FORMULATION AND EVALUATION OF SEMISOLID DOSAGE FORMS OFA MODEL NSAID CO-PREPARED WITH HERBO-METALLIC NANOPARTICLES

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ABSTARACT

The skin is one of the main and accessible organs in the human body. Stratum corneum forms a major penetration barrier and acts as an ideal site to deliver the drug both locally and systemically. The topical route has been a favored route of drug administration over the last decades. The key purpose of a topical delivery system is toenhance the skin permeability and to retain it in the dermis. All drugs cannot be delivered through this route as the Physicochemical properties of the drug include the dose, solubility, molecular size, partition coefficient, polarity etc. Physiological properties include pH of the skin surface, pore size, specific area of the skin in the body, lipid composition ofthe skin, temperature and any other disease associated with body or skin itself. Semisolids are promising dosage forms for local as well as systemictherapies its advantages over liquids and solid dosage forms its stickiness, spread ability, local delivery, minimal dose with minimal adverse effects, large surface area, easy drug withdrawal during therapy, sustained absorption. Formulation and evaluation of semi-solid dosage form of Herbo metallic nanoparticles containing popular anti-inflammatory agents as models for topical delivery proving better for patient acceptance with minimum synthetic pharmaceutical and better safety aspects of Herbo-synthetic dosage (explorative objective).[1]

Keyword: Herbo metallic nanoparticles, topical drug delivery system, NPs, curcumin, *Vitex negundo, Pluchea lanceolata*

INTRODUCTION

Nanoparticles may be defined as colloidal systems made from solid polymers that may be classified having size ranges from 1 to 100 nm. They can be categorized into different classes based on their properties, shapes, or sizes, including fullerenes, metal NPs, ceramic NPs, and polymeric NPs. These NPs possess exceptional physical and chemical properties attributable to their nanoscale size and high surface area. Their optical properties exhibit size-dependent behavior, resulting in distinct colors through absorption in the visible region. Furthermore, their reactivity, durability, and other characteristics rely on their unique size, shape, and structure. Owing to these remarkable attributes, NPs are well-suited for a wide range of commercial and domestic applications. However, it is worth noting that heavy metal NPs, such as those composed of lead, mercury, and tin, are known for their remarkable rigidity and stability, making their degradation a challenging task and potentially leading to environmental toxicity concerns. NPs have drawn increasing interest from each department of medication for their capacity to supply drugs in the ultimate dosage range regularly resulting in multiplied healing performance of the pills, weakened side outcomes and improved patient compliance.[3] Nanoparticles have a largesurface location-to volume ratio, which allows them to soak up excessive portions of drugs and to be unfold

without problems at some stage in the bloodstream.Nanotechnology is anticipated to have a wide impact on medication. The utility of nanotechnology for analysis, treatment, tracking, and manipulation of biological systems is now frequently called nanomedicine. Amongst many possible programs ofnanotechnology in medicine, the usage of numerous nanomaterials as pharmaceutical delivery structures for drugs, DNA, and imaging agents has gained growing interest. Many kinds of nanoparticles are to be had, along with one of a kind polymeric and metallic nanoparticles liposome, biosomes, solid lipid particles, quantum dots, micelles, dendrimers, microcapsules, lipoproteins, and one-of-a-kind Nano assemblies**.** NPs showed characteristic colors and properties with the variation of size and shape, which can be utilized in bioimaging applications.[7]

1. Metallic nanoparticles

Metallic NPs are in basic terms manufactured from the metal precursors. Because of localized surface plasmon resonance (LSPR) characteristics, these NPs own specific optoelectrical homes. NPs of the alkali and noble metals i.e. Cu, Ag and Au have a vast absorption band in the seen region of the electromagnetic solar spectrum. The facet, length and shape-controlled synthesis of steel NPs is crucial in contemporary substances. Due to their superior optical properties, metallic NPs locate applications in lots of research areas.[5,6]

A. Silver NPs

Silver nanoparticles (Ag-NPs or nano silver) have attracted increasing interest due to their unique bodily, chemical, and biological properties as compared to their macro- scaled opposite numbers· Silver ions (Ag+) are dissociated from distinct salts and from particulate silver. Ag-NPs have exceptional physical chemical properties, including excessive electrical and thermal conductivity, Raman scattering, thelowest melting and boiling points, chemical stability, catalytic hobby, and nonlinear optical behavior. Furthermore, among the "noble" metals, silver exhibits the highest reactivity, and its cations demonstrate toxic effects against numerous microorganisms. Silver nanoparticles (NPs) possess even more distinct properties, making them applicable in various fields, including solar energy harvesting, as well as in multiple areas of industry and medicine. Silver nanoparticulate suspensions can be natural in concept, but in practice, are most likely to be combinations such as silver ions, nanoparticles, sub- nano sized particles and aggregated nanoparticles that are either nano-length or more.[8] Silver nanoparticles are one of the most attractive nanomaterials for commercialization applications. AgNPs can be successfully used for the delivery of drug by different route of administration. AgNPs has potentially used to deliver drug for topical and cosmetic products to improve drug penetration into skin.

2. ANTI-INFLAMMATORY DRUGS:

Inflammation is a normal, protective response to tissue injury by the body which involves a complex array of enzyme activation, mediator release, and extravasation of fluid, cell migration, tissue breakdown and repair. Many of the drugs used in the treatment of this condition are referred as anti-inflammatory drugs. Traditionally, the standard treatments for rheumatoid arthritis have been to use non-steroidal anti- inflammatory drugs (NSAIDs), synthetic drugs such as Diclofenac, Ibuprofen, Ketoprofen and Celecoxib for pain relief to reduce other symptoms of the disease. And naturally used anti-inflammatory agents are turmeric, aloe, clove, cinnamon and ginger were also in practice. The development of NSAIDs, with reduced potential to cause gastric ulcers, was finally demonstrated that clinically useful NSAIDS inhibited the enzyme cyclo-oxygenase, which was also present in the gastric mucosa. The finding that cyclo-oxygenase present in inflammatory lesions (COX2)was distinct from that found in the stomach (COX1) led to the development of selective

COX2inhibitors.[9,10]

Diclofenac sodium is an effective NSAIDs often used in the treatment of acute and chronic inflammation. It is prescribed as a long-term treatment of rheumatoid arthritis, osteoarthritis and Ankylosing spondylitis. There is great interest in preparing the non-oral dosage forms of Diclofenac sodium to minimize its gastric side effect and to improve the relatively consistent drug levels at the application site for prolonged periods. However, effective permeation of the skin is difficult to achieve due to its poor permeability, though this is relatively goodcompared to other commonly used NSAIDs.[11]

a. Pluchea lanceolata

Pluchea lanceolata (Rasana) is a Sanskrit word means 'a plant having tongue (Rasana)shaped leaves or the plant which increases 'Rasa' i.e. all nutritive tissues. It belongs to the genus *Pluchea* (Family: Asteraceae). It is a small shrub which grows mostly in sandy and saline soil, found is hotter parts of India including Punjab, Rajasthan, Upper West Bengal, Uttar Pradesh, and neighboring Asian countries together with North Africa. Many controversies exist about the identification of Rasna but *Pluchea lanceolata* is the most widely accepted plant. The plant is used for inflammation and bronchitis, psoriasis, cough, and piles.

It is an important xerophytic medicinal herb. Whole plant has been used traditionally as astringent, anti- inflammatory, antipyretic, hepato-protective, diaphoretic in fevers, smooth muscle relaxant, nerve tonic, laxatives. It is used in several polyherbal formulations in traditional system of medicines for the managementand cure of 'Amavata' (arthritis)[12]

Figure No 5 : *Pluchea lanceolate*

b. Vitex nigundo

Vitex negundo, belongs to the (family "Verbenaceae") is a shrub which is quite abundant in India with major applications in folk and traditional medicine. The leaf extract of *V. negundo* has been reported to reveal a wide range of biological actions including mosquito repellent activity, anti-angiogenic, hepatoprotective, analgesic, anti- inflammatory, anti-arthritic, anti-microbial, anti-histaminic, CNS depressant, anti- filarial activities etc. These actions may be due to the various phytoconstituents presentin the plant, which include iridoids, flavonoids, polyphenolic compounds, alkaloids, terpenoids etc. Owing to these various phytochemicals this plant has a crucial role in phytomedicine. The decoction of various parts of this plant part is used against toothache, ulcers, sinusitis, gonorrhea, bronchitis, eye disease, leukoderma etc. *Vitex* species along with other chemical constituents shows the presence of numerous iridoids like agnuside, negundoside, nishindaside, that are responsible for the different pharmacological activities. Among these iridoids, agnuside is an important chemotaxonomic marker that can be used in standardization of *Vitex* extract andformulations

containing it. It is an ester of aucubin and p-hydroxy benzoic acid. It reveals pharmacological actions like anti-arthritic, anti-inflammatory.[12]

Figure No 6 : *Vitex nigundo*

***c.* CURCUMIN**

Curcumin, a yellow pigment obtained naturally from Curcuma longa has been used fromtime immemorial as a dietary supplement, coloring agent, spice and also for curing diseases. Vast research revealed that turmeric and curcumin have a wide spectrum of therapeutic effects such as anti-inflammatory, antibacterial, antifungal, anticancer, antispasmodic, antioxidant, ant amoebic, anti-HIV, antidiabetic, antifertility etc. Curcumin is safe up to 8g/day. Curcuminoids, the oleoresins, derived from ethanolic extraction of turmeric are mainly responsible for yellow color and are considered responsible for biological activity. Curcumin is practically insoluble in water and highly susceptible to pH change. There are reports indicating that curcumin demonstrates tautomeric forms, including keto-enol forms. Under neutral and acidic conditions, curcumin predominantly exists in its bis-keto form. In acidic condition curcumin acts as a powerful hydrogen donor. It also undergoesdegradation up to 90% in serum free 0.1M phosphate buffer of pH 7.2 at 37° C. The decomposition of curcumin was pH dependent andoccurs faster under neutral and basic pH condition.[13]

Curcumin exhibits characteristics of a monobasic bidentate ligand, enabling the formation of stable complexes with various metals and non-metals. These curcumin-metal complexes not only alter the physiochemical properties of curcumin but also impact the biological reactivity of the involved metals. Generally, it has been noted that curcumin complexation reduces the toxicity associated with metals, and certain curcumin complexes, such as those with Cu2+ and Mn2+, display promising potential as novel metal-based antioxidants.

Figure No 7 : *Curcuma longa*

4.6.1. Estimation of drug content:

In this study, one gram of Diclofenac sodium-SNPs gel was taken into a standard volumetric flask and mixed with mixture of phosphate buffer pH 6.8. The amount of drug per 1 gram per gel determined spectrophotometrically at 276 nm after filtration through Millipore filter (0.45 µm) and the drug content was obtained from the calibration curve.

% drug content= practical drug content/theoretical drug content ×100

4.6.2. In-vitro drug release studies

The *in-vitro* drug release studies were performed by using Franz diffusion cell with dialysis membrane. A dialysis membrane with a pore size of 2.4 nm and a molecular weight cut-off ranging between 12,000-14,000 (Hi-Media, Mumbai, India) was employed and positioned on the Franz diffusion cells. The recipient compartment, equipped with a water jacket, had a total capacity of 25 ml, and featured two arms, one for sample collection and another for a thermometer. The donor compartment, with an internal diameter of 2 cm, was carefully positioned to meet the diffusion medium within the receptor compartment. The receptor compartment contained pH 6.8 phosphate buffer as receptor medium and temperature of receptor medium was maintained at 37°C±1. Then, SNPs based gels (equivalent to 100 mg of drug) were placed in the donor compartment. Aliquots(1 ml) of the medium were withdrawn at 1, 2, 4, 6, 8 10 and 12 hours, and replaced with equal volume of the fresh medium to maintain the volume of the release medium constant throughout the duration of the experiment. All samples were filtered through Millipore filter (0.45 µm) and analyzed by UV spectrophotometer at 276 nm.[14]

Inhibition of albumin denaturation for anti-inflammatory activity

Inhibition of albumin denaturation technique the reaction mixture consists of test extracts (100µg/ml) and 1% aqueous solution of bovine albumin fraction, pH of the reaction mixture was adjusted using small amount of 1N HCl. The samples were subjected to incubation at 37 ºC for 20 minutes, followed by heating to 51°C for an additional 20 minutes. After cooling the samples, turbidity measurements were taken at 660nm using a UV Visible Spectrophotometer (Shimandzu 1800). The experiment was conducted in triplicate. The Percentage inhibitionof protein denaturation was calculated as follows:

Percentage inhibition = (Abs Control –Abs Sample) X 100/ Abs control

- Some Experiments were carried out to determine the *in vitro* anti- inflammatory activity of diclofenac sodium in presence of silver Nanoparticles of *Pluchea lanceolate*, *Vitex nigundo*, and curcumin. Selected data is being tabulated in the results section of the thesis. Some efforts were also made to formulate the best semisolid dosage however, for further validation, complete data is not being disclosed.

Drug Release Kinetics:

Investigation for the drug release from the Diclofenac sodium loaded SNPs based gel was done by studying the release data with zero order, first order kinetics and Higuchi equation. The release mechanism wasunderstood by fitting the data to Korsmeyer / Peppas model.[15]

a) Zero order kinetics:

When the data is plotted as cumulative % drug release versus time, if the plot is linearthen the data obeyszero- order release Kinetics, with a slope equal to K^0.

Zero order release would be predicted by the following equation:

$$A_t = A_0 - K_0 t$$

Where, A_t= Drug release at time 't'.A_0= Initial drug concentration.

K_0=Zero-order rate constant (hr^{-1}).

b) First order Kinetics:

When the data is plotted as log cumulative % drug remaining versus time yields a straight line, indicating that the release follows first order kinetics. The constant 'K' canbe obtained by multiplying 2.303 with theslope values.[16]

First order release would be predicted by the following equation.

$\text{Log } C = \log C_0 - Kt/ 2.303$

Where, C = Amount of drug remained at time 't'.

C_0 = Initial concentration of drug. K

= First-order rate constant (hr^{-1}).

c) Higuchi's model:

When the data is plotted as cumulative drug release versus square root of time, yields a straight line,indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.[17]

Drug release from the formulation by diffusion has been described by following Higuchi's classicaldiffusion equation:

$Q = [D\varepsilon / \varepsilon (2A - \varepsilon CS)\ CSt]^{1/2}$

Where, Q = Amount of drug released at time 't'.

D = Diffusion co-efficient of the drug in the matrix. A = Total amount of drug in unitvolumeof matrix. CS = Solubility of the drug in the matrix.

ε = Porosity of the matrix. t = Tortuosity.

d) Korsmeyer equation/ Peppa's model:

When the data is plotted as log of drug released versus time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y- intercept. To study the mechanism of drug release, the release data were also fitted to the well – knownexponential equation (Korsmeyer equation/ Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.[18]

$$\mathbf{M_t / M_a = Kt^n}$$

Where, M_t / M_a = the fraction of drug released at time 't'.

K = Constant incorporating the structural and geometrical characteristics of thedrug/polymer.

n = Diffusion exponent related to the mechanism of the release. Aboveequation can be simplified by applying log on both

sides,

$$\textbf{Log } M_t / M_a = \textbf{Log } K + n \log t$$

For Fickian release 'n' = 0.5 while for anomalous (non- Fickian) transport 'n' rangesbetween 0.5 and 1.0.[19]

CONCLUSION

Diclofenac sodium was chosen as a model drug fromsynthetic source and Aqueous extract of (*Pluchea lanceolata*) and (*Vitex nigundo*), ethanolicextract of turmeric (*curcumin*) was a model drug from herbal source. The primary objective of the study was to prepare and evaluate nanoparticles of Aq. extract of (*Pluchea lanceolata*) and (*Vitex nigundo*) & turmeric ethanolic extract. The secondary objective of the study was to formulate and evaluate the Herbo-metallic SNPs of semisolid dosage forms of anti- inflammatory drugs by choosing optimized nanoparticles of Aq. Extract of *Pluchea lanceolata* , *Vitex nigundo* and turmeric ethanolic extract and Diclofenac sodium as a model drug from herbal and synthetic source.

Drug estimation of Diclofenac sodium and *Pluchea lanceolata Vitex nigundo* and curcumin was carried out using UV spectrophotometry at 276 nm and 283 nm , 477 nm , 421 nm respectively. Calibration curve of Diclofenac sodium were found to be linear and concentration dependent.

Silver nanoparticles of *Pluchea lanceolata* and *Vitex nigundo* were prepared by aqueous extraction method where, curcumin was prepared by chemical reduction method andevaluated for solution stability, drug content, zeta potential and particle size. The nanoparticles solution was clear, golden yellow to brown in color with a pH of 6.7-6.8. Nanoparticles size of RSNP was found to be 19.59 nm and zeta potential was found to be -21.7mV and VSNP particle size was found to be 312.4 nm and zeta potential was found to be 13.0mV. Results FTIR studies confirmed that there are no possible interactions between Diclofenac Sodium, RSNP, VSNP, CSNP and excipients. The *in-vitro* anti-inflammatory results byalbumin denaturation method showed significant % inhibition in all the formulations rangingfrom 53 - 96 %. Stability studies for 1 month indicated no significant change in physicalappearance, pH, viscosity, drug content and *in- vitro* release profile. From the above it can beconfirmed that the topical delivery of Herbo synthetic semisolids of Diclofenac Sodium and RSNP, VSNP , CSNP are better than the marketed preparation in showing anti-inflammatory activity. Hence these formulations can be prepared effectively and releasedinto the market after clinical trials in human beings.

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