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Formulation and Evaluation of Niosomes containing Amoxicillin

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Abstract: Niosomes are microscopic non-ionic surfactant vesicles which foms on self-assembling of non-ionic surfactant. Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. Niosomes and liposomes both have similar physical properties but their chemical properties are different. The method of preparation of niosome is hand shaking method. A method of *in-vitro* release rate study includes the use of dialysis tubing. Niosomal vesicle is formed by making use of non-ionic surfactants whereas liposomal vesicles of lipids. Niosomes are known to be superior to liposomes because of their higher chemical stability of surfactants than lipids. This research article focuses on the concept of niosomes, advantages and disadvantages, composition, method of preparation, factors that influence the niosomal formulation and characterization, application of niosomes. Niosomes can be utilized in the treatment of several diseases like Psoriasis, leishmaniasis, cancer, migraine, Parkinson etc. Niosomes can be used as diagnostic aid. Various methods of niosomal administration include intramuscular, intravenous, per-oral and transdermal. Niosomal technology has been successfully used in cosmetics. Still researchers have to focus a lot on the commercial utility of niosomes in drug delivery. Formulated niosomes were evaluated for entrapment efficiency, vesicle diameter, *in-vitro* release. Entrapment efficiency and drug release were markedly dependent on surfactant: cholesterol ratio and quantity of ethanol used.

Key words: Niosomes, Amoxicillin, span 80, cholesterol, Tween-80

Contents

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1. Introduction

Niosomes are non-ionic surfactant vesicles that forms from self assembly of hydrated synthetic non-ionic surfactant have ability to entrap various drugs & have been evaluated as an alternative to liposomes[1].They are made up of biocompatible, biodegradable, non-toxic, non-immunogenic & non-carcinogenic agents that forms closed spherical structures or shelf assembly vesicles on hydration[2]. Various forces act inside the vesicles e.g., van der waal forces among surfactant molecules, repulsive forces resulting from the electrostatic interactions that found between charged groups of surfactant molecules, short-acting repulsive forces, entropic repulsive forces of the head groups of surfactants, etc[3]. An antibacterial is a compound or substance that kills or slows down the growth of bacteria[4]. The term is often used synonymously with the term antibiotic(s); today, however, with increased knowledge of the causative agents of various infectious diseases, antibiotic(s) has come to denote a broader range of antimicrobial compounds, including anti-fungal & other compounds[5].

The term antibiotics was first used in 1942 by Selman Walksmanand his collaborators in journal articles to describe any substance produced by a micro-organism that is antagonistic to the growth of other micro-organisms in high dilution[6]. This definition excluded substances that kill bacteria, but are not produced by micro-organisms (such as gastric juices & hydrogen peroxide). It also excludes synthetic antibacterial compounds such as the sulfonamides. Many antibacterial compounds are relatively small molecules with a molecular weight of less than 2000 atomic mass units. With advances in medicinal chemistry, most of today's antibacterial chemically are semi-synthetic modifications of various natural compounds[7]. Antiviral drugs are a class of medication used specifically for treating viral infections[8]. Like antibiotics for bacteria, specific antivirals are used for specific viruses. Unlike most antibiotics, antiviral drugs do not destroy their target pathogen; instead they inhibit their development. Antiviral drugs are one class of antimicrobials, a larger group which also includes antibiotic, antiparasitic drugs [9]. They are relatively harmless to the host, & therefore can be used for treat infections.They should be distinguished from viricides, which are not medication but deactivate or destroy virus particles, either inside or outside the body. Many common plants such as St John's wort are also widely believed in naturopathic circles to be viricides, but evidence to support this is far from sufficient in scientific circles [10]. Antivirals also can be found in essential oils of some herbs, such as eucalyptus oil and its constituents[11].

2. Materials and Methods

Materials

Amoxicillin was obtained from Vee Excel Drugs And Pharmaceuticals Private Limited, Delhi, Ghaziabad as a gift sample.Span 80, cholesterol were obtained from Merck specialities Pvt. Ltd. and Accurex Biomedical Pvt. Ltd., India respectively as a gift sample.All other chemicals and reagents used were under analytical grade.

Methods

Preparation of Niosomes[12]: Niosomes containing amoxicillin were prepared by Hand Shaking Method using Span 80 and cholesterol at different concentrations. In this method, the mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar Niosomes. Different batches of niosomes were prepared in order to select an optimized formula as per general method described above and proportion of surfactant and cholesterol for the preparations of niosomes were given in Table 1.

Table 1. Formulation ratio of drug, surfactant and cholesterol for preparation of niosomes

Formulation Code	Cholesterol (mg)	Surfactant		Drug (mg)	Methanol (ml)
		Tween 80	Span 80		
F1 (1:9)	10	90	-	30	5
F2 (2:8)	20	80	-	30	5
F3 (3:7)	30	70	-	30	5
F4 (4:6)	40	-	60	30	5
F5 (5:5)	50	-	50	30	5
F6 (6:4)	60	-	40	30	5

Drug Entrapment efficiency of niosomes[13]: After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation , or gel filtration as described above and the drug remained entrapped in Niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug. Where,

Entrapment efficiency (EF) = (Amount entrapped total amount) x 100

Vesicle diameter:

Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing (keeping vesicles suspension at – 20°C for 24 hrs and then heating to ambient temperature) of Niosomes increases the vesicle diameter, which might be attributed to fusion of vesicles during the cycle.

***In-vitro* release**[14]:

A method of in-vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method.

3. Results and Discussion

Results:

Entrapment efficiency:

Table 2. Entrapment efficiency of different batches of Amoxicillin Niosomes

S.No	Formulation	Entrapment efficiency
1	F1	42.33 %
2	F2	53.35 %
3	F3	43.35 %
4	F4	58.83 %
5	F5	71.37 %
6	F6	66.38 %

The entrapment efficiency was carried out for the six batches of amoxicillin niosomes formulation. Niosomes formulations of F1, F2 and F3 were prepared by using Tween 80 as for the F4, F5 and F6 from Span 80. Of all the formulations, niosomes formulation, F5 showed high percentage entrapment efficiency compared to other formulations. All the niosomes from the 6 batch of formulation exhibited spherical shape.

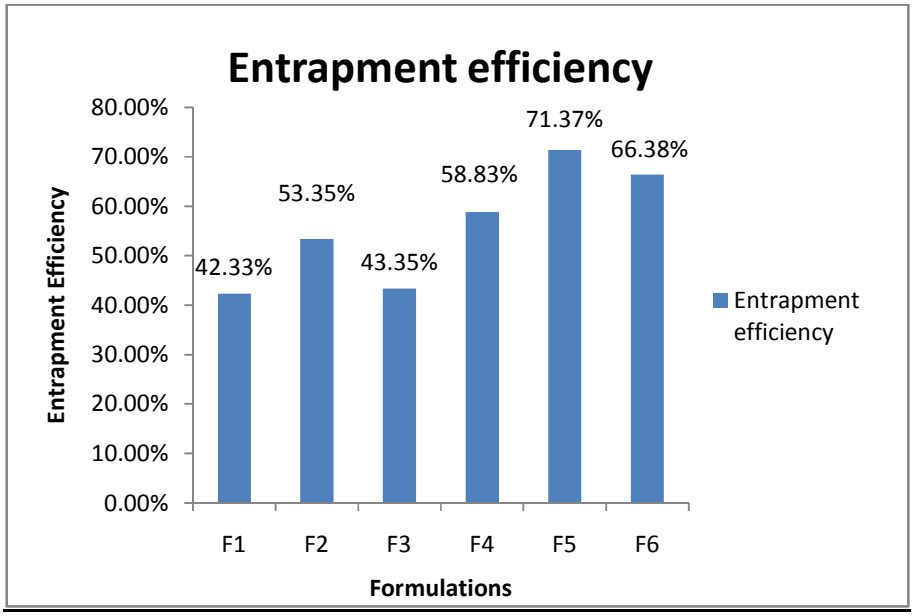

Fig. 1: Comparison of drug entrapment efficiency of Amoxicillin Niosomes Particle size analysis

Table 3. Mean partice size of different batches of Amoxicillin niosomes

Formulation Code	Mean Particle size (µm)
F1	6.231 ± 2.844
F2	5.00 ± 3.33
F3	3.33 ± 1.444
F4	4.333 ± 3.444
F5	5.333 ± 3.333
F6	3.342 ± 1.324

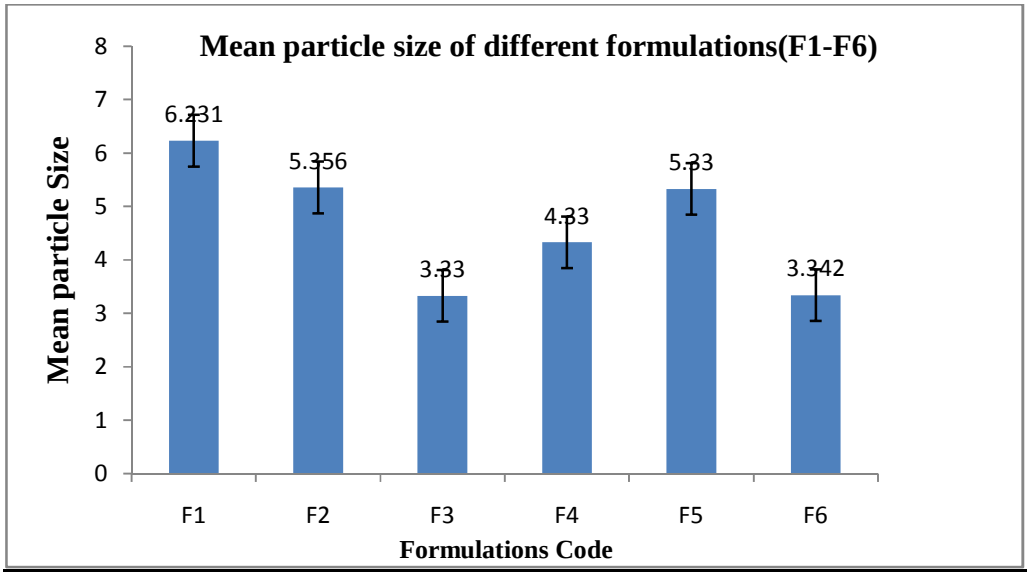

Fig.2 Distribution of particle size by bar diagram

As per results, amoxicillin niosomes formulation of F1 showed the highest mean particle size compared to other formulations.

***In-vitro* drug release study:** *In- vitro* study was carried out for niosomes formulation prepared from Tween 80 (F1, F2 and F3) and span 80 (F4, F5 and F6). The results showed that niosomes formulation of F1 prepared from span 80 showed a good percentage of drug release for about 12 hrs compared to other formulation. The results were represented in table and graph below.

Table 4. Percentage drug release of Amoxicillin Niosomes

Time (hr.)	% CDR					
	F1	F2	F3	F4	F5	F6
1	37.4758	23.555	33.358	19.838	21.3883	15.7574
2	41.8393	35.5754	42.322	23.3829	24.5553	21.8393
3	47.3849	37.3883	44.3282	27.3828	29.3293	25.2993
4	52.3292	42.8238	48.3892	32.9988	34.9892	32.3883
5	53.3829	48.3828	57.32828	48.2832	37.3829	33.3282
6	59.3829	52.3289	61.2882	55.2828	52.3838	59.9299
7	66.2222	63.3829	67.3282	60.3282	59.2828	65.2828
8	70.2828	65.2828	69.2828	62.2828	65.2822	67.288
9	74.2348	68.222	72.2828	65.2882	67.2828	70.2829
10	76.2878	69.3899	75.2828	69.8228	70.2828	74.2808
11	79.1728	72.2829	78.9822	78.298	74.6890	75.829
12	84.2929	75.2829	88.222	84.223	75.2282	77.2828

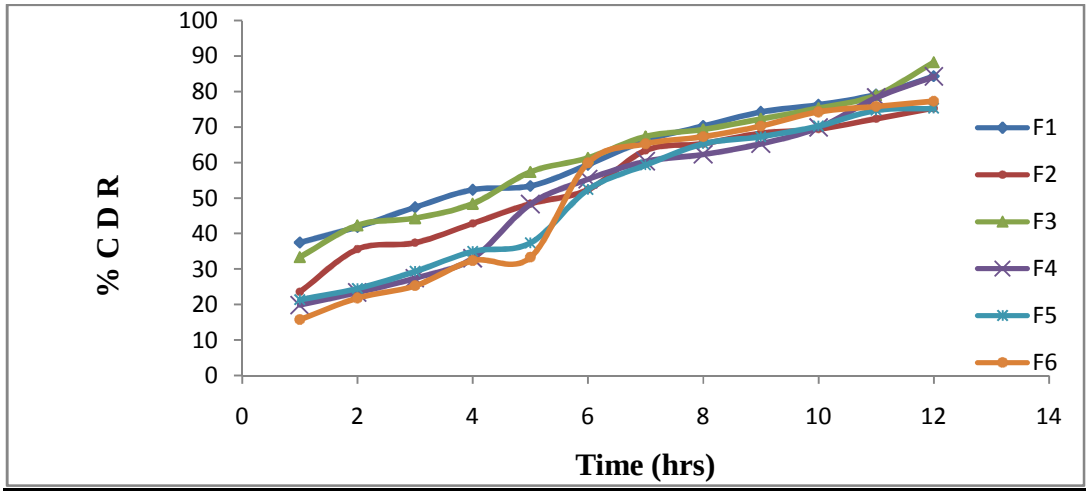

Fig.3 Comparison of percentage drug release of Niosomes formulation of Amoxicillin.

Discussion:

Niosomes prepared with Tween 80 (F1, F2, and F3) and span 80 (F4, F5, and F6) by hand shaking method showed gradual increase in mean particle size ranging from 4.3-6.2 m. This may be due to different hydrophilic-lipophilic balance (HLB) value of the each surfactant. Entrapment efficiency of niosomes formulation, F5 with span 80 showed high values compared to others. This was due to increase in surfactant concentration used in the preparation of niosomes formulation of amoxicillin. In the *in-vitro* study, niosomes formulation of amoxicillin, F1 (Tween 80) showed high percentage of drug release, 88.29% for about 12 hrs. This indicated that this batch of niosomes formulation exhibit sustained drug release pattern as the niosomes act as reservoir system for continuous delivery of drug. Niosomes formed which were observed under 40X magnification using light microscope were mostly spherical and in medium to slightly large size. As for the SEM analysis, the niosomes of amoxicillin were in spherical in shape. In stability studies, the optimized formulation, NFC's Stability started to deteriorate from 2nd week where the niosomes vesicles are seen in non-spherical shape. On 21st and 28th day the niosomes formulation were examined and seen in non-spherical shape and are clumped for both storage condition. This is mainly due to disruption or aggregation of vesicles since it is exposed to chemical degradation like hydrolysis and oxidation. As for the drug release, niosomes formulation stored in room temperature and refrigerated condition showed 88.29% which mainly due to membrane-stabilizing effect of cholesterol. Thus, from the prepared niosomes formulation, it can be concluded that the vesicular system was more stable at 2ºC - 8ºC. The released data of optimized niosomes formulation of amoxicillin were analyzed mathematically according to zero order, first order, Higuchi, and equations. As for the Higuchi's model (r2=0.988), zero order (r^2=0.982), and first order (r^2=0.695). The drug release from niosomes does not obey first order kinetics, which means that the release of amoxicillin from the niosomes vesicle is independent to concentration gradient.

4. Conclusion

Niosomes containing amoxicillin were prepared by Hand shaking method using nonionic surfactant span 80 and cholesterol at ratio 1:1 showed good results. This optimized formulation showed highest entrapment efficiency, having drug release for 12 hrs and exhibited good stability for 2 weeks in refrigeration condition at 2ºC - 8ºC. In conclusion, the optimized formed of niosomes formulation of amoxicillin showed a promising novel drug delivery system. Therefore further experiment as well as research about this formulation should be carried out for *in-vivo* and comparative analysis of *invivo* and *in-vitro* drug release studies in order to bring out an effective formulation for successful treatment of various diseases.

5. Acknowledgement

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