International Journal of Scientific Research and Engineering Development-– Volume 7 Issue 1, Jan-Feb 2024

Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

Synergistic Bilayer Tablets: Advancing Pregabalin and Methylcobalamin Combination Therapy for Enhanced Neurological Relief

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Abstract:

To effectively treat neuropathic pain, this study focuses on the creation and assessment of bilayer tablets co ntaining sustained-release pregabalin and immediate-
release methylcobalamin.The suitability of specific polymers (HPMC K4M, HPMC K100M, and SSG) wit h both medications was validated by compatibility experiments.The tablets fulfilled the requirements for h ardness, thickness, weight fluctuation, and friability, and the granules that were synthesized had satisfactor y flow qualities.Pregabalin was tested in nine different formulations for its ability to dissolve, and Design o f Experiment (DOE) software was used to identify the ideal ratios of HPMC polymers.
release layer.The bilayer pills were manufactured and confirmed to meet pharmacopeial requirements for d rug content. The tablets included optimal formulations of both medicines.
Zeroorder release kinetics were found in dissolution testing for the improved tablets.According to stability experiments, there were no appreciable alterations to the bilayer tablets' physical attributes, drug composition, or dissolving profiles. This thorough analysis indicates that the created bilayer tablets have potential for long-term, efficient neuropathic pain treatment.

Keywords: Bilayer tablets, methylcobalamin, pregabalin, neuropathic pain, sustained release, immediate release, compatibility studies, dissolution kinetics, stability studies.

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INTRODUCTION

NERVOUSSYSTEM:[1]

The nervous system is a complex, sophisticated system that regulates and coordinates body activities.Itis madeup of twomajor divisions, including:

Centralnervoussystem. Thisconsistsofthebrainandspinal cord.

Peripheral nervous system. This consists of all other neural elements, including the peripheral nerves and the autonomic nerves.

DISORDERS OFNERVOUS SYSTEM:

Thenervoussystemis vulnerabletovariousdisorders.Itcanbedamaged by:

- Injury
- Infections
- Degeneration
- Structuraldefects
- Tumors
- Bloodflowdisruption
- Autoimmune disorders

INJURY:[2]

Brain injuries are often caused by blunt trauma. Trauma can damage brain tissue, neurons, and nerves. This damage affects your brain's ability to communicate with the rest of your body. Examples of brain injuries include:

- hematomas
- blood clots
- contusions,orbruisingof braintissue
- cerebraledema,orswellinginsidethe skull
- concussions
- strokes

DEGENERATION:

Neurodegenerativediseasescausebrainandnervestodeteriorateovertime.Theycanchange your personality and cause confusion. They can also destroy brain's tissue and nerves. Some brain diseases, such asAlzheimer's disease, may develop as depend upon age. They can slowly impair memory and thought processes.Neurodegenerative diseases cause permanent damage, so symptoms tend to get worse as the disease progresses. New symptoms are also likely to develop over time.

E g. Parkinsondisease,multiplesclerosis,amyotrophiclateralsclerosis(ALS), Huntington chorea, and Alzheimer disease.

BILAYERTABLETS:

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. [10].

IDEALCHARACTERISTICSOFBILAYER TABLETS:

- Abilayertabletshouldhaveelegantproductidentitywhilefreeofdefectslike chips, cracks, discoloration and contamination.
- Itshouldhavesufficientstrengthtowithstandmechanicalshockduringin production, production, shipping, and dispensing.
- Itshouldhavethechemicalandphysicalstabilitytomaintainitsphysical attributes over time.
- Thebilayertabletmust beabletoreleasethemedicinalagentsinapredictableand reproducible manner.

Typesof BilayerTabletPress:[14]

- Singlesidedtabletpress.
- Doublesided tablet press.
- Bilayertabletpresswith displacementmonitoring.

Variousaspectsusedinthebi-layertablet:[10] Floating Drug Delivery Systems (FDDS):

Fromtheformulationand technologicalpointofview,thefloatingdrugdeliverysystemsaresignificantlyeasyand consistent approach in the development of Gastro retentive dosage forms (GRDFs).

Approachestodesignfloatingdrugdeliverysystem:

The following approaches have been used for the design of floating dosage forms of single- and multiple-unit systems.

- Intragastricbi-layeredfloatingtablets:
- Multipleunit typefloatingpill:
- PolymericBioadhesiveSystem
- Swelling System

METHODOLOGY

FORMULATIONOFBILAYERTABLETS:

Preparationofimmediatereleaselayerof methyl cobalamin:

Drug and excipients were accurately weighed and shifted through sieve #40 and mixed in a polybag. The sifted powders were thoroughly mixed for approximately 5 min and again passed through sieve #40 to get uniform particle size. Magnesium stearate was added into the powder mixture for lubrication after passing through sieve #40 and 0.125%w/w of iron oxide red previously sifted to sieve#100 was added to the above mixed mixture and blended thoroughly to ensure uniform colour

Ingredientsfortheformulationofmethyl cobalaminlayer

S.NO	Ingredients (mg)	Trial1	Trial2	Trail3	Trial4
1	Vitamin-B12	1	1	1	1
2	Lactose	28	22	26.5	31.25
3	MCC	32	33	30	31.25
4	Magnesiumstearate	1	1	1	1
5	Talc	3	3	3	3
6	SSG	10	15	13.5	7.5
	Totalweight(mg)	75	75	75	75

Preparationofsustainedreleaselayerof pregabalin:

TheSR granuleswereprepared bywet granulation technique.Required quantityofpregabalin and polymers(HPMC K100M) was weighed and passed through sieve#40 and were mixed homogenously in a polybag for about 5-10 min and was taken in a mortar.To the mortar 5% PVPK30 In isopropyl alcohol was added as granulating agent.The wet mass was passed through sieve#10 and dried in hot air oven at 50□c for 30 min;Dried granules were screened through sieve #14.Finally 10% fine was added to well form granules and was lubricated with magnesium stearate andtalcfor5min.The granuleswereprocessed forcompressionusing10 mm round flat faced punches of single punch tablet machine.

Ingredientsfortheformulationof pregabalinlayer

S.NO	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Pregabalin	75	75	75	75	75	75	75	75	75
2	$HPMCK_4M$	67.5	67.5	67.5	22.5	45	45	45	22.5	22.5
3	$HPMCK_{100}M$	90	45	135	45	45	90	135	135	90
4	PVPK-30	45	45	45	90	90	90	45	67.5	90
5	IPA	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.	Q. S.
6	Lactose	157.5	202.5	112.5	202.5	180	135	45	135	157.5
7	Colloidal silicon dioxide	7.425	7.425	7.425	7.425	7.425	7.425	7.425	7.425	7.425
8	Magnesium stearate	7.425	7.425	7.425	7.425	7.425	7.425	7.425	7.425	7.425
	Total weight(mg)	450	450	450	450	450	450	450	450	450

Compressionofbilayertablets:

Development of Bilayer tablets was carried in two different stages, blends of IR layer of methylcobalamin and SR layer of Pregabalin were prepared separately and after optimization

ofindividuallayerthebilayertabletswerepreparedusingselectedformulas.Optimizedbatch ofmethylcobalamin and Pregabalin was selected for formulation of bilayer tablet and was compressed using 12 mm round flat faced punch of the single punch CADMAC, Ahmedabad India; tablet compression machine. First, the granules of SR layer were poured in the die cavity and compressed with moderate force. Then, the upper punch was lifted and the IR granules were poured in the die cavity, containing initially compressed SR layer and compressed with full force to form bilayer tablet with hardness of 5-8 kg / cm^2. The hardness was kept constant for all tablets and was measured using Pfizer hardness tester

Ingredients forthe IRand SR layer:

MethylcobalaminIR layer			**PregabalinSRlayer**		
S.NO	**Ingredients**	**Trial2**	**S.NO**	**Ingredients**	**F4**
1.	Vitamin-B12	1	1.	Pregabalin	75
2.	Lactose	22	2.	$HPMCK_4M$	22.5
3.	MCC	33	3.	$HPMCK_{100}M$	45
4.	Magnesiumstearate	1	4.	PVPK-30	90
5.	Talc	3	5.	IPA	q.s.
6.	SSG	15	6.	Lactose	202.5
			7.	Colloidalsilicon dioxide	7.425
			8.	Magnesiumstearate	7.425
Totalweight(mg)		**75**	**Totalweight(mg)**		**450**

EVALUATION PARAMETER

Trialbatchesofdifferentformulationsofindividualtablets(sustainedandimmediate)and Bilayer tablets were prepared and evaluated for the following parameters.

Evaluationof granules

- Bulk Density
- TappedDensity
- AngleofRepose
- Carr'sIndex
- Hauser'sRatio

Physicalevaluationof tablet

- Weight variation
- Thickness
- Hardness
- Friability
- Swellingindex
- Drugcontent analysis
- In-Vitrodrugreleasestudy
- Tabletdissolution profile
- Stabilitystudies (As perICHguidelines)

RESULTS& DISCUSSION:

Rawmaterialanalysisofpregabalin:

Description:

AWhiteto off-white powder

Identificationtest:

Identification testfor pregabalin

Parameters	Inferences
Solubility	Complieswith IP
Meltingpoint	Complieswith IP
LOD	Complieswith IP
%purity	(99.15%)ComplieswithIP

Percentagepurity:

Assay:Thepercentagepurityofpregabalin was found to be99.15%.

Rawmaterialanalysisofmethylcobalamin: Description:

Adarkredcrystalline powder.

Identificationtest:

Identification testformethylcobalamin

Parameters	Inferences
Solubility	Complieswith IP
Meltingpoint	Complieswith IP
LOD	Complieswith IP
%purity	(98.54%)ComplieswithIP

Percentagepurity:

Assay:Thepercentagepurityof pregabalinwas found to be 98.54%.

Pre-formulation study:

FT-IRSpectrumof a puresampleofpregabalin

Materials	Testwavenumber(cm^{-1})	Functionalgroupassignment
Pregabalin	1651.12	N-H Stretching
	1558.54	N-O Bending
	1427.37	C-HBending
	1280.78	C-OStretching
	840.99	O-H Bending

FT-IRSpectrumof a puresampleof methylcobalamin

Materials	Testwavenumber(cm^{-1})	Functionalgroupassignment
Methylcobalamin	1580	C-Hstretching
	1390	CH_3C-Hbending
	1140	C-FStretching
	1020	C-FStretching

Precompressionstudiesof pregabalin

Formulation	Bulk density (gm/cm^3)	Tap density (gm/cm^3)	Carr's Index(%)	Hausner's Ratio	Angleof repose(θ)
F1	0.27±0.0021	0.33±0.0024	18.1±0.14	1.22±0.010	28.44±0.24
F2	0.29±0.0027	0.34±0.0017	14.7±0.0011	1.17±0.011	29.39±0.19
F3	0.30±0.0023	0.36±0.0015	16.6±0.004	1.20±0.004	27.71±0.24
F4	0.29±0.0028	0.35±0.0090	13.5±0.010	1.15±0.010	30.61±0.27
F5	0.30±0.0023	0.36±0.0012	13.8±0.011	1.16±0.011	28.59±0.18
F6	0.31±0.0011	0.36±0.0012	15.7±0.009	1.18±0.009	31.58±0.15
F7	0.32±0.0012	0.38±0.0027	17.1±0.005	1.20±0.005	33.14±0.26
F8	0.29±0.016	0.34±0.0070	11.7±0.010	1.13±0.010	30.55±0.21
F9	0.31±0.0013	0.36±0.0080	13.8±0.007	1.16±0.007	32.56±0.31

Post compressionparameters

Formulation	Hardness(kg/cm^2)	Weight variation (mg)	%Friability	Drugcontent (%)
F1	5.7±0.015	399.82±2.2	0.28	98.46±0.29
F2	6.5±0.053	400.27±1.3	0.47	99.11±0.54
F3	6.0±0.018	397.79±2.0	0.24	98.85±0.64
F4	5.6±0.011	396.85±1.1	0.41	99.33±0.47
F5	5.6±0.042	397.98±3.1	0.50	97.43±0.58
F6	6.3±0.034	398.64±2.4	0.43	97.51±0.54
F7	5.9±0.025	402.18±2.6	0.49	100.86±0.44
F8	5.8±0.024	401.22±1.4	0.37	97.47±0.47
F9	6.1±0.008	401.36±1.7	0.48	97.47±0.50

Precompressionstudiesofmethylcobalamin

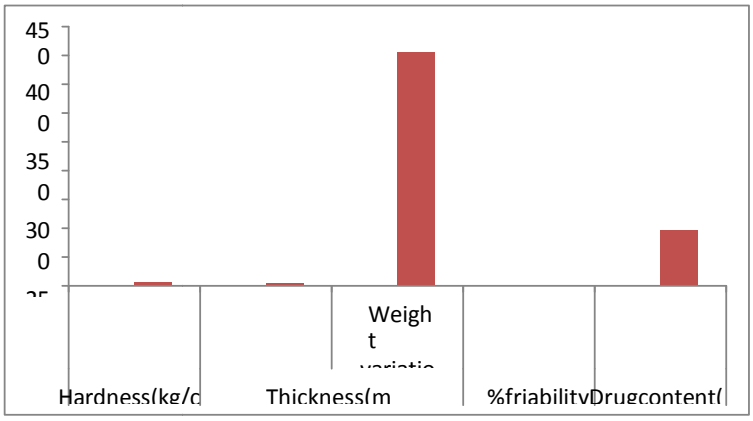
Formulation	Bulkdensity (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index(%)	Hausner's Ratio	Angle of repose(θ)
F1	0.251	0.370	18.1±0.14	1.22±0.010	28.44±0.24
F2	0.278	0.351	14.7±0.0011	1.17±0.011	29.39±0.19
F3	0.263	0.275	16.6±0.004	1.20±0.004	27.71±0.24
F4	0.294	0.364	13.5±0.010	1.15±0.010	30.61±0.27
F5	0.314	0.380	13.8±0.011	1.16±0.011	28.59±0.18
F6	0.267	0.354	15.7±0.009	1.18±0.009	31.58±0.15
F7	0.343	0.381	17.1±0.005	1.20±0.005	33.14±0.26
F8	0.314	0.390	11.7±0.010	1.13±0.010	30.55±0.21
F9	0.325	0.371	13.8±0.007	1.16±0.007	32.56±0.31

Postcompressionparameters

Formulation	Hardness(kg/cm^2)	Weight variation (mg)	%Friability	Drug content(%)
F1	5.7±0.015	399.82±2.2	0.28	98.46±0.29
F2	6.5±0.053	400.27±1.3	0.47	99.11±0.54
F3	6.0±0.018	397.79±2.0	0.24	98.85±0.64
F4	5.6±0.011	396.85±1.1	0.41	99.33±0.47
F5	5.6±0.042	397.98±3.1	0.50	97.43±0.58
F6	6.3±0.034	398.64±2.4	0.43	97.51±0.54
F7	5.9±0.025	402.18±2.6	0.49	100.86±0.44
F8	5.8±0.024	401.22±1.4	0.37	97.47±0.47
F9	6.1±0.008	401.36±1.7	0.48	97.47±0.50

POSTCOMPRESSIONPARAMETERSOFOPTIMIZED FORMULATION:

Formulation	Hardness(kg/cm^2)	Thickness (mm)	Weight variation (mg)	%Friability	Drug content(%)
F1	6.23	5.14	405.3	0.815	97.52



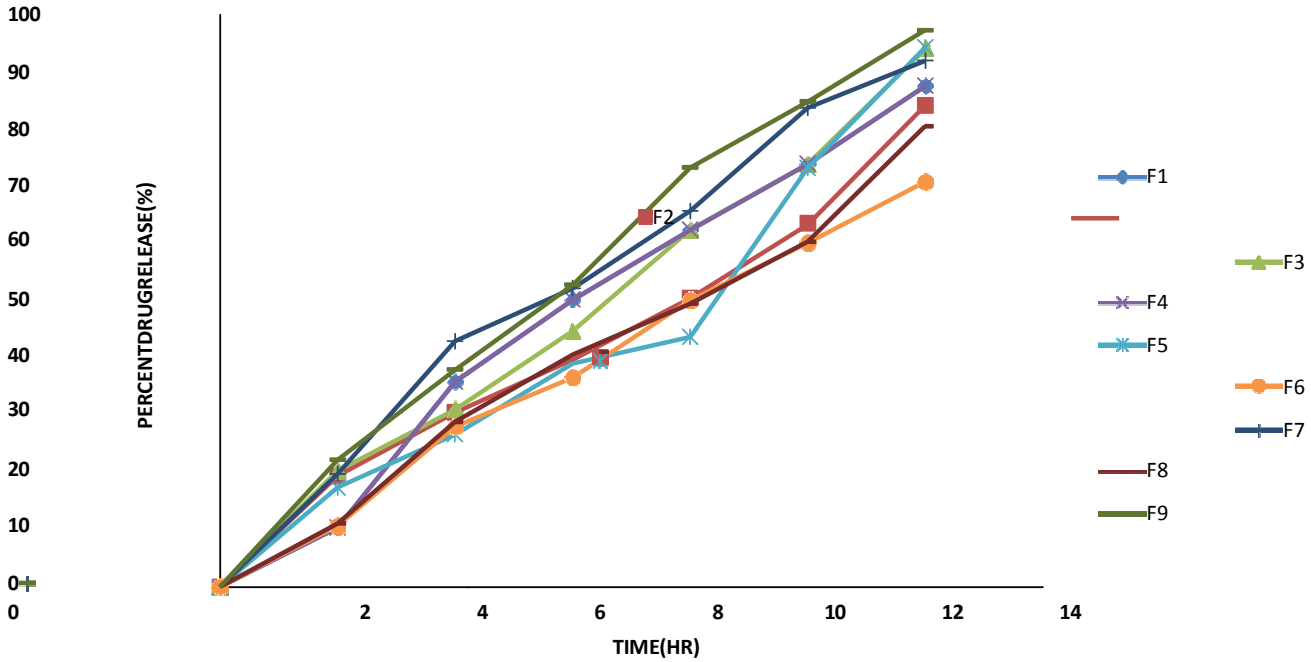
Post-compressionparametersofoptimized formulation

INVITROSTUDIES

In-vitrodissolutionofPregabalin& methylcobalamin:

In-vitrodissolutionofPregabalin& methylcobalaminF1-F9:

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	10.38	19.38	20.30	10.38	17.4	10.69	19.76	11.12	22.23
4	35.87	30.50	31.02	35.87	26.67	28.02	42.93	28.84	37.97
6	50.21	39.74	44.72	50.21	39.04	36.59	52.18	40.62	52.8
8	62.41	50.44	62.41	62.41	43.69	50.14	65.70	49.53	73.27
10	73.91	63.33	73.91	73.91	73.24	60.12	83.70	60.33	84.79
12	87.57	84.10	94.04	87.57	94.31	70.82	91.93	80.50	97.27



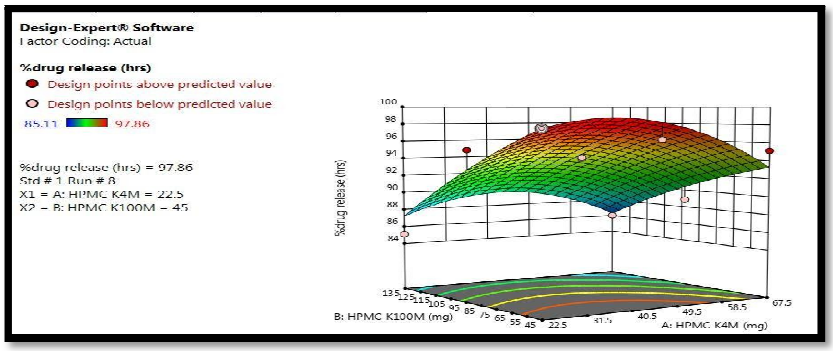
In-vitrodissolutionofpregabalinF1-F9

Optimization by 3^2Factorial Design:

Based on defined constraints for each independent variable, the Design Expert® Softwareversion11automaticallygeneratedtheoptimizedformulation.Theexperiments were performed and the responses were obtained.

Resultofindependentvariableanddependentvariableaccordingto 3^2Factorial Design

	Std	Run	Factor 1 A:HPMC K4M mg	Factor 2 B:HPMC K100M mg	Response 1 swelling index wt	Response 2 %drug release hrs
	9	1	67.5	135	40	86.03
	2	2	45	45	13.77	96.56
	12	3	45	90	14.44	94.12
	5	4	45	90	15	94.19
	10	5	45	90	14.5	95
	6	6	67.5	90	33.5	88.91
	4	7	22.5	90	17.77	95.34
	1	8	22.5	45	12.25	97.86
	13	9	45	90	15	94.24
	7	10	22.5	135	32.22	85.11
	11	11	45	90	14.44	95.02
	3	12	67.5	45	15.55	95.12
	8	13	45	135	38.88	92



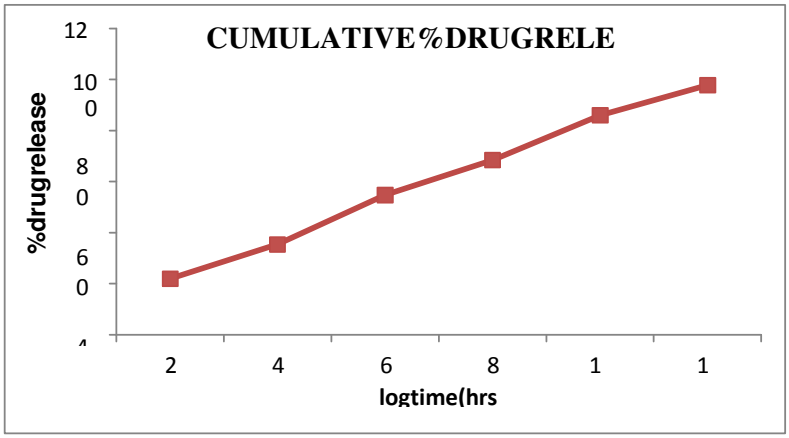
ResponsesurfacevalueofSwelling index

***IN-VITRO*KINETICSSTUDY:**

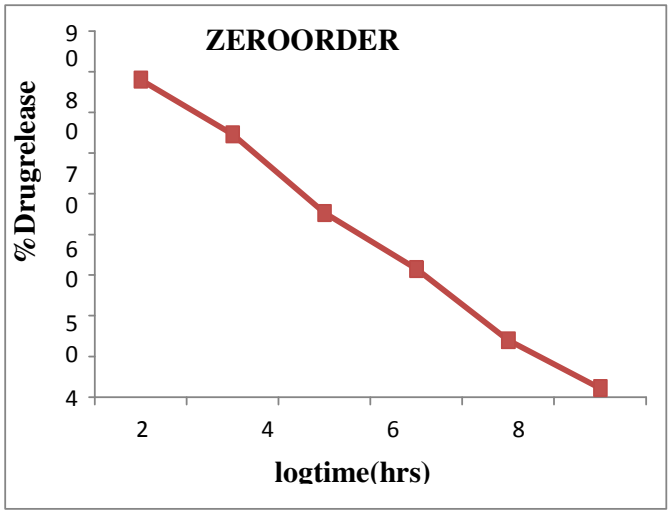
Thevaluesobtainedfrom*invitro*dissolutionofpregabalinfrombilayertabletswerefittedin various kinetics models. The results are given in the Table

***Invitro* releasekineticsof bilayertablets**

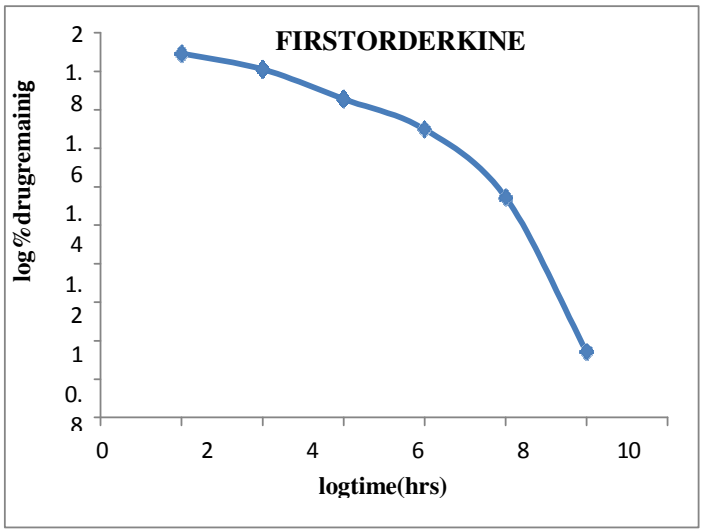
s.no	Time (hrs.)	%Drug release	Zero-order kinetics	First order Log% drug remaining	Higuchi Square root of time	Peppas Log%of time
1	2	21.95	78.05	1.414	8.8345	1.892
2	4	35.38	64.62	2	8.0386	1.810
3	6	54.72	45.28	2.449	6.729	1.655
4	8	68.48	31.52	2.828	5.614	1.498
5	10	86.01	13.99	3.162	3.740	1.415
6	12	97.8	2.2	3.464	1.483	0.342



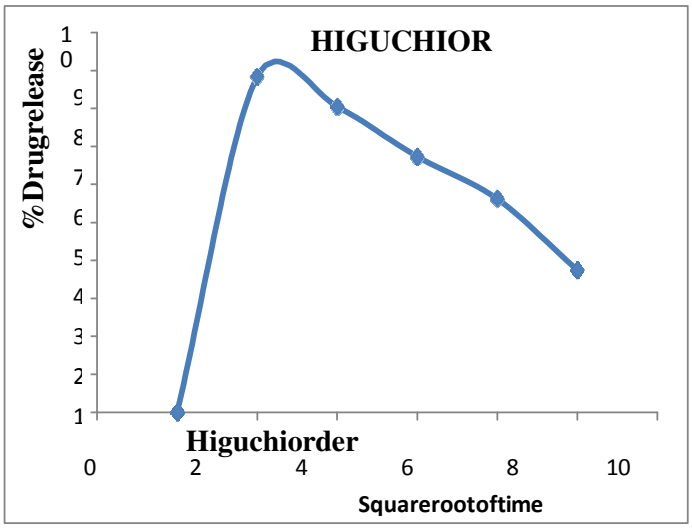
cumulative%drugrelease

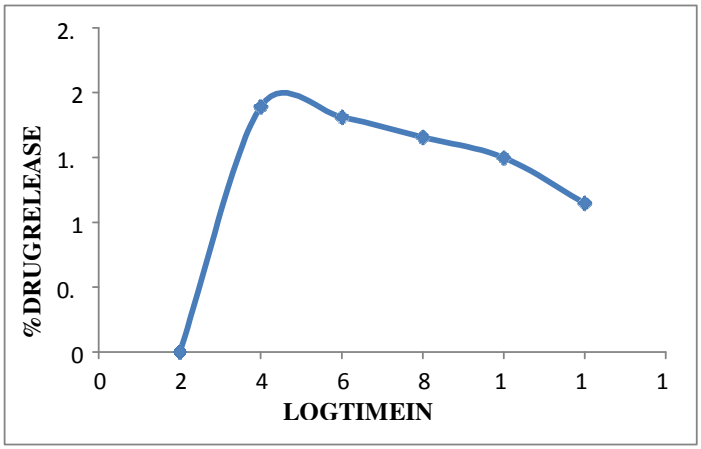


Zeroorder kinetics



Firstorder kinetics





peppasplot

AcceleratedStability Study

Stabilitytestingparametersforoptimizedsustainedreleasepregabalinlayer

Parameter	StorageCondition40□C±20□C&75%±5%RH		
	Initial	1ST month	2nd month
Appearance	white	white	White
AverageWeight(mg)	450 mg	450 mg	450 mg
Drugcontent(%)	98.4	98.4	98

In-vitrodissolution study

Dissolutiontime (hr)	StorageCondition40□C±20□C&75%±5% RH		
	Initial	1ST month	2nd month
	white	white	White
AverageWeight(mg)	450 mg	450 mg	450 mg
Drugcontent(%)	98.4	98.4	98

SUMMARYANDCONCLUSION

- The current study focuses on bi-layer tablets that contain SSG as a super disintegrant polymer for quick release of methylcobalamin and HPMC K4 M and HPMC K100M as retardant polymers for prolonged release of pregabalin. Studies on drug-excipient compatibility have verified that both medications work with certain polymers, including HPMC K4M, HPMCK100M, and SSG. Neuropathic pain can be

effectively and long-term managed with the use of the designed bilayer tablet. Physical properties, drug content, solubility, release kinetics, and stability tests were assessed for each formulation.

- Precompression experiments were conducted on the formed granules, indicating that they had satisfactory flow properties.
- It was discovered that the formed tablets' hardness, thickness, weight fluctuation, and friability were all within permissible bounds.
- Nine batches of pregabalin formulations with different amounts of HPMC K4 M and HPMC K100 M were tested in vitro for the SR tablet's dissolution. The best formulations were chosen for bilayer tablets utilizing DOE software.
- SSG 15% was selected as the best option for creating the methylcobalamin IR layer to construct the bilayer tablet.
- The optimized formulation of both pregabalin and methylcobalamin was compressed into bilayer tablets. The drug content of the bilayer tablets was estimated by simultaneous estimation method and it was found to be within the Pharmacopeial limits.
- The release kinetics of the optimized tablets showed that it follows zero order release kinetics.

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