2. Aim

The aim of the present work was to develop and evaluate time-controlled pulsatile release (PR) formulations of various drugs for the management of early morning chronological attacks such as rheumatoid arthritis (RA), bronchial asthma (BA) and variant angina (VA).

2.1. Specific Objectives

- Development of suitable analytical methods for determination of selected drugs i.e. prednisone (PRS), methylprednisolone (MPR), diclofenac sodium (DIC), diltiazem hydrochloride (DIL), nifedipine (NIF) and lornoxicam (LOR)
- Enhancement of solubility and dissolution rate of poorly soluble drug candidates (i.e. NIF and LOR) employing solid dispersion approach
- Development of fast dissolving immediate release (IR) core tablets
- Development of compression-coated PR formulations exhibiting 4-6 h of lag time followed by burst release profile
- Development of pan-coated PR formulations exhibiting 4-6 h of lag time followed by burst release profile
- *In vivo* pharmacokinetic study
- Short term stability study

2.2. Benefits to the patients and health care system in comparison to conventional IR formulations

- Chronotherapeutic drug delivery as per the circadian rhythm of the disease state improves therapeutic efficacy of the drug molecules.
- Targeting early morning chronological attacks using PR formulation requires relatively lower amount of dose as compared to conventional IR formulation since the effect is delivered only when it is required.
- Lower dose minimizes dose-dependent side effects as well as metabolic load on the body.
- Lower dose also minimizes risk of drug withdrawal effects upon discontinuation of the therapy.
- Rationalizing benefit to risk ratio through better control of the disease.
- Enhancing patient compliance in terms of dosing time/frequency and less sleep disturbances.

2.3. Plan of work

1. Literature survey, selection and procurement of drugs and excipients
2. Development of analytical methods for determination of selected drug substances
3. Development and optimization of compression-coated PR formulations having 4-6 h of lag time followed by burst release profile.
    a. Development of PRS compression-coated tablets (CCTs) employing Quality by Design (QbD) approach
        i. Establishment of Quality Target Drug Profile (QTPP)
        ii. Identification of Critical Quality Attributes (CQAs)
        iii. Initial risk assessment for impact of critical formulation and process parameters on drug product attributes
        iv. Development of fast dissolving IR core tablets
        v. Preliminary investigation and selection of critical formulation ingredients viz. glidant, lubricant, hydrophobic and hydrophilic excipients for fabrication of outer coat
        vi. Statistical optimization of critical formulation and process parameters in order to achieve desired quality traits
        vii. *In vitro* drug release testing of optimized PR CCTs
        viii. Risk mitigation of failure modes after implementation of control strategies
    b. Fabrication of other drug CCTs using above optimized formulation and process parameters
        i. MPR: preparation of IR core tablets followed by their compression coating
        ii. DIC: preparation of IR core tablets followed by their compression coating
        iii. DIL: preparation of IR core tablets followed by their compression coating
        iv. NIF: Development of amorphous solid dispersion (ASD); formulation of fast dissolving IR core tablets; followed by their compression coating
        v. LOR: Development of ASD; formulation of fast dissolving IR core tablets; followed by their compression coating

4. Development of pan-coated PR formulations by employing similar core tablets as well as outer coat ingredients as those of the CCT formulations
    a. *In vitro* drug release testing
    b. *In vivo* pharmacokinetic study using New Zealand White (NZW) rabbits
5. Short term stability studies