Emulsions As Anticancer Delivery Systems

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CONTENTS

INTRODUCTION
EMULSION AS A DOSAGE FORM
EMULSIONS IN CANCER THERAPY
REFERENCES

1. INTRODUCTION

Anticancer agents are typically hydrophobic and unstable in water, making formulation development a major undertaking. For this reason emulsion, the semihomogeneous mixture of two immiscible liquids, is an attractive dosage form for anticancer drugs. However, because of processing difficulties, lack of physiologically safe ingredients, and thermodynamic instability of the emulsion system, development of injectable emulsion formulations, particularly those containing anticancer drugs, has not been very successful. However, an intravenous (iv) emulsion containing a water insoluble and heat labile anticancer agent, penclomedeine, was successfully developed and tested in clinical trials (1–3).

This chapter will explore advances in and problems associated with development of emulsions as viable dosage forms for anticancer drugs. The first section will review the emulsion as a dosage form and the second section will focus on research related to emulsions as delivery systems for anticancer drugs.

2. EMULSION AS A DOSAGE FORM

2.1. Definitions

Generally, emulsions are heterogeneous, or "semi-homogenous" as stated in the foregoing: liquid-dispersed formulations with two distinct and immiscible liquid phases separated by interfacial boundaries. The continuous phase is the medium in which no boundaries among the phase ingredients exist, and the discontinuous or disperse phase is the other liquid that has been distributed throughout the continuous phase as small droplets with discrete boundaries separating each from the other. Disperse phase droplets suspend within the structure of the continuous phase by means of one or more dispersants. A dispersant, also called a surfactant, emulsifying agent, or surface active agent, is
Table 1
Description of Different Types of Emulsions

<table>
<thead>
<tr>
<th>Type of Emulsion</th>
<th>Description</th>
<th>Known as</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oil in Water</td>
<td>Oil dispersed in water</td>
<td>O/W</td>
</tr>
<tr>
<td>Water in Oil</td>
<td>Water dispersed in oil</td>
<td>W/O</td>
</tr>
<tr>
<td>Oil in Oil</td>
<td>Oil dispersed in oil</td>
<td>O/O</td>
</tr>
<tr>
<td>Water in Oil in Water</td>
<td>Water dispersed in oil and the formed W/O emulsion dispersed in water again</td>
<td>W/O/W</td>
</tr>
<tr>
<td>Oil in Water in Oil</td>
<td>Oil dispersed in water and the formed O/W emulsion dispersed in oil again</td>
<td>O/W/O</td>
</tr>
</tbody>
</table>

an amphiphilic molecule, a molecule with both hydrophilic and lipophilic moieties, that aids dispersion by situating itself in the interfacial boundaries, hence, preventing the coalescence of the dispersed droplets and giving physical stability to the emulsion.

Emulsions have been used in various industries and most of the scientific disciplines. However, it is beyond the scope of this chapter to cover all of these delivery systems and their processing within the pharmaceutical industry. Rather, this chapter will focus on the emulsions used to deliver anticancer agents because the lack of sufficient aqueous solubility makes the emulsion an ideal dosage form.

Emulsions and self-emulsifying systems may also be used to enhance the oral bioavailability of anticancer agents. This chapter will review emulsions for oral as well as parenteral administration of anticancer drugs.

2.2. Types of Emulsions

There are several different types of emulsions, and Table 1 provides a list and description of these varieties. Among these various emulsion types, only oil-in-water (O/W) and water-in-oil-in-water (W/O/W) emulsions have been used directly in delivery of anticancer medications. On the other hand, oil-in-oil (O/O) emulsions have been used indirectly in developing microencapsulated forms of anticancer agents (4–6).

Emulsions are thermodynamically unstable systems, and formulating a physically stable emulsion is always a challenge. This thermodynamic instability is generally exacerbated when preparing multiple emulsions. Various stabilization approaches have been suggested, but Kawashima (7) used an innovative method to stabilize a multiple emulsion by simply increasing the concentration of the solutes in the inner aqueous phase. Various types are schematically presented in Fig. 1.

2.3. Formulation Development

When a parenteral emulsion, based on preformulation work or based on a deliberate decision, appears to be an optimum approach for a specific anticancer agent, the pharmaceutical scientist responsible for development will need to consider various factors associated with designing, developing, and manufacturing the final product.

Besides the active ingredient(s) and water, two major components of emulsion formulations are oil and dispersant(s). These components play a major role in the toxicity, elegance, and stability of the final product, and we will provide some relevant examples.