WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 11, 796-817. Research Article ISSN 2277– 7105

A COMPREHENSIVE REVIEW ON GASTRORETENTIVE FLOATING TABLET OF CAPTOPRIL USING NATURAL AND SYNTHETIC POLYMER WITH COMPARISION OF POLYMER EFFICACY

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Article Received on
24 July 2017,

Revised on 14 August 2017,
Accepted on 04 Sept. 2017

DOI: 10.20959/wjpr201711-9561

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ABSTRACT

The oral route of drug administration is the most important method of administering drug for systematic effect. The present study was undertaken to prolong the release of orally administer. Captopril in the floating tablets by using different grade of HPMC. Formulation were optimized using different viscosity grades of HPMC. Lactose and citric acid and also natural polymers chitosan and carbopole. were used in different concentration as a channeling and chelating agent to obtain best optimized formulation and designed to prolong the gastric residence time (GRT).

KEYWORD: gastroretentive floating drung delivery system, Gastric retention time, HPMC, Lactose, Carbopole, Chitosan.

INTRODUCTION

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is to be dilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrintenstinal tract due to variable gastric emptying and motility. Gastroretentive system can remain in the gaswtric region for several hours and hence significantly prolong the gastric residence time of drugs. prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment. it has application also for local drug delivery to the stomach and proximal small intestines.

Experimental work

MATERIAL AND METHOD

Captopril was obtained as a gift sample from Ajanta Pharmaceutical ltd. Hydroxypropylmethylcellulose, k15, lactose, sodium bicarbonate, magnesium state, chitosan, carbopole, were obtained from SIRT.

Floating behavior of tablet

The in vitro buoyancy was determined by the floating lag time (time period between placing the tablet in the medium and the floating time) method described By Rosa et al, 1994. Tablets were placed in a 100 ml beaker containing 0.01 NHCL. The time required for thee tablets to rise to the surface and float was taken as the floating lag time.

1 REVIEW OF LITERATURE

Arza RA (2009) Studied that drugs that have narrow absorption window in the gastrointestinal tract (GIT) will have poor absorption. For these drugs, gastroretentive drug delivery systems offer the advantage in prolonging the gastric emptying time. Swellable, floating and sustained release tablets are developed by using a combination of hydrophilic polymer (hydroxypropyl methylcellulose), swelling agents (crospovidone, sodium starch glycolate and croscarmelose sodium) and effervescent substance (sodium bicarbonate). Formulations are evaluated for percentage swelling, in vitro drug release, floating lag time, total duration of floating and mean residence time (MRT) in the stomach. The drug release of optimized formulation follows the Higuchi kinetic model and the mechanism is found to be non-Fickian/anomalous according to Krosmeyer-Peppas (n value is 0.68). The similarity factor f is found to be 26.17 for the optimized formulation, which the release is not similar to that of marketed produced (CIFRAN OD). In vivo nature of the tablet at different time intervals is observed in the radiographic pictures of the healthy volunteers and MRT in the stomach is found to be 320 +/- 48.99 min (n = 6). A combination of HPMC K100M, crospovidone and sodium carbonate shows the good swelling, drug release and floating characters than the CIFRAN OD.

Srivastava AK **studied that** Floating matrix tablets of atenolol were developed to prolong gastric residence time and increase drug bioavailability. Atenolol was chosen as a model drug because it is poorly absorbed from the lower gastrointestinal tract. The tablets were prepared by direct compression technique, using polymers such as hydroxypropyl methylcellulose (HPMC K15M, K4M), guargum (GG) and sodium carboxymethylcellulose (SCMC), alone or

in combination and other standard excipients. Tablets were evaluated for physical characteristics viz. hardness, swelling index, floating capacity, thickness and weight variation. Further, tablets were evaluated for in vitro release characteristics for 8 hr. The effect of effervescent on buoyancy and drug release pattern was also studied. In vitro release mechanism was evaluated by linear regression analysis. GG- and SCMC-based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium.

Khan F. studied that the preparation and in vitro evaluation of gastroretentive floating tablet of theophylline. Two hydrophilic cellulose derivatives, Methocel K100M and Methocel K15MCR were evaluated for their gel forming and release controlling properties. Sodium bicarbonate and citric acid were incorporated as gas generating agents. The effects of soluble components (sodium bicarbonate and citric acid), gel forming agents and amount variation of theophylline on drug release profile and floating properties were investigated. Tablets were prepared by direct compression technique. Formulations were evaluated for in vitro buoyancy and drug release study was evaluated for eight hours using USP XXII paddle-type dissolution apparatus using 0.1N HCl as dissolution medium. The release mechanisms were explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The release rate, extent and mechanisms were found to be governed by polymer and floating agent content. The content of active ingredient was also a vital factor in controlling drug release pattern. It was found that polymer content and amount of floating agent significantly affected the mean dissolution time, percentage drug release after 8 hours, release rate constant and diffusion exponent.

Patel A. studied that A novel gastro retentive controlled release drug delivery system of verapamil HCl was formulated in an effort to increase the gastric retention time of the dosage form and to control drug release. Hydroxypropyl methylcellulose (HPMC), carbopol and xanthan gum were incorporated for gel-forming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. In vitro drug release studies were performed, and drug release kinetics was evaluated using the linear regression method. The optimized intragastric floating tablet composed of 3:2 of HPMC K4M to xanthan gum exhibited 95.39% drug release in 24 h in vitro, while the buoyancy lag time was 36.2 s and the intragastric floating tablet remained buoyant for >24 h. Zero-order

and non-Fickian release transport was confirmed as the drug release mechanism from the optimized formulation (F7). X-ray studies showed that total buoyancy time was able to delay the gastric emptying of verapamil HCl intragastric floating tablet in mongrel dogs for more than 4 h. Optimized intragastric floating tablet showed no significant change in physical appearance, drug content, total buoyancy time, or in vitro dissolution pattern after storage at 40 degrees C/75% relative humidity for 3 months.

Roy Studied that Conceptualizes a specific technology, based on combining floating and pulsatile principles to develop drug delivery system, intended for chronotherapy in nocturnal acid breakthrough. This approach will be achieved by using a programmed delivery of ranitidine hydrochloride from a floating tablet with time-lagged coating. In this study, investigation of the functionality of the outer polymer coating to predict lag time and drug release was statistically analyzed using the response surface methodology (RSM). RSM was employed for designing of the experiment, generation of mathematical models and optimization study. The chosen independent variables, i.e. percentage weight ratios of ethyl cellulose to hydroxypropyl methyl cellulose in the coating formulation and coating level (% weight gain) were optimized with a 3(2) full factorial design. Lag time prior to drug release and cumulative percentage drug release in 7h were selected as responses. Results revealed that both, the coating composition and coating level, are significant factors affecting drug release profile. A second-order polynomial equation fitted to the data was used to predict the responses in the optimal region. The optimized formulation prepared according to computer-determined levels provided a release profile, which was close to the predicted values. The proposed mathematical model is found to be robust and accurate for optimization of time-lagged coating formulations for programmable pulsatile release of ranitidine hydrochloride, consistent with the demands of nocturnal acid breakthrough.

Jagdate S.C Developed a gastroretentive drug delivery system of propranolol hydrochloride. The biggest problem in oral drug delivery is low and erratic drug bioavailability. The ability of various polymers to retain the drug when used in different concentrations was investigated. Hydroxypropyl methylcellulose (HPMC) K4 M, HPMC E 15 LV, hydroxypropyl cellulose (HPC; Klucel HF), xanthan gum and sodium alginate (Keltose) were evaluated for their gel-forming abilities. One of the disadvantages in using propranolol is extensive first pass metabolism of drug and only 25% reaches systemic circulation. The bioavailability of propranolol increases in presence of food. Also, the absorption of various drugs such as

propranolol through P-glycoprotein (P-gp) efflux transporter is low and erratic. The density of P-gp increases toward the distal part of the gastrointestinal tract (GIT). Therefore, it was decided to formulate floating tablet of propranolol so that it remains in the upper part of GIT for longer time. They were evaluated for physical properties, in vitro release as well as in vivo behavior. In preliminary trials, tablets formulated with HPC, sodium alginate, and HPMC E 15 LV failed to produce matrix of required strength, whereas formulation containing xanthan gum showed good drug retaining abilities but floating abilities were found to be poor. Finally, floating tablets were formulated with HPMC K4 M and HPC.

Boldhane SP **studied that** Formulated a Metoprolol succinate (MS) gastroretentive (GR) controlled release system was formulated to increase gastric residence time leading to improved drug bioavailability. Box-Behnken model was followed using novel combinations of sodium alginate (SA), sodium carboxymethylcellulose (NaCMC), magnesium alumino metasilicate (MAS) as independent variables. Floating lag time (Flag), t25, t50, t75, diffusion exponent as dependent variables revealed that the amount of SA, NaCMC and MAS have a significant effect ($p < 0.05$) on t25, t50, t75 and Flag. MSGR tablets were prepared and evaluated for mass, thickness, hardness, friability, drug content and floating property. Tablets were studied for dissolution for 24 h and exhibited controlled release of MS with floating for 16 h. The release profile of the optimized batch MS01 fitted first-order kinetics ($R2 = 0.9868$, $n = 0.543$), indicating non-Fickian diffusion or anomalous transport by diffusion and swelling.

Kharia AA studied that The purpose of the present work was to design and optimize floating drug delivery systems of acyclovir using psyllium husk and hydroxypropylmethylcellulose K4M as the polymers and sodium bicarbonate as a gas generating agent. The tablets were prepared by wet granulation method. A 3(2) full factorial design was used for optimization of drug release profile. The amount of psyllium husk (X1) and hydroxypropyl methylcellulose K4M (X2) were selected as independent variables. The times required for 50% (t(50%)) and 70% (t(70%)) drug dissolution were selected as dependent variables. All the designed nine batches of formulations were evaluated for hardness, friability, weight variation, drug content uniformity, swelling index, in vitro buoyancy and in vitro drug release profile. All formulations had floating lag time below 3 min and constantly floated on dissolution medium for more than 24 h. Validity of the developed polynomial equation was verified by designing two check point formulations (C1

and C2). The closeness of predicted and observed values for t (50%) and t(70%) indicates validity of derived equations for the dependent variables. These studies indicated that the proper balance between psyllium husk and hydroxypropyl methylcellulose K4M can produce a drug dissolution profile similar to the predicted dissolution profile. The optimized formulations followed Higuchi's kinetics while the drug release mechanism was found to be anomalous type, controlled by diffusion through the swollen matrix.

Sathivaraj S Investigated is to prolong the gastric residence time of Lornoxicam by fabricating it into a floating sustained release matrix tablets. Lornoxicam, a potent oxicam group of non-steroidal anti-inflammatory drugs, suffers from relatively short half life of 2 to 3 hrs showing maximal absorption in proximal gastro intestinal tract region necessitating its need to be formulated as a floating sustained release matrix tablets. In this current investigation, hydroxyl propyl methyl cellulose K15M, a high viscous grade polymer with apparent viscosity of 15,000 cps, was kept as a variable (10-50%) and calcium carbonate (13%) was used as a gas generator. The prepared blends were subjected for its pre-formulation characterization. The directly compressed tablets were evaluated for physical parameters such as weight uniformity, hardness, friability, drug content, in-vitro buoyancy with axial and radial enlargement measurement, swelling index. From the investigation it was observed that the buoyancy lasted for up to 24 hrs. Fourier transforms infra-red spectroscopy peaks assured the compatibility of the drug with excipients and confirmed the presence of pure drug in the formulation. It was supported by in-vitro dissolution studies; and the dissolution data was subjected to various release kinetic models to understand the mechanism of drug release.

Menon A. studied that the poor bioavailability of orally dosed furosemide (60%), a weakly acidic drug, is due to the presence of a biological window comprised of the upper gastrointestinal tract. The purpose of the present study was to develop and optimize in vitro a monolithic modified-release dosage form (MMR) for furosemide with increased gastric residence time and to evaluate the in vivo performance of the dosage form. The principle of floatation was used to restrict the MMR to the stomach. A two-factor three-level full factorial experimental design was employed for formulation development. A flow-through cell was designed to evaluate in vitro dissolution parameters. Quadratic regression models indicated the polymer viscosity and polymer: drug ratio to be significant ($p < 0.05$) formulation factors in determining the duration of buoyancy and the release profile. Statistical optimization using

response surface methodology with certain physiological constraints relating to gastric emptying time predicted an optimal MMR. In vivo evaluation of the optimized MMR in beagle dogs resulted in a significant increase ($p < 0.05$) in the absolute bioavailability for the MMR dosage form (42.9%) as compared to the commercially available tablet (33.4%) and enteric product (29.5%). Significant in vitro/in vivo correlations ($p < 0.05$) were obtained for the MMR using deconvolution analysis normalized for bioavailability. The floating dosage form was found to be a feasible approach in delivering furosemide to the upper gastrointestinal tract to maximize drug absorption.

Abdelbarya A. studied that Trimetazidine dihydrochloride is an effective anti-anginal agent; however, it is freely soluble in water and suffers from a relatively short half-life. To solve this encumbrance, it is a prospective candidate for fabricating trimetazidine extended-release formulations. Trimetazidine extended-release floating tablets were prepared using different hydrophilic matrix forming polymers including HPMC 4000 cps, carbopol 971P, polycarbophil and guar gum. The tablets were fabricated by dry coating technique. In vitro evaluation of the prepared tablets was performed by the determination of the hardness, friability, content uniformity and weight variation. The floating lag time and floating duration were also evaluated. Release profile of the prepared tablets was performed and analyzed. Furthermore, a stability study of the floating tablets was carried out at three different temperatures over 12 weeks. Finally, in vivo bioavailability study was done on human volunteers. All tablet formulas achieved < 0.5 min of floating lag time, more than 12 h of floating duration, and extended t (1/2). The drug release in all formulas followed zero-order kinetics. T4 and T8 tablets contained the least polymer concentration and complied with the dissolution requirements for controlled-release dosage forms. These two formulas were selected for further stability studies. T8 exhibited longer expiration date and was chosen for in vivo studies. T8 floating tablets showed an improvement in the drug bioavailability compared to immediate-release tablets (Vastrel® 20 mg).

Nanjibhai, C V. studied that Formulated And evaluated the floating drug delivery system containing theophylline as a model and to optimize the drug release profile by using Plackett-Burman designs. These Plackett-Burman designs are very efficient screening designs when only main effects are of interest. Theophylline tablets were prepared by direct compression and containing HPMC K100M, xanthan gum, carbopol 934P, PVP K30, MCC, lactose, aerosil and gas generating agent such as sodium bicarbonate were taken as independent

variables. It is evaluated by using USP-I (Basket) apparatus containing 0.1 N HCl. The effect of formulation variables on the response variables were statically evaluated by applying one-way ANOVA at 0.05 level using a commercially available software package design of Experiments® 6.05 (Stat Ease, USA). The design was evaluated by linear model. The release mechanisms of theophylline from floating tabled where evaluated on the basis of Peppas model. The n value of all formulations except "F11" ranges from lowest 0.5808 to highest 0.8183 which is in the range of $0.45 < n < 0.89$ which indicate the mechanism of release of theophylline is anomalous (non-Fickian) transport. However the n value of the optimized formula "OF- 1" and "F11" are above 0.9, which indicate that, the mechanism of release of theophylline from the dosage form is following the zero order release kinetics. The optimized formula is following the zero order release kinetics, which met the rule of controlled drug delivery system. Scanning electron microscopy (S.E.M.) Study represents the gel formation. Different excipients were tested for their compatibility with theophylline such as FT-IR and TLC studies which revealed that there is no chemical interaction occurs with other excipients. Present study has demonstrated the successful xiii utilization of technique of Differential scanning calorimeter (D.S.C) to assess the compatibility of theophylline with the excipients used in the development of floating drug delivery system of theophylline. Based on the results of D.S.C, majority of the excipients were found to be compatible with theophylline. However, results showed that there might be some interaction between theophylline with HPMC K100M, carbopol 934P, PVP K30 and sodium bicarbonate.

Shinde S.N. Developed floating matrix tablets of Salbutamol Sulphate. Tablets were prepared by wet granulation method and were characterized using the official method. Hydroxypropyl methylcellulose was used as a release retardant material. Sodium bicarbonate and Citric acid was incorporated as a gas-generating agent. The effects of citric acid on drug release profile, floating properties and matrix integrity of tablet were investigated. Addition of Citric acid caused the enhancement in drug release and disintegration of tablet that was retarded by incorporation of stearic acid in the formulation. Addition of high level of HPMC K100M didn't significantly retard the burst effect and tablet disintegration produced by citric acid but addition of stearic acid was necessary to retard the same. Formulations were evaluated for in vitro drug release profile, swelling characteristics. The similarity factor, dissolution kinetics, and t_{50} were used as parameters for selection of the best batch. The in vitro drug release followed Korsemeyer-Peppas kinetics and the drug release mechanism was found to be of anomalous type. For the developed formulation, the value of *n* was found to be

0.6039 while for the marketed formulation the value was 0.5889 indicating the anomalous transport. The similarity factor *f*2 was found to be 78.19 for the developed formulation indicating the release was almost similar to that of the marketed formulation.

Havaldar V.D. studied that The purpose of the study was to prolong the gastric residence time of atenolol by designing its floating tablets and to study the influence of different polymers on its release rate. Nine formulations of atenolol containing varying concentrations of polymers were designed by optimization. The floating matrix tablets of atenolol were prepared by direct compression method. The prepared tablets were evaluated for physicochemical parameters such as hardness, floating properties (floating lag time, floating time and matrix integrity), swelling studies and drug content. The physicochemical parameters of formulated tablets were found to be within normal range. A significant difference in drug release ($P < 0.0001$) and floating lag time ($P < 0.005$) at 0.5, one, four and eight hours were observed. The floating lag time of all the formulations was within the prescribed limit (<10 minutes). All the formulations showed good matrix integrity and retarded the release of drug for eight hours. The release pattern of atenolol was fitted to different models based on coefficient of correlation (r). All the formulations, except F2, F3 and F6 showed Korsemeyer-Peppas model as the best fit model. Formulation F2 and F3 showed first order model while F6 showed zero order model. Diffusion exponent (n) value was found in the range of 0.52-0.99 indicating diffusion as a release mechanism. The swelling studies of all the formulations showed that formulations containing Xanthan gum has higher swelling indices than HPMC K100M and HPMC K4M. It can be concluded that formulations with higher swelling indices retarded the release of drugs more than those with lower swelling indices.

Kaoutar A Studied the effect of the polymer additive, hydroxypropylmethyl cellulose (HPMC), on inhibiting the nucleation and growth of felodipine from supersaturated aqueous solutions was investigated. To characterize the growth and nucleation kinetics, seeded and unseeded desupersaturation experiments were carried out, respectively. A mathematical model for the batch crystallization of felodipine was constructed by using empirical expressions for nucleation and growth, a population balance equation, and a material balance. An optimization algorithm was employed to obtain the kinetic parameters in the nucleation and growth expressions by fitting the simulated results to the experimental data. Population balance modeling successfully allowed for the decoupling of the separate effect of HPMC on

the nucleation and growth rates. In both the absence and presence of polymer, the growth mechanism of felodipine was determined to be intermediate between mass diffusion and surface integration controlled growth. HPMC was able to inhibit nucleation and growth at very low polymer concentrations (0.2 μg mL^{-1}). However, the inhibitory impact was much greater on nucleation as opposed to growth. At a concentration of 3.5 μg mL^{-1}, HPMC was found to decrease felodipine nucleation by up to eight orders of magnitude while it only decreased the rate of crystal growth by a factor of two. Furthermore, at high concentrations, the inhibitory impact of HPMC on growth reached a plateau and any further increases in polymer concentration were ineffective.

Ashok R. Evaluated the possibility of using different concentrations and polymeric grades of hydroxypropyl methylcellulose (K4M, K15M and K100M) for transdermal delivery of methotrexate, an immunosuppressant drug for rheumatoid arthritis. The matrix films were evaluated for their physicochemical characterization followed by in vitro and in vivo evaluation. Selected formulations were subjected for their in vivo studies on healthy rabbits following balanced incomplete block design. The relevance of difference in the in vitro dissolution rate profile and pharmacokinetic parameters (C(max), t(max), AUC((s)), t(1/2), K(el) and MRT) were evaluated statistically. The thickness and weight of the patch increased with the increase in polymeric grade and content. Fourier transform infrared spectroscopy and differential scanning calorimetry results confirm that there is no interaction between drug and polymer used. X-ray diffraction study reveals an amorphous state of drug in the matrix films. The in vitro drug release followed Higuchi kinetics ($r=0.972$-997; $p<0.001$) as its coefficient of correlation values predominates over zero order and first order release kinetics. In vitro dissolution profiles and pharmacokinetic parameters showed a significant difference between test products ($p<0.01$), but not within test products. A quantitatively good correlation was found between per cent of drug absorbed from the transdermal patches and AUC((s)). A significant in vitro/in vivo correlation was observed when per cent drug released was correlated with serum drug concentration. Out of the various formulations made, the selected formulations are better in their in vitro dissolution and pharmacokinetic characteristics and thus hold potential for transdermal delivery.

Nyamweya N. studied that To assess the miscibility and phase behavior of binary blends of hydroxypropylmethyl cellulose (HPMC) with hydroxypropyl cellulose (HPC), methylcellulose (MC) and polyvinylpyrrolidone (PVP). Polymer-polymer miscibility was

assessed by measurement of the glass transition temperature (Tg) and the width of the glass transition temperature (W-Tg), using modulated temperature differential scanning calorimetry (MTDSC). HPMC K4M/PVP and HPMC E5/MC blends were miscible as evidenced by a single, composition dependent, Tg throughout the entire composition range. HPMC/HPC blends were immiscible at all compositions. For the miscible blends, the variation in Tg with blend composition was compared to the values predicted by the Fox and Couchman-Karasz equations. At intermediate blend compositions, HPMC K4M/PVP blends exhibited negative deviations from ideal behavior. The Tg of the HPMC E5/MC blends was found to follow the Fox equation. The W-Tg measurements of the miscible blends gave evidence of phase separation at certain compositions.

Darunkaisorn W. studied that The purpose of this study was to investigate and select the suitable granulating fluid for the matrix granules consisting of hydroxypropyl methylcellulose (HPMC). Method: Viscosity of the granulating fluids containing HPMC in different solvents was determined. The matrix granules obtained from mixing the granulating fluid with propranolol HCl, HPMC and lactose were assessed for bulk density, particle size distribution, flowability and friability. SEM, DSC, powder x-ray diffraction and drug dissolution studies were conducted to characterize the physical properties of the granules. Results: Type of granulating liquid affected the granule properties. The utilization of isopropyl alcohol as a granulating liquid and subsequently adding with water was a suitable system for agglomeration of powders. Good physical properties were obtained for the granule prepared by using this granulating fluid. Conclusion: Type of solvent and amount of water played an important role for physical properties of HPMC in the formation of the matrix granule due to the hydrophilicity and gel formation of this polymer. The use of isopropyl alcohol as granulating liquid and subsequently adding with water was a suitable process in producing the matrix granules consisting of HPMC.

Liang J.Q. Investigated of the changes of myocardial energy expenditure in patients with heart failure following myocardial infarction after treatment with different doses of perindopril done. The two groups had similar measurements before treatment. After 12 months of perindopril treatment, the patients in group N showed higher LA, LV, RA, RV, LVIDs, AD, cESS, lgNT-proBNP and MEE with lower LVFS and LVEF than those in group H. Compared to those before treatment, LVFS and LVEF were increased and LA, LV, RA, RV, AD, LVIDs, LVMI, lgNT-proBNP and MEEm lowered after the 12-month treatment in

group H. Significant changes were also found in the measured parameters except for PWTs, LVET, LVSV and LVFS in group N after the treatment. Bivariate analysis showed a significant positive correlation between MEE and lgNT-proBNP (r=0.513, P<0.01).

Meditsina K studied that This comparative ultrasound study included 210 patients aged 65-80 years with non-valvular atrial fibrillation treated with the use of 4 different therapeutic modalities. Intake of perindopril, valsartan, valsartan + rozuvastatin and lercanidipine resulted in a rise in distension index of common carotid artery, decrease of rigidity coefficient of the aortic wall and increase of the pulsed wave propagation speed. Combination of valsartan (80-160 mg/d) and rozuvastatin (10 mg/d) had the most pronounced effect on the vascular wall compliance compared with other modalities and reduced the frequency of ischemic stroke, myocardial infarction and mortality. It is concluded that therapy of non-valvular atrial fibrillation in elderly patients with valsartan, rozuvaststin is the optimal strategy for the improvement of elastic properties of the vascular wall and reduction of the frequency of cardiovascular complications.

Bulpitt CJ, Beckett N studied that White coat hypertension is considered to be a benign condition that does not require antihypertensive treatment. Ambulatory blood pressure (ABP) was measured in 284 participants in the Hypertension in the Very Elderly Trial (HYVET), a double-blind randomized trial of indapamide sustained release 1.5 mg±perindopril 2 to 4 mg versus matching placebo in hypertensive subjects (systolic blood pressure 160-199 mm Hg) aged >80 years. ABP recordings (Diasys Integra II) were obtained in 112 participants at baseline and 186 after an average follow-up of 13 months. At baseline, clinic blood pressure (CBP) exceeded the morning ABP by 32/10 mm Hg. Fifty percent of participants fulfilled the established criteria for white coat hypertension. The highest ABP readings were in the morning (average 140/80 mm Hg), the average night-time pressure was low at 124/72 mm Hg, and the average 24-hour blood pressure was 133/77 mm Hg. During follow-up, the systolic/diastolic blood pressure placebo-active differences averaged 6/5 mm Hg for morning ABP, 8/5 mm Hg for 24-hour ABP and 13/5 mm Hg for CBP. The lowering of blood pressure over 24 hours supports the reduction in blood pressure with indapamide sustained release perindopril as the explanation for the reduction in total mortality and cardiovascular events observed in the main HYVET study. Because we estimate that 50% had white coat hypertension in the main study, this condition may benefit from treatment in the very elderly.

Chalmers J. studied that A total of 6105 individuals with a history of stroke or transient ischaemic attack were randomly assigned active treatment (n=3051) or placebo (n=3054). Active treatment comprised the angiotensin-converting-enzyme inhibitor perindopril (4mg daily), with the addition of the diuretic indapamide at the discretion of treating physicians. Over a mean of 3.9 years of follow-up, active treatment reduced blood pressure by 9/4mmHg compared with placebo and reduced the primary outcome, stroke, by 28%. Major coronary events occurred in 269 participants (active 3.8%, placebo 5.0%) and heart failure was diagnosed in 264 participants (active 3.7%, placebo 4.9%). Active treatment reduced the risk of major coronary events by 26% (95% CI: 6–42%; $p = 0.02$) and the risk of congestive heart failure by 26% (5–42%; $p = 0.02$). For each of these outcomes, there was no clear evidence of differences between the treatment effects in participants classified as hypertensive or non-hypertensiv.

Thomson A. studied that Evidence shows that perindopril alone or in combination with other antihypertensive agents can achieve clinically significant reductions in blood pressure after 12 weeks of treatment. There is strong evidence from large randomized studies that perindopril-based therapy reduces the risk of cardiovascular outcomes, including mortality, in patients with coronary artery disease and those who have had a prior stroke or transient ischemic attack. There is also some evidence that these effects are greater than those achieved by blood pressure reduction alone, suggesting other drug-related effects including improvements in endothelial function. Recent results have also shown that an amlodipine ± perindopril regimen prevented more major cardiovascular events than an atenolol-based regimen in patients with hypertension, as a result of better control of blood pressure. Economic evidence from one major study shows that, for most patients, the incremental cost per quality-adjusted life-year gained with perindopril 8 mg was lower than the threshold value of €20 000 (73–92% of patients) in Europe or £20 000 (94% of patients) in the UK

Optimization and Formulation development of Captopril Floating Tablets

1 wet granulation method.

Tablets were prepared by conventional wet granulation method. The various excipients used were listed in Table No. 13. Ingredients except glidants and lubricant were thoroughly mixed and passed through sieve no. 60. Granulation was done with a solution of calculated quantity of PVP K30 in sufficient isopropyl alcohol. The wet mass was prepared passed through sieve

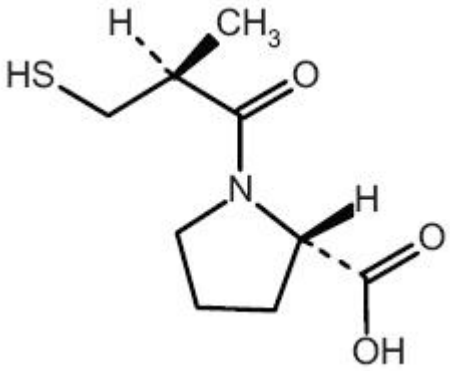
no. 12 and dried at 50°C for 2 h. The dried granules were lubricated with magnesium stearate and talc and compressed into tablets using single station tablet punch machine.

DRUG PROFILE

Name: Captopril

Description: Captopril is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII). ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS). Captopril may be used in the treatment of hypertension.

Structure



Synonym

Acepress, Apopril, Capoten, Captolane, Captoprilum Captopryl, Captoril, Cesplon etc.

Prescribed product: captopril, capoten.

Category

Cardiovascular agent; angiotensin-converting enzyme inhibitor.

Drug characteristics

Systematic (IUPAC) name :(2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl]pyrrolidine-2-carboxylic acid.

Description

Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor and metallic taste and it is soluble in water (approx. 160 mg/mL), methanol and ethanol and sparingly soluble in chloroform and ethyl acetate.

Molecular Formula: $C_9H_{15}No_3S$

Molecular weight: 217.29 g/mol

Melting point: About 103°C.

Half life 2 hours

Protein binding: 25-30% bound to plasma proteins, primarily albumin

Loss on drying: Dry at 60°C under reduced pressure (not exceeding 0.6kPa or about 5mm of mercury) for 3 hours; it loses notmore than 10 mg/g.

Solubility: Freely soluble in water, dichloromethane R and methanol R.

Requirements: Captopril contains not less than 98.0% and not more than 102.0% of C9H15NO3S, calculated with reference to the dried

Mechanism of action

The mechanism of action of CAptopril used in hypertension and congestive heart failure appear to result primarily from suppression of the renin-angiotensina system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion and as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

Pharmacokinetics

After oral administration of therapeutic doses of Captopril Tablets, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent; captopril therefore should be given one hour

before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75 percent. In a 24-hour period, over 95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug; most of the remainder is the disulfide dimer of Captopril Tablets and captopril-cysteine disulfide.

Pharmacodynamics

Administration of CAPOTEN results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of CAPOTEN and glomerular filtration rate is usually unchanged.

Contraindications

Captopril Tablets are contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

Pregnancy angioneurotic edema after other ACE inhibitors; bilateral renal artery stenosis. To avoid a hypotensive reaction when first administering **captopril**, it is recommended to withdraw the diuretics temporarily a few days beforehand (there is a small risk of hypovolemia).

Food Interactions

- Captopril decreases the excretion of potassium. Salt substitutes containing potassium increase the risk of hyperkalemia.
- Food decreases absorption by 25 - 40%. Clinical significance is debatable.
- Herbs that may attenuate the antihypertensive effect of captopril include: bayberry, blue cohash, cayenne, ephedra, ginger, ginseng (American), kola and licorice.

High salt intake may attenuate the antihypertensive effect of captopril.

Animal Toxicology

Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years) and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach and variation of retinal blood vessels.

Adverse effect

Common **side effects** of Capoten include a dry and persistent cough, abdominal pain, constipation, diarrhea, skin itching or rash, dizziness, drowsiness, fatigue, headache, sleep problems (insomnia), loss of taste, loss of appetite, nausea, vomiting, dry mouth, sores inside your mouth or on your lips etc.

Medicinal uses

Captopril is an ACE inhibitor. ACE stands for angiotensin converting enzyme. Captopril is used to treat high blood pressure (hypertension), congestive heart failure, kidney problems caused by diabetes, and to improve survival after a heart attack.

Evalution of tablets

Hardness

The tablet was placed between two anvils of hardness tester (Monsanto) and force (kg) was gradually increase in order to get exact reading. the reading at the marked scale was recorded for the pressure, which is required to break the tablets.

Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The observed value should not be more than 1%. The percentage friability was measured using the following formula.

$\%F=\{1-(Wt/W)\}*100$

Where, %F= friability in percentage, W=initial weight of tablet, Wt =weight of tablets after revolution.

Drug content

Five tablets for each batches were taken and triturate. Pawer equivalent 100mg of drug was weighed and transferred to beaker and then 0.01HCL was added and it was than shaken for 5 minutes and finally 0.01N HCL was added tto make the volume up to 100 ml and solution was then sonicated for 15 minutes and filtered through whatman filter paper. Finally a solution was diluted suitably and the absorbance of resultant solution was measured spectrophotometer jasco V-530 against 0.01N HCL bank.

Weight variation

Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance. The average weight and standard deviation of 20 tablets was calculated. Weight values were reported in milligrams.

In vitro dissolution studies

In vitro dissolution studies of all the formulation f floating tablets of captopril were carried out in 0.01N HCL at 37 + 0.5c. the study was performed 12 hours and cumulative drug release was calculated at every one hour time interval.

RESULT AND DISCUSSION

Preformulation study

The physical characteristic of captopril powder was observed on different parameters viz. color, odour, taste and texture. The color, odour, taste and texture were found to be white, odorless, bitter and Amorphous in nature.

The Solubility of pure drug captopril was found very soluble in water and methanol, freely soluble in 0.1N HCl and soluble in 0.1N NaOH.

The melting point was determined using melting point apparatus. The melting point of captopril was found to be 103˚C.

Captopril solution was scanned in the U.V. range of 200-400 nm using Systronic UV Visible spectrophotometer. The spectrophotometric method of analysis of captopril at λ_{max} 208 nm. The slope and intercept of the calibration curve were 0.016 and 0.006 respectively. The correlation coefficient 'r^2' values were calculated as 0.998.

The FTIR spectra of drug with exipients were compared with the FTIR spectrum of the pure drug. It indicates no interaction between captopril and exipients.

Flow Properties of Powder Blend of Different batches of captopril

The powder blends of all the batches (F1-f5) of using **synthetic polymer** were evaluated on different parameters i.e. bulk density, tapped density and angle of repose (θ), Carr Index and Hausner's ratio. Bulk density of all batches (F1-F5) was found to be 0.40-0.51, 0.49-0.62, and respectively.

Tapped density all batches (F1-F6) was found to be 0.659, 0.660, 0.630, 0.672, 0.659 and 0.665 respectively.

Angle of repose was found to be 26.2;21.29,31.05,24.55,29.38 and respectively. Carr Index was found to be 15.57,11.54,17.53,8.21,16.12and respectively. Hausner's ratio was found to be1.05,1.14,1.24,1.10,1.22respectively.

The values for angle of repose (<30) indicated Excellent flow properties of powder blends and index values and this was further supported by lower compressibility index values. Generally, compressibility index values less than 16% result in good to excellent flow properties. The results shows that the all the powder blends have the good flow properties and compressibility which are essential for the preparation of the tablets from the powder blend.

Physical parameter for the formulations prepared by floating technique of using **natural polymers** is shown. Bulk density was found to be between 0.45 to 0.59g/ml and tapped desity between 0.52 .to 0.65g/ml, Hausner ration between 1.15 to 1.253. and angle of repose was found to be between 25.03 to 32.88, indicating fair to good flow properties. After determining these flow properties tablet was prepared.

Evaluation of Prepared Tablet of Different Batches of captopril

All the tablet formulations of different batches were evaluated for different evaluation parameters by using **synthetic polymer** viz. weight variation, hardness and friability thickness, total floating time. Weight variation of different batches (F1-F5) was found to be respectively. Weight variation with in limit so, it was concluded that the uniformity of drug distribution in the granulation or powder blend occurs. So, the tablets were made perfect.

In all formulation, the hardness test indicated good mechanical strength. Hardness of synthetic polymer was ranged from 5.4 to 6.0 Kg/cm^2. Friability was ranged from0.10 to 0.14. and weight variation range was 203 to 209 and content was ranged 96.99 to 99.09 total floating time>9 to>10 [hrs].

Same as synthetic polymer all the table of different batches were evaluated of different evalution parameter by using **natural polymer** viz. weight variation, hardness and friability thickness, total floating time. Weight variation of different batches (F1-F5) was found to be respectively. Weight variation with in limit so, it was concluded that the uniformity of drug

distribution in the granulation or powder blend occurs. So, the tablets were made were perfect.

In all formulation, the hardness test indicated good mechanical strength. Hardness of synthetic polymer was ranged from 5.2 to 5.9 Kg/cm^2. Friability was ranged from0.10 to 0.15. and weight variation range was 202 to 209 and content was ranged 92.99 to 97.09 total floating time>9 to>11 [hrs].

An ultraviolet (UV) spectrophotometric method was used for the determination of drug content. Absorption maxima were determined by scanning different concentration of solution of drug captopril An absorption maximum was 208nm nm and method obeys Beer's law in concentration range 10 to 5. µg/ml, with good correlation coefficient (0.998).

In weight variation test, 20 tablets were selected random and average weight variation was calculated. Then individual tablet were weighed and weight was compared with average weight. It was varied from 203 to 209.10.

In-vitro release of captopril

In vitro release the release study in vitro aqueous Floating tablet of captopril time period 12 hours.

In the disintegration test, the disintegration test of different formulation it was observed that disintegration time of captopril ranged from 23 to 28 min. in 0.1N HCl.

The release profile of captopril from the timed –Floating tablet of different batches had been studied. *In vitro* dissolution studies was carried out USP paddle metod at 50rpm in 900ml of 0.1NHCL, maintained at $37+0.5^0$C.10 ml of aliquots withdrawn atb specified intervals filtered through whatmann filter paper and analysed at 208 nm using UV- VCisible spectrophotometer. The dissolution media was replaced by 10ml of each fresh dissolution fluid to maintain a constant volume. The synthetic polymer lower concentration (f-4) showed faster release 89.25% in 10 hrs and the highest polymer concentration (f-2} released 80% drug after10 hrs same as synthetic polymer comparatively the release rate of using **natural polymer** f4 lower polymer concentration and shows fasterr releas 83.23% and higher polymer concentration f1 shows slower release after 10 hrs 79.25.

The work carried out to study the effect of other response like bioadhesiveness and floating, release rate of drug.

Formulation which are using synthetic polymers turned out to be the best because they showed a minimum lag time and maximam floating time with maximum release of drug persrntage so it is considerd as a successful.

Summary

Hence in present investigation, for the formulation of floating tablet hpmc and carbopol used as matrix forming agent. other excipient used are, sodiumbicarbonate{as a gas generating agent} citric acid magnesium stearate as lubricant. The drug polymers are subjected to various preformulation stidies sach as angle of repose, bulk dencity, tapped dencity, compressibility index, hausner ratio cherecterization using FTIR, drug and excipient compatibility the tablet were using single station punching machine.

Prepared tablet were subjected to various evaluation parameters such as thickness hardness, weighet variation, friability buoyancy study and invitro drug release, it was councluded that there was no interference in the functional group as the principle peaks of the drug were found to be unaltered in the drug polymer physical mixture.

Floating, bioadhesive, swellable and megnatic system based GRTB are available however floating is gaining popularity associated whith their negligible advers effect on motality of gi tract andachevment of immediate buoyancy for GRTB be successful, detailed understanding of physiochemical property of drug physiological events of drug in the gi tract impact of gi tract physiology On drug delivery and formulation stratergies and their evaluation is prerequieste.

CONCLUSION

Floating tablets used for the drugs which get easily solubilized in stomach captopril floating tablets was used for the tratment of hypertension. The choice of the polymer and its quantity in floating tablet is critical to control the solubility profile of tablet. Drugs which are having low oral bioavailability (<50%), short biological half life (about 1 to 1.9 hrs.) and an adequate protein binding that are preferred while formulating floating tablet. On the basis of findings observed in present work, it can concluded that floating tablet of captoprilcould be the suitable dosage form for the treatment of diabetes with low dosing frequency for better

patient compliance, less toxic & better hypertension than other floating tablet formulations. This dosage form is preferred as it is very convenient and easy to formulate, cost-effective and does not require high cost equipments. For that reason, this dosage form has been gaining so much attention nowadays. from the above experimental result it can be concluded that, sodium bicarbonate has predominant effect on the buoyancy lag time, while hpmc has predominant effect on the total floating timeand drudg release.

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