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Counteracting the Arthritis : A Retrospection of Methotrexate Sustained Release System

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ABSTRACT

Aim of review is to treat the arthritis. Rheumatoid arthritis is an auto-immune joint disorder involving pain and inflammation. Various drugs are used for pain management and relief from arthritis with single and multiple dose therapy. Different drugs are especially suitable for achieving controlled and delayed release profile with low risk of dose dumping. These systems have received great attention of thus increasing patient compliance and economic feasibility and avoiding drug associated side effects. Present review mainly deals with the problem of rheumatoid arthritis in pain management, various approaches to overcome this and specifically explore the possibilities to apply modified drug delivery systems for this purpose.

KEYWORDS: Arthritis, Modified drug delivery system, Methotrexate.

INTRODUCTION

Rheumatoid arthritis (RA) is a common form of arthritis; it is a chronic and autoimmune disease that causes inflammation of the joints, the tissue around the joints, as well as other organs in the body. It is characterized by persistent synovitis, systemic inflammation, and auto antibodies (particularly to rheumatoid factor and citrullinated peptide). It is a progressive illness that can lead to long-term joint damage, loss of function and disability. [1] 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. [2]

Signs and Symptoms of Arthritis

- Inflammation and redness of a joint
- Joints will be sensitive to touch
- Deformation of limbs and extreme pain and warmth
- Stiffness of limbs during morning session
- Recurrent back pain
- Ankylosed joints (immobile joints due to the union of bones because cartilage has been destroyed) [3]

The current therapies for RA are as follows: Non-steroidal anti-inflammatory drugs ($NSAID_S$), Glucocorticoids, Non-biologic disease-modifying anti-rheumatic drugs ($DMARD_S$) and Biologic DMARDs.

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NSAIDs is a very effectively relieves pain and stiffness at RA. Glucocorticoids belonging to class of steroid hormones have potent anti-inflammatory and immunosuppressive properties. Corticosteroids, both systemic and intra-articular, are important adjuncts in the management of RA, they effectively relieve synovitis. The need for biologic DMARDs has arisen because conventional DMARDs have several short comings such as slow onset of action, partial remission in many cases, substantial toxicity that requires careful monitoring, and tendency to lose effectiveness with time—'slip-out'. [4]

Percentage according rheumatoid arthritis patient used different therapies. This graph showed 86% patient use NSAIDs, 79% patient use disease modifying anti-rheumatic drug (methotrexate), 72% patient use oral steroids and 66% patient use biologic DMARDs shown in fig 1.

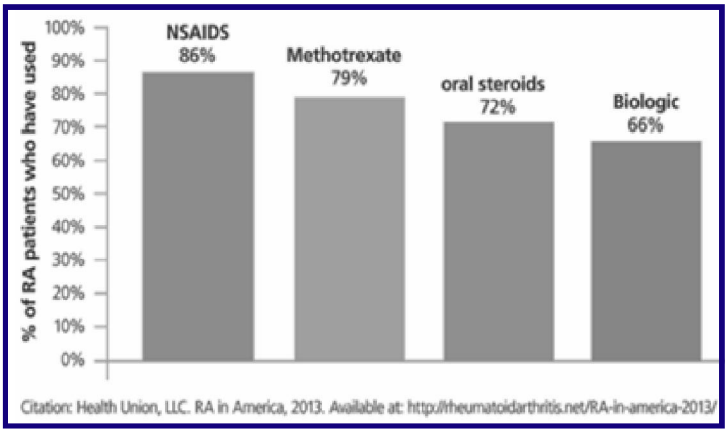

Fig. 1: Figure shows the percentage of drugs use by rheumatoid arthritis patient

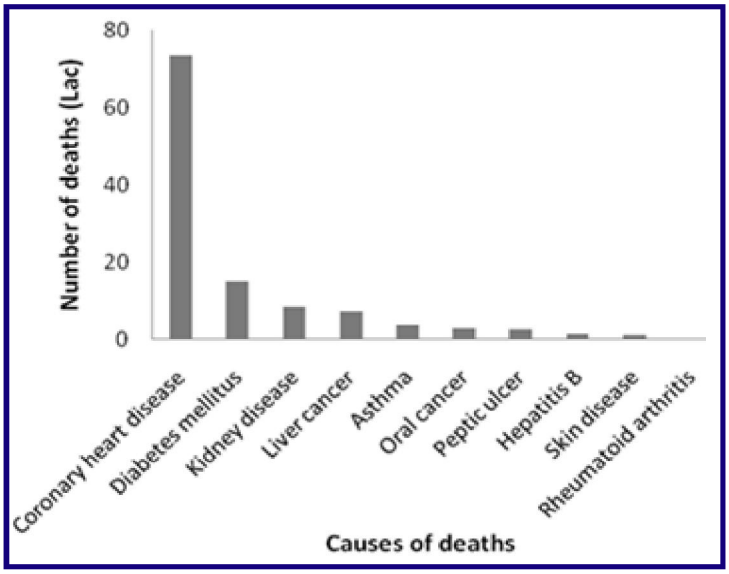

Fig. 2 Figure shows world ranking total deaths

Sustained release (SR) dosage form is better than conventional dosage form because SR dosage form are designed to achieve prolong therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose while conventional dosage form multiple dose administration is necessary. So sustained release dosage form effective for rheumatoid arthritis.

Sustained release term used to identify drug delivery system. [5] The drug release profile of the oral controlled release system maintains the drug plasma concentration level within the therapeutic range, through a specific rate and time frame, resulting in continued therapeutic action. Oral controlled release drug delivery is a system that provides constant oral drug release with expected pharmacokinetic parameters over a predetermined rate and time. It maintains a relatively continuous and effective drug level in the blood. [6]

Various advantages of sustained release drug delivery system: It Improved patient convenience and compliance due to less frequent drug administration. Reduction in fluctuation in steady-state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects. Increased safety margin of high potency drugs due to better control of plasma levels. Maximum utilization of drug enabling reduction in total amount of dose administration. [7]

Various reasons for making SR: It reduces the frequency of dosing. Increase effectiveness of the drug by localization at the site of action. Reducing the dose required. Providing the uniform drug delivery. [8]

Different dosage form for sustained release drug delivery system of antirheumatic drug like tablets, capsules, microcapsules, microspheres (beads), nanoparticles, pellets, Suppositories, niosomes, Micro sponge. It describes in below.

Table No 1: Details of various SR dosage form and polymer used in them for antirheumatic drug

S. No.	Worker & year	Drug	Polymer	Dosage form	Remark
1	Liao, J.C., Wei, Z.X.,Ma, Ma, Z.P., Zhao. C. and Cai, D.Z., 2016	Indomethacin	Carbopol 934	Gel	This work involves that sustained release indomethacin gel show significant analgesic and anti-inflammatory activities. [9]
2	Dhanaraj, S.A., Muralidharan, S., Venugopal, V. and Kanniappan, P., 2016	Methotrexate	Chitosan	Nanospheres	This study concluded that methotrexate nanospheres increase the amount of drug reaching the site of action, reducing its action on neighbouring tissue. [10]
3	Savjani, K., Gajjar, A. and Savjani, J., 2016	Febuxostat	Microcrystalline cellulose	Beads	Researcher achieves modified release formulation of Febuxostat to improve its efficacy and reduce toxicity and thereby improving safety as well. [11]
4	Asiniparthi, M., Anusha and Donti, v., 2016	Montelukast Sodium	Ethyl cellulose and HPMC	Tablets	The present work introduce tablet of montelukast sodium showed that the core was compared with the pure drug where it showed 46.26 % of drug release in 15 minutes whereas core exhibited 98.96% in 15 minutes.[12]
5	Qi, X., Qin, X., Yang, R., Qin, J., Li, W., Luan, K., Wu, Z. and Song, L., 2016	Diclofenac Sodium	Sodium alginate	Microspheres	The present work tells that microspheres of diclofenac sodium revealed that the combined system seemed to effectively reduce the swelling of arthritis joints and had superior anti-inflammation effects than drug solution.[13]

S. No.	Worker & year	Drug	Polymer	Dosage form	Remark
6	Dineshmohan, S., Gupta, V.R.M., Ramesh, A., Harika, V. and Sravani, T., 2015	Lornoxicam	HPMC, ethyl cellulose	Press Coated Tablets	This work investigates the preparation of sustained release lornoxicam show more effective for treating the pain and inflammation of rheumatoid arthritis. [14]
7	Basavaraja, Navade, K., Rao, B.S. and Kulkarni, S.V., 2015	Flurbiprofen	HPMC	Tablet	This study analyse sustained release flurbiprofen tablets was showed no much interaction between drug and polymer and perform better than conventional dosage forms. [15]
8	Mazahirraza, Fatima, T. and Shukla, A.K., 2015	Prednisolone	Lecithin	Liposomal Gel	This work examine prepared modified release of Prednisolone drug to improve therapeutic response and reduce the possible adverse symptoms.[16]
9	Fatima, T., Mazahir, R. and Shukla, A.K., 2015	Prednisolone	Carbopol-940	Liposomal Gel	The present work indicates prepared liposomal product of prednisolone to improve therapeutic response and reduces the possible adverse symptoms. [17]
10	Momoh, M.A., Kenechukwu, F.C., Gwarzo, M.S. and Builders, P.F., 2015	Ibuprofen	Polyvinyl alcohol	Lipospheres	This work explores modified release of ibuprofen used for pain and inflammatory condition and exhibited good anti inflammatory and analgesic properties. [18]
11	Ramkanth, S., Jayaprakash, s. and Vimalakannan, T., 2015	Tenoxicam	HPMC, Ethyl cellulose	Patches	This formulation shown to be efficacious, safe, stable and non-irritant to skin in rheumatoid cases. [19]
12	Husen, S. and Patel, M.R., 2015	Diclofenac sodium	Methocel	Tablets	Researcher tells that sustained release bilayer tablet of diclofenac sodium for the effective treatment of patient with acute musculoskeletal spasm or acute low back pain [20]
13	Ramesh, K.V.R.N.S., Walayat, F.S., Usman, S., Sarheed, O. And Kumar, M.V., 2015	Indomethacin	Badam gum and Gelucires	Matrix Tablet	present study suggest that employing a combination of hydrophilic and hydrophobic gelucires is a promising approach to design sustained release products of poorly soluble drugs such as IM. [21]
14	Garad, S.V., Jagme, C.M. and Somnathe, N.D., 2015	Metformin	Ethyl cellulose	Tablet	This work formulation designed to achieve prolonged therapeutic effect by continuously releasing medicament over an extended period of time. Metformin showed better release profile. [22]
15	Patel, K.C., Pramanik, S., 2014	Ibuprofen	Calcium alginate & calcium pectinate	Beads	Researcher present Floating beads shows two-phase release pattern. Formulation shows no major change in drug entrapment efficiency, floating behaviour and in-vitro dissolution pattern.[23]
16	Shafi, P., Pratyusha, A. and Rao, M., 2014	Lansoprazole	HPMC	Tablets	Present work concluded that, press coating of drug is necessary for providing pulsatile release profile. [24]
17	Shivhare, U.D., Suruse, P.B. and Varvandkar, S.S., 2014	Acelofenac	HPMC E-15 and Eudragit RL 100	Buccal Patch	This study is good way to bypass the extensive hepatic first pass metabolism and increase bioavailability. [25]
18	Manjula, D., Shabaraya, AR. and Shyale, S., 2014	Fenoprofen Proliposomes	Lecithin	Liposomes	This work concluded that fenoprofen loaded liposomes seem to be promising controlled delivery system. [26]
19	Abirami, A., Halith, S.M., Pillai, k.k. and Anbalagan, C., 2014	Indomethacin	HPMC, methyl cellulose and ethyl cellulose	Pellets	This study investigates the pellet formulation reduced dosing frequency, increased bioavailability and provides better patient compliance. [27]
20	Preeti, Kumar, M.S., 2014	Celecoxib	Carbopol	Transformal Gel	Dosages form preparation show transfersomal gel of Celecoxib possessed better skin permeation potential, better stability and higher entrapment efficiency, easy to scale up and ability as a self penetration enhancer. [28]

S. No.	Worker & year	Drug	Polymer	Dosage form	Remark
21	Moholkar, A.V., Attar, M.S., Banode, S.R., Jadhav, A.R. and Wandhre, M.D., 2014	Metformin HCL	HPMC K 100, Polyvinyl and pyrrolidone K 90	Tablets	This work explore metformin hydrochloride tablet prepared by melt granulation method and improve the patient compliance & systemic adverse side effects. [29]
22	Palo, A.K., Ghose, D., Saha, G. and Subudhi, S.K., 2014	Metformin	HPMC	Tablets	This work is conducting metformin prepared by direct compression method. reduce the frequency of administration and decrease the dose-dependent side effects [30]
23	Mallick, J., Sahoo, D., Sahoo, C.S., Dinda, S.C., 2013	Indomethacin	Sodium alginate	Beads	This work investigates the surface topography of indomethacin beads shows circular shape. X-Ray Diffraction studies and differential Scanning calorimeter studies show no drug polymer interaction. [31]
24	Christina, E., 2013	Diclofenac sodium	Sodium alginate	Microspheres	The present work tells microspheres prepared without use of organic solvents. It decreases the side effects and improves patient compliance by reducing the number of dosing. [32]
25	Khadabadi, S.S., Chishti, N.H., Khan, F.M., Tadvee, A.A., 2013	Ketoprofen	HPMC	Press Coated Tablets	The present work tells drug delivery system was achieved maximum efficacy, safety and affordability. [33]
26	Kumar L.D., Babji, M., Kumari, PV.K. and Rao, Y.S., 2013	Lornaxicam and Acelofenac	Micro crystalline cellulose, propylene glycol, HPMC	Liquisolid compacts (Lornoxicam) and Matrix Release Tablet (Aceclofenac)	Researcher tells that lornaxicam lowers the pain by an initial rapid release from the immediate release layer followed by controlled release of aceclofenac from the SR bilayered tablet. [34]
27	Nagaich, U., Deepak, P., Sharma, A., Gulati, N. and Chaudhary, A., 2013	Leflunomide	HPMC and Ethyl cellulose	Matrix Tablet	This research work focuses on the fabrication and in vitro characterization of leflunomide loaded sustained release matrix tablets using different concentration of hydrophilic polymer, hydrophobic polymer and a combination of both. [35]
28	Hadi, M.A., Rao, N.G.R. and Rao, A.S., 2013	Lornoxicam	HPMC, Ethyl cellulose and PVP	Compression coated tablets	Dosage form preparation shows sustained release of lornoxicam more effective for treating the pain and inflammation of rheumatoid arthritis [36]
29	Gokhale, K.S. and Jonnalagadda, S., 2013	Infliximab	Poly lactic-co-glycolic acid	Microspheres	This work shows that microspheres can present an alternative delivery method for infliximab. [37]
30	Karthika, R and Elango, K., 2013	Lornoxicam	Polyvinyl alcohol	Microsponge Tablets	This study presents a new approach for the preparation of modified microsponges with prolonged release characteristics. Drug is not interacting with the excipients. [38]
31	Patel, J., Patel, M. and Bhandari, A., 2013	Ketoprofen	HPMC, Ethyl Cellulose, MCC	Press coated Tablet	This preparation explore hydrophilic polymer used has less effect on lag time, while hydrophobic polymer considerably delays the lag time. As the viscosity grade and amount of polymer increases, the lag time also increases. [39]
32	Srinivas, L., Lohithasu, D., Madhupriya, D., Siddhartha, N. and Tejaswi, N., 2013	Ibuprofen	HPMC and Polyethylene oxide	Pulsatile Capsules	This study show sustained release of ibuprofen increase the efficacy and safety. [40]
33	CM, A., Ahad, H.A., A, Abhilash, KJ, P. and K, S., 2013	Acelofenac	Micro crystalline cellulose	Tablets	The present study revealed that aceclofenac appears to be suitable for use as a release retardant in the manufacture of once daily sustained release matrix tablets because of its good swelling, good flow and suitability for matrix formulations. [41]
34	Sapnil, C., Rao, V.U.M., Vishnu, P. and Kumar, A.B., 2013	Tramadol hydrochloride	HPMC	Tablets	The study includes development of the robust and stable product, which complies with the marketed product. [42]

S. No.	Worker & year	Drug	Polymer	Dosage form	Remark
35	Aksu, B., Yuedasiper, A., Ege, M.A., Okur, N.U. and Karasulu, H.Y., 2013	Indomethacin	plasdone (PVP K-90) and compritol-HD5	Capsules	This study concluded extended release hard gelatin capsules can be a promising alternative for the other oral formulations of indomethacin. [43]
36	Ibrahim, M., 2013	Mefenamic acid	Micro crystalline cellulose	Matrix Pellets	This study present formulation helps to obtain a controlled release dosage form capable of lowering the risk of side effects and improving patient convenience as an advantage of pellets as a drug delivery system. [44]
37	Sandhya, P, Habeeb, S., Sunitha, M., Patnaik, K.R. and Subrahmanyam, CVS, 2013	Etodolac	HPMC, Xanthan gum and guargum	Tablets	This study delivers the drug at a pre-determined rate for maintaining a relatively constant, effective drug levels in the body for a specific period of time. [45]
38	Kurakula, M., Srinivas, C., Kasturi, N. and Diwan, P.v., 2012	Prednisolone	Lecithin	Proliposomal Gel	This work tells that sustained release of prednisolone enhanced anti inflammatory activity implicating its potential in effective topical pharmacotherapy for the treatment of rheumatoid arthritis. [46]
39	Patel, S., Modasiya, M.K., Patel, V.M. and Patel, A.K., 2012	Meloxicam	PEG, PEG and HPMC	Tablet	This study achieve chronotherapeutic release Of meloxicame for treatment of rheumatoid arthritis, osteoarthritis, spondylytis and to improve the patient compliance. [47]
40	Jessy, S. and Amol, S., 2012	Aceclofenac	Eudragit	Microspheres	This work investigates microspheres show excellent lag at acidic pH, which may be due to insolubility of the drug and polymer. [48]
41	Kumar, K. And Rai, A.K., 2012	Curcumin	HPMC, Ethyl cellulose, Polyvinyl pyrrolidone, Eudragit	Microspheres	This work present floating microspheres show discrete, spherical and free flowing nature.[49]
42	Irfan, M., Verma, S. and Ram, A., 2012	Ibuprofen	Span 80 and Tween 80	Transferosome	This preparation shows transferosome is spherical shape and indicate that the elasticity of vesicle depend on both surfactant, concentration With increase in surfactant concentration. [50]
43	Chauhan, D. and Shah, 2012	Acelofenac	Eudragit L-100 and S-100	Microspheres	This study showed that the microspheres exhibited both pH sensitive and controlled release properties. [51]
44	Kumar, K.S., Sekhar, K.B.C. and Reddy, P.J., 2012	Naproxen sodium	Chitosan	Microspheres	This study explores the cross linked microspheres showed better results than the less cross linked microspheres. [52]
45	Mehmood, Y., 2012	Allopurinol and Diclofenac sodium	Avicel	Tablets	It concluded that formulation of combinational drug of Diclofenac sodium and Allopurinol can be use for the gout treatment; all the trial batches give good result for combinational drug. [53]
46	Kumar, T.V., Vasanthan, A. and Muthu, R.P.E., 2012	Budesonide	HPMC, Ethyl cellulose and Eudragit	Capsules	This study present by using extended release form there is a reduction in dosing frequency, reduction in plasma fluctuations consequently potential side effects can be minimized. [54]
47	Shaji, J. And Shinde, A., 2012	Aceclofenac	Eudragit-S100 and Eudragit-L100	Microspheres	This study shows floating pulsatile concept is increase the gastric residence of the dosage form having lag phase followed by a burst release.It develop a multiple unit, floating pulsatile drug delivery system for aceclofenac To provide relief for rheumatoid arthritis. [55]
48	Zhao, L., Wei, Y., Mei, Y., Yang, L., You, Y., Yang, X. and Jiang, Y., 2012	Metformin Hydrochloride	Carboxymethyl cellulose	Tablets	This work delivers metformin hydrochloride prepared by film coating method. It decreased hepatic and renal gluconeogenesis. [56]
49	Shaikh, A.C., Nazim, S., shaikh, S., Khan, T., Patel, M.S., Zameeruddin, M., Shaikh, A., 2011	Aceclofenac	HPMC	Matrix Tablet	This study present aceclofenac raw material was show passable flowability and encourages clinical trials and long term stability study on this formulation. [57]

S. No.	Worker & year	Drug	Polymer	Dosage form	Remark
50	Shanmugarathinam, A. and Puratchikody, A., 2011	Aceclofenac	Eudragit RL, Eudragit RSPO and Ethyl cellulose	Microspheres and Tablets	This work concluded aceclofenac loaded microspheres prepared by O/W solvent evaporation method. This study improve bioavailability and to target drug to specific sites. [58]
51	Kumar, V.D., Kumar, O., Premalatha, A. and Kumar, M.R., 2011	Deflazacort	HPMC K100M, Ethylcellulose and HPC	Tablets	This study concluded that the release rate of drug was found to be followed zero order kinetics from the matrix tablets. [59]
52	Honary, S., Ebrahimi, P., Naghibi, F. and Chaigani, M., 2011	Indomethacin	Ethyl cellulose	Microspheres	This work delivers formulation of indomethacin suitable of matrix formulation for controlled release. [60]
53	Mahajan, A.G., Jagtap, L.S., Chaudhari, A.L., Swami, S.P. and Mali, P.R., 2011	Indomethacin	Eudragit RS 100	Micro sponge	This study present micro sponge drug delivery system reduced side effects, improved stability, increased enhanced formulation flexibility. [61]
54	Basavaraj, Rao, B.S., Kulkarni, S.V., Patil, P. and Surpur, C., 2011	Aceclofenac	Microcrystalline cellulose	Matrix Tablets	This study show sustained release dosage form, compared to a conventional dosage form, is the uniform drug plasma concentration and therefore uniform therapeutic effect. [62]
55	Pandya, P.V., Patel, V.B. and Patel, P., 2012	Captopril	HPMC	Tablets	This study tells that tablets showed drug release up to 24 hrs in controlled manner. [63]
56	Kannan, S., Manivannan, R., Nishad, K.G.P.K. and Kumar, N.S., 2010	Aceclofenac	HPMC	Tablet	This study concluded aceclofenac raw material was show passable flowability and encourages clinical trials and long term stability study on this formulation. [64]
57	Bhardwaj, P., Chaurasia, H, Chaurasia, Deepti, Prajapati, S.K. and Singh, S, 2010	Indomethacin	Eudragit S100 and Eudragit RS100	Floating Microballoons	This work concluded that by changing the ratio of polymers (RS100 and S100) and solvent (DCM and EtOH), indomethacin release can be controlled. These microballoons could be dispensed by filling them in the empty capsule shell. [65]
58	Yurdasiper, A. and Sevgi, F., 2010	Mefenamic acid	Chitosan, Alginate and Eudragit RS	Microparticles	This formulation tells that less frequent drug administration is possible, lower plasma peak concentrations can be obtained to avoid adverse effects, and patient compliance can correspondingly be improved. [66]
59	Ahad, H.A., Kumar, C.S. and Yesupadam, P., 2010	Aceclofenac	Microcrystalline cellulose	Tablets	This study revealed that aceclofenac appears to be suitable for use as a release retardant in the manufacture of once daily sustained release matrix tablets because of its good swelling, good flow and suitability for matrix formulations. [67]
60	Jayaprakash, S., Halith, M.S., Firthouse, M.PU., Yasmin, Nagarajan, M., 2010	Celecoxib	HPMC, Methelcellulose, Polyvinylpyrolidone	Patches	This study reduced frequency of administration, and thus may improve the patient compliance. [68]
61	Lotlikar, V., Shidhaye, S., Kedar, U. and Kadam, V., 2010	Ketoprofen	Eudragit Rs	Pellets	This study present the drug loaded pellets in matrix prepared by extrusion method. Multiparticulate sustained release drug delivery system of ketoprofen is show sustained release for 12 hours and escaping the contact of drug with gastric mucosa.[69]
62	Reddy, S., Kumar, P.P., Kandagatla, R. and Rao, M.Y., 2010	Metformin hydrochloride	HPMC K 4M and Sodium carboxy methyl cellulose	Tablet	This study investigate metformin HCl as sustained release indicate promising potential of drug in the form of bilayer tablets an alternative to the conventional dosage form. [70]
63	Ghosh, S., Barik, B.B., 2009	Aceclofenac	HPMC	Hydrophilic Matrix Tablets	This study present hydrophilic matrix tablets reveals good physical characterstics and formulation recommended for high dose. [71]

S. No.	Worker & year	Drug	Polymer	Dosage form	Remark
64	Dhanaraju, M.D., Sundar, VD, Nandhakumar, S. and Bhaskar, K., 2009	Diclofenac sodium	Sodium alginate	Hydrophilic Polymeric Beads	The work is concluding diclofenac sodium loaded beads is prepared by the ionotropic gelation technique. The developed formulations show effective in providing a SR of drug with high entrapment efficiency. [72]
65	Gattani, Y.S., Kawtikwar, P.S. and Sakarkar, D.M., 2009	Acelofenac	Eudragit 100	Microspheres	The present work tells floating microspheres of aceclofenac showed excellent percent yield, good incorporation efficiency, good buoyancy and prolonged drug release. [73]
66	Gupta, B.K., Pal, R., Chakraborty, M. and Debnath, R., 2009	Ieflunomide	Eudragit	Microcapsules	Dosages form preparation show drug-loaded microspheres are a suitable delivery system for leflunomide with a new choice of an economical, safe and more bioavailable formulation in the management of rheumatoid arthritis. [74]
67	Manjunatha, K.M., Ramana,M.V. and Satyanarayana, D., 2007	Diclofenac Sodium	Sodium alginate and Chitosan	Beads	This formulation was found to be effective in providing controlled release of drug for a longer period of time. [75]
68	Chandran, S., Ravi, P. and Saha, R.N., 2006	Celecoxib	HPMC and Ethyl cellulose	Tablets	Researcher tells that the rate of release of the drug from the designed tablets was observed to decrease as the proportion of HPMC and Ethyl cellulose is increased. [76]
69	Khazaeinia, T. and Jamali, F., 2000	Ibuprofen	Methyl cellulose	Tablets	This work indicates sustained release formulations of ibuprofen may offer the advantages of prolonged efficacy without increasing GI toxicity [77]
70	Tarimci, N. and Ermis, D., 1998	Indomethacin	Eudragit RS and RL, PEG'S	Suppositories	This study present sustained release suppository dosage forms enhance the bioavailability of different drugs. [78]

Role of methotrexate in arthritis treatment

Methotrextae is used to treat certain types of cancer and anti rheumatic drug. It was used at higher doses as a cancer therapy. [79] For cancer methotrexate is a folic acid derivative that inhibits dihydrofolate reductase, thereby decreasing tetrahydrofolate formation and DNA synthesis. Its use is well established in the treatment of various forms of malignancy but it is now also being used increasingly for the treatment of rheumatological disorders and psoriasis. [80] It inhibits purine and pyrimidine synthesis, suppression of transmethylation reactions with accumulation of polyamines, reduction of antigen-dependent T-cell proliferation, and promotion of adenosine release with adenosine-mediated suppression of inflammation. It is possible that a combination of these mechanisms is responsible for the antiinflammatory effects of methotrexate. To date, the adenosine-mediated anti-inflammatory effect of methotrexate is best supported by the in vitro, in vivo and clinical data. [81]

Table No 2: Various methotrexate sustained release dosage form

S.no.	Workers & year	Drug	Polymer	Dosage form	Remark
1	Theodore, E.A., Halith, S.M., Barish, Hepzi, F.R., 2015	Methotrexate	Span 20	Niosomes	Researcher tells that niosomes was used as drug carriers for Methotrexate, to reduce its renal, hepatic, gastrointestinal toxicity and to sustain the effect of drug release. [82]
2	Bhardwaj, J. and Mukhopadhyay, S., 2014	Methotrexate	HPMC	Multilayered Tablet	This work concluded that formulated multi-layered tablet formulation may be used as an effective tool for colon targeted drug delivery of Methotrexate. [83]
3	Zhang, N., Wardwell, P.R. and Bader, R.A., 2014	Methotrexate	Tripolyphosphate	Nanoparticles	The present study improving the site-specificity of the nanoparticles through surface modification with a targeting ligand and demonstrating in vivo that the nanoparticles can be used to enhance the efficacy of entrapped DMARDs through targeted delivery. [84]

S.no.	Workers & year	Drug	Polymer	Dosage form	Remark
4	Kumari, S.D.C., Tharani, C.S., Narayanan, Kumar C.S. and Kumar, C.S., 2013	Methotrexate	Sodium alginate and Chitosan	Nanoparticles	This work present methotrexate loaded NaAlg-CS nanoparticles could be effective in controlled drug release for a prolonged period. [85]
5	Genc, L. and Buyuktiryak, S., 2013	Methotrexate	Methanol	Microcapsules	The goal of this study is to provide controlled release of methotrexate and to reduce the toxic effect of methotrexate. [86]
6	Patel, J.D., Chauhan, S.P. and Seth, A.K., 2012	Methotrexate	Ethyle cellulose	Nnoparticle	This study explores controlled drug delivery strategies used to enhance the efficacy of the drug. [87]
7	Sahu, G.K., Sharma, H., Dapurkar, V. and Rai, G., 2012	Methotrexate	Span 80	Microspheres	This study indicated that the microspheres system studied well be a promising tool for sustained release delivery of methotrexate. [88]
8	Kotadia, R.M., Patel, V.A. and Patel, H.V., 2010	Methotrexate	Chitosan	Microspheres	This work present that methotrexate based chitosan beads were spherical shape, useful in predicting the in vivo bioavailability of the drug. [89]
9	Chaudhary, R., Qureshi, M.S., Patel, J., Panigrahi, U.P. and Giri, I.C., 2010	Methotrexate	Ethyl cellulose	Buccal Patches	This research present work release kinetics of methotrexate through buccal mucosa was studied. [90]
10	Bhagat, H.R., Hollenbeck, R.G., Pande, P.G., Bogdansky, S., 1994	Methotrexate	Carboxymethyl cellulose	Microspheres	This work indicates microspheres were spherical shape, ensure complete bioavailability and avoid the inconvenience and expense of continuous infusion of long duration. [91]

Dosage Forms

Controlled release tablets

Indomethacin tablet is a non steroidal antiinflammatory drug (NSAID) and COX inhibitor; it is used for relief of symptoms of arthritis, primary dysmenorrhea, fever. Povidone one of the promising polymer both at research level as well commercial level was used for this particular study in order to improve its dissolution rate.In this study skimmed milk is used due to its surface active agent and amino acid content. Additionally, the milk is proposed against gastric disturbance caused by NSAID. [92] Lornoxicam is also as a NSAID in relieving symptoms of osteoarthritis, rheumatoid arthritis, Ankylosing spondylitis, acute sciatica and low back pain. It inhibits prostaglandin biosynthesis by blocking the enzyme cyclooxygenase (both COX-1 and COX-2). Hydrophilic polymers like (hpmc k4 & hpmc k15) with ph modifier sodium bicarbonate & magnesium oxide could control the Lornoxicam release effectively for 24 hours. [93] Controlling the delivery rate of either single or two different API'S, to separate incompatible API's with each other, to control the release of one layer by utilizing the functional property of the other layer (such as osmotic property). [94]

Microspheres

Multiple unit dosage forms such as microspheres or beads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local irritation and elimination of unwanted intestinal retention of polymeric material, when compared to non-disintegrating single unit dosage form. Aceclofenac is a new orally effective NSAID of phenyl acetic acid group. It posses remarkable anti-inflammatory, analgesic and antipyretic properties. The short biological half-life (about 4 hrs) and dosing frequency more than one per day makes aceclofenac an ideal candidate for sustained release. [95] Microspheres are characteristically free-flowing powders consisting of proteins/synthetic polymers that are biodegradable in nature and ideally having a particle size less than 200 mm. Biodegradable microspheres can be utilized to direct drugs to certain organs through capillary blockade. Its success depends on the size of the microspheres used and on the mode of administration (intravenous/intra-arterial). The microspheres can also be used for targeting anticancer drugs to the tumor. [96]

Nanoparticles

Fe3O4 superparamagnetic nanoparticles were synthesized and stabilized by chitosan. Methotrexate (MTX) is a folate antimetabolite with antineoplastic, antirheumatic and disease modifying properties. It has been used to treat trophoblastic neoplasms, leukemias, psoriasis, rheumatoid arthritis, various carcinomas of breast, head, neck and lung. It also has indications in osteosarcoma, soft tissue

sarcoma, carcinoma of gasterointestinal tract, esophagus, testicle and lymphoma. Particle size assessment of the magnetite nanoparticles indicated uniform particles with average size range about 10 nm. The suspension of uncoated nanoparticles in water was unstable and precipitated completely in a short time. [97] The size of methotrexate encapsulated folate nanoparticles in the size range of 80–350 nm. It has been shown that drug molecules can be encapsulated in these nanoparticles with significantly low drug loss of 4–5 %. Methotrexate molecules intercalate between or within the ordered folate stacks of the nanoparticles, which are cross-linked with a multivalent cation. Cross-linking cations play major role in keeping the drug encapsulated folate assembly intact. [98] Solid lipid Nanoparticles (SLN) have been proposed as a new type of colloidal drug delivery system mainly suitable for intravenous administration. These are alternate particulate carrier system, to polymeric nanoparticle emulsions and liposomes. These are particles with size range from 50-500nm. The system consists of spherical solid lipid Particles in the nanometer range, which is dispersed in water or aqueous surfactant solution. Generally, they are made of solid hydrophobic core having a monolayer of phospholipid coating. The solid core contains the drug dissolved or dispersed in the solid high melting fat matrix. The hydrophobic chains of phospholipid embedded in the fat matrix. They have Potentials to carry lipophilic or hydrophilic drugs or diagnostics. [99]

Microcapsules

This work present encapsulation of methotrexate and magnetite by utilizing the ability of adsorption of $CaCO_3$-PSS microparticles and further development into multi-layered polyelectrolyte microcapsules has been described. Moreover, the multilayer coating could prolong the release of the loaded methotrexate with in the same incubation time. Thus, this system has great application potential for the application of in-vivo drug delivery for possible use. [100]

Extended Release Pellets

Dissolution studies were performed using USP standard dissolution apparatus at 37±0.5oC. The basket was immersed in 900ml of dissolution medium and rotated at 50 rpm. The dissolution Media used was initially 0.1N HCl up to 2hrs, then continuation with fasted buffer having pH 6.8. [101]

Sustained release capsules

The Controlled drug delivery technology offer many advantages when compared to conventional dosage forms; include increasing therapeutic activity compared to the intensity of side effects, reducing the frequency of drug administration thereby increasing the patient compliance, or eliminating the need for specialized drug administration (e.g., repeated injections). Controlled release systems show a typical release pattern of drug release for a prolonged period of time by maintaining the drug concentration within the therapeutic window where the rate of drug release matches the rate of drug elimination. [102]

Niosomes

Nonionic surfactant vesicles (niosomes) which are similar to liposomes. Niosomes are found to improve therapeutic efficacy of drugs in cancer therapy, parasitic, viral and microbial diseases. Niosome is slowly degraded providing a more sustained effect. Niosornes are capable of releasing entrapped drug slowly. Niosomes are found to have selective drug delivery potential for cutaneous application of 5 -a l p ha - d i hydro te s t er one, i n tr ave no us administration of methotrexate for cancer treatment and sodium stilbogluconate in the treatment of lishmaniasis etc. [103]

Suppositories

Suppositories are solid rectal dosage form and are prepared using either fatty bases or water soluble bases. Polyethylene glycol (PEG) bases being hydrophilic have the inherent risk of traumatising sensitive rectal mucosa. Natural fatty bases for e.g. cocoa butter have the drawback of polymorphism; semi synthetic bases are produced from vegetable oils and are chemically modified during their manufacture and usually used as suppository bases. [104]

Micro sponge

Continuous administration of therapeutic agent is desirable to maintain fixed plasma levels. Microsponges are porous, polymeric nanostructures that are mostly used for prolonged action. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. This system can work efficiently for systemic as well as local effect. [105]

CONCLUSION

This review article were studied as modified release dosage form such as controlled release, programmed release, prolonged release, extended release, sustained release and other such dosage forms to retard the release of a therapeutic agent such that its appearance in the systemic circulation is prolonged and its plasma profile is sustained in duration. Extended-release drug-delivery system reduces the dosing frequency of certain drugs by releasing the drug slowly over an extended period of time. Controlled delivery devices are useful adjunct to conventional surgical or non-surgical treatments. It is concluded that all these modified release dosage forms are focused to deliver the drug to the site of action in sufficient quantity

at the appropriate/predetermined rate. Methotrexate drug could be effective in controlled drug release for a prolonged period would serve the purpose for long term treatment of Rheumatoid Arthritis. Methotrexate including the inhibition of enzymes involved in purine metabolism, leading to accumulation of adenosine; inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cell so modified release methotrexate drug could be used as a disease-modifying treatment for some autoimmune diseases, including rheumatoid arthritis.

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