e-ISSN: 2248-9126
Vol 3|Issue 1| 2013 |20-31. Print ISSN: 2248-9118

Indian Journal of Pharmaceutical Science & Research

www.ijpsrjournal.com

PREPARATION AND EVALUATION OF POROUS PELLETS LOADED WITH ANTI-ARRHYTHMIC DRUG FOR CONTROLLED RELEASE

Veena MC, Senthil Kumar SK, Parthiban S

Department of Pharmaceutics, Bharathi college of Pharmacy, Karnataka-571422.

ABSTRACT

The aim of the present study was to prepare and evaluate microporous pellets loaded with Dronedarone using blend of Avicel PH 101 (Microcrystaline cellulose) and Sodium chloride (NaCl) by Extrusion/Spheronisation technique for controlled release. Solid, porous, discrete, reproducible pellets were obtained. Sieve analysis data indicated that the size of prepared pellets were in the range of 1125 to 1265µm. The yield of pellets was upto 89%. The prepared formulations were subjected to micromeritic properties, SEM, DSC, FTIR and Stability studies. Prepared pellets were spherical in shape, have dent surfaces with pores on the surface, as evidenced by scanning electron microscopy (SEM). The pellets were free flowing with good packing properties. Compatibility of the drug after encapsulationin the pellets were confirmed by differential scanning calorimetry (DSC) and by FTIR. The prepared pellets were analyzed quantitatively for the amount of encapsulated drug. Studies such as drug loading and *in vitrodrug* release indicated F3 as optimized formulation. Formulation F3 shows 92.48% drug release upto 24 hours. It was also observed that, there was no significant release of drug in gastric pH. The release kinetics for all the formulations indicates that drug release followed non- Fickian diffusion. The stability studies performed on F3 showed no significant difference in drug content and drug release. It was concluded that the drug release performance was greatly affected by the polymer and pore forming agent used in preparation of pellets.

Keywords: Dronedarone, Pellets, Controlled release, Extrusion/Spheronisation.

INTRODUCTION

In recent years, considerable attention has been focused on the development of novel drug delivery system (NDDS). The reason for this paradigm shift is the low development cost and time required for introducing a NDDS, as compared to new chemical entity. In the form of NDDS, an existing drug molecule can get a new life, thereby increasing its market value, competitiveness, and product and product patent life. Among the various NDDS available in the market, the oral controlled release system hold a major because of their ease of administration and better patient compliance.

Development of controlled release drug delivery systems provide a uniform concentration of amount of drug at absorption site, maintained plasma concentration with a therapeutic range, minimizes the side effects and reduces the frequency of dose administration [1].

In the last decade, a considerable attention has focused on the development of novel drug delivery system because of their obvious advantages such as ease of administration, controlled release of drug at slower predetermined rate, effectiveness in the treatment at chronic conditions and better patient convenience due to simplified dosing schedule. A number of design options are available for the preparation of controlled release formulations to modify oral absorption by matrix pellet [2].

Pellets are defined as spherical, free-flowing granules with a narrow size distribution, thypically varying between 500-1500µm for pharmaceutical applications. The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously, since their multiparticulate nature offers some important pharmacological as well as technological advantages over conventional single unit

Corresponding Author:- **Veena MC** Email: veenamc234@gmail.com

solid dosage form. The uniform dispersion of a drug into the pellets reduces the risk of high drug concentration, dose dumping and irritating effects on gastric mucosa.furthermore drug absorption is maximized and peak plasma fluctuation are reduced. Spherical shape pellets exhibits a good flow property which ensures narrow sise distribution and good content uniformity [3].

Extrusion-spheronisation is the more specified term usually associated with spherical units formed by size enlargement process, that includes a spheronization step, where extrudates or agglomerated are rounded as they tumble on rotating fractional base plate. Due to spheronization, spherical particles have optimal mean size, uniform size distribution, and spherical shape when compared to granules. The spherical particals has good flowability which allows accurate capsule filling with minimal friction avoids the dust formation, variation, minimal friction avoids the dust formation, ability to withstand the mechanical stress and desired drug release can be achieved from pellets [4].

Extrusion step forms the wet mass into rod-shaped particles. The wet mass is forced through dies and shaped into small cylindrical particles having a uniform diameter. The extrudate particles break at similar lengths under their own weight. The extrudates must have enough plasticity to deform, but not so much that it adheres to other particles when collected or rolled in spheronizer. The extrudates are further subjected to spheronizer, to get and the spheroids, which are further, dried in tray or fluid bed drier. Extruder come in many varieties, but can generally be divided into three classes based on their feed mechanism. They include those that rely on a screw, gravity or a piston to feed the wet mass into the extrusion zone.

Screw feed extruders include

- Axial or end plate type
- Dome type
- Radial type
- Gravity feed extruders include
- Cylinder roll type
- Gear roll type
- Radial type [2].

MATERIALS AND METHODS

Materials

Dronedarone was gifted from Abbott, Banglore, India. Avicel PH 101 was obtained from Microlabs, Banglore, India. Sodium Chloride was obtained from Loba Chemie, Mumbai and all other chemicals used were of analytical grade.

PREPARATION OF PELLETS

The powdered MCC and Sodium Chloride were passed through a 40 mesh sieve. The powders were granulated with water to get a good dough mass of extrudable consistency. The volume of the binder required was noted and the quantity of the binder used was calculated. The wet mass was extruded in to short cylinders using a cylinder roll type gravity feed extruder with a roller speed setting of 100 rpm. A granulating cylinder with 1.0 mm pore size was used and extrudates were obtained. Spheronization of the extrudates was carried out in the spheronizer using a serrated plate. The spheronization speed was varied from 300rpm to 1500rpm and spheronization time was varied from 2 min to 20 min to get pellets of good sphericity. Drying of pellets was carried out in a tray drier.

Drug loading

Dried pellets were collected and the NaCl fraction was removed from the pellets by aqueous extraction: 30g of pellets were placed on to a 500 mL bottle top filter (membrane filter); the filter was placed on a 2-L flask and connected to a vacuum pump. An aliquot of 2 L of water was poured on to the filter in steps of 250 mL to extract the NaCl fraction. Later the pellets were oven dried at 40°C.

The drug was loaded by immersing the pellets into the drug solution. It is done by immersing 1g of pellets into the 200% in methanol solution for 24 hrs. After 24 hrs the pellets were collected and oven dried at 40°C [5].

Formulation of pellets

The optimal formula and processing conditions arrived at in some earlier experiments on the extrusion / spheronization process standardization was used as guidelines for processing. MCC and Sodium Chloride (NaCl) in different ratios were used to make pellets. Water is used as a binder. The quantity of the binder used was sufficient to maintain loss on drying [5].

Characterization of Pellets

Particle size analysis

The particle size of the prepared pelletswas measured using a Malvern Mastersizer 2000 version 5.1 (Malvern, UK.) The drug loaded Dronedarone pellets were dispersed in 1:20 with methanol and measured at temperature of 37°C [6].

Micromeritic properties

Tap densities of the prepared pellets were determined using Tap densities Tester and percentage Carr's index was calculated.

a. Angle of repose

Angle of repose was assessed to know the flowability of pellets, by a fixed funnel method. A funnel with the end of the stem cut perpendicular to its axis of symmetry was securely arranged above the graph paper of height which was placed on a flat horizontal surface. Dronedarone pellets were carefully poured through the funnel until the apex of the conical pile just reaches the tip

of the funnel. The radius (r) and height of the pile (h) were then determined. The angle of repose (θ) for samples were calculated using the formula,

$$\text{Angle of repose } (\theta) = \tan^{-1} (h / r)$$

Angle of repose represents whether the given sample was free flowing or not. The relationship between angle of repose and flowability is shown in Table 4. The mean of three determinations was used to calculate the angle of repose from each of the formulation [7].

b. Compressibility

Carr's index is a dimensionless quantity, which proved to be useful to the same degree as the angle of repose values for predicting the flow behavior. Apparent bulk density was determined by pouring the bulk samples into a graduated cylinder. Tapped density was determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapper apparatus (Electro lab tap density tester). Samples were tapped until no further reduction in volume of the sample was observed. Carr's index is calculated using the formula given below and the relationship between compressibility and flow property is shown in Table 5. The mean of three determinations was used to calculate the compressibility index from each of the formulation [8].

$$\text{Carr's index} = \frac{\text{(Tapped density – Bulk density)}}{\text{Tapped density}}$$

Scanning Electron Microscopic (SEM) studies

SEM photographs were taken with a scanning electron microscope Model Joel- LV-5600, USA, at the required magnification at room temperature. The photographs were observed for morphological characteristics and to confirm spherical nature of the pellets.

Compatibility Studies

Drug is in intimate contact with one or more excipients, which could affect the stability of the drug. The knowledge of the drug excipient interactions is essential for selecting appropriate excipients. This was studied using FT IR spectrophotometer and Differential Scanning Calorimetry (DSC) [9].

Differential Scanning Calorimetry (DSC)

DSC is a technique in which the difference in heat flow between the sample and a reference is recorded versus temperature All dynamic DSC studies were carried out on Du Pont thermal analyzer with 2010 DSC module. Calorimetric measurements were made with empty cell as the reference. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10º c/min. The runs were made in triplicate. The scanning temperature for reference pure drug and formulation are the same when dynamic measurements are performed, and hence the required heat energy for chemical transformation is directly recorded on a heat flow versus temperature graph. The energy is measured as Joules per kilocalorie [10].

Fourier Transform Infrared Spectroscopic (FT IR) studies

FTIR analysis was carried out for pure drug and for pellets with and without drug using KBr pellet method on FTIR spectrophotometer .Drug was mixed with KBr and spectra was taken. FT-IR spectrum of pure drug Dronedarone was compared with FT-IR spectra of Dronedarone formulations. Disappearance of peaks or shifting of peaks in any of the spectra was studied using the apparatus FTIR- 8400-S, Shimadzu, Japan [11].

Evaluation of Pellets

Percentage yield

Determining whether the preparation procedure chosen for incorporating a drug into the polymers is efficient and is of prime importance. The raw materials, amount of active compound, MCC, and other process parameters are deciding factors for the yield of the product during the preparation of pellets.

The yield was determined by weighing the Dronedarone pellets and then finding out the percentage yield with respect to the weight of the input materials, i.e., weight of drug and polymers used. The formula for calculation of % yield is as follows;

$$\% \text{ yield} = \frac{\text{Wt of pellets x 100}}{\text{Wt. of drug +Wt of polymers}}$$

Drug loading and encapsulation efficiency

Drug loading is important with regard to release characteristics. Generally, increased drug loading leads to an acceleration of the drug release. Drug entrapment efficiency represents the proportion of the initial amount of drug, which has been incorporated into the pellets.100 mg of Dronedarone pellets were weighed and transferred to 100 ml volumetric flask containing pH 7.4 phosphate buffers. From this, 1 ml of solution was transferred to 10 ml volumetric flask and diluted up to the mark. Further 1 ml of this solution is diluted to 10 ml and absorbance was measured at 280nm. The drug content was calculated by using the formula

$$\text{Amount of drug} = \frac{\text{Conc. from standard graph X dilution factor}}{1000}$$

Percentage encapsulation efficiency is found out by calculating the amount of drug present in 100 mg of pellets. It is further calculated by using formula

$$\% \text{ Encapsulation Efficiency} = (b)/a \text{ X } 100$$

Where, a is the theoretical drug content and b is the drug entrapped [12].

***In vitro* drug release studies**

The *in vitro* release of drug from the pellets was carried out in basket type dissolution tester USP XXIII, TDT-08L, with auto sampler containing 900 ml of pH 1.2 buffer for the first 2 hrs and in 7.4 pH phosphate buffer for the next 22 hrs. The volume of the dissolution media was maintained at 900 ml with constant stirring (100 rpm) and temperature of bath was maintained at 37 ± 0.5°C. Aliquots (10 ml) of dissolution media were sampled at specified time points and replaced with fresh media immediately after sampling. Samples were analyzed for drug content by UV Visible spectroscopy .The release data obtained were fitted into various mathematical models to know which mathematical model is best fitting for the obtained release profile. Dissolution studies were carried out for all the batches of the prepared formulations (09 batches).

Stability studies

It is necessary to perform stability testing to find out the extent of deterioration and to ensure the degradation has not exceeded an acceptable level assuring the safety of the patient and the activity of the product.

Degradation of active ingredients in pharmaceutical formulations may occur by hydrolysis, oxidation, reduction, racemization, ring cleavage, photolysis, decarboxylation and isomerization. Physical degradation of pharmaceutical products may occur due to loss of water, loss of volatile constituents, absorption of water, crystal growth, polymorphic changes and colour changes.

If pharmaceutical preparations or new formulations are stored under normal conditions, their instabilities are detectable only after long storage periods. Such a method is time consuming and uneconomical. In an attempt to reduce the time required to obtain information about instabilities, various stress tests are undertaken. The most common stress conditions used are temperature, humidity and light.

Pharmaceutical preparations may often exhibit physical or chemical reactions that may end in instability due to which the product gets deteriorated. This deterioration may lead to:

- Reduction in the activity of the product
- Formation of toxic products
- An inelegant product

Short-term stability study

Stability is defined as the ability of a particular drug or a dosage form in a specific container to remain with its physical, chemical, therapeutic and toxicological specifications.

A drug formulation is said to be stable if it fulfills the following requirements:

- It contains at least 90% of the stated active ingredient
- It contains effective concentration of the added preservatives, if any
- It does not exhibit discoloration or precipitation, nor develops foul odour
- It does not develop irritation or toxicity

Optimized formulation of the pellets was selected for stability studies Formulations were packed in a screw capped bottle and studies were carried out for 90 days by keeping at

- $25 \pm 2^{o}C$ and $60 \pm 5\%$ RH
- $30 \pm 2^{o}C$ and $65 \pm 5\%$ RH
- $40 \pm 2^{o}C$ and $75 \pm 5\%$ RH

Samples were withdrawn on 15^{th}, 45^{th} & 90^{th} day and were analyzed for drug content spectrophotometrically at 280 nm [13].

RESULTS AND DISCUSSION

Evidence has been proved in recent years MCC possess physical properties and behaviour suitable to prepare gastro resistant, biocompatible, biodegradable porous pellets to release the entrapped drug in the intestinal lumen. In the present study, extrusion/spheronization method was optimized by using MCC, NaCl to entrap the drug. The present method is quite different from other methods. Dronedarone is water insoluble drug could be entrapped into water in-soluble polymer by extrusion/spheronization method and porous pellets were prepared.

The pellets were prepared by using Avicel PH 101, as polymer and sodium chloride (NaCl), as a pore forming agent by extruder/spheronization technique. The technique was optimized using the parameters for pelletizations are shown in table 7. When the ratio of MCC was 70 % w/w produces spherical and hard pellets, suitable for pharmaceutical uses. But, when the ratio of MCC was 90 %, 80 %, 50 %, 40 %, 30 % w/w produces rod shaped, egg shaped, and semi spherical and brittle pellets respectively. These pellets are not suitable for pharmaceutical purpose. In the present study it was found that the ratio of MCC was 70 % w/w, resultant pellets did not have any surface irregularities and non-aggregated.

An attempt was made to prepare porous pellets by using 10, 20, 40, 50, 60, 70 % w/w of NaCl as a pore forming agent fail to produces the required pores in the porous pellets. The increased or decreased of NaCl responsible for shrinking of pore in the pellets. Maximum drug load was obtained, when the optimum ratio of 30 % w/w NaCl was used as pore forming agent. Produces suitable pore to entrap more amount of the drug [14-16].

In the present study, it was found that optimum spheronization speed was found to be 1250 rpm to produce spherical pellets. It was observed that with increase in stirring speed from 1250 to 1500 there was a decrease in

average size of the pellets and produces semi spherical pellets. When the stirring speed was 1000 rpm, 700 rpm and 300 rpm produces semi spherical, egg shaped and rod shaped pellets respectively. It was also found that optimum stirring time was found to be 15 min to produce spherical pellets. When the stirring time was 20 min, there was a decrease in yield and produces semi spherical pellets. When the stirring time was 10 min, 5 min and 2 min, it was observed that some amount of wetted mass adher to the spheronizer resulting in lower recovery of yield and produces semi spherical, egg shaped and rod shaped pellets respectively. Repeat batches treated at an optimized rate mentioned above proved to produce reproducible sizes, showing that spheronization speed and stirring time were well controlled. In the present study, to produce the spherical porous pellets, an optimum drug concentration was used. It was found that higher the amount of drug will show presence of crystals on surface of pellets which is determined by SEM study which were unsuitable for pharmaceutical uses.

Characterization

The characterization of pellets, micrometric properties such as particle size analysis, angle of repose, Tapped density, Granule density and carr's index were found to be within the limits. The obtained results are shown in table 3.

Scanning electron microscopy

Scanning electron microscopy (SEM) is one of the most commonly used method for characterizing drug delivery systems, owing in large part of simplicity of samples preparation and ease of operation. Scanning electron microscopy was carried out in order to characterize surface morphology, texture and porosity of the coating films. In this study the sample was prepared by placing the formulation F3 samples in pH 7.4 buffer solutions for 24 hours followed by drying the samples at 30° C for 24 hours. The samples were mounted on aluminium mount and sputtered with gold. Sample was scanned at an accelerating voltage of 20 kV. Scanning electron micrographs obtained are given in figures 1 and 2. Figure 1 shows the surface topography of the pellets, where a smooth surface can be observed with its optimal, spherical shape. SEM photographs reveal the absence of drug particles on the surface of pellets showing uniform distribution of the drug in the pellet. It also shows the approximate diameter of pellets ranging from 1.2 – 1.4 mm. A small degree of etching on the surface can be observed due to effect of the pH 7.4 phosphate buffer as a dissolution media. Figures 1 and 2 shows the SEM micrograph of porous pellets formed of formulation F3 at the resolution of 2000x. The fine pore formation of the dimensions in microns can be clearly observed.

Fourier Transform Infra Red spectrum (FT-IR)

FT IR spectra were obtained for of Dronedarone pure drug and Dronedarone loaded pellets and are presented in Figure 3,4 and 5. The following characteristic bands were observed. The characteristic peaks of the pure drug were compared with the peaks obtained for formulation F3 and are given in Table 4. From the data it is observed that a similar characteristic peak of Dronedarone and Formulation F3 was appears with minor differences. The characteristics peaks found both in pure drug of Dronedarone and formulation F3, hence it appears there is no chemical interaction between drug and polymer and it can be concluded that the characteristics bands of pure drugs were not affected after successful loading.

Differential scanning calorimetric (DSC) studies

To understand the compatible state of the drug, DSC studies were carried out on pure drug, drug loaded pellets and empty pellets. The thermograms obtained are shown in Figure 6, 7 and 8. The data obtained from the DSC scans for the Dronedarone and Dronedarone loaded pellets are given in Table 5 in terms of onset of melt (To), melting points (Tm) and completion of melt (Tc). Dronedarone exhibits a sharp endothermic peak at to 178.25^0C. It was observed that presence of the endothermic peak at to 180.02 ^{0}C in the drug loaded pellets indicated, that the drug retains its identity in the prepared pellets. The melting points of the drug and Polymers were estimated by open capillaries and found agrees well with the DSC data.

Where, T_o – Onset of melt, T_m - Melting point and T_c – Completion of melt

- Dronedarone exhibits a sharp endothermic peak at 178.25°C.
- Presence of the endothermic peak at 180.02°C in the drug loaded pellets indicated that there is no interaction between drug and polymer.

Determination of Drug Content

The prepared formulations were analyzed for drug content and the data is reported in Table 6. The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations.

Drug loading and Encapsulation efficiency

The percent of drug loading in the formulations was found to be in the range of 16.56 to 19.32 %. The percentage encapsulation efficiency was found to be 94.50 to 96.19 %. The results obtained are given in Table 7. The test for drug content was carried out to ascertain whether the drug is uniformly distributed in the formulation. The obtained results are reported in Table 7. Drug loading and entrapment efficiency increase with increase in the polymer concentration. From the results it can be inferred that there is a proper distribution of Dronedarone in the pellets and the deviation is within the acceptable limits. The decrease in the drug content in the product probably

can be due to the decrease in pore size and concentration. The bar graphs are shown in figure 9 and 10.

***In vitro* drug release**

The *in vitro* release studies were carried out for all formulations in both acidic and basic media. The *in vitro* release data for the Dronedarone formulations are given in the Table 8 and the corresponding graphs are represented in Figure 11. The release profile of pellets in both media clearly indicates that the concentration of polymers and pores formed decreases Dronedarone release from pellets. The increase in the concentration of the polymers and decrease in pore concentration decreases the drug release from the matrices, as the pore concentration and pore size increases results in immediate release of drug. It was observed that there is no significant release of drug at gastric pH from pellets. At the end of 24th, *in vitro* drug release from formulation F1 to F7 was found to be 73.35 to 92.48% in the intestinal environment as shown in the Fig11. The decrease in the drug release from the pellets was due to hydrophobicity of polymer. The release kinetics is mainly depends on the concentration of the polymers used, increase in the polymer concentration results in the controlled release of the drug from the pellets.

Stability studies

The objective of stability studies is to predict the shelf life of a product by accelerating the rate of decomposition, preferably by increasing the temperature and RH. The optimized formulation (F3) was subjected to stability studies according to ICH guidelines by storing at 25ºC/60% RH, 30ºC/65% RH and 40ºC/75% RH for 90 days. These samples were analyzed and checked for changes in physical appearance and drug content at regular intervals. The obtained data is presented in Table 9. From the Table, it is clear that the formulation did not undergo any chemical changes/interaction during the study period.

Table 1. Formulation chart for the preparation of pellets

Formulation code	MCC %	NaCl %
F1	90	10
F2	80	20
F3	70	30
F4	60	40
F5	50	50
F6	40	60
F7	30	70

Table 2. Optimization of process parameters for pelletization

Parameters	Formulation	Parametric value	Description of pellets
MCC : NaCl (w/w)	F1	90:10	Rod shape and brittle
	F2	80:20	Egg shape and brittle
	F3	70:30	Spherical and hard
	F4	60:40	Spherical and brittle
	F5	50:50	Semi spherical and brittle
	F6	40:60	Semi Spherical and hard
	F7	30:70	Spherical and brittle
Spheronization Speed (rpm)	F3	300	Rod shape
		700	Egg shape
		1000	Semi spherical
		1250	Spherical
		1500	Semi spherical
Spheronization speed (time)	F3	2	Rod shape
		5	Egg shape
		10	Semi spherical
		15	Spherical
		20	Semi spherical

Table 3. Micromeritic properties and Particle size analysis

Formulation code	Average size (μm)	Angle of repose θ^0	Tapped density (g/cm^3)	Granule density (g/cm^3)	Carr's index (%)	Friability (%)
F1	1155±0.55	25.57±0.82	0.85±0.65	1.06±0.88	9.13±0.33	0.53±0.78
F2	1185±0.46	26.39±0.15	0.87 ±0.93	1.07±1.78	8.80±0.98	0.51±0.45
F3	1241±0.25	24.58±0.78	0.91±1.42	1.05±1.45	9.42±0.52	0.42±0.82
F4	1237±0.58	26.12±0.65	0.86±1.03	1.05±0.96	8.92±0.97	0.46±0.36
F5	1215±1.04	25.35±0.46	0.84±0.51	1.04±0.72	8.78±1.74	0.46±0.78
F6	1234±0.95	25.88±0.74	0.85±0.84	1.07±0.81	8.70±2.02	0.48±0.22
F7	1218±0.37	24.76±0.45	0.84±0.61	1.08±0.18	8.81±1.14	0.56±0.91

***Standard deviation, n = 3**

Table 4. Peak positions of pure Dronedarone and formulations with intensity range:

Groups	Peak positions in pure drug(cm-1)	Peak positions in formulation (cm-1)	Intensity range (cm-1)
Aromatic C-H stretching C-C stretching	3068.85 1600.0	3057.6 1589.4	3030-3200 1620
Aliphatic---C-H stretching C-H bending	2968.55 1467.88	2972.1 1473.66	2962-2853 1485-1445
N-H stretching	3431.8	3446.91	3400
C=C Stretching aromatic	1539.25	1587.8	1450-1600

Table 5. ***DSC data obtained for Dronedarone and formulation***

SL. No.	Drug and Formulation	T_o	T_m	T_c	Melting range
1	**Dronedarone**	173.64	178.25	180.88	7.24
2	**Formulation F4**	174.35	180.02	183.12	8.92

Table 6. Result of % Yield of pellets formulations $F_{1\ to}$ F_7

Sl. No.	Formulation Code	% Yield			
		Trial I	Trial II	Trial III	Mean ± S.D*
1	F_1	88.2	88.5	88.3	88.33±0.1527
2	F_2	92.1	91.4	92.6	92.03± 0.6027
3	F_3	94.6	96.9	95.4	95.6±0.3318
4	F_4	94.8	93.9	92	93.9± 1.6462
5	F_5	92.6	94	93.1	93.21± 0.7094
6	F_6	95.9	92.8	93	93.9± 1.734
7	F_7	95.1	93.7	94	94.23± 0.737

***Standard deviation, n = 3**

Table 7. Drug loading and encapsulation efficiency of pellets

Formulation	Drug loading (%)	Encapsulation efficiency (%)
F1	16.56±0.23	94.50±0.75
F2	16.97±0.65	95.69±0.83
F3	19.32±0.44	96.19±0.33
F4	18.61±0.76	95.98±0.46
F5	18.21±0.53	95.32±0.87
F6	17.12±0.89	94.89±0.64
F7	18.11±0.43	95.10±0.11

***Standard deviation, n = 3**

Table 8. % Cumulative drug release of formulations

Time (hr)	% Cumulative drug release						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	2.48	2.85	3.01	3.59	4.32	4.58	4.79
2	4.95	7.52	7.62	7.57	7.58	8.32	8.56
3	8.56	12.48	12.84	13.25	12.38	13.48	13.81
4	12.78	16.24	17.25	19.52	19.65	19.24	20.18
6	19.26	23.7	24.25	23.15	25.24	26.48	26.14
8	25.26	32.47	32.14	29.54	34.75	32.14	32.84
10	35.28	40.25	44.15	35.25	43.14	40.28	42.81
12	45.35	49.52	52.26	45.24	52.14	51.95	50.48
16	52.15	59.25	66.47	59.24	65.28	63.14	62.48
20	68.25	72.25	81.75	72.51	76.15	73.68	72.15
24	74.58	84.39	93.48	83.16	86.31	83.63	82.73

***Standard deviation, n = 3**

Table 9. Stability studies of formulation F3

Stability condition	Sampling (in days)	Drug content (in %) Mean ± SD*
25ºC/60% RH	0	100.00 ± 0.20
	15	99.40 ± 0.48
	45	99.10 ± 0.85
	90	98.70 ± 1.17
30ºC/65% RH	0	100.00 ± 0.43
	15	99.20 ± 0.36
	45	98.40 ± 0.79
	90	98.10 ± 1.24
40ºC/75% RH	0	100.00 ± 0.52
	15	99.10 ± 1.12
	45	98.20 ± 0.72
	90	97.50 ± 0.79

* Standard Deviation, n=3

Figure 1. SEM of non porous pellet

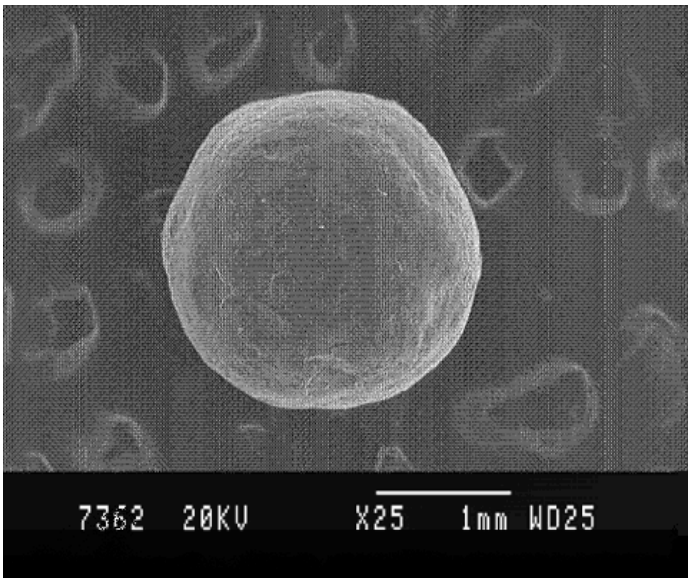


Figure 2. SEM of porous pellet (F3)

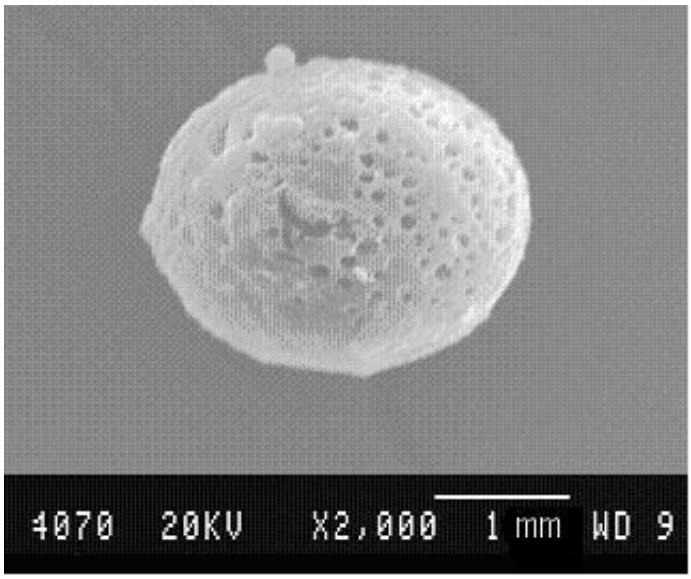


Figure 3. FT-IR of pure drug (Dronedarone)

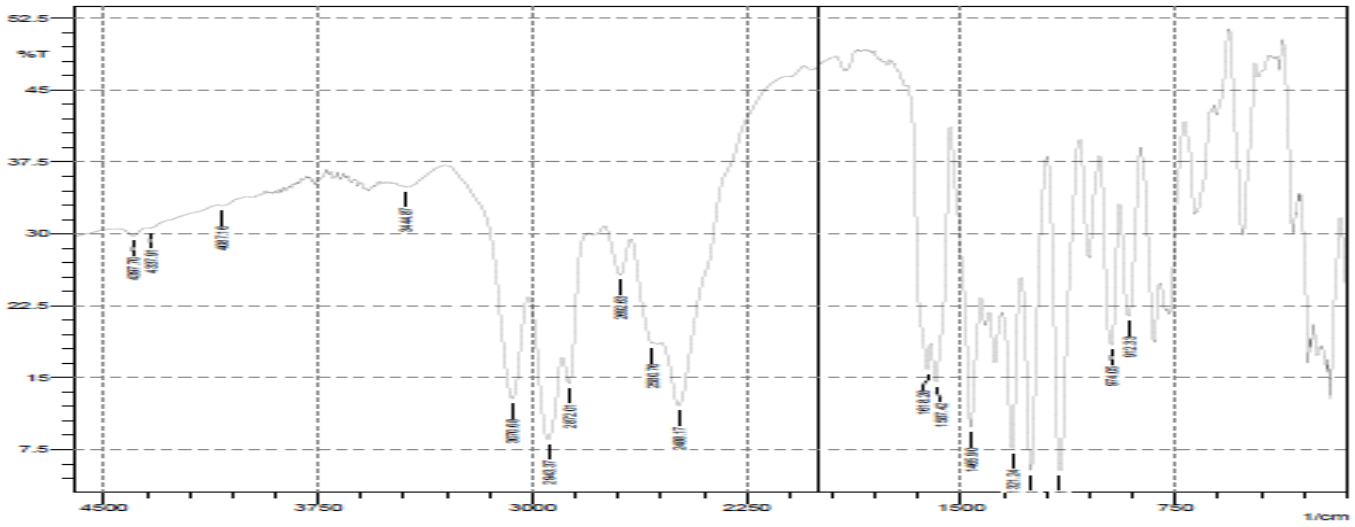


Figure 4. FT-IR of polymer (MCC)

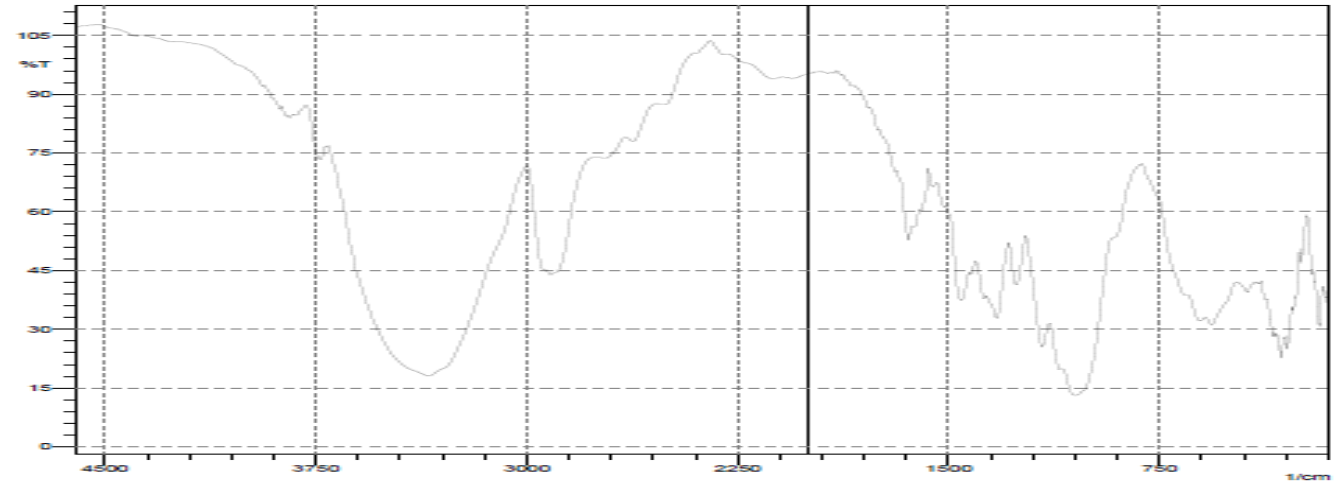


Figure 5. FT-IR of pure drug with polymer (F3)

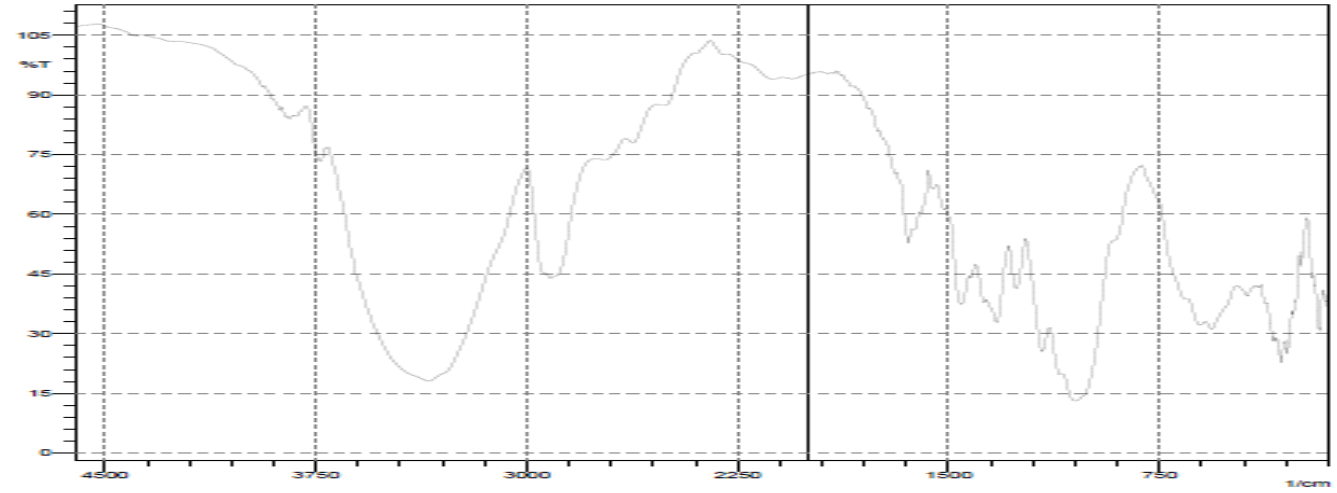


Figure 6. DSC thermogram of Dronedarone pure drug

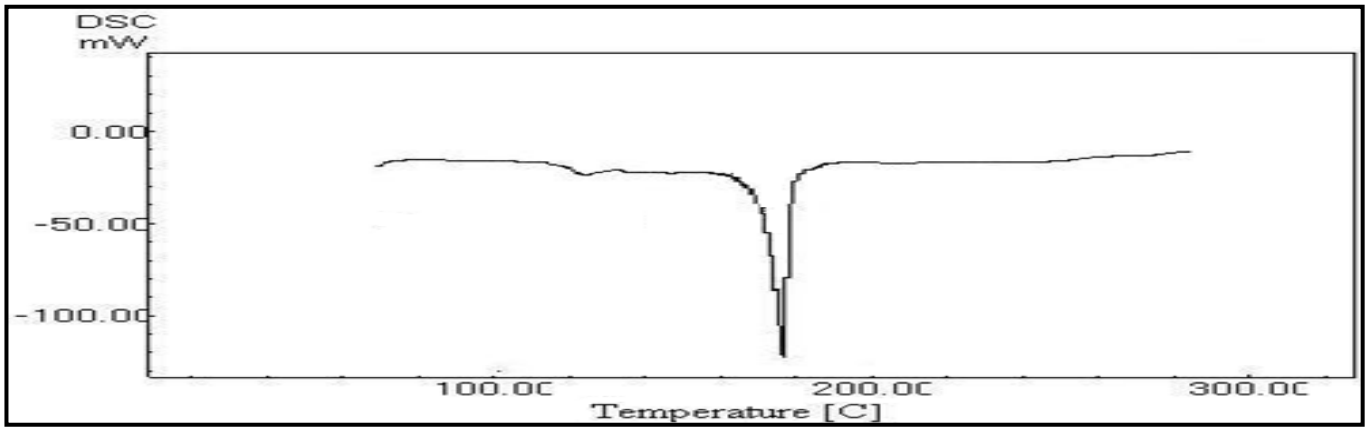


Figure 7. DSC thermogram of formulation F3

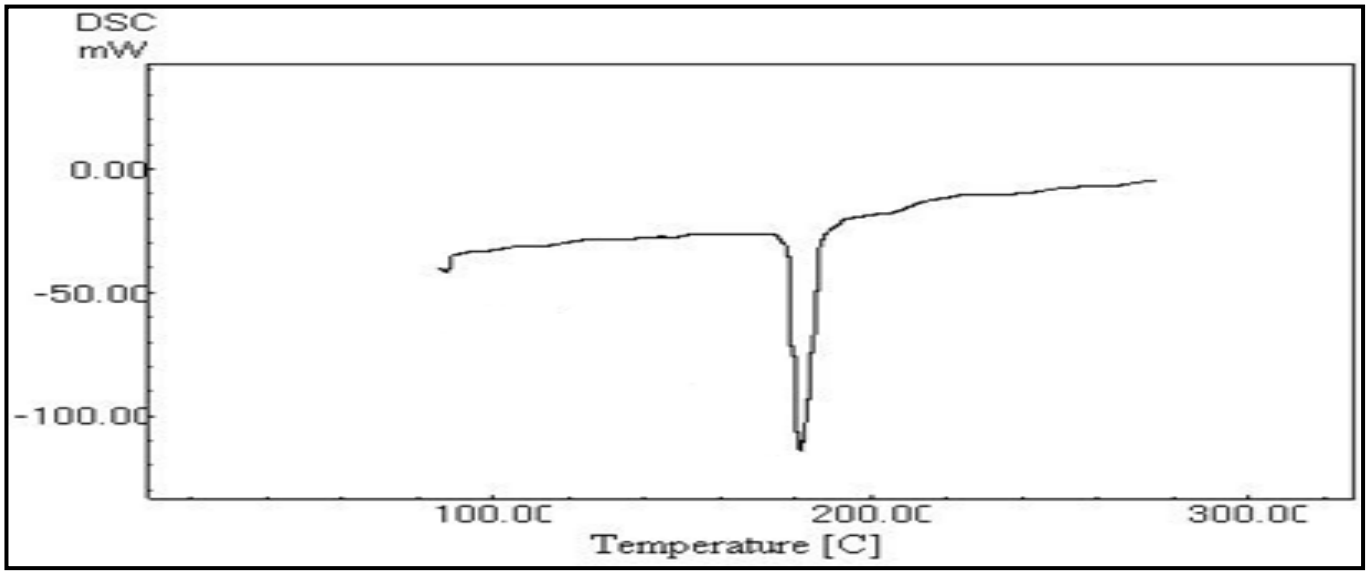


Figure 8. Comparison of DSC thermogram of pure drug and formulation F3

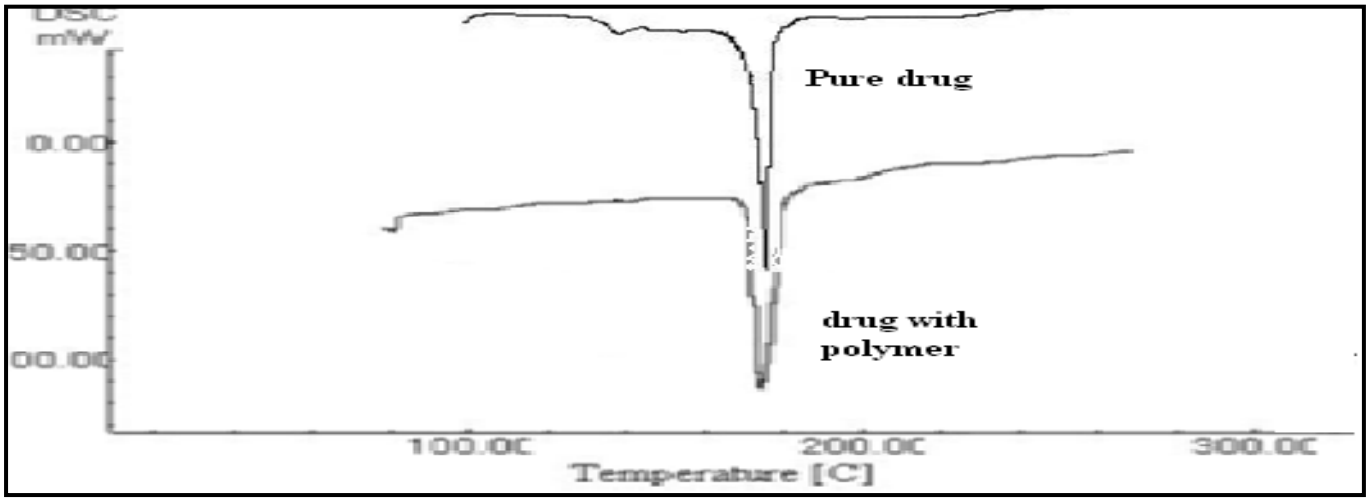


Figure 9. Bar graph of % drug loading

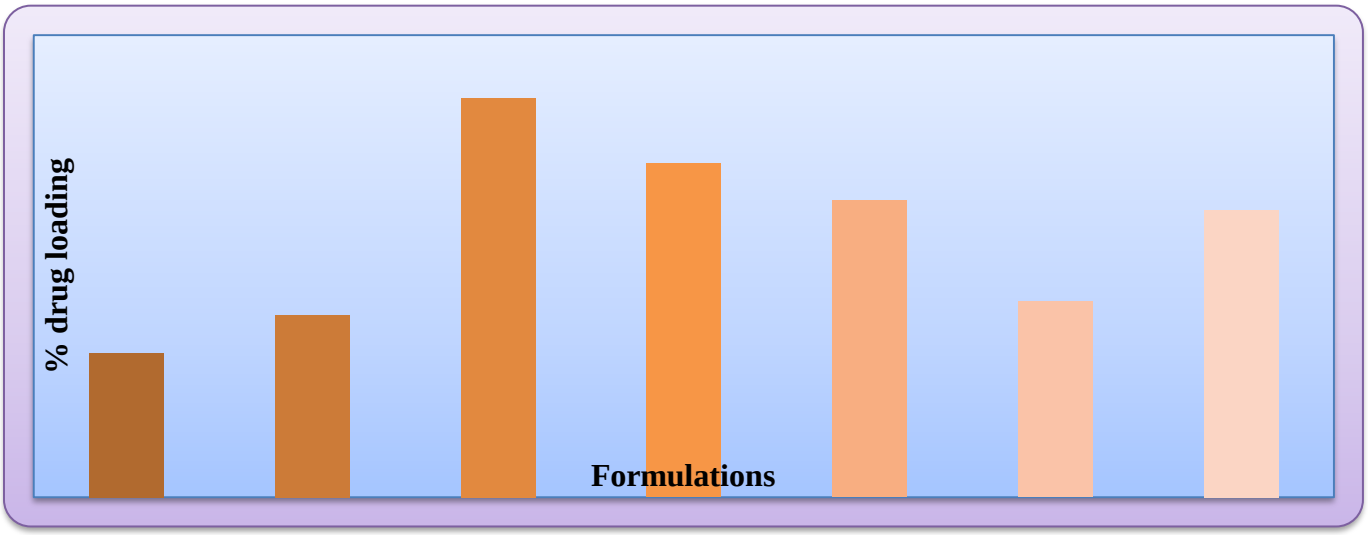


Figure 10. Bar graph of % Encapsulation efficiency

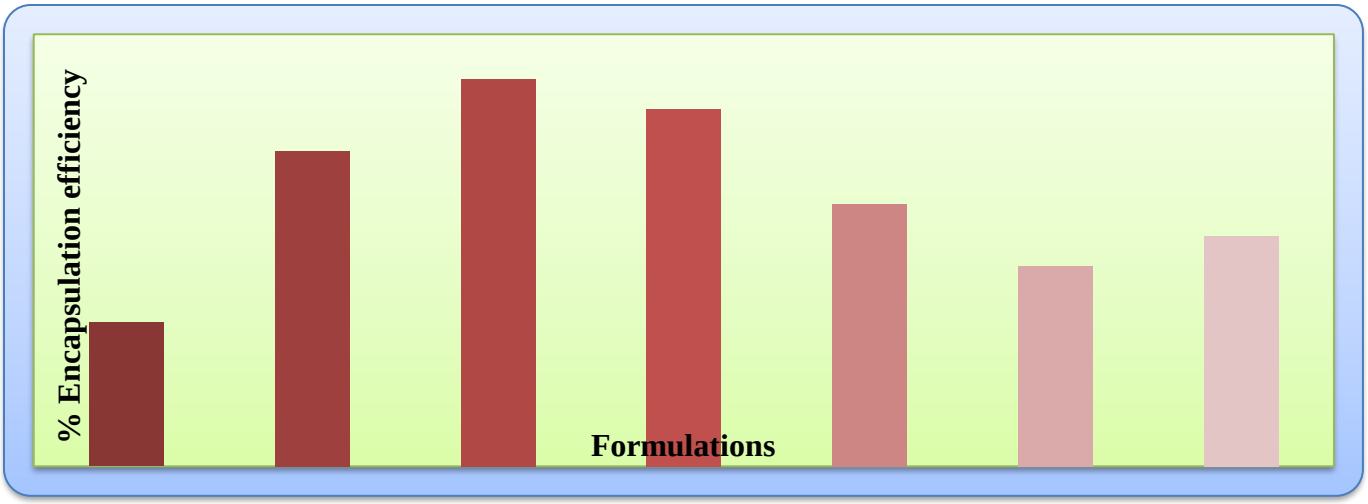
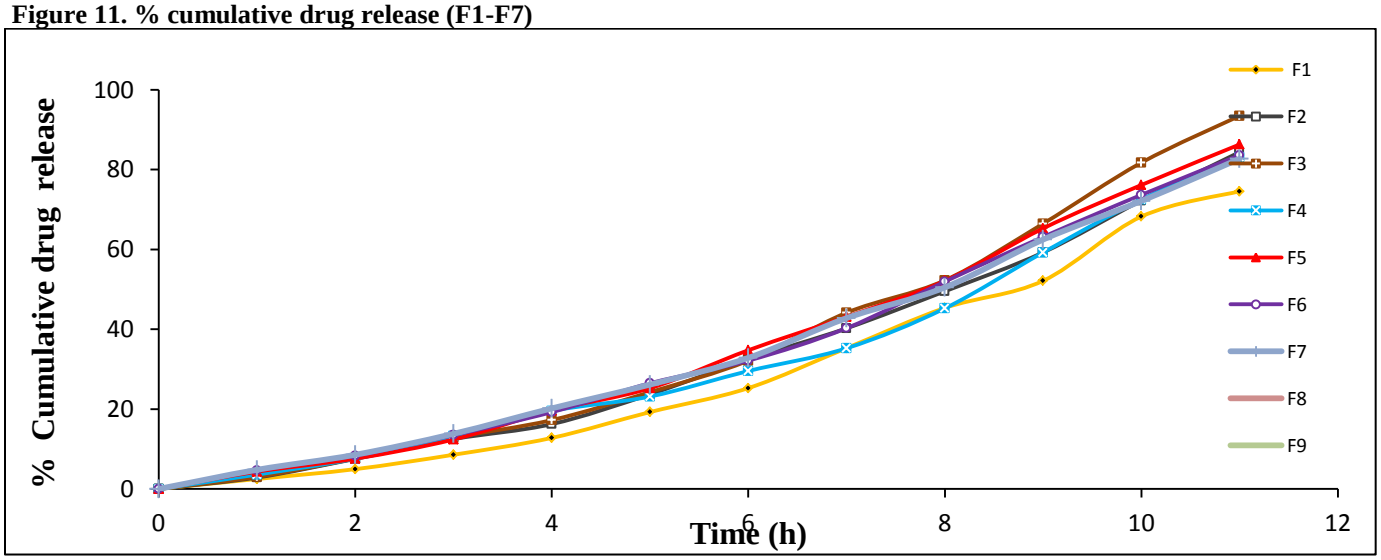


Figure 11. % cumulative drug release (F1-F7)



CONCLUSION

The objective of the study was to prepare pellets by the process of extrusion and spheronization and further the pellets were made porous by removing NaCl by aqueous extraction method. Drug was loaded in pellets by immersion technique. As the system comes into gastrointestinal environment it forms micro pores on the surface of the pellets.

Drug release profiles were studied through pore formed by addition of different concentrations of pore forming agent. Then desired results were obtained via micropores formed in pellets. The following conclusions were drawn from the results obtained

1) White spherical pellets with smooth surface were obtained and proving overall superiority of this method.
2) The SEM photograph clearly showed spherical pellets with microporous nature and surface dents.
3) The DSC thermogram obtained for the pure drug and for optimized formulation F3 showed that, drug was stable in the formulation.
4) From the FTIR spectra, it was observed that similar characteristic peaks appear with minor differences for the drug and formulation F3, indicating no chemical interaction between the drug and polymers.
5) The percentage encapsulation of drug inside pellets was found to be in the range of 94 to 96 %.
6) The *in vitro* drug release profile of the formulation F3 showed that the drugs release was more (93.48%) when compare to other formulations.
7) The results of stability studies carried out on optimized formulations indicated that, there was no significant change in drug content and drug release.

It can be concluded that among the prepared formulations, F3 was the optimized formulation. This can be prescribed for once a day administration.

REFERENCES

1. Vyas SP, Khar KK. Controlled drug delivery concepts and advances, CBS Pub, 2002, 1-12.
2. Ghebre-Sellassie I and Knoch A. Pelletisation techniques Encyclopedia of Pharmaceutical Technology, Marcel Dekker Inc, New York, 1995, 369-396.
3. Jamila Hamdani J. Andre, Moes, Karim Amighi. Physical and thermal characterization of precirol® and compritol® as lipophilic glycosides used for the preparation of controlled release matrix pellets. *Int. J. Pharm*, 260, 2003, 47-57.
4. Trivedi NR, Rajan MG, Johnson JR, Shukla AJ. Pharmaceutical approaches to preparing pelletized dosage forms using the extrusion-spheronisation process. *Crit. Ther. Drug Carr. Syst*, 24, 2007, 1-40.
5. Cosijins A, Nizet D, Nikolokakis I. Porous pellets as drug delivery system. *Drug Dev Ind Pharm*, 35(6), 2009, 655-62.
6. Takayama K, Nagai T. Novel computer optimization methodology for pharmaceutical formulations investigated by using sustained-release granules of indomethacin. *Chem. Pharm. Bull*, 37, 1989, 160-7.
7. Chowdhary KPR, Srinivasa Y. Mucoadhesive Microcapsules of Glipizide. *Ind J Pharm Sci*, 65, 2003, 279.
8. Wong TW, Chan LW, Lee HY, Heng PW. Release characteristics of pectin microspheres prepared by an emulsification technique. *J. Microencapsulation*, 19, 2002, 511-22.
9. United States of Pharmacopoeia 29 National formulary 24 (USP29–NF24) Supplement 1, is current from April 1, 2006 through July 31, 2006.
10. Du Pasquier AA. Differential Scanning Calorimetry studies of lithium ion and the reactivity of carbon anodes in plastic lithium ion batteries. *J. Electrochem. Sci*, 145 (2), 1998, 472-477.
11. Deasy PB, Law MFL. Use of extrusion spheronization to develop an improved oral dosage form of indomethacin. *Int. J. Pharm*, 148, 1997, 201-9.
12. Yan X, Gemeinhart RA. Cisplatin delivery from Poly (acrylic acid-co-methyl methacrylate) microparticles. *J. Control Release*, 106, 2005, 198–208.
13. ICH Harmonized Tripartite Guidelines, 2003. Stability testing of New Drug Substances and Products. Q1A (R2).
14. Gattani YS, Bhagwat DA, Maske AP. Formulation and evaluation of intragastric floating drug delivery system of diltiazem hydrochloride. *AAPS PharmSciTech*, 2 (4), 2008, 228-31.
15. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanisms of potassium chloride release from compressed, hydrophilic, polymeric matrices: effect of entrapped air. *J Pharm Sci*, 72(10), 1983, 1189-91.
16. Perumal D, Dangor CM, Alcock RS, Hurbons N, Moopanar KR. Effect of formulation variables on *in-vitro* drug release and Micromeritic properties of modified release Ibuprofen microspheres. *J Microencap*, 16, 1996, 475-87.