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The Effectiveness of Bovine Serum Albumin (BSA) Nanoparticles as Carriers in Drug Delivery Systems: A Review

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Abstract:
Background*:Toxicology and undesired side effects at non-target sites or organs can be reduced by using specific targeted drug delivery methods to cells, tissues, or organs. BSA nanoparticle carriers are one of the focused drug delivery techniques to cells or tissues.Reversible drug binding and drug release are both possible with BSA nanoparticles.Therefore, it is necessary to research how well BSA nanoparticles work as carriers in drug delivery systems.The goal of this review paper is to serve as a resource for scientists working on BSA nanoparticles as drug delivery system carriers.*
Materials and Methods*: ScienceDirect, Google Scholar, Elsevier, SpringerLink, and PubMed search engines are used to review articles from scientific publications that have already been published.*
Results*: BSA nanoparticles can enhance cytotoxicity and pharmacokinetic characteristics when used as a drug carrier.*
Conclusion:*In order to maximize the therapeutic effect of medications on target cells without creating undesirable side effects, BSA nanoparticles can be employed as a drug delivery system.*
Key Word*: Bovine serum albumin, nanoparticles, drug delivery system, pharmacokinetics, cytotoxicity*

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I. Introduction

Drug targeting is a technique for quantitatively and selectively delivering bioactive substances or active pharmaceutical ingredients (API) in order to maximize concentration in target cells and prevent interactions with healthy cells[1].Implementing a drug delivery system is mostly done to improve the drug's capacity to reach specified targets, such as cells, tissues, or organs, in order to lessen toxicity and undesired side effects at non-target sites or organs[2].

Drugs are substances that have been widely utilized to treat and prevent diseases in order to improve the health of their users, but some of them have more severe side effects or unstable features in the body, such as water solubility[3]. Low therapeutic impact effectiveness and poor drug bioavailability limit the potential of a medicine's ability to improve health[4].Examples of active ingredients with limitations in their use include gemcitabine, which has a short half-life and has substantial side effects when used at large doses[5]. Furthermore, there includes berberine, which has poor bioavailability and low water solubility[4]. Additionally, the poor water solubility of paclitaxel (2 g/ml) reduces the desired therapeutic effect[6]. Curcumin, an active ingredient utilized in medicine, has limitations including a short half-life, poor solubility, leading in less effective absorption, and poor bioavailability when administered orally[7].

Employing a carrier as a drug delivery method to enhance the therapeutic effect and minimize adverse effects is one way to address this limitation[3]. One of the additions that can be employed is the use of a carrier, such as albumin, to improve the ineffective qualities of the active ingredient (BSA). A natural bio-macromolecule called protein is involved in metabolism and the movement of chemicals inside living things. However, protein can make hydrophobic drugs more soluble in plasma, which can have an impact on blood transport[4]. The albumin protein has attracted the attention of researchers among the several types of biomolecules commonly implemented for targeted drug delivery systems because of its effective carrier properties[8].

Nanoparticles are in high demand as a replacement for ineffective drug delivery systems due to their poor bioavailability, selectivity, and biodistribution. Polymer nanoparticles as carriers are expected to overcome these shortcomings, resulting in more maximal effects with fewer unwanted side effects[9].Polymer nanoparticles could also protect drug compounds from premature degradation, increasing their water solubility[10].Polymer nanoparticles are solid colloidal particles with diameters ranging from 10 to 100 nm. Polymer nanoparticles are classified into two types based on their chemical composition, namely natural polymers such as albumin,

chitosan, and gelatin. Polymers that are synthetic or semi-synthetic, such as PGA, PLA, poly L-lactide, and polyglycolide[1].Bovine serum albumin nanoparticles (BSAN) have reversible drug binding properties, allowing them to release drugs into target cells[11].Thus, treatment becomes more selective and can improve drug pharmacokinetic properties (Mainardes& Khalil, 2019). Based on the above regarding BSAN as a carrier, it is necessary to conduct a more complete study. So that the results of this review are expected to be a reference for further development of BSA nanoparticles as carriers in drug delivery systems.

II. Material And Methods

Scientific journals with recent publications were found using search engines at ScienceDirect, Google Scholar, Elsevier, SpringerLink, and PubMed (2012-2022). Nanoparticles, Albumin, BSA, and Drug Delivery System are some of the terms used. The selected literature was then evaluated using the criteria, which included the effectiveness of bovine serum albumin (BSA) nanoparticles as a carrier in drug delivery systems.

III. Result

The review's findings (Table no 1) indicate that using BSAN as carriers can improve their pharmacokinetic properties and increase their cytotoxicity.

Table no 1: The effectiveness of BSAN as carriers in drug delivery systems

No.	Author	Study	Drug	Result
1.	(Huang et al., 2019)	Pharmacokinetic	Curcumin (CUR)	C_{max} and AUC were higher in BSAN-CUR (1.9 and 1.4 times, respectively) than in pure curcumin. In addition, T_{max} is obtained faster and MRT is obtained for a longer period of time than pure curcumin.
2.	(Wan et al., 2020)	Pharmacokinetic	Cabazitaxel(CBZ)	The pharmacokinetic properties of BSAN-CBZ ($T_{1/2}$, AUC, C_{max}, Cl, MRT) were significantly higher than those of CBZ-Tween 80. The drug clearance of CBZ-Tween 80 was faster than that of BSAN-CBZ.
3.	(Battogtokh et al., 2015)	Pharmacokinetic	Paclitaxel (PTX)	The AUC value obtained inl BSAN-PTX is greater than the AUC value obtained in PTX. BSAN-PTX has a longer elimination half-life than PTX.
4.	(Zhao et al., 2015)	Pharmacokinetic	Tacrolimus (TAC)	The AUC and MRT values of BSAN-TAC are greater and longer than those of Prograf®.
5.	(Zhang et al., 2017)	Pharmacokinetic	Bufalin (BF)	C_{max}, $T_{1/2}$, MRT, AUC of BSAN-BF are all greater than BF. While the value of ClBSAN-BF is slower than the value of BF. As a result, the drug will stay in the bloodstream longer, increasing its concentration in plasma.
6.	(Ramesh & Mandal, 2019)	Pharmacokinetic	EGCG	T_{max}, C_{max}, $T_{1/2}$, and AUC BSAN-EGCG were all significantly higher when compared to EGCG. Furthermore, the clearance value (Cl) of BSAN-EGCG was slower than that of EGCG. In order to keep the drug in the bloodstream longer and increase plasma concentration.
7.	(Yang et al., 2020)	Cytotoxicity	Doxorubicin (DOX)	When compared to the percentage of inhibition achieved by DOX, the cytotoxicity of BSAN-DOX against tumor cells A549, A2780, and NCL-H460 was 2 times, 1.5 times, and 1.5 times higher, respectively.
8.	(Dubey et al., 2015)	Cytotoxicity	Gemcitabine (GEM)	When compared to the GEM, the percentage of inhibition in BSAN-GEM was higher. Furthermore, when compared to GEM, the IC_{50} value of BSAN-GEM was significantly lower.
9.	(Solanki et al., 2021)	Cytotoxicity	Berberine (BBR)	BSAN-BBR inhibited MDA-MB-231 cells at a higher percentage than BBR. Furthermore, it proved that cancer cell death caused by BSAN-BBR (30%) was greater than pure BBR.
10.	(Siri et al., 2020)	Cytotoxicity	Emodin (E)	The results of metabolic tests and cell adhesion of BSAN-E were lower than those of pure E. This indicates an increase in cell death, which is supported by the LDH assay.

Note: C_{max} (Maximum concentration) ;T_{max} (maximum time) ; AUC (Area Under Curve) ; MRT (mean residence time)

IV. Discussion

An ideal drug delivery system should be capable of keeping product stability and delivery under a variety of physiological variables. Furthermore, drug delivery systems must be capable of increasing drug bioavailability, providing controlled drug delivery, and fully loading drugs to target cells while avoiding side effects on other organs[12].Natural polymers such as albumin[3], alginate[13], chitosan[14], gelatin[15], and cellulose[16] are currently used as carriers in drug delivery because they have the advantage of enhancing the therapeutic effect. Albumin (BSA) is a natural polymer with numerous advantages as a carrier[17].BSA has several advantages, including its availability[18] and abundance[19], non-toxicity[20], non-immunogenicity[21], biodegradability[17], high water solubility, and selective conduction ability[22]. These benefits make BSA a popular choice among researchers for use as a carrier in drug delivery systems.

Furthermore, the effectiveness of the addition of a carrier can be increased by making it in the form of nanoparticles, where the active ingredients of drugs with albumin carriers will be packaged in a nanoparticle basis[9], with the expectation that the therapeutic effect will be maximized and unwanted side effects will be minimized. Several hypotheses suggest that using drug delivery systems packaged in nanoparticle bases can improve drug stability, pharmacokinetic properties, and reduce drug toxicity[23]. The effectiveness of BSA nanoparticles as a carrier in drug delivery systems is shown in table no 1.

Pharmacokinetics of BSA Nanoparticle-Delivered Drugs

Pharmacokinetic properties, in general, can describe bioavailability. Furthermore, pharmacokinetic studies seek to determine the circulation of the half-life and the drug's ability to be localized in one compartment of the body so that the treatment can reach target cells while preventing drugs from entering other cells or tissues[24].Several drugs have limited therapeutic effects, so they are designed and produced as nanoparticles with bovine serum albumin (BSA) carriers. As a result, it can increase drug bioavailability, thereby increasing therapeutic effect[25].

Curcumin

Curcumin (CUR) has antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. Curcumin, on the other hand, belongs to the biopharmaceutical classification system (BCS) class IV, which has poor water solubility, reducing its therapeutic effect in treatment. As a result, a curcumin dosage form was developed using a galactosylated BSA nanoparticle carrier to increase the targeted effectiveness at the asialoglycoprotein receptor (ASGPR) in HCC cancer cells[26].

(Huang et al., 2019)[25] measured pharmacokinetic studies with the parameters AUC, MRT, T_{max}, and C_{max}. The T_{max} parameter results, namely BSAN-CUR, showed a faster time than the peak concentration at 0.5 hours. In contrast, the maximum peak concentration time in pure CUR is 2 hours. The results for BSAN-CUR (48.7 ± 7.4 ng/mL) were 1.9 times higher than pure CUR (25.2 ± 7.0 ng/mL) in the C_{max} parameter.This is because the nano size allows it to pass more easily through the intestinal barrier, allowing more curcumin to accumulate in the plasma.Furthermore, the AUC parameter obtained in BSAN-CUR (1047.6 ± 41.2 ng/mL/hour) was 1.4 times higher than the results in pure CUR (775.4 ± 35.7 ng/mL/hour), indicating that a higher AUC value can help maintain plasma concentrations and thus increase curcumin oral bioavailability.The final parameter, MRT, obtains a relatively longer value for BSAN-CUR (22.6 ± 0.4 hours) compared to pure CUR (21.7 ± 0.8 hours), implying that the longer residence time in plasma may aid in increasing oral bioavailability. Thus, BSAN-CUR can improve curcumin oral bioavailability.

Cabazitaxel

Cabazitaxel (CBZ) is an antitumor drug approved by the FDA for the treatment of prostate cancer as an injection. CBZ, on the other hand, has drawbacks such as high toxicity and poor tumor selectivity. Furthermore, because CBZ is poorly soluble in water, a solvent such as Tween80® is used.However, it can cause severe allergic reactions such as rash or systemic erythema. CBZ was thus delivered using BSA nanoparticles to achieve the desired target while minimizing side effects[27].

According to one study (Wan et al., 2020)[27] plasma drug concentrations of CBZ-Tween 80 and BSAN-CBZ differed significantly after intravenous administration. $T_{1/2}$, AUC, C_{max}, Cl, and MRT were used to make measurements.The results revealed that the $T_{1/2}$ value of CBZ-Tween 80 (14.76 ± 2.31 hours) BSAN-CBZ (25.39 ± 3.54 hours), AUC value of CBZ-Tween 80 (10.896.93 ± 109.63 ng/mL/hour) BSAN-CBZ (17,557.27 ± 182.56 ng/mL/hour), C_{max} CBZ-Tween 80 (3087.67 ± 136.86 ng/mL) BSAN-CBZ (3143.43 + 112 ,11 ng/mL). MRT CBZ-Tween 80 (8.76 ± 1.96 hours) BSAN-CBZ (13.24 ± 2.88 hours).The pharmacokinetic parameters of BSAN-CBZ performed significantly better than those of CBZ-Tween 80.The drug clearance results from CBZ-Tween80 (0.0014 0.0002 mL/min/kg) were faster than the BSAN-CBZ (0.0007 0.000013 mL/min/kg). This demonstrates that BSAN-CBZ have a slower clearance rate, due to longer circulation time in the blood, that could lead to higher plasma concentrations and increase therapeutic efficacy.

Paclitaxel

Taxol is a drug approved by the FDA that contains Paclitaxel. Paclitaxel (PTX) is widely used to treat a variety of cancers (ovarian cancer, stomach cancer, breast cancer and acute leukemia). However, PTX has a low water solubility (2 g/ml), which reduces its therapeutic effect[6].As a result, PTX was delivered via BSA-Cholesterol Nanoparticles. Cholesterol is used as a hydrophobic compound to boost PTX's therapeutic ability.

After intravenous administration of the drug, the pharmacokinetic properties of PTX and NP Chol BSA-PTX were compared in tumor-bearing mice.AUC values were obtained at PTX (5384.13 ± 225,83 ng/mL/hour) and BSAN-PTX (8177.03 ± 303.06 ng/mL/hour). This suggests that BSAN-PTX is more stable in plasma, making it easier for it to accumulate in target cells.Furthermore, the plasma half-life of BSAN-PTX was

longer (2.71 hours) than that of PTX (0.5 hours). As a result, the circulation of BSAN-PTX in the bloodstream is longer than that of PTX, indicating that it has a higher chance of reaching the target location.

Tacrolimus

Tacrolimus (TAC) is a drug used to treat acute rejection after organ transplantation. TAC, on the other hand, has therapeutic limitations due to its low water solubility. Prograf® is a commercial drug that contains tacrolimus and hydrogenated polyethylene castor oil (HCO-60), but it has nephrotoxicity, nephrotoxicity, diabetogenic effects, and hypertension as side effects.As a result, research was conducted to improve the therapeutic effect of TAC while reducing its side effects by using BSAN as a TAC drug delivery system.

(Zhao et al., 2015)[28] compared the pharmacokinetic profile of Prograf® with BSAN-TAC as a control. There was a difference in the pharmacokinetic profiles of the two materials after intravenous administration.BSAN-TAC had AUC values that were 1.8 times higher (151.5 46.69 min mg/L) than Prograf® (84.4 10.98 min mg/L). This is due to the ability of encapsulated TAC to be protected from metabolic enzymes in the liver. Furthermore, Prograf® proved 1.9-fold faster clearance (0.072 0.018 L/h/kg) than BSAN-TAC, which proved a slower clearance (Cl) (0.038 0.016 L/h/kg) due to the effect of protected liver metabolism, avoiding decreased clearance by the kidneys.This resulted in a longer MRT value for the BSA-TAC NP (10.58 0.57 hours), increase the time in blood circulation compared to the MRT value of the faster Prograf® (8.90 0.67 hours).

Bufalin

Several studies have shown that bufalin (BF) is effective as an antitumor agent. Bufalin, on the other hand, has limitations such as poor water solubility, a short half-life, and a high metabolic rate, which limit its therapeutic effect. To improve its therapeutic effect, bufalin was developed in a delivery system that used BSA nanoparticles as a carrier[29].

(Zhang et al., 2017)[29] compared the pharmacokinetic profiles of BF and BSAN-BF (C_{max}, $T_{1/2}$, MRT, AUC, and Cl). The obtained results revealed that the C_{max} value of BSAN-BF (2186.2 ng/mL) was greater than that of pure BF (2430.5 ng/mL). T1/2 NP BSA BF (127.2 minutes) was greater than that of pure BF (43.2 minutes).Furthermore, the AUC of BSAN-BF was higher (389.7 ng h/mL) than that of BF (302.6 ng h/mL). As a result, the MRT BSAN-BF value is greater (68.4 minutes) than BF (19.2 minutes). Because BSAN-BF had a slower Cl (1.54 L/h/kg), it could raise plasma concentrations more than BF (2.00 L/h/kg). The therapeutic effect of BF can be enhanced by improving the pharmacokinetic profile.

Epigallocatechin-3-gallate

Green tea contains the polyphenol epigallocatechin-3-gallate (EGCG), which has anticancer, antibacterial, antioxidant, anti-inflammatory, and antiallergic properties. However, EGCG has some disadvantages, including low solubility, poor stability, and a short absorption time. To deliver EGCG to target cells and increase its effectiveness, a BSA nanoparticle carrier must be developed[30].

(Ramesh & Mandal, 2019)[31] compared the pharmacokinetic profiles of BSAN-EGCG and EGCG (T_{max}, C_{max}, $T_{1/2}$, AUC, and Cl). The T_{max} value of BSAN-EGCG was found to be longer (2 hours) than EGCG (1.6 ±0.2 hours).The value of C_{max} in BSAN-EGCG indicates a 1.5 times increase in the maximum drug concentration in plasma (136 ± 4.8 ng/ml) compared to EGCG (53.1 ± 7.5 ng/ml). Furthermore, BSAN-EGCG has a longer half-life (15.6 ± 1.2 hours) than EGCG (12.2 ± 1.2 hours).The AUC value of BSAN-EGCG was significantly higher in plasma (1048 ± 11.46 mg/L/hour) than pure EGCG (536.8 ± 14.0 mg/mL/hour). The clearance value for BSAN-EGCG was slower (0.001 ± 0.0001 ml/hour) circulating in the blood for a longer period of time, increasing plasma concentration higher than the clearance value for EGCG (0.002 ± 0.0001 ml/hour). As a result, BSA EGCG NPs can improve EGCG bioavailability.

Cytotoxicity of BSA Nanoparticle-Delivered Drugs

One of the parameters for the biological evaluation of *in vitro* studies is cytotoxicity. Each drug has a unique cytotoxicity mechanism that determines cell death, such as cell damage. Cytotoxicity assays have been widely used to assess compound toxicity and the inhibition of cell growth, such as tumor cells. There are several cytotoxicity testing methods, including staining (trypan blue), colorimetric (MTT), fluorometry, and luminometry[32].

Doxorubicin

Doxorubicin (DOX) is a cancer chemotherapy drug that is commonly used. DOK, on the other hand, has side effects such as hair loss, cardiomyopathy, and so on. To overcome the drug's limitations, it is being developed in a drug delivery system that uses BSA nanoparticles as a carrier to increase therapeutic effect and reduce side effects[3].

(Yang et al., 2020)[3] studied cytotoxicity against normal cells (NIT 3T3) and tumor cells using MTT results comparing DOX and BSAN-DOX (A549, A2780 and NCL-H460). The MTT test results in the BSAN-DOX group showed low cytotoxicity to NIT 3T3 cells, even at the highest test concentration of 400 mg/mL BSAN-DOK.As a result, low cytotoxicity in normal cells indicates a low toxic effect.

When compared to the percentage of inhibition achieved by DOX, the cytotoxicity of BSAN-DOX against tumor cells A549, A2780, and NCL-H460 was 2 times, 1.5 times, and 1.5 times higher, respectively. Furthermore, the IC_{50} value in BSAN-DOX was found to be 2 times, 2.6 times, and 1.5 times lower than the IC50 value obtained in DOX, respectively. The BSAN-DOX group produced significantly more cytotoxicity to tumor cells, according to the results. This demonstrates that the use of BSAN as carriers can improve delivery effectiveness when compared to DOX.

Gemcitabine

Gemcitabine (GEM) is an effective drug for tumor treatment, but it has limitations, including a short half-life and high doses that cause serious side effects. To overcome these limitations, further research into delivering gemcitabine specifically into target cells using BSA NP carriers is required[5].

(Dubey et al., 2015)[5] investigated the cytotoxicity of GEM and BSAN-GEM groups against Ovcar-5, MCF-7, and MIAPaCa-2 cancer cells. The cytotoxicity test results revealed an increase in the inhibition of cancer cells by BSAN-GEM a concentration of 1 M in both Ovcar-5, MCF-7, and MIAPaCa-2 cancer cells, with percentages of inhibition in the three cancer cells of 70%, 72%, and 72%, respectively. The percentage of inhibition was higher when compared to the GEM group, which obtained percentages of inhibition on the three cancer cells of 46%, 48%, and 49%, respectively.

Furthermore, when compared to pure GEM, the IC_{50} value of BSAN-GEM was significantly lower; the average IC_{50} value of BSAN-GEM in the three cancer cells was 0.171, while the IC_{50} mean value of GEM in the three cancer cells was significantly lower. 3.185 times the number of cancer cells With an increase in inhibition and a low IC50 value, BSAN-GEM proved significantly greater anti-tumor activity, with an average tumor volume of 164 mm3 when compared to the GEM (298 mm3).

Berberine

Berberine (BBR) is a berberis plant-derived isoquinoline alkaloid compound. BBR has been reported in several studies to have antioxidant, antihypertensive, antimicrobial, and anticancer properties. BBR, on the other hand, has limitations such as low water solubility and bioavailability. As a result, BBR delivery to target cells is restricted. As a result, development is required to overcome these constraints. To increase the effectiveness of BBR, BSAN are used as carriers in the delivery of BBR to the desired target location[4].

(Solanki et al., 2021)[4] used the MTT assay on MDA-MB-231 breast cancer cells to assess the anticancer activity of BSAN-BBR and BBR. The MTT test results of BSAN-BBR revealed that the percentage of inhibition of MDA-MB-231 cells was greater than that of pure BBR after 48 hours of incubation at a dose of 25 g. The percentage of inhibition obtained from BSAN-BBR against MDA-MB-231 cells was (63%) while BBR only had a percentage of inhibition of (35%).The MTT test results were confirmed by the trypan blue test, which was performed to confirm the inhibitory efficacy of BSAN-BBR and BBR against MDA-MB-231 breast cancer cells. The trypan blue test results revealed that the cancer cell death produced by BSAN-BBR (30%) was greater than that produced by pure BBR. Obtaining greater inhibition from BSAN-BBR because BSAN can increase the delivery of hydrophobic molecules into MDA-MB-231 cells, allowing for better inhibitory effectiveness even at low drug doses when compared to BBR.

Emodin

Emodin (E) is an antibiotic with antimicrobial, immunosuppressive, and antitumor properties. However, E has drawbacks such as low solubility and negative side effects. As a result, development is required to deliver emodin. BSA NPs have been shown to be a promising drug delivery system for improving therapeutic effects while reducing side effects[19].

(Siri et al., 2020)[19] investigated the cytotoxicity of pure BSAN-E and E in breast cancer cells MCF-7 and PC-3 (prostate cancer cells). For 48 hours, cells were exposed to a 45 M concentration. The E cytotoxicity test included three types of tests: the metabolic activity test of cancer cells (MTT test), the cancer cell adhesion test, and the LDH (lactic dehydrogenase) test. The results obtained by BSAN-E demonstrated that the antitumor activity of MCF-7 cells given BSAN-E increased, as evidenced by a decrease in metabolic activity and adhesion activity of MCF-7 cells, both of which reached (60 percent), the results were greater. when compared to E, which reduced MCF-7 metabolic activity and cell adhesion by (50 percent)

The results of BSAN-E showed increased cell death, which was confirmed by the results of the LDH activity test of BSAN-E, which reached a value of (60 percent) after 48 hours of incubation, indicating cell membrane damage. PC-3 cells tested similarly to MCF-7 cells, with more cancer cell death in BSAN-E than E.

V. Conclusion

When used as a drug carrier, BSA nanoparticles can improve the pharmacokinetic profile, increase bioavailability, and increase cytotoxicity. As a result, BSA nanoparticles can be used as a drug delivery vehicle because they have the advantage of increasing the therapeutic effect of drugs to target cells while causing no unwanted side effects.

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