FORMULATION AND EVALUATION OF PHARMACOSOMES OF KETO PROFEN

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ABSTRACT
Pharmacosomes of Ketoprofen was formulated by conventional solvent evaporation technique to increase the solubility and bioavailability in different media with minimizing the GI disturbance. Two different ratio of drug: phosphatidylcholine (PC) in 1:1 and 1:2 were used to form pharmacosomes. Drug content was found to be 93.28% (w/w) for Ketoprofen phospholipid complex (1:1) and 85.44% (w/w) Ketoprofen-phospholipid complex (1:2). Ketoprofen phospholipid complex (1:1) showed better solubility profile than Ketoprofen-phospholipid complex (1:2). Further studies were carried out by optimizing the Ketoprofen phospholipid complex (1:1) ratio. Scanning electron microscopy and particle size analysis revealed differences between the formulations as to their appearance and size distribution-ray and DSC examination showed the amorphous nature of the drug. Solubility of pure Ketoprofen is 8.741 mg/ml in pH 6.8 which improve up to 18.232 mg/ml which increase in 2.09 fold. Dissolution profile of the prepared complex was found to be 93.30% which was much better than pure Ketoprofen which was 49.77% in 5 hrs. So finally we get positive approach for improving solubility and bioavailability of poor soluble drug.

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INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of pain and inflammatory disorders. Oral administration of this drug is also associated with gastrointestinal side effects like ulceration and gastrointestinal bleeding. It’s poor water solubility, which affects its dissolution in GI fluid, leads to poor bioavailability. These barriers which are obstacles to therapy are overcome by novel drug delivery systems (NDDS) [1]. Phospholipids have a special amphiphilic character. When placed in water, they form micelles or organized as lipid bilayers with the hydrophobic tails lined up against one another and the hydrophilic head-group facing the water on both sides. These unique features make phospholipids most suitable to be used as excipients for poorly water-soluble drugs. Thereby, it has to be kept in mind that the enhanced solubility of lipophilic drugs from lipid-based systems will not necessarily arise directly from the administered lipid, but most likely from the intraluminal processing, to which it is subjected before it gets absorbed [2]. Pharmacosomes are the colloidal dispersions of drugs covalently bound to lipids, which have unique advantages over liposome and noisome vesicles. They are depending upon the chemical structure of the drug–lipid complex they may exist as ultrafine vesicular, micellar, or hexagonal aggregates. “Pharmacosomes” means a drug (pharmakon) to a carrier (soma). They are an effective tool for drug targeting and controlled release. A surface and bulk interaction of lipids with drug is criteria for development of pharmacosomes. Any drug possessing an active hydrogen atom (-COOH, -OH, -NH2, etc.) can be esterified to the lipid, with or without a spacer chain that strongly result in an amphiphilic compound, which will facilitate membrane, tissue, or cell wall transfer, in the organism [3]. The studies had been done with respect to pharmacosome of diclofenac and aceclofenac which concluded that pharmacosome effective in improving solubility, bioavailability and gastrointestinal safety of the drug [4,5].

There is lot of work done regarding improving solubility of Ketoprofen by various approach like solid dispersion, freeze-drying, complexation etc [6,7,8]. But no study done with pharmacosome approach. So we apply this approach for improving solubility, bioavailability, protect active ingredients from degradation in the gastrointestinal tract and avoid GI disturbance of Ketoprofen. Therefore the present work aims to develop and characterize the pharmacosome of Ketoprofen along with its in vitro drug release study.

MATERIALS AND METHODS

Materials

Ketoprofen was obtained as a gift sample from Cipla Pharmaceuticals Ltd., Mumbai, India. Soya phosphatidylcholine (Lipoid S-80) was obtained as a gift sample from Lipoid GmbH Germany. All other solvents were used of analytical grade.

Preparation of pharmacosomes [4,5]

Pharmacosomes of Ketoprofen were prepared by conventional solvent evaporation technique as shown in fig 1. To prepare the pharmacosome of Ketoprofen, it was acidified first so that active hydrogen might be available for complexation. Ketoprofen acid was prepared by acidification of an aqueous solution of Ketoprofen and further extracted with chloroform and subjected to subsequent recrystallization. Ketoprofen-PC complex was prepared by associating Ketoprofen with PC in two different molar ratios viz. 1:1 and 1:2. The accurately weighed PC and Ketoprofen acid were placed in a 100 ml round bottom flask and dissolved in dichloromethane. The mixture was refluxed for 1 hr and solvent was evaporated under vacuum at 40°C in a rotary vacuum evaporator. The collected residues placed overnight in vacuum desiccator and then subjected to characterization.

Fig 1: Schematic representation of preparation of Ketoprofen pharmacosome

EVALUATION OF PHARMACOSOME

Determination of Solubility

To determine the change in solubility due to complexation, the apparent solubility of Ketoprofen and Ketoprofen physical mixture, pharmacosome was determined by adding an excess amount of drug, physical mixture and pharmacosome to 10 ml distilled water, pH 1.2, pH 6.8 phosphate buffers in screw capped vials. The vials were allowed to shake at 25°C for 24 hrs at orbital shaker (CIS-24, Remi). After equilibrium had been attained, the saturated solutions were centrifuge to remove excess drug. The supernatant was filtered immediately and rapidly through a 0.45 mm membrane filter. Then filtrate solutions were analyzed UV spectrophotometrically (UV-1800 PC Schimadzu, Japan).

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Drug Content
To determine the drug content in Ketoprofen-PC complex (Complex X and Complex Y with drug: PC ratio of 1:1 and 10:2), complex equivalent to 50 mg Ketoprofen was weighed and added in a volumetric flask with 100 ml of pH 6.8 phosphate buffer. Then the volumetric flask was stirred continuously for 24 h on a magnetic stirrer (Remi equipment Pvt. Ltd). At the end of 24 h, dilutions were made suitably and measured for the drug content at 260 nm UV spectrophotometrically.

Scanning Electron Microscopy
To detect the surface morphology of the pharmacosome, SEM of complex was performed by Scanning Electron Microscope (JSM 6390®, Japan). Samples of microspheres were dusted onto double-sided tape on an aluminum stub and coated with gold using a cold sputter coater to a thickness of 400°A, and then imaged using a 20 kv electron beam.

Differential Scanning Calorimetry (DSC)
Differential Scanning Calorimetry (DSC) of pure drug, drug loaded pharmacosome were conducted using differential scanning calorimeter (DSC 60 Shimadzu, Japan) at heating rate of 10 °C/min. The measurements were performed at a heating range of 30 to 3000C under nitrogen atmospheres.

X-ray diffraction study (XRD)
The X-ray diffraction (XRD) patterns of plane drug, phosphatidylcholine (80%) drug loaded pharmacosome were recorded on an X-ray diffractometer (AXS D8 Advance, Bruker, USA) diffractograms were run at a scanning speed of 2°/mm and a chart speed of 2°/2 cm per 2ø .

In vitro release
In vitro release experiments were conducted by using USP Type II Dissolution test apparatus (TDT 08L, Electro lab, Mumbai, India). The dissolution medium pH 6.8 phosphate buffer used. Pure Ketoprofen and Drug-loaded pharmacosome accurately weighed amount of the complex equivalent to 100 mg of drug was dropped into a dissolution vessel containing 900 ml of release medium and stirring rate was maintained at 100 rpm. Different interval up to 5 hour and sink condition was maintained with freshly prepared buffer solution. The UV absorbance of the withdrawal samples were measured by ultraviolet spectroscopy at 260 nm.

RESULT AND DISCUSSION
Solubility Study
Solubility of the Ketoprofen pharmacosome was found to be much higher (in water, pH 1.2 and pH 6.8) than the Ketoprofen and Ketoprofen physical mixture in table 2. The increase in solubility of Ketoprofen in the complex can be explained by the solubilization theory resulted from the formation of micelle in the medium and also by the amorphous nature of the complex. These amphiphilic surfactants (phospholipids) may increase the solubility of the drug by their wetting and dispersion properties. Unlike non-polar nature of Ketoprofen, the complex showed an amphiphilic nature, which in turn may prove to be responsible for improved bioavailability of the drug. The optimize batch was found to be pharmacosome batch X (1:1) this batch use for further studies [9].

<table>
<thead>
<tr>
<th>Media</th>
<th>Ketoprofen</th>
<th>Physical mixture (1:1)</th>
<th>Pharmacosomes (1:1)</th>
<th>Physical mixture (1:2)</th>
<th>Pharmacosomes (1:2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>0.00042</td>
<td>0.0032</td>
<td>0.0075</td>
<td>0.0054</td>
<td>0.0064</td>
</tr>
<tr>
<td>pH 1.2</td>
<td>0.0063</td>
<td>0.032</td>
<td>0.0654</td>
<td>0.023</td>
<td>0.053</td>
</tr>
<tr>
<td>pH 6.8</td>
<td>8.741</td>
<td>10.23</td>
<td>18.323</td>
<td>9.243</td>
<td>13.432</td>
</tr>
</tbody>
</table>

Drug Content and Percent Yields
Characterization of pharmacosome was done by production yield and drug content. Results are given in table 1. Drug content of Ketoprofen in the complex, as estimated by UV Spectrophotometry at 260 nm in pH 6.8 phosphate buffer was found to be 93.28 % (w/w) and 85.44 % (w/w) for Ketoprofen phospholipid complex (1:1) and for Ketoprofen - phospholipid complex (1:2) respectively. percentage of drug loading decreased with increase in concentration of lipid. On the basis of solubility, production yield and drug content optimize ratio was 1:1 which utilize for further studies. Pharmacosomes showed a high percentage of drug loading, better stability than liposomes which makes the delivery of drug possible for clinical use [10].

<table>
<thead>
<tr>
<th>Formulations</th>
<th>% yield</th>
<th>% drug content</th>
</tr>
</thead>
<tbody>
<tr>
<td>X (1:1)</td>
<td>92.12</td>
<td>93.28±0.34</td>
</tr>
<tr>
<td>Y (1:2)</td>
<td>83.42</td>
<td>85.44±0.23</td>
</tr>
</tbody>
</table>
SEM

The morphological evaluation of Pharmacosomes was performed by scanning electron microscopy. SEM image A of pure Ketoprofen and SEM image B of pharmacosomes. The surface morphology of optimized formulation prepared with the high purity grades of phospholipids (80%) was rough, non-sticky and free flowing in nature. Scanning Electron Micrographs of the complex are shown in figure 2. Pharmacosomes were found to be of disc shaped with rough surface morphology [10].

![SEM Image of Pure Drug And Pharmacosomes](image)

**Fig2. SEM Image of Pure Drug And Pharmacosomes**

DSC STUDY

The DSC thermograms of Ketoprofen as well as pharmacosome showed well defined chemical interaction between drug and lipid. In case of Ketoprofen it persisted sharp endothermic peak at 94.01º. And pharmacosome of Ketoprofen show endothermic peak at 61.80º. These all results indicate that Ketoprofen no longer present in the crystalline form may have got converted into the amorphous form. It also suggests that solubility of amorphous form better than crystalline form which is further confirmed by XRD study. The DSC thermograms of pure Ketoprofen and pharmacosome are presented in figures 3[11].

![DSC Spectra of pure Ketoprofen and pharmacosome](image)

**Figure3. DSC Spectra of pure Ketoprofen and pharmacosome**

X- RAY DIFFRACTION STUDIES

X- ray diffraction patterns of Ketoprofen, phosphatidylcholine and pharmacosome are given in figures 4. The X- ray diffractogram of Ketoprofen has sharp peaks at diffraction angles (2θ) between 0-60º showing a typical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of pharmacosome but of low intensity. This indicates that some amount of drug converts to its amorphous form. DSC studies support same hypothesis, which is confirmed by X- ray diffractometer [12].
DISSOLUTION STUDY

Drug release profile of pure Ketoprofen, pharmacosome of Ketoprofen was given in figure 5. Ketoprofen which showed 49.77% drug release and optimized pharmacosomes (1:1) showed 93.30% drug release in pH 6.8 phosphate buffer at the end of 5 hrs. Thus Pharmacosomes of Ketoprofen showed better dissolution profile than Ketoprofen [12].

CONCLUSION

Ketoprofen is a BCS class II drug, having poor solubility problem which lead to poor oral bioavailability and GI disturbances. To overcome this problem pharmacosome is one of the effective techniques. Preparation pharmacosome of by conventional solvent evaporation technique showed significant enhancement in solubility of Ketoprofen. Confirmation of formulation done by DSC study, the conversion of crystalline form of drug to amorphous form is confirmed by SEM study, XRD study. Consequently, a significant improvement in dissolution rate was seen as pharmacosome of Ketoprofen showed 93.30 % drug release in 5 hrs whether pure Ketoprofen showed 49.77% drug release in 5 hrs. Applying this approach to more addition drug the advantages of pharmacosomes exploited. Till date this approach requires some more effort for study the non bilayer and the mechanism of action of vesicle system. In future lot of work will be done for improving solubility permeability or avoid the problem associate with drug, phytoconstituents like GI disturbance etc.

REFERENCES


8. Influence of β-Cyclodextrin Complexation on Ketoprofen Release from Matrix Formulation


