IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
July 2023 Vol.:27, Issue:4
© All rights are reserved by Tanvi.Vilasrao.Deshmukh et al.

Formulation and Evaluation of Extended Release Multi-Particulate Drug Delivery System of Diltiazem HCL

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Tanvi.Vilasrao.Deshmukh, P.S.Kawtikwar

Department of Industrial Pharmacy, Sudhakarrao Naik Institute of Pharmacy Pusad, Nagpur Road Pusad, India

Submitted: 30 June 2023
Accepted: 20 July 2023
Published: 30 July 2023

ijppr.humanjournals.com

Keywords: Extended Release Multi-Particulate, Drug Delivery System, Diltiazem HCL

ABSTRACT

The purpose of this study is to formulate sustained-release pellets without coating utilising hydrophobic and hydrophilic matrix-forming polymers, such as Ethylcellulose and HPMC K100, and to manufacture matrix pellets containing the antihypertensive medication (Diltiazem HCl) using extrusion spheronization technology. FTIR analysis of the drug-polymer interaction was followed by DSC verification. The results of many preliminary batches show that polymers with the EC: HPMC K 100 batch ratio of 0.5:0.15 have appropriate morphological characteristics and the necessary drug release. To ascertain the impacts of the dependent and independent variables, a $(3)^2$ factorial design was adopted. It was determined that not only the operational parameters but also the type of wetting agent (liquid), the composition of the binder, and the impact of the plasticizer had a substantial impact. According to the USP XXIV monograph, friability, content uniformity, and in vitro drug release properties were investigated.

INTRODUCTION

The oral route is the most popular route used for the administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The term sustained release, prolonged release, modified release, extended-release or depot formulation are used to identify drug delivery system that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[1]The advantages of administering a single dose of a drug that is released over an extended period of time, instead of drug numerous doses, have been obvious to the pharmaceutical industry for some time. The desire to maintain a near constant or uniform blood level of drug often translates into better patient compliance as well as the enhanced clinical efficacy of drug for its intended use. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained or controlled release drug delivery systems.[2]

The oral formulation of the multi-particulate drug delivery systems is suited for controlled or delayed release. Low dose dumping is one of its benefits. Flexibility in blending for a rapid transit time through the stomach and various release patterns. Therefore, the multi-particulate drug delivery system (MPDDS) offers possibilities for creating oral formulations with regulated and delayed release. Oral dosage forms with multiple small discrete units called multi-particle drug delivery systems include multiple separate active substances. Subunits including grains, beads, microspheres, pellets, spheroids, and mini-tabs serve as its foundation. Pellets are spherical or semi-spherical, freely flowing solid objects with a restricted size range, often with a diameter of 0.5 to 2.0 mm. Pellets are created using the pelletization technique. Any medication delivery method that accomplishes a slow release of the drug over an extended period of time is considered a sustained release system. A controlled-release system is one that successfully maintains constant medication levels in the blood or the intended tissue.[3]

When creating an extended-release formulation, certain factors must be taken into consideration. If the active ingredient has a long half-life, it can be maintained independently, If an active substance's pharmacological activity and blood levels are not closely correlated, It would take a lot of medication to maintain a sustained effective dose if active transport is required for drug absorption and the active component has a very short half-life.[4,5]

The calcium channel blocker Diltiazem HCl is used to treat angina pectoris, hypertension, and cardiac arrhythmias. Patients are advised to take Diltiazem HCI in divided daily dosages, once every 6 to 8 hours because of its biological half-life, which is only 3-4.5 hours, which is relatively short. Since blood levels may fluctuate as a result of such frequent drug delivery, SR pellets, which offer advantages over tablets, must be developed. The goal of this work is to create matrix pellets without a covering that continually release the medicine over the course of 12 hours.

Extended Drug Delivery System

Extended-release delivery systems are dependent on a number of related, significant factors, including the type of delivery system, the disease being treated, the patient, the duration of therapy, and the characteristics of the drug. Any drug delivery system that achieves a slow release of the drug over an extended period of time is a sustained release system. A system can be considered a controlled-release system if it is successful in maintaining consistent medication levels in the target tissue or cells, whether this control is of a temporal, spatial, or both nature.[6] In recent years, there has been an increase in the development of sustained-release dosage forms for numerous medications, in combination with advancement and innovation in the field of pharmaceutical technology. This system's main goals were to assure patient compliance, increase therapeutic efficacy, and improve safety. This is accomplished via better control of plasma drug levels and less frequent dosing. According to pharmacokinetic theory, zero-order absorption is the most effective way to lower the ratio of plasma maximum concentration (C_{max}) to plasma minimum concentration (C_{min}). Drug concentration in plasma is stable after steady state is reached under these circumstances as long as absorption continues. This administration method is superior to previous methods in a variety of ways, including enhanced effectiveness, decreased toxicity, and increased patient comfort. Improved medication therapy effectiveness is the major objective of controlled drug delivery systems. Any drug or dosage form alteration that lengthens a drug's therapeutic activity is a sustained-release drug delivery method, according to the simple definition.[5,7]

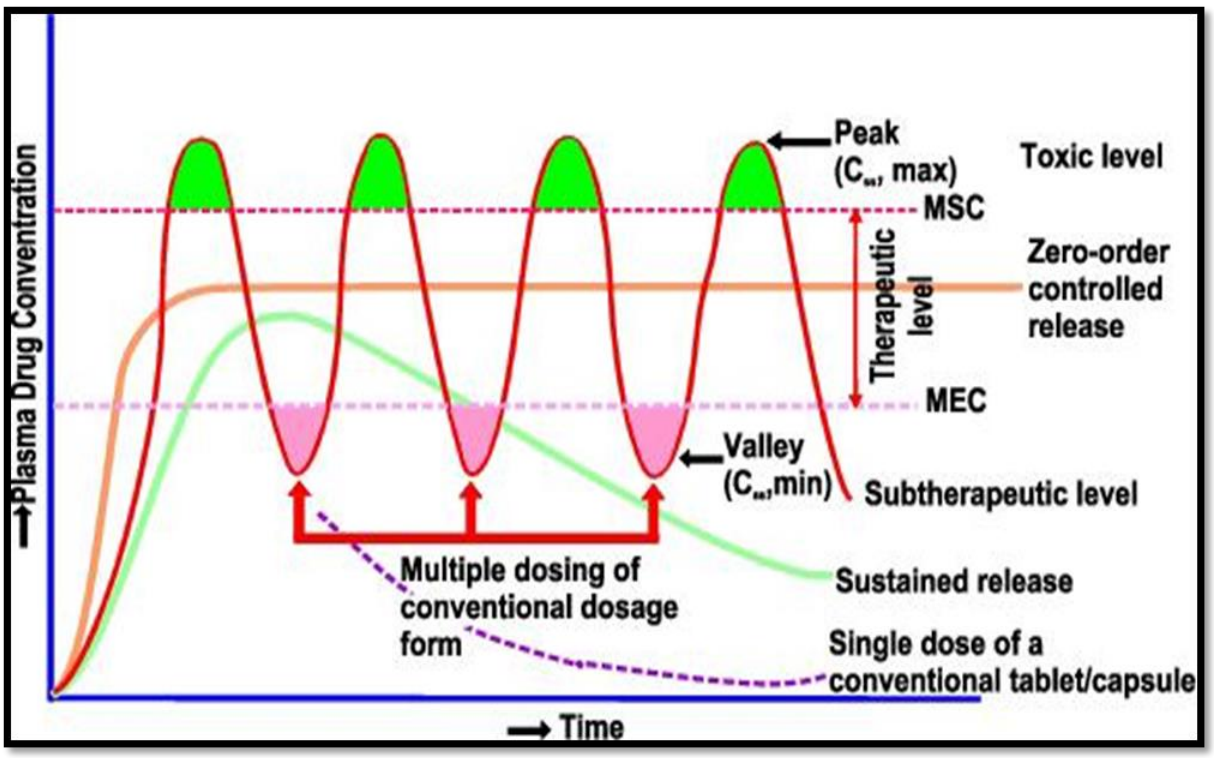


Fig. 1 Plasma drug concentration profiles for sustained release formulation and zero-order controlled release formulation.

Pellets [8, 9,10,11]

The active pharmaceutical ingredient (API) is present in pellets as a number of tiny independent molecular subunits. Pellets are small, spherical, free-flowing granules with a narrow size distribution, typically having a diameter between 500 and 1500 um. To provide the recommended total dose, these subunits are gathered in a sachet, encapsulated, or compacted into a tablet. Easy-to-disperse pellets in the G.I.T. increase drug absorption and minimise mucosal irritancy brought on locally by some irritating drugs. Compared to tablets, pellets have fewer fluctuations in gastric emptying rates, more flexibility for dosing forms, and easier coating. They can be designed with an immediate-release dose form, a sustained-release dosage form that delivers the medication over time, or they can be coated to deliver the medication to a particular place in the digestive system.

They can be separated into desired dose strengths without altering the formulation or procedure, then blended to deliver particles with distinct release profiles or incompatible bioactive chemicals simultaneously at the same location or at multiple sites within the digestive system. Pellets offer a high degree of flexibility due to their ability to flow freely. They may therefore be packed without any issues. Due to their spherical shape and low

surface area to volume ratio, pellets had a homogenous film covering. Pellets don't have the dosage dumping effect, which leads to a smoother plasma concentration profile and more progressive drug absorption than tablets, which further lessens prescription side effects.

Methods of Preparing Pellets [12, 13]

- Extrusion-spheronization
- Drug layering
- Globalisation Or Droplet
- Balling
- Spray Congealing

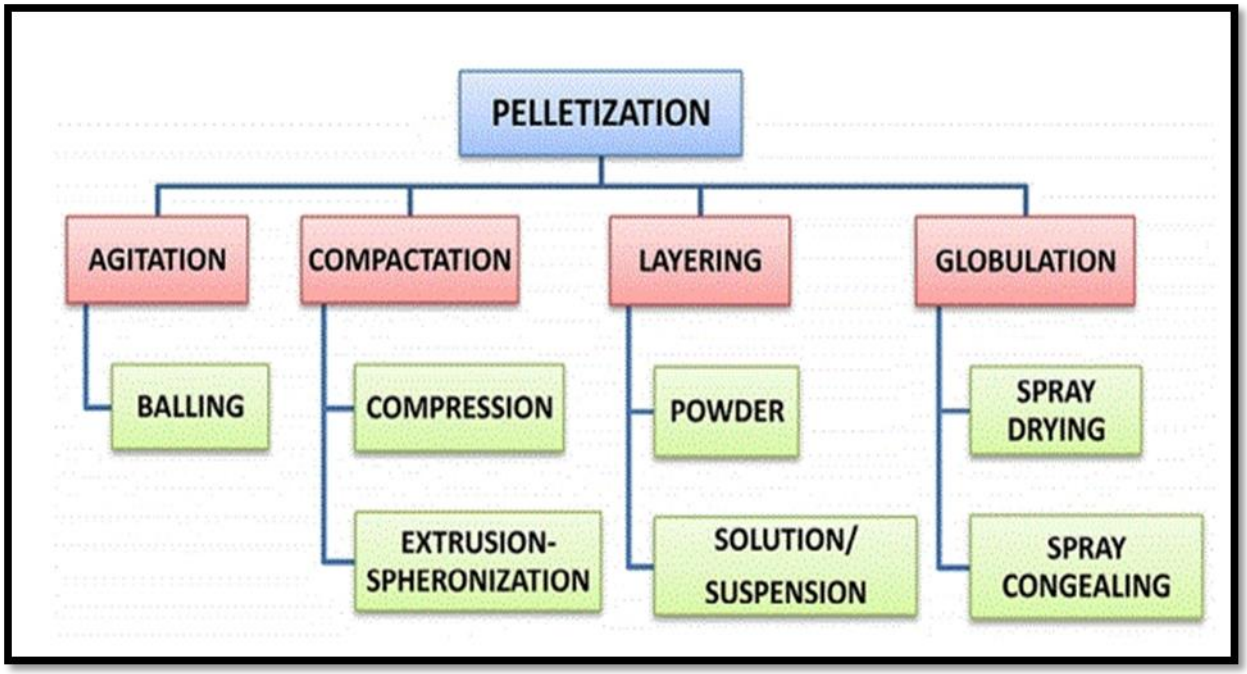


Fig.2 Various method of Pelletization

Extrusion- spheronization

The idea of multi-particulate dosage forms was first proposed in the 1950s, but as the use of Multi-particulate extended-release (CR) oral dosage forms has grown, there has been an increase in interest in the processes used to make these dosage forms.[12]For the preparation of Multi-particulate CR dosage forms, it has been widely used as a potential technique and as a future method of preference.[13]Dry mixing, wet granulation, extrusion, spheronization, drying, and screening are all steps in this multi-step procedure. In the first stage, the drug and

excipients are dry-mixed in appropriate mixers. Next comes wet granulation, in which the powder is transformed into a plastic mass that is simple to extrude.

The extruded strands are then introduced into a spheronizer, where they are instantly split into short cylindrical rods upon contact with the revolving friction plate and propelled outward and upward by centrifugal force against the stationary wall of the processing chamber. Once the required sphericity is attained, the particles finally return to the friction plate due to gravity, and the cycle is repeated. The technology is distinctive in that it can produce extended-release pellets in specific circumstances in a single process, eliminating the need for additional film coating. It is also suitable for the manufacture of pellets with high drug loading. Extrusion- Spheronization is a multi-step procedure requiring a variety of equipment and unit activities. The extruders and spheronizer, however, are the most important processing tools that, in essence, determine how the process will turn out altogether.[14]

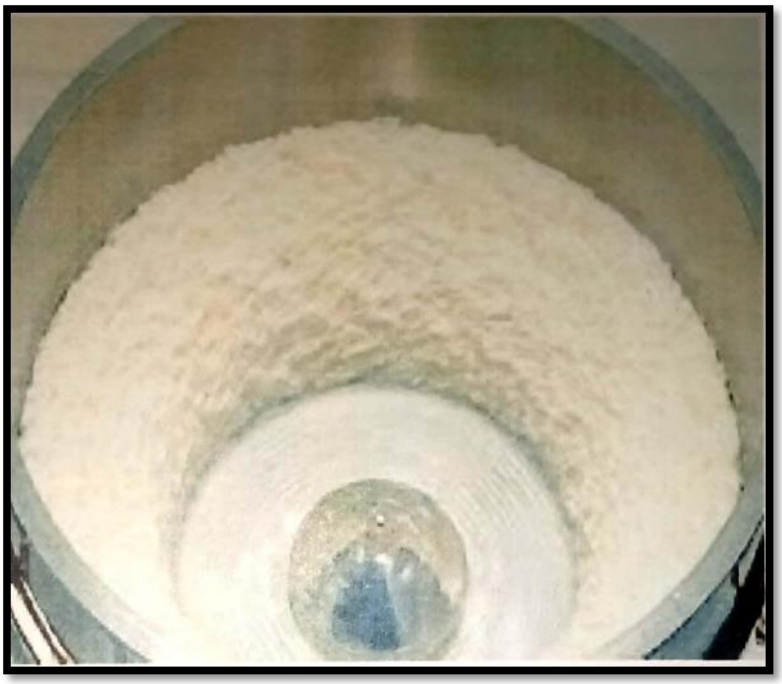


Fig.3 Process of Spheronization

Currently available extruders fall into three categories: screw-fed extruders, gravity-fed extruders, and Ram Extruders. These extruders vary in design elements and operational principles. Screw-fed extruders move the material horizontally by having screws that revolve around the horizontal plane. Both longitudinal and radial screw extruders are possible. A loading zone, a compression zone, and an extrusion zone make up an axial extruder, which

has a die plate positioned axially. Jacketed cylinders regulate the product temperature while it is being extruded.In radial extruders, the material is extruded radically through screens positioned around the horizontal plane of the screws, with a short transport zone. The rotary cylinder and rotary gear extruders, which are both gravity-fed extruders, differ mainly in the layout of their two counter-rotating cylinders. One of the two counter-rotating cylinders in the rotary-cylinder extruder is empty and perforated, while the other cylinder is solid and serves as a pressure roller. Two hollow, counter-rotating gear cylinders with Counter-bored apertures compose the so-called Rotary-gear extruder. In ram extruders, a piston moves the substance and pushes it through a die at the very end. Ram extruders are favoured when developing formulations because they make it possible to measure the rheological characteristics of the formulation. Filler, lubricants, and pH modifiers are formulation elements that are essential for creating pellets with the desired properties during an extrusion-spheronization process. For Extrusion, the granulated mass needs to be plastic, adequately cohesive, and self-lubricating. The extrudates must break at the proper length and have enough surface moisture to facilitate the formation of uniform, spherical pellets during the spheronization pellets.[15]

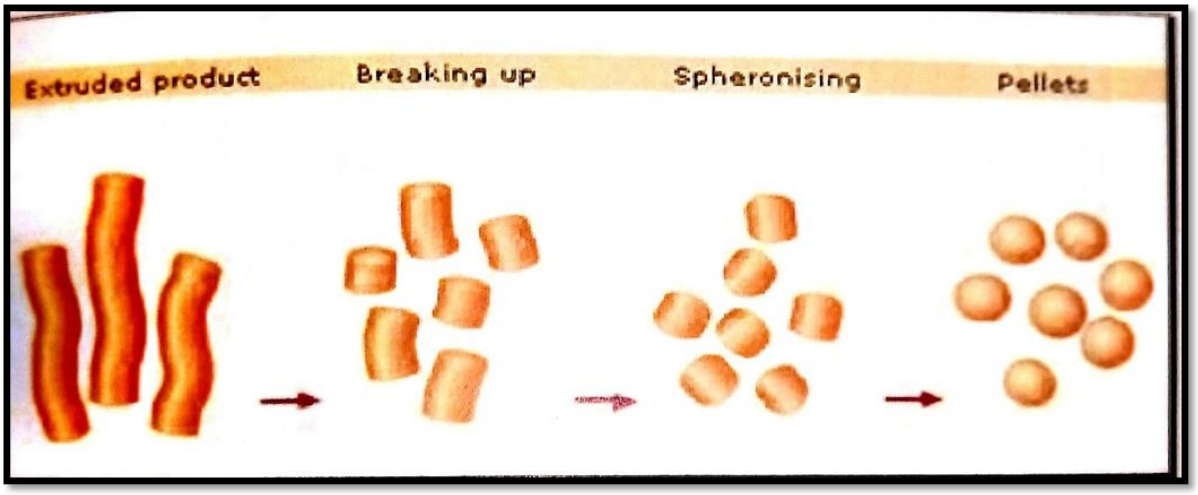


Fig.4 Extrusion-Spheronization Process

Material

Diltiazem HCl a calcium channel blocker drug obtained as a gift sample from "Swapnroop Drugs and Pharmaceuticals" Aurangabad, India.Ethylcellulose [10cps] and HPMC K100 and other HPMC Grades were obtained as gift sample from colorcon,goa,India. Microcrystalline cellulose obtained as gift sample from signetchem, mumbai,and distilled water.

Method

A) Drug Identification and Drug-Excipients compatibility study

1) Melting Point [16]

The melting point of Diltiazem HCI was determined by taking a small amount of sample in a capillary tube closed at one end and placed in Digital melting point apparatus. (Veego Digital Melting point apparatus) The melting point was recorded.

2) Spectroscopy[17,18]

a) Determination of λ_{max} of Diltiazem HCl

The UV absorption spectrum of Diltiazem Hydrochloride was obtained using a UV-visible spectrophotometer. The spectrum was scanned from 200 nm to 400 nm. A typical spectrum of Diltiazem Hydrochloride dissolved in methanol & distilled water. (Conc. 100µg/ml).

b))Standard Calibration curve of Diltiazem HCl

i.Preparation of standard solution-

10 mg of Diltiazem hydrochloride was accurately weighed and transferred to a 100 ml volumetric flask containing 30 ml of distilled water and sonicated for 15 minutes. This was further diluted upto the mark with distilled water to obtain drug concentration of 100 ug/ml. From this solution, 1 ml was further diluted using the same solvent to obtain drug concentration solution of 10 µg/ml as a working standard solution.

ii. Preparation of a working solution

From standard solution pipette out 2,4,6, 8, 10, 12 µg/ml respectively. These 2,4,6, 8, 10, 12, ml. Transfer to 100 ml volumetric flask & make volume up to 100 with distilled water to get 2.4…12 µg/ml conc. Measure the absorbance at 237 nm using a UV-visible spectrophotometer. Plot graph between Conc. Vs. Abs. Calculate coefficient of correlation (should be between 0.9-1) & slope.

3) Fourier transform infra-red spectra (FTIR)

The drug sample was placed in FTIR cuvette. The drug sample was said over the range of 4000-400 cm^{-1} on an FTIR (Prestige 21 SHIMADZU). The FTIR spectra of drug sample were recorded. (Drug, and mixture of drug and polymers (1:1).

B) Preparation of pellets

1) Selection of binder

Binders are adhesive materials that are incorporated to bind powders and maintain pellet integrity. They are an essential component of pellet formulation. In all cases binders are used in concentration range of 2-5%. Some of the binders like the solution of HPMC, polyvinyl pyrolidone, hydroxypropyl cellulose etc.

Pellets without drug (dummy pellets) were prepared with various binder solutions such as water, PVP K30, and HPMC (K4M, K15M, and K100M) solution in water. The responses of consistency of extrudates were studied and pellets were observed for their appearance and strength.

2) Optimization of Extrusion Spheronization Process

As the literature reveal that spheronization speed and time of spheronization affecting the pellets shape, roundness and pellet size hence to optimise speed and time, formulating the dummy pellets batches at three different speed and time Thus, 32-9 formulations were prepared.

Speed of spheronization (XI) 1300, 1500, 1700 rpm

Time of spheronization (X2)-10, 15, 20 min

3) Formulation of pellets

Powder of all the ingredients are passed through sieve no 40 separately then weighed accurately. Mixing of all weighed ingredients was performed by using geometric and bag-shaking method. Addition of binder solution in optimized concentration and water as quantity sufficient that lead to formation of dump mass having enough moisture. Amount of water added was also affecting the extrudibility of wet mass and indirectly process.The wet mass

was kneaded Then wet mass passed through extruder and extrudes formed that transfer to spheronization at optimized speed and time[19]

The wet mass obtained was extruded by roller extruder. Extrudate was then spheronized using a Spheronizer, equipped with cross-hatched plate 4.2 mm at 1500 rpm for 20 min. The time and speed of the Spheronization wasdetermined by the experimental design. The pellets were dried under the same conditions, at 40±2°C and sieve through 40 screens.

Factorial design

A $(3)^2$ factorial design was applied to optimize the concentration of two different polymers to observe the combine effect of polymer on the drug release pattern for getting the sustained release of Diltiazem HCI the factors included were the quantity of EC(A) and, HPMC K100(B) at constant speed and time. The approximate levels of these independent variables were chosen from drug release profile of preliminary batches.

C) Evaluation of Pellets

1) Bulk Density(20)

The bulk density was determined by three tap method. The powder was filled in cylinder. The cylinder was dropped onto a hardwood surface three heights of 1 inch at an interval of 2 seconds. Bulk density calculated by given formula

$$\text{Bulk Density} = \frac{\text{Weight of powder (gm)}}{\text{Bulk volume of powder (cm}^3\text{)}}$$

2) Tap Density

The tap density was determined by dividing the weight of powder by the tapped volume. The powder was introduced into a 50 ml cylinder. The cylinder was dropped onto a hard wood surface three times from a height of 1 inch at an interval of 2 seconds. Then Tap density is calculated by given formula.

$$\text{Tap Density} = \frac{\text{Weight of powder (gm)}}{\text{Tapped volume of powder (cm}^3\text{)}}$$

3) Carr's Index

Carr's compressibility index is a measure of powder flow properties and was calculated using the following equation.

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

4) Hauser's Ratio

Hausner's ration is an indirect index of ease of powder flow. Lower hausner's ratio indicated better flow properties than higher ones. Tapped density and bulk density were measured and the Hauser's ratio was calculated using the following formula.

$$\text{Hausner's ratio} = \frac{\text{Tapped density(gm/cm3)}}{\text{Bulk density(gm/cm3)}}$$

Table no:1 Hausner's ratio and Compressibility as an indication of powder flow properties

Sr.No	Hausner's Ratio	Flowability	Compressibility Index
1	1.00-1.11	Excellent	<10
2	1.12-1.18	Good	10-15
3	1.19-1.25	Fair	16-20
4	1.26-1.35	Passable	21-25
5	1.35-1.59	Poor	26-31
6	1.46-1.59	Very poor	32-37

5) Angle of Repose

The angle of repose was determined by the funnel method. Accurately weighed sample were taken in a funnel height of the funnel was adjusted in such way a that tip of the funnel just touches the apex of the heap of Pellets. The samples were allowed to flow through Funnel freely onto the surface the diameter of the pellets cone was measured and the angle of repose was calculated using equation.

$$\tan\theta = \frac{h}{r}$$

Table no:2 Relationship between angle of repose and Flowability

Angle of Repose	Flowability
<20	Excellent
20-30	Good
30-34	Passable
>40	Very Poor

6) Particle size[21]

The particle sizes of the formed pellets are to be measured using an optical microscope with ocular and stage micrometre where the particle size distribution can be calculated.

7) Friability test

Friability testing was conducted using a friability tester. 2 gm pellet sample was placed into the drum together with 10 g glass spheres of 5 mm diameter, and rotated for 10 min at 25 rpm. Pellets were then weighed and friability was calculated according to the formula:

$$\%\text{Friability} = \frac{W_O - W_1}{W_O} \times 100$$

whereas, W_O=Initial weight,

W_1= Final weight

8) Percent drug content

Pellets was accurately weighed, crushed, and dissolved in methanol to sonicate for 5 min, diluted to with phosphate buffer 6.8 and filtered. 1 mL of the filtrate was diluted to 10ml with same solvent. The content of Diltiazem HCL was determined spectrophotometrically by measuring the absorbance at 237nm. The results are expressed us mean values of three determinations +S.D.

9) In-vitro release studies

A calculated amount of pellets equivalent to 180 mg Diltiazem HCL was placed into the USP type-1 of a dissolution tester (electro lab dissolution tester USP Mumbai). The dissolution medium consist of 900ml phosphate buffer solution (pH 6.8). The dissolution medium temperature was kept at 37±0.5°C and adjusted at 50rpm. At pre-determined time intervals 1,2,3,4,5,6,7,8,9,10,11, 12hr. an 1ml of sample was collected and diluted with the same solvent then filtered and analyzed spectrophotometric. Record the absorbance and calculate the percentage of Diltiazem HCL dissolved in dissolution media.

10) Stability Study[22]

In any rational drug design or evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection. Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation until its chemical or biological activity is not less than a predetermined level of labelled potency and its physical characteristics have not changed appreciably or deleteriously.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental Factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

$$\%\text{Drug release} = \frac{\text{Drug release}}{\text{Dose of Drug}} \times 100$$

Long-term Testing: 25° C 2° C / 60 % RH + 5% for 12 Months.

Accelerated Testing: 40° C +2° C / 75% RH+ 5% for 6 Months.

Stability studies were carried out at 25°C/ 60% RH and 40° C / 75 % RH for the selected formulation for the period of 3 months.

Method

The selected formulations were packed in amber-coloured bottles, which were tightly plugged with cotton and capped. They were then stored at 25° C / 60% RH and 40° C/75 % RH for 3 months and evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of time.

Results and Discussion

1) Organoleptic Characterization and Melting Point Determination

The organoleptic character and melting point were found to be as per standard drug so drug used in the formulation was found to be pure according to I. P specification,

Table no:3 Organoleptic characteristics and melting point

Sr.No	Test	Observation
1.	Colour	White crystalline powder
2.	Odour	Odourless
3.	Taste	Bitter
4.	Melting point	210-215°C
5.	pH	4.5-6.0

2) Solubility analysis

The solubility of pure drug in 10mg/10ml of solvent was carried out and it reveals that it is soluble in water, sparingly insoluble in methanol and dichloromethane, soluble in phosphate buffer ph 6.8.

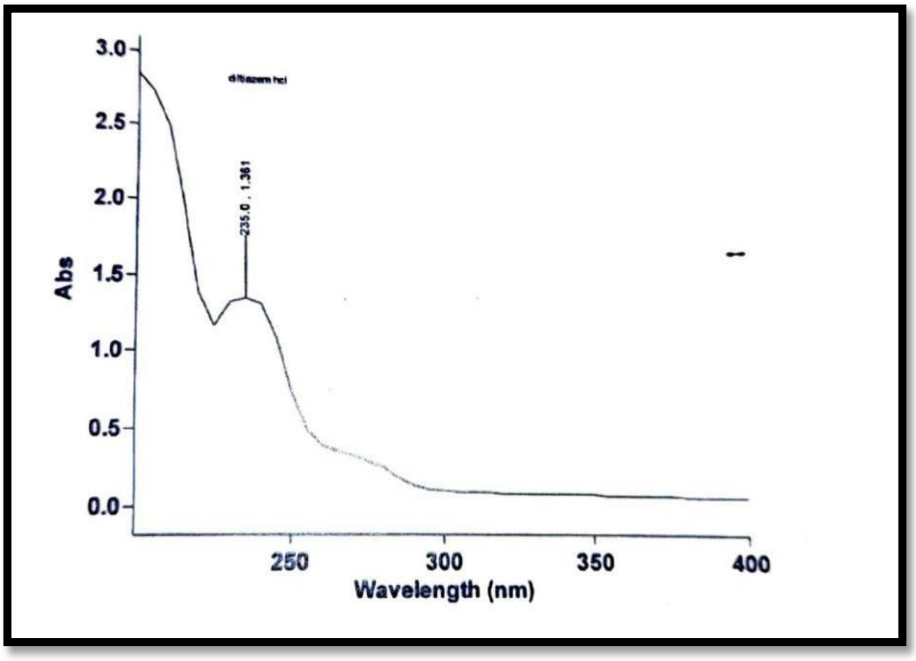
Table No 4: Solubility analysis

Sr.No	Solvent	Solubility
1.	Water	Soluble
2.	Buffer solution pH 6.8	Soluble
3.	Methanol	Insoluble
4.	Dichloromethane	Insoluble

3) Spectroscopy

I. Determination of λmax of Diltiazem HCl

Diltiazem HCL showed the maximum wavelength at 237nm, which matches the standard.



Figno:5 λmax of Diltiazem HCl

II. Standard Calibration curve of Diltiazem HCl

The standard calibration curve of Diltiazem HCl was done by plotting absorbance v/s concentration.

The absorbance values are mentioned in the table no 5

Table no: 5 Standard calibration of Diltiazem HCl in phosphate buffer pH6.8

Sr.No	Concentration(ug/ml)	Absorbance
1.	0	0
2.	2	0.1161
3.	4	0.2410
4.	6	0.3862
5.	8	0.5190
6.	10	0.6477
7.	12	0.7854
8.	14	0.9194

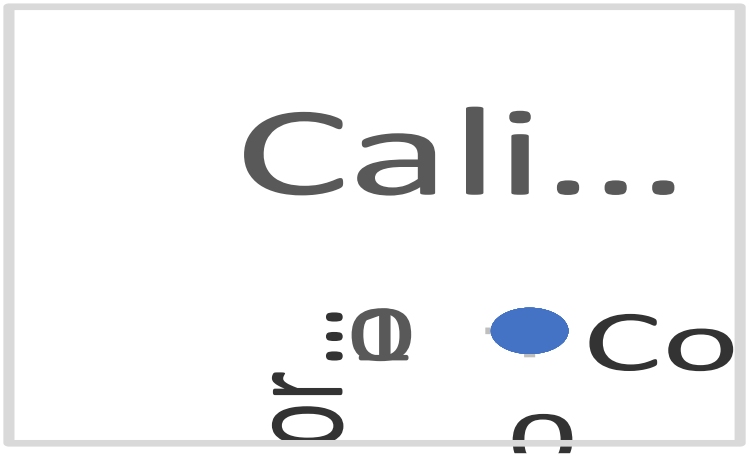


Fig no 6: Calibration curve of Diltiazem HCl

The linear regression analysis was done on absorbance data points the results are as follows:-

The Slope = 0.0663

The intercept = 0.012

The correlation coefficient = 0.999

A straight-linear equation (y = mx+c) was generated to facilitate the calculation for the amount of drug.

Absorbance=0.0663× Concentration

4) FTIR Study of Drug and Excipients

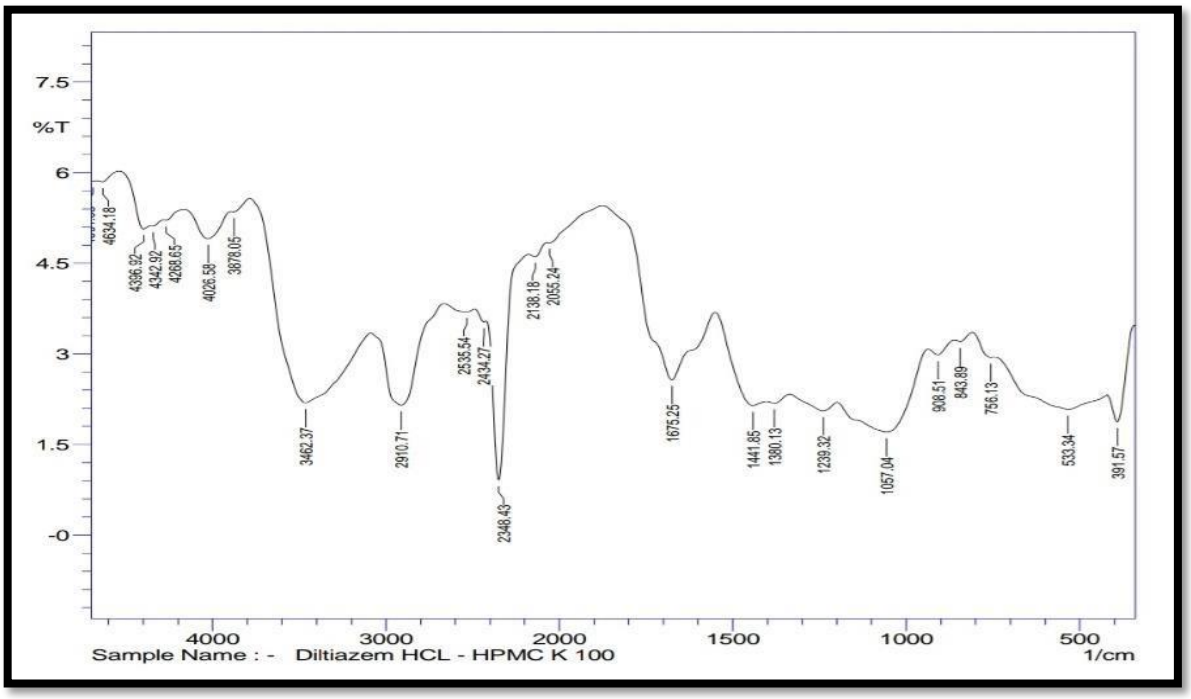


Fig No 7:FTIR OF Diltiazem HCL

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied making a KBr disc. The characteristic absorption peaks of Diltiazem HCL were obtained at different wave numbers in different samples. The peaks obtained in the spectra of each formulation correlate with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components.The spectra for all formulations are shown below:

A)FTIR study of Diltiazem HCl

B) FTIR study of Drug and Excipients

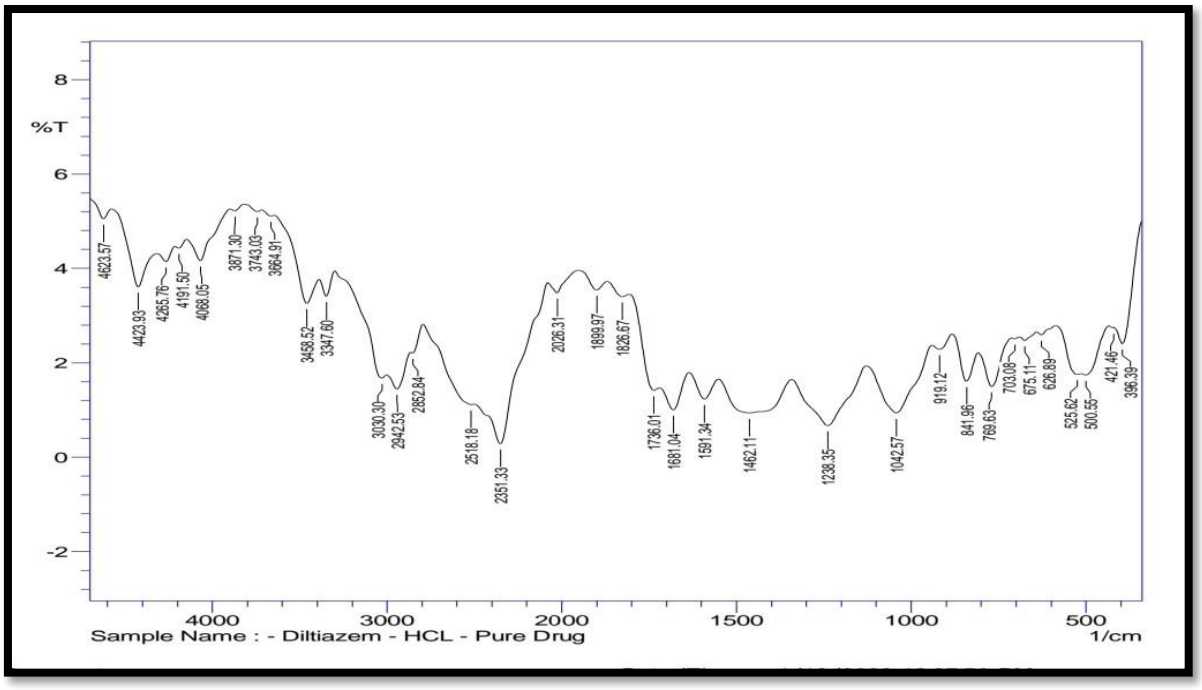


Fig No 8:FTIR of Diltiazem HCl + HPMC K100

5) Formulation of Diltiazem HCl pellets

Table no 6: Formulation of Diltiazem HCl pellets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Diltiazem HCl	180	180	180	180	180	180	180	180	180
MCC	203	158	113	203	158	113	203	158	113
Ethylcellulose	90	135	180	90	135	180	90	135	180
HPMCK100	27	27	27	45	45	45	63	63	63
PVPK30 (0.5%)Binder Solution	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

6) Evaluation of Pellets

Table No 7:Flow properties of pellets

Batches	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (°)	Carr's Index (%)	Hausner's Ratio	Friability(%)
F1	0.751	0.785	24.6°	7.14	1.04	0.55
F2	0.722	0.787	26.6°	9	1.09	1.07
F3	0.605	0.650	22.8°	7.43	1.07	0.75
F4	0.607	0.690	22.3°	13	1.13	0.90
F5	0.624	0.663	24.6°	6.25	1.06	1
F6	**0.599**	**0.647**	**24.8°**	**8.01**	**1.08**	**0.95**
F7	0.587	0.636	21.1°	8.34	1.16	0.52
F8	0.590	0.675	25.9°	14	1.14	1
F9	0.601	0.649	22.6°	7.89	1.07	0.85

- **Bulk Density**: It has been stated that the bulk density values less than 1.2gm/cm3 indicate good packing and values greater than 1.5gm/cm^3 indicate poor packing. The bulk density value for all formulations varies in the range of 0.587 gm/cm3 to 0.751gm/cm3.The values obtained lies within an acceptable range.

- **Angle of Repose** : The values obtained for angle of repose for all batches are tabulated in the table no 10.The values were found to be in the range of 21.1° to 24.8°.This indicates good flow property of the pellets.

- **Carr's Index:** The values obtained for Carr's Index for all batches are tabulated in the Table no 10.The values were found to be in the range of 6.25% to 14% indicating that the pellets have required flow properties for compression.

- **Hauser's ratio:** The values obtained for Hausner's ratio for all batches are tabulated in the table no 10. The values were found to be in the range of 1.04 to 1.16 indicating that the pellets have required flow property for compression.

➢ **Fraibility Test:** Pellets friability was determined by the Roche friabilator and weight loss calculated and represented in the term of percent friability. The value of friability test were tabulated in table no 10 . The %friability was less than 1%in all the formula ensuring that the pellets were mechanically stable.

7) Percent Drug Content

The Percentage of drug content was found to be between 90.26±0.12% to 95.34±0.14% of Diltiazem HCl, which was within acceptable limits. Table No 8 shows the result of drug content uniformity in each batch.

Table No 8: Percent Drug Content

Batches	**% Drug Content**
F1	90.26±0.12
F2	90.4±0.11
F3	92.71±0.16
F4	92.94±0.12
F5	92.27±0.15
F6	**95.34±0.14**
F7	90.75±0.10
F8	93.85±0.15
F9	94.04±0.14

Mean ±S.D, n=3

8) Particle size distribution:

Table No 9: Particle size distribution

Sr.No	Batches	Mean Particle Size
1	F1	0.70±0.01
2	F2	0.72±0.03
3	F3	0.74±0.01
4	F4	0.64±0.04
5	F5	0.75±0.01
6	**F6**	**`0.80±0.04**
7	F7	0.65±0.08
8	F8	0.72±0.03
9	F9	085±0.03

9) *In-vitro* studies

The *In-vitro* drug release of the entire matrix pellets was carried out in phosphate buffer pH 6.8 from 0-12 hrs by USP type-l apparatus and the value are shown in Table no 10. From the in-vitro dissolution data, it was found that the drug release of matrix pellets containing Diltiazem HCl in varying proportion of HPMC K100 and Ethyl Cellulose in batches (F1-F9).

Drug: Ethyl cellulose (1:0.5, 1:0.75, 1:1)

Drug: HPMC K100 (1:0.15, 1:0.25, 1:0.35)

The release profile of Batch F1 showed drug release as 23.47% for 1hrs & 86.29% for 12hrs. The batch F2 showed drug release as 21.27 for 1hrs & 85.55% for 12hrs. Batch F3 showed drug release as 18.59% for 1hrs & 83.60 % for 12hrs. The Batch F4 showed drug release as 24.91% for 1hrs & 84.74 % for 12hrs. Batch F5 showed drug release as 21.26% for 1hrs & 83.44 % for 12hr. The Batch F6 showed drug release as 16.52% for 1hrs & 76.13% for 12hr. Batch F7 showed drug release as 25.05% for 1hrs & 86.01 % for 12hr. Batch F8 showed drug releaseas 21.19% for 1hrs & 79.03% for 12hr. Batch F9 showed drug release as 19.47 % for 1hrs & 77.76 % for 12hr.

From the result it was observed that increasing the amount of polymer in the formulation, results in slower rate and decrease amount of drug release from the pellets. Combination of

HPMC K100 and Ethyl cellulose based pellets, release of drug was found to be more faster in Batch (F6) compared to Batch (F1-F2-F3-F4-F5-F7-F8-F9).

In-vitro release studies of all formulation (F1-F9) were compared and evaluate. The result showed that the drug release profile of formulation F6 shows sustained release. Batch F6 shows slow drug release in 10hr, 11hr, and 12hr as 67.41%, 71.88% and 76.13% respectively. Maximum drug release was found to be 76.13% over a period of 12 hrs in the ratio of (1:0.25). This indicate that the minimum quantity of HPMC K100 and maximum quantity of Ethylcellulose required to prepared the sustained release matrix pellets of Diltiazem HCl.Hence, Formulation F6 containing HPMC K100 in the ratio 0.25% and Ethyl cellulose 1% (0.25:1) was considered as an optimized formulation and used for further study.

Table No 10: *In-vitro* Dissolution data

Time in Hrs	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	**0**	0	0	0
1	23.47	21.27	18.59	24.91	21.26	**16.52**	25.05	21.19	19.47
2	30.32	28.15	24.17	28.08	26.85	**23.94**	30.19	29.48	28.31
3	37.08	35.04	31.66	33.33	32.71	**30.19**	35.97	34.54	33.53
4	41.52	39.10	37.90	40.66	38.32	**35.35**	40.79	40.05	39.14
5	48.91	45.23	43.88	46.38	43.58	**40.41**	48.12	44.14	42.65
6	54.88	51.73	49.87	52.58	48.68	**45.91**	53.98	49.69	46.25
7	60.82	58.37	56.5	57.93	53.64	**51.06**	60.17	55.70	48.77
8	66.03	63.64	61.10	64.41	59.43	**54.67**	68.43	60.48	53.29
9	70.5	68.64	66.18	68.38	66.07	**60.26**	72.99	65.04	57.91
10	75.71	73.48	71.05	72.64	71.25	**67.41**	75.72	68.50	64.94
11	81.72	80.31	79.54	77.56	76.08	**71.88**	85.32	73.44	69.67
12	86.29	85.55	83.60	84.74	83.44	**76.13**	86.01	79.03	77.76

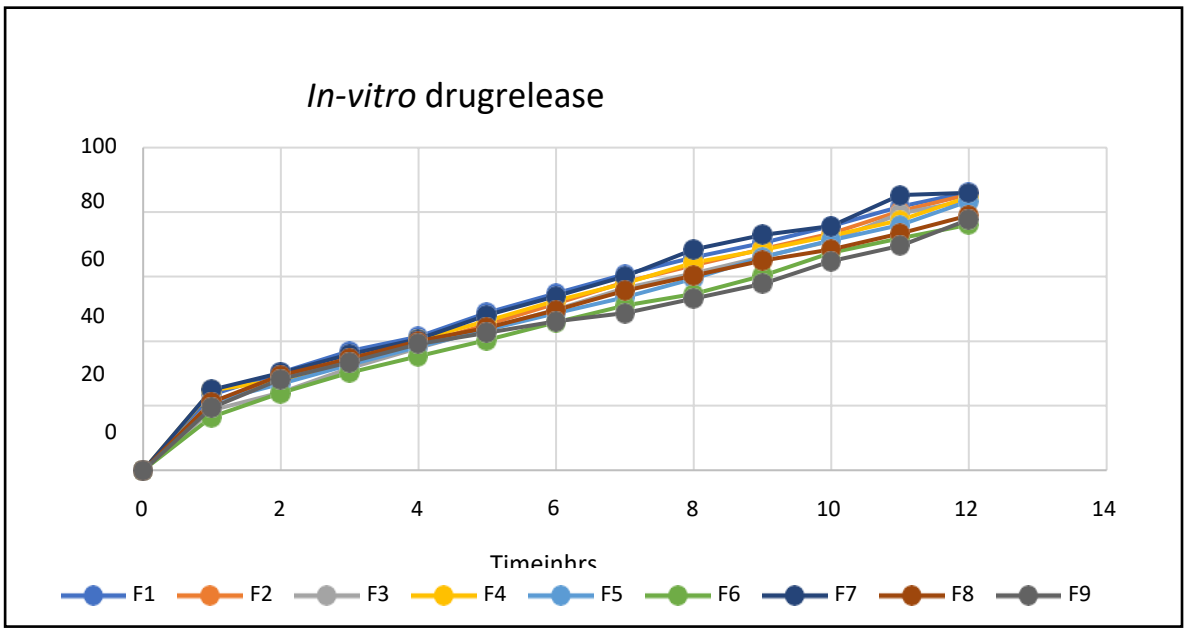


Fig no 9:*In-vitro* Drug Release

10) Stability studies

Table No 11: Dissolution study of optimized formulation F6 after stability Study

Time in hrs	Stability study (0days)	Stability study (After30days)	Stability study (After60days)
0	0	0	0
1	15.9	15.8	15.6
2	30.5	30.4	30.3
3	45.9	45.7	45.5
4	60.5	60.4	60.2
5	71.2	71.1	71.0
6	78.5	78.4	78.2
7	82.9	82.8	82.6
8	86.7	86.6	86.4
9	89.8	89.6	89.4
10	92.5	92.4	92.2
11	95.7	95.6	95.4
12	98.9	98.8	98.5

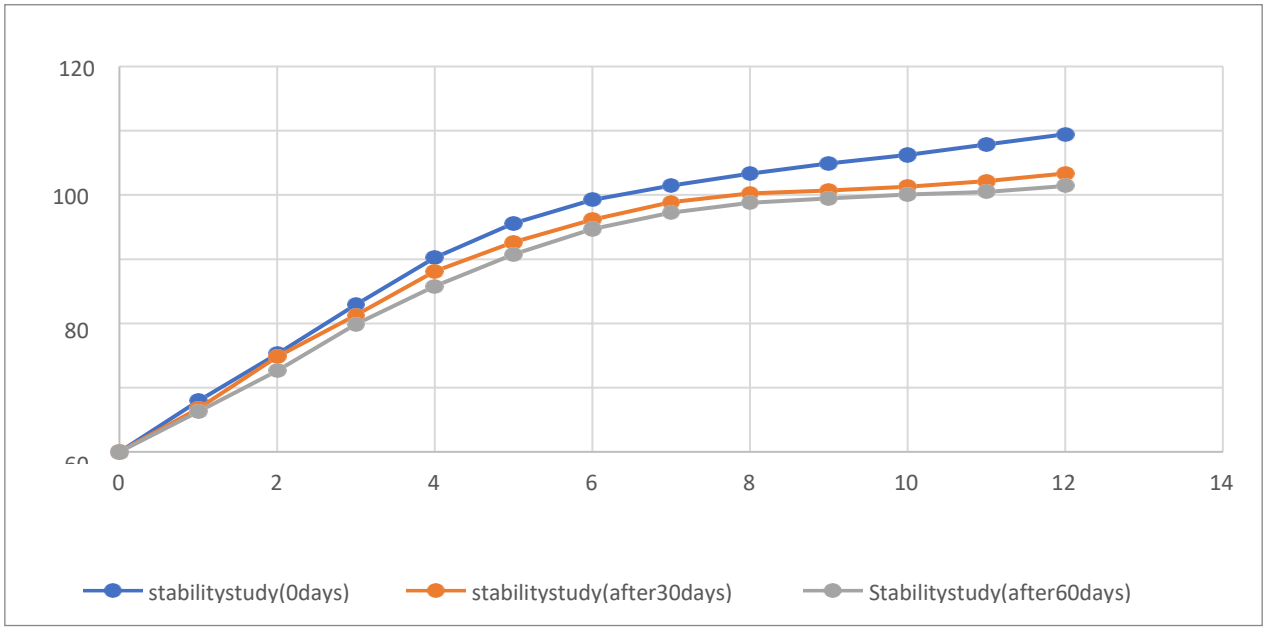


Fig no 10:Stability Studies Graph

CONCLUSION

It was concluded that the polymer plays an important role in the formulation of extended-release matrix pellets of Diltiazem HCl. Finally, it was found that the release of drug was low when matrix pellets contained higher concentrations of polymers. Batch F6 is considered to be optimized as the evaluation parameter passes through the acceptable range.

REFERENCES

1) Gupta PK and Robinson JR. "Oral controlled release delivery". Treatise on controlled drug delivery. 1992; 93(2): pp 545-555.
2) Jantzen GM and Robinson JR. "Sustained and Controlled-Release Drug Delivery systems". Modern Pharmaceutics, 1995; 121(4): pp 501-502.
3) Jeevana J.B., Jyosna D, "Multi-particulate drug delivery systems using natural polymers as release retardant materials", International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 6 (10): 61-65.
4) Wani MS. "Controlled Release System A Review"; Pharmaceutical Review.2008; 6(1): pp 41-46.
5) Sahil Husen IJ, Mukesh RP. "Pharmaceutical Controlled Release Drug Delivery Systems": A Patent Overview. Aperito J Drug Designing & Pharmacology 2014;1(2): pp 1-22.
6) Sampath Kumar KP, Debjit B, Shweta S, Shravan P, Dutta AS. "Sustained release drug delivery system potential". The Pharma Innovation 2012; 1(2):pp46-56.
7) Sahil husen IJ, Mukesh RP, Alpesh DP. "Sustained Release Drug Delivery Systems": A Patent Overview. Aperito J Drug Designing and Pharmacology 2014:1(1): pp1-14.
8) Dey N.S., Majumdar S., Rao MEB, "Multiparticulate Drug Delivery Systems for Controlled Release", Tropical Journal of Pharmaceutical Research, 2008; 7(3): pp 1067-1075.
9) Shailesh L.P., Mahesh. K.B, "Controlled release approach to novel Multiparticulate drug delivery system", International Journal of Pharmacy and Pharmaceutical Sciences, 2012;4(3): pp757-763.
10) Deepak S, Sanjay K.S., Manish J., Amit K., "A review on multi particulate floating drug delivery system", International Journal of Pharmaceutical, Chemical and Biological Sciences, 2014; 4(1): pp201-207.

11) Punia Supriya, BalaRajni, Rana A.C., "Pelletization Technique: A literature Review", International Research Journal of Pharmacy, 2012; 3(3): pp43-47.
12) Kumar S. ―Formulation and Evaluation of Multiunit Pellet System of Venlafaxine Hydrochloride‖, Journal of Pharmaceutical and Biomedical Sciences, 2012; 18: 2-3.
13) Newton J.M. ―Factors influencing the physical characteristics of pellets obtained by Extrusion and spheronization‖, International Journal of Pharmaceutics, 2002; 23(2): 91-106.
14) F. Podczeck, P.E. Knight and J.M. Newton. The Evaluation of modified microcrystalline Cellulose for the Preparation of pellets with high drug loading by Extrusion/spheronization. International Journal of Pharmaceutics, 2008; 350: 145–154.
15) Srujan Reddy, Palash Das, Harika Das and Arpita Ghosh, MUPS (Multiple Unit Pellet System) Tablets – A Brief Review. Journal of Pharmaceutical and Biomedical Sci, 2011; 12(02): 1-5.
16) Martin A., Physical Pharmacy, Physical Chemical Principles in the Pharmaceutical Sciences, third edition, B.I. Waverly Pvt. Ltd, New Delhi, 557.
17) BhavanPatell, AlpaJadav. Development and Validation of Derivative Spectroscopic Method for the Simultaneous Estimation of Rosuvastatin Calcium and Fenofibrate in Tablet, International Journal of Pharma Research & Review, July 2013; 2(7).
18) Ashwininikhade, sugandhamulgund, uv spectrophotometric estimation of diltiazem hydrochloride in bulk and tablet dosage form using Area under curve method, world journal of pharmacy and pharmaceutical sciences,. Volume 3, issue 8, 1217-1224 .
19) Makoto O., Jian G, Yoshihisa M.Effect of the amount added water during extrusion- Spheronizer process on pharmaceutical properties of granules. Drug Dev Ind Pharm., 1994, 20(19): 2977-2992.
20) C.V.S. Subrahmanyam., Micromeritics. In: C.V.S. Subrahmanyam. Editors."Text book of physical pharmaceutics". 2nd Edition. VallabhPrakashan. Delhi (2000) pp. 180-234.
21) Ajit C. Bhadage, Saurabh C. Khadse, Deepak L. Rokade, Pradum P. Ige. "Development of sustained release multiple unit pellets of Glipizide using pectin, microcrystalline cellulose and eudragit L-100 by extrusion-spheronization", Indian journal of novel drug delivery pub:2014.
22) Kanvinde SA, Kulkarni MS, Stability of oral solid dosage form-A global perspective, Pharma times,37(5):9-16.