ABSTRACT

Background: Arthritis is becoming more prevalent with time in Pakistan. An autoimmune and inflammatory condition, rheumatoid arthritis mostly affects the joints. Since most immune suppressants are injectable, it was very difficult for patients to follow their treatment regimen on a daily basis. Aims: To develop a liquid dosage form with minimal adverse drug reactions (ADRs) associated with immuno-suppressants. Methodology: For this purpose, a combination of aloe vera with anti-inflammatory effects and prednisolone with immunosuppressant effects is used. Firstly, aloe vera extract was taken and blended with distilled water, sweetened with sucralose and added in prednisolone solution along with other excipients. The results of efficacy, density, viscosity and specific gravity were as within ranges. Result: There is no discoloration and cloudiness. The results of efficacy, density, viscosity and specific gravity were as within ranges. Conclusion: Aloe juice has synergistic effects as an anti-inflammatory agent. This combination lessened the ADRs associated with prednisolone, however it doesn’t compromise the therapeutic effects.

Keywords: Prednisolone, Rheumatoid Arthritis, Aloe Vera extract, Immunosuppressant, Anti-inflammatory, Liquid dosage form.
INTRODUCTION

Rheumatoid arthritis (RA) is a symmetric polyarticular arthritis that is characterized by inflammation in the small arthrodial joints of the hands and feet. Along with invading and destroying nearby articular structures, the aggressive tissue front known as pannus also causes inflammation in the synovium, the lining of the joint. The synovium typically has a fragile intimal lining and is a comparatively acellular structure. In RA, CD4+ T cells, B cells, and macrophages invade the synovium and may group into distinct lymphoid aggregates that have germinal centres (1, 3).

Recent studies on rheumatoid arthritis worldwide reveal that Europe and North America have greater rates of arthritis than developing nations. For many years, the West has accumulated prevalence statistics for the main types of arthritic problems, but data from the developing world is just now becoming available. The WHO and ILAR (International League Against Rheumatism) have worked together to collect data for places like the Philippines, China, Malaysia, Indonesia, and rural South Africa, but there is little information available about the prevalence of arthritis in India and Pakistan (2, 4).

For people who prefer liquid prescriptions and don’t like chewing tablets, an oral solution of a medication is superior. Oral solutions are simple to consume and helpful for individuals who may have difficulty swallowing, such as children and the elderly. Drugs that have a bitter or unpleasant taste can be administered in sweetened, coloured, or flavoured carriers. Inappropriately dispersed hygroscopic and deliquescent medications can readily be administered in liquid dose forms. They are manufactured and employed as oral solutions, syrups, elixirs, spirits, and tinctures. The therapeutic ingredients in these formulations are meant to have systemic effects. Since they are typically administered in solution form, this means that they are soluble in aqueous systems and that their absorption from the gastrointestinal tract into the systemic circulation may be anticipated to happen more quickly than when the same medicinal agent is administered in suspension or solid dosage forms (5).

The autoimmune and inflammatory nature of rheumatoid arthritis causes your immune system to mistakenly target healthy cells in your body, which results in inflammation (painful swelling) in the body parts affected. Depending on the severity of your symptoms and the length of time you have had rheumatoid arthritis, you may take non-steroidal anti-inflammatory drugs (NSAIDs), steroids, biologic agents, disease-modifying anti-rheumatic medicines (DMARDs), or a combination of these. An established corticosteroid known for its
potent anti-inflammatory and immunosuppressive effects is prednisolone. Prednisolone works by activating a cytoplasmic glucocorticoid receptor, which causes a nuclear translocation as a result (6).

![Figure 0. Structure of prednisolone (7)](image)

Aloe vera gel has extremely effective anti-inflammatory qualities since it contains compounds like chromone and anthraquinones. It has been demonstrated that ingesting aloe gel (2%) can help lessen the severity of discomfort and the size of sores. Although aloe vera is typically regarded as safe, several adverse effects and difficulties have been noted (8).

**MATERIALS AND METHODS**

**Equipment**

Analytical balance, beakers, glass rod stirrer, graduated cylinder, mortar & pestle, magnetic stirrer, heating mantle, water bath, pycnometer, ostwald viscometer, pH meter, sieve (5).

**Table 0. Required Ingredients**

<table>
<thead>
<tr>
<th>Sr.#</th>
<th>Ingredient</th>
<th>Use</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Prednisolone</td>
<td>Active ingredient (immunosuppressant)</td>
<td>900mg</td>
</tr>
<tr>
<td>2.</td>
<td>Aloe Vera</td>
<td>Anti-inflammatory agent</td>
<td>300ml</td>
</tr>
<tr>
<td>3.</td>
<td>Ethanol</td>
<td>Co solvent</td>
<td>120ml</td>
</tr>
<tr>
<td>4.</td>
<td>Citric Acid</td>
<td>Buffer</td>
<td>436mg</td>
</tr>
<tr>
<td>5.</td>
<td>Sodium citrate dihydrate</td>
<td>Buffer</td>
<td>4.627g</td>
</tr>
<tr>
<td>6.</td>
<td>Propyl paraben</td>
<td>Preservative</td>
<td>1.2g</td>
</tr>
<tr>
<td>No.</td>
<td>Ingredient</td>
<td>Type</td>
<td>Quantity</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------</td>
<td>---------------------</td>
<td>----------</td>
</tr>
<tr>
<td>7.</td>
<td>Glycerin</td>
<td>Sweetening agent</td>
<td>50ml</td>
</tr>
<tr>
<td>8.</td>
<td>Sucralose</td>
<td>Sweetening agent</td>
<td>9g</td>
</tr>
<tr>
<td>9.</td>
<td>D, L Menthol</td>
<td>Flavoring agent</td>
<td>2g</td>
</tr>
<tr>
<td>10.</td>
<td>Benzoic Acid</td>
<td>Preservative</td>
<td>1.8g</td>
</tr>
<tr>
<td>11.</td>
<td>Purified Water</td>
<td>Volume makeup</td>
<td>Quantity sufficient</td>
</tr>
</tbody>
</table>

**Formulation of Oral Solution of Prednisolone**

**Extraction of Aloe Vera Juice**

First of all, wash the aloe vera leaves and dry them. Aloe gel was extracted from them. Blend the white flesh in the blender & make sure there are no lumps in the solution. Now add water in it and mix it well in the blender. The ratio of distilled water to aloe vera gel was 1:3. Aloe vera extract is obtained. Then the extract was filtered by using a mesh-100 and preservative was added in the filtrate (6-9).

**Prednisolone Solution**

Dissolved weighed amount of prednisolone in ethanol. Add glycerin in it to improve the bitter taste of prednisolone.

**Final Formulation**

Sucralose solution was added into the prepared aloe vera extract with constant stirring and then prednisolone solution was added. After that citric acid solution is added in it. Menthol is added as flavoring agent and 0.1% benzoic acid as preservative.

**RESULTS**

**Visual inspection**

Oral solution was clear & free from precipitates. There is no discoloration and cloudiness.

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*Figure 0. Visual inspection of oral solution*
Viscosity
Viscosity was determined by using Ostwald Viscometer.

Results
Density of water=0.96
Density of oral solution= 1.01
Mean time for water= 6.87s
Mean time for oral solution: 11.17s
The viscosity of oral solution =1.5224 cP

pH test
The pH of oral solution was determined by litmus paper. The pH of oral prednisolone solution was determined before and after addition of Aloe Vera extract.

Density Test
The density of prepared formulation was determined by dividing the weight in air of the quantity of the liquid being examined that fills a pycnometer at 20° by the weight in air of water required to filling the pycnometer after making allowance for the thrust of the air.

Results
Volume of oral solution = 58mL
Density of oral solution: = Mass/volume
= 59/58

Density of oral solution = 1.01g/ml
Volume of water =60mL
Density of water = Mass/volume
=58/60
Density of water =0.97g/ml

Specific gravity test
By dividing the weight of a liquid in air at 25° by the weight of an equivalent amount of water at the same temperature, the specific gravity of an oral solution was calculated.

Results
The specific gravity of oral solution =1.01
### Table 0. Determination of viscosity of oral solution

<table>
<thead>
<tr>
<th>Sr #.</th>
<th>Density of water(g/ml)</th>
<th>Density of oral solution(g/ml)</th>
<th>Time for water from point A to B</th>
<th>Time for oral sol. from point A to B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>0.96</td>
<td>1.01</td>
<td>6.88s</td>
<td>11s</td>
</tr>
<tr>
<td>2.</td>
<td>0.96</td>
<td>1.01</td>
<td>6.85s</td>
<td>11.2s</td>
</tr>
<tr>
<td>3.</td>
<td>0.96</td>
<td>1.01</td>
<td>6.87s</td>
<td>11.3s</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td>0.96</td>
<td><strong>1.01</strong></td>
<td><strong>6.87s</strong></td>
<td><strong>11.17s</strong></td>
</tr>
</tbody>
</table>

### Table 4. Determination of PH of solution

<table>
<thead>
<tr>
<th>Formulation</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before the addition of Aloe Vera extract</td>
<td>4-5</td>
</tr>
<tr>
<td>After the addition of Aloe Vera extract</td>
<td>5-6</td>
</tr>
</tbody>
</table>

### Table 5. Determination of Density of oral solution

<table>
<thead>
<tr>
<th>Sr#</th>
<th>Wt. of empty pycnometer + stopper (W1)</th>
<th>Wt. of pycnometer + oral solution (W2)</th>
<th>Wt. of oral solution (W3=W2-W1)</th>
<th>Wt. of pycnometer + water (W4)</th>
<th>Wt. of water (W5=W4-W1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>24</td>
<td>83</td>
<td>59</td>
<td>82</td>
<td>58</td>
</tr>
<tr>
<td>2.</td>
<td>24</td>
<td>82</td>
<td>58</td>
<td>82</td>
<td>58</td>
</tr>
<tr>
<td>3.</td>
<td>24</td>
<td>83</td>
<td>59</td>
<td>81</td>
<td>57</td>
</tr>
<tr>
<td><strong>Average</strong>: 83</td>
<td><strong>Average</strong>: 59</td>
<td><strong>Average</strong>: 82</td>
<td><strong>Average</strong>: 58</td>
<td><strong>Average</strong>: 58</td>
<td><strong>Average</strong>: 58</td>
</tr>
</tbody>
</table>
Table 6. Determination of Specific Gravity of oral solution

<table>
<thead>
<tr>
<th>Sr #</th>
<th>Wt. of empty pycnometer + stopper (W1)</th>
<th>Wt. of pycnometer + oral solution (W2)</th>
<th>Wt. of oral solution (W3=W2-W1)</th>
<th>Wt. of pycnometer +water (W4)</th>
<th>Wt. of water (W5=W4-W1)</th>
<th>Specific gravity (W3/W5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>24</td>
<td>83</td>
<td>59</td>
<td>82</td>
<td>58</td>
<td>1.01</td>
</tr>
<tr>
<td>2.</td>
<td>24</td>
<td>82</td>
<td>58</td>
<td>82</td>
<td>58</td>
<td>1.00</td>
</tr>
<tr>
<td>3.</td>
<td>24</td>
<td>83</td>
<td>59</td>
<td>81</td>
<td>57</td>
<td>1.02</td>
</tr>
<tr>
<td>Mean</td>
<td>24</td>
<td>83</td>
<td>59</td>
<td>82</td>
<td>58</td>
<td>1.01</td>
</tr>
</tbody>
</table>

DISCUSSION

Arthritis is becoming more prevalent in Pakistan with the passage of time. The main difference between osteoarthritis and rheumatoid arthritis is the cause behind the joint symptoms. Rheumatoid arthritis, is an autoimmune and inflammatory disease, mainly attacks the joints, usually many joints at once. As it is an autoimmune disease, so to treat it we need to suppress our immune system. Most of the immunosuppressant’s are in the form of injectable so this was very inconvenient for patients. Oral liquid dosage form is most convenient of all. And some marketed syrups of prednisolone are also available. But they are available at their highest recommended dose. Rheumatoid arthritis is not a curable disease we can only alleviate its symptoms and improve the quality of life of patient. So it is a chronic disease and patient need to administer its medicine for life long. This can also be hazardous for health to suppress the immune system for longer period of time. So, to overcome the ADRs of immunosuppressant’s associated with their dose and duration we modified the treatment by introducing aloe vera juice along with active ingredient (9). In current formulation we used the recommended dose of prednisolone as in BNF which is lower than the dose in marketed syrups. This is done to lessen the ADRs of prednisolone. In addition, we introduced aloe vera juice in it which has proven anti-inflammatory effects and other beneficial effects too (10). So without compromising on the efficacy of the dosage form and the results required for the alleviation of the symptoms of Rheumatoid Arthritis we formulated a dosage form which does not make the body this much weak; prone to infections and gives the desired results. Many studies have shown that aloe vera juice has best anti-inflammatory activity (10, 11). So we formulated an oral solution containing prednisolone as
an active along with aloe vera juice with the dose of 7.5 mg prednisolone and 2.5 ml aloe vera extract in 15 ml of oral solution. Then tests were performed including visual inspection, pH, density, viscosity and specific gravity of oral solution and results were as expected and then assay of final dosage form confirmed the efficacy (11). Finally, it was a dosage form of desired characteristics, in which aim was to minimize the ADRs and maximize the therapeutic effects with effort to make patient more compliant (10-15).

CONCLUSION
The objective of making this dosage form was achieved by using a combination of prednisolone at its moderate dose and aloe vera juice with its synergistic effects as an anti-inflammatory agent. This combination lessened the ADRs associated with prednisolone and but doesn’t compromise the therapeutic effects. So theoretically, a dosage form of desired characteristics is achieved.

Authors’ contributions
SMA contributed to study concept; DS, EH, HT and TT contributed to study design, data collection, data analysis and interpretation, literature review, write and critically review the manuscript. All the authors contributed equally and approved the final version of manuscript.

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DECLARATIONS

Ethics approval
Not applicable.

Competing interests
The authors declare that they have no competing interests

REFERENCES


