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A Comprehensive Review on Fixed Dose Combination Therapy for Cancer Treatment with Self Nanoemulsifying Drug Delivery System

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ABSTRACT

Fixed dosage combination (FDC) medication treatments have been generally recognized for many years because they provide superior disease treatment with increased therapeutic effectiveness and safety, as well as improved patient compliance and adherence and lower patient costs than single drug therapies. From a variety of viewpoints, the creation of FDC medicines appears to be a potential way to attaining therapeutic benefits and financial advantages in a wide range of medication classes. Only when the prospective advantages are based on genuine therapeutic concepts and supported by clinical data can the justification for pharmacological combinations be properly established. The fixed dose combination of chemotherapeutic medications using nanocarriers has emerged as a viable cancer treatment method. These co-delivery methods can overcome the challenges of low solubility and stability associated with such medications, transport both pharmaceuticals concurrently to the target site, release the payloads in a regulated and exact dosage, synchronize drug exposure, maximize therapeutic efficacy, and reduce toxicity. Several drug delivery systems have been investigated for the co-distribution of diverse medication combinations, and their effectiveness has been assessed both in vitro and in vivo. In the last few years, nanoemulsions and self-emulsifying drug delivery systems (SEDDSs) have been found to be effective approaches for the targeting of several anticancer drugs. SNEDDS presents several advantages for drug delivery system over other colloidal drug carriers. Self-nano emulsified drug delivery systems (SNEDDS) which comprise isotropic mixtures of oil, surfactants, and cosurfactants, are also a useful means of improving the dissolution and bioavailability of poorly water-soluble drugs. When these systems are introduced into gastrointestinal fluids, they disperse as very fine droplets in nanometre size range. The nanosized drug-loaded droplets of SNEDDS provide a large interfacial area thereby promote the rapid release of drug.

Keywords: Fixed-dose combination, Anti-cancer, Solubility, Bioavailability, Self-emulsifying drug delivery system.

INTRODUCTION

The pharmaceutical industry is becoming more intrigued in the prospect of Fixed-Dose Combination (FDC) therapies. Fixed dose combination (FDC) drug products, in which two or more pharmaceutically active components with various settings of pharmacological action are formulated in a fixed predetermined range into a single dosage form, are widely used for illnesses in almost all therapeutic applications (Desai et al. 2013; Kararli et al. 2014a; Pourkavoos 2012). These advantages of combination therapy may result from solely using appropriate, multiple objectives, fixed-ratio drug combinations and jointly lowering various risk factors for the relevant diseases without raising the likelihood of side effects (Mitra and Wu 2012). As acknowledged by the World Health Organization (WHO) and regulatory authorities in many nations, FDC have played important roles in curing human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), malaria, tuberculosis, and cardiovascular (CV) diseases, as well as making major contributions to improving quality of care through improved patient care and compliance at reduced premiums (EMA 2015; FDA 2015; Orloff 2005; WHO 2005). As a result, FDC products are progressively being licenced for the medical treatment of endemic and life-threatening illnesses across the world (Kararli et al. 2014b, Pourkavoos 2012; WHO 2003). From a clinical (physician) standpoint, FDCs can provide improved therapeutic effectiveness and safety profiles, as well as increased patient adherence and decreased drug resistance development (Bangalore et al. 2007; Desai et al. 2013; Pan et al. 2008). FDCs can also benefit patients by improving convenience and compliance, reducing dosing unit burden, and saving money. Elderly individuals, in particular, may require many drugs to manage age-related chronic complicated disorders and associated co-morbidities. Individual medications delivered separately are more expensive than FDCs (Newman et al. 2008; Pourkavoos 2012). When compared to individual items, the manufacture and distribution expenses of FDC products are often inexpensive (Desai et al. 2013). From an industrial standpoint, pharmaceutical businesses may have opportunities to optimize the value of their own single medicine products, to extend the life of their goods, and, eventually, to extend market exclusivity, resulting in increased sales and profits (Hiremath et al. 2011).

Similarly, the number of FDC medications has expanded over the last two decades, and this trend is expected to continue due to the fact that they provide significant therapeutic benefits and financial advantages across a variety of pharmacological classes (Hiremath et al. 2011; Kararli et al. 2014b). Because the safety and effectiveness evidences for individual treatments have previously been collected, most combinations of existing drugs are typically low risk due to less development efforts and a difficult regulatory route to approval (Desai et al. 2013; Pourkavoos 2012). Too far, FDC medications have mostly been created to replace commonly used free combinations, treat two closely related illnesses, and address unmet requirements of patients who are poorly managed by monotherapies (Pourkavoos 2012). FDC drug products have recently accounted for a significant share ([25 percent]) of new drug products authorised by the United States (US) Food and Drug Administration (FDA) (Desai et al. 2013; Kararli et al. 2014a, b). A considerable portion of newly authorized medicinal products worldwide are FDC drugs, which retain the majority of recent blockbusters in the global pharmaceutical market. As a result, the market for FDC products has grown (Hiremath et al. 2011; Pourkavoos 2012).

FDC'S IN THE TREATMENT OF CANCER

For many years, the use of FDC drug therapies has been widely accepted because they provide improved clinical effectiveness and safety, improved patient compliance and convenience, and lower treatment costs to patients when compared to single drug therapies, which can contribute to greater treatment compliance to the combination therapy and, ultimately, improved disease prevention and recovery (Bangalore et al. 2007; Kararli et al. 2014b; Mitra and Wu 2012; Pan et al. 2008).Fixed dose combinational therapies are increasingly being employed in clinical trials to treat various malignancies. In comparison to the typical single medication approach, combinational strategies are typically cited with enhanced therapeutic effects or delayed drug resistance, with synergistic medicines being the most

desirable (Chou, 2006). In recent years, computational progress has been made in qualitatively classifying and predicting synergistic components (Han et al., 2017; Sarah, 2017; Sheng et al., 2017). However, before the formula is experimentally utilised, the best dose of each component must be determined, as different dose combinations can result in varied results even for the same formula (Tallarida and Raffa, 2010). To avoid potential harmful or antagonistic effects, largescale studies must be screened across a vast combinational space of drug concentrations, which is time consuming and labour intensive. Yin et al (2018) outlined the most recent advances in the field of synergistic dosage combinations for anticancer drugs The preceding study has opened the path for the development of a complete prediction model of optimal dosage combination. It should be noted that current searching approaches are still restricted to local optimization, and more experimental data are required to confirm the computational models. Although difficult, taking into account the following criteria may lead to more successful algorithms. Cancer heterogeneity, for example, should be thoroughly examined in order to produce better results. In the meanwhile, taking into account the medication response of numerous cells/tissues may help to reduce the possible negative effects of combination treatments on normal tissues. This is especially significant when the medications are given at different times and in varied orders. More solid models, when combined with future AI and hardware development, are projected to possibly aid in the therapeutic choice of combinational medication dose for cancer patients.

Cancer is a disease characterized by uncontrolled, abnormal cell development with the capacity to infiltrate or spread to other tissues, organs, or areas of the body [Cooper, 2000]. Not all tumours are carcinogenic; benign tumours grow slowly, resemble normal cells, and do not move to other areas of the body, whereas malignant tumours multiply fast, are invasive, and exhibit dedifferentiation and the propensity to metastasis [Health NIo, 2007]. Although there are no exact fingerprints for the etiology of every cancer, the majority of cancers are caused by genetic alterations produced by environmental causes and inherited genetics. Cancer harms the surrounding cells and is fatal if left untreated, however it is true that cancer may be avoided [Anand et al 2008]. As a result, numerous techniques to treating various forms of cancer have been developed, but the chances of success in delivering the treatment appropriately and efficiently are extremely low due to the features of anticancer agents. The majority of chemotherapeutic drugs are either weakly water-soluble or have permeability concerns [Navya et al 2019]. As a result, the self-emulsifying drug delivery system is used to overcome the medication's challenges and improve its distribution. In many study publications, S-SMEDDS have been discovered to be an effective strategy to improving the solubility, dissolution, and bioavailability of chemotherapeutic drugs, and as a result, S-SMEDDS are progressively capturing the interest of researchers.

RECENT RESEARCH AND ITS RESULT RELATED TO SEDDS IN CANCER

Approximately 40-70 percent of novel therapeutic compounds explored in recent years belong to Biopharmaceutical Classification Tract (BCS) Class II or Class IV, with poor solubility that limits absorption from the gastrointestinal (GI) system following oral administration [Sanghai et al, 2013] [Gupta et al 2006].

Poor or irregular bioavailability can be caused by a variety of reasons. To achieve high bioavailability and minimal variability in oral pharmaceutical products, API must be dissolvable and stable in the GI lumen in order to be properly absorbed. The bioavailability of these candidates can be increased by using a lipid-based drug delivery method in conjunction with nanotechnology, which has an additive impact on bioavailability [Yeung et al, 1993] [Kassem et al, 2016]. Particle size reduction, liposomes, nano-micelles, and self-emulsifying drug delivery systems have all been employed to increase the bioavailability of poorly soluble medicinal compounds [Hou et al, 2017] [Zhang et al, 2016] [Zhang T et al, 2016] [Pooja et al, 2016]. Selfnano emulsifying drug delivery system (SNEDDS) is a homogenous combination of oils, medicines, surfactants, and cosurfactants that are anhydrous in nature and have

emerged as a viable technique in nano emulsions for oral drug administration. When SNEDDS is exposed to GI fluids, oil-in-water (O/W) nano emulsions develop spontaneously. The physicochemical features of pharmaceuticals encapsulated in nano emulsions drastically alter and overcome the many bio-barriers in the GI tract, resulting in increased oral bioavailability. [Ding et al, 2019] [Baloch et al, 2019] [Xue et al, 2018] [Majed et al, 2019]. SEDDS research is expanding due to their potential to increase the bioavailability of class II, III, and IV medicines. Several study publications on SEDDS as chemotherapeutic agents to improve solubility, bioavailability, and antitumor activity have been published, as shown in figure 1. (Image courtesy: Singh et al 2020 and references 37-42

S. No.	Title	Drug Used	BCS Class of Drug	Technique Used	Major Outcomes	References
1	Development of a Solid Supersaturatable Self-Emulsifying Drug Delivery System of Docetaxel with Improved Dissolution and Bioavailability	Docetaxel	IV	Spray dry-ing	DTX-S-SEDDS1 showed 90.96% drug dissolution at 2 h, which was 29.8 times higher than crude DTX powder, and the *in-vivo* results indicate that area under the concentration-time curve (*AUC*0—∞) of the DTX-S-sSEDDS1enhanced by 8.77 times when compared DTC DT with DTC-SEDDS2 and 1.45 fold in comparison to DTC powder. So, they concluded that S-SEDDS showed to be an effective system for the enhancement of dissolution and bioavailability of docetaxel.	[101]
2	Preparation and Evaluation of Solid-Self-Emulsifying Drug Delivery System Containing Paclitaxel for Lymphatic Delivery	paclitaxel	IV	Spray dry-ing	Dissolution studies of Solid-SEDDS formulation showed 70% and 75% drug release in 60 and 30 min in pH 1.2 and 6.8 dissolution medium, respectively. The *C*max and AUC0–∞ were also increased significantly ($P \leq 0.05$), and targeting efficiency of Ptx was enhanced with the help of solid-SEDDS.	[102]
3	Design and Development of Docetaxel Solid Self-Microemulsifying Drug Delivery System Using Principal Component Analysis and D-optimal Design	Docetaxel	IV	Liquid-solid compact technique	It was observed that the optimized DOXP-13 batch showed a 95.21% cumulative drug release within 30 mins, and 103.23% w/v recovery was found *via* HPLC analysis. Disintegration time was found to be 42 ± 0.20, and a 100.39% cumulative drug release was observed at 60 min. of the final 250 mg tablet (LSC-Tab), showing good stability. Therefore, the solid-SMEDDS was found to be a promising tool to improve the solubility and dissolution of docetaxel.	[103]
4	Development of Solid Self-Emulsifying Formulation for Improving the Oral Bioavailability of Erlotinib	Erlotinib	II	Spray dry-ing	The results of pharmacokinetic parameters like the area under the curve and maximum concentration of optimized batch of erlotinib solid-SEDDS were enhanced significantly, compared to erlotinib powder ($p<0.05$). Therefore, Erlotinib solid-SEDDS offer a good delivery system to improve its bioavailability.	[104]
5	Lecithin/TPGS-based spray-dried self-micro emulsifying drug delivery systems: *In vitro* pulmonary deposition and cytotoxicity	atorvas-tatin	II	Spray dry-ing	The prepared spray-dried SMEDDS of atorvastatin was evaluated for the pulmonary deposition and cytotoxicity, and results showed that the drug delivery to the lungs was increased by 7 fold; moreover, cytotoxicity of the solid-SMEDDS formulation was observed to enhance as compared to the plain drug.	[105]
6	Development of docetaxel-loaded solid self-nano emulsifying drug delivery system (SNEDDS) for enhanced chemotherapeutic effect	Docetaxel	IV	Spray dry-ing	The outcomes of the present work indicate that the solid D-SNEDDS provides an enhanced rate of absorption of DCT into the bloodstream as compared to the marketed formulation Taxotere® and also shows less toxicity with enhanced anti-tumor activity.	[106]

***(Image courtesy Singh et al 2020).**

Fig 1: Articles on SEDDS in the treatment of cancer and their outcomes

SEDDS PATENTS FILED DURING THIS DECADE

In recent years, a number of patents on SEDDS, SMEDDS, and their solid form have been submitted, indicating the vast value and applicability of SEDDS and solid-SMEDDS in the pharmaceutical area. Figure 2 depicts a current (2016-2020) list of patents submitted for various types of self-emulsifying systems. (Image courtesy: Singh et al 2020 and references 43-62)

S. No.	Year	Patent No.	Type of Patent Application	Title	Reference
1.	2018	BR102017007556A2	BR102017007556-7A	Pharmaceutical compositions based on cocus Nucifera l. understanding SMEDDS type drug control release system with an indication of topic and oral use in dentists	[81]
2.	2016	BR102015014719A2	BR102015014719A	Bioavailability of hydroalcoholic extract of croton caracara Benth in SMEDDS system for herbal application	[82]
3.	2018	US9918965B2	US15/094,732	Self-emulsifying formulations of DIM-related indoles	[83]
4.	2019	CN109549923A	CN201811228643.6A	1,8- cineole from microemulsion and Submicron Emulsion drug delivery system and its preparation method and application	[84]
5.	2016	KR101608178B1	KR1020150113348A	An oral pharmaceutical composition comprising atorvastatin calcium using a self-emulsifying drug delivery system	[85]
6.	2018	BR102017025993A2	BR102017025993-5A	Bioformulated with the property of controlled release of Phyto-components present in the oil extracted from Azadirachta seeds applied as a mean of follicular crop	[86]
7.	2019	WO2019019091A1	PCT/CN2017/094665	Curcumin pharmaceutical preparations	[87]
8.	2017	BR102015013231A2	BR102015013231A	Preparation of copaiba oil-based microemulsion for dental use	[88]
9.	2018	CN109044971A	CN201810825724.8A	A kind of hydroxyl carthamin yellow A-containing self-micro emulsion formulation and preparation method thereof	[89]
10.	2019	US20190060300A1	US16/081,105	Self-Emulsifying Compositions of CB2 Receptor Modulators	[90]
11.	2017	CN107184549A	CN201710233806.9A	A kind of Nintedanib self-micro emulsion formulation and its soft capsule being made and preparation method	[91]
12.	2018	CN108703949A	CN201810577201.6A	A kind of indigo red solid self-emulsifying drug delivery system preparation and preparation method	[92]
13.	2019	WO2019206458A1	PCT/EP2019/025117	Soft gel capsule comprising a selective estrogen receptor modulator	[93]
14.	2018	US20180036233A1	US15/554,983	Self-emulsifying drug delivery system (SEDDS) for ophthalmic drug delivery	[94]
15.	2019	CN110151730A	CN201910166045.9A	A kind of hesperetin Solid Self-microemulsion osmotic pumps capsule and preparation method thereof	[95]
16.	2020	CN110812280A	CN201910927731.3A	Solid multiple self-emulsifying carrier and preparation method thereof	[96]
17.	2019	CN110420187A	CN201910844324.6A	A kind of isoflavone Solid Self-microemulsion	[97]
18.	2019	CN109985008A	CN201910357578.5A	A kind of astaxanthin Solid Self-microemulsion and preparation method thereof	[98]
19.	2011	CN101584661B	CN2009102037349A	Preparation of sorafenib self-micro emulsifying drug delivery system for oral administration or intravenous injection and use thereof	[99]
20.	2017	CN107257680A	CN201680012023.1A	Self-emulsifying drug delivery system (SEDDS) for ocular drug delivery	[100]

***(image courtesy Singh et al 2020).**

Fig 2: Recent patents on SEDDS

In a study by Zewail et al 2021, encapsulating candesartan (CAN) and hydrochlorthiazide (HCTZ) FDC in SNEDDS can improve their solubility and dissolution rate. The formulation and in vitro characterization of two optimum SNEDDSs (A5 and B3) loaded with fixed-dose combinations of CAN and HCTZ were comprehensively investigated. The original formulation (A5) had 7% castor oil, 67.5% tween 80, and 26.5% ethanol. The second (B3) has 5% oleic acid, 79% tween 80, and 16% PEG 400. B3

has a greater percentage transmittance (99.90 percent 0.01) than A5 (99.48 percent 0.18). However, A5 had a shorter emulsification time (14 1.00 s) than B3 (23 1.73 s). Both A5 and B3 proved the capacity to tolerate diverse dilution circumstances, passed thermodynamic stability tests, indicated the lack of drug-additive interaction using FTIR investigations, and had high cloud point values of 88 0.57 C and 76 1.52 C, respectively. Both SNEDDS formulations had smaller droplets, low PDI values, and a moderate zeta potential. Both A5 and B3 TEM images revealed spherical, non-aggregated globules, which were compatible with the size analysis results. When compared to pure medicines and marketed products, both A5 and B3 demonstrated a superior in vitro release profile for CAN and HCTZ.because to its reduced globule size In vivo studies shown that optimised fixed-dose combination loaded SNEDDS outperformed free medicines suspension and marketed product in increasing oral bioavailability of CAN/HCTZ combination and controlling blood pressure. Finally, SNEDDS can be employed effectively to increase the solubility and dissolution of the CAN/HCTZ combination, hence increasing its oral bioavailability and pharmacological activities.

In another studies by Hwang et al 2015, despite the physicochemical variances of the medications, demonstrated the effective construction of a SMEDDS incorporating a fixed-dose combination of atorvastatin (ATR) and ezetimibe (EZT). For the less soluble medication, ATR, rational formulation development was performed by selecting the excipient with the maximum drug solubility. Furthermore, sketching phase diagrams and measuring microemulsifying area for all possible combinations allowed for reasonable selection of the best SMEDDS system. The large difference in loading capacity between ATR and EZT was explained by the lower solubility of ATR in the oil phase and the research of their small molecules' locations employing UV absorption and zeta potential analysis, emphasising the importance of rational oil selection in enhancing the extent of solubilization. The in vitro dissolution studies revealed a rapid dissolving rate for both medications independent of the kind of dissolution media used, showing that the SMEDDS disperses quickly and has a greater bioavailability.

To date, cancer remains to be one of the deadliest diseases that lack effective treatments. As the most widely adopted approach in cancer therapy, chemotherapy is subject to many in vitro and in vivo barriers, such as tumor microenvironment and multidrug resistance (MDR). Tumor microenvironment is a complicated system that comprised different types of cells, including tumor-associated fibroblasts, macrophages, and endothelial cells, which are the main components that contribute to the resistance of drug delivery approaches (DDS) and decrease the permeation, as well retention of both DDS and chemotherapeutic agents. On the other hand, by continuously secreting growth-inducing cytokines and growth factors, these cells can facilitate the survival of tumor cells that further diminish the chemotherapy outcome in another way. In particular, during the chemotherapy processes, chronic damage to stroma cells elicits the secretion of damage response program molecules to promote the survival and growth of neighboring cells, thus causing acquired MDR to the chemotherapies.

Combination chemotherapy for cancer therapy is considered as an important protocol to enhance therapeutic effects and reduce systemic toxicity by simultaneously modulating multiple cell-signaling pathways. In recent years, the combination of chemotherapeutic drugs via nanocarriers has emerged as a promising strategy for treating cancer. These co-delivery systems can address the issues of poor solubility and stability associated with such drugs, transport simultaneously both drugs to the target site, release the payloads in a controlled manner and accurate dose, synchronizing the drug exposure, maximizing the therapeutic efficacy, and reducing the toxicity. Several drug delivery platforms have been explored for co-delivery of various combinations of drugs, and their efficacy has been tested both in vitro and in vivo.The efficacy of chemotherapeutic drugs can be increased by administering them in their synergistic ratio. However, free drugs might not maintain the synergistic ratio after in-vivo administration owing to their different pharmacokinetic profiles. In contrast, drugs that are encapsulated in a drug delivery system have to be released for their biological effects to be exerted. Therefore, an

appropriately designed drug delivery system that coordinates drug release can be used to maintain the synergistic molar ratio of the two drugs in vivo to increase the efficacy of the anticancer treatment. Currently, most of the work carried out on the use of drug delivery systems to coordinate drug release is focused on the combination of conventional amphipathic chemotherapeutic drugs, such as irinotecan with floxuridine, doxorubicin with vincristine, fludarabine with mitoxantrone, and cytarabine with daunorubicin in liposomes. Of these, the liposomal combinations of irinotecan with floxuridine and cytarabine with daunorubicin are currently in phase II clinical trials.

Co-administration of an antioxidant, having anti-proliferative and antioxidant properties, could be of great interest for augmenting overall antitumor efficacy and reducing the toxicity of anticancer drugs.

CONCLUSION

Combination medication therapy have become common for the prevention and treatment of chronic and complicated illnesses, and their necessity and usefulness will only grow as pathophysiological, pharmacological, and pharmacogenomic techniques develop, as will the prevalence of unmet medical requirements. The regulatory authorities are already aware of the therapeutic potential of rational combination medicines and are encouraging the development of combination medications that are beneficial for critical disorders especially cancer treatment.Because of their potential to boost the bioavailability of class II, III, and IV medications, SEDDS research is growing. Several research papers on SEDDS as chemotherapeutic drugs to increase solubility, bioavailability, and anticancer efficacy have been published**.**

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