

Preparation and Evaluation of Chitosan Succinate Pellets Using Extrusion-Spheronization Technology: Processing and *In Vitro* Characterization

Dasari Subramaniyam KARUNA¹, Ubaidulla UDHUMANSHA^{1*}, Grace RATHNAM¹, Mani GANESH^{2,3}, Hyun Tae JANG²

¹C.L. Baid Metha College of Pharmacy, Department of Pharmaceutics, Chennai, INDIA

²Hanseu University, Department of Chemical Engineering, Seosan-si 356 706, SOUTH KOREA ³Hill Side College of Pharmacy, Department of Pharmaceutical Chemistry, Kanakapura Main Road, Bangalore-560062, INDIA

The study is aimed to investigate a novel approach for the preparation of multiparticulate drug delivery system using chitosan succinate a chitosan derivatives polymer. Herein the chitosan succinate multiparticulate pellets entrapped diclofenac sodium was prepared by extrusion and spheronization technique. FTIR results revealed that there were no interactions between the drug and polymer. The prepared pellets were with good spherical geometry and 1.02 ± 0.40 mm as their mean diameter. Chitosan succinate showed pH dependent release profiles for the entrapped diclofenac sodium. Maximum drug release was observed at pH 7.4, whereas no drug release was observed at pH 1.2. The optimized formulation followed Higuchi kinetics while drug release mechanism was found to be anomalous type i.e controlled by diffusion through swollen matrix. It can be concluded from these results that new pharmaceutical carrier is capable of sustained release in oral drug delivery system.

Key words: Chitosan succinate pellets, pH sensitive drug release, Chitosan, Sustained release, Extrusion-spheronization.

Ekstrüzyon-Sferonizasyon Teknolojisi Kullanarak Kitozan Süksinat Pelletlerinin Hazırlanması ve Değerlendirilmesi: İmalat ve *In Vitro* Karakterizasyon

Bu çalışma, kitozandan türetilen polimer, kitozan süksinat, kullanımıyla çok birimli ilaç salım sistemlerinin hazırlanması için yeni bir yaklaşımı incelemeyi amaçlamaktadır. Bu çalışmada ekstrüzyon-sferonizasyon tekniği ile diklofenak sodyum yüklenmiş çok birimli kitozan süksinat pelletler hazırlandı. FTIR sonuçları etken madde ile polimer arasında bir etkileşim olmadığını ortaya çıkardı. Hazırlanan pelletler iyi küresel geometriye sahipti ve ortalama çapları 1.02 ± 0.40 mm idi. Kitozan süksinat, yüklenen diklofenak sodyum için pH'ya bağlı salım profilleri gösterdi. pH 1.2'de hiç etken madde salımı yokken, maksimum etken madde salımı pH 7.4'de gözlemlendi. Optimize edilen formülasyonda etken madde salım mekanizmasının şişen matrinden difüzyonla kontrol edilen anamolus tipte olduğu ve Higuchi kinetiğine uyduğu bulundu. Bu sonuçlardan yeni farmasötik taşıyıcının oral ilaç salım sisteminde sürekli salıma eğilimli olduğu sonucu çıkarılabilir.

Anahtar kelimeler: Kitozan süksinat pelletler, pH'ya duyarlı etken madde salımı, Kitozan, Sürekli salım, Ekstrüzyon-sferonizasyon

*Correspondence: Email: ubaidnkl@gmail.com; Tel: +91 9677781834,

INTRODUCTION

Diclofenac sodium is a new generation non-steroidal anti-inflammatory agent, which is widely used in the long-term therapy for chronic musculoskeletal pain and chronic inflammatory conditions like rheumatoid arthritis and osteoarthritis. Short biological half-life of 1–2 h necessitates multiple dosing for maintaining therapeutic effect throughout the day (1). Albeit is one among the best in long term therapy in management of arthritis, diclofenac sodium suffers from severe drawbacks like gastrointestinal disturbance, occult GI bleeding and peptic ulceration (2). These adverse effects create a potential need for delayed release to intestine and bypass the stomach. Development of new drug molecule is expensive and time consuming. Improving safety, efficacy ratio of 'old' drugs has been attempted using different methods such as individualizing drug therapy, dose titration and therapeutic drug monitoring. Delivering drug at controlled rate, slow delivery, and in targeted fashion are the other very attractive methods and pursued very vigorously.

Pellets offer several advantages over conventional single unit matrix formulations. These include less risk of dose dumping, less inter and intra subject variability and a higher degree of dispersion in the gastrointestinal tract, thus minimizing irritation associated with high local drug concentrations (3). Moreover, multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption leads improved bioavailability (4). Chitosan polymer has been widely used for potential site-specific and controlled drug delivery to the colonic region. Limitations of chitosan based delivery system such as soluble in dilute acid and precipitates at a pH above 7 which hindered the applicability in drug delivery system. Various enteric coatings (acrylates, shellac and cellulose derivatives) requires over chitosan layer which could protect it against the excess acid solubility in the stomach (5,6). Also practical difficulties were occurred during production chitosan pellets by extrusion/spheronization such as breaking the extrudates and agglomeration of

particles due to acid concentration in the granulating liquid (7).

Chemically modified chitosan can overcome the above said limitations in utilising the plain chitosan, especially in the field of controlled drug delivery and increase the potential applications of chitosan. Researchers have focused on modification of chitosan and their potential application towards drug delivery system. The reactivity of chitosan's primary amine groups allows us to prepare of a variety of derivatives with different physicochemical properties (8,9). In our earlier studies, we found chitosan succinate (CS) polymer has the potential carrier for colon targeted drug delivery system (10,11). This gives basic idea to develop CS multiparticulate pellets by extrusion and spheronization and to evaluate it efficiency by incorporating diclofenac sodium as a model drug.

The aim of the present study was to investigate the effect of new chitosan derivatives namely CS pellets on the dissolution behaviour of diclofenac sodium to improve its release properties at simulated intestinal fluid (SIF).

MATERIALS AND METHODS

Materials

Diclofenac sodium was purchased from Indian Fine chemicals, Mumbai, India. Chitosan polymer was supplied by Central Institute of Fisheries Technology, Cochin, Kerala, India. Other excipients used to prepare the pellets, such as micro crystalline cellulose (MCC) and lactose were India Pharmacopoeia grade, Chennai. Succinate anhydride was purchased from Merck, India. Methanol and acetonitrile (HPLC grade) and other reagents for diclofenac sodium determination were analytical grade. Double-distilled water was used.

Methods

Preparation of chitosan succinate polymer

The synthesis of chitosan succinate was carried out replacement of primary amino groups by other substituent's method. Briefly, chitosan (1.00 g, corresponding to approximately 6.20 mmols glucosamine) was

dissolved in aqueous solution of Hydrochloric acid (HCl) (0.37%, 50 mL) at ambient temperature, and a solution of the anhydride (6.25 mmol; succinate 0.63 g) in pyridine (5 mL) was added drop wise with vigorous stirring. The reaction pH was maintained at 7.0 by the drop wise addition of 1M sodium hydroxide (NaOH) solution. After 45 min the reaction was terminated by the addition of sodium chloride (NaCl) solution (20%, 200 mL). The resulting precipitate was filtered and washed with acetone and diethyl ether. The polymer was stored in desiccator and used for further studies.

Determination of the degree of substitution

Chitosan derivative polymers (0.10 g) were completely hydrolyzed in a NaOH aqueous solution (3.0 M, 30 mL) and over 48 h. The concentrations of succinic acids in the hydrolysis solutions were determined by UV spectrophotometer at 232 nm (12). Non-conjugated chitosan was also treated in the same way, and the resulting solution was used as the blank. The degree of substitution measured from amount of succinic acid that release by the hydrolyzed CS polymer before and after.

Infrared (IR) spectroscopy

IR spectra of chitosan and CS were determined between 4000-400 cm^{-1} using the Potassium Bromide Pellet (KBr) disc in a Nicolet Impact 400 IR (Perkin Elmer Spectrum Rx₁, USA).

Drug and polymer compatibility studies

The compatibility of drug and polymer is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions. A physical mixture (1:1) of drug and polymers was prepared and mixed with suitable quantity of IR grade potassium bromide and prepared transparent pellets. They were scanned from 4000 to 400 cm^{-1} (Perkin Elmer Spectrum Rx₁, USA).

Preparation of pellets by extrusion and spheronization

Different pellet formulations containing diclofenac sodium were prepared by extrusion and spheronization. The components of the formulations were shown in Table 1. The diclofenac sodium, CS, MCC and lactose

Table 1. Composition of chitosan succinate pellets

Ingredients	Formulations (%)			
	F1	F2	F3	F4
Diclofenac sodium	33.3	33.3	33.3	33.3
Chitosan succinate	20	30	50	66.7
MCC	23.5	18.5	8.5	-
Lactose	23.5	18.5	8.5	-
Water	q.s	q.s	q.s	q.s

Solubility of polymer

Chitosan and CS polymer were placed in a 100 mL screw-capped bottle containing different pH solution (pH 1.2, 4.5 and 7.4). The polymeric suspension was then shaken using a mechanical shaker (Technico Lab, Chennai) at room temperature for 48 h. The suspension was then filtered and left overnight to dry under vacuum. The dissolved amount was then calculated by weight difference.

were mixed for 10 min using blender. The powder mixture was mixed with water in the ratio of 60 g of water per 400 g of powder material as optimised ratio that gives damp mass with suitable consistency. The mixing was continues for 20 min. The wet mass was then passed through a single screw extruder (EXT 30, Rikan Pharma, India) with a 1.0 mm screen at 150 rpm. The extrudates were processed in a spheronizer (SPH 150, Rikon

Pharma, India) fitted with a cross-hatched plate rotated at 300 rpm for about 5 min. The obtained pellets were dried at 40 °C for 30 min and stored in desiccator.

Evaluation of Pellets

Pellets size analysis

The prepared samples of pellets (20g) were passed through a set of sieves number 10, 12, 14, 16, 18, 20 and 25 with aperture sizes of 2, 1.7, 1.4, 1.18, 1, 0.85 and 0.71 mm respectively. The samples were shaken for 10 min on a mechanical shaker (Scientific Engg Corporation, New Delhi, India). The samples retained on sieve number 18 (size \approx 1mm) were used for further studies.

Surface morphology

The Surface morphology of the pellets was studied by scanning electron microscopy (HITACHI, S-3400N, Japan). The samples were mounted on the SEM sample stab, using a double-sided adhesive tape and then coated with gold (200A) under reduced pressure (0.001 torr) for 5 min using an Ion sputtering device. The pellets were observed for their morphology at acceleration voltage of 15 KV.

Shape of the pellet

The pellets were characterized by geometric parameters determined by analyzing digital photographs of pellets scattered on a black surface, obtained with a digital camera SONY Cyber-shot 12 megapixel camera. The photographs were processed by UTHSCSA Image Tool 3.0 program. The geometric parameters Aspect Ratio, Sphericity were determined by applying the following equations.

$$\text{Aspect Ratio} = \frac{D_{\max}}{D_{\min}}$$

$$\text{Sphericity} = \frac{4\pi A r}{P m^2}$$

Where, P is the perimeter of the spherical granules image and A is the area determined by the total number of pixels within the feature.

Friability

Friability of the pellets were determined by subjecting 10g of the pellets (w_i) for friability by placing them in the plastic chamber of a Roche Friabilator and subjected to impact testing at 25 rpm for 4min. The pellets were then screened using a sieve number 18 and weight of the pellets (w_f) retained on the sieve was measured. The weight loss (%) after friability testing was calculated.

$$\text{Loss of Percentage} = \frac{\text{Initial Weight}(W_i) - \text{Final Weight}(W_f)}{\text{Initial Weight}(W_i)} \times 100$$

Angle of repose

Angle of repose is used to determine the flow properties of pellets. The method to find angle of repose is to pour the powder on a conical heap on a level, flat surface and measure the inclined angle with the horizontal.

$$\tan \theta = \frac{h}{r}$$

Where θ = angle of repose; h = height of the heap; r = radius of the surface

Bulk density

Bulk density of the pellets was determined by pouring pellets into a graduated cylinder via a large funnel and measuring the volume and weight.

$$\text{Bulk density} = \frac{\text{Weight of pellets}}{\text{Bulk volume of pellets}}$$

Tapped density

Tapped density was determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which was operated for a fixed number of taps until the pellets bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

$$\text{Tapped density} = \frac{\text{Weight of pellets}}{\text{Tapped volume of granules}}$$

Carr's index

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$CI = \frac{TD - BD}{TD} \times 100$$

Where TD – Tapped density; BD – Bulk density

Hausner's ratio

It is a measurement of frictional resistance of the pellets. It was determined by the ratio of tapped density and bulk density.

$$\text{Hausner Ratio} = \frac{V_i}{V_o}$$

Drug content

300 mg of pellets equivalent to 100 mg of drug were accurately weighed and dissolved in 70 mL of methanol for 15 min, make up to 100 mL with the same solvent, and filtered. 1 mL of the filtrate was diluted to 100 mL of methanol. The content of Diclofenac sodium was determined spectrophotometrically by measuring the absorbance at 276 nm. The results were expressed as mean values of three determinations.

volume was observed (V_t) at 6 h. The degree of swelling was calculated using following formula,

$$\text{Degree of Swelling} = \frac{V_t - V_o}{V_o}$$

Where V_o and V_t are initial volume and final volume of the granules respectively

In vitro drug release

Dissolution studies of the pellets were performed in triplicate employing USP XIII dissolution rate test apparatus - 1 (Electrolab, TDL - 08L, India) simulating the gastro intestinal tract conditions. Weighed quantities of the pellets were loaded into the basket of the dissolution apparatus, the pH changes were performed starting with 900 mL of simulated gastric fluid (SGF); pH 1.2 for 2 h and then a pH 4.5 buffer for 2 h followed by simulated intestinal fluid (SIF); phosphate buffer of pH 7.4 till the end of the test. The temperature of the dissolution fluid was maintained at $37 \pm 0.5^\circ\text{C}$ with a stirring speed of 100 rpm. The samples were withdrawn at intervals of 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24 h and filtered with 0.22 μm filter (Millipore). The amount of drug was estimated by spectrophotometrically at 276 nm. In case of analysis of the calibration

Table 2. Analytical parameters of DS in different pH medium

Parameters	pH 1.2	pH 4.5	pH 7.4
Linearity ($\mu\text{g/mL}$)	2-10	2-10	5-25
Correlation	0.995	0.997	0.992
Co-efficient (r^2)			
Slope (m)	0.064	0.076	0.037
Intercept (n)	0.004	0.001	0.003
LOD ($\mu\text{g/mL}$)	0.5	0.5	1.5
LOQ ($\mu\text{g/mL}$)	0.9	0.9	3.5

Swelling index

Swelling property of chitosan succinate pellets were studied using different media. A weighed amount of pellets (10 g) were placed in a 100 mL measuring cylinder containing pH 1.2, 4.5 and 7.4 buffer. Initial volume (V_o) was noted and change in physical

graphs were constructed by dissolving the DS in the different media with pH 1.2 and 4.5 and 7.4. The analytical parameters such as linearity, correlation co-efficient, limit of detection (LOD), Limit of quantification (LOQ), slope and intercept were given in Table 2.

Analysis of release data

The release data obtained via the above procedure were subjected to the Ritger and Peppas model to devise its release mechanism. The initial 60% cumulative release data were used to estimate the diffusion exponent 'n' by using following equation.

$$M_t / M_\infty = Kt^n$$

Where M_t is the amount of drug released at time t, M_∞ the nominal total amount of drug released, K the kinetic constant, and n the diffusion exponent that is used to characterize the release mechanism. For spheres, a value of $n \leq 0.43$ indicates Fickian release and 'n' value between 0.43 and 0.85 is an indication of non-Fickian release (both diffusion-controlled and swelling-controlled drug release). An 'n' value ≥ 0.85 indicates case-II transport that involves polymer dissolution and polymeric chain enlargement or relaxation (13).

RESULTS AND DISCUSSION

Synthesis and characterization of chitosan succinate polymer

CS was prepared and yield was found 90 %. The conjugation reactions were carried out using succinate anhydrides in the presence of pyridine. Both anhydrides are strong electrophiles and react readily with the nucleophilic amine groups of chitosan. Pyridine was added as an acylation catalyst. Probably, the amino groups were selectively acylated due to their superior nucleophilic character in comparison to the surrounding hydroxyl groups. The average degree of chitosan substitution by succinate moieties was found to be 12.3%. The solubility of CS was carried out in acidic and alkaline solution. In contrast to chitosan, semi-synthetic polymers exhibit the highest solubility in alkaline media; this is probably due to ionization of the carboxylic acid moieties under alkaline conditions yielding the sodium carboxylate anions. The hydrophilic ionic species facilitate efficient polymeric hydration and dissolution in aqueous media.

FTIR spectral studies

The FTIR spectra of chitosan and chitosan succinate are presented in Figure 1. The characteristic absorption of the chitosan was the band at 1579.1 cm^{-1} , which is assigned to the stretching vibration of amino group and 1438.6 cm^{-1} was assigned to C-H vibration. Another band at 3448.2 is due to amine NH symmetrical stretching vibration. The peak at 2927.8 cm^{-1} is typical for C-H vibration. The peaks around 896.0 and 1152.8 cm^{-1} correspond to saccharide structure of chitosan. The broad peak at 1093.4 indicates C-O stretching vibration (14). IR spectrum of the chitosan succinate also shows characteristic peak present in chitosan, in addition to the above peaks a peak at 1653.8 cm^{-1} which is attributed to C-O stretching vibrations of carboxylic moieties. The peak around 1639.3 cm^{-1} which is indicated that C-O stretching vibrations of carboxylic moieties. Thus, the results confirm that the chitosan succinate polymer contain carboxylic moieties, which are linked to the chitosan backbone chain.

Preformulation studies

The IR spectrum of diclofenac sodium showed characteristic peaks at 1167 and 682 cm^{-1} for aromatic -C-Cl. The stretches between 800 and 600 cm^{-1} also support the presence of -C-Cl group. The strong peaks in the region of 1600 – 1700 – 1800 cm^{-1} indicate the presence of -C=O. Moreover, the presence of peaks in the region of 1250 , 1283 , and 1044 cm^{-1} confirms the -C-O- group. The peaks at 1603 , 1507 , and 869 – 716 cm^{-1} confirm the presence of an aromatic ring (15). The peaks of diclofenac sodium loaded CS pellets were similar to the spectrum of diclofenac sodium. The peaks of various functional groups as described in the IR spectrum of diclofenac sodium were also present in the pellets loaded with diclofenac sodium without any shift or change (Figure 2). These observations revealed the intact nature of the diclofenac sodium present in the pellets. From these results, the absence of drug-polymer interaction and the stability of the drug in the pellets were confirmed.

Evaluation of pellets

Characterization of CS pellets was performed. Average size of the pellets was found to be 1.02 ± 0.40 mm and the results were shown in Figure 3. SEM photographs of CS pellets were shown in Figure 4. The pellets were found discrete, spherical with a

slightly rough surface. The Sphericity value of 1.00 corresponds to a perfect sphere (16). The sphericity of the pellets (F1 to F3) was found in the range 0.8968 to 0.9948. The results revealed CS particles are dispersed within the MCC matrix and the mass can be pressed

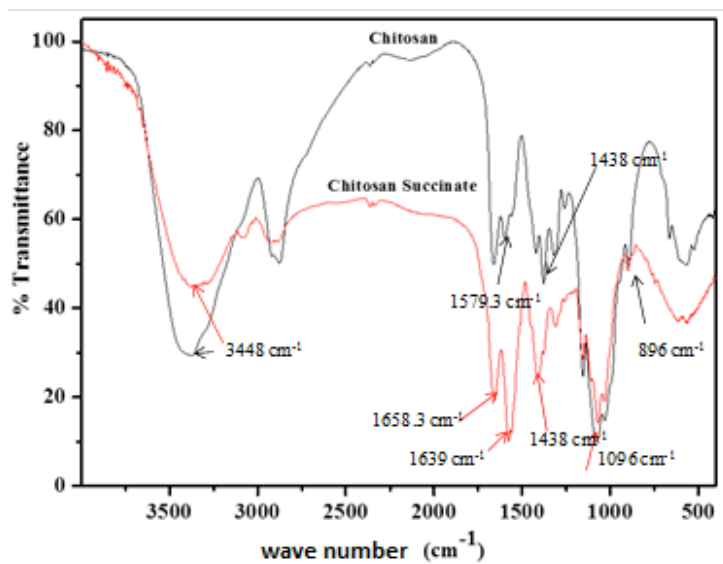


Figure 1. FTIR spectrum of chitosan and chitosan succinate polymer.

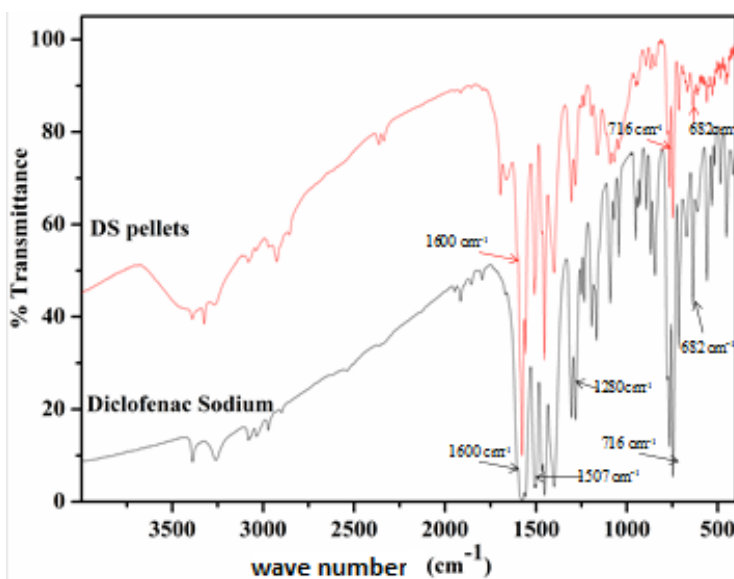


Figure 2. FTIR spectrum of pure diclofenac sodium (DS) and DS pellets.

through the die of the extruder (17). In case of F4 pellets was found poor sphericity and friability. If the CS fraction is greater than 50% it determines the behaviour of the wet mass in the extruder, leading to insufficient plastic formability and blocking of the die.

found to be 1.07 to 1.11. Angle repose of the pellets showed less than 30° indicates good flow property (18). The improved flow ability of pellets may be due to good sphericity and small size of granules. The drug content of all the pellets was found in the range of 96 to 99

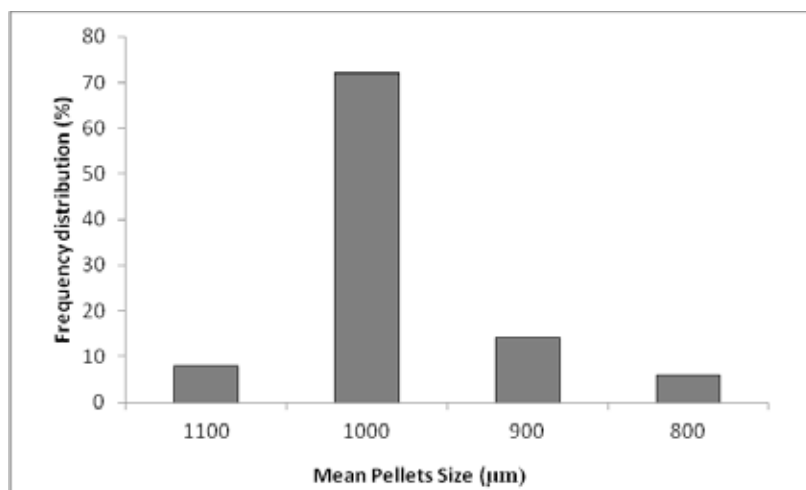


Figure 3. Particle size analysis of chitosan succinate pellets.

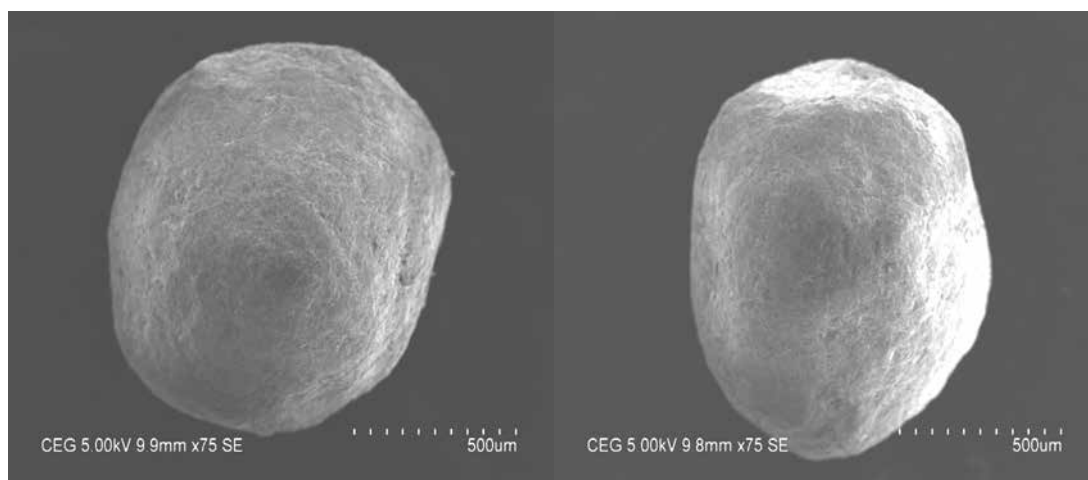


Figure 4. SEM images of chitosan succinate pellets.

The pellets were evaluated for bulk density (BD), tapped density (TD), compressibility (Carr's) index and angle of repose and the results were shown in Table 3. The bulk density of the formulations (F1 to F4) was found in the range of 0.25 to 0.30 and tapped density from 0.27 to 0.32 respectively. The compressibility index was found to be in the range 7.4% to 10.3%. Hausner's ratio was

%. The result indicates that drug was uniformly distributed in the pellets.

Swelling index

The swelling ratio of the pellets was shown in Figure 5. Under acidic conditions swelling of pellets occurs scarcely. Under alkaline conditions the swelling index of the pellets were improved appreciably. The equilibrium

swelling studies showed that the increase in the polymer concentration result increased swelling. The low swelling in acidic media pH 1.2 was probably due to hydrophilic character CS of polymer which hindered liquid uptake of the pellets. The swelling of beads were ultimately increases in pH 4.5 and pH 7.4 at the end of 6 h. This was due to increased solubility of the polymer in basic pH leading to relaxation of the polymeric network.

drug release was observed at pH 1.2. This behaviour agrees with the following explanation. Under alkaline conditions the carboxylic acid moieties are deprotonated yielding hydrophilic carboxylate anions. Hydration of the carboxylate residues promotes the dissolution and the subsequent release of the pellets diclofenac sodium. However, under acidic conditions, the carboxylic moieties are predominantly unionized (at pH 1.2 and 4.5). The uncharged

Table 3. Evaluation parameters of chitosan succinate pellets

Parameters	Formulations			
	F1	F2	F3	F4
Sphericity*	0.994±0.04	0.896±0.05	0.526±0.08	0.402±0.12
Friability (%w/w)*	0.12±0.005	0.30±0.004	0.40±0.005	0.97±0.006
Angle of repose*	22.20±0.4	22.19±0.5	21.26±0.7	29.26±0.5
Bulk Density (g/mL)*	0.28±0.01	0.30±0.01	0.26±0.01	0.25±0.01
Tapped Density (g/mL)*	0.31±0.01	0.32±0.01	0.29±0.01	0.27±0.01
Carr's Index (%)	9.677	6.25	10.34	7.40
Hausner's ratio*	1.10±0.04	1.06±0.04	1.11±0.05	1.07±0.01
Drug content (%)	95.34	97.86	97.32	98.56

*Results are the mean of triplicate observations (Mean±SD).

In-vitro drug release

The *in vitro* drug release profile of diclofenac sodium from CS pellets was shown in Figure 6. The release of diclofenac sodium from CS pellets was at its highest levels under the alkaline conditions of pH 7.4. Moderate drug release was observed under slightly acidic conditions of pH 4.5. However, lowest

carboxylic acid groups are considerably less hydrophilic compared to their charged polymer bases, i.e. the carboxylate anions. Therefore, the modified chitosan pellets acted as expected under acidic conditions, and resisted hydration and the subsequent release of imbedded drugs.

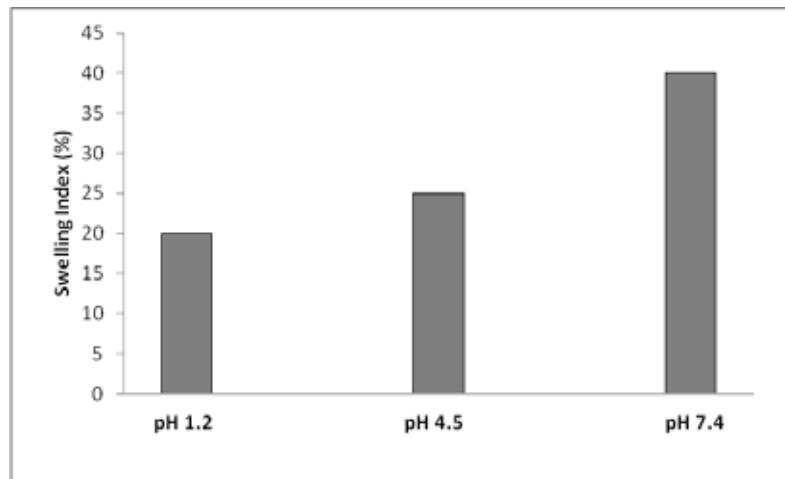


Figure 5. Swelling index of chitosan succinate pellets at different pH conditions

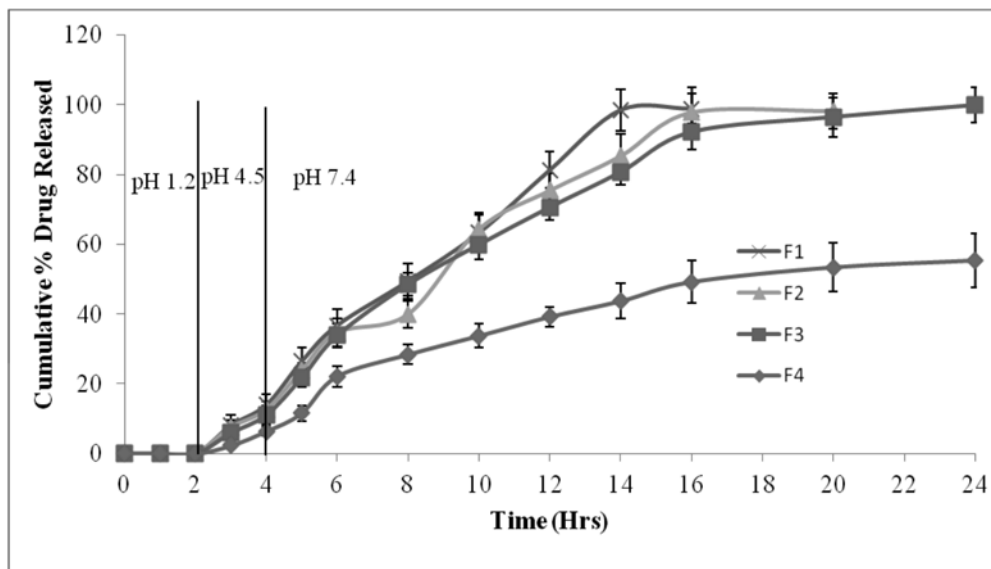


Figure 6. *In vitro* release of diclofenac sodium from chitosan succinate pellets

In vitro release of diclofenac sodium from pellets clearly indicates that the drug release rates were inversely proportional to the amount of the polymer in each pellet. The release profile of chitosan succinate alone formulations (F4) was not meet USP pharmacopeia specification of diclofenac sodium extended release tablets. Different combination of MCC and lactose were used to achieve the release rate. Formulation F3 (CS 50%) was found retard the drug release up to 24 h whereas F1 (CP 20%) and F2 (CP 30%) could not retard the drug release. This might

be due to increased polymer concentration could have increased diffusion path length (gelling rate) for the drug which could have retarded the drug release from pellets. The swelling process of polymer occurring upon liquid uptake into the system is the rate-controlling step (12). It was expected that in alkaline medium, the CS pellets could swell upon liquid uptake during the initial period and a hydrated viscous layer around pellets was formed. The drug subsequently diffuses through the hydrated viscous layer. It was observed from the dissolution profiles that the

chitosan succinate pellets showed an initial slower drug release and a subsequent faster drug release. The overall results suggest that the dried pellets swell slightly in the stomach. When they are subsequently transferred to colon region, the pellets are begun to swell and they behave as matrices for sustained release of the drug.

Kinetic evaluation of in vitro release data

Data obtained from *in vitro* release studies of formulation (F3) was explored various kinetic models used are zero-order, first-order, and Higuchi equations. The data obtained from the *in vitro* release were fitted to various kinetic equations to determine the mechanism of drug release and release rate. As indicated by the higher correlation coefficient ($r^2 = 0.970$), the drug release from CS pellets followed the Higuchi model rather than the first-order and zero-order equations. These findings indicated that the drug release from the formulated CS pellets was diffusion controlled. In sustained release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms followed. The drug release from the polymeric system is mostly by diffusion and is best described by Fickian diffusion. But in case of formulations containing swelling polymers, other processes in addition to diffusion play an important role in exploring the drug release mechanisms. These processes include relaxation of polymer chains, imbibitions of water causing polymers to swell and changing them from initial glassy to rubbery state. Due to swelling, considerable volume expansion take place leading to moving diffusion boundaries complicating the solution of Fick's second law of diffusion. So the release data were further treated by equation given by Ritger and Peppas or also called as the Power law (13). This equation is a generalization of the observation that superposes two apparently independent mechanism of drug transport, Fickian diffusion and a case-II transport describes drug release from a swelling polymer. When n takes the value 0.5 it indicates diffusion-controlled drug release and for the value 1.0 indicates swelling-controlled drug release. Values of n between 0.5 and 1.0 can be regarded as an indicator for the both

phenomena (anomalous transport). These extreme values for the exponent n , 0.5 and 1.0, are only valid for slab geometry and for spheres and cylinders different values have been derived. For pellets, a spherical geometry is considered and as per Ritger and Peppas n takes values in the range of 0.45 – 0.89 for anomalous transport. The value of n with regression coefficient for optimized formulation (F3) was found to be 0.663 indicating the anomalous transport. The anomalous diffusion mechanism of drug release demonstrated both diffusion-controlled and swelling-controlled drug release from chitosan succinate pellets containing diclofenac sodium.

CONCLUSION

Sustained release diclofenac sodium pellets were successfully prepared using CS polymer by extrusion and spheronization method. The result of characterization of pellets such as particle size, aspect ratio, sphericity, SEM, friability, Carr's Index, Hausner Ratio, angle of repose was found satisfactory. CS showed pH dependent release profiles of the entrapped diclofenac sodium. Maximum drug release was observed only under alkaline pH condition. The optimized formulation followed Higuchi kinetics while drug release mechanism was found to be anomalous type, controlled by diffusion through swollen matrix. Swelling studies were indicated significant fluid up take in alkaline conditions by pellets and contributed in drug release. This novel system ensures applicability for oral delivery as a platform for sustained release of drug molecules.

Acknowledgements

The authors acknowledge the financial support received from the Research council, The Tamilnadu Dr. M.G.R. Medical University, Chennai under the project number 28/2012.

REFERENCES

1. Savaser A, Ozkan Y, Isimer A, Preparation and *In vitro* evaluation of sustained release tablet formulations of diclofenac sodium, *Farmaco* 60,171-77, 2005.

2. Fu J, Wang X, Xu L, Meng J, Weng Y, Li G, He H, Tang X, Preparation and *In vitro* and *In vivo* evaluation of double layer coated and matrix sustained release pellet formulations of diclofenac potassium, *Int J Pharm* 406, 84-90, 2011.
3. Almeida PS, Blanco MJ, Otero Espinar FJ, Starch-dextrin mixtures as base excipients for extrusion-spheronization pellets, *Euro J Pharm Biopharm* 59,511-521 2005.
4. Zhang XR, Chen XY, Hu LD, Tang X, Li SM, Zhong DF, Evaluation of *in vitro* dissolution and *in vivo* absorption for two different film-coated granules of clarithromycin, *Archiv Pharm Res* 28, 977-982, 2005.
5. Sinha VR, Kumria R, Binders for colon specific drug delivery an *in vitro* evaluation, *Int J Pharm* 249, 23-31, 2002.
6. Ganesh M, Jeon UJ, Ubaidulla U, Hemalatha P, Saravanakumar A, Peng MM, Jang HT, Chitosan cocrystals embedded alginate beads for enhancing the solubility and bioavailability of aceclofenac, *Int J Biol Macromol* 74,310-17, 2015.
7. Steckel H, Mindermann-Nogly F, Production of chitosan pellets by extrusion/spheronization, *Euro J Pharm Biopharm* 57, 107-114, 2004.
8. Aiedeh KM, Khatib H, Taha MO, Al-zoubi N, Application of novel chitosan derivatives in dissolution enhancement of a poorly water soluble drug, *Pharmazie* 61, 306-311, 2006.
9. Aiedeh KM, Tahab MO, Synthesis of iron-cross-linked chitosan succinate and iron cross linked hydroxamated chitosan succinate and their *in vitro* evaluation as potential matrix materials for oral theophylline sustained-release beads, *Euro J Pharm Sci* 13, 159-168, 2001.
10. Ubaidulla U, Khar RK, Ahmad FJ, Sultana Y, Panda AK, Development and Characterization of chitosan succinate microspheres for the improved oral bioavailability of insulin, *J Pharma Sci* 96 (11), 3010-3023, 2007.
11. Ubaidulla U, Khar RK, Ahmad FJ, Tripathi P, Optimization of chitosan succinate and chitosan phthalate microspheres for oral delivery of insulin using response surface methodology, *Pharm Dev Technol* 14 (1), 96-105, 2009.
12. Aiedeh K, Tahab MO, Synthesis of Chitosan succinate and Chitosan phthalate and Their Evaluation as suggested matrices in orally administered, colon-specific drug delivery systems, *Arch Pharm* 332,103, 1999.
13. Ritger PL, Peppas NA, A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices, *J Cont Release* 5,37-42, 1987.
14. Saravanan M, Bhaskar K, Maharajan G, Pillai KS, Development of gelatin microspheres loaded with diclofenac sodium for intra-articular administration, *J Drug Target* 19, 96-103, 2011.
15. Tomer G, Podczeczek F, Newton JM, The influence of model drugs on the preparation of granules by extrusion/spheronization: II spheronization parameters, *Int J Pharm* 231, 107, 2002.
16. Santos H, Veiga F, Pina M, Podczeczek F, Sousa J, Physical properties of chitosan pellets produced by extrusion-spheronisation: influence of formulation variables, *Int J Pharm* 246, 153-169, 2002.
17. Geldart D, Abdullah EC, Hassanpour A, Nwoke LC, and Wouters I. Characterization of powder flowability using measurement of angle of repose, *China Particuology* 4, 104-107, 2006.
18. Ferrari PC, Souza FM, Giorgetti L, Oliveira GF, Chaud MV, Ferraz HG, Evangelista RC *In vitro* drug permeation from chitosan pellets, *Carbo Poly* 87, 2526-2531, 2012.

Received: 26.11.2015

Accepted: 18.02.2016