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MICROSPHERES: A RELIABLE DRUG DELIVERY SYSTEM FOR ANTICANCER HERBAL DRUGS

***Kripi Vohra, PhD Scholar, Harish Dureja, PhD. and Vandana Garg, PhD.**

Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India.

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***Corresponding Author**
Kripi Vohra
Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India.

ABSTRACT

Cancer is a life-threatening disease which severely affects the overall quality of life of patients. Despite the availability of many conventional methods of treatment and cytotoxic drugs, their clinical outcomes are coupled with adverse effects due to their target unspecific nature. Nowadays, herbal anticancer agents are gaining special attention as an alternative system of therapy in cancer due to the benefits associated with them such as minimal adverse effects with high therapeutic efficacy. However, the barriers restricting their bioavailability warrant new drug delivery systems which may improve their pharmacokinetic profile. Recently, formulation of herbal products using novel drug delivery system (NDDS) has gained popularity due to the advantages offered by them in comparison to conventional formulations. The present study reviews the role of microspheres formulated with herbal anticancer extracts or phytochemicals in treating cancer. Microspheres are one of the NDDSs with discrete spherical particle size of 1-1000 µm. Their integration to herbal anticancer agents have shown better patient compliance in terms of route and frequency of administration, improved efficacy, fewer adverse effects, better solubility and stability, targeted action on tumour cells and sustained drug release profile. Many studies also support the use of anticancer herbal microsphere technology in treatment of cancer by exhibiting various benefits.

KEYWORDS: Cancer, herbal, microspheres, plant extracts, phytochemicals, novel drug delivery system.

INTRODUCTION

Cancer has been considered as the second leading cause of death and is responsible for one in six deaths at global level. In 2015, cancer led to 8.8 million deaths.[1] In India, more than one million new cases are diagnosed with cancer every year. In 2012, around 6,00,000-7,00,000 cancer deaths were reported.[2] In the modern era of science and advanced technology, numerous cancer treatments are being used depending upon the type of cancer and its stage. Despite such an advancement in drug discovery, many adverse effects are still associated with these treatment regimens, such as anemia, thrombocytopenia, edema, alopecia, infection, neutropenia, peripheral neuropathy, *etc*.[3] Depreciation in quality of life of cancer patients due to the use of conventional methods of treatment has inclined the pharmacists, clinicians as well as patients towards alternative treatment strategies.[4]

The in-depth pharmaceutical research coupled with advancement in molecular science has considerably increased the interest and faith of health care system as well as the cancer patients in herbal treatment.[4] Till date, many plants have been reported to possess anticancer activity. Alkaloidal derivatives obtained from plant vinca (viscristine, vinblastine), taxanes (paclitaxel), podophyllotoxin and its derivatives (topothecan, irinothecan), anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin), *etc*. have been isolated due to their anticancer potential.[5] However, the limitations (poor solubility, inappropriate site specificity, low bioavailability, *etc*.) associated with herbal extract formulations and phytochemicals have lowered the efficacy of herbal anticancer formulations. To overcome the drawbacks of conventional herbal formulations, numerous novel drug delivery systems (NDDSs) have come in to play.

Microsphere is one of the NDDSs and is widely integrated with phytoconstituents/ extracts to demonstrate drug targeting at the site of action, thereby enhancing therapeutic activity of the herbal drugs with minimal adverse effects. Due to such an interesting profile, microspheres play an essential role in the treatment of cancer.[6, 7] The present review focuses on the role of microspheres in the treatment of cancer using herbal extracts and phytochemicals.

ROLE OF NOVEL DRUG DELIVERY SYSTEMS IN TREATMENT OF CANCER

Cancer is associated with the proliferation of abnormal cells which are quite similar (not identical) to the normal cells. The cancer cells are just minutely different from normal cells, in terms of genetics or function. Cancer needs to be treated with an anticancer drug coupled with a drug delivery system (DDS) to ensure target specificity, increased drug release at the

tumour tissue and least safety concerns. Therefore, NDDS is the choice of drug carrier in the management of cancer.[6]

Role of NDDS in cancer is well-understood by various mechanisms, out of which, the most commonly accepted mechanism involve development of passively targeted NDDS. The property of NDDSs to enhance permeability and retention can be explained by greater accumulation of the drug in tumour tissues as compared to normal cells. This further results in exploitation of leaky vasculature present at the tumour site. Another contributing factor is the potential of NDDS to alter the pharmacokinetic properties of the drug.[8]

MICROSPHERES

Microspheres, the discrete spherical particles sized 1-1000 µm, are one of the NDDSs which allow a uniform dispersion of drug in polymer matrix which gets released following first order kinetics. Matrix gets diffused to the outer dissolution media which brings the entrapped drug in contact of the media. The drug gets solubilized, followed by its release in the body systems. Addition of a polymer leads to surface erosion, thereby promoting the release of the drug.[9]

A number of natural (albumin, gelatin, modified starches, *etc*.) and synthetic polymers (polypropylene, dextran, polylactic acid and polylactide-co-glycolide, *etc*.) can be used for the preparation of microspheres using various methods (Fig. 1).[10]

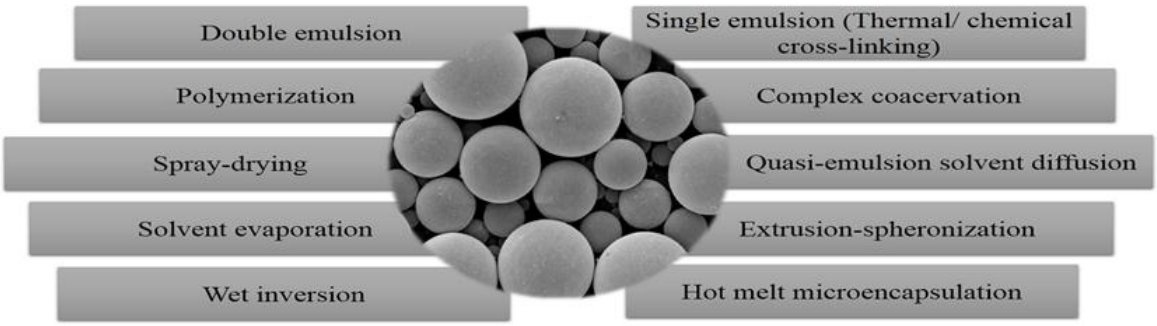

Figure 1: Various methods used for preparation of microspheres.

ROLE OF MICROSPHERES IN THE TREATMENT OF CANCER USING HERBAL DRUGS

Administration of microspheres is possible *via* ingestion as well as injection and that too in a desired release profile. Microspheres also ensure site-specific/organ targeted delivery of

drugs. This makes it more compatible for treating cancer.[11] Drug-loaded microspheres are generally delivered to the tumour site by passive as well as active targeting.[12]

Herbal microspheres, *i.e.*, combination of microspheres and bioactive herbal agent, have helped the pharmacists to formulate herbal anticancer products with site specific action, maximum therapeutic value, minimum adverse effects and appropriate clinical outcomes.[6] Fig. 2 compares the effects of conventional anticancer herbal formulation and microspheres prepared using anticancer herbal drugs.

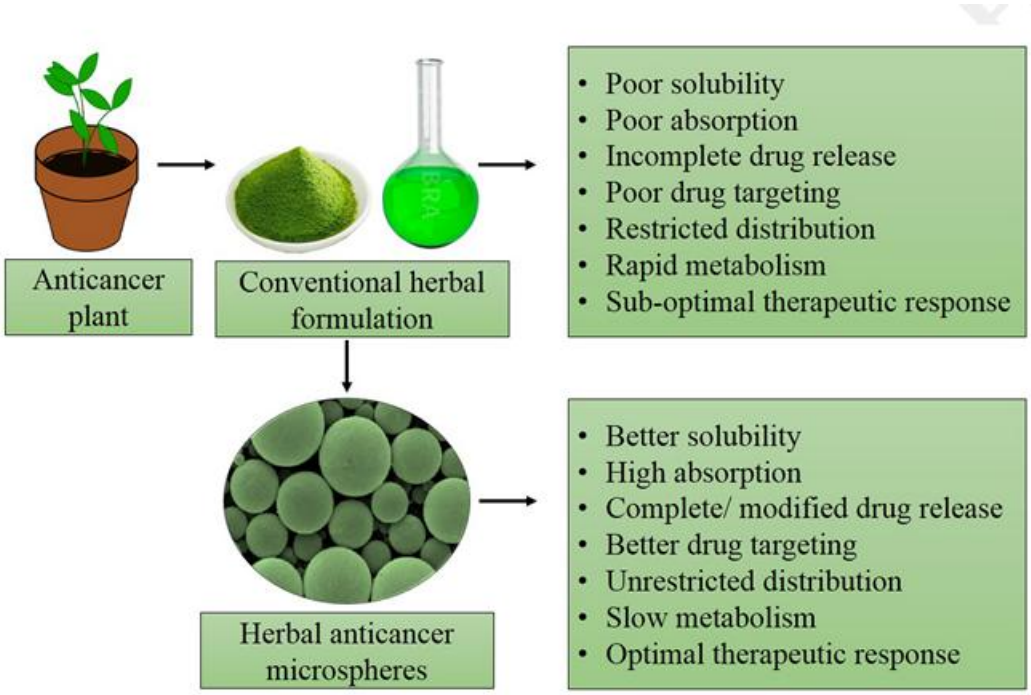

Figure 2: Comparison between the effects of conventional anticancer herbal formulation and microspheres prepared using anticancer herbal drugs.

Many studies have been conducted which report the ability of microspheres to modify the pharmacokinetics of the drug in the body, reduce drug dosage or frequency as well as improve the efficacy, which suggest the use of microspheres in treatment of cancer using herbal drugs. A study, targeting lung cancer, assessed morphology, size distribution, drug loading, encapsulation efficiency, and *in vitro* release profile of sophoridine-loaded poly(lactide-co-glycolide) (PLGA) microspheres in a rat model. The study also compared its *in vivo* distribution with drug in solution form (intravenous, IV). It was reported that the microspheres with an average size of 17 µm (range 12-24 µm) exhibited drug loading of 65% and encapsulation efficiency of 6.5%. With an initial burst of 16.6% at four hours, the

microspheres demonstrated a sustained-release period of 14 days. The drug concentration (after 30 minutes) of microspheres and solution in lung tissue of rats was found to be 220.10 µg/g and 6.77 µg/g, respectively with a similar trend up to 12 days. Moreover, the microsphere formulation had higher drug levels in lung tissue than in the other major organs and blood samples.[13]

The major advantages associated with the use of herbal microsphere in the treatment of cancer, include improved efficacy, a better route of administration (parenteral or intraperitoneal; IP), ability to modify drug release, and site-specific/organ targeted drug release.[11] The use of herbal microspheres are found to be safer and digestible as compared to conventional herbal formulations. Micro-encapsulated herbal drugs also impart many benefits such as high solubility with improved bioavailability. Lastly, herbal microspheres exhibit least toxicity with better therapeutic efficacy and better patient compliance.[10, 14-17] Some of them have been discussed below with the help of relevant studies.

1. **Improved bioavailability:** The micro-emulsion prepared from berberine, an anticancer agent, showed 6.47 times better bioavailability as compared to berberine tablet suspensions.[18]
2. **Better efficacy:** Paclitaxel was encapsulated in poly(methylidene malonate 2.1.2) using single emulsion method and was evaluated by assessing cytotoxicity on MBT-2, a bladder cancer cell line. An improvement was observed in the survival rate of cancer cells. Moreover, a lower incidence of carcinoma *in situ* and high grade transitional cell carcinoma in the cells treated with paclitaxel bio-adhesive microspheres was observed as compared to the controls as well as the cells receiving injections of similar doses of the conventional paclitaxel formulation.[19]
3. **Improved permeation and enhancement ratio *via* transdermal delivery:** Curcumin is an antioxidant, hepatoprotective anti-arthritic and anti-cancer, and is obtained from *Curcuma longa*. Curcumin was formulated into micro-emulsion (containing 5%, 10%, and 20% of water content along with 1% curcumin) to assess its transdermal delivery characteristics. The 10% micro-emulsion (permeability coefficient=$0.11\times10^{-3}\pm0.05\times10^{-3}$ cm/h) was two times more permeable as compared to the other two (permeability coefficient of 5%=$0.04\times10^{-3}\pm0.02\times10^{-3}$; permeability coefficient of 20%=$0.05\times10^{-3}\pm0.03\times10^{-3}$). The conventional form of curcumin, *i.e.*, micellar system, S/O-mix, and a plain solution, had lower permeability coefficient ($0.02\times10^{-3}\pm 0.01\times10^{-3}$, $0.00\times10^{-3}\pm0.00\times10^{-3}$, and $0.00\times10^{-3}\pm 0.00\times10^{-3}$cm/h, respectively).[20]

4. **Modified release profile of drug:** Kumar et al., 2012 formulated curcumin floating microspheres using emulsion solvent diffusion method due to their poor bioavailability in body in traditional form. The microspheres allowed sustained release of drug in the body.[21]

Silymarin is obtained from *Silybum marianum* and is active against human prostate adenocarcinoma cells. Panapisal et al. reported silymarin microemulsion to exhibit prolonged release profile as compared to silymarin solution.[22]

Microemulsion prepared from berberine, an effective antineoplastic agent, reported to show best absorption rate at the ileum and it was significantly higher than that of conventional form of berberine ($p<0.01$).[23]

Another study conducted by Machida *et al*., 2000 compared the release of camptothecin (CPT-11) in solution form [10mg/ Kg; IV and IP administration] with that in microsphere form (50 mg eq CPT-11/ Kg; IP administration). CPT-11 solution attained maximum plasma concentration in 30 minutes after IP administration and showed a swift decrease in its plasma concentration after IV administration. Moreover, the area under plasma concentration-time curve was lower after IP administration as compared to IV administration. On the other hand, microspheres increased CPT-11 concentration gradually and maintained almost constant CPT-11 levels. Overall, CPT-11 in the form of microspheres demonstrated faster and prolonged release as compared to solution form.[24]

5. **Prolonged activity**: Camptothecin containing PLGA microspheres, assessed for their cytotoxic activity, revealed the release of camptothecin in its active lactone form for the entire duration. Moreover, the microspheres were quickly uptaken by skin cell line (B16 cells).[25]
6. **Improved apical to basolateral transport**: Docetaxel, an antimitotic compound, in the form of microemulsion showed improved apical to basolateral transport across cancer coli-2 (Caco-2) cells as compared to the commercial product Taxotere (0.624 microg/cm^2 vs. 0.025 microg/cm^2; $p<0.01$).[26]
7. **Low dose**: Quercetin, an anticancer drug, is required in high dose due to high particle size which restricts its passage through blood brain barrier. The quercetin microspheres formulated using solvent evaporation method Significantly decrease the dose size to one/tenth times as compared to the dose required for systematic administration.[27]

8. **Drug targeting property**: Docetaxel-loaded chitosan microspheres were found to be more advantageous than the conventional formulation of docetaxel. *In vitro* release study revealed a sustained release of drug while the *in vivo* studies revealed drug targeting as well as maximum drug release at the lung tumour tissue with minimal exposure to normal cells.[28]
9. **Minimal damage to normal cells**: Cisplatin loaded PLGA microspheres were evaluated for drug distribution in tissue and the toxicity caused to normal tissues by the drug delivery system. The microspheres were administered *via* venoportal route of administration which resulted in reduced total systemic and renal toxicity. It was observed that the normal tissues were less exposed to the drug and still maintained high liver-to-kidney platinum level ratios (28 and 19 times higher after 4 and 24 hours, respectively, than free form of drug) and liver-to-blood platinum level ratios (38 and 36 times higher after 4 and 24 hours, respectively, than free form of drug). The efficacy, in terms of tumour growth inhibition of CC531 colon carcinoma liver micro-metastases model, was found to be equal in both forms, free and microsphere, over a period of 26 days. However, the histological studies reported more renal damage with free form. Moreover, the kidney platinum levels were seven times lower in case of microspheres.[29]

Table 2 also illustrates the studies conducted on herbal anticancer agents which used microspheres as NDDS.[25, 30-42]

Table 2: Studies conducted on microspheres prepared with herbal anticancer drugs.

Active ingredient	Polymers	Results	Ref.
Camptothecin	PEGylated 6 µm polystyrene	Dose reduction, enhancement of cytotoxicity	[30]
Docetaxel and curcumin	Biodegradable PLA-PEO-PPO-PEO-PLA polymers	Slow release (*in vitro*) and slow, sustained release of curcumin and docetaxel (*in vivo*)	[31]
Ginsenosides	PLA	Improved drug release behaviour and encapsulation efficiency	[32]
Taxol	PLGA	Targeted delivery	[33]
Irinotecan	PVA	Low morbidity, no systemic chemotoxicity	[34]
Curcuma aromatica oil	Gelatin	Safe to be embolized via hepatic artery	[35]
Mixture of triterpene saponins, from *Physospermum verticillatum* roots	Acrylic acid	The combination released drug in lung, reduced systemic drug toxicity, reduced frequency of doses, increased half-life of the drug, eliminated complications related to	[36]

+ gemticabine		the fast clearance of gemcitabine administration.	
Cyclodextrin complexes in reduced bromonoscapine, a cyclic ether brominated analogue of noscapine	Encapsulated in bio-responsive guar gum	Enhanced colonic drug delivery	[37]
Lectins extracted from *Pisum sativum* roots	Encapsulated in alginate microbeads	Anti-proliferative effect against HCC, suitable route of administration	[38]
Piroxicam	Crosslinked guar gum	Maximum drug release (97.1%) in simulated colonic fluid leading to targeted therapy	[39]
Irinotecan	Assam Bora rice starch	Slow and extended release of drug over longer periods of time with reduced systemic side-effects	[40]
Zedoary turmeric oil	-	Improved oral bioavailability	[41]
Paclitaxel	PLA–PEG–PLA	Controlled release of the drug	[42]

PLA-PEO-PPO-PEO-PLA: Poly lactic acid-poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide)-poly lactic acid; PLGA: Poly(lactide-co-glycolide); PLA–PEG–PLA: Poly(lactic acid)–poly(ethylene glycol)–poly(lactic acid); PVA: Polyvinyl alcohol; PLA: Poly lactic acid; HCC: Hepatocellular carcinoma

Overall, the use of microspheres, as a drug delivery system, is quite acceptable as it improves patient compliance [43]. Besides the advantages that microspheres offer, pharmaceutical industry utilizes microspheres for taste and odor masking, delaying the volatilization rate of drugs, separating incompatible substances, improving the stability of the drug as well as for improving the solubility of water insoluble substances by incorporating dispersion of such material in aqueous media.[44]

CHALLENGES ASSOCIATED WITH HERBAL MICROSPHERES AND THEIR SOLUTIONS

Herbal microspheres may attain a specific position in the world of cancer treatment. Moreover, as NDDS, they play a vital role in cancer treatment due to their controlled release properties.[45] However, microspheres, incorporated with herbal extracts or actives, are also associated with some drawbacks. The modified drug release profile may get affected by various factors such as food, transit rate through gut, etc.[43] Encapsulated herbal

microspheres may not release drug in liver and therefore, may exhibit solubility and absorption issues.[46, 47]

While formulating herbal microspheres, it is essential to take care of the following points which may act as challenges for herbal microsphere technology:

- Preparation of controlled or sustained release formulation in case of sensitive drugs;
- Use of biodegradable and biocompatible polymers
- Targeting towards improvement in efficacy by drug targeting strategy
- Identification and isolation of phytoconstituents compatible with microsphere formulation
- Development of highly efficient and low- cost formulations with improved sensitivity and specificity

CONCLUSION

Cancer is a deadly disease which affects the quality of life of patients. Though with the help of technological advancement, numerous conventional treatment strategies are available, but they are still not able to overcome the adverse effects associated with them. Nowadays, herbal anticancer drugs have also gained attention due to their therapeutic potential in addition to their low toxicity profile, easy availability and complete biodegradability. However, the challenges associated with their pharmacokinetic profile need to be resolved by formulating them using a robust NDDS. Anticancer herbal microspheres have resulted in improved solubility, better efficacy, tumour targeting potential along with low adverse effects as compared to traditional herbal formulations. Therefore, the present scenario warrants the commercial utilization of anticancer herbal microspheres for better management of cancer with least adverse effects, improved efficacy and better quality of life of patients with cancer.

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