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FORMULATION DEVELOPMENT OPTIMIZATION AND EVALUATION OF TELMISARTAN MINI TABLETS

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ABSTRACT

Telmisartan is the Angiotensin II receptor antagonist which mainly used in treatment of hypertension. The aim of this research was to develop & optimize sustain release Minitablet of Telmisartan. Mini tablets of Telmisartan were prepared by direct compression method using HPMC K 200M and Carbopol 940 release retarding agents. 32 factorial design was applied to study % cumulative drug release and hardness by using design expert software The Mini tablets were evaluated for weight variation, hardness, thickness, friability, drug content, and in-vitro dissolution studies. The prepared Mini tablets exhibited satisfactory physic-chemical characterise full factorial design and optimization technique successfully used in the development of Mini tablet. Comparing the all the formulations, formulation H5 was considered as optimized formulation which exhibited 97.87% of drug release in 12 hours also stable in stability.

KEY WORDS

Mini tablets, Telmisartan, Physiochemical parameters, optimizations.

INTRODUCTION:

Oral controlled release drug delivery systems can be classified in two broad groups

1. Single unit dosage forms, such as tablets or capsules
   It includes matrix tablet or coated/uncoated tablet or capsules and consists of only one unit, e.g. osmotic tablet.[1]
2. Multiple unit dosage forms such as granules, pellets or minitablets.

Multiple-unit: The basic concept of multiple-unit systems is that the dose of the active ingredient is released by the individual subunits (like, pellets, minitablets), and the functionality of the entire dose depends on the quality of the subunits. It associated with various advantages like chances of dose dumping is less, reduction local irritation & others. One of the popular approaches of multi-unit dosage forms is Mini tablets.[2]

MINI TABLET

Mini-tablets are small tablets with a diameter typically equal to or less than 3 mm that are typically filled into a capsule, or occasionally, further compressed into larger tablets. It is possible to incorporate many different mini-tablets, each one formulated individually and programmed to release drug at different sites within the gastrointestinal track, into one capsule. These combinations may include immediate release, delayed release, and/or controlled release mini-tablets. It is also possible to incorporate mini-tablets of different drugs to treat concurrent diseases or combinations of drugs to improve overall therapeutic outcome, while delivering distinct release rates of each according to disease requirements. Mini-tablets combine the advantages of

multi-particulate dosage forms with the established manufacturing techniques of tablet.[3]

ADVANTAGES OF MINITABLETS

- They can be manufactured relatively easily.
- They have excellent size uniformity, regular shape and smooth surface.
- They offer a substrate which is easy to coat with polymeric membranes for modified release purposes.
- They combine the advantages of MUDFs with the established manufacturing techniques in tablet and have fewer constraints compared to extrusion/Spheronization.
- Mini-tablets also offer an alternative for pellets because of their relative ease of manufacturing and because dosage forms of equal dimensions and weight with smooth regular surface are produced in a reproducible and continuous way.
- They offer high drug loading, a wide range of release rate designs, and fine tuning of these release rates.
- They have less risk of dose dumping, less inter- and intra-subject variability, high degree of dispersion in digestive tract thus minimizing the risks of high local drug concentrations.[4,5,6]

TYPES OF MINI-TABLETS

1. Capsule-in-a-capsule technology
2. Tablet-in-a-tablet technology
3. Tablets-in-a-capsule technology
4. Granules and Tablets-in-a capsule technology [7,8]

Telmisartan is the Angiotensin II receptor antagonist which mainly used in treatment of hypertension. Frequent dosing schedule of Telmisartan leads to decreased patient compliance, increased incidence of side effects (like nausea, vomiting) and tolerance development, especially in long-term use. The half-life of the Telmisartan is about 1.5-2 hours. Because of its short biological half-life and frequent administration, it is considered as a suitable candidate to formulate it into a sustained release drug delivery system. From the technology point of view pellets and granules are more difficult and costly in production than tablets. So, therefore mini matrices were produced to combine the physiological advantage of MUDFs with the economic advantage of SUDFs.[9,10]

MATERIALS AND METHODS:

Telmisartan drug was gift sample from Glanmark Pharma Mumbai, HPMC K 200 M, Carbopol 940 S100, Mg.stearate, Talc and MCC PH 101 were purchased from S.D. Fine Chem. Ltd. Mumbai.

DRUG POLYMERS COMPATIBILITY STUDIES

1. Drug polymer compatibility studies were carried out using FTIR.
2. The study was carried out on individual pure drug and its physical mixture with the selected polymers under study.

I. PREPARATION OF TELMISARTAN MINI TABLET

Telmisartan mini tables were prepared by direct compression method. All the powders passed through #60. The required quantity of drug, various polymer mixtures and diluent were mixed thoroughly in polybags. The blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant were the blended was then compressed into mini-tablet weighing 60 mg using 6 mm round convex punches in a rotary tablet press (Rimek mini press, model RSB-4, M/S: Karnavati engineering, Ahmedabad). 4 mini tablets were manually filled in size “0” capsules. The mini tablets (4) contained 80 mg a labeled amount of Telmisartan. All the tablets were stored in airtight containers for further study.

Factorial Design

In the present study, a 3^2-full factorial design was employed containing 2 factors evaluated at 3 levels and experimental trials were performed for all 9 possible combinations. The amount of HPMC K200M (X1) and Carbopol 940 (X2) were selected as independent variables. The time dissolution of drug in 12hous (Q12) was selected as dependent variable.

Table 1: Translation of coded values for 3^2 factorial experimental designs

Formulation code	Variable level code	
	X_1	X_2
H1	-1	-1
H2	-1	0
H3	-1	+1
H4	0	-1
H5	0	0
H6	0	+1
H7	+1	-1
H8	+1	0
H9	+1	+1

Table 2: Value codes of factorial design

Coded value	X_1	X_2
-1	4	4
0	8	6
+1	12	8

X1= HPMC K 200M; X2= Carbopol 940

Table 3: Formulation of 3^2Factorial Design Batches

Ingredients(mg)	H1	H2	H3	H4	H5	H6	H7	H8	H9
Telmisartan	20	20	20	20	20	20	20	20	20
HPMC K200M	4	4	4	8	8	8	12	12	12
Carbopol 940	4	6	8	4	6	8	4	6	8
Talc	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2
MCC PH 101	28	26	24	24	22	20	20	18	16
Total	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**

II. EVALUATION OF TELMISARTAN MINI TABLETS

1 Appearance

The colour, odour and any other flaws like chips, cracks, surface texture, etc. are other important morphological characteristics were observed.

2.Thickness and Diameter

The thickness and diameter of mini tablets were determined with the help of vernier caliper. The average diameter and thickness of the tablet was calculated.

3. Hardness

Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Monsanto hardness tester.

4. Weight variation test

Twenty tablets were selected randomly and weighed individually. Calculated average weight and compared the individual tablet weight to the average weight weight test are performed as per I.P.

5. Drug Content

Randomly selected 4 tablets from each batch were crushed in a mortar and pestle. The crushed powder equivalent to 20 mg of Telmisartan was taken and dissolved in suitable quantity of buffer then filtered through Whattman filter paper suitably diluted. The concentration of Telmisartan was determined by using UV.

6. Friability

Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 minutes dropping the tablets through a distance of 6 inches with each revolution. This process was repeated for all formulations and the percentage friability was calculated.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets - Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Where; W_1 = Initial weight of tablet; W_2 = weight of tablet after rotation.

7. *In vitro* dissolution profile of formulation batches

Mini-tablets were subjected to in-vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution test apparatus II at 50 rpm, 37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours, since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and experiment continued for another 10 hours. At different time intervals, 1ml of the samples were withdrawn and replaced with 1ml of dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using multi component mode of analysis at 296,244 nm wave length.

Parameter of *in-vitro* dissolution test

1. Apparatus: USP Type –II (Basket)
2. Volume of medium: 900 ml
3. Temperature: 37 ± 0.5°C
4. Paddles Speed: 50 rpm
5. Dissolution medium used: 0.1 N HCL and Phosphate buffer pH 6.8
6. Aliquot taken at each time interval: 1 ml
7. Time interval: 1 hour.
8. Dilution factor: 10

8. Kinetics of drug release

The drug release was analyzed by PCP Disso Version 3 software to study the kinetics of drug release mechanism.

9. Stability Studies

On the basis of *in vitro* evaluation of all the formulation batches for the various parameters, formulations were packed in thick aluminum foil and stored in stability chambers (Thermolab) for the accelerated stability studies. The tablets were stored in the stability chamber at the controlled conditions of temperature and relative humidity. The stability of the tablets was studied for the duration of 90 days at temperature 40^0C ± 2^0C and 75% ± 5% relative humidity. The tablets were then evaluated for various parameters viz. thickness, hardness, and weight variation and release studies.

RESULT AND DISCUSSION

DRUG POLYMERS COMPATIBILITY STUDIES

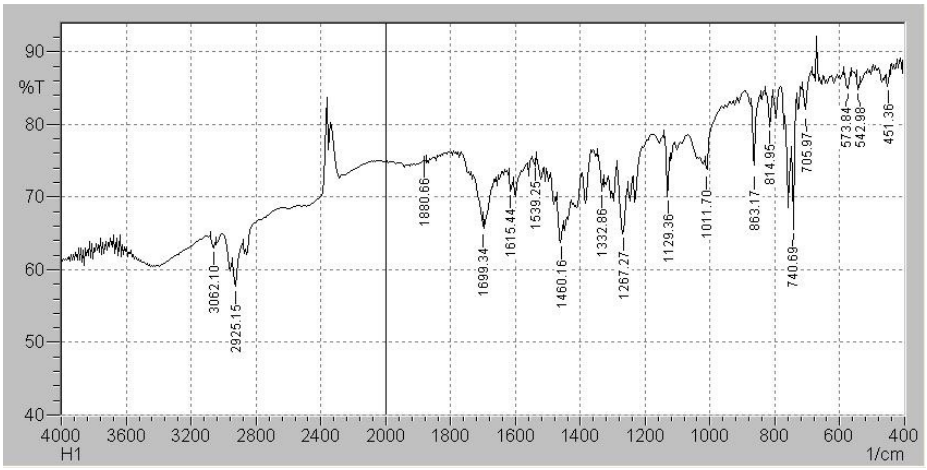

Figure No.1 FTIR spectra of FT-IR spectra of Telmisartan

The IR spectrum of pure drug was found to be similar to their reference standard IR spectrum of Telmisartan given in pharmacopoeia.

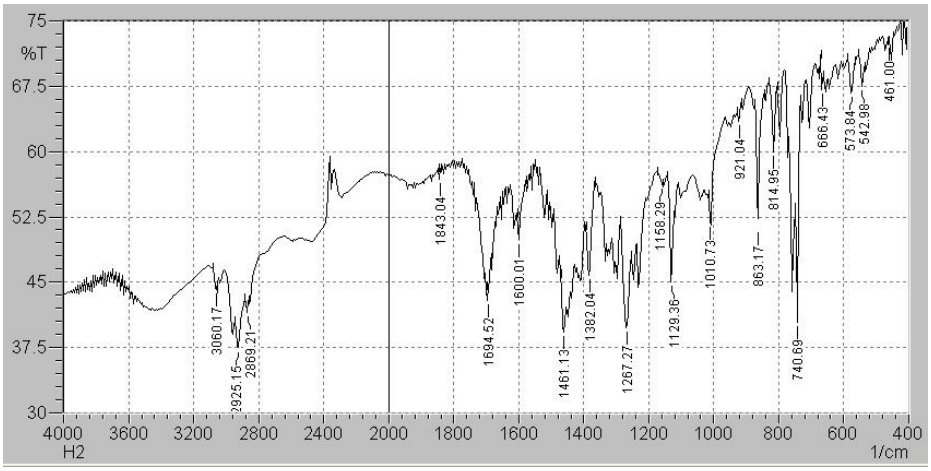

Figure No.2 FTIR spectrum of Telmisartan with HPMC K15M

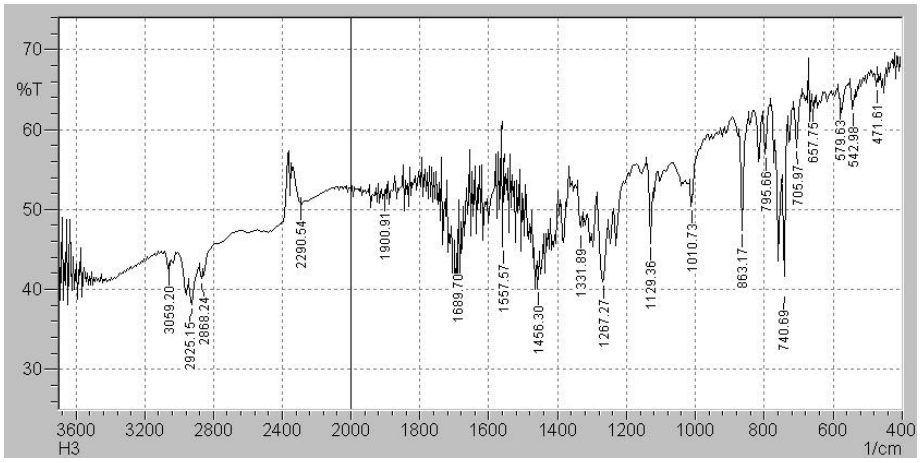

Figure No.3 FTIR spectrum of Formulation blend

From FTIR study it can concluded that the drug Telmisartan have maintained its identity without losing its characteristic properties in formulation blend.

EVALUATION OF MINI TABLETS

Tablets from all the formulation were subjected to following quality control test**.**

Appearance: All tablets are white in colour, circular in shape.

Figure No.4 Prepared Mini tablets of Telmisartan

Table 4: Physical parameters of sustain release mini tablets (mean±SD)

Formulation	Weight Variation mg ±SD	Hardness (Kg/cm^2) ±SD	Friability %	Thickness (mm) ±SD	Assay (%) ±SD
H1	60.42 ± 1.08	3.10 ± 0.02	0.65	2.64 ± 0.04	99.62± 0.52
H2	61.27 ± 0.83	3.30 ± 0.02	0.51	2.65 ± 0.02	100.03± 2.115
H3	58.98 ± 1.12	3.25 ± 0.08	0.758	2.67 ± 0.01	98.02±0.594
H4	61.14 ± 1.10	3.30 ± 0.04	0.52	2.60 ± 0.01	101.32±1.79
H5	60.54 ± 0.67	3.65 ± 0.03	0.68	2.65 ± 0.02	98.5±1.79
H6	59.88 ± 1.21	4.20 ± 0.02	0.79	2.67 ± 0.04	100.1± 0.52
H7	60.63 ± 1.09	3.70 ± 0.03	0.47	2.66 ± 0.04	99.69± 0.83
H8	58.86 ± 1.17	4.10 ± 0.05	0.30	2.67 ± 0.06	101.32± 0.367
H9	60.28 ± 1.66	4.40 ± 0.05	0.15	2.65 ± 0.02	99.88±0.342

All Physical parameters of sustain release mini tablets were within acceptable range.

***In vitro* dissolution profile of formulation batches**

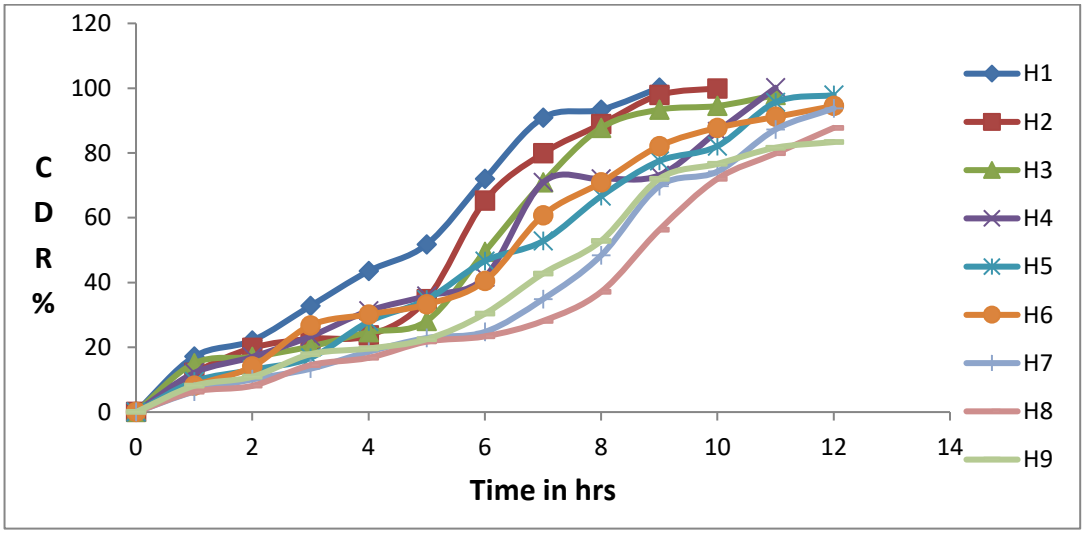

Figure No.5. Graph show *In vitro* Drug Release %

The in vitro drug release study was carried out using USP dissolution apparatus II initially 2 hrs in 0.1N HCL then in pH 6.8 buffer for a period of 10 hrs. The rate of drug release from the matrix mini tablet is rapid initially followed by progressively slow drug release through the matrix. The slow release of the drug from the matrix may be due to the formation of viscous gel of HPMC K200 M& Carbapol 940.Formulation containing more amounts of HPMC K200M and Carbopol 940 retarded the drug release up to 12 hrs.

The formulation H5 was the best formulation by using HPMC and Carbopol and it was follows zero order kinetics for sustained release.

Kinetics of drug release

The results showed that the factorial design batches followed Zero Order models shown table

Table 5: Drug release kinetics of the optimized batch

Batch code	R^2				
	Zero order	**1st order**	**Matrix**	**Peppas**	**Hixson Crowell**
H 5	0.9856	0.9490	0.9621	0.9166	0.9819

Statistical analysis by Design Expert Software

The 3^2 full factorial designs were selected to study the effect of independent variables HPMC K200M (X1), Carbopol 940 (X2) on dependent variables i.e. Drug Release & Hardness.

The coefficient of variable X1 and X2 i.e. HPMC K200M, Carbopol 940 in case of response indicates that as HPMC K200M concentration increased drug release decreased and as the concentration of Carbopol 940 was increased the initial burst release decreased.

Table 6: Result of ANOVA

Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Model Sgnificant/Non-Significant
Cumulative % drug release	1456.06	2	728.03	28.19	0.0001	0.8193	Significant
Hardness	1.67	3	0.56	47.27	0.0001	0.9204	Significant

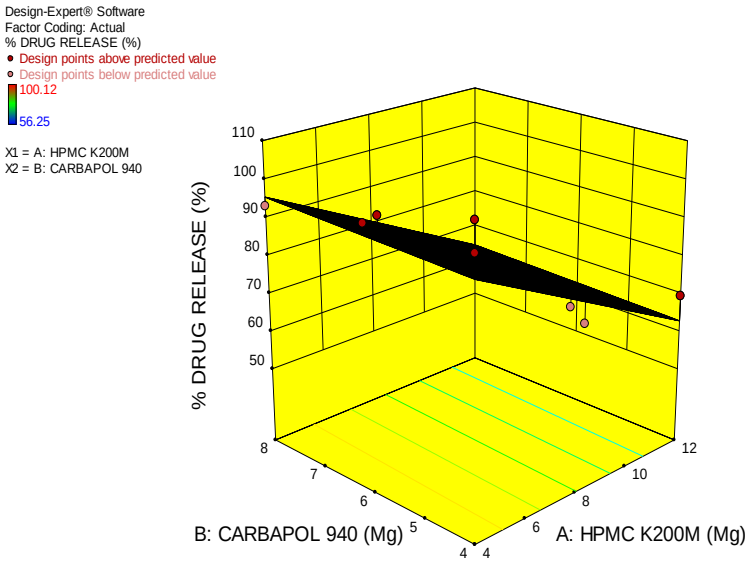

Figure No.6. A response surface plot showing effect of concentration of independent variables on the Cumulative % drug release.

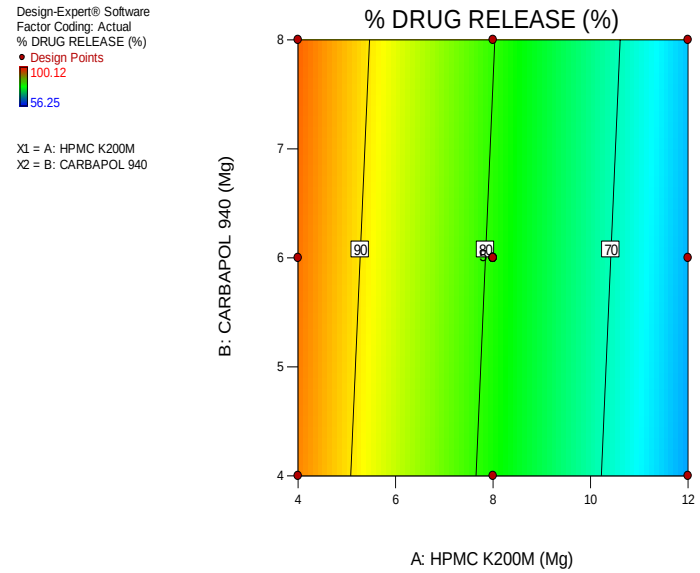

Figure No.7. A counter plot showing relationship between various levels of independent variables to gain fixed value of the Cumulative % drug release.

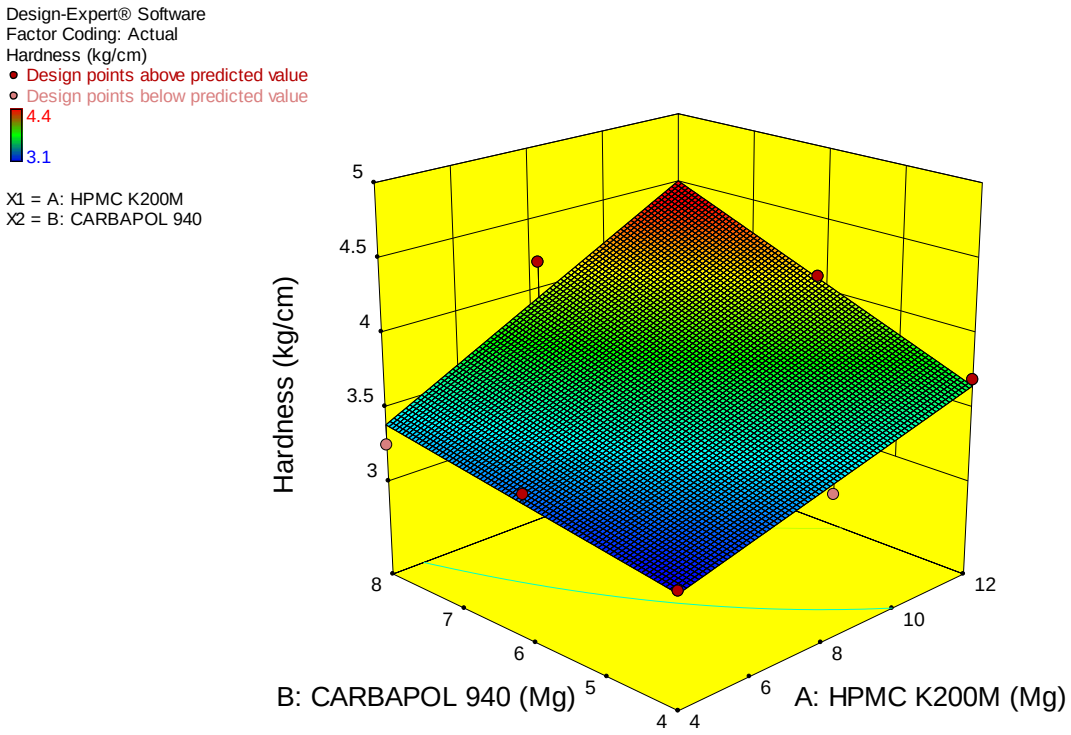

Figure No.8. Response surface plot showing effect of concentration of independent variables on the Hardness

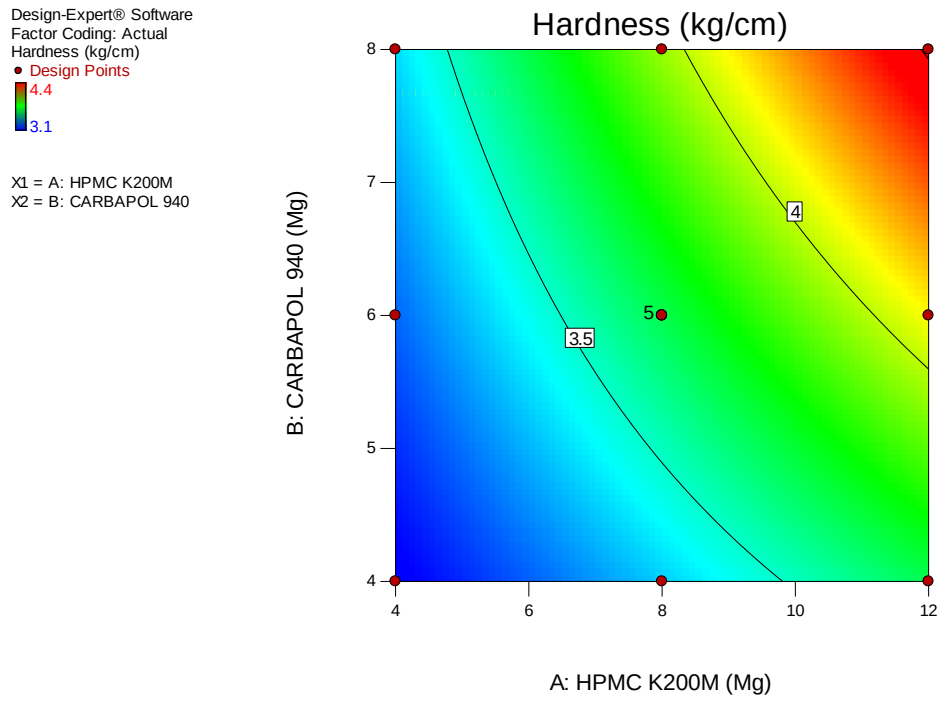

Figure No.9. A counter plot showing relationship between various levels of independent variables to gain fixed value of the Hardness

Stability Studies

The stability of the tablets was studied for the duration of 3 Months at temperature $40^0C \pm 2^0C$ and 75% ± 5% relative humidity. The tablets were then evaluated for various parameters viz. thickness, hardness, Weight variation and drug release studies. Stability study indicate optimize formulation H5 was stable after stability period.

Table 7: Stability studies

Sr No	Parameters	Initial	After 3 Months
1	Thickness mm	2.65 ± 0.02	2.60 ±**0.06**
2	Hardness kg/cm2	3.65 ± 0.03	3.60 ±**0.11**
3	Weight variation mg	60.54 ±0.67	61.05 ±0.22
4	Drug release %	97.87 %	96.44 %

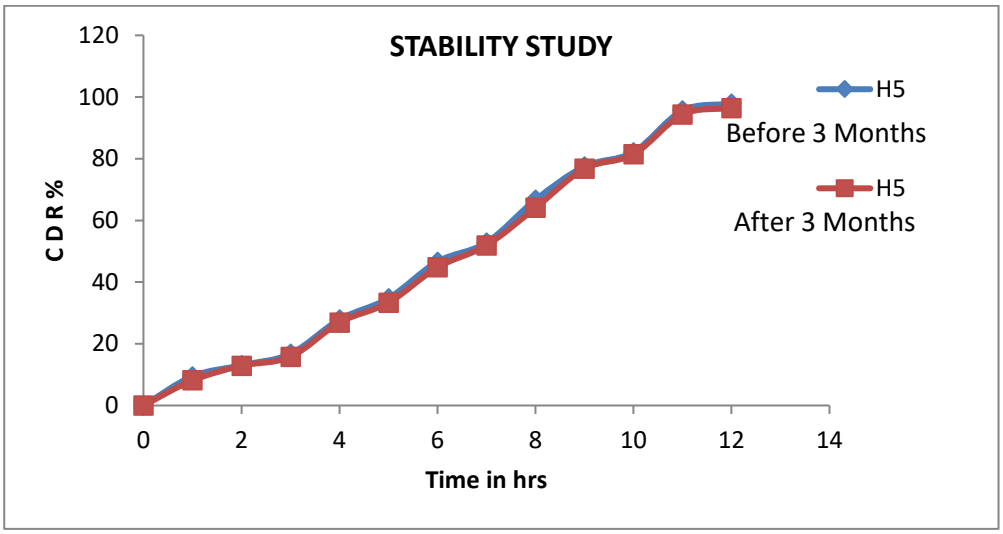

Figure No.10.Stability profile of optimized formulation H5

CONCLUSION:

The aim of this research was to develop & optimize sustain release Mini tablets of Telmisartan. Mini tablets of Telmisartan were prepared by direct compression method using HPMC K 200M and Carbopol 940 release retarding agents. 32 factorial design was applied to study % cumulative drug release and hardness by using design expert software. IR spectroscopic study indicates no drug-excipient interaction in the prepared formulations. The prepared Mini tablets exhibited satisfactory physic-chemical characteristic. 32 full factorial design and optimization technique successfully used in the development of Mini tablet. Comparing the all the formulations, formulation H5 was considered as optimized formulation which exhibited 97.87% of drug release in 12 hours also stable in stability.

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