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The usefulness of curcumin is limited in therapy because of its poor physicochemical characteristics. Curcumin, a multitargeted molecule, shows pluripharmacology, manifested by a cascade of events occurring due to a variety of its actions on a plethora of targets, complementing one other and also the overall effects. In spite of wondrous in vitro success, in vivo data on curcumin and its clinical effectiveness are still lacking. The ambiguity in translating in vitro and preclinical effectiveness to humans and clinics points towards a need for pharmaceutical couturing of curcumin.

Considering the potential of solid lipid nanoparticles as oral drug delivery system, the present investigation involved development and characterization of C-SLNs with a view to improve the oral bioavailability of curcumin. C-SLNs were prepared by microemulsification method. Achievement of high total drug content and entrapment efficiency confirmed the suitability of the formula and the process of SLN formation. Latter was found to be highly reproducible and resulted in particles with a spherical shape as observed by TEM. The entrapment of curcumin in the nanocompartments, formed by the solid matrix of the nanoparticles, was verified by its high entrapment (80% EE) and the absence of endothermic peak corresponding to the drug in DSC studies. PXRD indicated the amorphous nature of developed SLNs; this substantiates high entrapment capacity of the latter.

Preparation of SLNs by the described method involving a small dilution (1:1) of the microemulsion; claimed by us for the first time, overcomes the need to subsequently concentrate the SLN dispersion either by diafiltration or lyophilisation. This helps in administering the desired dose (which is usually high for natural molecules like curcumin). Lyophilisation needs to be followed by redispersion which almost invariably results in an increase in the particle size, such that the formulation loses its essence of being nano in nature. The use of polysorbate 80, presently, in the preparation of the microemulsion and its presence in the subsequent aqueous dispersion of SLNs may enhance the solubility of any unentrapped curcumin and its
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subsequent bioavailability also. Poor aqueous solubility of curcumin of 0.003 µg/ml increases to 5.28 mg/ml in 25% tween 80. High concentration of tween 80 is proposed to change the nature of SLNs, developed in the present work, producing a synergy, which a normal solution of curcumin in a similar concentration of tween 80 in water does not (as shown by the control used in the kinetic studies). Tween 80 may in some way be arranging itself both inside and on the surface of the SLNs so that they are easily transported across the gut epithelium and subsequently across the BBB. Presence of a tween 80 coat helps in the adsorption of apolipoprotein E which is carried across the BBB by endocytosis across special receptor sites. Developed SLNs show significantly better BA as they are able to overcome the first barrier that is permeation across the stomach and ileum and also the enzymatic degradation in the gut. Incorporation of curcumin within SLNs will also protect curcumin against hydrolytic degradation, in solution and also in plasma against enzymatic/metabolic degradation.

Release of curcumin from C-SLNs was by diffusion and was prolonged up to 7 days (85.9%) befitting the first order kinetics model. The initial release (almost 50% in 2 days) may be by diffusion from the shell of the SLNs, while the subsequent phase of prolonged release is attributed to the fact that the curcumin dispersed within the core is being released slowly from the solid matrix of lipid through diffusion and dissolution.

A highly validated, sensitive and specific liquid chromatographic technique coupled with tandem mass spectroscopy method for the quantization of curcumin as such and from its prepared SLNs was developed and validated with a routine sensitivity limit of 10.0 ng/ml in 0.1 ml rat plasma. To best of our knowledge this is the first ever reported data on a novel drug system achieving such a high C_{max} value at an extremely low oral dose of 1 mg/kg of curcumin. In vivo pharmacokinetics performed after oral administration of C-SLNs (50, 25, 12.5 and 1 mg/kg dose) and (free) solubilized curcumin (C-S; 50 mg/kg) in rat plasma revealed significant improvement (at p ≤ 0.05) in BA (39 times at 50 mg/kg; 155 times at 1 mg/kg; and, 59 and 32 times at 12.5 and 25 mg/kg, respectively) after administration of C-SLNs at all the doses with respect to C-S.
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This highly bioavailable (32-155 times more than free curcumin solution (C-S) in 25% tween 80) and stable solid lipid nanoparticulate formulation of curcumin may help establish the clinical efficacy of curcumin, reinventing its role from a preventative dietary supplement to a therapeutic agent.

Presence of yellow fluorescent particles in the plasma and brain were indicative of effective delivery of intact C-SLNs across the gut wall and the BBB. **It confirms the protective asylum provided by the lipidal core of SLNs, preventing curcumin from enzymatic as well as physiological degradation, and removal/elimination from the system.**

Blood\(\text{AUC}_{\text{oral}}\) value for radiolabeled C-SLNs was 8.135 times greater than that for C-S, confirming a prolonged circulation of former. Preferential distribution of curcumin from C-SLNs into the brain tissue was confirmed by a low ratio (≤1) of \(\text{AUC}_{\text{t.v.}} / \text{AUC}_{\text{t.v.}}\) C-SLN in blood to a 30 times higher value achieved in brain. Similar observations were also made for oral administration. To our knowledge this is the first study reporting an 8-30 times enhanced distribution of curcumin to brain, using a suitable delivery system. A 32-155 times enhanced BA observed for C-SLNs in pharmacokinetic studies was complemented by these studies. Further, gamma scintigraphic images confirm the delivery of C-SLNs to brain in rabbits.

Study also highlights the significantly better apoptotic role of C-SLNs as compared to free curcumin, against a variety of cancer cell lines. Most of the investigations report on pharmacological and clinical studies showing effectiveness of curcumin for gut-related cancers only. This is as expected, considering that curcumin is a very poorly absorbed drug (less than 1%) and is excreted unchanged in the faeces. Hence its local concentration in the gut is sufficient to show this effect. Similarly, it has also shown its clinical effectiveness upon local application to skin. Present investigation deliberately dealt with a proof of concept of in vitro efficacy of developed C-SLNs over free curcumin. Having achieved the in vitro efficacy and enhanced in vivo systemic bioavailability, we expect that the formulation effectively hits the target for this most appalling disease i.e cancer. However, future successful studies on
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developed formulation in the in vivo settings will confirm the eventual clinical translation of this well known herbal agent to the status of a therapeutic agent.

Curcumin administered in its highly bioavailable form (C-SLNs) completely reversed the induced alterations in brain histopathology, loss of cognition and an oxidative damage induced biochemical changes, including inhibition of antioxidant enzyme activities as a result of AlCl3 exposure. This gives a direct evidence of effective brain delivery of C-SLNs and for the first time establishes the curative-therapeutic role rather than a mere protective role established by simultaneous or prior administration) of curcumin, in AD like symptoms. The study also established the much higher potential of C-SLNs to act as an anti-depressant upon administration of a single low dose (1 mg/kg) when compared to free curcumin.

All the above studies put together, confirm the direct delivery of curcumin loaded solid lipid nanoparticles to the brain.