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Chitosan and Hydroxy Propyl Methyl Cellulose as a Carrier for Aceclofenac for Prolonged Release

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Authors' contributions

This work was carried out in collaboration among all authors. Authors RGK and AVY designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors RVC and JSD managed the analyses of the study. Authors ABK and PVR managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Numerous natural polymers either alone or in combination with other polymers were found effective in controlling the drug release. In this study the attempts were made to combine chitosan (degree of deacetylation 84.14 %) and as hydroxylpropyl methylcellulose (HPMC K 15M) to retard the release of aceclofenac in tablet formulation. The tablets were prepared by wet granulation and evaluated for pre and post- compression parameters. All the pre-compression parameters were found within the limit. Hardness and friability values were found in the range of 4.30-4.89 kg/cm^2 and 0.1-0.6% respectively. These results proved the good mechanical strength of the formulations. The drug content was found in the range of 97.56 – 99.10 %. Weight variation was found within the official limit. The percent drug release and swelling index was found to be dependent on the concentration of polymer. With increasing the concentration of both the polymers the swelling index

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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 achieve the optimized formulation. The response of the drug release after 4h was considered to check the drug release. It was found that the enhanced concentration of both the polymers had negative effective on the drug release. The formulation containing highest concentration of the chitosan and HPMC was found be fit in the limits of optimized formulations. The optimized formulation was found to be stable at accelerated stability storage conditions.

Keywords: Chitosan; HPMC K 15M; tablet; drug release.

1. INTRODUCTION

Tablets are solid dosage forms containing a single dose of single or multiple active pharmaceutical ingredients obtained by compressing uniform volumes of particles and intended for oral administration. They are most commonly prescribed dosage form offering convenience of drug administration, providing tablet to tablet drug uniformity and stability over extended and diverse storage conditions [1].

Advancement in tablet production technology has resulted in newer modified release oral dosage forms. Sustained-release tablets are one of such dosage forms which are designed to control drug release profile at a specific rate to obtain desired concentration of drug either in blood plasma or site of action [2]. They provide several advantages such as reduced frequency of dosing, sustained concentrations of drugs in blood, uniform drug delivery, reduced adverse effects, enhanced efficacy of drug at the desired site of action, increasing the time of action and enhanced 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 formulated by coating the tablets by the polymers involved in retarding the drug release in order to regulate the solubility rate or by encapsulating the drug in the form of microparticles of different sizes using polymers to control the dissolution rate. Several natural polymers such as natural gums, natural silk, mucilages, natural rubber, proteins, starch, cellulose etc. obtained natural sources are used in the formulation of sustained release tablets [4].

Chitosan, a naturally occurring polysaccharide is one of such natural polymers used in the formulation of sustained release tablets. It is a deacetylated chitin derivative, comprising copolymers of N-acetylglucosamine and glucosamine. Chitosan is a most widely used biodegradable and biocompatible cationic polymer because of its properties such as reduced toxicity and improved patient compliance. Structurally it possesses 1-4 linked 2-acetamido-2-deoxy-β-D-glucopyranose as well as 2-amino-2-deoxy-β-D-glucopyranose [5].

Solubility of chitosan is critically associated with its deacetylation degree, molecular weight and the pH value of its aqueous solution. Chitosan is practically insoluble in water and common organic solvents but can be easily solubilised in acidic aqueous solutions below pH 6.3. Low degree of deacetylation (55–70%) makes chitosan completely insoluble in water, Medium deacetylation degree (70–85%) is renders it partly soluble in water while high degree of deacetylation (85–95%) enhances solubility of chitosan in water. Ultrahigh degree of deacetylation (95–100%) of chitosan is difficult to achieve. Reducing the molecular weight of chitosan by inducing degradation is plays an important role in enhancing its aqueous solubility in water [6].

Cellulose ethers such as hydroxylpropyl methylcellulose (HPMC), are widely used as the basis for sustained release hydrophilic matrix tablets. Its characteristics as gelling agent are very useful in the formulation of sustained release tablets as it forms an erosion and diffusion resistant gel layer by hydration which is involved in control drug release [7].

Acceclofenac being a nonsteroidal anti-inflammatory drug (NSAID), is used for the treatment of pain and several inflammatory disorders such as rheumatoid arthritis osteoarthritis and ankylosing spondylitis. Aceclofenac inhibits the cyclo-oxygenase enzyme (COX) involved in prostaglandins (inflammatory mediators) synthesis responsible

for pain, fever inflammation and swelling. Aceclofenac being a BCS Class II drug exhibits poor water solubility which leads to dissolution-related absorption problems [8].

The present investigation aims to develop the sustained release tablet formulation to retard the release of acelofenac. It has short half-life of 2-4 h hence to reduce the dosing frequency it is need to develop sustained release formulation. The chitosan (degree of deacetylation 84.14 %) and HPMC K 15M were used in combination to retard the release of aceclofenac. The effect of these polymers on drug release was studied.

2. MATERIALS AND METHODS

2.1 Material

Aceclofenac was obtained as gift sample from Aarti Drugs, Mumbai. Chitosan (degree of deactetylation (84.14%, molecular weight 540 kDa) was procured as gift samples from India Sea Foods, Kerala. HPMC was obtained from Anshul Life Sciences, Mumbai as gift sample. All the solvent used for the study were of analytical grade.

2.2 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].

2.2.1 Preparation of matrix tablets containing chitosan and HPMC K 15M

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].

2.2.2 Evaluation of granules

The prepared granules were evaluated for different flow properties as follows: [10].

2.2.2.1 Bulk density

It was determined by pouring the 5 gm. mass of granules in 100 mL measuring cylinder and volume occupied by powder mass was noted. Bulk density was calculated by the formula:

Bulk density = Mass of granules/ bulk volume

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*

2.2.2.2 Tapped density

The samples were taken for the evaluation of bulk density were subjected to tapped density test apparatus and tapping was done for 100 times and volume occupied by granules were noted.

Tapped density = Mass of granules/ Tapped volume

2.2.2.3 Carr's index

The 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

2.2.2.4 Hausner's ratio

It was calculated by the formula, Tapped density/ Bulk density.

2.2.3 Evaluation of tablets

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

2.2.3.1 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.

2.2.3.2 Hardness test

Pfizer hardness tester (Model PTB 411, Dolphin instruments) was used for the determination of the hardness of the tablets.

2.2.3.3 Friability test

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 and after the test 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

2.2.3.4 Thickness test

The crown-to-crown thicknesses of five tablets from each batch were determined using a digital vernier caliper (Mituyoto) and average values were calculated.

2.2.3.5 Swelling behaviour of matrix tablets

One tablet from each formulation was kept in a petri dish containing pH 6.8 phosphate buffer. The matrices obtained were circular in shape with 8-mm diameters. Hence, 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].

2.2.3.6 *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^{o}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].

2.3 Statistical Analysis

It was carried out by ANOVA by using design expert software.

2.4 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. Parameters mainly % drug contents and cumulative drug release were measured [14].

3. RESULTS AND DISCUSSION

Tablets containing Aceclofenac were prepared to study the effect of chitosan and HPMC 15M on

the drug release. Tablets were prepared by wet granulation technique and evaluated for flow properties; the result is summarized in Table 2. Flow properties are important for uniform flow of material from hopper to die. Poor flow properties results in the weight variation and content uniformity of tablet. 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 [15,16].

3.1 Evaluation of Tablets

Prepared tablets were evaluated for different parameters as per the pharmacopoeia. Hardness and friability are indicative of mechanical strength of the tablet. The mechanical strength is important factor for tablet which generally denotes capability of tablet to withstand the force during transportation and handling of tablets. 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 [17]. 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 [18]. The results of evaluation were shown in Table 3.

3.1.1 Swelling behaviour of matrix tablets

After exposure to media the penetration of the solvent into the tablet resulted in hydration swelling and formation of gel. The larger exposure area of the radial surface increases the process of swelling. The extent of swelling was measured in terms of radial swelling of the tablet. These measurements are represented graphically in Fig. 1.

Table 2. Evaluation of flow properties of granules

Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's Ratio
I	0.501±0.02	0.554±0.04	9.56±3.21	1.10±0.06
II	0.527±0.02	0.602±0.01	12.45±1.24	1.14±0.01
III	0.502±0.03	0.775±0.05	35.22±1.07	1.54±0.03
IV	0.505±0.03	0.701±0.08	27.96±1.01	1.38±0.15
V	0.510±0.02	0.665±0.04	23.30±1.45	1.30±0.04
VI	0.517±0.07	0.676±0.07	29.59±1.23	1.32±0.12
VII	0.508±0.04	0.624±0.05	18.58±1.25	1.22±0.17
VIII	0.513±0.06	0.612±0.02	16.17±1.23	1.19±0.03
IX	0.505±0.09	0.625±0.05	19.20±1.35	1.24±0.15

**Mean ± S.D for n=3*

Table 3. Evaluation parameters for post compression parameters

Formulation	Weight Variation (%)	Thickness (mm.)	Friability (%)	Hardness (Kg/cm^2)	Drug content (%)
I	0.15±0.16	4.32±0.12	0.3±0.18	4. 30±0.05	97.56±1.73
II	0.21±0.03	4.40±0.14	0.4±0.16	4.54±0.52	97.81±2.98
III	0.25±0.13	4.38±0.23	0.6±0.18	4.41±0.42	99.42±2.00
IV	0.10±0.10	4.06±0.22	0.1±0.24	4.56±0.36	97.12±0.27
V	0.51±0.40	4.29±0.41	0.5±0.26	4.61±0.14	98.52±1.92
VI	0.52±0.23	4.26±0.14	0.1±0.18	4.36±0.13	97.56±1.73
VII	0.63±0.43	4.35±0.52	0.1±0.16	4.54±0.52	97.81±2.98
VIII	0.83±0.32	4.24±0.12	0.4±0.12	4.89±0.23	98.02±1.20
IX	0.34±0.23	4.52±0.25	0.2±0.01	4.78±0.56	99.10±2.35

**Mean ± S.D for n=3*

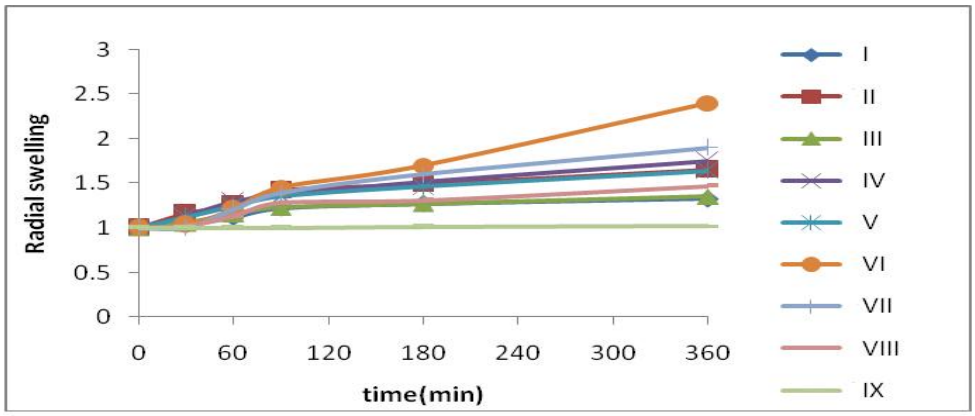

Fig. 1. Radial swelling of formulations

It was observed that chitosan matrices preferentially undergo radial swelling. This could be attributed to the acetyl substitution on the polymeric backbone. This substitution would be contributing towards radial relaxation favourably. These results were in agreement with the research carried out by the Nunthanid et. al. [19]. HPMC was also contributing the swelling of the matrices. HPMC enhances the water uptake rate by the tablet resulting in rapid swelling and transition from glassy to rubbery state. This transition leads to disentanglement of the polymer chains [20]. The graph showed that with highest concentration of both the polymer swelling was also increased (Formulation VI).

3.1.2 *In-vitro* drug release studies

The effect of degree of deactylation of chitosan on the release of aceclofenac was studied along with the effect of combination of chitosan with HPMC. The release of drug with respect to time is shown in Fig. 2.

Chitosan and HPMC were combined in different concentration and release of the drug was determined. It has been observed that highest concentration of both the polymer could retard the drug release for 8 hrs. and individual polymer at highest concentration could retard the drug release for 6-7 hrs. The various combinations at low concentration of polymer could retard the drug release up to 6 hrs. The combination of low and high concentration of polymer could retard the drug release up to 7 hrs. 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 [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 HPMC 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 HPMC matrix 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 [22].

3.1.3 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.

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 factor are changed simultaneously and used at different levels in a formulation, a factor can produce different degrees of response.

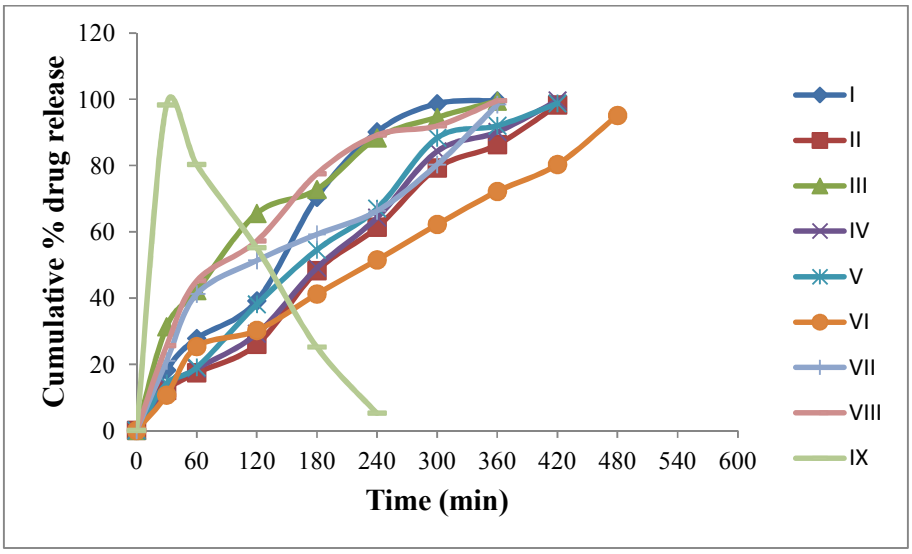

Fig. 2. Cumulative percentage of drug release from various formulations

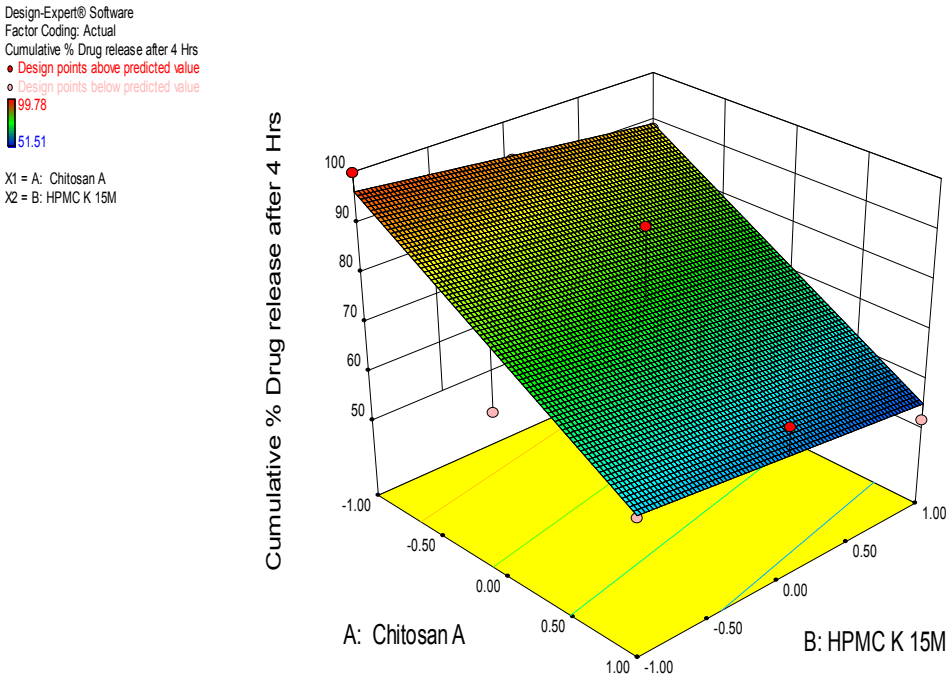

Fig. 3. Response surface showing the effect of X1 and X2 on drug release at 4h (Y)for Chitosan and HPMCK15M

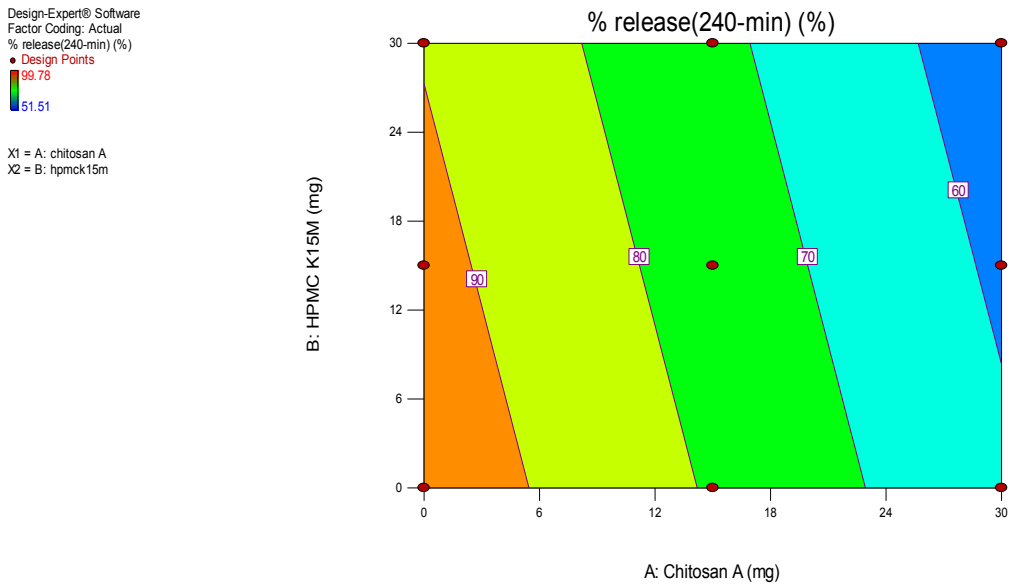

Fig. 4. Contour plot showing the effect of X1 and X2 on drug release at 4h (Y) for Chitosan A and HPMCK15M

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	0.799395	0.732526	0.66006	8.76802	11.5915

Regression equations of the fitted linear and interactive model; Final Equation in Terms of Actual Factors; Cumulative % Drug release (Y)= 75.64222-17.1633 X1-3.43167* 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	1838.138	919.069	11.95474	0.0081 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 Figs 3 and 4 for the studied response, i.e. drug release. The presented figures depicts 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.

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.

3.2 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.

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

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.

4. CONCLUSION

Chitosan having the degree of deacetylation of 84.14% was combined with HPMC in different concentration to form a matrix tablet. Tablets were prepared by wet granulation techniques and evaluated for pre and post-compression parameters. Flow properties of the granules were found within the limit. Better hardness and friability contributing to mechanical strength was observed. Content uniformity and weight variation complies as per the official standards as per Indian Pharmacopoeia. Swelling studies indicates that both the polymers were contributing the swelling mechanism and with increasing concentration of polymer the rate of swelling is increased. The in-vitro dissolution studies indicated that the drug retardation was higher with higher concentration of polymer owing to formation of more viscous layer. The optimized formulation was determined by employing design expert software and it was found that formulation VI was within the range of set expected limits of drug release. The optimized formulation was found to be stable for 6 months accelerated stability conditions. The combination of chitosan and HPMC was found effective in controlling the drug release for prolong period.

CONSENT

Not Applicable.

ETHICAL APPROVAL

Not Applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Nagashree K. Solid dosage forms: Tablets. Research and Reviews: Journal of Pharmaceutical Analysis. 2015;4(2):60-71
2. Agarwal G, Agarwal S, Karar PK, Goyal S. Oral Sustained Release Tablets: An Overview with a Special Emphasis on Matrix Tablet. American Journal of Advanced Drug Delivery. 2017;5(2):64-76.
3. Zalte HD, Saudagar RB. Review on sustained release matrix tablet. Int J Pharm Biol Sci. 2013;3(4):17-29.
4. Menkudale A, Khuspe P, Otari K, Khemnar M, Kulkarni V. An Updated Review on Applications of Natural Polymers in Sustained Release Drug Delivery System. 2020;2(1):43-47.
5. Kadam VS, Shendarkar GR. Role of Natural Polymer in Sustained and Controlled Release. Indo American Journal of Pharmaceutical Research.2017;7(01):7390-400.
6. Enayatifard R, Saeedi M, Akbari J, Tabatabaee YH. Effect of hydroxypropyl methylcellulose and ethyl cellulose content on release profile and kinetics of diltiazem HCL from matrices. Tropical Journal of Pharmaceutical Research. 2009;8(5):425-32.
7. Bhardwaj TR, Kanwar M, Lal R, et al. Natural gums and modified natural gums as sustained-release carriers. Drug Development and Industrial Pharmacy. 2000;26(10):1025- 38.
8. Faiyaz S, Wafa R, Sheikh S. Solubility and dissolution improvement of aceclofenac using different nanocarriers. J Bioequiv Availab. 2009;1:39-43.
9. Bookya P, Raparla R, Sriramula H, Tarrigopula S, Vanga S. Formulation and evaluation of metformin hydrochloride sustained-release oral matrix tablets. Asian Journal of Pharmaceutical and Clinical Research. 2018;11(3):342.
10. Kandekar UY, Abhang TR, Pujari RR Khandelwal KR. Exploration of Elephant Foot Yam (*Amorphophallus paeoniifolius*) Starch: An Alternative Natural Disintegrant for Pharmaceutical Application. Indian Journal of Pharmaceutical Education and Research. 2021;55(1):S209-S219.
11. Ghimire P, Chandra SA, Pandey S, Chapagain B, Dhakal S. Pharmacopoeial comparison of in-process and finished product quality control test for

pharmaceutical tablets. GSC Biological and Pharmaceutical Sciences. 2020;11(3):155-165.
12. Katedeshmukh RG, Yadav AV. Development of matrix tablet of Aceclofenac with chitosan and hydroxypropyl methyl cellulose (HPMC) as co-polymer. American Journal of PharmTech Research. 2013;3(6):638-658.
13. Elgaied-Lamouchi D,. Descamps N, Lefevre P, Rambur I, Pierquin JY, Siepmann F, Siepmann J, Muschert S. Starch-based controlled release matrix tablets: Impact of the type of starch. Journal of Drug Delivery Science and Technology. 2021;61:102152.
14. Mutalik S, Krishnan M, Reddy MS, Kushtagi P, Achutha NU, Parambil A, Averineni KR, Udupa N. Chitosan and enteric polymer based once daily sustained release tablets of aceclofenac: *In vitro* and *in vivo* studies. AAPS PharmSciTech. 2008;9(2):651.
15. Developing solid oral dosage forms : Pharmaceutical theory & practice. Edited by Yihong Qiu, Yisheng Chen, Geoff G.Z. Zhang, Lawrence Yu and Rao V. Mantri. 2nd ed. 2016. United Kingdom: Amsterdam : Academic Press.
16. Amidon, GE, PJ Meyer, DM Mudie. Chapter 10-Particle, Powder, and Compact Characterization. United States: Academic Press: Boston;2017.
17. Paul S, Changquan CS. Dependence of Friability on Tablet Mechanical Properties and a Predictive Approach for Binary Mixtures. Pharmaceutical Research. 2017;34 (12):2901-2909.
18. Goh HP, Heng PWS, Liew CV. Understanding die fill variation during mini-tablet production. International Journal of Pharmaceutics 2017;534(1-2):279-286.
19. Nunthanid J, Luangtana-Anan M, Sriamornsak P, Limmatvapirat S, Huanbutta K, Puttipipatkhachorn S. Use of spray-dried chitosan acetate and ethylcellulose as compression coats for colonic drug delivery: Effect of swelling on triggering *in vitro* drug release. European Journal of Pharmaceutics and Biopharmaceutics. 2009;71(2):356-361.
20. Barba AA, d'Amore M, Serafina C, Gaetano L, Giuseppe T. Swelling of cellulose derivative (HPMC) matrix systems for drug delivery. Carbohydrate Polymers. 2009;78(3):469-74.
21. Roy H, Bhabani N. Formulation and design of sustained release matrix tablets of lamivudine: Combination of chitosan and HPMC. American Journal of Pharmacy and Health Research. 2017;5(2):1-10.
22. Rao TV, Kiran Kumar GB, Mohammed GA, Joshi V. Development and evaluation of chitosan based oral controlled matrix tablets of losartan potassium. International Journal of Pharmaceutical Investigation. 2012;2(3):157-161

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