Research Article ISSN 2639-8478

Cancer Science & Research

Trends in Nanocarrier based Delivery Systems of Methotrexate: Update 2020

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Received: 27 March 2021; **Accepted:** 22 April 2021

Citation: Patel DB, Tiyyagura P, Patel B, et al. Trends in Nanocarrier based Delivery Systems of Methotrexate: Update 2020. Cancer Sci Res. 2021; 4(2): 1-7.

ABSTRACT

Methotrexate is commonly used as anticancer and anti-inflammatory agent to cure various types of cancerous and auto-immune disorders. An optimum dose of MXT is proven to inhibit the di-hydro-folate-reductase that obstruct the purine multiplication. The nanotechnology-based carriers have outranged in since decade and fabricated as multifunctional complexes to cater medicinal agents for biomedical and pharmaceutical applications. The present review aims on upbringing the understanding the various formulation development of MXT-loaded nanocarriers that have been reported with significance in the treatment of cancers. Also, in this paper, we have comprehensively listed various marketed MXT nanoformulation available in the market with a great safety, efficacy and been promising with great results in patients across the globe.

Keywords

Methotrexate, Lipid, Polymers, Nanocarriers, Marketed products, Targeted Delivery.

Introduction

The aim of achieving utmost therapeutic efficacy with minimal hazards of the drug has always been the priority of any pharmaceutical researcher. The available therapeutic options for cancer such as chemotherapy and radiotherapy need skilled personnel to produce better results because of the difference in target-specific action of the drugs used in the procedure. The recent development of polymer-based specific drug delivery systems such as lipid-polymer hybrid nanoparticles has attracted researchers due to target specific action, enhanced efficacy, and least side- effects [1]. Methotrexate--MXT (also known as amethopterin; MW: 454 g/mol) is a widely used drug in multiple medical conditions such as psoriasis, RA, and cancer [2]. At higher doses, it blocks the activity of DHFR and other folate-dependent enzymes and thus inhibits the DNA synthesis leading to overproduction of adenosine, an anti-inflammatory agent, which drives the immunosuppression [3]. Currently, nanotechnology is the most promising strategy for treatment through active & passive targeting rendering minimum damage to the healthy tissues [4]. The nanoparticles take advantage of unique characteristics such as large surface-to-volume ratio, enhanced permeation, and retention (EPR) effect, extended blood circulation time, biodegradability, low toxicity, and sustained release of drugs [5,6]. Efforts have been made to develop nano-drug delivery vehicles based on polymeric nanoparticles (PNPs) [7], lipid-polymer hybrid nanoparticles (LPHNPs) [8], nanostructured lipid carriers (NLCs) [9], solid lipid nanoparticles (SLNs) [10], and liposomes [11] for the controlled and targeted delivery of --MXT. This review focuses on the action of MXT in different medical conditions, the role of NDDS, and

the design and development of surface engineered lipid-based nanocarriers (SLNs & LPHNPs) for potential delivery of the drug.

Pharmacokinetics and pharmacodynamics of --MXT

MXT is rapidly eliminated from the human body through the renal route (90% of the intravenously injected dose excreted in 24 h and 95% in 30 h) after being metabolized to 7-hydroxy MXT. Recently, various molecular determinants of MXT (drug-metabolizing enzymes, transporters, etc) have been discovered which are involved in the pharmacokinetic process to prevent the drug interactions and understanding their disposition. The membrane transporters OATP1B1, OATP1B3, MRP2, MRP3, MRP4, BCRP & RFC regulate the hepatic clearance whereas OAT1, OAT3, MRP2, MRP4, BCRP & RFC are involved in renal elimination [13] MXT is highly sensitive to actively proliferating cells such as malignant cells, cells of the fetus, bone marrow, buccal and intestinal mucosa, and urinary bladder. Several interlinked biochemical mechanisms substantiate the use of MXT in the treatment of neoplastic diseases, psoriasis, and adult rheumatoid arthritis [14]. Mainly, it acts by inhibiting the DHFR enzyme which reduces dihydrofolates to tetrahydrofolates before their utilization as carbon carriers during the synthesis of purine nucleotides [12]. The pharmacology of this historical drug has been studied by several researchers and some of their inferences are summarized in Figure 1. The pharmacokinetic measurement of -MXT is performed in the biological fluids using HPLC or fluorescence polarization immunoassay (FPI). The bioavailability of drugs has been studied extensively and has been found to depend on the route of administration. The oral administration of MXT is highly dose-dependent in adults and leukemic pediatric patients [15]. A variable absolute bioavailability range of 13-76% was observed at doses < 25 mg. However, the drug is well absorbed in dose <40 mg/m^2 with median bioavailability ~ 42%, while above this, a reduction in the median bioavailability was observed due to the saturation effect. Therefore, MXT is routinely administered as intermittent low dose drug by the oral route. Balis and coworkers evaluated the subcutaneous absorption as an alternative route for the oral MXT at 40 mg/m^2 dose level and found 3X higher peak concentration and AUC in acute lymphoblastic leukemia children, for up to 6 h compared to 2.6 h for the oral dose [16]. This may be attributed to the saturation of absorption of orally administered MXT was not observed with the subcutaneous dose. The bioavailability of MXT when delivered through the IM route was found to be 76% which falls in the range between subcutaneous and oral routes [17]. Attention should be paid to MXT clinical application, which must be a site-specific treatment rather than exposure to the whole body. The said aim could efficaciously be achieved by various multiparticulate systems such as nanoparticles, solid lipid nanoparticles, and liposomes for targeting of various forms of malignancy and RA. Though multiparticulate and novel approaches such as prodrug and drug conjugates have proved successful platform to meet this ultimate goal, the application and research are limited to research laboratory rather than industrial and clinical applications (Figure 1).

There are numerous dosages form available for MXT in the national and international markets (Figure 2).

Role of MXT in cancer therapeutics

Cancer is the second leading cause of death around the globe [17] with lung cancer as the most commonly diagnosed (11.6%) and a major cause of death (18.4% out of total), followed by breast cancer (11.6%). [38- Long MS] Until now, more than 277 types of cancer have been diagnosed. [18] The pathophysiology of cancer involves interruption in the signal transduction mechanism mediated by the normal cell as a result of activation of proto-oncogenes or introduction of point mutation and inactivation of the gene leading to specific DNA damage. The inappropriate function of a gene affects the cell cycle and leads to abnormal proliferation.

Mechanism of action of MXT in cancer

MXT has always been the choice of 'targeted therapy' in cancer chemotherapy since its inception. It is used to treat different types of cancer such as leukemia, non-Hodgkin's lymphoma, breast cancer, head and neck cancer, stomach cancer, bladder cancer, bone cancer, and choriocarcinoma. The drug, well known as the folate pathway-dependent antimetabolite drug aminopterin, was first used in acute lymphoblastic leukemia. Though the clinical trials using MXT started in 1953, its intracellular target DHFR was discovered in 1958. The mechanism of action of MXT involves the inhibition of purine synthesis to stop the cell cycle in the S phase eventually leading to cell apoptosis. Mainly, it blocks the activity of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase and DHFR enzymes involved in the catalysis of dihydrofolate (DHF) to tetrahydrofolate (THF) which cause inhibition of synthesis of thymidylate synthetase enzyme.

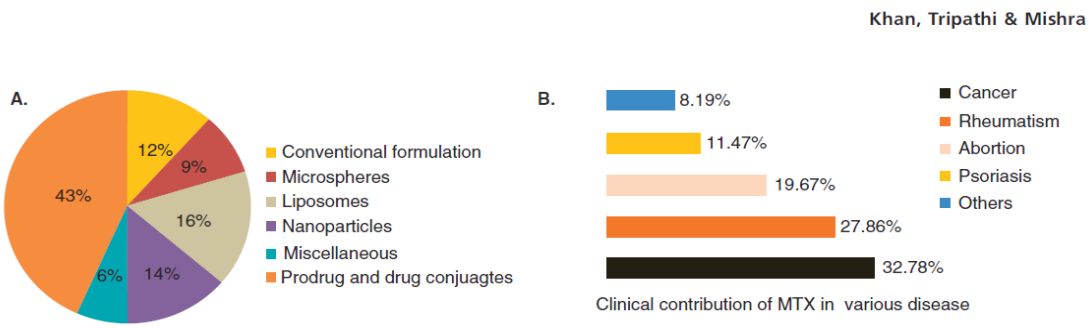

Figure 1. (A) Comparative involvement of R&D of --MXT (--MXT) in different drug delivery systems. (B) Clinical contribution of --MXT in various diseases.

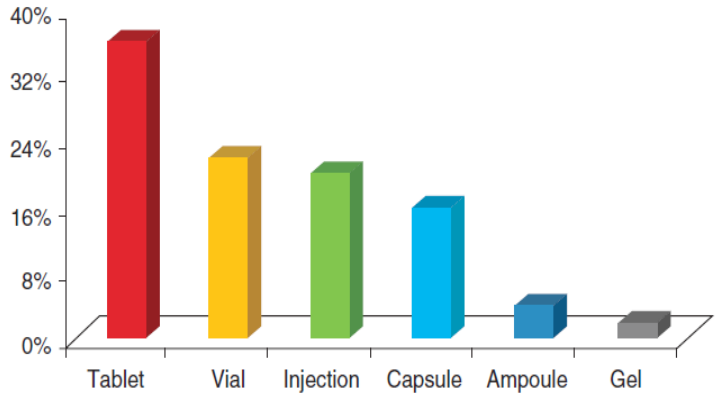

Figure 2. Available dosage forms of --MXT (--MXT) in various national and international markets.

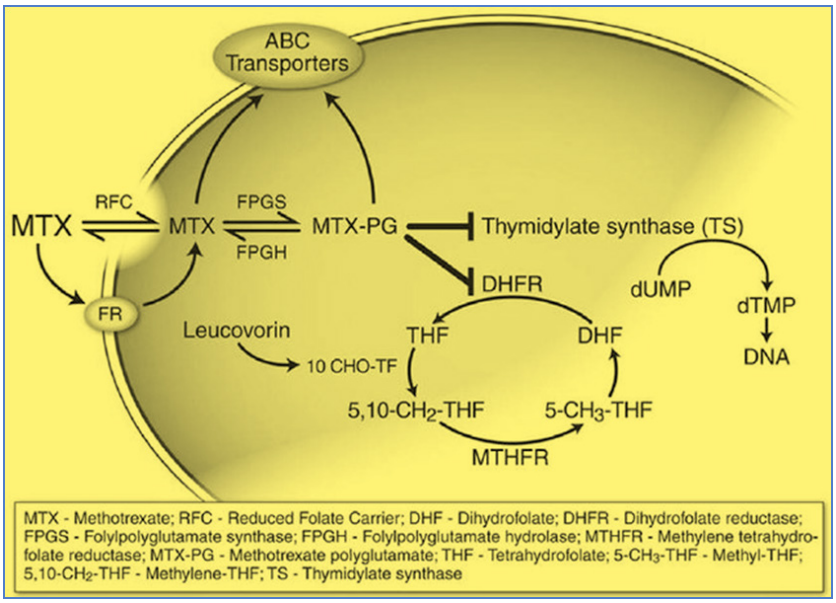

Figure 3: Mechanism of action of MXT.

Table 1: List of marketed MXT dosage forms available in India and across the globe.

Brand name	Company name	Type	Dose (mg)
--MXT			
Folitrax	Ipca Laboratories Limited	Tablet	2.5. 5
Zexate	Dabur Pharma Limited	Tablet	2.5
Alltrex	Miracalus Pharma Private Limited	Tablet, injection	2.5 mg, 25 mg/ml
Beltrex	Neesee Healthcare Pvt., Ltd.	Tablet	5
Bio --MXT	Biochem Pharmaceutical Industries Ltd.	Tablet, injection	2.5 mg. 2.5 mg/ml
Caditrex	Cadila Pharmaceuticals Ltd.	Injection	2 ml
Cytotrex	BDH Industries Ltd.	Tablet	2.5
Darmatrex	East West Pharma	Tablet	2.5, 7.5
Folitrax	Ipca Laboratories Ltd	Injection	25 mg/ml
Hi-Trex	VHB Lifesciences Inc. (Cytocare)	Tablet	2.5
Imutrex	Aronex Lifesciences Pvt., Ltd.	Tablet	2.5
Merex	Intas Pharmaceutical Ltd.	Injection	100 mg/ml
Methorex	Zydus Cadila Healthcare Ltd. (Biogen)	Injection	50 mg/2 ml
Neo --MXT	Glaxo SmithKline Pharmaceuticals Ltd.	Injection	50
Nidtrex	Nidus Pharma Pvt., Ltd.	Tablet	2.5
Oncotrex	Sunrise International Labs Ltd.	Tablet, injection	2.5 mg, 50 mg/ml
Remtrex	Alkem Laboratories Ltd. (Cytomed)	Tablet	2.5
Trixilem	Elder Pharmaceuticals Pvt., Ltd.	Tablet	2.5
Zexate	Dabur Pharma Ltd.	Injection	25 mg/ml

Table 2: List of marketed MXT dosage forms available in other countries.

MXT Dose	Manufacturer	Country	Product ID	AAPCC Code	ROA
2.5 MG coated tablet	Schein Pharmaceutical	United States	5016624	77750	Oral
2.5 MG Tablet	American Health	United States	5624138	77750	Oral
2.5 MG Tablet	Amneal Pharmaceuticals	United States	8165212	77750	Oral
2.5 MG Tablet	Barr Laboratories	United States	5328277	77750	Oral
2.5 MG Tablet	Barr Laboratories	United States	5563964	77750	Oral
2.5 MG Tablet	Hikma Pharmaceuticals USA	United States	5425594	77750	Oral
2.5 MG Tablet	Lederle Laboratories	United States	5180859	77750	Oral
2.5 MG Tablet	Novartis Generics	United States	5447431	77750	Oral
2.5 MG Tablet	Par Pharmaceutical	United States	6738178	77750	Oral
2.5 MG Tablet	Sun Pharmaceuticals	United States	8078663	77750	Oral
2.5 MG Tablet	Supergen	United States	5571610	77750	Oral
2.5 MG Tablet	Zydus Pharmaceuticals	United States	8059720	77750	Oral
2.5 MG Tablet	Altimed Pharmaceutical	Canada	6387826	77750	Oral
2.5 MG Tablet	David Bull Laboratories	Canada	5181146	77750	Oral
2.5 MG Tablet	Wyeth Pharmaceuticals	Canada	5181097	77750	Oral
10 MG Tablet	Wyeth Pharmaceuticals	Canada	6412475	77750	Oral

It has been observed that --MXT increases the level of UTP and decreases the level of ATP and GTP in human T cells, restraining T cell proliferation and enhancing cell apoptosis [19-25] (Figure 3).

A comprehensive list of MXT based marketed dosage forms available in India and across the globe is depicted in both Table 1 and 2, respectively.

Autoimmune diseases are persistent, destructive diseases known to cause multiple organ failure and functional disability. The existing immunosuppressive and biological therapies have numerous limitations like the routes of administration, the requirement for frequent long-term dosing, and inadequate targeting options often lead to suboptimal effects, patient non-compliance, and systemic adverse reactions. To address these limitations several attempts have been made in recent years using nanotechnology [26]. These Nanotechnology strategies offer several advantages including bypassing first passage metabolism, reducing nonspecific targeting, increasing the efficacy of the drugs. On the other hand, there are no long-term effective therapies till today, so this remains at the top of the list for unmet needs. This comprehensive review details the concepts and clinical potential of a novel nanomedicine approach for inducing immunosuppression and immunological tolerance in autoimmune diseases (psoriasis and rheumatoid arthritis) to modulate aberrant and pathologic immune responses.

Novel nanoformulations of MXT

Nanogel

Avasatthi *et al*. developed a nanogel by hot homogenization composed of MXT-loaded nanostructured lipid carrier (MXT-NLC) and then they evaluate its potential in imiquimod-induced psoriasis model to ameliorate symptoms of psoriasis [27-31].

Hydrogel

Kumar *et al*. studied the efficacy and safety of a recently marketed topical MXT (0.25 %) preparation in a hydrogel base in 14 adult patients with palmoplantar lesions. They conclude that MXT 0.25% in a hydrophilic gel is well tolerated but is not very effective in controlling the lesions of psoriasis on the palms and soles [31-36].

Liposome

Srisuk *et al.* investigated the physicochemical characteristics and *in vitro* permeability of MXT-entrapped deformable liposomes. They formulated lipid vesicles from PC and oleic acid (OA), comparing with those of MXT-entrapped conventional liposomes prepared from PC and CH by thin-film hydration method. Trotta *et al.* tested deformable liposome of MXT entrapped in PC or hydrogenated lecithin and dipotassium glycyrrhizinate surfactant [37-40].

Solid lipid nanoparticles

Misra *et al.* developed MXT-loaded SLN, incorporated it in suitable gel base by hot microemulsion technique, and evaluated it *in vitro* and clinically on 24 patients to justify the role of the developed gel in the treatment of psoriasis [41-46].

Nanosuspension

Yang *et al*. had conducted studies on solid in oil nanosuspensions which was a kind of oil-based nanocarriers. The oil-based nanocarriers help in the penetration of MXT through SC [47-49].

Nanostructured lipid carriers

Pinto *et al*. aimed to develop and assess the potential of NLCs loaded with MXT by hot homogenization technique in combination with ultrasonication as a new approach for topical therapy of psoriasis [50-53].

Niosomes

Lakshmi *et al*. prepared niosomal by lipid layer hydration method of MXT in chitosan gel and test the same for irritation and sensitization on healthy human volunteers followed by assessing the efficacy of the gel through a double-blind placebo-controlled study on psoriasis patients and also comparing its efficacy with a marketed MXT gel. Recently, Avasatthi *et al.*

have prepared the --MXT-NLCs nanogel to evaluate its potential in imiquimod-induced psoriasis model and showed the gradual release (47.32±0.94 %) more effectively when applied topically compare to immediate release by MXT gel (94.23±0.79 %) in 48 hr. Also, PASI was calculated and reduced to 0.3, 1 and 1.3 from 2 for --MXT-NLCs gel, MXT gel, and blank gel respectively at the end of the treatment with the normal skin and trivial keratosis as of enhanced penetration of MXT compare to certain hyper and parakeratosis in --MXT gel treated group [52-56]. The result of this study opened a new avenue for NLCs delivery system due to its controlled-manner drug release in the gel form with reduced toxicity, the major concern with another nanodelivery system which may help in optimizing the better NLCs preparation, however the efficacy of NLCs based gel needs to be verified by other *in vivo* and clinic-based study before their commercial use. Microemulsion, an alloy of oil and water together with surfactant and co-surfactants used by Nasr and group and achieved higher skin penetration compared to transdermal treatment for psoriasis (different drug-tazarotene) [33-38]. By the recent progress of their usage in transdermal and dermal drug delivery [57-61], Ramez *et al* prepared the microemulsion of MXT (mMXT) for clinical plaque psoriasis [62-68]. The prepared mMXT was tested in 30 patients having the mean PASI score of 8.587±5.081, completed the 8-week courses with all the clinical analysis by comparing the treatment of mMXT with and without fractional erbium (Er) YAG (yttrium aluminum garnet) laser. The result ($P<0.05$) showed the 24.4 % elevated reduction in TES when Er-YAG used with m---MXT compare to merely use of m-MXT at the end of 3 weeks which was increased by 6.72% after 8 weeks [69-70].

Conclusion

MXT is recognized as a revolution anticancer agent in the field of pharmaceutical and biomedical fields. MXT is proven to show broad effect by selective targeting cells, robust biological response, and with high safety. Also, MXT in the nanoformulations indicated high mean residence time in blood circulation that helps them to accumulate at the desired targeted sites. With the advancing interest in combinatorial approach especially in cancer therapy and associated inflammatory diseases, the recent research in this area is likely to grow exponentially. Also, the multiple therapeutics of MXT enables both imaging and drug delivery features that can have significant applications in both chemotherapy and in relevant clinical settings.

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