Preparation, Characterization and Application of Chitosan–Alginate Based Polyelectrolyte Complex as Fast Disintegrating Drug Delivery Carrier

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Summary

Aim. Present investigation was carried out with aim to synthesize chitosan–alginate polyelectrolyte complex, their characterization and then formulation of phenytoin sodium fast dispersible tablet using polyelectrolyte as active excipient.

Methods. In this study, polyelectrolyte complex was formed by ionic cross-linking of polymers. Dried complex was evaluated for micromeritic properties and flow behaviour. Tablets were prepared for six batches based on different proportion of complex viz 5%, 10%, 20%, 30%, 40%, 50% and 60%. Tablets were evaluated for hardness, friability, thickness, in vitro disintegration time, in vitro dissolution study and stability study.

Results. Results of micromeritic study and flow behaviour predict that complex can be used as an efficient excipient. Hardness, friability, thickness all were in acceptable limit. Release studies were showed that tablets release drug up to 99.97%. Batch showed .sec of invitro disintegration time. Stability study easily predicted that formulation characteristics dose not changed during the whole period of study.

Conclusions. From the findings it is concluded that chitosan-alginate polyelectrolyte complex is efficient excipient for fast dispersible formulation especially required in case of epilepsy and chronic diseases.

Key words: polyelectrolyte complex, fast dispersible tablet, phenytoin sodium, epilepsy, stability study

Lay summary. In present investigation polyelectrolyte complex (PEC) of chitosan and sodium alginate was prepared and it was characterized as pharmaceutical excipient in terms of micromeritic properties and flow behaviour. Tablets were also fabricated using different ratios of previously prepared PEC. Furthermore tablets were evaluated for their post-compression parameters such as hardness, friability and thickness. These tablets were also characterized for their release behaviour and stability study. Results obtained from various studies showed that prepared tablets have good hardness (comparable to sustained release tablets), zero friability and low disintegration time (about 2min). It can be easily predicted from the obtained results that chitosan-alginate based polyelectroltic complex can be easily prepared at commercial level and may be used as carrier to prepare fast disintegrating drug delivery system.

Przygotowanie, charakterystyka i zastosowanie kompleksu polielektrolitowego na bazie chitozynowo-alginowej jako szybko dezintegrowalnego nośnika leków

Streszczenie

Cel. Badanie zostało przeprowadzone w celu zsyntezowania polielektrolitowego kompleksu chitozynowo-alginowego, opra-

cowania jego charakterystyki i utworzenia szybko rozpuszczalnych tabletek fenytoiny z zastosowaniem polielektrolitu, jako aktywnego nośnika.

Metody. W pracy kompleks polielektrolitowy był uformowany poprzez jonowe krzyżowe wiązanie polimerów. Wysuszony kompleks był oceniany pod względem własności mikrometrycznych i zachowania się w fazie przepływu. Tabletki zostały przygotowane w 6 porcjach w zależności od zawartości kompleksu: 5%, 10%, 20%, 30%, 40%, 50% i 60%. Oceniano tabletki pod względem twardości, kruchości, grubości, czasu dezintegracji *in vitro*, czasu rozpuszczania *in vitro* i stabilności.

Wyniki. Wyniki badań mikrometrycznych i zachowania w przepływie pozwalają przewidywać, że kompleks może być używany jako efektywny nośnik. Twardość, kruchość i grubość były w akceptowalnych granicach. Badania uwalniania wykazały, że tabletki uwalniały do 99,97% leku. Poszczególne porcje wykazały czas dezintegracji rzędu ułamków sekundy. Badania stabilności pozwalają przewidywać, że charakterystyka formuły nie zmienia się w czasie całego badania.

Wnioski. Na podstawie wyników badań można stwierdzić, że kompleks polielektrolitowy chitozynowo-alginowy jest skutecznym nośnikiem dla szybko rozpuszczalnych farmaceutyków, szczególnie potrzebnych w przypadku padaczki i przewlekłych chorób.

Słowa kluczowe: kompleks polielektrolitowy, szybko rozpuszczalne tabletki, fenytoina, padaczka, badania stabilności

INTRODUCTION

Polyelectrolyte complexes are generally formed by electrostatic interaction between two oppositely charged polyelectrolyte solutions [1–3.] These complexes exhibit unique physical and chemical properties, as the electrostatic interactions within the polyelectrolyte complex gels are considerably stronger than most secondary binding interactions. Many studies have been done to use polyelectrolyte complex of chitosan and polyanions for pharmaceutical applications [4, 5]. Chitosan, poly-b-(1-4)-2-amino-2-deoxy- D-glucose, is a naturally occurring cationic polysaccharide derived from the N-deacetylation of chitin.

Chitosan shows specific biological behavior in term of biocompatibility, biodegradability, lack of toxicity, and adsorption. At acidic pH ranges, the ionizable amino groups in chitosan molecules are protonated. Formation of polyelectrolyte complexes (PEC) with polyanionic molecules have been widely reported in different study [6, 7]. The formation and the properties of polyelectrolyte complex depend on various factors including nature and position of the ionic groups, charge density and concentration of both anionic and cationic polymers; it also depends upon proportion of opposite charges, molecular weight of the macromolecules and condition of synthesis [8–13]. Alginate, an important polysaccharides extracted from seaweeds, has very high hydrophilicity due to presence of both its carboxylic and hydroxyl groups in the solution. Formation of interpolymer complexes of chitosan with alginate and other polymer was investigated in many researches [14–17].

It has been reported that drug release from in situ polyionic complexes showed more sustained effect than the single polymer. Polymer solutions can interact to give a superior quality complex for the dosage form. Generally 50% of total tablet weight of chitosan was used to prepare sustained release tablet. It has been reported in different studied that; polyionic interaction of chitosan with anionic polymers will permit a considerable reduction of chitosan concentration in tablet [18]. Phenytoin sodium is commonly used anticonvulsant which is useful in the treatment of status epilepticus of the grandmal seizures type. Phenytoin has poor water solubility while its sodium salt (phenytoin sodium) has enhanced water solubility. It is quite useful in the treatment of chronic attack of seizures. The conventional dosage forms available in market suffer from the problem of high friability which is undesirable for pharmaceutical use, since they show problem in packaging and transportation. These problems can be overcome by use of polyelectrolyte as a polymer in drug delivery. In present research an attempt was made to formulate fast disintegrating tablet of phenytoin sodium and the optimization of different baches was based on simple lattice design approach.

MATERIALS AND METHODS

Material. Drug Phenytoin sodium was obtained as a gift sample from Alchem Laboratories, Baddi India. Sodium alginate and microcrystalline cellulose

was procured from CDH laboratory reagent, central drug house (P) Ltd, New Delhi, India. Chitosan (medium molecular weight, viscosity 200.000 cps) was purchased from Sigma Aldrich, Spruce Street, St. Louis. All other materials were of pharmaceutical grade and used as supplied without further purification.

Preparation of chitosan-alginate polyelectrolyte complex. 5% chitosan gel was prepared using 2% acetic acid solution. Continuous agitation and heating makes a gel formation at temperature about 45°C. Further temperature was increased upto70°C with continuous stirring. Sodium alginate was added in deionized water to form homogeneous solution of 5% (w/v) polymer. Temperature of alginate solution was increased slowly upto 60°C.

To prepare polyelectrolyte complex, equal proportion of both solutions was mixed with continuous stirring and temperature of mixture was reduced within the range of room temperature (25–35°C). This solution was further dried under vacuum. Dried polyeletrolyte complex was powdered and passed through sieve #20, and stored in airtight container for further study.

CHARACTERIZATION OF CHITOSAN-ALGINATE POLYELETROLYTE COMPLEX

Fourier transform infrared spectroscopy analysis. All the ingredients were studied for compatibility between them. For that purpose infrared spectra of individual polymers were compared with infrared spectra of polyeletrolyte complex.

Bulk density. Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measuring the volume and weight of powder blend [19–21].

Bulk density =weight of powder blend/ /volume of powder blend (Equation 1)

Tapped density It was determined by placing a graduated cylinder, containing a known mass of powder on mechanical tapping apparatus, which was operated for fixed number of taps (around 50). Using the weight of powder in a cylinder and its tapped volume, the tapped density was computed [19–21].

Tapped density = weight of powder blend/ /tapped volume of powder blend (Equation 2)

Carr's index. It is an important parameter to study compressibility behaviour of powder blend. Carr's index was calculated, from the results of bulk density and tapped density [19–21].

Carr's index = (bulk density- -tapped density)/ /tapped density (Equation 3)

Bulkiness. It is reciprocal of bulk density and calculated as

Bulkiness= 1/bulk density (Equation 4)

Angle of repose. For the measurement of angle of repose, a glass funnel was taken with its tip at a given height (H), above a piece of graph paper placed on a horizontal surface. Powder was poured through the funnel until the apex of the conical pile touched the tip of the funnel. The angle of repose was calculated with the formula; $\tan \theta = H/R$, where θ is the angle of repose and R is the radius of the conical pile [19–21].

PREPARATION OF POLYELECTROLYTE COMPLEX BLENDS

Granulation. In present research wet granulation technique was used to prepare matrix tablet. Drug (phenytoin sodium) dose was decided 30 mg for each tablet and was added accordingly. According to table 1, all the ingredients were mixed physically for 25 min, using a mortar pestle. Then appropriate amount of distilled water was added to prepare a wet mass. Wet mass was passed through 20 mesh- sieve to obtain granules. The granules were dried at 45°C for 6 h.

Evaluation of polyelectrolyte blends. Polyelectrolyte blends of all batches were evaluated for bulk density, tapped density, bulkiness, carr's index, hausner's ratio and angle of repose according to standard procedures [19–21].

Preparation of tablets. Equivalent to 500 mg, granules were weighted and compressed by Cadmach punching machine with 12 mm diameter flat faced tolling. Tablets were compressed at compression force of 2Newton for 10 s [19].

EVALUATION OF POLYELECTROLYTE BASED TABLETS

Evaluation for weight variation. Test was carried out according to the European Pharmacopoeia. Twenty tablets were randomly selected from each

batch and the mean of tablet weights was calculated. Results are presented as mean value and standard deviation [22].

Tablet thickness testing. The thickness of the matrix tablets was determined using vernier caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations, with standard deviations.

Evaluation for tablet hardness. Hardness of all batches was determined using Digital Force Gauge (Model:EL=500N, Electrolab). The test was carried out in triplicate for all batches as per USP XXIV monograph for uncoated tablets. The tablet hardness was expressed in Newton (N) unit and mean and standard deviation of the tablet hardness were calculated [22].

Friability measurement. Twenty tablets were randomly selected from each batch, were accurately weighed and placed in the drum of friabilator (Erweka type, GmbH, Germany). The tablets were rotated at 25 rpm for a period of 4 min and then removed, dedusted and accurately re-weighed (EP 2000). The percentage loss in weight was calculated and taken as a measure of friability. The readings were shown as mean of triplicate with standard deviation [22].

Drug content. The tablets were powdered, and 30 mg equivalent weight of phenytoin sodium in tablet powder was accurately weighted and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH6.8) was added and shaken for 10 min. Then, the volume was made up to 100 ml with buffer. Subsequently, the solution in volumetric flask was filtered, and 1 ml of the filtrate was diluted and analysed at 252 nm using UV-visible spectrophotometer (Shimadzu UV-2450, Japan). The drug content of the each sample was estimated from standard curve [22–24].

***In vitro* disintegration time.** Tablets of all batches were selected and evaluated for disintegration time in distilled water kept at 37± 0.5°C using a disintegration apparatus (Electrolab, TDT-06T, Mumbai, India), according to EP (2002) specifications. The disintegration time was defined as the time necessary for the ODT to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains on the screen. A digital stopwatch was used to measure the disintegration time to the nearest second. Only one ODT was analysed at a time in order to ensure accuracy. All results are presented as mean value of six readings with standard deviation [22–24].

***In vitro* drug release study.** *In vitro* drug release was studied using Lab India Dissolution Apparatus, with 900 ml of dissolution medium (phosphate buffer pH 6.6) maintained at 37 ± 1°C for 90 min, at 100 rpm. 5ml of sample was withdrawn at particular time interval, and was replaced by an equal volume of fresh dissolution medium of same pH (phosphate buffer pH 6.6). Collected samples were analysed spectrophotometrically at measured wavelength of 252 nm, and cumulative percent drug release was calculated.

The data obtained in the *in-vitro* dissolution study was analysed in terms of, percentage drug release with respect to time (min). The graph was plotted between % drug release and time (min).

Stability study. Selected tablets of all formulations were stored in polyvinyl chloride (PVC) blisters covered with aluminum foil at room temperature and 60% relative humidity for a time period of 12 months. To maintain relative humidity, ammonium nitrate (NH_4NO_3) saturated salt solution was used as a humidifier. Stability of all formulations was assessed by comparing the results from in vitro disintegration and dissolution studies. To investigate any change in the physic-chemical property of complex and drug, infrared spectrum of them was match after 0, 3, 6 and 12 months. The results were checked for statistical significance using the one-way analysis of variance (ANOVA) F-test for testing the equality of several means. A p-value > 0.05 was considered statistically insignificant [25].

RESULTS

Infrared spectroscopic study showed that peaks of individual polymers were not changed in infrared spectra of complex so there was no interaction between chitosan and sodium alginate (Figure 1, Figure 2 and Figure 3). Micromeritic study of polyelectrolyte complex showed that bulk density and tapped density were found to be 0.423 ± 0.07 and 0.498 ± 0.06mg/ml respectively. The angle of repose was calculated as 24.67° which gives important information about the flow characteristics of the polyelectrolyte complex. Carr's index was studied with the aim to evaluate compressibility characteristics of the polyeletrolyte complex. The value for Carr's index was found 6.56%, indicating that this complex have good compressibility. Hausener's ratio was found to be 1.27 ± 0.14, where as bulkiness was 2.36 ± 0.21ml/mg.

Results of micromeritic charactrization and flow properties of polyelectrolyte complex blends were showed (Table 2) that all batches have good flow behaviour. Micromeritic properties were not more changed and so easy to formulate.

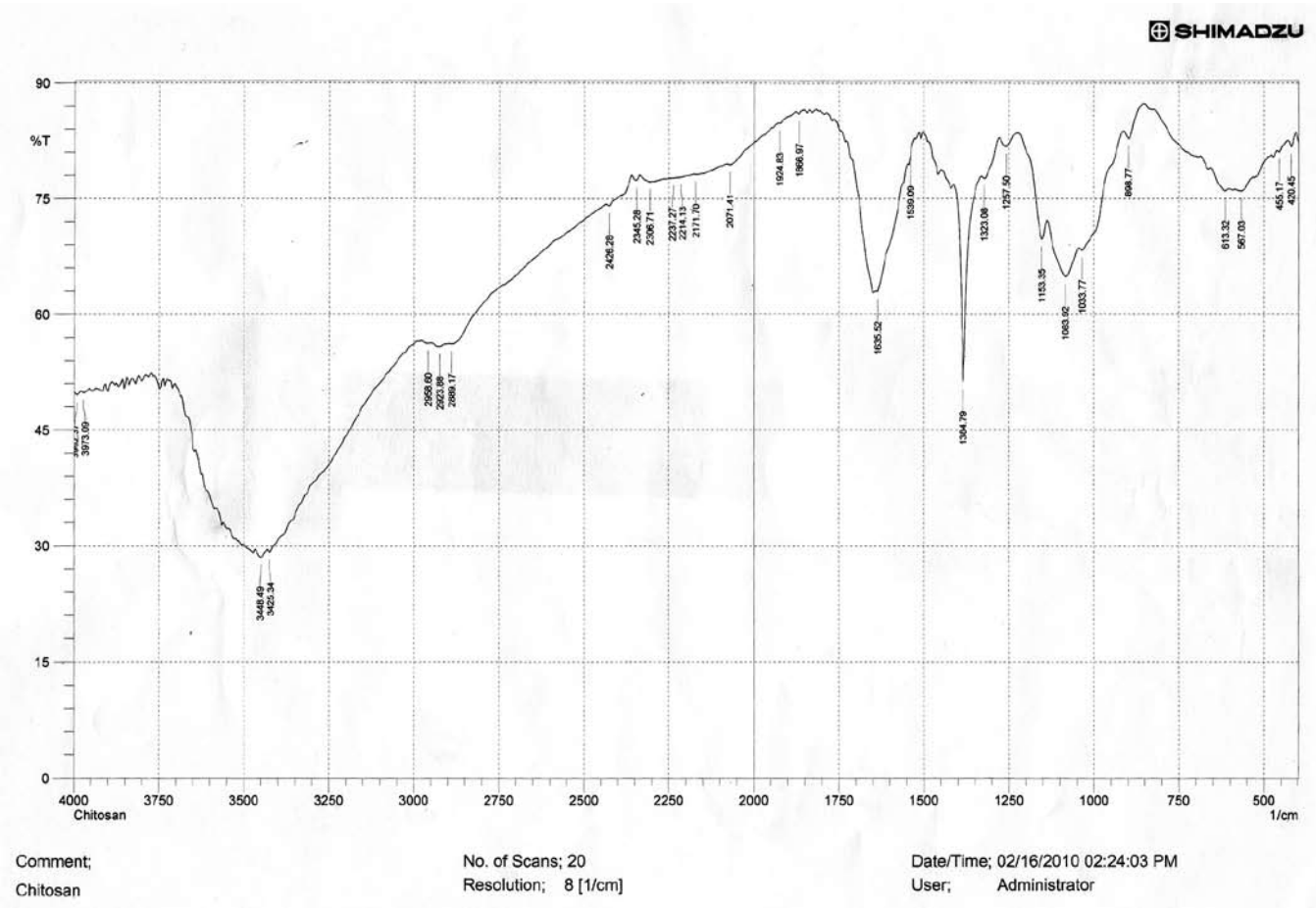

Fig. 1. Infrared spectrum of chitosan

Ryc. 1. Spektrum chitozanu w podczerwieni

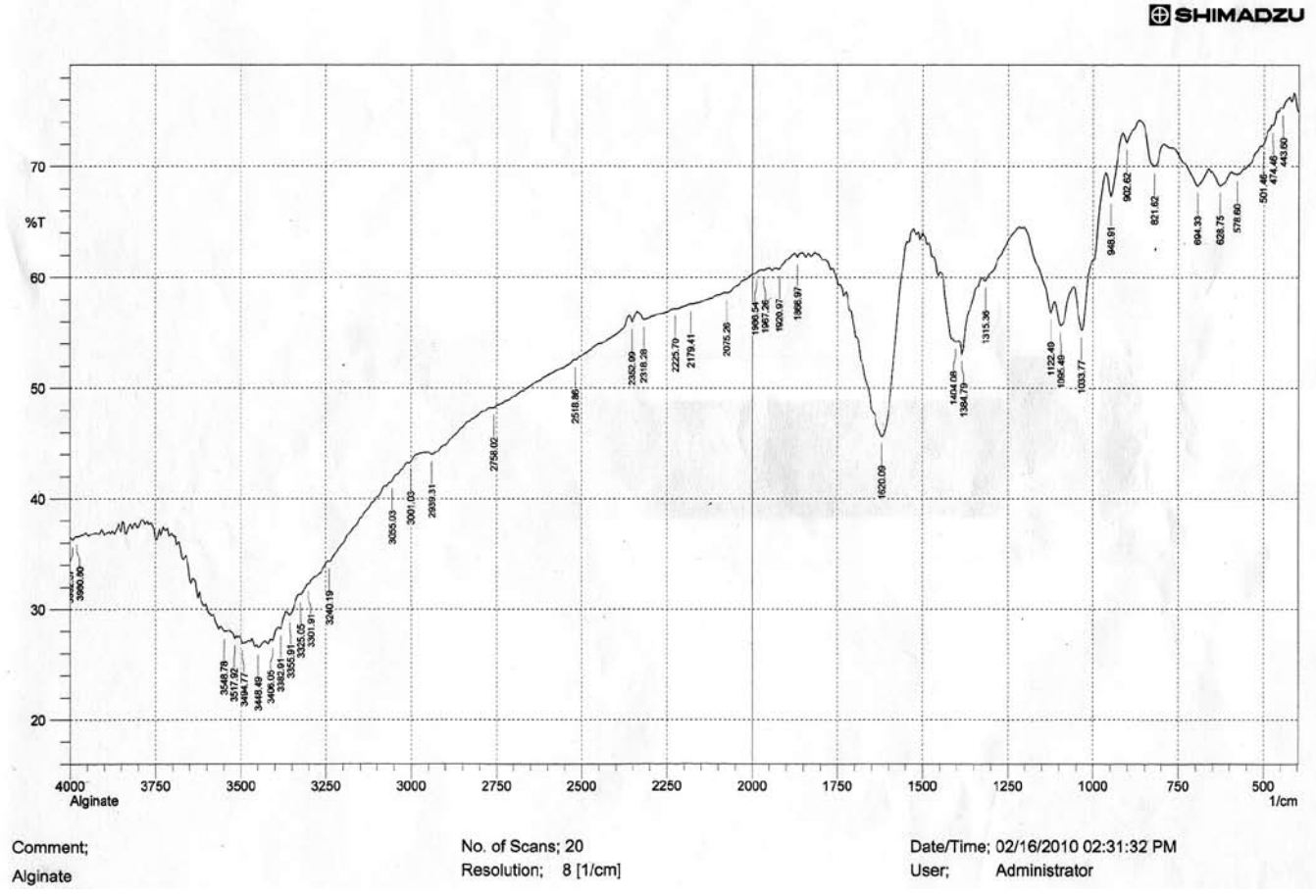

Fig. 2. Infrared spectrum of alginate

Ryc. 2. Spektrum alginatu w podczerwieni

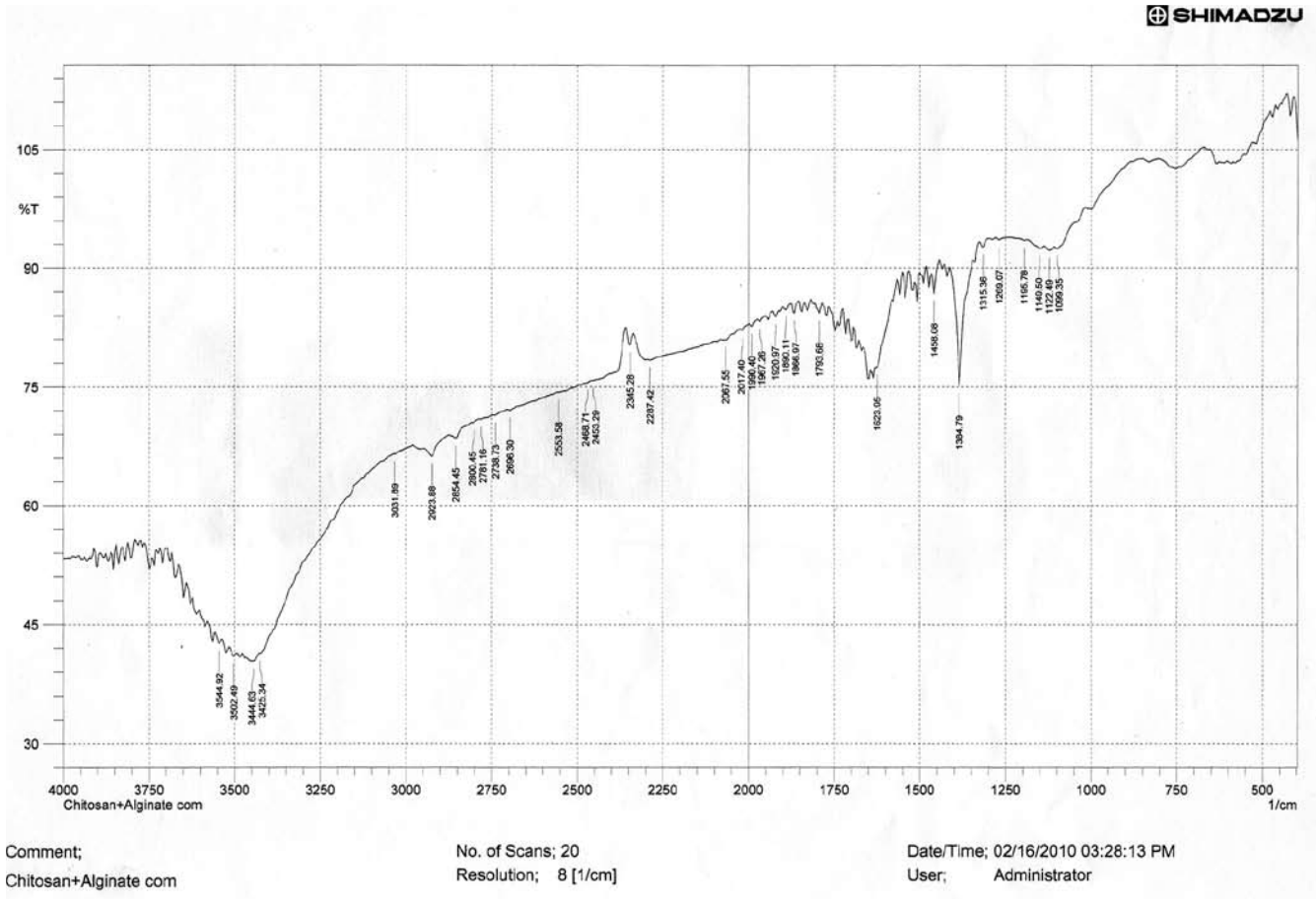

Fig. 3. Infrared spectrum of chitosan-alginate polyelectrolyte complex

Ryc. 3. Spektrum kompleksu polielektrolitowego chitozynowo-alginowego w podczerwieni

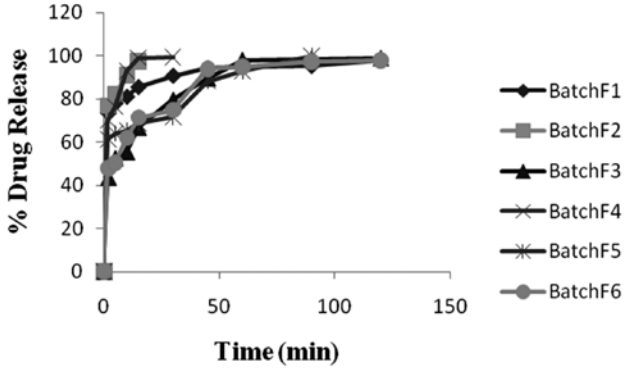

Fig. 4. Release study of phenytoin sodium from tablets

Ryc. 4. Badanie uwalniania fenytoiny z tabletek

As per the Table 3, the formulated matrix tablets met the Pharmacopoeial requirement of uniformity of weight. They confirmed, to the requirement of assay, as per USP. Hardness, percentage friability and thickness were all within acceptable limits. The hardness of tablets was determined and was found to be in the range of 20.10 to 20.50N. The valve of hardness for all batches showed that tablets have sufficient hardness and further friability was studied for all batches. Friability was obtained between 0.082 to 0.236%, which was below 1% indicating sufficient mechanical integrity and strength of the prepared tablets. Thickness of tablet was found in between 3.94 to 4.24 mm.

Drug release studies were easily showed that an about 95% drug comes in to dissolution media within 45 min (Figure 4). BatchF1 and BatchF4 showed 99% release 30 min. BatchF6 having maximum concentration of complex (60%) and showed release retardant effect after 45 min.

After 12 months of stability study at controlled environmental conditions no significant differences ($p < .05$) in disintegration time and drug release rate of the prepared tablets were observed (Table 4). On the basis of infrared spectroscopic study during the stability study, it was concluded that there was no change in the physic-chemical properties of both polyelectrolyte complex and drug.

Table 1. Formula to prepare polyelectrolyte complex based tablets

Tabela 1. Przygotowanie tabletek na bazie kompleksu polielektrolitowego

Ingredients	Formulations					
	BatchF1 (5%)[a]	BatchF2 (10%)	BatchF3 (20%)	BatchF4 (30%)	BatchF5 (40%)	BatchF6 (50%)
Drug (mg)	30	30	30	30	30	30
Polyelectrolyte Complex (mg)	25	50	100	150	200	250
Sodium CMC (mg)	435	410	360	310	260	210
Magnesium stearate (mg)	10	10	10	10	10	10

[a] percentage of total tablet weight.

Table 2. Characterization of polyelectrolyte complex blends[$]

Tabela 2. Charakterystyka mieszania kompleksów polielektrolitowych[$]

Parameters	BatchF1	BatchF2	BatchF3	BatchF4	BatchF5	BatchF6
Bulk density (mg/ml)	0.456 (0.01)	0.424 (0.03)	0.436 (0.02)	0.426 (0.01)	0.404 (0.02)	0.376 (0.01)
Tapped density (mg/ml)	0.488 (0.01)	0.430 (0.01)	0.456 (0.01)	0.445 (0.02)	0.434 (0.01)	0.427 (0.02)
Carr's index (%)	6.36 (0.02)	1.40 (0.01)	4.40 (0.02)	4.39 (0.01)	8.415 (0.01)	11.857 (0.01)
Bulkiness (ml/mg)	2.22 (0.01)	2.36 (0.03)	2.29 (0.02)	2.35 (0.01)	2.48 (0.02)	2.66 (0.01)
Hausner's ratio (%)	1.070 (0.08)	1.014 (0.07)	1.046 (0.08)	1.045 (0.09)	1.074 (0.06)	1.130 (0.04)
Angle of repose (°)	25.94 (0.06)	25.06 (0.07)	24.98 (0.08)	25.72 (0.08)	26.03 (0.06)	25.00 (0.05)

[$] value in parenthesis show standard deviation of triplicate readings.

DISCUSSION

Ionic gelation method is an important method to form complex between two different ionic species. Findings of present investigation are able to demonstrate that the properties of polyelectrolyte complex are entirely different from the properties of both polymer from which that complex is synthesized. Synthesized complex have characteristics properties in terms of micromeritic properties and flow behaviour.

Micromeritic study data is important in predicting the flow property of polymer as well as granules obtained after granulation. The polyelectrolytic complex showed better flow properties hence depicting the fact that this complex when used as polymer would enhance the flow characteristic of the formed granules. Flow property is emphasized upon because, it decides the ease of compaction of powder or granules into a tablet dosage form. Carr's index was studied with the aim to evaluate compressibility charac-

Table 3: Tablet evaluation parameters[x]

Tabela 3. Parametry oceny tabletek[x]

Parameters	F1	F2	F3	F4	F5	F6
Weight variation (mg)	500.21 (0.011)	500.09 (0.009)	501.01 (0.008)	500.13 (0.008)	499.89 (0.013)	500.4 (0.014)
Friability (%)	0.236 (0.031)	0.107 (0.082)	0.302 (0.011)	0.173 (0.142)	0.082 (0.060)	0.096 (0.019)
Thickness (mm)	3.17 (0.012)	3.18 (0.020)	3.20 (0.036)	3.26 (0.006)	3.27 (0.019)	3.36 (0.006)
Hardness (N)	20.13 (0.153)	20.5 (0.100)	20.43 (0.058)	21.97 (0.058)	20.1 (0.100)	20.27 (0.153)
In vitro disintegration (min)	1.16 (0.071)	2.56 (0.022)	1.02 (0.014)	1.6 (0.191)	0.70 (0.063)	3.2 (0.109)
Drug content (mg)	29.93 (0.032)	29.97 (0.086)	29.89 (0.100)	29.89 (0.009)	29.98 (0.011)	29.87 (0.071)
Drug release (%)	97.99 (0.261)	97.23 (0.183)	99.04 (0.092)	99.33 (0.151)	99.86 (0.217)	98.05 (0.162)

[x] values in parenthesis shows standard deviation.

Table 4. Stability studies of polyelectrolyte based tablets after 0, 3, 6 and 12 month storage at room temperature and 60% relative humidity[!]

Tabela 4. Badania stabilności tabletek po 0, 3, 6 i 12 miesiącach przechowywania w temperaturze pokojowej i wilgotności względnej 60%[!]

Attributes	0 months	3 months	6 months	12 months
BatchF1				
Disintegration time	1.16 (0.13)	1.15 (0.09)	1.17 (0.20)	1.17 (0.17)
Drug released after 2 min (%)	73.51 (0.16)	72.89 (0.21)	73.67 (0.18)	74.53 (0.27)
BatchF3				
Disintegration time	1.02 (0.53)	1.01 (0.61)	1.03 (0.08)	1.04 (0.11)
Drug released after 2 min (%)	43.65 (0.13)	44.17 (0.23)	44.09 (0.09)	44.01 (0.16)
BatchF5				
Disintegration time	0.70 (0.16)	0.71 (0.13)	0.70 (0.24)	0.72 (0.19)
Drug released after 2 min (%)	61.38 (0.10)	62.11 (0.27)	62.09 (0.18)	63.07 (0.31)

[!] valves in parenthesis shows standard deviation of triplicate readings.

teristics of the polyeletrolyte complex. All these parameters ranged between the reported limits.

Results also reveal the fact (Table 2) that micromeritic properties and flow charactrisics does not changed significantly when prepared different powder blends using complex. Post compression study such as hardness and friability all were in acceptable limits. These are the important physical properties which demonstrate that the tablet formulated can be handled easily without any physical damage. These two data show the importance of formulation over commercial fast disintegrating tablets which have problem during transportation and storage. Thickness of tablets was also measured to evaluate efficacy of process of formulation development. Almost uniform thickness of tablets showed that this process is efficient to produce tablet of such types. Drug content was also measured to evaluate the efficacy of process of formulation. Uniform drug content values for all batches are able to show that this particular process was highly efficient and can be used at industrial level to formulate fast disintegrating tablet for a particular disease condition. The drug release was studied in terms of % drug release vs time (min) graph, and showed that all batches released drug within a small duration of time. Hence, release characteristics are able to demonstrate that all the formulation can be used for the commercialization of products. The drug release data for the various calcium alginate polyelectolyte complex tablets fitted into the classical power law expression. This indicates that drug release from these matrix tablets followed non-Fickian kinetics, due probably to rapid swelling and erosion of the matrix structure formed by the ionic interaction of chitosan and sodium alginate. It is likely that the incorporation of polyelectrolyte complex into tablets enhanced the initial swelling and erosion and shifted the drug release mechanism toward anomalous transport or case II transport, indicating that the drug was diffusing through the tablet at the same time as polymer relaxation was taking place. Data obtain during stability study demonstrate the fact that these tablets are stable during the period of stability study (Table 4). Properties of tablets were not changed significantly during the study. So these types of tablets can be stored in the environmental condition (temperature – 25°C, relative humidity 40 to 60%).

It can be concluded by all the physico-chemical parameters and invitro disintegration and invivo dissolution study that batch F4 has been characterized as optimized formulation among the six batches of tablets prepared using polyelectrolyte complex as polymer. The batch showed less friability and greater hardness when compared to other batches. Invitro disintegration time and invivo dissolution time were less comparatively. The tablets released 99.27% of drug which is quite better than other batches.

It can be concluded on behalf of obtained results that neither the drug nor the polymers show any interaction, thus removing the uncertainty of cause of any chemical interaction. This is utmost important while formulating any dosage form, so that individual characteristics of compound is retained.

CONCLUSIONS

The study demonstrated that an ionic interaction took place during the formation of chitosan-alginate polyelectrolytic complex which also helped in enhancing the release of drug from the tablets within few minutes. Thus this may prove to be efficient means of formulating fast disintegrating tablets for the treatment of chronic disorders at the initial stage of attack.

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Conflict of Interest Declaration. The authors declare that they have no competing interests.

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