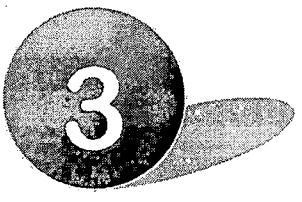

Profile of Drugs and MSNs

Drugs and MSNs profile | 3

Two poorly water soluble anticancer drugs, Methotrexate and Dasatinib were selected for this study. According to BCS classification[1], methotrexate and dasatinib are classified as class IV and class II drugs respectively. Brief properties of the drugs are given below.

Methotrexate is a well-known antineoplastic drug used also in acute lymphoblastic leukemia, certain types of lymphoma and breast carcinoma. It is an excellent disease modifying drug for a whole host of rheumatic diseases, especially rheumatoid arthritis and psoriatic arthritis. Whereas dasatinib is a novel, oral multi targeted inhibitor of kinases including SRC family kinases. Dasatinib is highly potent and has demonstrated *in vivo* anti-tumor activity in several human tumor xenograft models. It is used for the treatment of imatinib resistant chronic myeloid leukemia. Dasatinib was the first agent approved to treat patients with CML who are intolerant or resistant to imatinib.

Drug profile- Methotrexate

3.1 Chemical name

Methotrexate[2] (MTX) {(2S)-2-[[4-[(2, 4-diaminopteridin-6-yl) methyl-ethylamino] benzoyl] amino] pentanedioic acid)} is a folic acid derivative and a folic acid antagonist. In the cell it is a competitive inhibitor of the dihydrofolate reductase[2]. The inhibition of the reduction of dihydrofolate to tetrahydrofolate causes blocking of the DNA synthesis. It is widely used in the treatment of leukemia, lymphoma[3], choriocarcinoma[4, 5], head and neck cancer[6] and osteogenic sarcoma[7]. It is also used for the treatment of various autoimmune diseases, e.g., rheumatoid arthritis[8, 9] and psoriasis[10, 11] and for the prevention of graft-versus host disease[12, 13] after transplantation. MTX is a key drug in the curative regimen of children with acute lymphocytic leukemia[14].

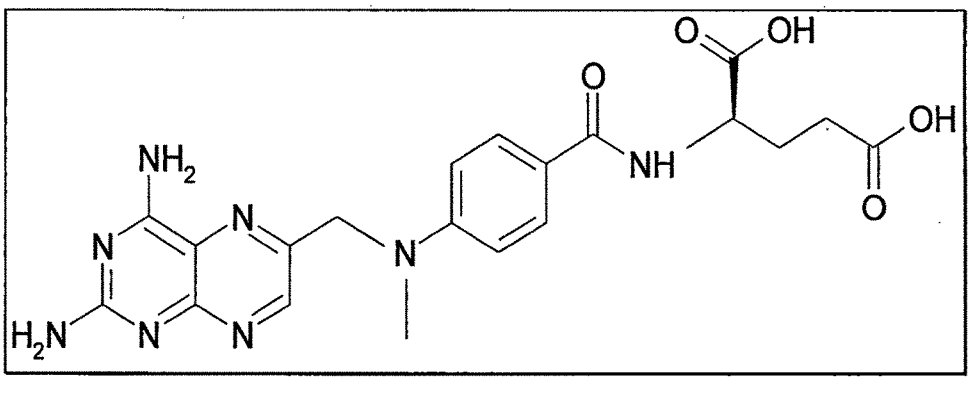

Figure 3.1: Chemical structure of methotrexate

The molecular structure of MTX is shown in Fig. 3.1 and important physical properties[15] and some leading brands of methotrexate are shown below.

3.1.1: Physical properties of Methotrexate[2]

Synonyms	Amethopterin, L-Amethopterin, Methylaminopterin
Chemical formula	$C_{20}H_{22}N_8O_5$
Molecular weight	454.44
Drug Category	Anti-metabolites, Antineoplastic
Physical state	Solid yellow color powder
Solubility	⊕Methotrexate is insoluble in water, ethanol, chloroform, and ether. ⊕ Soluble in solutions of mineral acids and in dilute solutions of alkali hydroxides and carbonates.
Melting point	185-196 °C
BCS class	Class IV drug
Water solubility	0.04 mg/ml

3.1.2: Leading brands of Methotrexate

Brand name	Company
BIOTREXATE tab	Biochem
BIOTREXATE inj	Biochem
IMUTREX tab	Cipla
IMUTREX inj	Cipla
METHOCIP inj	Cipla
METHOTREXATE tab	Wyeth
METHOTREXATE inj	Wyeth
METREX tab	Chandra Bhagat
METREX inj	Chandra Bhagat
MEXATE tab	Cadila-H
MEXATE inj	Cadila-H
NEOTREXATE tab	Glaxo Smithkline
ONCOTREX tab	Sun
ONCOTREX inj	Sun
REMTREX tab	Cytomed (Alkem)
REMTREX inj	Cytomed (Alkem)
TREX tab	Samarth Pharma
TREX inj	Samarth Pharma

3.1.3 Mechanism of action[16]

Methotrexate competitively inhibits dihydrofolate reductase (DHFR), an enzyme that participates in the tetrahydrofolate synthesis. The affinity of methotrexate for DHFR is about one thousand-fold that of folate. DHFR catalyses the conversion of dihydrofolate to the active tetrahydrofolate. Folic acid is needed for the synthesis of the nucleoside thymidine, required for DNA synthesis. Also, folate is needed for purine base synthesis, so all purine synthesis will be inhibited. Methotrexate, therefore, inhibits the synthesis of DNA, RNA, thymidylates, and proteins.

Methotrexate acts specifically during DNA and RNA synthesis, and thus it is cytotoxic during the S-phase of the cell cycle. Logically, it therefore has a greater toxic effect on rapidly dividing cells (such as malignant and myeloid cells, and gastrointestinal and oral mucosa), which replicate their DNA more frequently, and thus inhibits the growth and proliferation of these noncancerous cells, as well as causing the side effects listed below. Facing a scarcity of dTMP, rapidly dividing cancerous cells undergo cell death via thymine less death.

For the treatment of rheumatoid arthritis, patients should supplement their diets with folate. In these cases, inhibition of DHFR is not thought to be the main mechanism, but rather the inhibition of enzymes involved in purine metabolism, leading to accumulation of adenosine, or the inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cells.

3.1.4 Pharmacokinetics[17]

Absorption

In adults, oral absorption of methotrexate appears to be dose dependent. Peak serum levels are reached within one to two hours. At doses of 30 mg/m^2 or less, methotrexate is generally well absorbed with variable bioavailability of about 30-60%. The absorption of doses greater than 80 mg/m^2 is significantly less, possibly due to a saturation effect.

In leukemic pediatric patients, oral absorption of methotrexate also appears to be dose dependent and has been reported to vary widely (23% to 95%). A twenty fold difference between highest and lowest peak levels (Cmax: 0.11 to 2.3 micromolar after a 20 mg/m^2 dose) has been reported. Significant inter individual variability has also been noted in time to peak concentration (Tmax: 0.67 to 4 hrs after a 15 mg/m^2 dose) and fraction of dose absorbed. The absorption of doses greater than 40 mg/m^2 has been reported to be significantly less than that of lower doses. Food has been shown to delay absorption and reduce peak concentration. Methotrexate is generally completely absorbed from parenteral routes of injection. After intramuscular injection, peak serum concentrations occur in 30 to 60

minutes. As in leukemia pediatric patients, a wide inter individual variability in the plasma concentrations of methotrexate in doses of 6.4 to 11.2 pediatric patients with JRA, mean serum concentrations were 0.59 micromolar (range, 0.03 to 1.40) at 1 hour, 0.44 micromolar (range, 0.01 to 1.00) at 2 hours, and 0.29 micromolar (range, 0.06 to 0.58) at 3 hours. In pediatric patients receiving methotrexate for acute lymphocyctic leukemia (6.3 to 30 mg/m^2, or for JRA (3.75 to 26.2 mg/m^2), the terminal half-life has been reported to range from 0.7 to 5.8 hours or 0.9 to 2.3 hours, respectively.

Distribution

After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40% to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin.

Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration. In dogs, synovial fluid concentrations after oral dosing were higher in inflamed than un-inflamed joints. Although salicylates did not interfere with this penetration, prior prednisone treatment reduced penetration into inflamed joints to the level of normal joints.

Metabolism

After absorption, methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. A small amount of metabolism to 7-hydroxymethotrexate may occur at doses commonly prescribed.The aqueous solubility of 7-hydroxymethotrexate is 3 to 5 fold lower than the parent compound. Methotrexate is partially metabolized by intestinal flora after oral administration.

The terminal half-life reported for methotrexate is approximately three to ten hours for patients receiving treatment for psoriasis, or rheumatoid arthritis or

low dose antineoplastic therapy (less than 30 mg/m^2). For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours.

Excretion

Renal excretion is the primary route of elimination, and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed.

Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase methotrexate serum levels. Excellent correlation has been reported between methotrexate clearance and endogenous creatinine clearance.

Methotrexate clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for methotrexate toxicity. It has been postulated that the toxicity of methotrexate for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, a third space effusion, or other causes, methotrexate serum concentrations may remain elevated for prolonged periods. Methotrexate has been detected in human breast milk. The highest breast milk to plasma concentration ratio reached was 0.08:1.

3.1.5 Adverse effects

Bone marrow depression, leucopenia, thrombocytopenia, megaloblastic-anemia, ulceration of mouth, gastrointestinal disturbances, stomatites, diarrhoea, haemorrhagic enteritis, intestinal perforation, hepatic fibrosis, cirrhosis, alopecia, osteoporosis, spermatogenesis abortion and teratogenesis. Leucoencephalopathy, arachnotis and meningismus are associated particularly with intrathecal administration.

3.1.6 Contraindication

The drug is contraindicated for pregnancy, severe renal or hepatic dysfunction, psoriasis patients with preexisting bone marrow depression.

3.1.7 Drug interaction

Vinca alkaloids impair methotrexate elimination from the cerebrospinal fluid. Cisplatin, NSAIDS, omeprazole, high dose penicillin's, probenecid, and

sulphonamides increase methotrexate serum levels and toxicity. Salicylates decrease renal elimination of methotrexate and displace it from plasma protein binding sites. Alcohol enhances hepatotoxicity of methotrexate. Cholesterol binding resins-decrease oral methotrexate absorption, broad spectrum antibiotics decrease methotrexate serum levels and efficacy after oral administration.

3.1.8 Therapeutic uses

Acute lymphoblastic leukemia, meningeal leukemia, burkitts lymphoma, non-hodgkin's lymphomas, osteosarcoma, tumours of the bladder, brain, breast, G.I.T, head and neck, lung, pancreas and prostate, retinoblastoma, mycosis fungoides, psoriasis, rheumatoid arthritis, primary biliary cirrhosis, polymycositis, wegener's granulomatosis. It is an effective immunosuppressive agent used for the prevention of graft versus-host reaction in bone-marrow transplantation.

3.1.9 Dosage and administration

Methotrexate may be given orally as the base or sodium salt, or by injection as methotrexate sodium. Doses larger than 100 mg are usually given partly or wholly by intravenous infusion over not more than 24h.

3.1.10 Reported Formulation approaches of Methotrexate

Methotrexate is widely used in the treatment of various types of cancers[3-7], autoimmune diseases like rheumatoid arthritis[8, 9] and psoriasis[10, 11]. Literature review suggests various approaches to deliver the drug to the specific site with an aim to modify its release rate and possibly the toxic effect of the drug. Some formulation approaches of the MTX reported in literature are shown in Table 3.1.

Table 3.1: Different formulation approaches of methotrexate

Sr. no.	Formulation approach/ type of formulation	Therapeutic use	Administration route	Ref.
1	Colon targeting delivery formulation-capsule	Colorectal cancer	Oral	18
2	PEG-PAMAM Dendrimer	Tumor-selective targeting	Parenteral	19
3	PAMAM Dendrimer	Tumor-selective targeting	Parenteral	20
4	Niosamal MTX in Chitosan gel	Psoriasis	Topical	21
5	Polypeptide conjugate	Leishmania donovani-infection	Parenteral	22
6	Alpha-Lactalbumin microparticle	Leukemia	Oral	23
7	Gellan- MTX implants	Cancer	Implantation	24
8	Carbon nanotube	Cancer	Oral and Parenteral	25
9	pH-sensitive polymer	Cancer	Oral	26

10	Liposomal conjugate	Arthritis	Transdermal & Oral	27
11	Albumin conjugate	Tumor targeting	Oral	28
12	Cross-linked guar gum microsphere	Colorectal cancer	Oral	29
13	Time-dependent formulation	Cancer	Oral	30
14	Bacterial degradable hydrogel	Colorectal cancer	Oral	31
15	Biodegradable polymer	Colorectal cancer	Oral	32
16	Hydrogel	Cancer	Oral	33
17	Mesoporous nanoparticle	Cancer	Oral	34
18	Lipid-based drug-delivery system	Leukemia	Subcutaneous	35
19	Lipid drug conjugate nanoparticle	Cancer	Oral	36
20	Solid Lipid Nanoparticle	Psoriasis	Topical	37
21	Microemulsion	Psoriasis	Transdermal	38

DASATINIB

3.2 Chemical name

Dasatinib[39], (DTB) chemically is *N*-(2-chloro-6-methylphenyl)-2- [[6-[4-(2-hydroxyethyl) - 1-piperazinyl] - 2-methyl-4-pyrimidinyl] amino]-5-thiazole carboxamide, mono-hydrate. Dasatinib is a novel, oral multi-targeted inhibitor of kinases including SRC family kinases[39].

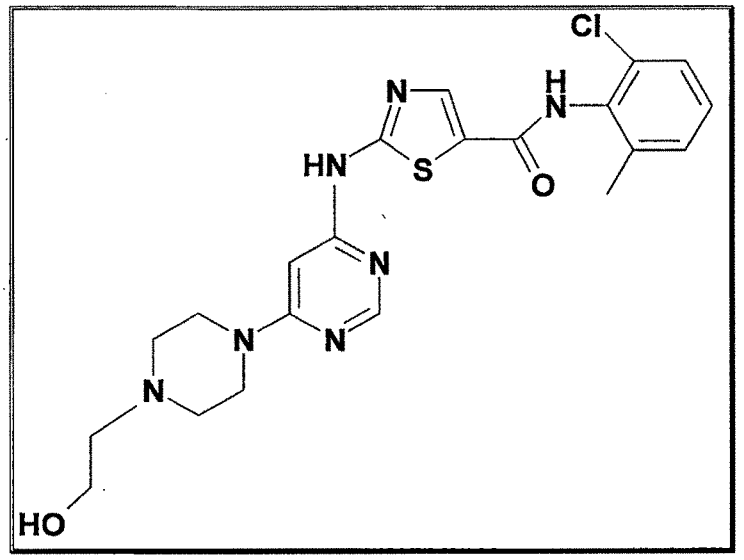

Figure 3.2: Chemical structure of Dasatinib

Dasatinib is a potent, oral multi targeted kinase inhibitor. It is an effective therapy for patients with imatinib-resistant or intolerant Ph+ leukemias. It has demonstrated promising preclinical anti-tumor activity, and is under clinical evaluation in solid tumors. Dasatinib inhibits the over-production of leukemia cells in the bone marrow of patients with CML and Ph +ALL and allows normal red cell, white cell, and blood platelet production to resume[39].

The molecular structure of DTB is shown in Fig. 3.2 and important physical properties are shown below.

3.2.1: Physical properties[39,40]

Synonyms	BMS-354825, Sprycel
Chemical formula	$C_{22}H_{26}ClN_7O_2S$
Molecular weight	488.01
Drug Category	Kinase inhibitor- Anti leukemic
Physical state	Solid, off-white to pale yellow powder
Solubility	⊕Very poorly soluble in water and ethanol ⊕ Soluble in DMSO
Melting point	261-285 °C
BCS class	Class II drug
Water solubility	0.008mg/ml

3.2.2 Mechanism of action

Dasatinib inhibits the activity of the BCR-ABL kinase and SRC-family kinases at low nano-molar or subnano-molar concentrations. Dasatinib also inhibits a number of other kinases including c-KIT, the EPHA2 receptor and the PDGFβ receptor. Unlike imatinib, it binds not only to the inactive but also to the active conformation of the BCR-ABL kinase[40]. This suggests a reduced propensity for acquired drug resistance due to the emergence of mutations that promote the adoption of kinase's active conformation.

Dasatinib has been demonstrated to inhibit the survival/proliferation of human leukaemic cell lines in vitro, and to inhibit the growth of human CML (chronic myeloid leukaemia) xenografts in SCID mice, in both imatinib-sensitive and resistant models of the disease. Antileukaemic activity was seen in dasatinib-treated mice in a model of CML with CNS involvement. Nonclinical studies show

that dasatinib can overcome imatinib resistance resulting from BCR-ABL independence, most BCR-ABL kinase domain mutations, activation of alternate signalling pathways involving SRC-family kinases and P-glycoprotein over expression.

3.2.3 Pharmacokinetics[41]

Absorption

The oral bioavailability was low with values ranging from 14% to 34%. The steady state volume of distribution of dasatinib in mice, rats, dogs and monkeys was greater than the volume of total body water, suggesting extra vascular distribution of the drug. Mean peak concentrations at the suggested clinical dose regimen of 70 mg twice daily were observed between median Tmax of 1.00 to 1.42h either in healthy subjects or in leukaemia patients.

Distribution

On the basis of in vitro studies at clinically relevant concentrations (100 and 500 ng/mL), binding of dasatinib to serum proteins was approximately 96%. Dasatinib distributes freely in human red blood cells; the blood to plasma concentration ratio was 1.8. The Vz/F after multiple dosing with the proposed therapeutic dose of 70 mg q12h for 5 or 8 days was 2505 L. In animals, the absolute bioavailability of dasatinib ranged from 14% to 34%. Assuming the most conservative value of F in humans (15.2%), Vz corrected for oral bioavailability is calculated (0.152•Vz/F) to be approximately381 L. The apparent volume of distribution is about 9-fold greater than total body water suggesting an extensive extra vascular distribution in humans.

Metabolism

The metabolism of 14C-dasatinib was investigated in vivo in rats, monkeys, and humans following oral administration. Unchanged dasatinib was the most abundant drug-related component in the plasma of rats (34-55% at 1-8h), monkeys (32% at 4h), and humans (26% at 2h). Nevertheless studies demonstrated, that dasatinib undergoes extensive oxidative metabolism and conjugation. In total 29 metabolites were detected. CYP3A4 appears to play a major role in dasatinib metabolism. Dasatinib treatment inhibited the activities of liver microsome CYP2C8 (Ki of 3.6 μM) and CYP3A4 (Ki = 1.9μM). A Cmax value of 0.12 μM has been reported in humans.

Excretion

Following repeated doses of 70 mg orally administered dasatinib in the target population, the terminal elimination half-life was 5.4h, and apparent oral clearance was 578 L/h. Subjects eliminated radioactivity primarily in faeces. Mean total recoveries of total radioactivity through 9 days post-dose were approximately 4% and 85% in urine and faeces, respectively, with a mean total of approximately

89%. Negligible amount of dasatinib was excreted in the urine (≤ 1% of dose) and approximately 19% of the dose was recovered in the faeces as dasatinib.

3.2.4 Adverse effect[41]

The data described below reflect exposure to dasatinib in 2,182 patients in clinical trials (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily). Of the 2,182 patients treated, 494 (23%) patients were over 65 years of age, while 83 (4%) were over 75 years of age. The median duration of therapy was 7 months (range 0-19 months).

The majority of dasatinib treated patients experienced adverse reactions at some time. Most reactions were of mild-to-moderate grade. Treatment was discontinued for adverse reactions in 6% of patients in chronic phase CML, 9% in accelerated phase CML, 13% in myeloid blast phase CML, and 5% in lymphoid blast phase CML or Ph+ ALL. In the Phase III dose-optimization study in patients with chronic phase CML, the rate of discontinuation for adverse drug reaction was lower for patients treated with 100mg once daily than for those treated with 70mg twice daily (3% and 11%, respectively).

The majority of imatinib-intolerant patients in chronic phase CML were able to tolerate treatment with dasatinib. About 30% of patients developed the same toxicity as with imatinib (13% developed similar non-haematologic toxicity as on prior imatinib therapy); these were usually of lower severity and did not lead to discontinuation of dasatinib treatment.

The most frequently reported adverse reactions were fluid retention (including pleural effusion), diarrhoea, skin rash, headache, haemorrhage, fatigue, nausea, dyspnoea, musculoskeletal pain, infection, vomiting, cough, abdominal pain and pyrexia. Drug-related febrile neutropenia was reported in 5% of patients.

Miscellaneous adverse reactions such as pleural effusion, pulmonary oedema and pericardial effusion with or without superficial oedema may be collectively described as "fluid retention". The use of dasatinib is associated with fluid retention with severe cases in 6% of patients. Severe pleural and pericardial effusion was reported in 4% and 1% of patients, respectively. Severe ascites and generalized oedema were each reported in < 1%. One percent of patients experienced severe non-cardiogenic pulmonary oedema. Fluid retention events were typically managed by supportive care measures that include diuretics or short courses of steroids.

Bleeding drug-related events, ranging from petechiae and epistaxis to severe gastrointestinal haemorrhage and CNS bleeding were reported in patients taking dasatinib. Severe CNS haemorrhage occurred in < 1% of patients; 7 cases

were fatal and 4 of them were associated with CTC grade 4 thrombocytopenia. Severe gastrointestinal haemorrhage occurred in 4% of patients and generally required treatment interruption and transfusions. Other severe haemorrhage occurred in 2% of patients. Most bleeding related events were typically associated with severe thrombocytopenia. Treatment with dasatinib is associated with anaemia, neutropenia and thrombocytopenia. Their occurrence is more frequent in patients with advanced phase CML or Ph+ ALL than in chronic phase CML.

3.2.5 Contraindications[42]

Use of dasatinib is contraindicated in patients with hypersensitivity to dasatinib.

3.2.6 Drug interactions[43]

CYP3A4 Inhibitors

In vitro, dasatinib is a CYP3A4 substrate. Concomitant use of dasatinib and drugs that potently inhibit CYP3A4 (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, atazanavir, lopinavir, grapefruit juice) may increase exposure to dasatinib. Therefore, in patients receiving treatment with dasatinib, systemic administration of a potent CYP3A4 inhibitor is not recommended. Selection of an alternate concomitant medication with no minimal CYP3A4 inhibition potential is recommended. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, the patient should be closely monitored for toxicity.

CYP3A4 Inducers

Drugs that induce CYP3A4 activity may increase metabolism and decrease dasatinib plasma concentration. Therefore, concomitant use of potent CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or Hypericum perforatum, also known as St. John's Wort) with dasatinib is not recommended. In healthy subjects, the concomitant use of dasatinib and rifampicin, a potent CYP3A4 inducer, resulted in a five-fold decrease in dasatinib exposure. In patients for whom rifampicin or other CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be used.

Antacids: Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. In healthy subjects, the concomitant use of aluminium hydroxide/magnesium hydroxide antacids with dasatinib reduced the AUC of a single dose of dasatinib by 55% and the Cmax by 58%. However, when antacids were administered 2 hours prior to a single dose of dasatinib, no relevant changes in dasatinib concentration or exposure were observed. Thus, antacids may be administered up to 2h prior to or 2h following dasatinib. Simultaneous administration of dasatinib with antacids should be avoided.

Histamine-2 Antagonists/Proton Pump Inhibitors: Long-term suppression of gastric secretion by histamine-2 antagonists or proton pump inhibitors (e.g. famotidine and omeprazole) is likely to reduce dasatinib exposure. The concomitant use of histamine-2 antagonists or proton pump inhibitors with dasatinib is not recommended. In a single-dose study in healthy subjects, the administration of famotidine 10 hours prior to a single dose of dasatinib reduced dasatinib exposure by 61%. The use of antacids should be considered in place of histamine-2 antagonists or proton pump inhibitors in patients receiving dasatinib therapy.

CYP3A4 Substrates

In a study in healthy subjects, a single 100mg dose of dasatinib increased exposure to simvastatin, a known CYP3A4 substrate, by 20%. Therefore, CYP3A4 substrates known to have a narrow therapeutic index such as astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids (ergotamine, dihydroergotamine) should be administered with caution in patients receiving dasatinib. In vitro data indicate a potential risk for interaction with CYP2C8 substrates, such as glitazones.

3.2.7 Therapeutic uses

Dasatinib is indicated for the treatment of adults aged 18 years or over with chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib[44]. It is indicated for the treatment of Philadelphia chromosome positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy[44].

3.2.8 Dosage and administration

The recommended starting dosage of dasatinib for chronic phase CML is 100 mg administered orally once daily, either in the morning or in the evening[42]. The recommended starting dosage of dasatinib for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL is 140 mg/day administered orally in two divided doses (70 mg twice daily), one in the morning and one in the evening. Tablets should not be crushed or cut; they should be swallowed whole. Dasatinib can be taken with or without a meal[42].

3.2.9 Reported formulation

In December 2005, Bristol-Myers Squibb Company submits a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for the dasatinib and was approved in May 2009. Dasatinib is the first approved oral tyrosine kinase inhibitor and marketed under the trade name SPRYCEL®.

Sprycel® (dasatinib) is a patented product of Bristol-Myers Squibb and patent is expected to expire in April 2020. Sprycel® formulation of dasatinib is not available

India but marketed in countries like Canada, France, Germany, Italy, Sweden, Switzerland, United Kingdom and United States.

SPRYCEL® is presented as a film-coated tablet containing 20 mg, 50 mg and 70 mg of Dasatinib as active substance. The other ingredients are lactose monohydrate, microcrystalline cellulose, cascarmellose sodium, hydroxypropyl cellulose, magnesium stearate and purified water. The film coat consists of hypromellose, titanium dioxide, polyethylene glycol and purified Water. The film-coated tablets are marketed either in aluminum/aluminum blisters or high-density polyethylene (HDPE) bottles with two piece child resistant closures having an aluminum-foil induction seal and containing silica gel desiccant canister.

MCM-41 and MSU-H MSNs profile

Nanoparticulate mesoporous silica materials have recently gained attention because of their efficiency in dissolving the poorly water soluble drugs. Mesoporous MCM-41 and MSU-H are selected to prepare the MSNs in the study. Both are silica based and are structurally similar except the pore size. MCM-41 and MSU-H MSNs possess attractive features such as large surface areas and porous interiors that can be used to entrap a drug molecule. MCM-41 and MSU-H MSNs are having stable mesoporous structure, good biocompatibility and tailored size of mesopores makes them promising drug carrier for the dissolution enhancement of poorly soluble drugs. The main characteristics of MCM-41 and MSU-H are listed in Table 3.2.

Table 3.2: Comparative characteristics of MCM-41 and MSU-H MSNs

Characteristics	MCM-41[45]	MSU-H[46]
Physical properties		
Molecular Formula	SiO_2	SiO_2
Molecular weight	60.08	60.08
Structure	Small pore, 2D hexagonal	Large pore, 2D hexagonal
Physical state	Solid, white powder	Solid, white powder
Unit cell size	4.6-4.8 nm	10-11.6 nm
Pore size	2.3-3.8 nm	7.1-7.5 nm
Pore volume	0.98 cm^3/g	0.91 cm^2/g
Surface area	1000 m^2/g	750 m^2/g
Boiling point	2230 °C	2230 °C
Melting point	>1600 °C	>1600 °C
Bulk density	0.34 g/mL	0.12 g/mL

Synthesis conditions	MCM-41[45]	MSU-H[46]
Surfactant	Cationic	Nonionic
Silica source	Silicon alkoxide	Silicon alkoxide
pH	Alkaline	Neutral or acidic
Calcination	500-550 °C	550-600 °C

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