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Research Article

An Explorative Study of Oral Microemulsion-based Formulation for the Delivery of Cabazitaxel and Piperine

Rehan Uddin*, Jitendra S. Rajawat

Faculty of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan, India

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ABSTRACT

Cabazitaxel is the newest version of taxanes and is a promising drug for managing various cancers. Like other taxanes, this drug also poses a challenge of solubility and permeability, resulting in a poor oral bioavailability. The present study explores a scalable and economic nanoformulation in the microemulsion form for the oral delivery of cabazitaxel. The developed system substantially improved the drug's anticancer activity on the breast cancer cell lines and *in vivo* cancer models. Piperine was also loaded in the microemulsion and it was observed that the incorporation of piperine resulted in an oral formulation with substantially higher oral bioavailability of CBZ *vis-à-vis* plain drug as well as the microemulsion. The findings infer that biocompatible microemulsions can enhance the oral bioavailability and anticancer activity of CBZ, which was further improved after incorporating piperine.

Introduction

Taxanes belong to group of diterpenes, promotes inhibition of microtubules. These are commonly used as chemotherapy agents for several cancer types. In 2010, the USFDA approved cabazitaxel (CBZ) under the brand name of Jevtana for the management of hormone-refractory prostate cancer. This marketed product is a micelle-based formulation comprising polysorbate 80 and alcohol. The surfactant and co-surfactant/co-solvent have been incorporated to enhance the solubility of the CBZ to make it fit for the intravenous infusion. The main disadvantages of the developed marketed composition are Neutropenia, thrombocytopenia, and loss of red blood cell count. In 8 percent of the cases, the neutropenic infection had been diagnosed. Hypersensitivity syndrome, vomiting, bronchospasm, diarrhoea, etc. are other popular toxicities. The USFDA released a black box warning letter because of serious concerns like occurrence of neutropenia.[1–3]

Many of these life-threatening side effects have necessarily reduced the use of CBZ in clinical trials. Besides, the CBZ marketed preparation cannot target tumors, and its unequal distribution in the tissue triggers toxic side effects tissues. A daily dosing regimen, which is fatal to the patient, includes thorough plasma protein binding and the rapid removal of CBZ. Multidrug resistance is a key problem in many types of chemotherapy failure. Other major complications commercially viable for chemotherapeutics are serious effects leading to death. There is also an intense necessity to tackle multidrug-resistant leukemia, including certain nanotechnology-based chemotherapy, with innovative medications. Extremely effective protocols are required and their introduction in cancer will be exceedingly difficult.[4–6]

With the improved understanding of the biological

***Corresponding Author:** Rehan Uddin

Address: Research Scholar, Faculty of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan, India

Email ✉**:** rehanuddinnizami@gmail.com

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systems and the molecular mechanisms, novel drug delivery systems are being explored scientifically to enhance the efficacy of the drugs in practice and overcome the limitations of the drugs. [7,8] Microemulsions are thermodynamically firm nanocarrier systems. These systems have a uniform orientation with clear combinations of oil, surfactant, and an aqueous medium. They are stable in nature. The oil is emulsified in the aqueous phase or vice versa by the interfacial lowering capability of the surfactants. Gibb's free energy and interfacial tension are reduced due to the presence of the interfacial layer of the surfactant at the utmost layer of the internal phase. A variety of drugs can be loaded by these liquid nanocarriers, which can be used for different routes ranging from oral to topical.[9,10] It was henceforth envisaged to prepare microemulsion-containing CBZ for oral distribution to leverage the beneficial properties of this carrier mechanism and to establish a continuous release formula to counteract the side effects of the drug. Apart from the oral delivery of CBZ using microemulsion, piperine was also loaded in the system to temporarily inhibit the P-gp efflux mechanism and improve the bioavailability of the CBZ.[11]

Materials

Cabazitaxel was provided as gift sample by Fresenius Kabi Oncology Limited, Gurugram, India and Phospholipid was a generous gift sample from Phospholipid GmBH, Nattermannalle, Germany. Dimethyl sulphoxide and 3-(4,5-Dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were supplied by Sigma- Aldrich, Bangalore, India. Acetonitrile and Ortho Phosphoric Acid were obtained from Spectrochem Pvt Ltd, Mumbai, India, hydrochloric acid, potassium dihydrogen phosphate, glycerol stearate and dipotassium hydrogen phosphate were procured CDH Pvt Ltd, New Delhi, India, dialysis membrane, Dulbecco Modified Eagle's Media, and fetal Bovine Serum Albumin were procured Himedia laboratories Pvt Ltd, Mumbai. Ultrapure water milli-Q® Integral system; Merck Millipore, Billerica, USA was used throughout the study.

Methods

Preparation of Pseudo-ternary Phase

Microemulsions are thermodynamically stable and isotropic systems composed of oil, surfactant and aqueous phases.[10,12-14] Being a good penetration enhancer and Generally Recognized as Safe material, isopropyl palmitate was selected as the oil component.[15] However, three ternary phase diagrams were constructed to select appropriate polysorbate. In brief, the oil and the polysorbate were mixed in ratios ranging from 1:9 mass ratios to 9:1 and vortexed. These mixtures were titrated with water till the appearance of haziness or gelling. Analogously, the dilutions were prepared with varying ratios of water and the polysorbate(s), and the mixtures were titrated against oil until haze or gelling drop appeared. The percentages of each component were calculated and the ternary phase diagrams with each component representing the constructed vertex of the triangle. The titrated values fetched the boundary of the miscible and immiscible regions.[16]

Preparation of Microemulsion

Based on desired characteristics, the selected optimized formulation after optimization studies was selected for final formulation. The microemulsion was prepared by mixing the aqueous phase into the organic phase. The organic phase consisted of IPM and the aqueous phase consisted of Tween 60, and CBZ. CBZ was dispersed in water containing the polysorbate. Aqueous phase was slowly poured into the organic phase, i.e., IPM. Blank microemulsion was also prepared analogously; however, the drug was not added. For the microemulsion with piperine, the piperine was also dispersed in the aqueous phase, rest other procedure was same.[17]

Characterization Studies

Globule size, PDI and Zeta Potential

For the measurement of the globule size and the polydispersity index (PDI), the microemulsion was diluted 50-times with distilled water. For the recording of the zeta potential, the sample was used undiluted. All the recordings were made at 25˚C using Nano ZS, model of Malvern Zetasizer (Malvern Instruments, UK). The reported results were of three runs.

Density, %Transmittance and pH

The density was determined simply as the ratio of the mass of the microemulsion to its volume. The %transmittance was recorded on UV-visible spectrophotometer at 650 nm against water. The pH value of microemulsion samples were measured at 25˚C by a pH meter.

Drug Entrapment and Drug Loading

Dialysis method was used for the drug loading and drug entrapment studies. Blank and CBZ-loaded microemulsion were individually packed in different dialysis bags and stirred on two magnetic stirrers in a 100 ml beaker containing 70 ml methanol for 2 hours. The entrapment efficacy (EE) and extent of drug loading (DL) were determined by measuring optical density of the sink solution through UV spectrophotometer at a wavelength 230 nm. [5,17]

In-vitro Drug Release Studies

In-vitro release of equivalent amount of plain CBZ and CBZ loaded microemulsion was also determined at pH 6.8 and 0.1M HCL. The samples (1 mL) were collected at regular intervals and were analysed by HPLC method

Mobile phase: 92 % Orthophosphoric acid buffer pH 6.0 and 8% Acetonotrile; Flow rate: 1.4 mL/min) at 302 nm. To understand the drug release mechanism from the developed system, various drug release kinetic modes were employed, as explained by Thakkar *et al.,* 2009.[18,19]

In-vitro Cytotoxicity Assay

MCF-7 cell lines were used to determine the cytotoxicity of the prepared formulation. Cells were cultured in 96 welled plates in the presence of 5% CO_2. Plain drug and lipospheres were added to these cultured welled plates and incubated at 37°C for 24 hours. After 24 hours MTT solution (10 µL) was added to these plates and incubated for next 4 hours. Purple-coloured insoluble formazan crystals were collected and dissolved in 200 µL DMSO. These solutions were analyzed to determine optical density at λ_{max} of 302 nm. IC^{50} values were calculated from the obtained optical density values. [11]

Pharmacokinetics

For the pharmacokinetic studies, unisex Wistar rats (200–250 g; 4–6 weeks old) were employed. The animals were divided into three groups of five animals each: animals of the Group 1 received only cabazitaxel (10 mg. kg^{-1}), animals of Group 2 received drug-loaded microemulsion (equivalent to 10 mg/kg of CBZ) and Group 3 received CBZ-piperine-loaded microemulsion (equivalent to 10 mg/kg of CBZ). For easy oral administration, 0.2 mL of normal saline was used to disperse the desired doses. After the oral administration of the doses, at specified time intervals, 200 µL of whole blood was harvested from the *retro*-orbital plexus of the rodents. The blood with anti-coagulant was centrifuged at a speed of 10,000 rpm for 5 min and equivalent amount of acetonitrile was added for protein precipitation and drug extraction. The extracted samples were analyzed by RP-HPLC to fetch with the plasma concentration of the drug at various time points. Using PK Solver software, various pharmacokinetic parameters were determined as per the one compartment open body model. [5,20]

Pharmacodynamic Studies

The tumor was developed in female Balb/c mice of 21–42 days age with mass range of 30-40 g. For the tumor development, subcutaneous injection of DMBA in olive oil (1 mg/0.2 mL) was injected in the mice every 07 days, for a total of 3 weeks. After 15 days, the tumor-developed animals were divided into three groups with 3 animals each. The groups received oral CBZ, microemulsion CBZ and saline after two weeks, for one month, respectively. [5] All the animal protocols including the pharmacokinetic studies were duly approved by the Institutional Animal

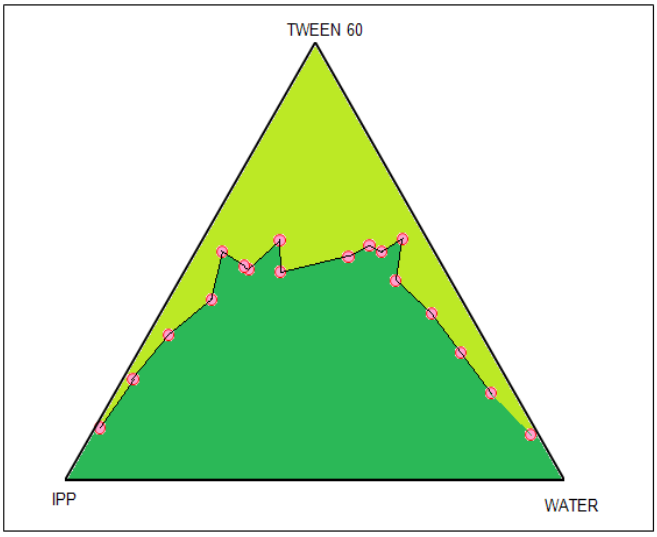

Fig. 1 (B): Ternary phase diagram obtained from the three component system, i.e., IPP, Tween 60 and water

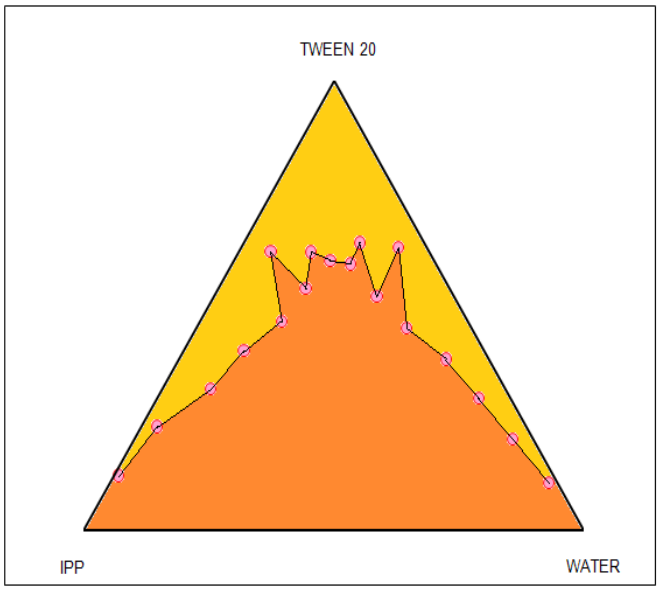

Fig. 1 (A): Ternary phase diagram obtained from the three component system, i.e., IPP, Tween 20 and water

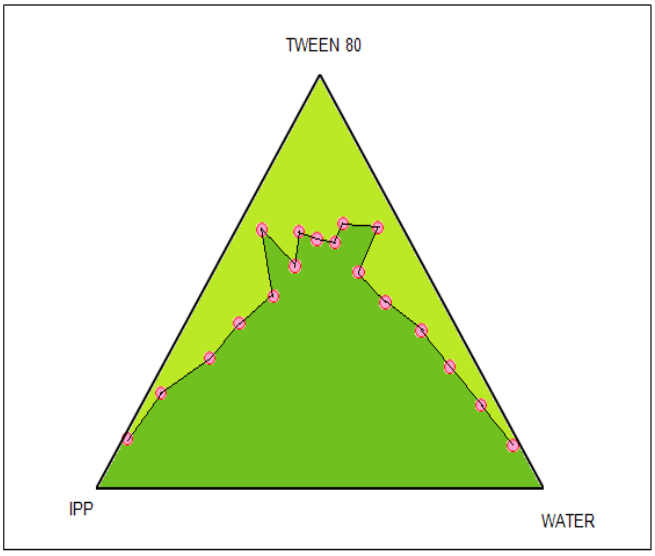

Fig. 1 (C): Ternary phase diagram obtained from the three component system, i.e., IPP, Tween 80 and water

Ethics Committee, ADINA Institute of Pharmaceutical Sciences, Sagar, MP, India (AIPS/2020/2636/IAEC/13).

Results and Discussion

Ternary Phase Studies

A total of three ternary phase diagrams were constructed using the polysorbastes (Tween 20, Tween 60 and Tween 80), isopropyl palmitate and water. The respective ternary phase diagrams have been shown as Fig. 1. Isopropyl palmitate (IPP) was selected as the oil, owing to its better solubilization capabilities and penetration enhancement effects. For a BCS class IV drug like CBZ, IPP can offer both the solubility enhancement and permeability enhancement.[21,22]

Out of the studied ternary phases, the area of emulsification of the oil was quite good by all the three non-ionic surfactants, with the maximum emulsification offered by Tween 60. Based on the emulsification area, it was decided to select the Tween 60 as the surfactant for the microemulsion.

The ternary phase diagrams showed that the IPP was better emulsified by the non-ionic surfactants with larger carbon chains. For instance, the carbon chain length of the fatty acid (Lauric acid) of Tween 20 is 12, and relatively less emulsification was offered by Tween 20, out of the studied polysorbates. Interestingly, the carbon chain length of the fatty acid component of IPP is 16, and it appears that the better non-ionic surfactants to emulsify this kind of oil should have higher carbon chain length. The surfactants with > 16 carbon atoms in the fatty acid chains, i.e., Tween 80 and Tween 60 offered better solubilization/emulsification. IPP hosting a saturated fatty acid was better emulsified an 18 Carbon chained (fatty acid component) non-ionic surfactants, with the best performance by the surfactant with saturated 18 Carbon chained fatty acids (Tween 60). The required HLB for the IPP is between 11 to 12 and both the surfactants can offer it as the HLB value of Tween 60 is 14.9 and that of Tween 80 is 15. The results provide an inference that the polysorbates, in general can easily emulsify the IPP, with the best emulsification offered by Tween 60.

Selection of the Microemulsion Composition

From the ternary phase diagram of IPP, Tween 80 and water, a total of 14 formulations were screened with % of IPP from 4% to 16%, and the % of Tween 80 from 3% to 6.4% w/w, rest being water. The amount of drug was maintained in way that 0.2 mL of the microemulsion can cater the dose of a rodent. The microemulsions were prepared by simple mixing technique, as disclosed above. The results of various parameters including pH, density, % transmittance, globule size, PDI, drug loading and entrapment efficiency have been listed in the Table 1.

Table 1 shows the pH value of the developed microemulsions ranged from 5.35 to 7.91. Though the pH range of skin is below 5, most acceptably as 4.7, these pH ranges are quite acceptable on the skin and across the GIT.[23] The density of the developed formulations ranged between 0.8649 mg/mL to .1682 mg/mL. Notably, the average density of the nanocarriers was near to water. The %transmittance of the developed systems was observed to be > 84%, except for the formulation F8, where the value of the %transmittance was ~ 78%, indicating a compromised level of transparency. The majority of the developed systems were transparent in nature. The globule size of the nanocarriers ranged between 106.1 nm and 1217 nm, with a PDI range of 0.297 to 0.928. The entrapment efficiency of the drug ranged between 86.40% to 98.98%, emphasizing the super solvent nature of the microemulsions, whereas

Table 1: Composition and various attributes of the developed formulations

Code	*Tween 60 (%)*	*IPM (%)*	*pH*	*Density (g /mL)*	*% Transmittance*	*Globule size (nm)*	*PDI*	*Drug loading (%)*	*% Entrapment efficiency*
F 1	4.4	8	5.35	0.9927	98.907	295.2	0.406	14.4	86.40
F 2	4.2	12	6.41	1.1682	89.371	483.7	0.536	9.4	89.70
F 3	3.8	16	5.40	0.6927	88.327	252.7	0.650	9.1	91.00
F 4	4.6	4	7.80	0.9135	88.102	737.9	0.574	15.6	90.64
F 5	4.4	12	4.63	0.9661	99.759	136.8	0.297	14.2	96.28
F 6	4.2	4	7.91	1.0061	89.765	1085	0.756	12.3	98.98
F 7	4	8	7.43	1.1271	95.840	320.2	0.928	6.7	94.69
F 8	3.6	12	5.72	1.0019	78.626	956.1	0.732	11.2	94.04
F 9	3.2	12	6.12	0.8649	98.029	171.2	0.245	9.9	94.08
F10	3.8	8	6.40	0.7517	97.905	121	0.803	12.9	97.35
F11	3	16	6.35	0.9871	99.191	514.7	0.314	8.9	89.71
F12	5.2	4	7.40	1.0210	99.203	106.1	0.119	13.0	91.35
F13	5.8	4	5.40	1.0109	84.775	454.8	0.295	11.1	92.28
F14	6.4	4	6.50	0.9525	84.703	1217	0.927	13.07	91.50

the drug loading of CBZ ranged between 6.7% to 15.6%. The microemulsions offered a substantial drug loading potential, meanwhile maintaining an upper range of drug entrapment.

Based on the results in Table 1, the formulation coded as F5 was selected as the final formulation for further studies. The reasons being such selection were the presence of moderate amount of surfactant, 12% of IPP and the final product offered a globule size of 136.8 nm, i.e., the ideal size for drug delivery with an acceptable range of PDI (< 0.3), higher drug loading and substantial drug entrapment. Out of various formulations, this very formulation offered the desired physicochemical attributes like appropriate particle size for better pharmacokinetic profile, [20] appropriate PDI ensure better homogeneity in the particle size, suitable pH and efficient drug loading.

In-vitro Drug Release Studies and Release Kinetics

In the gastric pH, for the initial 2 hours of the study, only 27.88% of the CBZ was released from the developed microemulsion (CBZ-PIP-ME), whereas from the plain drug, 79.21% of CBZ was released, showing uncontrolled release from the plain drug, whereas presence of release controlling mechanisms for the CBZ from the microemulsion. In just 6 hours, the contents of the plain CBZ were released, whereas the microemulsion constantly released the drug over 24 hours. This temporal drug release pattern, where the drug release was controlled, that too minimal release in the gastric pH was a desirable attribute, as the stomach is not the site for the absorption of CBZ.[24] The drug release results have been shown in Fig. 2, where the clean distinction between the drug release from the plain drug and the microemulsion is clearly evident. The developed system was able to retard the drug release in the gastric pH and release it in a controlled manner in the instestinal pH, which is the target site of absorption. Out of the studied drug release kinetic models, it was found to follow the zero-order release characteristics ($r^2 = 0.9827$).

One interesting observation in the release profile is that the release of piperine from the selected microemulsion (CBZ-PIP-ME) was always greater than the amount of CBZ released at every time point. Such release characteristic is desired, as the piperine is a milder P-gp efflux and cytochrome P450 enzyme inhibitor. It will execute its effect before reaching CBZ to the target site and liver. It will result in partial inhibition of the efflux mechanisms at the target site, resulting in better accumulation of CBZ at the site of action, meanwhile inhibiting the target enzyme for the first-pass metabolism of CBZ, resulting in enhanced bioavailability of CBZ.[25]

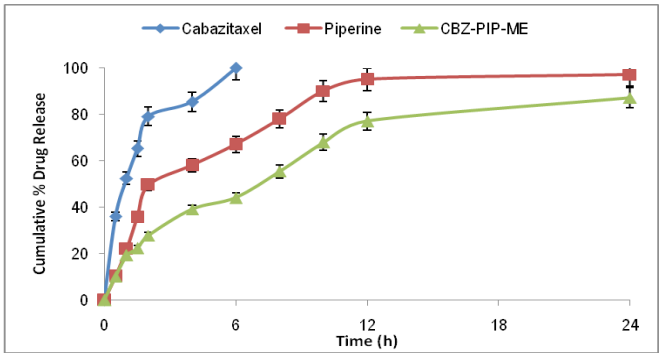

Fig. 2: The drug release profile from the plain drug and the drug-loaded microemulsion for 2 hours in simulated gastric fluid and next 22 hours in simulated instestinal fluid.

In-vitro Cytotoxicity Assays (MTT Assay)

The IC_{50} values obtained for the studied interventions were in the order of:

Pure CBZ (5.20 µM) > CBZ-ME (2.45 µM) > CBZ-ME-PIP (1.08 µM)

There was approximately 2.12 folds reduction in the IC_{50} values of CBZ-ME compared to free CBZ. After incorporation of piperine, there was a substantial decrease of 4.8 times, advocating the synergism between piperine and cabazitaxel. The results are in close agreement with the drug release pattern, advocating the inhibition of the drug efflux mechanisms by the previously released piperine, resulting in higher accumulation of drug in the cell and better cytotoxicity. The results clearly advocate the supremacy of the developed system over the plain drug, providing a platform for an effective nanoformulation for anticancer effect compromising of CBZ and piperine.

Pharmacokinetic Studies

The results of the pharmacokinetic studies are represented in Fig. 3. It is evident that at every time point, the amount of drug present in the central compartment was maximum for CBZ-PIP-ME, followed by CBZ-PIP and least for the CBZ ($p < 0.05$). The findings are in the close agreement with the hypothesis derived from the *in-vitro* drug release studies, as the previously released piperine mifght have inhibited the cytochrome P450 enzymes, resulting in the highest plasma drug concentrations. Also, plain micromeulsion was also able to enhance the plasma drug concentrations,

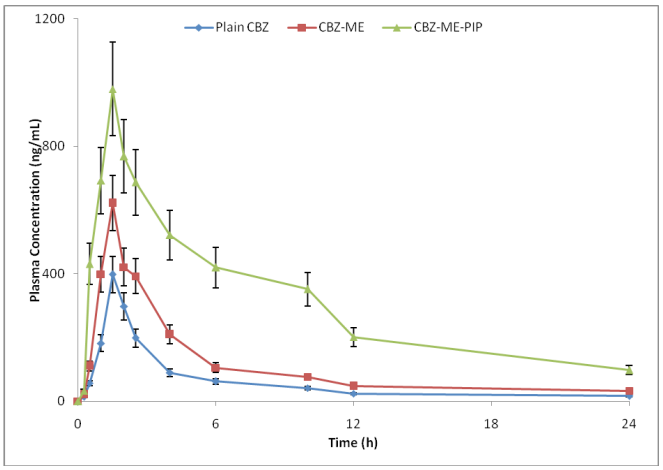

Fig. 3: Graph between plasma drug concentrations versus time for tested formulations

Table 2: Tabular representation of the various *in vivo* pharmacokinetic parameters

Pharmacokinetic Parameter	*CBZ*	*CBZ-ME*	*CBZ-ME-PIP*
AUC (0-24) (ng/mL.h)	1121.12 ± 12.31	2614.48 ± 9.79	5690.87 ± 26.21
C_{max} (ng/mL)	397.09 ± 12.49	621.38 ± 20.17	979.21 ± 42.13
$t_{1/2}$ (h)	6.97 ± 0.21	8.54 ± 0.68	12.85 ± 2.19
K (1/h)	0.099 ± 0.021	0.0811 ± 0.012	0.059 ± 0.009
V_d (L)	0.102 ± 0.012	0.084 ± 0.011	0.090 ± 0.024
Cl (L/h)	0.010 ± 0.001	0.007 ± 0.002	0.005 ± 0.002

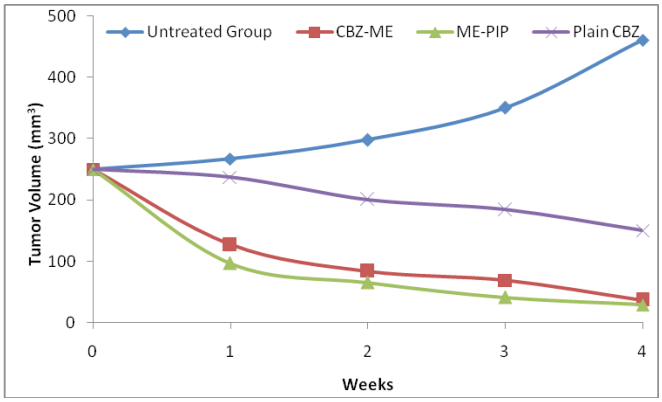

Fig. 4: The effect of various treatments on the tumor volumes of the rodents at various time intervals

owing to better absorption and bypassing the first-pass metabolism.[26] The results of the pharmacokinetic parameters are shown in the Table 2. There was almost 2.33 times enhancement in the oral bioavailability of CBZ in the microemulsion *vis-à-vis* the plain drug ($p < 0.05$). It was also observed that the microemulsion enhanced the plasma half-life of CBZ by 1.2-folds ($p < 0.05$). After incorporating piperine, the bioavailability of the CBZ was enhanced by almost 5.1-folds *vis-à-vis* plain drug, advocating the merit of the dual drug delivery model over the CBZ-ME ($p < 0.05$). Apart from the substantial biaoavailability enhancement, the piperine incorporation resulted in 1.8-folds enhancement in the biological half-life. The findings are promising as it paves a path for oral delivery of CBZ. After incorporation of piperine, the pharmacokinetic attributes improved substantially. The $C_{max,}$ which was 1.56 times enhanced by ME, was enhanced by 2.5 times by adding piperine, whereas the bioavailability enhancement was around 5 times with the piperine incorporation. The plasma protein binding was not altered, whereas the clearance was reduced with the ME as well as the piperine ME. The findings are encouraging as the piperine has substantially improved the pharmacokinetic outcomes of the microemulsion.

Pharmacodynamic Studies

Fig. 4 shows the change in the tumor volume on week basis. It is evident that the group receiving plain CBZ showed a decrease in the tumor volume, but the rate of decrease was quite lower than both the microemulsion-based CBZ formulations ($p < 0.05$). The effect of piperine-based CBZ

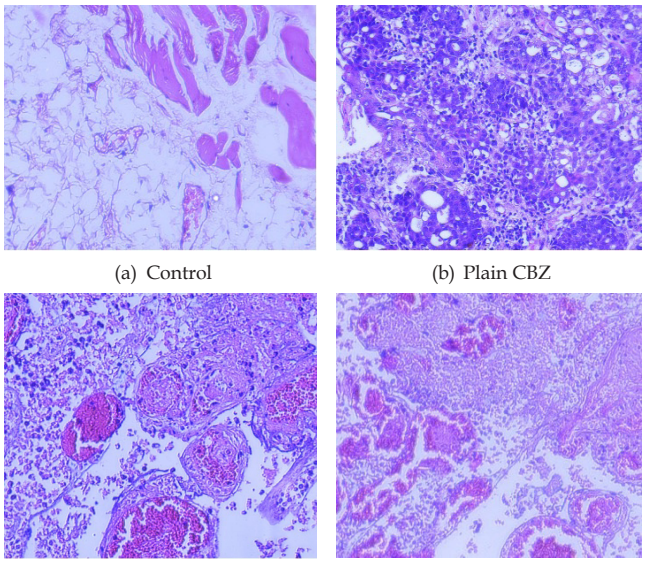

Fig. 5: Histopathological pictures showing the effect of various treatments on the tumor on the 4th week

microemulsion was more pronounced than that of the CBZ microemulsion owing to the better bioavailability and better tissue penetration. The tumor volume was decreased to around 29 mm^3 by the former, whereas the latter group exhibited an average tumor volume of 37 mm^3. The tumor volume of the group with plain CBZ was 151 mm^3 on the fourth week, indicating the efficacy of oral doses, though advocating the superiority of the microemulsion-based systems.

The histopathological results also corroborated the findings of the tumor volume, as the maximum healing was exhibited in the groups receiving piperine-based CBZ microemulsion, followed by CBZ microemulsion and least by the group receiving plain CBZ. The plausible reasons are better absorption, passive targeting, lower first-pass metabolism, partial inhibition of P-gp efflux and prolonged residence at the site of action. The histopathological pictures are presented as Fig. 5.

Conclusions

The findings provide evidence of a nanoscale pharmaceutical product for the oral delivery of CBZ, the bioavailability of which has been further improved by incorporating piperine. Such scalable products with

proof of concept of enhanced anticancer activity in cancer cells and tumor bearing rodents can be further explored, so that an oral product can be made available. The pharmacokinetic outcomes were conducive and provided a platform for systematic development of nanocarriers loaded with piperine and cabazitaxel for managing various tumors.

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