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FORMULATION AND EVALUATION OF SOLID DISPERSION BASED FAST DISSOLVING TABLET OF AMIODARONE

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Abstract

Fast-dissolving drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Fast-dissolving drug delivery systems may offer a solution for these problems. Fast-dissolving tablets are intended and designed to disintegrate and dissolve in saliva and then easily swallowed without need of water, which is a major benefit over conventional dosage form. Various excipients are employed in the formulation for example superdisintegrants such as crospovidone (CP), sodium starch glycolate (SSG), croscarmellose sodium and PVP as binder and many more. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology. Thus, in near future, it is expected that this delivery system will get much importance as that of conventional delivery systems.

Prepare solid dispersion consisting of Amiodarone, carriers by employing different methods. Study the physico-chemical characterization, preparation method on dissolution characteristics, and investigate the influence of polymers and drug-carrier ratio on drug Release characteristics, select the optimized batch amongst the batches that exhibit good dissolution profiles. To formulate fast dissolving tablets of solid dispersion for optimized formulation using super disintegrants and evaluate the physical characteristics like weight uniformity, thickness, hardness and drug content of the formulations.To perform accelerated stability study for the selected formulation as per ICH guidelines.

Key Words:

Chemical sensors, drug delivery, fast are dissolving tablet, Novel dosage forms, and Oral delivery.

Introduction

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is t+he most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly, patient compliance. Also solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipients and equipments choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in the drug discovery such as genomics. Injections generally are not favoured for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generate predominantly chemical entities with low molecular weights.

Fast- Dissolving Tablets

Fast-disintegrating and fast-dissolving tablets are becoming popular as novel delivery systems for drug administration. They are more convenient for children, elderly patients, patients with swallowing difficulties, and in the absence of potable liquids. The most desirable formulation for use by the elderly is one that is easy to swallow easy to handle. Taking these requirements into consideration, attempts have been made to develop a fast-disintegrating tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various types of fast-disintegrating dosage forms.[15,16]

Advantage of fast disintegrating drug delivery system (FDDS):[15,16]

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients, mentally ill, disabled and uncooperative.
- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage from, which is highly convenient feature for patients who are traveling and do not have immediate access to water.

- Good mouth feel property of FDDS helps to change the basic view of medication as "bitter pill", particularly for pediatric patients.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Rapid dissolution of drug and absorption, which may produce rapid onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

Limitations of FDDS: [15, 16]

The tablets usually have insufficient mechanical strength. Hence, careful handling is required, and may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

Disintegration Mechanisms: [20,1]

The materials used as disintegrants include starches, agar, amylose, cellulose and its derivatives, gum and its derivatives, gelatin, resins, and silicone compounds. A few mechanisms of action of disintegrants have been proposed. The first mechanism is evolution of gas from an effervescent couple, e.g., sodium bicarbonate with citric acid upon absorption of water. The expansion of gas can be enough to cause the tablet to disintegrate.

Definition of solid dispersions

Solid dispersion Is " the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting- solvent method"

Materials and Methods

Materials

Amiodarone was procured as a gift sample from Chandra lab hydrabad , Sperdisintegrating agent was procured as a gift sample from ESSEL fine chem. Mumbai, monnitol, poly thylene lycol6000 , urea, crospovidone, micro crystalline cellulose, cros carmellose sodium, Magnesium stearate comphore , methenal fromS.D. fine chem., Mumbai. All other materials were of analytical reagent grade.

Preparation of solid dispersions of Amiodarone

Solid dispersions were prepared by different methods like solvent evaporation and fusion method

Solvent evaporation method: Amiodorone and each of water soluble carrier PEG 6000, Urea and Mannitol were weighed accurately in various ratios (1:1, 1:2 and 1:3) and transferred to beaker containing sufficient quantity of acetone to dissolve. The solvent was evaporated at room temperature. The resulting solid dispersion was stored for 24 hrs in a desiccator to congeal. Finally, dispersion were passed through sieve no.85 and stored in desiccator till further use.

Fusion Method: Each of water soluble carrier PEG 6000, Urea and Mannitol were weighed accurately in various ratios (1:1, 1:2 and 1:3) and melted in a porcelain dish at 80-85ºC and to this calculated amount of Amiodorone was added with thorough mixing for 1-2 minutes followed by quick cooling. The dried mass was then pulverized by passing through sieve no.85 and stored in a dessicator until used for further studies. Solid dispersions were prepared using compositions as given in Table No.5.

Preparation of Fast Dissolving Tablets of Amiodarone Solid Dispersion by Direct Compression Method

Solid dispersion of Amiodarone: Urea (1:2 ratio) equivalent weight of drug prepared by fusion method were taken and mixed with directly compressible diluent, superdisintegrants and other excipients in a plastic container. Table No.6 gives composition of the tablet formulation. Powder blend were directly compressed using 9mm, round-shaped flat punch in a multi station tablet compression machine.

Evaluation parameters for fast dissolving tablets of Solid dispersion of amiodarone

Active pharmaceutical ingredient (API) characterization:-

Organoleptic evaluation:

These are preliminary characteristics of any substance which is useful in identification of specific material. Organoleptic Evaluation Amiodran shows White to off white powder , Solubility insoluble in water and freely soluble at phosphate buffer

PRECOMPRESSION PARAMETERS

Bulk density:

Bulk density of powdered blend was determined by pouring gently through a glass funnel into 50 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density *= weight of sample in gram /volume occupied by the sample*

Tapped density:

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.

A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and taped density is calculated using following formula.

Tapped density *= Wt. of sample in gm / Tapped volume*

Compressibility Index and Hausner ratio:

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

$$\text{Carr's index} = \frac{\text{Tapped desnity} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hauser's Ratio *= Tapped Density / Bulk Density*

Angle of Repose: (USP29-NF-24)

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane.

$$\text{Tan } \theta = h / r$$

$$\theta = \text{Tan}^{-1} h / r$$

Where, θ = angle of repose, h = height, r = radius.

A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed .Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

Post Compression Parameters

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters.

Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

Weight variation test:

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets of a sample of tablets with an upper and lower percentage limit of the observed sample average. The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Thickness and diameter: The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calipers.

Friability: Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging,

handling and shipping. It is usually measured by the use of the Roche friabilator.

Method:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ Friability} = (W_1-W_2) / W_1 \text{ X } 100$$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

IN VITRO disintegration time

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms.

Method:

The U.S.P. device to test disintegration uses 6 glass tubes that are open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets.

Disintegration time: Uncoated tablet: 5-30 minutes.

Coated tablet: 1-2 hours

IN VITRO dissolution studies

IN VITRO dissolution study was performed by using USP dissolution testing apparatus 2 (Paddle method). Weighed tablets from different batches were kept in a flask of the dissolution apparatus containing 500 ml of pH 6.8 Phosphate buffer dissolution medium maintained at 37 ± 0.5ºC and at a speed of 50 rpm. Aliquot of dissolution medium (5 ml) was withdrawn at specific time intervals and the samples were replaced with fresh dissolution medium. Aliquot were analyzed spectrophotometrically at 242 nm against Suitable blank using UV-visible spectrophotometer.

Stability studies

Stability studies were carried out according to ICH guidelines by exposing the Formulations F6 in their final packing mode to the temperature 40±2°C and relative humidity 75±5 % in programmable environmental test chamber (CHM-10S, Remi Instruments Ltd., Mumbai, India). Aliquot were withdrawn at 30 and 60 days and analyzed for change in drug content and disintegration time.

Results and Discussion

Discussion

Calibration Curve of Amiodarone

The calibration curve of Amiodarone was obtained in the range of 2 to 10 µg at the wavelength of 242 nm. It has shown good linearity with a regression coefficient of 0.9975(r^2 value).

Solid Dispersions of Amiodarone With Mannitol, Urea And PEG 6000

IN VITRO dissolution studies of Amiodarone and its solid dispersions

IN VITRO dissolution test results indicate complete dissolution of drug from all its solid dispersion within 30min figure. Among the different methods of preparation of solid dispersion, fusion method was found to be most effective. The formulation SD1H showed highest drug release within 30min.

Evaluation Parameters for Fast Dissolving Tablets of Amiodarone

Precompression Parameters

The values for angle of repose were found in the range of 32°-39°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41±0.006 to 0.721±0.007 (g/cc) and 0.483±0.01 to

0.873±0.02 (g/cc) respectively. From the result it was concluded that the powder blends had good to fair flow properties and these can be used for tablet manufacture.

Post compression Parameters

Hardness test

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 20. The results showed that the hardness of the tablets was in range of 4.4 to 4.8 Kg/cm^2.

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 20. The average weight of the tablet is approximately 300 mg; so the permissible limit is 5%. The results of the test showed that, the tablet weights were within pharmacoepial limit.

Friability

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 20. The average friability of all the formulations lies in the range of 0.25 % to 0.70 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

IN VITRO disintegration time

Tablets of each batch were evaluated for IN VITRO disintegration time and the data's were shown in the Table 20. The results showed that the disintegration time of prepared tablets were in the range of 3.22-3.58 mins. The tablets of batch F6 prepared using crospovidone which is suitable for tablet punching.

IN VITRO dissolution studies

Finally, the tablets were evaluated for IN VITRO dissolution studies in Phosphate buffer and the results were shown in the Table 21. Formulations F1 showed 63.8% of drug release with 6mg of CCS, F2 showed 59.5% of drug release with 6mg of CP, F3 which contain 15mg of CCS showed 88.7% of drug release with in 15 min, F4 showed 93.2% of drug release with 15mg of CP, F5 showed 87.8% of drug release with 15mg of CCS with camphor as sublimating agent and finally F6 showed 98.7%of drug release with 15mg of CP with camphor as sublimating agent. This result exhibit a direct relationship between concentration of super disintegrants and drug release. Among the various formulations tablets of batch F6 prepared with 15mg CP showed complete release of drug within 15 min.

Conclusion

Among the various solid dispersions prepared, the formulation SD1H i.e., the solid dispersion of Amiodorone with Urea prepared by fusion method shows faster dissolution rate it was decided to use formulations SD1H to formulate fast dissolving tablets using super disintegrants like CCS, crospovidone by direct compression technique.

The powder blend was subject to various physical characteristics tests such as bulk density, tapped density, Hausners ratio, compressibility index. The powder was compressed and the core tablets were evaluated for weight variation, hardness, thickness, disintegration time and the results were within specification.

In the formulation the best results showed was with CP 5% in formulation with 2% camphor.

List of materials.

Materials	Suppliers
Amiodorone	Provided by Chandra labs, Hyd
Mannitol	ESSEL fine chem. Mumbai
Polyethylene glycol 6000	ESSEL fine chem. Mumbai
Urea	S.D. Fine Chem. Ltd, Mumbai, India
Cross povidone	MYL CHEM Mumbai.
Micro crystalline cellulose	MYL CHEM Mumbai.
Cross caramellose sodium	MYL CHEM Mumbai.
Magnesium stearate	S.D. Fine Chem. Ltd, Mumbai, India
Camphor	S.D. Fine Chem. Ltd, Mumbai, India
Menthol	S.D. Fine Chem. Ltd, Mumbai, India

List of equipments.

Equipments	Model /Company
Electronic balance	Citizen, India
Tablet compression machine	Cadmach single punch machine
Hardness tester	Monsanto hardness tester
Dissolution test apparatus	Lab India
Disintegration test apparatus	Campbell Electronics
Friability test apparatus	Riche Rich
U.V visible spectrophotometer	Shimadzu UV-1601, Japan
Fourier transformer infrared spectrophotometer	Bruker (Tensor 27)
pH meter	Citizen, India

Composition of Amiodarone solid dispersions.

Solid dispersion composition	Method	Drug-Polymer ratio	Formulation Code
Amiodarone: Mannitol	**Fusion method**	1:1	**SD1A**
		1:2	**SD1B**
		1:3	**SD1C**
	Solvent evaporation method	1:1	**SD2A**
		1:2	**SD2B**
		1:3	**SD2C**
Amiodarone: Polyethylene glycol 6000	**Fusion method**	1:1	**SD1D**
		1:2	**SD1E**
		1:3	**SD1F**
	Solvent evaporation method	1:1	**SD2D**
		1:2	**SD2E**
		1:3	**SD2F**
Amiodorone: Urea	**Fusion method**	1:1	**SD1G**
		1:2	**SD1H**
		1:3	**SD1I**
	Solvent evaporation method	1:1	**SD2G**
		1:2	**SD2H**
		1:3	**SD2I**

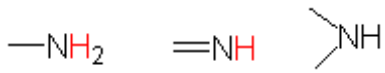
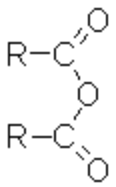
Formulation Table

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Amiodarone SD	150	150	150	150	150	150
Cross Caramellose Sodium	6	--	15	--	15	--
Cross Povidone	--	6	--	15	--	15
Micro crystalline cellulose	qs	qs	Qs	qs	qs	qs
Magnesium Stearate	6	6	6	6	6	6
Menthol	6	6	6	6	-	-
Starch	7.5	7.5	7.5	7.5	7.5	7.5
Camphor	-	-	-	-	6	6
Total weight	300	300	300	300	300	300

Standard Calibration Curve of Amiodarone

S.NO	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.144
3	4	0.351
4	6	0.521
5	8	0.739
6	10	0.894

FT-IR Spectra data of Amiodarone

Sno	Functional group	Characteristic peak cm^{-1}	Observed peak for drug cm^{-1}	Peaks for optimized formulation
1		3500 - 3300	3492.17	3497.30
2		2960 - 2850	2935.57	2935.27
3		1770 - 1710	1721.95	1721.94

Cumulative % drug release in solid dispersion containing Mannitol.

TIME (MINS)	SD1A	SD1B	SD1C	SD2A	SD2B	SD2C
5	50.12	57.19	50.12	38.41	68.7	63.8
10	63.02	69.7	65.4	48.12	72.3	68.5
15	70.29	74.8	77.6	53.7	76.6	72.2
20	75.71	80.1	87.5	60.7	82.1	78.8
30	80.15	88.15	92.17	60.7	88.30	81.8

Cumulative % drug release in solid dispersion containing PEG 6000.

TIME (Mins)	**SD1D**	**SD1E**	**SD1F**	**SD2D**	**SD2E**	**SD2F**
5	32.6	35.4	37.8	33.9	34.6	40.5
10	45.2	47.3	52.6	44.6	58.7	52.1
15	53.6	62.6	65.6	52.7	64.8	62.3
20	68.1	78.3	75.0	66.8	72.4	75.4
30	70.2	82.4	83.4	70.1	78.6	80.7

Cumulative % drug release in solid dispersion containing PEG 6000.

TIME (Mins)	**SD1D**	**SD1E**	**SD1F**	**SD2D**	**SD2E**	**SD2F**
5	32.6	35.4	37.8	33.9	34.6	40.5
10	45.2	47.3	52.6	44.6	58.7	52.1
15	53.6	62.6	65.6	52.7	64.8	62.3
20	68.1	78.3	75.0	66.8	72.4	75.4
30	70.2	82.4	83.4	70.1	78.6	80.7

Cumulative % drug release in solid dispersion containing Urea.

TIME (Mins)	**SD1G (%)**	**SD1H (%)**	**SD1I (%)**	**SD2G (%)**	**SD2H (%)**	**SD2I (%)**
5	42.3	46.0	42.5	35.5	56.8	51.4
10	52.12	59.19	51.12	40.41	70.17	65.28
15	65.02	71.7	67.4	49.12	74.23	70.25
20	73.29	84.8	75.6	55.7	77.26	75.23
30	77.71	94.1	88.5	63.7	84.13	82.58

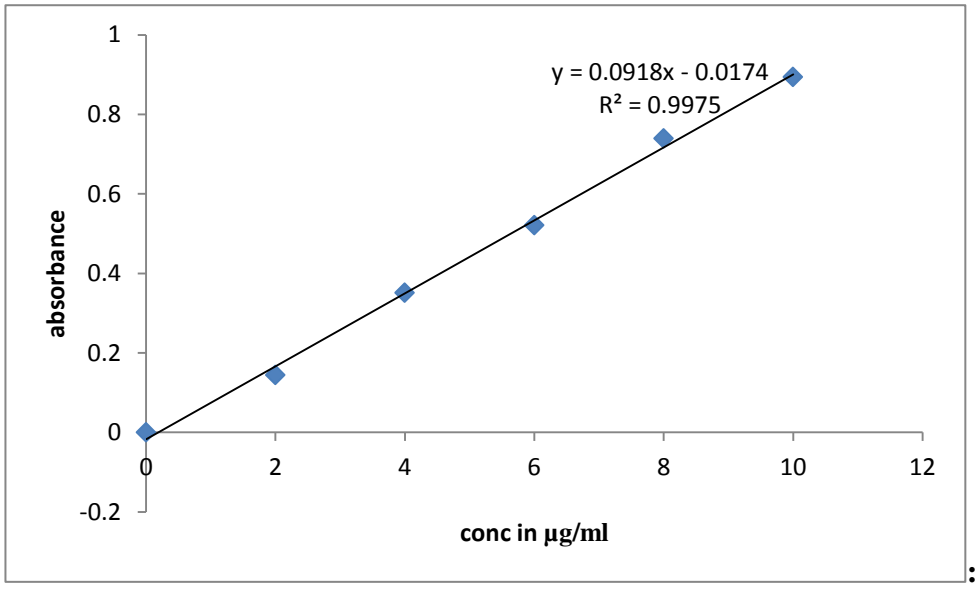
Pre-Compression Parameters

Formulation	**BulkDensity (gm/ml)**	**TappedDensity (gm/ml)**	**Carr'sIndex (%)**	**HauserRatio**	**Angle of repose**
F1	0.721	0.87	17.126	1.206	37.28^0
F2	0.461	0.608	24.177	1.32	34.21^0
F3	0.41	0.483	15.113	1.178	36.16^0
F4	0.710	0.873	19.714	1.251	39.32^0

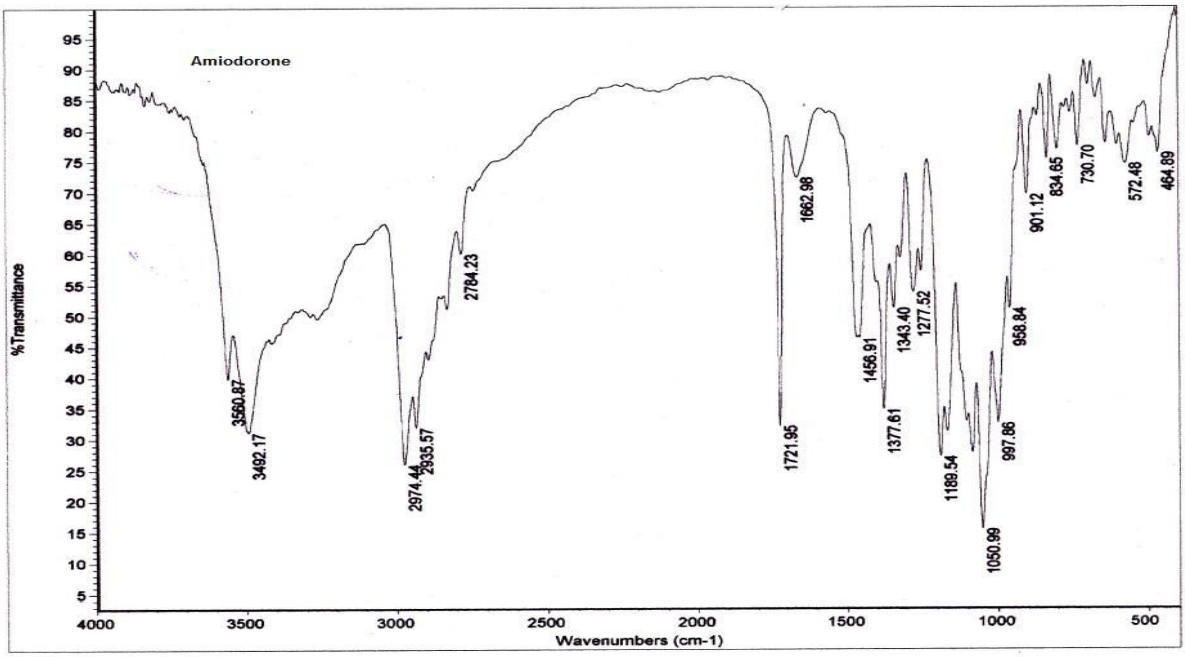
F5	0.453	0.583	22.299	1.288	32.43^0
F6	0.500	0.600	23.22	1.295	33.46^0

Stability Studies

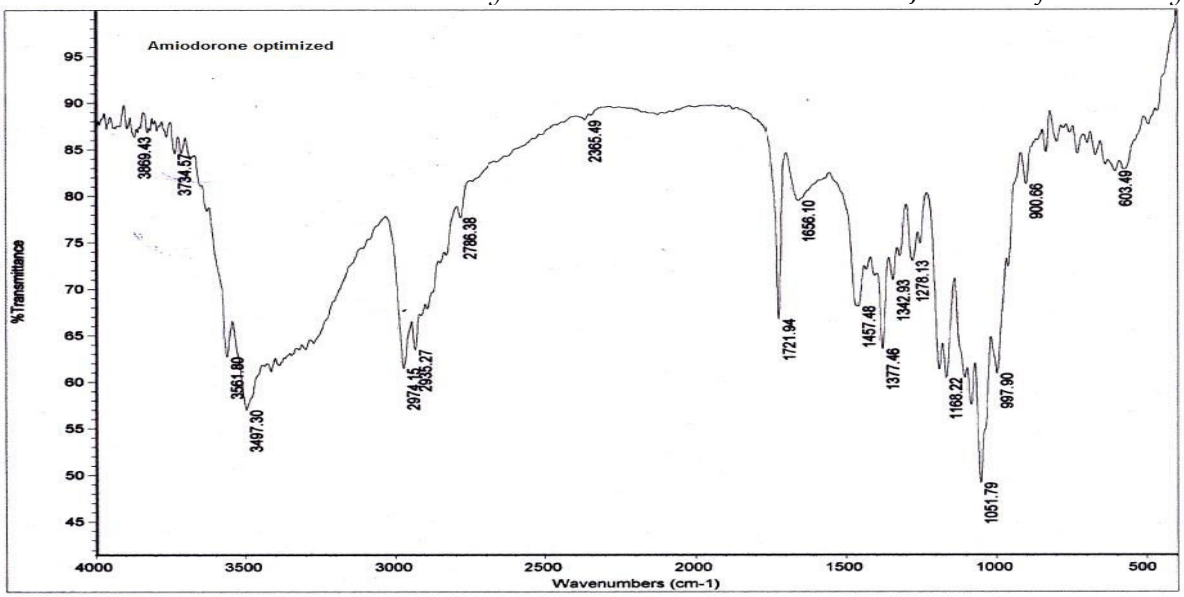
Time	Colour	Percent drug content ± St.D. at Room Temperature	Cumulative % drug release ± St. t 40^0 C 75% RH
First day	White	98	98
30 days	White	97.5	97.3
60 days	White	97.25	96.85
90 days	White	96.89	96.64



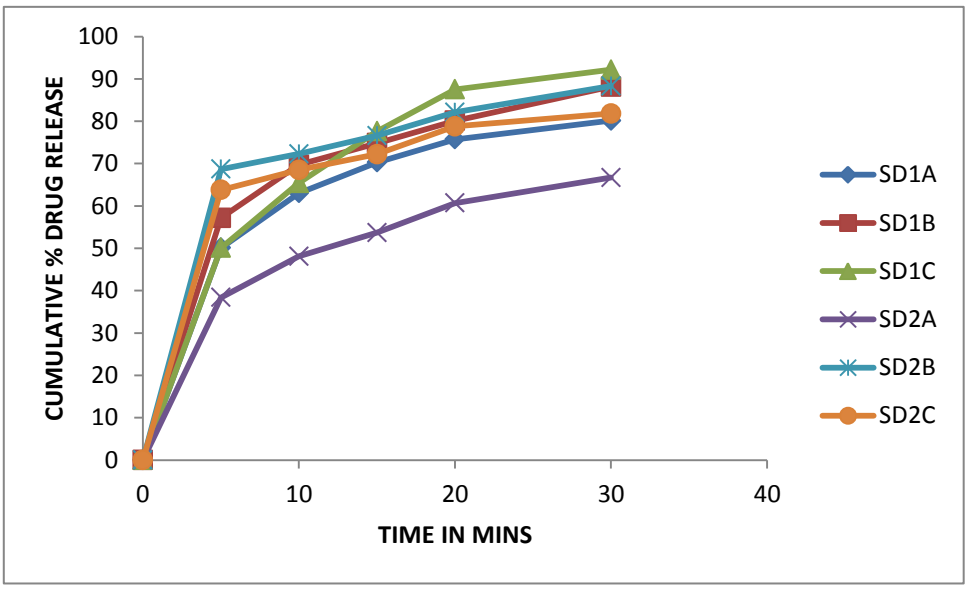
Standard calibration curve of Amiodarone.



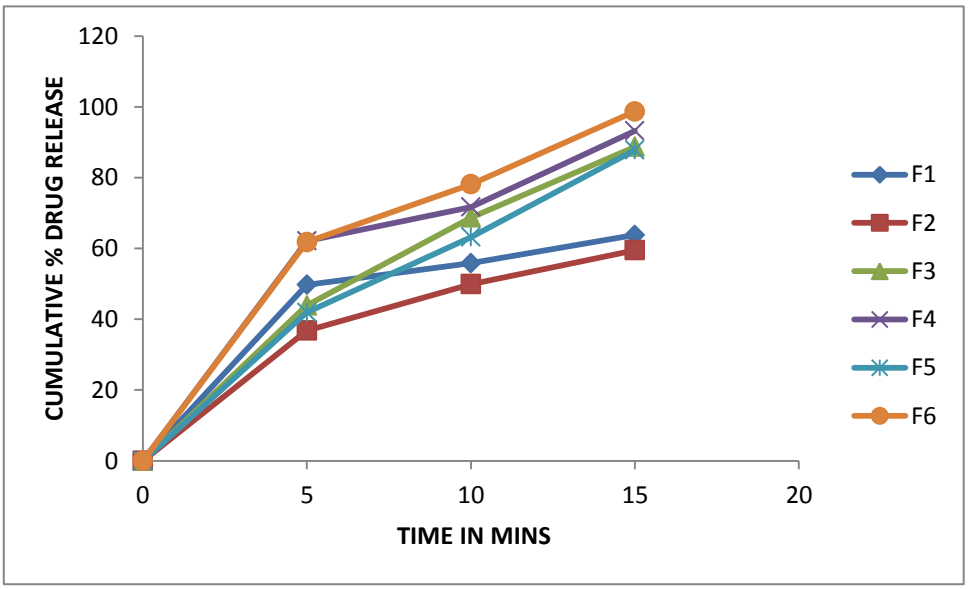
FTIR Spectra of Amiodarone.



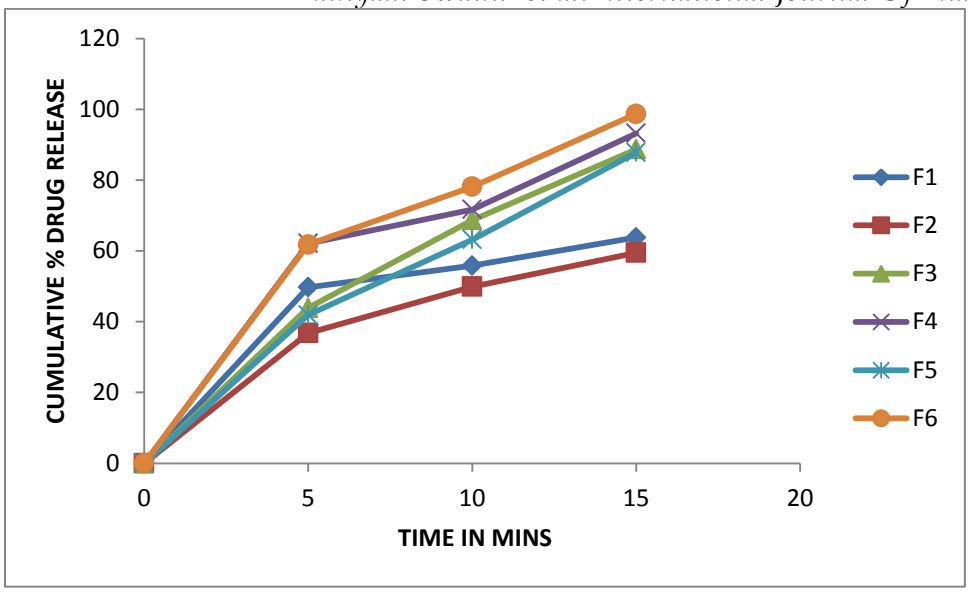
FTIR Spectra of Amiodarone optimized



Graph for in-vitro drug release for solid dispersion containing Mannitol



Graph for in-vitro drug release for solid dispersion containing PEG 6000.



Graph for in-vitro drug release.

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