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Formulation and Development of Microemulsion Based Tablets of Atorvastatin Calcium

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ABSTRACT:

Atorvastatin calcium is the drug used for treating hypercholesterolemia. Microemulsions are used as edge as potential drug delivery vehicles because of their thermodynamic stability, reversibility, simple manufacturing, and scale up feasibility, and do not require any special equipment. Microemulsion based tablet of atorvastatin calcium was formulated using avicel 101 as career and aerosil as coating material. A32 full factorial design was carried out to optimise oil: smix ratio and % SSG for the formulation of tablet. Regression analysis was carried out for dependent variable and full and reduced polynomial equations ware generated for each variable. The response plot and counter plot were prepared for each response to check effect of each variable on response. Using check point batch the polynomial equations were validated and optimised batch were formulated using extensive grid search on overlay counter plot and polynomial equation. The optimised formulation was evaluated for flow property, hardness, friability, disintegration time, emulsification time, and invitro drug release. Drug release kinetic of optimised batch showed fickian diffusion type drug release. A stability study and comparison study with marketed formulation was carried out on optimise formulation.

KEYWORDS: Atorvastatin calcium, microemulsion, tablet dosage form, Liquid retention potential, Career: coat ratio.

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INTRODUCTION:

Introduction to dosage form:-[1]

Microemulsions are thermodynamically stable dispersions of oil and water stabilized by a surfactant and frequently with a co-surfactant. Microemulsions are dispersions of nanometer-sized droplets of an immiscible liquid within another liquid. Droplet formation is facilitated by the addition of surfactants and often also co-surfactants with dispersed domain diameter varying approximately from 1 to 100 nm, usually 10 to 50 nm. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions.

Administration of the microemulsion in a form of a free solid dosage form can offers significant advantages as,

1. The solid dosage form presents a more robust and stable dosage.
2. It is more patient acceptable and thus provides potential for better patient compliance.

3. Easy production and packaging.
4. It provides the use of various ingredients in combination with the dosage forms to enhance bioavailability and the rate of dissolution.

Formulation Component

Formulation containing following components

1) Oil phase

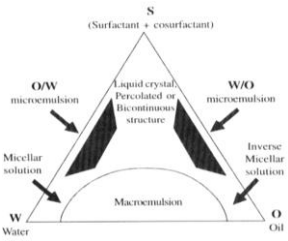
2) Aqueous Phase

2) Surfactant

3) Co-surfactant

4) Co-Solvent

Construction of pseudo ternary phase diagram[2]: Pseudoternary phase diagrams comprises of oil, Smix and water were developed using the aqueous titration method.

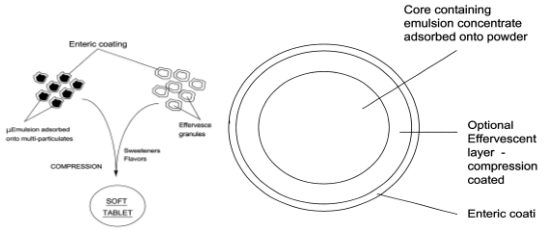


Pseudoternary phase diagram of oil, water and surfactant showing microemulsion region[3]

Solid dosage form of microemulsion[4 5]

Microemulsions however, require filling into soft or hard gelatin capsules. To overcome limitation of microemulsion like phase separation and to avail additional advantages its adsorption on to inert career/ powder can be carried out. The amount of microemulsion is kept low so that the mixture of adsorbent and microemulsion forms an easily compressible, free flowing powder.

Suitable nontoxic adsorbent may be used. Preferably fine particulate adsorbents are used. We can use kaolin, bentonite, colloidal silicon dioxide, magnesium trisilicate, aluminium hydroxide, calcium silicates, magnesium hydroxide, magnesium oxide or talc.



MATERIAL AND METHODS:

Material:

Atorvastatin Calcium was obtained from Intas Pharmaceutical, Ahmedabad Gujarat india. Polysorbate 80, Propylene glycol, Avicel 101 and Aerosil were obtained from Astron chemicals, Ahmedabad, Gujarat india. All ingrdients used in this formulation were analytical grade.

Analytical method for the estimation of atorvastatin:

Calibration curve for the estimation of Atorvastatin Calcium in 0.1N HCl:

Over lay spectra was obtained by preparing series of solution their spectrum were obtained in UV spectrophotometer and absorbance maxima was determined. Preparation of standard calibration curve of Atorvastatin Ca at 243nm

Instrument used: UV Spectrophotometer, Shimadzu 1800, Japan.

Solubility Study: The solubility of Atorvastatin Ca in various oil, surfactant, co-surfactant was determined. i.e Capmul- MCM, Sunflower oil , Soyabean oil, oleic acid , Olive oil , Span 80, Labrasol, Polysorbate 80, Polysorbate 20, Propylene glycol. Solubility studies were conducted by placing an excess amount of drug in each vehicle in vial containing 5 gm of the vehicle[6].

Pseudo ternary phase diagrams: Surfactant (Tween 80) and cosurfactant (PG) were mixed (Smix) in different weight ratios (4:1, 3:1, 2:1, 1:2). Soyabean oil was optimized as an oil phase based on the solubility study. For each phase diagram, oil (Soyabean oil) and specific Smix ratio were mixed thoroughly in different weight ratios viz., 4:1, 3:2, 2:3, 1:4. Each ratio of oil and Smix was taken and titrated with water at 5% intervals and then mixed on a vortex mixer. The solutions were observed visually and were categorized into different phases.

Physicochemical Characterization of Microemulsion: To determine the physicochemical characterization of prepared microemulsion.

Formulation of Micro-emulsion based tablets [4] [5] : Microemulsion based tablets prepared by adsorbing drug loaded oil and surfactant mixture to suitable career. The prepared powder mixture coated with suitable material to get dry look like free flowing powder. Thus obtained powder compressed using suitable binder with other excipients. Spireas & Bolton[7] has given method to optimise career: coat ratio for liquid adsorbed solid dosage system

Screening of Career & coating material:

Calculation of Required amount of career and coating material[8]

According to the theories, the carrier and coating powder materials can retain only certain amount of liquid while maintaining acceptable flow and compression properties. Hence, the excipient ratio (R) or the carrier: coat ratio of the powder system used should be optimized.

Calculation of Liquid load factor (L_f)

R represents the ratio between the weights of carrier (Q) and coating material (q) present in the formulation.

L_f = Φca +Φco(1/R)

Where, **Φca** and **Φco** are the flwable potential-values of carrier and coat material respectively.

$$\Phi ca = \frac{Wt\ of\ liquid}{wt\ of\ career} \quad \textbf{and} \quad \Phi co = \frac{Wt\ of\ liquid}{wt\ of\ coating}$$

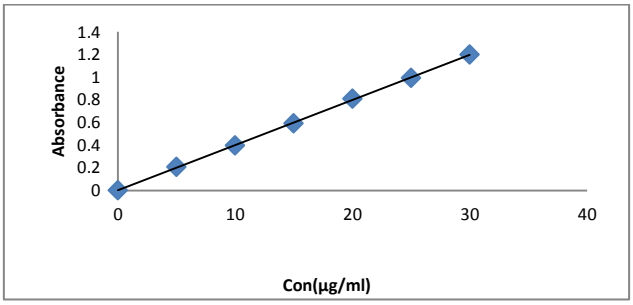
Experimental Design : A statistical analysis of microemulsion based tablet was carried out using 3^2 full factorial design. In an art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions. The number of experiments required for these studies is dependent on the number of independent variables selected.

***In-vitro*dissolution:** The *invitro drug* release test was performed in 900mL of 0.1NHCl maintained at 37±0.5 °C using USP XXV type II dissolution apparatus. The paddle rotation was set at 50 rpm. The microemulsion based Atorvastatin calcium tablet containing 10 mg. Five mL aliquots were collected periodically (5,10,15,30,45,60,and75min) and replaced with fresh dissolution medium. Aliquots, after filtration through 0.45µm whatman filter paper, were analyzed by UV-Vis spectrophotometer at 243nm.[9] Dissolution of marketed formulation of Atorlip 10® was performed by similar method. 1% Tween 20 was added to maintain sink condition. Dissolution was performed in triplicate.

Stability study: The stability study of optimized microemulsion based Atorvastatin calcium tablet was carried out in tightly closed air tight amber glass bottles. The bottles were kept at 40ºC±2ºC/75%RH ± 5%RH tested at 1 month. The sample was then evaluated for stability by determining DT, %drug content and *invitro* drug release.

Results and Discussion

Analytical method for the estimation of atorvastatin: Standard curve of Atorvastatin Ca in 0.1 N HCL shown in below graph.



Standard curve of Atorvastatin Ca in 0.1 N HCl

Solubility Study Results: Solubility of Atorvastatin Calcium in various vehicles are shown. Soyabean oil (16.65±2.34 mg/100 mg) exhibited higher solubility for Atorvastatin Ca among the various oils testes. Tween 80 (10.4±1.63mg/100 mg) and PG(13.8±2.05mg/100 mg) showed the highest solubilizing potential for Atorvastatin Ca among the various surfactants, cosurfactants screened. Based on the solubility data, Soyabean oil was selected as oil phase, Tween 80 as surfactant, PG as co-surfactant for formulating microemulsion.

Phase Diagram: From the results of the pseudo-ternary phase diagram, 4:1 ratio of S_{mix} was selected for microemulsion preparation. Optimum microemulsion formula was selected using phase studies employing Soyabean oil as oily phase, Tween 80 as surfactant and PG as a Co-surfactant.

Physicochemical Characterization of Microemulsion: The physicochemical characteristics of the developed microemulsion showed clear transmission that the developed system had lowviscosity (~25.56 cP). From the low viscosity we can conclude that the system is of the o/w type.Further water dilution test and dye test with scarlet red dye conforms o/w type emulsion.

Parameter	Value
Particle size (nm)	40.2 ± 2.3
Viscosity (cP)	25.56

Screening of Career & coating material: From the taken different career materials, Avicle 101 retain maximum oil:smix i.e. is 0.68 ml (701 mg) thus it was selected from 3 career. Aerosil as coating retain 0.42 ml (433.4mg) oil:smix. Using this data flowable liquid retention potential for career (Φca) and for coating (Φco) are calculated that is 0.152 and 0.44 respectively.

Experimental Design: Factorial Design :

Selection of Independent Variables and Dependent Variables

Independent variable		**Dependent variables**	
X1 Career:coat ratio, R	X2 %SSG	Y1 Angle of Repose	Y2 Disintegration time

Data Analysis: In this factorial design the obtained responses were analysed statically. A regression analysis was carried out using data analysis tool in M S Excel program. All batches were statically evaluated at confidence level 95 % or level of significance 5% / P < 0.05 for two response i.e. angle of repose and disintegration time. The significance of statistical model was tested and significant polynomial terms were used to predict the responses.

Formulation of Microemulsion based Tablet: Optimise formulation as it gives excellent flow property with minimised career: coating ratio,In the formulation F2, Career: coat ratio 5 was taken. Pre-gelatinised starch (10%) is used as binder (10% of mix of drug, oil, Smix, career and coating material) and sodium starch glycolate (4%) as disintegrate(4% calculated after addition of binder to the mixture) and magnesium stearate (1%) as lubricant (1% calculated after addition of SSG.)

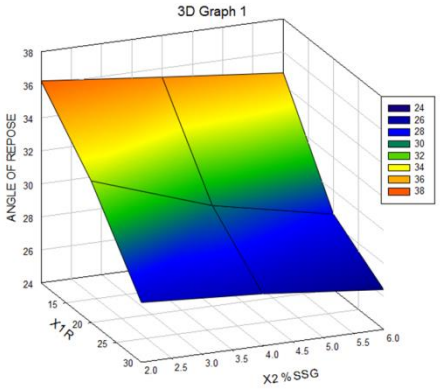


Figure 3 Response plot for response Angle of Repose

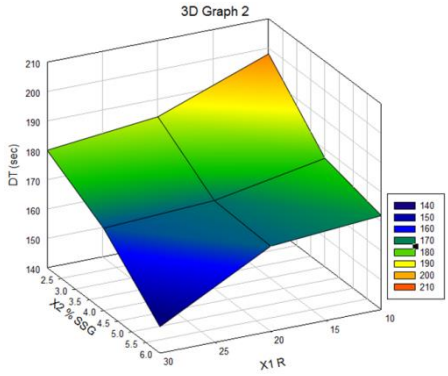


Figure 4 Response plot for response Disintegration time

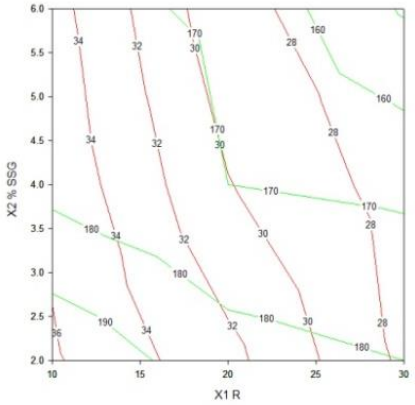


Figure 3 Overlay plot for responses

***In-vitro* dissolution**:

Comparison of % CDR of marketed formulation and optimised formulation: The Microemulsion based Atorvastatin calcium tablet was compared with marketed

formula Atorlip 10®(Cipla). The *invitro* drug release study of optimised formula and marketed formula-Atorlip 10®(Cipla) shows dissimilarity factor 32.91, indicating significant difference between drug release profiles. The optimised formulation gives better dissolution than Atorlip 10®(Cipla).

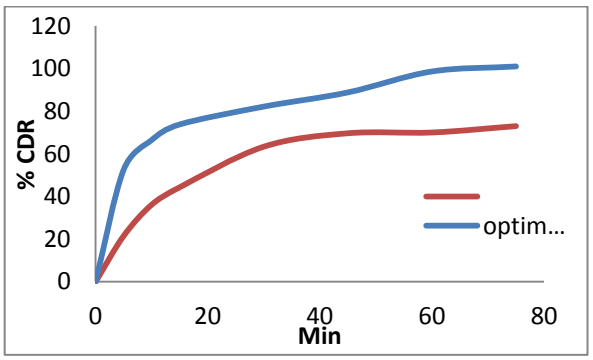


Figure 4 Comparison of optimized batch with marketed formulation

Stability study: Results of the stability study had shown no remarkable change in the release profile of the microemulsion based Atorvastatin calcium tablet after the stability. The Disintegration time was almost same.

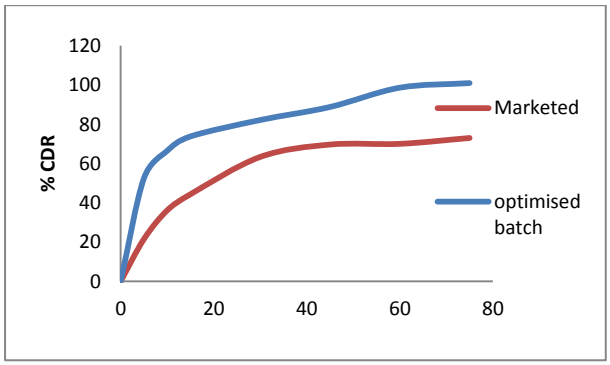


Figure 5 Stbility study data

CONCLUSION:

In current study microemulsion based tablet of Atorvastatin calcium was successfully formulated with the help of suitable career and coating material. Based on the solubility study, soya oil with tween 80 and propylene glycol were optimised as oil, surfactant and co-surfactant respectively. 4:1Smix ratio and 1:4 oil: Smix ratio was optimised based on phase diagram study that gave stable microemulsion. The low viscosity, dilution test and dye test conformed o/w emulsion. The optimized oil:smix was converted in free flowing powder using Avicel as career and aerosil as coating material.

The experimental design was used to optimize two variables i.e. career: coat ratio and % sodium starch glycolate. From the result of regression analysis, counter plot and response plot it was concluded that career: coat ratio is important for good flow property. As the ratio increases floe property increases with increase in tablet weight and change in disintegration time. For second variable, % sodium starch glycolate; it was concluded that as % SSG increases disintegration time decreases and career: coat ratio has a little effect on disintegration time.

The optimized batch was formulated based on validated polynomial equations and overlay counter plot grid search that gave free flowing drug loaded mixture with 154 second disintegration time. The drug release showed to be fickian diffusion drug release based on drug release kinetic study. The formulation found to be stable based on 1 month accelarated stability study and showed much better dissolution profile than marketed formulation.

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