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Development and Characterization of Mesalamine Nanoparticles for Effective Targeting of Ulcerative Colitis– Review

Rameshwar Sisodiya[1] Mrs. Eisha Ganju[2]
People's University, Bhopal School of Pharmacy & Research Pharmacy[1]
People's University, Bhopal School of Pharmacy & Research Pharmacy[2]

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ABSTRACT
Mesalazine,also known as Mesalamine or 5-aminosalicylic acid is a medication used to to treat inflammatory bowel disease,including ulcerative colitis and crohn,s disease.it is generally used for mildly to moderately severe disease.it is generally used for mildly severe disease.
Ulcerative colitis (UC) causes irritation and ulcers (open sores) in your large intestine.It belongs to a group of conditions called inflammatory bowel disease (IBD)it often causes diarrhea with blood, cramping and urgency.
Nanoparticles particulate dispersions or solid particles size in the range of 10-1000 nm encapsulated or attached to a nanoparticle matrix. Have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ.
Keywords: Mesalazine,Ulcerative colitis (UC),Nanoparticles,inflammatory bowel disease (IBD).

I. INTRODUCTION

1.1.Ulcerative colitis Ulcerative colitis (UC) causes irritation and ulcers (open sores) in your large intestine. It belongs to a group of conditions called inflammatory bowel disease (IBD). It often causes diarrhea with blood, cramping and urgency. Sometimes, these symptoms can wake you up at night to go to the bathroom. The inflammation in ulcerative colitis usually starts in your rectum, which is close to your anus. The inflammation can spread and affect a portion of your entire colon. When the inflammation occurs in your rectum and lower part of your colon, it's called ulcerative proctitis. If the entire large intestine is affected, it's called pancolitis. If only the left side of your colon is affected, it's called limited or distal colitis [1]. The severity of UC depends on the amount of inflammation and the location. Everyone is a little different. You could have severe inflammation in your rectum (small area) or very mild inflammation in your entire colon (large area). Doctors can notice a pattern of flare-ups (active disease), when symptoms are worse. During times of remission, you might have little to no symptoms. The goal of therapy is to remain in remission as long as possible (years). About half of the people diagnosed with ulcerative colitis have mild symptoms. Others experience frequent fevers, bloody diarrhea, nausea and severe abdominal cramps. Ulcerative colitis may also cause issues such as arthritis, inflammation of the eye, liver disease and osteoporosis. It isn't known why these problems occur outside of your colon. Scientists think these complications may be the result of inflammation triggered by your immune system. Some of these issues go away when the colitis is treated [2]. Ulcerative colitis can occur in people of any age, but it usually starts between the ages of 15 and 30, and less frequently between 50 and 70 years of age. It affects all sexes equally and appears to run in families, with reports of up to 20% of people with ulcerative colitis having a family member or relative with ulcerative colitis or Crohn's disease. In addition, about 20% ofpeople are diagnosed before they're 20 years old, and it can occur in children as young as 2 years of age. Ulcerative colitis is a lifelong condition that can have mild to severe symptoms. For most people, the symptoms come and go. Some people have just one episode and recover. A few others develop a nonstop form that rapidly advances. In up to 30% of people, the disease spreads from their rectum to their colon. When both your rectum and colon are affected, ulcerative symptoms can be worse and happen more often [3]

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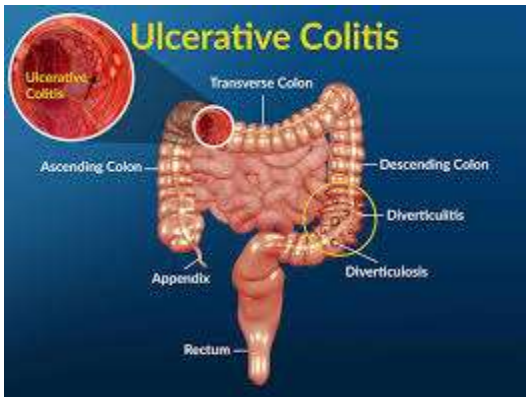

Fig.1 Ulcerative colitis.

1.2 Nanoparticles Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm. The drug is dissolved, entrapped, encapsulated or attached to a nanoparticle matrix. Depending upon the method of preparation, nanoparticles, nanospheres or nanocapsules can be obtained. Nanocapsules are systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. In recent years, biodegradable polymeric nanoparticles, particularly those coated with hydrophilic polymer such as poly(ethylene glycol) (PEG) known as longcirculating particles, have been used as potential drug delivery devices because of their ability to circulate for a prolonged period time target a particular organ, as carriers of DNA in gene therapy, and their ability to deliver proteins, peptides and genes [4].

- **Nanoparticles designing the** major goals in designing nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the sitespecific action of the drug at the therapeutically optimal rate and dose regimen. Though liposomes have been used as potential carriers with unique advantages including protecting drugs from degradation, targeting to site of action and reduction toxicity or side effects, their applications are limited due to inherent problems such as low encapsulation efficiency, rapid leakage of water-soluble drug in the presence of blood components and poor storage stability. On the other hand, polymeric nanoparticles offer some specific advantages over liposomes. For instance, they help to increase the stability of drugs/proteins and possess useful controlled release properties [5].

✓ **Advantages of nanoparticles**

1. Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
2. They control and sustain release of the drug during the transportation and at the site of localization, altering organ distribution of the drug and subsequent clearance of the drug so as to achieve increase in drug therapeutic efficacy and reduction in side effects.
3. Controlled release and particle degradation characteristics can be readily modulated by the choice of matrix constituents. Drug loading is relatively high and drugs can be incorporated into the systems without any chemical reaction; this is an important factor for preserving the drug activity.
4. Site-specific targeting can be achieved by attaching targeting ligands to surface of particles or use of magnetic guidance.
5. The system can be used for various routes of administration including oral, nasal, parenteral, intra-ocular etc. [6].

✓ **Disadvantages of nanoparticles**

Nanoparticles do have limitations. For example, their small size and large surface area can lead to particle-particle aggregation, making physical handling of nanoparticles difficult in liquid and dry forms. In addition, small particles size and large surface area readily result in limited drug loading and burst release. These practical problems have to be overcome before nanoparticles can be used clinically or made commercially available [7].

Mesalazine: Mesalazine is an aminosalicylate drug used to treat mild to moderate active ulcerative colitis and also to maintain remission once achieved [8].

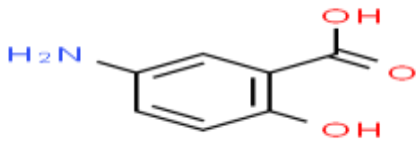

Fig.02 Mesalazine

Brand Names: Apriso, Asacol, Canasa, Delzicol, Lialda, Mezavant, Pentasa, Rowillbea, Salofalk, Zaldyon

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Generic Name: Mesalazine

Background: An anti-inflammatory agent, structurally related to the salicylates and nonsteroidal anti-inflammatory drugs like acetylsalicylic acid, which is active in inflammatory bowel disease. Although demonstrably effective in treating and maintaining remission for ulcerative colitis, mesalazine has historically faced a number of issues regarding its lack of stability as a pharmaceutical agent. Throughout the late seventies and the eighties, important research initiatives developed stable mesalazine formulations like the eudragit-S coating of Asacol brand mesalazine and the Pentasa brand's encapsulation of mesalazine within microgranules. In the present day, contemporary research regarding novel methods to stabilize mesalazine continues and interest in the agent's capacity to decrease inflammatory activity and subsequently potentially reduce the risk of colorectal cancer in conditions like ulcerative colitis is maintained.

Weight: 153.1354

Chemical Formula: C7H7NO3

PharmacodynamicsMesalazine is thought to dampen the inflammatory process through its ability to inhibit prostaglandin synthesis, interfere with leukotriene synthesis, and consequent leukocyte migration as well as act as a potent scavenger of free radicals. Intraperitoneally administered mesalazine at 30 and 340 mg/kg daily had similar efficacy in attenuating colitis as prednisolone 4 to 550 mg/kg daily given intraperitoneally or sulphasalazine 0.34 to 5 mg/kg given orally in immune complexinduced colitis mice.

Mechanism of action Although the mechanism of action of mesalazine is not fully understood, it is believed to possess a topical anti-inflammatory effect on colonic epithelial cells.14 Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyeicosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalazinediminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon. Furthermore, mesalazine also has the potential to inhibit the activation of Nuclear Factor kappa B (NFkB) and consequently the production of key pro-inflammatory cytokines. And leukotriene production and scavenge for free radicals.

Absorption Depending on the formulation administered, prescribing information for orally administered delayed-released tablets of 2.4g or 4.8g of mesalazine given once daily for 14 days to healthy volunteers will be to found to be about 21% to 22% of the administered dose while prescribing information for an orally administered controlled-release capsule formulation suggests 20% to 30% of the mesalazinein the formulation is absorbed.

Volume of distributionfor the extended-release formulation, mesalazine has a Vd of 18 L, confirming minimal extravascular penetration of systemically available drug. For the delayed-release formulation, the apparent volume of distribution will be estimated to be 4.8 L.

Protein binding in an in vitro study, at 2.5 mcg/mL, mesalamine and N-Ac-5-ASA are 43±6% and 78±1% bound, respectively, to plasma proteins. Protein binding of N-Ac-5-ASA does not appear to be concentration dependent at concentrations ranging from 1 to 10 mcg/mL.

Metabolism Mesalazine is metabolized both pre-systemically by the intestinal mucosa and systemically in the liver to N-acetyl-5-aminosalicylic acid (N-Ac-5-ASA) principally by NAT-1. Some acetylation also occurs through the action of colonic bacteria.

Route of elimination Elimination of mesalazine is mainly via the renal route following metabolism to N-acetyl-5- aminosalicylic acid (acetylation). However, there is also limited excretion of the parent mesalazine drug in the urine. After the oral administration of the extended-release formulation of mesalazine, of the approximately 21% to 22% of the drug absorbed, less than 8% of the dose will be excreted unchanged in the urine after 24 hours, compared with greater than 13% for N-acetyl5-aminosalicylic acid.

Half-life For the delayed-release formulation, after intravenous administration, the elimination half-life of mesalamine is reported to be approximately 40 minutes. After oral dosing, the median terminal t1/2 values for mesalamine are usually about 25 hours, but are variable, ranging from 1.5 to 296 hours.

Clearance The mean (SD) renal clearance in L/h for mesalazine following the single dose administration of mesalazine delayed-release tablets 4.8g under fasting conditions to young and elderly subjects will be documented as 2.05 ± 1.33 in young subjects aged 18 to 35 years old, 2.04 ± 1.16 in

Toxicity Mesalazine caused no increase in the incidence of neoplastic lesions over controls in a

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two-year study of Wistar rats fed up to 320 mg/kg/day of mesalazine admixed with diet. the mouse lymphoma cell (TK+/-) forward mutation test, or the mouse micronucleus test. No effects on fertility or reproductive performance of the male and female rats will be observed at oral mesalamine doses up to 320 mg/kg/day (about 1.7 times the recommended human intra-rectal dose of mesalazine, based on body surface area). Mesalazine is an aminosalicylate, and symptoms of salicylate toxicity include nausea, vomiting and abdominal pain, tachypnea, hyperpnea, tinnitus, and neurologic symptoms (headache, dizziness, confusion, seizures). Severe salicylate intoxication may lead to electrolyte and blood pH imbalance and potentially to other organ involvement (e.g., renal and liver). There is no specific antidote for mesalamine overdose; however, conventional therapy for salicylate toxicity may be beneficial in the event of acute overdosage and may include gastrointestinal tract decontamination to prevent further absorption. Correct fluid and electrolyte imbalance by the administration of appropriate intravenous therapy and maintain adequate renal function. Mesalazine is known to be substantially excreted by the kidney, and the risk of adverse reactions

II. AIMS & OBJECTIVES

Aims Development and Characterization of Mesalamine Nanoparticles for effective targeting of Ulcerative Colitis. Objectives

- Formulation development of mesalamine nanoparticles
- Characterization of developed mesalamine nanoparticles
- Study the drug release profile of formulations
- Accelerated stability study of developed nanoparticle formulation

III. PLAN OF WORK

The proposed plan of work can be outlined as:
1. Literature survey.
2. Drug, chemicals, reagents, and solvents will be purchase from the standard vendor(s).
3. Pre-formulation studies of drug and excipients.
a. Physical properties
b. Melting point
c. Solubility studies
d. Partition coefficient
e. Lambda max determination
f. Drug-polymer interaction study (Fourier Transform Infrared (FTIR) Analysis)
4. Development of SLN formulations.
5. Characterization of SLN formulations:
a. Particle size and Zeta Potential
b. Drug Entrapment Efficiency
c. Shape and Surface Morphology
d. In-vitro Drug Release Studies
e. Accelerated Stability Studies

IV. MATERIALS AND METHODS

4.1Preformulation Identification of Mesalazine will be carried out by melting point determination, solubility profile, UV-Vis spectroscopy, partition coefficient, and infrared spectroscopy as per the protocol given by Naseri et al., 2015 [22].

4.1.1. Physical appearance studiesthe physical state, odor, taste, color, etc. characteristics of the drug will be studied.

4.1.2. Melting point study Melting point of the drug determined by taking small amount of drug in a capillary tube closed at one end. The capillary tube will be placed in melting point apparatus and the temperature at which drug melt will be recorded this procedure will be performed thrice and average value will be noted.

4.1.3. Solubility study The drug content will be evaluated for solubility in water, acetone, methanol, diethyl ether, chloroform, and ethanol in accordance with the British pharmacopoeia specifications.

4.1.4. Determination of absorption maxima Accurately weighed about 10 mg of Mesalazine will be dissolved in 100 mL of water to obtain 100 µg/mL concentration of drug (Stock solution) from stock solution to obtain concentrations of 5 µg/mL, 10 µg/mL, 15 µg/mL, 20 µg/mL, and 25 µg/mL of Mesalazine. All dilutions will be scanned from 400 nm to 200 nm against water as blank. The spectrum of the drug will be studied to verify λmax and calibration curve will be plotted with absorbance versus concentration.

4.1.5. Partition coefficient study 10 mg drug will be added in 50 mL of n-Octanol (pre saturated with water) and it will be shaked and then 50 mL of distilled water (presaturated with n-Octanol) will be added and will be shaked the mixture by mechanical shaker for 24 hrs. After 24 hr both phases are separated. Absorbance will be taken of both the phases and calculated the concentration in each phases. Partition Coefficient = Drug concentration in Octanol / Drug concentration in Water

4.1.6. FT-IR spectroscopy The study will be conducted with an intention to identify the fingerprint features. Also, it helps to check the suitability of polymer for the preparation of

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microsphere. FTIR spectrum will be studied using a Shimadzu FTIR spectrometer (IR-Affinity-1 Model, Japan) spectrometer. The sample will be prepared into KBr disks. The scanning range will be kept from 4000 cm −1 to 400 cm −1.

4.2. Formulation development

4.2.1. Considerations for formulation development as a drug delivery system, nanoparticles can be prepared using different biodegradable materials such as natural or synthetic polymers, metals or lipids. In these Nano-particulate drug delivery systems, the drug is absorbed/ conjugated into its outer surface or encapsulated within its core. One of the key challenges associated with the development of SLN preparation is the physicochemical characterization of lipids and the changes these lipids undergo during processing. There is a need to emphasize the selection of the appropriate grade of lipids utilized in the preparation of SLN at the early stages and its thorough physical-chemical characterization before and after lyophilization.

4.2.2. Preparation of SLNs by solvent emulsification evaporation technique Solid lipid nanoparticles of Mesalazine will be fabricated by solvent emulsification/evaporation technique. Accurately, a weighted amount of Mesalazine will be dissolved in methanol. Lipid GMS will be first warmed to 75ºC. Drug and excipient proportions will be taken as depicted in Table 01. The surfactants will be added to the water under constant stirring and allowed to equilibrate to 75ºC. Aqueous surfactant solution will be added to the molten lipid and once again allowed to equilibrate at 75ºC. The organic solvent mixture will be completely evaporated at 70ºC using a rotary evaporator. Drug entrapped lipid layer will be subsequently poured into 100 mL of aqueous solution containing surfactant at 70ºC using a magnetic hot plate and homogenized for 10 min at homogenization speed of 25,000 rpm using a high-speed homogenizer (IKA). Then, the suspension will be allowed to cool at room temperature. The obtained SLNs dispersion will be freeze-dried using a freeze dryer for 24 h at -50 ºC temperature and pressure below 15 Pascal [23].

Table.01 Formulation of solid lipid nanoparticle formulations by solvent emulsification /evaporation technique.

Formulation Code	Drug	Glycerol Monostearate	Soya lecithin	Cholesterol	Tween 20	span 20	Methanol	Distilled water (q.s.)
F1	10	10	5	0.3	0.1	-	10	(q.s.)
F2	10	15	10	0.3	-	0.1	10	(q.s.)
F3	10	20	15	0.3	0.1	-	10	(q.s.)
F4	10	25	20	0.3	-	0.1	10	(q.s.)

V. CHARACTERIZATION

The SLN formulations will be carried out by determining particle size, zeta potential, drug entrapment efficiency, shape and surface morphology, in-vitro drug release studies, and stability studies as per the protocol given by Aditya et al., 2014 [24].

5.1 Particle size and Zeta Potential The particle size will be measured by dynamic light scattering technique using Horiba scientific nanopartica instrument. Zeta potential will be estimated on the basis of electrophoretic mobility under an electric field. The samples will be diluted with distilled water before measurement and measured at a fixed angle of 165°C at 25ºC for the particle size analysis. For zeta potential measurement, samples will be diluted with distilled water.

5.2 Drug Entrapment Efficiency The entrapment efficiency of the drug will be determined by measuring the concentration of free drugs in the dispersion medium. 10 mg of freeze-dried SLNs will be dissolved in aliquot volumes of phosphate buffer pH 7.4 and then filtered utilizing 0.45 µm membrane filters. Absorbance of the filtered solutions will be recorded by UV-visible spectrophotometer at 228 nm (Lab India). The percentage entrapment efficiency (% EE) will be calculated by using the following formula: % EE = (Mass of the drug in submicron particles) / (Mass of drug used in Formulation) × 100

5.3 Shape and Surface Morphology The shape and surface morphology of the optimized freeze dried Mesalazine-loaded SLNs formulation will be studied by scanning electron microscopy (SEM).

5.4. In-vitro Drug Release Studies In-vitro drug release studies will be carried out using pH 7.4 phosphate buffer consisting of 0.5% v/v Tween 80 by the dialysis bag method utilizing the dialysis

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membrane. SLNs dispersion equivalent to 5 mg of drug will be then filled into the dialysis membrane bag & tied at both ends, and kept in a beaker consisting 100 mL of phosphate buffer solution pH 7.4. The speed and temperature will be maintained at 100 rpm and 37ºC ± 2ºC, respectively, using magnetic stirrer. The samples will be withdrawn at predetermined time intervals, and similar volume will be simultaneously replaced with the fresh buffer solution in order to maintain the sink conditions. The samples will be analyzed at 228 nm using a UV-visible spectrophotometer. Cumulative % release will be further calculated from the amount of drug release. The drug release kinetics will be determined for the best formulation by following kinetic equations like zero-order (cumulative % release vs. time), first order (log % drug remaining vs. time). Higuchi's model (cumulative % drug release vs. square root of time) and Korsmeyer-Peppas model (log drug release vs. log time). The values of r2 will be calculated from the linear curve obtained by regression analysis of plots. For the Korsmeyer-Peppas model, the value of n will be computed.

5.5 Stability Studies The stability studies of the best SLNs formulation will be performed by storage at 40ºC ± 2ºC / 65% ± 5% RH for 90 days and will be examined at periodic time intervals for the changes in particle size and % entrapment efficiency. 5.4. Statistical analysis The obtained data will be statistically analyzed by ANOVA method (one-way) followed by the Dunnett's multiple comparisons test. The P-value of less than 0.01 will be regarded as statistically significant.

REFERENCES

[1]. Gajendran M, Loganathan P, Jimenez G, Catinella AP, Ng N, Umapathy C, Ziade N, Hashash JG. A comprehensive review and update on ulcerative colitis. Disease-a-month. 2019;65(12):100851

[2]. Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. Aliment PharmacolTher. 2006;23(5):577-85.

[3]. Ungaro R, Colombel JF, Lissoos T, Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis: a systematic review. Am J Gastroenterol. 2019;114(6):874.

[4]. Mohanraj VJ, Chen YJ. Nanoparticles-a review. Trop J Pharm Res. 2006;5(1):561-73.

[5]. Rajput N. Methods of preparation of nanoparticles-a review. Int J AdvEng Technol. 2015;7(6):1806.

[6]. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: An update. BioengTransl Med. 2019;4(3):e10143.

[7]. Jeevanandam J, Barhoum A, Chan YS, Dufresne A, Danquah MK. Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein J Nanotechnol. 2018;9(1):1050-74.

[8]. Ham M, Moss AC. Mesalamine in the treatment and maintenance of remission of ulcerative colitis. Exp Rev ClinPharmacol. 2012;5(2):113-23.

[9]. Ye B, van Langenberg DR. Mesalazine preparations for the treatment of ulcerative colitis: Are all created equal?.World J GastrointesPharmacolTher. 2015;6(4):137.

[10]. Zhu Y.F., Ikoma T., HanagataN., Kaskel S., Rattle-TypeFe3O4@SiO2 Hollow mesoporous spheres as carriers for drug delivery, Small 2010, 6(3), 471-478.

[11]. Deng Z.W., Zhen, Z.P., Hu X.X., Wu S.L., Xu Z.S., Chu P.K., Hollow chitosan-silica nanospheres as pH-sensitive targeted delivery carriers in breast cancer therapy, Biomaterials 2011, 32(21),4976-4986.

[12]. Yuan L., Tang Q.Q., Yang D., Zhang J.Z., Zhang F.Y., Hu J.H., Preparation of pH responsive mesoporous silica nanoparticlesand their application in controlled drug delivery. The Journal of Physical Chemistry C 2011, 115(20), 9926-9932.

[13]. Wang Z., Wang E., Gao L., Xu L., Synthesis and properties ofMg2Al layered double hydroxides containing 5-fluorouracil, Journal of Solid State Chemistry 2005, 178(3), 736– 741

[14]. Wang Z.L., New developments in transmission electron microscopy for nanotechnology, Advanced Materials 2003, 15(18), 1497–1514.

[15]. Cheng X., Kuhn L., Chemotherapy drug delivery from calciumphosphate nanoparticles, International Journal of Nanomedicine 2007, 2, 667-674.

[16]. Koppolu B., Rahimi M., Nattama S., Wadajkar A., Nguyen K.T., Development of multiplelayer polymeric particles for controlled drug delivery, Nanomedicine:

Nanotechnology, Biology and Medicine 2010, 6(2), 355-361.

[17]. Dilnawaz F., Singh A., Mohanty C., Sahoo S.K., Dual drug loaded superparamagnetic iron oxide nanoparticles for targetedcancer therapy, Biomaterials 2010, 31(13), 3694- 3706.

[18]. Yang X.Q., Hong H., Grailer J.J., Rowland I.J., Javadi A., Hurley S.A., Xiao Y. L., Yang Y.A., Zhang Y., Nickles R., Cai W.B., Steeber D.A., Gong S.Q., cRGD-functionalized, DOXconjugated,and Cu-64-labeled superparamagnetic iron oxidenanoparticles for targeted anticancer drug delivery and PET/MRimaging, Biomaterials 2011, 32(17), 4151- 4160.

[19]. Gallo J.M., Hung C.T., Gupta P.K., Perrier D.G., Physiological pharmacokinetic model of adriamycin delivered via magnetic albumin microspheres in the rat, Journal of Pharmacokinetics and pharmacodynamics 1989, 17, 305-326.

[20]. Lubbe A. S., Bergemann C., Riess H., Schriever F., Reichardt P., Possinger K., Matthias M., Do¨rken B., Herrmann F., Gurtler R., Hohenberger P., Haas N., Sohr R., Sander B., Lemke A. J., Ohlendorf D., Huhnt W., Huhn D., Clinical experienceswith magnetic drug targeting: a phase I study with 40-epidoxorubicinin 14 patients with advanced solid tumours. Cancer Research 1996, 56, 4686–4693.

[21]. Xu Z. P., Niebert M., Porazik K., Walker T.L., Cooper, H.M., Middelberg A.P., Gray P.P., Bartlett P.F., Lu G.Q., Subcellular compartment targeting of layered double hydroxide nanoparticles, Journal of Controlled Release 2008, 130, 86–94.

[22]. Naseri N, Valizadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: structure, preparation and application. Adv Pharm Bull. 2015;5(3):305.

[23]. Dudhipala N, Veerabrahma K. Pharmacokinetic and pharmacodynamic studies of nisoldipine-loaded solid lipid nanoparticles developed by central composite design. Drug Devel Indus Pharm. 2015;41(12):1968-77.

[24]. Aditya NP, Macedo AS, Doktorovova S, Souto EB, Kim S, Chang PS, Ko S. Development and evaluation of lipid nanocarriers for quercetin delivery: A comparative study of solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and lipid nanoemulsions (LNE). Food Sci Technol. 2014;59(1):115-21.