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FORMULATION AND EVALUATION OF HYDROGEL BASED ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM FOR ACYCLOVIR

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ABSTRACT

The goal of this study was to develop hydrogel based oral controlled release acyclovir matrix tablet capable of delivering drug at prolonged rate, suitable for once a day administration. The highly swollen hydrogel (CHGL) was prepared by cross linking the chitosan with glutaraldehyde (crosslinking agent). It was analysed by FITR spectra. Among 10 formulations, 6 formulations containing Hydrogel and HPMC K 100 in different ratio were prepared by wet granulation method using suitable polymers. The prepared matrix tablets were evaluated for pre compression and post compression parameters. The compatibility study was done by FTIR method. *In- vitro* release study was performed for 12 hours by using USP type-2 dissolution apparatus. SEM revealed that surface of tablet appeared porous with polymeric erosion after the dissolution testing. The drug release was found to be best fitted by Higuchi square root model. The formulation F_8 has shown best results for all parameters as per pharmacopeia standard.

KEYWORDS: Oral controlled drug delivery system, Cross linked chitosan (CHGL), hydroxy propyl methyl cellulose (HPMC).

INTRODUCTION

Oral administration is a common convenient method for introducing drug in to systemic circulation because of ease of administration, pain free, accurate dosage and low cost therapy. But drugs that have low half life and chronic diseases that require long term drug therapy, conventional medications should be given in multiple doses, which results in patient incompliance and adverse effects. This could be resolved by designing controlled release drug delivery systems.[1]

Controlled release drug delivery systems provide uniform concentration of drug to the absorption site and thus allows the maintenance of plasma concentration within the therapeutic range which minimizes not only the side effects but also the frequency of administration. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile. HPMC is the best choice for the formulation of hydrophilic matrix system.[2]

Hydrogels deliver the drug molecules to the gastro intestinal tract for prolonging the drug release and to improve the absorption. These drug delivery systems maintain its uniformity throughout the stomach and swells rapidly in the stomach environment for a controlled drug release. Hydrogels are called as three dimensional hydrophilic networks which can absorb large amount of water or biological fluid, they are chemically stable, may undergo degradation, finally disintegrate and dissolve in water or biological fluids. Recently, much importance has been given to the preparation of hydrogels from natural polymers. Among natural polymers, chitosan has been reported to be good for synthesizing hydrogels because of its greater cross linking ability.[3]

Acyclovir, a guanosine analogue, is a potent antiviral drug most commonly used in the treatment of herpes simplex, herpes zoster and varicella zoster infection.The highly selective antiviral action of acyclovir causes termination of the deoxyribonucleic acid (DNA) chain and leads to irreversible inactivation of viral DNA polymerase. Conventional acyclovir tablets have major drawbacks such as short biological half life (2.5 h), narrow absorption window in gastrointestinal tract, requirement of frequent administration.[4] To overcome the oral absorption barrier, some prodrugs with enhanced solubility (such as valacyclovir) and different delivery systems such as matrix tablets and polymeric films have been reported to improve its bioavailability.[5&6]

The rationale of the current investigation was focused on controlling the drug delivery and thereby improving the

oral absorption of acyclovir and decreasing dosing frequency.

MATERIALS AND METHODS

Materials

Acyclovir was received as a gift sample from Zydus Cadila Healthcare Ltd Goa, Chitosan was obtained from Himedia Laboratories Pvt Ltd Banglore, Hydroxy propyl methyl cellulose (HPMC K100) gift sample from Ontop pharmaceutical Pvt Ltd Banglore, Acetone and Glutaraldehyde from SD fine Chem Limitsd Warli Road Mumbai. Talc from Fisher Scientific Mumbai and magnesium stearate purchased from Loba chemie Mumbai.

Methods

Preparation of cross linked chitosan (CHGL) with Glutaraldehyde

Chitosan solution (2% w/v) was prepared by stirring in 2% (v/v) aqueous acetic acid using a homogenizer until the chitosan dissolves completely. To this solution, 0.1M glutaraldehyde (GL) 20% w/w of dry chitosan and 0.5 ml of 0.1 N HCL were added and stirred for 1 h at 50 ^{o}C. Acetone was added and precipitated hydrogel (CHGL) was repeatedly washed with distilled water to remove any un-reacted material. Further it was dried at 40 ^{o}C for 24 h; powdered and stored in a well closed container.

Preparation of CHGL and HPMC K100 blend hydrogel matrix tablet

The CHGL – HPMC K100 matrix tablets were prepared by conventional wet granulation method. Accurately weighed quantities of Acyclovir, crossed linked chitosan, HPMC K 100 and microcrystalline cellulose (MCC) were passed through sieve ♯ 80 and mixed to get uniform mass. To this sufficient amount of binding agent (starch paste 5% w/v) was added. After required cohesiveness was attained, the mass was sieved through 22/44 mesh. The granules were dried at 40 ^{o}C for 12 h and then kept in a desiccator for 12 hrs at room temperature. The granules retained on 44 mesh were taken and mixed with 10% of fines, talc and magnesium stearate were added and then compressed in to tablets using a compression machine. Total weight of each tablet was 600 mg to 650 mg which contains 200 mg of Acyclovir. shown in the below table no. 01.

Pre formulation studies[7]

The sample of Acyclovir was evaluated for colour, physical state, solubility and melting point.

FTIR study

FTIR carried out by KBr disc method. The samples were prepared by mixing it thoroughly with potassium bromide. This mixture was then placed in a scanning slot of FTIR spectrophotometer and scanned at range from 400 to 4000 cm^{-1} to obtain FTIR of API.

Pre compression parameters[8]

The flow properties of granules were characterized in terms of angle of repose, Carr's index, and Hausner ratio. The bulk density and tapped density were determined and from this data Carr's index and Hausner ratio were calculated.

Post Compression Parameters[9]

The tablets after punching of every batch were evaluated for thickness, Hardness, Friability, weight variation and drug content.

Swelling Index

The extent o

f swelling was measured in terms of percentage weight gain by the tablet. One tablet from each formulation at triplicate manner was taken and kept in a Petri dish containing 6.8 pH buffer. At the end of 1 hour, the tablet was withdrawn and the excess water was removed by placing the tablet on tissue paper and weighed. Then for every 1 hour, weight of the tablets were noted and the process was continued till the end of 8 hours.

$$\% (S.I.) = \{(Mt) – (Mo)/ (Mo)\} \times 100$$

Where, S.I. = Swelling index

Mt = weight of the swollen tablet at time t

Mo = initial weight of the tablet at time Zero (0)

In vitro drug release studies[10]

In vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electro lab, Mumbai, India) at 50 rpm. The dissolution medium consist of 750 ml of 0.1N HCL (pH 1.2) for 2 hours and then the pH was changed to 6.8 by adding 250 ml of 0.2M solution of tri sodium phosphate dodecahydrate for the rest of dissolution duration. Adjust, if necessary, with 2M hydrochloric acid or 2M sodium hydroxide to a pH 6.8 ± 0.05. The temperature of the dissolution medium was maintained at 37 ± 1 ^{0}C. continue to operate the apparatus for 10 hours. The drug release at different time intervals was measured using an ultraviolet visible spectrophotometer (Shimadzu) at 256 nm (for 2 hrs) and 252.5 nm (for next 10 hrs). *In vitro* drug release can be explained through various pharmacokinetic models to describe the drug release kinetics.

RESULTS AND DISCUSSION

Pre formulation Study

Description

The sample of Acyclovir was found to be white powder having no odour.

Determination of solubility

Acyclovir is freely soluble in dimethyl sulphoxide, slightly soluble in water, very slightly soluble in ethanol. It dissolves in dilute solutions of mineral acids and alkaline hydroxides.

Determination of melting point

Melting point of Acyclovir drug was found to be 252°C.

Compatibility Studies

a) FTIR spectrum to establish cross linking between chitosan & glutaraldehyde.

FTIR analysis: The FTIR spectra of Chitosan and CHGL given in figure 2 and 3 confirms the crosslinking of chitosan with glutaraldehyde. In case of chitosan (CH) the peak at 3363.44 cm^{-1} is assigned for stretching vibration of hydroxyl and amino groups, the peak at 2879.53 cm^{-1} is due to C-H stretching. The band at 1654.63 cm^{-1} is due to C=O stretching and another band around 1319.85 cm^{-1} correspond to N-H bending and the peak at 1257.69 $cm^{-1}$is due to C-O stretching of ether group. While in case of CHGL, peak at 3437.30 cm^{-1} is assigned for starching vibration of hydroxyl group, The peak at 2929.03 cm^{-1} is due to stretching vibrations of –CH group, the peak at 1646.32 cm^{-1} is attributed to carbonyl stretching vibrations of acetamide group, and amine bonds (C=N) formed by crosslinking reaction between the amino groups of chitosan and glutaraldehyde. This peak confirms the formation of schiff base after crosslinking reaction.

b) FTIR to analyse compatibility of Acyclovir with excipients.

FTIR spectra of acyclovir showed characteristic peaks between 3500 cm^{-1} and 2900 cm^{-1} which designates the presence of stretching vibrations of O-H, N-H, and Ar-C-H. the peak due to C=O was also observed at 1716.82 cm^{-1} and the peak due to C=C is observed at 1634.35 cm^{-1}. The IR spectrum of acyclovir matrix tablet prepared using cross linked chitosan show the characteristic bands at 1632.07 cm^{-1} which is due to C=C stretching and all other peaks observed with individual compound remained unaffected in tablet formulation. This confirms the compatibility of acyclovir with excipients in the formulation.

PRE-COMPRESSION STUDY

For the formulations F5-F10, the angle of repose were found in the range of 27.53±0.557 to 31.07±1.095, bulk density for all the formulations were found to be in the range of 0.3623±0.006 to 0.6243±0.008 gm/ml and tapped density were fund to be in the range of 0.4410±0.014 to 0.7043±0.012 gm/ml. For the formulations F5-F10, the carr's index was found to be in the range of 7.667 to 13.36% and Hausner's ratio lie within the range of 1.100 to 1.125. Amongst all the formulations, the formulation F5 to F10 containing cross linked chitosan and HPMC K100 in different ratio have shown the good flow property. The results were depicted in table. No.02.

POST COMPRESSION STUDY

The tablet thickness of all the formulations lies within the range of 4.070 to 4.403 mm, the hardness was found to be in the range of 7.98±0.488 to 9.57±0.390 kg/cm^3, the formulated tablets showed good hardness. the average weight of tablets were found to be in the range of 600.4±0.251 to 650.5±0.208 mg, the % friability was found to be between 0.349±0.095, which was found to be within the official limit the drug content estimation data was found be between 94.58±0.291 to 0.427%. The formulation F5 to F10 containing cross linked chitosan and HPMC K100 in different ratio have shown the good results for post compression studies. The results were depicted in table. No.03.

Swelling Index

Formulation F2 containing drug & plain chitosan showed higher swelling ratios compared to the tablets prepared with cross linked chitosan hydrogel tablets. In case of F5, F6 & F7 containing HPMCK100 to crosslinked chitosan in the ratio1:1, 1:1.3 and 1:1.66 respectively, F7 showed higher swelling index at the end of 8 hrs, where as in case of F8, F9 and F10 formulations containing crosslinked chitosan to HPMC K100 in the ratio 2:1, 2:1.33 and 2:1.66 the higher swelling index was observed with F10. However a steady increase in swelling rate was observed for formulation F8. The results were depicted in table. No.04.

***In-vitro* dissolution study.**

Drug release profile was studied using percentage drug release versus time (hr) plots are shown in figures 7, 8 and 9. Formulations F1, F2, F3, F4 and F5 showed 98.77±0.930, 98.40±0.1312, 96.89±0.8664, 98.86±0.2458 and 71.07±0.7602 release of drug respectively at 15 hrs. Formulations F6, F7, F8, F9 & F10 showed 74.12±0.4136, 76.30±0.3999, 60.58±0.3870, 67.09±0.3292and 84.28±0.6439 respectively. Among all formulations F8 has shown controlled release of drug. This release pattern can be correlated with the swelling rate for the formulation. F8 which contains a hydrophobic polymer i.e. cross-linked chitosan and hydrophilic polymer of high viscosity HPMC K100 showed a steady increase in the swelling rate and the erosion was also slow. The tablet though in the swollen state remained intact up to 8 hrs.

Release Kinetics.

The cross linked hydrogel matrix tablet formulations F7 to F10 have shown matrix release when analysed using PCP- Disso V3 soft ware, the drug release was found to be best fitted by Higuchi square root model (R^2=0.9791 for formulation F8) which implies that release of drug from matrix as a square root of time dependent process and diffusion controlled. The results were depicted in table. No.05.

SEM Analysis.

The surface morphology of hydrogel tablets before and after the dissolution testing was studied using SEM photomicrographs, which are shown in figure 10 and 11.The surface of the hydrogel tablets was smooth and uniform before drug release testing whereas after testing

the surface has became porous with polymeric erosion as

evident from SEM photomicrographs. This indicates that the hydrogel network has undergone swelling and drug might have diffused out through the matrix by polymer chain relaxation and erosion.

Table no: 1 Formulation table.

S. NO.	Ingredients.(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Acyclovir	200	200	200	200	200	200	200	200	200	200
2	Chitosan	---	150	---	---	---	---	---	---	---	---
3	HPMC K 100	---	---	90	---	90	90	90	180	180	180
4	CHGL	---	---	---	180	90	120	150	90	120	150
5	Magnesium stearate	5	5	5	5	5	5	5	5	5	5
6	Talc	10	10	10	10	10	10	10	10	10	10
7	Microcrystalline cellulose	385	235	295	205	205	175	145	165	135	105

Table no: 2 Pre compression parameters of tablets.

Batch no	Bulk density (gm/ml) ±SD	Tapped Density (g/ml)±SD	Compressibily (%)	Hausner's Ratio	Angle of Repose±SD
F_1	0.4203 ±0.017	0.5277 ±0.015	20.23	1.258	27.53 ±0.557
F_2	0.3623 ±0.006	0.4410 ±0.014	17.77	1.199	27.71 ±1.022
F_3	0.3647 ±0.021	0.4973 ±0.015	26.56	1.376	31.07 ±1.095
F_4	0.3783 ±0.020	0.5870 ±0.025	35.18	1.540	30.25 ±1.080
F_5	0.6013 ±0.001	0.6513 ±0.008	7.667	1.083	25.07 ±1.429
F_6	0.6243 ±0.008	0.698 ±0.0176	10.54	1.125	27.98 ±1.429
F_7	0.5850 ±0.012	0.6477 ±0.003	9.674	1.078	21.68 ±1.848
F_8	0.6143 ±0.015	0.7043 ±0.012	10.44	1.156	16.80 ±0.894
F_9	0.6093 ±0.017	0.7043 ±0.012	13.36	1.110	20.21 ±0.859
F_{10}	0.5690 ±0.023	0.6177 ±0.021	9.385	1.100	17.17±0.406

Table no: 3 post compression parameters of tablets.

Batch no	Average Weight (mg) ±SD	Friability% ±SD	Hardness (Kg/cm^2) ±SD	hickness (mm)	%Drug content ±SD
F_1	600.4 ±0.472	0.640 ±0.068	8.80 ±0.695	4.403	97.04±0.921
F_2	600.6 ±0.400	0.349 ±0.095	7.98 ±0.488	4.173	95.22±0.244
F_3	600.8 ±0.416	0.756 ±0.075	9.04 ±0.550	4.317	95.56±0.175
F_4	600.9 ±0.655	0.656 ±0.350	8.50 ±0.267	4.230	94.58±0.291
F_5	600.5 ±0.200	0.983 ±0.134	9.18 ±0.273	4.070	96.61±0.450
F_6	600.9 ±0.300	0.962 ±0.116	8.49 ±0.480	4.133	96.83±0.230
F_7	600.4 ±0.251	0.812 ±0.049	9.07 ±0.406	4.313	96.38±0.353
F_8	650.3 ±0.264	0.630 ±0.053	8.77±0.661	4.393	97.95±0.710
F_9	650.1 ±0.057	0.636 ±0.047	8.24 ±0.384	4.400	98.36±0.427
F_{10}	650.5 ±0.208	0.645 ±0.041	9.57 ±0.390	4.320	97.53±0.830

Table no: 4 Swelling Index of formulations F1 to F10.

Tim Hour	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
1	21.42	32.11	24.17	38.51	38.61	42.64	48.44	36.55	38.71	40.21
2	30.99	52.82	30.62	54.01	51.81	58.49	65.35	43.07	50.08	46.55
3	68.71	58.02	31.95	66.92	52.31	71.24	81.93	61.60	54.53	62.31
4	70.11		34.43	63.37	60.73	85.62	94.24	71.42	61.77	80.01
5			40.06		75.62	90.49	100.98	80.21	79.73	92.93
6			58.31		86.21	101.64	111.72	86.29	88.13	109.61
7			77.64		100.53	112.15	126.73	90.91	100.16	127.38
8			98.58		103.42	128.01	129.58	95.68	102.16	130.37

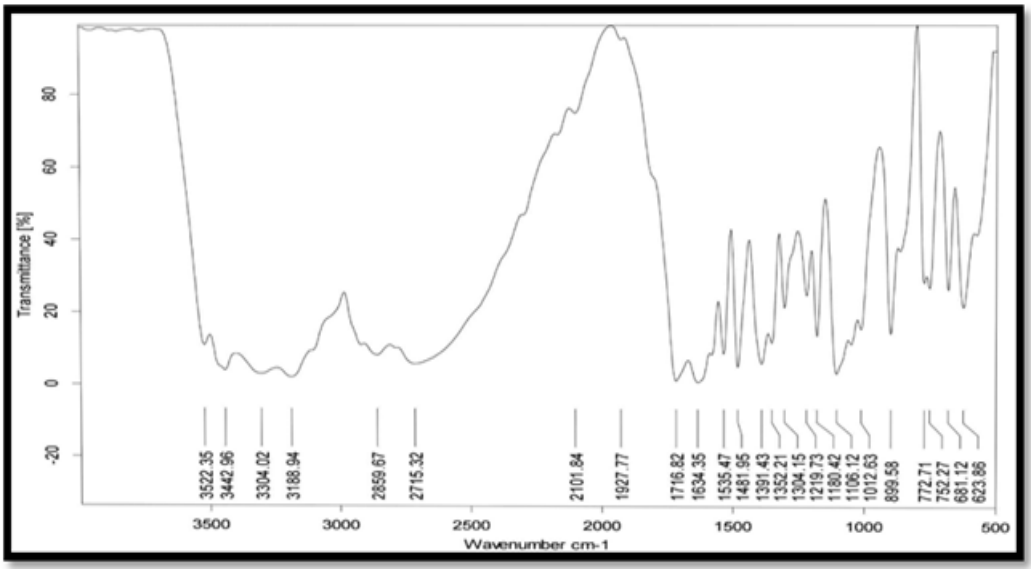

Figure: 1 FTIR spectra of Acyclovir.

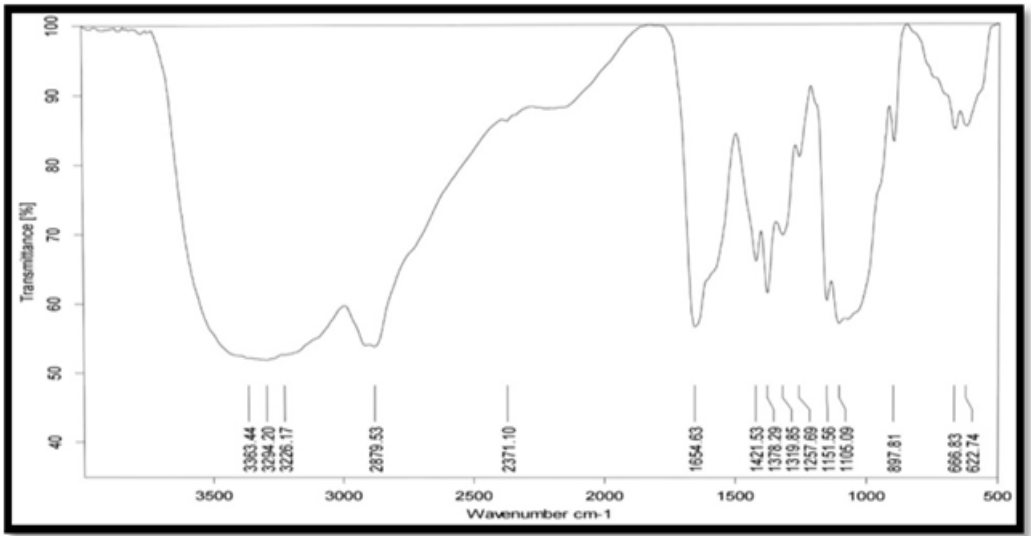

Figure: 2 FTIR spectra of Chitosan.

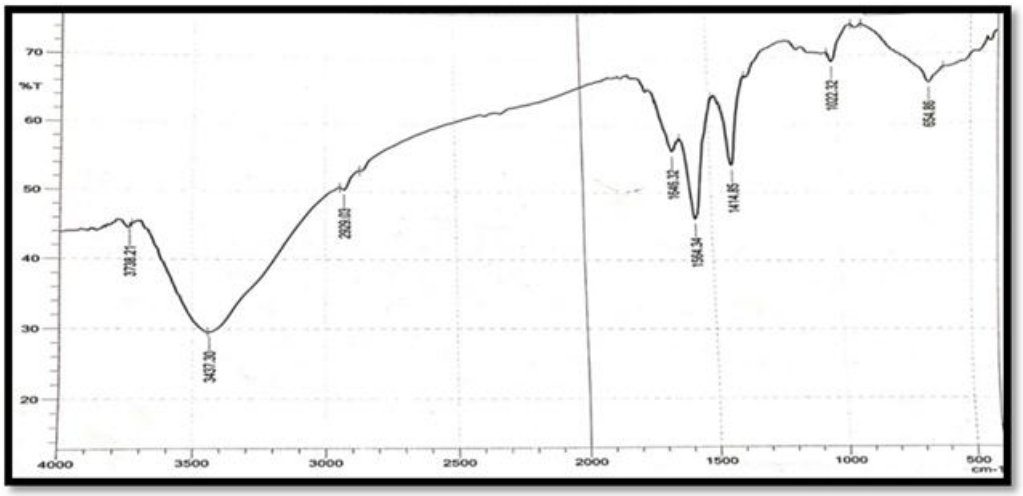

Figure: 3 FTIR spectra of CHGL.

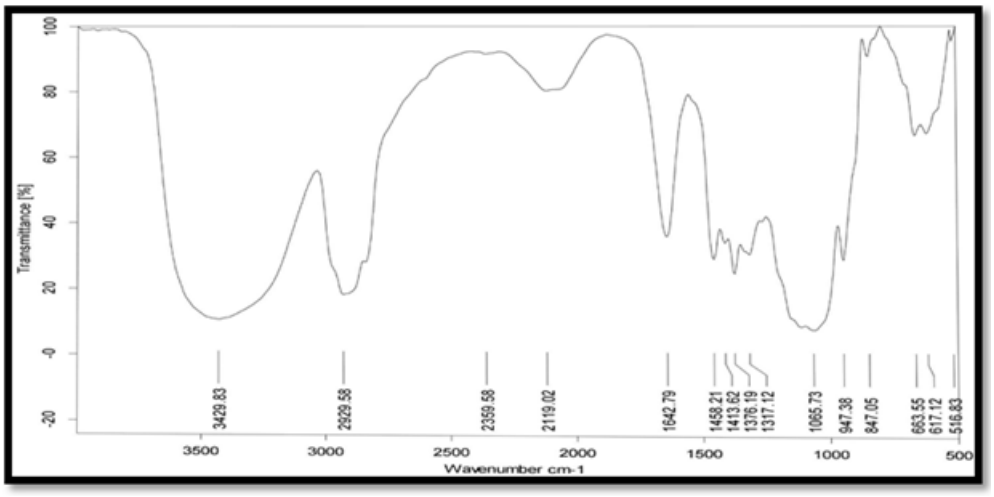

Figure: 4 FITR spectra of HPMC K100.

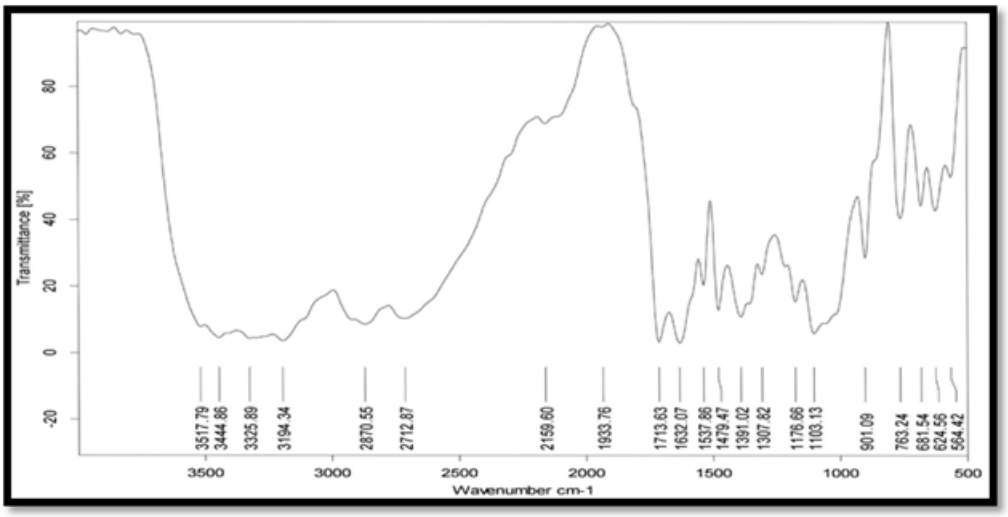

Figure: 5 FTIR spectrum of Formulation 8.

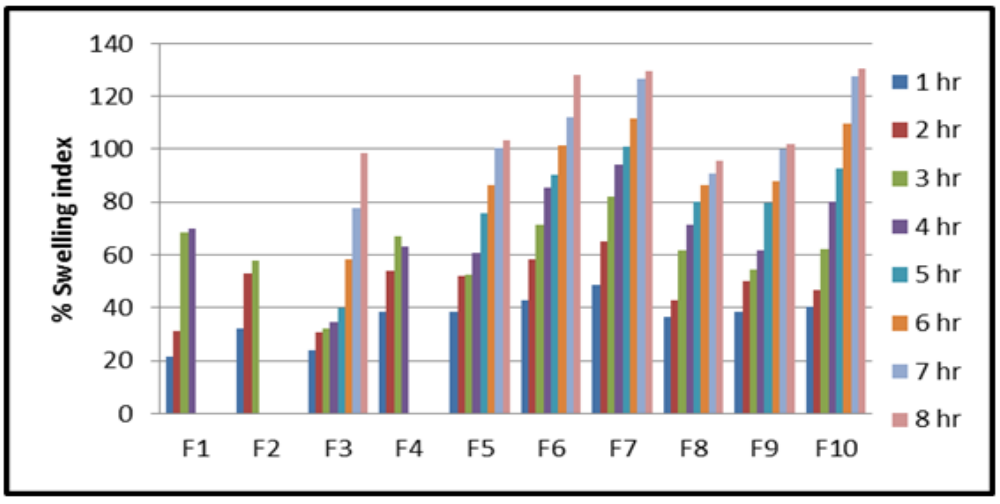

Figure: 6 Swelling index in %.

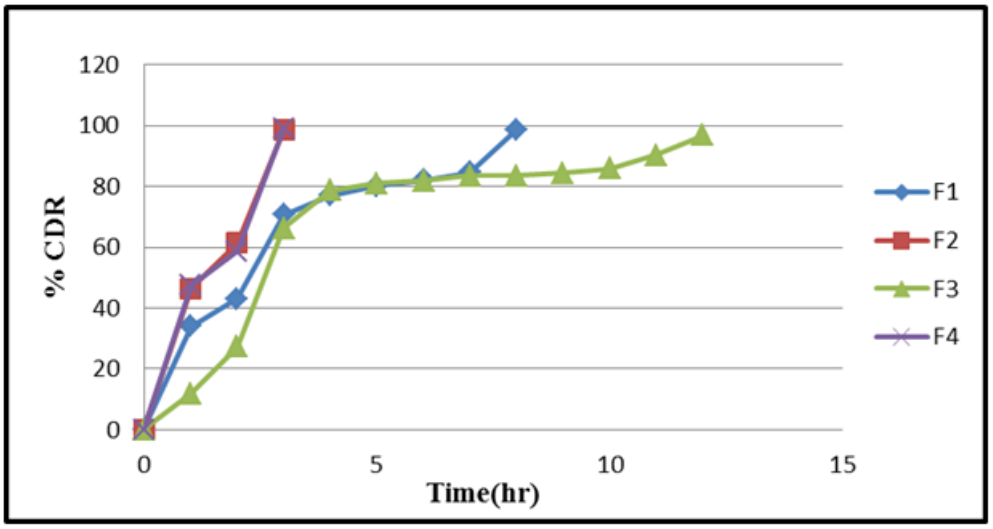

Figure: 7 Cumulative % of drug release Vs Time of F1,F2,F3 & F4.

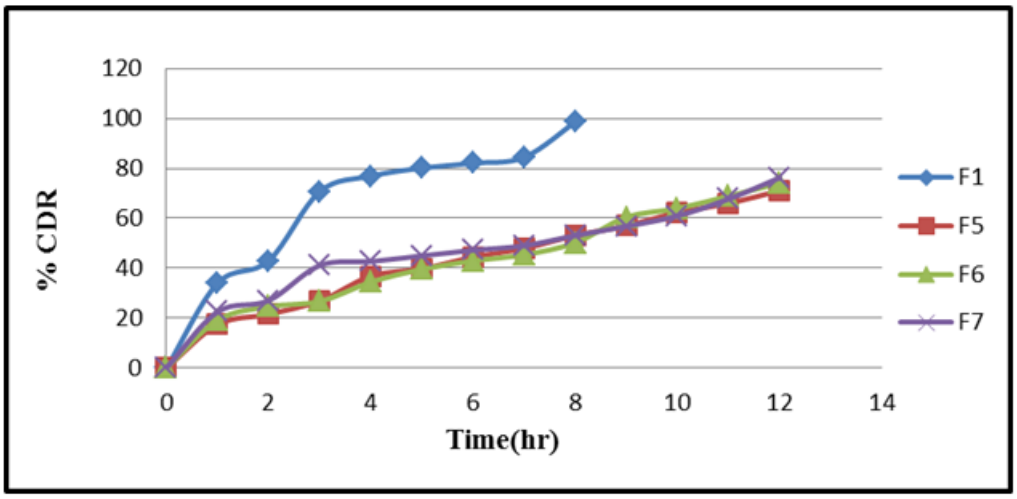

Figure: 8 Cumulative % of drug release Vs Time of F1,F5,F6 & F7.

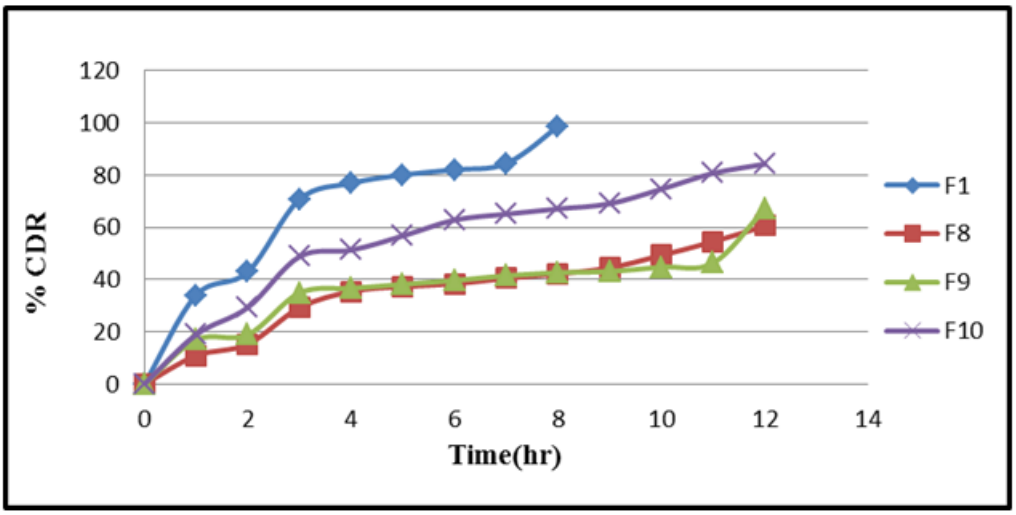

Figure: 9 Cumulative % of drug release Vs Time of F1,F8,F9 & F10.

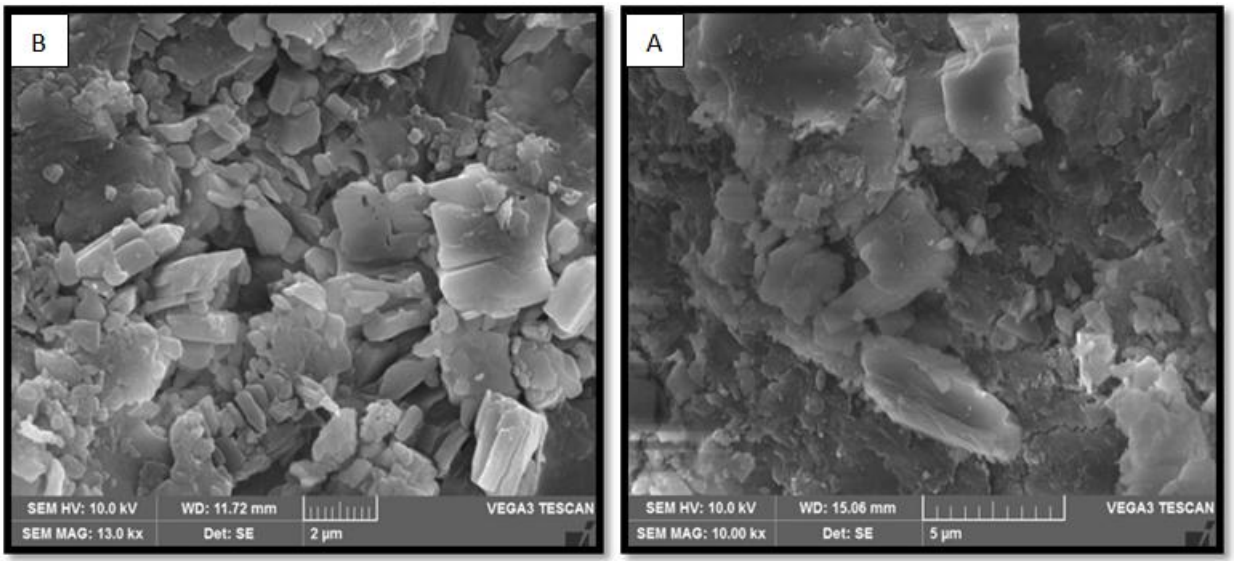

Figure: 10 SEM Photomicrographs of Hydrogels matrix tablets F8 before (B) and after (A) the dissolution testing.

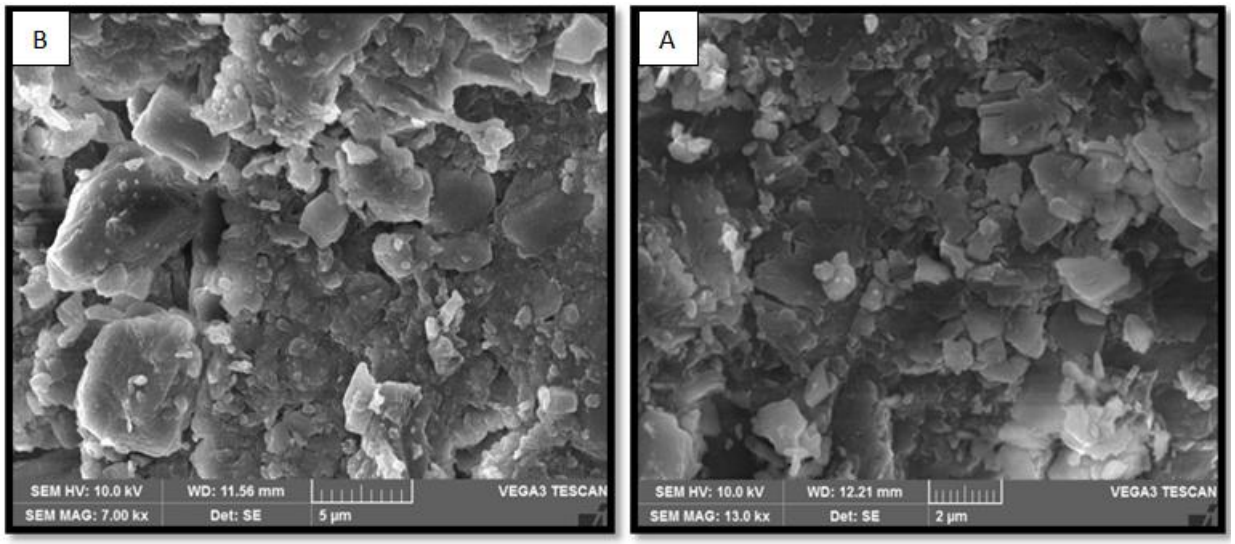

Figure: 11 SEM Photomicrographs of Hydrogels matrix tablets F9 before (B) and after (A) the dissolution testing.

CONCLUSION

The FTIR studies indicate that the drug was compatible with the polymers and other excipients used in the dosage form. FTIR spectra confirmed the crosslinking of chitosan. Pre-compression parameter results showed good flow properties. Post-Compression parameter results were found to be optimum. Hardness of the tablets is sufficient to withstand the shock. All the formulated tablets were found be within the official limit for weight uniformity. The drug content was uniform in all the tablet formulations indicating uniform distribution of drug within the matrices. Based on the *in- vitro* dissolution studies formulations F8 containing HPMC K100 180 mg , CHGL 90 mg (2:1) was found to be promising and showed a drug release profile 60.58% at the end of 12 hours when compared to other formulations. All the formulations were subjected for kinetic studies and showed Higuchi model indicating that the drug release was by Fickian diffusion. Finally, it was concluded that the Hydrogel based CDDTs of Acyclovir, formulation F8 containing HPMC K100 180 mg, CHGL 90 mg (2:1) showed swelling time and *in-vitro* drug release study slower than the other formulations. Selected formulations were found to be complying with all the properties of tablets and the formulations were satisfactory.

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