

Original Research Article

Interpolymer complex of Chitosan and Eudragit L-100: Preparation, Characterization and drug release behavior.

Abstract:

Aims: The aim of the present investigation is to prepare interpolymer complex between Chitosan and Eudragit L100 , and to evaluate its performance as a matrix for controlled release of drugs, using Diclofenac sodium as a model.

Methodology: . Interpolymer complex were prepared by combining different % chitosans solutions with different % Eudragit L100 solutions in different ratios The formation of interpolyelectrolyte complexes (IPEC) between carbopol and Chitosan was investigated, using turbidimetry and viscosity measurement. The structure of the prepared IPEC was investigated using FTIR spectroscopy and DSC. A Rotary compression press was used to formulate matrix tablets of diclofenac sodium using polymers in physical mixture and IPECs. The amount of Diclofenac Sodium released in the dissolution medium was determined spectrophotometrically at 276 nm.

Results: The results of the present investigation confirm the formation of an interpolyelectrolyte complex between Chitosan and Eudragit L 100 . The release of the model drug Diclofenac sodium was significantly controlled from tablets made up of the IPEC as compared with polymers alone and in combination. Release profiles were represented by a mathematical model, which indicates that the prepared system releases drug in a zero-order manner. By changing the ratio of the IPEC in the tablets

Conclusion: Controlled release drug delivery systems designed to manipulate the drug release to achieve specific clinical objectives that are unattainable with conventional dosage forms

Keywords: Interpolymer complex, Diclofenac sodium, Chitosan, Eudragit, controlled release

1. Introduction:-

There are several ways that can be utilised to broaden the scope of polymers used in dosage form design, such as modifying their chemical structure, combining different polymers in physical mixtures, or forming polymer-polymer interactions, such as polyelectrolyte complexes. Polyelectrolyte complexes combine the distinct physicochemical features of several polymers while maintaining good biocompatibility. As a result, polyelectrolyte complexes are becoming more prevalent in modern pharmaceutical technology. [1]

When oppositely charged polyelectrolytes are combined in solution, strong but reversible electrostatic connections emerge, which results in self-assembly or spontaneous association. Polyelectrolyte complex networks will arise as a result of the direct interactions between the polymeric chains. Polymer complexes are classified on the basis of its nature of association. Stereocomplexes, interpolyelectrolyte complexes (or polyelectrolyte complexes, IPECs), and hydrogen-bonded complexes are the three main types of polymer complexes. Interpolymer complexes (IPCs) are macromolecular structures generated by the non-covalent association of the polymers having affinity for each other. The complexes are insoluble and are generated by repeating units on different chains (interpolymer complexes) or on various portions of the same chain (subpolymer complexes) (intrapolymer complexes). They are well – tolerated and biocompatible but are very sensitive to the environmental

changes. [2][3] Most polyanions and polycations readily produce IPECs. The ionic interaction of repeating units on polymer chains forms these complexes.

The formation and characterization of systems involving a variety of anionic and cationic polymers has increased in recent years due to an increasing interest in polyelectrolyte complexes such as, E-Eudragit L-Eudragit E-Eudragit L-Eudragit E-E E-sodium alginate Eudragit chitosan–alginate/chitosan–carrageenan.[4]

Many researchers have used different types of Eudragit for controlled drug delivery.[5] IPECs (interpolyelectrolyte complexes) are precipitates formed by combining cationic and anionic polymers in aqueous solutions. The advantages of IPEC as a polymeric carrier in controlled drug release systems are well known.[6]

The media pH, ionic strength, concentration, and, in certain cases, mixing order are all known to influence the stoichiometry of both components in IPEC. IPEC's benefits as a polymeric carrier for drug release in regulated systems are well known.[7]

The components that make up the IPEC can be chosen based on their properties, which are critical for its pharmaceutical application, such as incompatibility, pH-dependent solubility and swellability, and physicochemical stability. The purpose of this study is to investigate the formation of a novel IPEC between Chitosan (CH) and Eudragit L100 (EL) and to evaluate its performance as a matrix for controlled release of drugs, using Diclofenac sodium as a model.

2. Methodology

2.1. Materials-

Diclofenac sodium was gifted from VamaPharma, Nagpur, India. Chitosan (Research Lab Fine Chemicals, Mumbai, India), Eudragit L100 (EvonikRoehmPharma, Mumbai). Sodium

deoxycholate and microcrystalline cellulose purchased from loba chemicals, India. All the other chemicals and reagents used were of analytical grade.

2.2. Method- Synthesis of solid IPEC

The IPEC of Chitosan(CS) and Eudragit L100 (EL) was prepared following the modified procedures given in literature.[8][9] Chitosan (0.5%) and Eudragit L100 (0.5%) solutions were made by dissolving them in acetic acid solution and 0.1 M NaOH, separately, then diluting them with demineralized water and adjusting the pH to 6.0. Chitosan and Eudragit L100 solutions were mixed at room temperature for 2 hours at pH 6.0, then vigorously agitated. By combining different volumes of % chitosans solutions with different volumes of % Eudragit L100 solutions in different ratios of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, and 9:1 respectively, nine different mixtures of solutions were formed. The mixture was then stirred continuously for 1 hour with a magnetic stirrer. The precipitate was washed with distilled water after being isolated by centrifugation at 6000 rpm. After that, the solid IPEC was dried for two days under vacuum at 500°C. The powder was sieved with an ass no. 80 sieve and used for further research.

3. Preparation of tablets

A Rotary compression press was used to compress the IPEC powder (1:1) at 25 kg/cm² to produce flat faced tablets with a weight of 250 mg. Magnesiumstearate (lubricant) and MCC (bulking agent) were added to the powder. The formula for preparation of tablets is given in table 1.

Table 1- Preparation of Diclofenac sodium tablets using polymers and IPEC. (Drug:Polymer = 1:1)

Ingredients	C ₁	C ₂	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈	C ₉	C ₁₀	C ₁₁	C ₁₂
Diclofenac sodium	100	100	100	100	100	100	100	10	100	100	100	100
Chitosan	100	-	50	-	-	-	-	-	-	-	-	-
Eudragit L100	-	100	50	-	-	-	-	-	-	-	-	-
IPEC	-	-	-	100	100	100	100	10	100	100	100	100
MCC	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47	47.5	47.5	47.5	47.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

4. Evaluation of IPEC

4.1 Physical Appearance

The physical appearance of IPEC complex was noted of all the batches prepared.

4.2 Turbidity measurements

The Chitosan / Eudragit L100 ratio in the complex was examined by monitoring the transmittance of the solution at a wavelength of 600 nm using a spectrophotometer (Shimadzu Double Beam UV 2300 UV-Spectrophotometer).

4.3 Viscosity measurements

The specific viscosity of the supernatant solution was determined by using a Brookfield viscometer.

4.4 pH Measurement

The pH of the solution was measured with a pH metre for each ratio. Chitosan and Eudragit were separately dispersed in acetic acid and the dispersion was stirred to form a uniform solution. Using NaOH solution, the pH of both the solution was adjusted to 6.

4.5 Infrared spectroscopy

FTIR spectra of the prepared CH and EL solid IPEC, physical mixture, pure medication, and polymers were determined by Perkin Elmer, Norwalk, CT.

4.6 Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) study was carried out to evaluate thermal behavior and thermo tropic characteristics. It was carried out using a differential scanning calorimeter (Mettler Toledo DSC 822), in an aluminum-sealed tray, the samples were preheated to 200° C. The sample was cooled to room temperature before being reheated from 40° to 450° C at a rate of 10° C/min.

5. Post Compression Evaluation of Sustained Release Tablets

5.1 Weight Variation

The weight variation test was done by weighing twenty tablets individually, calculating the average weight and then comparing the individual tablet weight to the average. The weight variation should be under the pharmacopeial limits.

5.2 Hardness

The hardness of the tablets was measured using Monsanto hardness tester. It is expressed in kg/cm².

5.3 Friability

Roche friabilator (Electrolab Friabilator – USP, Model No. EF-1W) was used to test the percent friability of the tablets. The weight lost should not exceed the limit 1.0%.

5.4 Thickness

The thickness of tablet was measured by using a digital calliper (ASAHI, India). Average values and SDs were determined using five tablets from each batch.

5.5 Determination of Drug Content

For the determination of drug 20 tablets were weighed and powdered. Powder equivalent to 50mg of diclofenac sodium was weighed and taken in volumetric flask, methanol was added upto 200ml and shaken. About 5.0 ml of the solution was diluted to 100 ml with methanol and absorbance was measured at 285 nm.

5.6 Degree of swelling of tablets:

The degree of swelling of tablets was determined in conditions that simulated the intestinal tract. [10]The volume of the medium was 40ml, the tablets were taken out of the medium after every 15 minutes, dried with filter paper and measured. After 24 hours, a final weighing was done to determine the degree of swelling equilibrium. The swelling percentage (S%) was determined as follows:

$$S\% = (m_2 - m_1 / m_1) 100$$

Where, m_1 is the weight of the dry sample and m_2 is the weight of the swollen sample.

5.7 In-vitro dissolution studies of sustained release tablet formulations.

The dissolution study of the tablets was carried out using the USP Apparatus-(Type II Paddle dissolution apparatus) (Electrolab Tablet Dissolution tester – USP, Model No. TDT – 06P) and was used to release diclofenac sodium from matrix tablets at $37 \pm 0.5^{\circ}\text{C}$. The pH of the release medium was maintained at 6.8, and aliquots (5 ml) of the solution were taken at predetermined time interval. Meanwhile, 5mL of a fresh medium was used to replace the dissolution medium. The amount of Diclofenac Sodium released was measured spectrophotometrically at 276 nm with a spectrophotometer (Mode No. UV 2300, Techcomp). The PCP DISSO – V3 software was used to measure the cumulative percent drug release at various time intervals.

5.8 Determination of release mechanism

The release data obtained were treated according to zero-order, first-order, Higuchi and korsmeyer-Peppasequation models. The release data was plotted in kosmeyer et al's equation as log cumulative percent of drug release Vs log time, with exponent n determined using the slope of the straight line.[11][12][13]

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

Where,

M_t/M_{∞} = fraction solute release

t = release time

K= kinetic constant characteristic of the drug/ polymer system

n = exponent that characterizes the mechanism of release of traces.

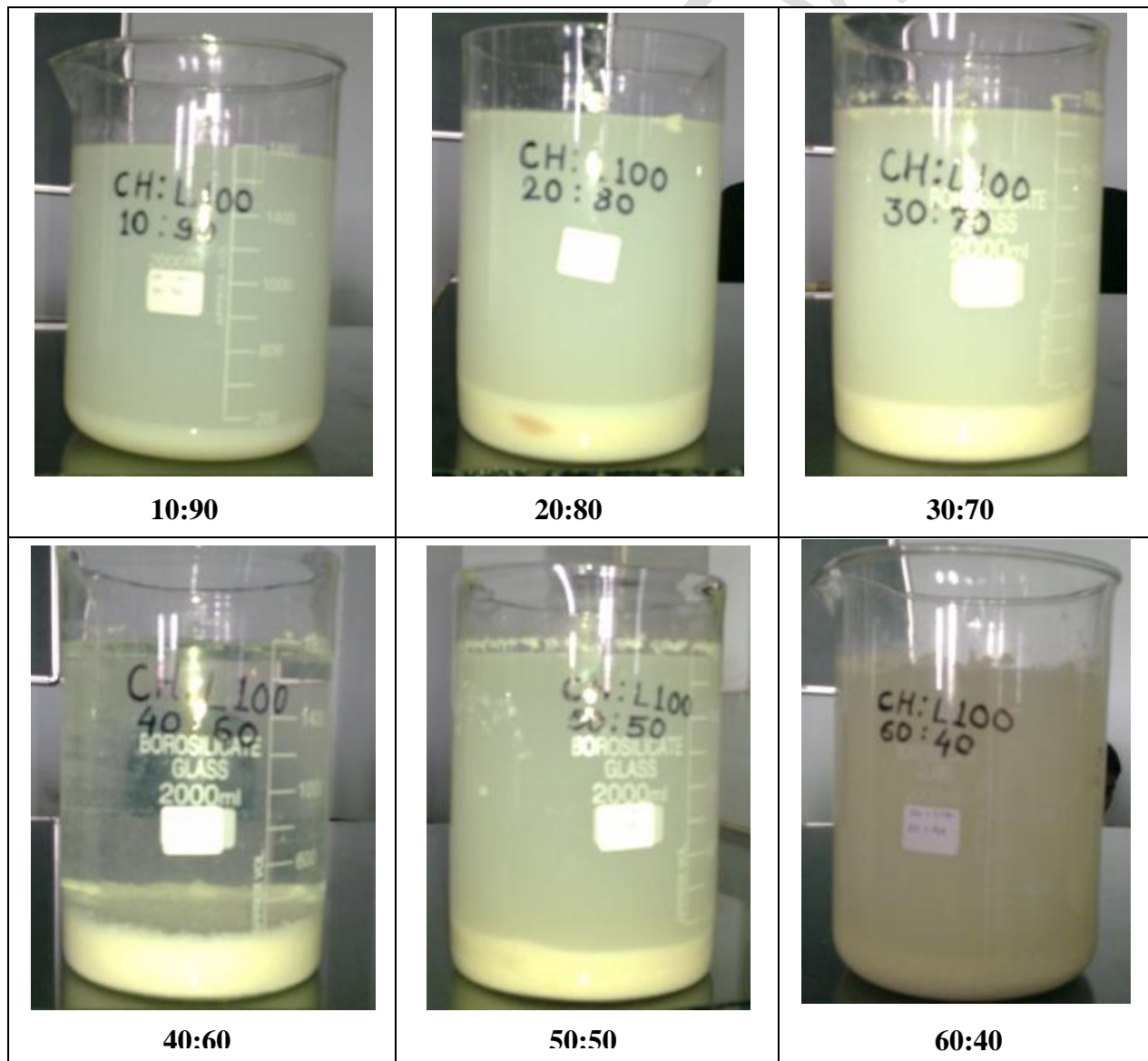
5.9 Tablet surface analysis

The tablet surface analysis was performed where the tablet samples were removed from the dissolution apparatus at the end of the dissolution test and the tablets were completely dried. The dried tablet was then seen through the Scanning Electron Microscope. The change in the tablet's surface was investigated.

6. RESULT & DISCUSSION

6.1 Physical Appearance of IPEC Solution

There was distinct change in the physical appearance of the IPECs solution as shown in **figure 1** and **table 2**.



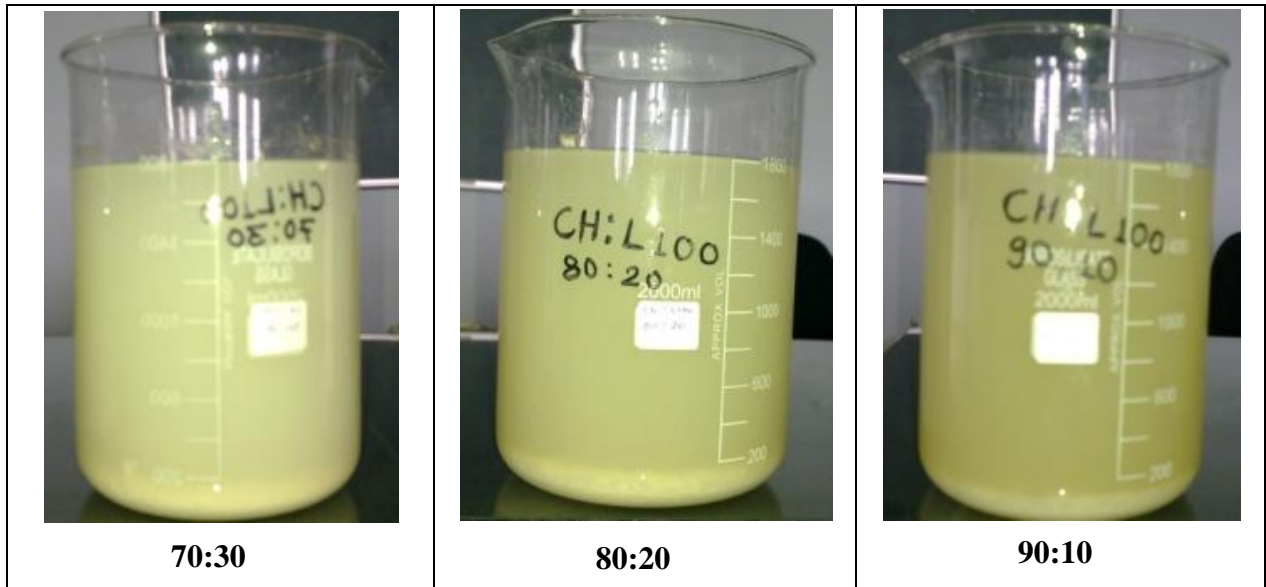


Figure1: Physical appearance of the IPECs solution

Table 2: Physical appearance of the IPECs solution

Chitosan:	Appearance without settling	Appearance after settling
EudragitL100		
Chitosan	Clear cream solution	Clear cream solution
Eudragit L100	Transparent solution	Transparent solution
10:90	White solution	White milky solution
20:80	White solution	White milky solution
30:70	White solution	White milky solution
40:60	White solution	Cream solution
50:50	White solution	White less milky solution
60:40	Cream solution	Milky cream solution
70:30	More creamy solution	Milky more cream solution
80:20	Yellowish solution	Yellowish turbid solution
90:10	More yellowish solution	Yellowish more turbid solution

1. Turbidity Measurements (% Transmittance Of IPEC Solution)

The Chitosan / Eudragit L100 solution was filtered for examining the transmittance of the solution at a wavelength of 600 nm using a spectrophotometer and is depicted in **fig 2**

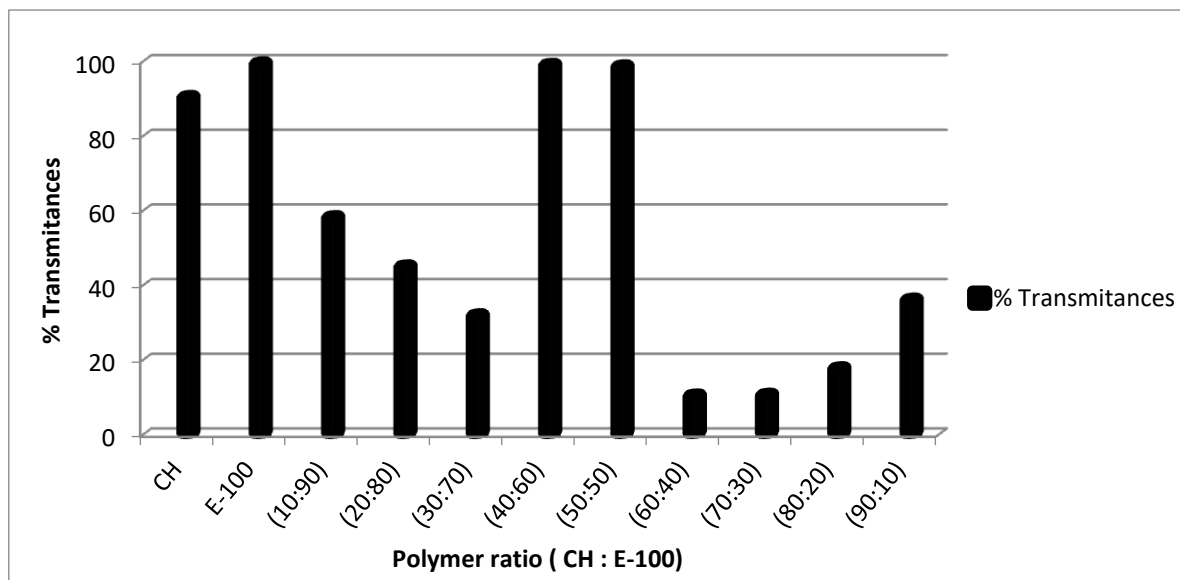


Figure: 2 % Transmittances of different polymer solution

Figure 2 shows the percent transmittances of the solution and indicates the complete formation of IPEC; as the concentration of chitosan was increased, the solution's transmittance decreased; however, the transmittances of the IPEC 40:60 and 50:50 were found to be the highest, indicating that the reaction was complete and IPEC was formed in greater proportion. As a result, the percent transmittance of IPEC solution is directly proportional to formation of IPEC.

2. Viscosity of IPEC Solution

It was observed that the viscosity of IPEC solution increased as the concentration of Chitosan was increased. **Table 4 and Figure 3** represents the viscosity.

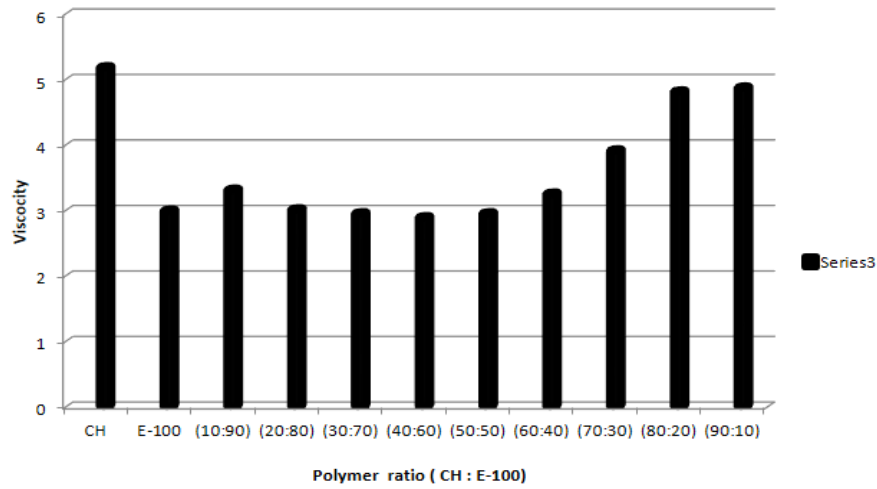


Figure 3 Viscosity of different polymer solution

pH of Solution

The pH of the solution was determined before and after filtration using 0.5 percent (w/v) Chitosan and Eudragit L100 solutions in various ratios, resulting change in the pH of the solution during IPEC creation. **Figure 4** shows the pH.

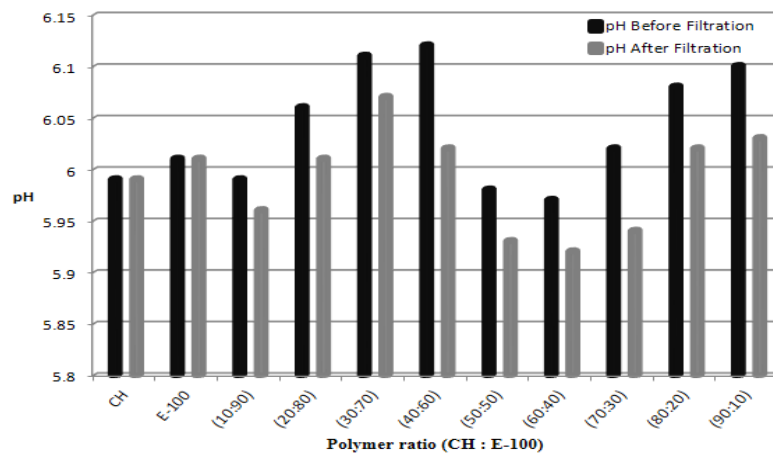


Figure 4 - pH of different polymer solution

Infrared absorption spectrophotometry:

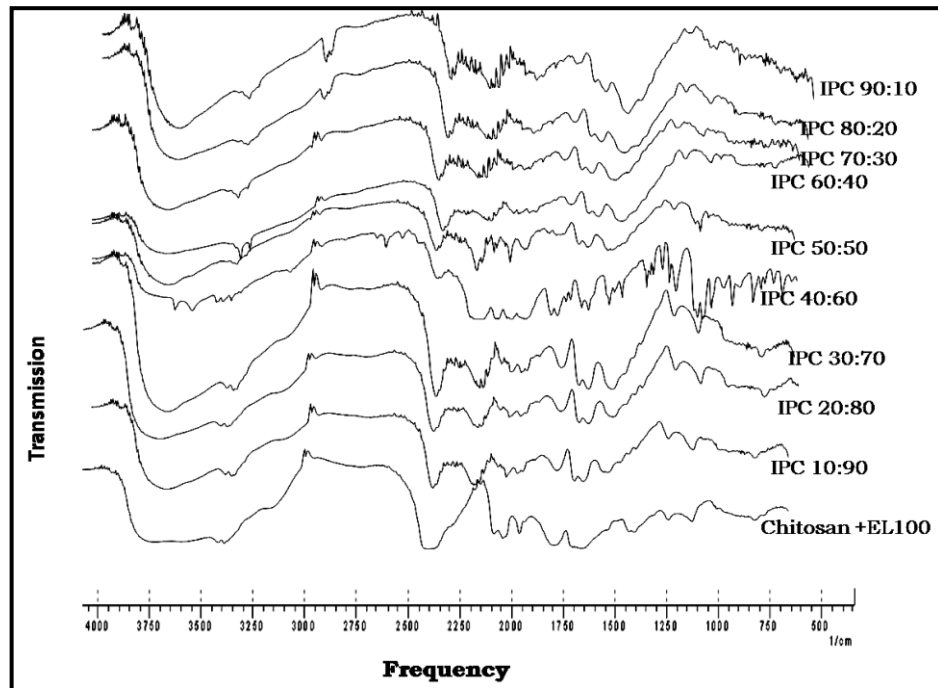


Figure 5 FTIR spectra of all the IPEC solution, Chitosan+EL100

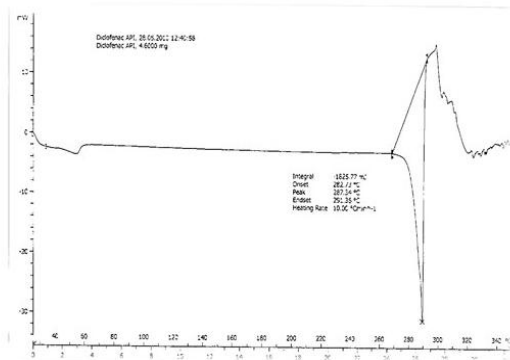
The FTIR spectrum of Chitosan shows the absorption band at 1577 and 1656 cm^{-1} because of the amine group and at 3435 cm^{-1} due to the undissociated primary amino group (NH_2). Eudragit L100 shows a characteristic band at 1726 cm^{-1} because of the carboxylic acid. The IPECs showed the peak of amino groups of Chitosan and the peak of the carboxylic groups of Eudragit at 3435 cm^{-1} and at 1726 cm^{-1} respectively.

An additional peak of new band appeared at 1562 cm^{-1} because of the ionic interaction between the ionised carboxylic groups of Eudragit L100 and the protonated amino groups ($-\text{NH}_3^+$) of Chitosan. The binding ratio of the complex was stoichiometric, this finding seems to point to ionic bonding as a primary binding force in the complex formation between NH_3^+ group of Chitosan and the COO^- group of Eudragit L100.

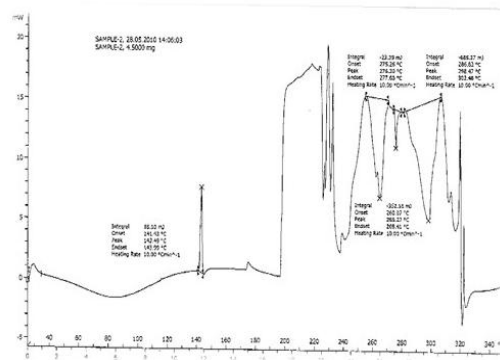
No significant difference was observed in IR spectrum, thus no interaction was found between the Diclofenac Sodium, Chitosan, Eudragit L100 and IPEC.

Differential scanning calorimetry (DSC)

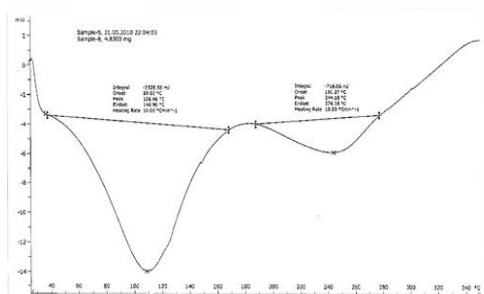
Thermal analysis was carried out using a differential scanning calorimeter (Mettler Toledo DSC 822).



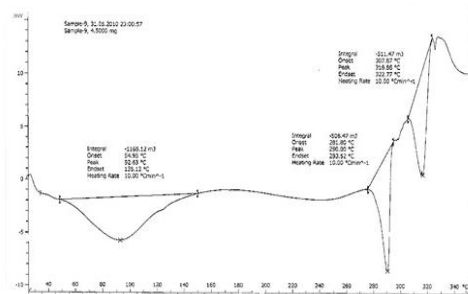
DSC thermogram of Diclofenac Sodium



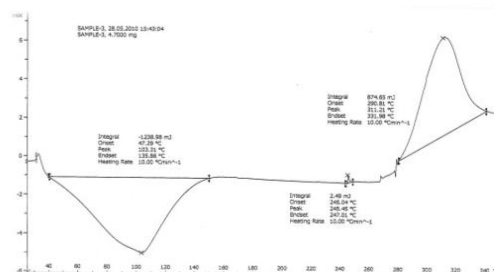
DSC thermogram of Eudragit L100



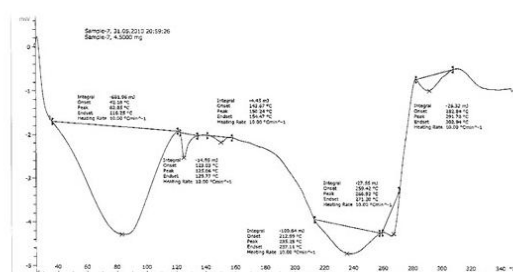
DSC thermogram of IPEC 40:60



DSC thermogram of IPEC 40:60 + Diclofenac Sodium



DSC thermogram of Chitosan



DSC thermogram of Chitosan + Eudragit L100 + Diclofenac Sodium

Figure 6 DSC graph

The DSC thermogram of pure Diclofenac Sodium showed a sharp endothermic peak at 287.3⁰ C that shows the decomposition of drug. DSC thermogram of Eudragit L100 showed one exothermic peak and three endothermic peak, the small exothermic peak may be due to water loss at 143⁰C, followed by a glass transition temperature around 265.2⁰ C with complete decomposition at 298.5⁰ C characterized by 3rd endothermic peak in the thermogram. The pure Chitosan thermogram showed an exothermic peak at 311.2⁰ C, attributable to the decomposition of Chitosan.

The DSC thermogram of Chitosan, Eudragit L100 and Diclofenac Sodium showed a characteristic peak where three endothermic peak were obtained at 235.25⁰ C, 266.93⁰ C, 291.78⁰C. DSC thermogram of IPEC 40:60 showed an endothermic peak at 244.1⁰ C. The DSC thermogram of IPEC 40:60 and Diclofenac sodium showed two endothermic peak at 290.0⁰C and 316.86⁰C which indicates the presence of diclofenac Sodium. Therefore it is indicated that there is no reaction between drug and polymers.

Post-compression assessment of sustained release tablets:

Friability, Hardness, Thickness, Weight variation and Drug content

Table No.5 shows the evaluated results of tablets for friability, hardness, thickness, weight variation, and drug content.

F. code	Friability* (%)	hardness †(kg/cm ³)	Thickness (mm) †	Weight variation [†] (g)	Drug content*
C1	0.455 ± 0.09	5.96 ± 0.083	4.10 ± 0.025	0.25 ± 0.0077	99.8
C2	0.488 ± 0.03	0.454 ± 0.123	4.61 ± 0.053	0.25 ± 0.0079	98.6
C3	0.469 ± 0.02	4.48 ± 0.078	4.55 ± 0.036	0.252 ± 0.0059	97.2

C4	0.46 ± 0.07	5.22 ± 0.115	3.85 ± 0.036	0.25 ± 0.0077	95.1
C5	0.445 ± 0.03	4.56 ± 0.09	3.82 ± 0.031	0.249 ± 0.0061	100.1
C6	0.445 ± 0.27	6.19 ± 0.105	3.75 ± 0.032	0.246 ± 0.0063	99.3
C7	0.467 ± 0.03	5.11 ± 0.104	3.73 ± 0.017	0.245 ± 0.0058	96.98
C8	0.439 ± 0.17	5.79 ± 0.196	3.89 ± 0.035	0.251 ± 0.0087	94.36
C9	0.468 ± 0.04	5.11 ± 0.104	4.04 ± 0.055	0.249 ± 0.0099	97.28
C10	0.464 ± 0.05	6.19 ± 0.196	3.73 ± 0.025	0.25 ± 0.0082	94.79
C11	0.488 ± 0.06	5.87 ± 0.057	3.80 ± 0.015	0.251 ± 0.0078	97.54
C12	0.464 ± 0.06	6.19 ± 0.066	3.89 ± 0.031	0.25 ± 0.0071	99.06

Mean ± S.D. * $n=3$, † $n=6$, $n^*=10$

The friability of all the batches was found in the range of 0.246 to 0.489, which were found to pass the specified limits. Low values of friability indicate high resistance to abrasion and good binding property. The hardness of tablets was found in the range of 4.11 ± 0.125 to 8.44 ± 0.104 kg/cm². The hardness of tablets can be attributed to presence of different ratio of IPEC. The tablet thickness was found to be in the range of 3.73 ± 0.017 to 4.61 ± 0.053 mm.

The drug content was found to be more than 94.36%. The uniformity of active ingredients can be attributed to proper blending of ingredients prior to compression.

***In-vitro* drug release from matrices**

The amount of Diclofenac Sodium released in the dissolution medium was determined spectrophotometrically at 276 nm.

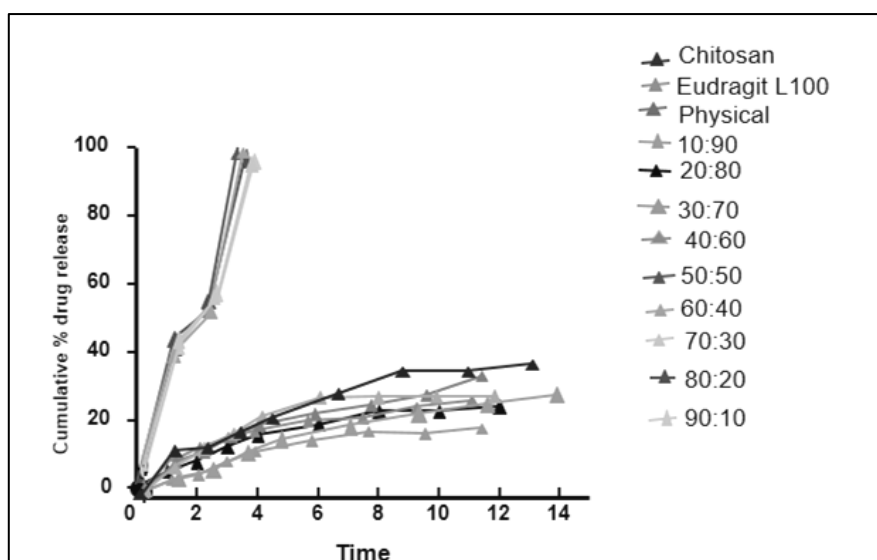


Figure 7 In vitro release of IPEC solutions

Matrices made up of chitosan C1 led to smaller drug release. In comparison to Chitosan the release of drug from the matrices made up of Eudragit L100 showed more sustained effect. The batch C2 and C3 showed 31.87% and 39.71% release of drug in 12 hours respectively.

IPEC 10:90 showed good sustained effect of around 24.02% release of drug. IPEC 20:80 matrices show release behaviour slower than that of the IPEC 10:90. This IPEC 20:80 can sustain the release more, with the more constant drug release rate. IPEC 30:70 and 40:60 batch matrices show only 23.29% and 32.25% release of drug in 12 hours, which states that this batch has a good sustained effect as the concentration of IPEC is increased.

Batch 50:50, 60:40, 70:30, 80:20 and 90:10 showed the bursting effect and the complete release was shown in first 3 hours itself, this may be due to inability of polymer to form a coat over the drug particle.

Kinetic treatment of data of dissolution profiles

Table No. 6 show the release kinetics of drug for individual polymers. The exponent of power law determines the probable mechanism by which drug has been released from the

matrices. The release model was chosen on basis of best fitted criterion. Regression analysis of the equations determines the best fitted model. The other simplified form of the determination of release mechanism was proposed by Peppas et al. The exponential relation was utilized by these scientists to describe the Fickian and Non-Fickian release behavior of swelling controlled release systems.

Table no. 6 shows that the release similar kinetics as earlier. However batch C6, C7, C8, C9, C10 and C11 follow Fickian diffusion ($n = 0.1$ to 0.5) and batch C1, C2, C3, C4, C5, and C12 follows Non-Fickian ($n = 0.$ to 0.8) as projected by Korsmeyer-Peppas eq. The release of drug was found to be following Korsmeyer-Peppas eq. The value of exponent was 0.3434 which shows that it follows Non-Fickian as projected by Korsmeyer-Peppas eq.

F.Code	Zero order		1st order		Matrix		Hix.Crow		Korsmeyer-Peppas		
	R	k	R	k	R	k	R	k	R	n	k
C1	0.872	4.586	0.933	-0.058	0.989	13.41	0.916	-0.018	0.978	0.5154	12.8491
C2	0.717	3.341	0.773	-0.039	0.961	9.964	0.756	-0.012	0.961	0.5992	9.8082
C3	0.919	3.410	0.955	-0.040	0.990	9.890	0.945	-0.012	0.992	0.818	8.1377
C4	0.958	2.130	0.971	-0.023	0.972	6.100	0.967	-0.007	0.986	0.670	3.2837
C5	0.887	2.314	0.910	-0.025	0.982	6.750	0.903	-0.008	0.981	0.719	4.8973
C6	0.903	2.216	0.921	-0.024	0.974	6.435	0.916	-0.007	0.975	0.477	4.2218
C7	0.795	3.040	0.855	-0.035	0.993	8.993	0.837	-0.011	0.991	0.254	9.4661
C8	0.859	16.35	0.895	-0.207	0.976	25.72	0.883	-0.063	0.863	0.290	30.8678

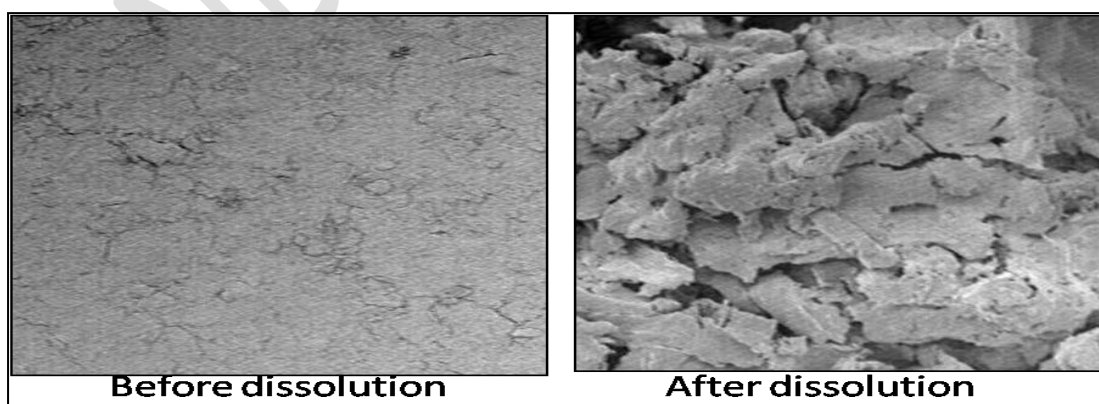
C9	0.864	16.75 9	0.900	-0.213	0.986	26.395 2	0.889	-0.065	0.999	0.314	30.9670
C10	0.881	16.84	0.918	-0.215	0.989	26.459	0.906	-0.066	0.989	0.269	30.4708
C11	0.868	16.58 6	0.904	-0.211	0.977	26.054	0.892	-0.064	0.853	0.274	30.8706
C12	0.871	16.63 6	0.906	-0.212	0.978	26.123	0.895	-0.065	0.857	0.518	30.8448

TABLET SURFACE ANALYSIS

The SEM images of the tablet showing the surface morphology of before and after dissolution study are shown in **figure 8**. **Figure (a)** shows intact surface without any channels or troughs. After dissolution, the solvent front enters the matrix and moves slowly toward the centre of the tablet through the pores as shown in **Figure (b)**. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The drug release from the tablet is may be due to diffusion.

a.

b.



Before dissolution

After dissolution

Figure 8: SEM photographs of C7 tablets showing surface morphology **(a)** before and **(b)** after dissolution study.

Conclusion

The results of the present investigation confirm the formation of an interpolyelectrolyte complex between Chitosan and Eudragit L 100. In the present work we found matrix tablet prepared by interpolymer complex of Ch and EL 100 provides extending drug release of Diclofenac sodium. The formulations showed good linearity which appears to indicate a coupling of diffusion and erosion mechanisms-so called anomalous diffusion.

References:-

- [1] Lankalapalli S, Kolapalli VRM. Polyelectrolyte Complexes: A Review of their Applicability in Drug Delivery Technology. *Indian J Pharm Sci.* 2009; 71(5):481.
- [2] Berger J, Reist M, Mayer JM, Felt O, PeppasNA, Gurny R. Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications. *Eur J Pharm Biopharm.* 2004; 57(1):19–34.
- [3] Berger J, Reist M, Mayer JM, Felt O, PeppasNA, Gurny R. Structure and interactions in chitosan hydrogels formed by complexation or aggregation for biomedical applications. *Eur J Pharm Biopharm.* 2004; 57(1):35–52.
- [4] Rao YM, Veni JK, Jayasagar G. Formulation and evaluation of diclofenac sodium using hydrophilic matrices. *Drug Dev Ind Pharm.* 2001; 27(8):759–766.
- [5] Wadher KJ, Kakde RB, Umekar MJ. Formulation and Evaluation of a Sustained-Release Tablets of Metformin Hydrochloride Using Hydrophilic Synthetic and Hydrophobic Natural Polymers. *Indian J Pharm Sci* 2011; 73:208.

- [6] Mitrevej A, Sinchaipanid N, Rungvejhavuttivittaya Y, Kositchaiyong V. Multiunit controlled-release diclofenac sodium capsules using complex of chitosan with sodium alginate or pectin. *Pharm Dev Technol.* 2001; 6(2):385–392.
- [7] Tamilvanan S, Biswanath SA. In vitro and in vivo evaluation of single-unit commercial conventional tablet and sustained-release capsules compared with multiple-unit polystyrene microparticle dosage forms of Ibuprofen. *AAPS PharmSciTech* 2006; 7(3): 126-134.
- [8] Mustafin RI, Kabanova T V. Diffusion Transport Properties of Polymeric Complex Matrix Systems Based on Eudragit E100 and L100 Copolymers. *Pharm Chem J* 2005; 39(2):89–93.
- [9] Mustafin RI, Protasova AA, Mooter G Van den, Kemenova VA. Diffusion transport in interpolyelectrolyte matrix systems based on chitosan and Eudragit L100. *Pharm Chem J.* 2005; 39(12):663–666.
- [10] Prado HJ, Matulewicz MC, Bonlli PR, Cukiermna AL. Preparation and characterization of controlled release matrices based on novel seaweed interpolyelectrolyte complexes. *Int J Pharm.* 2012; 429(1-2):12–21.
- [11] Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci.* 1963; 52(12):1145–1149.
- [12] Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm.* 1983; 15(1):25–35.
- [13] Wadher KJ, Kakde RB, Umekar MJ. Formulation and Evaluation of Sustained Release

Tablets of Metformin Hydrochloride by Solid Dispersion Technique Using pH dependent and pH independent Eudragit Polymers. J Pharm Sci. 2011; 73(2):208.

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