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Research Article

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Controlled release tablet formulations of carvedilol

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ABSTRACT

The present investigation was undertaken with an objective of formulating controlled release (CR) oral matrix tablet formulations of Carvedilol (CAR), an antihypertensive using cellulose ether polymer, Hydroxy Propyl Methyl Cellulose (HPMC K4M, HPMC K15M) of different viscosity grades as drug release retardants. The tablets were prepared by direct compression technique and evaluated for various physico-chemical/mechanical parameters. Based on the viscosity and gel formation during dissolution, HPMC K4M was selected as release retardant. The effect of different fillers like Avicel PH 101, Avicel PH 105 and Avicel PH 200 (microcrystalline cellulose), pre gelatinized starch (PGS), maize starch with spray dried lactose (FLOWLAC) on CAR release was studied and percent release of CAR at the end of 24h is in the order of FLOWLAC > Avicel PH 101 > Avicel PH 105 > Avicel PH 200 > PGS. Based on the dissolution data obtained with different fillers and keeping in view of the results from the pre-compression studies, and gel layer retaining with the matrix tablets, Avicel PH 105 was selected to carry out further formulation development. The formulation containing 25%w/w HPMC K4M as release retardant and Avicel PH 105 gave 96.59 ± 3.1% release at the end of 24h and fulfils regulatory requirement. The dissolution data was also evaluated for drug release kinetics and mechanism.

Key Words: Carvedilol, Controlled release tablets, Cellulose ether polymer, Diluents, Release kinetics.

INTRODUCTION

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery systems of existing drug molecules to maximize their therapeutic action, patient compliance and protection. Patient protection is equally important in the case of antihypertensive agents, because if constant blood levels are not maintained, it results in dose dumping which leads to hypotension. Controlled release formulations help to maintain constant blood levels [1].

CAR, an anti-hypertensive agent is a nonselective β-adrenergic blocking agent with α_1-blocking activity which is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 25-35% due to a significant degree of first-pass metabolism and its plasma half-life is about 6h [2]. The maximum dose administered per day is 25mg and administered 2-3 times in divided doses. COREG and COREG CR are the two US approved formulations marketed by GlaxoSmithKline.

Research works published on CAR include CR dosage forms [3] in which polyethylene oxides were used as release retardants, fast dissolving tablets [4], muco-adhesive tablets [5], and transdermal patches [6]. The present investigation was aimed to develop once daily controlled release oral matrix tablet dosage forms of CAR based on cellulose ether polymers like HPMC K4M, and HPMC K15M as drug release retardants.

EXPERIMENTAL SECTION

Carvedilol (Aurobindo Pharmaceuticals, Hyderabad), HPMC K4M (Colorcon, India), HPMC K15M (Colorcon, India), Partially pre gelatinized starch (Rouette Pharma, France), Spray dried lactose with maize starch (Rouette Pharma, France), Microcrystalline cellulose PH 200 (Rouette Pharma, France), Microcrystalline cellulose PH 105 (Rouette Pharma, France), Microcrystalline cellulose PH 101(Rouette Pharma, France) Methanol (Loba Chemie, Mumbai), Talc (Loba Chemie, Mumbai), Colloidal silicone dioxide (Loba Chemie, Mumbai) were used. All the chemicals and reagents of analytical grade were used.

Analytical Procedures

An UV-VIS Spectrophotometric method [7] based on the measurement of absorbance at 241nm in methanol stock solution was used in the present research work for the estimation of CAR in dissolution samples.

Solubility Studies

Excess amount of CAR was added to 10 mL of each fluid in 25mL stoppered conical flasks and the mixtures were shaken for 48 hours at room temperature (28 ± 1°C) on a rotary flask shaker.1mL aliquots were withdrawn at different time intervals and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were suitably diluted and assayed for CAR by measuring absorbance at 241nm. Shaking was continued until three consecutive estimations were same. The solubility experiments were run in triplicate.

Drug excipients compatibility by FTIR spectroscopy

The FTIR spectra of CAR alone and CAR with different excipients like HPMC K4M, HPMC K15M, Partially pre gelatinized starch, Spray dried lactose with maize starch, Microcrystalline cellulose PH 200, Microcrystalline cellulose PH 105, Microcrystalline cellulose PH 101, Talc, Colloidal silicone dioxide were measured using ATR-FTIR spectrophotometer (Bruker, Germany). ATR spectra were recorded over the wave number range of 4000-500 cm^{-1} at a resolution 1.0 cm^{-1}. The powder is simply placed onto the ATR crystal and the sample spectrum is collected.

Preparation and Evaluation of CAR CR Matrix Tablets

CR oral tablet formulations of CAR were prepared by direct compression method, as per formulae given in Table 1. Two different grades of HPMC i.e., K4M, K15M were used as release retardant materials. Colloidal silicone dioxide and talc at 1% concentrations were used as glidant/lubricants. Sufficient quantities of microcrystalline cellulose, spray dried lactose with starch, pre gelatinized starch were used to raise the total bulk of the tablets to a weight of 200mg each. All the ingredients were passed through sieve # 80 before mixing. Initially drug and polymers were mixed thoroughly and then required quantities of fillers were added and finally the blend was mixed with talc thoroughly for 5min in a poly bag and then required amount of colloidal silicon dioxide was added and mixed for another 5min. Powder blends (for 50 tablets each) of all the above formulations were compressed on single punch tablet press (Cadmach, India) using 8mm punches (round shape) to the hardness of 6Kg/cm^2.

Table 1: Formulae of CR tablets of CAR with different excipients

INGREDIENTS (mg/Tab)	FORMULATION											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
CAR	20	20	20	20	20	20	20	20	20	20	20	20
HPMC K4 M	50	-	40	-	50	60	60	50	50	-	40	40
HPMC K15 M	-	50	-	50	-	-	-	-	-	50	-	-
MCC PH 200	-	-	-	-	-	116	-	-	-	-	-	-
MCC PH 105	-	-	-	-	-	-	116	126	-	126	136	-
MCC PH 101	-	-	-	-	-	-	-	-	126	-	-	136
SDL	-	-	-	126	126	-	-	-	-	-	-	-
PGS	126	126	136	-	-	-	-	-	-	-	-	-
Colloidal silicon dioxide	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight (mg)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Evaluation of flow properties of powder blends

The powder blends were evaluated for parameters like bulk density, tapped density, Carr's index, Angle of repose, and Hausner's ratio [8].

Evaluation of CAR CR Tablets
The compressed CR tablets were evaluated for following properties: drug content, uniformity of weight, friability, hardness, and disintegration time and *in vitro* drug release profiles [9].

Drug content
Ten tablets were weighed and powdered in a mortar. Accurately weighed tablet powder samples equivalent to 20mg of CAR was transferred to a 100mL volumetric flask, and the CAR was extracted into 75mL methanol and then finally the volume was made to 100 mL with methanol. This solution was suitably diluted with 0.1N HCl and the absorbance was measured at 241nm. The estimations were carried out in triplicate.

Uniformity of weight of tablets
The individual and total weight of 20 tablets from each batch was determined. Percentage deviation of the individual weights from the average weights was calculated.

Hardness
The hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-66, India). The results reported were average of 6 tablets for each formulation.

Friability
For each formulation 10 tablets were weighed, placed in Friabilator (M/S Cambell Electronics, India) and were subjected to 100 rotations in 4min. The tablets were reweighed and friability was calculated by the following formula:

$$Friability = \frac{W_2 - W_1}{W_1} \times 100$$

Where W_1 is the initial weight and W_2 is the final weight of the tablets.

Dissolution studies
In vitro dissolution studies of CAR controlled release formulations prepared were carried out in 900mL of 0.1N HCl using USPXXI type II (paddle method) Dissolution Rate Test Apparatus (DISSO 8000, Lab India). The tablet was placed in a sinker and placed in to the dissolution medium. A speed of 100 rpm and a temperature of 37 ± 1ºC were used in each test. A 5mL aliquot was withdrawn at different time intervals, and replaced with 5mL of fresh dissolution medium. The filtered samples (filtered using a 0.45µ nylon disc filter) were suitably diluted if necessary and assayed for CAR by measuring absorbance at 241nm. The dissolution experiments were carried out in triplicate.

Release kinetics and mechanism
In order to describe the kinetics of the release process of CAR, various equations were used such as the zero-order rate equation [10], which describes the systems where the release rate is independent of the concentration of the dissolved species. The first-order equation [11] describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species. The Higuchi square root equation [12], describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion. Two factors, however, diminish the applicability of Higuchi's equation to matrix system. This model fails to allow for the influence of swelling of the matrix upon hydration and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the Peppas equation [13], which is often used to describe the drug release from polymeric system.

$$Mt/Ma = K\, t^n \qquad (1)$$

Where Mt/Ma is the fractional drug release at time t; K is a constant incorporating the properties of the macromolecular polymeric system and the drug and n is a kinetic constant which depends on and is used to describe the transport mechanism. The value of n for a tablet, n = 0.45 for Fickian (Case I) release, > 0.45 but < 0.89 for non Fickian (anomalous) release and 0.89 for case II (zero-order) release and > 0.89 for super case II type of release. Equation one was used to calculate the n values and to identify the drug release mechanism of drug.

Due to the differences in drug release kinetics, the Peppas constant k, though is one of the measures of release rate, should not be used for comparison. Therefore, to characterize the drug release rate in different formulations, mean dissolution time (MDT) was calculated from dissolution data using the formula:

$$MDT = (n/n+1) \times k^{-1/n}$$

Where n is the release exponent and k is the Peppas constant [14]. MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher value of MDT indicates a higher drug retarding ability of the polymer and vice-versa [15].

RESULTS AND DISCUSSION

Solubility Studies

CAR is not yet official in any pharmacopoeia; official dissolution rate test is not available. However, dissolution rate tests were reported for marketed formulations of CAR where 0.1N HCl was used as dissolution medium for evaluating *in vitro* dissolution profiles for extended release CAR formulations. Based on these published FDA reports solubility of CAR in 0.1N HCl and different buffer solutions and also in water was carried out and results were shown in Fig.1.

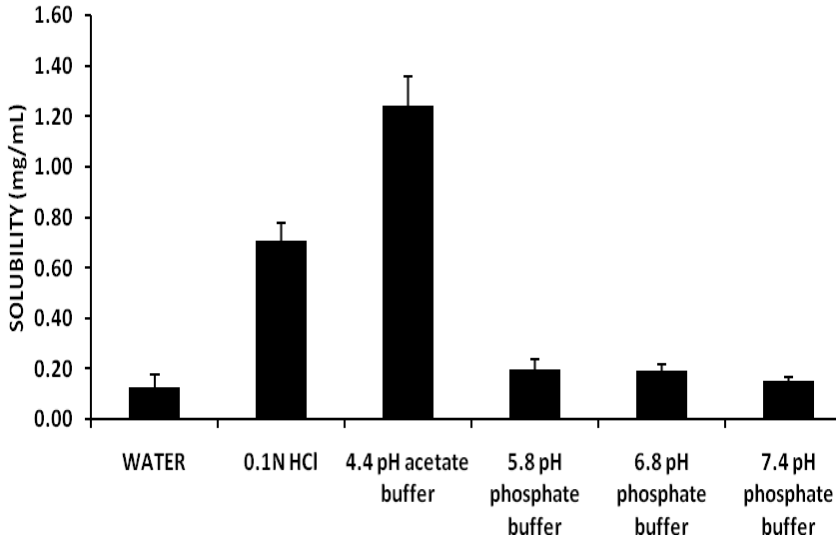

Fig.1: Solubility of CAR in different media

FTIR Studies

Fig.2 shows the IR spectra of pure CAR and CAR excipient mixtures in 1:1M. The CAR showed IR absorption bands at 3338 cm^{-1} for N-H stretching. The absorption band at 2920 cm^{-1} was denoted for C-H (acids) stretching. The band at 1338 cm^{-1} was denoted for OH sharp stretching. The band at 1589 cm^{-1} was denoted for N-H stretching in chain. Band at 1212 cm^{-1} was denoted for O-C stretching and the band at 1095 cm^{-1} was for C-N stretching.

All these characteristic peaks of CAR were observed in IR spectra of drug-excipient mixtures also. These characteristic IR absorption bands of CAR were all retained in the presence of the selected excipients indicates that there is no *in situ* interaction between the CAR and excipients.

Determination of pre compression parameters

These results indicated that the powder blends of all formulations were suitable to prepare tablets by direct compression technique. The results are shown in Table 2.

Table 2: Pre compression parameters of tablet powder blends

Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Compressibility index (%)	Hausner ratio	Angle of repose (°)
Pure drug	0.451	0.632	26.45	1.43	33.24
F1	0.806	0.926	12.90	1.18	18.45
F2	0.820	0.962	14.75	1.12	19.65
F3	0.833	0.962	13.33	1.20	22.35
F4	0.667	0.781	14.67	1.22	25.96
F5	0.658	0.769	14.47	1.25	26.82
F6	0.676	0.781	13.51	1.25	26.96
F7	0.667	0.794	16.00	1.22	25.72
F8	0.676	0.806	16.22	1.19	24.89
F9	0.658	0.794	17.11	1.30	25.78
F10	0.667	0.820	18.67	1.24	26.50
F11	0.676	0.833	18.92	1.25	26.47
F12	0.673	0.834	18.78	1.26	26.76

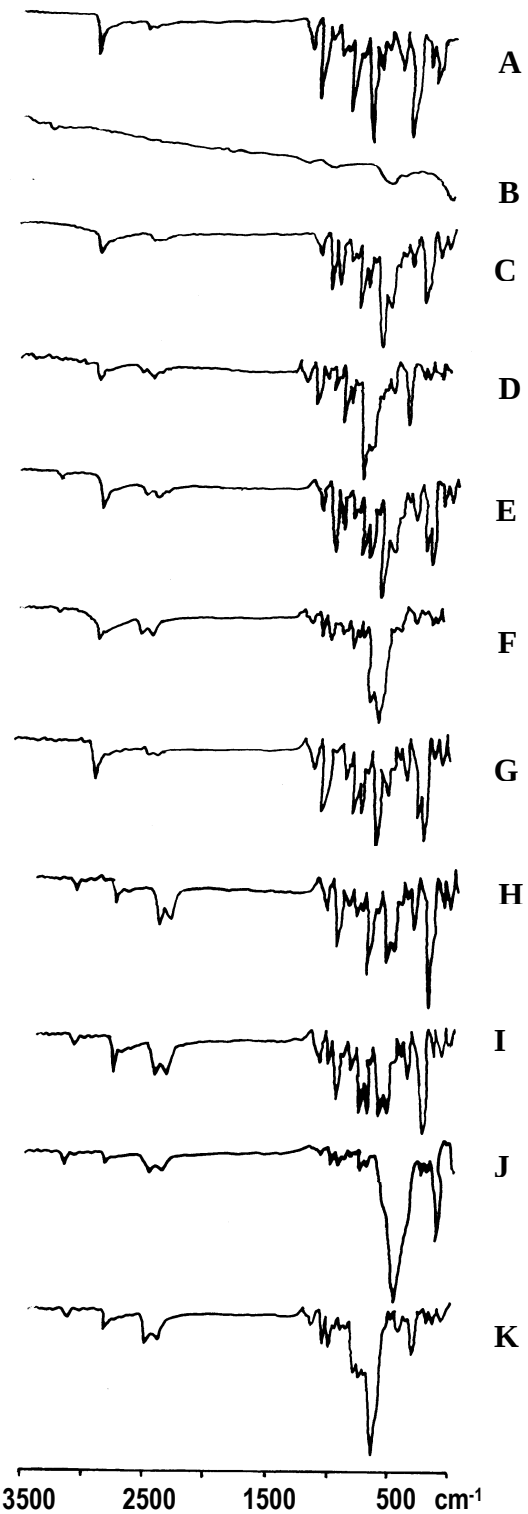

Fig.2. FTIR spectra of pure CAR (A); HPMC K15M (B); CAR: HPMC K4M (C) CAR: HPMC K15M (D); CAR: Avicel PH101 (E); CAR: Avicel PH 105 (F); CAR: Avicel PH 200 (G); CAR: FLOWLAC (H); CAR: PGS (I); CAR: Talc (J); CAR: Silicon dioxide (K).

Determination of post compression parameters

The compressed tablets fulfilled the official compendial requirements regarding drug content, uniformity of weight, hardness and friability. The results are shown in Table 3.

Table 3: Various evaluation parameters of CAR CR tablets

Formulation	Drug content (mg/tab)	Weight variation (mean ± SD)	Hardness (kg/cm^2)	Friability (% wt. loss)
F1	19.98	200 ± 1.51	6.0	0.29
F2	20.62	199 ± 1.51	6.0	0.32
F3	20.84	200 ± 0.92	6.5	0.26
F4	19.97	200 ± 1.01	5.5	0.31
F5	19.81	201 ± 1.21	5.5	0.49
F6	19.99	201 ± 0.94	6.0	0.22
F7	20.25	199 ± 1.22	6.0	0.27
F8	20.76	198 ± 1.82	6.0	0.31
F9	20.56	199 ± 1.36	6.2	0.39
F10	20.79	200 ± 1.61	6.5	0.21
F11	19.73	198 ± 0.84	6.0	0.28
F12	20.23	201 ± 1.91	6.0	0.42

***In vitro* drug release studies**

All the tablet formulations were subjected to *in vitro* drug release studies using 0.1N HCl as dissolution medium, in order to assess drug release profiles including release kinetics and drug release mechanisms from tablets.

The CR tablets gave a controlled release of CAR over a period of 10 to 24 hours. The dissolution profiles of these formulations (F1-F12) clearly indicated a controlled release pattern over a period of 10-24 hrs, because HPMC tablet formulations swelled upon contact with dissolution medium and a gel layer was formed on their surface. This gel retarded further ingress of fluid and subsequent drug release.

Diluents fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. Diluents can affect the drug release from dosage form. Among the various water soluble and insoluble and directly compressible grade diluents, few diluents such as, different grades of Avicel i.e., PH 101,105, and 200, PGS, maize starch with spray dried lactose (FLOWLAC) were used to study their effect on CAR release.

Initial formulation studies were carried out to look in to the release retarding effect of different swellable polymers used. With formulation F1 containing 25% w/w HPMC K4M, as release retardant material, 77.74 ± 2.19 percent of CAR was released at the end of 24 hours. The diluent PGS used also acts as binder. But the release was less at the end of 24 hours. So, in formulation F2, 25%w/w HPMC K15M was used as release retarding agent. The diluent used was PGS. The release was decreased than formulation F1. Only 69.79 ± 3.39 percent CAR release was observed. So, in F3 formulation polymer concentration was decreased. Here, 20%w/w HPMC K4M was used and same diluent was used as that in F2 formulation, i.e. PGS 79.17 ± 2.8 percent release was observed in formulation F3. In F4 formulation, 25% w/w HPMC K4M was used. The diluent used was SDL (spray dried lactose with maize starch). Complete drug release was observed with this formulation at end of 10 hours. Here, the tablet integrity was lost within 10 hours of dissolution. In formulation F5, 25%w/w HPMC K15M was used as release retardant and SDL (spray dried lactose with maize starch) was used as diluent. Here also the tablet integrity was lost within 10 hrs of dissolution and hence complete CAR release was observed. In formulation F6, 30%w/w HPMC K4M was used as release retardant and MCC PH 200 was used as diluent, which also acts as binding agent. Here, 95.76 ± 1.52 percent CAR release was observed. But no tablet was remained at the end of 24 hrs. The tablet was broken down with in 24 hours. It may be due to large particle size of the diluent. The comparative release profile of CAR for F1-F6 was shown in Fig.3. So, in next formulation MCC PH 105 with good binding property was used as diluent. In formulation F7, 30%w/w HPMC K4M was used as release retarding agent and MCC PH 105 was used as diluent. With this formulation only 90.68 ± 3.3 percent CAR release was observed. So, in next formulation the polymer concentration was decreased to 25 percent. In formulation F8, 25%w/w HPMC K4M was used as release retarding agent and MCC PH 105 (micro crystalline cellulose) was used as diluent. Increase in drug release was observed than formulation F8. Here, 96.59 ± 3.1 percent drug CAR release was observed. The release was almost complete and good amount of tablet gel was remained at the end of 24 hours. To further increase the drug release, trials were done with different concentrations of polymers. In formulation F9, 25% w/w HPMC K4M was used as release retarding agent and MCC PH 101 was used as diluent, 99.61 ± 1.54 percent release was observed at the end of 24 hrs. But no tablet was remained; the tablet was completely broken down at the end of 24 hrs. In formulation F10, 25%w/w HPMC K15M was used as release retarding agent and MCC PH 105 was used as diluent. Here, only 79.19 ± 1.2 percent of drug was released. It may be due to high viscosity of HPMC K15M. In next formulations the polymer concentration was decreased to 20% w/w. In formulation F11, 20%w/w HPMC K4M was used as release retarding agent and MCC PH 105 was used as diluent. 96.92 ± 2.2 percent CAR release was observed at the end of 24 hours. But no tablet was remained at the end of 24 hours. The tablet was broken down with in 24 hours of dissolution. In formulation F12, 20%w/w HPMC K4M was used as release retarding agent and MCC PH 101 was used as diluent.

97.92 ± 1.53 percent drug CAR release was observed. The release was almost complete, but no tablet was remained at the end of 24 hrs. The comparative release profile of CAR for F7-F12 was shown in Fig.4.

For formulations F8 and F7, 24 hours release was observed. Tablet was not broken down at the end of 24 hours. The drug release observed was 96.59 ± 3.08 percent and 90.68 ± 4.34 percent respectively. In these two formulations the polymer used was 25%w/w and 30%w/w HPMC K4M respectively and the diluent used was MCC PH 105. So, among these 12 formulations F8 was selected as better formulation as it has given almost complete release and release over a period of 24 hours as required. The results were further confirmed by MDT values as shown in Table 4.

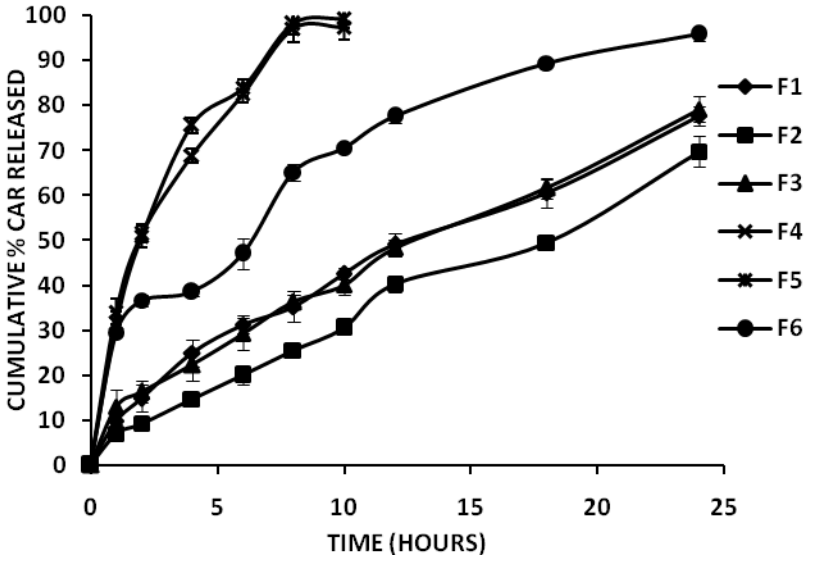

Fig.3: Comparative dissolution profiles of F1-F6

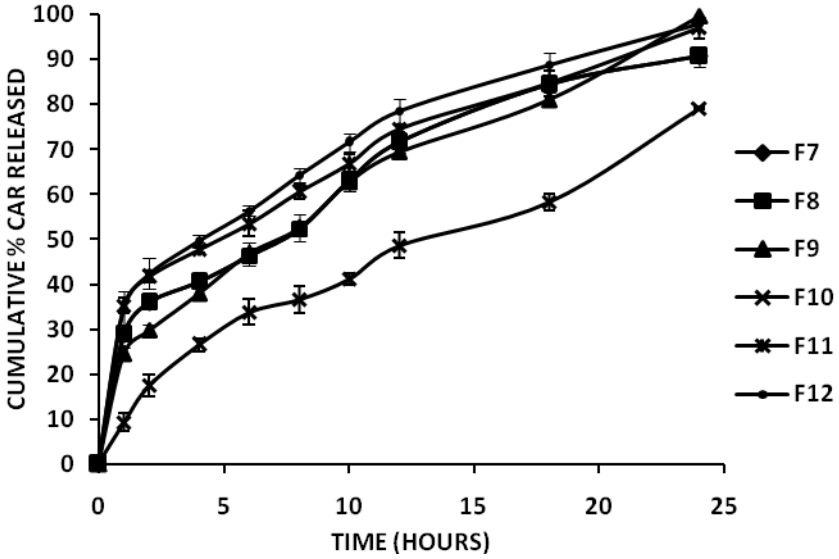

Fig.4: Comparative dissolution profiles of F7-F12

Drug release kinetics and mechanism

The release rate constants Qt versus t (zero order), Log Qt versus t (first order), Qt versus square root of time (Higuchi), Log %Qt versus log t (Korsmeymer-Peppas) were calculated. Where Qt is the amount of CAR released at time t.

The R^2 values for F1, F2, F3, F4, F6, F7, F9, F10, F11, F12 obtained with first order plots were found to be superior when compared to the R^2 values obtained with zero order plots. These results indicated that the CAR release from these formulations followed first order kinetics. Incase F8 the R^2 values obtained with zero order plots were found

to be superior when compared to the R^2 values obtained with first order plots. These results indicated that the CAR release from F8 followed zero order kinetics. The results are given in Table 4. The Higuchi square root model showed higher correlation coefficients (0.931-0.992) and diffusion is the release mechanism for CAR from the tablets. The results are given in Table 4. By incorporating the first 60% of release data mechanism of release can be indicated according to Korsmeyer- Peppas (power law) where 'n' is the release exponent, indicative of the mechanism of release. Fickian diffusional and a case-II relaxation release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxation release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. The term also indicates polymer disentanglement and erosion. The diffusional exponent 'n' values for the formulations were 0.247-0.734. For formulations F1, F2, F3 'n' value was above 0.45. So, the release mechanism was non-Fickian diffusion. For remaining all formulations, F4-F12 the exponent 'n' was less than 0.45 ranging from 0.24-0.36. It indicates 'n' value beyond the limits of Korsmeyer Peppas model (power law). The results are shown in Table 4. The power law only gives limited insight in to the exact release mechanism of the drug. Even if values of the exponent n are found that would indicate a diffusion controlled drug release mechanism, this is not automatically valid for HPMC.

The 'n' value of Korsmeyer Peppas can not be predicted clearly as it appears to be a complex mechanism of swelling, diffusion and erosion. Overall, the CR tablets gave a controlled release of CAR over a period of 10 to 24 hours. The main aim of the study was to develop controlled release formulation that can give drug release over a period of 24 hours. For formulations F8 and F7, 24 hours release was observed. Tablet was not broken down at the end of 24 hours. The drug release observed was 96.59 ± 3.08 percent and 90.68 ± 4.34 percent respectively. In these two formulations the polymer used was 25% w/w and 30% w/w HPMC K4M respectively and the diluent used was MCC PH 105. So, among these 12 formulations F8 was selected as better formulation as it has given almost complete release and release over a period of 24 hours as required. The release rate constants and correlation coefficient values for F8 formulation were given in Table 4.

The MDT values of formulations containing HPMC K4M were lower when compared to HPMC K15M. The MDT value of F8 was lower when compared to F7 indicating faster and complete release of the drug in case of F8.

Higuchi correlation coefficient was 0.969. So, the drug release mechanism was diffusion for CAR CR tablets. Korsmeyer Peppas constant 'n' = 0.245 which is the beyond the limits of Korsmeyer Peppas model (power law); the power law can only give limited insight of drug release mechanism. It can not be predicted clearly. It may be due to a complex mechanism of swelling, diffusion and erosion. F8 the drug release was 96.599 ± 3.08 percent at the end of 24 hours and it has followed zero order kinetics. The diffusional exponent 'n' was 0.245 which indicates the drug release mechanism was complex and it can not be explained by power law. It may be due due complex mechanism of swelling, diffusion and erosion.

Table 4: Release kinetic parameters for CAR CR Formulations

Formulations	Zero order		First order		Higuchi	Peppas		MDT (min)
	k_0	R^2	k	R^2	R^2	n	R^2	
F1	3.02	0.966	0.025	0.979	0.988	0.637	0.997	374.00
F2	2.76	0.990	0.189	0.965	0.931	0.734	0.980	615.69
F3	3.04	0.976	0.025	0.972	0.980	0.562	0.981	350.15
F4	8.94	0.869	0.405	0.957	0.989	0.520	0.996	134.22
F5	9.22	0.861	0.134	0.989	0.983	0.505	0.973	128.60
F6	3.55	0.851	0.053	0.985	0.934	0.324	0.849	131.61
F7	3.27	0.868	0.039	0.983	0.978	0.307	0.954	148.08
F8	3.24	0.857	0.062	0.845	0.969	0.245	0.992	92.12
F9	3.61	0.920	0.037	0.985	0.992	0.396	0.977	172.61
F10	2.96	0.955	0.030	0.894	0.977	0.627	0.987	380.18
F11	3.23	0.830	0.053	0.920	0.924	0.247	0.986	127.28
F12	3.36	0.816	0.062	0.935	0.972	0.285	0.991	126.19

CONCLUSION

Overall, formulation F8 containing HPMC K4M at 20% w/w level as release retardant polymer and Avicel PH105 as filler was selected as core formulation which gave superior CAR release of 96.59 ± 3.1 at the end of 24 hours and fulfils the regulatory requirement in terms of percent drug release.

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