



EFFECT OF PROCESS PARAMETERS ON DESIGN OF VESICULAR SYSTEMS CARRYING ACECLOFENAC

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ABSTRACT

The Vesicular carrier based drug delivery systems are a recent breakthrough to achieve target specificity and minimization of adverse effects associated with drug. In spite of such novelty associated, carrier systems suffer from drawback like non-uniformity in size. The present study is based on determination of optimum process conditions to obtain vesicles of uniform size carrying drug Aceclofenac. The results indicate a strong influence of temperature, time and rotations per minute of rotary evaporator and sonication cycles, amplitude and time on the size of Liposomes and transferosomes prepared using lipids and surfactants.

KEYWORDS: Nanocarriers, size, Process optimization.

INTRODUCTION

The vesicular carrier based drug delivery system incorporating nonsteroidal anti-inflammatory drugs are a need for therapy of inflammatory disorders because of their enhanced localization to the desired site of action thereby reducing the incidents of side effects. Aceclofenac is selected in the present study as the drug has many side effects when administered by conventional oral route such as gastro-intestinal disorders, in particular dyspepsia, abdominal pain, nausea and diarrhea and therefore a lesser adherence of patient to the treatment. Topical delivery of drugs has many advantages such as avoidance of hepatic first-pass metabolism, improved patient compliance and ease of access, provide a means to quickly terminate dosing sustained therapeutic drug levels, possible self – administration, non-invasive (no needles or injections needed), avoids food related Interaction, reduction of doses as compared to oral dosage forms and intravenous therapy. Topical route allows drug to diffuse out of its vehicle onto the surface tissues of skin. There is no significant obstacle to penetration, once the drug permeates through stratum corneum of epidermis of skin.^[1-4] Topical NSAIDs have been reported to have reduced incidences of systemic side effects like gastric bleeding and peptic ulcer.^[2-5]

For permeation of drug through stratum corneum layer, novel strategies can be adopted by the use of vesicular carrier based drug delivery system and novel penetration enhancers. But there are some shortcomings associated with the vesicular carrier drug delivery systems such as lack of control over drug release rate; insufficient loading of drugs and lack of means to override biological barriers.^[5-9]

In the present study, the effect of process parameters on the design of vesicular systems loaded with Aceclofenac has been studied and loaded drug carrier such as Liposomes, was designed by optimizing the components of formulation and the process parameters in order to prepare the drug loaded carriers with uniform size, high drug entrapment efficiency and good permeation characteristics.

MATERIALS AND METHODS

For the studies, Phospholipids were obtained as gift samples from Lipoid Corporation, Germany. The drug Aceclofenac was obtained from Chemdyes Corporation. All the chemicals and reagents used were of Analytical grade. There was no interaction observed between the pure API Aceclofenac and the Phospholipids as confirmed by FTIR Studies.

The preliminary trial batches of Liposomes were prepared using different Phospholipids such as 1-2 disteroyl-sn- glycerol-3-phosphoethanolamine, Na salt, 1-2 disteroyl-sn- glycerol-3-phosphate monosodium salt hydrogenated Phosphotidylcholine, 1, 2-dioleoy-3-trimethyl ammonium Propane chloride, Leciva S-35, Leciva S-50 D, Lipova E-120 using drug: lipid ratio of 1:1.

The thin film hydration technique was used for preparation of Liposomes. Leciva S-35 and Leciva S-50D, did not produce, homogenous dispersion on hydration of thin film and particles were visible. The LipovaE-120 resulted in Homogenous dispersion and no phase separation was observed, vesicles were found to be visible when seen through trinocular microscope.

Using 1,2-disteroyl-sn-glycero-3-Phospho-ethanolamine, Na salt, 1,2-distroyl -sn-glycero-3-Phosphate, monosodium salt, 1,2-Dioleoxy-3-trimethyl ammonium Propane chloride, a homogenous dispersion was prepared on thin film hydration and vesicles were found to be visible in trinocular microscope as shown in Table 1. The process parameters such as temperature, rotations per minute were varied from 50⁰c to 70⁰c, 60 to 90 respectively in thin film hydration method.

RESULTS AND DISCUSSION

It was observed that at 50⁰c temperature and 90 rpm, when film formation was allowed for 20 minutes in rotary vacuum evaporator, a thin film formed which was uniform in appearance. Also there was no change observed in appearance of film when, temperature was varied from 50⁰c to 70⁰c and rpm was varied from 70 to 90 rpm.

TABLE 1: SCREENING OF PHOSPHOLIPIDS FOR LIPOSOMES AND TRANSFEROSOMES

Lipids	Observation
Leciva S-35	On hydration of thin film produced, Homogenous dispersion was not achieved. particles were visible
Leciva S-50 D	
Lipova-E-120	Homogenous dispersion ,no phase seperation, vesicles visible in trinocular microscope
1,2-disteroyl -sn-glycero -3-Phospho-ethanolamine, Na salt	Homogenous dispersion, vesicles visible in trinocular microscope
1,2-distroyl -sn-glycero-3-Phosphate, monosodium salt	Homogenous dispersion, vesicles visible in trinocular microscope
1,2-Dioleoxy-3-trimethyl ammonium Propane chloride	Homogenous dispersion, vesicles visible in trinocular microscope
Hydrogenated Phosphotidylcholine	Not homogenous, slight lumps vesicles visible in trinocular microscope

It was also observed that, at 50⁰c temperature and 60 rpm, when film formation was allowed for 10 minutes in rotary vacuum evaporator, a dry thin film could not be formed and also no change was observed, when rpm was changed from 60 rpm to 70 rpm as shown in Table 2.

TABLE 2: PROCESS OPTIMIZATION OF FORMATION OF THIN FILM BY VACUUM ROTARY EVAPORATOR

Process Parameters			Observation
Temperature	RPM	Time(min)	
50 ⁰ C	60	10	Dry Thin film not formed
50 ⁰ C	70	10	Dry Thin film not formed
50 ⁰ C	70	20	Thin film formed-not uniform in appearance
50 ⁰ C	80	20	Thin film formed-not uniform in appearance
50 ⁰ C	90	20	Thin film formed- uniform in appearance
60 ⁰ C	80	20	Thin film formed- uniform in appearance
60 ⁰ C	90	20	Thin film formed- uniform in appearance
70 ⁰ C	80	20	Thin film formed- uniform in appearance
70 ⁰ C	90	20	Thin film formed- uniform in appearance

Hydration of thin film formed was carried out and then prepared Liposomes were reduced in size by probe sonication. The probe sonicator was operated using 13 mm probe at an amplitude of 60%. The effect of sonication cycles on the transparency of vesicular dispersion and average size of vesicles was studied and it was found that application of 2 cycles for 2 minutes produced Vesicles dispersion which was slightly Hazy and mean vesicle size was found to be 3.5 μ m whereas at 3 and 4 cycles for 2 minutes produced Vesicles dispersion which was almost transparent with mean

vesicle size of 2 μ m and 0.6 μ m. The sonication cycle of 5 cycles for 2 minutes produced Vesicle dispersion which was transparent and mean vesicle size observed was 0.4 μ m. The process was repeated thrice and % Transmittance was found to be 90% in every analysis. Therefore the method of 5 sonication cycle each of 2 minutes can produce transparent vesicular dispersion with reproducibility and uniformity in vesicle size as given in Table no-3 & 4.

TABLE 3: PROBE SONICATION OF HYDRATED THIN FILM TO OBTAIN SUV FROM MLV PROBE-STANDARD PROBE DIAMETER-13 MM, AMPLITUDE -60%, TEMP-4°C

Cycles	Time(min)	Observation
2	2	Vesicles dispersion was slightly Hazy, mean vesicle size- 3.5 μ
3	2	Vesicles dispersion was almost transparent , mean vesicle size- 2 μ
4	2	Vesicles dispersion was almost transparent ,mean vesicle size- 0.6 μ
5	2	Vesicle dispersion was transparent, mean vesicle size observable-0.4 μ Process repeated thrice % Transmittance was 90% in every analysis.

TABLE 4: EFFECT OF SONICATION TIME ON MEAN VESICLE SIZE

sonication time(min)	Mean vesicle size(μ)
0	8
4	3.5
6	2
8	0.6
10	0.4
10	0.4
10	0.4
10	0.4

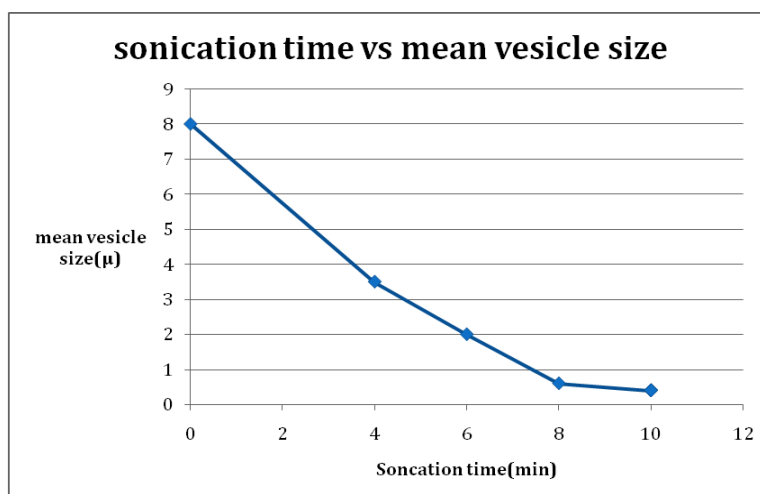


Figure 1: sonication time vs mean vesicle size

For preparation of Transferosomes, the ratio of lipid: surfactant was kept 1:1. The selected lipids based on the above mentioned experiments were used in the preparation whereas surfactants tried were Sodium cholate, Tween 80, Tween 20, Span 40 and Span 60.

It was found that using Sodium cholate, Span 40, Span 60 and Tween 20, Transferosome dispersion was homogenous and vesicles were visible when observed under trinocular microscope. The transferosome dispersion using Tween 80 was not suitable as frothing has been observed as shown in Table 5.

TABLE 5: SCREENING OF SURFACTANTS FOR TRANSFEROSOMES

Surfactant	Observation
Sodium Cholate	Transferosome dispersion was homogenous. On observation under trinocular microscope-vesicles were visible
Tween 80	Frothing observed
Span 40	Transferosome dispersion was homogenous. On observation under trinocular microscope-vesicles were visible
Span 60	Transferosome dispersion was homogenous. On observation under trinocular microscope-vesicles were visible
Tween 20	Transferosome dispersion was homogenous. On observation under trinocular microscope-vesicles were visible

CONCLUSION

For the preparation of Liposomes and Transferosomes loaded with NSAID- Aceclofenac, the lipids may be selected among 1,2-distearoyl-sn-glycero-3-Phosphoethanolamine, Na salt, 1,2-distearoyl-sn-glycero-3-Phosphate, monosodium salt, 1,2-Dioleoyl-3-trimethyl ammonium Propane chloride, LipovaE-120 etc. as these lipids produce better film characteristics in thin film hydration method.

The surfactants can be selected among Sodium cholate, Span 40, Span 60 and Tween 20 as these surfactants have shown to produce homogenous vesicular dispersion and uniform vesicles. The process parameters in thin film hydration method were found to have prominent effect on the formulation and the optimum conditions were found to be temperature 50°C, speed of rotation 90 rpm and time of 20 minutes in rotary vacuum evaporator for formation of a uniform thin film. Also there was no change observed in appearance of film when, temperature was varied from 50°C to 70°C and rpm was varied from 70 to 90 rpm.

The sonication parameters were found to effect the average size and uniformity in size of vesicles as shown in Figure 1. and the method of 5 sonication cycle each of 2 minutes using 13 mm probe at amplitude of 60% was found to produce transparent vesicular dispersion with reproducibility in uniformity in vesicle size.

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