ABSTRACT
The present work was aimed to formulate, optimise & evaluate Self-Micro Emulsifying Drug Delivery System (SMEDDS) of Amiodarone HCl and to evaluate its in vitro release. The main objective of formulation was dissolution enhancement. SMEDDS comprises of isotropic mixture of natural or synthetic oil (Capmul MCM C8), surfactant (Tween 80), and co surfactant (Propylene glycol), which upon dilution with aqueous media or in 0.1 N HCl spontaneously form fine o/w micro emulsion with less than 200 nm in droplet size. Solubility of Amiodarone HCl were determined in various vehicles. Ternary phase diagrams (1:1:2,1:2:1) were plotted to identify the efficient Self-Emulsification region with selected excipients. For optimisation, 2 full factorial design was applied. SMEDDS was investigated for Clarity (Transmittance), Phase Separation, Globule size with Shape, Zeta Potential, Effect of various Dilutions, Thermodynamic Stability and in vitro release of formulation. Dissolution study was compared with marketed tablet. The batch having 116.23±8.33 nm Globule Size, clear bluish (PDI 0.26), and 96.52±0.52 Transmittance, 5.60 pH, 174 centipoise Viscosity & 36.1 mV Zeta Potential was <0.0001.

Keywords: Amiodarone HCl, SMEDDS, Capmul MCM C8, Tween 80, Propylene Glycol, Dissolution Efficiency.

Abbreviations: SMEDDS - Self-Micro Emulsifying Drug Delivery System; XRD - X - Ray Diffraction; FTIR – Fourier Transform Infrared; DE – Dissolution Efficiency

How to Cite This Article

1. INTRODUCTION

1.1. Drug: Amiodarone HCl
Amiodarone hydrochloride is an anti-anginal and anti-arrhythmic drug used to increase the duration of ventricular and atrial muscle action by inhibiting Sodium-Potassium-activated myocardial adenosine tri-phosphatase. There is a resulting decrease in heart rate and in vascular resistance. It is a benzofuran derivative related to the now obsolete vasodilator khellin. The most striking structural features of the drug are its high iodine content and its resemblance to the thyroid hormone thyroxine (Florey, 2001). Amiodarone Hydrochloride is a highly lipophilic (log p (octanol/water) 7.9) (www.drugbank.com) poorly water soluble drug with absolute bioavailability of 20-55%. The drug exhibits physico-chemical properties highly suitable for diffusion across lipophilic absorbing membranes, but its low aqueous solubility can act as the rate limiting step for absorption, making the process erratic and variable (Martian-algarra et al. 1997).

1.2. Adverse event with Amiodarone HCl
On intravenous administration of Amiodarone, it leads to Hypotension, cardiovascular collapse and AV block which have been reported as rare complications during intravenous Amiodarone treatment. Amiodarone contains about 37% iodine by weight, and a considerable fraction is diiodinated in the body. A 200 mg dose has been reported to produce 9 mg free excess iodine may cause at least three thyroid abnormalities: (Mcgovern et al. 1984).

1) Iodine-induced thyroiditis (Mcgovern et al. 1984)
2) Hypothyroidism usually after prolonged exposure (David Conen et al. 2007)
3) Thyrotoxicosis (David Conen et al. 2007)

There have been reports of exacerbation of cardiac failure

Comparison:
It is an act of assessment or evaluation of things side by side in order to see to what extent they are similar or different. It is used to bring out similarities or differences between two things of the same type mostly to discover essential features or meaning either scientifically or otherwise.

Bioavailability:
In pharmacology, bioavailability (BA) is a subcategory of absorption and is the fraction of an administered dose of unchanged drug that reaches the systemic circulation, one of the principal pharmacokinetic properties of drugs.

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by Amiodarone. Other major effect is pulmonary toxicity. Above listed problem can be prevented by either route change or by reduction of the dose. This can be approached by lipid based formulation. SMEDDS has received particular attention as a mean of enhancing the oral bioavailability of poorly soluble and permeable drugs. Here, attempt is made for improving in vitro dissolution of Amiodarone Hydrochloride by formulating SMEDDS with reduction in the dose (Mcgovern et al. 1984).

1.3. Requirement of SMEDDS

Approximately 40% of new drug candidates have poor water solubility and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability and a lack of dose proportionality (Kommuru et al. 2001). This is due to large food effect, i.e. much higher exposures in the fed than fasted state, which can lead to greater sensitivity of the pharmacokinetic profile to the fat content of meals and fed than fasted state, which can lead to greater sensitivity of the pharmacokinetic profile to the fat content of meals and inter subject variation in absorption leading to fluctuation in plasma profile. SMEDDS produce reproducible plasma profile (Anand et al 2010).

Advantages:

1) SMEDDS is a novel approach to improve water solubility and ultimate bioavailability of drugs for which water solubility is a rate-limiting step. SMEDDS have the ability to present the drug to GIT in 1-100 nm globule size (average size: <200 nm) and subsequent increase in specific area enables more efficient drug transport through the intestinal aqueous boundary layer leading to improvement in bioavailability (Tang et al. 2007).

2) Many drugs show large inter-subject and intra-subject variation in absorption leading to fluctuation in plasma profile. SMEDDS produce reproducible plasma profile (Anand et al 2010).

3) Fine oil droplets empty rapidly from the stomach and promote wide distribution of the drug through the intestinal tract and thereby minimizing irritation frequently encountered with extended contact of drugs and gut wall (Pouton et al. 1997).

4) Ease of manufacture and scale up is one of the most important advantages that make SMEDDS unique, when compared to other drug delivery system (Sami Nazzal et al. 2006).

5) SMEDDS has potential to deliver peptides that are prone to enzymatic hydrolysis in GIT (Anand et al. 2010).

6) When polymer is incorporated in the composition of SMEDDS, it gives prolonged release of medicaments (Tang et al. 2007).

7) Enhanced oral bioavailability enabling reduction in dose of the drug (Shobhit Kumar et al. 2012).

8) Selective targeting of drugs towards specific absorption window in GIT (Anand et al. 2010).

Limitation: (Shukla et al. 2010)

Volatile co solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.

1) Due to presence of high surfactant concentrations there may be chances of instabilities of drugs.

2) Also the high content of surfactant in self emulsifying formulations irritates the gastrointestinal tract. This problem may be avoided by utilizing optimum less amount of surfactants.

3) Sometime co-solvents remain into the formulation and cause degradation of drugs.

4) It may allow less drug loading.

5) Chemical instabilities of drugs and high surfactant concentrations.

Table 1

<table>
<thead>
<tr>
<th>Composition of formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone HCl (mg)</td>
</tr>
<tr>
<td>Capmul MCM C-8</td>
</tr>
<tr>
<td>Tween-80</td>
</tr>
<tr>
<td>Propylene Glycol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vehicle (%)</th>
<th>LS-1</th>
<th>LS-2</th>
<th>LS-3</th>
<th>LS-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS 1</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>LS 2</td>
<td>15</td>
<td>20</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>LS 3</td>
<td>42.5</td>
<td>40</td>
<td>40</td>
<td>42.5</td>
</tr>
<tr>
<td>LS 4</td>
<td>42.5</td>
<td>40</td>
<td>40</td>
<td>42.5</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>2 Factorial designs: particle size evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch no</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>LS 1</td>
</tr>
<tr>
<td>LS 2</td>
</tr>
<tr>
<td>LS 3</td>
</tr>
<tr>
<td>LS 4</td>
</tr>
</tbody>
</table>

Figure 1

Graph of Solubility in excipients

Solubility: The solubility is defined as the maximum concentration of solute present in solvent under specific condition of temperature, pH and pressure.

Dissolution: Dissolution is defined as the rate of mass transfer from a solid surface into the solvent under standardized conditions of liquid/solid interface, temperature and solvent composition.

Self-Microemulsifying Drug Delivery System (SMEDDS):

A self microemulsifying drug delivery system (SMEDDS) is a drug delivery system that uses a microemulsion achieved by chemical rather than mechanical means. That is, by an intrinsic property of the drug formulation, rather than by special mixing and handling.

What is SMEDDS?

"Self-micro emulsifying drug delivery system is isotropic (one phase system) mixture of oil or modified oils, surfactants and co-surfactants, which form the fine oil in-water micro emulsion when introduced into aqueous phase under condition of gentle agitation. The digestive motility of the stomach and intestine provides the agitation, necessary for self-micro emulsion in vivo."

Dharmang Pandya et al.

2. MATERIALS AND METHODS

2.1. Materials
Amiodarone HCl was supplied by Claris Lifesciences Limited. Grating sample of oils were supplied by Abitec & Gattefosse. Tween 80 & Propylene glycol were purchased from Loba.

2.2. Methods

2.2.1. Drug identification
Drug was identified by melting point determination (capillary method), FTIR, UV spectroscopy method & XRD (Florey, 2001).

2.2.2. Solubility screening of excipients
One ml of each of solvents (oil, surfactant, and co-surfactant) was filled in 1 ml screw capped test tube. Increasing quantity (milligrams) of Amiodarone HCL (drug) was added in each tube until saturation point is achieved. The tightly closed tubes were shaken for 48 h at 50 strokes.
Table 5
Check point batches

<table>
<thead>
<tr>
<th>Batch</th>
<th>Expected particle size (nm)</th>
<th>Obtained particle size (nm)</th>
<th>t-test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch 1</td>
<td>198</td>
<td>202</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>Batch 2</td>
<td>157.6</td>
<td>156.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Centre point)

Table 6
Accelerated Stability study

<table>
<thead>
<tr>
<th></th>
<th>0 day</th>
<th>After 15 days</th>
<th>After 30 days</th>
<th>After 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>LS 1</td>
<td>151.3</td>
<td>149.4</td>
<td>155.1</td>
<td>163.2</td>
</tr>
<tr>
<td>LS 2</td>
<td>202</td>
<td>197.5</td>
<td>184.4</td>
<td>177.8</td>
</tr>
<tr>
<td>LS 3</td>
<td>133.6</td>
<td>156.7</td>
<td>147.3</td>
<td>142.6</td>
</tr>
<tr>
<td>LS 4</td>
<td>220</td>
<td>212.7</td>
<td>197.1</td>
<td>215.8</td>
</tr>
</tbody>
</table>

Figure 4
Particle size of optimized batch after 500 times dilution in 0.1 N HCl

2.2.4. Optimization of Formulation

- Preliminary trials were carried out to decide minimum quantity of oil and surfactant. Based on these experiments, it was found that a minimum of 15% of oil is required to dissolve 25mg of AmiodaroneHCl and 85% of surfactant is required to produce a Micro emulsion with globule size of less than 200nm.

- To study the effect of independent variable on the dependent variable and optimization of AmiodaroneHCl SMEDDS formulation, 2^3 full factorial design was employed. Obtained results were evaluated using design expert software.

- There were two independent parameter (oil concentration & surfactant concentration) & dependent parameter was taken as Globule size (nm). There were two level for each: low level (-1) & high level (+1). For oil 15 & 20%, surfactant 80 & 85% level respectively.

- Prepared liquid SMEDDS was characterized for statistical analysis using ANOVA regression analysis. Effect of formulation components on response was also studied using design expert software.

2.2.5. Evaluation of SMEDDS

1) Dispersibility test (Adhvait et al. 2010)

The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus. One millilitre of each formulation was added to 500 mL of water at 37 ± 0.5 °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system:

- Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.
- Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.
- Grade C: Fine milky emulsion that formed within 2 min.
- Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).
- Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

2) Robustness to Dilution (Adhvait et al. 2010)

Robustness of SMEDDS to dilution was studied as per Date and Nagarsenker’s method with slight modification. SMEDDS was diluted to 10, 100, and 1,000 times with various dissolution media viz., water, pH 1.2 buffer. The diluted micro emulsions were stored for 12 h and observed for any signs of phase separation or drug precipitation.

3) Droplet size (Nidhi Bhatt et al. 2010)

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release, as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter
Nanosizer are mainly used for the determination of the emulsion droplet size.

4) Viscosity Determination (Mittal Pooja et al. 2011)

The SMEDDS system is generally administered in soft gelatin or hard gelatin capsules. Therefore, it should be easily pourable into capsules and such system should not be too thick to create a problem. The rheological properties of the micro emulsion are evaluated by Brookfield Viscometer. This viscosity determination confirms whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosity then it is w/o type of the system.

5) TEM studies (Ajeet K. Singh et al. 2009)

For Transmission Electron Microscopy (TEM), samples were prepared in a controlled environment verification system. A small amount of sample is put on carbon film supported by a copper grid and blotted by filter paper to obtain thin liquid film on the grid. The grid is quenched in liquid ethane at -180 °C and transferred to liquid nitrogen at -196 °C. The samples were characterized with a TEM microscope.

6) Refractive index and Percent transmittance (Ajeet K. Singh et al. 2009)

Refractive index and percent transmittance proves the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it is compared with water. The percent transmittance of the system is measured at particular wavelength (650nm) using UV-Vis spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water and formulation has percent transmittance > 99 percent then formulation has transparent nature.

7) Zeta potential study (Nidhi Bhatt et al. 2010)

The emulsion stability is directly related to the magnitude of the surface charge. The zeta potential of the diluted SMEDDS formulation was measured using a (MalvenZetasizer 3000HS). The SMEDDS were diluted with 100 times distilled water and mixed for 1 min using a magnetic stirrer.

8) Thermodynamic stability studies (Sami Nazzal et al. 2006)

The physical stability of a lipid based formulation is also crucial to its performance which can be adversely affected or precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability leads to phase separation of the excipients, affect not only formulation performance but visual appearance well as mentioned in Figure 3.

9) Accelerated Stability Study

As per ICH Guideline for Checking Globule size & visual appearance of SMEDDS, it was performed at [40±2° C / 75 % RH±5%].

9) Dissolution Efficiency (Paulo Costa, 2001)

The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the release assay of the reference formulation and rectangle described by 100% dissolution in the same time.

\[
D.E. = \frac{\int y \times dt}{y_{100} \times t} \times 100\%
\]
### 3. RESULTS & DISCUSSIONS

As per the table 1 to 6, the results were obtained after different studies.

**DE of SMEDDS** = $982.74^{*100}/30{98.24} = 33.33$

**DE of Marketed Tablet** = $1151.96^{*100}/90{83.79} = 15.27$ as per Table 7

\[
\% \text{ DE} = \frac{\text{DE of SMEDDS} - \text{DE of Marketed Tablet}}{\text{DE of Marketed Tablet}} \times 100 = +33.33/15.27 = 2.18
\] as per Table 8

SMEDDS of Amiodarone HCl was prepared and optimized by using in vitro parameters like particle size, polydispersity index. Other parameter like Transmittance, pH, zeta potential, in vitro release. Stability study Optimal SMEDDS contains Capmul MCM C-8 as oil phase, Tween 80 as a surfactant, and PG (propylene glycol) as co-surfactant. The combination of all three components, i.e., oil/surfactant/cosurfactant in the ratio of 15:40:40, formulates SMEDDS with lower particle size $16.23^{*8.33}$ nm, PDI 0.261 ± 0.021, and 36.1 mv zeta potential. This optimized SMEDDS showed good in vitro release which is within 30 min complete release of drug. Marketed tablet even after 90 min only $83{\%}$ drug release then after it become constant. All SMEDDS batches having greater than $95{\%}$ drug release within 30 min. Final equation from design expert software is

\[
+157.18 + 33.04 * \text{oil} -1.34* \text{S mix} -9.0 * \text{oil} * \text{S mix}
\]

From ANOVA of selected model, P value of independent parameter oil (X1) is less than 0.0001 and for S mix (X2) it is 0.73 and for interaction term (X1X2) is 0.0426. So, P less than 0.0500 indicate model terms are significant. In this case X1, X2 are significant model terms and X2 is non significant term as per Table 9.

There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size such as in the case of a mixture of saturated C8-C10 polyglycolized glycerides. This could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface. On the other hand, in some cases, the mean droplet size may increase with increasing surfactant concentrations. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase. The particle size determination following self microemulsification is a critical factor to evaluate a self microemulsion system as droplet size is reported to have an effect on drug absorption. The smaller is the droplet size, the larger is the interfacial surface area provided for drug absorption.

The optimization of SMEDDS was based on microemulsion domain obtained and particle size of SMEDDS & PDI. Polydispersity is the ratio of standard deviation to the mean droplet size. This signifies the uniformity of droplet size within the formulation. The higher the value of polydispersity, the lower is the uniformity of the droplet size in the formulation Higher PDI is due to less solubility of drug in solvents may be the reason behind this. This leads to precipitation of drug and thereby increases particle size of SMEDDS. SMEDDS with increased particle size causes agglomeration of globules and suffers with instability of system. So here in this case as ratio of S mix increased from 1:1, 2:1, 3:1, the PDI value also increased 0.253, 0.267, 0.440 respectively. So from this study also 1:1 ratio of S mix is optimized.
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**SUMMARY OF RESEARCH**
This work showed that the dissolution of Amiodarone HCl – BCS Class-II drug is increased by SMEDDS formulation because in this formulation, the particle size is reduced by various ratios of surfactant, cosurfactant and oil so the surface area increases to provide better dissolution.

**FUTURE ISSUES**
From the above mentioned work, the dissolution of poorly water soluble drug was enhanced. This work can also be continued by bioavailability, efficacy and stability enhancement by various formulation and development processes, which will result in low dose and less side effects of Amiodarone HCl.

**DISCLOSURE STATEMENT**
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