www.pharmaerudition.org

ISSN: 2249-3875

International Journal of Pharmaceutical Erudition

Research for Present and Next Generation

AUG. 2017

Vol: 07 Issue:02

(40-49)

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Research Paper

Formulation and Evaluation of Sustained Release Matrix Tablet of Verapamil HCl

Roy S, Kishor A, Wadhwani S, Bhadauria RS.

Department of Pharmaceutical Chemistry,

Srinathji Institute of Pharmacy,Nathdwara (Rajasthan)

The present study was undertaken with the aim of **"Formulation and Evaluation of Sustained Release Matrix Tablets of Verapamil HCl by using Sustained Release Polymers."**preformulation study was done initially and result directed for the further course of formulation. Infrared spectra of the drug reveal that there is no significant interaction between drug and polymers. Granules were evaluated for bulk density, tapped density, compressibility index, angle of repose, hausner's ratio and loss on drying before being punched as tablets and were found within the pharmacopoeial limit. The various formulation of Verapamil HCl was formulated using various polymers like PVP K 30, PVP K 90 and HPMC 5 CPS in different ratio by wet granulation. The evaluation test results were found to be within pharmacopoeia specifications. The tablets were evaluated for physical characterization, in vitro release study and accelerated stability studies. Observation of all the formulation for characterization had shown that F7 to F9 comply with the specification of official pharmacopoeia and standard references. Results of in vitro release profile indicated that among all formulation F7 to F9 was the most promising. it was concluded that no significant difference in the drug content, appearance, hardness, assay and loss on drying in PVC –PVDC 40 GSM/ ALU- 20µ between initial and formulation stored at 25˚C± 2˚C& 60 %, 30˚C ± 2˚C& 65 %, and 45˚C ± 2˚C& 75 % for 90 days.

Key Words: Verapamil HCl, Matrix Tablets,PVP K 30, PVP K 90.

INTRODUCTION

Dosage forms are designed to deliver optimum dose of drug to the site of action to produce desired pharmacological action and also to achieve the effective drug concentration over the preferred period of time. Oral drug delivery system is the most commonly used route of administration when compared to all other routes for various pharmaceutical products of different dosage forms. Easy administration, high patient compliance, avoiding tough sterile standards, and relatively cheap and easy formulation makes the oral dosage form as the first priority.[1]

The oral route is the most popular route used for 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 terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems 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. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug.[2]

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Introduction to Sustained Release Drug Delivery System

Sustained drug delivery that introduced in the early 1950s, Ideally, a drug should arrive rapidly at the site of action (receptor) in the optimum concentration, remain for the desired time, be excluded from other sites, and be rapidly removed from the site when indicated i.e. the basic goal of the therapy is to achieve a steady state blood level that is therapeutically effective and non-toxic for an extended period of time. Generally, the time course of a dosage form (pharmacokinetics) in man is considered to be controlled by the chemical structure of the drug. Decreasing the rate of absorption and/or changing the dosage form provide a useful adjunct. When it is feasible or desirable to modify the drug compound on a molecular level, often sought is a product that will require less frequent administration to obtain the required biologic activity time profile; for example, a tablet that has the same clinical effect when administered every 12 Hrs. In another instance, it may be desirable to decrease the absorption on rate in order to obtain a more acceptable clinical response.[3]

The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration. Presently pharmaceutical industries are focusing on development of sustained release formulations due to its inherent boons.

Review of Literature

Drug profile

- **Compound Name**

Verapamil HCl

- **Chemical Name**

(2*RS*)-2-(3,4-dimethoxyphenyl) -5-[[2-(3, 4-dimethoxyphenyl) ethyl] (methyl) amino]-2-(1-methylethyl) pentane nitrile hydrochloride

- **Chemical Structure**

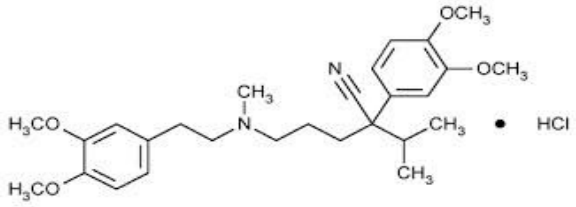

Fig. 1: Chemical Structure of Verapamil HCl

- **Molecular Formula**

$C_{27}H_{38}N_2O_4$, HCl

- **Molecular weight**

491.1

- **Description**

Verapamil HCl is appears in a white crystalline powder.

- **Loss on drying**

Not more than 0.5 %, determined on 1.0 g by drying in an oven at 105ºC.

- **Assay**

Weigh accurately about 0.4 g dissolve in 40 mL of anhydrous glacial acetic acid, added 6 mL of mercuric acetate solution. Titrate with 0.1 M perchloric acid, determining the end-point potentiometrically. Carry out a blank titration.1 mL of 0.1 M perchloric acid is equivalent to 0.04911 g of $C_{27}H_{38}N_2O_4$, HCl.

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

- **Class**

Benzene and Substituted Derivatives

- **Biopharmaceutical Classification**

Verapamil HCl follows the BCS Class 2 it means high permeability and low solubility**.**

- **Pharmacodynamic**

Verapamil HCl is an L-type calcium channel blocker that also has antiarrhythmic activity. The R-enantiomer is more effective at reducing blood pressure compared to the S enantiomer. However, the S-enantiomer is 20 times more potent than the R enantiomer at prolonging the PR interval in treating arrhythmias.

- **Mechanism of action**

Verapamil HCl inhibits voltage-dependent calcium channels. Specifically, its effect on L-type calcium channels in the heart causes a reduction in ionotropy and chronotropy, thus reducing heart rate and blood pressure. Verapamil HCl's mechanism of effect in cluster headache is thought to be linked to its calcium-channel blocker effect, but which channel subtypes are involved is presently not known.

- **Route of administration**

Approximately 70 % of an administered dose is excreted as metabolites in the urine and 16 % or more in the faces within 5 days. About 3 % to 4 % is excreted in the urine as unchanged drug.

Half life: 2.8 Hrs -7.4 Hrs

- **Toxicity**

LD_{50} = 8 mg/kg (i.v. in mice)

- **Food Interaction**
  - Avoid alcohol
  - Avoid excessive quantities of coffee or tea (Caffeine)
  - Avoid natural liquorice
  - Avoid taking with grapefruit juice.
- **Adverse effects**
  - Nausea
  - Constipation and bradycardia
  - Flushing, headache and ankle oedema

Table 1: Property of Active Pharmaceutical Ingredient

Property	Value
Melting point	< 25 °C
Boiling point	243°C -246 °C at 1.00E-02 mm Hg
Water solubility	4.47 mg/L
logP	3.79
pKa	8.92

- **Interaction**

Verapamil HCl should not be given with β blockers- additive sinus depression, conduction defects or asystole may occur. It increases plasma digoxin level by decreasing its excretion: toxicity can develop. It should not be used with other cardiac depressant like quinidine and disopyramide.

Patents

Country	Patent number	Approved	Expires
United States	6096339	04-04-1997	04-04-2017
United States	5785994	22-10-1992	22-10-2009

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Aim and Objective

Aim : Verapamil HCl is a calcium ion influx inhibitor (slow- channel blocker or calcium ion antagonist) that exerts its pharmacologic effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells. Verapamil HCl has the most prominent cardiac electrophysiological action. It blocks L type Ca^{+2}channels and delay their recovery. The basic action of Verapamil HCl is to depress Ca^{+2} mediated depolarization. This suppresses automaticity or re-entry dependent on slow response. Phase- 4 depolarization in SA node and PFs is reduced resulting in bradycardia and extinction of latent pacemakers. Verapamil HCl is mainly used in the treatment of the hypertension, angina, cluster headache prophylaxis.More than 90% Verapamil HCl rapidly absorbed after oral administration with maximum plasma drug concentration achieved in 1 to 2 Hrs. Half life of the Verapamil HCl is 6 Hrs. and bioavailability is 20-30%. Protein binding of Verapamil HCl is 90%.

ObjectiveThe objective of the present study is to develop a pharmaceutically stable, cost effective and quality improved, once in a day formulation of Sustained release matrix tablets of Verapamil HCl.

- In the present study the main objective is directed towards formulation and evaluation of sustained release matrix tablets of Verapamil HCl to achieve faster dissolution to match the innovator product.
- To carry out pre-formulation study of drug and excipients.
- Design and development of various formulations with different polymers.
- To prepare tablets with using different ratio of polymers.

To carryout accelerated stability studies as per ICH guideline.

MATERIALS & METHODS

Materials

Table 2: Materials used in present study

Name of Material	Supplier
Verapamil HCl	ONS Pharmaceuticals
Micro Crystalline cellulose	CDH, Delhi
Colloidal silicon Dioxide	ONS Pharmaceuticals
Sodium Alginate	ONS Pharmaceuticals
HPMC	CDH, Delhi
PVK-30	CDH, Delhi
HPMC 5 cps	CDH, Delhi
Magnesium Stearate	CDH, Delhi

Equipments

Table 3: Equipments used in present study

Name of instrument/ equipment	Model and manufacturer
Digital balance	Citizen
Mechanical sieve shaker	Mohan
LOD	Labtech
Tap density tester	Instrument India
Tablet Punching machine	Cadmech
Vernier callipers	Instrument India
Hardness tester	Instrument India
Hot air oven	Labtech

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Mechanical stirrer	Instrument India
pH meter	Instrument India
Double Cone Blender	Thakur
UV-Visible double beam spectrophotometer	Shimadzu, Japan

Methods

Preformulation Study

Preformulation study is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. Preformulation study is the backbone of pharmaceutical formulations, which gives the basic information for selection of ingredients and process. Increasing demand or cost effective formulation development needs accurate selection of excipients and projection of risk involved during bioequivalence and stability study.

Organoleptic Properties

The organoleptic studies of Verapamil HCl like general appearance like nature, colour, odour etc. were performed and observed.

- **Colour:** Small quantity of Verapamil HCl was taken in butter paper and viewed in well illuminated place.
- **Odour:** Very less quantity of drug was smelled to get the odour.

Detection of Melting Point Range

For determination of melting point USP method was followed. Small quantity of Verapamil HCl was placed into a sealed capillary tube. The tube was placed in the melting point apparatus. The temperature in the apparatus was gradually increased and the observation of temperature was noted at which Verapamil HCl started to melt and the temperature when the entire drug gets melted. This method is also known as open capillary method.

Partition Coefficient

The partition coefficient is the parameter used to determine the lipophilicity of the API. The API with high lipophilic nature has high lipophilicity and thus a high partition coefficient and vice-versa. The logarithm of the ratio of the concentrations of the un-ionized solute in the organic and aqueous solvents is called **log P**. The log P value is also known as a measure of lipophilicity (partition coefficient). It provides a means of characterizing the lipophilic/hydrophilic nature of the drug. Drugs having values of P much greater than 1 are classified as lipophilic, whereas those with partition coefficient much less than 1 are indicative of a hydrophilic drug. The partition coefficient is commonly determined using an oil phase of n-Octanol and water[87]. It can be determined by the formula;

$K_{o/w}$= C1/C2

Where,

C1 = Conc. of solute in organic phase
C2 = Conc. of solute in aqueous phase
$K_{o/w}$= Partition coefficient
Log P = log ($K_{o/w}$)

RESULT AND DISCUSSION

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Organoleptic Properties

On organoleptic evaluation of Verapamil HCl was found white in colour, odourless powder and bitter in taste.

Table 4:Organoleptic Properties of Verapamil HCl

Sr. No.	Test	Specification	Observation
1.	Colour	white to off-white	White
2.	Odour	Odourless	Odourless
3.	Appearance	Powder	Powder
4.	Taste	Bitter	Bitter

Detection of Melting Point Range

Melting point of Verapamil HCl was performed using Digital Melting Point and the melting point was found to be 142 ℃ which was in the range as prescribed in Indian Pharmacopoeia, so the drug was found to be of standard prescribed purity and quality.

Table 5: Melting point of Verapamil HCl

Drug	Specification	Observation
Verapamil HCl	140℃-144℃	142℃

Partition Coefficient

The partition coefficient of Verapamil HCl was calculated from the ratio between the concentration of Verapamil HCl in oil (n- octanol) and aqueous phase (water). The ratio between the concentration of Verapamil HCl in oil (n- octanol) and aqueous phase (water) was determined and the partition coefficient of Verapamil HCl (log P) was found to be **3.97** which was in the range as prescribed in Indian pharmacopeia so the drug was found to have standard prescribed hydrophobic character.

FTIR Spectrum

IR spectra: The IR spectrum of pure Verapamil HCl showed following absorption band at different wave number. The IR spectra alone showed that the principal peaks were observed thus confirming the purity of the drug.

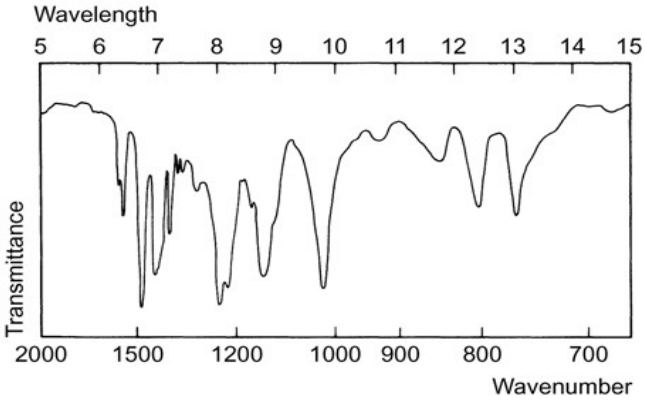

Fig. 2: FTIR of Verapamil HCl

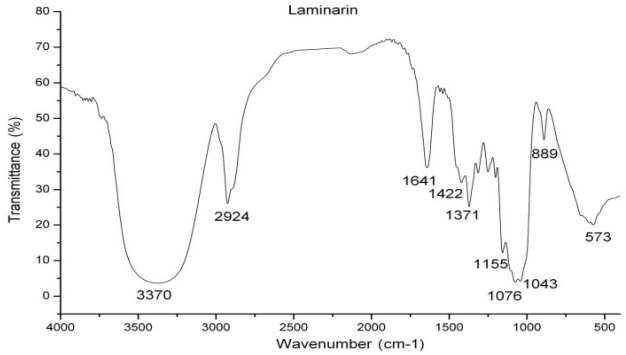

Fig. 3: FTIR of Microcrystalline Cellulose

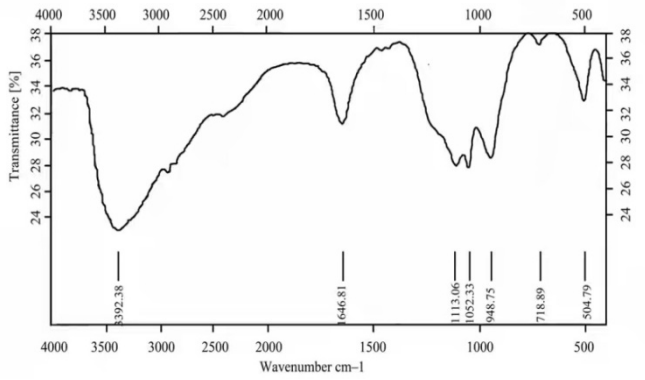

Fig. 4 FTIR of Colloidal Silicon Dioxide

Determination of Absorption Maxima (λ_{max})

A solution of 10µg/mL of Verapamil HCl was scanned

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

in the range of 200 to 400 nm. The drug exhibited the λ_{max} at 279 nm in 0.1 N HCl and has good reproducibility graph

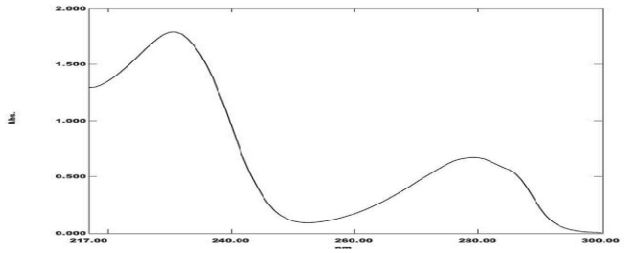

Fig. 5: Absorption maxima of Verapamil HCl

Solubility

On solubility studies it was found that Verapamil HCl is sparingly soluble in chloroform, freely soluble in Water, Isopropranol, acetone, ethyl acetate, freely soluble in methanol.

Table 6: Solubility of Verapamil HCl in different solvents

S.No.	Solvent	Amount (mg/ml)	Inference
1.	Chloroform	32.23	Sparingly soluble
2.	Water	83	Soluble
3.	Isopropranol	20.34	Soluble
4.	Ethanol	26	Slightly Soluble
5	Methanol	83	Freely soluble

Calibration Curve

From the scanning of drug in 0.1 N HCl it was conclude that the drug had $\lambda_{max}$of 279 nm and which was exactly similar as reported. From the graph 0.1 N HCl it was observe that the drug obeys Beer's- Lambert's Law in concentration range 0-100 µg/ml in medium as shown in table and graph. The R^2 value was found to be 0.996.

Table 7: Absorbance vs. Concentration of Verapamil HCl

Concentration (µg/ mL)	Absorbance
0	0.000
10	0.041
20	0.078
40	0.151
60	0.213
80	0.277
100	0.375

Pre-Compression Evaluation

Verapamil HCl was estimated by bulk density, tapped density, Carr's index, hausner's ratio, angle of repose and loss on drying. The values achieved by experimental works were compared by standard values.

- **Bulk Density**

The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.45 to 0.58 gm/mL.

- **Tapped Density**

The tapped density for the prepared blend was carried out for all formulation and found in the range of 0.59 to 0.72 gm/mL.

- **Carr's Index**

Compressibility index was carried out and the results were shown in table 9. It were found between 19 % to

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

21 % indicating the powder blend have the required flow property for compression except

Compatibility Study

Table 8: Drug and Excipient Compatibility Study

Ingredients	Initial	40 ^{0}C/75 % RH	
		15 Days	30 Days
Micro Crystalline cellulose (Avicelph 101)	White to off white powder	White to off white powder	White to off white powder
Micro Crystalline cellulose (Avicelph 102)			White to off white powder
Colloidal silicon Dioxide (Aerosil)			
Sodium Alginate			
Magnesium Stearate			
PVP K-30	White to light yellow powder	White to off white powder	White to off white powder
HPMC 5 cps			White to off white powder

for formulation F1 to F6 that is having percentage compressibility between 25 % to 29 %.

- **Angle of Repose**

The angle of Repose for formulated blend was carried out and the result was describes in table. It shows that the F7 to F9 formulated blend was in the range of 34 ^{0}C to 35 ^{0}C.

- **Loss on Drying**

The loss on drying for the formulated blend was carried out and the result was indicated in table. It concludes that the entire formulated blend was in the range of 2.50 % to 3.00 %.

Table 9: Pre-Compression Evaluation

Parameter / Formulation	Bulk Density (gm/mL)	Tapped density (gm/mL)	Carr's Index (%)	Hausner's Ratio	Angle of Repose	Loss on Drying (%)
F1	0.56	0.76	28.78	1.356	51.00	2.52
F2	0.51	0.70	25.55	1.456	48.00	2.53
F3	0.57	0.72	26.47	1.426	44.00	2.59
F4	0.58	0.68	26.54	1.412	43.00	2.67
F5	0.50	0.65	27.32	1.528	51.00	2.88
F6	0.51	0.67	25.44	1.312	50.00	2.74
F7	0.45	0.60	20.21	1.213	34.08	2.84
F8	0.49	0.61	19.67	1.242	35.00	2.51
F9	0.48	0.59	19.10	1.238	34.21	2.93

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Post Compression Evaluations

➢ **Hardness Test**

The measured hardness of tablets of batches F7 to F9 ranged between 140-200 N and for formulation F1 to F3 ranged between 30-100 N and for formulation F4 to F6 ranged between 50-150 N was tabulated in table 10.

➢ **Thickness Test**

The thickness was determined for formulated tablets and tabulated in table 10. The thickness uniform in F7 to F9 formulation and were found to be in the range of 5.98 mm to 6.3 mm.

➢ **Friability Test**

The values of friability test were tabulated in table 10. The percent friability was less than 1 % in all formulation ensuring that the tablets were mechanically stable.

➢ **Content uniformity**

The percentage of drug content for F7 to F9 was found to be range 99.79 % to 99.99 %.

➢ **In- Vitro Dissolution Study**

The dissolution data of various batches of Verapamil HCl were indicating in table 5.8 and graph. The percentage drug release from batches F1 to F9 vary from 86.46 % to 99.42 %. From the data it is clear that by increase the amount of polymer in the formulation the amount of drug release is decreased. Based on the dissolution studies F7 to F9 was selected as an optimized because it shows maximum drug release at the end of 12 Hrs..

Table 10: Post compression Evaluations of formulated tablets

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability	Drug content (%)
F1	3.5 ± 0.52	5.1 ± 0.12	600 ± 4.15	0.85 ± 0.08	91.22
F2	4.89 ± 0.54	4.80 ±0.22	600 ±3.55	0.68 ± 0.02	90.12
F3	8.78 ± 0.23	5.1 ± 0.32	600 ± 4.05	0.75 ± 0.15	91.12
F4	6.65 ± 0.45	3.8 ± 0.12	600 ±3.55	0.56 ± 0.01	90.58
F5	10.12 ± 0.34	3.6 ± 0.18	600 ± 4.05	0.45 ± 0.03	92.45
F6	13.45 ± 0.25	3.9 ± 0.20	600 ± 4.15	0.59 ± 0.18	91.85
F7	16.22 ± 0.22	6.1 ± 0.12	600 ±1.22	0.23 ± 0.01	99.89
F8	17.34 ± 0.44	6.1 ± 0.10	600 ± 1.32	0.25 ± 0.02	99.99
F9	18.22 ± 0.32	6.1 ± 0.20	600 ± 1.76	0.26 ± 0.02	99.78

SUMMARY AND CONCLUSION

The present study was undertaken with the aim of **"**Formulation and Evaluation of Sustained Release Matrix Tablets of Verapamil HCl by using Sustained Release Polymers**."** Preformulation study was done initially and result directed for the further course of formulation. Infrared spectra of the drug reveal that there is no significant interaction between drug and polymers. Granules were evaluated for bulk density, tapped density, compressibility index, angle of repose, hausner's ratio and loss on drying before being punched as tablets and were found within the pharmacopoeial limit. The various formulation of Verapamil HCl was formulated using various polymers like PVP K 30, PVP K 90 and HPMC 5 CPS in different ratio by wet granulation. The evaluation test results were found to be within pharmacopoeia specifications. The tablets were evaluated for physical characterization, in vitro release study and accelerated stability studies. Observation of all the formulation for characterization had shown that F7 to F9 comply with the specification of official pharmacopoeia and standard references. Results of in vitro release profile indicated that among all formulation F7 to F9 was the most promising. Formulation as it showed that 99.85 % drug release within 12 Hrs. In vitro release profile were compare with reference standard and result was most promising and as it showed that 101 %. From the stability studies, it was concluded that no significant difference in the drug content, appearance, hardness, assay and loss on drying in PVC –PVDC 40 GSM/ ALU- 20µ between initial and formulation stored at 25 ℃± 2 ℃& 60 %, 30 ℃ ± 2 ℃& 65 %, and 45 ℃ ± 2 ℃& 75 % for 90 days.

REFERENCES

1. Krishnaiah, Y.S.R., Karthikeyan, R.S., Bhaskar, P., &Satyanarayana, V.Bioavailability studies on guar gum-based three-layer matrix tablets of trimetazidinedihydrochloride in human volunteers. Journal of controlled release, 2002 Volume83, Issue 2, Pages 231-239.

2. Navin Dixit, SheoDuttMaurya, Bhanu P.S. Sagar; "Sustained Release Drug Delivery System"; Indian Journal of Research in Pharmacy and Biotechnology; May-June 2013; Volume 1(3); 305-310

3. Girish K Jani, Dhiren P Shah, Vipul D Prajapati, Vineet C Jain. Gums and Mucilages, AJPS, 4(5), 2009, 309-323.

4. Sarika Pundir1, AshutoshBadola and Deepak Sharma; Sustained Release Matrix Technology and Recent Advance in Matrix Drug Delivery System: A Review; Int. J. Drug Res. Tech. 2013, Vol. 3 (1), 12-20.

5. Shargel, L and Yu, ABC, "Modified release drug products", Applied Biopharmaceutics and Pharmacokinetics, 4th Ed.,1999; McGraw Hill, 169-171.