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Original article

Comparative studies on polyelectrolyte complexes of chitosan for sustained release of simvastatin

Poornima G, Mohammed Gulzar Ahmed, Ramesh B
Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, B.G.Nagara, Karnataka, India
Correspondence to: Mohammed Gulzar Ahmed, Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, B.G.Nagara, Karnataka, India

Abstract
The present work was based on "Comparative studies on polyelectrolyte complexes of chitosan for sustained release of simvastatin". Simvastatin (SV) is a drug belonging to class of statins, used as lipid regulating drug and in the treatment of hypercholesterolemia and it is poorly absorbed from the gastrointestinal tract and undergoes extensive first pass metabolism in the liver, only 5% of the oral dose has been reported to reach the systemic circulation as active metabolite. The half-life of the active metabolite is 3hrs. In the present study, chitosan polyelectrolyte complex were developed in the form of hydrogels by interaction of positively charged chitosan with negatively charged polymers sodium alginate, gellan gum, and carrageenan. The compatibility studies of polyelectrolyte complex formation were confirmed by FTIR spectroscopy and the surface morphology was investigated by (SEM) Scanning electron microscopy. The simvastatin sustained release tablets containing polyelectrolyte complex were prepared by direct compression method. The prepared PEC tablets were evaluated for drug content, swelling behaviour and *in-vitro* release studies. Evaluation parameters for matrix tablets were within the acceptable limits. The matrix tablets showed pH sensitive swelling with low swelling in hydrochloric acid buffer while more swelling in phosphate buffer. The *in-vitro* release of simvastatin from prepared PEC tablets was in the order of chitosan-gellan gum > chitosan-sodium alginate > chitosan-carrageenan. Drug release from prepared PEC tablets at the end of 12 hrs are 77.639%, 74.464%, 83.567%, 81.702%, 70.374% and 61.451 respectively chitosan–sodium alginate, chitosan-carrageenan and chitosan-gellan gum. Indicating prolonged drug release from prepared polyelectrolyte complex (PEC) Tablets.
Key words Simvastatin; Sustained Release; *In-vitro* release; Polyelectrolyte complex; Chitosan.

Introduction

Oral route is the most commonly employed route of drug administration. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product.[1]

Simvastatin is the drug which increasingly used in the management of hypercholesterolemia[2]. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-

limiting step in the biosynthesis of cholesterol[3]. Since the half-life of Simvastatin is 3 hrs[4], multiple doses need to be taken in order to maintain a constant plasma concentration for a good therapeutic response. By formulating Simvastatin as a sustained release tablet we can overcome this major side effect and also increase the bioavailability. By use of polymers such as sodium alginate, carrageenan, gellan gum in the form of polyelectrolyte complexes with chitosan, the release of the drugs in the acidic environment can be protected. These polymers swell and get hydrated on reaching the intestine when in contact with the alkaline medium and the release the drug slowly over a long period. The phenomena of Inter polymer interactions and formation of polyelectrolyte complex have been the focus of intensive fundamental and applied research. Inter polyelectrolytes combine unique physicochemical properties with high biocompatibility[5]. Hydrogels are high water content prepared from cross-liked polymers that are able to provide sustained, local delivery of verity of therapeutic agents, use of natural polymers were used as the scaffold material in hydrogels. The great advantages of these natural polymers were better polymer biocompatibility, low toxicity, and biodegradability[6]. Matrix systems based on physical mixtures of chitosan–gellan gum have been studied. These systems showed good properties as prolonged drug release matrices. On the other hand, matrices containing sodium alginate and carrageenan were found to be useful for controlling the simvastatin release. Our interest in the polymers chitosan, alginate, and carrageenan is based on the fact that our country is an important producer of these polysaccharides. We consider that the study of the physical mixtures and polyelectrolyte complexes could allow development of prolonged drug release matrices.

The aim of this work was to evaluate the possibility to obtain different prolonged drug dissolution profiles by changing the polymer matrix system (chitosan–gellan gum or chitosan–sodium alginate or chitosan-carrageenan) and the method used to include the polymers into the formulation (physical mixture or polyelectrolyte complex). Also, we tried to explain the drug dissolution profiles from the matrices considering the swelling behavior of the polymers used.

Material and methods

Simvastatin as procured as a gift sample from Biocon Lab, Bangalore. Chitosan, Sodium Alginate, Carrageenan, Gellan Gum, Magnesium Stearate, Dicalcium Phosphate from Yarrow chem products, Mumbai.

Preparation of polyelectrolyte complexes: Polyelectrolyte complexes was prepared by using chitosan as cationic and alginate, gellan gum, carragenan as anionic polymers in 1:1 and 1:4 ratio by the following methods.

Chitosan–alginate polyelectrolyte complex*:* The chitosan–alginate polyelectrolyte complex (CCSAS) was prepared from chitosan (CS) solution at 4.0% w/v in 1% w/w acetic acid solution and alginate (AS) Solution at 4.0% w/v in water.

Chitosan– Carrageenan polyelectrolyte complex*:* The chitosan–carrageenan polyelectrolyte complex (CCSCSI) was prepared from chitosan (CS) solution at 4.0% w/v in 1% w/w acetic acid solution and carrageenan (CSI) solution at 4.0% w/v in 5.7% NaCl solution.

Chitosan– Gellan gum polyelectrolyte complex: The chitosan–gellan gum polyelectrolyte complex (CCSGG) was prepared from chitosan (CS) solution at 4.0% w/v in 1% w/w acetic acid solution and gellan gum (GG) Solution at 4.0% w/v in water.

Each solution was heated separately at 70 - 80^0 C both the solutions were mixed at 75^{0}C with agitation until it attained room temperature. Then it was left to rest for 2hrs. The polyelectrolyte complex (PEC) was thoroughly washed with distilled water and was then separated from water by centrifugation for 30 min at 10000 rpm. Thereafter, the PEC was again submerged in distilled water and left at 9^{0}C for 48 h. Then, the centrifugation step was repeated. Finally, the PEC was dried to constant weight in a vacuum oven at 70-80^{0}C, and classified by sieving through 100# mesh sieves. The ratios of polymers combination was shown in Table 1[7].

Table 1: Ratio of polymers used in preparation of PECs

Code	Chitosan-Sodium alginate	Chitosan-Carrageenan	Chitosan-Gellan gum
F1	1:1	-	-
F2	1:4	-	-
F3	-	1:1	-
F4	-	1:4	-
F5	-	-	1:1
F6	-	-	1:4

Characterization of polyelectrolyte complexes:

The polyelectrolyte complexes formed were characterized by FTIR and SEM studies.

Evaluation of physical properties:

The blended powder was evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, Hausner's Ratio[8].

Formulation of simvastatin PEC tablets:

The tablets were prepared by direct compression. The drug and polyelectrolyte complex were taken in a ratio of 1:1. Magnesium stearate and di-calcium phosphate are used as lubricant and diluents respectively. As the polyelectrolyte complex itself is expected to have binding properties.

For formulation of simvastatin tablets, 40mg of the drug and 40mg of the complex was taken. The PEC can be used for any dose of the drug, in a drug: complex of 1:1 is shown in Table 2.

Table 2: Formulation of sustained release tablet of simvastatin using drug loaded polyelectrolyte complex:

INGREDIENTS	F1	F2	F3	F4	F5	F6
Drug (Simvastatin)	40	40	40	40	40	40
CS-SA (Chitosan-Sodium alginate)	40	40	_	_	_	_
CS-CR (Chitosan-Carrageenan)	_	_	40	40	_	_
CS-GG (Chitosan- Gellan gum)	_	_	_	_	40	40
Diluent (Di-Calcium phosphate)	66	66	66	66	66	66
Lubricant (Magnesium Stearate)	4	4	4	4	4	4
Total Weight	150	150	150	150	150	150

Evaluation of sustained release PEC loaded simvastatin tablets:

The prepared tablets were subjected to thickness, weight variation test, hardness, friability and drug content and swelling index.

***In Vitro* Release study:**

The release study was carried out for 12 hours using USP type-II (paddle method).The water bath was thermo stated at 37^0C ± 0.5^0C. The paddle was set to rotate at 100 rpm. One tablet previously weighed was kept in the dissolution media. Two dissolution medias-acidic buffer pH 1.2 for 2 hrs and phosphate buffer pH 6.8 for remaining 10hrs. A 5 mL sample was collected from each vessel at every 1 hour and spectrophotometrically analysed for simvastatin at 247 nm. The withdrawn sample was immediately replaced by equal volume of fresh buffer[6].

RESULTS:

Compatibility studies:

The FTIR spectroscopy is a useful tool for identifying both organic and inorganic chemicals. It can be utilized to quantify some components of an unknown mixture and can be used to analyze liquids, solids and gases. The FT-IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between drug and the used polymers.

Scanning Electron Microscopy:

The surface morphology of prepared drug loaded PEC was studied by scanning electron microscopy (SEM) in Figure 1. The PEC formed by chitosan and sodium alginate has rough texture and small gaps. The PEC hydrogels formed by chitosan and carrageenan have showed a great number of large channels with some pores of irregular form and size. The PEC formed by chitosan and gellan gum has sponge like surface with fibrilar structure.

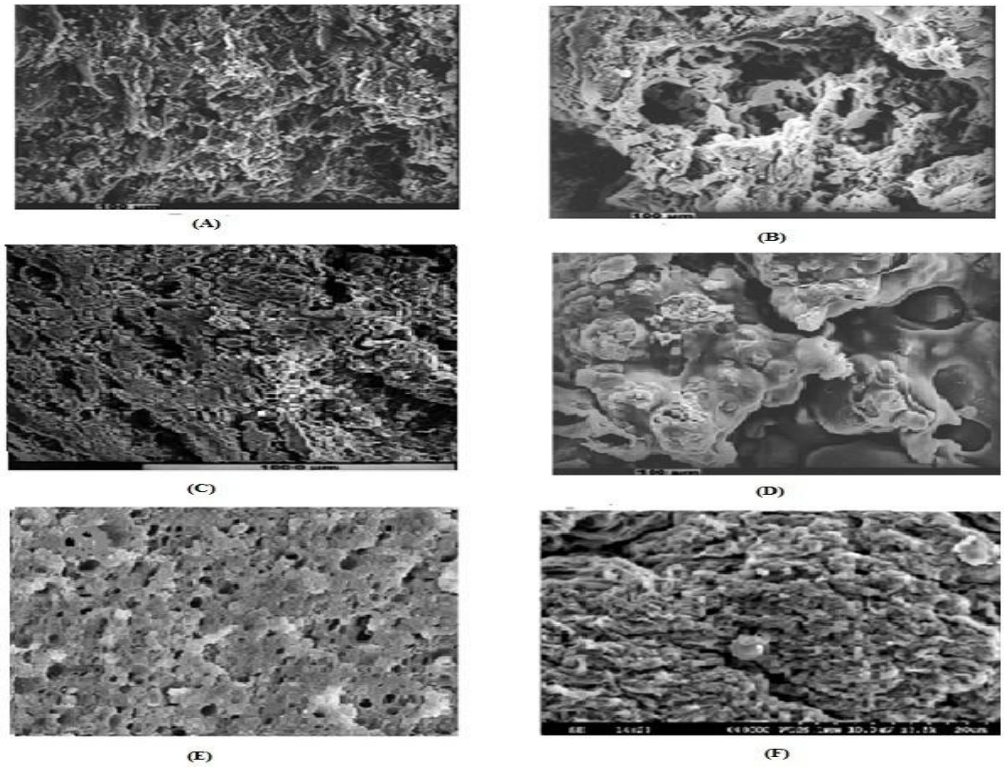

Figure1: SEM of polyelectrolytes. A) Dry state of chitosan- sodium alginate; B) Maximum swellon state of chitosan- sodium alginate; C) Dry state of chitosan- carrageenan; D) Maximum swellon state of chitosan-carrageenan; E) Dry state of chitosan-gellan gum; F) Maximum swellon state of chitosan-gellan gum

Powder Properties of Simvastatin loaded PEC:

The results of low bulk density (LBD) and Tapped Bulk Density (TBD) ranged from 0.3658±0.0020 to 0.3826±0.0015 and 0.4113±0.0025 to 0.498±0.0065gm/cc respectively and the compressibility index (%) ranged from 7.209±0.659 to 23.426±0.120. The results of angle of repose ranged from 23.34±0.13 to 28.73±0.41 (º). The Hausner's ratio ranged from 1.077±0.0076 to 1.305±0.0020 is shown in Table 3.

Formulations	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.3816±0.0011	0.4113±0.0025	7.209±0.659	1.077±0.0076	28.73±0.41
F2	0.3803±0.0005	0.4120±0.0026	7.683±0.514	1.083± 0.0060	26.34±0.63
F3	0.3826±0.0015	0.4130±0.0050	7.338±0.760	1.079±0.0088	25.41±0.35
F4	0.3658±0.0020	0.4293±0.0037	14.788±0.386	1.173±0.0053	27.42±0.52
F5	0.3760±0.0017	0.4603±0.0024	18.311±0.794	1.224±0.0110	23.34±0.13
F6	0.3813±0.0045	0.4980±0.0065	23.426±0.120	1.305±0.0020	24.26±0.43

Table 3: Powder Properties of Simvastatin loaded PEC

Post compression characteristics:

The results of weight variation of tablets for all formulations were ranged from 146.9±0.11 to 151.2±0.51 (mg) indicating that the weight variation is within the pharmacopoeial limits. Hardness was ranged from 6.9±0.2 to 7.6±0.4 (kg/cm^2). Friability ranged from 0.397±0.46 to 0.180±0.076 (%) indicating that the friability of all formulations was less than 1%. The thickness of all formulations shown were within the pharmacopeial limit. The percentage drug content of all formulations was ranged from 97.11±1.975 to 99.69±0.722 (%) which was all within the acceptable limits of official standards is shown in Table 4.

Table 4: Results of Post Compression characteristics

Formulations	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug content (%)
F1	148.6±0.20	3.12±0.01	7.0±0.6	0.397±0.46	99.52±2.130
F2	146.9±0.11	3.15±0.03	7.3±0.8	0.494±0.66	98.92±1.112
F3	150.4±0.42	3.14±0.01	6.9±0.2	0.180±0.076	99.81±1.638
F4	151.2±0.51	3.15±0.03	7.5±0.6	0.139±0.06	99.41±1.520
F5	147.3±0.25	3.12±0.01	7.4±0.5	0.147±0.01	97.11±1.975
F6	149.5±0.13	3.14±0.02	7.6±0.4	0.154±0.04	99.69±0.722

Swelling index at 1.2 pH and 6.8 pH:

The swelling data of simvastatin loaded prepared PEC tablets are represented in the Table 5 and 6. All the tablets show low swelling in pH 1.2 (HCL buffer) and after incubating the same tablets in 6.8 (phosphate buffer) the degree of swelling was increased. At pH 1.2 (HCL buffer) the amino NH_3^+ group of chitosan was get protonated thereby increased charge density which interact strongly with carboxylic (COO^-) group of sodium alginate, carrageenan and gellan gum which leads to formation of strong polyelectrolyte complex and hence the degree of swelling was reduced. At pH 6.8 (phosphate buffer), deprotonation of chitosan weakens the extent of ionic interactions leads to dissociation of complex and hence degree of swelling was increased. The degree of swelling in chitosan-gellan gum was very less indicating strong ionic interaction which restricts the entry of dissolution fluids. The degree of swelling was in the rank order of chitosan-gellan gum> chitosan-sodium alginate> chitosan-carrageenan.

Table 5: Results of swelling index at 1.2 pH

Formulations	Time (min)					
	5min	10min	15min	30min	45min	60min
F1	8.71±0.13	12.41±0.2	22.37±0.56	41.61±0.87	44.80±0.65	48.88±0.91
F2	7.87±0.83	11.21±0.6	19.34±0.59	37.87±0.86	41.58±0.52	45.85±0.93
F3	12.71±0.47	18.4±0.34	33.33±0.46	39.87±0.23	43.60±0.47	51.60±0.74
F4	10.93±0.06	17.29± 0.2	30.5± 0.32	36.1± 1.76	40.4 ±1.22	49.5± 1.24
F5	6.51±0.12	13.87±0.2	22.07±0.38	42.20±0.54	43.15±0.24	43.55±0.72
F6	9.61±0.90	15.66±2.2	25.87±0.53	35.72±0.34	40.70±1.29	41.50±1.08

Table 6: Results of Swelling index at pH 6.8

	Time					
	2hr	4hr	6hr	8hr	10hr	12hr
F1	81.63±0.2	154.1±0.2	172.37±0.5	191.6±0.8	204.8±0.6	248.8±0.9
F2	77.43±0.3	142.1±0.6	169.34±0.5	187.8±0.8	201.8±0.5	245.8±0.9
F3	108.5±0.1	177.4±0.3	193.33±0.4	213.6±0.9	227.6±0.4	267.6±0.7
F4	102.3±0.2	160.9±0.3	191.52±0.3	209.1±1.7	221.2±0.5	257.3±0.2
F5	75.35±0.2	125.7±0.5	142.07±0.3	172.2±0.5	193.5±0.2	223.5±0.5
F6	78.53±0.1	132.6±2.9	151.87±0.5	168.3±1.5	184.7±1.2	204.7±1.0

***In vitro* release studies**

The in-vitro release data for chitosan-sodium alginate, chitosan-carrageenan, and chitosan-gellan gum prepared PEC tablets are represented in Table 7 and illustrated in Figure 2. *The in-vitro* release of Simvastatin also depends on swelling behaviour of the tablets. The *in-vitro* release study was performed in HCL buffer (pH 1.2) for initial first one hour, and then the medium was replaced by phosphate buffer (pH 6.8) and study was continued for 10 hours. The *in-vitro* release of Simvastatin was very slow in first one hour in HCL buffer (pH 1.2). After 1 hour, approximately 8.13% of Simvastatin, from chitosan-sodium alginate tablets, 7.5% from chitosan- carrageenan and 6.25% from chitosan-gellan gum tablets has been released. The reason was explained previously in swelling study. In the second phase of *in-vitro* release study using phosphate buffer (pH 6.8), the release of simvastatin was rapid and a maximum of 74.46% from chitosan-sodium alginate, 81.70% from chitosan-carrageenan and 61.45% from chitosan-gellan gum was released within 12 hours. The ionic interaction between chitosan and negatively charged polymers was greatly reduced at this pH of 6.8 and forms a loose network with increase porous surface which allows great part of dissolution media. Tablets prepared with chitosan and gellan gum shows sustained release of simvastatin, with a percent drug release at 12 hour's value of 70.37% and 61.45% (formulations F5 and F6) due to formation of strong PEC membrane that restricts the easy of dissolution medium. The overall *in-vitro* release of simvastatin, from all the formulations show the following order with changing the negatively charged polymers gellan gum >sodium alginate> carrageenan.

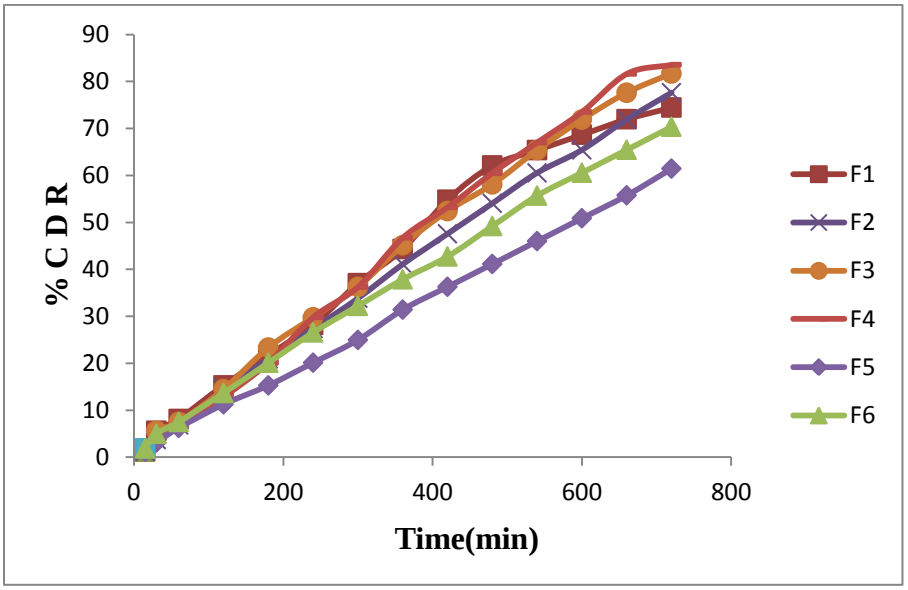

Figure 2: Comparative drug release profile of the formulations F1 to F6

Table 7: *In Vitro* drug release studies of F1 to F6

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
15	1.25±0.02	2.16±0.02	1.87±0.01	1.77±0.01	1.66±0.01	1.14±0.01
30	3.75±0.01	5.62±0.11	4.37±0.02	5.60±0.03	5.00±0.20	3.12±0.00
60	6.88±0.26	8.13±0.07	6.88±0.05	7.50±0.03	7.50±0.10	6.20±0.00
120	14.4±0.67	15.2±0.80	12.8±0.10	14.4±0.15	13.6±0.15	11.2±0.02
180	20.9±0.41	21.7±0.81	20.1±0.05	23.3±0.15	20.1±0.45	15.2±0.01
240	27.3±0.20	28.1±0.36	29.7±0.10	29.7±0.02	26.5±0.58	20.1±0.01
300	33.8±0.37	37.0±1.02	36.2±0.30	36.2±.0.10	32.2±0.41	24.9±0.10
360	41.1±0.45	44.3±0.31	46.7±0.45	45.1±0.05	37.8±0.15	31.4±1.10
420	47.5±0.55	54.8±0.35	53.2±0.60	52.4±0.06	42.7±0.55	36.2±0.10
480	54.0±0.90	62.1±0.85	60.5±0.62	58.0±0.15	49.2±0.20	41.1±0.70
540	60.5±0.65	65.3±0.79	66.9±0.11	65.3±0.10	55.7±0.25	46.0±2.60
600	65.4±0.45	68.6±1.20	73.5±0.43	71.8±0.02	60.5±0.70	50.8±0.20
660	71.9±0.51	71.9±0.51	81.6±0.36	77.5±0.05	65.4±0.20	55.7±2.10
720	77.6±0.63	74.4±0.45	83.5±0.36	81.7±0.25	70.3±0.77	61.4±2.00

Release kinetics:

The release studies shown that it follows zero order kinetics and the probable release mechanism was initial diffusion (due to swelling) followed by erosion (dissociation of PEC membrane). This may be super case- II transport and is shown in Table 8.

Table 8: Drug Release Kinetics of Formulations F1 to F6

FORMULATION CODE	KINETIC MODELS					
	Zero order	First order	Higuchi	Korsmeyer-Peppas		Hixson
	R^2	R^2	R^2	n	R^2	R^2
F1	0.998	0.972	0.970	1.354	0.808	0.990
F2	0.981	0.988	0.973	1.286	0.754	0.990
F3	0.997	0.960	0.963	1.018	0.935	0.984
F4	0.997	0.969	0.970	0.964	0.901	0.989
F5	0.998	0.984	0.971	0.951	0.907	0.994
F6	0.999	0.983	0.960	1.352	0.832	0.992

Stability studies:

Stability study was conducted for two best formulations selected based on and *in-vitro* drug release. The stability studies were conducted according to the described in methodology. There was no significant reduction in drug release profile of formulation F5 and F6. There was no significant taste, colour and odour changes has been observed at the

end of stability studies**.** The drug content estimation after stability studies found that there was no significant variation in the drug content for best formulations F6.

Discussion

In the present study simvastatin loaded chitosan- polyelectrolyte complex were prepared by interaction of positively charged chitosan with negatively charged sodium alginate, carrageenan and gellan gum to overcome Hypercholesterolemia. The surface morphology of the prepared complex was studied using scanning electron microscopy. Polyelectrolyte complex formation was confirmed by using Fourier transform infrared spectroscopy. The prepared complex were evaluated for swelling behavior and *in-vitro* release study, whereas the tablets were evaluated for drug content, friability, hardness and percentage weigh variation . The results of *in-vitro* release study were in full support of swelling study.

The *in-vitro* release of simvastatin sustained release matrix tablets containing prepared PEC was in the order of chitosan--gellan gum > chitosan-sodium alginate > chitosan-carrageenan. *In-vitro* release data was fitted into various kinetic models to study the release mechanism. The release obeyed zero order kinetics and the probable release mechanism was initial diffusion (due to swelling) followed by erosion (dissociation of PEC membrane) with super case- II transport. All the prepared gel tablets were stable at room temperature.

Conclusion

The study conducted so far on development of chitosan polyelectrolyte complex reveals following conclusion:

Polyelectrolyte complex loaded with Simvastatin were prepared by using positively charged chitosan and negatively charged sodium alginate, carrageenan and gellan gum.

The simvastatin sustained release tablets were prepared by direct compression method using polyelectrolyte complex.

The *in-vitro* release of Simvastatin from all PEC formulations was slow in HCL buffer (pH 1.2) and was rapid in phosphate buffer (pH 6.8). The *in-vitro* release was fully supported by swelling study. The *in-vitro* release was in the rank order of chitosan-gellan gum> chitosan-sodium alginate> chitosan-carrageenan. The release obeyed zero order kinetics and the probable release mechanism was initial diffusion (due to swelling) followed by erosion (dissociation of PEC membrane) with super case- II transport.

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