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Liposomal Delivery of Ajmaline: Formulation Strategies, Pharmacological Rationale and Future Perspectives

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Abstract

Ajmaline is a naturally occurring indole alkaloid isolated from Rauwolfia serpentina, and classified as a class IA antiarrhythmic agent. Today, ajmaline is especially important as a sodium-channel blocker that is used in the context of pharmacological provocation testing in order to ascertain the type-1 electrocardiographic pattern of the Brugada syndrome. Its pharmacological activity has been confirmed, but the traditional way of administering ajmaline carries with it the standard drawbacks of systemic drug delivery such as the requirement for a suitable concentration in the tissues to exert its intended effect and the risk of excessive exposure and undesirable pharmacological effects. Liposomes have been developed as a versatile drug delivery system, which can be loaded with both hydrophilic and lipophilic compounds, into the aqueous core and the lipid bilayer, respectively. They can be modified in their composition, particle size, surface charge and through their preparation to affect drug loading, stability, circulation and release. The pharmaceutical considerations related to the development of liposomal ajmaline are discussed here with special emphasis on the structure and classification of liposomes and their preparation techniques, mechanisms of drug loading, characterization of the liposomes, steric stabilization of the liposomes, mechanisms of drug release and potential targeting techniques. The liposomalization of ajmaline is discussed based on its physicochemical and pharmacological properties. Special emphasis is placed on the passive and active loading and the compromise of a long retention time with a proper drug release. Based on the literature available, it is suggested that liposomal delivery might also be used for the modification of the disposition and release characteristics of ajmaline; however, there is a lack of direct evidence of ajmaline loaded in liposomes. Thus, systematic formulation development, physicochemical characterization, pharmacokinetic study and pharmacodynamic assessment is necessary prior to clinical potential for liposomal ajmaline.

Keywords

Ajmaline; liposomes; antiarrhythmic drug; sodium-channel blocker; drug delivery; liposomal encapsulation; controlled release; Brugada syndrome.

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1. INTRODUCTION

Indole alkaloid, Ajmaline, is related to the medicinal plant Rauwolfia serpentina. It belongs to the antiarrhythmic drugs of class IA and has a very strong blocking action on the cardiac sodium channels.[1] The use of Ajmaline has gained new clinical significance as it could reveal the characteristic type-1 electrocardiographic pattern of Brugada syndrome and as such intravenous administration is indicated as a provocation agent in the proper diagnostic

context. Ajmaline has other pharmacological properties besides its effect on sodium channel inhibition. Experimental studies have shown effects on several cardiac ion currents, such as potassium currents, and more recent mechanistic studies have included consideration of possible effects of calcium currents, mitochondria and metabolic pathways. [2] Therefore, the concentration and duration of exposure to ajmaline warrants consideration in the design of therapeutic and/or diagnostic delivery systems. The opportunity of the drug-delivery technology is to alter the pharmacokinetics and pharmacodynamics of known drugs.

Liposomes are especially appealing to use as nanocarriers, as they are vesicular systems with one or more phospholipid bilayers and an aqueous compartment. They are amphiphilic and thus are able to incorporate compounds of varying physicochemical properties.[3] The biocompatibility and biodegradability of liposomes, along with their capacity for carrying hydrophilic and lipophilic compounds have made them a subject of wide research as a pharmaceutical carrier. The localization of the drug in the bilayer or in the aqueous compartment will depend greatly on the lipophilicity of the drug and the properties of the lipid membrane. Liposomes can change the distribution of a drug incorporated in their interior in space and time. Thus, liposomal formulations have been explored to enhance the stability, change the pharmacokinetics, reduce toxic effects to sensitive tissues and promote targeted delivery of the drug. Such a strategy may be a viable strategy for the modification of drug disposition and release for ajmaline. It is important to note, however, that the rationale for developing liposomal ajmaline is not the same as the clinical proof of efficacy, which was provided by the literature searched in this study, but rather by the literature concerning liposomal drug delivery in general. [4]

2. AJMALINE: PHARMACOLOGICAL BACKGROUND

2.1 Chemical and pharmacological characteristics

Ajmaline is an alkaloid with established antiarrhythmic activity. It is classified as a class IA antiarrhythmic drug and acts predominantly through inhibition of voltage-gated cardiac sodium channels. The cardiac sodium channel Nav1.5 is a major pharmacological target associated with its electrophysiological effects. [5]

Blockade of cardiac sodium current reduces the rate of depolarization and slows impulse conduction. Ajmaline also affects cardiac potassium channels, and studies have demonstrated inhibition of Kv1.5, Kv4.3 and hERG-related potassium currents. These additional actions contribute to the broader electrophysiological profile of the drug. [6]

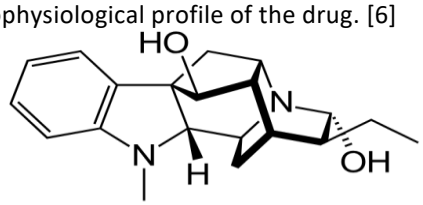

Fig 1: Structure of Ajmaline [7]

2.2 Ajmaline and Brugada syndrome

One of the most important modern applications of ajmaline is its use as a sodium-channel blocker during pharmacological challenge testing for suspected Brugada syndrome. Intravenous sodium-channel blockade can reveal an otherwise concealed type-1 Brugada ECG pattern. [8]

The mechanism of the ajmaline-induced ECG response is more complex than simple sodium-channel inhibition. Reduction of sodium current can increase conduction delay within susceptible myocardial substrates and promote conduction abnormalities associated with the Brugada ECG phenotype. [9]

Because the diagnostic effect depends on controlled pharmacological exposure, formulation and delivery characteristics are important considerations. A delivery system that changes the rate of drug appearance, distribution or release could theoretically alter the pharmacodynamic profile of ajmaline. This concept provides a scientific rationale for investigating modified-release or carrier-based approaches, although such an application would require rigorous pharmacological validation. [10]

3. LIPOSOMES AS DRUG-DELIVERY SYSTEMS

Liposomes are spherical vesicles made of amphiphilic lipids, mainly phospholipids. Phospholipids have the ability to spontaneously form closed bilayer structures upon hydration. The vesicles that are formed have an aqueous compartment inside, surrounded by a lipid membrane. Liposomes with different physicochemical properties can be prepared by varying the types of lipids used in their preparation, by adjusting the surface charge, by altering the particle size, by increasing or decreasing the number of bilayers, and by changing the method of preparation. Unsaturated phospholipids tend to make the membranes more fluid and more permeable, while saturated, long-chain phospholipids can make very rigid, less permeable bilayers. The amphiphilic property of liposomes is very advantageous in the field of drug delivery. Hydrophobic molecules can preferentially bind to the lipid bilayer, while hydrophilic molecules can be inserted into the aqueous contents of the lipid bilayer. Molecules of intermediate lipophilicity can

be found in both compartments. This structural flexibility allows liposomes to be used to formulate drugs where the distribution, retention and release of the drug can be controlled by changing the liposomal composition and by changing the conditions of the manufacture of the liposome. [11,12]

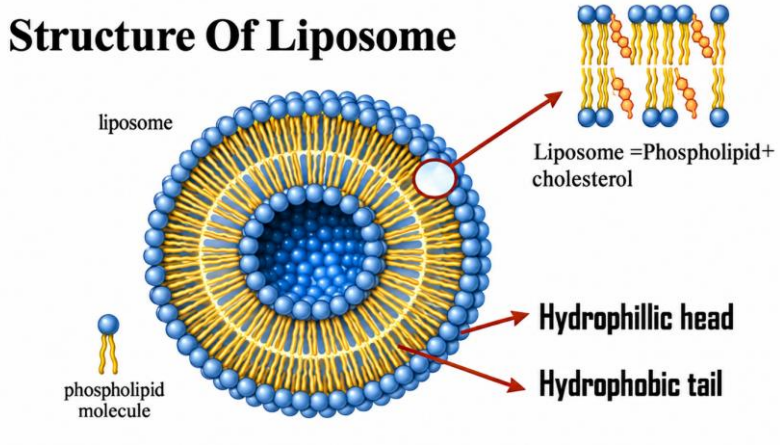

Fig 2: Structure of Liposomes

4. CLASSIFICATION OF LIPOSOMES

Liposomes can be classified according to size and lamellarity. The major categories include multilamellar vesicles (MLVs), large unilamellar vesicles (LUVs) and small unilamellar vesicles (SUVs). [13]

4.1 Multilamellar vesicles

MLVs contain multiple concentric phospholipid bilayers separated by aqueous layers. They are commonly generated during initial lipid hydration and can subsequently be converted into smaller vesicles through mechanical processing. [14]

4.2 Large uni-lamellar vesicles

LUVs contain a single phospholipid bilayer surrounding an aqueous compartment. Their relatively large internal aqueous volume can be advantageous for encapsulation of hydrophilic substances. [15]

4.3 Small uni-lamellar vesicles

SUVs contain a single bilayer and have smaller particle dimensions. Sonication and extrusion are frequently employed to produce smaller and more homogeneous vesicles. [16]

For ajmaline, the choice among these vesicular systems should depend on its distribution between the aqueous phase and lipid membrane, desired drug loading, stability and intended route of administration. [17]

5.RATIONALE FOR LIPOSOMAL DELIVERY OF AJMALINE

The main interest in studying liposomal ajmaline stems from the ability of liposomes to alter the physicochemical environment in which the drug is delivered to the biological systems. It has been reported that liposomes enhance the stability of several drugs, modify their pharmacokinetics and decrease the exposure of the non-target tissues. Their composition may also be changed to give sustained circulation, or different rates of drug release.

Aimed targets for liposomalization of ajmaline could be:

1. Modification of drug release: Encapsulation can give a reservoir effect for the slow release of ajmaline.
2. Pharmacokinetics changes: Distribution and clearance changes may be observed depending on the size, lipid composition and surface properties of liposomes.
3. Enhanced formulation stability: The lipid bilayer can offer a protective microenvironment.
4. Control of exposure: A controlled-release system may allow for a less dramatic change in the systemic drug concentration.
5. Potential for targeted delivery: Surface modification with suitable ligands might enable preferential interaction with targeted biological targets.

These are only formulation hypotheses, however, and not clinical advantages of using liposomal ajmaline. The main problem is to achieve adequate drug delivery without providing too slow a release rate. [18]

6.FORMULATION STRATEGIES FOR AJMALINE-LOADED LIPOSOMES

The lipid composition is one of the most important variables determining liposome behaviour. Phospholipid selection affects membrane rigidity, permeability, stability and drug retention. Cholesterol can also influence membrane packing and stability. [19]

Long-chain saturated phospholipids can produce relatively rigid bilayers, whereas unsaturated phospholipids produce more fluid membranes.
Barenholz emphasized that membrane composition and cholesterol content influence bilayer defects and permeability. Saturated phospholipids together with an appropriate cholesterol concentration can reduce membrane defects and decrease drug leakage.
Therefore, formulation development of ajmaline-loaded liposomes should systematically investigate phospholipid type, cholesterol concentration and drug-to-lipid ratio. [20]

7. METHODS OF LIPOSOME PREPARATION

The basic steps in most of the liposome-preparation methods are the removal of lipids from organic solvents, dispersion or hydration of the lipid, purification and analysis of the final vesicles.

7.1 Thin-film hydration

One of the most commonly used laboratory methods is thin-film hydration. A thin film of lipids is formed by dissolving lipids in an organic solvent and removing the solvent, and then adding an aqueous phase with the drug. These vesicles may be heterogeneous at first, and can be homogeinized by sonication or membrane extrusion. [21]

7.2 Sonication

Vesicles are typically reduced size by sonication to create SUVs. But sonication might lead to degradation of phospholipids or encapsulated substances, and probe sonication may lead to metal contamination. [22]

7.3 Extrusion

Extrusion is the process of forcing larger vesicles through membranes with specific pore size. Can be used for size reduction and to achieve uniformity in size. Mechanical method for preparation of liposomes include French pressure cell method and membrane extrusion. [23]

7.4 Ethanol injection

Ethanol injection involves the injection of lipids dissolved in ethanol into aqueous phase. The method is simple but may produce vesicles of varying size and ethanol needs to be removed effectively. [24]

7.5 Reverse-phase evaporation

In inverted micellar evaporation (IRE) vesicles are formed by the creation and collapse of inverted micelles. It can offer a relatively high lipid-to-aqueous volume ratio and have been used to achieve high encapsulation efficiencies. In the case of ajmaline, the method of preparation should depend on its physicochemical properties and the processing method and loading mechanism desired. [25]

8. DRUG LOADING IN LIPOSOMES

Generally, drug loading falls into two categories: passive and active loading.

8.1 Passive loading

In passive loading the drug is added when the liposomes are formed. The hydrophobic molecules can associate to the lipid bilayer, while the hydrophilic molecules are included in the aqueous compartment. Review notes provided that for a drug to be able to be passively entrapped, the aqueous volume within the vesicles must be small enough to be supplied and the solubility of the drug must be high enough. [26]

8.2 Active or remote loading

Active loading takes place after the vesicles are formed and relies on a transmembrane chemical gradient to force the accumulation of drugs into the vesicle. One of Barenholz's greatest accomplishments in liposome research was the discovery of the remote loading by pH and ion gradients. The method can achieve high and stable drug-to-lipid ratio with acceptable drugs. The feasibility of remote loading for ajmaline is likely to depend on its ionization behaviour, its membrane permeability and interaction with the intraliposomal environment. Thus, optimization of the gradient would have to be performed by experimentation instead of relying on the assumption that a gradient which works for another drug will prove to be acceptable for ajmaline. [27]

9.CHARACTERIZATION OF AJMALINE-LOADED LIPOSOMES [28]

Systematic characterization program should contain both physicochemical and drug related parameters.

9.1 Particle size and polydispersity

The particle size and polydispersity of materials. The size of the particle's influences, circulation, biodistribution, cellular interactions and physical stability. Polydispersity gives information about the uniformity of the vesicles.

9.2 Zeta potential Surface charge affects the stability of the colloids and interaction between liposomes and biological membranes.

9.3 Morphology Vesicle morphology can be studied using TEM (including cryo-TEM) or by other microscopy techniques.

9.4 Entrapment efficiency Entrapment efficiency is one of the key measurements that is important to assess the percentage of the ajmaline loaded into the liposomal formulation.

9.5 Drug loading Drug loading should be expressed in terms of lipid content and should be analyzed in conjunction with the entrapment efficiency.

9.6 In vitro drug release Release studies are necessary since encapsulation is no guarantee for therapeutic effectiveness. Barenholz also showed the significance of stable loading and the need for sufficient release - too high a stability can led to very slow release of the drug and significantly reduced bioavailability.
9.7 Stability Physical stability should include evaluation of particle-size changes, aggregation, leakage and precipitation. In the case of chemical stability, drug degradation and lipid oxidation/hydrolysis should be checked.

10. STEALTH AND LONG-CIRCULATING LIPOSOMES

Liposomes are the conventional liposomes that can be eliminated by the components of the mononuclear phagocytic system. Polyethylene glycol (PEG) can be used to modify the surface to decrease the uptake of the macrophages and increase circulation time. PEGylated or sterically stabilized liposomes therefore offer an important approach to the modification of the biological fate of liposomal drugs. Barenholz said sterically stabilized liposomes represent a big leap forward in liposome technology, and stressed the need to find a balance between long-term circulation and release of the drug. The extended circulation time might, in theory, lead to longer duration of drug release and affect systemic exposure with liposomal ajmaline. However, long circulating times are not necessarily a measure of therapeutic efficacy. The amount of free drug available at the drug's site of action can be low if the drug is too tightly bound to the vesicle. This relationship reflects the need to design liposomes that are stable as well as to control the release. [29]

11. DRUG RELEASE AND TARGETING

One of the major challenges faced in liposomal drug delivery is the stabilization of the liposomes while not hampering the drug elution. If liposomes are quite permeable, they might deliver their drug before it reaches its target site in the body, while if they are very stable, they may keep the drug too long. It was a basic formulation issue, barenholz said, noting that a system that is stable during circulation, but more permeable at the intended site, was needed. Liposomes can be administered to biological sites either by passive or active targeting. The passive targeting is dependent mainly on the physicochemical characteristics and tissue microanatomy, while active targeting requires the attachment of a ligand, antibody or other recognition molecule on the surface of the liposome. The use of active targeting is not yet a proven method with ajmaline. Regardless of the targeting approach, evidence would need to be demonstrated that targeting enhances drug delivery without disrupting the specific pharmacological effect. [30]

12.PHARMACOLOGICAL BENEFITS OF LIPOSOMAL AJMALINE (POTENTIAL)

Considering the fundamentals of the liposomal drug delivery system, several potential benefits can be suggested for the use of ajmaline: Controlled exposure: Free drug availability may be diminished due to liposomes. Altered pharmacokinetics: Circulation time and tissue distribution modifications may result due to association with a particulate carrier. There may be a reduction in systemic exposure when using encapsulation, if it is designed appropriately. Greater formulation flexibility: The composition of liposomes can be tailored to meet the desired release profile. May be available for extended periods of action: Long-circulating formulations can be used to provide extended release. The above are potential benefits only and not clinical outcomes. Research on liposomes has shown that enhanced circulation and accumulation in the tissues do not guarantee enhanced pharmacological activity if the release of the drug is inadequate. [31]

13. CHALLENGES AND RESEARCH GAPS

Although some significant progress has been made in the field of liposomal drug delivery, several problems need to be overcome before the translation of ajmaline-loaded liposomes to actual pharmaceutical products becomes possible. The first is that the drug loading efficiency should be maximized. The best method of loading ajmaline will be determined by its ionization, lipid affinity and its permeability through membranes. Secondly, the rate of drug release should be adequate to achieve the desired pharmacological response without early release of the drug. Third, the stability of liposomes is of importance because of the potential for oxidation or hydrolysis of phospholipids and aggregation, fusion or leakage of the drugs from liposomes. Fourth, manufacturing and scale-up must be taken into account. The key parameters of Liposome products are particle size, composition, drug loading, sterility and batch to batch reproducibility. Fifth, biological evaluation should determine if liposomal encapsulation alters the pharmacokinetics and pharmacodynamics of ajmaline. [32] Finally, there is a significant gap in the evidence that is available for ajmaline-specific liposomal formulations. References provided by the two main suppliers set the scientific and pharmaceutical foundation for liposomal delivery, but do not directly provide proof of clinical

efficacy of liposomal ajmaline. Accordingly, reports on the therapeutic efficacy of the compounds should be taken with a pinch of salt and should be regarded as hypotheses that must be tested in experiments [33].

14. FUTURE PERSPECTIVES

The future development of liposomal ajmaline should be done in a step-wise manner. Preformulation studies should be performed to elucidate the solubility, partitioning behaviour, ionization characteristics and compatibility of ajmaline with the selected phospholipids. The next step is to test a number of lipid compositions for particle size, polydispersity, entrapment efficiency and stability. The next step should be the comparison of passive loading versus active loading. If it is possible to achieve appropriate ionization and membrane transport properties with ajmaline, gradient based remote loading may be explored. [34] It will have to be determined by experiment whether this is feasible as remote loading is drug-specific. Optimized formulations should then be tested in vitro for release and then compared with the release of free ajmaline in the body by a pharmacokinetic study. The electrophysiological effect of ajmaline should be studied in the liposomal form. Thereafter, more advanced systems, like PEGylated liposomes, could be investigated when a long circulation time is required. Controlled release of stimuli responsive systems may also be acceptable if controlled release at a specific biological environment is needed. Importantly, the pathway for development should not depend on the fact that long circulation or increased encapsulation necessarily yields better pharmacological activity. Previous studies on liposomal drug delivery have shown that the formulation has to exhibit proper circulation, drug delivery to the desired biological compartment, drug loading, and drug release. [35]

15. CONCLUSION

Ajmaline is a well-known class IA antiarrhythmic agent that has a significant place in present day as a sodium-channel blocker used for pharmacological evaluation of Brugada syndrome. It has multiple electrophysiological effects, with controlled exposure to drugs being of special interest. The versatility of liposomes for controlling drug disposition is due to the fact that the size, structure of lipid, surface properties, lamellarity and the drug loading procedure can be controlled. They may be used to contain drugs with varying physicochemical properties, and may alter the stability, circulation and release of the drug. The literature reviewed on liposomes is strong enough to indicate a strong pharmaceutical rationale for the study of liposomal ajmaline. But the available data should not be construed as evidence of superiority of ajmaline in liposomes in the clinic. There are also significant issues to be addressed about the best combination of lipids, loading, particle size, release rates, and pharmacodynamics/pharmacokinetics of encapsulation.

The systematic formulation development and systematic physicochemical, pharmacokinetic and electrophysiological evaluations, therefore, need to be the focus of future research. Such studies would help determine if liposomal encapsulation offers a significant improvement over other conventional methods of delivery of ajmaline and could give some idea of whether this strategy has a future in controlled and/or targeted cardiovascular drug delivery.

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