig. 5: Effect of binder type and concentration on drug dissolution: ◇ 1.0% maize starch, △ 1.2% maize starch, ◆ 1.0% CH-Aph-Teg, ▲ 1.2% CH-Aph-Teg

[14] suggested the use of tablet disintegration time as a useful guide in the preparation of an optimum tablet, since it correlates reasonably with different tablet properties including drug dissolution. On the other hand, Alam et al. [15] have established that any correlation between disintegration and dissolution times should not always be expected. However, the apparent disintegration/dissolution times relationship, reported herein, is probably due to the highly adhesive and viscous nature of the CH-Aph-Teg gel formed within the tablet. The generated gel is expected to delay drug release from the entrapped granules through two mechanisms: slowing down tablet disintegration, thus minimizing the surface area of the drug-releasing face, and hindering the migration of drug molecules from the drug-releasing face to the solution bulk. The enhanced adhesion and viscosity properties of the CH-Aph-Teg are propably a direct consequence of its improved hydrophilicity.

The relatively prolonged disintegration time and dissolution rate observed for tablets containing CH-Aph-Teg in the presence of a fast disintegrant (AC-Di-Sol) suggest that the CH-Aph-Teg can be useful in the formation of sustained-release tablets and granules. However, more work on the CH-Aph-Teg and formulation with other drugs is needed before a firm and concrete postulation can be made.

3. Experimental

3.1. Chemicals

Low molecular weight chitosan (CH, mol.mass 70000), triethylene glycol (Teg), phthalic anhydride (Aph), lactose, maize starch, Ac-Di-sol, stearic acid, sodium salicylate, dicyclohexylcarbodiimide (DCC), dimethylformamide (DMF) and 1-hydroxybenzotriazole (HOBt) were all purchased from Fluka-Aldrich and Merck.

3.2. Preparation of chitosan triethylene glycol phthalate (CH-Aph-Teg)

Pyridine (3.23 ml, 40 mmol) was added dropwise to a magnetically stirred solution of triethylene glycol (2.67 g, 20 mmol) and phthalic anhydride (1.48 g, 10 mmol) in $CHCl_3$ (33 ml). The reaction was maintained at 60 °C for 24 h. Subsequently, $CHCl_3$ was removed *in vacuo* and the resulting oily residue was dissolved in aqueous Na_2CO_3 solution (60 ml, 4.24 g, 50 mmol). Next, the resulting alkaline solution was extracted with $CHCl_3$ (3×45 ml). After discarding the organic layers, HCl (10 ml, 10 N) was added to the aqueous layer and the resulting solution was extracted with $CHCl_3$ (5×50 ml). The organic layers were then combined. $CHCl_3$ was removed *in vacuo* to give triethylene glycol phthalate (Aph-Teg) [6]. The linkage of chitosan to Aph-Teg was achieved as follows: DCC (1.85 g, 0.9 mmol) and HOBt (1.32 g, 0.9 mmol) were added to a magnetically stirred solution of Aph-Teg (0.75 mmol) in DMF (50 ml). The reaction was maintained for 3 h at 25 °C. Subsequently, the generated *N,N*-dicyclohexylurea was removed by centrifugation. The supernatant DMF solution was decanted and added to a stirred solution of chitosan (0.25 g; corresponding to about 1.55 mmol of glucosamine) in 0.37% HCl. The reaction pH was maintained at 7.0 by dropwise addition of NaOH solution (1.0 M). NaOH addition was continued until the pH was stabilized. After 24 h the reaction was terminated by the addition of NaCl aqueous solution (20%, 200 ml). The resulting precipitate was filtered, washed with acetone and diethylether, and desiccated to give chitosan triethylene glycol phthalate (CH-Aph-Teg). The formation of CH-Aph-Teg was confirmed by an IR spectrum (KBr disc., Fig. 6a, b). The spectrum shows absorption bands at 1660 and 1550 cm^{-1} corresponding to the amide linkages, and at 1730 cm^{-1} corresponding to ester carbonyl groups. Thus, this information confirm the formation of amide links between the phthalate moieties and the amino groups within chitosan, and ester links between the phthalate moieties and triethylene glycol chains.

3.3. Tablet preparation

Table 2 shows the adopted formulas for the preparation of the six investigated batches of sodium salicylate tablets. All batches were prepared by the wet granulation method. In each case, appropriate amounts of sodium salicylate and other excipients were weighed to give 200 tablets per batch. Sodium salicylate, lactose, Ac-Di-Sol and the particular percentage of each binder (maize starch or CH-Aph-Teg) were triturated in a mortar to a homogeneous mix, which was then mixed with a predetermined volume of warm water to give a damp mass. The resulting mass was then screened through a 1.7 mm stainless steel sieve. Subsequently, the wet-screened granules were tray-dried in a hot oven at 60 ± 1 °C for 1 h. The dried granules were re-screened through a 1.0 mm sieve and subsequently shaken on a 0.25 mm sieve to separate the fines. A weighed quantity of stearic acid powder was mixed with the fines over 5 min. The granules were incorporated into the fines and mixed for further 3 min. Subsequently, the granules mixture was compressed into tablets using a Korsch Eko tabletting machine to a target weight of 350 to 360 mg. The pressure setting in each case was set at 55 units to provide constant compression as much as possible.

3.4. In vitro tablet tests

Random samples were collected from each batch. Hardness, friability, disintegration time and dissolution rate tests were carried out 12 h after compression to allow enough time for the tablets to equilibrate.

3.4.1. Hardness test

Tablets hardness was determined using an Irmeco Schoenfeld hardness tester (model 2E). Tablets from each batch were tested individually. The mean hardness value was calculated for the different batches.

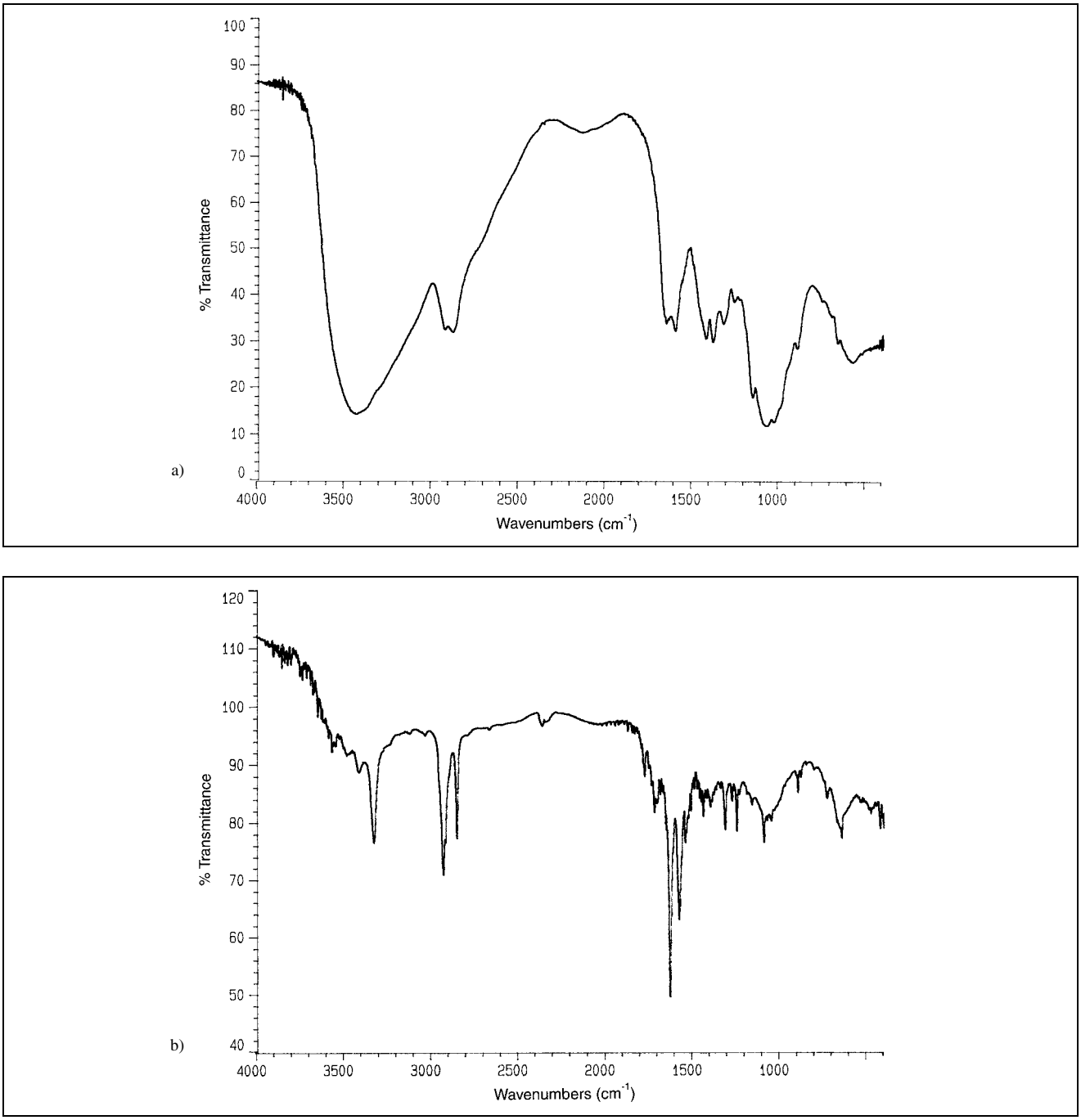


Fig. 6: Infrared spectra of: a) chitosan, b) chitosan triethylene glycol phthalate (CH-Aph-Teg)

3.4.2. Friability test

Erweka Friabilitor (TAR model) was used. Ten tablets from each batch were randomly sampled, weighed in a balance and subjected to shock at 25 r/min for 4 min in the friabilitor. The selected tablets were re-weighed. Friability is calculated as the percentage weight loss according to eq. (1).

$$\text{Friability} = \frac{W_0 - W}{W_0} \times 100\% \quad (1)$$

W_0: tablet weight before exposure to shock, W: tablet weight after exposure to shock.

3.4.3. Disintegration time test

The USP method was adopted using an Erweka tablet disintegration unit (model 2T6-6). Freshly prepared HCl (0.1 N) was used as the disintegration medium. The medium was placed in a 1 l beaker. The apparatus temperature was maintained at 37 ± 1 °C. Five tablets from each batch were placed in five Perspex tubes, which were placed in five baskets, then the stirring motor was switched on. The disintegration was considered to have terminated when the last tablet particle passed through the screen. The mean disintegration time was calculated for each batch.

3.4.4. Dissolution rate test

The magnetic stirrer method was adopted. Freshly prepared 0.1 N HCl (900 ml) was placed in a beaker and maintained at a temperature of 37 ± 0.1 °C. One tablet, from each batch, was placed in a basket and immersed in the acidic medium. Subsequently, the dissolution medium was magnetically stirred at a speed of 100 ± 1 r/min. During the stirring course, 5 ml samples were withdrawn from the beaker at predetermined time intervals. In order to maintain a constant dissolution medium volume, a quantity of 5 ml HCl (0.1 N) was added to the medium after withdrawing each sample. The concentration of the released sodium salicylate was determined by adding $FeCl_3$ to each sample, followed by measuring the absorbence at 540 nm using a SP6-450 UV-Vis spectrophotometer. The absorbencies were converted to concentration using the standard Beer plot for sodium salicylate.

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