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Formulation and Evaluation of Megesterol Proniosomal Systems

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PHARMACEUTICAL SCIENCES RESEARCH ARTICLE
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ABSTRACT

Over 40% of old and new drug molecules are implicated with poor oral bioavailability due to poor drug solubility in aqueous environment of gastro-intestinal lumen. Chemical methods to improve drug solubility are again limited, because any drastic change in the chemistry of molecules might result into loss of pharmacophore and thus loss of biological activity. Megesterol acetate, a synthetic derivative of the naturally occurring steroid hormone used to manage various disorders that affect women. Magesterol does not appear to be well absorbed from the gut. This may be related to its relative insolubility (2µg/ml) micronized formulations are more completely absorbed than are nonmicronized preparations. Liposomal drug products have shown improved oral bioavailability. The various proniosomal systems developed were span 20: megesterol (50:50%), span 20: megesterol (70:30%), span 20 50% and 50% megesterol+cholesterol (50:50), and span 20, 70% and 30% megesterol+cholesterol (50:50). Out of all the compositions the one with 70% span 20 and 30% megesterol:cholesterol (50:50) exhibited slower release. All other compositions have enhanced the release to significant extent.

KEYWORDS: *Megesterol, cholesterol, proniosomes, bioavailability.*

Introduction:

Drug administration via oral route is most popular because of the ease of administration, patient compliance and low degree of acute toxicity. However in contrast to these advantages the limiting factor for oral delivery is poor solubility and poor permeability of drug molecules across gastrointestinal tract. Over 40% of old and new drug molecules are implicated with poor oral bioavailability due to poor drug solubility in aqueous environment of gastro-intestinal lumen. Chemical methods to improve drug solubility are again limited, because any drastic change in the chemistry of molecules might result into loss of pharmacophore and thus loss of biological activity. Use of solvents, pH, solubilization by micelles etc also have limitations, as sometimes large quantities of solubilizing excipients are needed to achieve adequate solubility.

Therefore another strategy would be to develop lipid based drug delivery systems to address the issue of poor solubility. In few instances, mere admixture of a lipid with an insoluble drug might resolve the solubility issue but is not universally applicable.

The current trend in lipid based colloid drug delivery systems is an impetus for renewed interest in oral delivery research. Colloidal drug delivery systems appear to offer solutions for the problems of oral bioavailability in totality. They can improve solubility of drugs, enhance permeation due to their adhesive property, prevent enzymatic attack in gut wall and mask drug-efflux transporter interactions

in gut wall. Drug in a colloidal carrier may also be protected against gastrointestinal degradation.

Though liposomes/ niosomes have been studied extensively for drug delivery via various routes, their use in oral delivery was not successful due to high acidic condition, enzymes and bile in gastrointestinal environment. Recently some strategies to overcome these issues have been suggested[1, 2, 3, 4, 5, 6.] Due to physical and chemical stability problems associated with vesicular dispersions, proniosomal products were developed and applied successfully for drug delivery.

Megesterol acetate, a synthetic derivative of the naturally occurring steroid hormone, progesterone is white, crystalline solid chemically designated as 17- Hydroxy-6-methylpregna-4, 6-diene-3, 20-dione acetate. Solubility at 37˚C in water is 2µg per mL, solubility in plasma is 24µg per mL. Its molecular weight is 384.51. A synthetic progestational agent, megesterol acetate is often used to manage various disorders that affect women. It was initially evaluated as a possible contraceptive agent[7]. However, since the mid-1970s, it has been used to treat refractory metastatic breast cancer and endometrial cancer [8, 9]. Because of its weight-enhancing qualities, the drug was approved in 1993 for the management of AIDS-related cachexia[10]. Off-label uses include cancer-related cachexia, refractory ovarian cancer, and menopausal symptoms[11,12,13]. In men, megesterol is also used to manage advance prostate cancer[14]. Most recently, the drug has been given in large doses to potentiate other oncologic compounds[15].

Megesterol does not appear to be well absorbed from the gut. This may be related to its relative insolubility (2µg/mL); micronized formulations are more completely absorbed than are non micronized preparations[16]. Liposomal drug products have shown improved oral bioavailability. But conventional liposomal are generally unstable in the GI tract and susceptible to action of acids, bile and enzymes after oral administration. To pac vent the deformation of liposomal bilayers and improve liposomal stability many studies have been carried out. Since liposomal dispersions have physical & chemical stability problems, we formulated megesterol into a proliposomal solid formulation, with a view to improve its dissolution velocity and in turn it's oral absorption. For such a formulation development we have chosen a phospholid and charged /uncharged ligands to prevent its gastro intestinal degradation.

MATERIALS AND METHODS

Megesterol (Meg) was a gift sample from Natco Pharma Ltd, Hyderabad, India. Egg phosphatidyl choline and cholesterol were purchased from lipoid, Germany, α-tocopheryl

polyethylene glycol 2000 succinate (TPGS) was a gift from Eastman Laboratories, Japan. Sodium lauryl sulphate, polysorbate-80 and other chemicals were purchased from Merck, India.

Preparation of Proniosome Systems

The proniosome formulations containing Span 20, Cholesterol in (50:50 mole percent) and megesterol acetate 40mg were dissolved in 1-2ml of ethanol and by adopting slurry method. Slurry method is relatively simple and is mainly useful for the carriers which are not soluble in organic solvents.

For slurry method, 1g of neusilin powder was added to a 500ml round-bottom flask, the entire volume of lipid solution containing drug in ethanol/chloroform was added directly to the flask. Additional solvent 3-5ml if necessary was added particularly when low lipid content was used; to form good slurry. The flask was attached to notary evaporator and vacuum was applied until the powder appeared to be dry and free flowing. The flask was removed from the evaporator, and kept under vacuum overnight. Provesicular powder was stored in sealed containers at 4-8˚C. Formulations containing megesterol acetate (40mg) with various proportions of Span 20 and cholesterol were prepared. Such formulations also contained 10% polysorbate by weight, to improvise the case of hydration of powder proniosomal formulation.

CHARACTERIZATION

The powder proliposome (100mg) was hydrated with 5ml distilled water and the dispersions were further diluted if necessary. The reconstituted dispersion contained numerous lipid vesicles. The size and zeta potentials of the vesicles were measured by light microscopy or photon correlation spectroscopy. The entrapment of megesterol into vesicles was measured by centrifugal ultra-filtration using sartorious polycarbonate membranes of 12000 mol wt cutoff. The total drug content of reconstituted preparations was obtained UV-Spectrophotometrically. Briefly 500µl of preparation was dissolved in methanol:chloroform solvent mixture (9:1) and the optical density of the mixture was noted against a solvent blank. The estimation was carried out at λ_{max} of 292nm according to modified USP method using a previously constructed standard plot (fig 1).

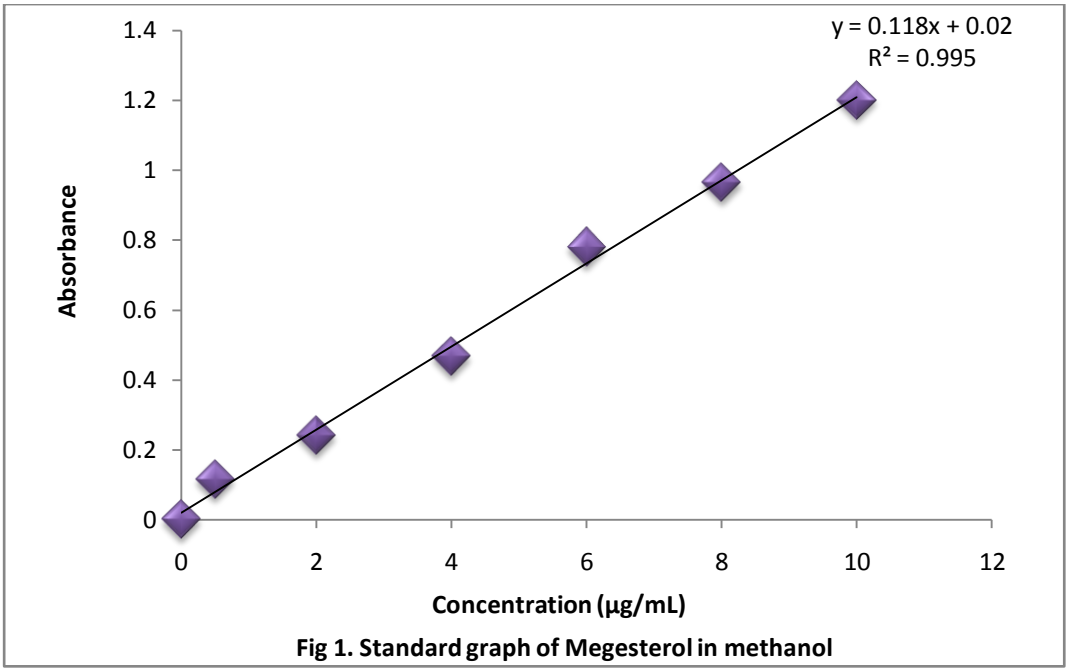

Fig 1. Standard graph of Megesterol in methanol

RELEASE STUDIES

Initially we have decided to conduct release studies according to the method reported in USP using paddle stirrer and 1% w/v sodium lauryl sulphate as dissolution medium. But 1% w/v sodium lauryl sulphate solution interacted with the lipid films and modified their release. Because of this we have conducted a drug-solubility in varied concentrations of SLS solutions. Based on this we obtained negligible interference below 0.25% SLS and thus this medium was used in the release studies of proniosomal products of megesterol acetate.

RESULTS AND DISCUSSION

The Size, Zeta potential and Percent entrapment of different formulations are shown in table 1. A decrease in size and zeta potential was observed with increase in tween 80 concentration.

Table 1: Size, Zeta potential and % entrapment of various formulations

Span 20:Meg/Chol(50:50)	Size (nm)	Zeta potential (mV)	% Entrapment
50:50 (10% Tween 80)	837 ± 23	-47.3 ± 3.3	87.0 ± 2.7
60:40 (10% Tween 80)	917 ± 83	-43.3 ± 6.0	83.0 ± 3.1
50:50 (30% Tween 80)	414 ± 17	-27.3 ± 1.3	93.0 ± 4.8
60:40 (30% Tween 80)	547 ± 48	-26.3 ± 8.3	91.0 ± 7.3

Proniosomal systems composed of Span 20, cholesterol, megesterol and neusilin, Span 20 and megesterol loaded on to neusilin and megesterol plain were subjected to dissolution

testing using distilled water or 1% w/v sodium lauryl sulphate (SLS) in water (**fig 2**).

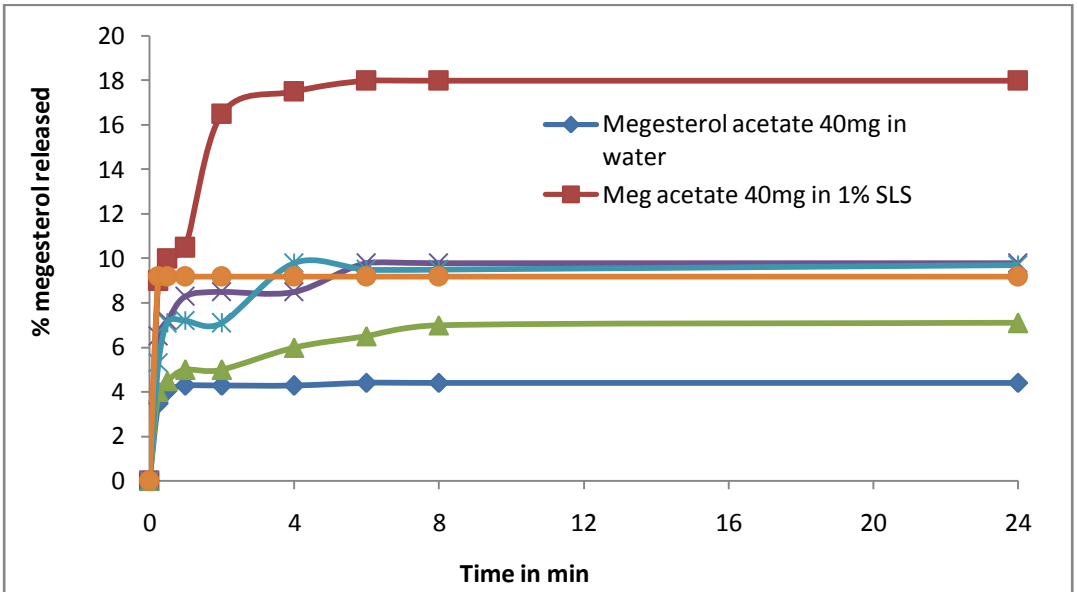

Fig 2. Effect of higher concentration of sodium lauryl sulphate (1% w/v) on megesterol release from span 20 based proniosomal formulations

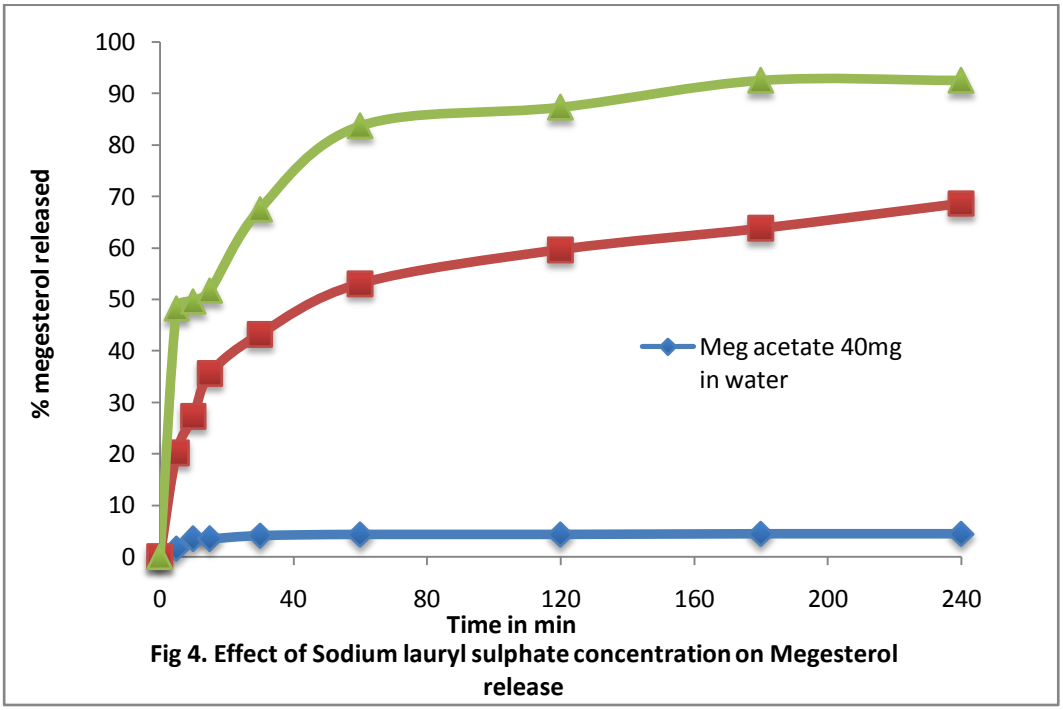

Fig 4. Effect of Sodium lauryl sulphate concentration on Megesterol release

The highest megesterol release obtained was 18% in 1% SLS medium with megesterol powder. The lowest release (4%) was obtained when distilled water was used as the release medium for plain drug.

All the lipid containing formulations of megesterol have marginally improved release in distilled water and 1% SLS media. In SLS containing medium release was better than water medium.

As there was no substantial increase in megesterol release from lipid formulations in 1% SLS medium, we suspected an interaction between SLS and lipid components. A study was conducted to determine the solubility of megesterol in SLS solutions of various strengths (0.1, 0.25, 0.5 & 1%w/v SLS). This study was necessary to determine concentration of SLS at which its interference on megesterol release is minimal. With increase in SLS concentration solubility of MEG increased (fig 3). However a sudden increase in solubility was noticed at 0.25% w/v SLS. Incidentally this concentration is nearer to critical micelle concentration of SLS (225mg/100ml). It is interesting to note the results of dissolution of MEG in 0.2% and 0.25% SLS media and distilled water (fig 4). The release was very poor in water medium, and it abruptly increased to 70% in 0.2% w/v SLS medium. The maximum release was obtained in 0.25% w/v SLS medium which is very close to critical micelle concentration.

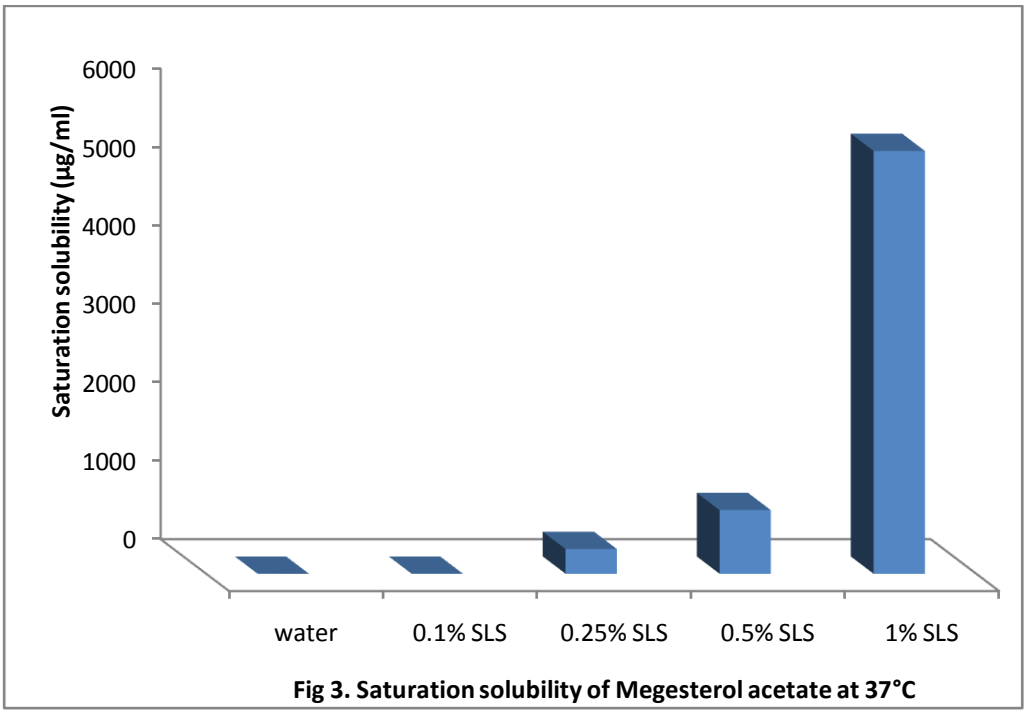

Fig 3. Saturation solubility of Megesterol acetate at 37°C

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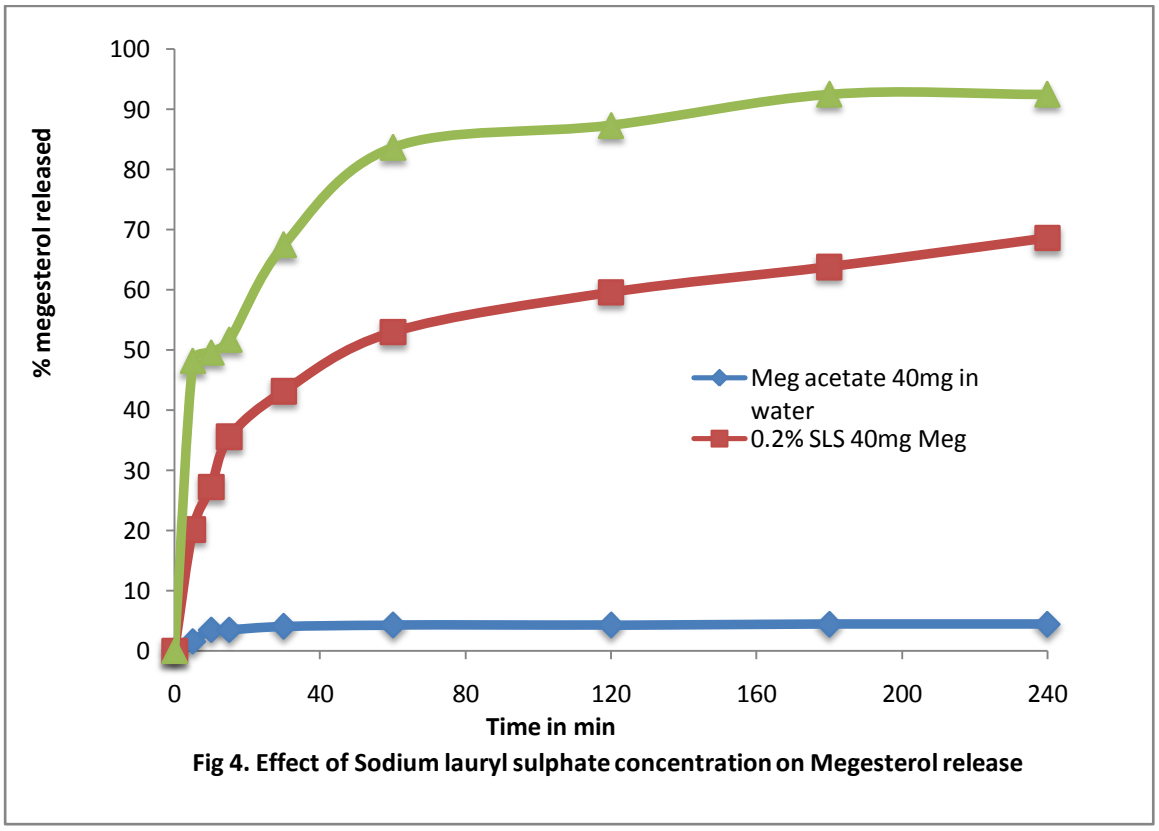

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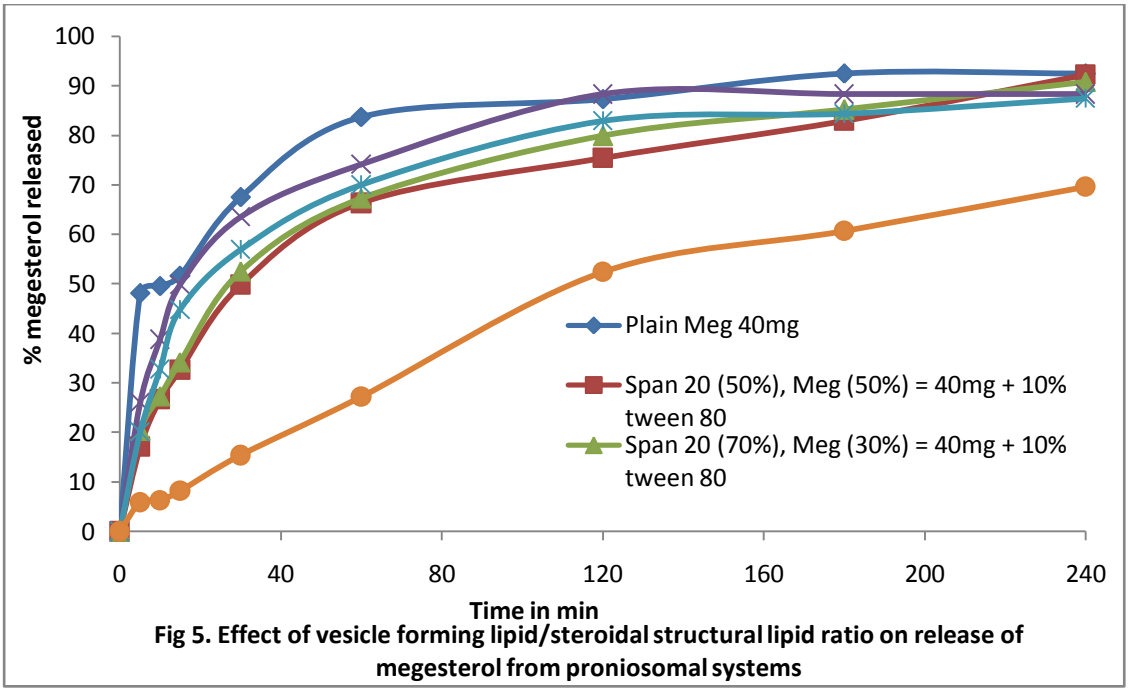

Fig 5. Effect of vesicle forming lipid/steroidal structural lipid ratio on release of megesterol from proniosomal systems

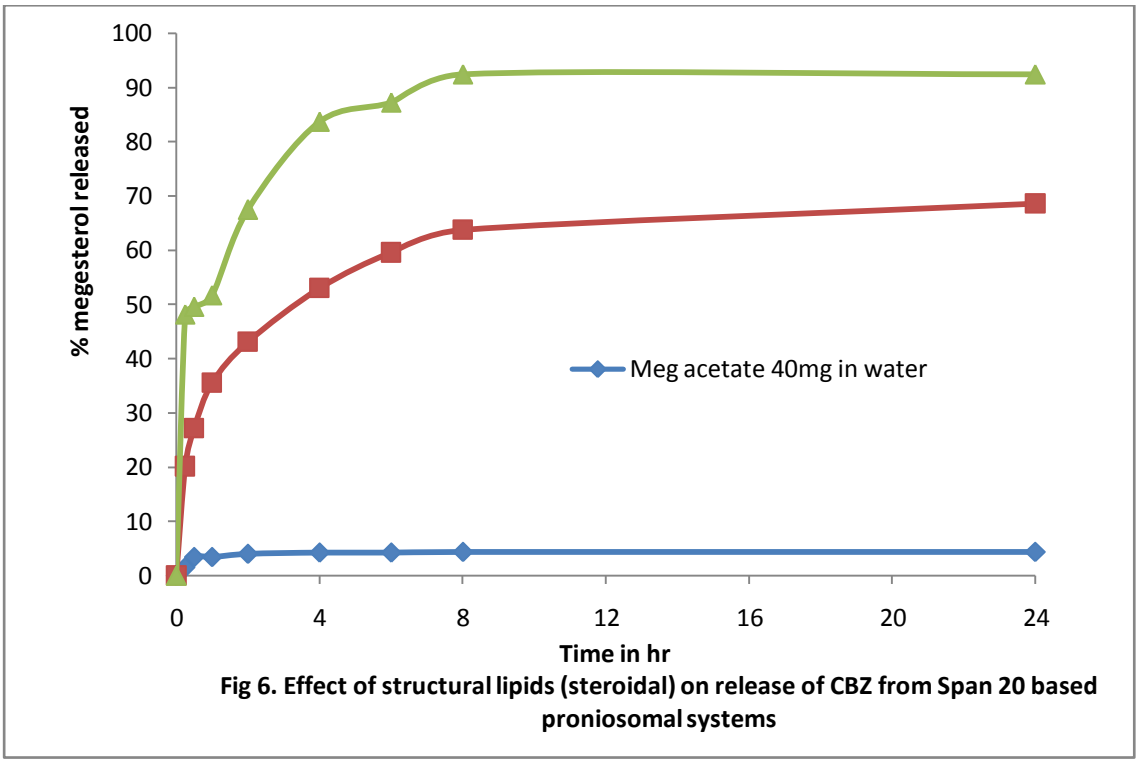

Fig 6. Effect of structural lipids (steroidal) on release of CBZ from Span 20 based proniosomal systems

Since the objective of improving dissolution velocity of megesterol in aqueous environment (water) could not be achieved, we switched over to develop Span 20, cholesterol, and Tween-80 based proniosomal formulations. In such formulation higher percent of Tween-80 (30% w/w) was used. Thus a system with Span 20: (megesterol + cholesterol) at 50:50 level containing 30% Tween-80 based on lipid weight significantly improved the release in aqueous medium (distilled water). Another system Span 20: megesterol (50:50) containing

30% Tween-80 exhibited a very poor release compared to cholesterol containing system (fig 6). Thus we infer cholesterol presence in the formulation is essential to render effective vesiculization, which in turn seem to be responsible for improved dissolution rate of megesterol in aqueous medium (water). It appears from such vesicles, the drug is dispersed in molecular form in lipid domains of bilayers. Such drug molecules are steadily diffusing into aqueous environment. Even with this proniosomal composition the highest release achieved for megesterol was around 25%. Thus there is need to improve it further.

CONCLUSIONS

Proniosomal systems of Megesterol were developed wherein either Megesterol or cholesterol and Megesterol were combined with span 20 to form a provesicular system. Since the megesterol dissolution medium was an issue, because at higher sodium lauryl sulphate concentration the release was retarded and it became necessary evolve a proper dissolution medium (containing SLS) so as to perceive the differences in dissolution velocity of Megesterol due to formulation changes.

A proniosomal formulations of span 20 improved the dissolution velocity of megesterol when the system contained either cholesterol or cholesterol/megesterol combination. No significant difference in dissolution velocity of drug was noticed by changing the ratio between vesicle forming lipid (span 20) and structural lipid (cholesterol/megesterol).

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