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Review Article

Review: Therapetic Approach in the Management of Osteoarthritis

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A B S T R A C T

Objectives: The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, and providing uniform drug delivery. A sustained release system is a type of modified drug delivery system that can be used as an alternative to a conventional drug delivery system.

Summary: Osteoarthritis is a generative disease of synovial joints characterized by focal loss of articular hyaline cartilage with the proliferation of new bones and remodelling of joint contour. Risk factors of osteoarthritis are age, female gender, joint alignment, hereditary gene defect, joint injury and obesity.There are various symptoms of osteoarthritis and It diagnose by blood test, joint fluid test and MRI. Osteoarthritis is treated by self-care, medications, therapies, and surgeries. A sustained-release dosage form is a dosage form that maintains the therapeutic blood or tissue levels of the drug by continuous release of medication. Formulation of granules by wet granulation and the granules are evaluated by the pre-compression and post-compression studies.

Conclusion: Sustained release tablet optimize drug release for extended time period.It maximized effectiveness, reduced side-effects of drug and cures the disease.

Keyword: Osteoarthritis, Modified drug delivery, Sustained release tablet, Pre-compression and post-compression studies.

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INTRODUCTION

Osteoarthritis

Osteoarthritis is a generative condition that affects the synovial joints and is characterised by a focused loss of articular hyaline cartilage, the proliferation of new bones, and modification of the shape of the joints.[1]Although the damage to joints cannot be repaired, osteoarthritis symptoms are typically manageable.[2-4]Being physically active, keeping a healthy weight, and obtaining specific therapies may decrease the disease's course and help with pain relief and joint function.[5-7] Osteoarthritis affect the various bones as shown in fig. 1 and 2.

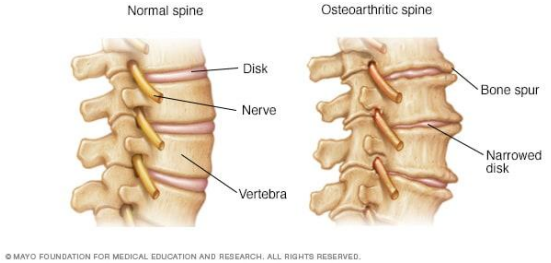

Figure 1: Osteoarthritis of the spin

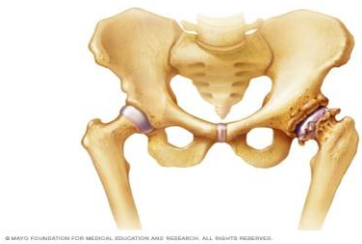

Figure 2: Osteoarthritis of the hip

Risk Factors

1. **Age** – age is the strongest risk factor for OA. Can start in young adulthood if people over 45 years old you are at higher risk.[9,10]
2. **Female Gender** – In general OA occurs in women. Before age 45. OA occurs more frequently in men after age 45.[11-13]
3. **Joint Alignment** – People with joints that more or fit together incorrectly. Such as bow legs, a dislocated hip.[14]
4. **Hereditary Gene Defect** – A defect in one of the genes responsible for the cartilage component callogen can cause deterioration of cartilage.[15-17]
5. **Joint injury or overuse caused by physical labour or sports** – Traumatic injury to the Knee or Heep increases your risk for developing OA in these joints.
6. **Obesity** – Being overweight during midlife or the later years is among the strongest risk factor for OA of the knee.[18]
7. Osteoarthritis uncommonly affects the shoulder, wrist, elbow, metacarpophalangeal joints and ankle Commonly affected areas are shown in fig.3.[18]

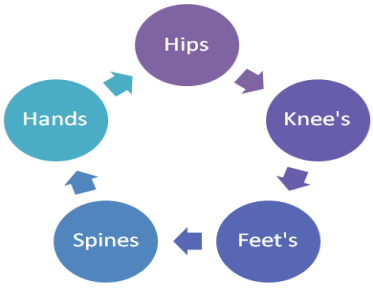

Figure 3: Commonly Affected Areas

Symptoms

Symptoms of osteoarthritis frequently appear gradually and get worse over time. Osteoarthritis symptoms and signs include:

1. **Pain:** Movement may hurt the affected joints during or after.[20,21]
2. **Stiffness:** Joint stiffness may be more apparent in the morning or after inactivity.
3. **Tenderness:** When you lightly press on or close to your joint, it could feel tender.
4. **Loss of flexibility:** The joint may not be able to move through its entire range of motion.
5. **Grating sensation:** When you utilise the joint, you could get a grating sensation and hear popping or cracking.[22]
6. **Bone spurs:** Around the afflicted joint, these additional pieces of bone that feel like hard lumps, can develop.[23]
7. **Swelling:** Inflammation of the soft tissues near the joint may be the cause of this.

Diagnosis of Osteoarthritis

- Medical History
- Physical Exam
- Tenderness, Swelling, Redness, Flexibility[24-26]
- X – ray
- Cartilage doesn't show up on x-ray images, but cartilage loss is revealed by a narrowing of the space between the bones in your joints.
- Other tests
- Blood test
- Joint fluid test
- Magnetic Resonance Imaging (MRI)[27]

Treatment of Osteoarthritis

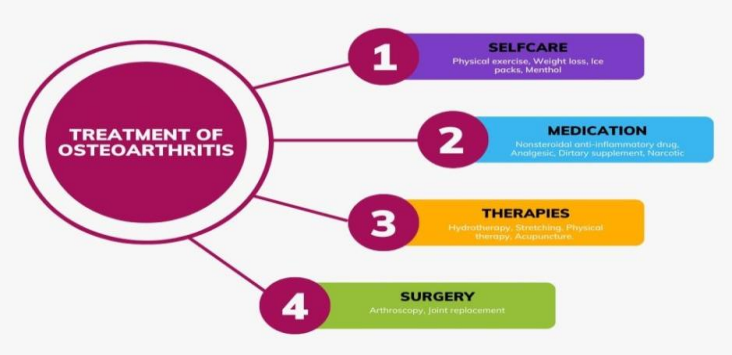

Figure 4: Treatment of Osteoarthritis

Self – care

1. **Physical exercise:** Aerobic activity for 20-30 minutes 5 days a week improves cardiovascular health. If injured, pursuing an activity that avoids the injured muscle group or joint[29]
2. **Weight loss:** Can improve cardiovascular health and reduce the risk of complications related to obesity.

3. **Ice packs:** Reduces inflammation and dulls sensation of pain.
4. **Menthol:** Oil made from mint that soothes sore throats and relieves itching.

Medication

1. **Nonsteroidal anti-inflammatory drug:** Relieves pain, decreases inflammation and reduces fever.

   Mechanism of Action (MOA): The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). Cyclooxygenase is required to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins. The therapeutic effects of NSAIDs are attributed to the lack of these eicosanoids.

   Eg. Ibuprofen (Motrin, Advil) Naproxen (Aleve) and Diclofenac (Voltaren, others)[30,31]
2. **Analgesic:**Relieves pain

   MOA:NSAIDs exert analgesic, anti-inflammatory, and antipyretic effects by blocking cyclooxygenases (COX), enzymes that are needed to produce prostaglandins. Understanding of the pharmacology of NSAIDs continues to evolve, but it is thought that most NSAIDs block the COX-1 and COX-2 isoenzymes [32]

   Eg. Acetaminophen (up to 4,000 mg/daily)
3. **Dietary supplement:** works along or in conjugation with other treatments to promote health.

   MOA: It is an endogenous amino sugar that is required for synthesis of glycoproteins and glycosaminoglycans, which are found in synovial fluid, ligaments, and other joint structures.

   Eg. Glucosamine
4. **Narcotic:** Relieves pain, dull the senses and causes drowsiness. May become additive.

   MOA: Inhibition of neurotransmitterrelease is considered to be the major mechanism of action responsible for the clinical effects of opioids.

   Eg. Oxycodone (OxyContin, Roxicodone)

Therapies

1. **Hydrotherapy:** Using water to relieve pain, treat diseases and maintain health. For example, mineral baths and hot tubs.
2. **Stretching:** Stretching exercise can improve flexibility and improve physical function.
3. **Physical therapy:** Restores muscle strength and function through exercise.
4. **Acupuncture:** Insertion of needles into specific points on the body to relieve pain and treat other conditions. A form of traditional Chinese medicine.

Surgery

1. **Arthroscopy:** Procedure to diagnose and treat joint problems using a tiny camera inserted through a small surgical opening.
2. **Joint replacement:** Removing a damaged or defective joint and inserting a new, functioning one in its place.

Oral Drug Delivery

Oral drug delivery is the most preferred administration route due to non-invasive, high patient compliance, convenient to handle, and does not require any specific sterile conditions. However, some of the drugs administered orally face several physical, biological, and biochemical barriers which lower the therapeutic efficacy of the drugs before getting absorbed into the systemic circulation

Because oral administration offers various benefits for patients, such as simplicity of medication administration by patients and a high degree of dosage flexibility, oral drug delivery is regarded as an appealing method and may be the most chosen route for drug administration. Drugs administered orally should be safeguarded from the effects of first-pass liver effects following oral delivery and drug degradation caused by the GI system before reaching the targeted areas. The advantages of oral administration over other routes of medication delivery include convenience, patient compliance, and cost efficiency. It is the most practical, patient-friendly, economical, and secure route of administration for treating a variety of disorders.

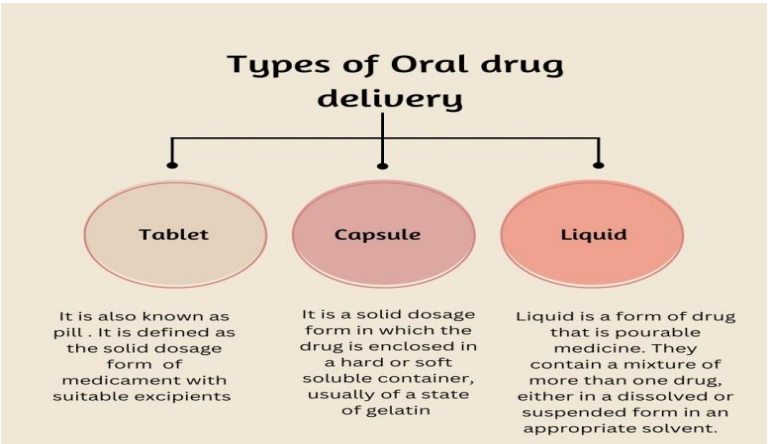

Figure 5: Types of oral drug delivery

Modified Release Drug Delivery

The term "Modified Release" refers to both delayed and extended release systems for oral administration as well as other delivery systems designed specifically to modify the release of poorly water soluble drugs.[35]

Modified release drug products are those that alter the timing and the rate of release of drug substance.

Types of modified release dosage form

a) **Delayed release:** These are dosage forms designed to release the drug at a time other than promptly after administration. (*Eg. enteric coated dosage forms like enteric coated aspirin, other NSAIDs etc.)*

b) **Extended release:** One that allows a reduction in dosing frequency to that presented by a conventional dosage form. Designed to release their medication in controlled manner, at pre-determined rate, duration and location in the body to achieve and maintain optimum therapeutic blood levels of drug. *(Eg.Controlled release, Sustained release and long acting drug products.)*

c) **Repeat action:** These are dosage forms usually containing two single dosage of medication, one for immediate and the second for delayed release *(eg. Bi-layered tablets)*

d) **Targeted release:** Drug release that is directed towards isolating or concentrating a drug in a body region, tissue, or site for absorption or drug action. *(Eg. Liposomes, Niosomes)*

Sustained Release Drug Delivery

Sustained release dosage form are dosage form that maintains the therapeutic blood or tissue levels of drug by continuous release of medication for a prolonged of time, after administration of a single dose. In case of injectable dosage forms it may vary from days to months. Delivery of drug can be achieved using various types of dosage forms including (*Tablets, Capsules, Creams, Ointments, Liquids, Aerosols, Injections, Suppositories*).[36]

The goal in designing sustained or controlled delivery systems is to reduce frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, providing uniform drug delivery.

Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system. These systems sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy of drug. They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in therapeutic window as shown in fig. 6. Sustained release system have benefits like patient compliance, avoid multiple dosing, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional system.[37,38]

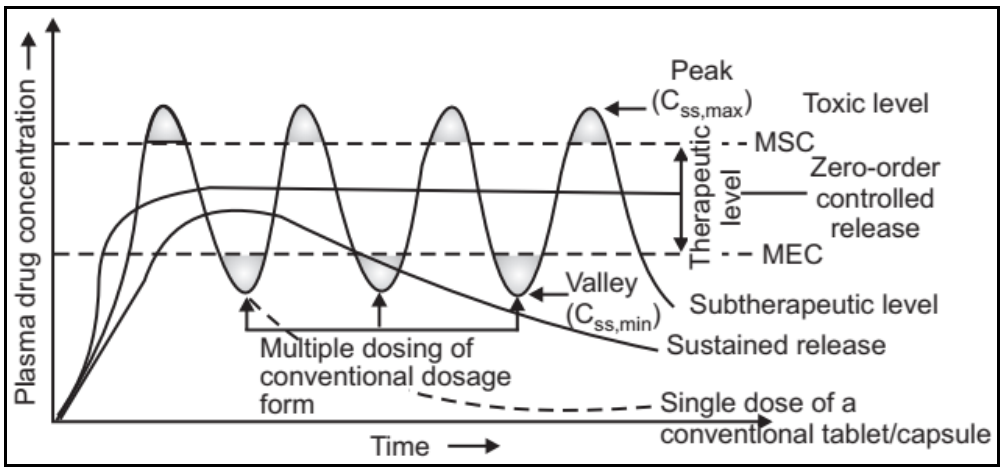

Figure 6: Plasma Drug Concentration Profile

Advantages

i. Reduction in blood level fluctuations of drug, thus better management of disease
ii. Make use of special effects, e.g. Treatment of Arthritis
iii. Reduce side effects
iv. Maximum bioavailability with a minimum dose
v. Improved patient compliance
vi. Reduces nursing and hospitalizing time

Disadvantages

i. Poor *in- vitro* and *in-vivo* relationship
ii. Dose dumping
iii. Delayed onset of action, hence sometimes not useful in acute conditions
iv. Higher manufacturing costs[39]

Challenges and Future prospects in sustained release drug delivery system

There are various challenges and future aspects in sustained drug delivery system like development of non-protein mimetic drugs, new drug modalities, targeting to intracellular sites and understanding structures of protein drugs these are givenin fig.7 [40-42]

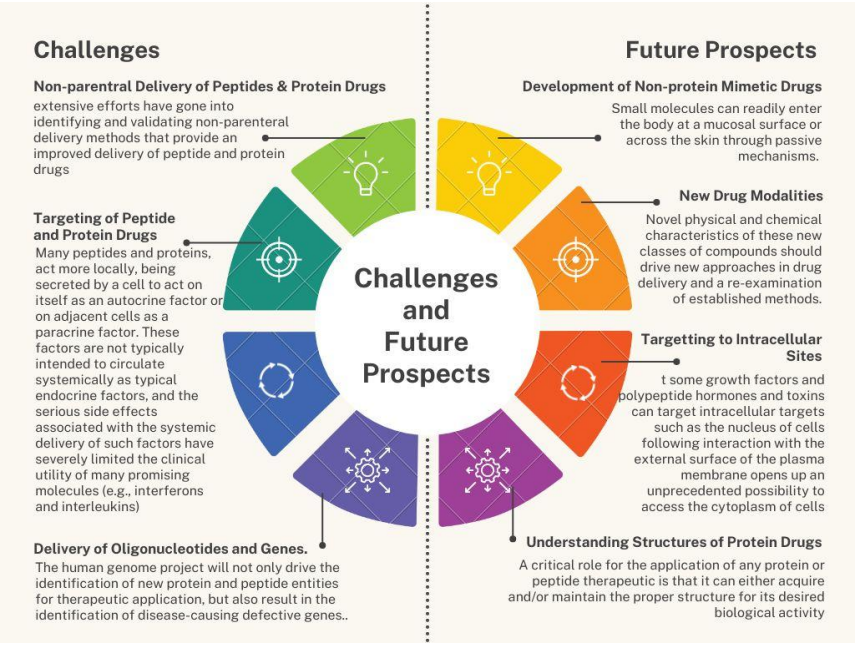

Figure 7: Challenges and future prospects

Sustained release tablets

These medications prolong the medication's release from a tablet or capsule so that patient will get the medication's benefits over a longer period of time. This means that patient need to take fewer doses throughout the day. Sustained release, sustained action, prolonged action controlled release, extended release, depot release these are the various terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over a long period of time after administration of a single dose of drug. By localizing at the site of action, lowering the dosage needed, or ensuring uniform drug distribution, sustained release delivery systems seek to decrease frequency of dosing or boost the effectiveness of the treatment. One dose and the length of the therapy, whether it be for a few days or a week, as in the case of an illness, or for the patient's lifetime, as in the case of hypertension or diabetes, are the two requirements for the optimal drug delivery system. Second, it should minimize side effects by delivering the active ingredient right to the location of the action.[43]

Formulation of granules

Different tablet formulations were prepared by wet granulation technique as shown in f. All the powders were passed through 24 mesh. Required quantity of drug, diluents and polymers were mixed thoroughly and a sufficient quantity of binding agent was added slowly. After enough cohesiveness was obtained, the mass was sieved through 16 mesh. The granules were dried at 50ºC for 45minuts and were mixed with talc and magnesium stearate. The tablets were compressed using tablet compression machine.[44,45]

Figure 8: Steps of Wet Granulations

Evaluation of granules Steps of wet granulation

Angle of repose

The static angle of repose of the considered granules was assayed using the funnel methodology. First, the granules were accurately weighted and then taken in the funnel. The tip of the funnel was considered to just touch the apex of the heap of the granules and, to do so, the height of the funnel was adjusted. The granules were allowed to freely flow through the funnel onto the surface. The diameter of the powder cone was measured, and the angle of repose was calculated using

$$\text{Tan}\Theta = \frac{h}{r}$$

Where,

h is the height of the powder cone.

r is the radius of the powder cone.

Bulk density

Bulk density is determined by pouring powder into a graduated cylinder via a large funnel and measure the volume and weight.

$$\text{Bulk Density} = \frac{\text{Weight of the powder}}{\text{Bulk Volume of powder}}$$

Tapped density

A known weight of the powder was transferred to a measuring cylinder, tapped manually 100 times, and the ratio of weight to volume of the powder gives the TD.

$$\text{Tapped Density} = \frac{\text{Weight of the powder}}{\text{Tapped volume of powder}}$$

Compressibility index

The compressibility index of granules was determined using Carr's compressibility index according to Equation.

$$\text{Carr s Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density} \times 100}$$

Hausner's ratio

The Hausner's ratio, determined by using Equation, is related to interparticle friction and can be used to predict the powder flow properties.[46-50]

$$\text{Hausner's ratio} = \frac{\text{TappedDensity}}{\text{Bulk Density}}$$

EVALUATION OF TABLETS

Thickness

The thickness of tablets was determined using Vernier caliper. Five tablets from different formulations were used and their average values reported in millimeters.

Weight variation test

To study the weight variation, twenty tablets of different formulations were weighed using an electronic balance. Weight values were determined in milligrams (mg).

$$\%\ \text{Weight Variation} = \frac{\text{Average Weight} - \text{Individual Weight}}{\text{AveragWeight}} \times 100$$

Hardness test

For each formulation, the hardness of six tablets was determined using a hardness tester (Monsanto hardness tester). Hardness values were reported in kilograms (kg). Mean and standard deviation (SD) values were calculated.

Friability test

For each formulation, six tablets were placed in the friabilator and subjected to 100 rotations for 4 min. The tablets were then deducted and reweighed. The friability was calculated as the percentage weight loss, using Equation.[51-56]

$$\text{Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) experiments were carried out to find out the presence of any interaction among drug and the excipients. Pure drug, 1:1 ratio of drug and polymer, and optimised formulation were subjected to the analysis. About 5-15 mg of sample to be analysed was taken in the pierced DSC aluminium pan and scanned in the temperature range of 50-300 °C. The heating rate was 10°C/min.; nitrogen served as purged gas and the system was cooled down by liquid nitrogen.[57]

Drug content

Twenty tablets were randomly selected and crushed for the estimation of drug content. Powder weight equivalent to 50 mg was transferred into 50 ml volumetric flask and made to the volume by phosphate buffer pH 7.0. The flask was placed in a sonicator till completely soluble. The solution was filtered through a filter paper and from this 1 ml was taken and transferred to 25 ml volumetric flask which was made up to the mark by phosphate buffer pH 7.0. The absorbance of the solution was measured using UV/ Vis spectrophotometer[58]

In-vitro release studies

The release of Sustained Release tablets was monitored in a dissolution medium consisting of 900 mL of phosphate buffer (pH = 6.8) kept at 37.0 ± 0.5 °C and stirred at 50 rpm, using USP dissolution apparatus under described sink conditions. A volume of 5.0 mL of sample was withdrawn through a 0.45 µm filter and replaced with another 5.0 mL of a suitable fresh dissolution medium kept under the same conditions at preselected intervals, up to 24 h.[59]

Stability studies

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation, by keeping at 40°± 2°C, in air tight high density polyethylene bottles for three months, at RH 75±5%. Physical evaluation and in vitro drug release was carried out in each month[60]

Table 1: Example of the marketed products

Brand name	Dosage form	Drug (dose)	Company, Country
Rachic-SR	Sustained release tablet	Lornoxicam	Alaina Pharma, Himachal Pradesh, India
Smonac-200 SR	Sustained release tablet	Aceclofenac	PCD Pharma Franchise, India
Etonox-ER	Extended release tablet	Etodolac	Salveo Lifecare, Punjab, India
Etova-ER 600	Extended release tablet	Etodolac	Ipca Laboratories Ltd, Mumbai, India
Ldotac-600-ER	Extended release tablet	Etodolac	Rech Elist Pharma, Chandigarh, India

DISCUSSION

The basic role of sustained release drug delivery system shows the biopharmaceutical, pharmacokinetic and pharmacodynamics properties of a drug in such a way that its utility is maximized, side-effects are reduced and cure of the disease is achieved. Sustained release tablet implies slow release of the drug over time period. The development of sustained-release drug delivery systems (DDSs) for Osteoarthritis may be an attractive strategy to prevent rapid drug clearance and improve the half-life of a drug at the joint cavity.

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Conflict of interest

Author has no any conflict of interest.

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