REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Cubosomes as an Oral Drug Delivery System

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Abstract

Oral administration is widely accepted drug delivery system however, its use is limited due to physico-chemical properties of the drug such as poor solubility, low permeability, instability, and rapid metabolism as all of which decrease oral bioavailability. The low oral bioavailability of most drugs is still a major obstacle which creates challenges for pharmaceutical manufacturers to design drug delivery system with improved pharmacokinetics profile and therapeutic responses. The fundamental problem over the years has been to develop techniques that will allow most medications, regardless of their properties, to be administered orally in order to attain systemic availability. Many techniques have been explored to increase the water solubility of poorly water-soluble drug and thus their bioavailability. Cubosomes are novel lipid-based nano-system that are similar to well-known vesicular systems such as liposomes and niosomes. Cubosomes have been widely formulated in the presence of a suitable stabilizer using certain amphiphilic lipids (e.g., glyceryl monooleate and phytantriol). They could represent a novel drug delivery system containing hydrophilic, lipophilic, and amphiphilic drug molecules. They are widely used in a variety of drug delivery applications, including oral, ocular, transdermal, and chemotherapy drug delivery. In this review, cubosomes, their composition, methods of preparation and oral drug delivery applications will be critically reviewed.

Keywords: Cubosomes, oral delivery system, poorly water-soluble drugs.

Oral drug delivery:

Oral drug delivery is the most popular and preferred route of administration(Kalepu, Manthina et al. 2013, Rewatkar, Kumeria et al. 2020) owing to its nature of being pain-free, convenient handling, noninvasive, the achievement of desired therapeutic effects and patient compliance(Sahoo, Bandaru et al. 2021), especially for chronic diseases. Drug candidates that are stable in stomachic environments, have a suitable hydrophilic-lipophilic balance to cross the intestinal epithelium membrane, and exhibit low irritation and toxicity signs are ideal for oral administration. Although oral administration is widely accepted drug delivery system, its use is limited due to physico-chemical properties of the drug such as poor solubility, low permeability, instability, and rapid metabolism as all of which decrease oral bioavailability. The low oral

bioavailability of most drugs is still a major obstacle which creates challenges for pharmaceutical manufacturers to design drug delivery system with improved pharmacokinetics profile and therapeutic responses(Nasr, Gardouh et al. 2016),(Pathak and Raghuvanshi 2015). Aqueous solubility strategies are the main problem in the pharmaceutical industry today, with approximately 50% of newly developed drug candidates suffering from poor aqueous solubility (Paul and Paul 2021).

Since the drugs are absorbed in the dissolved state, Dissolution rate is considered as the rate limiting step before absorption and subsequent bioavailability of poorly water soluble drugs (PWSDs). Furthermore, to attain the therapeutic blood level, PWSDs are given orally in greater doses. This leads to economic wastage, local GIT irritation, risk of toxicity, patient incompliance, as well as inefficient treatment**(Kakran, Li et al. 2012)**.

The fundamental problem over the years has been to develop techniques that will allow most medications, regardless of their properties, to be administered orally in order to attain therapeutic systemic availability. Many techniques have been explored to increase the water solubility of PWSDs and thus their bioavailability. These techniques are explained in the following reviews:**(Kim and Park 2004, Pouton 2006, Singh, Bandopadhyay et al. 2009, Tiwari, Tiwari et al. 2009, TImpe 2010, Rahman, Harwansh et al. 2011, Singh, Worku et al. 2011, Alam, Ali et al. 2012, Savjani, Gajjar et al. 2012, Williams, Trevaskis et al. 2013)**, and can be summarized as follows: (a) Physical modifications as reduction of particle size, crystal habit optimization, formation of cocrystal and solid dispersions. (b) Chemical modifications as the buffers utilization, salt formation and complexation (Cyclodextrins). (c) Miscellaneous methods such as the usage of surfactants, co-solvents, hydrotrophy, supercritical fluids and lipid-based drug delivery systems.

Nanotechnology in drug delivery:

Nanotechnology is defined as the development of materials or devices on the nanometer scale. Materials with nanometer dimensions have different physical, chemical, and biological properties than materials with larger dimensions. These distinctive characteristics of nanoparticulate structures have been extensively studied for the potential use of nanotechnology-based systems in the pharmaceutical industry **(Shrivastava, Vyas et al. 2020, Abourehab, Ansari et al. 2022).** Nanotechnology-based systems have the potential to improve drug potency and the efficacy of bioactive administered via various routes of administration. Recently, nanotechnology has gained attention for improving the oral bioavailability of drugs in their dosage form, particularly lipophilic drugs. The most promising nanotechnology strategies used in oral drug delivery include lipid-based nanoparticles (e.g., self-nanoemulsifying drug delivery system (SNEDDS), solid lipid nanoparticles, lipid nanocapsules nanosuspensions liposomes, liquid crystalline nanoparticles, lipid drug conjugates) ; polymer-based nanocarriers (polymeric nanoparticles, polymeric micelles, polymer-drug conjugates) ; carbon nanotubes; drug nanocrystals; dendrimers; silica and silicon nanoparticles; nanogel and so on. Lately, Lipid-based liquid crystalline nanoparticles (LCNP) have gained increasing attention of pharmaceutical research due to their ability to improve the bioavailability of lipophilic drugs. In this review Cubosomes (CUBs), as liquid crystalline nanoparticles (LCNP), will be discussed in more detail.

Lyotropic liquid crystal:

An amphiphilic molecule is composed of two distinct regions: hydrophilic “polar” head and a hydrophobic “lipophilic” tail **(Boge 2018)** as shown in Figure 1. Amphiphilic molecules play a significant role in drug delivery thanks to their ability to self-assemble under certain conditions, leading to highly arranged structures “mesophases” -intermediate states of matter- that have properties in the middle of isotropic liquids and solid crystal **(Garti, Libster et al. 2012, Chong, Mulet et al. 2015, Karami and Hamidi 2016)** , which enabled them to be used in drug delivery systems. The amphiphilic lipids self-assembly due to the hydrophobic effect could potentially lead to some thermodynamically stable, well-defined structures known as lyotropic liquid crystal (LLC) systems_“mesophases”_ such as lamellar (La), hexagonal (HII) and bicontinuous (QII) cubic phases, all of them having sufficient average degree of molecular orientation and structural symmetry **(Karami and Hamidi 2016)**. Upon dispersion of these poorly water-soluble structures in aqueous media, the formed nanostructures are liposomes, due to the dispersion of a huge lamellar phase; cubosomes, formed by reversed

bicontinuous cubic phase dispersion ; and hexosomes, formed by the reversed hexagonal phase dispersion **(Karami and Hamidi 2016)**.

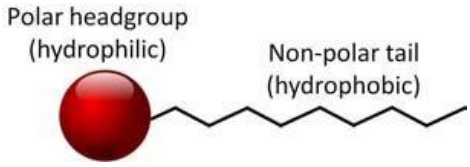

Figure 1: Structure of amphiphilic molecule

Cubosomes:

The colloidal dispersion of bicontinuous cubic liquid crystalline structures in water using suitable surfactants results in nanostructured systems, referred to as 'cubosomes', having sizes ranging from 100 to 500 nm. In comparison to their parent cubic structure, CUBs have the same structure with larger surface area and lower viscosity. Biocompatibility, bioadhesiveness and capability to sustain the drug release are essential properties of CUBs that make them a potential drug delivery vehicle. Unlike traditional lipid or aqueous-based carrier systems, CUBs are excellent solubilizers. They have high drug-carrying capacity for variety of drugs that are only slightly soluble.

Main Components of cubosomes

Amphiphilic lipids

At present, GMO, also known as monoolein, and phytantriol (PHYT) are the most commonly employed amphiphilic lipids in CUBs formulation **(Montis, Castroflorio et al. 2015, Murgia, Falchi et al. 2015).**

Glyceryl monooleate 'GMO'

Glyceryl monooleate 'GMO' is -a synthetic, biodegradable amphiphilic lipid- the most commonly used amphiphilic lipid in CUBs preparation. It is a synthetic combination of glycerides ester of Oleic acid with other fatty acids, mainly monooleate, which can self-assemble to bicontinuous cubic structures**(Kulkarni, Wachter et al. 2011)**. **Figure 2** shows that GMO has both hydrophobic and hydrophilic domains and the hydrophilic domain is responsible for formation of H-bond with water. Due to its amphiphilic nature, it is used to formulate a variety of lyotropic liquid crystals**(Lutton 1965)** such as lamellar, reversed bicontinuous cubic or reversed hexagonal structures **(Boge 2018)**. Low hydration of GMO, results in lamellar phase formation. At elevated temperatures, Increasing hydration leads to formation of reversed bicontinuous cubic or reversed hexagonal structurers **(Boge 2018)** as shown in **Figure 3,** thus all phases are interconverted with changes in operating water levels and temperature.

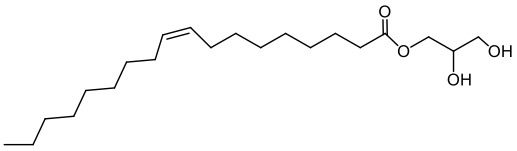

Figure 2. chemical structure of GMO

Reversed LC phases are created as a result of the tiny hydrophilic head group and double bond in the hydrophobic tail, which increases the bulkiness. Adding guest molecules to the GMO-water system leads to alteration in the phase behavior. According to Lutton's results, monoglycerides with hydrocarbon Chain containing 12- 22 C, have an extreme tendency to cubic phases formation **(Lutton 1965)**. Lipophilic, lipophobic or amphiphilic drugs can be loaded within its polar or non-polar domains.

Phytantriol (PHYT)

PHYT, 3,7,11,15-tetramethyl-1,2,3-hexadecanetriol, is commonly used in cosmetic products, was suggested as a great alternative for GMO in CUBs preparation. PHYT has higher structure stability than GMO due to its phytanyl backbone**(Boyd, Whittaker et al. 2006).** This is because lipid-based compounds, such as glyceryl monooleate, are susceptible to esterase degradation, but the phytanyl backbone of PHYT may provide more structural strength. It has a phytanyl backbone that differs in chemical structure from monoglycerides. Fatty acid substances, such as GMO, have the disadvantage of being digested in esterase-catalyzed reactions, which reduces the performance of GMO-derived composition. However, PHYT and GMO have different molecular structures, both of them display very similar phase transition behaviors by increasing water content and temperature.

Stabilizers:

Although cubic phases are thermodynamically stable, their aqueous dispersion are not kinetically stable as they tend re-coalescence due to exposure of hydrophobic portions to the external aqueous media**(Ganem-Quintanar, Quintanar-Guerrero et al. 2000),** so amphiphilic lipid only cannot form stable dispersion. Utilizing stabilizing agents is required in CUBs formulation to prevent re-

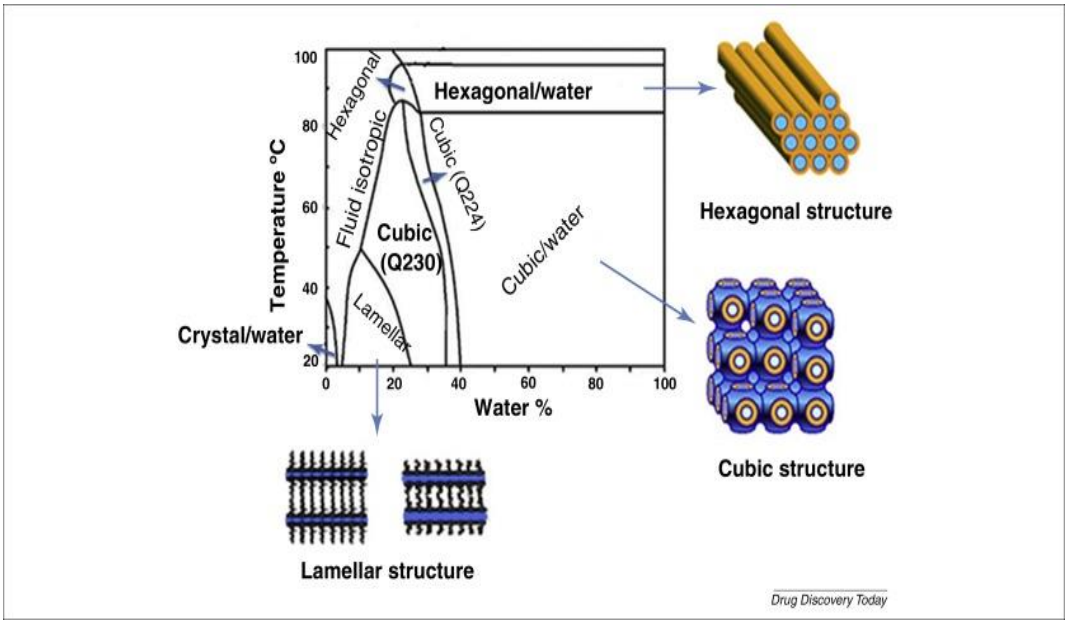

Figure 3: Phase transition in the hydrophilic matrix of the GMO–water interaction (Karami and Hamidi 2016).

coalescence that provides sufficient colloidal stability to the liquid-crystalline phase. The stabilizer's principal job is to create an electric barrier between particles, preventing close particle contact and keeping the dispersed particles in a stable state. This effect is achieved by the employed stabilizer participating in the lipid water assembly without affecting cubic liquid crystallinity. The selection of a proper stabilizer is a critical step. Pluronics are the most widely used surfactants in CUBs preparation, especially F127 (Poloxamer 407) which is known as "gold standard".

Methods of CUBs preparation

There are several methods for CUBs preparation. Top-down and bottom-up approaches are the main approaches for CUBs preparation. Utilization of a suitable stabilizer, such as F127 is essential in both approaches to prevent CUBs dispersion aggregation, as previously described.

The top-down approach

It involves the bulk cubic phase formation by mixing lipid(s) with stabilizer(s) to prevent aggregation. Then, dispersion of this formed bulk cubic phase into aqueous medium with high-energy processing such as high-pressure homogenization or sonication till cubosomal nanoparticles formation. Water-swollen crossed linked polymer chains responsible for the clear rigid gel appearance in the bulk cubic phase, whereas the cubic phase resembled a liquid crystalline structure. Moreover, according to the cubic phase, increasing the amount of surfactant and oils bilayer formation, increases the yield stress **(Thadanki, Kumari et al. 2011)**. Sonication **(Yang, Peng et al. 2011),** high-pressure homogenization , spontaneous emulsification **(Salah, Mahmoud et al. 2017)**, and spray drying are among the ways used to disperse particles into CUBs. The most prevalent procedures for CUBs preparation are sonication and high-pressure homogenization. This could be attributed to its low polydispersity, rapid method for producing homogenous dispersions with particle sizes less than 200 nm **(Chong, Mulet et al. 2015)**and stability of the formed CUBs against aggregation**(Karami and Hamidi 2016).** The fundamental disadvantage of the top-down technique is the high energy required for dispersion of very viscous lipid or bulk cubic phase into aqueous solution, especially in large-scale production. This can make it difficult to include thermo-labile components, such as peptides and proteins (Karami and Hamidi 2016).

Bottom-Up Technique:

In this approach CUBs prepared by simpler protocols with lower energy expenses. CUBs preparation began with a molecular solution rather than bulk material, allowing CUBs creation and crystallisation from precursors at the molecular level**(Zakaria, Ashari et al. 2022)**. As Spicer et al.**(Spicer, Hayden et al. 2001)** explained, this method is known as solvent dilution method. To

form discrete nanoparticles, it relies on the dispersion of a mixture containing the liquid-crystal-forming lipid, the polymer, and a hydrotrope in excess water with minimal energy input. The principle function of hydrotrope is to create liquid precursors by dissolving lipids and to prevent the formation of a viscous liquid crystal phase at high concentrations **(Karami and Hamidi 2016)**.

Advantages of cubosomes as an oral delivery system

As CUBs are lyotropic, they can solubilize poorly water-soluble medicines in their lipid bilayers**(Lai, Lu et al. 2010)**and this will improve drug solubility and bioavailability. Most crucially, because the cubic phase is isotropic, the solubilized state can be kept after the cubic nanoparticles have been broken down into smaller particles by the intestinal lipases during the digestion process. Furthermore, the cubic nanoparticles are bioadhesive, which increases the chances of drug-loaded nanoparticles contact with the intestinal cell membrane. Also, cubic nanoparticles are thought to have essential roles in lipid and drug absorption process as a secondary carrier during lipid digestion. As cubic phases proved its ability in enhancing transdermal and transmucosal permeation, similar mechanisms for cubic nanoparticles as oral delivery carriers may be proposed. Mesophases' amphiphilic nature allows the oral administration of highly hydrophobic and high-molecular-weight drugs.

CUBs can enter intravascular regions and tightly bind to the GIT mucosa due to their small size, resulting in enhanced therapeutic absorption. CUBs have a mucoadhesive function due to the presence of glyceryl monoolein. CUBs have a long retention period with the GIT barrier due to their mucoadhesiveness, resulting in higher penetration**(Ali, Kataoka et al. 2017)**. Moreover, the lipids in CUBs encourage the secretion of bile salts from the gallbladder into the small intestine. These bile salt components form a mixed -micelle phase with CUBs which may be absorbed into the bloodstream along with the drug. CUBs have a high loading capacity and can protect the embedded drugs from degradation. CUBs have emerged as a promising candidate for the oral delivery of active compounds with low aqueous solubility. Inside the gut lumen, the CUBs keep the entrapped drug in a soluble form by entrapment in the micelles produced by CUBs digestion. As a result, they improve drug absorption, resulting in enhancing oral bioavailability**(Abourehab, Ansari et al. 2022).**

Cubosomes by oral route

The oral route is the most commonly used pathway of administration for all drugs. Cubosomes have applications in improving the bioavailability of many poorly soluble substances and large-molecular-weight compounds using this route. There are some examples of using cudosomes orally with improving their properties.

Jin et al.**(Jin, Zhang et al. 2013)** loaded 20(S)-protopanaxadiol (PPD), an anticancer agent, to cubosomes, intended for its enhanced oral absorption. According to the results, the PPD-incorporated cubosome association could rise the permeability values from the Caco-2 cell monolayer model of PPD at 53%. Pharmacokinetic study in rats established that the extent of bioavailability of the PPD-loaded cubosome association (AUC0–1) was 169% compared with the free PPD as shown in **Figure 4** . In another investigation, the pharmacokinetic study of ibuprofen-loaded cubosomes in beagle dogs showed the improved absorption of ibuprofen from cubosomes compared with conventional ibuprofen with a longer half-life and appropriate relative oral bioavailability as shown in **Figure 5 (Dian, Yang et al. 2013)**. The oral cubosomal formulation of efavirenz (EFV) with improved bioavailability was shown to be capable of providing sustained release effect using PHYT as shown in **Figure 6 (Avachat and Parpani 2015)**. In another study, the Tween-modified cubosomes (T-cubs) incorporated with piperine were administered orally for targeting the brain parenchyma **(Elnaggar, Etman et al. 2015)**. Results of this study showed that the T-cubs significantly improved piperine cognitive effect and even returned cognitive function to the normal level. In-vivo pharmacokinetic investigation of Telmisartan (TEL)-loaded cubosomes showed a noticeable change in oral bioavailability compared to TEL commercial tablets also, retained a controlled release profile **(Yasser, Teaima et al. 2019)**. Clopidogrel (CB) cubosomes showed a higher CB release in intestinal pH and preserved the high% released (95.66±1.87%) in buffer transition release study in comparison with free drug (66.82±4.12%) also, higher antihaemostatic properties with longer bleeding time (BT)(628.47±6.12 seconds) compared to Plavix® (412.43±7.97 seconds) as shown in **Figure 7**. Thus, cubosomes proved to be a successful platform to improve the intestinal release of CB and improve its absorption **(El-Laithy, Badawi et al. 2018).**

Hakeem, et al. increased clopidogrel (CB) gut

solubility and bioavailability via formulating a unique, robust, dry CB procubosome-based tablet that dissolved and re-distributed in the gastrointestinal tract, generating in situ CB-based cubosome particles, and thus increasing the stability of the standard cubosomes dispersion at ambient temperature **(Hakeem, El-Mahrouk et al. 2020).** Similarly, other studies for the oral delivery of cubosomes that displayed promising results included, Oridonin cubosomes **(Shi, Peng et al. 2017)**, folic-acid/3-bromo pyruvate cubosomes **(Hou, Wang et al. 2020)**, coenzyme Q10/cubosomes **(Mohsen, Younis et al. 2021)**, cinnarizine/silica-stabilized cubosomes **(Joyce, Yasmin et al. 2017)**, AT 101/cubosomes **(Flak, Adamski et al. 2020)**,docetaxel/cubosomes **(Rarokar, Saoji et al. 2016)**, and rebamipide/cubosomal nanoparticles **(Hashem, Nasr et al. 2018).**

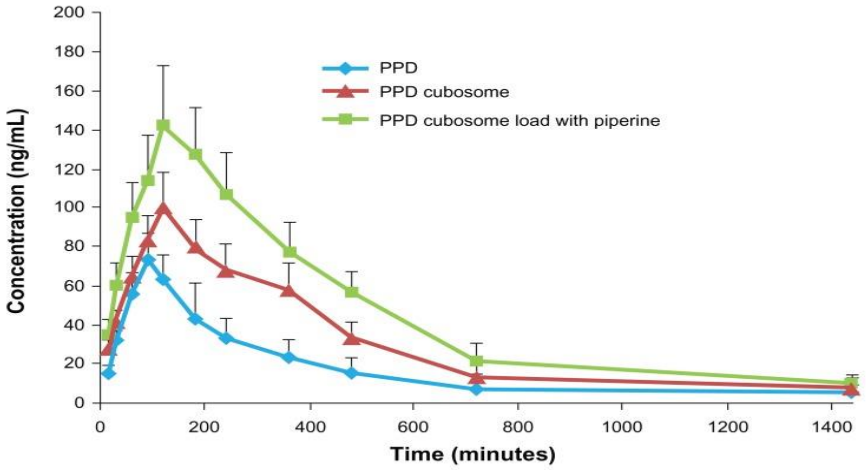

Figure 4: The plasma concentration-time curve of PPD in rats after oral administration of PPD, PPD-cubosome, and PPD-cubosome loaded with piperine (2 mg/kg, PPD)]. Note: Data are presented as mean ± standard deviation (n = 6). Abbreviation: PPD, 20(S)-protopanaxadiol (Jin, Zhang et al. 2013)

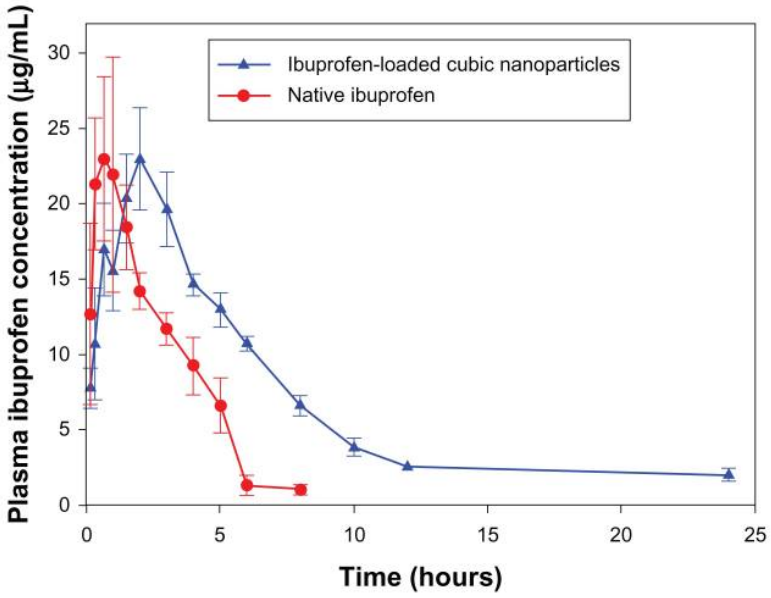

Figure 5: Mean plasma ibuprofen concentration after a single oral dose of 15 mg/kg equivalent ibuprofen or ibuprofen-loaded cubic nanoparticles (n = 3) (Dian, Yang et al. 2013)

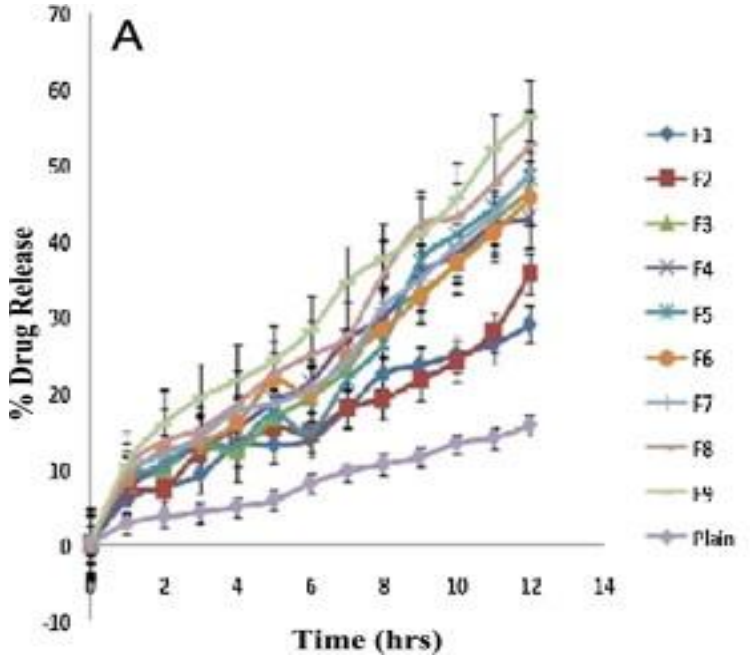

Figure 6: *In vitro* dissolution profile of plain EFV and cubosome formulation of F1–F9 [data are reported as mean ± S.D. (n = 3) (Avachat and Parpani 2015)

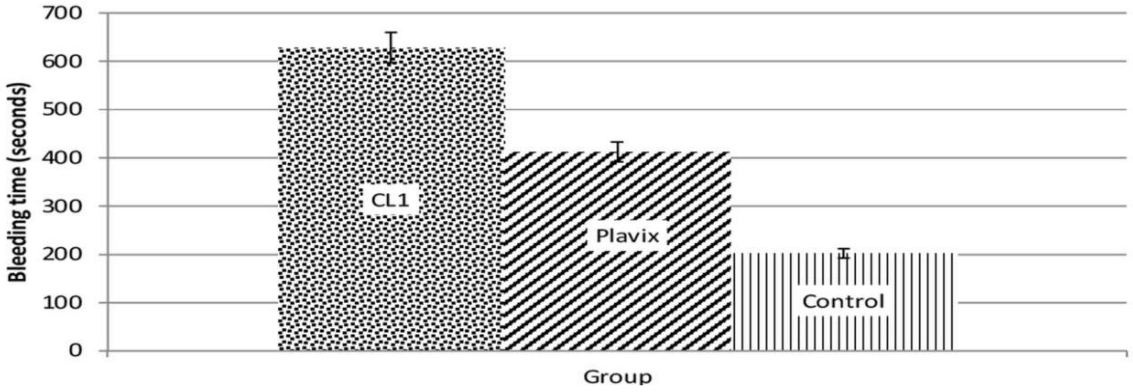

Figure 7: Histogram comparing BT of optimized CB loaded cubosomal dispersion CL1, Plavix® and control in rabbits (n=6) (El-Laithy, Badawi et al. 2018)

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