1.1 Multi-component system

The concept of multi-component therapy is beneficial when the selected agents possess different mechanism of action that provide additive or synergistic efficacy, reducing the required doses of individual agents compared with monotherapy and potentially limiting side effects. Multi-component therapy may seem costlier than monotherapies in the short term, but causes significant savings: lower treatment failure rate, lower case-fatality ratios, slower development of resistance and consequently, less money needed for the development of new drugs. There are three general categories commonly applicable for multi-component therapy. First category includes individual components, which requires individually e.g., analgesic with antipyretic and beta-blocker with diuretic. The second category is to ameliorate the unwanted pharmacodynamic effects of the active agents like anticholinergic with narcotic reduces the narcotic abuse. The third category includes those combinations that improve the pharmacokinetic properties like coadministration of levodopa and decarboxylase inhibitor greatly reduces the dopamine formation in GIT and outside CNS, which ultimately results in reduction of dose and dosing frequency in levodopa.

Generally the principles involved for the development of combination chemotherapeutic therapy regimens are as follows

- Each single agent should have activity against the disease
The agents should have different mechanisms of action

The agents should have non-overlapping toxicity profiles

The regimen should combine cell cycle specific and cell cycle non-specific agents

Multi-component therapy now is in demand for its more development regarding formulation as well as dosage designing because it has been proved for its effectiveness, affordability and acceptability of dosage regime for a variety of diseases like aids, malaria, joint disorders, pain, hypertension, tuberculosis and diabetes etc. In every country treatment works for the women, men and children so regular monitoring via blood tests, individual drugs and combination drugs studied for longer the length of time, developing resistance and level of cure of disease may provide assessment of combination therapy\textsuperscript{1-2}.

There are several multi-component formulations are available in the market for the treatment of variety of diseases like malaria\textsuperscript{3-18}, AIDS\textsuperscript{19-30}, tuberculosis\textsuperscript{31-40}, bacterial infections\textsuperscript{41-50}, joint disorders, pain, musculoskeletal disorders and pain associated with a range of disorders such as myofascial, refractory pain and neuropathic, chronic tension-type headache and chronic daily headache\textsuperscript{51-56} (Table 1T-1). The therapy for musculoskeletal disorders are effective in reducing pain associated with osteoarthritis, rheumatoid, and other degenerative joints disorders, low back pain, dysmenorrhoea, gynaecological condition, thrombophlebitis, dental pain and inflammations etc. because arthritis is a chronic multifactorial disease induced when the immune system attacks and begins degrading the
body's joints. The disease knows no racial boundaries and comes in many forms, including calcific periarthritis, enteropathic arthritis, chronic, gouty, and hand osteoarthritis, hip and knee osteoarthritis, thumb, Jaccoud's, and juvenile osteoarthritis, oligoarthritis, polyarthritis, and peripheral, psoriatic, rheumatoid and septic arthritis. Rheumatoid arthritis (RA) alone is estimated to affect 1% of the world's population and is twice as prevalent in women as in men. In the US, arthritis and other rheumatic conditions affect about 43 million people, or about 15% of the population, at a total disease burden close to $65 billion. Prescription sales of the various drugs used to control the disease are in excess of $3.5 billion, growing at about 11% annually.\textsuperscript{57}

With such a massive economic and societal burden, it is not surprising that arthritis is a disease in which there is a tremendous amount of research to find effective drugs that focus not only on the symptoms, but also on the causes themselves.

At present, a great deal of attention is being focused on nonsteroidal anti-inflammatory drugs (NSAIDs) based on inhibiting the cyclooxygenase (COX) enzymes. The two isoforms, COX-1 and COX-2, are central to the production of prostaglandins, produced in excess at sites of inflammation. COX-1 synthesizes prostaglandins that are involved in the regulation of normal cell activity, whereas COX-2 produces prostaglandins mainly where inflammation occurs.\textsuperscript{58}

In addition to single-drug clinical trials focusing on new targets, there are other trials that aim to optimize current approaches like combination therapy, specifically comparing various regimens of multi-component therapy in
arthriti. One recent trial involved 199 patients in a multicenter, randomized study with a two-year follow-up, comparing combination therapy (sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone) with a single antirheumatic drug (sulfasalazine or methotrexate) with or without prednisolone in early RA. Here, multi-component therapy was found to be better in causing initial remission in at least a proportion of the patients studied.

Musculoskeletal disorders presents a major socioeconomic burden that has and will continue to attract major research and development efforts aimed at elucidating the basis of the disease as well as developing effective therapies (Table 1T-1). Increasing understanding of the molecular cascades involved are already producing significantly better drugs than in the past with increased selectivity and fewer side effects, and this will continue into the foreseeable future as arthritis is a multifactorial disease that is unlikely to be solved with a magic bullet-type approach. There are several multi-component formulations available in the market containing non-steroidal anti-inflammatory drugs with antipyretic or skeletal muscle relaxants (Table 1T-2). These muscle relaxants are a heterogeneous group of medications used to treat two different types of conditions: spasticity from upper motor neuron syndromes and muscular pain or spasms from peripheral musculoskeletal conditions. Centrally muscle relaxants (CMRs) are used mainly for treating muscle spasticities of neurological origin, and painful muscle spasms due to rheumatologic conditions. Their use is frequently...
associated with dose-limiting adverse effects. New drugs with improved side-effect characteristics are needed\textsuperscript{62}.

1.1.1 Advantages

One of the first indications that the use of more than one agent could be more effective than the use of either agent as monotherapy was in the treatment of gout\textsuperscript{63}, severe infections (e.g. bacterial endocarditis) with combinations of penicillin and an aminoglycoside\textsuperscript{64}. Frusemide and metolazone is still used to produce diuresis in resistant congestive cardiac failure.

The effects of some drug combinations are merely additive rather than synergistic. Nevertheless, the combination produces more efficacy than the use of each single agent alone and this can be of therapeutic benefit e.g., osteoarthritis requires pain management. Combination therapy for acetaminophen and an opioid may maximize pain relief and provide greater speed and duration of action than the separate components\textsuperscript{65}; diclofenac-paracetamol combinations consistently produced a greater reduction in mean pain score than either nonsteroidal antiinflammatory drugs or paracetamol alone\textsuperscript{66}. A survey of current evaluation and treatment of gout showed that 64\% rheumatologists use combination therapy for acute gout; nonsteroidal antiinflammatory drugs alone are used in only 27\%\textsuperscript{63}.

Combinations of medicines with different spectra of adverse drug reactions may therefore allow reduction of dose of each compound to levels that are less likely to produce clinically relevant toxicity and it is most useful in case of cancer therapy. Combination of tumor necrosis factor-alpha with sulindac
augments its apoptotic potential and suppresses tumor growth of human carcinoma cells\textsuperscript{67}.

Combination therapy can prevent the development of resistance in malaria, bacterial infection and AIDS. Development of resistance is an increasing problem for antimalarial chemotherapy because resistance against most available drugs has developed in the majority of worldwide parasite populations. The use of synergistic drug combinations for the treatment of drug-resistant malaria is a major strategy to slow the selection and spread of \textit{plasmodium falciparum} resistant strains\textsuperscript{68-70}.

\textbf{1.1.2 Disadvantages}

The scientific justification for the benefits of combined therapy is still poor because research on this therapies are undergoing and only few randomized placebo-controlled studies have been undertaken to compare the relative merits of monotherapy and combination therapy with respect to efficacy of drugs. Chances of side effects may be greater with combination therapy than monotherapy. For an example, non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of arthritis can increase the risk of peptic ulcer by around four-fold in patient aged 65 years or older.

- Toxicity may be due to the pharmacokinetic interactions.
- Patient compliance is essential to achieve optimal benefit.
- Misuse of medications may be major cause of medication error
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs in combination</th>
<th>Efficacy</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Therapy for Malaria</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1.    | Chloroquine + Sulfadoxine-pyrimethamine  
Amodiaquine + Sulfadoxine-pyrimethamine   | Lower treatment failure rate was observed than monotherapy and efficacies against uncomplicated falciparum malaria                                                                             | 3    |
| 2.    | Chloroquine and Sulfadoxine  
Chloroquine and Pyrimethamine | Lower treatment failure rate than monotherapy and but no significant efficacies against uncomplicated falciparum malaria were observed so recommended artemisinin-based combination                                       | 4.   |
| 3.    | Artemisinin and Curcumin | Additive interaction was observed in killing of Plasmodium falciparum                                                                                                                                       | 5    |
| 4.    | Artemisinin combination therapy | Clearance of gametocytes in uncomplicated Plasmodium falciparum malaria                                                                                                                                 | 6    |
| 5.    | Azithromycin + Quinine | Effective treatment of the uncomplicated Plasmodium falciparum                                                                                                                                             | 7    |
| 6.    | Pyrimethamine + Sulfadoxine (PS) | Predictor of the failure of treatment with PS against (PS)-resistant Plasmodium falciparum malaria                                                                                                           | 8    |
| 7.    | Dapsone + Atovaquone + Chlorproguanil | Strong synergy was observed in the combinations against Plasmodium falciparum                                                                                                                             | 9    |
| 8.    | Artesunate + Mefloquine | Cerebral malaria successfully treated but side effect transient reticulocytopenia was observed                                                                                                                | 10   |
| 9.    | Amodiaquine (AQ) + Sulfadoxine-pyrimethamine (SP), | Highly effective, inexpensive, and available therapy for the treatment of uncomplicated malaria                                                                                                             | 11   |
| 10.   | Amodiaquine (AQ) + Sulfadoxine-pyrimethamine (SP) | AQ plus SP achievd less treatment failure than SP                                                                                                                                                        | 12   |
| 11.   | Artemether-Lumefantrine  
Mefloquine-Artesunate | An Artemisinin-based combination was highly effective and results in equivalent therapeutic responses in the treatment of highly drug-resistant falciparum malaria.                                                | 13   |
| 12.   | Exifone- Vitamin C | Synergistic antimalarial activity was observed                                                                                                                                                             | 14   |
| 13.   | Artesunate plus Amodiaquine (ASAQ) and Artemether-Lumefantrine (AL) | Both treatments were highly efficacious, but AL provided stronger prevention against reinfection                                                                                                          | 15   |
| 14. | Chloroquine (CQ) + Sulfadoxine-pyrimethamine (SP) | Artemisinin-based therapies effectively prevented development of gametocytes, whereas CQ + SP did not. |
| 15. | Chloroquine (CQ) + Sulfadoxine-pyrimethamine (SP) | AQ + AS was the most efficacious regimen for preventing recrudescence, but this benefit was outweighed by an increased risk of new infection. |
| 16. | Artesunate + Clindamycin | The activity of artemisinin-based therapies effectively prevented development of gametocytes, whereas CQ + SP did not. |
| | Quinine + Clindamycin | AQ + AS was the most efficacious regimen for preventing recrudescence, but this benefit was outweighed by an increased risk of new infection. |

### B: Therapy for AIDS

| 17 | Stavudin (80 mg) + Lamivudin (600 mg) + Nevirapin (400 mg) + Zidovudin (600 mg) | Significant (p < 0.05) reduction in the plasma concentration of protein sulfhydryl groups was observed |
| 18 | Plasmid-derived IL-21+ IL-15 gene | Plasmid-delivered IL-21 and IL-15 increases the magnitude of the response to DNA vaccines. |
| 19 | Combination Drugs | Since resistance can develop against a specific drug designed to inhibit only one stage of the viral cycle, combinations of drugs directed at more than one step have proven to be more effective than a single drug given alone. |
| 20 | Combination of the non-nucleoside reverse transcriptase inhibitor nevirapine (NVP), and two nucleoside reverse transcriptase inhibitors, Stavudine (d4T) and Lamivudine (3TC) | The combination of nevirapine, 3TC and d4T was as efficacious as a combination of efavirenz, 3TC and d4T. Once-daily NVP with twice-daily 3TC and d4T is as efficacious as twice-daily NVP, 3TC and d4T. However, toxicity may be increased in the once-daily NVP regime. |
| 21 | Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) chemotherapy+ highly active antiretroviral therapy (HAART) | Therapy was safe and improves survival of patients with acquired immunodeficiency syndrome-related lymphoma (ARL) |
| 22 | Antiretroviral treatment (HAART) and other combination antiretroviral therapies | Positive association between social support and use of highly active antiretroviral treatment (HAART) and other combination antiretroviral therapies was contingent upon disclosure of HIV status within the household or among friend and acquaintance networks |
| 23 | Double nucleoside (NRTI) backbone plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir pharmacologically enhanced protease inhibitor (PI/r). | Triple NRTI combinations were less potent than 2NRTIs/NNRTI or 2NRTIs/PI/r combinations. | 25 |
| 24 | Growth factors and Cytokines + HAART | Cytokines acts synergistically with antimicrobial agents to improve outcomes, which is of particular importance since recurrent infections frequently result in resistance to standard antimicrobial treatments. | 26 |
| 25 | Interferon-gamma and interferon-2 | Use of a combination of interferon-gamma and interferon-2 resulted in a remarkable improvement in the patient's condition, accompanied by an increase in circulating CD4+ T cells. | 27 |
| 26 | Nelfinavir (NFV) + Ritonavir (RTV) + Buffered Didanosine (DDI) | Combination therapy containing NFV + RTV + DDI appeared more efficacious | 28 |
| 27 | Fenofibrate and Pravastatin | Combination therapy with fenofibrate and pravastatin for HIV-related dyslipidemia provided substantial improvements in lipid parameters and appears safe. | 29 |
| 28 | Paromomycin+ Azithromycin + Antiretroviral therapy (HAART) | Respiratory cryptosporidiosis investigated in HIV-infected patients with pulmonary symptoms and low CD4 cell count, and, if detected, treatment should include HAART plus the combination of paromomycin and azithromycin. | 30 |

**C: Therapy for Tuberculosis**

<p>| 29 | Rifampicin and Rifabutin | Rifabutin might be a valid component of combination therapy in rifampicin resistant tuberculosis. | 31 |
| 30 | Isoniazid and Rifampicin | Pulmonary tuberculosis could be cured. However, if tubercle bacilli are resistant to isoniazid and rifampicin, the success rate of medical treatment falls considerably. | 32 |
| 31 | Isoniazid and Imipenem | Significantly reduced the numbers of M. tuberculosis organisms in lungs and spleens and improved survival of mice. | 33 |
| 32 | Linezolid in combination regimens | Peripheral neuropathy and bone marrow depression led to linezolid withdrawal | 34 |
| 33 | Lentinan+ BCG vaccine | Pre-treatment with Lentinan enhanced the local immunohistological response to BCG in lung and reduced the generalized side effects. | 35 |</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Combination of Antituberculosis therapy</td>
</tr>
<tr>
<td>35</td>
<td>Multigene TB DNA immunotherapy including Ag85A and PstS-3 genes + normal chemotherapy</td>
</tr>
<tr>
<td>36</td>
<td>16α-Bromoepiandrosterone (EpiBr) + Conventional therapy.</td>
</tr>
<tr>
<td>37</td>
<td>Immunotherapy with a plasmid DNA encoding the Mycobacterium leprae 65 kDa heat-shock protein (hsp65) + antibiotics</td>
</tr>
<tr>
<td>38</td>
<td>Polychemotherapy + Laser radiation</td>
</tr>
<tr>
<td></td>
<td><strong>D: Therapy for bacterial infection</strong></td>
</tr>
<tr>
<td>39</td>
<td>Beta-lactam antibiotic plus an aminoglycoside</td>
</tr>
<tr>
<td>40</td>
<td>Rifampicin + Clarithromycin</td>
</tr>
<tr>
<td>41</td>
<td>Beta-lactam + Vancomycin (VCM) Beta-lactam + Teicoplanin (TEIC)</td>
</tr>
<tr>
<td>42</td>
<td>Daptomycin + Vancomycin, + Rifampin</td>
</tr>
<tr>
<td>43</td>
<td>Cefotaxime, Ceftriaxone and high doses of Amoxicillin</td>
</tr>
<tr>
<td>44</td>
<td>Fortified amikacin + Clarithromycin 1%, and a fourth-generation Fluoroquinolone</td>
</tr>
<tr>
<td>Page</td>
<td>Text</td>
</tr>
<tr>
<td>------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>45</td>
<td><strong>Topical benzoyl peroxide, antibiotics (erythromycin or clindamycin) and Azelaic acid</strong>&lt;br&gt;Azelaic acid is naturally present, systemic side effects are not likely to occur, making it safe for acne treatment during pregnancy and lactation.</td>
</tr>
<tr>
<td>46</td>
<td><strong>Beta-lactam and Macrolide</strong>&lt;br&gt;Low-risk patients shall receive a monotherapy with, e.g., amoxicillin, high-risk patients should be treated with a broad-spectrum combination therapy (beta-lactam and macrolide) against pneumonia.</td>
</tr>
<tr>
<td>47</td>
<td><strong>Esomeprazole, Amoxicillin and Clarithromycin</strong>&lt;br&gt;Clarithromycin decreases the metabolism rate of esomeprazole, leading to approximately doubled AUC values, both in healthy CYP2C19 extensive metabolizers (Ems) and CYP2C 19 poor metabolizers (PMs).</td>
</tr>
<tr>
<td>48</td>
<td><strong>Colistin and Rifampicin</strong>&lt;br&gt;Nosocomial pneumonia caused by multiresistant Acinetobacter baumanii treated by colistin and rifampicin.</td>
</tr>
<tr>
<td></td>
<td><strong>E: Therapy for Arthritis</strong></td>
</tr>
<tr>
<td>49</td>
<td><strong>Prednisolone+ Methotrexate+ Sulfasalazine (SSZ)</strong>&lt;br&gt;Step-down combination therapy with prednisolone, methotrexate, and sulfasalazine (SSZ) was superior to SSZ monotherapy for suppressing disease activity and radiologic progression of rheumatoid arthritis (RA).</td>
</tr>
<tr>
<td>50</td>
<td><strong>Sulphasalazine (SSZ) + Methotrexate (MTX)+ Prednisolone</strong>&lt;br&gt;Significantly better clinical outcomes at week 28 compare to SSZ alone.</td>
</tr>
<tr>
<td>51</td>
<td><strong>Cyclosporine+ Methotrexate (MTX)</strong>&lt;br&gt;Significant steroid sparing effect and have shown that combination therapy with MTX does not increase side effects and allows for a decrease in MTX dose.</td>
</tr>
<tr>
<td>52</td>
<td><strong>Methotrexate, Gold salts, anti-malarials, d- Penicillamine and Salazopyrine (SAARDs)</strong>&lt;br&gt;Treatment with two or more SAARDs, may be feasible since an additive/synergistic effect may be obtained. Methotrexate in combination with salazopyrine and hydroxychloroquine or in combination with cyclosporine may cause a better therapeutic effect than methotrexate alone, without additional toxicity.</td>
</tr>
<tr>
<td>53</td>
<td><strong>Diclofenac and Cyclosporine</strong>&lt;br&gt;Diclofenac can be safely combined with cyclosporine in the management of RA when appropriate clinical monitoring and dose titrations are performed. Due to the pharmacokinetic interaction that increases diclofenac systemic exposure.</td>
</tr>
<tr>
<td>54</td>
<td><strong>Diclofenac sodium (DS)+ Misoprostol/</strong>&lt;br&gt;Combination of HSV and misoprostol offers significant protection only to gastric mucosa.</td>
</tr>
</tbody>
</table>
Table 1T-2: Non steroidal anti-inflammatory combinations available in market

<table>
<thead>
<tr>
<th>S. No</th>
<th>Type of combinations</th>
<th>Onset of actions</th>
<th>Duration of actions</th>
<th>Indications</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Ibuprofen</strong>&lt;br&gt;Ibuprofen S.R. 600 mg&lt;br&gt;Ibuprofen 400 mg + paracetamol 500mg&lt;br&gt;Ibuprofen 400 mg + paracetamol 325 mg&lt;br&gt;Ibuprofen 400 mg + paracetamol 650 mg&lt;br&gt;Ibuprofen 400 mg + paracetamol 500 mg + magnesium trisilicate 50 mg&lt;br&gt;Ibuprofen 400 mg + paracetamol 500 mg + caffeine 65 mg&lt;br&gt;Ibuprofen 200 mg + paracetamol 500 mg&lt;br&gt;Ibuprofen 400 mg + paracetamol 333 mg</td>
<td>Analgesic effect: 30 Min.&lt;br&gt;Anti-inflammatory effect: 7 days</td>
<td>4-6 hrs</td>
<td>Rheumatoid arthritis, ankylosing spondilitis, cervical spondilitis, primary dysmenorrhoea</td>
<td>400 mg t.i.d. S.R. preparation: b.i.d.</td>
</tr>
<tr>
<td>2</td>
<td><strong>Flurbiprofen</strong>&lt;br&gt;Flurbiprofen 100 mg&lt;br&gt;Flurbiprofen 200 mg (S.R)</td>
<td>30-60 min</td>
<td>8-12 hrs.</td>
<td>Rheumatoid arthritis, ankylosing spondilitis, cervical spondilitis, primary dysmenorrhoea Post operative analgesia</td>
<td>50-100 mg. t.i.d S.R.: Once daily</td>
</tr>
<tr>
<td>3</td>
<td><strong>Ketoprofen</strong>&lt;br&gt;Ketoprofen 50 mg + Analgin 50 mg</td>
<td>30 min</td>
<td>6-8 hrs</td>
<td>Rheumatoid arthritis, gout, capsulitis of shoulder, primary dysmenorrhoea, analgesia</td>
<td>100-150 mg in div. doses. Max: 300 mg daily</td>
</tr>
<tr>
<td>4</td>
<td><strong>Naproxen</strong>&lt;br&gt;Naproxen 250 mg&lt;br&gt;Naproxen 500 mg&lt;br&gt;Naproxen 750 mg (S.R.): Daily</td>
<td>Analgesic effect: 30 Min.&lt;br&gt;Anti-rheumatic effect: 2 weeks</td>
<td>7 hrs.</td>
<td>Rheumatoid arthritis, ankylosing spondilitis, cervical spondilitis, primary dysmenorrhoea acute gout, pelvic inflammation, tooth extraction, tendonitis, bursitis, juvenile arthritis</td>
<td>200 mg b.i.d. Gout: 700 mg Initially then 250 mg 8 hourly</td>
</tr>
<tr>
<td>5</td>
<td><strong>Mefenamic acid</strong>&lt;br&gt;Mefenamic acid 250 mg+ Acetaminophen 500 mg&lt;br&gt;Mefenamic acid 500 mg +acetaminophen</td>
<td>1-2 hrs.</td>
<td>6 hrs.</td>
<td>Rheumatoid arthritis, ankylosing spondilitis,</td>
<td>200-500 mg t.i.d.</td>
</tr>
<tr>
<td>6</td>
<td>Phenyl butazone</td>
<td>Analgesic effect: 2 hrs. Anti-rheumatic effect: 3-4 days</td>
<td>Some effect last for 3-4 days</td>
<td>Rheumatoid arthritis, ankylosing spondylitis, rheumatic fever, osteoarthritis, after blunt injuries, fractures, tooth extraction, vasectomy, acute gout.</td>
<td>200mg t.i.d.</td>
</tr>
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</tr>
<tr>
<td>7</td>
<td>Oxyphenbutazone</td>
<td>1-2 hrs.</td>
<td>Some effect last for 2 days</td>
<td>Rheumatoid disorder, inflammation</td>
<td>100 mg t.i.d</td>
</tr>
<tr>
<td>8</td>
<td>Indomethacin</td>
<td>Analgesic effect: 30 min. Anti-rheumatic effect: 4-6hrs.</td>
<td>4-6 hrs.</td>
<td>Rheumatoid arthritis, ankylosing spondylitis, gout.</td>
<td>25-50 mg t.i.d. 75-100 mg daily (S.R.)</td>
</tr>
<tr>
<td>9</td>
<td>Diclofenac</td>
<td>Analgesic effect: 1 hrs. Anti-rheumatic effect: 2 weeks.</td>
<td>Up to 12 hrs. Up to 24 hrs. (S.R.)</td>
<td>Rheumatoid arthritis, ankylosing spondylitis, cervical spondylitis, primary dysmenorrhea post operative analgesia</td>
<td>100-500 mg daily; In divided dose</td>
</tr>
<tr>
<td>10</td>
<td>Piroxicam</td>
<td>Analgesic effect: 1 hrs. Anti-rheumatic effect: 7-12 days.</td>
<td>48-72 hrs</td>
<td>Rheumatoid arthritis, ankylosing spondylitis, cervical spondylitis, primary dysmenorrhea post operative analgesia</td>
<td>20 mg daily In gout: 40 mg daily Post operative analgesia: 40 mg</td>
</tr>
<tr>
<td>11</td>
<td>Acelofenac</td>
<td>1-3 hrs</td>
<td>Rheumatoid arthritis, ankylosing spondylitis.</td>
<td>100 mg b.i.d</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Tenoxicam</td>
<td>1-2 hrs 24 hrs</td>
<td>Rheumatoid</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug</td>
<td>Dose</td>
<td>Frequency</td>
<td>Indications</td>
<td></td>
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</tr>
<tr>
<td>13</td>
<td>Meloxicam</td>
<td>Meloxicam 7.5 mg + Paracetamol 325 mg</td>
<td>5-6 hrs</td>
<td>Rheumatoid arthritis, ankylosing spondilitis, osteoarthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Celecoxib</td>
<td>Celecoxib 100 mg</td>
<td></td>
<td>Rheumatoid arthritis, osteoarthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Celecoxib 200 mg</td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>Rofecoxib</td>
<td>Rofecoxib 12.5 mg</td>
<td></td>
<td>Osteoarthritis, acute pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rofecoxib 25 mg</td>
<td></td>
<td>(dental pain, and primary dysmenorrhoea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rofecoxib 50 mg</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Rofecoxib 25 mg + Paracetamol 500 mg</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>16</td>
<td>Valdecoxib</td>
<td>Valdecoxib 40 mg (in betacyclodextrin)</td>
<td>Analgesic effect: 30 min</td>
<td>Rheumatoid arthritis, osteoarthritis, Rheumatoid arthritis: 10 mg once a day. dysmenorrhoea: 20-40 mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valdecoxib 20 mg + Paracetamol 500 mg</td>
<td>Anti-rheumatic effect: 7-12 days.</td>
<td></td>
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<tr>
<td>17</td>
<td>Etoricoxib</td>
<td>Etoricoxib 60 mg</td>
<td></td>
<td>Rheumatoid arthritis, osteoarthritis, pain, acute pain gout arthritis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Etoricoxib 90 mg</td>
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<td></td>
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<td>Etoricoxib 120 mg</td>
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</tr>
<tr>
<td>18</td>
<td>Nimesulide</td>
<td>Nimesulide 100 mg</td>
<td>30-60 min</td>
<td>Rheumatoid arthritis, osteoarthritis, dysmenorrhoea, postoperative analgesia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Nimesulide 100 mg + paracetamol 350 mg</td>
<td>8-10 hrs</td>
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<td></td>
<td></td>
<td>Nimesulide 100 mg + Serratiopeptidase 15 mg</td>
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<td></td>
<td></td>
<td>Nimesulide 100 mg +</td>
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<td>Paracetamol 500 mg</td>
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<tr>
<td>Nimesulide 100 mg + serratiopeptidase 10 mg</td>
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<tr>
<td>Nimesulide 100 mg + Diclofenac sod. 50 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nimesulide 100 mg + paracetamol 400 mg + dextropropoxyphene 32.5 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>reduction of pain of ear, nose, throat</td>
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Research, development, and sales of drug-delivery systems are increasing at a rapid pace through the world. This worldwide trend will intensify in the next decades as cuts in public health expenses demand lower cost and higher efficacy. To meet this demand, many efficient drugs currently in use will be reformulated within delivery system that can be value-added for optimal molecular activity. In addition to the health sector, the cosmetic, agricultural, chemical, and food industries operate in an open market place where free and aggressive competition demands novel coating techniques with enhanced effectiveness at the lowest possible cost. Currently, microparticulate systems are most widely used in the development and production of improved – drug and food-delivery system. The microparticulate delivery systems include mainly pellets, microcapsules, microspheres, lipospheres, emulsions and multiple emulsions. Generally, the microparticulate delivery systems are intended for oral and topical use. Different types of coated particles can be obtained depending on the coating process used. The particles can be embedded within a polymeric or proteinic matrix network in either a solid aggregated state or a molecular dispersion, resulting in the formulation of microspheres. Alternatively, the particles can be coated by a solidified polymeric or proteinic envelope, leading to the formation of microcapsules. The profile and kinetic pattern governing the release rate of the entrapped active substance from the dosage form depend on the nature and morphology of the coated particles, which need to be established irrespective of the manufacturing method used. Until now, the use of some interesting and promising therapeutic substances has been
limited clinically because of their restrictive physicochemical properties, which have required frequent administration.

Investigators have been trying to develop delivery systems that allow the fate of a drug to be controlled and the optimal drug dosage to arrive at the site of action in the body by means of novel microparticulate dosage forms. During the past two decades, researchers have succeeded in part in controlling the drug absorption process to sustain adequate and effective plasma drug levels over a prolonged period of time by designing delayed or controlled release microparticulate delivery systems intended for either oral or parenteral administration.

Conventional drug therapy of these above formulations involves the periodic dosing of a therapeutic agent that has been formulated to ensure stability, activity and bioavailability of the active pharmaceutical ingredient (API). Nevertheless, many drugs present difficulties when administered by conventional methods due to toxicity and low therapeutic index problems. Controlled-release or sustained release systems have been designed to maintain plasma drug levels in the therapeutic range and thus minimize the effects of such problems\(^{71,72}\).

### 1.2 Design of controlled-release systems

The rate of drug input into the body or dosing rate is determined by the rate of drug release from the delivery device. Multiple kinetic models and equations can be used to describe the drug release kinetics from controlled release systems, but formulations that give zero-order drug release in vivo are widely accepted as ideal form many drug therapies\(^{73}\). However,
controlled-release products have been studied to produce many different release profiles. Systems exhibiting first-order drug release kinetics are also frequently employed to achieve the goals of controlled drug release therapies. Thus, a zero- or first-order release model is often considered when calculating the desired drug release kinetics\textsuperscript{74}. The controlled drug release system is then formulated and developed to achieve the desired drug release profile\textsuperscript{75}. Although there are significant differences in the design and composition of marketed controlled-release dosage forms, these preparations can be broadly categorized as either single or multiple unit dosage forms.

1.2.1 Single unit dosage forms

Single unit dosage forms are defined as delivery systems that consist of one unit that contains a single dose of the drug and intended to be administered singularly\textsuperscript{71}. Many single unit dosage forms have been developed for the controlled-release of bioactive materials. The most widely investigated example is the monolithic matrix-based tablet\textsuperscript{76-78}. The advantages of this dosage form include high drug loading and the availability of well-characterized and cost-effective production methods. Drug release from these systems is controlled by a variety of mechanisms, including drug diffusion, tablet erosion, matrix swelling or a combination of these mechanisms. Film-coated and osmogen controlled single unit dosage forms have also been studied for modified release applications\textsuperscript{79, 80}. 
1.2.2 Multiple unit dosage forms

The concept of the multiple unit dosage form was introduced in the early 1950s. These solid dosage forms consist of a multiplicity of small discrete particulates, which include mini-tablets, pellets and granules. These systems provide flexibility during formulation development and therapeutic benefits to patients. A significant advantage of multiparticulates is that they can be divided into desired doses without formulation or process changes. They can also be blended to deliver simultaneously incompatible bioactive agents or particles with different drug release properties. Furthermore, these dosage forms are less susceptible to dose dumping than the reservoir or matrix type, single unit tablet since the drug release profile does not depend on the drug release properties of a single unit. Microparticulate offer advantages as constitutes of multiple unit dosage forms since studies have indicated that they are rapidly and evenly dispersed in the gastrointestinal tract upon oral administration, thus maximizing drug absorption and reducing inter- and intra-subject variability due to differences in gastric emptying rates. Microparticles can be filled into hard gelatin capsules or compressed into tablets.

1.2.3 Modified release dosage forms

In recent years there has been an accelerating interest in the development of modified release formulations. Such interest is based largely on the fact that modified release drugs products have established and retained a place in the market based on their uniqueness and their clinical advantage in the practice of medicine. In order to treat a disease effectively, the drug dose
regimen should be scheduled in such a way that the plasma level does not decrease below the minimum effective concentration. However frequent administration is a burden to a patient. Thus, ways to maintain an effective plasma level for a long period of time are often desired to increase patient compliance. Some dosage forms are designed for rapid and complete release of their medicament in body, where as other product are designed to release the drugs slowly to give sustained drug action. Thus the absorption rate of drug into the body can be decrease from the dosage form. These products have been referred to as sustained release, sustained action, prolonged action, controlled release, extended release, timed release, depot and respiratory dosage forms.

The compendia describe all such dosage forms under one category as modified release dosage forms. In other words all such drug delivery system can be called as non-immediate release delivery system. It is classified into two categories.

1.2.3.1 Extended release dosage forms

They are defined as those that allow at least a two-fold reduction in frequency of dosing compared to the drug presented in conventional form (solutions or fast releasing conventional solid dosage form) e.g. these dosage forms are also known as timed release or prolonged release dosage forms. Extended release dosage forms can be classified into the following three types.
1. Sustained Release or Controlled Release Formulation: Controlled release systems maintain a constant drug level in blood or target tissue.

2. Prolonged Release Formulations: It extends the duration of action.

3. Repeat Action: Repeat action oral dosage form is designed to release the equivalent of a usual single dose of the drug at the same time later.

1.2.3.2 Delayed release dosage forms

They are defined as those that release a drug (or drugs) at any time other than promptly after administration e.g. enteric-coated prodrugs. In oral sustained release drug delivery systems, the time of drug release critically depends on the residence time of a dosage form in the GIT, therapeutic concentration and pharmacokinetics characteristics of the drug. Different colloidal carrier systems are now days widely used for obtaining target specificity and sustained action. These include emulsions/multiple-emulsions, microcapsules, polymeric microparticles, nanoparticles, macromolecular complex and liposome etc. Being fluidized system, colloidal carriers overcome the limitations or residence time due to gastric emptying.

The desirable attributes of a colloidal drug delivery system are-

- It should bind the drug reversibly so as to carry it intact to the site of action and then release it at a controlled rate.

- It should be compatible and/or biodegradable with non-toxic end product.
• It should be pharmaceutically acceptable with respect to the ease of presentation as dosage form, high drug loading and stability.

1.3 **Microparticulate drug delivery systems**

Microparticulates are drug-loaded small polymeric particles (erodible, nonerodible or ion-exchange resins) that could be delivered as solids or suspended in a liquid carrier medium. They include microspheres, spheroids and/or pellets. Microparticulate systems have been employed in different medical and engineering applications (87-92). In the field of medicine, this delivery system (especially in radiolabeled form) has been used in different disorders in form of diagnostic tools for functional imaging of lungs, reticuloendothelial system, gastrointestinal system, inflammatory lesions and tumors. Several distinct approaches have been used to formulate drugs as microparticulate delivery system for oral, intraocular and topical applications. These include erodible microparticles, swelling mucoadhesive microparticles, pH responsive microparticles, nanoparticles/latex systems and ion-exchange resins, etc. In ophthalmology, ocular delivery of microparticles has been shown to improve bioavailability at the target site, and reduce the potential for ocular and systemic side effects. In this regard, the delivery system was used topically as controlled drug delivery in vitreoretinal disorders (Some of the major causes of blindness in the developed world), to reduce frequency of intravitreous application (via injection) and optimize intraocular drug levels. This minimizes the risk of complications that can occur from frequent intravitreous injection. Microparticles are used therapeutically mostly for
immediate and sustained release drug delivery. Microparticulates may be of varying diameter depending on the application and the goal of the formulator. The microparticles could be classified into two classes according to general structures exist i.e., microcapsules and microspheres.

1.3.1 Microcapsules

A microcapsule is a system that contains a well-defined core and a well-defined envelope: the core can be solid, liquid, or gas; the envelope is made of a continuous, porous or nonporous, polymeric phase. Figure 1F-1 (a) shows the different microcapsule configurations; the drug can be dispersed inside the microcapsule as solid particulates with regular or irregular shapes. Other forms may consist of a pure or dissolved solution, suspension, and emulsion. Specific applications sometimes require modifications, e.g., when proteins are encapsulated they may contain stabilizers as well as the active ingredient. Also, the core can be something other than a chemical meant for release. An interesting application is the encapsulation of gases for the use of ultrasonic imaging. Alternatively, a microsphere is a structure made of a continuous phase of one or more miscible polymers in which particulate drug is dispersed, at either the macroscopic (particulates) or molecular (dissolution) level (Figure1F-1b). However, the difference between the two systems is the nature of the microspheres matrix, in which no well-defined wall or envelope exists. Different methods of encapsulation result, in most cases, in either a microcapsule or microspheres. For example, interfacial polymerizational most always produces a microcapsule, whereas solvent
evaporation may result in a microspheres or a microcapsule, depending on the amount of loading.

![Diagram of microcapsules and microspheres configurations]

**Figure 1F-1: Various Configurations of (a) Microcapsules and (b) Microspheres**

### 1.3.2 Microspheres

Microspheres based drug delivery systems have received considerable attention in recent years. The most important characteristic of microspheres is the microspheres separation morphology, which endows it with a controllable variability in the degradation rate and also drug release. There is growing interest in the development of homogeneous monolithic drug release systems for various routes of administration. One very attractive types of such dosage form is microspheres. The considerable interest in using polymer based microspheres as drug carrier is due to following reasons.93
(a) Microspheres improve the safety and efficiency of bioactive agents.
(b) Desired release pattern can be engineered.
(c) Flexibility in design and development.
(d) Better patient compliance.

Microspheres are solid spherical particles containing dispersed drug in light solution or microcrystalline form. They are ranging in size from 1 to 1000 µm. They are made of polymeric, waxy or other protective materials like biodegradable synthetic polymers and modified natural products such as starches, gums, proteins and fats. Protein and polysaccharides microspheres have been extensively investigated for targeted drug delivery. Natural polymers have the advantage that they have less toxicity problems of their own. Majority of the natural polymers are susceptible to biodegradation and are generally biocompatible. A major problem with biopolymers is the presence of antigenic determinants in them. Biopolymers also differ in their molecular wt. and their physical and chemical properties to varying extents depending on the source and method of isolation and purification.

1.3.2.1 Microspheres based on biodegradable polymers

Biodegradable microspheres can be prepared from synthetic as well as natural polymers. An important requirement of such polymers is that the degradation products should be non-toxic because such products eventually enter systemic circulation or result in tissue deposition.

1.3.2.2 Microspheres as drug carriers
The most important characteristics of microspheres are the microphase separation morphology, which endows it with a controllable variability and degradation rate and also drug release. Advantage of microspheres based carriers is that they could be injected into the body in a suitable vehicle.\textsuperscript{98} Polypeptide undergoes enzymatic degradation while synthetic polyesters such as poly (lactic acid) and poly (glycolic acid) degrade mostly by simple hydrolysis.\textsuperscript{99-100}

1.3.2.3 Principle for microspheres

The preparation of microspheres should satisfy certain principle. They are:

- Controllable particle size & dispensability in aqueous vehicle for injection.
- Release of active agent with good control over a wide time scale.
- Susceptibility to chemical modification.
- Stability of preparation after synthesis with clinically acceptable shelf life.
- The ability to incorporate reasonably high concentration of the drug.
- Biocompatibility with a controllable biodegradability.\textsuperscript{101}

The preparation of microspheres from natural polymers involves three steps. First, the solution of the polymer is dispersed in a continuous medium such as vegetable oil or an organic solvent using a suitable stabilizing agent. Dispersion is accomplished using mechanical stirring or by ultrasonication or by high-speed homogenization depending on the particle size required. The second step involves the hardening of the polymer droplets either by heat denaturation (in the case of proteins) or by chemical cross-linking using
suitable cross-linking agent. The third step involves separation of the solid microspheres formed, purification and drying$^{102}$.

1.3.2.4 Drug incorporation

Drugs are incorporated into the microspheres either during their synthesis or after the microspheres are formed. High loading can be achieved by in-situ loading if the drug is insoluble in the dispersion medium employed for microsphere stabilization. Washing the microspheres after their preparation to remove surfactants, oils, other impurities etc., using solvents in which the drug solubility is high may result in poor loading efficiency. If the drug is heat sensitive, the resulting drug loaded microspheres cannot be sterilized by heat.

Loading into preformed microspheres has the advantage of removing all impurities from microspheres preparation before the drug is incorporated. A high payload of water-soluble drugs can be obtained if the microsphere is hydrophilic and swells to a high degree in aqueous solution. The method allows the most native form of the drug to be incorporated into the matrix$^{103-104}$.

1.3.2.5 Drug-polymer binding

The binding force that holds the drug to the microsphere matrix can either be physical or chemical. In addition to this, hydrophobic and electrostatic interaction may also exist and depending on the force of attachment, drug release from the matrix also varies. The drug release is expected to be faster if only physical entrapment is achieved. Drug release in such cases is modulated by a diffusion-controlled mechanism$^{105}$. Slow release can be
achieved by chemically binding the drug to the microsphere matrix. The polymeric matrix should have reactive functionalities to which the drug can be bound through a functionally available on the drug.

There are various methods for attaching drugs to the matrix. In the case of protein microspheres, certain drugs bind strongly to the matrix without covalent attachment. Albumin and casein microspheres were found to show this behaviour with certain cytotoxic drugs such as methotrexate, mitoxantron and 5-fluorouracil etc.$^{106-107}$.

1.3.2.6 Route of administration

Microspheres can be used for the delivery of drugs via different routes. Route of administration is selected depending on the drug properties, disease state being treated and the age and condition of the patient. Desirable properties of the microspheres to be used for the delivery will also change depending on the route of administration.$^{108}$

1.3.2.6.1 Oral delivery

It is the simplest way of drug administration and in this the microspheres have to pass through frequently changing environments in the GI tract. There is also patient-to-patient variation in GI content, stomach emptying time and peristaltic activity. The relatively brief transit time of about 12 h through the GI tract limits the duration of action that can be expected via the oral route. Recently, it has been reported that microspheres of less than 10mm in size are taken up by the Peyer's patches and may increase the retention time in the stomach. Although constraints of the oral route are
numerous, on the whole, it offers less potential danger than the parenteral route\textsuperscript{109}.

1.3.2.6.2 Parenteral delivery

Most of the microsphere based controlled delivery systems are developed with the aim of using them for parenteral administration. Drug released is completely absorbed in this case. Microspheres used for parenteral delivery should be sterile and should be dispersible in a suitable vehicle for injection. Hydrophilic microspheres have the potential advantage of aqueous dispersibility as opposed to hydrophobic microspheres for reconstituting them for injection\textsuperscript{110}.

Knowledge of the fate of microspheres after parenteral administration is very important in designing a drug delivery system. The biological fate of the administered particles has been studied by radio labelled techniques where \textsuperscript{14}C, \textsuperscript{131}I, \textsuperscript{125}I and \textsuperscript{99}Tc have been used for labeling\textsuperscript{111}.

1.4 Application of microparticulate system

1.4.1 In sustained and controlled release

Microparticles can be designed to release their ingredients at specific rate. This is most recent addition to oral prolonged release as well as sustained released dosage forms of drugs such as theophylline, indomethacin, chlorothiazide\textsuperscript{112}, aspirin, diclofenac sodium \textsuperscript{113}, renin inhibitor FK906 (tripeptide)\textsuperscript{114}, tofizopam\textsuperscript{115} and chloramphenicol\textsuperscript{116}.

1.4.2 To mask bitter or unpleasant taste of the drug

Various microencapsulated dosage forms were prepared by using polymers like gelatin; Eudragit resins L-100, S-100, E-100, RS-100, hydroxyl-
propylcellulose, mixtures of ethylcellulose and hydroxypropylmethylcellulose in order to mask the undesirable taste of diclofenac sodium, cefuroxime axetil, enoxacin, remoxipride, sparfloxacin, clarithromycin and beclamide etc.\textsuperscript{117-124}.

**1.4.3 Alter the residence time and to improve the bioavailability**

Reverse micellar solutions of diclofenac sodium encapsulated in soft gelatin capsules increased the mean residence time (parameter of sustained release) of the capsules as compared to conventional suppositories\textsuperscript{125}, thiolated polymer polycarbophil-cysteine (PCP-Cys) also increased mean residence time due to better mucoadhesion properties \textsuperscript{126}. Albumin and gelatin microspheres containing pilocarpine nitrate (ophthalmic drug delivery) for delivery in eye, increased residence time of drug in the eye, and provide improved bioavailability.

**1.4.4 In enteric release dosage form**

Enteric-coated microcapsule designed to achieve intestinal targeting for drugs irritant to the stomach or detioriate under acidic environment like paracetamol\textsuperscript{127}, alpha-tocopherol\textsuperscript{128}, theophylline, chlorothiazide and indomethacin\textsuperscript{112} etc. These microcapsules would be structurally resistant against acidic environment, and it would rapidly release core material under alkali condition.

**1.4.5 Drug targeting**

Lung targeted albumin loaded tetrandrine sustained-release drug delivery system by microencapsulation, decreased the toxicity and enhanced the therapeutic function of anti-pulmonary hypertension of tetrandrine\textsuperscript{129}. Casein
and gelatin microspheres containing adriamycin and interferon’s respectively were magnetically delivered to tumor site. Albumin microspheres used for anti-inflammatory agents for directing against knee joint.

1.4.6 Targeting using microparticulate carriers

1.4.6.1 Ocular

The rapid conversion of the particulate suspension to gel form reportedly leads to their longer retention in the eye. The eye and the cornea are easily accessible targets. The washout effect, however, presents difficulties in retention of microparticulate drug carrier in the corneal. A novel approach to increase the retention of the microparticulate system is changing them to the gel form in the cul de sac of eye. The rapid conversion of the particulate suspension to gel form reportedly leads to their longer retention in the eye.\textsuperscript{130}

1.4.6.2 Intranasal

The bioadhesive microspheres are used as the alternative to gel dosage formulation. The intranasal route is exploited for the delivery of the peptides and proteins. The conventional dosage forms are rapidly cleared from the nasal mucosa. Bio-adhesives gels have been proposed to increase the retention of the insulin and calcitonin. The bioadhesive microspheres are used as the alternative to the gel dosage formulations. In comparison to the gel dosage form the bioadhesive microspheres have greater control over the surface character and the release pattern.

1.4.6.3 Oral

Oral route is one of the most preferred and convenient routes for administration of the drug. Thus, a number of the controlled release systems
have been developed for oral administration. Single unit system has
disadvantage of being removed with the chyme. Thus, their gastrointestinal
transit time is determined by the frequency of the stomach emptying and
causal localization in the vicinity of pylorus. In comparison to single unit
systems, multiple unit system has marked advantages as it spreads over a
large area and avoids the exposure of high concentration of drug to the
mucosa\textsuperscript{131}.

1.4.7 As drug and antigen carriers
Albumin as a carrier has been used to protect/target enzymes within
circulation and different enzymes could be protected against proteolytic
digestion, immunological tolerated or remain in the circulation for long times.
PLA and PLGA microspheres of varying composition have been used to
improve the ability of the antigens to provoke a mucosal immune response.
- Protect reactive materials against environment.
- It is useful for drugs vitamins, aspirin, which are sensitive to oxygen &
  water.

1.4.8 As a topical drug delivery system
Nerve growth factor and monosialoganglioside microencapsulated in
biodegradable co-polymer poly (L-lactide)co-glycolide. The topical
application of microcapsules of a biodegradable polymer containing a
mixture of two neuroprotective factors could be a viable alternative to the use
of osmotic minipumps for delivery of these agents into the CNS\textsuperscript{132}.
Microspheres of benzoyl peroxide for their bactericidal activity against acne.

1.4.9 Liver cell immobilization
Microparticles has been investigated as artificial cells as a means to immobilize liver cells such as liver, kidney and red blood cell substitutes and can be targeted to the site. Microencapsulated Cytochrome c, hemoglobin, urease and liver microsomes are the examples of immobilization of proteins and cell fragments and thus it opens new possibilities for the application of biomacromolecules, particularly for extracorporal detoxification\textsuperscript{133}.

1.4.10 Vaccine delivery

Rapid development in biotechnology during the last decade has allowed novel ideas in the development of antiviral vaccines to be considered and provides interesting technological approaches to their realization. Designing of microencapsulated forms for delivering bacterial and viral antigens or antigenic complexes using biodegradable biopolymers is an important novel direction. This approach involves the production of polymeric spherical particles with a diameter of 1 micron to 3 mm, containing isolated viral antigens or whole viral particles. Microencapsulated antigens administered orally are protected from low pH values of the gastric juice, bile acids, their salts and proteolytic enzymes of the gastrointestinal tract. The ability to drastically potentiate the immune response to encapsulated antigens, together with the ability to penetrate into the intestinal and respiratory mucosa upon oral and tracheal administrations, respectively, with induction of local and systemic immune reactions\textsuperscript{134}.

Microparticulate system also improved the stability of tetanus toxoid coated with poly(lactide-co-glycolide) by an oil-in-oil solvent extraction method\textsuperscript{135}.

1.4.11 Antigen release
The release of antigens from the microspheres is influenced by the structure, micro-morphology, nature and type of the biodegradable polymer. The antigen release from microspheres can be of different type's viz., burst mechanism, and pore diffusion mechanism, erosion or combination of them\textsuperscript{136-139}.

1.5 Recent advances in microspheres technology

1.5.1 Magnetic microparticles
Targeting of drug under controlled, burst or modulated release using biophysical approaches is a new way to achieve site-specific drug delivery. These approaches utilize a wide range of modalities as hyperthermia, arterial perfusion, arterial chemoembolization, intra cavity injection and use of extra corporeal magnetic field. In developing different approaches to target, it is instructive to observe how the body localizes its own biopharmaceuticals in the desired tissues. Magnetic monitoring has the advantage of being efficient in allowing high local concentration of therapeutic agents. A variety of magnetically response carriers have been proposed for chemotherapeutic agents. These include magnetite-containing matrices (microspheres of nanoparticles of the starch, albumin, ethyl cellulose, etc.), ethyl oleate based emulsion and natural cells such as erythrocyte ghosts. Magnetic targeting is one of the most efficient methods developed for targeting of active agents.

1.5.2 Monoclonal antibodies mediated microspheres targeting-immunomicrospheres
Monoclonal antibodies mediated targeting is a method used to achieve selective targeting to the specified sites. Monoclonal antibodies are extremely specific molecules. This extreme specificity of the monoclonal antibodies (Mabs) can be utilized to target microspheres loaded bioactive molecules to selected sites. Mabs can be directly attached to the microspheres by means of covalent coupling. The free aldehyde groups, amino groups, or hydroxyl groups on the surface of the microspheres can be linked to the antibodies. Microspheres from different material (e.g. bovine serum albumin and poly Acrolein) and prepared using different methods carry different functional groups, which help in the coupling of the antibodies. The mabs can be attached to the microspheres by any of the following methods.

- Non-specific adsorption
- Specific adsorption
- Direct coupling
- Coupling via reagents

Mabs can be adsorbed non-specifically on to the surface of the hydrophobic microspheres by physical adsorption, which renders them more hydrophilic. Hydrophilic microspheres are more suitable for the cell targeting. Monoclonal antibodies form immunomicrospheres on coupling with the microspheres. Immunomicrospheres are formed non-specifically by Vander Waals- London forces. Mabs can be adsorbed on the surface of poly hexyl cyanoacrylate microparticles by simple incubation of microspheres with an excess of antibodies at 4°C in phosphate buffer saline\textsuperscript{140-142}. 
Coupling of microspheres with monoclonal antibodies can also be achieved by means of the reagents when microspheres of choice do not contain functional groups or carry functional groups, which are not capable of coupling\textsuperscript{143-148}.

1.5.3 Microsponges: Topical porous microspheres

Microsponges are porous microspheres having myriad of inter-connected voids of particle size range 5-300\textmu{}m. These microsponges having capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens and anti-infectives, etc. are used as the topical carrier system. Further, these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions and powders. A microsponge consists of non-collapsible structures with porous surface through which active ingredients are released in a controlled manner\textsuperscript{149}.

The various steps in the preparation of microsponges are summarized as:

- Selection of monomer or combination of monomers
- Formation of chain of monomers as polymerization begins
- Formation of ladders as a result of cross linking between chains of monomers
- Folding of monomer ladders to form spherical particles (microspheres)
- Agglomeration of microspheres, which gives rise to formation of bunches of microspheres
- Binding of bunches to form microsponges
1.6 Polymers used in microparticulate system \(^{150-156}\)

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres. These materials include the polymers of natural and synthetic origin and also modified natural substances.

**Synthetic Polymers**

**Non Biodegradable**
- Poly Methyl- (Methacrylate)
- Acrolein
- Glycidyl- methacrylate
- Epoxy Polymers

**Biodegradable**
- Lactides & Glycolides & their co-polymers
- Polyalkyl Cyanoacrylates
- Polyanhydrides

**Natural Materials**

**Proteins**
- Albumins
- Gelatin
- Collagen

**Carbohydrates**
- Starch
- Agarose
- Carrageenan
- Chitosan

**Chemically Modified Carbohydrates**
- DEAE Cellulose
- Poly (acryl) dextran
- Poly (acryl) starch

1.7 Microencapsulation techniques

Various techniques are employed to form the capsules, including spray drying, spray chilling or spray cooling, extrusion coating, fluidized bed coating, liposome entrapment, coacervation, inclusion complexation,
centrifugal extrusion and rotational suspension separation. Each of these techniques is discussed in this review. Microencapsulation is receiving considerable attention fundamentally, developmentally, and commercially. Microencapsulation process can be classified as type A and type B i.e., chemical and mechanical processes respectively. Capsules produced by type A, or chemical processes, are formed entirely in a liquid-filled stirred tank or tubular reactor. Capsules produced by type B, or mechanical processes, utilize a gas phase at some stage of the encapsulation process. No encapsulation process developed to date is able to produce the full range of capsules desired by potential capsule users. Some readily produce small, liquid-filled capsules, whereas others produce relatively large capsules with a solid core material.

1.7.1 Type A encapsulation process

1.7.1.1 Complex coacervation

It is based on the ability of cationic and anionic water-soluble polymers to interact in water to form a liquid, polymer-rich phase called a complex coacervate. Gelatin is normally the cationic polymer used. A variety of natural and synthetic anionic water-soluble polymers interact with gelatin to form complex coacervates suitable for encapsulation. Researchers have reported that complex coacervation has been used for encapsulation of cell by using alginate-chitosan\textsuperscript{157}, electric ink microcapsules by using gelatin and gum Arabic\textsuperscript{158}, microencapsulation of sunflower oil, lemon and orange oil
flavor was investigated using complex coacervation of whey protein/gum Arabic\textsuperscript{159}, microchannel emulsifications in producing monodisperse gelatin/acacia complex coacervate microcapsules of soybean oil\textsuperscript{160}, cellular functions of the encapsulated hepatocytes were enhanced by microcapsules formed by polyelectrolyte copolymer and modified collagen\textsuperscript{161}. Furthermore, complex coacervation method was also used to prepare microcapsules for sustained release of dalarelin\textsuperscript{162}, nitrofurantoin and amoxicillin trihydrate\textsuperscript{163}, controlled release of ketoprofen\textsuperscript{164} and beta-glucuronidase\textsuperscript{165}, mucoadhesive microspheres of gentamicin\textsuperscript{166}, benzocaine topical preparation\textsuperscript{167}.

Limitation

This technology routinely produces single capsules of 20-800µm diameter that contain 80-90 wt. percent core materials. The mechanical and barrier properties of dry capsules formed by complex coacervation generally are sensitive to moisture. Post treatment of such capsules with urea and formaldehyde under acidic conditions has been used to reduce their moisture sensitivity.

1.7.1.2 Solvent evaporation

The processes are come out in a liquid manufacturing vehicle. Microcapsule coating is dispersed in volatile solvents, which is immiscible with the manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in coating polymer solution. With agitation, the material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer. In the case in which the
core material is dispersed in the polymer solution, polymer shrinks around the core. In the case in which the core material is dissolved in the coating polymer solution, matrix type microcapsules are formed\textsuperscript{168-173}. The solvent evaporation technique to produce microcapsules is applicable to a wide variety of core materials. The core materials may be either water-soluble or water insoluble materials. The Schematic representation of various solvent evaporation techniques are shown in figure 1F-2

![Figure 1F-2: Schematic representation of various solvent evaporation techniques\textsuperscript{174}](image)

**1.7.1.3 Polymer-polymer incompatibility**

This technology utilizes a polymer phase-separation phenomenon quite different from complex coacervation. In complex coacervation, two oppositely polymers join together to form the complex coacervate and both polymers become part of the final capsule shell. In contrast, polymer-
polymer incompatibility occurs because two chemically different polymers dissolved in a common solvent are incompatible and do not mix in solution. They essentially repel each other and form two distinct liquid phases. One phase is rich in polymer designed to act as the capsule shell. The other is rich in the second, incompatible polymer. Polymer phase-separation technique has been studied by pharmaceutical scientists to overcome biotechnological potential problems associated with toxicity of the organic phase for microbial cells or enzymes by using microcapsules composed of a hydrophobic liquid core surrounded by a cross-linked polyacrylamide/alginate membrane\textsuperscript{175}. Furthermore, this technology also utilized for the preparation of sustained release of antitumor drugs\textsuperscript{176}, isoniazid\textsuperscript{177}, theophylline\textsuperscript{178}, peptides and proteins\textsuperscript{179}, ciprofloxacin\textsuperscript{180}, nitrofurantoin\textsuperscript{181}, FK906 (tripeptide)\textsuperscript{182}, ketorolac tromethamine\textsuperscript{183}, 6-mercaptopurine\textsuperscript{184}, phenytoin sodium\textsuperscript{185} and biodegradable implantable delivery system containing ciprofloxacin hydrochloride\textsuperscript{186}.

**Limitation**

Polymer-polymer phase separation processes normally are carried out in organic solvents and are used to encapsulate solids with a finite degree of water solubility. Many of the capsules produced commercially have an ethyl cellulose shell, are irregularly shaped 200-800 μm particles, and are loaded with solid drug particles. They are used to provide taste masking or prolonged drug delivery. Smaller capsules (e.g., 20-120μm in diameter) with a biodegradable poly (d, l-lactideglycolide) shell have been prepared by
polymer-polymer phase separation and used as injectable drug delivery devices.

1.7.1.4 Interfacial polymerization (IFP)

It is a third type A encapsulated process that has been commercialized. A unique feature of this technology is that the capsule shell is formed at or on the surface of a droplet or particle by polymerization of reactive monomers. This approach to encapsulation has evolved into a versatile technology able to encapsulate a wide range of core materials, including aqueous solutions, water-immiscible liquids, and solids. Interfacial polymerization techniques were used by the scientist for the time course release of die\textsuperscript{187}, capturing capsules\textsuperscript{188}, rabbit hemolysate-filled polyethyleneimine (PEI) or polyurea (PU)-type artificial red blood cells\textsuperscript{189}, temperature-sensitive hydrophilic gel microcapsules\textsuperscript{190}, gelospheres of theophylline\textsuperscript{191}, biologically active material (calf thymus DNA)\textsuperscript{192}, submicron range production of oil-containing polyterephthalamide microcapsules\textsuperscript{193} and to produce thermostable glucose oxidase\textsuperscript{194}.

Limitation

It is routinely used to produce 20-30 µm diameter capsules loaded with pesticides and herbicides. It also used to form 3-6 µm diameter capsules loaded with carbonless paper ink. Capsules formed by IFP often have a continuous core-shell structure and a spherical geometry. Significantly, the exterior surface of many IFP capsules is smooth and uniform. Capsule fracture studies show that the interior surface of many IFP capsule shells is cratered and irregular. That is, the capsule shell is not uniformly deposited
around the core by an IFP process except for a comparatively thin outer region of the shell.

1.7.1.5 In-situ polymerization

It is a type A encapsulation technology closely related to IFP. Like IFP, capsule shell formation occurs because of polymerization of monomers added to the encapsulation reactor. However, with in situ encapsulation processes, no reactive agents are added to the core material. Polymerization occurs exclusively in the continuous phase and on the continuous-phase side of the interface formed by the dispersed core material and continuous phase. In-situ polymerization techniques were used for the microencapsulation of three higher hydrocarbon phase change materials by using amino-aldehyde resins and developed a mathematical model for the transfer of process up to pilot reactor\textsuperscript{195}. This technique are also utilized by the scientist for the encapsulation of recombinant cells by using alginate\textsuperscript{196}, production of functional microcapsules, which contain a suspension responsive to electric fields\textsuperscript{197}, crystallization and prevention of super cooling of n-alkanes\textsuperscript{198}, microencapsulation of healing agent dicyclopentadiene provides adequate strength, long shelf-life and excellent bonding to the host material\textsuperscript{199}.

Limitation

In situ polymerization is used extensively to produce small i.e., 3-6 µm capsules loaded with carbonless paper inks or perfume for scented strips. Larger capsules loaded with mineral oil are used for cosmetic applications,
whereas capsules filled with epoxy resin are used for fasteners. The technology can also be adopted to encapsulate solids.

1.7.1.6 Centrifugal force and submerged nozzle processes

Several interesting type A processes use centrifugal force or two-fluid submerged nozzles to form microcapsules. In one process, a cup perforated with a series of fine holes is immersed in an oil bath. Capsules can also be produced by co-extruding an aqueous gelatin solution and an oil to be encapsulated through a two fluid nozzle into a moving fluid stream of an oil solution. Since the handling of many active agents in its pure form has many problems, microencapsulation is used to have better properties in the product. With the patented BRACE-Processes it is possible to encapsulate a very wide range of materials in monodisperse. Microspheres or microcapsules in a diameter range of 50-6000 microm with a very narrow size distribution. The microsphere units from BRACE can be customer tailored to the materials and all necessary specifications as FDA, GMP/GLP, EX, CIP, WIP etc. The throughput of the BRACE microsphere units ranges between 10 ml per h (small laboratory scale) up to over 1000 l per h (production scale) while the production cost are very low, especially if compared directly to competitive processes as spray-drying or fluidized bed coating.

1.7.2 Type B encapsulation processes

Centrifugal force, extrusion, and formation of sprays are the principal means by which type B capsules are made
1.7.2.1 Spray drying

The first step in a spray dry encapsulation process is to emulsify or disperse the core material in a concentrated (40-60% solids) solution of shell material. The core material generally is water-immiscible oil such as a fragrance, flavor, or vitamin. It is emulsified in a solution of shell material until 1-3µm oil droplets are obtained. The shell material normally is a water-soluble polymer like gum arabic or a modified starch. Water is the preferred solvent for most spray-drying encapsulations. However, several groups are exploring the use of spray drying from organic media to produce pharmaceutical capsules from biodegradable polymers. To date, scientist utilized this techniques for the retention of aroma contents using different types of saccharides like cyclodextrin (alpha), gum arabic, oxidative protection of oils and drugs like tuna oil, fish oil, D-limonene, linoleic acid, enhancement of aerosolization behavior of drug 208, 209, enhancement of oral bioavailability of poorly water soluble drugs 210, 211, enhancement of enzymatic activity 212, controlled release of vitamins 213, anticancer drugs 214, thermosensitive microparticles 215, encapsulation of high water soluble drugs 216, encapsulation of probiotic microorganism for the in vitro tolerance at pH values of stomach and bile concentrations 217, microgranulating the live virus materials with their virulence being preserved 218, stabilization of monoterpenes 219, stability and taste masking 220 and improved feasibility and immunogenicity of diphtheria toxoid vaccines 221.

Limitation
Spray drying is a viable commercial method of forming microcapsules. It is an established, comparatively low-cost encapsulation technology that continues to develop. Spray-dry encapsulation has several problems and limitation. If water is the preferred solvent, spray dry encapsulation is limited to shell materials soluble or dispersible in water. Another limitation is the 20-30% core loading carried by most spray-dried capsules. Water evaporation from a capsules in the chamber of spray drier occurs rapidly, it is not uncommon to harvest spray dried capsule is free or encapsulated oil. The higher the core loading, the more pronounced this problem could become.

1.7.2.2 Fluidized bed coater

Fluidized bed coaters function by suspending a bed or column of solid particles in a moving gas stream, usually air. A liquid containing coating formulation is sprayed onto the individual particles, and the freshly coated particles are cycled into a zone where the coating formulation is dried either by solvent evaporation or cooling. The coating and drying process sequence is repeated until a desired coating thickness has been applied. A major advantage of fluidized bed coaters is their ability to handle an extremely wide range of coating formulations. They have been used to apply hot melts, aqueous latex dispersions, organic solvent solutions of shell material, and aqueous solutions of shell material. Several investigators are utilizing fluidized bed coating techniques for production of microparticle and pellets of extremely low doses drugs, pediatric drug formulations; enteric-coated and sustained release micro dose drug delivery systems, enhancement of bioavailability and coating of ordered powder mixture.
Limitation
They are limited to encapsulating solid particles or porous particles into which a liquid has been absorbed.

1.7.2.3 Centrifugal extrusion
In this method the core and shell material, two mutually immiscible liquids, are pumped through a spinning two fluid nozzle. This produces a continuous two-fluid column or rod of liquid that spontaneously breaks up into a stream of spherical droplets immediately after it emerges from the nozzle. Each droplet contains a continuous core region surrounded by a liquid shell. However these droplets are converted into capsules is determined by the nature of the shell material. Suitable core materials typically are polar liquids like water or aqueous solution, since they are immiscible with a range of hot melt shell materials like waxes.

Limitation
Capsules prepared by centrifugal prepared by centrifugal extrusion tend to be large with diameters typically ranging from over 250 µm up to several millimeters.

1.7.2.4 Rotational Suspension Separation
In this process, core material dispersed in a liquid shell formulation is fed onto a rotating disk. Individual core particles coated with a film of shell formulation are flung off the edge of the rotating along with droplets of pure coating material. When the shell formulation is solidified, e.g., by cooling, discrete microcapsules are produced. The droplets of pure coating material
also solidify, but they are said to collect in a discrete zone away from the capsules.

**Limitation**

Formulation of spherical geometry may require a granulation step before encapsulation is attempted. A variety of hot melt shell materials can be applied, but melt viscosities below 5000 cP are favored. Capsule shells produced by rotational suspension separation are not at thermodynamic equilibrium immediately after capsule formation is complete.

**1.8 Microparticulate system: Application in NSAIDs**

Currently, there is a trend towards a safe delivery of drugs, which includes a growing awareness by patients of what they take and what benefits are associated with certain excipients also. The excipients includes polymer mostly in novel approaches are being used in maintaining the release profile of drugs which produces the toxicity after oral therapy. In many cases, microencapsulation can be used to overcome these challenges.

The NSAIDs like nimesulide, aceclofenac, indomethacin, ibuprofen, fenoprofen with a short half-lives of 6hrs or less in patients and are given three or four times daily. The steady state is reached within 24 to 36 hrs after the drug is initially administered but is characterized by marked fluctuations in plasma between peak post absorption levels and trough levels at the time of next dosage. The development of new functional drug molecule of these drugs requires technologies for incorporating drug into dosage form without reducing their bioavailability or functionality. In many cases, microencapsulation can provide the necessary protection for these compounds,
but in all cases bioavailability should be carefully studied. A wide range of core material have been encapsulated, including adhesives pharmaceuticals, agrochemicals, living cells, active enzymes, flavors, fragrances, and inks for the development of various type of dosage form like sustained release, taste masking of bitter drugs, single layered tablet containing chemically incompatible ingredients, new formulation concepts for creams, ointments, aerosols, protection of degradable drugs in gastro-intestinal tract, increment of shelf life of drugs, alteration of surface properties of drugs and prevention of volatile liquids from evaporation\textsuperscript{228, 229}. The applications of various microencapsulation technologies to pharmaceutically important non steroidal anti-inflammatory drugs are summarized in table 1T-3. The highlights show a road map of achievements of the development of microparticulate delivery for NSAIDs. The literature reveals about microcapsules which shows that micro-particulate delivery reduces marked fluctuations in plasma between peak and trough levels at the time of next dosages. The study also reveals about the selection of different polymers according to intended use of drugs. Micro particulate drug delivery technology represents one of the frontier areas of science, which involves multidisciplinary scientific approach, contributing to human health care. The development of appropriate carriers for drug delivery is a challenge for scientists.
Table 1T-3: The Microparticulate delivery of non-steroidal anti-inflammatory drugs.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name of Core Material</th>
<th>Microencapsulation Technique</th>
<th>Coating Material Used</th>
<th>Purpose of Microencapsulation</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><strong>Aspirin</strong>&lt;br&gt;Maximal Daily Dose: 80-100 mg.&lt;br&gt;Protein Bound: 80-90%&lt;br&gt;$T_{max}$&lt; 30 min&lt;br&gt;$T_{1/2}$ - 15 min.</td>
<td>Complex Cocervation</td>
<td>Dipalmitoylphosphatidylcholine Acacia Gelatin</td>
<td>Constant release of acetylsalicylic acid</td>
<td>230</td>
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<tr>
<td></td>
<td>Solvent Evaporation</td>
<td>Ethyl cellulose</td>
<td>Modified release</td>
<td>231</td>
<td></td>
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<tr>
<td></td>
<td>Oil-In-Water Emulsification/Solvent Evaporation</td>
<td>Ethylcellulose</td>
<td>Modified release</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spray-Congealed</td>
<td>Hydrogenated soybean oil</td>
<td>Controlled release</td>
<td>233</td>
<td></td>
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<td>2.</td>
<td><strong>Diclofenac</strong>&lt;br&gt;Maximal Daily Dose: 200 mg.&lt;br&gt;Protein Bound: 99%&lt;br&gt;$T_{max}$: 1-3 h&lt;br&gt;$T_{1/2}$: 1.2-2 h&lt;br&gt;Renal Excretion Unchanged Drug(% Dose) &lt; 1</td>
<td>Congealable Disperse Phase Method</td>
<td>Glycerol monostearate Tween 80</td>
<td>Sustained release</td>
<td>234</td>
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<td>Oil-In-Oil (O/O) Emulsification-Solvent Evaporation</td>
<td>Low M.W polyester Poly(l-lacticacid), Copoly(lacticacid/glycolic acid)</td>
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<td>235</td>
<td></td>
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<td></td>
<td>Multiple-Emulsion Technique</td>
<td>Poly(delta-valerolactone) Acacia</td>
<td>Prolonged release</td>
<td>236</td>
<td></td>
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<td></td>
<td>A Non-Aqueous Emulsion Method</td>
<td>Ethylcellulose Poloxamer 188 Hydroxypropylmethylcellulose phthalate</td>
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<td>237</td>
<td></td>
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<td>3.</td>
<td><strong>Diclofenac Sodium</strong>&lt;br&gt;Maximal Daily Dose: 200 mg.&lt;br&gt;Protein Bound: 99%&lt;br&gt;$T_{max}$: 1-3 h&lt;br&gt;$T_{1/2}$: 1.2-2 h&lt;br&gt;Renal Excretion Unchanged Drug(% Dose) &lt; 1</td>
<td>Phase Separation-Coacervation</td>
<td>Ethylcellulose Cyclohexane</td>
<td>Controlled release</td>
<td>238</td>
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<td>Phase Separation-Coacervation</td>
<td>Ethyl cellulose Toluene Petroleum ether.</td>
<td>Taste masking</td>
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<td>Emulsification Method</td>
<td>Chitosan Glutaraldehyde Sulphuric acid</td>
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<td>Emulsification Method</td>
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<td>Solvent Evaporation</td>
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<td>Compound</td>
<td>Method</td>
<td>Drug</td>
<td>Release Type</td>
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<td>Wurster Process</td>
<td>Calcium carbonate Hydroxypropyl Cellulose Polyethylene glycol 6000</td>
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<td>Eudragit RS30D</td>
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<td>Co-acervation Phase separation</td>
<td>Ethylphthalate</td>
<td>Modified drug release</td>
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<td>Solvent Evaporation</td>
<td>Eudragit RL</td>
<td>Sustained release</td>
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<td></td>
<td>The Wet Granulation and Thermal Change Methods</td>
<td>Cellulose Acetate Phthalate Ethyl Cellulose</td>
<td>Retarded drug release</td>
<td>247</td>
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<td><strong>Diflunisal</strong></td>
<td>Quasi-Emulsion Solvent Diffusion Method and Spray Drying</td>
<td>Eudragit RS100 Acrylic/Methacrylic Copolymer</td>
<td>Sustained release</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein Bound</td>
<td>99%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2-3 h</td>
<td></td>
<td></td>
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<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>7-15 h</td>
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<td>Renal Excretion</td>
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<td></td>
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<td>Drug (% Dose)</td>
<td>&lt;3</td>
<td></td>
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<td><strong>Ibuprofen</strong></td>
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<td>Protein Bound</td>
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<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1-2 h</td>
<td></td>
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<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
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<tr>
<td>Renal Excretion</td>
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<tr>
<td>Drug (% Dose)</td>
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<td><strong>Indomethacin</strong></td>
<td>Co-acervation Phase separation</td>
<td>Hydroxypropyl methylcellulose phthalate Sodium sulphate</td>
<td>Increased rate of release</td>
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<td>Maximal Daily Dose</td>
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<tr>
<td>Protein Bound</td>
<td>&gt;98%</td>
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<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1-4 h</td>
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<td>T&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>2.0-13 h</td>
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<td>Renal Excretion</td>
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<tr>
<td>Drug (% Dose)</td>
<td>&lt;15</td>
<td></td>
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<td><strong>Ketoprofen</strong></td>
<td>Phase Separation-Coacervation</td>
<td>Benzoalkonium chloride Sodium lauryl sulphate Polysorbate 20</td>
<td>Increase release</td>
<td>256</td>
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<td>Maximal Daily Dose</td>
<td>300 mg.</td>
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<td></td>
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<tr>
<td>Protein Bound</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.5-2 h</td>
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<td><strong>Spray Drying</strong></td>
<td>Dispersion</td>
<td>Acetone Liquid Paraffin</td>
<td>Dissolution patterns</td>
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<td><strong>Modified W/O/W Complex Emulsion Technique</strong></td>
<td>Cellulose acetate butyrate Polystyrene</td>
<td>Controlled release</td>
<td>261</td>
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<td><strong>Spray Drying</strong></td>
<td>Eudragit S and L</td>
<td>Gastro resistant</td>
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<td>Drug Name</td>
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<td>Protein Bound (%)</td>
<td>( T_{\text{max}} )</td>
<td>( T_{1/2} )</td>
<td>Renal Excretion</td>
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<td>Ketorolac Tromethamine</td>
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<td>Meclofenamate</td>
<td>400 mg.</td>
<td>99%</td>
<td>0.5-2.0 h</td>
<td>2.0-3.0 h</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

Finally, the future will also see the increasing application of multi-component therapy as a front-line defense against the disease, aiming at long-term corrective treatment through the designing of multi-component novel drug delivery system. During design of these formulations several factors have to be considered like careful pharmacokinetic parameters for dosage regimen to achieve a desired therapeutic efficacy of drug in the body. Thus designing of such proper dosing services will minimizes the drug toxicity, reduces the overdosing or drug complications, keep health care at minimum cost and ultimately increase the patient compliance.
1.9 Objective and plan of work

Conventional multi-component nonsteroidal antiinflammatory dosage forms constitute one of the largest group of pharmaceuticals with a world market excess of $13 billion per annum due to increase the potency, multiple action, quick relief and several multi-component NSAIDs are available in the market which are primarily used to treat pain and inflammation in musculoskeletal diseases, Alzheimer's disease, rheumatoid arthritis, ankylosing spondylitis but the main problem with this conventional approach is that it produces lot of side effects like intestinal bleeding/ulceration, renal insufficiency, headache, dyspepsia, confusion, depression, broncho-spasm, rashes etc.

The ultimate objective of proposed work is to develop multi component microcapsular system by using various micro encapsulation techniques and reformulate in to multiple unit system for a non-steroidal analgesic and antiinflammatory drugs. This system is able to maintain and control the plasma concentration without the need for frequent dosing and less side effects unlike in case of conventional dosage forms and increases the patient compliance.

The concept of multi-component therapy is beneficial when the selected agents posses differing mechanism of action that provide additive or synergistic efficacy, reducing the required doses of individual agents as compared with monotherapy and potentially limiting side effects. Multi-component therapy may seem costlier than monotherapies in the short term;
but causes significant savings, lower treatment failure rate, lower case-
fatality ratios, reduction in development of resistance and consequently less 
monies needed for the development of new products in long-term therapy.
The rational fixed dose combination of nimesulide and tizanidine, 
aceclofenac and tizanidine are available in the market for the relief of 
inflammations and spasticity associated with multiple sclerosis, stroke, spinal 
cord injury, or disease as they fall in the similar range of pharmacokinetic 
profile. The half-lives of nimesulide (1.56 to 4.95 hr), aceclofenac (4 - 4.3 hr) 
and tizanidine (2.12 to 4.2 hr), fall in the same range and hence, the time 
course of action of the two drugs might be similar, which is an important 
criterion for the possibility of a rational fixed-dose-combination available in 
the market e.g., Citanz, Nimulid-MR, Nicip T and Etiz etc. Various 
inflammatory painful conditions in which NSAIDs are used are often 
accompanied with muscle spasm. Since, Tizanidine is a myotonolytic agent 
and is helpful in management of muscular spasm, the combination of the two 
drugs will be helpful in managing such conditions. Tizanidine has been found 
to possess antinociceptive activity in animal models as well as clinical trials. 
It is seen that the overall consumption of NSAIDs for the management of 
pain is reduced when Tizanidine is given in combination to NSAIDs. 
Tizanidine also helps in improving the gastric safety profile of NSAIDs when 
given with them. Evidence is now emerging that tizanidine may also have a 
role to play in the treatment of other conditions associated with muscle 
spasm. Hence, it can be said that combination of tizanidine with aceclofenac
or Nimesulide show synergistic potential which is one of the most important factors in deciding the feasibility of a formulation.

The main technological significance of this investigation is to develop microcapsular delivery systems and reformulate into multiple unit system to control and extend the release of the active ingredient from the microcapsules without attempting to modify the normal biofate of the active molecules in the body after administration and absorption. Furthermore, these dosage forms are less susceptible to dose dumping than the reservoir or matrix type, single unit tablet since the drug release profile does not depend on the drug release properties of a single unit. Micro particles can be filled into hard gelatin capsules or compressed into tablets.

This research helps to community regarding to avoid patient non-compliance problems and will provide delivery of drug in their usual forms with application of new techniques.

This novel approach also employ less total drug (i.e. decreasing cost of dose) to community which minimize or eliminate local and systemic side effects, improves efficiency in treatment, protects the degradation of drugs in the body as well as from environmental conditions, improves the self life of drugs, helps in taste masking of bitter drugs and finally reduction of therapy cost at economic level.

Finally, the future will also see the increasing application of multi-component therapy as a front-line defense against the disease, aiming at long-term corrective treatment through the designing of multi-component novel drug delivery system. Thus designing of such proper dosing services will
minimizes the drug toxicity, reduces the overdosing or drug complications, keep health care at minimum cost and ultimately increase the patient compliance.

1.9.1 Plan of work

1.12.1 Phase I

1) Literature survey of drugs
2) Selection of model multi-component NSAID’s drugs.
3) Procurement of drugs.
4) Analysis of drugs (As per I.P, B.P and U.S.P)
   a. Physical properties
   b. Chemical properties
5) Establishment of analytical methods of selected drugs
   a. Selection of solvents, and buffer system
   b. Interaction study i.e. drug-solvent, drug-drug
   c. Development and validation of analytical method by UV & HPLC
6) Formulation of microcapsule of model drugs
   a. Preformulation studies of selected drugs
   b. Selection of coating polymers
   c. Study of drug-polymer interaction
   d. Selection of suitable microencapsulation techniques
7) Optimization of methods:
   a. Study of various variables
      ➢ Effect of RPM
      ➢ Effect of agitation rate
➢ Effect of temperature
➢ Effect of drying time
➢ Effect of solvents
➢ Effect of various polymers

8) Evaluation

a. Particle size analysis
b. Dissolution study
c. Size distribution
d. Entrapment efficiency
e. Stability studies

1.12.2 Phase II

1) Development and characterization of suitable dosage forms

2) Selection of dosage from: Tablets

3) Selection of excipients

a. Preformulation study of excipients

4) Development of various formulations with excipients

5) Optimization of master formulations

6) Evaluation of dosage forms as per compendial requirements

a. In-vitro study
b. Comparative study with marketed conventional dosage forms
c. Stability study of dosage forms: As per ICH guidelines

7) Patent filing.


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