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Chitosan and Hydroxypropyl Methylcellulose as release retardant for Aceclofenac

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Abstract---Plenty of natural polymers has been found effective to modulate the drug release. Numerous natural polymers either alone or in combination with other polymers were found effective in controlling the drug release. In the current study attempts were made to combine chitosan (degree of deacetylation 88.42 % ,Molecular weight 50,000 Da, and viscosity 93 CPS) and HPMC K 15M to retard the release of aceclofenac in tablet formulation. The tablets were prepared by wet granulation method and evaluated for pre and post- compression parameters. All the pre-compression parameters were found within the limit. The mechanical strength was determined in terms of hardness and friability values these were found in the range of 4.16-5.22 kg/cm^2 and 0.1-0.75% respectively. The drug content was found in the range of 97.51 – 99.66 %. Weight variation test complied the official limit as per Indian Pharmacopoeia. With increasing the concentration of both the polymers the swelling index was increased and drug release decrease. Highest concentration of both the polymers was found to retard the drug release up to 8 h. The effect of chitosan and HPMC on drug release was evaluated by design expert software to get the optimized formulation. The response of the drug release after 4h was considered to check the drug release. The optimized formulation was found to be stable at accelerated stability storage conditions. It was found that the enhanced concentration of both the polymers had negative effective on the drug release.

Keywords---chitosan, HPMC K 15 M, tablet, drug release.

Introduction

Tablets are the one of the most widely used solid dosage forms because of their various factors such as lower production cost, simplicity for administration and elegance. They comprise of one or more active pharmaceutical ingredientsand are manufactured by compression of uniform volumes of drug particleintended for oral administration [1]. Advancement in tablet formulation technology has lead to the development of various newer modified-release oral dosage forms. Sustained-release tablet formulations are being one of the dosage forms of such kind, designed to control the release of the drug at a specific rate to obtain requireddrug concentration at the site of action or in blood plasma [2]. They possess several added advantages such as sustained drug concentrations of in blood, reduced frequency of dosing, decrease in adverse effects, uniformity in drug delivery, enhanced duration of action,enhanced efficacy of drug at desired site of action and increased patient compliance over conventional oral tablet dosage forms. Sustained release has received the attention of researchers because

of feasibility in dosage form in providing release of the medication for extended time period and obtaining desired therapeutic action after administration of single dose [3].

Sustained release oral tablet dosage forms are prepared by coating the tablets by polymers responsible for the retardation of the drug release to control the rate of solubility or by drug encapsulation the in the form of different sized microparticlesusing polymers to regulate the rate of dissolution. There are various natural polymers available includingnatural silk, natural gums, natural rubber, cellulose, mucilages, starch, proteins etc. which are obtained from natural sources are used in the formulation of sustained release tablets [4]. Chitosan is such a natural polysaccharide is one of such natural polymers used in formulation of sustained release tablets. It is a deacetylated chitin derivative, containing copolymers of N- glucosamine andacetylglucosamine. It is also one of thebiocompatible and biodegradable cationic polymer possessing useful properties such as less extent of toxicity and enhanced patient compliance. Structurally, the amino groups (cationic) present on C2 position of repeating chitosan glucopyranose units possess the ability to interact with the anionic groups electrostatically (especially carboxylic acid groups) of other polyions to form polyelectrolyte complexes [5].

Solubility of chitosan is specificallydependant on its molecular weight, pH value of its aqueous solution and deacetylation degree. Chitosan is practically insoluble in water and common organic solvents but soluble easily in acidic aqueous solutions below pH 6.3. Lessdeacetylationdegree (55–70%) makes chitosan completely water insoluble. Medium deacetylation degree (70–85%) makes it partly water soluble, whereas the high degree of deacetylation (85–95%) enhances water solubility of chitosan. Ultrahigh deacetylation degree (95–100%) of chitosan is very difficult to obtain. Aqueous solubility can be markedly enhanced by reducing the molecular weight of chitosan by inducing degradation [6]. Hydroxylpropyl methylcellulose (HPMC) is cellulose etherwhich is widely used as the base for the formulation of sustained release hydrophilic matrix tablets. Its gelling characteristics are very useful in the sustained release tablets formulation [7].

Acceclofenac is a nonsteroidal anti-inflammatory drug (NSAID), widely used in the treatment of several inflammatory disorders such as ankylosing spondylitis, osteoarthritis rheumatoid arthritis andpain. Aceclofenac acts by inhibiting the cyclo-oxygenase enzyme (COX) responsible forsynthesis of prostaglandins involved in inducinginflammation, edema, fever and pain. Aceclofenac is a drug belonging a BCS Class II exhibiting poor water solubility leading to dissolution-related absorption problems [8]. The present investigation attempted towards the use of chitosan (degree of deacetylation 84.14 %) and HPMC K 15M combination to retard the release of aceclofenac.

Material and Methods

Aceclofenac was obtained as gift sample from Aarti Drugs, Mumbai. Chitosan (degree of deactetylation (88.42 % ,Molecular weight 50,000 Da, and viscosity 93 CPS) was received as gift sample from India Sea Foods, Kerala. HPMC was

obtained from Anshul Life Sciences, Mumbai as gift sample. All the other reagents and solvents used for the study were of analytical grade.

Methods

Matrix tablet containing Chitosan and HPMC K 15M was prepared by wet granulation method. 3^2 factorial design was used to prepare the different batches by selecting Chitosan and HPMC K 15M as independent variables and drug release was chosen as dependent variables. All the batches prepared with 100 mg of Aceclofenac and various concentration of chitosan and HPMC as shown in Table 1. Briefly, all the ingredients were weighed and passed through sieve no 40. Further homogeneous mixing was carried out and granules were prepared by starch paste as binder. Wet granules were dried by tray dryer at the temperature of 40-50^{0}C and passed through sieve no 30. Before compression granules were lubricated with talc and magnesium stearate and flow characteristics of granules were evaluated. The compression was carried out by 10 station tablet compression machine (Karnavati Co. Ahmedabad), 8mm punch was used to obtain the weight of 250 mg of each tablet [9].

Table 1
Formulations of Aceclofenac matrix tablet containing Chitosan and HPMC K15M

Formulations	I	II	III	IV	V	VI	VII	VIII	IX
Aceclofenac	100	100	100	100	100	100	100	100	100
Chitosan	15	30	0	30	15	30	15	0	0
HPMCK15M	15	0	30	15	30	30	0	15	0
Lactose	84	84	84	69	69	54	99	99	114
Starch	30	30	30	30	30	30	30	30	30
Talc	3	3	3	3	3	3	3	3	3
Mag. Stearate	3	3	3	3	3	3	3	3	3

*All weights in mg.

Evaluation of Tablet
Evaluation of granules

The prepared granules were evaluated for different flow properties as elaborated below[10]:

- **Bulk density**
  It was determined by pouring the 5 gm. mass of granules in 100 mL measuring cylinder and initial volume occupied by powder mass was noted. Bulk density was calculated by the formula
  Bulk density = Mass of granules/ Bulk volume
- **Tapped density**
  The 5 gm of samples were poured in measuring cylinder and were subjected to tapped density test apparatus and tapping was done for 100 times and final volume occupied by granules were noted.
  Tapped density = Mass of granules/ Tapped volume

- **Carr's Index:** Carr's compressibility index was determined by the values obtained for bulk and tapped densities by the following formula,
  Carr's index (%) = (Tapped density-Bulk density/Tapped density) X 100
- **Hausner's ratio**: It was calculated by the formula,
  Hausner's ratio = Tapped density/ Bulk density

Evaluation of tablets

Prepared tablets were evaluated for the following parameters as listed in Indian Pharmacopoeia [11].

- **Weight variation test:**
  It was carried out by randomly weighing 20 tablets individually and calculating the average weight. Later the weight of each tablet was compared with average weight. Tablet was considered as passed the test when they did not deviate ± 7.5% of average weight.
- **Hardness:**
  Pfizer hardness tester (Model PTB 411, Dolphin instruments) was used for the determination of the hardness of the tablets.
- **Friability:**
  The Friability of the tablets was determined using Roche friabilator (Model-EF-2, Electrolab). 10 tablets were weighed and subjected to Roche friabilator for 25 revolutions per minute, further tablets were de-dusted and reweighed. The % friability was calculated by using formula
  % Friability = (1- Weight of tablet before the test/ Weight of tablet after the test) X 100
- **Thickness**
  The crown-to-crown thicknesses of five tablets from each batch were determined using adigital verniercaliper(Mituyoto) and average values were calculated.
- **Swelling behaviour of matrix tablets**
  One tablet from each formulation was kept in a petridish containing pH 6.8 phosphate buffer.
  The concentric circles were drawn with diameters of 7, 8, 10, 12, 14, 16, 18, 20mm. The paper was laminated to make it hydrophobic. On either side of this piece, special arrangements were made to facilitate the raising and lowering of the assembly. The concentric circles were drawn to measure the increase in the radial direction, and the diameter of the outermost circle arbitrarily was fixed at 20 mm as the matrices underwent total disintegration/dissolution above this parameter [12].
- ***In-vitro* drug release studies**
  The *in-vitro* dissolution studies were carried out using USP TDT-08L (Electro lab, Mumbai.) apparatus at 37±0.5°C and at 50 rpm for 8 hrs. The dissolution medium used was 900 mL phosphate buffer pH 6.8. At predetermined interval 10 mL of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain sink condition. After filtration and appropriate dilution, the sample solutions were analysed by UV- visible spectrophotometer [13].

- **Stability Studies**
  Stability study was carried out as per ICH guidelines on selected formulations. The formulations were selected on the basis of cumulative % drug release at 4 hrs. analysed Design Expert software. Formulations were placed in thermostatically controlled stability chamber (Thermolab) at an accelerated condition (40 ± 2 °C/75 ± 0.5% RH) for 1 month. Tablets were observed for physical changes and parameters mainly % drug contents and cumulative drug release were determined [14].

Results and Discussion

Matrix tablets composed of chitosan and HPMC 15M were prepared for prolong release of aceclofenac. Wet granulation technique was employed for preparation of tablets and evaluated for flow properties; the resultswere summarized in Table 2.Flow properties are important for uniform flow of material from hopper to die. Poor flow properties results in problems with respect to uniformity of weight and content. Carr's index in the range of 5-15 was desirable to achieve excellent flow properties whereas value of carr's index greater than 40 showed extremely poor flow properties. Hausner's ratio near about 1.2 and 1.6 was indicative of low inter-particular friction and more cohesive forces respectively [15].

Table 2
Evaluation of flow properties of granules

Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio
I	0.641 ± 0.03	0.881 ± 0.04	27.24 ± 1.63	1.375 ± 0.05
II	0.575 ± 0.07	0.855 ± 0.02	32.74 ± 1.47	1.488 ± 0.03
III	0.566 ± 0.06	0.875 ± 0.04	35.31 ± 1.8	1.546 ± 0.1
IV	0.584 ± 0.08	0.908 ± 0.04	35.68 ± 1.14	1.555 ± 0.41
V	0.545 ± 0.04	0.613 ± 0.01	11.09 ± 1.44	1.125 ± 0.15
VI	0.511 ± 0.03	0.698 ± 0.05	36.86 ± 1.22	1.36 ± 0.01
VII	0.51 ± 0.03	0.712 ± 0.08	28.37 ± 1.14	1.39 ± 0.8
VIII	0.521 ± 0.03	0.623 ± 0.03	16.37 ± 1.03	1.19 ± 0.06
IX	0.505 ± 0.09	0.625 ± 0.05	19.20 ± 1.35	1.24 ± 0.15

*****Mean ± S.D for n=3

Evaluation of tablets

Prepared tablets were evaluated for different parameters as per the Indian Pharmacopoeia. Hardness and friability are indicative of mechanical strength of the tablet. The mechanical strength is important parameter to withstand the tablet for mechanical shock during handling and transportation.Hardness of the tablets depends on compactness of granular mass and the compression force. For the different batches hardness and friability value ranged from 4.03-4.89 Kg/cm^2 and 0.1-0.6% respectively. These values were indicative of good mechanical strength as hardness values between 4-5 $Kg/cm^2$and friability less than 1% are desired for good mechanical strength [16]. Weight variation and content

uniformity test was important to determine the uniformity of the weight of tablet and uniform drug distribution within the tablet respectively. These parameters were very important for uniform dose distribution and ultimately bioavailability of the drug. These depend on uniform mixing and flow properties of the powder or granules [17]. The results of evaluation were shown in Table 3.

Table 3
Evaluation parameters for post compression parameters

Formulation	Weight Variation (%)	Thickness (mm.)	Friability (%)	Hardness (Kg/cm^2)	Drug content (%)
I	0.22±0.12	4.20 ± 0.12	0.23 ± 0.13	5.22 ± 0.65	97.63±2.35
II	0.54±0.23	4.54± 0.11	0.7± 0.22	4.16± 0.43	98.32±3.01
III	0.86 ± 0.34	4.21± 0.43	0.5± 0.11	5.12±0.15	98.09±2.6
IV	0.50 ± 0.39	4.16± 0.11	0.5±0.16	4.67±0.54	99.66±0.52
V	0.53±0.12	3.94±0.27	0.3±0.14	4.46±0.64	97.51±1.59
VI	0.86 ± 0.12	4.29±0.42	0.1± 0.13	5.16 ± 0.65	97.63± 1.35
VII	0.49±0.03	4.32± 0.15	0.7± 0.2	4.63±0.45	98.32± 1.01
VIII	0.61±0.23	4.34± 0.11	0.5±0.13	4.75±0.24	99.03± 0.54
IX	0.52 ± 0.30	4.45 ± 0.13	0.75 ± 0.25	4.25 ± 0.25	98.90 ± 1.05

*Mean ± S.D for n=3

Swelling behaviour of matrix tablets

Tablets were placed in phosphate buffer 6.8 and allowed to swell upon absorption of fluid tablets were hydrated and swelled to form a gel mass. The more exposure area of the radial surface increased the extent of swelling.The extent of swelling was measured in terms of radial swelling of the tablet. These measurements are represented graphically in Figure 1.

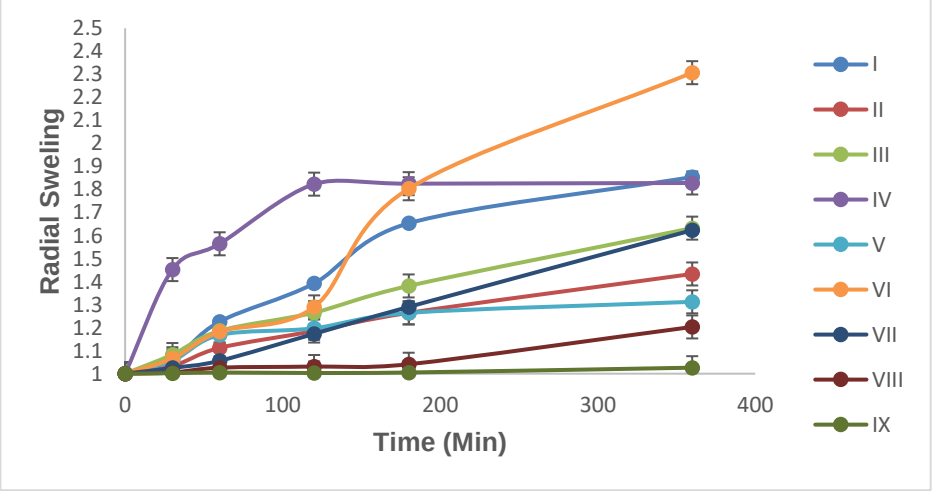

Figure 1. Radial swelling of formulations

It was observed that owing to presence of acetyl substitution, chitosan matrices mainly undergoes radial swelling. Acetyl substitution might be contributing to radial relaxation preferably. These results were in consensus with the research carried out by the Nunthanidet. al. (2009) [18]. HPMC was also found to be equally contributing to the swelling of the matrices. HPMC hydrate; enhances the water uptake rate resulting in rapid swelling andconversion from glassy to rubbery state. This conversiondevelops disentanglement of the polymer chains [19]. The graph showed that with highest concentration of both the polymer swelling was also increasedremarkably (Formulation VI). At the higher concentration of polymer water absorption will be higher resulting in more predominant swelling as compared to other matrices. This phenomenon might be result of delayed erosion of the gelled layer and higher ability of water uptake of the tablets composed of higher amounts of polymer [20].

***In-vitro* drug release studies**

The effect of degree of deactylation of chitosan on the aceclofenac release was investigated. The combined effect of Chitosan and HPMC in different concentration was also investigated. The cumulative release of drug with respect to time is shown in Figure 2.

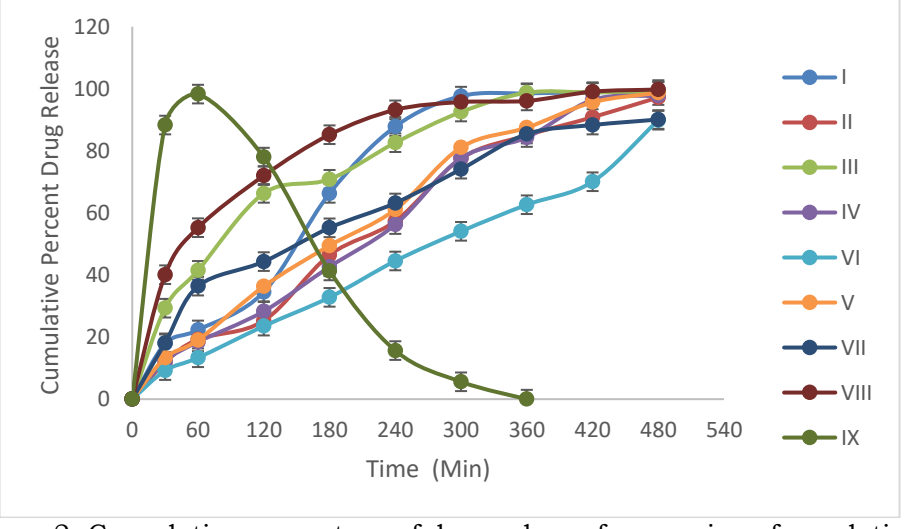

Figure 2. Cumulative percentage of drug release from various formulations

Chitosan and HPMC were combined in different concentration and release of the drug release was investigated. It has been observed that highest concentration of both the polymers in combination could retard the drug release for 8 h. and individual polymer at highest concentration could retard the drug release for 6-7 h. The different combinations at low concentration of polymer could retard the drug release up to 6 h. The combination of low and high concentration of polymer could retard the drug release up to 7 h. These results might be attributed to formation of viscous gel layer depending on the polymer concentration and subsequent release of the drug. At higher concentration the drug release rate is low due to formation of more viscous layer that hinder the diffusion of drug. As

both the polymers are hydrophilic in nature swelling and erosion are predominant mechanism for drug release.Soon the tablet come in contact with dissolution media, imbibition of media in the matrix result in swelling and formation of gel layer and slowly gel layer starts eroding and consequently drug is released. The thickness of swollen gel may act as a diffusion barrier. Swelling action was controlled by rate of water uptake into the matrices. An inverse relationship was observed between the drug release and thickness of gel layer [21].

Formulations having n values close to 0, release become increasingly matrix type. This is due to resulting in formation of matrix. The system no longer remains a reservoir, barrier membrane diffusion controlled one but transforms into a monoblock of drug and polymer. In case of matrix tablets, the release pattern in 6.8 phosphate buffer, shows n values depicting matrix or first order. In this case the contribution of the polymer degree of deacetylation plays very important role. The disruption of release controlling mechanism leads to significant changes in n values. For the optimized matrix formulation, the n value was less than 0.5 indicating Peppas or Higuchi or Matrix pattern. For these formulations, the n value is further away from 0.5 towards zero indicates diffusion through membrane as predominant mechanism of drug release as against the swelling controlled drug release seen in case of chitosan matrix. These results were in agreement with research carried out by Rao et.al. (2012) [21].

Optimization

The effect of chitosan (X1) and HPMC K15M (X2) on drug release was evaluated by using design expert software. The data was statically analysed by ANOVA. All the responses observed for nine formulations prepared were fitted to various models using Design- Expert® software and following graphs were obtained.

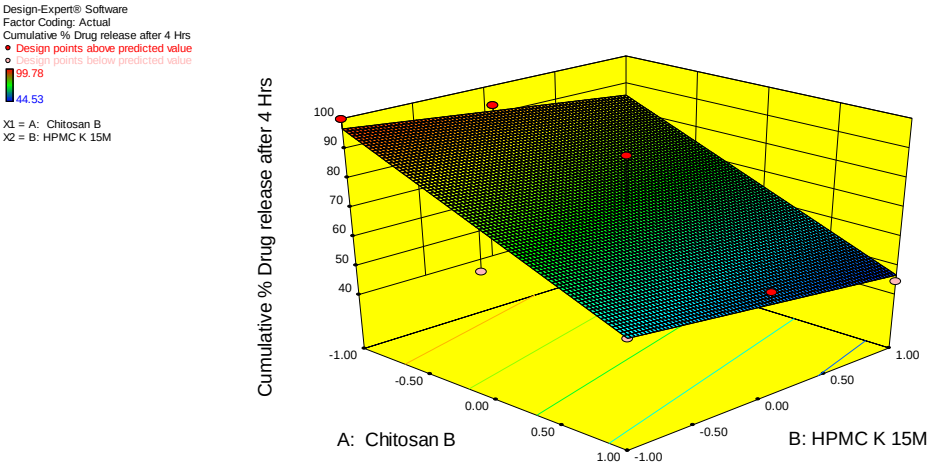

Figure 3. Response surface showing the effect of X1 and X2 on drug release at 4h (Y)for chitosan and HPMCK15M

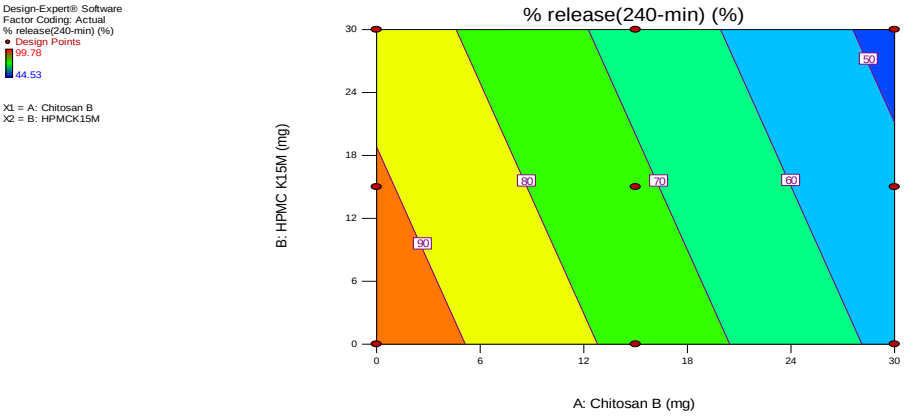

Figure 4. Contour plot showing the effect of X1 and X2 on drug release at 4h (Y) for Chitosan A and HPMCK15M

It was observed that the best-fitted model was linear for the response drug release at 4 h. The values of R2, adjusted R2, predicted R2, SD and % CV are given in Table 4, along with the regression equation generated for each response. The results of ANOVA in Table 5 for the dependent variable demonstrate that the model was significant for the response variable. It was observed that independent variables X1 (Chitosan concentration) and X2 (concentration of HPMC K15 M) had a negative effect on drug release (Y). The coefficients with more than one factor term in the regression equation represent interaction terms. It also shows that the relationship between factors and responses is not always linear. When more than one factors werechanged simultaneously and used at different levels in a formulation, a factor can produce different degrees of response.

Table 4
Summary of results of regression analysis for response Y for Chitosan A

Models	R^2	Adjusted R^2	Predicted R^2	SD	% CV
Response (Y) Linear model	0.82444	0.76592	0.708093	9.369159	13.05361

Regression equations of the fitted linear and interactive model:
Final Equation in Terms of Actual Factors:
Cumulative % Drug release (Y)=71.77444-19.5867* X1- 5.34667* X2

Table 5
Results of analysis of variance for measured response

parameters	DF*	SS*	MS*	F*	p Significance
Drug release at 4 h Model	2	2473.346	1236.673	14.08814	0.0054 significant

* DF indicates degrees of freedom; SS sum of square; MS mean sum of square and F is Fischer's ratio.

Three dimensional response surface plot and contour plot generated by the Design Expert® software are presented in Figures 3 and 4 for the studied response, i.e. drug release. The presented figures depicted response surface and contour plots of chitosan (X1) and HPMC K15 M concentration (X2) on drug release at 4 h, which indicate that as the concentration of chitosan and HPMC increase the drug release was decreased [25]. A numerical optimization technique by the desirability approach was used to generate the optimum settings for the formulation. The process was optimized for the dependent variable Y. The optimum formulation was selected based on the criteria of attaining the minimum value of % drug release. Formulation VI having 30 mg of chitosan and 30 mg of HPMC K15 M fulfilled the criteria set from desirability search.

Stability Studies

The selected formulations were kept for accelerated stability at 40°C±2°C and 75%RH ±5% RH. The samples were withdrawn at a regular time interval. The formulations were tested for different parameters like % drug contents and cumulative drug release were measured and the results of accelerated stability studies are shown in Table 6. No significant changes with respect to any of the physical parameters like colour and hardness of the tablets and also above parameters were observed. The formulations were found to be quite stable.

Table 6
Accelerated Stability Studies

Parameters	Initial	1 Month	2 Months	3 Months	6 Months
% Drug Content	98.52±1.92	98.59±1.80	98.52±1.92	98.32±1.72	98.22±1.12
% Drug release	95.12±0.25	96.33±0.27	96.50±0.28	97.45±0.55	97.13±0.65

Conclusion

Chitosan having the degree of deacetylation of 88.42% was combined with HPMC in different concentration to form a matrix tablet. All the formulations compiles with the limits of pre and post-compression parameters and found to have good mechanical strength. Swelling of matrix indicative of both the polymers were contributing the swelling mechanism and inverse correlation was observed in swelling and polymer concentration. The *in-vitro* dissolution studies indicated that the drug retardation was more with the combination of highest concentration of polymer owing to formation of firm viscous layer that restricts the drug release. The optimized formulation was determined by using design expert software and it was found that formulation VI was within the range of set expected limits to control the release of drug. The optimized formulation was found to be stable for 6 months of accelerated stability conditions. The combination of chitosan and HPMC was found effective in controlling release of aceclofenac for extended period.

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