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Design, Formulation and evaluation of Amiodarone HCl co-crystal tablet

Vinod K.Patidar*[1], Anshu Sharma[2]
[1]*Faculty of Pharmacy, Bhupal Noble's University, Udaipur-313001, Rajasthan, India*
**Corresponding Author E-mail:patidarvinod304@gmail.com*

Abstract:
Amiodarone HCl is an against of arrhythmic medication. This prescription is utilized to treat specific sorts of genuine (potentially deadly) unpredictable heartbeat, (for example, determined ventricular fibrillation/tachycardia). It is utilized to reestablish typical heart cadence and keep an ordinary, consistent heartbeat. Co precious stones is an elective methodology dependent on gem designing to upgrade explicit physicochemical and biopharmaceutical properties of dynamic drug fixings (APIs) when the ways to deal with salt or polymorph arrangement don't meet the normal targets. A precious stone designing methodology was utilized to configuration; build up a Co gem of the API. Co precious stones are strong substances, which comprise of not many segments combined. Co gems are multi segment frameworks in which two parts, a functioning drug fixing and a co previous were available in stoichiometric proportion and fortified along with non-covalent associations or Hydrogen holding in the precious stone cross section. There are a great deal of methods of co precious stones creation and application. The goal of the current work was centered around the improvement of watery solvency of medication by figuring Co-precious stone of Amiodarone HCl.

Keywords: Co crystals, Co formers, amiodarone hydrochloride, solubility, stability, bioavailability.

INTRODUCTION:

Co-crystal engineering is the design and synthesis of molecular solid state structures with desired properties, based on an understanding and use of intermolecular interactions. The two main strategies currently in use for Co-crystal engineering are based on hydrogen bonding and coordination bonding. The term Co-crystal engineering' was first used in 1971 by Gerhard Schmidt. The first reported Co-crystal, quinhydrone, was studied by Friedrich Wöhler in 1844. A Co-cryatal is a multiple component Co-crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a stoichiometric ratio of a target molecule or ion and a neutral molecular Co-cryatal former. Co-crystal form can be vital to the performance of a dosage form. Co-crystals are defined as Co-crystalline complexes of two or more neutral molecular constituents bound together in the Co-crystal lattice through non covalent interactions. Co-crystallization is a result of competing molecular associations between similar molecules, or homomers, and different molecules or heteromers. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of families of molecular networks with the same molecular components (single component Co-crystals and their polymorphs) or with different molecular components. The components in a Co-crystal exist in a definite stoichiometric ratio, and assemble via non covalent interactions such as hydrogen bonds, ionic bonds, and π-π or van der Waals interactions rather than by ion pairing.

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Crystal engineering or solid state supramolecular synthesis deals with the understanding of intermolecular interactions in the context of Co-crystal packing and in applying this understanding to the design of pre-desired Co-crystal structures with specific physical or chemical properties1.' Co-crystals are solids that are Co-crystalline materials composed of two or more molecules in the same Co-crystal lattice.

Co-crystal incorporated pharmaceutically acceptable guest molecules into Co-crystalline lattice along with the API. Co-crystals have regained attention as attractive alternate solid forms for drug development. Physiochemical properties of pharmaceuticals can be improved by obtaining Co-crystals using Co-crystallization. Co-crystallization with pharmaceutically acceptable (GRAS) compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, compaction behavior.

Quinone and hydroquinone Co-crystal called Quinhydrone. This material was taken in to 1:1 stoichiometric ratio. The physicochemical properties improvement has become a major concern in the pharmaceutical industry. Most of the chemical entities are discovered as lipophilic compound and have poor water solubility [1-3]. Currently various techniques resolve the problem of poor solubility and dissolution rate of poorly water soluble drugs and is classified as BCS Class II or BSC Class IV, where solubility is the rate limiting step for absorption. There are various methods available to increase the bioavailability and solubility of BCS Class-II and class IV drug includes particle size reduction, salt formation, Co-crystal formation with co former [4], amorphization [5] and solid dispersion formation. Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a liquid or gaseous solvent to form a homogeneous solution of the solute in the solvent. A pharmaceutical Co-crystal is a single Co-crystalline solid that incorporates two neutral molecules, one being an API and the other a Co-crystal former. Co-crystal former may be an excipient or another drug. Pharmaceutical Co-crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of forms of an API. Scientists showed that modifying the physical properties of a pharmaceutical compound through pharmaceutical Co-crystal formation improved the performance of a drug

Pharmaceutical co-crystals is reliable method to improve drug physicochemical and mechanical properties such as solubility, dissolution rate, stability hygroscopicity [6], compressibility and *in vivo* performance without altering their pharmacological behavior and hence this is a potential new alternative in the selection of optimal solid forms in drug product development[7]. Co-crystals are those that are formed between an active pharmaceutical ingredient (API) and a co-crystal former (CF). Poor dissolution rate, solubility, chemical stability and moisture uptake influence therapeutic efficacy of many pharmaceuticals, and significantly lower the market value of a drug. Multi-component crystals e.g. solvates, hydrates [8], co-crystals, salts play important role in the design of new solids particularly in the pharmaceutical area.

MATERIALS AND METHODS:

Preformulation studies of Amiodarone HCl pure drug

Preformulation testing of the active substances provides useful information. It may be necessary to consider the physiochemical characteristics of active substance in the formulation in relation to the proposed dosage form and route of administration. Although the most of the analytical and identification

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parameters was already performed by Niranjan laboratories Ankleshwar (Gujrat) India who provide the gift sample of Clopidogrel bisulfate pure drug for research wok.

Determination of λ_{max}

For determination of λ_{max} stock solutions of Amiodarone HCl (concentration 1000µg/ml) in methanol were prepared. 1ml of the prepared stock solution was further diluted to 100 ml. Resulting solutions were scanned in the range of 400 to 200 nm using methanol as a blank with the help of UV-visible spectrophotometer. Average of triplicate readings was taken. The $\lambda_{max\ of\ drug\ was}$ found to be-242 NM.

Preparation of standard calibration curve of Amiodarone HCl in 0.1 N HCl

Preparation of stock solution: A standard stock solution of Amiodarone HCl was prepared by dissolving 10 mg of Amiodarone HCl in 1000 ml 0.1N HCl to obtain stock solution of drug of concentration of (100 µg/ml).

Preparation of standard solutions: The-working solutions in the concentration range of 10-50 µg/ml were prepared by suitable dilutions of the stock solution in 0.1 N HCl. Resulting solutions were scanned in the range of 400 to 200 nm using 0.1 N HCl as a blank with help of UV-visible spectrophotometer (Shimadzu 1601) and absorbance were taken at 242 NM.

Melting point determination

Open capillary method was used to determine the Melting point of Amiodarone HCl. The capillary filled with drug powder was placed in Thiel's tube [10] containing liquid paraffin. The tube was heated and the melting point of the drug powder was noted. The average of three values was considered as the melting point of drug.

FTIR Spectra of pure drug

The FTIR spectrums of Amiodarone HCl were recorded with the FTIR spectrophotometer (IR200 Thermo electron). Potassium bromide pellet method was used and under identical condition background spectra was collected. Each spectrum was derived from 16 single average scans collected in the range of 400-4000 cm^{-1} at the spectral resolution of 02 cm^{-1}. The obtained spectral values of wave number were compared with standard reference values functional groups present in the API.

Drug co-former compatibility study

The FTIR method was employed to identify the drug and co-formers interaction to know the physiochemical interaction occur in the drug and excipient [12]. 1:5 ratios of drug and co-formers were taken and placed in a vial and rubber stopper was placed on the vial and sealed properly for 6 month at $40^0C\pm2^0C/75\%RH\pm5\%$ RH. After 6 month the FTIR method were employed to know the physiochemical interaction between drug and co-former.

Preparation of Co crystals by Dry grinding technique

Dry grinding method was employed for the preparation of Amiodarone HCl. Drug and conformer (Urea, Glutamine [13], Ascorbic acid and Citric acid) were mixed in different molar ratio 1:1 Stoichiometric (molar) ratio and grind in mortar and pestle for 45 min to form co crystals. This was dried an overnight at ambient temperature and stored in tight containers. This technique works on the principle that, when different molecules of complimentary functional groups shared hydrogen bonds that is more favorable

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than each of the individual molecular components. Finally stored in desiccators until further investigated by microscopic, melting point, SEM, XRPD and DSC study.

Table 1: Drug and conformer ratio

S. No.	Drug : Co former	Quantity (mg)
1	AmiodaroneHCl: Glutamine	300
2	AmiodaroneHCl: Urea	
3	AmiodaroneHCl: Citric scid	
4.	AmiodaroneHCl: Ascorbic acid	

Evaluation of co-crystal Melting point of cocrystal

Amiodarone HCl Melting point was determined using capillary method. The capillary filled with drug powder was placed in Thiel's tube containing liquid paraffin. The tube was heated and the melting point of the drug powder was noted.

Fourier Transform Infrared (FT-IR)

Fourier Transform Infrared (FT-IR) spectra were recorded for the prepared co-crystals. Potassium bromide pellet method was employed and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 400-4000 cm^{-1} at the spectral resolution of 02 cm^{-1}.

Differential scanning calorimetry

The DSC of Co-crystal was recorded by differential scanning calorimeter equipped with a computerized data station. The DSC measurements were performed on a DSC [15] 60, Shimadzu, Japan instrument. Accurately weighed sample were placed in a sealed aluminum pans before heating under nitrogen flow (20ml/min) at a scanning rate of 100c/min. An empty aluminum pan was used as a reference. Melting point was determined for identification of API and co-crystal former.

X-ray Diffraction

The powder x-ray diffraction (XRD) pattern of Cocrystal was determined to know the characterization of crystalline state [16]. X-ray Powder Diffraction was done for the prepared co-crystals; it reveals the information about the crystal structure, chemical composition, and physical properties of the material and also helps in structural characterization. Powder X-ray diffraction (XRD) was carried out using a Bruker AXS Advance D-8 scanner with filter Ni, Cu- Kά radiation, voltage 40kV and a current 20 mA. 10/min scanning rate employed over 50 to 500 diffraction angle (2Θ) range.

Scanning Electron Microscopy (SEM)

SEM (JSM 6360 LV, Joel, Japan) was used to studies the surface characteristic of prepared crystal [17]. Powder samples was mounted onto aluminum stub using double sided adhesive tape and sputter coated with a thin layer of gold at 10 Torr vacuum before examination. Electron beam of acceleration potential of 20 kV was used for scanned the specimens and the images were collected as secondary electron mode.

Solubility Studies

Saturated solubility studies were conducted according to method given by Higuchi and Connors in triplicate (Higuchi and Connors, 1965). The equilibrium solubility at a room temperature is determined

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by the shake flask method. In order to determine saturated solubility, an excess amount (10) of drug and cocrystals are added to 5ml of the distilled water in the glass vials and The vials are subjected to rotary shaking (Remi Ltd.) for 24 hrs at 200 rpm. The saturation is confirmed by observation of the presence of un-dissolved material. The samples were kept with occasional shaking at equilibrium for a period of 24 hrs in incubator [19] at 37± 0.5^0C. The supernatant collected from vials was filtered through Whatman filter paper after filtration a sample for analysis can be taken and analyzed by UV-Visible spectrophotometer (Shimadzu) at respective wavelength. The shake-flask method is the most accurate method to determine solubility but it is time consuming.

Drug Co-former compatibility study

The FTIR method was used to know the physiochemical interaction between drug and excipient. The ratio of drug and excipient taken is 1:5 [20] and placed in a vial and rubber stopper was placed on the vial and sealed properly for 6 month at 40^0C±2^0C/75%RH±5%RH. After storage the FTIR studies were carried out to know the physiochemical interaction between drug and exciepient.

Formulation of Cocrystal tablet:

Various formulations were prepared by direct compression method. 22 mesh sieve used for granulation. Drug, polymer and low-density copolymer were mixed thoroughly according to required quantity [23]. Talc and magnesium stearate were added as a glident and lubricant respectively. By the using of multipunch tablet compression machine (Cadmach, Ahmedabad, India) blend was compressed (12 mm diameter, flat punches) & 80 mg of Amiodarone HCl present in each tablet & other excipient as listed in table.

Ingredients	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**
Amiodarone HCl:Urea Cocrystal	80	80	80	80	80	80	80	80
HPMC K-100 M	80	70	60	50	-	-	-	-
Microcrystalline cellulose	-	-	-	-	80	70	60	50
Lactose Anhydrous	20	30	40	50	-	-	-	-
Mannitol	-	-	-	-	20	30	40	50
Magnesium Stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Starch Past	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Table 2: Drug and Polymer concentration of formulation F-1 to F-8
***Quantities are in milligram**

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Evaluation of Amiodarone HCl Co-crystals powder blends (pre-compression parameters) [24]:

Angle of Repose

Angle of repose is angle made by the surface of pile of powder to the horizontal surface. It is micrometric parameter related to interparticulate friction or resistance to flow. The angle of repose of powder was determined by the funnel method. The lower tip of funnel was kept at 2.5 cm from the surface of table. 15 gm weighed powder were taken in a funnel. The funnel height was adjusted and the powder was allowed to flow freely through funnel onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Tan θ=h/r, Where θ = angle of repose, h = height of the cone, r = radius of the cone base.

Bilk Density

Bulk density or poured density is the ratio of the mass to volume of poured and an untapped powder sample considering the contribution of the interparticulate void volume. It is determined by pouring an API sample of known mass into a graduated cylinder/flask, and the volume occupied by the sample is noted for calculating ratio. A quantity of 10 g of powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 50 ml measuring cylinder. The bulk volume and mass of the powder was determined. The bulk density was calculated using following formula:

Bulk density= Weight of granules/ Volume of granules

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume occupied in the cylinder and the mass of the blend was measured. The tapped density was calculated using the following formula:

Tapped density= Weight of granules/ Volume of granules after 100 tapping.

Carrs Index

The Carr‟s index has been projected as a roundabout assessment parameter of bulk density, size, shape, surface area, moisture content, and cohesiveness of materials as these factors can potentially affect the flow property. The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by Carr¡¦s index which is calculated as follows;

Carr's index (%) = Tapped Density – Bulk Density/Tapped Density X 100

Where, BD = Bulk density and TD = Tapped density

Hausners ratio

It is the ratio of tapped density to the bulk density. It suggests the flow behavior of the powder blend. Less than 1.25 Hausners ratio value is indicates good flow and greater than 1.5 Hausners ratio value indicates poor flow property which was calculated by using following formula:

Hausnre's ratio = Tapped density/ Bulk density

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Evaluation of Amiodarone HCl Co-Crystals Tablets (Post Compression Parameters) [21 25]:
The tablets of every batch after punching were evaluated for in-process and finished product quality control tests i.e. thickness, hardness, friability, weight variation, disintegration time and in- vitro dissolution studies.

Weight variation
20 Tablets of each formulation batch were randomly selected and weighed individually using an electronic balance. The average weight of 20 tablets was calculated and individual tablet weight was then compared with average value and the deviation was recorded.

Friability test
The friability of tablets was determined using Roche Friabilator. It is express in percentage (%). Ten tablets were initially weighed and revolved at 25 rpm for 4 min. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated.

Hardness
The hardness was measured using pfizer hardness tester in triplicate.

Thickness
The thickness of tablet was determined by Vernier caliper in triplicate and average values were calculated.

Drug content
10 Tablets from each batch formulation were weighed and crushed to make powder in mortar-pestle. Quantity of powder equivalent to 100 mg of Amiodarone HCl was weighed and taken in 200 ml volumetric flask and make up the volume 200 ml with 0.1 N HCl. It was then shaken vigorously on a Magnetic stirrer for 5 min and filtered by using Whatman filter paper. Further appropriate dilutions were made and absorbance was measured at 242 nm.

Disintegration time
Disintegration test was performed to know the disintegration time of tablet. Disintegration test apparatus contain 6 perforated basket tube. One tablet was placed in each tube and the basket rack was positioned in a 1-L beaker of water at 37 ± 2 ℃, such that the tablet remain 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. 900 ml of 0.1 N HCl was used as disintegration medium. 6 tablets of each formulation were used and the disintegration test was performed.

***In-vitro* dissolution study**
In vitro drug release of all formulations was carried out using USP-type II dissolution apparatus (paddle type) [18, 23]. 0.1 N HCl used as dissolution medium, 900 ml of 0.1 N HCl was placed into the dissolution flask maintaining the temperature at$37^0 \pm 0.50^0$C and speed of 80 rpm. Aliquot was taken at intervals of 1 hour, 2 hour, 3 hour, 4 hour, 5 hour and so on until the drug is release. After collecting the sample, the dissolution medium was repleased with the same volume of fresh medium to maintain the sink condition, and the sample was filtered. 1ml of the filtrate was suitable diluted with 0.1 N HCl and analyzed using UV spectrophotometer at 242 nm [19,25].

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Stability Study of Optimized Formulation

The stability study was carried out for optimized formulation as per ICH guidelines. The tablets of the batch were placed in screw capped glass container and stored at 40ºC ± 2ºC (75% ± 5%RH) ICH storage condition. For a period of 6Month the samples were further analyzed for physical appearance and the drug content. After 6 month calculated the drug dissolution profile.

Study	Storage condition	Time period
Long term	25^0C±2^0C/60%RH±5RH	12 month
Intermediate	30^0C±2^0C/65%RH±5%RH	6 month
Accelerated	40^0C±2^0C/75%RH±5%RH	6 month

Table 6.6 ICH guidelines for stability study

RESULT AND DISCUSSION:

Standard Calibration Curtve (CC) of AmiodaroneHydrochloride in 0.1 N HCl:

Stock solution of amiodarone Hydrochloride was prepared in 0.1 N HCl and Shimadzu UV-1601 UV/Vis double beam spectrophotometer was used for absorption measure (λ_{max}). λ_{max} of amiodarone Hydrochloride was found to be 242 nm.

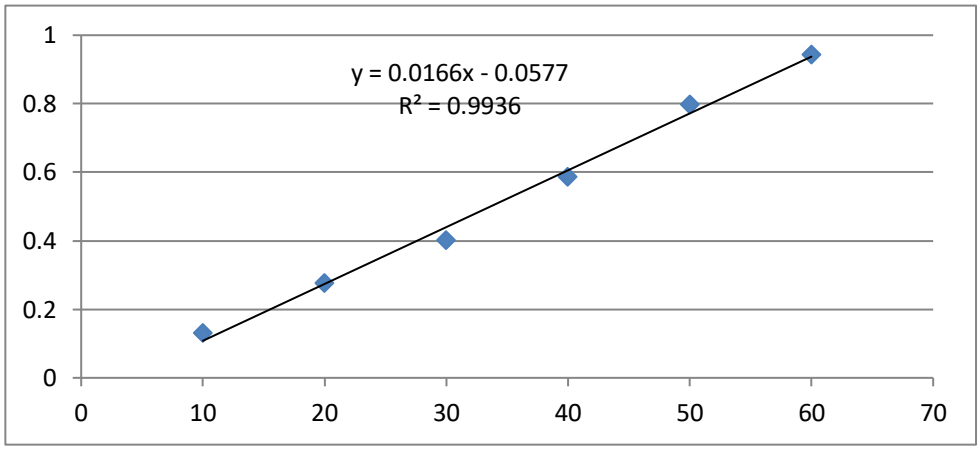

Fig 1: Drug calibration curve in 0.1N HCl

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1	10	0.132	0.130	0.132	0.132
2	20	0.276	0.278	0.276	0.276
3	30	0.402	0.404	0.402	0.402
4	40	0.584	0.586	0.586	0.586
5	50	0.798	0.799	0.798	0.798
6	60	0.943	0.946	0.943	0.943
Correlation Co-efficient (R^2) = 0.9936 Absorbance(y) = 0.0166x - 0.0577					

Table 2: Standard CC of Amiodarone Hydrochloride in 0.1 N HCl

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Melting point:

The average melting point of pure drug is 156^0C which is complies with Stander melting point of drug. The result of melting point study shows that drug melting point is not affected by co former.

Drug co-former compatibility study:

Table 3: Physical observation after Six month

S. No.	Additives (50 mg each) with drug	Physical Observation	Observation at 45^0C after 6 month	Remarks
1.	Drug (Amiodarone Hydrochloride)	White	No change	Accepted
2.	Drug + Microcrystalline cellulose	White	No change	Accepted
3.	Drug + HPMC K-100 M	White	No change	Accepted
4.	Drug + Talc	White	No change	Accepted
5	Drug + all excipient	White	No change	Accepted

Solubility Studies of co-crystal:

The solubility study of pure drug is found to be 1.353 mg/L. The solubility study of Amiodarone Hydrochloride co-crystal was also carried out and the solubility of Co crystal was found to be13.137 mg/L. So the result of solubility was revealed that the aqueous solubility of drug was increase in Co-crystal form.

Pre compress parameter:

Table 4: Observation for Pre-compression parameter

S. No	Parameters	Values obtained
1.	Bulk density (gm/ml)	0.425± 0.005
2.	Tap density (gm/ml)	0.532±0.008
1.	Angle of repose (θ)	26º45'±0.132
4.	Carr's index	13.34 ± 0.23
5.	Hausner's ratio	1.17 ± 0.005

Table 5: Physical Characteristics of powder blend

Formulation code	Angle of Repose(º)	Bulk density	Tap density	Hausner ratio	Carr's Index
F1	21 º23 ± 0.4637	0.315 ± 0.012	0.439± 0.003	1.15± 0.004	14.18± 0.483
F2	20 º 25 ± 0.4983	0.332 ± 0.016	0.418± 0.002	1.16± 0.003	13.60± 0.379

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F3	20 º 16 ± 0.4327	0.349 ± 0.018	0.411± 0.003	1.17± 0.001	14.25± 0.412
F4	21 º 11 ± 0.3125	0.364 ± 0.013	0.441± 0.001	1.16± 0.004	14.48± 0.226
F5	22 º 10 ± 0.7834	0.347 ± 0.012	0.437± 0.005	1.15± 0.005	13.72± 0.318
F6	21^{0o} 21 ± 0.6319	0.392 ± 0.014	0.421± 0.004	1.16± 0.007	14.71± 0.465
F7	20 º 25 ± 0.6392	0.317 ± 0.011	0.435± 0.007	1.17± 0.002	12.85± 0.512
F8	21º 24 ± 0.4893	0.364 ± 0.012	0.412± 0.006	1.18± 0.003	15.61± 0.635

The pre compress parameter result showed that powder blend of all formulations was good flow properties.

Post compress parameter

Table 6: Post Compression Parameter

Formulation code	**weight variation (mg) ± S.D**	**Hardness (Kg/cm^2) ± S.D**	**Friability (%) ± S.D**	**Thickness (mm) ± S.D**
F1	199 ± 1.01	5.1 ± 0.211	0.31± 0.03	2.30±0.011
F2	198 ± 1.03	5.3 ± 0.216	0.33 ± 0.04	2.23±0.014
F3	200± 1.05	5.4 ± 0.327	0.32± 0.02	2.21±0.012
F4	201 ± 1.25	5.1 ± 0.128	0.34± 0.06	2.31±0.018
F5	202± 1.45	5.5 ± 0152	0.32± 0.03	2.33±0.015
F6	202 ± 1.52	6.3 ± 0.427	0.37± 0.02	2.32±0.017
F7	199 ± 1.36	5.8 ± 0.382	0.31± 0.09	2.18±0.011
F8	201± 1.19	5.4 ± 0.417	0.33± 0.10	2.28±0.019

Values mentioned are average range of 3 determinations

The thickness was found in the range of 2.21±0.012 to 2.33±0.015. Weight variation was found within the limit as per I.P in each formulation. Mostly, the variation was within ± 4%. The hardness was found in the range of 5.1-6.3 kg / cm^2. All the formulations exhibited less than 1% friability.

Drug content:

Table 7: Drug Content of formulation

Formulation	**Drug Content (%)**
F1	91.63
F2	93.39
F3	91.94
F4	94.29
F5	96.32
F6	97.89
F7	96.33
F8	94.02

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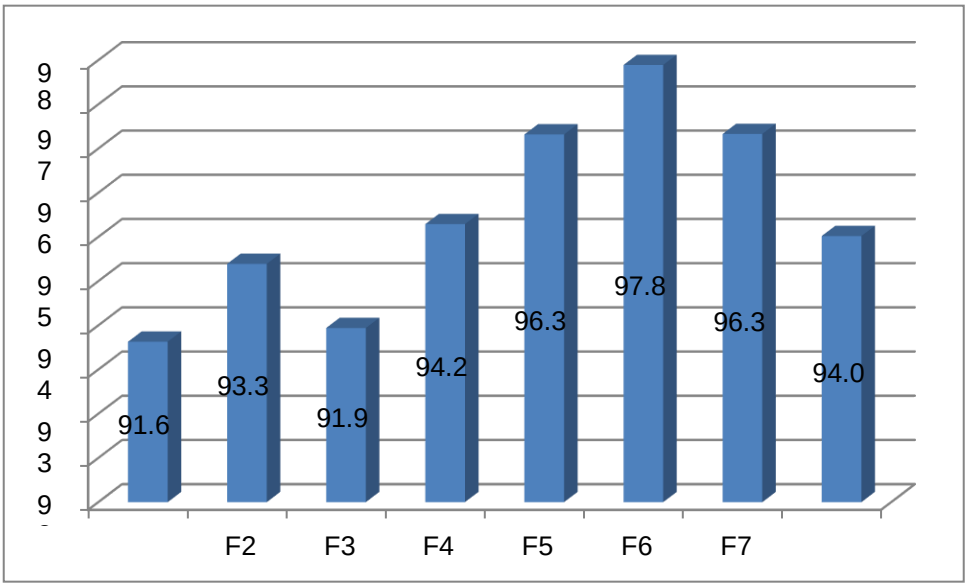

Fig. 2: Drug Content of formulationF-1 toF-8

The drug content study of the prepared formulation have shown that the process used to prepared the Tabletin this research work was capable of giving dosage form with uniform drug content. The result of drug content indicates that drug is uniformly distributed in formulation.

Disintegration time:

Table 8: Disintegration time

Formulation	Disintegration time (Minute)
F1	11
F2	14
F3	16
F4	13
F5	11
F6	15
F7	18
F8	14

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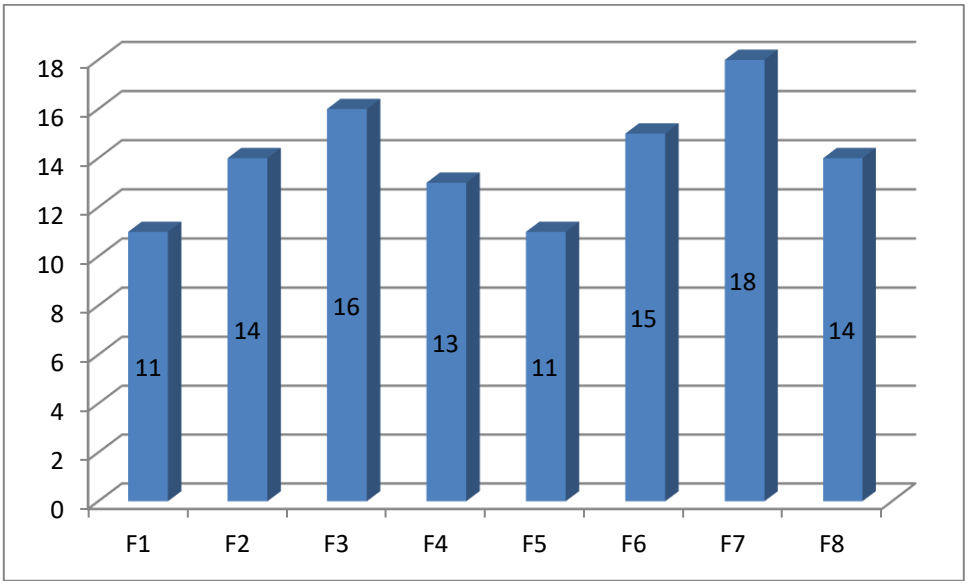

Fig. 3: Disintegration time

Disintegration time Result of different formulation complies with I.P.

***In-Vitro* dissolution studies:**

Table 9: Cumulative Drug release (F-1 to F-4)

Time (hr)	F-1	F-2	F-3	F-4
0	0.0	0.0	0.0	0.0
1	5.83	6.02	5.11	7.29
2	11.22	13.48	12.22	14.99
3	17.16	19.34	18.22	20.87
4	23.54	25.83	24.37	25.13
5	28.94	30.24	29.75	31.48
6	35.21	35.99	34.63	36.19
7	41.14	43.48	42.11	44.03
8	48.61	50.82	49.43	51.16
9	53.12	55.57	54.68	56.32
10	59.71	61.63	60.51	62.37
11	64.32	65.72	64.72	66.17
12	69.52	70.96	69.62	71.42
13	75.82	76.38	75.15	77.14
14	80.43	82.83	81.37	83.28
15	86.13	88.46	87.01	89.23
16	91.52	93.25	91.89	94.15
17	91.63	93.39	91.94	94.29

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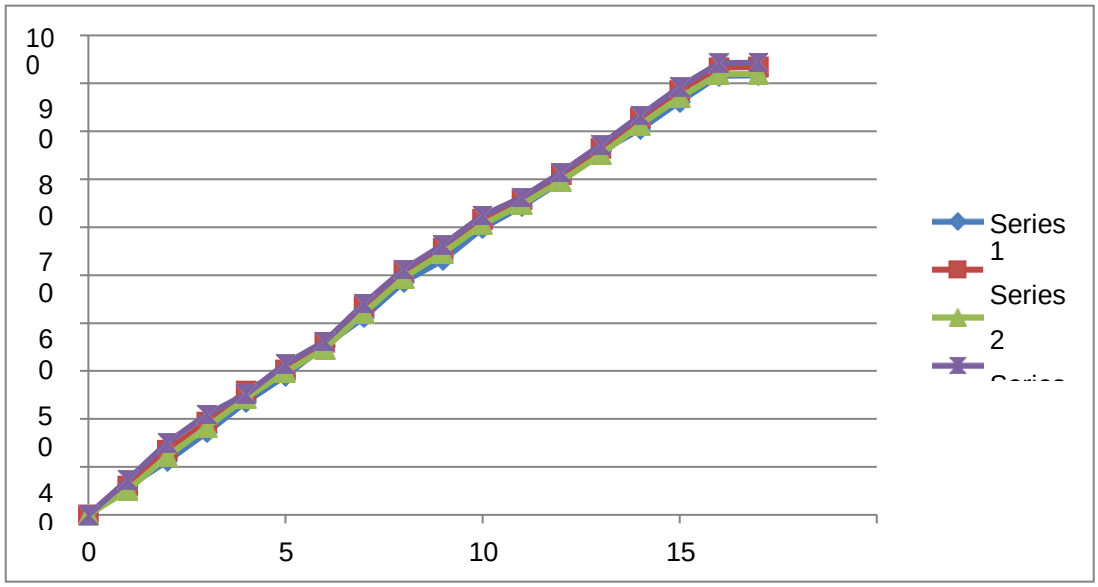

Fig. 4: Cumulative Drug release % (F-1 to F-4)

Table10: Cumulative Drug release (F-5 to F-8)

Time (hr)	F-5	F-6	F-7	F-8
0	0.0	0.0	0.0	0.0
1	5.22	5.99	5.11	4.85
2	7.33	8.04	7.26	6.94
3	10.21	11.48	10.18	9.84
4	15.36	16.83	15.31	14.83
5	21.45	22.63	21.36	20.33
6	27.82	28.62	27.17	26.31
7	33.28	34.69	33.25	32.74
8	38.24	39.73	38.19	37.53
9	46.82	47.94	46.63	45.21
10	53.27	55.30	53.14	52.64
11	59.31	61.27	59.16	58.83
12	67.37	68.42	66.27	65.14
13	75.48	77.73	74.29	73.53
14	82.73	83.94	81.64	80.38
15	88.91	91.15	87.69	85.99
16	96.14	97.65	96.21	93.99
17	96.32	97.89	96.33	94.02

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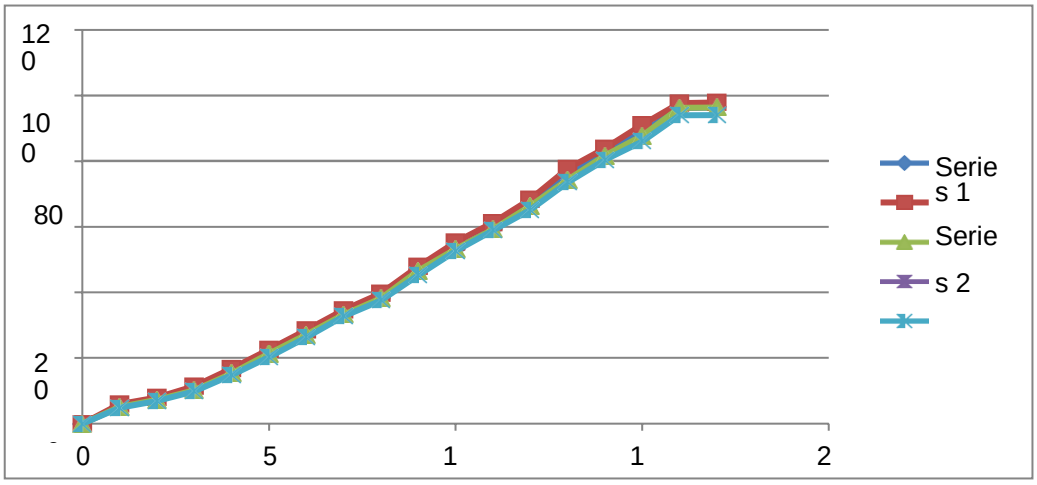

Fig. 5: Cumulative Drug release % (F-5 to F-8)

Maximum percentage of drug release (i.e. 97.89 %) was observed with formulation F-6 and the minimum (i.e. 91.63 %) was found with formulation F-1. So based on *in-vitro*dissolution studies formulation F-6 was used as optimized formulation and used for further studies.

Stability studies of optimized formulation (F-6)

Table 11: Accelerated stability studies Drug release Comparison

Time (hr)	Cumulative drug release %	
	Initial	After 6 Month
0	0.0	0.0
1	5.13	5.03
2	8.93	7.83
3	15.39	13.11
4	20.32	18.64
5	27.53	25.01
6	34.32	32.04
7	40.93	38.27
8	47.83	45.28
9	53.28	51.38
10	59.34	57.76
11	65.95	64.01
12	73.39	72.04
13	79.98	78.93
14	86.36	84.48
15	91.26	89.93
16	97.63	95.73
17	97.89	95.84

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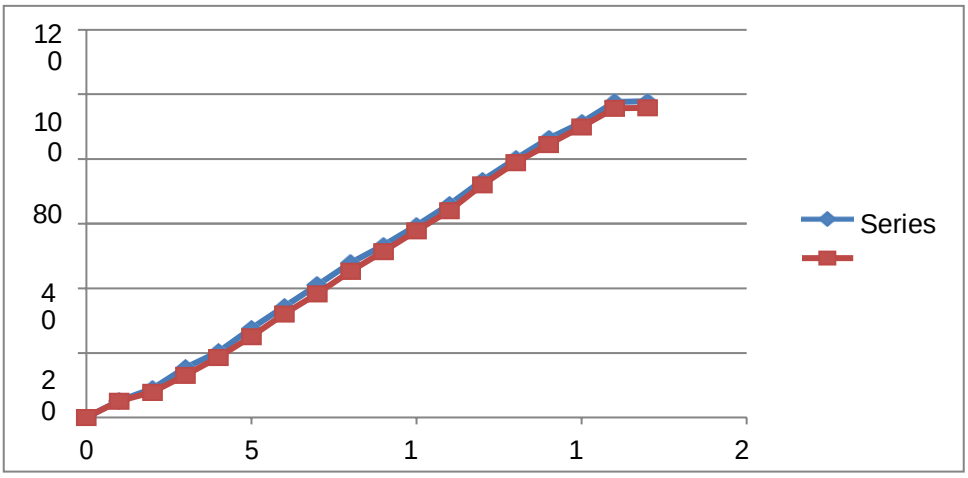

Fig. 6: Accelerated stability studies Drug release Comparison

Comaprisionwith Market Product of AmiodaroneHydrochloride Drugs:

Brand names: Diovan

Strength: (80 mg**)**

Mfg by: Novartis (India)

Dosage form: Tablet

Table 12: Comparison of prepared tablet with marketed formulation

Time in hours	**F-6**	**Marketed Formulation**
0	0.0	0.0
1	5.99	4.26
2	8.04	7.24
3	11.48	9.32
4	16.83	14.14
5	22.63	20.26
6	28.62	26.42
7	34.69	32.83
8	39.73	37.38
9	47.94	45.26
10	55.30	53.38
11	61.27	59.17
12	68.42	65.99
13	77.73	65.37
14	83.94	81.25
15	91.15	85.43
16	97.65	91.93
17	97.89	92.31

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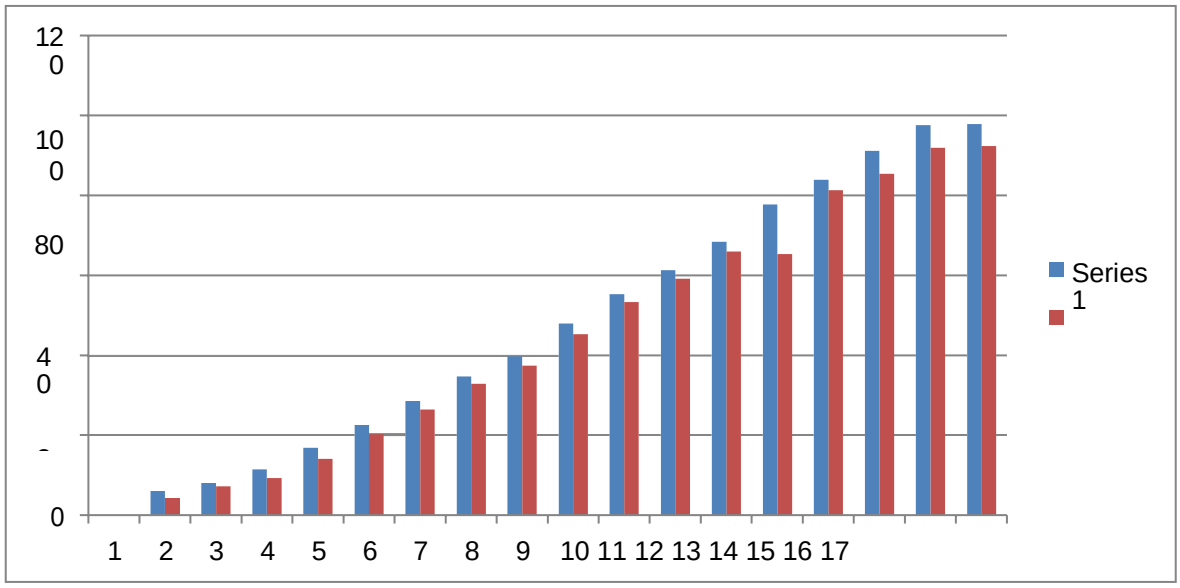

Fig. 7: Prepared tablet Comparison with marketed formulation

Table 13: comparison of prepared tablet with marketed formulation

Particulars	**A_a**	**A_b**	**A_c**	**Inhibition (%)**
Marketed formulation of AmiodaroneHydrochloride (Diovan)	0.284	0.223	0.201	61.37
Co-crystal formulation of Amiodarone Hydrochloride	0.473	0.392	0.324	81.04

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CONCLUSION:

The average melting point of pure drug is 156^0C which is complies with Stander melting point of drug. The solubility study of pure drug is found to be 1.353 mg/L The solubility study of amiodarone hydrochloride cocrystal was also carried out and the solubility of Co crystal was found to be13.137 mg/L. So the result of solubility was revealed that the aqueous solubility of drug was increase in Cocrystal form. The pre compress parameter result showed that powder blend of all formulations was good flow properties. The thickness was found in the range of 2.18 ± 0.011 to 2.33±0.015. Weight variation was found within the limit as per I.P in each formulation. Mostly, the variation was within ± 4%. The different formulations hardness were found in range of 5.1-6.3 kg / cm^2. All the formulations exhibited less than 1% friability. Disintegration time Result of different formulation complies with I.P was 11 minutes. Maximum percentage of drug release (i.e.97.89%) was observed with formulation F-6 and the minimum (i.e. 91.63%) was found with formulation F-1. So based on *in-vitro* dissolution studies formulation F-6 was used as optimized formulation and used for further studies.

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