

Formulation, Development and Evaluation of Atorvastatin Ethosomal Gel

S Agarwal^{1,*}, G Gautam^{1,2}

¹Department of Pharmacy, Bhagwant University, Ajmer, Rajasthan, INDIA.

²Shri Ram College of Pharmacy, Department of Pharmacy, Muzaffarnagar, Uttar Pradesh, INDIA.

ABSTRACT

Background: The present investigation was held to develop vesicular ethosomal gel system for anti-hypertensive drug atorvastatin. Atorvastatin is a HMG-CoA reductase inhibitor and utilized for minimizing cholesterol level in the treatment of congestive heart failure (CHF). In order to enhance the systemic bioavailability and to decrease the first pass metabolism atorvastatin drug was designed into ethosomal gel. **Methods:** Ethosomes composed of phospholipid soya lecithin, ethanol and cholesterol were formulated by cold method followed by ultra-sonication. The atorvastatin ethosomes were then distinguished for their particle size, zeta potential followed by *in vitro* drug release profile. The optimized ethosomal formulation was then incorporated into gelling agent, carbopol 934 to prepare ethosomal gel formulation. **Results:** The ethosomal gel formulation was then subjected to physico-chemical characterization, spreadability and *in vitro* drug release profile. The ethosomal gel formulation showed 15.69g.

cm² spreadability and 98.47% *in vitro* drug release within 48 hr as compared to plain drug ethosomal formulation which shows 65.37% in 48 hr.

Conclusion: It was concluded that ethosomal gel delivery system provide a good design for topical delivery of drug with enhanced bioavailability and patient compliance.

Key words: Bioavailability, Ethosomes, Metabolism, Sonication, Spreadability.

Correspondence

S Agarwal

Department of Pharmacy, Bhagwant University, Ajmer-305004, Rajasthan, INDIA.

Phone no: +91-8006033481

Email: agarwalshivacsr@gmail.com

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INTRODUCTION

Many dosage forms are available in the market, in that most of them are given by oral and parenteral routes. Oral route is widely used, but it shows decreased bioavailability due to first pass metabolism and gastrointestinal side effects. To overcome this, drug was designed into parenteral preparations in order to avoid gastrointestinal metabolism, but parenteral preparation are costlier due to their high manufacturing cost.

A persistent release rate of medicament is achieved by transdermal drug delivery system and it also maintain concentration level of medicament for a longer period of time in order to avoid peak and valley related with parenteral administration and oral dosing. A number of problems like first pass metabolism, decreased absorption rate, gastrointestinal disturbances and formation of toxic metabolites, etc can be avoided by utilizing transdermal delivery system technique. In order to reduce the frequency of drug administration of medicaments having short half-life transdermal technique is very useful. In the present study we formulated ethosomal gel of atorvastatin in order to reduce first pass metabolism.^{1,2}

Ethosomes are soft, smooth, malleable vesicles utilized for novel delivery of medicaments. Ethosomes provide a controlled release of medicament for a prolonged time period so as to maintain the constant concentration of therapeutic agent in the systemic circulation in order to provide sustained and controlled release and also the right amount also. Ethosomal drug delivery were investigated to be efficacious at administering molecules across the skin to the blood circulation.

The I.P. defines Gels are thick, slightly sticky or semisolid system containing medicinal products or cosmetics which is interpenetrated by a liquid base. They are normally prepared with the aid of suitable gelling agents like HPMC, Carbopol and Sodium Carboxy methyl cellulose,

etc. Substances such as antioxidants, stabilizers and antimicrobial preservatives are used as additives in the formulation of gels.

As transdermal drug delivery system eliminates gastrointestinal irritation, metabolic degradation and first pass effect, it is gaining popularity. As a result of first pass metabolism very limited amount of drug reaches the blood circulation. Topical formulation has been introduced to eliminate this problem. As being less greasy and can be readily removed from the surface of the skin topical gel system is relevant for drug delivery across the skin.^{3,4}

MATERIALS AND METHODS

Atorvastatin was obtained as a gift sample from Chandra Labs, Hyderabad, India. Soya lecithin and other ingredients were obtained as a gift sample from Fine Chem Industries, Mumbai. Cholesterol was purchased from Cortex Laboratories, Hyderabad. All the other raw materials were of pharmacopoeia grade.

Preparation of ethosomes

Atorvastatin loaded ethosomes are formulated by cold method followed by ultra-sonication. Phospholipids, drug and different lipid material were liquified in ethanol in a closed beaker at a room temperature by hardly agitating with the use of magnetic stirrer. During agitation propylene glycol was added. This compound mixture was inflated up to 30°C in a water bath. The water inflated up to 30°C in a particular beaker was added to the solution which was then mixed for 5 min in a closed vessel employing magnetic stirrer. The vesicle size of ethosomal composition was then lowered by ultrasonic probe sonicator for 10 min and off time was 10 sec. Finally the prepared composition was kept in cool place.

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The vesicles were observed under Carl Zeiss trinocular microscope at 40 X and 100 X magnification.⁵

Incorporation into gel

Carbopol 934 forms very good consistency transparent gel at low concentration. Carbopol 1% w/v was moistened with minimal volume of water for an hour. Atorvastatin (100mg) was mixed into the swollen polymer with constant agitation at a temperature of 30°C till the homogeneous gel was obtained. Triethanolamine was utilized to maintain the pH of the preparation and it was agitated slowly until a clear transparent gel was obtained. Finally the ethosomal gel was mixed utilizing a mechanical stirrer for 5 min.

Preparation of plain drug in gel

Plain gel of Atorvastatin was prepared by similar method applied for preparation of ethosomal gel. In this method, required quantity of Atorvastatin was taken and triturated into water miscible gel base. Final concentration of Atorvastatin in formulations was fixed to 0.4%.⁶

Evaluation of Ethosomal Gel

The ethosomal gel formulation of Atorvastatin was evaluated for organoleptic characteristics, occlusiveness and washability.

Measurement of pH of the ethosomal gel: 1 g Atorvastatin ethosomal gel was mixed in 100 ml distilled water utilizing a homogenizer. Electrodes are then immersed in the developed gel solution and readings were documented from digital pH meter in three times and mean value was estimated.

Viscosity study: Viscometer spindle was dipped into the preparation of about 50 gm which was placed in suitable beaker up to an immersion mark on the spindle shaft. The motor rotates the spindle at definite speed in rpm and the resistance to rotation gives the viscosity value. Readings were utilized for obtaining viscosity.

Spreadability: It is defined as the extend of area covered when gel is applied over the skin or affected part, as the spreading value effects the therapeutic efficacy of a formulation. When gel is placed between the slides against a certain load, the two slides slip off over the gel and this time is noted down to calculate the spreadibility. Minimum time taken by the slides for separation, shows better spreadability.^{7,8}

Extrudability study: The extrudability of ethosomal gel was determined by filling ethosomal gel in the collapsible tubes. In order to analyse extrudability of the ethosomal gel weight in grams required to extrude a 0.5 cm ribbon of gel in 10 sec was determined.

Percentage yield: The empty container was weighed in which the ethosomal gel formulation was stored then again the container was weighed with ethosomal gel formulation. The value of practical yield was expressed as empty container weight was subtracted with the container with gel formulation.

Homogeneity and grittiness: A minimum quantity of ethosomal gel was pressed between the index finger and thumb. The existance of coarse particles was checked between the figures to notify the consistency of gel. Also, the homogeneity could be detected when a small quantity of the ethosomal gel was rubbed on the skin of the back of the hand. The grittiness of prepared ethosomal gel was also observed in the same manner.

In vitro release studies: Skin permeation studies Franz diffusion cell was used for permeation studies. Study was conducted using prepared rat skin. 28 ml of PBS 7.4 was taken in receptor compartment and was continuously stirred with a magnetic stirrer and temperature was maintained at 37°±1°C by utilizing water bath. The prepared skin facing stratum corneum upward was mounted into the donor compartment. 1

g of ethosomal gel formulation was placed in donor compartment. 5 ml sample was withdrawn via the sampling port at predetermined intervals over 8 hr and each sample was replaced with equal volume of fresh dissolution medium. Then drug content was determined by analyzing the samples by using phosphate buffer as blank with UV-Visible double beam spectrophotometer at 246 nm. Similar study was performed with marketed atorvastatin gel.

In vitro Drug Release Kinetics

In order to analyse the mechanism of release of drug, the release data were analyzed with the following three mathematical models:

- (1) Zero-order kinetic
- (2) First-order kinetic
- (3) Higuchi kinetic

Zero-order model

According to zero order model drug release don not disaggregate from dosage forms and releases the drug slowly. It is represented by the following equation:

- ✓ $Q_t = Q_0 + K_0 t$ In the above equation
- ✓ Q_t = the amount of drug which dissolves in time t,
- ✓ Q_0 = the initial amount of drug into the solution
- ✓ K_0 = the zero order release constant

For zero order model the data obtained from *in vitro* release study were plotted as a cumulative amount of drug released versus time.

First order model

This model has been used to explain absorption and elimination of some drugs, in theoretical way it is difficult to have concepts for this mechanism. The following equation is mentioned for release of the drug for first order kinetics:

$$\text{Log } Q_t = \text{Log } Q_0 - \frac{K_1}{2.303} t \quad 2.303$$

Where,

- ✓ Q_0 = the initial concentration of drug,
- ✓ K_1 = rate constant for the first order,
- ✓ t = the time.

The plots were made by log cumulative percentage of drug remaining versus time which gives a straight line with a slope of $-K_1/2.303$.

Higuchi model

This model is based on the hypothesis that

- > Initial drug concentration is more high than drug solubility;
- > Diffusion of drug takes place in one dimension only;
- > Particles size of drug is much smaller than thickness of system;
- > Drug diffusivity is constant; and
- > In the release environment a perfect sink condition is always attained.

The higuchi model equation is:

$$Q = K_H t^{1/2}$$

Where,

- K_H = the Higuchi dissolution constant,
- $t^{1/2}$ = square root of time.^{9,10}

RESULTS

pH determination: The pH of gel base and freshly prepared E8 ethosomal gel was analyzed to be 7.3 and 7.9 respectively.

Viscosity

The viscosity of carbopol 934 gel base and ethosomal gel by brookfield viscometer was found to be 734,00 and 75,100 cps (centipoise).

Spreadability

The spread ability of ethosomal gel was found to be 15.69 g.cm². The spread ability results showed that ethosomal gel was most effective i.e. it showed best result for spread ability.

Extrudability study

The extrude ability of ethosomal gel was analyzed to be positive.

Homogeneity and grittiness

Ethosomal gel was analyzed to be homogeneous and no grittiness was noted.

In vitro release study

In vitro release study was performed to determine quantity of drug released at different interval of time. Rate of release from different formulation are given in graph and table. From graph it was detected that cumulative release of Atorvastatin was more from ethosomal formulation than marketed. Ethosomal formulation was designed to achieve high permeability and ultimately increase the bioavailability of the drug. Table 1. Shows drug release profile and the *in vitro* release kinetic data was shown in Table 2. Figure 1 shows release profile of atorvastatin ethosomal gel formulation.

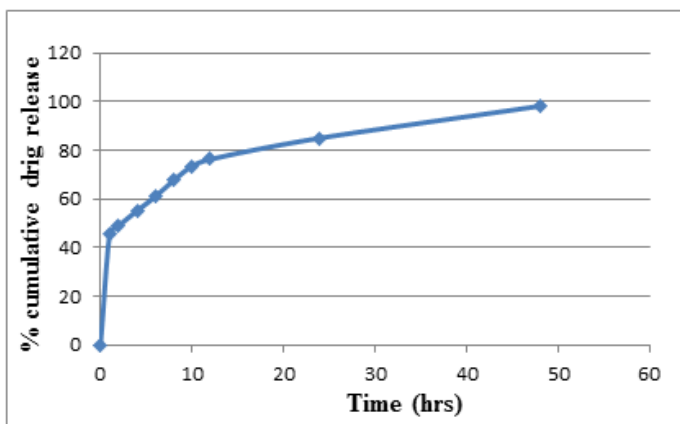


Figure 1: Dissolution profile of Atorvastatin ethosomal gel formulation.

Drug release models of Atorvastatin ethosomal gel

According to the data from table, the kinetic of drug release was calculated for zero order, first order and Higuchi model. The correlation coefficient of release profiles of these models for Atorvastatin ethosomal gel formulation is shown in Table 3. According to the obtained data, first order release profile was determined to be the best fit model for our optimized AEGF formulation. The graphs of all three release models for Atorvastatin ethosomal gel formulation are shown in Figures 2-4.

Mechanism of drug release from vesicular systems

According to the Korsmeyer-Peppas model, it was found that the mechanism for drug release from the vesicular systems are following Fickian diffusion-controlled mechanism followed by a prolonged release.

DISCUSSION

Atorvastatin having low bioavailability due to first pass metabolism was formulated into ethosomes then formulated into gel to penetrate it through the skin. Initially atorvastatin was formulated into ethosomes and are evaluated for particle size, shape, zeta potential, entrapment efficiency and drug release profile. From the observation it was conclude that formulation number 8 shows favorable result. The formulation was then incorporated into gel by using carbopol 934 as gelling agent. The formulated gel was then evaluated for viscosity, homogeneity, spreadability and drug release profile and the ethosomal gel shows enhanced release as compared to plane drug gel and increased bioavailability.

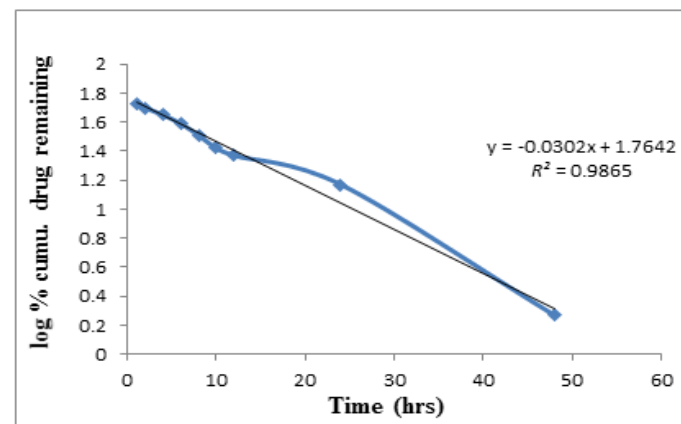


Figure 3: First order for drug release from ethosomal gel.

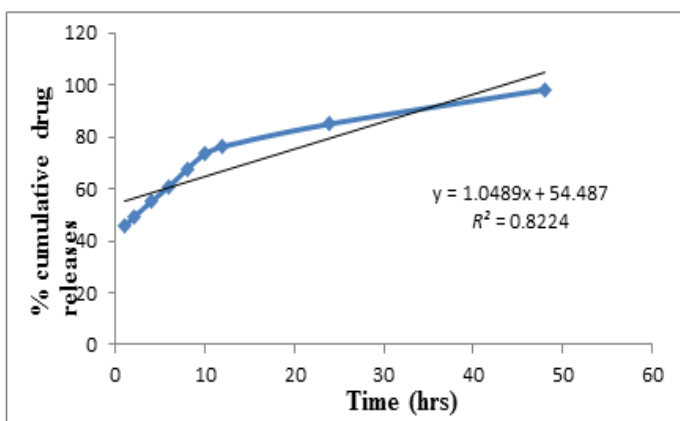


Figure 2: Zero order plot for drug release from ethosomal gel.

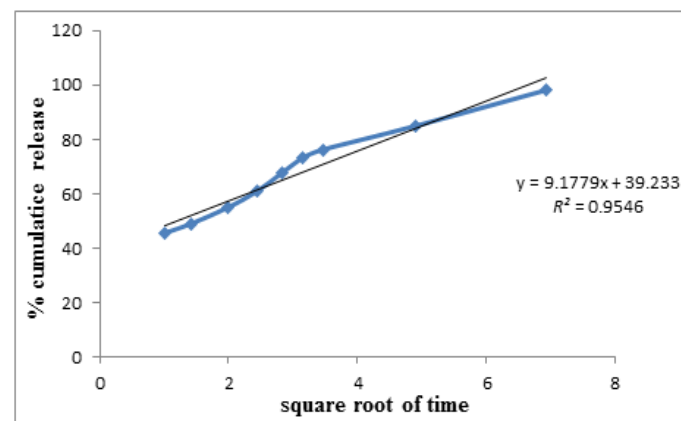


Figure 4: Higuchi model for drug release from ethosomal gel.

Table 1: *In vitro* drug release profile of ethosomal gel formulation and plane drug gel formulation.

Time (hr)	% Cumulative drug release	
	Ethosomal gel formulation	Plane drug gel formulation
0	0	0
1	45.53	6.46
2	48.98	8.45
4	55.13	12.56
6	60.97	18.54
8	67.62	25.62
10	73.41	30.43
12	76.26	47.32
24	84.97	59.93
48	98.47	65.37

Table 2: Dissolution data of Atorvastatin ethosomal gel for *in vitro* release kinetics.

Time (hr.)	%cumulative Release	Log% cumul. Release	% cumul. Drug remaining	Log cumul. % drug remaining
1	45.53	1.65	54.47	1.73
2	48.98	1.69	51.02	1.70
4	55.13	1.74	44.87	1.65
6	60.97	1.78	39.03	1.59
8	67.62	1.83	32.38	1.51
10	73.41	1.86	26.59	1.42
12	76.26	1.88	23.74	1.37
24	84.97	1.92	15.03	1.17
48	98.13	1.99	1.87	0.27

Table 3: Drug release kinetic models and their *R* values for Atorvastatin ethosomal gel.

Model	<i>R</i> value
Zero order	0.8224
First order	0.986
Higuchi	0.9546

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CONCLUSION

Atorvastatin a HMG Coenzyme A reeducates inhibitor has low oral bioavailability due to first pass metabolism, to enhance its bioavailability atorvastatin was formulated into ethosomal gel for topical application. Atorvastatin was initially formulated into ethosomes using soya lecithin a phospholipid and ethanol as permeation enhancer and then finally formulated into gel utilizing carbopol 934 as gelling agent. The so formed ethosomal gel showed enhanced bioavailability as compared to normal plane drug gel and also oral marketed formulation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

I.P: Indian Pharmacopoeia; **HPMC:** Hydroxy propyl methyl cellulose; **HMG:** Hydroxy methyl glutaryl; **UV:** Ultra violet; **PBS:** Phosphate buffer solution; **RPM:** Revolution per minute.

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