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Hydrophobic Modification of Chitosan and its Physicochemical Evaluation as Sustained Release Tablet Formulation

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Chitosan is being investigated widely for use as an excipient in oral and other pharmaceutical formulations. Chitosan is generally regarded as a nontoxic and non-irritant material. It is biocompatible with both healthy and infected skin. Chitosan has been shown to be biodegradable (LD50 (mouse, oral): > 16 g/kg). Unmodified chitosan exhibited a low degree of disorder and a weak tablet crushing strength. In the present work, the hydrophobically modified chitosan were synthesized in order to formulate a system for sustain release of hydrophilic drug (indomethacine prototype drug in present case). The caproyl (C-8), decanoyl (C-10), lauryl (C-12), myristyl (C-14), palmitoyl (C-16) and stearoyl (C-18), fatty acyl derivatives of chitosan were prepared and physicochemically evaluated as excipient in matrix tablet dosage. The best sustained release studies was defined by palmitoyl chitosan and it can able sustain 50-60 % release upto 12 h and in concentration range 10-30 % much less as compared to chitosan (> 50 %).

Key Words: Chitosan, Sustained release tablets, Novel drug delivery system, Biodegradable polymer.

INTRODUCTION

Chitosan is a linear polysaccharide obtained from chitin deacetylation. Chitosan is the term applied to deacetylated chitins in various stages of deacetylation and depolymerization and it is, therefore, not easily defined in terms of its exact chemical composition. In general, chitosan is a polysaccharide comprising copolymers of glucosamine and N-acetyl glucosamine (Fig. 1). In essence, chitosan is chitin sufficiently deacetylated to form soluble amine salts. The degree of deacetylation necessary to obtain a soluble product must be greater than 80-85 %. Chitosan is commercially available in several types and grades that vary in molecular weight by 10,000-10,000,00 and vary in degree of deacetylation and viscosity[1].

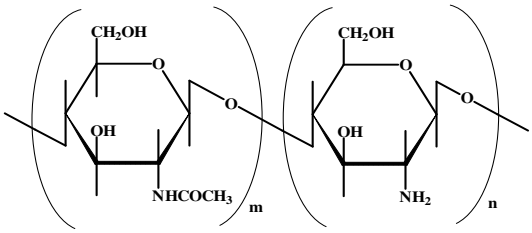


Fig. 1. Representative structure of chitosan

Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations. The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies[2-6]. These include controlled drug delivery applications[7-12], use as a component of mucoadhesive dosage forms[13,14], rapid release dosage forms[15,16], improved peptide[17,18] colonic drug delivery systems[19,20] and use for gene. Delivery[21] chitosan has been processed into several pharmaceutical forms including gels[22,23], films[8,9,24-25], beads[26-27], microspheres[28,29], tablets[30,31] and coatings for liposomes[32]. Furthermore, chitosan may be processed into drug delivery systems using several techniques including spray-drying[13,14], coacervation[33], direct compression[30] and conventional granulation processes[34].

Chitosan is a cationic polyamine with a high charge density at pH < 6.5. It is a linear polyelectrolyte with reactive hydroxyl and amino groups (available for chemical reaction and salt formation)[4]. The properties of chitosan relate to its polyelectrolyte and polymeric carbohydrate character. The presence of a number of amino groups allows chitosan to react chemically with anionic systems, which results in alteration of physicochemical characteristics of such combinations. The nitrogen in chitosan is mostly in the form of primary aliphatic amino groups. Chitosan therefore undergoes reactions typical of amines, for example, N-acylation and Schiff reactions[2]. Almost all functional properties of chitosan depend on the chain length, charge density and charge distribution[5].

Numerous studies have demonstrated that the salt form, molecular weight and degree of deacetylation as well as pH at which the chitosan is used all influence how this polymer is utilized in pharmaceutical applications[4].

Chitosan is sparingly soluble in water, practically insoluble in ethanol (95 %), other organic solvents and neutral or alkali solutions at pH above approximately 6.5. Chitosan dissolves readily in dilute and concentrated solutions of most organic acids and to some extent in mineral inorganic acids (except phosphoric and sulfuric acids). Upon dissolution, amine groups of the polymer become protonated, resulting in a positively charged polysaccharide (RNH_3^+) and chitosan salts (chloride, glutamate, *etc*.) that are soluble in water and the solubility is affected by the degree of deacetylation[4]. Solubility is also greatly influenced by the addition of salt to the solution. The higher the ionic strength, the lower the solubility as a result of a salting-out effect, which leads to the precipitation of chitosan in solution[35]. When chitosan is in solution, the repulsions between the deacetylated units and their neighboring glucosamine units cause it to exist in an extended conformation. Addition of an electrolyte reduces this effect and the molecule possesses a more random, coil-like conformation[36].

A number of derivatives had been synthesized till now and some of them include N-carboxymethyl chitosan, hydrophobic chitosans, chitosans with methoxyphenyl functions, tyrosine glucan, highly cationic chitosans, polyurethane-type chitosans, hydroxyalkyl chitosan, sugar-modified chitosan, cyclodextrin-linked chitosan, crown-ether-bound chitosan, in order to modulate the physicochemical property.

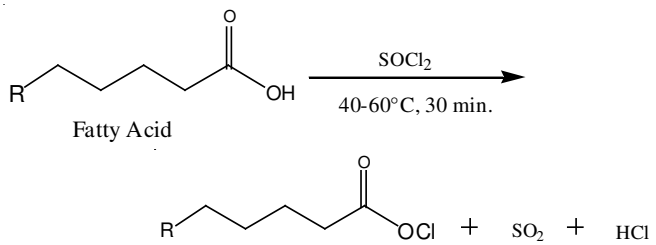
Water uptake of chitin and chitosan was found to be significantly higher than that of microcrystalline cellulose[3]. This water uptake property of chitosan enables it to function in tablet formulations as a disintegrant. It was found that when chitosan is used in a concentration of more than 50 % of tablet weight, an insoluble non-erosion type matrix was formed. Tablets prepared with a chitosan concentration of less than 33 % were fast releasing chitosan used in a concentration of about 10 % acted as a disintegrant and the drug was dissolved within 1 h.

Chitosan being a novel excipient of natural origin is investigated by us for hydrophobic modification for release retardant action for hydrophilic drugs in matrix tablet dosage forms. In the present work, six different homologous of N-fatty acyl (caproyl, decanoyl, lauryl, myristyl, palmitoyl, stearoyl) derivative of chitosan is synthesize in various batches which differ in degree of substitution through reaction monitoring. The physicochemical properties such as degree of substitution, spectra analysis, solubility analysis, flow properties (bulk density, tap density, carr index and angle of repose), water binding capacity, viscosity requires to qualify them as pharmaceutical excipient were evaluated and finally these materials were incorporated in the tablet in various concentrations and evaluate for "test for tablets" as per IP and "*in vitro* release studies". Through present study, it is concluded that there is gradually increment in release retardation property and compaction property as we go high in the carbon chain length in homologous series but the best property found using palmitoyl as modified functional grouping and the probable reason is resistance in water attacking property in derived chitosan.

EXPERIMENTAL

Synthesis of fatty acyl chitosan[37-39]

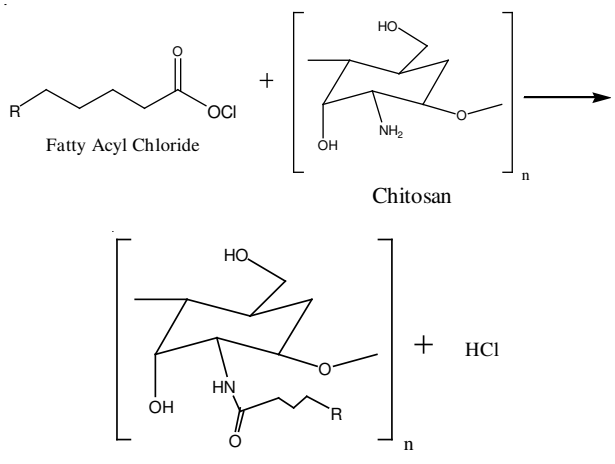
Step-1: Synthesis of fatty acyl chloride from fatty acids: Fatty acid (0.05 M) was transferred in round bottom flask and heated on water bath. Thionyl chloride 5.50 mL (0.75 M) was then added to heated solution during 30-40 min interval. The solution was heated gently for 0.5 h at 40-60 ºC. Shaken from time to time as to ensure mixing until evolution of fumes ceases.



Scheme-I

Step-2: Synthesis of fatty acyl chitosan from synthesized fatty acyl chloride: One gram chiotsan was weighed and dissolved into 120 mL of 0.12 M aqueous acetic acid. The solution was stirred for 24 h as to ensure total solubility. The pH of the solution was adjusted to 7.2 by slow addition of 0.1 M sodium hydroxide with strong agitation yielding a gel slurry, volume of which was adjusted to 180 mL with distilled water. Fatty acyl chloride prepared in step 1 was added in varying amount 4, 8 and 12 mL to three beakers containing stirred chitosan solution prepared by same procedure as above as to obtain products with different degree of substitution.

After 4-6 h stirring each preparation was neutralized to pH 6.8-7.0 and further the solution was precipitated with acetone. Precipitates were collected by filteration and washed at 50-60 ºC with an excess of methanol and decanted. Washing was repeated three times with methanol to eliminate free fatty acids. Finally the product were dried with pure acetone to obtain the corresponding derivatives.



Scheme-II

Physicochemical characterization of chitosan and its derivatives

Solubility studies[39]: Chitosan and its derivatives were checked for its solubility in different solvents like water, dimethyl sulphoxide, dimethyl formamide, methanol, ethanol, pyridine, acetone and 0.1 M hydrochloric acid.

Bulk density, tap density and carr index[40]: For the determination of bulk and tap density, powder sample was carefully introduced into a measuring cylinder separately. The cylinder was dropped on a hard wooden surface from a height of 1 inch at 2 s interval, giving it tapping till the volume becomes constant. Carr's index was also calculated as per following formula

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

Angle of repose: For this, powder was carefully poured separately in to a dry glass funnel whose tip was blocked. The block was removed and the powder was allowed to flow onto a sheet of plane paper under the force of gravity. The height and diameter of the pile formed was measured.

Water binding capacity[41]: Water binding capacity of chitosan was measured using a modified method of Wang and Kinsella. Water binding capacity was initially carried out by weighing a centrifuge tube containing 0.1 g of sample, added 10 mL of water and mixing on a vortex mixer for 1 min to disperse the sample. The content were left at ambient temperature for 0.5 h with shaking for 5 s every 10 min and then centrifuged at 3000 rpm for 25 min. After the supernatant was decanted, the tube was weighed again and water binding capacity was calculated as follows.

$$\text{WBC \% (Water binding capacity)} = \frac{\text{Water bound (g)}}{\text{Sample weight (g)}} \times 100$$

Viscosity: Viscosity was measured using Ostwald's viscometer at 25 ºC. Solution of chitosan and its derivatives were prepared at 0.1 per cent concentration.

Degree of deacetylation[42]: Degree of deacetylation is determined using FTIR spectrophotometry. It is determined by the ratio of absorbance at 1655 cm^{-1} (amide I band) and absorbance at 3450 cm^{-1} (hydroxyl band) as per method proposed by Moore and Roberts and using the relation

$$\text{Degree of deacetylation (DD) (\%)} = \left(\frac{A_{1655}}{A_{3450}}\right) \times 100$$

Degree of substitution[43]: The degree of substitutions were determined by hydrolyzing 100 mg of acylated chitosans in aqueous NaOH solution (3 M) for 72 h. The concentration of caprylic acid, decanoic acid, lauric acid, myristic acid, palmitic acid and stearic acid, in the hydrolyzed solutions were determined by UV measurement at the wavelengths 208, 212, 211, 218, 268, 273, respectively. Non-conjugated chitosan was treated in the same way and the resulting solution was used as a blank. The degree of substitution (% g) is defined as the ratio of the measured amount of fatty acid (g) in the hydrolyzed solution, to the amount of the hydrolyzed chitosan conjugate (g).

FTIR studies: Identification of functionality in the structure of chitosan and its derivatives was confirmed by FTIR recorded on FTIR spectrophotometer (Shimadzu 8400S).

Scanning electron microscopy studies: The surface morphology of chitosan was visualized by scanning electron microscopy (SEM). The sample for SEM was prepared by lightly sprinkling the powder of chitosan and derivatives on a double adhesive tape, which stuck on a metal stub. The powder was observed at an excitation voltage of 5 kV on different magnifications using Jeol JSM 5600 scanning electron microscope.

X-Ray diffraction studies: The chemical composition and crystallographic structure of chitosan and its derivatives was also studied using X-ray diffraction study on Rigaku diffractometer, in which high intensity monochromatic CuK_α radiation was generated at 40 kV and 100 mA, at a wavelength of 1.5418 Å. Diffraction patterns of chitosan and acylated chitosan derivatives in powder form was compared by powder X-ray diffraction patterns acquired at room temperature at 2θ range from 0-35 ºC in continuous mode.

Formulation of tablets[43,44]: In the study, the tablets were prepared using indomethacine (75 mg) as prototype hydrophilic drug. The content of chitosan derivatives (Table-1) were varied to in order to observe the effect of the concentration on release profile. All the excipients were weighed accurately and passed through sieve # 44, except magnesium stearate which was passed through sieve # 60. After weighing, the ingredients were mixed properly and then magnesium stearate was mixed. Finally the batches were compressed at a target weight in a single punch machine using a flat punch by hand filling. The matrix tablets were prepared by direct compression method using 9 mm punch. The hardness was kept between 3.0-4.5 kg/cm^2.

TABLE-1
GENERAL FORMULE AND THE CORRESPONDING DIFFERENT PERCENTAGE OF EXCIPIENTS USED FOR THE PREPARATION OF MATRIX TABLETS

Excipient	Batch-I	Batch-II	Batch-III
Indomethacin	30 % (75 mg)	30 % (75 mg)	30 % (75 mg)
Chitosan and its derivatives	10 % (25 mg)	20 % (50 mg)	30 % (75 mg)
PVP K-30	5 % (12.5 mg)	5 % (12.5 mg)	5 % (12.5 mg)
Directly compressible lactose	54 % (135 mg)	44 % (110 mg)	34 % (85 mg)
Magnesium stearate	1 % (2.5 mg)	1 % (2.5 mg)	1 % (2.5 mg)

Evaluation of physicochemical properties matrix tablets[45]: Tablets were evaluated for the following quality control parameters.

Hardness: The hardness was determined using monsanto hardness tester.

Thickness: Vernier calliper method.

Weight variation test: In this study 20 tablets were sampled and were tested as per IP and USP acceptance limits.

Friability: The test was performed on Roche friabilitor using 10 tablets. Weights tablets were allowed to revolve at 25 rpm for 4 min as to complete 100 revolutions.

***In vitro* release studies:** The tablets were evaluated for *in vitro* release studies using IP-1, USP-2 apparatus, 900 mL

of pH 6.2 buffer as dissolution media. The temperature of media was maintained at 3.7 ± 0.5 ºC and speed of the paddle was set to 75 rpm. 24 h dissolution profile was recorded at different sampling time interval. The samples were withdrawn at each time interval and filtered into glass vials. The samples were analyzed for the Indomethacin content using UV spectrophotometer absorbance at 218 nm taking pH 6.2 buffer as blank.

RESULTS AND DISCUSSION

Solubilty studies: The comparative solubility data (Table-2) shows while chitosan was soluble only in acidic aqueous condition but the derivatives have good solubility profile in organic solvents.

Bulk density, tap density and carr index: A comparative profile of the chitosan and its synthesized derivatives shows that chitosan have better compressability status as compared to chitosan (Table-3).

Angle of repose: The comparative profile (Table-3) shows that there is not much variation in flow properties after derivatization.

Water binding capacity and viscosity: The water binding capacity and viscosity profile is decreased upon derivatization as shown by comparative data in Table-4.

Degree of deacetylation: The value of degree of deacetylation was found with in the desired limit *i.e.*, more than 85 %.

Degree of substitution: Table-5 shows the values of degree of degree of substitution of all the batches.

FTIR spectra analysis: The data in Figs. 2-8, Table-6 shows characteristic bands of chitosan and its derivatives giving a confirmation that derivatization was performed successfully.

TABLE-2
SOLUBILITY PROFILE OF DIFFERENT CHITOSAN DERIVATIVES

Chitosan/derivative	Batch	Water	DMSO	DMF	Methanol	Ethanol	Pyridine	Acetone	0.1 M HCl
Chitosan	–	–	–	–	–	–	–	–	+
Caproyl chitosan	I	–	PS	PS	–	–	PS	–	–
	II	–	PS	PS	*	*	+	PS	–
	III	–	S	PS	*	*	+	PS	–
Decanoyl chitosan	I	–	PS	PS	*	–	PS	–	–
	II	–	PS	PS	*	*	+	PS	–
	III	–	S	PS	*	*	+	PS	–
Lauryl chitosan	I	–	PS	PS	–	–	PS	–	–
	II	–	PS	PS	–	*	+	PS	–
	III	–	S	PS	–	*	+	PS	–
Myristoyl chitosan	I	–	PS	PS	–	–	PS	–	–
	II	–	–	–	*	*	+	PS	–
	III	–	–	–	*	*	+	PS	–
Palmitoyl chitosan	I	–	PS	PS	–	–	PS	–	–
	II	–	PS *	PS *	*	*	+	PS	–
	III	–	PS *	PS *	*	*	+	PS	–
Stearoyl chitosan	I	–	–	–	–	–	PS	–	–
	II	–	–	–	PS	*	+	PS	–
	III	–	–	–	PS	*	+	PS	–

–: Insoluble, PS: partially soluble, +: soluble, *swelling.

TABLE-3
BULK DENSITY, TAPPED DENSITY, CARR'S INDEX AND ANGLE OF REPOSE OF CHITOSAN AND ITS DERIVATIVES

Chitosan/derivative	Batch	Bulk density (g/mL)	Tapped density	Carr's index	Angle of repose
Chitosan	–	0.138	0.178	22.47	24.36
Caproyl chitosan	I	0.625	0.730	14.38	32.23
	II	0.635	0.734	13.48	33.16
	III	0.640	0.754	15.11	30.20
Decanoyl chitosan	I	0.500	0.625	20.00	18.20
	II	0.470	0.620	24.19	20.16
	III	0.500	0.609	17.79	22.24
Lauryl chitosan	I	0.440	0.530	16.98	21.56
	II	0.405	0.533	15.57	22.58
	III	0.480	0.615	21.95	22.92
Myristoyl chitosan	I	0.330	0.450	26.66	32,63
	II	0.280	0.470	40.42	36.53
	III	0.250	0.370	32.40	36.86
Palmitoyl chitosan	I	0.416	0.520	20.00	26.10
	II	0.350	0.510	31.20	32.61
	III	0.312	0.450	58.50	40.26
Stearoyl chitosan	I	0.540	0.660	18.18	28.16
	II	0.540	0.650	67.60	29.24
	III	0.500	0.610	69.50	22.92

TABLE-4
WATER BINDING CAPACITY (WBC) AND VISCOSITY OF CHITOSAN AND ITS DERIVATIVES

Chitosan/derivative	Batch	WBC (%)	Relative viscosity
Chitosan	–	15.320	5.700
Caproyl chitosan	I	7.560	1.280
	II	7.120	1.083
	III	6.800	0.876
Decanoyl chitosan	I	6.360	0.600
	II	6.300	0.440
	III	6.270	0.380
Lauryl chitosan	I	7.122	0.438
	II	6.616	0.413
	III	6.325	0.361
Myristoyl chitosan	I	6.554	0.433
	II	6.328	0.382
	III	6.193	0.375
Palmitoyl chitosan	I	6.710	0.427
	II	6.395	0.400
	III	6.323	0.366
Stearoyl chitosan	I	6.537	0.796
	II	6.428	0.408
	III	6.325	0.379

TABLE-5
DEGREE OF SUBSTITUTION OF DIFFERENT BATCHES

Chitosan/derivative	Batch	Degree of substitution
Caproyl chitosan	I	3.11
	II	8.12
	III	15.28
Decanoyl chitosan	I	2.15
	II	4.86
	III	13.20
Lauryl chitosan	I	1.60
	II	4.23
	III	5.82
Myristoyl chitosan	I	2.53
	II	3.92
	III	11.24
Palmitoyl chitosan	I	6.14
	II	13.35
	III	18.12
Stearoyl chitosan	I	5.10
	II	12.90
	III	15.23

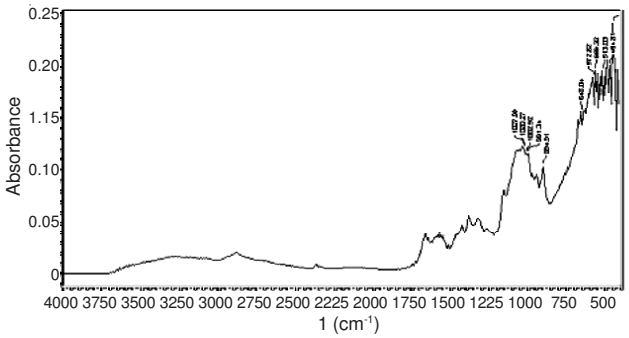


Fig. 2. FTIR spectrum of chitosan

X-Ray diffraction analysis: When compared with the diffraction pattern of acylated chitosan it was observed that, the chitosan shows two distinct peaks, which actually are two distinct crystal from I and II. It is reported[46] that these two peaks are orthorhombic form of crystals. The strongest reflections

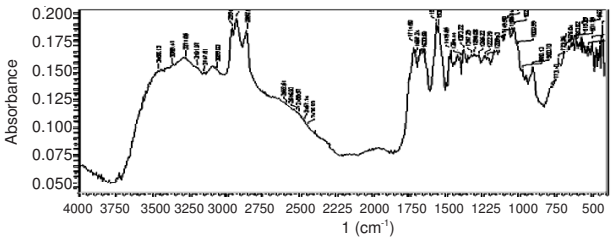


Fig. 3. FTIR spectrum of caproyl chitosan

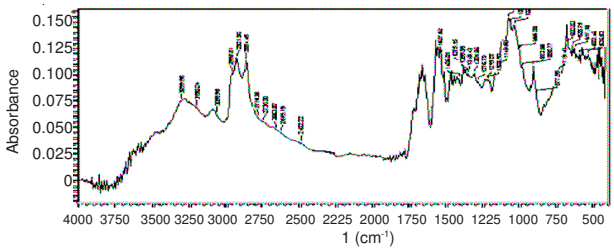


Fig. 4. FTIR spectrum of decanoyl chitosan

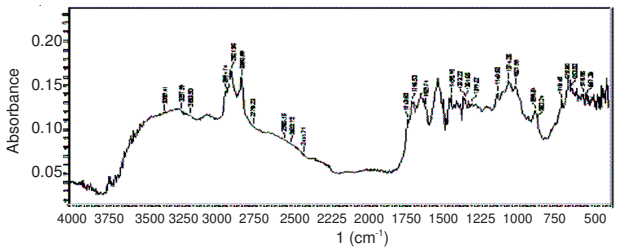


Fig. 5. FTIR spectrum of lauryl chitosan

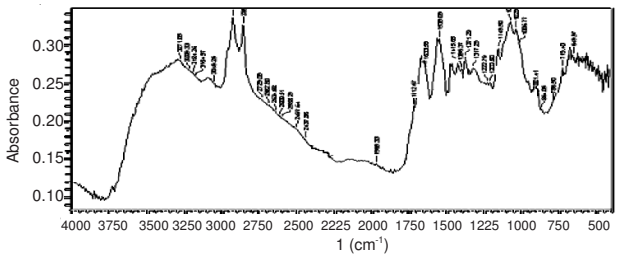


Fig. 6. FTIR spectrum of myristyl chitosan

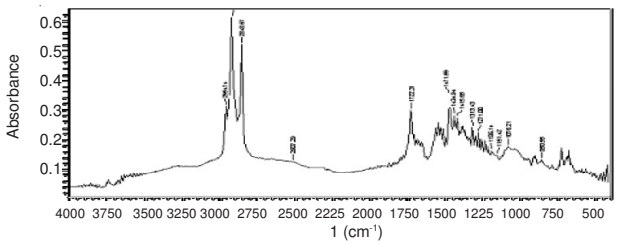


Fig. 7. FTIR spectrum of palmitoyl chitosan

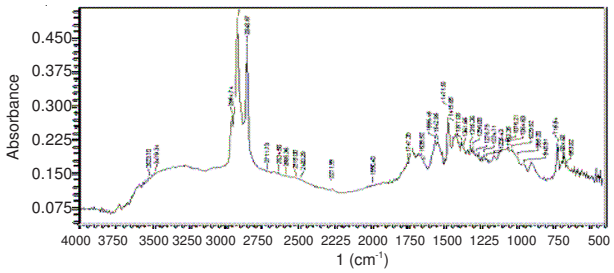


Fig. 8. FTIR spectrum of stearoyl chitosan

TABLE-6
FTIR INTERPRETATION OF CHITOSAN AND ITS DERIVATIVES

Chitosan/derivative	Interpretation of FTIR spectra
Chitosan	1. Primary -NH_2 Group = 1560.3 cm^{-1} 2. -OH Stretching vibration = 3447 cm^{-1} 3. -CH_2 Stretching band = 2877 cm^{-1} 4. -CO- band = 1027.9 cm^{-1}
Caproyl chitosan	1. Peak at 1560.3 cm^{-1} disappeared 2. -C=O of amide = 1646.23 cm^{-1} (amide-I) 3. 3. Peak area in the region at 2850-2950 cm^{-1} at 2846 and 2941.31 cm^{-1} increased suggesting the formation of caproyl chitosan.
Decanoyl chitosan	1. Peak at 1560.3 cm^{-1} disappeared 2. -C=O of amide = 1647.31 cm^{-1} (amide-I) 3. Peak area in the region at 2850-2950 cm^{-1} at 2852.03, 2920.3 and 2950.8 cm^{-1} increased suggesting the formation of decanoyl chitosan.
Lauryl chitosan	1. Peak at 1560.3 cm^{-1} disappeared 2. -C=O of amide = 1633.16 cm^{-1} (amide-I). 3. Peak area in the region at 2850-2950 cm^{-1} at 2852 and 2921 cm^{-1} increased suggesting the formation of lauryl chitosan.
Myristoyl chitosan	1. Peak at 1560.3cm^{-1} disappeared 2. -C=O of amide = 1638.52 cm^{-1} (amide-I). 3. Peak area in the region at 2850-2950 cm^{-1} at 2850.59 and 2920.03 cm^{-1} increased suggesting the formation of myristoyl chitosan.
Palmitoyl chitosan	1. Peak at 1560.3 cm^{-1} disappeared 2. -C=O of amide = 1636.22 cm^{-1} (amide-I). 3. Peak area in the region at 2850-2950 cm^{-1} at 2865.74 and 2916.17 cm^{-1} increased suggesting the formation of lauryl chitosan.
Stearoyl chitosan	1. Peak at 1560.3 cm^{-1} disappeared 2. -C=O of amide = 1658.33 cm^{-1} (amide-I). 3. Peak area in the region at 2850-2950 cm^{-1} at 2848.67 and 2923.88 cm^{-1} increased suggesting the formation of lauryl chitosan.

falls at 2θ = 20.81°. This reflection is the typical crystalline peak of chitosan. The acyl substituted chitosan shows a broad reflection only at around 2θ = 15°. With increase in acyl chain length the peak was observed to be sharper and increased in number, as from X-ray diffraction indicated that the palmitoyl and stearoyl chitosan structure contained more crystalline areas (Figs. 9-15, Table-7).

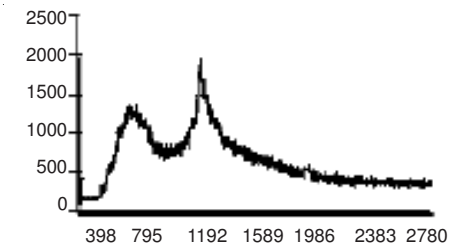


Fig. 9. X-Ray spectrum of chitosan

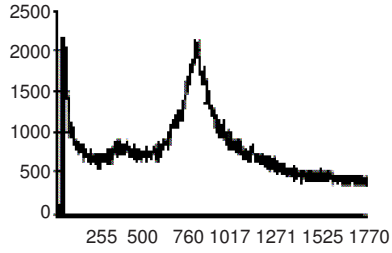


Fig. 10. X-Ray spectrum of caproyl chitosan

SEM Analysis: From the photomicrograph of chitosan and synthesized derivatives, it isdepicted that the surface pattern of chitosan was found to be smoother, where that of

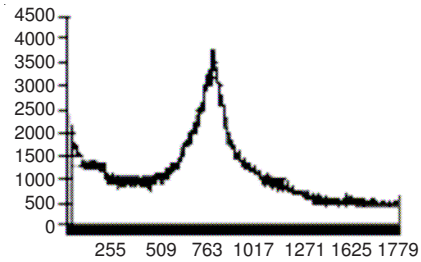


Fig. 11. X-Ray spectrum of decanoyl chitosan

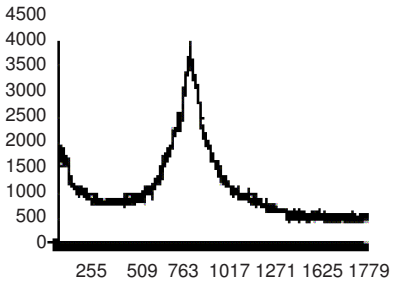


Fig. 12. X-Ray spectrum of lauryl chitosan

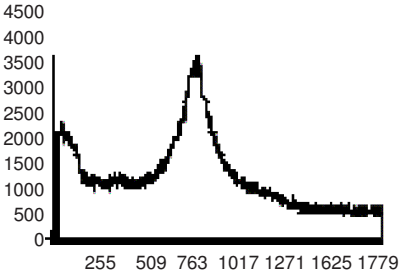


Fig. 13. X-Ray spectrum of myristyl chitosan

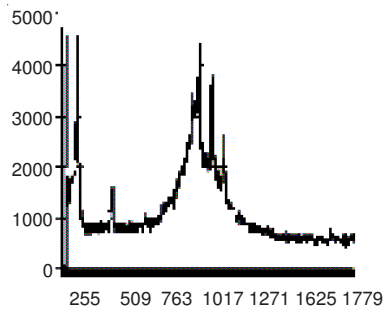


Fig. 14. X-Ray spectrum of palmitoyl chitosan

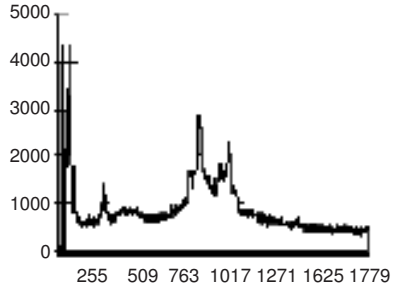


Fig. 15. X-Ray spectrum of stearoyl chitosan

TABLE-7
2θ VALUES OF DIFFERENT CHITOSAN DERIVATIVES

Chitosan/derivative	2θ Values
Caproyl chitosan	15.42
Decanoyl chitosan	15.34
Lauryl chitosan	15.48
Myristoyl chitosan	15.18
Palmitoyl chitosan	1.6, 5.82, 15.6, 19.42
Stearoyl chitosan	0.86, 4.58, 15.5, 18.06

acylated derivatives showed a slightly rough and stretched surfaces and essentially same surface pattern was observed with other N-acylated chitosan. The slightly rough and stretched pattern is considered to be formed by the dehydration and neutralization process during N-acylation of chitosan (Figs. 16-22).

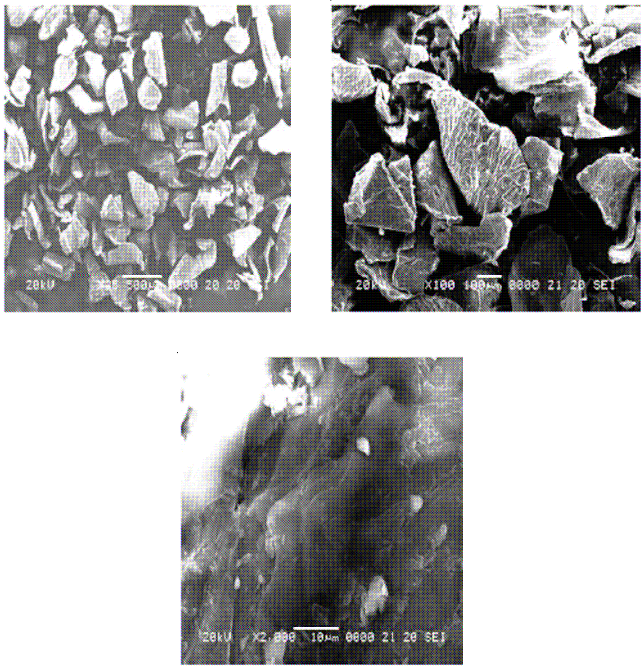


Fig. 16. Scanning electron microscope photograph of chitosan

Quality control test for tablets: Table-8 shows the values of quality control parameter as per "IP tests for tablets". The values are in acceptance limits.

***In vitro* release studies:** Figs. 23-25 shows release profile of tablets with varied polymer content. The best results were obtained with palmitoyl derivatives which were able to retard the release of drug from the tablets *i.e.*, 50-60 % release in 12 h.

TABLE-8
HARDNESS, FRIABILITY, THICKNESS, WEIGHT VARIATION OF THE PREPARED HYDROPHILIC MATRIX TABLETS, EXPRESSED AS MEAN ±

Chitosan/derivative	Batch	Hardness (Kg/cm^2)	Friability	Weight variation	Thickness (mm)
Chitosan	I	3.25	0.67	252 ± 8.13	2.7 ± 0.1
	II	3.1	0.82	248 ± 7.29	3.3 ± 0.2
	III	3.2	0.62	249 ± 6.63	3.1 ± 0.2
Caproyl chitosan	I	4.1	0.73	249 ± 8.08	3.2 ± 0.3
	II	4.23	0.66	246 ± 6.62	3.3 ± 0.1
	III	4.3	0.43	248 ± 7.20	3.4 ± 0.3
Decanoyl chitosan	I	3.2	0.65	247 ± 8.14	3.3 ± 0.4
	II	3.2	0.76	250 ± 6.23	3.5 ± 0.4
	III	3.6	0.55	251 ± 6.68	3.3 ± 0.3
Lauryl chitosan	I	3.1	0.97	248 ± 7.69	3.1 ± 0.2
	II	3.2	0.71	246 ± 8.27	3.4 ± 0.2
	III	3.4	0.68	246 ± 9.61	3.3 ± 0.1
Myristoyl chitosan	I	4.3	0.63	250 ± 5.65	3.3 ± 0.4
	II	4.4	0.66	251 ± 7.33	3.4 ± 0.2
	III	4.3	0.71	253 ± 9.45	3.1 ± 0.1
Palmitoyl chitosan	I	3.6	0.53	249 ± 6.26	3.2 ± 0.3
	II	3.5	0.86	246 ± 8.24	3.2 ± 0.3
	III	3.8	0.91	248 ± 6.29	3.1 ± 0.4
Stearoyl chitosan	I	3.8	0.53	245 ± 9.13	3.2 ± 0.1
	II	3.6	0.78	247 ± 6.21	3.1 ± 0.2
	III	3.3	0.51	244 ± 8.63	3.5 ± 0.2

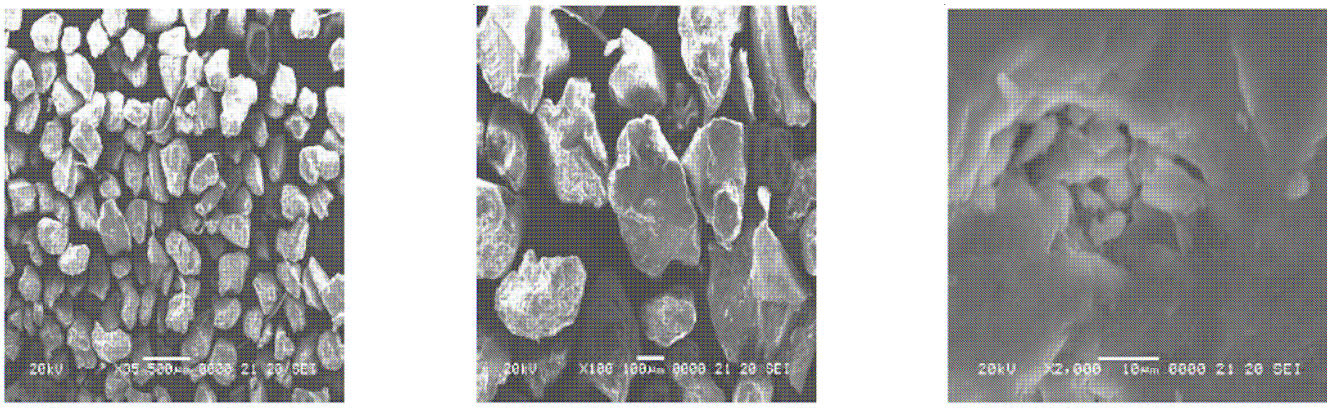


Fig. 17. Scanning electron microscope photograph of caproyl chitosan

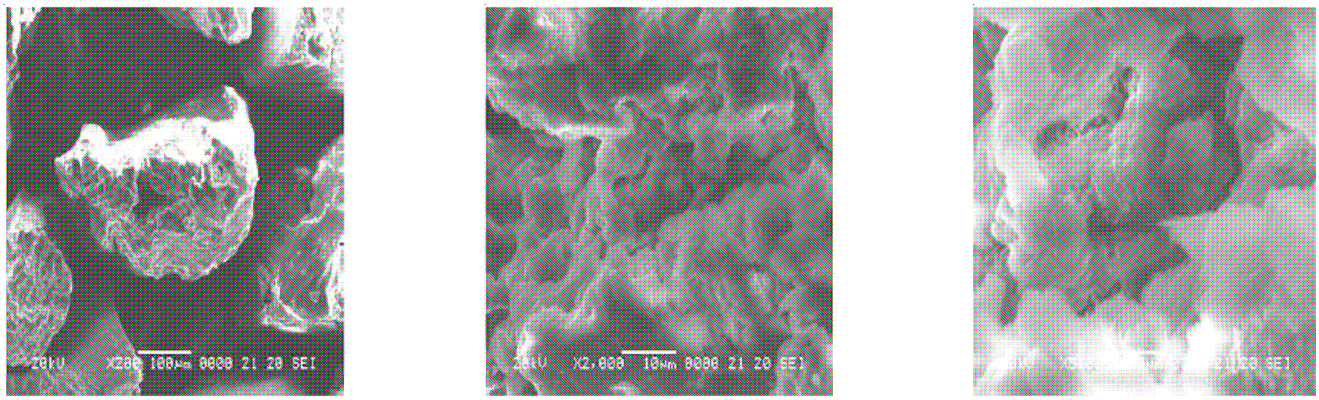


Fig. 18. Scanning electron microscope photograph of decanoyl chitosan

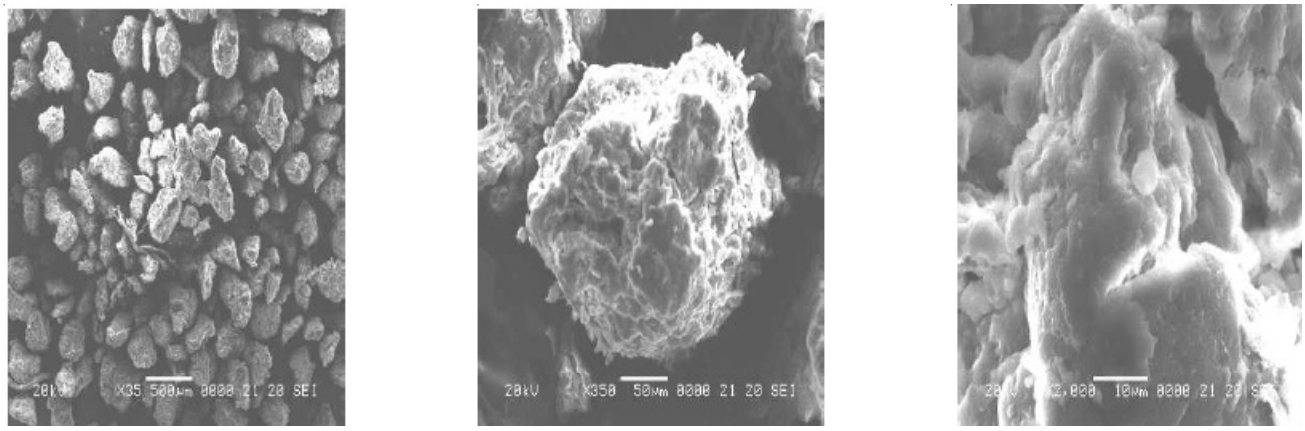


Fig. 19. Scanning electron microscope photograph of lauryl chitosan

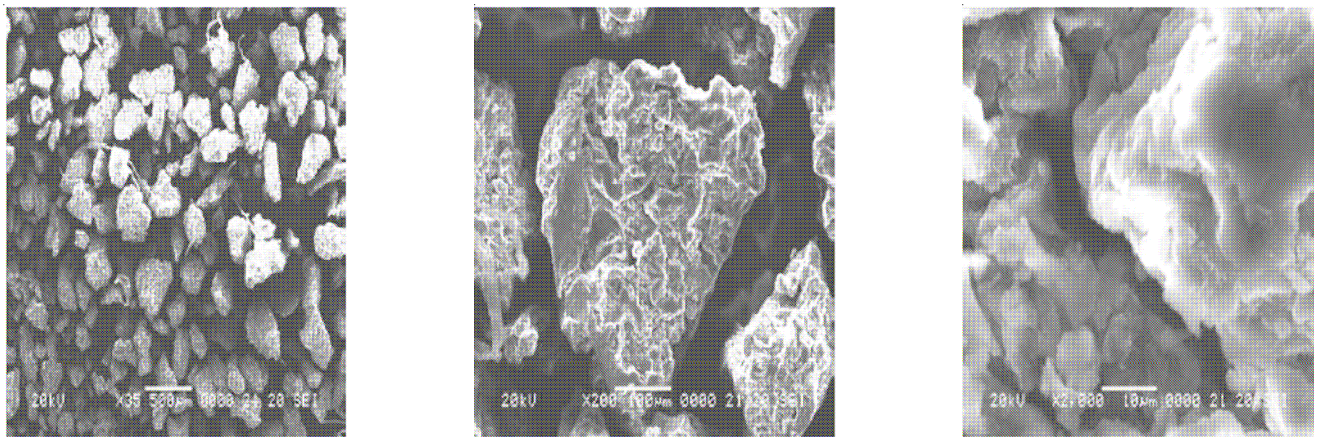


Fig. 20. Scanning electron microscope photograph of myristyl chitosan

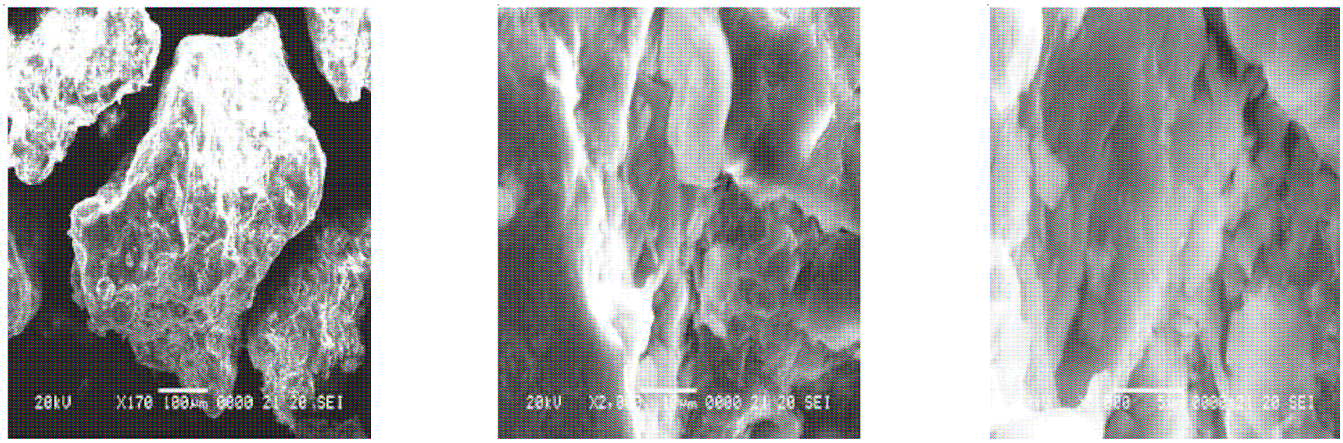


Fig. 21. Scanning electron microscope photograph of palmitoyl chitosan

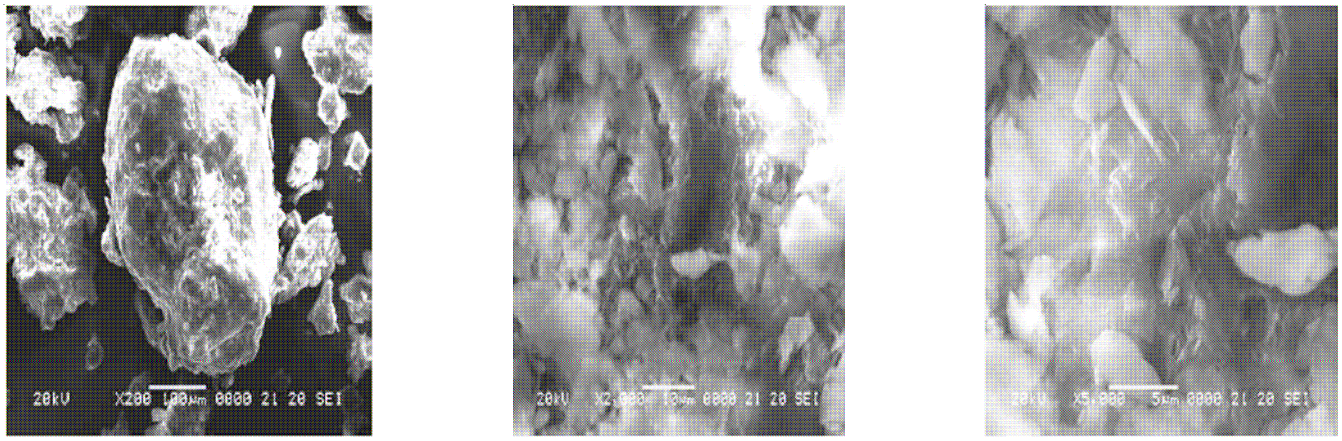


Fig. 22. Scanning electron microscope photograph of stearoyl chitosan

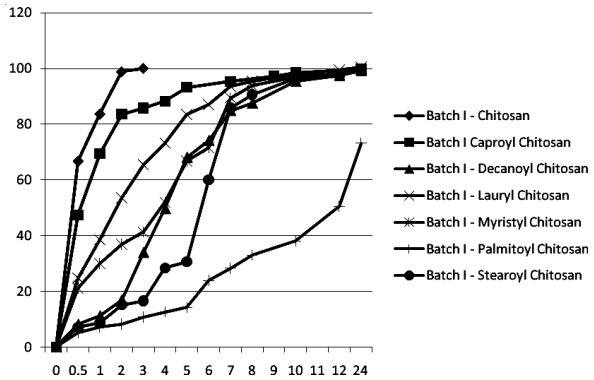


Fig. 23. Comparative graph of dissolution profile of batch I of chitosan and its derivatives

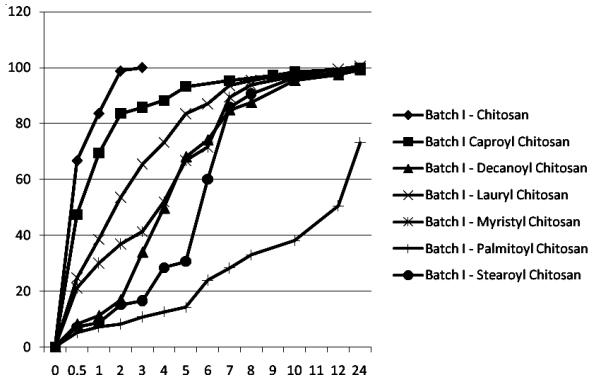


Fig. 24. Comparative graph of dissolution profile of batch II of chitosan and its derivatives

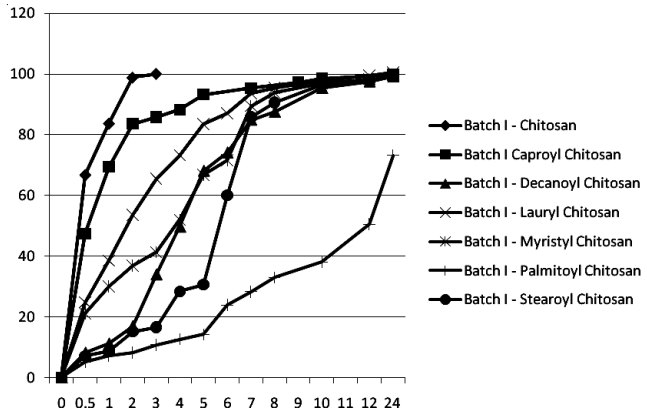


Fig. 25. Comparative graph of dissolution profile of batch III of chitosan and its derivatives

Conclusion

From the studies, it can be concluded that hydrophobic modification of chitosan can be a valuable tool in generating a polymer to be used in sustained release system of hydrophilic drugs. When chitosan itself is active at a concentration above 50 % in non-erosion type matrix systems. The modified polymers are active even at lower concentrations and gives more profound release profile in case of hydrophilic polymers. The best modification were obtained by palmitoyl substitution *i.e.*, with carbon chain C-16.

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