(HPC), carboxymethylcellulose sodium (NaCMC), (ii) natural polymers: sodium alginate, carrageenan, chitosan and (iii) synthetic polymers: polymerized acrylic acid (Carbopol), polyvinyl alcohol (PVA), polyethylene oxide (PEO). It has been suggested, however, that the term ‘swellable matrices’ is more appropriate as it better explains the characteristic of the systems (Colombo et al., 2000).

Clarithromycin is a semi synthetic macrolide antibiotic. It is practically insoluble in water. Patient compliance for immediate release formulations of Clarithromycin is poor because of two to three times dosing per day; poor gastrointestinal tolerability; bitter metallic taste. Hence, controlled release tablet formulation of Clarithromycin was designed and introduced into the market by Abbot under the brand name BIAXIN XL. The tablets are formulated using a polymer-based matrix that slows the drug release and extends absorption from the gastrointestinal tract resulted in improved patient compliance, enhanced gastrointestinal tolerability and improved taste profile. (Gotfried MH., 2003) Clarithromycin controlled release tablets provide extended absorption of clarithromycin from the gastrointestinal tract after oral administration. Relative to an equal total daily dose of immediate-release clarithromycin tablets, clarithromycin controlled release tablets provide lower and later steady-state peak plasma concentrations but equivalent 24-hour AUC's for both clarithromycin and its microbiologically-active metabolite, 14-OH clarithromycin. (Laman Al-Razzak et al., 2000)

The present research endeavour was directed towards the development of a simple and cost-effective controlled release dosage form of Clarithromycin which would be comparable to BIAXIN® XL Film tab® with respect to stability and drug release characteristics.

Prednisone
Reservoir (coated) systems comprise a drug-containing core enclosed within a polymer barrier coat. Two types of reservoir systems can be used: (c) Simple diffusion/erosion systems where a drug-containing core is contained within hydrophilic and/or water-insoluble polymer coatings. Drug release is achieved by diffusion of drug through the coatings or following coat erosion. (d) Osmotic systems where the drug core is contained within a semipermeable polymer membrane with a mechanical/laser drilled hole for drug release, driven by osmotic pressure generated within the tablet core. (Clive G. Wilson et al., 2011)
Polymyalgia rheumatica (PMR), an inflammatory disease with a lifetime risk estimated at 2.4% for women and 1.7% for men, is the most common rheumatological disorder in people over 60 years (Crowson CS et al., 2011, Smeeth L et al., 2006 and Vanhoof J et al., 2002). The principal symptoms are pain and stiffness of the proximal muscle girdles, usually worse in the morning, with subsequent profound disability (Hutchings A et al., 2007). PMR is one of the commonest indications for longterm glucocorticoid (GC) therapy (Walsh LJ et al., 1996). There are wide variations in clinical management in primary and secondary care (Chakravarthy K et al., 1994), reflecting the dearth of strong evidence available on which to develop treatment policies. Although guidelines have been published (Dasgupta B et al., 2010), treatment recommendations are not based on the results of randomized controlled trials, and alternative interpretations of the available data have led others to recommend different regimens (Kirwan J et al., 2007 and Michet CJ et al., 2008). Nevertheless, all these treatment recommendations advocate the use of medium dose GC (e.g., 15 mg/day prednisone or prednisolone) as starting treatment with a reduction in the dose over 1–2 years (Delecoeuillerie G et al., 1988, Salvarani C et al., 1987 and Lundberg I et al., 1990). While the majority of patients show a rapid clinical response (Kyle V et al., 1989 and Myklebust G et al., 2001), it is clear that, even with a rapid reduction in GC dose, there are substantial adverse effects. In the absence of placebo-controlled trials, the frequency of adverse effects attributable to GC can only be estimated, but up to 85% of those treated with current protocols report GC-related adverse events. There is a clear need to find ways of optimizing dosing of GC to maintain efficacy while minimizing the potential for adverse events. Active PMR is characterized by increased serum levels of the pro-inflammatory cytokine IL-6, but not of other pro-inflammatory cytokines (Alvarez-Rodriguez L et al., 2010 and Spies CM et al., 2010). In rheumatoid arthritis (RA), where there is also an increase in IL-6 concentration, there is a circadian variation in levels of the cytokine that coincides with the circadian variation in symptoms, with plasma IL-6 concentrations at their peak at the time of waking (Arvidson NG et al., 1994, Arvidson NG et al., 1997 and Perry MG et al., 2009). However, as noted by Spies and colleagues, studies in PMR have collected blood samples at only one time point (mainly in the morning), without specifying the exact timing. They concluded that a more detailed analysis of the circadian variation in cytokines in patients with PMR was required. The primary aim of this study was therefore to determine for the first time the circadian variation in plasma IL-6 and other cytokines in patients with newly diagnosed untreated PMR. In RA, the administration of GCs at night using a modified- (delayed-) release preparation of prednisone causes both a marked reduction in morning IL-6 (Clarke LL
et al., 2011) and a reduction in morning stiffness (Buttgereit F et al., 2008, Buttgereit F et al., 2010, Derendorf H et al., 2013, Clinicaltrials.gov, Bird HA et al., 1979, Hutchinson RM et al., 1977, Nicklin JK et al., 2009, Zigmond AS at al., 1983, Perry MG et al., 2010, Lavendar P et al., 2010, Quick V et al., 2012 and Kirwan JR et al., 2011).

The present area of research is on designing the reservoir system of Prednisone using water-insoluble, pH independent polymer, Ethyl Cellulose along with a water soluble, hydrophilic polymer, Hypromellose 3 cps as a pore former. This controlled release preparation of prednisone is taken in the evening (approximately 22.00 hrs), but the drug, Prednisone is released approximately 4h later (approximately 02.00) with the same bioavailability profile as standard immediate-release prednisone tablets and would be comparable to RAYOS with respect to stability and drugrelease characteristics.

3.2 SCOPE

Clarithromycin

Apart from different gastro retentive systems designed for Clarithromycin, matrix based controlled release tablets of Clarithromycin was found to be a feasible and practical solution for effective oral antimicrobial therapy and to achieve patient compliance through reduced adverse drug events and better organoleptic characteristics. Literatures on matrix based drug delivery system available for Clarithromycin involves complex manufacturing process incorporating significant amount of high viscous polymers along with non-aqueous solvents for processing. From industrial view point such process lacks commercial feasibility and will not contribute for cost effective end product to serve the society at large. Hence the present research objective is to design a simple, reproducible and robust manufacturing process to formulate the controlled release tablets of Clarithromycin which would be comparable to the drug release characteristics of BIAxin® XL FILMTAB®.

Prednisone

Time controlled drug delivery system of Prednisone is particularly advantageous to reduce the severe adverse drug events associated with frequent drug administration. Dose of Prednisone is also less when administered through time based drug delivery system than the conventional immediate release dosage forms. The effectiveness and patient compliance is improved when Prednisone is given in the form of time controlled drug delivery than the conventional drug delivery since the disease state is associated with factors / mediators that
strictly follows biological / circadian rhythm. The marketed / reference product, RAYOS is a
tablet in tablet design of patented GEOCLOCK™ technology which utilizes a combination of
Dibasic Calcium Phosphate Dihydrate, Glyceryl Behenate and Povidone to control / delay the
drug release after 4 hours. The manufacturing process and equipments involved, requires high
precision. As such the process is very costly and the output is less. Elsewhere a drug product
for controlled release of Prednisone is designed using pH dependent polymers. Hence the
present research objective is to design a simple, reproducible and robust manufacturing
process to formulate the controlled release tablets of Prednisone in which no organic / non
aqueous solvent will be used. With respect to polymer selection, Water insolublepH
independent which would be comparable to the drug release characteristics of BIAXIN® XL
FILMTAB®.

3.3 OBJECTIVE
The present research endeavour is to formulate the controlled release tablets of
Clarithromycin and Prednisone.
In the formulation of controlled release tablets of Clarithromycin, the following particulars
were considered,

- Minimum excipients
- No organic solvents
- Aqueous based top spray granulation process (using fluid bed processor) with few
  unit operations
- Less manufacturing time
- Cost effective manufacturing

In the formulation of controlled release tablets of Prednisone, the following design was
considered to achieve cost effective product in less time of manufacturing,

- Immediate release core tablet with controlled release coating.
- Unlike conventional controlled release systems, this controlled release coating will be
time specific.
- No organic solvents; aqueous based ethyl cellulose dispersion as polymer and
  hypromellose as pore former will be used.
- Conventional perforated coating pan will be used for manufacturing the controlled
  release tablets.
PLAN OF WORK
Based on the literature review and above mentioned objectives the following plan was framed for both Clarithromycin and Prednisone,

1. Preformulation study
   • API
   • Drug – Excipient Compatibility Study

2. Marketed Product Characterization

3. Formulation development of dosage form including optimization of the manufacturing process

4. Evaluation of dosage form in comparison with the marketed product
   • Invitro – Dissolution
   • Invivo – Bioequivalence

5. Accelerated stability study of the finalized formulation as per ICH guidelines.
EXPERIMENTAL WORK
CHAPTER – IV

EXPERIMENTAL WORK

Formulation and Evaluation of Controlled-Release Tablets of Clarithromycin

4.1 Drug Substance – Method of Analysis & Specification

Chemical Name: Erythromycin, 6-O-methyl-6-O-Methylerythromycin

CAS#: 81103-11-9

Molecular Structure:

a. Molecular Formula: C_{38}H_{69}NO_{13}
b. Molecular Weight: 747.95
c. Physical Description: White or almost white, crystalline powder
d. Solubility Characteristics: Soluble in acetone and in methylene chloride, slightly soluble in dehydrated alcohol, in methanol, in acetonitrile and in phosphate buffer at pH values of 2 to 5; practically insoluble in water.

Table: 1 Solubility Characteristics

<table>
<thead>
<tr>
<th>S.No</th>
<th>Buffer Solution</th>
<th>pH</th>
<th>Solubility of Clarithromycin 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acid Phthalate</td>
<td>2.4</td>
<td>1.18 mg/mL</td>
</tr>
<tr>
<td>2</td>
<td>Neutralized phthalate</td>
<td>5.4</td>
<td>1.26 mg/mL</td>
</tr>
<tr>
<td>3</td>
<td>Phosphate buffer</td>
<td>7.4</td>
<td>0.76 mg/mL</td>
</tr>
<tr>
<td>4</td>
<td>Alkaline borate buffer</td>
<td>8.4</td>
<td>0.12 mg/mL</td>
</tr>
</tbody>
</table>