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A Novel on "Formulation and Evaluation of Sustained Release Matrix Tablet of Anti-Hypertensive Drug"

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ABSTRACT— The goal of present work has formulation of pH independent sustained release drug delivery system based on matrix system of Valsartan and comparison of different viscosity grades of polymers. The polymers were used either alone or as in combination. To make formulation which decrease dosing frequency & reducing gastrointestinal toxicity, ultimately increasing patient compliance. The polymers were used in combination. Tablets were prepared by wet granulation method. . In-vitro drug release studies from the prepared matrix tablets were conducted for a period of 12 hours using an USP dissolution test apparatus (type II Paddle) at 37±0.5°C and 50 rpm speed. The optimized formulation F15 contains combination of hydrophilic polymer HPMC K100M 15% and hydrophobic polymer Eudragit RSPO 30% showed 90.34% drug release in 12h and avoid problem of burst release. Best fitted model optimize formulation was Korsmeyers-peppas (r2 0.9960) and the value of n= 0.8229. It proves that drug release in non-fickian type. The dissolution efficiency represents there is increase % dissolution efficiency, decrease in drug release rate from tablet.

KEYWORDS – Valsartan, HPMC K100, Carbopol 971, Eudragit 100, Polymer matrix tablet.

I. INTRODUCTION

Sustain release drug delivery system

Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. It remains the preferred route of administration investigated in the discovery and development of new drug candidates and formulations. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost effective manufacturing methods and generally improved shelf life of the product. In recent years, considerable attention has been focused on development of sustained release drug delivery systems. The rationale for the development of sustain release drug delivery system of a drug is to enhance its therapeutic benefits, minimizing its side effects while improving the management of the diseased condition [1].

I. **Biopharmaceutical Characteristics of the drug:**

Dose:

The formulation of sustained release drug products may not be practical for drugs with large conventional dose (>500mg). Because, the size of the SR drug product would have to be quite large, too large for the patient to swallow easily.

Aqueous solubility:

The rate of dissolution is directly proportional to aqueous solubility. Therefore the aqueous solubility of a drug is the limiting factor in its dissolution.

Partition Coefficient:

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Drugs with extremely high partition coefficient readily penetrate the membranes, but are unable to proceed further. While drugs with excessive aqueous solubility i.e. low oil/water partition coefficient cannot penetrate the membrane well. Therefore an ideal drug candidate is one which has a balanced partitioning between oil and water phase.

Drug stability:

Drugs unstable in Gastro-intestinal environment cannot be administered as oral sustained release formulation because of bioavailability problems.

Mechanism and Site of absorption:

Drugs absorbed by carrier-mediated transport process and those absorbed through a window are poor candidates for controlled release system e.g. several B vitamins

II. Pharmacokinetic Characteristics of the drug:

Absorption:

For a drug to be administered as controlled release formulation, its absorption rate (Ka) must be efficient since the desired rate –limiting step is rate of drug release Kr. i.e. Kr<<Ka. A drug with slow absorption is a poor candidate for such dosage forms since continuous release will result in a pool of unabsorbed drug.

Elimination Half Life:

Smaller the t1/2, larger the amount of drug to be incorporated in the sustained release dosage form. Drugs with half-life in the range of 2 to 8 hours make good candidates for such a system.

Rate of Metabolism:

A drug, which is extensively metabolized, is suitable for controlled release system as long as the rate of metabolism is not too rapid. A drug capable of inducing or inhibiting metabolism is a poor candidate for such a product since steady-state blood level would be difficult to maintain.

Dosage form index:

It is defined as the ratio of max steady state conc.(Css.max) to min. steady state conc.(Cssmin). Since the goal of sustained release formulation is to improve therapy by reducing the dosage form index while maintaining the plasma drug levels within the therapeutic window, ideally its value should be as close to one as possible.

II. LITERATURE REVIEW

- Uttam Mandal and Tapan Kumar Pal, 2008: Formulated the Bilayer Matrix Tablet containing Metformin HCL as sustained Release. To form the sustain release of the Metformin HCL they used different grades of HPMC *viz* HPMC K4M, HPMC K15M and HPMC (K100M). There was no significant difference in drug release pattern, for different viscosity grades of HPMC with the same concentration [9].
- Harris M. Shoaib , at al; 2006: Prepared once-daily Tablet formulation and In-Vitro Release Evaluation of Cefpodoxime using HPMC polymer. They observed that hydrophilic matrix of HPMC controlled the drug release effectively for 24 hours. The Kinetics of release indicated that, the release was best explained by Higuchi's equation i.e. Matrix System [6].

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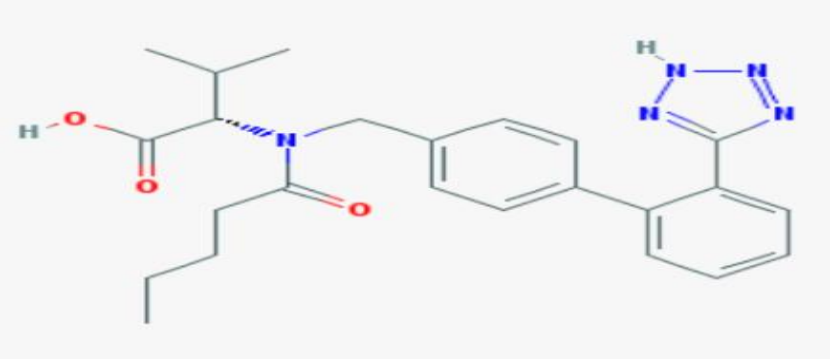
- Maswadeh , Raslan HK ; 2006: Studied In-Vitro Dissolution Kinetic Study of Theophylline from mixed Controlled Release Matrix Tablets Containing HPMC and Glycerylbehenate. They observed that during the dissolution process the tablets undergo erosion as well as swelling and also shows the alteration in the surface area and diameter of the matrix system [9].
- Amelia Avachat and Vikram Kotwal , 2007: Designed and Evaluated Matrix Based Controlled Release Tablets of Diclofenac Sodium and Chondroitin Sulphate . They used the sustaining polymer as HPMC KIOOM CR and found out that 40% concentration of the polymer revealed good results as desired. The release of the prepared tablets was then matched with the marketed tablet and was found to be similar [10].

III. DRUG & POLYMER PROFILE

Valsartan [35-38]:

Structure:



Chemistry:

Molecular Formula	-	Valsartan;2S)-3-methyl-2[pentanoy1-[[4-[2-(23H-tetrazol -5-yl)pheny1]methy1]amino] butanoic acid
Molecular Weight	-	435.51
Melting range	-	116-117^{0}C
Half-life	-	About 4-6hr
Solubility:	-	Soluble in ethanol and methanol
Physical Properties	-	white crystalline powder
Category:	-	Cardiovascular Agent , Renal Protective Agent

Mechanism and Action- Block the vasoconstrictor and aldosterone secreting effect of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissue, such as vascular smooth muscle.

Metabolism and Elimination- Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83%of dose) an urine (about 13% of dose). The recovery is mainly as an changed drug, with only about 20% of dose recovered as metabolites. The primarily metabolite, accounting for about 9% of dose, is Valery 4 hydroxyl valsartan. In vitro metabolism study involving recombinant CYP 450 enzyme indicated that the CYP 2C9 is enzyme is responsible for formation of valeryl-4-hydroxy valsartan. Valsartan does not inhibit CYP450 is enzyme at clinically relevant concentration. CYP 450 mediated drug interaction between valsartan and code ministered drug are unlikely because of the long extend of metabolism

Therapeutic use: Valsartan is used to treat high blood pressure and congestive heart failure

Contraindications:

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Co-administration of quetiapine with thioridazine does result in low plasma levels of quetiapine, hence should not be used with it. Concurrent administration of quetiapine with phenytoin increases it's oral clearance by 5- folds. Caustion must be taken when administrating quetiapine along with the drugs that inhibit or induce cytochromes, particularly CYP3A4.

Dosage recommendation: 80-160 mg/day PO generally, adjust dosage monthly (maximal reduction of BP attained after 4 weeks); adjust more aggressively in high-risk patients and patients with comorbidities.

Preparations available: 80-160 mg/day

IV. EXPERIMENTAL

Table 1: List of chemicals

Sr. No.	Chemical and reagents	Suppliers
1.	Valsartan	Micro Lab Ltd, Mumbai, India.
2.	HPMC K100M	S kant pharma, Vapi, India.
3.	Carbopol 971	BASF Chemicals Mumbai, India.
4.	Eudragit 100	EvonikPharma House, Degussa, India.
5.	Lactose	Loba Chem., Mumbai, India.
6.	Magnesium stearate	SD Fine Chemicals, Mumbai, India.
7.	Talc	SD Fine chemicals, Mumbai, India.
8.	Isopropyl Alcohol	Loba Chem., Mumbai, India.

Physical parameters

- **Solubility determination**

The solubility of Valsartan in double distilled water was determined. An excess amount of Valsartan was placed in glass bottles containing 20 ml of solvent. The bottles were thoroughly shaken for 24 h and kept aside for 24 hrs at room temperature. At the end of this period the solution were filtered and the filtrate was collected into dry containers. The solutions were suitably diluted and assayed for Valsartan content.55

Determination of λmax

Stock solution of Valsartan was prepared by dissolving 10 mg of drug in 100 ml of solvent (pH 1.2 & pH 6.8) after proper dilutions, analyse spectrophotometricaly to determine the λmax.

Preparation of calibration curve -

Valsartan solution of 100µ g/ml was prepared in pH 1.2 and in pH 6.8 and UV-Visible spectrum was recorded in the wavelength of 200-400 nm.

Angle of repose

The angle of repose of each powder blend was determined by glass funnel method. Powders were weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel was so adjusted that the tip of funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated by using the following formula.

$$\tan\theta = h/r \quad \text{.....(5.1)}$$

Where,

h = height of cone & r = radius of powder cone.

Bulk density (D_b)

Bulk density of the granules was determined by pouring gently 5 gm of sample through a glass funnel into a 10 ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated by the following formula:

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$$D_b = M/V_0 \text{ ……..(5.2)}$$

Where,

M the mass of powder (gm).

V_0 the bulk volume of the powder (ml).

Tapped density (D_t)

About 5 gm of granule was poured gently through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after 50 tappings were recorded and tapped density was calculated by the equation5.4,

$$D_t = M/V_t \text{ ……..(5.4)}$$

Where,

M the mass of powder (gm)

Vt the Tapped volume of the powder (ml).

Carr's index

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index I, which is determined by the equation5.5,

Carr's index = (Dt–Db/Dt)×100 ……..(5.5)

Stability studies

The optimized formulation F15 was kept for short term stability study. The conditions for stability study were temperature 42±20C and relative humidity of 75%. All tablets were suitably packed in group of 10 in aluminum foil. At the end of one month the sealed tablets were opened and evaluated for thickness, dissolution, disintegration, Friability, uniformity of weight and determination of drug content.

Statistical analysis of data

The obtained results of stability data subjected for statistical analysis using Systat Software, Inc. 501 USA. Stability data of drug contain and dissolution data is statistically analyzed by using student't' test. A t-test is any statistical hypothesis test in which the test statistic follows a student's t distribution if the null hypothesis is supported. It can be used to determine if two sets of data are significantly different from each other, and is most commonly applied when the test statistic would follow a normal distribution if the value of a scaling term in the test statistic were known. When the scaling term is unknown and is replaced by an estimate based on the data, the test statistic (under certain conditions) follows a Student's distribution.

This statistical approach where applied for stability data of drug content and drug dissolution profile of optimizes formulation

Dissolution efficiency

The dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

Preparation of matrix tablet -

Valsartan tablets with different concentrations of polymer were prepared by the wet granulation technique. All ingredients in required quantities were weighed individually. All the ingredients were first sieved and mixed for 5 min. isopropyl alcohol was added drop wise till suitable mass for granulation was obtained. Then wet mass

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was granulated through sieve 8# and prepared granules were dried at 60^0c for 1 h. the dried granules were dried at 60^0c for sieve 10# and fractions of granules retained on the sieve were discarded then blended with talc and magnesium stearate for lubrication of granules which were then compressed on single punch tablet machine using circular 4 mm punch. The weight of tablet adjusted to 200 mg. each tablet containing 80 mg Valsartan and other excipients.

Table 2 Composition of tablets formulation batches F1 to F9

Formulation codes	HPMCK100M			Carbopol 971			Eudragit RSPO			Diluent (mg)
	10%	15%	20%	35%	40%	45%	20%	25%	30%	
F1	20	-	-	-	-	-	-	-	-	96
F2	-	30	-	-	-	-	-	-	-	86
F3	-	-	40	-	-	-	-	-	-	76
F4	-	-	-	70	-	-	-	-	-	46
F5	-	-	-	-	80	-	-	-	-	36
F6	-	-	-	-	-	90	-	-	-	26
F7	-	-	-	-	-	-	40	-	-	76
F8	-	-	-	-	-	-	-	50	-	66
F9	-	-	-	-	-	-	-	-	60	56

From the above obtained result following combination batches were prepared.

Table 3 Composition of tablets formulation batches from F10 to F15

Formulation codes	HPMC K100M (15%)	Carbopol 971			EudragitRSPO35%			Diluent (mg)
		35%	40%	45%	20%	25%	30%	
F10	30	70	-	-	-	-	-	16
F11	30	-	80	-	-	-	-	6
F12*	30	-	-	90	-	-	-	00
F13	30	-	-	-	40	-	-	46
F14	30	-	-	-	-	50	-	36
F15	30	-	-	-	-	-	60	26

****Each formulation contains 1% Magnesium sterate, 1% Talc (except Batch F12 contains 1.5% talc).**

Evaluation of tablet

Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet was measured by Monsanto hardness tester (Nevtex). The hardness was measured in terms of kg/cm^2.

Thickness

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Venire calipers.

Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 minutes, the tablets were weighed and the percentage loss in tablet weight was determined.

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% Friability = (A-B) ×100/A …….. (5.7)

Where,

A Initial weight of tablets and

B Final weight of tablets after revolutions

Uniformity of weight

Weigh 20 tablets at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown and none deviates by more than twice that percentage.

Determination of drug content

For drug content, accurately weighed tablets was selected and ground to fine powder. An amount equivalent to 75 mg drug was dissolved 500 ml volumetric Flask in pH 6.8 buffer and filtered through filter paper. The filtered solutions of appropriate dilutions were analyzed at 250 nm using UV spectrophotometer. The amount of DXT was determined by measuring the absorbance at 250 nm.

Dissolution Test

The developed formulations (n=3) were subjected to release studies using USP type II dissolution apparatus at 50 rpm with a constant temperature double distilled water bath at 37°C ± 0.5°C. Dissolution medium used was pH 1.2 (900 ml) for first 2 hours and pH 6.8 (900 ml) for next 10 hours. Withdraw 10 ml of samples at different time interval and replaced with an equivalent amount of fresh medium.

V. RESULTS

Table 4 Micromeritic profile of formulation batches F1 to F15

Formulation Code	Angle of Repose ( )	Bulk density (gm/cm3)	Tapped density (gm/cm3)	carr's index (%)	Hausner's ratio
F1	26.20±0.842	0.350±0.011	0.402±0.011	15.1	1.18±0.014
F2	25.52±0.945	0.372±0.006	0.438±0.075	13.69	1.16±0.025
F3	24.82±0.607	0.390±0.006	0.443±0.046	11.21	1.13±0.012
F4	27.13±0.959	0.382±0.003	0.451±0.004	15.3	1.17±0.011
F5	28.55±0.904	0.357±0.005	0.418±0.004	14.22	1.19±0.015
F6	24.59±0.835	0.352±0.005	0.409±0.120	12.71	1.15±0.015
F7	26.46±0.587	0.365±0.002	0.430±0.007	14.8	1.17±0.021
F8	28.98±0.866	0.332±0.005	0.386±0.006	13.58	1.15±0.012
F9	24.61±0.505	0.388±0.0034	0.451±0.0046	14	1.16±0.127
F10	27.66±0.758	0.400±0.0040	0.460±0.011	11.22	1.13±0.006
F11	23.94±0.688	0.350±0.00288	0.405±0.003	12.65	1.15±0.012
F12	26.46±0.965	0.396±0.0011	0.446±0.007	12.77	1.12±0.011
F13	25.733±0.574	0.331±0.00288	0.378±0.005	10.72	1.14±0.017
F14	28.33±0.601	0.365±0.00288	0.430±0.007	14.8	1.17±0.015
F15	28.16±0.602	0.353±0.00288	0.400±0.004	12.62	1.37±0.404

Mean , ± S.D, n=3

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Table 5 Characterization of formulation

Formulation Code	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability	Drug content (%)
F1	199.65±0.70	3.06±0.057	6.33±0.29	0.50	97.60± 0.53
F2	199.70±0.83	3.03±0.057	6.17±0.29	0.25	98.31±1.74
F3	199.47±0.72	3.01±0.100	6.33±0.58	0.30	97.87±1.48
F4	199.78±0.65	3.06±0.110	6.00±0.50	0.20	98.84±1.97
F5	199.65±0.58	3.12±0.057	5.83±0.29	0.75	98.13±1.67
F6	199.85±0.58	3.06±0.057	6.17±0.29	0.20	98.49±0.81
F7	199.70±0.59	3.13±0.110	6.00±0.50	0.15	98.22±0.41
F8	199.77±0.63	3.03±0.057	6.00±0.50	0.10	98.49±1.20
F9	199.73±0.79	3.01±0.132	6.00±0.50	0.25	97.51±1.37
F10	199.72±0.62	3.1±0.057	6.00±0.50	0.10	98.67±0.92
F11	199.87±0.37	3.13±0.057	6.17±0.29	0.15	98.93±1.22
F12	199.75±0.43	2.96±0.057	6.33±0.29	0.10	99.47±0.71
F13	199.68±0.47	3.06±0.057	6.17±0.29	0.20	98.84±1.01
F14	199.63±0.63	3.06±0.111	5.83±0.29	0.45	97.69±1.78
F15	199.80±0.58	3.03±0.057	6.33±0.29	0.10	98.93±1.22

Table 6 Release kinetics of F1-F15 formulation batches

Formulation Code	Zero order	First order	Higuchi	Peppas	Hix.-Crowell	n value
F1	0.8627	0.9824	0.9459	0.9961	0.9739	0.7297
F2	0.9389	0.9193	0.9846	0.9941	0.9758	0.7684
F3	0.9591	0.9296	0.9886	0.9958	0.9744	0.9308
F4	0.9449	0.8322	0.9819	0.9917	0.9438	0.5663
F5	0.9691	0.8787	0.9769	0.9976	0.9372	0.5887
F6	0.9776	0.8249	0.9576	0.980	0.9099	0.533
F7	0.9587	0.9407	0.9906	09914	0.9845	1.1013
F8	0.9729	0.9457	0.9959	0.9896	0.9834	1.1394
F9	0.9868	0.9992	0.9942	0.9822	0.9771	1.264
F10	0.9353	0.9795	0.9912	0.9980	0.9814	0.6445
F11	0.9851	0.9151	0.9824	0.9976	0.9668	0.6778
F12	0.9950	0.9200	0.9753	0.9879	0.9649	0.7591
F13	0.9168	0.9874	0.9807	0.9950	0.9934	0.7672
F14	0.9149	0.9914	0.982	0.9924	0.9897	0.8117
F15	0.956	0.9815	0.9947	0.9960	0.9944	0.8229

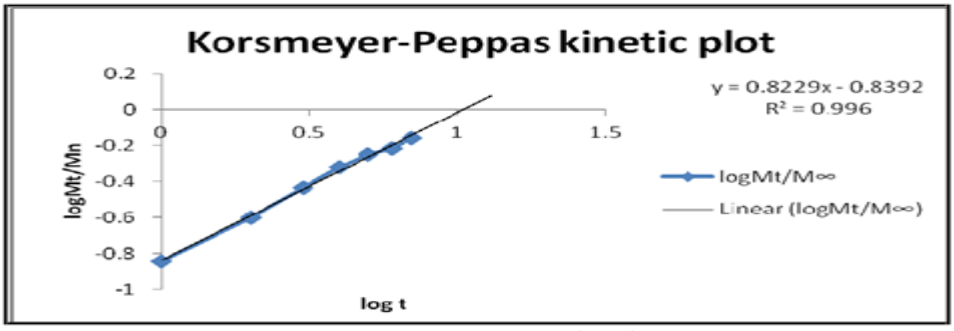

Fig. 3 Korsmeyer-Peppas kinetic plot of F15 formulation

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Table 7 Results of stability study

Parameters	After 0 days	After 30 days
Weight Variation (mg)	199.80±0.58	199.53±.06
Content Uniformity (%w/w)	98.93±1.22	99.11±1.37
Hardness (kg/cm2)	6.33±0.29	6.27±0.29
% Friability (%w/w)	0.10	0.12

Table 8 Results of student t-test for drug content for F15 formulation

Parameters	Mean	SD	pValue
Before stability drug content	98.93	1.22	0.902
After stability drug content	99.11	1.37	

Table 9 Results of student t-test for drug dissolution data at 2h, 6h & 12h.

drug dissolution time	Before Stability Drug dissolution	After Stability drug dissolution	p value
2h	23.650±0.586	23.740±0.941	0.895
6h	56.920±0.615	55.970±1.933	0.463
12h	90.730±0.103	89.460±1.146	0.128

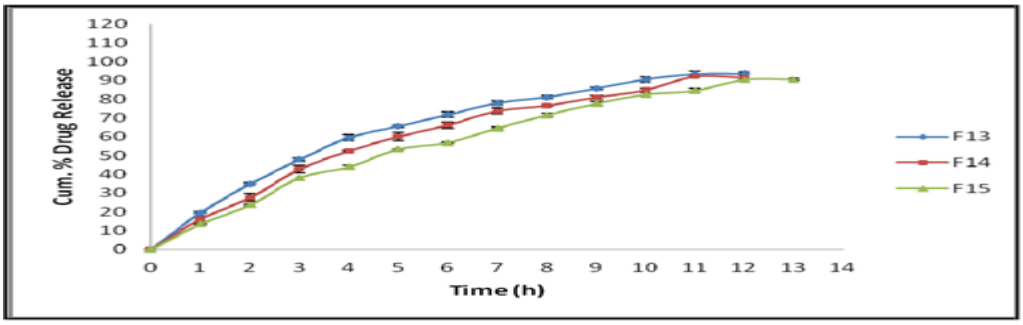

Fig. 4 in-vitro drug release profile of F15

Dissolution efficiency

The data of dissolution efficiency proves that increase in polymer concentration of polymer there is decrease in release rate of drug from matrix.

Table 10 Result of dissolution efficiency for F1-F15 formulations

Formulation codes	% Dissolution efficiency	
	At 2h	At 6h
F1	9.46	61.38
F2	8.14	47.68
F3	6.25	14.88
F4	7.14	39.25
F5	6.15	35.38
F6	5.30	32.02
F7	5.36	42.55
F8	4.36	50.61
F9	3.23	31.98
F10	5.48	31.94
F11	5.40	29.96
F12	3.69	27.63

F13	6.76	38.28
F14	4.64	33.41
F15	4.02	29.01

VI. CONCLUSION

Polymer matrix systems are widely used in sustained drug delivery to obtain a desirable drug release profile and broad regulatory acceptance. Hence, in the present work an attempt has been made to develop sustained release matrix tablets of Valsartan using HPMC K100M, Carbopol 971 and Eudragit RSPO either in combination or alone. The tablets were evaluated for hardness, thickness, and drug content uniformity, in-vitro drug release studies for 12 hours in pH 1.2 buffer and in pH 6.8 buffer. The amount of Valsartan released from the tablet formulations was estimated at 250 nm using a UV spectrophotometer. Formulations F1-F9 contained a single polymer with drug and polymer from higher to lower percent. Among these formulations, none of the formulation showed, desired drug release rate retardation. Formulation F1-F6 shows the burst release while formulation F7- F9 unable to retard the drug upto 12 hours. It may be concluded from the present study that slow and sustained release of Valsartan over a period of 12 hrs was obtained (F12 and F15). It was successful in the formation of matrix and at the same time it is effective in retarding the drug release. Formulation F15 shows 23.65% releases drug at 2h and 90.34% drug release at 12 hrs. While F12 shows 21.41%. Among them, formulation F15 shows Highest R2 value. Therefore Batch F15 selected as optimized formulation. Best fitted model For F15 formulation is Korsmeyers-peppas and also follows first order release kinetics model.

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