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REVIEW ARTICLE

# APPROACHES TO OVERCOME NSAID INDUCED ULCERATION IN ARTHRITIC PAIN MANAGEMENT: PERSPECTIVES AND PROSPECTS

**Ganeshanand, Kamal Jeet, Baldi Ashish***

Department of Quality Assurance, I.S.F. College of Pharmacy, Moga, Punjab, 142001

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**ABSTRACT**

Rheumatoid arthritis is an auto-immune joint disorder involving pain and inflammation. Various approaches are used for pain management and relief from arthritis with single and multiple dose therapy. In single dose therapy, use of non-steroidal anti-inflammatory drugs like diclofenac aceclofenac, celicoxib etc. reported many side effects mainly leading to decrease in production of prostaglandin and holding the ulcer. High dosing frequency of these drugs is also a major factor of risk. Recently developed novel formulations are especially suitable for achieving controlled and delayed release profile with low risk of dose dumping. These systems have received great attention of pharmaceutical industry as they deliver accurate amount of drug at the right time and location thus increasing patient compliance and economic feasibility and avoiding drug associated side effects. Present review mainly deals with the problem of ulceration in pain management, various approaches to overcome this and specifically explore the possibilities to apply novel drug delivery systems for this purpose.

**Keywords:** Arthritis, Drug delivery systems, Gastroretentive, NSAIDs, Pain, Rheumatoid arthritis, Rheumatic pain management.

## INTRODUCTION

Arthritis is a form of joint disorder that involves chronic inflammation of one or more joints[1]. There are over 100 different forms of arthritis. The commonest form is osteoarthritis, which is the result of trauma to the joint, infection of the joint, or age. Other arthritis forms are rheumatoid arthritis, septic arthritis, psoriatic arthritis, and related autoimmune diseases. Rheumatoid arthritis (RA) is a potentially destructive disease with profound impact on joint pain and may be localized to the affected joint. The pain associated with arthritis is due to inflammation that occurs around the joint, damage to the joint from disease, daily wear and tear of joint, muscle strains caused by forceful movements against stiff painful joints and fatigue. Arthritis in children is common, and a major cause of potential morbidity with significant long-term consequences, joint damage and disability if left untreated[2].

RA is the most common cause of disability in the USA. More than 20 million individuals with arthritis have severe limitations in function on a daily basis[3]. Each year, arthritis results in nearly 1 million hospitalizations and close to 45 million outpatient visits to health care centres.

Arthritis can make it very difficult for an individual to remain physically active, contributing to an increased risk of obesity, high cholesterol or vulnerability to heart disease. Individuals with arthritis are also at increased risk of depression, which may be related to fear of worsening symptoms. Therapy is aimed at relieving pain, maintaining or improving mobility and minimizing disability. It may induce medication, physical therapy, and patient education[3].

## ANTI-INFLAMMATORY DRUGS USED FOR PAIN MANGEMENT IN ARTHIRITIS

Patients with rheumatic diseases, including RA and osteoarthritis, almost universally describe pain and stiffness as important contributors to reduced health-related quality of life. The treatment options available, non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used agents for symptomatic treatment[4].

Most frequently used NSAIDs in arthritic pain management are enlisted below:

- Aspirin, Celecoxib, Diclofenac, Indomethacin
- Diflunisal, Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen
- Ketorolac, Meloxicam, Nabumetone, Oxaprozin, Piroxicam
- Salsalate, Sulindac, Tolmetin etc.

*For Correspondence
***Dr. Ashish Baldi***
*Professor and Principal,*
*I.S.F. College of Pharmacy,*
*G.T. Road, N.H. 95, Moga,*
*Punjab, India- 142001.*
*Tel: +91-8968423848;*
*E-mail: baldiashish@gmail.com*

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### Role of NSAIDs in arthritic pain management

NSAIDs are used as effective therapy for pain management to relieve pain, swelling (inflammation), and joint stiffness caused by arthritis. These drugs may also be used to treat other painful conditions such as dental pain, muscle aches, pain after surgery or parturition, but are not appropriate for long-term disease control[5]. The safety of NSAIDs has been closely monitored by regulatory authorities across the globe. These are used for the treatment of mild to moderate pain, fever and inflammation. NSAIDs mainly work by blocking the effect of chemicals called cyclo-oxygenase (COX) enzymes thereby decreasing prostaglandins synthesis. Some prostaglandins are produced at sites of injury or damage, and cause pain and inflammation. By blocking the effect of COX enzymes, fewer prostaglandins are produced, leading to pain and inflammation cessation[6].

Topical form of NSAIDs produces a higher local concentration of the drug, and target the inflammation site and pain, where it preferentially distributes. Achieving sufficiently high concentration to exert local therapeutic activity, for the effective distribution, skin absorption is most critical factor of the drug to the site of inflammation and thus it can affect the efficacy of topical formulation[7].

## PROBLEMS ASSOCIATED WITH USE OF NSAIDs IN ARTHRITIS

### Symptomatic relief but not cure

The most obvious symptoms indicating arthritic state and its severity are inflammation and pain in and around the affected joint. Anti-inflammatory drugs used for pain management in arthritic individuals provide relieves from pain for a certain time and reduce inflammation but no existing treatment modality ensures cure of arthritis. Hence, all NSAIDs offers only symptomatic relieve in RA[5].

### High dose frequencies

The recommended dose of NSAIDs for treating RA is generally given 3-4 times daily for e.g. diclofenac is given daily thrice at a dose of 50 mg. Rheumatoid arthritic treatment modulates the involvement of long term use of anti-inflammatory drugs for years. Furthermore due to increase in pain with severity of disease and age, patient start more frequent self medication of higher dosages. Furthermore simultaneous application of different dosages forms like tablets, gels, etc. also results in higher concentrations of drug in the body. Due to these reasons, NSAIDs induced toxicities and related complications arise in many patients. Frequent administration of these drugs at higher dose also results in decreased therapeutic effectiveness. Both toxicities and lack of efficacy result in high withdrawal rate, which question impact of these drugs on the underlining disease mechanistically. Conventional NSAIDs based treatment therapies have much well recognised toxicity and is incompletely effective with few patients. Diclofenac sodium, the most preferred NSAID in arthritic pain management is a non-steroidal, non-pyrazole compound with anti-inflammatory, antipyretic and analgesic activity in laboratory animals. It has been shown to be well tolerated and effective in short term therapy of degenerative joint disorders and RA. In long term, frequent dosing show side effect in the patient[8].

### NSAIDs associated side effect

NSAIDs are reasonably safe medications, when low doses are taken for brief period. Side effects most commonly occur with large doses over a prolonged time (months or years). Some side effects are mild and go away on their own or after reducing the dose. Others may be more serious and need medical attention[9]. Common side effects of NSAIDs include:

- GI gastropathy, abdominal cramps, stomach pain, stomach ulcers and heartburn.
- Headaches, ringing in the ears and dizziness.
- Allergic reactions such as rashes, wheezing, and throat swelling and
- Liver or kidney problems, high blood pressure and increased bleeding tendency (especially with aspirin).

Many of the adverse effects of NSAIDs are also related to inhibition of prostaglandin production, making their use problematic in some patient populations. The biology of prostaglandin as it relates to gastrointestinal, renal, and cardiovascular physiology and the pharmacologic properties of specific NSAIDs is a key to using these drugs safely[5].

### NSAIDs induced ulceration: A cause of worry in arthritis

Being acidic in nature, most of the NSAIDs (diclofenac, ibuprofen) are known to damage stomach lining and may also cause ulceration and perforation in extreme cases[10]. The lifetime risk of developing peptic ulcer is approximately 10%. However this situation becomes alarming in patients, who are receiving for long term in situations like RA for months and years. Development and peptic ulcers and associated pain is one of the major causes of withdrawal of NSAIDs and non compliance in rheumatic pain management. NSAIDs damage gastrointestinal mucosa by causing both local injuries and by systemically inhibiting prostaglandin production. However, current consensus on the pathogenesis of symptomatic peptic ulcer disease resulting from exposure to NSAID is mainly a consequence of systemic (post-absorptive) inhibition of GI mucosal COX activity rather than a local effect; NSAIDs are valuable agents in the treatment of arthritis and many other musculoskeletal disorders and as analgesics in a wide variety of clinical scenarios. However, as stated above, their use has been limited mainly by their association with mucosal injury to the upper gastrointestinal tract, including the development of peptic ulcer disease[11].

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## APPROACHES TO OVERCOME NSAIDs INDUCED ULCERATION

### Combination with other drugs

#### *Antacid*

Antacids were usually co-prescribed with NSAIDs although no broad evidences were available as to the effects of antacids in preventing NSAID associated gastropathy[12]. A represent active survey of an outpatient prescription database was performed to measure the extent of such a combination and to explore its associated factors[13]. However, erratic absorption pattern of some NSAIDs upon co-administration with antacid should also be taken into consideration[14,15]. NSAID can also increase gastric acid secretion, although it is not clear whether such acts have any impact on ulcer formation or healing. Prostaglandins exert inhibitory acts on parietal cells, so the inhibition of their synthesis by NSAIDs can result in an increase in gastric acid secretion[16].

#### *Cytoprotectant*

Cytoprotectant are said to enhance endogenous mucosal protection mechanism and provide a physical barrier over the surface of ulcer. These drugs are now day most frequently co-administrated with NSAIDs to prevent ulcer formation. Prostaglandin of E and I series have a generally protective action in the GI track and a deficiency in endogenous prostaglandin production may contribute to ulcer formation.

Misoprostal, a synthetic prostaglandin E1 (PGE1) methyl ester analogue has potent anti-secretory and cytoprotective effects on the gastric and duodenal mucus[17]. Misoprostal is a stable prostaglandin analogue, has been shown in large studies to significantly reduce serious gastrointestinal side-effects due to the concurrent administration of NSAIDs and appears to be superior to ranitidine and sucralfate in preventing NSAID-induced gastric and dudenol ulcers.

Misoprostal is absorbed rapidly when administered orally, vaginally, rectally or intracervically. The vaginal route is advantageous because peak levels are reached slowly and sustained for long time and this is associated with fewer side effects. It exerts a direct action on the parietal cell inhibiting the basal secretion of gastric acid as well as stimulation of production seen in response to food, histamine, pentagastrin and caffeine. It also increases mucosal blood flow and augments the secretion of mucus and bicarbonate[12].

### Drug delivery approaches for prevention of NSAIDs induced ulceration

#### *Current status*

Presently most preferred treatment approaches for pain management in arthritis consists of diclofenac (NSAID) and misoprostol (a cytoprotectent) as mono- or combination therapy, with recommended dose of 50 mg and 200 µg respectively given 3-4 time daily. If this regiment is not tolerated, diclofenac may be given 50 mg or 75 mg twice a day. Currently tablet and enteric coated tablet forms of diclofenac alone or in combination with misoprostol drug are available in market. Despite of several technological advancement in novel drug delivery system, only tablet and enteric coated tablets available in the market for oral administration of these drugs. By keeping in view above mentioned problems associated with use of NSAIDs in arthritic pain management, more specifically high frequency of dosing and ulceration, application of novel drug delivery systems may offer suitable, safe, therapeutically effective, more acceptable and cost efficient alternative.

#### *Controlled/sustained release formulations*

Sustained release systems include any system that achieves slow release of drug over an extended period of time or if the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system.

The basic rationale behind sustained/controlled release drug delivery is altering the pharmacokinetics and pharmacodynamics of drugs by using customized novel drug delivery pattern and modification of molecular structure or physiological parameters inherent in a selected route of administration[18]. Thus, optimal design of a sustained/controlled release system necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug. When the drug is administered in a conventional dosage form, it results in a fluctuation of drug concentration at the site of action (peak and valley pattern) and therefore in systemic circulation and tissue compartment. Improved efficiency in treatment, optimized therapy and more uniform blood concentration is the benefits of this drug administration method. Advantages of controlled/sustained release formulation include:

- Reduction in fluctuation in drug level and hence more uniform pharmacological response with reduced frequent dosing and cure of control of condition more promptly with diminish the chances of ulcer induction.
- Improved patient compliance. It has been found that there is an inverse relationship between the number of dosages per day and the compliance rate.
- Although the initial unit cost of sustained release products is usually greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period may be less. Economy may also result from a decrease in nursing time and hospitalization time[19].

#### *Gastroretentive/floating formulation*

Gastroretentive drug delivery is an approach to prolong gastric residence time. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including high density (sinking) systems that is retained in the bottom of the stomach low density (floating) systems that causes buoyancy in gastric fluid[20]. Two type of floating system, single unit and multiple unit dosage form are available[21] thereby targeting site-specific drug release in

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the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs[22]. The gastro retentive systems are advantageous for drugs absorbed through the stomach, e.g. ferrous salts, antacids[23].

Floating drug delivery system is also called the hydrodynamically balanced system (HBS)[24]. This type of drug delivery system is specifically beneficial to reduce NSAIDs induced peptic ulcers due to avoidance of direct contact of NSAIDs to stomach lining[25], no dose dumping, decreased frequency of dosing, possibility of co-administration with antacids/cytoprotectent and better bioavailability[26]. The associated advantages with floating drug delivery systems are as follows:

- Administration of floating dosage forms, tablet or capsules, will result in dissolution of the drug in the gastric fluid[27]. Drug dissolved in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine[28].
- Improves patient compliance by decreasing dosing frequency.
- Bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration are avoided; a desirable plasma drug concentration is maintained by continuous drug release[29].
- Better therapeutic effect of short half-life drugs can be achieved.
- Superior to single unit dosage forms due to uniform drug release and no risk of dose dumping.
- Avoidance of gastric irritation, because of sustained release effect, floatability and uniform release of drug through multi particulate system.

***Enteric coated drug delivery system***

Enteric refers to the small intestine; therefore enteric coating on the dosage form prevents the release of drug before it reaches the small intestine[30]. Most enteric coatings work by presenting a surface that is stable to highly acidic pH of stomach, but breaks down rapidly at a less acidic (relatively more basic) pH. Enteric coating is suitable for drugs that have irritant effect in stomach (like NSAIDs) and drugs which are unstable in acidic pH of stomach. Thus, enteric coating is aimed to prevent the formulations from gastric fluid in the stomach and release the drug component in the intestinal region or once it has passed into the duodenum. The enteric coated tablet is the most common example of a delayed-action tablet product[31]. Advantages offered by enteric coated drug delivery system include:

- Prevention from gastric distress or nausea due to irritation caused by certain drugs e.g. NSAIDs.
- Protection of acid-labile drugs from the acidic pH of gastric fluid e.g. enzymes and certain antibiotics.
- To deliver drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.
- To deliver drugs intended for the local action in intestines. E.g. intestinal antiseptics could be delivered to their site of action in a concentrated form and bypass systemic absorption in the stomach.
- To provide a delayed release component to repeat action tablets.

Hence this strategy avoids contact of NSAIDs to mucosal lining of stomach result in prevention from associated irritation and erosion and may offer a suitable alternative to avoid NSAIDs induced ulceration[32].

***Novel/Multiple unit dosage forms formulation (MUDF)***

Oral modified drug delivery systems can be classified in to two broad groups: single unit dosage forms (SUDFs) and multiple unit dosage forms (MUDFs). Several mini-tablets can be either filled into hard capsules or compacted into bigger tablets that, after disintegration, release these subunits as multiple dosage forms. The concept of MUDFs was initially introduced in 1950s. The production of MUDFs is a common strategy to control the release of drug as shown by the reproducibility of the release profiles when compared to the ones obtained with SUDFs[33].

MUDFs have an enough surface area-to-volume ratio and provide an ideal shape for the application of film coatings. The preparation process necessitates extra care and fine adjustments of various equipment's like tableting machines for the preparation of minitablets, the volume per dose is usually higher than for tablets because of the lower bulk densities of pellets compared to compressed tablets, compared to larger single unit dosage forms, the specific surface area per dose of multiple units is higher and more[34]. These systems consist of pellets, granules, beads, microspheres, mini or micro tablets filled in to sachets, capsules or compressed into tablets.

***Mechanism of drug release from MUDFs:*** Mainly three mechanisms are applied for the drug release MUDFs i.e. diffusion, osmosis, erosion. In diffusion it occurs through a membrane that controls the movement of the drug or solvent between two sides. Both the membrane permeability of the drug and the solvent as well as the geometry of the device determines the diffusion rate of molecules through the membrane. Modeling the release characteristics of reservoir devices as well as monolithic devices, in which the transport of the drug is by a solution diffusion mechanism, involves a solution to Flick's second law for the valid boundary conditions[35]**.** Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semi permeable membrane coat[36]. In some cases coatings can be designed to wear away gradually with time, thus

 

delivering the drug contained within the particle by erosion.

Various novel drug delivery technologies and dosage forms holding promising potential to be effectively utilized for the purpose of prolonged release with desired pattern and reducing the risk of NSAID induced ulceration are given in Table 1. Diagrammatic representations of the same are depicted in Fig. 1.

**Table 1: Novel technologies/dosage forms that can be explored to overcome NSAIDs induced ulceration in arthritic pain management**

| Type | Characteristics | Function | Ref |
|---|---|---|---|
| Tab-in-a-Cap | Multiple release profiles are easily achieved by filling immediate release formulation (prostaglandin analogue) in outer larger capsule and sustained or controlled release formulation (NSAID) in inner smaller tablet. | Provides both controlled and multi-phase release for single and combination prescription. Patient convenience and compliance and cost effective therapy. Sustained, pulsed or delayed release profiles achievable. | 37 |
| ACCU-BREAK | ACCU-BREAK tablet technology use an inactive layer (segment) as the break region. The layer containing drug can be scored into 2, 3 or 4 equal segments, all adjacent to an inactive breakable support segment. Thus, a tablet could be broken easily into the specific dose desired. | Permits reduction in cost to patients.<br>May also promote adherence to therapy by reducing the need of frequent administration.<br>Dose adjustment as per requirement is possible. | 38, 39 |
| Spheroids/ Pallets/ Bead | Controlled-release beads/granules in the range from 1 to 2 mm containing drugs may be formulated. Each bead begins as an inert core onto which the drug is applied. Drug release from these beads occurs by a diffusion process in a controlled, predetermined manner. These dosage form enable high drug loading and granules produces beads that are of controlled size and density with a defined-based granulation extrusion and spheronisation techniques. | Both NSAID and prostaglandin analogue, may be simultaneously administered as beads in single dosage form with desired release profile and drug loading.<br>Possibility of aqueous or solvent-based granulation. High-speed process is well suited for sensitive molecules like proteins and enzymes.<br>Suitable for high drug loading as required in arthritic pain management. | 40, 41 |
| Multilayer dosage forms | Customizable multilayered oral drug delivery platform technology may also be explored. It uses well-established ingredients and is easily manufactured using conventional production equipment. The combination of layers, each with different rates of swelling, gelling and erosion, controls the drug release rate within the body | Use of highly swellable hydrophilic polymers (e.g. HPMC).<br>Dynamic control of the surface of the layer containing the drug that is exposed to surrounding fluids.<br>May allow efficient administration of NSAID and prostaglandin analogue with required release profile and high dose delivery in pain management. | 42 |
| **Delayed release (Lag) based technology** | It is used to release the drug from the tablet after a pre-determined lag-time that is independent of food or pH. It can additionally be used for multiple pulse delivery of one or more drugs with pre-determined time intervals between the pulses. | NSAID and prostaglandin analogue may be simultaneously administered on possible release pattern to avoid dose dumping and associated side effects. | 43 |
| **OROS (Osmotic and Chronset)** | OROS delivery systems consist of the push-pull system is comprised of a bilayer or trilayer tablet core consisting of one push layer and one or more drugs layers. The drug layer and the osmotic engine are encased in hard capsule which is surrounded by the rate controlling semi permeable membrane. A barrier layer composed of an inert substance separates the drug layer from osmotic engine. Using this technology, the drug formulation is completely protected from chemical and enzymatic degradation in the GIT before release, and the timing of release is unaffected by GIT contents. | This technique may be adopted for co-administration of two drugs for example NSAID and prostaglandin analogue.<br>A delivery orifice is laser drilled at the opposite end of the osmotic engine providing an outlet for the drug.<br>Contact of NSAID with gastric mucosa may be avoided to reduce the possibility of ulceration. | 44 |

 

| | | | |
|---|---|---|---|
| **One Step Dry Coating Technology (OSDrC)** | OSDrC technology allows placement of any number of cores of any shape into the tablet just where they need to be positioned for optimum delivery of active pharmaceutical ingredients. This technology opens the door to new world of pharmaceutical tablet manufacturing with advantages like uniqueness, high quality, low cost and innovativeness. | This is ideal for manufacturing a variety of high-quality drug products at low cost. This innovative technology can also replace conventional sugar- and film-coated tablets. Multiple drugs e.g. NSAID and prostaglandin analogue may also be administered in different cores. | 45 |
| **Diffucaps/ Diffutabs** | In this technology, a unit dosage form, such as a capsule for delivering drugs into the body in a circadian release fashion, is comprised of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Drug profiles are created by layering an active drug onto a neutral core such as cellulose spheres and then one or more rate-controlling, functional membranes are applied. | Diffutabs are particularly useful for high-dose products and drugs that require sustained release and once-a-day dosing. Different formulations containing NSAID and prostaglandin analogue may be developed and then mixed as a unit dosage form for simultaneous administration of these drugs with different pattern of release. | 46 |

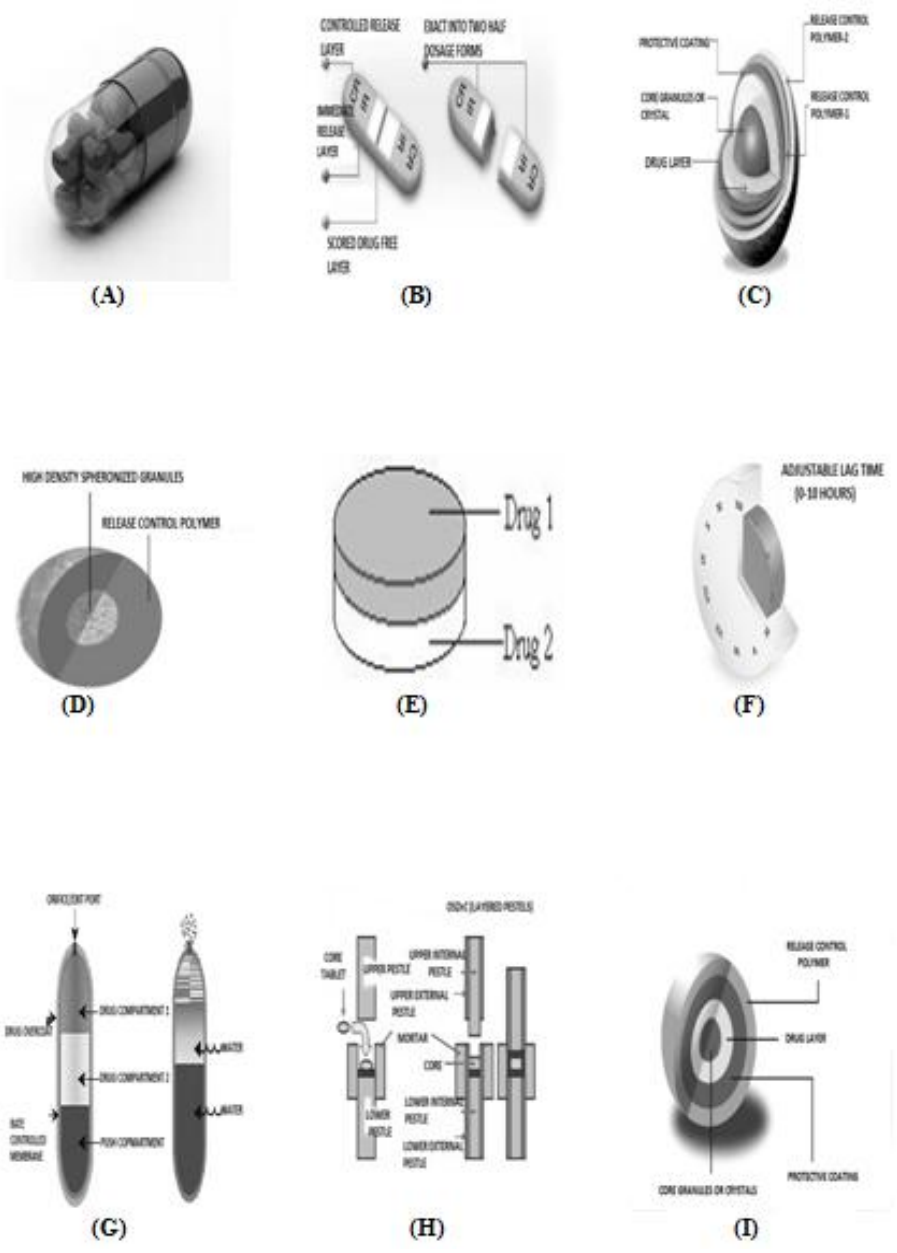


**Figure 1: A**: TAB IN CAP; **B**: ACCU BREAK; **C**: Spheroids; **D**: Bead; **E**: Multilayer dosage forms; **F**: Delayed release (Lag) based technology; **G**: OROS; **H**: OSDrC; **I**: Diffucaps/Diffutabs

 

## CONCLUSION AND FUTURE PROSPECTS

Undoubtedly use of NSAIDs for management of arthritic pain is essential to increase the quality of life in patients suffering from rheumatic disorders. However side effect associated with these drugs are major cause of worry for physicians for successive therapeutic management of rheumatic inflammation and pain. Multi drug based therapy approach especially NSAIDs along with prostaglandin analogue is one of the most promising approach to overcome ulceration induced by high dose and frequency of anti-inflammatory drugs. Various novel drug delivery based technologies, as discussed in the article, also hold promising potential for pain management and patient compliance in these ailments without the problem of NSAID-induced ulceration. These drug delivery systems may be explored in future to find out better strategies for effective management of rheumatic disorders.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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