WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 7, 1607-1622. Research Article ISSN 2277– 7105

# FORMULATION AND EVALUATION OF PELLETS LOADED WITH DILTIAZEM HYDROCHLORIDE FOR SUSTAINED RELEASE

**Rashmitha N. M.*, Somashekar C. N., Shravya Lakshmi S. and T. Tamizh Mani**

Department of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagar, Maddur Taluk, Mandya District, Karnataka, India.

Article Received on
02 April 2019,

Revised on 24 April 2019,
Accepted on 13 May 2019,

DOI: 10.20959/wjpr20197-15075

***Corresponding Author**
**Rashmitha N. M.**
Department of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagar, Maddur Taluk, Mandya District, Karnataka, India.

## ABSTRACT

The objective of this study was to prepare and evaluate Diltiazem hydrochloride loaded pellets for sustained release by using Extrusion-Spheronization Method. The different formulations were prepared using MCC as extrusion aid, CMC as a binder and demineralized water is used as a granulating agent. The mean particle size of the drug loaded pellets was in the range 1026 - 1061µm. SEM photographs and calculated sphericity factor confirmed that the prepared formulations were spherical in nature. *In vitro* drug release studied in pH 6.8 phosphate buffer.F5 formulation showed the better drug release of 88.1%. F5 formulation was the optimized formulation. The drug content and entrapment efficiency was in the range of 92.97 – 97.12% and 89.17 – 95.27% respectively. The compatibility between drug and polymers in the drug loaded pellets was confirmed by DSC and FTIR studies. The stability studies were carried out for a period of 90 days at 40±2 °C and 75±5% RH. Stability studies indicated that pellets are stable.

**KEYWORDS:** Diltiazem hydrochloride, Pellets, Extrusion-spheronization method, *In vitro* study.

## INTRODUCTION

Oral drug delivery system has importance due to its, maximum therapeutic effects and patient compliance. Even though it is frequently impaired by several physiological and pharmaceutical factors that are associated with inherent physicochemical nature of the drugs and/or the variability in GI conditions, such as pH, presence of food, transit times, expression

of P Glycoprotein (P-Gp) and CYP3A, as well as enzymatic activity in the alimentary canal.[1]

Novel drug delivery systems are designed to achieve a continuous delivery of drugs at predictable and reproducible kinetics over an extended period of time in the circulation. The potential advantages of this concept include minimization of drug related side effects due to controlled therapeutic blood levels instead of oscillating blood levels, improved patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administered. Hence, the combination of both sustained release and controlled release properties in a delivery system would further enhance therapeutic efficacy.[2]

Pelletization is one of the novel drug delivery techniques that provide an effective way to deliver the drug in modified pattern. It is advantageous in providing site specific delivery of the drug. Drugs with unpleasant taste, poor bioavailability and short biological half-life can be delivered efficiently through pellets. Their reduced size makes them more valuable as compared to the conventional drug delivery system.

Pellets are small, free flowing, spherical dosage form prepared by the agglomeration of fine powders or granules of drug substances and excipients. Pellets as drug delivery systems provide not only technological advantages including better flow properties, durable dosage form, reduced particle size distribution, simplicity of coating, and homogeneous packing but also provide therapeutic advantages such as comparatively less irritation of the alimentary canal, a lower danger of side effects related with dose dumping and a uniform distribution in the gastrointestinal tract resulting in a decreased peak plasma fluctuations.[3] Pellets offer a high degree of flexibility and can be divided into desired dose strengths without formulation or process changes. Pellets are in a size range between 0.5 and 1.5 mm and are produced primarily for the purpose of oral controlled release dosage forms having gastro resistant or sustained release properties or the capability of site-specific drug delivery.[4]

Hypertension is defined as the systolic blood pressure is more than 140 mm Hg and the diastolic blood pressure is more than 90 mm Hg. It is a chronic disease, which is considered to be one of the major public health problems and a significant cardiovascular risk factor.[5]

Diltiazem hydrochloride a highly water soluble Class I drug that releases the drug at a predetermined rate on the basis of pharmacokinetic principles. The drug has a saturation

solubility of 590 mg/mL in phosphate buffer pH7.4.[6] Diltiazem hydrochloride (DTZ), one member of calcium channel blockers, is widely used in the treatment of angina pectoris and hypertension.[7] Diltiazem HCl produces its antihypertensive effect primarily by relaxation of vascular smooth muscle with a resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives. Diltiazem HCl has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal work load.[8]

## MATERIALS AND METHOD

Diltiazem hydrochloride gift sample obtained from strides shasun Ltd. The other chemicals were obtained from authenticated manufactures, CMC (Shreeji chemicals, Mumbai), MCC (Sigma chemical Ltd., Mumbai).

### Preparation of pellets[9]

The Pellets were prepared by pelletization technique using extrusion/spheronization. Extruder (EXT-65/031/37, RR Enterprises, India) and Spheronizer (SPH-150/010,RR Enterprises, India) were used in the preparation of pellets. Different ratio of MCC, drug and CMC were used in the formulation. All the powders were passed through sieve No. 40 prior to pelletization and mixed uniformly in a planetary mixer. The powder were mixed are of 100g batch by geometric mixing in polyethylene bag for 10 minutes. The above dry blend mixture was granulated using demineralized water as a granulating agent. The wet mass was extruded using cylinder roll type extruder of 1mm opening diameter. The obtained extrudates were spheronized in a spheronizer fitted with a cross hatched rotor plate of 1mm diameter and 2.5mm thickness. The obtained pellets were dried at 40˚C for 8 hours.

**Table 1: Formulation chart for pellets.**

| Sl. No. | INGRIDIENTS | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|---|
| 1. | Diltiazem hydrochloride(mg) | 10 | 10 | 10 | 10 | 10 | 10 |
| 2. | MCC | 90 | 60 | 30 | 20 | 10 | - |
| 3. | CMC | - | 30 | 60 | 70 | 80 | 90 |
| 4. | Distilled water | q.s | q.s | q.s | q.s | q.s | q.s |

**Compatibility studies**

**Drug-Excipients interactions studies by FTIR[10]**

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 $cm^{-1}$ and the resolution was 1 $cm^{-1}$.

**Differential scanning calorimetry(DSC)**

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Samples were accurately weighed and heated in sealed aluminum pans at a rate of 10°C/ min between 25 and 350°C temperature rang under nitrogen atmosphere. Empty aluminum pan was used as a reference.

**Evaluation of pellets[11-19]**

**Micromeritic properties**

**Angle of repose**

Angle of repose is used to determine the flow properties of powders, pellets or granules. The method to find angle of repose is to pour the powder on a conical heap on a level, flat surface and measure the included angle with the horizontal.

$\theta = \tan^{-1} (h/r)$

Where, h = height of the heap,

r = Radius of the heap.

**Table 2: Standards of Angle of Repose.**

| Angle of repose | Flow |
|---|---|
| <25 | Excellent |
| 25-30 | Good |
| 30-40 | Possible |
| >40 | Poor |

**Bulk Density**

Bulk density of the coated pellets was determined by pouring pellets into a graduated cylinder via a large funnel and measuring the volume and weight.

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

**Tapped Density**

Tapped density was determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which was operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

$$\textbf{Tapped density} = \frac{\textbf{Weight of granules}}{\textbf{Tapped volume of granules}}$$

**Carr's Index**

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$\textbf{CI} = \frac{(\textbf{TD} - \textbf{BD})}{\textbf{TD}} \times \textbf{100}$$

Where, TD = Tapped density

BD = Bulk density

**Table 3: Standards for Carr's Index values.**

| Flow | Carr's index |
|---|---|
| Excellent | <10 |
| Good | 11-15 |
| Fair | 16-20 |
| Passable | 21-25 |
| Poor | 26-31 |
| Very poor | 32-38 |
| Extremely poor | >40 |

**Hausner's Ratio**

Hauser's Ratio is indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

**Hausner's Ratio = Tapped density/ Bulk density**

**Table 4: Standards for Hausner's ratio.**

| Flow | Hausner's ratio |
|---|---|
| Excellent | 1.00 – 1.11 |
| Good | 1.12 – 1.18 |
| Fair | 1.19 – 1.25 |
| Passable | 1.26 – 1.34 |
| Poor | 1.35 – 1.45 |
| Very Poor | 1.46 – 1.59 |
| Very, Very Poor | > 1.60 |

**Loss on drying**

Loss on drying is determined by IR moisture analyzer, at 105˚C.2gms of sample was placed in analyzer and observed until required temperature was attained. Then loss on drying was determined.

$$\textbf{Loss on drying} = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\textbf{Final weight}} \times 100$$

**Moisture content**

The moisture content (% loss on drying; % LOD) of the dried and sieved pellets (18/24) was determined by using Mettler Toledo Halogen Moisture Analyzer (Model: HB43, USA) where the working temperature was 105℃.

$$\textbf{Percentage moisture content} = \frac{\textbf{Final weight} - \textbf{Initial weight}}{\textbf{Initial weight}} \times 100$$

**Friability test**

Friability is the loss of weight of pellets in the container due to removal of fine particles from the surface. This in-process quality control test was performed to ensure the ability of pellets to withstand the shocks during process, handling, and transportation. Roche friabilator was used to measure the friability of pellets. It was rotated at 25rpm. Pellets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the pellets were exposed to rolling, resulting from free falling of pellets within chamber of the friabilator.

After 100 rotations the pellets were taken out from the friabilator and intact pellets were again weighed collectively after removing fines using sieve. Permitted percentage friability limit is 0.8%. The percentage friability was determined using the formula.

$$\textbf{Percent friability} = \frac{(\textbf{W1} - \textbf{W2})}{\textbf{W1}} \times 100$$

**Particle Size Determination**

Particle size of the optimized formulation and size distribution was determined by optical microscope fitted with an ocular and stage micrometer. The Weswox model having resolution of 45x was used for this purpose.

**Pellet sphericity**

Pellet size and shape were determined using an image analysis System. Photomicrographs were taken with a digital camera. The obtained images were processed by image analysis

software (Digimizer, USA) to characterize each individual pellet by aspect ratio (AR) and two-dimensional shape factor (*e*R).

**eR = 2πr/Pm-(b/1)2**

Where, r is the radius, Pm is the perimeter, l is the length (longest FD) and b is the width (longest perpendicular diameter to the longest FD) of a pellet.

Shape factor for the prepared sample were obtained from the area (A) and perimeter (P) of a pellet.

**Scanning electron microscopy (SEM)**

The surface and shape characteristics of pellets were determined by scanning electron microscopy (model-ZEISS Evo 18 Special edition). Photographs were taken and recorded at suitable magnification.

**Determination of drug content**

Diltiazem hydrochloride content of the prepared pellets was determined spectrophotometrically (UV-1800 Spectrophotometer) at 236nm. Diltiazem HCL-loaded pellets were crushed in a mortar and an amount equivalent to 9 mg of Diltiazem HCL was dispersed in 100ml volumetric flask containing methanol. It was further diluted with phosphate buffer (pH 7.4) and volume was made upto 100 ml. The solution was filtered and Diltiazem HCL amount was measured spectrophotometrically at 236 nm after appropriate dilution.

**Entrapment efficiency**

Pellets were dissolved in 10 mL of phosphate buffer (pH 6.8) under occasional shaking for 2-3 hrs. The resultant solution was filtered through 0.46µm filter paper and after suitable dilution, the amount of drugs present in the formulation was determined using a UV Visible spectrophotometer at 279nm (Shimadzu 1800, Japan). (Malay and Prakash, 2007) Drug incorporation efficiency can be given by the following formula,

$$\%EE = \frac{\text{Total amount of drug} - \text{Amount of drug in supernatant}}{\text{Total amount of drug}} \times 100$$

**In-Vitro Drug Release Studies**

The in vitro release of the drug from pellets of all formulation batches were performed using USP apparatus Type I (Basket). The dissolution medium consisted of 900 ml of phosphate

buffer pH 6.8. Dissolution was performed at 37±0.5°C, with stirring speed of 100 rpm. 5 ml of aliquot was withdrawn at time intervals of 1, 2, 4, 6, 8, 10, 12 Hrs. The medium was replenished with same amount of fresh dissolution media each time. The filtered samples were analyzed by UV-VIS spectrophotometer at 236 nm and absorbances were recorded.

**Stability studies**

Stability studies of pharmaceutical products were done as per ICH guide lines. These studies are designed to study the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions.

**METHOD**

Selected formulations were stored at different storage conditions at elevated temperatures such as 25˚C± 2˚C / 60% ± 5% RH, 30˚C ± 2˚C / 65% ±5% RH and 40˚C ± 2˚C / 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of 30 days and checked for physical changes.

**RESULT AND DISCUSSIONS**

FT-IR spectroscopy study was carried out to check the compatibility between the drug and polymers used for the preparation of pellets. The FT-IR was performed for drug and physical mixture of drug and polymer separately. The spectra obtained from FT-IR spectroscopy studies at wavelength from 4000 to 400 $cm^{-1}$ are shown in Figure 1and 2. From this we have observed that there was no significant chemical interaction between the drug and excipients. DSC thermograph of Diltiazem hydrochloride and the physical mixture of diltiazem hydrochloride and polymers were shown in Figure 3&4. The Diltiazem hydrochloride loaded pellets were prepared by the extrusion-spheronization method by using MCC and CMC. MCC is used as extrusion aid and CMC is used as a binder. Demineralized water is used as a granulating agent. The prepared pellets were evaluated for various micromeritic characters. The results are shown in Table 5. Angle of repose of all the formulations were found to be 19.18±0.24 - 26.79±0.22, bulk density were found to be 0.410±0.005 - 0.496±0.006 g/cc, tapped density were found to be 0.460±0.007 - 0.486±0.008 g/cc, Carr's index were found to be within 4.61±0.065 - 12.37±0.066 and Hausner's ratio were found to be within 1.04±0.097 - 1.12±0.041. The results of micrometric characters confirmed that all the prepared pellets formulations have good flow property. Moisture content and loss on drying of all prepared pellet formulations F1-F6 were in the range of 1.2 – 1.6% and 0.18 – 0.26 respectively. All the formulations of pellets showed satisfactory results. Friability is needed for the prepared

pellets to assess the mechanical strength in terms of fragmenting or powdering during filling operation into capsule shell. The friability of all the formulation was found to be between 0.269 – 0.698% are Table 6 and all the formulations were within the official limits (*i.e.* not more than 1%). The particle size determination of prepared pellet formulations was done by optical microscope. The pellets of all the formulations were in the size range of 1026 - 1061µm are shown in Table 6. The results of all the formulations confirmed that as the concentration of the MCC increases will influence the diameter of the pellets. From the photomicrograph image analysis, calculated aspect ratio (AR) and two-dimensional shape factor (*e*R) of all the pellet formulation were found to be 1.18 – 0.98, respectively are shown in Table 6. The obtained *e*R and AR values of the pellets were closer to the value of 1, which confirmed that the prepared pellets were spherical in nature. The surface morphology was studied by Scanning electron microscopy (SEM). The SEM photographs of pellets of formulation F5 are shown in Figure 5. SEM photomicrographs of F5 formulation of pellets were spherical in nature and had a smooth surface. Pellets reveal the uniform distribution of the drug in the pellets. The percentage drug content and entrapment efficiency in different formulations F1 – F6 was found to be 92.97 – 97.12% and entrapment efficiency of all the formulation was found to be 89.17 – 95.27%, results are shown in Table 7. Formulation F5 has higher drug content and entrapment efficiency. This implied that drug distribution was uniform and satisfactory in all formulation. *In vitro* release behavior of all formulations is summarized in Table 8 and Figure 6. *In vitro* release profile of Diltiazem hydrochloride pellets from different batches of formulations F1 to F6was conducted for 12 hrs by using USP basket type dissolution test apparatus, using phosphate buffer pH 6.8. The percentage of drug release from the formulations F1- 71.2%, F2- 84.3%, F3- 73.1%, F4- 76.8%, F5- 88.1%, F6- 75% at the end of 12hrs. The amount of drug release from formulation F1 was showed 71.2% which was lower among all the formulations F1-F6. From the result we observed that the release of drug from pellets was varied according to the concentration of polymer. It shows that the increase in the concentration of the MCC will decrease the release of the drug. The formulation F6 were prepared with CMC which shows 75% drug release from the pellets at the end of 12hrs. The formulations F2, F3, F4 and F5 were prepared with combination of MCC and CMC with different ratio. The formulation F5 showed 88.1% which was higher drug release among the formulations F2 – F5. In F5 formulation the MCC concentration is less than the CMC concentration, so it showed better sustained release. The result shows that decrease in the concentration of MCC will increase the release of drug from the formulation. By comparing the all formulation individual and combination F1-F6, F5 combination

formulation showed better sustained release till 12 hrs. Hence F5 formulation is taken as an optimized formulation. Upon the application of different drug release model kinetics. It was found that all formulation follows zero order. The 'n' values for all formulation to be more than 0.5. This indicates that the release approximates Non-Fickian diffusion mechanism. The results are shown in Table 9. Accelerated stability studies were carried out at 40 ± 2 ºC and 75 ± 5% RH for the optimized formulation F5 for 3 months and monitored for % drug content and % CDR. The results are shown in Table 10, which indicated that negligible changes in the results hence confirmed all the pellets were stable during storage period.

**Compatibility studies**

**FTIR studies to find out the compatibility of drug with the Polymer**

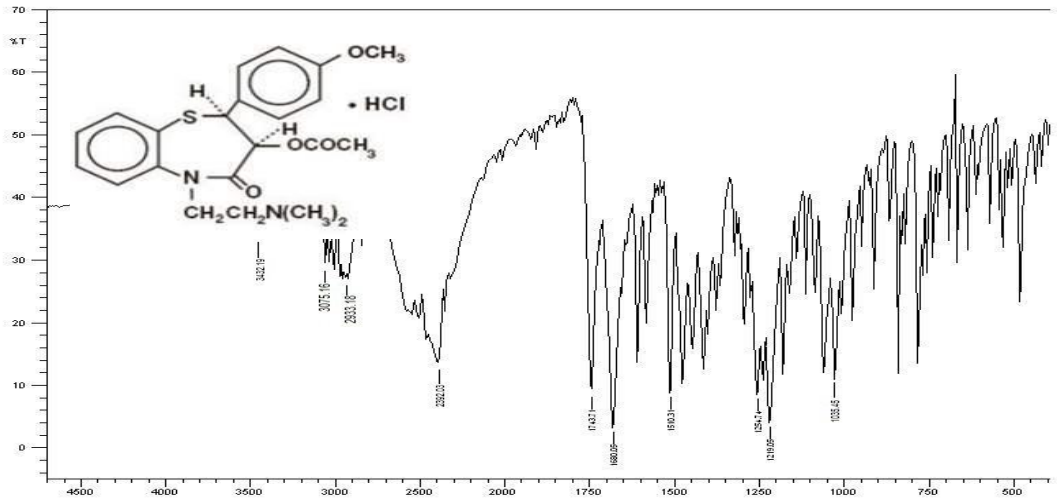


**Figure 1: FTIR spectra of Diltiazem hydrochloride.**

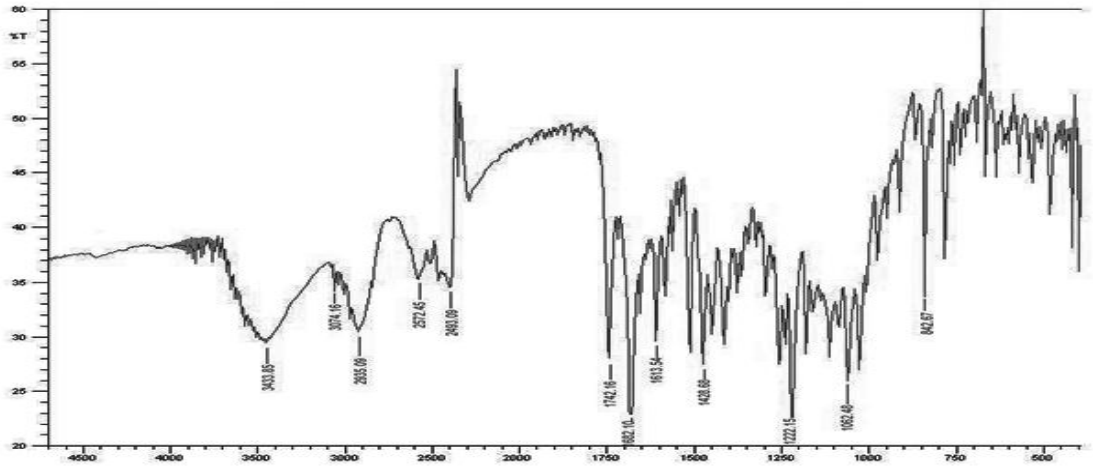


**Figure 2: FTIR spectra of physical mixture.**

**Differential scanning calorimetry (DSC)**

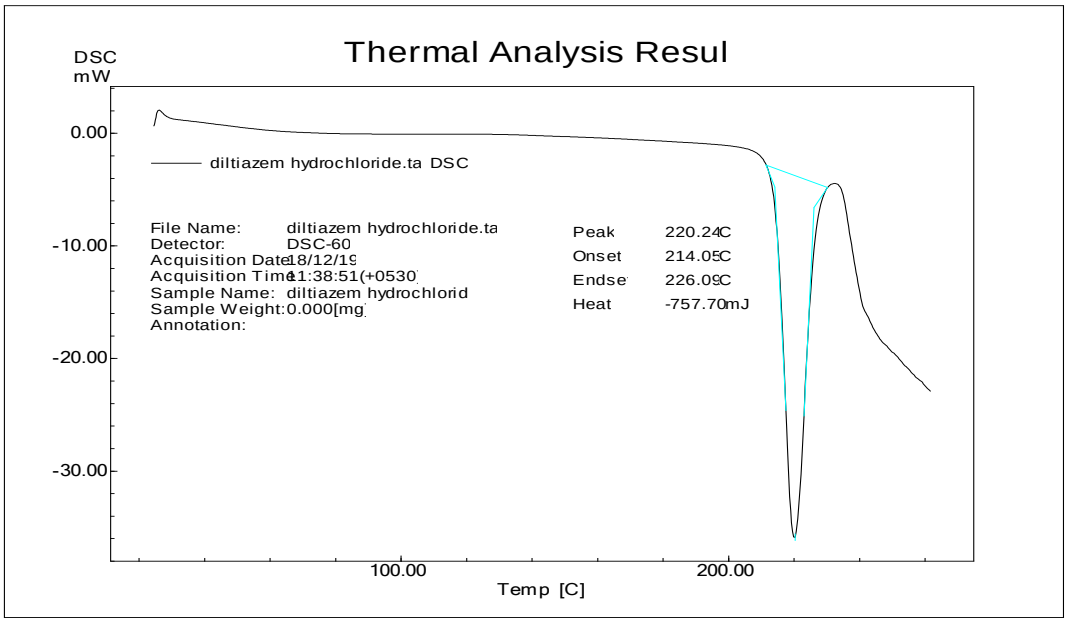


**Figure 3: DSC Thermograph of Diltiazem hydrochloride pure drug.**

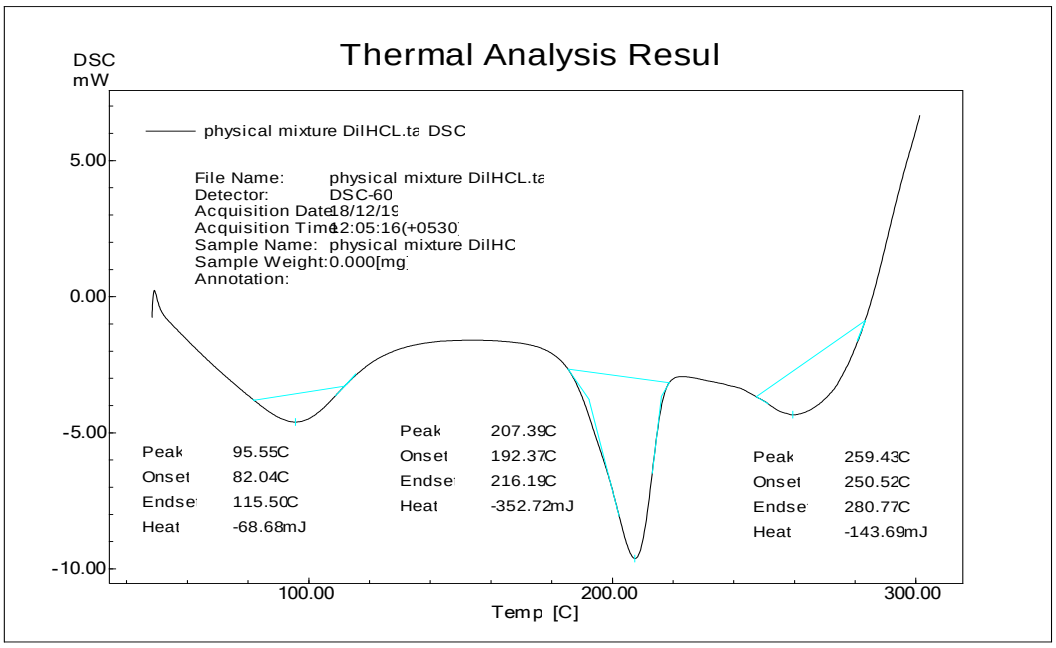


**Figure 4: DSC thermograph of physical mixture.**

**Evaluation of pellets**

**Micromeritic characters of pellets**

**Table 5: Micrometric characters of formulation F1-F6.**

| Sl. No | Formulation code | Angle of repose (Ɵ)±SD* | Bulk density (g/cc)±SD* | Tapped density (g/cc)±SD* | Carr's index ±SD* | Hausner's ratio ±SD* |
|---|---|---|---|---|---|---|
| 1. | F1 | 21.21±0.20 | 0.410±0.005 | 0.460±0.007 | 11.02±0.072 | 1.11±0.005 |
| 2. | F2 | 21.93±0.12 | 0.447±0.006 | 0.480±0.004 | 7.05±0.092 | 1.07±0.01 |
| 3. | F3 | 26.79±0.22 | 0.434±0.006 | 0.478±0.008 | 8.49±0.085 | 1.12±0.041 |
| 4. | F4 | 22.17±0.37 | 0.458±0.004 | 0.485±0.007 | 4.61±0.065 | 1.04±0.097 |
| 5. | F5 | 20.91±0.34 | 0.449±0.007 | 0.483±0.007 | 7.84±0.091 | 1.08±0.025 |
| 6. | F6 | 19.18±0.24 | 0.496±0.006 | 0.486±0.008 | 12.37±0.066 | 1.10±0.040 |

**Mean ±SD n=3**

**Friability, Particle size determination and Pellet sphericity**

**Table 6: Particle size of formulation F1-F6.**

| Sl. No. | Formulation code | Friability (%) | Particle size in µm ±SD* | Sphericity ±SD* |
|---|---|---|---|---|
| 1. | F1 | 0.342 | 1061±0.71 | 0.92±0.24 |
| 2. | F2 | 0.698 | 1055±0.55 | 1.12±0.38 |
| 3. | F3 | 0.285 | 1046±0.84 | 1.05±0.22 |
| 4. | F4 | 0.360 | 1035±0.67 | 1.15±0.36 |
| 5. | F5 | 0.416 | 1032±0.51 | 1.02±0.25 |
| 6. | F6 | 0.269 | 1026±0.48 | 1.18±0.41 |

**Mean ±SD n=3**


**Figure 5: Scanning electron microscopy of optimized formulation F5.**

**Percentage drug content & percentage Entrapment efficiency**

**Table 7: %Drug content & Entrapment efficiency of formulation F1-F6.**

| Sl. No. | Formulation code | % Drug content ±SD* | %Entrapment efficiency ±SD* |
|---|---|---|---|
| 1. | F1 | 95.71±0.65 | 93.19±0.17 |
| 2. | F2 | 92.97±0.72 | 89.17±0.48 |
| 3. | F3 | 94.98±0.12 | 92.29±0.76 |
| 4. | F4 | 96.35±0.83 | 94.35±1.09 |
| 5. | F5 | 97.12±0.36 | 95.27±0.32 |
| 6. | F6 | 94.28±0.23 | 93.85±1.15 |

**Mean ±SD n=3**

***In vitro* drug release study**

**Table 8: *In vitro* release study of formulations F1-F6 in phosphate buffer pH 6.8.**

| Sl. No | Time (hrs) | % CDR | | | | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 |
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 7.4 | 11.2 | 5.6 | 7.4 | 9.3 | 11.2 |
| 3 | 2 | 16.8 | 24.3 | 13.1 | 11.2 | 16.8 | 20.6 |
| 4 | 4 | 29.9 | 35.6 | 28.1 | 26.2 | 31.8 | 33.7 |
| 5 | 6 | 37.5 | 48.7 | 39.3 | 35.6 | 46.8 | 45 |
| 6 | 8 | 46.8 | 60 | 50.6 | 46.8 | 61.8 | 52.5 |
| 7 | 10 | 58.1 | 73.3 | 63.7 | 60 | 76.8 | 65.5 |
| 8 | 12 | 71.2 | 84.3 | 73.1 | 76.8 | 88.1 | 75 |

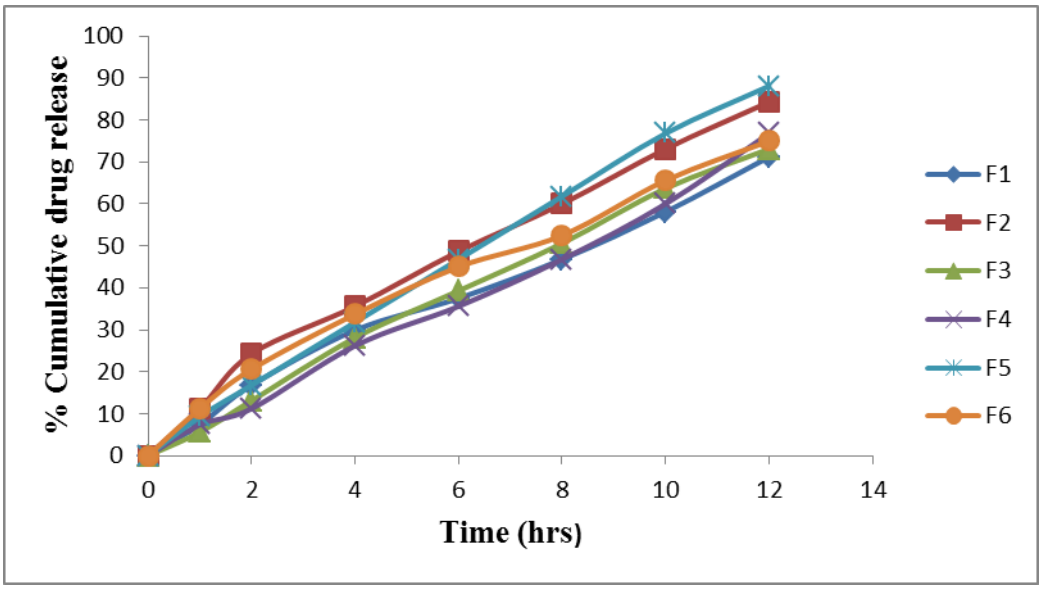


**Figure 6: *In vitro* release profile of formulation F1-F6 in phosphate buffer 6.8.**

**Result of model fitting**

**Table 9: Data for different kinetic model.**

| Formulation code | Zero order | First order | Higuchi plot | Peppas plot | |
|---|---|---|---|---|---|
| | | | | $r^2$ | 'n' |
| F1 | 0.990 | 0.970 | 0.949 | 0.801 | 1.267 |
| F2 | 0.987 | 0.965 | 0.966 | 0.738 | 1.257 |
| F3 | 0.996 | 0.982 | 0.937 | 0.865 | 1.368 |
| F4 | 0.995 | 0.932 | 0.909 | 0.842 | 1.317 |
| F5 | 0.998 | 0.943 | 0.937 | 0.806 | 1.340 |
| F6 | 0.984 | 0.984 | 0.971 | 0.735 | 1.218 |

**Stability studies**

**Table 10: Accelerated stability studies for optimized formulation F5.**

| Temperature and RH | Parameters | Duration in months | | | |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 |
| 40±2˚C and 75±5% | %Drug content | 97.12 | 97.10 | 97.06 | 97.03 |
| | %CDR | 88.1 | 87.58 | 87.97 | 87.32 |

## CONCLUSION

From the study, it can be shows that the SEM photographs and calculated sphericity factor confirmed that the prepared formulations were spherical in nature. Stability studies indicated that pellets are stable. Pellets showed sustained drug release upto 12hrs. From the *in vitro* drug release and drug content it can be concluded that F5 formulation is the optimized formulation. These improve the bioavailability through its longer residence time and ability to sustain drug release.

## REFERENCES

1. Giram PS, Bare AR, Puranik PK. Formulation and evalution of sustained released matrix pellets of diltiazem HCl by extrusion and spheronization. World J Pharm Res, 2015; 4(5): 1542-560.
2. Kumar V, Arvind S, Ashish S, Gourav J, Vipasha D. Recent advances in novel drug delivery system for delivery of Anti- Hypertensive drugs. Int J Drug Dev Res, 2011; 3(1): 252-59.
3. Zaman M, Saeed-Ul-Hassan S, Sarfraz RM, Batool N, Qureshi MJ, Akram MA, Munir S, Danish Z. Pellets and pelletization emerging trends in the pharma industry. Acta Pol Pharm, 2016; 73: 1415-425.
4. Venkat NR, Rama RN, Chandrika NK. Design and evaluation of sustained release pellets of aceclofenac. J Pharm Res, 2013; 6: 525-31.

5. Kumar VR, Ram VR, Prasad BG, Mohanta GP, Manna PK. A study of adverse drug reactions due to antihypertensive drugs in a tertiary care teaching hospital. Int J Pharm Life Sci, 2011; 2(5): 767-72.
6. Anurag S, Yasvanth AR, Ramesh P. Use of extrusion–spheronization to develop controlled-release dosage forms for Diltiazem hydrochloride. Pharm Tech, 2004; 1: 62-85.
7. Xiaopeng Han, Linan Wang, Yinghua Sun, *et al.*, Preparation and evaluation of sustained-release diltiazem hydrochloride pellets. Asian J Pharm Sci, 2013; (8): 244 -51.
8. Elias NM, Sharmin S, Ahmed I. Development & *In vitro* evaluation of sustained release pellets of Diltiazem hydrochloride using ethyl cellulose & hydroxy propyl methyl cellulose polymer. Int J Pharm Stu Res, 2012; 1(3): 08-17.
9. Gowda DV, Ram AS, Venkatesh MP, Khan MS. Development and evaluation of clozapine pellets for controlled release. Int J Res Ayurveda Pharm, 2012; 3(4): 611-18.
10. Ramireddy GV, Ramana Murthy KV. Formulation and *In vivo* Evaluation of sustained release pellets of bosentan by pan coating process. Int J Med Sci Innovative Res, 2017; 2(5): 318-29.
11. Ramu S, Chandra Gopal RP, Srinivasa RD, Ramakrishna D. Formulation and evaluation of Lansoprazole delayed release pellets. Int J pharm chem biological sci, 2015; 5(4): 860-78.
12. Kibria G, Akhter A, Islam KA. Formulation and evaluation of Domperidone pellets prepared by powder layering technology. Asian J Pharm, 2010; 4(1): 41-47.
13. Brahmareddy DR, Madhulatha AV, Priyanka R. Formulation and Evaluation of Venlafaxine hydrochloride Sustained Release Pellets. Int J Pharm Sci Lett, 2015; 5(6): 632-35.
14. Ravella VN, Nadendla RR, Kesari NC. Formulation and evaluation of sustained release pellets of Ketorolac tromethamine employing pan coating technology. Int J Adv Pharm Sci, 2013; 4(3): 543-56.
15. Bathool A, Gowda DV, Khan MS. Development and evaluation of porous membrane pellets of Disopyramide phosphate for sustained release. Asian J Pharm, 2014; 6(2): 107-115.
16. Raval KM, Ramani RV, Sheth NR. Formulation and evaluation of sustained release enteric-coated pellets of Budesonide for intestinal Delivery. Int J Pharm Investig, 2013; 3(4): 203-11.

17. Anusha K, Krishna SA. Preparation and evaluation of Mefenamic acid loaded microspheres using synthetic and natural polymers. Pharm Lett, 2016; 8(1): 197-05.
18. Tarkase KN, Sachin PG, Akash BB. Formulation and evaluation of controlled release pellets of metoprolol succinate by extrusion-spheronization method. Int J Drug Res Tech, 2016; 6(3): 141-49.
19. Sirichandana G, Ashok KP, Suresh VK. Formulation and evaluation of sustained release pellets of Domperidone. Int J Drug Dev Res, 2015; 7(1): 162-72.