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Polyelectrolyte Complexes of Carbopol and Chitosan, as Metoprolol Tartrate Carriers

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Abstract

The objective of the present research work was to develop an extended release matrix tablet of Metoprolol tartrate, an antihypertensive drug by using Carbopol/Chitosan interpolymer complex. Since Metoprolol tartrate has biological half-life nearly about to 4 hours, so attempt has been made to optimize an extended release. Here Carbopol/Chitosan interpolymer complex was used as the rate controlling polymer. The interpolymer complex (IPC) was formed using a precipitation method in an acidic solution. The chitosan and Carbopol IPC was characterized by Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), and turbidity measurements. FT-IR demonstrated that the IPC formed a complex through an electrostatic interaction between the protonated amine (NH3^{+}) group of chitosan and the carboxylate (COO^{-}) group of Carbopol. DSC indicated the IPC to have different thermal characteristics from chitosan or Carbopol. The turbidity measurement revealed the optimum complexation ratio of IPC between chitosan:Carbopol to be 1:4. The tablets were prepared by direct compression method. Formulation MT6 showed NMT 25% release in 1 h, 20-40% release in 4 h, 40-60% release in 8 h and NLT 80 % release in 20 h. The dissolution data were fit to the above equation by drawing a log-log plot of the fraction released versus time. The 'n' value were between 0.647 to 0.975, which indicated that the release followed non-Fickian diffusion mechanism or anomalous transport and suggesting that both diffusion of the drug in the hydrated matrix and chains relaxation process affect the drug release process.

Keywords
Matrix tablets, Metoprolol tartrate, Chitosan/Carbopol IPC, Extended release.

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INTRODUCTION

Interpolymer complexes (IPCs) are the intermolecular associates that result from intermolecular interactions between different polymers. The physicochemical properties of IPC (e.g., solubility, stability, and crystallinity) and the mechanical properties are different from those of individual polymers[1]. The intermolecular interactions responsible for the formation of IPCs could be classified into 4 categories: (a) an ionic interaction between positively charged and negatively charged polymers[2] ; (b) a hydrogen bond interaction between proton-donating and proton-accepting polymers[3] ; (c) a van der Waals interaction between polymers with different stereo chemical structures such as enantiomer and diastereomer[4]; and (d) a charge transfer interaction between electron-donating and electron-accepting polymers[5]. Ionic interactions and hydrogen bond interactions are the two most studied types of complexation in the field of drug delivery. The interaction between polymers during the formation of IPCs has been confirmed as a cooperative process in which the behavior of a monomer unit in the polymer chain is dependent on the state of the neighboring units[6]. Mixing oppositely charged polymers in the solution will result in their self-assembly or spontaneous association due to the formulation strong, but reversible electrostatic links. Interpolymer complex is formed by the electrostatic interaction between the protonated amine (NH_3^+) groups of Chitosan and the carboxylate (COO^-) groups of polyanionic polymer such as sodium alginate, pectin, carbopol[7].

Chitosan is second most available natural polysaccharide. Chitosan has better biocompatibility, it also has excellent compatibility with organic compounds and anionic and cationic polymers. Multivalent anions easily crosslink with chitosan to form gels and precipitates[8]. Additionally, chitosan is considered to be biodegradable as chitosan is metabolized by certain human enzymes like lysozyme. Highly refined grades of chitosan have been used in pharmaceutical formulation as a release controlling agent in oral preparation[9]. Carbopol is a synthetic high-molecular weight polymers of acrylic acid. The ratio of polymers involved in the interpolymer complex formation could be controlled by the pH of the medium[7].

In this study, we investigated Carbopol/chitosan interpolymer complexe as non-covalently crosslinked hydrogels and applied them to the controlled release tablet matrix. The main driving force of this interpolymer complexation was the electrostatic interaction between the NH_3^+ of chitosan and COO^- of Carbopol®971NF[10].

MATERIALS AND METHODS

Metoprolol tartrate was received was procured from Yarrow Chem Products, Mumbai, India. Chitosan high molecular weight (viscosity of 1% acetic acid solution:800–2000 cP), was procured from Sigma Aldrich, Bengaluru & Carbopol®971NF was obtained by Noveon, Inc. (Cleveland, OH, USA). All other chemicals and reagent used in this study were of analytical grade.

Formulation of interpolymer complex

Preparation of Carbopol/chitosan complex

A Carbopol aqueous solution (1 mg/ml) and chitosan acetic acid solution (5 mg/ml) were mixed (Table 1). The resulting precipitate (Carbopol/chitosan IPC) was washed with distilled water and dried under vacuum over a 24-h period. The dried complex was ground with a grinder and ball milled. The powder was passed through a 200 µm sieve and used for further study.

EVALUATION STUDIES

Characterization of the Carbopol/chitosan IPC

Fourier transform infrared spectroscopic (FT- IR) analysis

The FT-IR spectra of Chitosan, Carbopol®971NF and IPC were analysed using a FT-IR spectrophotometer (Shimadzu, Model 8400S, Japan). The pellets were prepared by pressing the sample with KBr[11].

Viscosity studies

The IPC'S were prepared at different concentrations, by mixing the polymer solutions at different ratios. Optimization of the IPC ratio was done by measuring the viscosity of the supernatant solutions using Brookfield viscometer[13].

Turbidity measurements

An aqueous Carbopol solution (0.5, 1, 1.5, 2, 2.5, 3, 3.5, and 4 mM) and a chitosan acetic acid solution (0.5, 1, and 2 mM) were prepared. The concentration was calculated by dividing the weight of chitosan and Carbopol by the formula weight of each monomer unit. Each Carbopol solution (3 ml) was mixed with the 0.5mM chitosan solutions (3 ml), and each chitosan solution (3 ml) was mixed with a 0.5mM Carbopol solution (3 ml). Each mixture was shaken vigorously. The mixtures were then left to stand for 10 min before measuring the transmittance of the solution as a function of the various mixing ratios (Carbopol/chitosan) at a wavelength of 600 nm using a spectrophotometer[10].

Differential scanning calorimetry (DSC)

The thermal behavior of chitosan, carbopol 71 G and IPC were analysed using a differential scanning calorimeter (DSC Q2000) with a temperature range of 40–250 ºC and a heating rate of 10 ºC/min in a nitrogen atmosphere. The runs were made in triplicate[13].

X-ray powder diffractometry (XRD):

Wide angle x-ray scattering measurements were carried out on a high resolution powder diffractometer with guinier geometry. X-ray diffraction patterns were recorded automatically at a scanning rate of 0.02 ° 29 per sec over the range of 10° - 70°[13].

Formulation of sustained release matrix tablets

Metoprolol tartrate matrix tablets coded MT1 to MT6 were prepared by direct compression method, and the CL-CH interpolymer complex was used as the extended release matrix former in the tablets. The extended-release matrix tablets with a total weight of 650 mg were prepared using a mixture of Metoprolol tartrate, CL-CH IPC, lactose, Magnesium stearate (1% w/w). The mixture was compressed using a hydraulic press with a compression force of 10 kN/cm^2.

In vitro Drug Release Study

Six matrix tablets were taken for dissolution studies using the USP dissolution apparatus II (paddle method) with a paddle rotating at 50 rpm. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug released by measuring the absorbance at 224nm (Shimadzu, UV-1800) using pH 6.8 phosphate buffer. The volume withdrawn at each time intervals was replaced with the same amount of fresh dissolution medium.

RESULTS AND DISCUSSION

Characterization of the Carbopol/chitosan IPC

Fourier transform infrared spectroscopic (FT- IR) analysis

FTIR spectral analysis has been carried out and it suggested that the Carbopol/chitosan IPC was formed by an electrostatic interaction between the COO$^-$ group of Carbopol and NH$_3^+$ group of chitosan. Because the degree of deacetylation of chitosan is 85%, the amine group of the 2-aminoglucose unit and the carbonyl group of the 2- acetaminoglucose unit of chitosan showed absorption bands at 1595 and 1656 cm^{-1}, respectively. The peak at 1715 cm^{-1} in the IR spectrum of Carbopol was assigned to the carbonyl group of carboxylic acid. The IR spectrum of the IPC showed that the peak of 1595 cm^{-1} assigned to the amine band of chitosan was shifted to 1640 cm^{-1}, indicating that the amine group was protonated to a NH$_3^+$ group in IPC. The bands at 1550 and 1408 cm^{-1} were assigned to the symmetric and asymmetric stretching of the COO$^-$ group. In addition, the NH$_3^+$ peak was known to appear between 1600 and 1460 cm^{-1}. Moreover, the peak of NH$_3^+$ groups in the complex between chitosan and poly (acrylic acid) was known to appear at 1520 cm^{-1}. Therefore, the broad peak around 1550 cm^{-1} was believed to be the overlapped peak of COO$^-$ and NH$_3^+$ peak. These results suggested that the Carbopol/chitosan IPC was formed by an electrostatic interaction between the COO− group of Carbopol and NH3+ group of chitosan.

Viscosity studies

Figure 6 represents a plot illustrating the influence of varying the CL-CH ratios on the supernatant viscosity of the corresponding mixture. As the CL concentration was increased, the supernatant viscosity was decreased indicating that the protonated amine groups of CH were undergoing complexation with the carboxylate groups of the anionic polymer CL to variable extents. This relation was held true till a certain CL concentration. This could indicate that the interaction sites of chitosan and these anionic polymers were almost saturated. Therefore, the reacting polymers formed an insoluble complex and the supernatant viscosity would represent that of the solvent. Above this optimum ratio, there was no further decrease in the viscosity. And as the CH concentration was increased, the supernatant viscosity was increased. This indicated that the optimum ratio of CH:CL could be considered as 1:4 since this ratio is having the least viscosity.

Turbidity measurements:

The change in transmittance as a function of the unit molar ratio of Carbopol to chitosan was measured to determine the composition of the IPC, as shown in figure 7. The chitosan acetic acid solution and the Carbopol aqueous solution were transparent regardless of their concentration prior to mixing. The transmittance of the IPC did not show a significant change with increasing Carbopol concentration up to a CL:CH ratio of 1:1. However, the transmittance decreased as the ratio was changed from 1:1 to 1:4. The change in transmittance was not significant at higher ratios. It appears that the excess chitosan (or Carbopol) did not react with Carbopol (or chitosan) because of the saturation of the electrostatic interaction sites of Carbopol (or chitosan) by that of chitosan (or Carbopol). As the chitosan:carbopol ratio was changed from 4:1 to 1:1 (the amount of Carbopol was fixed at 0.5 mM), the amount of IPC formed was determined by the amount of Carbopol. As the chitosan:carbopol ratio was changed from 1:1 to 1:4 (the amountof chitosan was fixed at 0.5 mM), the amount of IPC increased with increasing amount of Carbopol. At a chitosan:carbopol ratio of 1:4, each interaction site of chitosan and Carbopol was saturated, and further increase in the amount of chitosan did not cause any change in turbidity. The transmittance results clearly showed that the complexation unit molar ratio of chitosan with Carbopol was 1:4. Therefore, the chitosan and Carbopol IPC with the mixing ratio 1:4 was used to characterize the IPC and to study the release profile.

Differential scanning calorimetry (DSC):

The results of Differential scanning calorimetric (DSC) analysis are shown in figures 8-12. The exothermic peak attributable to the decomposition of chitosan appeared at approximately 320°C. In the DSC thermogram of Carbopol, the glass transition temperature was observed near 135°C and the decomposition of Carbopol was observed at approximately 280°C at which the Carbopol had melted and decomposed sequentially. The broad endothermic peak near 100°C was attributed to the physically bound-water. The endothermic peak of the IPC due to bound water was smaller than that of chitosan. The water absorption ability of chitosan is expected on account of its amine group being reduced by the complexation of chitosan with Carbopol. Therefore, the water absorption capacity of the IPC may be lower than chitosan. The reduced water absorption capacity might result in the slow disintegration of the IPC matrix and the extension of drug release from the IPC matrix.

DSC tracings of pure Metoprolol tartrate and formulation MT4 are displayed in figure 11 and 12. Metoprolol tartrate showed a sharp endothermic peak at 123.85° C whereas the formulation showed a peak at 123.8°C which indicated that the drug existed in the crystalline form in the formulation.

X-Ray diffractometry (XRD):

The results of X-ray diffractometry (XRD) analysis are shown in fig. 25, 26, 27. The XRD patterns have shown that there is no interaction between the drug and the interpolymer complex. And also the drug has not lost its crystalline nature when combined with the interpolymer complex.

***In vitro* Drug Release Study**

The *in vitro* drug release study was carried out in 6.8 pH phosphate buffer using USP type-II dissolution apparatus according to USP for Metoprolol ER tablets. Formulation MT6 showed NMT 25% release in 1 h, 20-40% release in 4 h, 40-60% release in 8 h and NLT 80 % release in 20 h. It was also seen that as the interpolymer complex concentration was increased, there was a decrease in dissolution release rate.

To confirm the exact mechanism of drug release from these tablets, the data were fitted according to the equation of Korsmeyer and Peppas, given as $M_t/M_\infty=Kt^n$ where M_t/M_∞ is the fractional release of drug in time t, K is a constant incorporating structural and geometric characteristics of the controlled-release device, and n is the diffusional release exponent indicative of mechanism of release. The value of n is 0.5 for Fickian transport, more than 0.5 and less than 1 for non-Fickian transport, and 1 for case II transport (zero order); when the value of n approaches 1, it may be concluded that the release is approaching zero order. The dissolution data were fit to the above equation by drawing a log-log plot of the fraction released versus time. The 'n' value were between 0.647 to 0.975, which indicated that the release followed non-Fickian diffusion mechanism or anomalous transport and suggesting that both diffusion of the drug in the hydrated matrix and chains relaxation process affect the drug release process. The initial burst effect is probably due to the fact that the gel layer, which controls the release of the drug, needs some time to become effective. The mixture of the two polymers, used as release modulator agents, enables the system to reach a nearly zero-order release kinetic (n for MT6 is 0.975).

Table 1: Formulations of Metoprolol Tartrate Tablets by direct compression

Formulation	Ratio of drug: CL-CH IPC	Drug MT (mg)	CL-CH IPC (mg)
MT1	1:0.25	200	50
MT2	1:0.5	200	100
MT3	1:0.75	200	150
MT4	1:1	200	200
MT5	1:1.25	200	250
MT6	1:2	200	400

Table 2: Viscosity studies of various ratios of CL:CH

IPC Code	CH:CL	Viscosity (centistokes)
1.	1:1	54.6
2.	1:2	10.5
3.	1:3	8.2
4.	1:4	7.0
5.	1:5	8.1
6.	2:1	49.4
7.	3:1	53.5
8.	4:1	54.1
9.	5:1	55.1

Table 3: Turbidity measurements of CH:CL in various ratios

IPC Code	CH:CL	TRANSMITTANCE%
1.	5:1	78.3

2.	4:1	77.1
3.	3:1	76
4.	2:1	75
5.	1:1	75.5
6.	1:2	34.4
7.	1:3	20.5
8.	**1:4**	4.7
9.	1:5	4.8

Fourier Transform Infra-Red (FTIR) spectroscopy

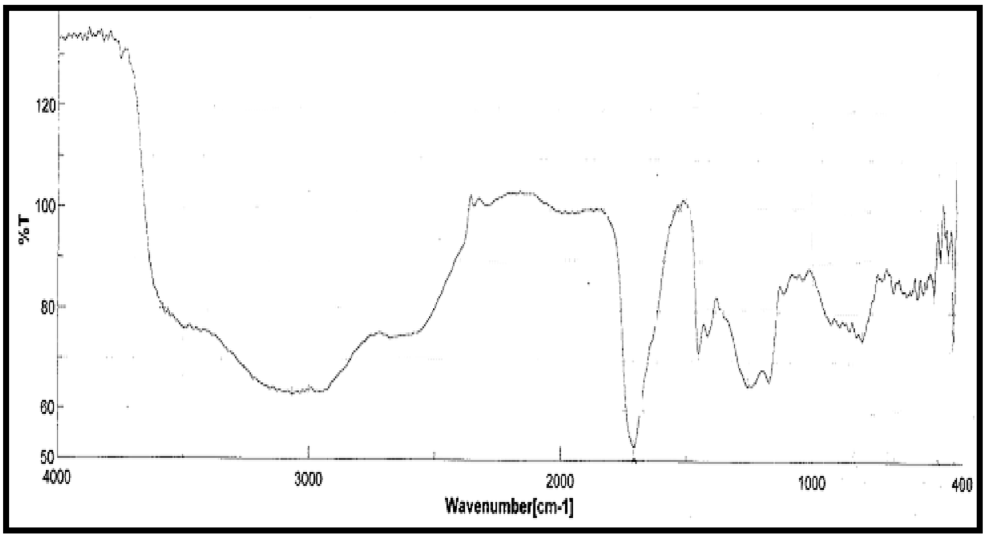

Figure 1: FTIR spectra of Carbopol®971NF

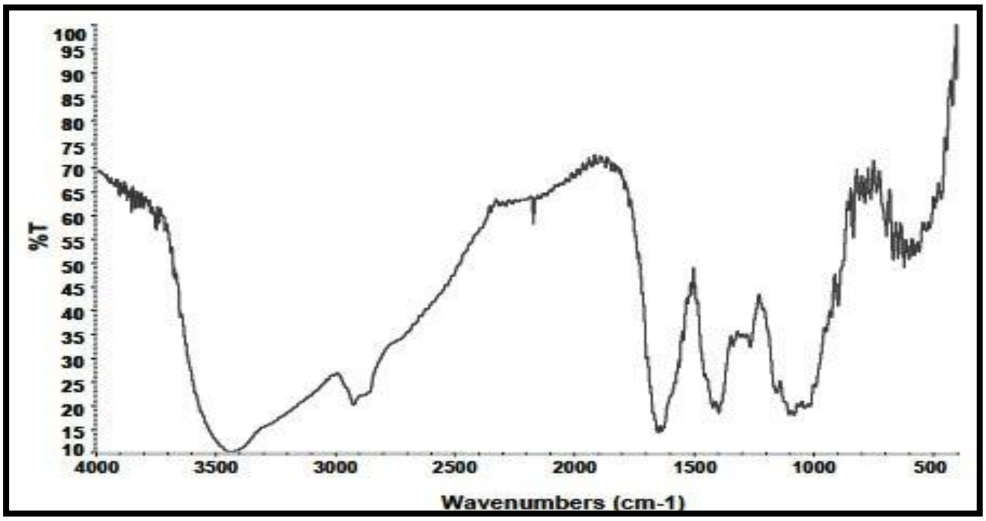

Figure 2: FTIR spectra of Chitosan

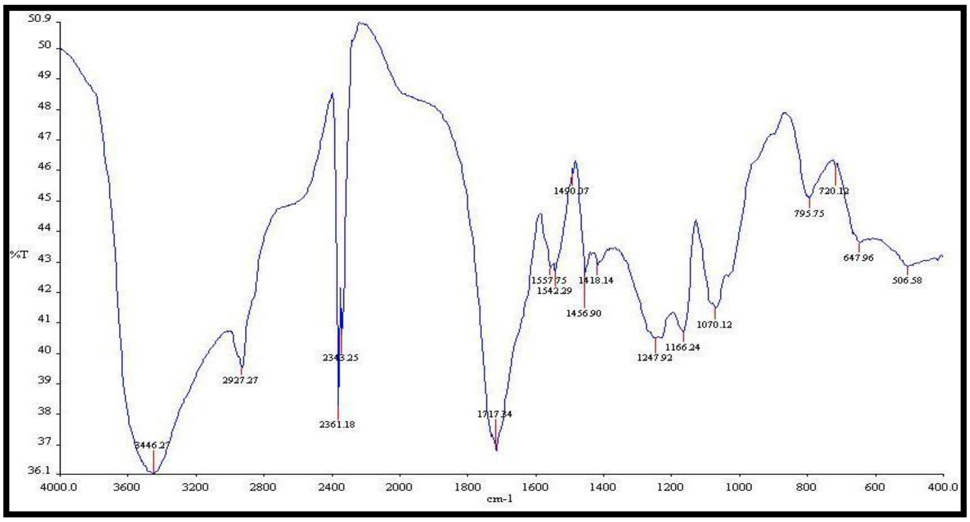

Figure 3: FTIR spectra of Carbopol /chitosan IPC

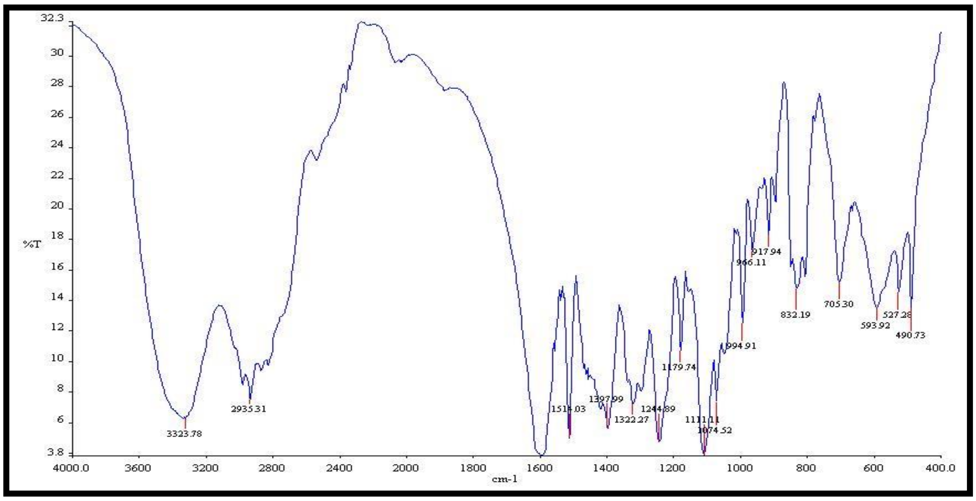

Figure 4: FTIR spectra of Metoprolol tartrate

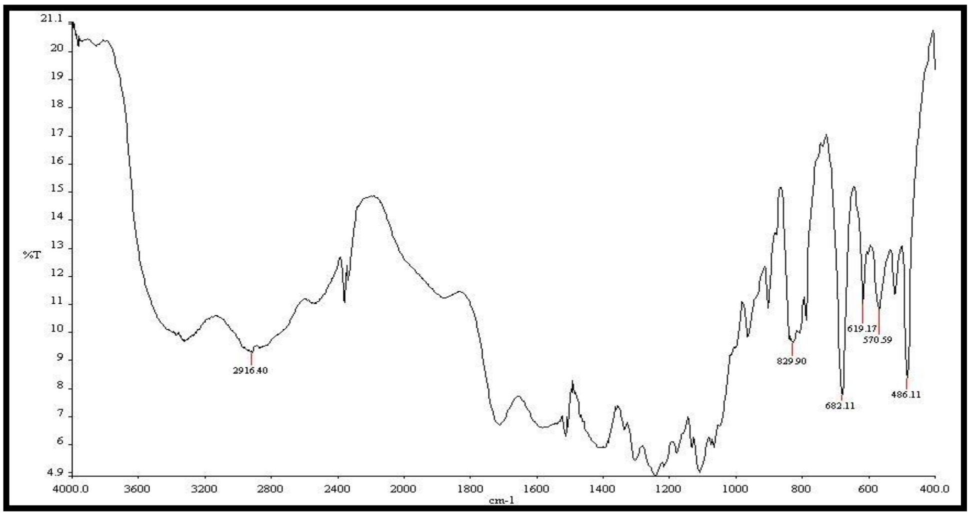

Figure 5: FTIR spectra of Metoprolol tartrate mixed with Carbopol/chitosan IPC

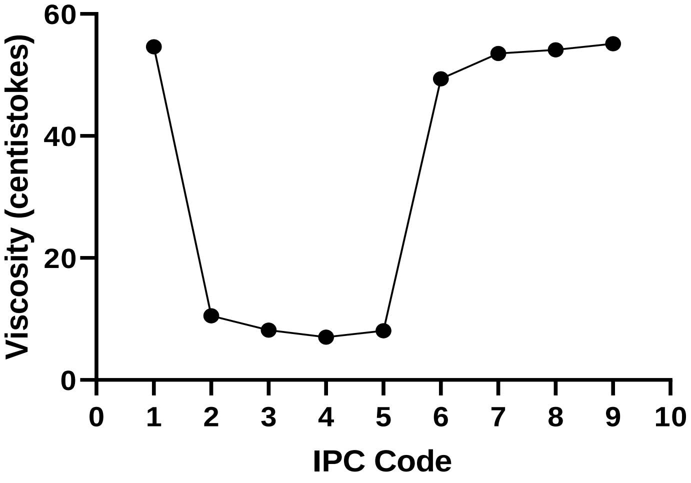

Figure 6: Viscosity graph of CL:CH ratio

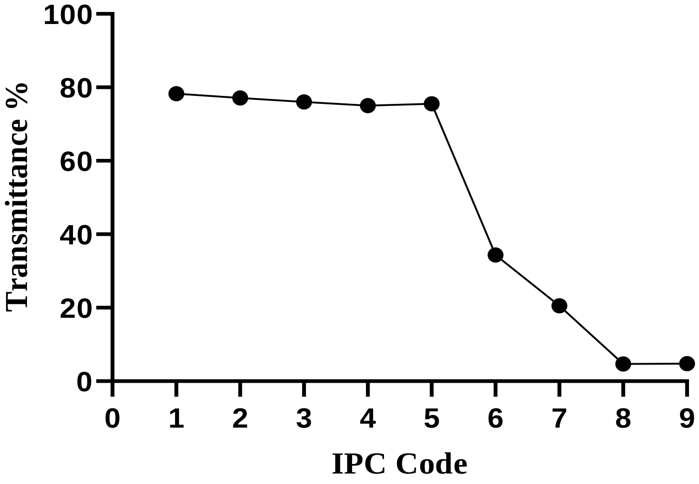

Figure 7: Turbidity measurement graph of CH:CL in various ratios

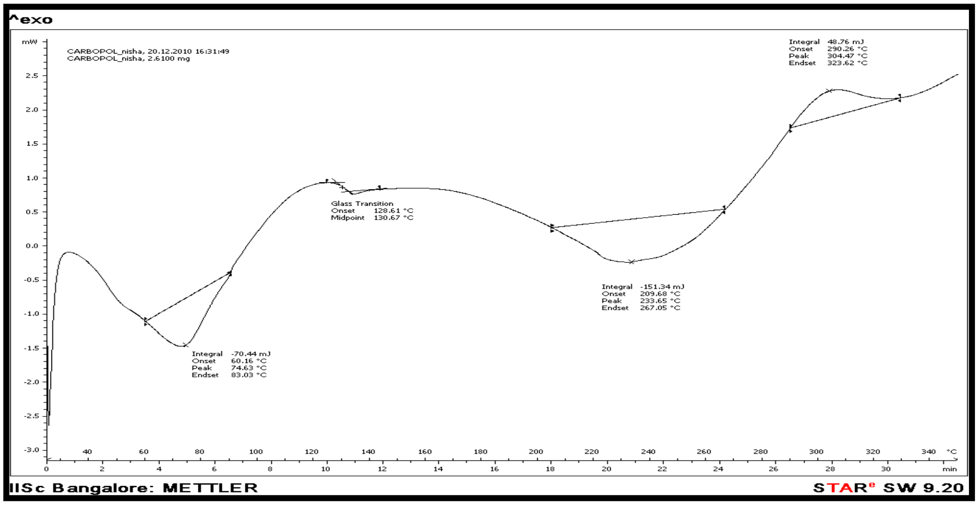

Figure 8: DSC of Carbopol

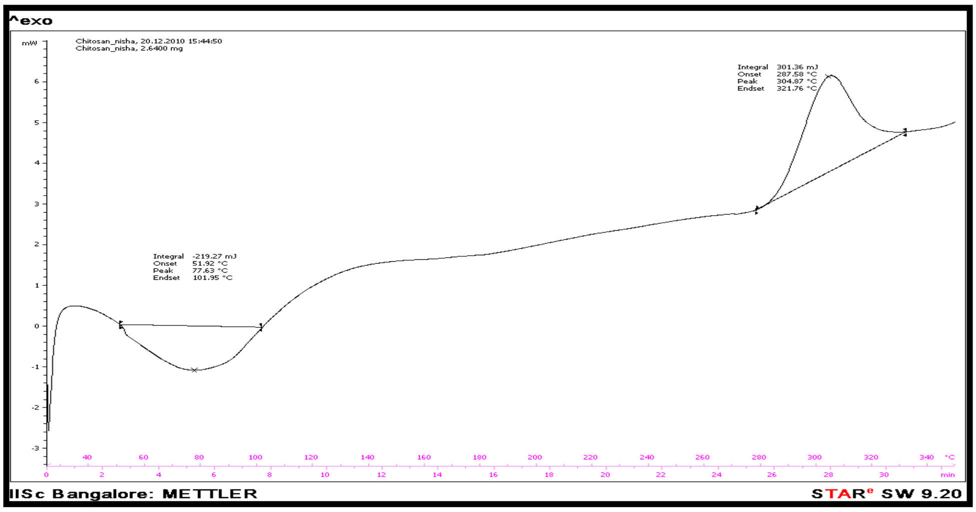

Figure 9: DSC of Chitosan

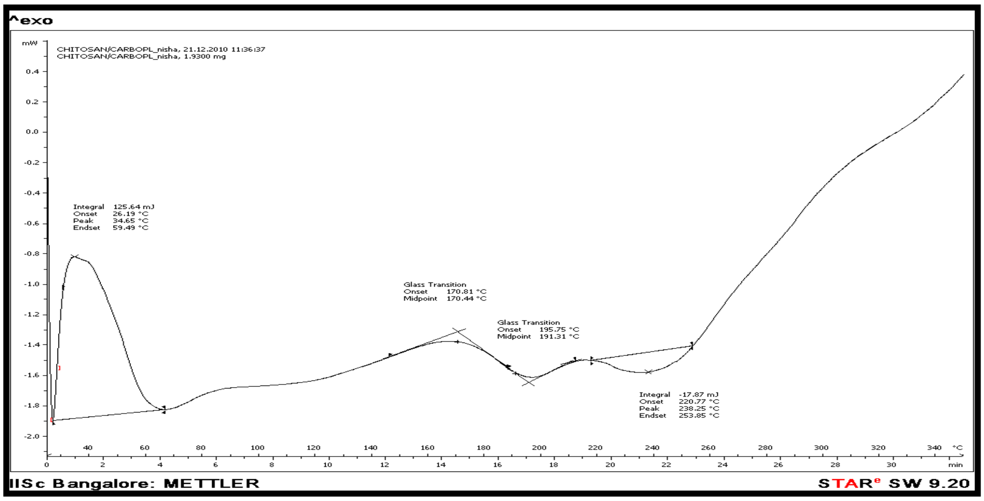

Figure 10: DSC of Carbopol/chitosan IPC

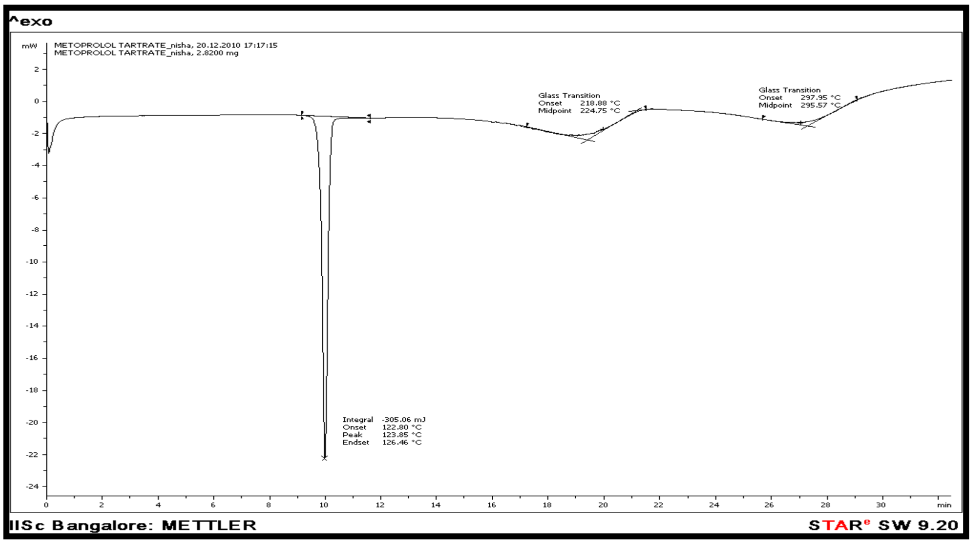

Figure 11: DSC of Metoprolol tartrate

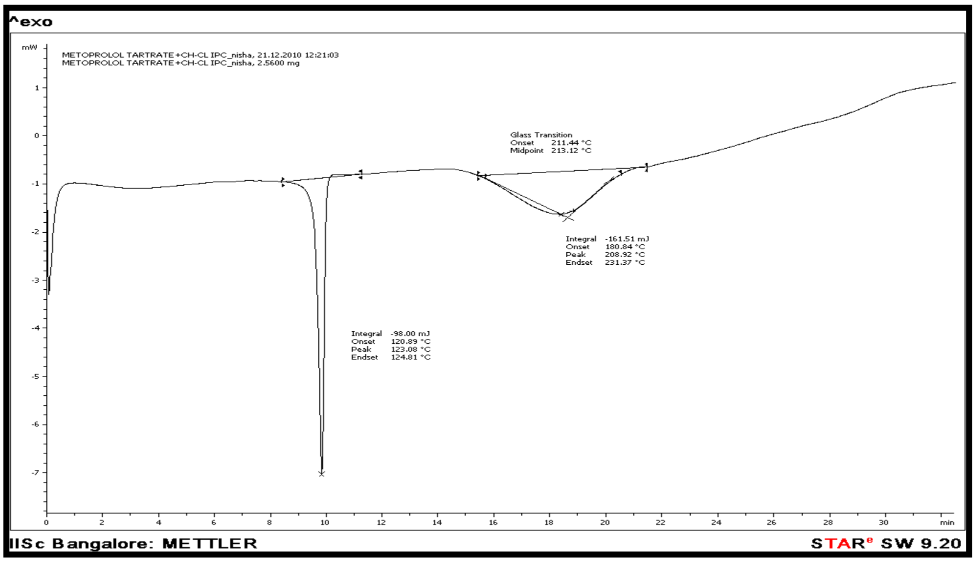

Figure 12: DSC of Formulation MT4

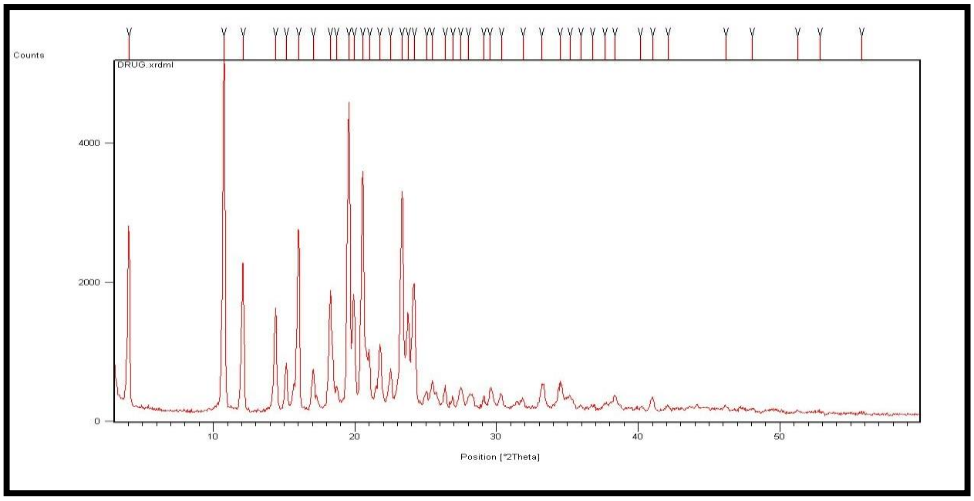

Figure 13: XRD of Metoprolol tartrate

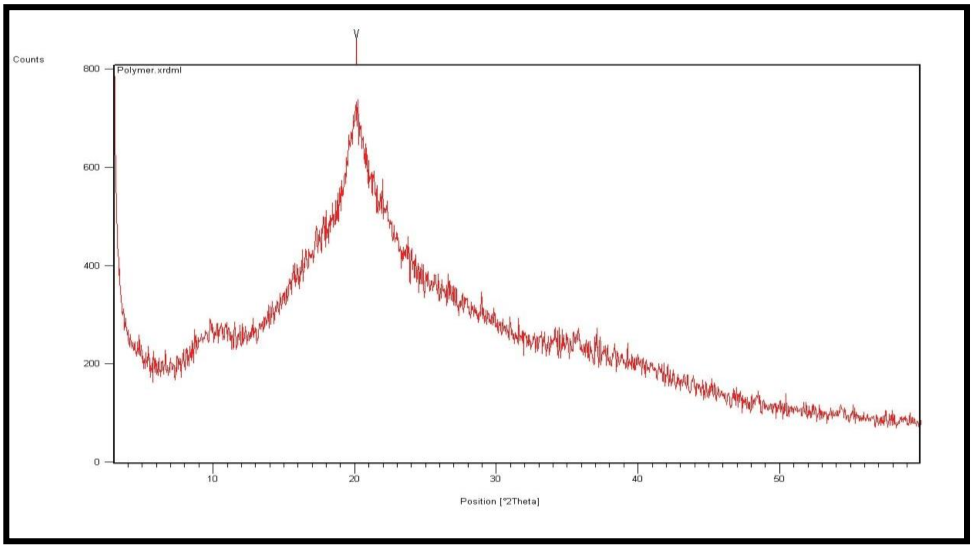

Figure 14: XRD of Carbopol/chitosan IPC

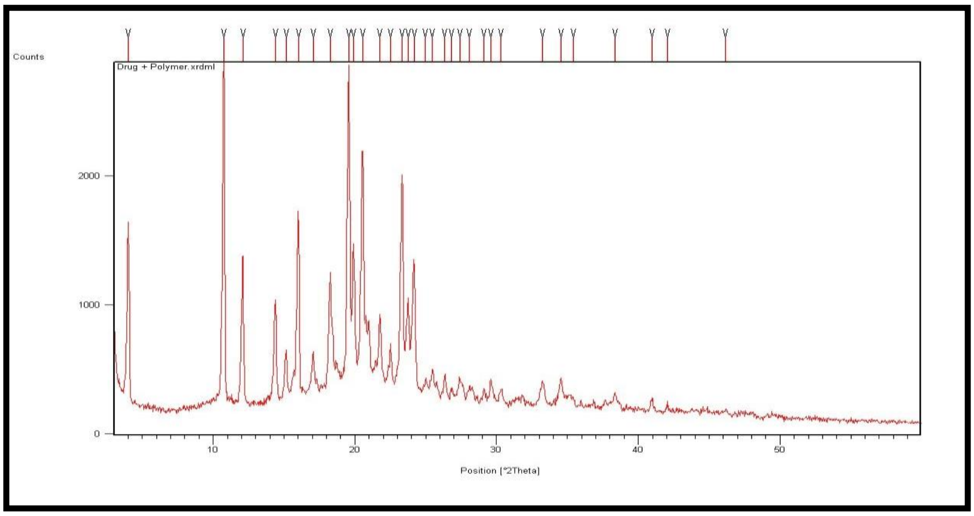

Figure 15: XRD of Metoprolol tartrate mixed with Carbopol/chitosan IPC

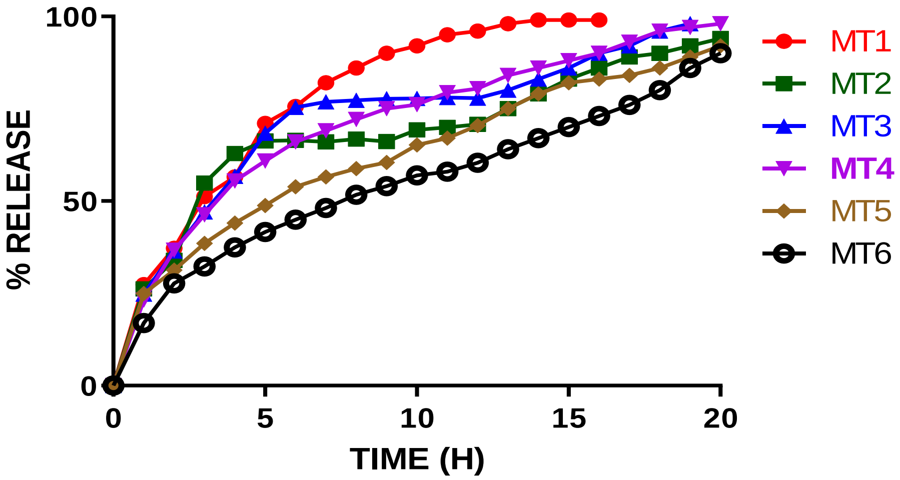

Figure 16: Comparative release profile of Metoprolol Extended Release Formulations MT1- MT6

CONCLUSION

The extended release matrix tablets of an antihypertensive drug like Metoprolol tartrate can be formulated for the treatment of angina pectoris using an optimum ratio of Carbopol/chitosan interpolymer complex as a matrix former. Carbopol/chitosan interpolymer complex was compatible with the drug and showed excellent matrix forming characteristics. The pH dependent swelling and release property of Carbopol can be decreased by the formation of a complex with chitosan, and can be used as a pH independent extended-release tablet matrix.

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REFERENCE

1. Zhang F., Lubach J., Watson N., Momin S., Interpolymer Complexation Between Polyox and Carbopol, and Its Effect on Drug Release from Matrix Tablets. J Pharm Sci, 105(8): 2386-2396, (2016)
2. Bekturov E.A., Bimendina L.A., Interpolymer complexes. Adv Polym Sci, 41: 99-147, (1981)
3. Jiang M., Li M., Xiang M.L., Zhou H., Interpolymer complexation and miscibility enhancement by hydrogen bonding. Adv Polym Sci, 146: 121-196, (1999)
4. Saravanan M., Domb A.J., A contemporary review on polymer stereocomplexes and its biomedical application. E J Nanomed. 5(2):16-21, (2013)
5. Rodriguezparada J.M., Percec V., Interchain electron donor-acceptor complexes: a model to study polymer-polymer miscibility. Macromolecules. 19(1): 55-64, (1986)

6. Kabanov V.A., The cooperative interactions of complementary synthetic macromolecules in solutions. In: Macromolecular Chemistry, Vol 8. Helsinki, Finland: Bros Ltd: 121-145, (1972)
7. Naidu V.G.M., Madhusudhana K., Sashidhar R.B., Ramkrishna S., Khar R.K., Ahmed F.J., Diwan P.V., Polyelectrolyte complexes of gum kondagogu and chitosan, as diclofenac carriers. Carbohydr Polym, 76: 464-471, (2009)
8. Lu Z., Chen W., Olivier E.I., Hamman J.H., Matrix polymeric excipients: Comparing a novel polyelectrolyte complex with hydroxypropylmethyl cellulose. Drug Deliv, 15: 87-96, (2008)
9. Etrych T., Leclercq L., Boustta M., Vert M., Polyelectrolyte complex formation and stability when mixing polyanions and polycations in salted media. Eur J Pharm Sci, 2: 281-288, (2005)
10. Lee, MH., Chun, MK. & Choi, HK. Preparation of Carbopol/Chitosan Interpolymer Complex as a Controlled Release Tablet Matrix; Effect of Complex Formation Medium on drug Release Characteristics. Arch Pharm Res, 31(7): 932-937, (2008)
11. Cho, S.M., Choi, H.K. Preparation of mucoadhesive chitosan–poly (acrylic acid) microspheres by interpolymer complexation and solvent evaporation method I. J Kor Pharm Sci, 35: 95–99, (2005b)
12. Park, S.H., Chun, M.K., Choi, H.K., Preparation of an extended-release matrix tablet using chitosan/Carbopol interpolymer complex, Int J Pharm, 347: 39-44, (2008).
13. Noble, L., Gray, A.I., Sadiq, L., Uchegbu, I.F., A noncovalently cross-linked chitosan based hydrogel, Int J Pharm, 192: 173-182, (1999)