FORMULATION AND EVALUATION OF GUAR-GUM BASED ATORVASTATIN BEADS

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ABSTRACT

A sustained-release dosage form is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Atorvastatin, a selective, competitive HMG-CoA reductase inhibitor, is used to lower cholesterol and triglycerides in patients with hypercholesterolemia and mixed dyslipidemia and in the treatment of homozygous familial hypercholesterolemia. 10mg of the drug was taken and dissolved in ethanol.A mixture of polymers(HPMC,Guargum, sodium alginate)were taken into a mortar and triturated till a smooth paste is formed.Drug is added into the polymer solution and make up the volume to 100ml with distilled water.Prepare 1.5%, 2% and 2.5% calcium chloride solutions. Beads were prepared by using 1ml insulin syringe. Then curing is done for 15min and filtered air-dried.Further it is taken for in-vitro dissolution studies.

Key Words: Atorvastatin beads, HPMC, Guargum, sodium alginate, Sustained-release

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INTRODUCTION

A sustained-release dosage form is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug. To achieve successful systems, technical difficulties ranging from protein denaturing during formulation process and the course of prolonged in vivo release, burst release, and incomplete release, to low encapsulation efficiency and formulation complexity have to be simultaneously resolved. Sustained-release technology offers the promise for reducing dosing frequency, maximizing the efficacy–dose relationship, and decreasing adverse side effects. To achieve in vivo or in situ sustained-release of drugs, various polymer-based formulation strategies have been examined since1970s.

As an alternative, the use of biodegradable materials, such as polymers, encapsulating the medicament can be employed as a sustained delivery system. The use of biodegradable polymers, for example, in the form of microparticles or microcarriers, can provide a sustained release of medicament, by utilizing the inherent biodegradability of the polymer to control the release of the medicament thereby providing a more consistent, sustained level of medicament and improved patient compliance.

Hyperlipidemia, hyperlipoproteinemia, or hyperlipidaemia is the condition of abnormally elevated levels of any or all lipids and/or lipoproteins in the blood. It is the most common form of dyslipidemia (which also includes any decreased lipid levels). Hyperlipidemias are divided in primary and secondary subtypes. Primary hyperlipidemia is usually due to genetic causes (such as a mutation in a receptor protein), while secondary hyperlipidemia arises due to other underlying causes such as diabetes. Lipid and lipoprotein abnormalities are common in the general population, and are regarded as a modifiable risk factor for cardiovascular disease due to their influence on atherosclerosis. In addition, some forms may predispose to acute pancreatitis.

Atorvastatin, a selective, competitive HMG-CoA reductase inhibitor, is used to lower cholesterol and triglycerides in patients with hypercholesterolemia and mixed dyslipidemia and in the treatment of homozygous familial hypercholesterolemia. Atorvastatin has a unique structure, long half-life, and hepatic selectivity, explaining its greater LDL-lowering potency compared to other HMG-CoA reductase inhibitors.

Polymeric hydrophilic matrices are widely used for controlled-release preparations. The process of drug release is controlled by matrix swelling or polymer dissolution. It has been shown that the swelling of guar gum and Sodium Alginate is affected by concentration of drug and viscosity grade of the polymer. This study examines the mechanism of behavior of guar gum and Sodium Alginate in a polymer-drug matrix. The swelling action of guar gum, in turn, is controlled by the rate of water uptake into the matrices. An inverse relationship exists between the drug concentration in the gel and matrix swelling. This implies that guar gum and Sodium Alginate swelling is one of the factors affecting drug release. The swelling behavior of guar gum is therefore useful in predicting drug release.

MATERIALS AND METHODS:

Atorvastatin, Guargum, HPMC, Sodium alginate, Phosphate buffer PH -7.4, Ethanol, Distilled water, Calcium chloride, Scanning electron microscopy, Differential scanning calorimeter, USP- II Dissolution apparatus, UV Spectrophotometer

Preparation of Atorvastatin Beads

10mg of the drug was taken and dissolved in ethanol.A mixture of polymers(HPMC,Guargum, sodium alginate)were taken into a mortar and triturated till a smooth paste is formed.Drug is added into the polymer solution and make up the volume to 100ml with distilled water.Prepare 1.5%, 2% and 2.5% calcium chloride solutions. Beads were prepared by using 1ml insulin syringe. Then curing is done for 15min and filtered air-dried.Further it is taken for in-vitro dissolution studies.

EVALUATION OF BEADS:

Preformulation studies:

FTIR Studies

The FTIR spectral measurements were taken at ambient temperature using IR spectrophotometer. Two mg of pure drug, polymers and drug loaded polymer beads were selected separately. FTIR was used to study the drug Polymer Interaction.

Differential scanning calorimetry (DSC)

The DSC measurements were taken at ambient temperature using IR spectrophotometer. Two mg of pure drug, polmers and drug loaded polymer beads were selected separately. DSC was used to study the drug Polymer Interaction.

In vitro evaluation studies

Drug content:

The beads were evaluated for ATR content. The swollen beads were crushed in mortar with pestle and the homogenous solution thus formed was sonicated for 2 min at 60MHZ of frequency. About 20ml of ethanol was added to precipitate Na-Alg. ATR was analyzed by UV spectrophotometer at λmax value of 254 nm. The percentage entrapment efficiency was calculated as

Drug Entrapment Efficiency

The drug entrapment efficiency (DEE) was calculated by the

$$DEE = (Pc / Tc) \times 100$$

Here, Pc is practical content, Tc is the theoretical content.

Particle size analysis

The microsphere size distribution was determined by the optical microscopy method using a calibrated stage micrometer (µm) and was calculated by using following equation

$$\text{Eye piece division} = \frac{y}{x} \times 10\mu m$$

Here   y=number of stage micrometer division

X= number of eye piece divisions

10µm= least count

In-vitro drug release

Dissolution experiment were performed at $37^{o}C$ using a dissolution apparatus equipped with 8 paddles at a paddle speed of 100 rpm. A 900ml solution of phosphate buffer solution (7.4) was used as dissolution medium. Samples (5ml) were withdrawn at predetermined time intervals for the analysis of the released drug. The withdrawn volume was immediately replaced with an equivalent volume of the fresh medium maintained at the same temperature. The absorbance values of the sample were reported at 254 nm.

### Determination of Absorption Maxima and Calibration Curve

Before the analysis of solutions containing ATR, the spectrophotometry was adjusted with phosphate buffer PH 7.4. The spectrum was recorded from 200-400 nm. Standard solution (10µg/ml) was scanned against a solvent (phosphate buffer 7.4) as blank between   200-400nm. Spectrum was recorded and the suitable absorption maximum was selected as 254nm.

Varioua aliquots of standard stock solution were taken and diluted to 10ml with phosphate buffer to give final analyte concentration of wanted volume (10-50μg/ml). Then the absorption of these solutions were measured at 254nm and the corresponding values were plotted.

Scanning electron microscopy (SEM)

SEM of the drug loaded beads were taken. The shape and surface features of beads were observed by optical microscopy. The beads were hard, free flowing and discrete and almost spherical in shape. The color was dark brown. Clumping was seen in some cases, which could be easily separated by gentle agitation.

RESULTS AND DISCUSSION
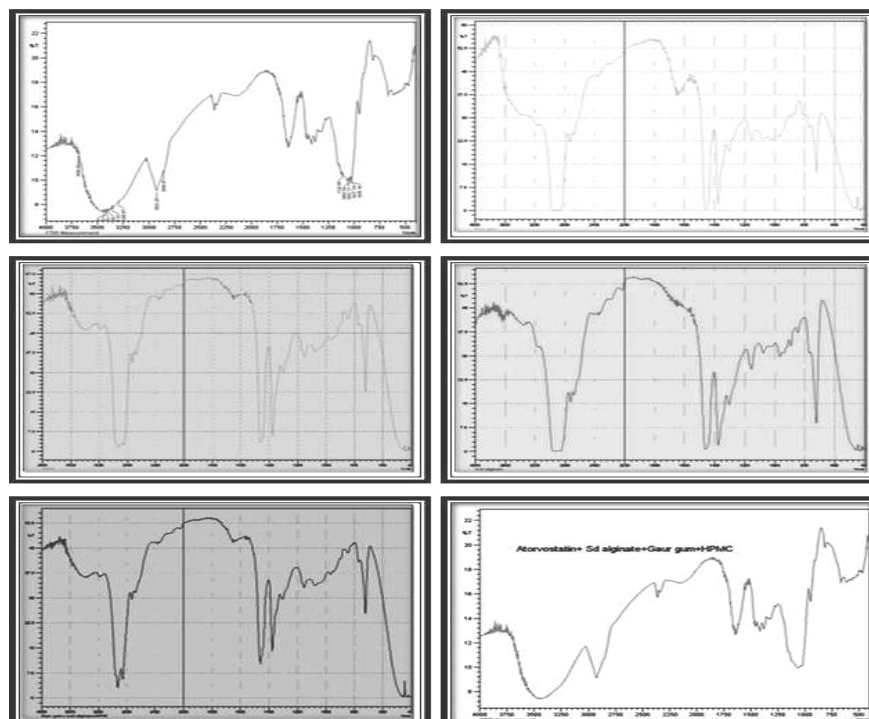
FTIR GRAPHS

In order to observe the compatibility of drug with the polymers the samples were subjected to the Fourier Transform Infra Red spectroscopy (FTIR). The spectrum of pure drug, polymers HPMC, sodium alginate and guar gum, drug and the polymers mixture were obtained. The drug and the polymers mixture presented the peaks characteristic to the pure drug. This states that the presence of polymers did not alter the properties of the drug atorvastatin. Thus we concluded that the drug is compatible with the polymers taken.
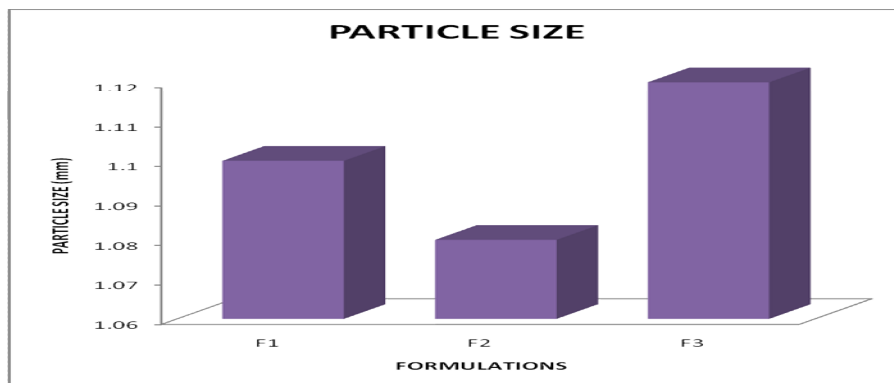
PERCENTAGE DRUG ENTRAPMENT
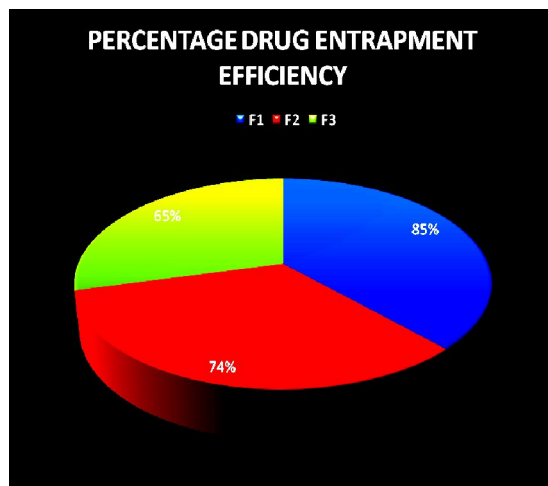
The percentage drug content and the drug entrapment efficiency of the optimised formulation F_2 was found to be 85%. On comparing these two properties with other formulations, F_1 and F_3 the optimised formulation has better results the comparision of the three formulations are given in the following graphs
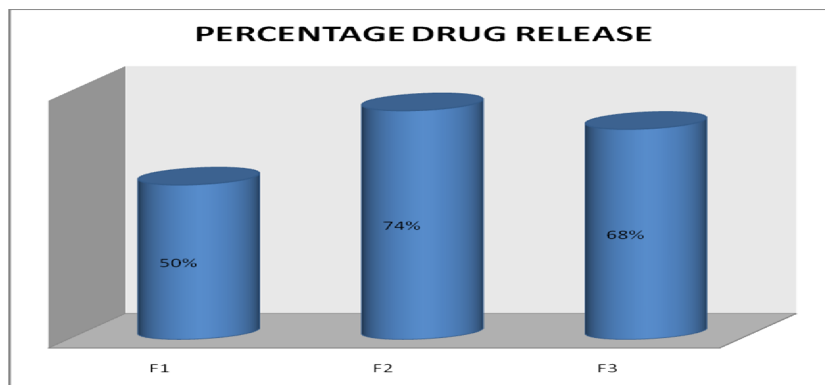
PARTICLE SIZE

On determining the particle size of the beads the mean particle size diameter of the beads belonging to optimized formulation was found to be 1.08-1.12 mm and the comparison of all the three formulations was given in the following histogram where the formulations are taken on X axis and the particle size in mm on Y axis.

DISSOLUTION STUDIES

The invitro drug release was determined by conducting the dissolution studies in the dissolution apparatus for 6 hrs. the percentage drug release of the formulations performed test was given in the following graph. The percentage drug release of F_1 formulation for 12 hrs was found to be 50% . Tthe plasma half life of Atorvastatin drug is 14hrs. So after conducting the invitro drug release test for 6 hrs it is the optimised formulation showed only 50 % drug release so it can be used for sustain release action. The other formulations F_2 and F_3 showed 74% and 68% respectively which are not suitable for the sustain release action as the cannot release the drug for about 6hrs.

PERCENTAGE DRUG RELEASE
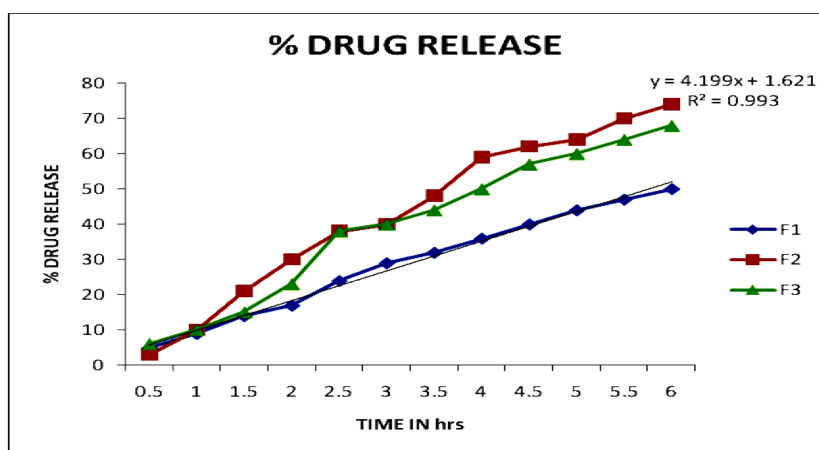
Correlation Coefficient (R^2) Values in the Analysis of Release data as per various Kinetics

Zero order	First order	Higuchi	Korsemeyer
R^2=0.994	R^2=0.977	R^2=0.988	R^2=0.996
m =2.42	m=-0.016	m =0.029	m=0.027

ZERO ORDER KINETICS

Zero order kinetics was obtained on plotting the graph between time and percentage drug release. Time is taken on abscessa and cumulative percentage drug release on ordinate. The slope and the R^2 value was recorded as in the graph given below.
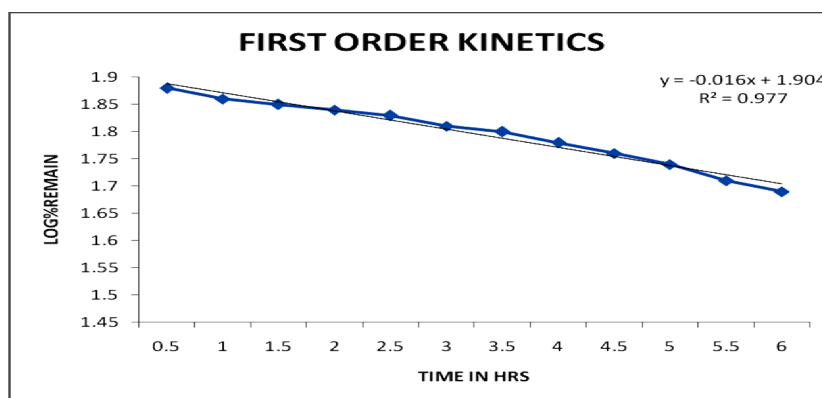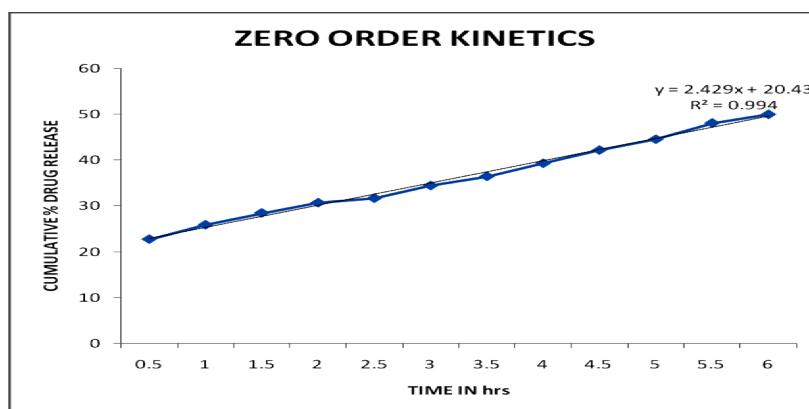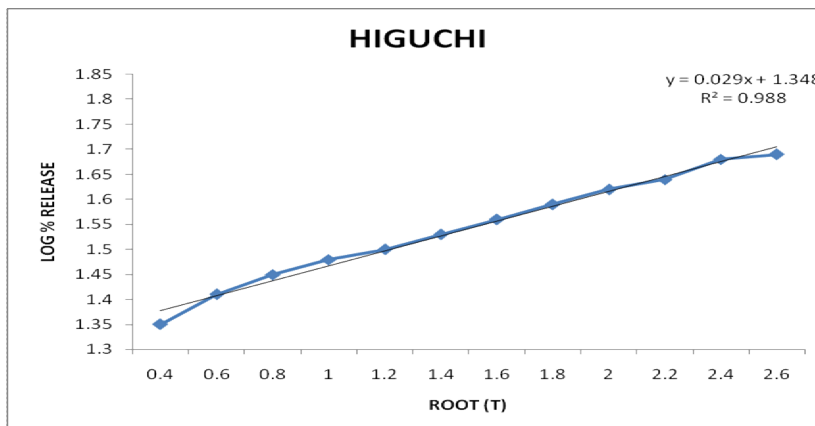

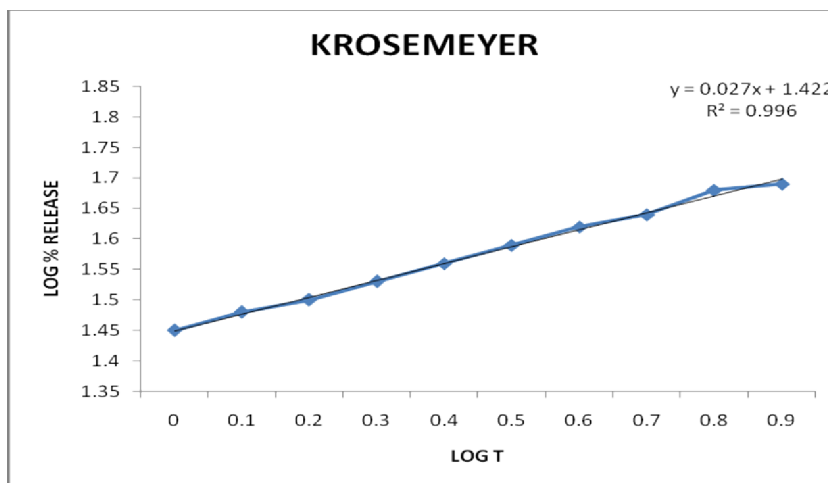*Athiraju Naveen et al. /JGTPS Jan-March 2012, Vol.3 (1)-576-588*

On plotting the graph between time and log percentage remain on X and Y axes respectively the graph for first order kinetics was obtained. The slope and the R2 values were recorded as shown in the above graph.

HIGUCHI

$y = 0.029x + 1.348$
$R^2 = 0.988$

(Y axis: LOG % RELEASE, from 1.3 to 1.85; X axis: ROOT (T), from 0.4 to 2.6)

Taking time root on X- axis and log percentage release on Y axis the graph for Higuchi was obtained with R2 and the slope values on the graph. It is shown in the graph.

Krose mayer release graph was obtained by plotting log time on X axis and log percentage release on Y axis as sown in the following graph.

KROSEMEYER

$y = 0.027x + 1.422$
$R^2 = 0.996$

(Y axis: LOG % RELEASE, from 1.35 to 1.85; X axis: LOG T, from 0 to 0.9)

SEM PHOTOGRAPHS

The SEM photographs of the Atorvastatin beads revealed the external surface of the beads and it was found that their surfaces are smooth.
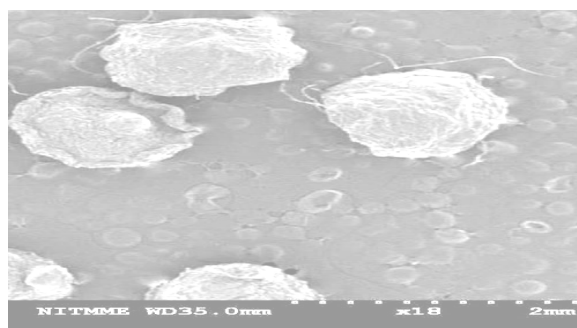
SEM photographs of the Atorvastatin beads

CONCLUSION

The emulsion gelation method was successfully utilized for formulation of guargum based Atorvastatin beads. The adopted method for estimation of Atorvastatin showed good linearity. The formulated beads showed higher percentage of drug entrapment efficiency (85%) and the optimum particle size. The beads also showed good swelling behavior. The beads showed excellent sustaining properties as compared to conventional beads which were due to incorporation of HPMC.

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