

Development of Bioequivalent Extended Release Tablets of Verapamil Hydrochloride and Its Quality Control

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Abstract-

The efficacy of drug is directly dependent on methods by which it is delivered, in order to achieve ideal concentration range for its maximum therapeutic benefit, and avoid concentrations above or below of the therapeutic range. Extended release dosage form as the one which allows two fold reduction in dosing frequency as compared to that conventional drug dosage forms. The terminologies frequently associated with sustained drug delivery systems are Sustained release, Controlled release, Prolonged release, Delayed release, Extended release. A robust Extended Release (ER) tablets formulation of Verapamil Hydrochloride giving release of 12 hr also containing immediate release part was prepared. HPMC K 4 M, HPMC K 100LV CR were used as control release agent in different concentrations. and tablets were subjected to in vitro release studies in distilled water, phosphate buffer of pH 6.8 and 0.1 N HCl. U.V, I.R, HPLC and XRD were done for the API and formulations.

Keywords- Verapamil Hydrochloride, Bioequivalent Extended release, Bilayered tablets, IR, XRD

I. INTRODUCTION

Sustained release drug formulations- prolongs drug release and hence plasma drug levels for an extended period of time but not necessarily at predetermined rate. The pharmaceutical industry provides a variety of dosage form and dosage level of particular drug thus it enables the physician to control the onset and duration therapy by altering the dose and/or mode of administration. In some instances, control of drug therapy by taking advantage of beneficial drug interaction that affects drug deposition and elimination.

Delayed release drug formulations-Drug dosage form that releases active substrates at time delayed or after prompt administration.

The drug interaction may depend on gastrointestinal environment. These are mainly of two types Intestinal and colonic.

Controlled release drug formulations- It is one of the most popular and successful delivery system because of convenience and ease of administration. They are primarily solids and based on dissolution in solvent, monitored release of the active substrate occur slowly.

Extended release drug formulations

This type of system includes formulations in which drug release is prolonged along the entire gastrointestinal tract. The basic rationale of extended release drug delivery Systems (DDS) is utilization of biopharmaceutical, Pharmacokinetic and pharmacodynamic properties to achieve desired concentration to enhance therapeutic effect and maintain adequate blood level concentration. A hypothetical curve obtained between plasma drug concentration versus time. The conventional dosage forms are administered at multiple dosing frequency in order to attain drug concentration in therapeutic range and this resulted in fluctuation of blood concentration of drug (Fig. 1).

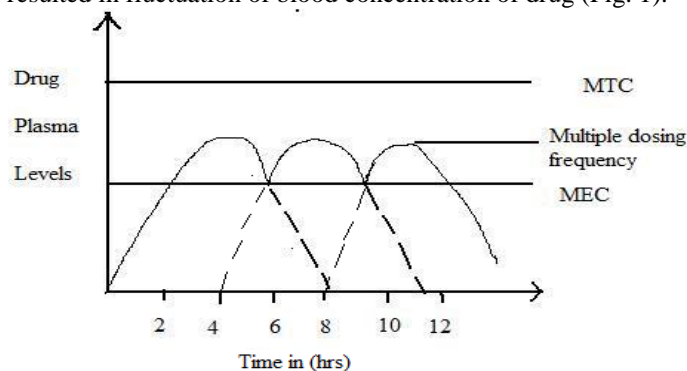


Fig. 1. A hypothetical drug plasma level-time curves for conventional dosage forms.

(MTC= Minimum toxic concentration; MEC= Minimum therapeutic concentration)

Significance of maintaining therapeutic blood concentration is to achieve desired pharmacological effects. The Extended release dosage form can deliver the drug in more sustainable form to achieve therapeutic effect to add to this, it maintain the effect over a predetermined period of time as depicted in hypothetical curve below.(Fig. 2)

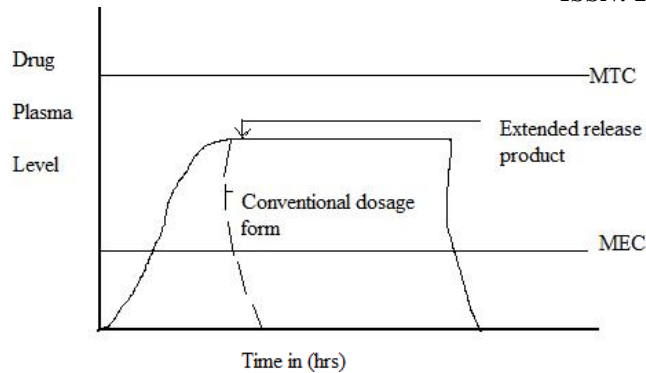


Fig. 2. A hypothetical drug level time curve for extended release product

(MTC= Minimum toxic concentration; MEC= Minimum therapeutic concentration)

Extended release dosage form can be established with various methodologies which include:

(a) Swell able matrix as extended drug release system

The swell able matrices include polymeric matrices or gel based surrounded by boundaries, hydrocolloid matrix, swell able controlled release systems or hydrophilic matrix tablets. They mainly constitute blend of drug and one or more hydrophilic polymer and these matrices forms a glass-rubbery transition on imbibitions of water.

Mechanism: drug is released by formation of gel layer around the Matrix. This gel layer inhibits matrix disintegration and further water penetration. Finally the drug release is controlled by drug diffusion through gel layer or erosion of gel layer.

The gel layer is limited by two sharp fronts that separates different matrix i.e one separating matrix by solvent and another transition. The drug release is more controlled by drug dissolution rather than by polymer swelling. Schematic diagram in Fig. 3. shows various matrix tablets fronts. The drug release is controlled by drug diffusion through gel layer or erodible matrix in order to follow gel layer dynamics during drug release in swell able matrices the boundaries of such layer have to be defined. This can be measured in three front positions which give the possibility to determine various parameters i.e rate of water uptake, rate of drug dissolution and rate of matrix erosion.

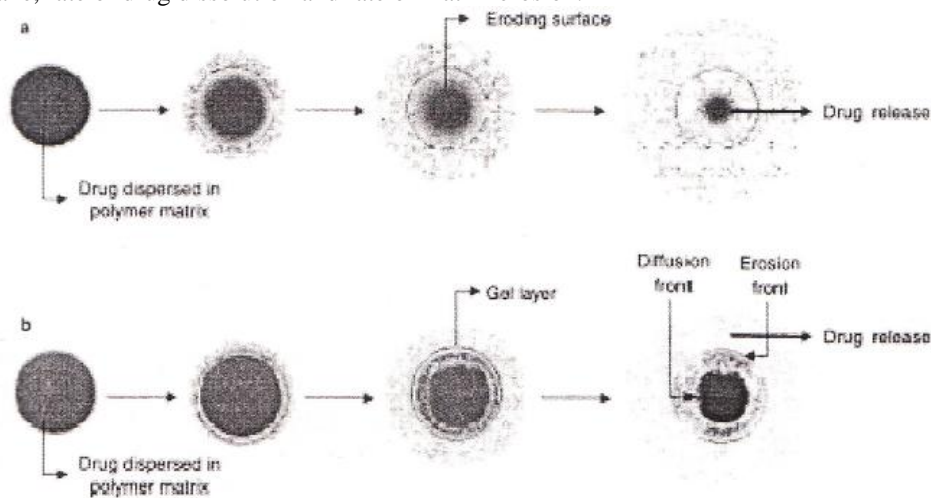


Fig 3. Schematic diagram showing drug release from swell able matrix by diffusion.

Stages of polymer that is from glassy to rubbery.

Thus in swell able matrices three fronts are expected:

- A) Swelling front between glassy polymer and rubbery state.
- B) Diffusion front between undissolved and dissolved drug as a gel layer.
- C) Erosion front between matrix and dissolution medium.

The rate of drug release is successfully modulated by microencapsulation of matrix with slowly permeable polymeric material and in this way release kinetics could be shifted to linearity.

(b) Coating of drug formulations:

It is an additional step in manufacturing process.

Objectives of coating the tablets are:

- 1) Masking taste, color and odor of the drug.
- 2) Provides both physical and chemical protection of the drug.
- 3) To control the release rate of the drug.
- 4) To improve the elegance of the dosage form.
- 5) To prevent the tablet from gastric environment e.g. enteric coated tablets.

The primary component of tablets coating are:

- 1) Properties of tablet
- 2) Coating process
- 3) Coating composition

Extended release drug dosage form comprises of two parts i.e. immediate drug release and sustained release part. It is available in beads, pellets, granules or other particulate system.

Also it comprises of various commercial coating systems and utilizes ethyl cellulose and plasticizers. The rate of drug release is directly dependent upon thickness of coating material and hence thicker the coat, drug release will be delayed further.

Ideal coating thickness is 1mm, and may be used along with the combination of three four release groups.

Quality control charts

It is a statistical tool used for analysis of data used in control of product quality.

The statistical tools developed by Dr. Walter. A. Shewhart in quality control are:

- a) The Shewhart control charts for measuring quality characteristics
- b) The Shewhart control charts for fraction rejected.
- c) The Shewhart control charts for number of non conformities per unit
- d) The portion of sampling theory that deals with quality protection given by any sampling acceptance. The quality control charts comprises of vertical and horizontal axis .The vertical axis has a scale of varying measurement like mean, range standard deviation or fraction defective.

The upper line is upper control limit which is usually three standard deviation above middle line. Similarly the lower control limit has three standard deviation below the middle line .

A graphic representation of a typical QC chart is shown in fig. 4

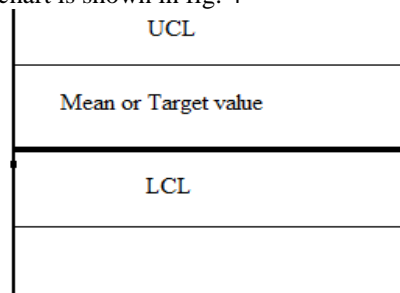


Fig 4. Typical quality control chart

II. MATERIALS & METHODS

Verapamil Hydrochloride was obtained as a gift sample from Piramal Healthcare Ltd. Baddi. HPMC K 4 M, HPMC K 100 M, Avicel 102, Aerosil from Dow Chemicals, All other chemicals used were of analytical grade.

API Analysis

FT-IR spectroscopy-The IR spectrum of drug was taken by using KBr pellet method and it is given in Fig.5.

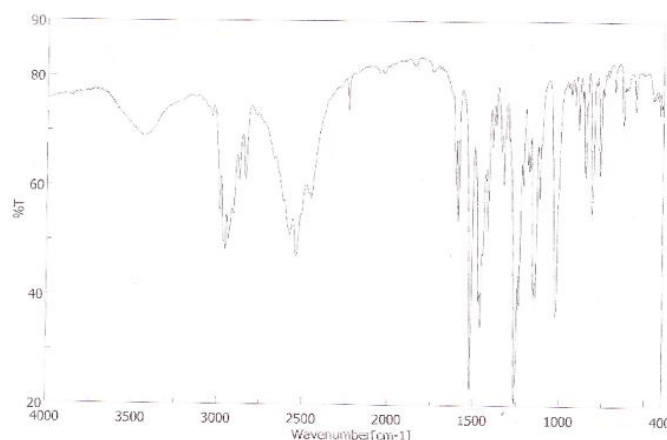


Fig- FTIR spectrum of Verapamil Hydrochloride sample obtained

XRD- (X RAY Diffraction Study)

The physical state of Verapamil Hydrochloride was explored by X-ray diffraction. Powder X-ray diffractometry was carried out with a PAN Analytical X- Ray B. V. diffractometer (PW 3040) using Ni filtered, CuK α radiation (1.5405980 \AA), a voltage of 40 kV and a current of 30 mA. The XRD patterns were recorded using diffraction angles (2θ) from 5 to 60 $^\circ$.

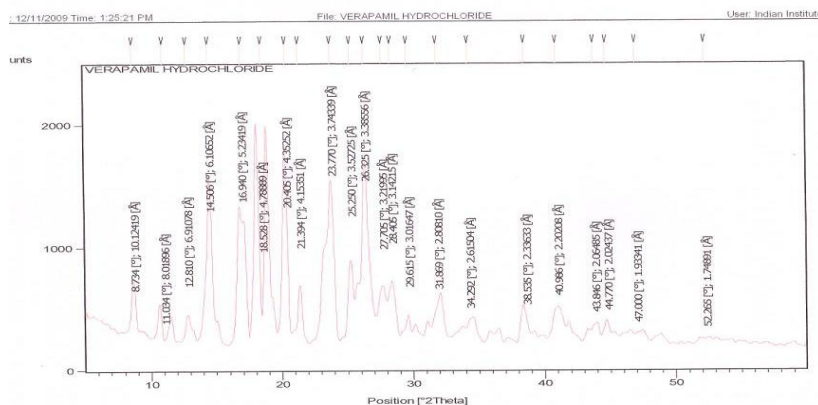


Fig 6: XRD Diffraction Pattern of Verapamil HCL

Method of preparation of bilayered tablet of verapamil hydrochloride- The concept of layered tablet was planned i.e. in one layer Quick release part and second layer sustained release part. For tableting Direct Compression method was used.

Preparation of Immediate Release (IR) Part: for making IR part, 40 mg of the drug was used, along with other excipients i.e. Fillers (lactose DCL 111 and Avicel 102), Disintegrants (sodium starch glycolate and PVP K 30); Glidant (Aerosil); Lubricant (Talc) and a colorant (Tartrazine). The compressibility of Lactose DCL 111 and Avicel 102 was used because of good compressibility and flow ability of these excipients. The talc and aerosil were used to produce good lubricating and flow ability of the powder blend as the angle of repose of the powder blend was above 30 degrees i.e. poor flow ability as obtained under preformulation studies. The excipients and the drug powder were mixed thoroughly by using mortar and pestle at laboratory scale and using various combinations four batches were prepared.

In sustained release part (second layer) HPMC K 4 M, HPMC K 100 LV CR, and Avicel 102 were generally used. These were also mixed in appropriate quantities along with the drug and compressed to form tablets. It was observed that the tablet with sufficient strength was obtained. For development of extended release tablet dosage form 40 mg of the drug was used in quick release part and 80 mg of drug was incorporated in Extended Release part. The composition of different formula are given in Table No.I. (Formula ERT-1, ERT-2, ERT-3, ERT-4, and ERT-5).

For making sustained release part, all the ingredients along with drug were mixed together using a mortar and paste. It was then lubricated. For the preparation of Bi-layered tablets part first (Quick release part) was placed in the die of tablet machine and a mild compression was produced. Then second part (sustained release part) was poured in to the die cavity and final compression was produced to obtain bilayered tablets of hardness in the range of 7-8 Kg/cm².



Fig 7 - In house ERT-4

Table I. Composition of extended release tablet of Verapamil Hydrochloride

Ingredients(mg/tab)	ERT-1	ERT-2	ERT-3	ERT-4	ERT-5
First Layer Of Tablet (BATCH- 1)					
Verapamil HCl	40	40	40	40	40
Lactose (DCL111)	20	20	20	20	20
Avicel 102	160	160	160	160	160
Sodium Starch Glycolate	1.2	0	0.6	0	0
PVP K30	0	1.2	0	0.6	0.6
Aerosil	0	0	0.2	0.2	0.2
Talc	0.2	0.2	0.4	0.4	0.4
Tartrazine	0.8	0.8	0.8	0.8	0.8
Total weight (in mg)	222.2	222.2	222	222	222
Second Layer of Tablet					
Verapamil HCl	80	80	80	80	80
HPMC K 4 M	15	25	0	0	0
HPMC K 100 LV CR	0	0	15	25	0
Ethyl Cellulose	0	0	0	0	308.8
Avicel 102	152	152	152	152	0
Aerosil 101	9	9	9	9	9

Magnesium Stearate	9	9	9	9	9
Talc	10	10	10	10	10
Total Wt. (in mg)	275	285	275	285	416.8
Concave Tooling (mm)	9	9	9	9	9
Total Weight Of Bilayered Tablets	497.2	507.2	497	507	638.8

III. IN VITRO RELEASE STUDIES

Bilayered tablets in the batches ERT-1, ERT-2, ERT-3, ERT-4, ERT-5 were subjected to *in vitro* release studies in distilled water, phosphate buffer of pH 6.8 and 0.1 N HCl. The dissolution data were compared with the dissolution data of reference of marketed extended release tablet of verapamil hydrochloride.

The dissolution was carried using USP 2 dissolution apparatus (basket type). By taking 900 ml of different dissolution media (Distilled water, Phosphate buffer of pH 6.8, 0.1 N HCl) at 37 ± 0.5 °C, and at 100 ± 1 RPM. The 5 ml samples were withdrawn at different time intervals and assayed by using U.V spectroscopic methodology at λ max 278 nm.

The dissolution curves for each formula showed same pattern of release of the drug in three different dissolution media viz. Distilled water, Phosphate buffer of pH 6.8 and 0.1 N HCl. This might be due to almost similar solubility profile of the drug in these three media.

Under the dissolution curves the straight lines were not observed for these curves (cumulative % of drug release v/s time), which indicated that the drug release occurred due to First order kinetics. The release of the drug from all the formula of the tablets might be due to the disintegration of the quick release part and slow erosion of the matrices of second layer of the tablet. At the similar time diffusion might also occur. ERT-4 showed release of the drug almost up to 12 hrs. When the dissolution curves of all the formula viz. ERT-1, ERT-2, ERT-3, ERT-4, and ERT-5 were compared with marketed reference extended release tablet, The ERT-4 matched to the dissolution curve of marketed preparation significantly. Hence it appeared as a bioequivalent extended release tablet to the reference marketed extended release tablet dosage form (Innovator's) dosage form. The dissolution data of (ERT-4) was also subjected to release kinetic studies in order to ascertain the exact release kinetic of the drug.

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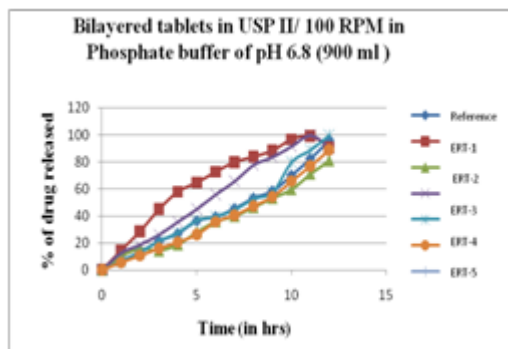


Fig 8. ERT- 1, 2, 3, 4, and 5 & Marketed Preparation in Phosphate buffer of pH 6.8

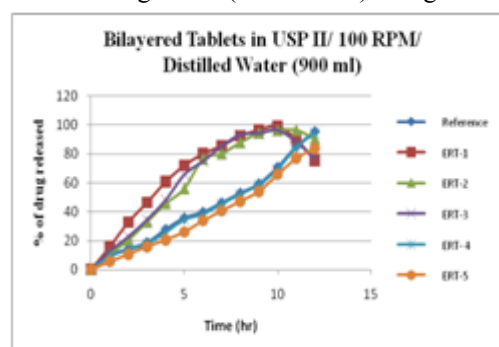


Fig 9. ERT- 1, 2, 3, 4, and 5 & Marketed Preparation in Distilled Water

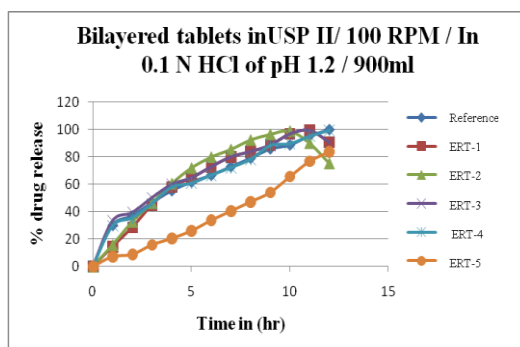


Fig 10. ERT- 1, 2, 3, 4, and 5 & Marketed Preparation in 0.1 N HCl of pH 1.2

Release Kinetics Studies and Interaction Studies

Release Kinetic Studies the release kinetic studies were performed on optimized extended release tablets i.e. ERT-4. Dissolution data of ERT- 4 was converted into cumulative % of drug remaining and log time shown in following Table as Different curves were plotted i.e. cumulative % of drug remaining v/s time Fig no.11 , log cumulative % of drug remaining v/s time Fig no. 12 , cumulative % of drug release v/s time. Fig. 13, Log cumulative % of drug remaining v/s log time. Fig. 14

Release kinetic studies were performed on the optimized extended release tablet (ERT-4) using its dissolution data obtained under *in vitro* release studies. Different values were calculated like cumulative % of drug remaining, log % of drug remaining and log time. Different curves were plotted between cumulative % of drug remaining v/s time, log cumulative % of drug remaining v/s time, cumulative % of drug release v/s time, Log cumulative % of drug remaining v/s Log time.

Table I Dissolution data of Extended release bilayered tablets (ERT-4)

Time (hrs)	Cumulative % of drug release	Cumulative % of drug remaining	Log % of drug remaining	Log Time
0	0	100	2	-
1	8.97	91.03	1.959	0
2	13.65	86.35	1.936	0.3010
3	17.76	82.24	1.915	0.4771
4	25.67	74.33	1.871	0.6021
5	34.45	65.55	1.816	0.6989
6	38.23	61.77	1.79	0.7781
7	45.32	54.68	1.738	0.8450
8	52.07	47.93	1.681	0.9542
9	58.56	41.44	1.618	1
10	69.23	30.77	1.488	1.041
11	84.12	15.88	1.2	1.041
12	94.56	5.44	0.7355	1.079
14	97.56	2.44	0.3873	1.146

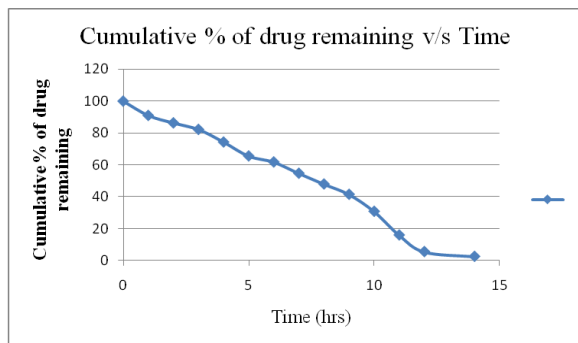


Fig.11 Data showing Cumulative % of drug remaining v/s Time ERT- 4

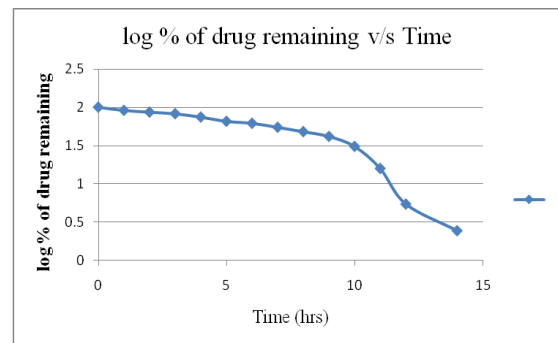


Fig.12 Data showing log cumulative % of drug remaining v/s Time ERT-4

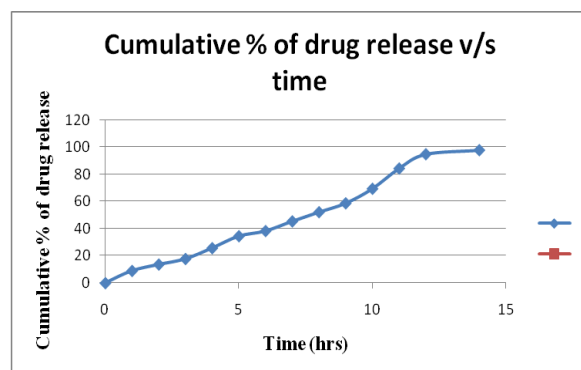


Fig.13 Data showing cumulative % of drug release v/s Time ERT-4

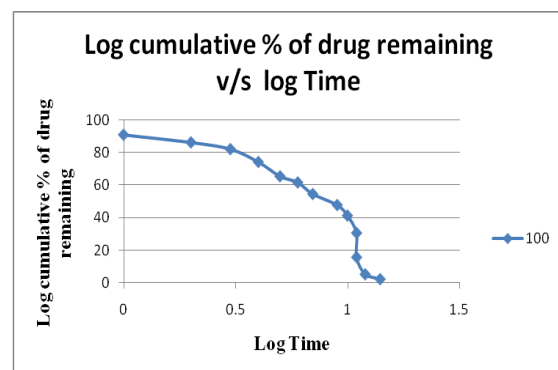


Fig.14 Data showing Log cumulative % of drug release v/s Log Time ERT-4

IV. QUALITY CONTROL AND QC CHART

Quality control tests on the optimized formulation ERT-4 were performed in order to ascertain the quality of the dosage form. The quality control test was performed for weight variation, content uniformity, thickness, hardness, and friability. The data of these studies were processed to obtain quality control charts. The weight variation value was found out to be within pharmacopoeial limit i.e. $\pm 5\%$. The drug content in each batch was found out to be almost similar. No significant variation was found in the thickness of tablets. The hardness was found to be sufficient. The friability was found out to be 0.328% i.e. less than 0.6% indicating good quality of product. On the basis of quality control data and QC chart it was concluded that the ERT-4 tablet met the quality control requirement.

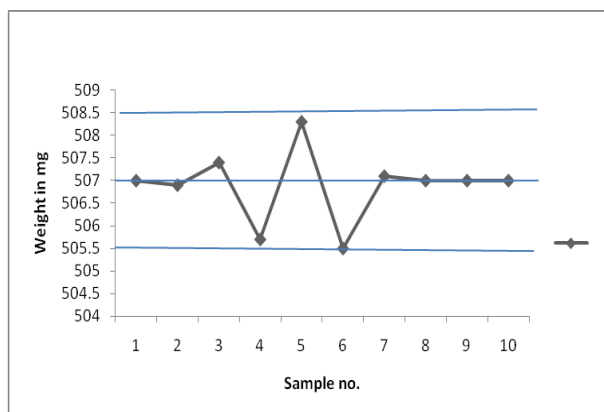


Fig.15. Quality control chart of weight variation of Bi – layered tablets Batch – ERT-4

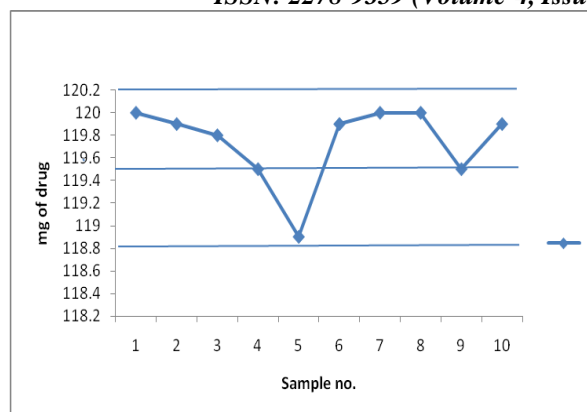


Fig. 16. Quality control chart of Content Uniformity of Bi – layered tablets Batch – ERT-4

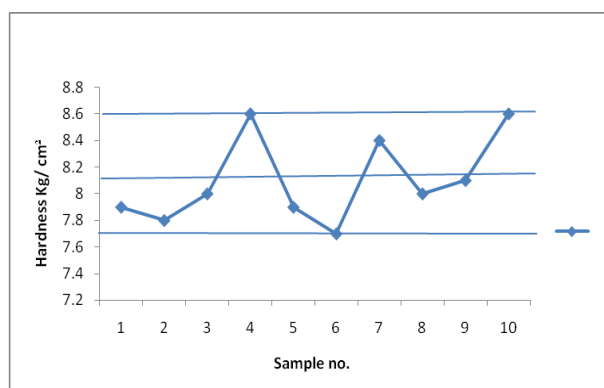


Fig.17 Quality control chart of Thickness of Bi – layered tablets Batch – ERT-4

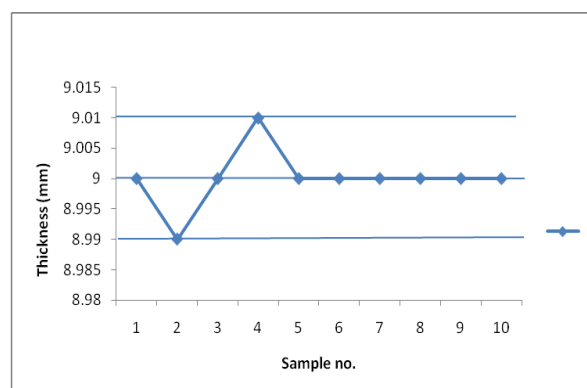


Fig18 Quality control chart of Hardness of Bi – layered tablets Batch – ERT- 4

V. RESULT AND DISCUSSIONS

The dissolution of this tablet dosage form was determined in distilled water, phosphate buffer of pH 6.8 and 0.1 N HCl of pH1.2 medium. At 100 RPM, using USP dissolution apparatus 2 (Basket Type). From the dissolution rate curves it was observed that this tablet dosage form gave almost constant release of drug up to 12 hrs duration. In distilled water and phosphate buffer initially less amount of drug was released up to 5 hrs as compared to the 0.1 N HCl of pH 1.2 medium. However the difference was not so much wide. Almost similar pattern of the dissolution curves were observed in all these three media up to 12 hr duration. From these results it was inferred that the reference tablet dosage form behaved in similar manner in all these three media.

The optimized extended release formulation was subjected to interaction studies to investigate any interaction of the drug with any excipients used in formulation of extended release of verapamil hydrochloride. The interaction studies were performed by using U.V spectral analysis, assay of drug in tablet, physical appearance and hardness of tablets before and after 2 months of storage at room temperature in laboratory.

The stability studies on the optimized extended release Bi- layered Tablet ERT-4 was done according to ICH Guidelines. The formulation was found out to be highly stable as less than 5% of degraded drug was observed (the study was done for three month and the data was extrapolated to six month). The few parameter and humidity were also observed visually. The formulation was intact and stable, without any color change and without unevenness.

VI. CONCLUSION

On the basis of above observations, interpretation and results it was concluded that the extended release bilayered tablets of verapamil hydrochloride was prepared successfully. The optimized tablet dosage form of batch (ETR-4) was found *in vitro* equivalent hence bioequivalent to the marketed sustained release tablet formulation and can be given twice a day for effective treatment of hypertension and arrhythmia.

ACKNOWLEDGEMENT

Author appreciated support from Piramal Healthcare Ltd for providing verapamil Hydrochloride as gift sample.

CONFLICT OF INTEREST- None Declared.

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