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FORMULATION AND EVALUATION OF SUSTAINED RELEASE ANTI-HYPERTENSIVE TABLETS BY USING VARIOUS NATURAL BIODEGRADABLE POLYMERS

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ABSTRACT

In the present research work has been carried out in formulation and evaluation of verapamil sustained release metrics utilizes various natural biodegradable polymers. There are many biodegradable natural polymer used among these such as tragacanth and guar gum results of the present study demonstrated that combination of both could be successfully employed for formulating sustained release matrix tablets of verapamil. The sustained release tablets can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional verapamil. The prepared granules were evaluated by following test bulk density, angle of repose, tapped density, compressibility index or carr's index, hausner ratio has been satisfied and release profile meet with standard bioequivalent study.

KEYWORDS

HPMC, Verapamil, Biodegradable polymers and Sustained release tablets.

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INTRODUCTION

Hypertension is sustained elevation of resting systolic BP (> 140mm Hg), diastolic BP (>90mm Hg) or both. Hypertension with no known cause (Primary, formerly, essential hypertension) is most common. Hypertension with an identified cause (Secondary hypertension) is usually due to a renal disorder. Usually, no symptoms develop unless hypertension is a serve or long-standing. Diagnosis is by sphygmomanometer. Tests may be done

determine cause, assess damage, and identify other cardiovascular risk factors[1,2].

Types of Hypertension

There are mainly two types of hypertension 1) Primary hypertension 2) Secondary hypertension[3-5].

Primary hypertension

Hemodynamic and physiologic components (e.g. plasma volume. Activity of the rennin angiotensin system) vary, indicating that primary hypertension is unlikely to have a single cause. Even if one factor is initially responsible, multiple factors are probably involved in sustaining elevated BP (Mosaic theory). In afferent systematic arterioles, malfunction of ion pumps on sarcolemmal membranes of smooth muscle cells may lead to chronically increased vascular tone. Heredity is a predisposing factor, but the exact mechanism is unclear. Environmental factors (e.g. Dietary Sodium, obesity and stress) seem to affect only genetically susceptible people.

Secondary Hypertension

Causes include renal parenchyma disease (e.g. chronic glomerulonephritis or pyelonephritis, polycystic renal disease, connective tissue disorders and obstructive uropathy), renovasular disease, pheochromocytoma, Cushing's syndrome. Primary aldosteronism, congenital adrenal hyperplasia, hyperthyroidism, myxedema and coarctation of the aprta. Excessive alcohol intake and use of oral contraceptives are common causes or licorice commonly contributes to hypertension.

Drug Treatment in hypertension

This can be classified into of 6 major classes. Six different classes of drugs used for the treatment of hypertension are: Angiotensin-converting enzyme (ACE) inhibitors, B-blockers, Calcium channel blockers (CCBs), Diuretics, Aldosterone antagonists (ALDO ANT) and the newest class, Angiotensin II – receptor blockers (ABBS), Each of these classes has merits and demerits, as ancillary properties that pressure and thus, the choice of combination therapy, with appropriate synergistic effects of the drugs, becomes similarly important[6,7].

Sustained Release Dosage Form

Sustained-release (SR), extended-release, time–release or timed–release, controlled-release (CR), or continuous–release (CR or Contin) pills are tablets or capsules formulated to dissolve slowly and release a drug over time. The advantages of sustained-release tablets are capsules are that they can often be taken less frequently than instant release formulations of the same drug and that they keep steadier levels of the drug in the blood stream. Sustained –release tablets are formulated so that the active ingredient is embedded in a matrix of insoluble substance so that the dissolving drug has to find its way out through the holes in the matrix. In some SR formulations the matrix, and then exit through the outer surface[8].

Potential advantages and disadvantages of sustained release dosage forms

Patient Compliance

Reduced see-saw fluctuation

Reduced total dose

Improved efficiency in treatment

Disadvantages

Dose Dumping,

Less flexibility in an accurate dose adjustment

Poor in Vitro-in Vivo correlation, iv. Patient variation[9,10].

Matrix system used for sustained release

Frequently used approaches to achieve adequate control of drug release include hydrophilic and lipophilic matrix system, in which the mechanisms of drug release, is based on a combination of diffusion and erosion process. Their properties as gelling agent are very important in the formulation because they are responsible for the formulation, by hydration, of a diffusion and erosion resistant gel layer which is able to control drug release[11,12].

Hydroxypropyl methylcellulose (HPMC) is the polymer most widely used as the gel-forming agent in the formulation agent in the formulation of solid, liquid. Semisolid and even controlled release dosage form[13-15]. Water penetration, polymer swelling drug dissolution, drug diffusion matrix Erosion from these dosage forms are controlled by a hydration of HMPC, which form a gel barrier through which the drug diffuses[16-21].

From various literature searches there are few sustained release matrix tablets available. Sandesh

Y. Pawar, *et al*, (2023)[22] to develop antihypertensive matrix tablets with sustained release of valsartan and Jagruti J. Pansare, *et al*, (2021)[23] to developed Verapamil HCl novel fast disintegrating sustained release pellets containing tablet by using Fluidized Bed processor. The objective of the research work is to formulate and evaluate the oral sustained drug delivery system containing Verapamil as a model drug by using polymer among the hydrophilic polymer, cellulose derivative such as methyl cellulose, HPMC, are generally considered to be stable and safe as release dosage form. These semi synthetic polymers are quite expensive when compared with natural polymers such as tragacanth and guar gum. The natural polymers are non –toxic and easily available.

MATERIAL AND METHODS

List of Materials and List of Instruments

List of material and list of equipment used in this experiments given in the Table No.1 and Table No.2 given respectively.

METHODS AND PREPARATION OF SR MATRIX

Pre Formulation Studies of Verapamil

Before reformulation of drug substance in to dosage forms, it is essential that it should be chemically and physically characterized studies give the formulation needed to define the nature of the drug substance and provide a frame work combination with pharmaceutical recipients in the fabrication of dosage forms. The drug and polymer ratio is 1:1 proportion were prepared and examined.

Standard Calibration Graph of Verapamil in Diluent: (1% Polysorbate 80 in water solution medium)

Weighed 20gm of Verapamil in was dissolved in 100ml dilution 1% Polysorbatee 80 medium further dilution were made using 1% Polysorbate e80 medium to obtains conc. ranging from1ug\ml. The peak area of the solution measured at 254nm using Agilent 1100 series HPLC. Peak Area of verapamil are listed below Table No.3 and graphical representation in Figure No.1.

Drug - Excipient Interaction Study

In the drug -excipient interaction study it was found that Verapamil was having compatibility with all the excipients used in the formulation .active drug blended with individual excipient taken in 1:1 ratio. The compatibility studies were done samples were observed by physical changes at the end of 1^{st}, 2^{nd}, 4^{th} and 6^{th} weeks thus the chosen the exipients for the formulation were found to be compatible with the active ingredient and having low physical interaction with the active pharmaceutical ingredient also there was no change in the physical appearance of the blend given in the Table No.4.

Compression of tablets by wet granulation method:

The tablets were prepared by wet granulation technique using 6mm round concave punch. Compression was done by 16-station rotator tablet punching machine. The trial error method the preliminary screening of natural polymer for sustained release matrix of verapamil HCl is given in the Table No.5.

RESULTS AND DISCUSSION

Evaluation of granules

The micrometric properties such as angle of repose, Hausner's ratio, bulk density, tapped density and Carr's index of blend containing drug and excipient were studied. To determine the flow ability, angle of repose, Hausner's ratio, carry's index was calculated. The results are tabulated in Table No.6. The obtained value angle of repose (θ) ranges between 28.39-30.46, Hausner's ratio below 1.25 and carr's index below 20 indicating good flow properties.

Post Compression Evaluation

The Post Compression parameters of Hardness kg/cm2, Friability, Thickness (mm), Weight Variation were satisfactory and the results given in the Table No.7.

In-vitro Evaluation studies

Drug release study was carried out in USP II basket-type dissolution test apparatus dissolution

medium was 1% (w/v) Polysorbate 80 in water volume of dissolution medium was 500ml, and bath temperature was maintained at 37+ 1° throughout the study. Basket speed was adjusted to 100rpm. After 1, 2, 4, 6, 8, 10, 12 hours, 5ml of sample was a withdrawn and analyzed for content by HPLC at 254nm. Using Chemstation software (Agilent Technologies, New Delhi, India). It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicane (6 tablets in each set) and the mean values were plotted versus time with SDs of less than 3, indicating the reproducibility of the results. The results are tabulated in Table No.8 and graphical representation in Figure No.2.

Table No.1: List of materials used

S.No	Materials	Suppliers
1	Verapamil	Intermed Pharma, Chennai
2	Polysorbate 80	Harish Chemicals Pvt Ltd Ahamadabad
3	HPMCTM K 100LV	Chemplastsunmark Pvt Ltd, Nadoor
4	Tragacanth Gum	Sigachi Chloro chem. Ltd Hydrabad
5	Guar Gum	Sigachi Chloro chem. Ltd Hydrabad
6	HPMCTM E 15 LV	Chemplastsunmark Pvt Ltd, Nadoor
7	MCC VC 114	SigachiChloro chem. Ltd Hydrabad
8	Magnesium stearate	Harish chemicals Pvt ltd Ahamadabad
9	Colloidal silicon dioxide	Cabot Sunmark Pvt Ltd Naddor

Table No.2: List of materials used

S.No	Name of Equipments	Manufacturing Company
1	Electrical balance	Precisa
2	Single rotary tablet compression machine	Cadmach
3	Vernier caliper	Mitutoya
4	Hardness tester	Monosanto
5	Friabilator	Roche
6	Hydrolic press hardness tester	Dharma scientific products
7	Dissolution apparatus	Minicon
8	Sonicator (bath)	Remi equipment Pvt Ltd
9	Micro centrifugator	Remi equipment Pvt Ltd
10	Micro syringe	Eon pipette (Bio ers's)
11	Hot air ovan	Minicon
12	KFR titer apparatus	Lasco equipment Pvt Ltd
13	Bulk density test apparatus	Vergo
14	Cyclo mixer	Remi equipment Pvt Ltd

Table No.3: Peak Area of Verapamil vs Concentration (µg/ml)

Concentration (µg/ml)	Peak Area of the Solution
1	75
2	155
3	250
4	325
5	425

Table No.4: Drug – Excipients compatibility study of verapamil with other excipients

S.No	Drug + Excipients	Drug/ Excipients ratio	Physical Description Initial	35ºC±2ºC/60%±5% RH			
				1 Week	2 Week	4 Week	6 Week
1	Verapamil	-	White powder	*	*	*	*
2	Drug+HPMC K 100 LV	1:1	Yellow Fibrous powder	*	*	*	*
3	Drug + HPMC E15 LV	1:1	White granular powder	*	*	*	*
4	Drug + Tween 80	1:1	White crystalline powder	*	*	*	*
5	Drug + MCC 114	1:1	White crystalline powder	*	*	*	*
6	Drug + Magnesium Stearate	1:1	White crystalline powder	*	*	*	*
7	Drug+ Aerosil	1:1	White powder	*	*	*	*
8	Drug+ Tragacanth	1:1	White crystalline powder	*	*	*	*
9	Drug+ Guar gum.	1:1	White powder	*	*	*	*

*No incompatibility Problem

Table No.5: Preliminary screening of Natural Polymer for Sustained Release Matrix of Verapamil HCL

S.No	Ingredients (mg)	Quantity in mg				
		F1	F2	F3	F4	F5
1	Verapamil HCL	120	120	120	120	120
2	HPMC K 100 LV	10	10	10	10	10
3	HPMC E15 LV	1	1	1	1	1
4	Tween 80	1	1	1	1	1
5	Verapamil HCL	1	1	1	1	1
6	HPMC K 100 LV	1	1	1	1	1
7	MCC 114	5	6	4	3	7
8	Aerosil	5	4	6	7	3
9	Tragacanth	5	5	5	5	5
10	Guar gum	1	1	1	1	1
11	IPA	1	1	1	1	1
12	Magnesium stearate	1	1	1	1	1
13	Total	150mg/tablet				

Table No.6: Angle of response, bulk density, tapped density, Carr's compressibility index and Hausner's compressibility

S.No	Property	F1	F2	F3	F4	F5
1	Angel of Response(°)	43.05	28.39	29.05	29.74	29.74
2	Bulk Density (gm/cm3)	0.47	0.48	0.47	0.45	0.47
3	Tapped Density	0.58	0.56	0.56	0.56	0.56
4	Carr's Compressibility Ratio	18.96	14.28	16.07	19.64	19.96
5	Hausner's Compressibility Ratio	1.26	1.16	1.19	1.24	1.23
6	Flow Property	Good	Good	Good	Good	Good

Table No.7: Post compression parameter of F1 to F5

S.No	Parameters	Formulations				
		F1	F2	F3	F4	F5
1	Hardness kg/cm2	4.8	5	5.2	4.4	5.8
2	Friability (%)	0.24	0.24	0.24	0.25	0.26
3	Thickness (mm)	6.46	3.55	3.62	3.55	3.5
4	Drug Content (%)	88.93	90.35	89.65	94.87	95.86
5	Weight Variation	Weight of all the tablets was found between the ranges of 150mg to 159mg which is well within the IP limits				

Table No.8: Percentage of *In-vitro* drug release profile of verapamil SR matrix of formulation F1 to F5

S.No	Time in Hrs	Cumulative Percentage Release of Verapamil				
		F1	F2	F3	F4	F5
1	1	4.26	5.56	6.4	4.5	15.9
2	2	9.82	11.12	16.71	21.02	32.79
3	4	14.63	19.36	25.54	29.83	43.69
4	6	26.14	26.32	34.65	39.5	65.5
5	8	32.71	37.33	41.96	61.59	78.89
6	10	53.53	49.46	53.99	73.9	89.4
7	12	68.48	72.87	74.2	78.89	98.9

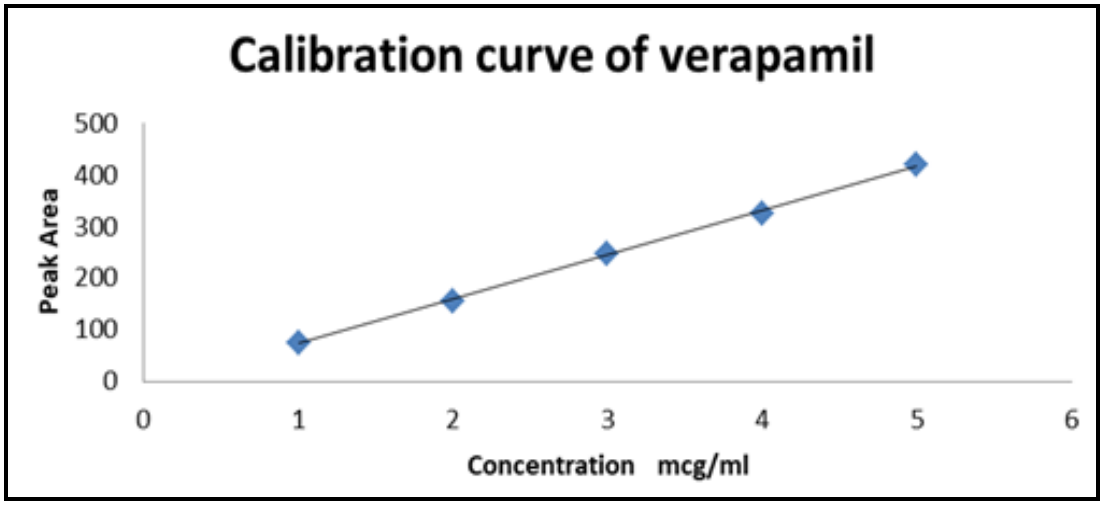

Figure No.1: Standardgraphy of Verapamil HCL, Conc Vs Peakarea

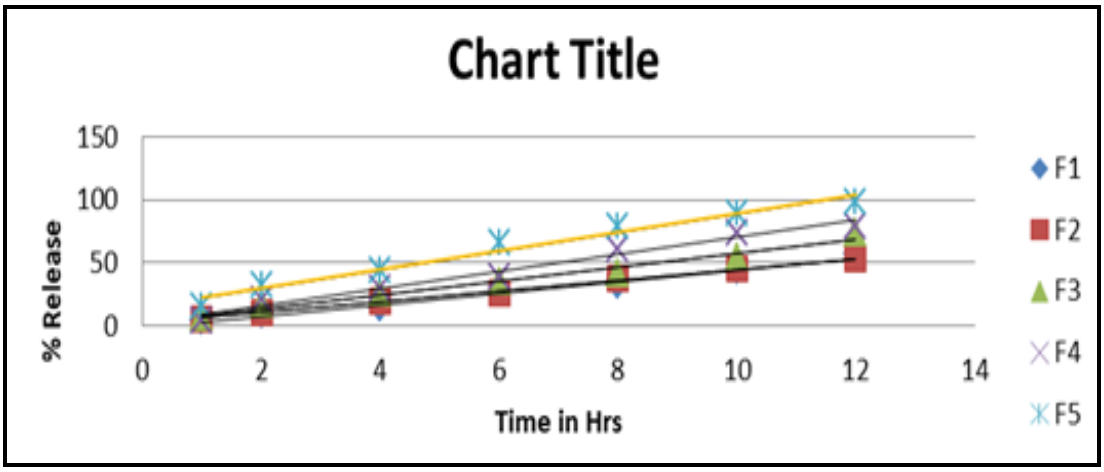

Figure No.2: *In-vitro* %drug release of formulation F1 to F5

CONCLUSION

Recent advances in novel drug delivery systems aims to enhance the safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is oral sustain release formulation.

Chosen excipients for the formulation were found to be compatible with the active ingredient and having low physical interaction with the active pharmaceutical ingredient also there was no change in the physical appearance.

The formulation F1, F2, F3, F4 containing HPMC E15 LV in low concentration has shown less drug release and are not able to maintain matrix integrity formulations F5 were prepared using combination of HPMC E 15LV and HPMC k100LV along with natural biodegradable polymer such as tragacanth and guargum in increased ratio in order to overcome the drug release rate therefore this formulations were prepared in bulk and subjected to further stability studies. All the pre and post compression evaluation given satisfactory.

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CONFLICT OF INTEREST

All authors' declared no conflict of interests.

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