Formulation and Evaluation of Hydrogel Based Oral Controlled Release Tablets of Simvastatin

P.Sandhya[1,2,3*], Bushra Anjum[1] , K.S.K.Rao Patnaik[2], C.V.S.Subrahmanyam[3]

[*1] Department of Pharmaceutics, Shadan Women's College of Pharmacy, Hyderabad, India.
[2] University College of Technology, Osmania University, Hyderabad, India.
[3] Department of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Hyderabad.

Abstract- Hydrogel based tablets of Simvastatin was formulated using hydropropyl methyl cellulose(different grades), guar gum and carbopal-934-P with the aim to study of release kinetic, to attain a near zero order release and to increase the bioavalability upto 95%. In-vitro dissolution studies were carried out using USP type 2 dissolution test apparatus. The release of drug followed a typical Higuchian pattern. Hydrogel based tablets formulated employing hydropropyl methyl cellulose, guar gum and carbopal-934-P slow release of Simvastatin over period of 12 h and were found suitable for maintenance portion of oral controlled release tablets. Simvastatin release from these tablets were diffusion controlled and followed zero order kinetics after a lag time of 1h[1]. The most successful of the study, exhibited drug release pattern very close to theoretical release profile. A decrease in release kinetics of the drug was observed on

Index Terms- Bioavalability, Carbopal-934-P, Formulation, Guar gum, Hydrogel, Hydropropyl methyl cellulose. Release kinetics study.

I. INTRODUCTION

During the last two decades there has been remarkable increase in interest in controlled release drug delivery system. This has been dua to various factors viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric matericals suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems[1]. Now-a-days the technology of controlled release is also being applied to veterinary products also. The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and /or physiological parameters inherent in a selected route of administration. Hydropropyl methyl cellulose (different grades like HPMC-K-15M and HPMC-K-100M), Carbopal-934-P and natural gum (Guar gum)can be used as matrix materials. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix material[1]. Hypercholesterolemia disease in which normally, about 70-75% of plasma LDL is removed by hepatocytes, by receptor-mediated endocytosis. Cholesterol esters from LDL molecules are hydrolysed in the liver to free cholesterol. The liver is also produced cholesterol by *de novo* synthesis by the pathway involving formation of mevalonic acid by the enzyme (HMG-CoA Reductase). Simvastatin(1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate. The 6-membered lactone ring of simvastatin is hydrolyzed *in vivo* to generate the beta,delta-dihydroxy acid, an active metabolite structurally similar to HMG-CoA (hydroxymethylglutaryl CoA). Once hydrolyzed, simvastatin competes with HMG-CoA for HMG-CoA reductase, a hepatic microsomal enzyme. Interference with the activity of this enzyme reduces the quantity of mevalonic acid, a precursor of cholesterol[2]. The resulting decreases in hepatic cholesterol synthesis leads to increased synthesis of high affinity LDL receptors on liver cells and increased clearance of plasma LDL. This causes reduction in plasma LDL cholesterol level. Off various recent techniques for controlling drug release[3], advantages of ease of formulation, better control on release profile of drug and better patient compliance.

II. MATERIALS AND METHODS

Simvastatin was obtained as gift sample from Dr. Reddy's Laboratory, Hyderabad, India. HPMC-K-15M and HPMC-K-100M from Suleb Lab, Baroda. Carbopal-934-P from National Health Care Pvt. Ltd, Nepal. Guar gum was obtained as gift sample from S.D.Fine chemical Ltd, Mumbai. Other materials used were of analytical grade, and procured from commercial sources.

Preparation of Controlled Release Tablets of Simvastatin

All the ingredinents were sieved through sieve number 120. Weighed quantities of drug, polymer, lubricant (Talc and Magnesium sterate) and diluent (lactose) were mixed in geometric proportion using a mortar and pestle. Controlled released tablets were prepared by wet granulation method. Hydroxypropyl methylcelluloses(HPMC-K-100M and HPMC-K-15M), Guar Gum and Carbopol-934-P were used as retardant material for prepartion of tablets[1].

The resultant mixture was wetted with 4% starch paste and granulated then the damp mass was passed through sieve number 10. The wet granules were dried in the oven at 50° C for half an hour. Remaining amount of lubricants were added to the dried granules.

After evaluating the precompression parameters, the lubricated granules were subjected to compression to form tablet with target weight of 300mg using hydraulic press having 10mm

diameter flat punches. The hardness of all tablets was maintained at 6 to 8 Kg/cm². The formulae for various formulatins attempted have been given in table No.1

Dissolution study of controlled release fomulation of Simvastatin

The in-vitro dissolution profile of the designed formulations of controlled release tablets was carried out using USP type II apparatus under conditions specified (temp 37± 0.5°C, 75rpm). Tablets were subjected to dissolution for first two hrs in 0.1 N Hcl, followed by pH 7.4 phosphate buffer for next ten hours till the end of dissolution study. From the dissolution medium withdrawn and replaced 5ml for every 1hour. Absorbance was measured at 238 nm using buffer solution as blank. Results of in-vitro dissolution studies obtained were tabulated and shown graphically according to following modes of data treatment[4].

1. Cumulative Percentage Drug Release V/s Time in Hours.
2. Cumulative Percentage Drug Retained V/s Time in Hours.
3. Higuchi's Classical Diffusion Equation - Cumulative Percentage Drug Release V/s Square Root T.

III. RESULTS AND DISCUSSIONS

In present work an attempt has been made to formulate hydrogel based oral controlled release tablets of Simvastatin using retardants namely Hydroxypropyl methylcelluloses(HPMC-K-100M and HPMC-K-15M), Guar Gum and Carbopol-934-P in different concentration and combinations. The formulation of tablets was done by using wet granulation technique which was found acceptable.

The results of *evaluation studies* can be summarized as follows:

Figure No.1 shows plot of cumulative percentage of Simvastatin release V/s. time for optimized formula. Four polymers were employed with varying concentrations to get promising concentration for Hydrogel based oral controlled release tablets, which can be used for further studies. Formulation F1, F2, and F3 contains Guar Gum, HPMC-K-100M, Carbopol-934-P, and HPMC-K-15M as polymer. Formulation F1, F2 and F3 gave 93.77%, 84.56% and 90.04% of drug release respectively in 12hours of dissolution study performed. It was found that drug release was prolonged to desired level in F1 and F3; but in F2 it was found that drug release was not prolonged to desired level, this may be due to inadequate concentration of polymer and also due to lactose, present in relatively large amount which alter drug release rate mainly by altering the gelation of polymer. Formulation F4 contains HPMC-K-15M and Carbopol-934-P which gave 84.89% of drug release, F5 contains HPMC-K-100M and Carbopol-934-P which gave 88.67% of drug release in 12hours dissolution study. The drug release was found to be not prolonged; this may be due to presence of large amount of lactose. F6 contains HPMC-K-100M and HPMC-K-15M gave 92.78% of drug release in 12hours dissolution of study. The drug release was found to be prolonging this is due to low concentration of polymer level. Formulations F7 and F8 contains Guar Gum and HPMC-K-100M gave 85.25% and 80.11% of drug release in 12hours of dissolution study, this may due to high concentration of polymer level. F9 and F10 gave 85.24% and 90.38% of drug release and F11 contains HPMC-K-100M and PVP-K-30 gave the 91.58% of drug release in 12hours of dissolution study. The mechanism of release may be based on hydration and gelation due to cellulosic nature of polymer at tablet liquid interface. The existence of gel barrier could be expected to drug release by limiting exposure of solid drug to dissolution liquid. The drug release may be due to diffusion controlled and swelling controlled mechanism because of inherent swelling characteristic of hydroxylpropyl methylcellulose. The tablets were found swollen at the end of 12hours indicating a hydrophilic system. Guar Gum, a natural polymer used in formulation, the tablets were found swollen at the end of 12hours dissolution study this may be due to inherent swelling property of gum.

Figure No.2 shows a plot of Swelling index, the graph was plotted between % weight absorption ratio and time.

The best selected formulations are F1, F3 and F6; these plots were found to be linear with correlation coefficient (r) values which are 0.997, 0.995 and 0.995 respectively. But the optimized formula is F1 with the r value 0.997. This linearity indicates that the release of Simvastatin from the tablets have followed nearly zero order kinetics.

Figure No.3 shows plot of Zero order kinetic release graph of optimized formula (cumulative % drug release V/s time) which shows the linear drug release of Simvastatin.

Figure No.4 shows plot of Higuchi's Classical Diffusion Equation graph of optimized formula (cumulative % drug released V/s square root time.

Figure No.5 shows plot of Peppas kinetic model graph of optimized formula (Log cumulative % drug release V/s Log time). Slope (n) value is 1.077.

Figure No.6 shows plot of First order kinetic release graph of optimized formula (Log % drug remaining V/s time).

IV. CONCLUSION

From the finding obtained so far, it can be concluded that,

- Hydroxypropyl methylcellulose (different grades) and Guar Gum is of the total tablet weight is promising concentration for oral controlled release tablets Simvastatin.
- Formulated tablets exhibited nearly zero order kinetics and the release profile was of matrix diffusion type.
- From this study, it is possible to design promising Hydrogel based oral controlled release tablets containing Simvastatin for the treatment of hypercholesterolemia.
- Hydrogel based oral controlled release tablets of Simvastatin also used in reducing heart related disease, heart stroke and with more efficacy and better patient compliance.
- The in-vitro kinetic release obeyed zero order kinetics with mechanism of release was followed by non-fickian diffusion due to more hydrophilic nature of polymer and drug. The increase in concentration of polymer decreases the release of drug.

Table.1: Composition of hydrogel based oral controlled release tablets of Simvastatin

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Drug	40	40	40	40	40	40	40	40	40	40	40
Guar gum	120	120	80	-	-	-	160	-	-	-	-
HPMC-K100M	40	-	-	-	40	20	-	160	-	-	40
HPMC-K15M	-	-	40	40	-	20	-	-	-	120	-
Carbopol-934-P	-	40	-	40	40	-	-	-	80	-	-
Lactose	70	70	90	90	90	110	70	70	85	70	180
Starch	20	20	-	-	-	-	20	20	-	-	-
MCC	-	-	50	80	80	100	-	-	85	60	-
PVP-K30	-	-	-	-	-	-	-	-	-	-	30
Mg. sterate	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5
Tatol tablet weight	300	300	300	300	300	300	300	300	300	300	300

Figure No.1 % Cumulative drug release graph for optimized formula

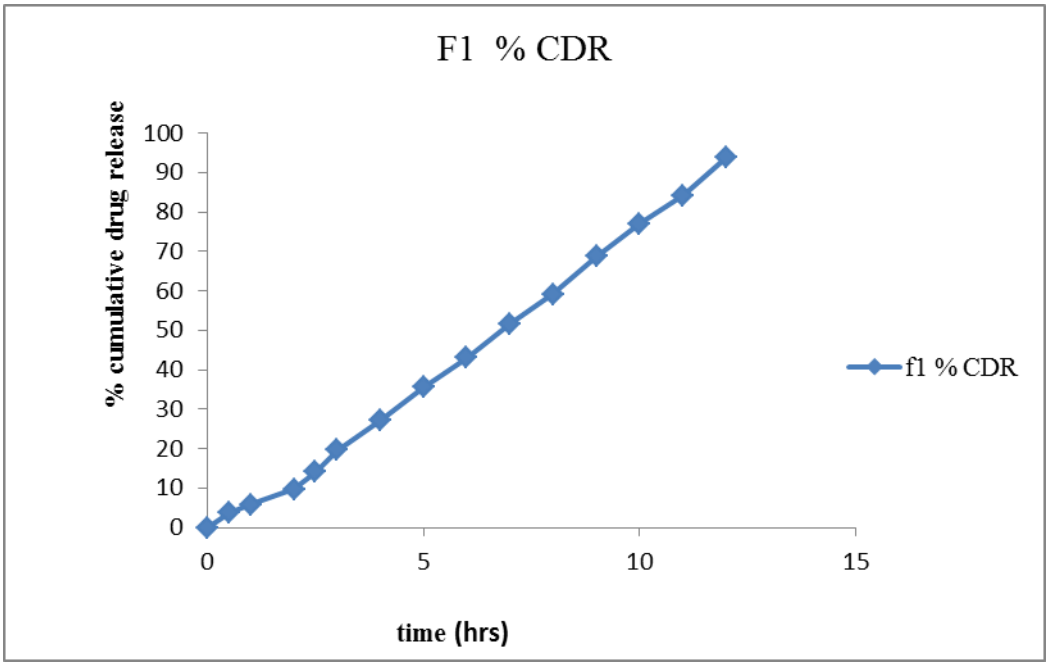


Figure No.2 % Weight absorption ratio graph for optimized formula

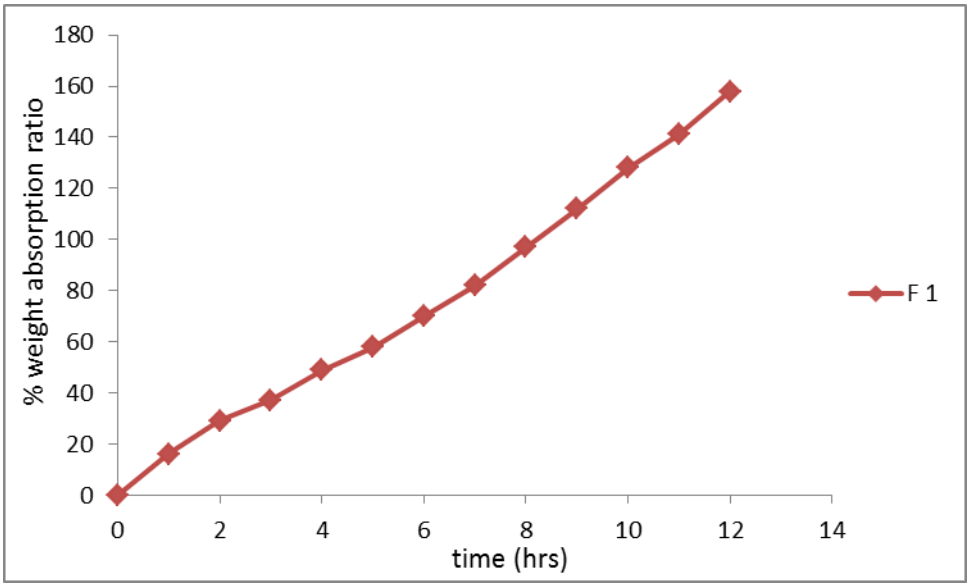


Figure No.3 Zero order kinetic release graph for optimized formula

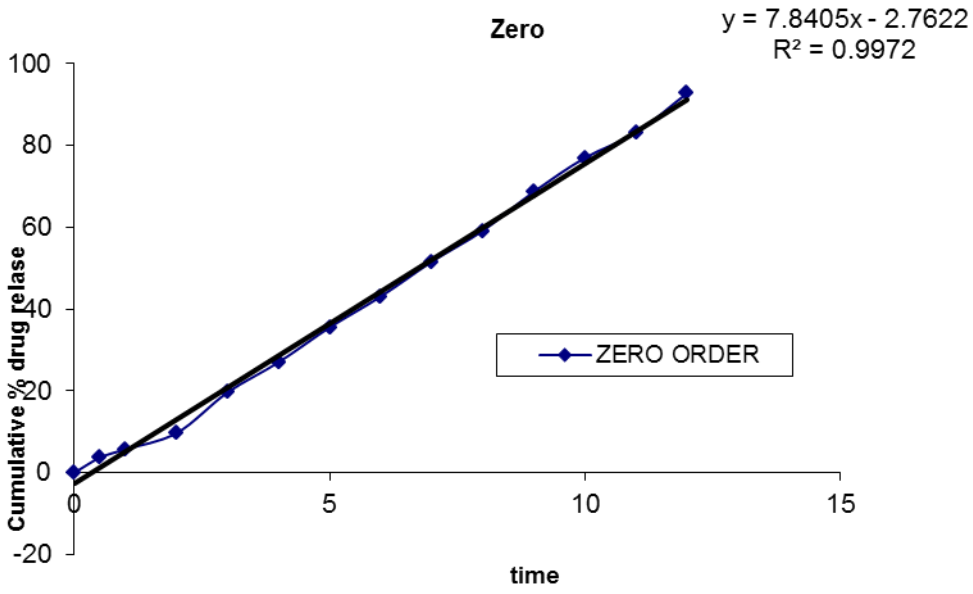


Figure No.4 Higuchi Model graph for optimized formula

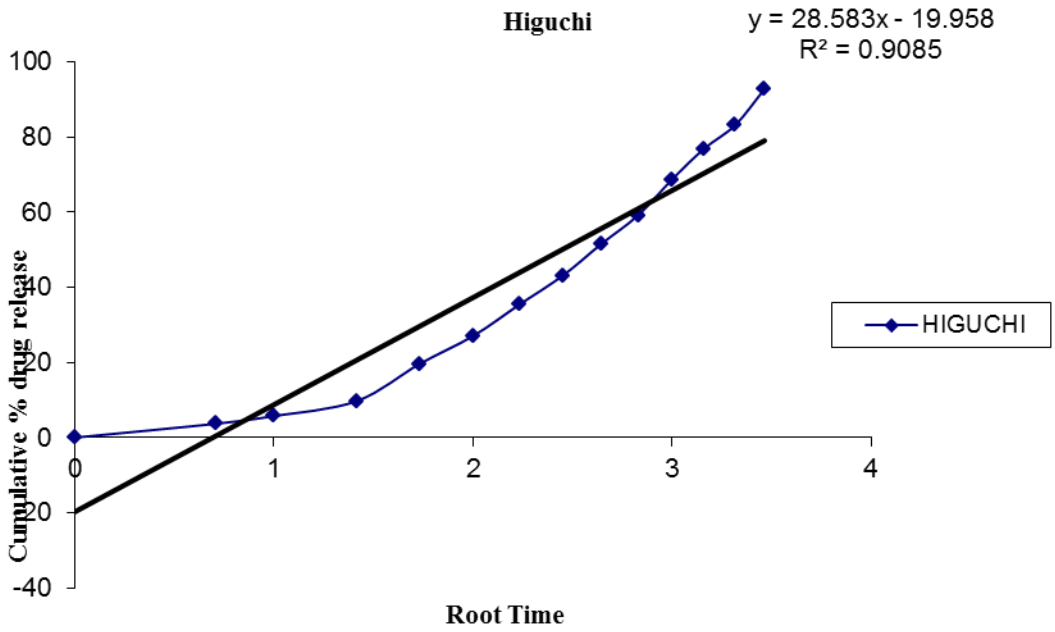


Figure No.5 Korsmeyer Peppas Kinetic Model graph for optimized formula

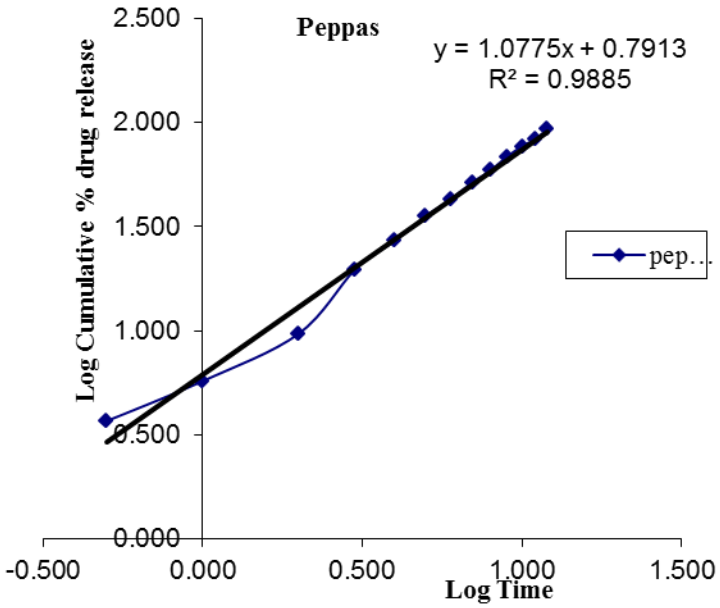
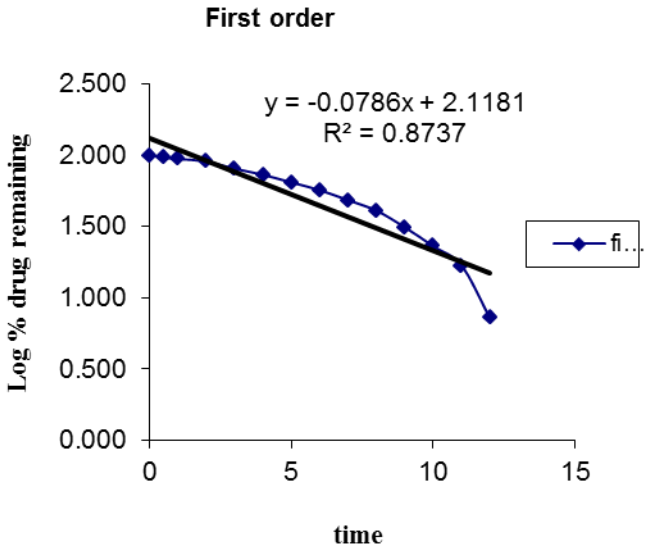


Figure No.6 First order kinetic release graph for optimized formula



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AUTHORS

First Author – P.Sandhya, University College of Technology, Osmania University, Hyderabad, India.
Second Author – Bushra Anjum, Department Of Pharmaceutics, Shadan Women's College of Pharmacy, Hyderabad, India.
Third Author – K.S.K.Rao Patnaik, University College of Technology, Osmania University, Hyderabad, India.
Fourth Author – C.V.S.Subrahmanyam, Department Of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Hyderabad.