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Development of Matrix Tablet of Aceclofenac with Chitosan and Hydroxypropyl Methyl Cellulose (HPMC) As Co-Polymer.

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ABSTRACT

Chitosan, a linear binary heteropolysaccharide, composed of β-1, 4-linked glucosamine (GlcN) with various degrees of N-acetylation of GlcN residues. It is a non-toxic, biocompatible and biodegradable natural polymer of high molecular weight (~500,000 kDa). The degree of deacetylation (DD) and molecular weight (MW) are two fundamental parameters that can affect the properties and functionality of chitosan. HPMC is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery systems. Hydrophilic polymers are widely used in controlled release systems due to their favorable functionality. Enhancing the mobility of the polymer chains and diffusing of the drug out from such polymer matrices could be done by inclusion of different types of excipients at different concentrations. The present manuscript describes the attempt undertaken to develop the matrix tablet of Aceclofenac along with different grades of chitosan and HPMC as a copolymer & to study effect of it on the swelling behavior and the drug release pattern.

Keywords: chitosan A, B, C, D and E, Aceclofenac, HPMC, drug release, swelling

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INTRODUCTION

Matrix systems generally consist of dissolved or dispersed drug within a swelling or slowly eroding polymer matrix. The drug release from such systems is controlled by water penetration into the matrix followed by either diffusion of the drug into the surrounding medium, erosion of the matrix, or combination of both. A potential disadvantage of the simple monolithic matrix system is the lack of zero-order release kinetics resulting from time-dependent changes in the diffusion path length and surface area. Hydrophilic polymers are widely used in controlled release systems due to their favorable functionality. At the molecular level, the drug release rate from polymer matrix is determined by the polymer swelling front, drug dissolution diffusion, and matrix erosion. These occur by the interaction of water molecules with polymer matrix and drug molecules. Enhancing the mobility of the polymer chains and diffusing of the drug out from such polymer matrices could be done by inclusion of different types of excipients at different concentrations. Chitosan, a linear binary heteropolysaccharide, is composed of β-1,4-linked glucosamine (GlcN) with various degrees of *N*-acetylation of GlcN residues[1-5]. Chitosan occurs naturally in some microorganisms, yeast and fungi [6-8]. It is a non-toxic, biocompatible and biodegradable natural polymer of high molecular weight (~500,000 kDa) [9, 10]. It is the second most common polysaccharide occurring in nature after cellulose. Chitosan is prepared by alkaline *N*-deacetylation of chitin using concentrated sodium hydroxide (NaOH) solutions at high temperature for a long period of time [1, 11]. Another approach to produce chitosan is by enzymatic *N*-deacetylation under relatively mild conditions. [12-15] The commercially available chitosan is mostly derived by alkaline *N*-deacetylation from chitin of crustaceans because it is easily obtainable from the shells of crabs, shrimps, lobsters and krill [16, 17]. The degree of deacetylation (DD) and molecular weight (MW) are two fundamental parameters that can affect the properties and functionality of chitosan [11, 13, 18]. These properties include solubility [12, 19, 20], viscosity [10], reactivity such as heavy metal ion chelation [21] and proteinaceous material coagulation, loading (enzyme-loaded) properties and film properties such as tensile strength, elasticity, elongation and moisture absorption [22-27]. With the apparent pKa value of the amino group of about 6.5, chitosan is only soluble in aqueous acidic solutions and insoluble in water and alkaline solutions [24].

HPMC is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery system. The transport phenomena involved in drug release from the HPMC matrices are complex, because the micro and macrostructure of HPMC exposed to water is strongly time dependent. Upon contact with gastrointestinal fluid. HPMC swells significantly and finally

dissolves. Numerous studies have been reported in the literature investigating the transport mechanisms and trying to predict the resulting drug release kinetics quantitatively.[28, 29]

Aceclofenac (2-[(2, 6-dichlorophenyl) amine] phenylacetoxyacetic acid) is an orally effective non-steroidal anti-inflammatory drug (NSAID) of phenyl acetic acid group [30-32]. Aceclofenac appears to be particularly well-tolerated among the NSAIDs, with a lower incidence of gastrointestinal adverse effects [32, 33]. Unfortunately, aceclofenac suffers from low aqueous solubility (0.058 μg/ml), leading to poor dissolution and insufficient oral bioavailability. Aceclofenac is an example of BSC class II compound, its oral bioavailability is determined by dissolution rate in the gastrointestinal tract [34-37]. Therefore, the improvement of aceclofenac dissolution is an important issue for enhancing its bioavailability and therapeutic efficacy.

In view of a wider research project to develop matrix tablets of aceclofenac with varying concentration of chitosan along with different grades available, the purpose of this study was to investigate the influence of the excipients type on matrix hydration, erosion and drug release from matrix systems with HPMC as co-polymer.

MATERIALS AND METHOD

Materials:

Aceclofenac was obtained as gift sample from Aarti Drugs, Mumbai. Chitosan A, B, C, D and E 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.

Table I: **Grades of Chitosan:**

Chitosan	**Degree of Deacetylation (%)**	**Viscosity** (cps)
A	84.14	37
B	88.42	93
C	89.37	51
D	92.70	52
E	96.49	47

Preparation of Matrix Tablets using Wet granulation method:

Several lots of matrix tablets with weight of 250 mg were prepared, each containing 100 mg aceclofenac as drug along with HPMC, as polymeric matrix materials in combination with chitosan A, B, C, D and E (Table I). Matrix tablets were prepared by wet granulation technique. The composition of each tablet with varying conc. of chitosan grade A, B, C, D and E along with HPMC is shown in Table 1. All the ingredients along with drug were separately weighed and sifted using mesh no. 40. The dry mixture was granulated with starch paste, dried in the tray drier

at the temperature of 40-50^{0}C. The dried granules were passed through mesh no. 24. The dried granules were blended for ten minutes and the above blend was lubricated with Magnesium stearate, talc for two minutes. The powder blends were evaluated for the flow properties as pre compressional parameters and were found to be in good agreement with the standards. The evaluated lubricated granules were compressed on 10-station tablet compression machine using respective punches (Karnavati Co, Ahmedabad, India), to get tablets of 250 mg each. A minimum of fifty tablets were prepared for each batch.

Table 1: Formulation of Aceclofenac matrix tablets containing Chitosan A/B/C/D/E.

Formulation / Contents (mG)	A/B/C/D/E I	A/B/C/D/E II	A/B/C/D/E III	A/B/C/D/E IV	A/B/C/D/E V
Drug	100	100	100	100	100
Chitosan A/B/C/D/E	9.60	19.20	--	19.20	9.60
HPMC	9.60	--	19.20	9.60	19.20
Lactose	87.60	87.60	87.60	78.00	78.00
Starch	14.40	14.40	14.40	14.40	14.40
Talc	9.60	9.60	9.60	9.60	9.60
Mag. Stearate	19.20	19.20	19.20	19.20	19.20

Evaluation of Tablets:

The prepared tablets were evaluated for weight variation, hardness, thickness, *In-vitro* drug release studies and Swelling behavior.

Weight variation test:-

20 tablets were selected at a random and average weight was calculated using an electronic balance. The test was performed according to the official reported method. Then individual tablets were weighed and the weight was compared with an average weight.

Hardness: -

This parameter shows the actual hardness of the tablets. This factor depends on powder compactness and the forces apply during compression. Generally tablet having hardness near 5 is considered as good. But the hardness varies depending upon the type of tablet. It is measured in Kg/cm^2. For each formulation, the hardness of 6 tablets was determined using the Pfizer hardness tester. Pfizer hardness tester was used for the determination of the hardness.

Friability: -

This is one of the important parameter for the compressed tablet. Friability helps to determine the mechanical strength of the tablet. The mechanical strength is important factor for tablet which generally shows capability of tablet to withstand with the force during transportation and handling of tablets. The Friability of the tablets was determined using Roche friabilator.

This instrument consists of a plastic chamber for placing the tablets which is attached to a horizontal axis. The drum has an inside diameter of 287 mm and is about 38 mm in depth, made of a transparent synthetic polymer with polished internal surface. A set of pre weighed tablets [if one tablet weigh 650 mg or less then approx 6.5 g of total weight should be taken and for more than 650 mg/tablet weight, 10 tablets should be taken] are placed in the plastic chamber revolving at 24-25 rpm for 4 min. The tablets are subjected to combined effects of abrasion and shock. The tablets are dropped at a distance of six inches on each revolution.

Preweighed sample of tablets was placed in the friabilitor and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula:

$$F = (1- W0 / W) \times 100$$

Where W0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

Thickness: -

The crown-to-crown thicknesses of five tablets from each batch were determined using a Digital Vernier caliper and average values were calculated.

Disintegration test:

The Disintegration of the designed and developed tablet was studied using Disintegration apparatus. Tablets were placed in distilled water as disintegrating medium at 37±0.5^{o}C.

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

The *In-vitro* dissolution studies were carried out using 8 station USP TDT-08L (Electro lab, Mumbai.) apparatus at 37±0.5^{o}C and at 50 rpm. The dissolution medium consisted of phosphate buffer p^{H} 6.8 for 360 minutes (900 mL). At every interval 10 mL of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed by UV- visible spectrophotometer.

Swelling behaviour of matrix tablets: [38]

The extent of swelling was measured in terms of axial and radial swelling by the tablet. The swelling behavior of formulation was studied using reported method. One tablet from each formulation was kept in a petridish containing pH 6.8 phosphate buffer.

The matrices obtained were circular in shape with 8-mm diameters. Hence, using computer-aided design software, concentric circles were drawn with diameters of 7, 8, 10, 12, 14, 16, 18, 20, 22, 25 and 30 mm. 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 are drawn to measure the increase in the radial direction, which makes it unnecessary to disturb the gel layer that formed, and the diameter of the outermost circle arbitrarily was fixed at 30 mm as the matrices underwent dissolution above this parameter.

The tablet matrix under investigation was placed in the center so that it occupied the innermost circle with a 7-mm diameter.

RESULTS AND DISCUSSION:

Pre compressional parameters:

Some of the Pre compressional parameters of granules are shown in **Table 2**. Bulk density, tapped density, % compressibility (09.560±3.216 to 36.620±1.048), and Hausner's ratio (1.106±0.006 to 1.578±0.045) of the prepared granules are found in good agreement as given in official standards.

Table 2: Pre-compressional evaluation parameters for granules.

Sr. No.	Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Compressibility Index (%)	Hausner's Ratio
1	A I	0.501±0.002	0.554±0.004	09.560±3.216	1.106±0.006
2	B I	0.641±0.003	0.881±0.004	27.24±3.163	1.375±0.005
3	C I	0.532±0.003	0.726±0.005	26.720±1.068	1.365±0.001
4	D I	0.541±0.003	0.833±0.003	35.05±1.654	1.541±0.002
5	E I	0.515±0.002	0.636±0.001	19.020±1.204	1.235±0.054
6	A II	0.527±0.002	0.602±0.001	12.450±1.248	1.142±0.001
7	B II	0.575±0.007	0.855±0.002	32.74±1.457	1.488±0.023
8	C II	0.547±0.004	0.794±0.025	32.97±1.042	1.455±0.057
9	D II	0.553±0.050	0.632±0.083	12.500±1.538	1.143±0.051
10	E II	0.545±0.045	0.860±0.004	36.620±1.048	1.578±0.045
11	A III	0.502±0.013	0.775±0.005	35.220±1.078	1.545±0.003
12	B III	0.566±0.006	0.875±0.004	35.31±1.238	1.546±0.160
13	C III	0.506±0.014	0.569±0.016	11.070±1.045	1.125±0.021
14	D III	0.511±0.063	0.665±0.012	23.15±1.016	1.302±0.004
15	E III	0.508±0.003	0.683±0.048	25.62±1.489	1.346±0.048
16	A IV	0.505±0.013	0.701±0.081	27.96±1.010	1.389±0.156
17	B IV	0.584±0.0058	0.908±0.054	35.68±1.104	1.555±0.041
18	C IV	0.514±0.035	0.576±0.078	10.76±1.848	1.121±0.010
19	D IV	0.515±0.043	0.698±0.051	26.21±1.768	1.356±0.201
20	E IV	0.511±0.023	0.702±0.048	27.20±1.193	1.374±0.057
21	AV	0.510±0.012	0.665±0.040	23.30±1.451	1.305±0.047
22	B V	0.545±0.004	0.613±0.013	11.09±1.044	1.125±0.015
23	C V	0.521±0.014	0.682±0.058	23.60±1.489	1.310±0.030
24	D V	0.516±0.019	0.712±0.087	27.52±1.146	1.381±0.045
25	E V	0.515±0.003	0.692±0.041	25.57±1.123	1.345±0.012

Post compressional parameters:

Table 3 shows post compressional parameters i. e. hardness (4.036±0.05 to 5.947±0.169 kg/cm^2), friability (0.1±0.036 to 0.9±0.143%), weight variation (0.125±0.646 to 0.846±0.354) and thickness (3.16±0.101 to 4.65±0.523 mm). Drug content was found to be (97.12±0.27 to 99.66±0.52%) within the acceptable official limits.

Table 3: Post-compressional evaluation parameters for developed formulations

Sr. No.	Formulation	Weight Variation (%) (±SD)	Thickness (mm.) (±SD)	Friability (%) (±SD)	Hardness (Kg./cm^2) (±SD)	Drug content (%)(±SD)
1	A I	0.151±0.165	4.32±0.125	0.1±0.187	4.036±0.05	97.56±1.73
2	B I	0.202±0.223	4.20±0.123	0.1±0.163	5.163±0.665	97.63±2.35
3	C I	0.423±0.107	4.23±0.214	0.2±0.369	5.115 ± 0.162	98.76±1.65
4	D I	0.725±0.040	4.13±0.363	0.2±0.353	5.652±0.262	99.43±1.66
5	E I	0.247±0.516	3.46±0.221	0.2±0.620	4.165±0.546	98.45±2.65
6	A II	0.215±0.035	4.40±0.141	0.1±0.165	4.546±0.521	97.81±2.98
7	B II	0.584±0.253	4.54±0.110	0.7±0.202	4.163±0.453	98.32±3.01
8	C II	0.532±0.321	4.28±0.643	0.4±0.601	5.214 ± 0.135	98.79±2.58
9	D II	0.513±0.840	4.36±0.303	0.4±0.415	5.563±0.136	98.56±1.99
10	E II	0.218±0.535	4.26±0.100	0.5±0.463	4.620±0.164	99.10±1.70
11	A III	0.251±0.135	4.38±0.233	0.1±0.189	4.641±0.427	99.42±2.00
12	B III	0.846±0.354	3.81±0.043	0.5±0.161	5.127±0.156	98.09±2.67
13	C III	0.469±0.452	4.12±0.464	0.1±0.068	5.016 ± 0.148	97.45±0.73
14	D III	0.125±0.646	3.36±0.312	0.8±0.684	4.451±0.468	98.00±0.67
15	E III	0.523±0.157	3.74±0.347	0.2±0.187	4.538±0.199	98.41±0.65
16	A IV	0.106±0.102	3.68±0.222	0.1±0.247	4.461±0.365	97.12±0.27
17	B IV	0.500±0.389	3.16±0.101	0.5±0.162	4.673±0.543	99.66±0.52
18	C IV	0.342±0.335	4.32±0.109	0.3±0.115	5.146 ± 0.194	98.25±2.32
19	D IV	0.542±0.153	3.52±0.169	0.8±0.653	4.620±0.164	99.43±0.96
20	E IV	0.532±0.045	4.36±0.141	0.9±0.143	4.469±0.489	99.23±1.65
21	AV	0.518±0.405	4.29±0.412	0.5±0.267	4.616±0.146	98.52±1.92
22	B V	0.503±0.123	3.54±0.207	0.3±0.141	5.460±0.064	97.51±1.59
23	C V	0.636±0.461	4.42±0.172	0.1±0.036	4.620±0.164	98.65±2.15
24	D V	0.538±0.307	4.10±0.220	0.2±0.104	5.947±0.169	99.35±1.95
25	E V	0.357±0.472	4.65±0.523	0.1±0.101	4.616±0.196	99.65±1.87

The swelling in axial and radial direction was studied and the data normalized by calculating R_t/R_o for the radial direction and A_t/A_o for the axial direction respectively, where R_o and A_o are the dimensions at time =0; R_t and A_t are the dimensions at time = t (Table 4).

The graphs were plotted for:

1. Radial swelling
2. Axial swelling

It was observed that Chitosan matrices preferentially undergo radial swelling as compared to axial swelling. This could be attributed to the acetyl substitution on the polymeric backbone. This substitution would be contributing towards radial relaxation favorably than the axial one.

It can be observed from the graphs that in certain cases as time increases, the radial swelling also increases. This is especially the case with the tablets having HPMC K15M (A I-E I, A III-E III, A IV-E IV, A V-E V)

This is because 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. The chains, which were initially fixed in their positions, are now able to move and undergo reptational motion.

Table 4: Normalized values for Axial and Radial Swelling (AI-EV).

Sr. No.	Formulation	Axial Swelling	Radial Swelling
1	A I	1.5	1.325
2	B I	2.1	1.854
3	C I	1.1	1.644
4	D I	2.2	1.689
5	E I	2.3	1.675
6	A II	1.6	1.653
7	B II	2.8	1.433
8	C II	1.4	1.313
9	D II	1.5	1.375
10	E II	1.2	1.35
11	A III	1.5	1.354
12	B III	2.2	1.632
13	C III	1.6	1.6
14	D III	2	1.6
15	E III	1.5	1.738
16	A IV	1	1.755
17	B IV	2.7	1.828
18	C IV	1.5	1.65
19	D IV	2	1.538
20	E IV	2	1.6
21	AV	1.5	1.641
22	B V	2	1.312
23	C V	2	1.3
24	D V	1.5	1.363
25	E V	2	1.75

Also, in some cases, there is a variation observed in the readings at different time periods in which initial readings have greater value than the final ones (A V- E V). This can be explained on the same fact that after transition from glassy to rubbery state, the outermost regions of the disentangled polymeric chain becomes so relaxed that they are ultimately dissolved in the aqueous medium. This is facilitated further by presence of HPMC.

If the axial and radial swellings of the same tablet are considered, it is observed that the tablet radial diameter increases substantially over a period of time while the axial length remains fairly

constant (C I, E II, A IV, A V). This may be attributed to the more concentration of Chitosan than HPMC in the developed formulations .

Several important features regarding the development of the gel layer are noted. First, a continuous increase in the gel layer thickness is observed irrespective of the polymer viscosity grade or substitution ratio. Slight decrease in the apparent gel layer thickness is attributable to the dissolution of the outermost, totally relaxed polymer. Second, the gel layer thickness and its growth rate depend on the polymer-viscosity grade. The differences in the gel thickness are due to the presence of undissolved HPMC or other excipients at the gel-core interface. Third, there are three distinct gel growth phases that can be readily identified.

However, since the study was unidirectional, this final stage is somewhat obscure.

Qualitatively, when a study is carried out bi-directionally, a sharp decrease in the rate of front movement is observed at the very early swelling stage due to an increase of the diffusional resistance as the diffusion path length increases. During the second stage, the penetration front moves at a relatively constant rate due to the attainment of a pseudo steady state of gel formation. In the final swelling stage, the gel layer thickness sharply increases due to a fast increase of water diffusivity as both the fronts meet (Table 5 - 9).

In terms of transition from glassy to rubbery state, the outermost layer undergoes this transition rapidly. The waterfront moves ahead, leaving behind the polymer in rubbery state. As the relaxation increases, chains become more and more mobile and ultimately dissolve in the medium.

Dissolution study of all the formulations was carried out using 8 station USP TDT-08L (Electro lab, Mumbai.) apparatus at 37±0.5^{o}C and 50 rpm. The dissolution medium consisted of phosphate buffer pH 6.8 for 360 minutes (900 mL) (Table 10 - 14).

Table 5: Radial Swelling with Time for A I- E I.

	Radial Swelling				
Time (min)	**AI**	**BI**	**CI**	**DI**	**EI**
0	1	1	1	1	1
30	1.034	1.064	1.135	1.188	1.175
60	1.121	1.221	1.251	1.338	1.275
90	1.223	1.391	1.433	1.378	1.425
180	1.271	1.645	1.532	1.55	1.5
360	1.325	1.854	1.644	1.689	1.675

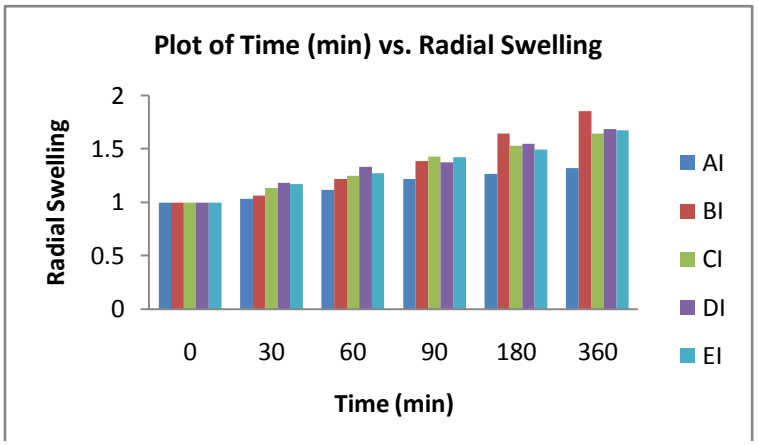

Figure 1: Plot of Time (min) vs. Radial Swelling for A I-E I.

Table 6: Radial Swelling with Time for A II- E II.

	Radial Swelling				
Time (min)	**AII**	**BII**	**CII**	**DII**	**EII**
0	1	1	1	1	1
30	1.161	1.033	1.082	1.075	1.05
60	1.26	1.112	1.181	1.123	1.125
90	1.422	1.185	1.235	1.225	1.225
180	1.494	1.264	1.263	1.275	1.263
360	1.653	1.433	1.313	1.375	1.35

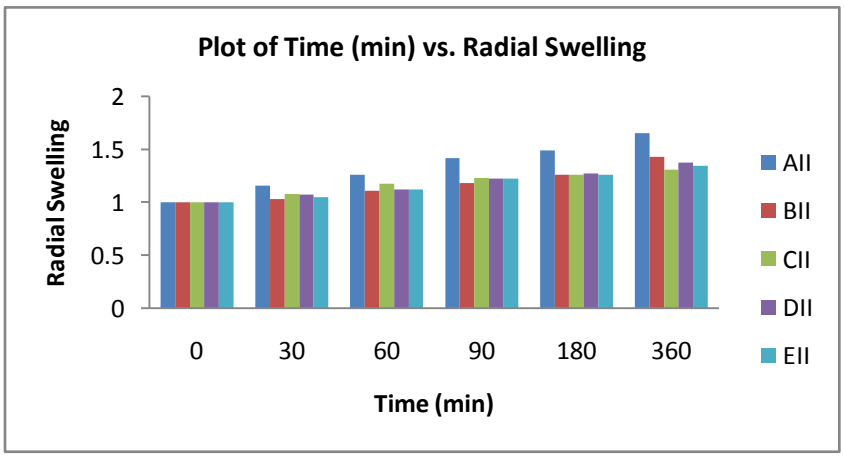

Figure 2: Plot of Time (min) vs. Radial Swelling for A II-E II.

Table 7: Radial Swelling with Time for A III- E III.

	Radial Swelling				
Time (min)	**AIII**	**BIII**	**CIII**	**DIII**	**EIII**
0	1	1	1	1	1
30	1.054	1.084	1.138	1.112	1.15
60	1.155	1.186	1.25	1.262	1.325
90	1.231	1.265	1.338	1.35	1.438
180	1.272	1.381	1.45	1.438	1.525
360	1.354	1.632	1.6	1.6	1.738

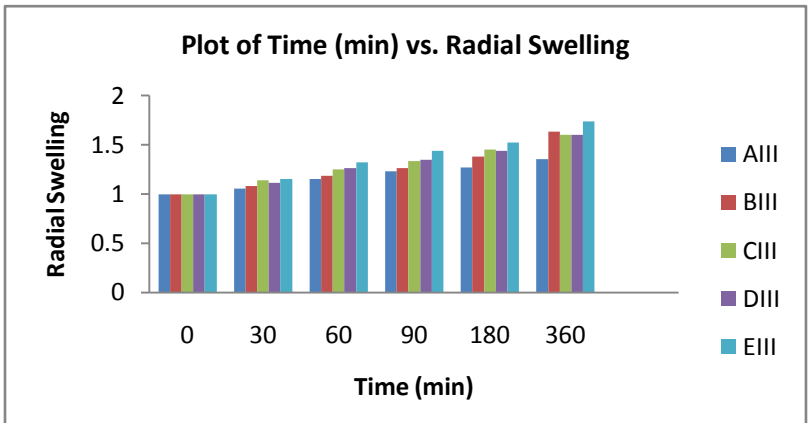

Figure 3: Plot of Time (min) vs. Radial Swelling for A III-E III.

Table 8: Radial Swelling with Time for A IV- E IV.

	Radial Swelling				
Time (min)	**AIV**	**BIV**	**CIV**	**DIV**	**EIV**
0	1	1	1	1	1
30	1.136	1.452	1.175	1.075	1.075
60	1.295	1.564	1.259	1.2	1.225
90	1.362	1.823	1.372	1.338	1.3
180	1.51	1.825	1.475	1.4	1.413
360	1.755	1.828	1.65	1.538	1.6

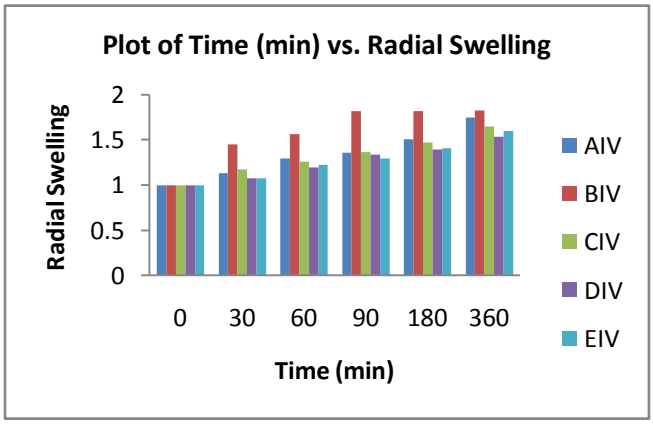

Figure 4: Plot of Time (min) vs. Radial Swelling for A IV-E IV.

Table 9: Radial Swelling with Time for A V- E V.

	Radial Swelling				
Time (min)	**AV**	**BV**	**CV**	**DV**	**EV**
0	1	1	1	1	1
30	1.124	1.047	1.05	1.05	1.163
60	1.247	1.168	1.138	1.15	1.3
90	1.354	1.197	1.163	1.234	1.375
180	1.462	1.264	1.225	1.3	1.638
360	1.641	1.312	1.3	1.363	1.75

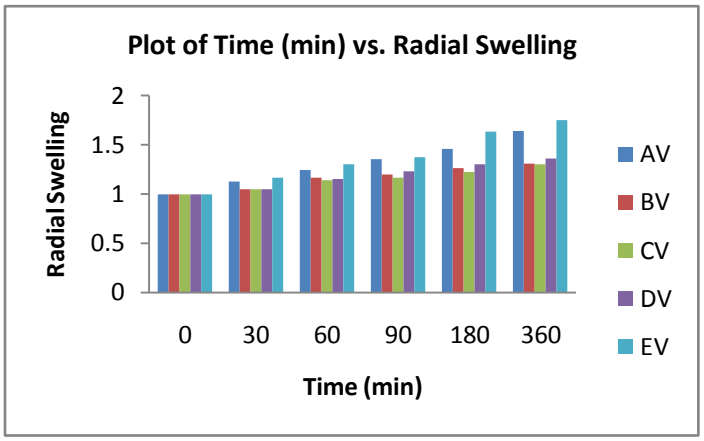

Figure 5: Plot of Time (min) vs. Radial Swelling for A V-E V.

It is observed that the drug release rate remains unchanged irrespective of the viscocity grades for the same degree of deacetylation of the Chitosan in presence of HPMC in same conc. With that of Chitosan (1:1) e.g. B I & C I.

Table 10: Drug release (%) with time of matrix containing Chitosan A-E with HPMC.

Time (Minute)	Drug release (%)				
	A I	B I	C I	D I	E I
0	0	0	0	0	0
30	100	88.83	98.51	76.69	89.37
60	--	100	100	89.34	100
120	--	--	--	100	--
180	--	--	--	--	--
240	--	--	--	--	--
300	--	--	--	--	--

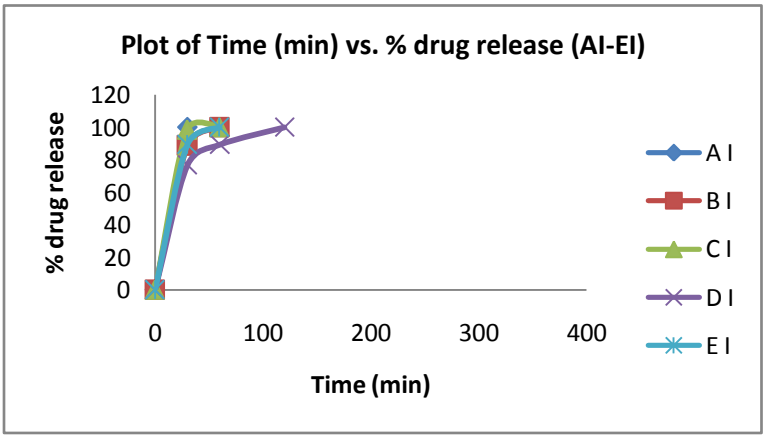

Figure 6: Plot of time vs. % drug release for AI-EI.

When only Chitosan is used in absence of HPMC it was observed that the drug release rate decreases as in case of formulations having Chitosan with DAD 84% and low viscosity grade whereas drug release rate substantially increases in case of formulations containing Chitosan

having more DAD as 90 % (B II, C II & E II). This might be attributed to the presence of less number of acetyl groups attached. In certain formulations it was noted that the drug release rate sustains because of HPMC alone (A III - E III).

Table 11: Drug release (%) with time of matrix containing Chitosan A-E without HPMC.

Time (Minute)	Drug release (%)				
	A II	B II	C II	D II	E II
0	0	0	0	0	0
30	68.12	74.85	96.09	52.8	95.82
60	73.47	89.62	100	74.33	100
120	76.28	100	--	87.35	--
180	89.99	--	--	100	--
240	100	--	--	--	--
300	--	--	--	--	--

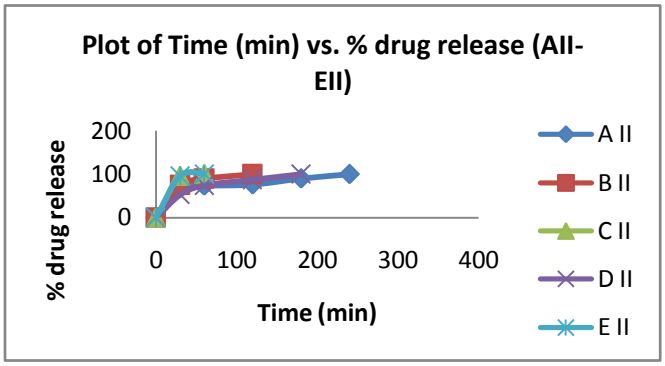

Figure 7: Plot of time vs. % drug release for AII-EII.

Table 12: Drug release (%) of matrix containing HPMC without Chitosan A-E.

Time (Minute)	Drug release (%)				
	A III	B III	C III	D III	E III
0	0	0	0	0	0
30	98.24	100	67.25	71.06	65.21
60	100	100	74.31	81.03	75.66
120	--	--	78.71	86.93	80.76
180	--	--	89.58	90.04	86.32
240	--	--	100	100	100
300	--	--	--	--	--

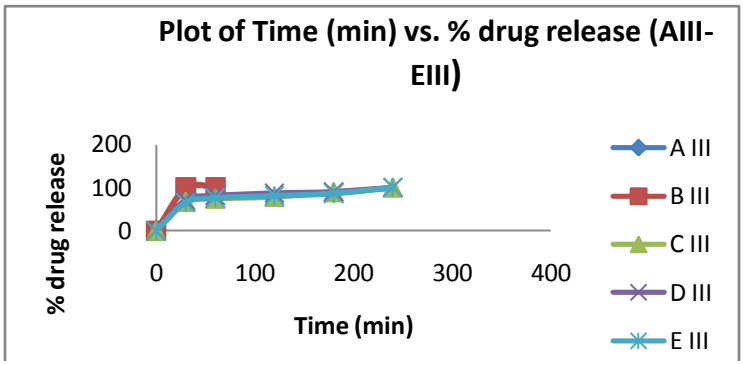

Figure 8: Plot of time vs. % drug release for AIII-EIII.

It was further observed that the drug release rate is substantially extended when DAD of Chitosan is less than 90 % and concentration of Chitosan and HPMC is in the ratio 2:1 (A IV, B IV). However drug release rate increases at higher % DAD (C IV – E IV). This could be attributed to the increased number of acetyl group in the Chitosan polymer chain.

Table 13: Drug release (%) of matrix containing Chitosan A-E + HPMC (2:1).

Time (Minute)	Drug release (%)				
	A IV	B IV	C IV	D IV	E IV
0	0	0	0	0	0
30	57.23	65	98.25	84.15	98.45
60	63.72	69.45	100	90.63	100
120	69.25	78.32	--	95.19	--
180	79.12	82.65	--	100	--
240	84.26	86.26	--	--	--
300	86.32	87.68	--	--	--
360	100	100	--	--	--

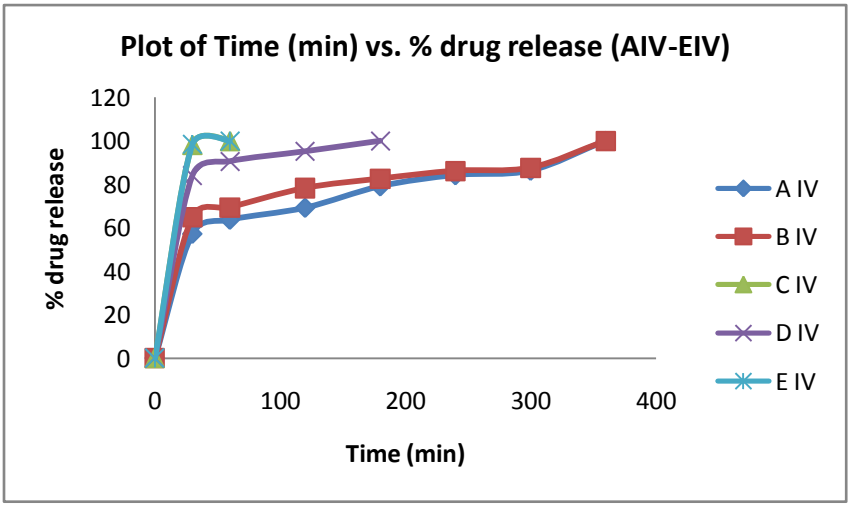

Figure 9: Plot of time vs. % drug release for AIV-EIV.

It was worth noting that the change in concentration of Chitosan to HPMC from 2:1 to 1:2 brought a sudden change in the drug release pattern. It was observed that the formulations shown

sustained drug release. The increased level of HPMC in the formulation brings about the sustained effect on drug release (A V – E V).

Table 14: Drug release (%) of matrix containing Chitosan A-E + HPMC (1:2).

Time (Minute)	Drug release (%) A V	B V	C V	D V	E V
0	0	0	0	0	0
30	34.38	30.33	31.19	30.86	30.33
60	59.05	39.03	50.07	36.94	39.03
120	78.07	66.33	77.32	79.9	76.46
180	84.56	76.46	88.71	86.34	81.9
240	97.04	81.09	96.30	94.6	100
300	100	100	100	100	--
360	--	--	--	--	--

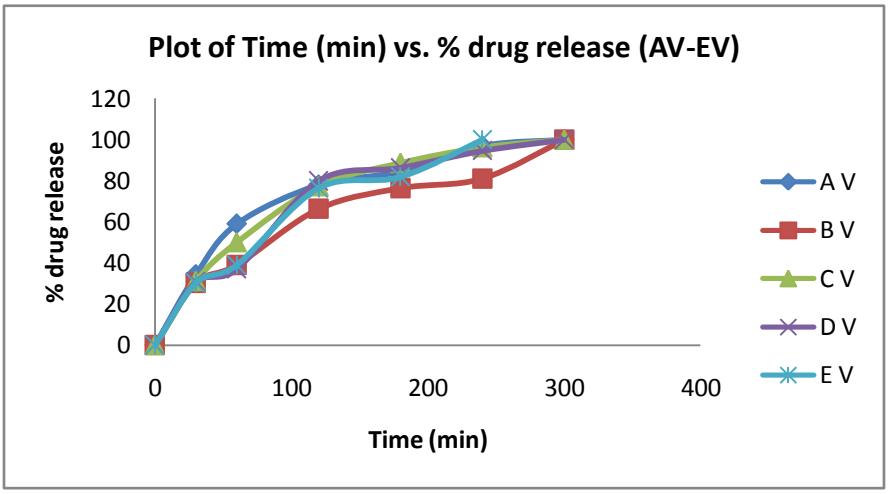

Figure 10 :Plotoftimevs.% drugrelease for AV-EV

Table 15: Model fitting for the developed formulations.

Code	Zero order		First order		Matrix		Peppas			Hixon Crowel	
	R	K	R	K	R	K	R	n	K	R	K
A1	0.9306	0.3420	0.9743	-0.0071	**0.9891**	4.9208	0.9790	2.1021	0.6683	0.9871	-0.0018
AII	0.9043	0.2245	0.7562	-0.0050	0.7575	2.8978	**0.9182**	0.0028	1.8190	0.8091	-0.0012
AIII	0.6149	0.7072	-	-	0.8265	10.6355	**0.8699**	0.9154	0.9824	0.6209	-0.0081
AIV	0.9721	0.2975	0.8097	-0.0089	0.8461	3.9362	**0.9902**	0.0601	1.2821	0.8891	-0.0018
AV	-	0.4992	-	-	0.7245	7.7886	0.8436	33.2403	0.2164	**0.9169**	-0.0051
BI	-	0.3917	-	-	0.4546	6.8813	0.7454	0.0368	82.0034	-	-0.0039
BII	0.9856	0.3003	0.9236	-0.0064	0.8723	4.0115	**0.9902**	0.0301	1.4282	0.9535	-0.0016
BIII	-	0.4410	-	-0.0114	0.1262	7.0835	**0.7667**	59.5008	0.0794	-	-0.0026
BIV	0.9782	0.2772	0.9150	-0.0054	0.8517	3.6596	**0.9804**	0.0017	1.9528	0.9464	-0.0014
BV	-	0.4166	0.4396	-0.0099	0.8308	6.4404	**0.8882**	17.2998	0.3075	0.3820	-0.0024
CI	-	0.3926	-	-	0.3079	6.9224	**0.7454**	0.0047	97.5167	-	-0.0039
CII	0.9637	0.2680	0.9352	-0.0048	0.8376	3.5310	**0.9734**	0.0007	2.1139	0.9500	-0.0013
CIII	-	0.4165	-	-0.0092	0.6413	6.5808	**0.8886**	33.9214	0.1788	-	-0.0023
CIV	**0.9742**	0.3371	0.8374	-0.0115	0.8694	4.5255	0.9670	0.0976	1.2136	0.9297	-0.0022

CV	-	0.5557	-	-	0.7554	8.6105	**0.9422**	44.6076	0.1753	0.8681	-0.0067
DI	-	0.3886	-	-	0.6541	6.7657	**0.9016**	0.1016	57.3871	0.5648	-0.0038
DII	-	0.4720	-	-	0.7768	7.2747	**0.7667**	14.7373	0.3651	0.5552	-0.0043
DIII	-	0.3764	-	-	0.7721	6.4773	**0.9840**	0.1406	44.5894	0.8889	-0.0033
DIV	-	0.3878	-	-	0.5947	6.7643	**0.9670**	0.0718	67.0268	0.6755	-0.0037
DV	0.8400	0.1825	0.9194	-0.0023	0.9787	2.6664	**0.9690**	3.4227	0.4488	0.8980	-0.0007
EI	-	0.3917	-	-	0.4477	6.8836	**0.7454**	0.0349	82.8401	-	-0.0039
EII	0.0926	0.7995	-	-	0.7057	12.4806	**0.7881**	4.7218	0.6911	-	-0.0074
EIII	-	0.3705	-	-	0.8405	6.3292	**0.9786**	0.1789	35.5042	0.9176	0.0033
EIV	0.9357	0.5093	-	-	0.9911	7.3198	**0.9990**	4.6327	0.5880	0.9531	-0.0052
EV	0.8278	0.3567	-	-	**0.9793**	5.8786	0.9738	0.5281	5.0887	0.9604	-0.0032

n value in pappas model for drug release is an exponent showing the relation between the time and drug release. In other words, it depicts the drug release pattern. Generally, matrix type of release indicates that the drug release varies according to square root of time while first order release profile shows dependence on drug concentration. Zero order release is independent of drug concentration in the system.

The changes in n values indicate change in the mechanism of drug release. n value of 0.5 or close to 0.5 indicates matrix release wherein the drug is embedded in the polymer matrix and drug release occurs by process of diffusion and erosion. n values below 0.5 and towards 0 indicate drug release occuring predominantly by process of diffusion. This is a characteristic of membrane coated, reservoir systems. n value above 0.5 but below 1 indicate case II transport that is, the release is governed by swelling, diffusion and erosion of polymer.

It is observed that almost all the formulations which contain chitosan along with HPMC follow Peppas model for the drug release from the matrices except AI, AV and C IV,attributed to Formulations having **n** values close to 0, release become increasingly matrix type. 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 playes very important role. the disruption of release controlling mechanism leads to significant changes in n values. For formulations the n value drastically changes indicating that the release becomes progressively first order, a characteristic of immediate release dosage forms.

For HPMC matrix, the n value in Power law equation is closer to 0.5 indicating Higuchi or Matrix pattern. For 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 HPMC matrix.

It is observed that the drug release rate remains unchanged irrespective of the viscosity grades for the same degree of deacetylation of the Chitosan in presence of HPMC in same conc. With that of Chitosan (1:1) e.g. B I & C I.

When only Chitosan is used in absence of HPMC it was observed that the drug release rate decreases as in case of formulations having Chitosan with DAD 84% and low viscosity grade whereas drug release rate substantially increases in case of formulations containing Chitosan having more DAD as 90 % (B II, C II & E II). This might be attributed to the presence of less number of acetyl groups attached. In certain formulations it was noted that the drug release rate sustains because of HPMC alone (A III - E III).

It was further observed that the drug release rate is substantially extended when DAD of Chitosan is less than 90 % and concentration of Chitosan and HPMC is in the ratio 2:1 (A IV, B IV). However drug release rate increases at higher % DAD (C IV – E IV). This could be attributed to the increased number of acetyl group in the Chitosan polymer chain.

It was worth noting that the change in concentration of Chitosan to HPMC from 2:1 to 1:2 brought a sudden change in the drug release pattern. It was observed that the formulations shown sustained drug release. The increased level of HPMC in the formulation brings about the sustained effect on drug release (A V – E V).

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CONCLUSION:

Several important features regarding the development of the gel layer are noted and it is concluded that Increase in the gel layer thickness does not depend on the polymer viscosity grade or substitution ratio. The differences in the gel thickness are due to the presence of undissolved HPMC or other excipients at the gel-core interface. From the results of the drug release studies, it was concluded that, The drug release rate remains unchanged irrespective of the viscosity grades for the same degree of deacetylation (DAD) of the Chitosan in presence of HPMC in same concentration with that of Chitosan (1:1) The drug release rate is substantially extended when degree of deacetylation DAD of Chitosan is less than 90 % and concentration of Chitosan and HPMC is in the ratio 2:1. However drug release rate increases at higher % DAD.

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