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Preparation and characterization of poly(acrylic acid-*co*-methyl methacrylate) microparticles as sustained drug delivery system of antihypertensive drugs

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Abstract

The objective of the present study was to develop a sustained drug delivery system for highly water-soluble (diltiazem hydrochloride and metoprolol tartrate) drugs using pH sensitive monomers (acrylic acid and methyl methacrylate). The monomers were polymerized using ammonium persulphate as initiator. The polymers were then cross-linked with ethyleneglycol dimethacrylate as crosslinking agent. The prepared microparticles were characterized by FT-IR and DSC for drug and polymer compatibility and surface morphology of the particles was studied by SEM. FT-IR and DSC studies showed no chemical interaction between the drug and polymers. The release of drug followed Non Fickian diffusion type.

Keywords: Diltiazem hydrochloride, metoprolol tartrate, acrylic acid, methyl methacrylate, ethyleneglycol dimethacrylate

Introduction

High blood pressure, termed "hypertension," is a leading cause of morbidity and mortality. Hypertension is much more than a "cardiovascular disease" because it affects other organ systems of the body such as kidney, brain, and eye. The term "hypertension" can apply to elevations in mean arterial pressure, diastolic pressure, or systolic pressure of effective therapies, only 58% of adults with hypertension are receiving treatment, and in only 31% hypertension is controlled (Chobanian 2003, Yan and Gemeinhart 2005).

From many decades, pharmaceutical dosage forms like tablets, capsules, liquids and injectables have been used as drug carriers for the treatment of acute diseases. Even today, these conventional drug delivery systems are the primary pharmaceutical products known to provide prompt drug release. Thus, to achieve and maintain a therapeutically effective drug concentration range these dosage forms have to be taken several times a day which results in significant fluctuations of drug levels and untoward side effects. The oral drug delivery has its

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own importance because of its ease of administration and patient compliance. Though the conventional oral drug delivery systems achieve both local and systemic effects, there is no control over drug release from dosage forms that may lead to local or systemic toxicity (Fishburn 1965).

These limitations shifted the focus of pharmaceutical scientists towards the novel drug delivery systems (NDDS), where the required amount of drug is made available at desired time and site of action in the body. These systems maintain plasma concentrations with in the therapeutic range, which minimizes side effects and also reduces frequency of administration. The low development cost and time required to formulate a novel drug delivery system is also an advantage. Hence these systems gains an importance over immediate release systems for their effectiveness in treatment, reduced side effects and also increased patient compliance.

One such novel approach is the administration of drug orally in the form of microparticles. Microparticles can be formulated sensitive to several stimuli, of which the pH sensitive drug delivery systems are gaining more importance especially in the oral route of administration considering the variation in pH along the GIT (Bakan and Anderson 1986).

The model drugs used in the present study are metoprolol tartrate and diltiazem hydrochloride. Metoprolol tartrate is a α-1 selective adrenoreceptor antagonist which is commonly used as an anti anginal and anti hypertensive drug. The daily dose varies from 100 mg to 450 mg daily, in divided doses, with half life of 3 to 4 h. Diltiazem hydrochloride is a calcium channel blocker commonly used as an antihypertensive agent. The dose varies from 30 mg to 480 mg daily depending on the severity in divided doses, with a half life of 3 to 5h. Since these antihypertensive drugs are to be taken daily in divided doses, a controlled release product will definitely reduce the dose requirements and the patient health care costs.

In the present study, an attempt has been made to formulate poly(acrylic acid-*co*-methyl methacrylate) microparticles with pH sensitivity using metoprolol tartrate and diltiazem hydrochloride as model drugs. The copolymers are made out of polymers that exhibit pH dependent swelling (i.e.), they swell and release the drug only at a particular pH range. Hence site specific drug delivery is possible.

Materials and Methods

Materials

Diltiazem hydrochloride and Metoprolol tartrate have procured as gift sample from Divis labarotories, India and Aurobindo Pharma Ltd, India, respectively. Acrylic acid, methylmethacrylate, ethyleneglycol dimethacrylate has been purchased from Sigma-Aldrich, USA. Other reagents were of analytical grade.

Formulation of microparticles

Poly(acrylic acid-*co*-methyl methacrylate) microparticles were synthesized in 200 mL double distilled water by polymerization. Known amount of acrylic acid and methylmethacrylate were polymerized using ammonium persulphate (APS) and ethyleneglycol dimethacrylate, as initiator and crosslinker, respectively. The monomers and crosslinker were added directly into a 250 mL round bottom flask. While stirring with a magnetic stirrer at 800-1000 rpm, the reaction mixture was purged with nitrogen for 30 min and reacted at 70°C for 5 h. The poly(acrylic acid-*co*-methyl methacrylate) microparticles were collected

by centrifugation at 1500 rpm for 15 min followed by washing and they are freeze-dried (Table 1 and 2) (Yan and Gemeinhart 2005, Kumara et al. 2006, Chowdhary et al. 2003).

Table 1. Formulation chart of diltiazem microparticles

Ingredients	DF1	DF2	DF3	DF4	DF5
Diltiazem hydrochloride (mg)	500	500	500	500	500
Acrylic acid(% w/v)	80	70	60	70	70
Methyl methacrylate (% w/v)	20	30	40	30	30
Ethyleneglycol dimethacrylate (% w/v)	2	2	2	1	4
Ammonium persulphate (mg)	200	200	200	200	200
Water (mL)	200	200	200	200	200

Table 2. Formulation chart of metoprolol tartrate microparticles

Formulation	MF1	MF2	MF3	MF4	MF5
Metoprolol tartrate (mg)	500	500	500	500	500
Acrylic acid(% w/v)	80	70	60	70	70
Methyl methacrylate (% w/v)	20	30	40	30	30
Ethyleneglycol dimethacrylate (% w/v)	2	2	2	1	4
Ammonium persulphate (mg)	200	200	200	200	200
Water (mL)	200	200	200	200	200

Characterization of prepared microparticles

The prepared microparticles were characterized by Fourier transform infra red spectroscopic analysis, Differential scanning calorimetric analysis and surface morphology by Scanning electron microscopic analysis and Particle size analysis. The surface charge of the microparticles is studied by Zeta potential studies.

Drug content

The prepared microparticles were finely powdered. 50 mg of the powder was taken in a 100mL standard volumetric flask. To this 75 mL of 7.4 pH PBS solution was added and kept over night with occasional stirring. The volume was made upto the mark with 7.4 pH PBS. The final solution was filtered using whatmann filter paper and estimated spectrophotometrically for drug content (Morishita et al. 2002).

Swelling studies

The swelling properties of the microparticles were carried out using 0.1 N HCl and pH 7.4 phosphate buffer. The microparticles of known weight were placed in 50 mL of the buffer solution for 24h. At regular time intervals the microparticles were removed and excess surface liquid was removed by blotting paper and their weight was recorded. The percentage swelling (S) was determined by the following equation (Dalton et al. 2002, Liu and Che 2006).

$$S = \frac{\text{Weight of swollen microparticles - Weight of dry microparticles}}{\text{Weight of dry microparticles}} \times 100$$

Morphology observation

The surface of the beads was examined using Scanning electron microscopy (SEM, S-590, JOEL). Prior to observation, samples were mounted on metal grids, using double-sided adhesive tape and coated by gold under vacuum before observation.

Particle size analysis

The particle size was measured using a Malven Mastersizer 2000 (Malvern, UK). The samples of Poly(acrylic acid-*co*-methyl methacrylate) microparticles particles were dispersed in 1:20 with light liquid paraffin and measured at temperature of 37°C (Mei et al. 2006).

Entrapment efficiency

To evaluate the amount of the drug inside the microparticles, an indirect method was used. Aliquots from the filtered solutions remaining after removal of the beads were assayed spectrophotometrically. The amount of drug entrapped was calculated from the difference between the total amount of drug added and the amount of drug found in the filtered solution. The percentage drug encapsulation (PDE) was calculated by the below equation (Rao et al. 1996).

$$PDE = (\text{Practical drug loading} / \text{Theoretical drug loading}) \times 100$$

In vitro drug release studies

The *in vitro* release of drug from the microparticles was carried out in basket type dissolution tester-USP XXII, TDT-08L, with auto sampler containing 900 mL of 0.1 N HCl for the first 2 h and in 7.4 pH phosphate buffer for the next 10 h. The volume of the dissolution media was maintained at 900 mL while constant stirring (100 rpm) and temperature of bath was maintained at 37±0.5°C. Aliquots (10 mL) of dissolution media were sampled at specified time points and replaced with fresh media immediately after sampling. And the samples are analyzed for drug content by UV-VIS spectrophotometer (Shimadzu, Model 1601, Japan).The release data obtained were fitted into various mathematical models to know which mathematical model is best fitting the obtained release profile (Paloma et al. 2003).

Stability studies of optimized formulations

Stability is defined as the ability of a particular drug or a dosage form in a specific container to remain with its physical, chemical, therapeutic and toxicological specifications. Optimized formulation of the microparticles one of each drug (metoprolol and diltiazem) was selected for stability studies. Formulations were packed in a screw capped bottle and studies were carried out for 90 days by keeping at 30±2°C / 65±5% RH and 40±2°C / 75±5% RH.

Samples were withdrawn on 0th, 15th, 45th and 90th day and were analyzed for drug content.

Results and Discussion

FT-IR analysis

Pure diltiazem hydrochloride, metoprolol tartrate and their formulations were subjected to FT-IR analysis. The obtained spectra are given in Fig. 1 and 2.

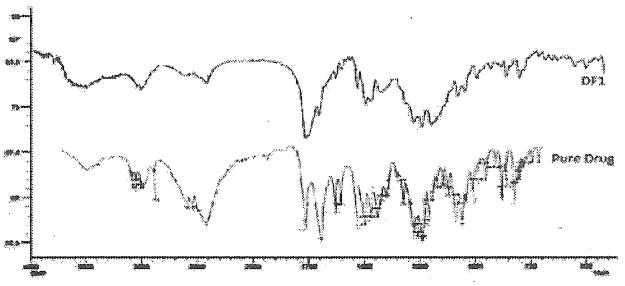


Figure 1. FT-IR spectra of pure diltiazem hydrochloride and formulation DF 1 containing diltiazem hydrochloride

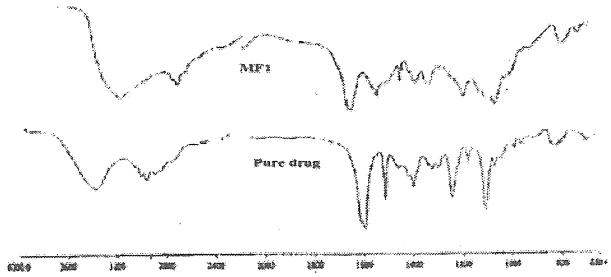


Figure 2. FT-IR Spectra of pure metoprolol tartrate and formulation (MF 1) containing metoprolol tartrate

The characteristic peaks of pure drugs were compared with the peaks obtained for their respective formulations. From the FT-IR peaks it can be concluded that the peaks of pure drug and formulations were found to be similar indicating that there was no significant interaction between drug and polymer used.

Differential scanning calorimetry (DSC)

In order to study any possible interactions between the drug and polymers, differential scanning calorimetric studies were carried out. The DSC thermograms obtained are reported in Fig. 3 and 4. DSC thermograms of the formulation were compared with the DSC thermograms of the pure drug.

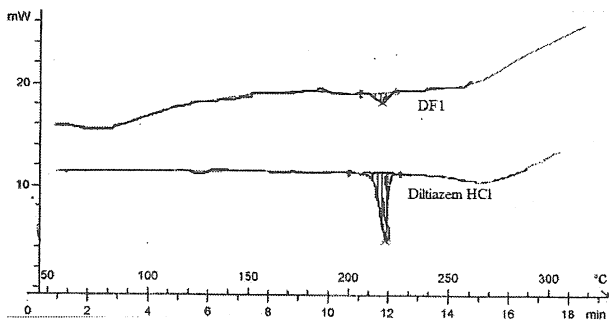


Figure 3. DSC Thermogram of pure diltiazem hydrochloride and formulation containing diltiazem hydrochloride

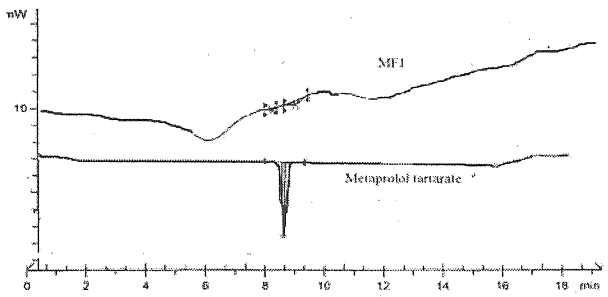


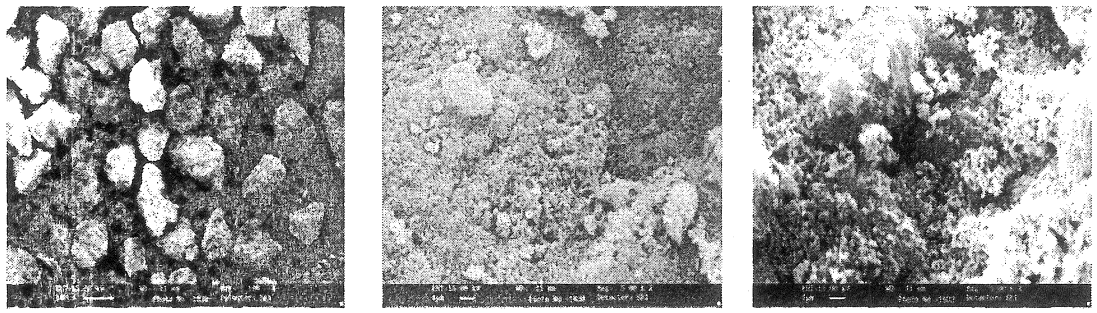
Figure 4. DSC thermogram of pure metoprolol tartrate and formulation containing metoprolol tartrate

Diltiazem hydrochloride displayed a single sharp endothermic peak at 217.39°C corresponding to its melting point, and a peak at same temperature was also observed in the formulation, confirming the stability of the drug in the prepared formulation. Metoprolol tartrate displayed a

single sharp endothermic peak at 123.24°C corresponding to its melting point of the drug, and a peak at same temperature was also observed in the formulation, confirming the stability of the drug in the prepared formulation.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy (SEM) is one of the commonly used methods for surface characterization of any solid particle. Scanning electron microscopy was carried out to observe the surface morphology, texture and porosity of the microparticles. SEM micrographs and typical surface morphology of the dried microparticles are given in Fig. 5. It was observed from the micrographs that microparticles were irregular and the surface was not smooth.



(a) (b) (c)

Figure 5. *(a)* SEM photograph of microparticles, *(b)* SEM photograph of surface of microparticle in 0.1N HCl, *(c)* SEM photograph of microparticle after swelling in 7.4 pH Phophate buffer

Particle Size Determination

The average particle size/volume mean diameter (D[4,3]) and volume median diameters (D[v, 0.5]), (D[v, 0.9]) of the microparticle formulations of diltiazem hydrochloride (DF 1 and DF 5) and metoprolol tartrate (MF 1 and MF 5) are given in Table 3. (D[v,3]) is the volume mean diameter and is the diameter of the sphere having the same volume as that of the microparticles whose size is being determined. (D[v,0.5]) is the median diameter and it is this value of particle size that divides the population in to two equal halves i.e., there is 50% of distribution above this and 50% below this value. (D[v, 0.9]) is the cut off value for the distribution, which means 90% of the distribution is below this value (Mei et al. 2006).

Table 3. Particle size distribution parameters of diltiazem hydrochloride and metoprolol tartrate microparticles

Formulation	Volume mean diameter (D[v,3]) μm	Volume mean diameter (D[v,0.5]) μm	Volume mean diameter (D[v,0.9]) μm
DF1	127.336	120.499	216.717
DF5	130.657	125.502	198.955
MF1	128.816	122.817	218.768
MF5	126.342	122.321	216.276

Zeta Potential

The zeta potential of the microparticles without drug was found to be in the range of -30 to -40 mV. The negative charged surface of microparticles is attributed to the anionic nature of acrylic acid in the copolymer. The results of Zeta potential are shown in Table 4.

Table 4. Zeta potential of microparticles without drug

Formulation	Zeta Potential (mv)
F1	-38.6 ± 0.2
F2	-34.8 ± 0.6
F3	-31.0 ± 0.5

Drug content

Diltiazem hydrochloride

The test for drug content was carried out to ascertain whether the drug is uniformly distributed in the formulation. The results obtained are reported in Table 5. From the results it can be inferred that there is a proper distribution of diltiazem hydrochloride in the microparticles and the deviation is within the acceptable limits.

Table 5. Drug content data for diltiazem hydrochloride formulations DF1 to DF 5

Formulation	Average mean ± SD
DF1	14.66 ± 0.32
DF2	13.83 ± 0.20
DF3	12.40 ± 0.25
DF4	15.93 ± 0.21
DF5	11.50 ± 0.30

Metoprolol tartrate

The resulted obtained are reported in Table 6. From the results it can be inferred that there is proper distribution of metoprolol tartrate in the microparticles and the deviation is within the acceptable limits.

Table 6. Drug content data for metoprolol tartrate formulations MF 1 to MF 5

Formulation	Average Mean ± SD
MF1	16.57 ± 0.40
MF2	14.90 ± 0.26
MF3	14.60 ± 0.36
MF4	16.90 ± 0.44
MF5	12.93 ± 0.31

Swelling Studies

The swelling studies for the microparticles (without drug) were carried out in both 0.1N HCl and pH 7.4 phosphate buffer to check their pH sensitivity. The results indicate that with a change in pH from acidic to basic medium considerable increase in swelling was observed for all the formulations. This may be due to the dissociation of the -COOH groups of acrylic acid, there by increasing the osmotic pressure inside the microparticles resulting in increased swelling. The pH sensitive monomer used in the formulations i.e., acrylic acid is responsible for swelling in basic media due to its dissociation and deswells in the acidic medium. This is due to the electrostatic repulsion between carboxylic acid polymer side chain and ions present in the buffer solution. At high pH values the carboxylate side chains are repelled by the ions in the solution and minimize the charge concentration by expanding. Swelling mainly depends on the extent of crosslinking. At lower crosslinking density, the network is loose with a greater hydrodynamic free volume, so that the chains can accommodate more of the solvent molecules resulting in higher swelling. The concentration of EGDMA remains constant for all the formulations except F 4 and F 5.

Formulation F 4 having less concentration of crosslinking agent swells more in basic pH may be due to loose network structure which can accommodate more amount of solvent and results in rapid swelling and F 5 which is having high crosslinker concentration swells less may be due to formation of tight junctions between the monomers results in lower swelling of the particles. The results are given in Fig. 8 and 9 (Fundueanu et al. 2006).

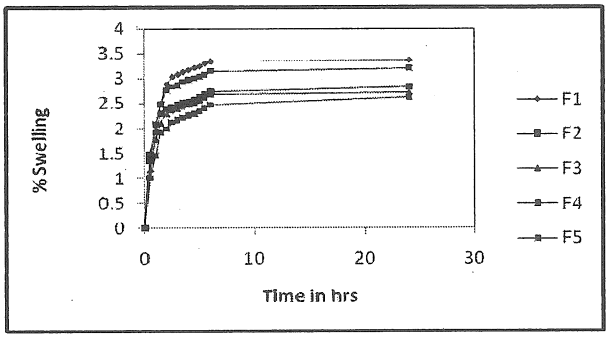


Figure 8: Percent swelling of microparticles in 0.1N HCl

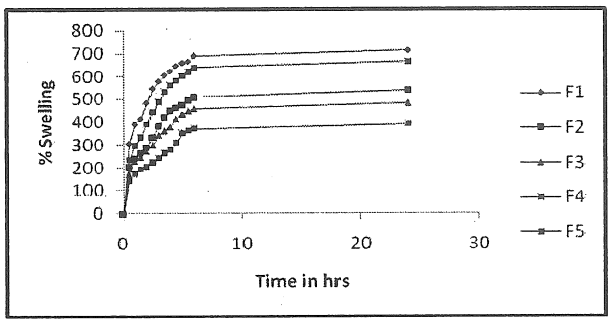


Figure 9. Percent swelling of microparticles in pH 7.4 phosphate buffer

Encapsulation Efficiency

The encapsulation efficiency was performed to find out the amount of drug that gets encapsulated in the microparticle so that sufficient amount of drug is present in the microparticles to ensure the drug remains in the therapeutic range once it enters the systemic circulation. The results are given in Table 7 and 8 (Kristmundsdottir et al. 1996).

Table 7. % Encapsulation efficiency of diltiazem hydrochloride formulations

Formulations	% Encapsulation efficiency
DF1	29.30 ± 0.5
DF2	27.60 ± 1.2
DF3	24.86 ± 1.0
DF4	31.86 ± 0.5
DF5	23.00 ± 1.1

Table 8. % Encapsulation efficiency of Metoprolol tartrate formulations

Formulations	% Encapsulation efficiency
MF1	29.1 ± 1.4
MF2	27.8 ± 2.1
MF3	25.2 ± 2.4
MF4	32.6 ± 2.0
MF5	22.6 ± 1.2

In vitro release studies

The *in vitro* release studies were carried out for all the formulations in both acidic and basic media. The *in vitro* release data for the diltiazem hydrochloride and metoprolol tartrate formulations are represented in Fig. 10 and 11.

The results obtained indicated percentage drug release in first 2 h was found to be low in all the cases (less than 4 %), which can be attributed to the fact that the microparticles swells less in the acidic medium. When the dissolution medium was changed to pH 7.4 phosphate buffer the release rate increased. For the formulations DF 1, DF 2 , DF 3 and MF 1, MF 2, MF 3 it was noticed that the percentage release of the drug increases with increase in acrylic acid concentration from 60-80 (% w/v). For the formulation DF 4 and MF 4 the percentage release was found to increase due to decrease in the crosslinking agent concentration (1%w/v) and the percentage release in formulation DF 5 and MF 5 found to decrease due to increase in the crosslinking agent concentration (4%w/v) respectively. The drug release profile of prepared Diltiazem hydrochloride and Metoprolol tartrate formulations were compared with marketed formulations. Diltiazem hydrochloride (Angizem SR 90) (DMP) and metoprolol tartrate (Metolar ER 100) (MMP). The overall % release of DF 2 and MF 2 and their corresponding marketed product was found to be similar. But for the first 2 h in 0.1N HCl the release of prepared formulation was less (1-4 %) when compared with marketed formulation (23-25 %) confirming the pH sensitivity of the prepared formulations (Fundueanu et al. 2006).

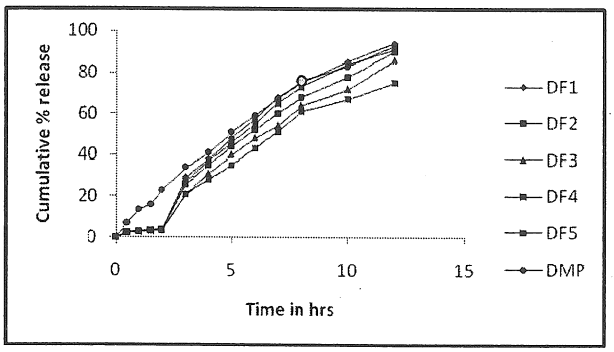


Figure 10. Graph showing the *in vitro* release profile of diltiazem hydrochloride and marketed product

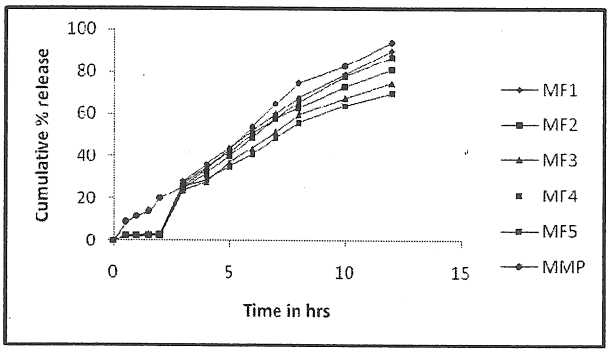


Figure 11. Graph showing the *in vitro* release profile of Metoprolol tartrate and marketed product

Mathematical model fitting of obtained drug release data

The *in vitro* release studies data was fitted in to various mathematical models to determine which the best-fit model. The various parameters n., the time exponent .k., the release constant and .R., the regression coefficient, were also calculated. The results indicate that, the best-fit model in all the cases was found to be Peppas model.

Korsmeyer-Peppas equation:

$$Mt/M\infty = 1- A (\exp -Kt)$$

$$\log(1 - Mt/M\infty) = \log A . kt/2.303$$

R = regression co-efficient; n = time exponent; k = release rate constant.

The value of n determined from Korsmeyer-Peppas equation was found to be above 0.5, which indicates that the drug release from the microparticles follows non-Fickian or anomalous mechanism (relaxation controlled) and Super case II transport respectively.

Stability studies of the optimized formulations

Stability studies of the optimized formulations of diltiazem hydrochloride and metoprolol tartrate were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated temperature. Stability studies data for diltiazem hydrochloride (DF 2) and metoprolol tartrate (MF 2) are given in Tables 9 and 10, respectively.

Table 9. Stability studies data of diltiazem hydrochloride formulation (DF 2)

Stability Condition	Sampling time (in days)	Drug content (mg) Mean ± S.D*
30°C / 65 % RH	0	90.0 ± 0.30
	15	86.2 ± 0.23
	45	85.3 ± 0.43
	90	85.3 ± 0.43
40°C / 75 % RH	0	90.0 ± 0.70
	15	88.0 ± 0.30
	45	87.2 ± 0.45
	90	84.3 ± 0.56

Table 10. Stability studies data of metoprolol tartrate formulation (MF 2)

Stability Condition	Sampling time (in Days)	Drug content (mg) Mean ± S.D*
30°C / 65% RH	0	100.0 ± 0.30
	15	99.5 ± 0.23
	45	99.3 ± 0.43
	90	99.2 ± 0.43
40°C / 75% RH	0	100.0 ± 0.43
	15	99.5 ± 0.70
	45	98.1 ± 0.45
	90	97.5 ± 0.56

Conclusion

The objective of the study was to prepare microparticles of diltiazem hydrochloride and metoprolol tartrate as pH sensitive drug delivery system, using Methyl methacrylate and Acrylic

acid as monomers. FT-IR studies indicated no interaction between the polymers and the drugs in both the prepared microparticles and the principal peaks of the drugs are not altered. From the DSC thermograms, it was evident that the decomposition temperatures of both the drugs and their microparticles formulations are closer; hence no significant interactions exist between the drug and polymers. From the SEM studies it was observed that microparticles were found to be coarse and having rough surface. The results obtained from the drug content studies; showed that the drugs were uniformly distributed in all the prepared formulations. From the results of swelling studies, it was observed that with an increase in pH from acidic to basic, a considerable increase in swelling was observed in all the formulations, confirming the pH sensitivity of the monomer combination used. It was also found that the swelling degree increased with increase in acrylic acid concentration whose dissociation increases with increase in pH. Swelling nature strongly depends on the extent of crosslinking. At lower crosslinking density, the network is loose with a greater hydrodynamic free volume, so that the chains can accommodate more of the solvent molecules resulting in higher swelling. The *in vitro* drug release profiles of both the drugs were almost similar. Hence it can be concluded that release is independent of the drug used. The release was found to be low when higher amount of crosslinking agent was used and high when higher amount of acrylic acid concentration was used. Similarity factor calculated for formulations and marketed product was found to be between 50- 100 indicating both the release profiles are similar. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases was found to be Peppas model.

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