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DESIGN AND EVALUATION OF SELF NANO-EMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) OF AMIODARONE

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Abstract

To design and evaluation of self-nanoemulsifying drug delivery system using novel biomaterial isolate from the seeds of *Cicer arietinum* acts as a bio emulsifier and amiodarone as a model drug. The *Cicer arietinum* (chickpea) is a legume of the family Fabaceae, subfamily Faboideae. *Cicer arietinum* are a helpful source of zinc, folate and protein. They are also very high in dietary fibres and hence a healthy source of carbohydrates for persons with insulin sensitivity or diabetes. Chickpeas are low in fat and most of this is polyunsaturated. Nutrient profile of desi Chana (the smaller variety) is different, especially the fibre content which is much higher than the light-coloured variety. Nano-emulsion is clear and isotropic mixture. Size range of nano-emulsion 10-100nm. The drug interaction studies were performed by FT-IR spectrometry in different ratio of drug: polymer. The formulations were then subjected for various evaluation parameter like pH, drug contentand Dispersibility test, viscosity determination. Formulation F3(1:50), F4 (l:30) F5 (1:65) showed the best release in all formulation. Therefore, it was concluded that a novel biopolymer isolate from *Cicer arietinum* can serve a novel-bio emulsifier for formulation various drug loaded SNEDDS.

Key words: semi-solid self-nanoemulsifying drug delivery, self-nanoemulsifying drug delivery system (SNEDDS.), Biopolymer, bio retardant amiodarone.

Introduction of Nano Emulsion

Nano emulsifying drug delivery system is the isotropic, transparent and thermodynamically stable mixture (Soni and Prajapati, 2017. Self-Nano emulsifying drug delivery system (SNEDDS) is belonging to the BCS class II or IV. These mixtures are consisting of emulsifying agents, surfactant, co-surfactant, oil and API. The SNEDDS is improve the oral bioavailability, there is no doubt (Mohd Izham *et al.,* 2019). Nano emulsion is a novel drug delivery system, nano-emulsion is one of the novel entries of drug delivery system to enhancement the bioavailability of poorly water-soluble drug (Mahajan and Savale, 2016). The size range of nano-emulsion is 10-100nm (submicron) (Khalil *et al.,* 2015). Oral route is the most common route for drug delivery, it is easy route, but various drug is not given by this route and common problem of these route is very low bioavailability. Increase the solubility and bioavailability of oral route by nano-emulsion. Emulsion is the increase the oral bioavailability of poorly absorbed drug. Emulsion is given specially for enhancing the oral bioavailability of poorly absorbed drug (Agrawal *et al.,* 2016). SNEDDS is effective for low solubility and bioavailability of poorly water-soluble drug. SNEDDS is solved the low solubility issue of poorly soluble (Kohli *et al.,* 2010). The SNEDDS is very attractive study, is scientific approved to enhance the solubility and improved the bioavailability (Liu *et al.,* 2018). Nano-emulsions are called as mini emulsions, sub-micron emulsions and ultrafine emulsions (Kaur *et al.,* 2013). SNEDDS is improving the bioavailability of hydrophobic drug. These systems can offer better compliance and minimize problems associate with capsule filled with liquid SNEDDS (Patel *et al.,* 2010). SNEDDS is preventing degradation of drug in physiological milieu and these systems are improve the solubility hydrophobic drug. Nano emulsions are the heterogeneous mixture of two immiscible liquid like oil-in – water and water-in-oil and droplet size of nano-emulsion is 20-200nm (Date *et al.,* 2010).

Advantages of Nano-Emulsions

A. Nano- emulsions are improved physical stability.

B. It is having small size droplets and greater surface

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area, are provide good absorption.

C. Solubilize the lipophilic drug.

D. Low energy is needed (Jaiswal *et al.,)*.

E. Improve the distribution of oily drop in gel platform (network), because is work as carrier in lipophilic drug (Chellapa *et al.,* 2015).

F. Do not show any problems like flocculation, sedimentation

G. NEs can be prepared in various formulation such as spray, creams, liquids, foam (Bhatt and Madhav, 2011).

Disadvantages

A. Required large concentration of surfactant and co- surfactant for stabilizing the nano droplets (Patel and Joshim, 2012).

B. Manufacturing of nano emulsion is very difficult and expensive process, because size reduction process is very difficult and required instrument (Sharma *et al.,* 2010).

C. Nano-emulsion stability is influenced by environmental parameters such as temperature, ph. and viscosity.

D. Lack of understanding of interfacial chemistry.

E. It having a limited solubilizing capacity for high – melting substances (Mahajan and Savale, 2016).

Amiodarone

Amiodaron is a benzofuran derivative, it is an anti-arrhythmic drug (Naccarelli *et al.,* 2000). These are antiarrhythmic drug. These drug treat to suppress abnormal heart beat (heart rhythm) by different mechanism (Mehraein, 2015). It is also used for outpatient and inpatient. Amiodarone is used life – threatening irregular heart rhythms (arrhythmias). Amiodarone is maintaining a normal heart rate in patient. It is affecting the rhythm of your heartbeats (Latini *et al.,* 1984). Amiodarone is the best medicine of irregular heart rhythm (arrhythmias). amiodarone is used to keep the heart beating normally in people with life threatening heart rhythm disorder of the ventricles (Rosenbaum *et al.,* 1976) . Amiodarone is used to the heart rhythm disorder. Amiodarone is used to treat ventricular tachycardia/ ventricular fibrillation. Amiodarone is given n by orally and intravenously. This drug shows low bioavailability and low permeability. Amiodarone is taken prescribed by doctor (Latini *et al.,* 1984). First amiodarone is developed in 1961 and came onto medicinal use in 1962 for chest pain, heart problems. Amiodarone is caused various side effect like nausea, thyroid, constipation, allergic. Vision swelling of your face, lips and tongue. To make sure this medicine is safe for you, tell you doctor if you have even had -asthma /another lung disorder, liver disease, thyroid disorder, vision problem and high blood pressure or low blood pressure. Amiodarone is not taking in pregnancy may harm an unborn baby inhibit the growth of child, or cause thyroid problems and abnormal heart beat of baby (Tavolinejad *et al.,*) . The bioavailability of amiodarone is variable but generally poor, ranging from 22 to 90 percent, amiodarone is administered with food then absorption is enhanced. Amiodarone is highly lipid soluble and stored in high concentration in liver lung and skin. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first -pass metabolism, pre- systemic metabolism and susceptibility to efflux mechanism. The most frequent causes of low oral bioavailability are attributed to poor solubility and low bioavailability. Nearly 22% of new drug candidates exhibit low solubility in water, which leads to poor oral bioavailability, high intra – and intra – subject variability and lack of dose proportionality (Siddoway, 2003). One of the most popular and commercially viable formulation approaches for the solving problem is Self-nano emulsifying drug delivery system, this formulation increases the oral bioavailability of poorly water-soluble drug (Naccarelli *et al.,* 2000). Amiodarone is given by orally and intravenously. This drug shows low bioavailability and low permeability. Amiodarone is taken prescribed by doctor. First amiodarone is developed in 1961 and came onto medicinal use in 1962 for chest pain, heart problems (Hamed *et al.,* 2019). Amiodarone is caused various side effect like nausea, thyroid and constipation, allergic. Vision swelling of your face, lips and tongue. To make sure this medicine is safe for you, tell you doctor if you have even had -asthma /another lung disorder, liver disease, thyroid disorder, vision problem and high blood pressure or low blood pressure. Amiodarone is not taking in pregnancy may harm an unborn baby inhibit the growth of child, or cause thyroid problems and abnormal heart beat of baby. The bioavailability of amiodarone is variable but generally poor, ranging from 22 to 55 percent, amiodarone is administered with food then absorption is enhanced. Amiodarone is highly lipid soluble and stored in high concentration in

Fig. 1: Image of amiodarone drug with label.

liver lung and skin. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first -pass metabolism, pre-systemic metabolism and susceptibility to efflux mechanism. Amiodarone HCL is a white to cream coloured, crystalline powder. It is slightly soluble in water,

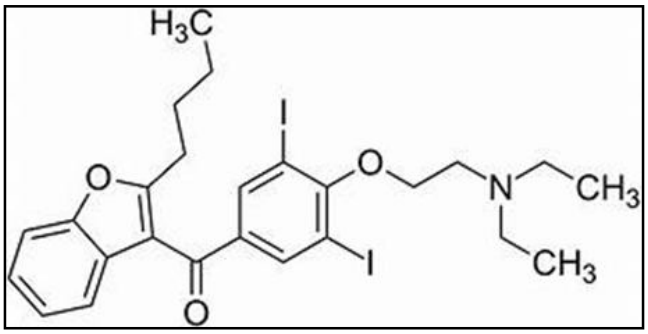

Fig. 2: Molecular structure [27].

soluble in alcohol and freely soluble in chloroform (Vassallo and Trohman, 2007; Latini *et al.,* 1984). Drug interaction of amiodarone, amiodarone is commonly used cardiovascular drug, given with other drug like warfarin, digoxin, quinidine and procainamide. Caused anticoagulant effect of warfarin by amiodarone (Orbison, 1949) .

IUPAC NAME- {2-[4-(2-butyl-1-benzofuran-3-carbonyl)-2, 6-diiodophenoxy] ethyl}-diethyl amine hydrochloride.

Chemical formula: $C_25H_30C_11NO_3$ [28].

Synonyms: Amiodarone HCL

Dosage form: amiodarone is available in tablets and injection.

Solubility: Slightly soluble in water and freely soluble in chloroform.

Brand name: Pacerone, Cordarone, Nexterone.

Storage and stability condition: Amiodarone is store in tight and light resistant container at 04 to 25^{0}C. (Siddoway, 2003).

Pharmacology of Amiodaron

1. Pharmacodynamics: It is a branch of pharmacology concerned with the effects of drug. Study of the biochemical and physiologic effects of drug. Amiodarone is an antiarrhythmic drug. Amiodarone is a class III antiarrhythmic drug. It blocks potassium currents that cause repolarization of the cardiac action potential. Amiodarone gives a result, increase the duration of the action potential as well as the effective refractory period for cardiac cell (myocytes). Amiodarone is block of voltage potassium and calcium channels (Amiodarone, 2019).

2. Pharmacokinetic: It is a branch of pharmacology and study of the ADME process. Amiodarone is well absorbed and extensively metabolized in the liver. Absolutely bioavailability is 22 to 55% and a single dose is well absorbed (at least 92%).

Side effect: Eye pain, blurred vision, cough, chest tightness, seizure, thyroid, skin discoloration, pulmonary toxicity, cardiac toxicity, hepatotoxicity, dermatologic, gastrointestinal.

Medicinal uses: Antiarrhythmic (Mehraein, 2015; Heuzé, *et al.,)*.

Introduction of Biopolymer

Cicer arietinum **(chickpea)-** Chick pea (*Cicer arietinum*) is an annual plant, belonging to family of Fabaceae and sub family Faboideae (Al-Snafi, 2018). It is a rich source of protein, carbohydrate, sulphate, amino acid, fixed oils, chloride, iron and phosphate (Basha *et al.,* 2018). *Cicer arietinum* L. is an important pulse Legume cultivated and large production of chickpeas in India, growth area about 9.54mha with a production of 9.08 Mt and productivity of 951 kg ha^{-1} (Jukanti *et al.,* 2012). Chickpeas (*Cicerarietinum*) is an important pulse crop grown. It is found all over world especially in afro-countries (Thudi *et al.,* 2017). Chickpea is mainly grown in south area and sub – Saharan Africa, more than 76% area covered (Jukanti *et al.,* 2012). It is a healthy source of carbohydrates for diabetes person. Chickpeas having a low fat and chickpeas used as a natural bio emulsifying agent Chibbar (Chibbar *et al.,* 2010; Singh *et al.,* 2014). The dictionary cites chick- pea in the mid – 18 centuries, the original word in English taken from French was chish,

Table 1: Classification of chickpeas [42].

Kingdom	Plantae
Division	Magnoli1ophyta
Class	Magnoliopsida
Order	Fabales
Family	Fabaceae
Subfamily	Fabaceae
Genus	Cicer
Species	Arietinum

found in print in English in 1388 and became obsolete in the 18th century. Other names for the species include garbanzo bean, Chana and Bengal gram. The chickpea traces back through the French chiche to Cicer, Latin for chickpeas [39]. It is the important source of cheap source of protein with high energy and nutritive value. It is cultivated in the temperate region. Large production of chickpea in various countries like central Asia, west Asia, South Europe, Australia and north Africa [40, 41].

Fig. 3: Chickpea Plant.

Fig. 4: Unripe chickpeas.

Scientific name: The common name of chickpeas and the generic name of the chickpeas is *Cicer arietinum*. Scientific name is *Cicer arietinum*, is belonging to family Fabaceae and subfamily Faboideae (Singh *et al.,* 2014).

Chemical constituents: *Cicer arietinum* having various chemical constituents like fixed oil, alkaloids, phytosterols, phenolic compound, tannins, carbohydrate, protein and amino acid. *Cicer arietinum* is a good source of carbohydrate and protein and present small quantities present of vitamin. Some chemical constituents present in chickpea like 38-59 % carbohydrate, 3% fiber, 4.8-5.5 % oil, 3% ash, some calories, 69% moisture, amino acid, protein, fatty acid, linoleic 38.0, myristic 2.74, arachidic 0.07 %. The leaves contain 4-8% protein (Taylor *et al.,* 2016; Williams *et al.,* 1994).

Materials and methods

Materials: The materials used in this study include Amiodarone drug, olive oils, poly ethyl glycol (PEG) 400 and biopolymer. The various tools used in the study are PH meter, analytical balance, dispersibility tester, Brookfield, SEM and UV spectrophotometer.

Methodology

Pre-formulation studies

It is mandatory to carryout pre-formulation study before formulation development to find out any changes in physico-chemical characteristics of drug. Preformulation testing is the first step in the rationale for development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of a drug substance, alone and when it is combined with excipients. Here we have carried out some preliminary pre-formulation studies required for the development of new drug delivery system.

Isolation of biomaterial from the seed of *Cicer arietinum*

Cicer arietinum seed (250gm) was procured from herbal garden of Meerut U.P. and soaked for 24hrs in distilled water and removed the outer cover. The pulp was grinded properly and added to 250ml of distilled water. The resulting mixture was filtered and filtrate was centrifuged at 300 RPM to remove the residual matter. The 250 ml of resulted filtrate and 250 ml of acetone were mixed well and stored at 25-40^{o}C for 12 hrs. The mixture was centrifuged at 300 RPM for 8-10min, the supernatant was discarded and the pellet was collected, dried in the oven and stored (Bansal *et al.,* 2015).

Nano-emulsion Formulation methods

Self-nanoemulsifying drug delivery system Formulation of drug was prepared by varying concentration of olive oil, Biopolymer (surfactant) and PEG 400 (co-surfactant). APT was dissolved in PEG 400, biopolymer. The mixture was heated on water bath at 37^{0}C. Other preservatives were added to the mixture followed by continuous stirring for 10 min. Then the formulation was sonicated at 45^{o}C for 15-20 min. Eight formulations were prepared with the different concentration of the oil, surfactant co – surfactant and different quantity of drug. Store in dark place at room temperature (Jyothi and Sreelakshmi, 2011; Uppulurj *et al.,* 2015).

Screening of surfactant and Co – surfactant

These are the important methods of self-nanoemulsifying drug delivery system, various ingredients like API, surfactant (Biopolymer), co-surfactant (PEG 400) were used and screened for self-nano emulsifying drug delivery system. The 200mg of surfactant and 100mg of co-surfactant were added to oil and heated at 40-45^{0}C for 20 to 30 seconds. 50mg of mixture was diluted in 50 ml of water. The formation of emulsion formation was scrutinized (check) by the counting the number of

volumetric flask inversions to give a uniform emulsion and observe visually for relative turbidity. The emulsion was left on standby for 2hr and the transmittance was measured at 382nm (Soni and Prajapati, 2017).

3 Procedure for the Preparation of Snedds of Amiodarone

Amiodarone hydrochloride was purchased sigma Aldrich (Buchs Switzerland). Surfactant and co – surfactants were added in this formulation. 8 mg of amiodarone was added in accurate weight of oil into a screw capped glass vials and this mixture melted on water bath at 37^{0}C. Surfactants and co-surfactants were added in the oil mixture with continuous stirring with the help of magnetic bar and the formulation was sonicated (frontline FS-4) for 12-15min. The homogeneous mixture was formed. The resulted formulation was store at room temperature for later studies.

Table 2: Zeta potential measurement value.

Formulation	F1	F2	F3	F4
Zeta potential data	20.09	25.01	24.03	25.05

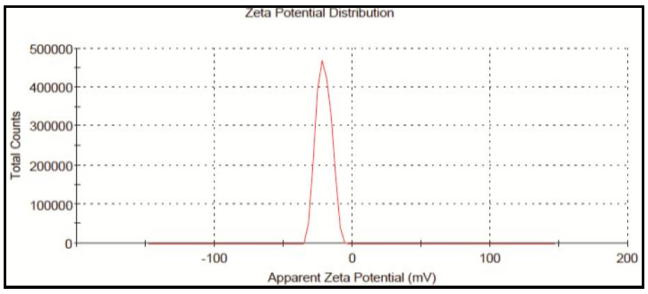

Fig. 5: Zeta potential.

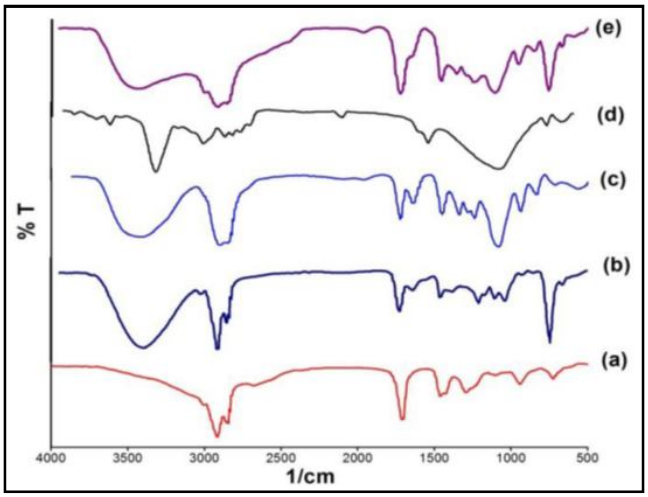

Fig. 6: FT-IR Spectra of olive oil, biopolymer, PEG 400 and

Evaluation Paraeters

1. Zeta potential measurement

Zeta potential measure the electric charge on nano emulsion at 25^{0}C temperature. Zeta potential is measured by zetasizer ZS 90. 70ul sample dilute in 5 ml distil. Water then sonicated, after sonication. I have received the homogenous mixture and measure by Zetasizer at 20^{0}C temperature (Datri *et al.,* 2012).

Table 3: Globules size and PDI data.

Formulation	F1	F2	F3	F4	F5
Droplet size (nm)	12.3	12.5	13.1	19.0	19.5
PDI	0.120	0.155	0.180	0.030	0.190

2. Compatibility study

Compatibility is must require of API and other ingredients used in formulation the drug and ingredient involved in design and manufacturing of the drug required the consideration of physical and chemical character. Compatibility must establish to develop a stable, attractive and safe product. Check the interaction between drug and ingredients by FT-IR spectrophotometry (Chintalapudi *et al.,* 2015).

3. Globule size and polydispersity index analysis

Taking the nano formulation and was dilute 45 time and 100 tomes of distilled water. And resulting samples were stirring by magnetic bar for 5-8 min and prepared gentle agitation. Globule size measurement using light scattering techniques by Malvern and can measure the size 10-5000nm. PDI (Polydispersity index) is measured Malvern Zeta sizer 90 (Deore *et al.,* 2019).

4. In – vitro study is a scientific study

In- vitro word obtain from Latin language which mean in the glass. Study of amiodarone, PEG 400, 300 and olive oil used in this formulation. *In vitro* of amiodarone (complex with biopolymer and PEG 400) was analysed by dialysis Bag method. This method was operated in dialysis bag with different solvent e.g. buffer acetate with ph. 4.6 and buffer phosphate with ph. 7 at 37^{0}C temperature. Taken the sample of pure drug. 2 ml sample was added in dialysis bag. Sample bag put in 250 ml beaker inclusive 100ml phosphate buffer ph. 7.5. Now beaker put on magnetic bar for stirring under controlled condition (100rpm at 37^{0}C). Collect 1 ml sample was taken at predetermined time interval (0.5, 10, 15, 20, 25, 30, 35, 40 and 45hrs) and simultaneously 1ml respected media was added to maintain the sink condition. This media was stored at -200^{0}C until analysis. Multiple part of drug was measure by UV spectroscopy at 270 nm and receive the in-vitro drug release curve. Release part of drug was calculated (Rubim *et al.,* 2015; Murthy *et al.,* 2015).

5. UV-Visible Spectroscopy

Standard curve for Amiodarone was prepared in

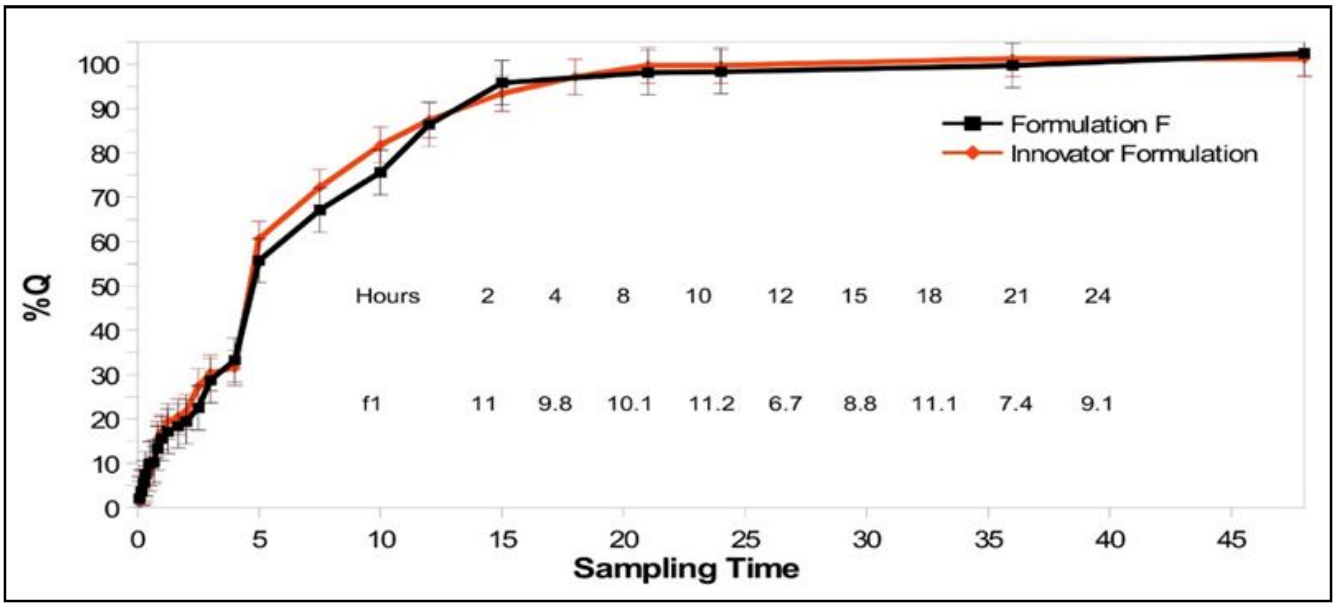

Fig. 7: In-vitro study.

Table 4: Calibration curve of Amiodarone hydrochloride using UV spectroscopy.

Concentration (µg/ml)	Absorbance (nm)Mean±SD	%RSD
0.2	0.0312±0.002	8.32
0.4	0.0595±0.005	9.33
1.6	0.2218±0.005	2.52
3.2	0.4818±0.004	0.95
6.4	0.9161±0.005	0.61

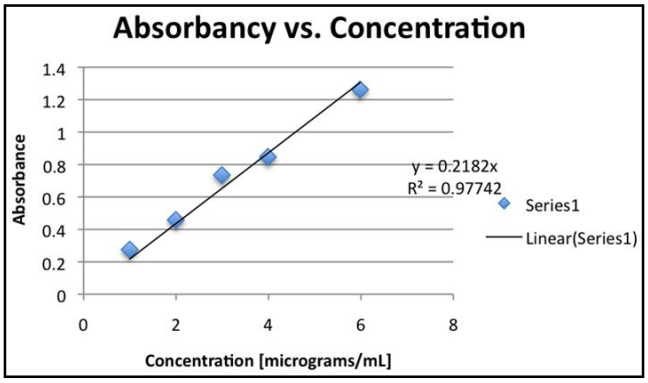

Fig. 8: Calibration curve of Amiodarone at 245 nm.

acetonitrile (ACN) at λmax of 245 nm. The calibration curved obtained by plotting absorbance vs concentration at 245 nm in the concentration range of 0.2-6.4 µg/ml had $R^2 = 0.97742$ and the equation is y = 0.2182 x. (Akhil *et al.,* 2015).

6. Observation of UV Calibration curve in ACN at 245 nm

To validate the UV-visible spectroscopic method for identification of Amiodarone stock solution (1mg/ml) was further diluted with acetonitrile (ACN) to obtain a concentration range (different to concentrations prepared in section 6.1.6) of 0.5 to 7 µg/ml. Correlation plot *i.e.* theoretical concentration vs observed concentration was given in Fig. 9. From the table 5. It was found that percentage recovery was in between 97 to 105% which is highly significant

Table 5: Observation in Acetonitrile at 245 nm.

Theoretical Conc. (µg/ml)	Avg. absorbance	Observed Conc. (µg/ml)	% Recovery
0.5	0.07387	0.48	98.70
1	0.15122	1.02	103.21
3	0.41821	2.91	96.40
5	0.71913	4.94	99.00
7	0.99632	6.95	98.76

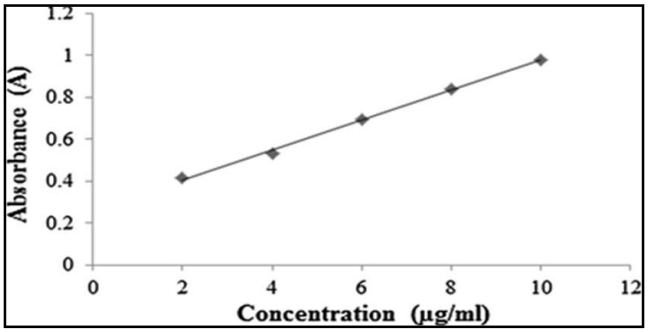

Fig. 9: Observation Curve of Amiodarone at 245 nm.

Result and Discussion

Amiodarone drug, an antiarrhythmic drug is used in the treatment of arrhythmia. Used in many types of cardiac diseases and it have various chemical properties. Amiodarone is low solubility of drug. The main object this work formulation and evaluation of amiodarone drug for oral use. The present work of nano emulsion to enhance the oral bioavailability of amiodarone drug by

administrable orally. Better solubility, droplet size of characterization of nano formulation (biopolymer and co-surfactant). In this formulation various studies done like preformulation study and identify the APT and other excipients. Various methodology and characterization paraments used in this formulation. FT-IR spectroscopy study for compatibility of the drug and other excipients used in this formulation. UV spectroscopy checked the absorbance the drug and excipients. Drug dissolve in methanol and check the absorbance 270 nm and plotted the graph. Physical characterization like droplet size, zeta potential, PDI used for all formulation.

Conclusion

Our aims were to formulation and evaluation of self-nano emulsifying drug delivery system of amiodarone drug was capable of trouncing complication of high solubility anti- arrhythmic drug. In conclusion, this study increases the oral bioavailability of amiodarone drug with the nano emulsion. Nano emulsion enhance the solubility and bioavailability of the amiodarone drug, its stability increased, oral bioavailability of amiodarone was also increased as the stability improved. Amiodarone's nano emulsion was made from olive oil, biopolymer and peg 400. the result it has been clearly seen that the formulation was completely safe for biomedical as well as pharmaceutical application. Nano- emulsion of amiodarone was effective in cardiac arrest. Nano-emulsion of amiodarone were control the irregular heartbeat. Nano emulsion enhance the After stabilizing the nano-emulsion of the amiodarone.

Conflict of interest

The author has declared that no conflicts of interest exist.

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Ethical Approval

Not required.

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