Chapter 2

Need of Present Investigation & Plan of Work
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2. Need of present investigation and plan of work:
Macrolide antibiotics (MA) are macrocyclic lactones isolated first from Streptomyces spp. The common skeleton is a 12–16-membered lactone ring with attached neutral and/or amino sugars. Besides their activity against common Gram-positive and Gram-negative cocci, these new compounds have gained interest; because of their activity against nonclassical pathogens such as Helicobacter pylori (HP) and their therapeutic efficacy in HP-induced peptic ulcer disease. Macrolides are used to treat infections such as respiratory tract infections and soft tissue infections. The antimicrobial spectrum of macrolides is slightly wider than that of penicillin, and therefore macrolides are a common substitute for patients with a penicillin allergy. Beta-hemolytic streptococci, pneumococci, staphylococci and enterococci are usually susceptible to macrolides. Unlike penicillin, macrolides have been shown to be effective against mycoplasma, mycobacteria, some rickettsia and Chlamydia(1).

The mechanism of action of the macrolides is inhibition of bacterial protein synthesis by binding reversibly to the subunit 50S of the bacterial ribosome, thereby inhibiting translocation of peptidyl-tRNA. This action is mainly bacteriostatic, but can also be bactericidal in high concentrations. Macrolides tend to accumulate within leukocytes, and are therefore actually transported into the site of infection.

Commonly prescribed Macrolides are Erythromycin, Azithromycin, Clarithromycin and Roxithromycin. Macrolide antibiotics are white crystalline powders basic in nature and poorly soluble in water. These are mostly absorbed from the alkaline intestinal environments.

Until the late 1980s the 14-membered macrolide erythromycin, available since 1952, remained the only widely used macrolide antibiotic. However, its absorption after oral administration is highly variable due to instability in the acid environment of the stomach, and resulting plasma concentrations are unpredictable.

In the last decade semisynthetic derivatives of erythromycin such as roxithromycin, clarithromycin, and azithromycin have been developed which are more stable to acid compared to erythromycin. In vivo performance of conventional formulations of Roxithromycin was hampered by poor bioavailability owing to poor solubility and low residence time especially under adverse physiological conditions such as high peristaltic movement. Roxithromycin, a BCS class IV drug has 50% absolute oral bioavailability due to poor aqueous solubility. To increase the oral absorption of roxithromycin, it is important to improve the drug solubility in gastrointestinal tract, enabling rapid and complete absorption from the GIT (2).

Clarithromycin (CTM), a 14-membered macrolide antibiotic, was developed with greatly improved acid stability compared to erythromycin. CTM possesses potent antibacterial activity against clinically important respiratory pathogens such as penicillin-susceptible and intermediate pneumococci. CTM has also been used to treat Helicobacter pylori infection and pediatric infections. However, like many other macrolide antibiotics, CTM exhibits poor absorption and low bioavailability when administered orally. Because of its very low aqueous solubility (0.342 µg/mL water at 25°C), it is difficult to achieve an injectable CTM product in a clinically and commercially acceptable formulation (3).

Azithromycin is a semisynthetic macrolide antibiotic representing the first of a subclass of macrolides classified as azalides. A relative newcomer to veterinary medicine azithromycin was first described in the late 1980s and differs from erythromycin by the
insertion of methyl-substituted nitrogen on the lactone ring at position 9a. This addition creates a 15-membered macrolide. The alteration of the lactone ring provides a more stable compound in acidic environments and provides a larger spectrum of activity against Gram-negative bacteria (4).

The flowability and compressibility of the macrolide antibiotics are poor because of irregular crystalline habit. The oral bioavailability of Macrolide antibiotics is low which may be due to poor aqueous solubility and dissolution behavior.

The therapeutic dose of the Macrolide antibiotics is relatively high. Tablet formulation of Macrolide antibiotics with higher amount of drug substance do not lend themselves to direct compression due to poor compressibility as their crystal morphology show significant impact on compression characteristics. Macrolide antibiotics raw crystals are unsuitable for direct tabletting due to their poorly compactable properties, although strongly demanded in commercial production by direct tabletting. Most of the commercial tablet production of macrolide antibiotics utilize granulation method (wet granulation or slugging method) which required 3-5% binder along with different directly compressible diluents. Direct compression in the production of high dose formulation for poor compressible drugs is limited, since large quantities of directly compressible excipients are ordinarily required to produce suitable tablets. The granulation procedure also includes number of steps and require lot of powder binders and diluents such as microcrystalline cellulose, lactose monohydrate, dibasic calcium phosphate and other necessary excipients resulting in bigger size tablet and increase the cost of formulation.

Spherical crystallization is the novel agglomeration technique that can transform directly the fine crystals produced in the recrystallization process into a spherical agglomerated shape. It is the versatile process that enables to control the type and the size of the crystals. It is the particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into compacted spherical form. This technique of particle design of drugs has emerged as one of the areas of active research currently of interest in pharmaceutical manufacturing and recently came into the forefront of interest or gained great attention and importance due to the fact that crystal habit (form, surface, size and particle size distribution) can be modified during the crystallization process. In consequence of such modifications in the crystal habit certain micrometric properties (bulk density, flow property, compactibility) and physicochemical properties like solubility, dissolution rate, bioavailability and stability can also be modified. It has been also described as a very effective technique in improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile. It has also been applied to improve the flowability and the compression ability of some powders so that critical steps involved in wet granulation can be avoided.

Extensive Literature survey indicate that by using spherical crystallization technique it is possible to increase the flow, solubility, dissolution rate, bioavailability of poorly water soluble drugs. It is also possible to mask the bitter taste of drug by using taste masking polymers. By using spherical crystallization technique the recrystallization of drug occurs with changes in the crystal habit/crystal form and improvement in the compressibility of the drug molecules.
Chapter 2: Need of present investigation and plan of work

To succeed in direct compression with tablet formulation, particle modification of a drug is required to impart the formula which reduces the weight and cost of the formulation. Hence the proposed investigation aims at the preparation, evaluation and characterization of recrystallized agglomerated crystals of macrolide antibiotics with different excipients and polymers to improve physicochemical properties (flowability, density, porosity, intrinsic dissolution, packability, tablettability, wettability, moisture, antimicrobial activity, stability and in vivo performance). Further it also aims at studying the suitability of recrystallized agglomerates in direct tabletting and their performance (dissolution rate, disintegration, hardness, tensile strength, friability, porosity) comparing with the tablets prepared from powder blend of MA with excipients and the tablets available in market.

Table: 2.1 Important features and physicochemical properties of macrolide antibiotics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Erythromycin Base</th>
<th>Roxithromycin</th>
<th>Clarithromycin</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Fine white to off white Powder</td>
<td>White Crystalline Powder</td>
<td>White Crystalline Powder</td>
<td>White crystalline powder</td>
</tr>
<tr>
<td>Crystal habit</td>
<td>Irregular stone shaped</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taste</td>
<td>Bitter taste</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water Solubility (mg/mL)</td>
<td>0.925</td>
<td>0.273</td>
<td>0.005</td>
<td>1.45</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>25%</td>
<td>50%</td>
<td>55%</td>
<td>34%</td>
</tr>
<tr>
<td>BCS Class</td>
<td>class II drug</td>
<td>class IV drug</td>
<td>class II drug</td>
<td>class II drug</td>
</tr>
<tr>
<td>Dose</td>
<td>250mg, 500mg</td>
<td>150mg, 300mg</td>
<td>250mg, 500mg, 600mg</td>
<td>250mg, 500mg</td>
</tr>
</tbody>
</table>

2.1. Significance of present research work:

a) Spherical crystallization technique has been successfully utilized for improvement of flowability and compressibility of crystalline drug.
b) This technique could enable subsequent processes such as separation, filtration, drying etc to be carried out more efficiently.
c) By using this technology, physicochemical properties of pharmaceutical crystals were dramatically improved for pharmaceutical processing i.e. mixing and tablettting because of their excellent flowability and packability.
d) This technique may enable crystalline form of a drug to be converted into different polymorphic form and thus attain better bioavailability due to changes in solubility and dissolution.
e) The technique is now days used for masking of the bitter taste of drug substances.
f) The spherically agglomerated crystals can be prepared in tablet form or compounded directly into a pharmaceutical system without further processing such as granulation due to their spherical shape.
g) The process is simple and inexpensive enough for scaling up to a commercial level. It reduces time and cost by enabling faster operation, less machinery and fewer personnel.
h) It gives important advances in tablettting technology, especially the introduction of number of directly compressible excipients.
2.2. Plan of work:

- Procurement of drug and polymers sample.
- Detection of solubility of drug in different solvent system.
- Selection of solvent and their quantity for the preparation of agglomerates.
- Selection of optimized conditions for spherical crystallization process.
- Preparation of spherical agglomerated crystals.
- Study the polymer and surfactants effect on taste masking and dissolution behavior of spherical agglomerates.
- Evaluation and characterization of agglomerates.
  1. Shape, size and size distribution.
  2. Solubility.
  3. Dissolution rate profile study.
  4. Taste masking ability of used polymers.
  5. Flowability.
  6. Packability.
  7. Density and porosity.
  8. Strength/friability of agglomerates.
 10. Moisture absorption.
 12. Characterization (FTIR, XRPD, DSC, SEM)

- Tablet Formulation and Compression.
  Evaluation of Compressed tablet and Compare with the Marketed tablet Formulation with reference to the following parameters.
  1. Tensile strength
  2. Porosity and wettability study
  3. Hardness and Friability test
  4. Drug content.
  5. Disintegration test.
  6. In vitro dissolution study

- Compilation of data.

2.3. References: