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Formulation Evaluation of Bi-Layered Tablet Of Divalproex Sodium

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ABSTRACT
Divalproex sodium is considered as the most important antiepileptic drug and widely used fortreatment of epilepsy and bi-polar disorders and prophylaxis of migraine. The present work hasbeen done to formulate bi-layered tablet of Divalproexsodium containing immediate releaselayer and sustainedrelease layer.. HPMC K4M and HPMC K100M polymer used to retard the drugrelease from sustained release layer in different proportion and combination and evaluated forphysicalparameteralong withinvitro drug release studies.The optimizedsustainedreleaselayer (SF8) which extends the Divalproex sodium release more than 18 hrs was selected. In vitrodrug release studies were performed using USP type II apparatus (paddle method) in 900 ml of phosphate buffer pH6.8at100rpm.

I. INTRODUCTION

Bi-layer tablets are prepared with one layer of drug for immediate release while secondlayer designed to release drug later, either as second dose or in an extended release manner.Thebasicgoaloftherapyistoachieve asteadystatedrugin blood level for an extentperiod oftime[20].

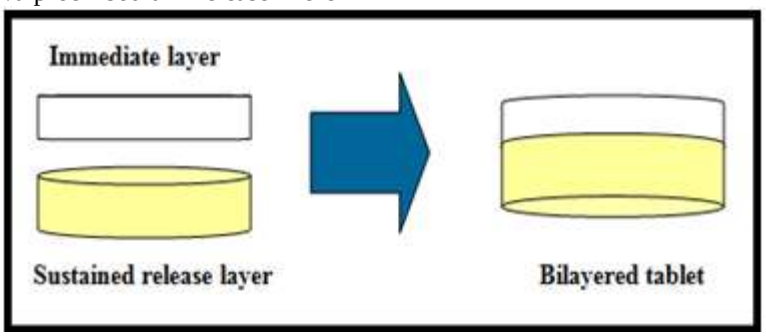


Figure3:Bi-layeredtablet

Advantageof Bi-layeredtablets[21]:

1. Bi-layeredexecutionwithoptionalsingle-layerconversionkit.
2. Costis lowercompared toall otheroral dosageform.
3. Greatest chemicalandmicrobialstabilityoveralloraldosageform.
4. Objectionableodor and bittertastecan bemaskedbycoatingtechnique

DisadvantageofBi-layeredtablets:

1. Somedrugsresistcompressionintodensecompacts, owingtoamorphousnature,lowdensitycharacter,
2. Bitter tasting drugs,drugswithanobjectionable odor or drugsthatare sensitive tooxygenmayrequireencapsulation orcoating.

3.Difficulttoswallowincaseofchildrenandunconscious patients.

Typesof Bi-layeredtabletpress[22]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

1. Singlesidedtabletpress.
2. Doublesided tabletpress.
3. Bi-layeredtabletpresswithdisplacementmonitoring

Singlesidedtabletpress:

The single design is a single sided press with both chambers of the doublet feeder separated fromeach other. Each chamber is gravity or forced fed with different power, producing the twoindividual layers of tablets. When die passes under the feeder, it is first loaded with the first layerpowder followed by the second layer powder. Then the entire tablet is compressed in one or twosteps

Doublesidedtabletpress:

In most double sided tablet presses with automated production control use compression force tomonitorandcontroltabletweight.Theeffectivepeakcompressionforceexertedoneachindividual tablet of layer is measured by the control system at main compression of the layer.This measured peak compression force is the signal used by the control system to reject out oftolerance and correct thedie fill depthwhen required.

Bi-layeredtabletpress withdisplacementmonitoring:

The displacement tablet weight control principle is fundamentally different from the principlebased uponcompressionforce. When measuring displacement, the control system sensitivitydoesnot dependon thetablet weight butdependsonthe appliedpre-compression forc.

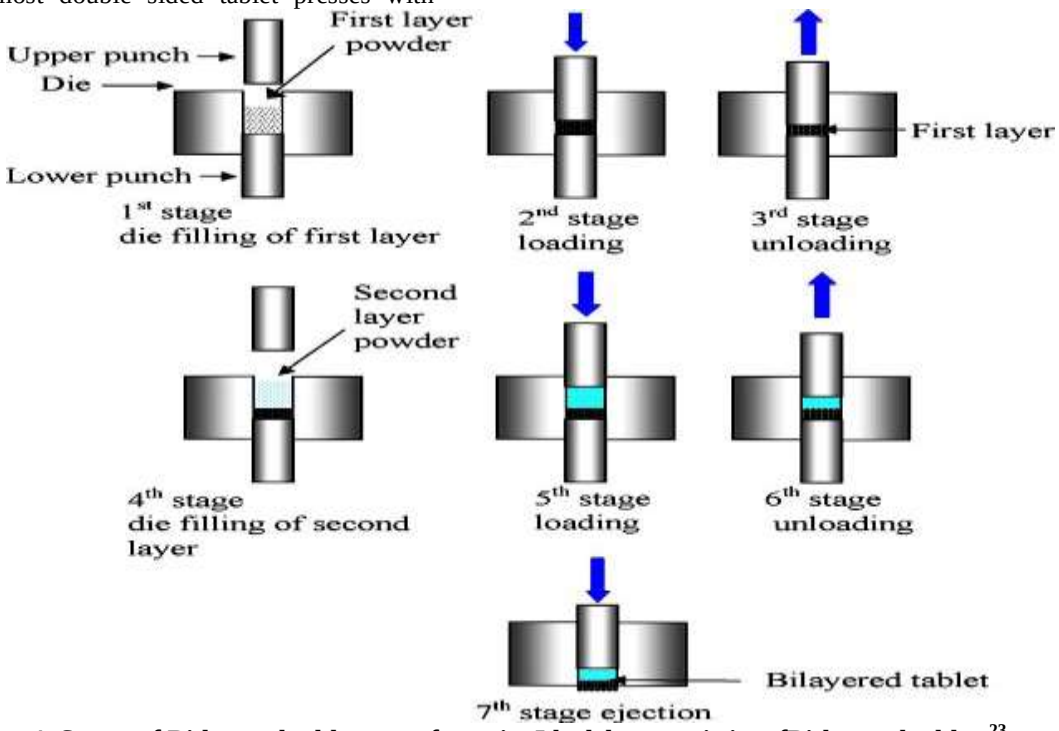


Figure 4: Stages of Bi-layered tablet manufacturingIdealcharacteristics ofBi-layered tablets[23]:

1. A Bi-layered tablet should have elegant product identity while free of defects like chips,cracks,discoloration andcontamination.
2. It should have sufficient strength to with stand mechanical stock during its productionpackaging,shipping anddispensing.
3. Itshould havethechemicalandphysicallystabilitytomaintain itsphysicalattributesover time.TheBi-layeredtabletmustbeabletoreleasethemedicinalagentinapredictable and reproducible manner.

Introduction to epilepsyand bipolardisorders[26,27]

Epilepsy is abnormal, high frequency electrical

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

discharge in brain characterized by transientepisode(seizure)withorwithoutlossofconscio usnessandcharacteristicbodymovement(convulsion)
Bipolar disorder also known as manic-depressive illness, is a brain disorder that causes unusualshifts in mood, energy, activity levels and the ability to carry out day to day tasks

Anticonvulsants:[28]
Anticonvulsants (also known as antiepileptic drugs or antiseizure drugs) are a diverse group of pharmacological agents used in the treatment of epileptic seizures
It also prevents the spread of the seizurewithinthebrain.Italsousedin thetreatmentof bipolardisorder.Theyare classifiedasfollowing

1. Barbiturate: Phenobarbitone
2. Deoxybarbiturate:Primidone
3. Hydantoin:Phenytoin
4. Iminostilben:Carbamazepine
5. Succinamide:Ethisuximide
6. Aliphaticcarboxylic acid:Valproicacid,
7. Sodiumvalproate,Divalproexsodium

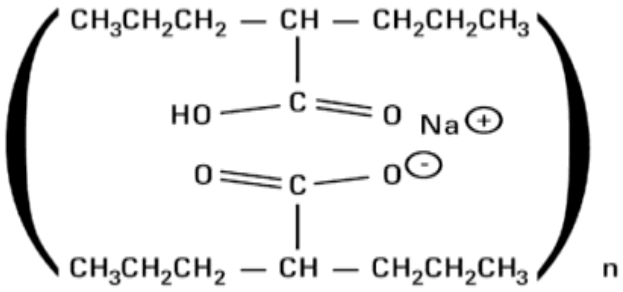
8.Benzodiazepine:Clonazepam,Diazepam,Clobazam
9.Phenyltriazine:Lamotriazene
10.CyclicGABAanalogue: Gabapentin
11.Newerdrugs:Vigabatrin,Topiramate,Tiagabine,Le vetiracetam

Mechanismof actionof antiepilepticdrugs[29]
Drugsthatareeffectiveinseizurereductionacco mplishthisbyavarietyofmechanisms,includingblockad eofvoltage-gatedchannels(Na^+orCa^{2+}),enhancementofinhibitoryG ABAergic impulses, or interference with excitatory glutamate transmission. Some antiepilepticdrugs appear to have multiple targets within the CNS, whereas the mechanism of action for someagents ispoorlydefined.

II. DRUG PROFILE:

DIVALPROEXSODIUM[54,55,56,57]
Chemicalstructure:

Structureof Divalproexsodium



oDivalproexsodiumcontainsnot lessthan 98%andnot morethan102%ofavailablevalproicacid, $C_8H_{16}O_2$.
Chemical Name: 2-propyl-pentanoic acid sodium salt (2:1)
CASNumber:76584-70-8

Brandname: Depakote, DepakoteCP,Depakote ER,Epival,Stavzor

Category:Anticonvulsant

MolecularFormula:$C_8H_{16}O_2C_8H_{15}O_2Na$

Molecularweight:310.41

Description: Odorless,whiteoroff-white crystalline powder.Sodium hydrogen bis (2-propylvalerate)c

MeltingPoint:222°C

Solubility:solubleinethanol(95%),methanol,Isopropy lalcohol,partiallysolubleinwater,ether.
Storage: Storeprotected frommoistureata temperature not exceeding30°C.

MECHANISMOF ACTION:
Divalproex sodium is broad-spectrum anticonvulsant.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

It increases the availability of gamma-amino butyric acid (GABA), an inhibitory neurotransmitter.It has inhibitory action againstGABA transaminase which breakdown GABA, it leads to increased concentration of GABA inthesynapses.Otherproposemechanismsofactionthataccountfortheiranticonvulsantpropertiesisiteitherenhancetheactionof GABAormimicitsactionatpostsynapticreceptorsites.Itals blockvoltage gated sodium channels and T-type calcium channels,andcauseinhibitoryactivityin thebrain.

Pharmacokinetics

Absorption: Rapidabsorptionfromgastrointestinaltract.

Distribution: Proteinbinding80-90%

Metabolism: Metabolized almostentirelybythe liver.

Excretion: Both bile and urine**Half Life:** 9-16 hours**Bioavailability (oral):** 84%**Pharmacology**

Divalproexsodium is a stable co-ordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. It is an anticonvulsant and mood-stabilizing drug used primarily in the treatment of epilepsy and bipolar disorder

It is believed to affect the function of the neurotransmitter rGABA(asGABA transaminase inhibitor)in the human brain.It dissociate to the valproate ion in the gastrointestinal tract.

Contraindicationsof Divalproexsodium

a) Hepaticdiseaseor significanthepaticdysfunction
b) Ureacycledisorders
c) Hypersensitivityto thedrug

WarningsandPrecautions

a) Hepatotoxicity
b) Teratogenic
c) Pancreatitis
d) **Thrombocytopenia**

Hyperammonemia and hyperammonemic

e) **encephalopathyAdverseEffects of Divalproex sodium**

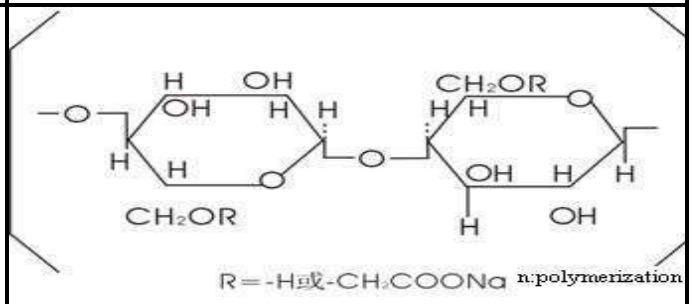
a) Nausea,Headache
b) Somnolence
c) Dizziness
d) Vomiting
e) Asthenia
f) Abdominalpain
g) Anorexia
h) Weightgain
i) Alopecia

DrugInteractions

a) Hepaticenzyme-inducingdrugs:phenytoin,carbamazepine,primidone,phemobarbital,rifampincan decreasevalproate clearance.
b) Aspirin,carbapenemantibiotics
c) Topiramate
d) Amitriptyline,warfarinandzidovudine
e) **SODIUMSTARCH GLYCOLATE**[58]

Non-proprietary names	BP: Sodium starch glycollateUSP/NF:Sodiumstarchglycolate PhEur:Carboxymethylamylumnatricum
Synonyms	Carboxymethylstarch,sodiumsalt,Explosol,Explotab,Tablo.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

Description	Whitetooff-white,odorless,tasteless,free-flowingpowder.ThePhEur2005 states that it consists of oval or spherical granules, 30-100 µm indiameter,withsomeless-sphericalgranulesrangingfrom10-35 µmin diameter.
StructuralFormula	
ChemicalnamesCASNumber	Sodiumcarboxymethylstarch 9063-38-1
Empiricalformula Molecularweight	$5x10^5$–$1x10^6$
Meltingpoint	Approximately200^0C
Solubility	Practicallyinsolubleinwater,sparinglysolubleinethanol(95%).In waterit swellsup to300 timesits volume.
FunctionalCategory	Tabletandcapsuledisintegrant
Stabilityandstorage conditions	Itisstableand shouldbe stored inawell-closedcontainer inorderto protectitfromhumidityandtemperature,whichmaycausecracking.
Incompatibilities	Ascorbicacid
Safety	Itis widelyusedin oral pharmaceutical formulationsand is generally regardedasanontoxicandnonirritantmaterial.
Application	Itiswidelyusedinoralpharmaceuticalsasadisintegrantincapsulea nd tablet prepared by both direct- compression and wet-granulationprocess.Usual concentrationemployedinaformulationisbetween2% and8%.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

Table3:CROSCARMELLOSESODIUM[59]

Non-proprietarynames	BP: Croscarmellose sodiumUSPNF:Croscarmellosesodium PhEur:Carmellosumnatricumconexum
Synonyms	Ac-Di-Sol,crosslinkedcarboxymathylcellulosesodium,Explocel, modifiedcellulosegum,primellose,Solutab
Description	Odorless,whiteorgrayish-whitefreeflowingpowder.
Chemicalnames CASNumber	Cellulose,carboxymethylether,sodiumsalt,crosslinked 74811-65-7
Empiricalformula Molecularweight	$C_{12}H_{10}Ca_3O_{14}.4H_2O$ 570.49
Solubility	Insoluble in water, although croscarmellose sodium rapidly swells to 4-8timesits originalvolumeoncontact withwater. Practicallyinsoluble inacetone, ethanolandtoluene,
FunctionalCategory	Tabletandcapsuledisintegrant.
Stabilityandstorage conditions	Itisa stablethoughhygroscopic materialand shouldbestored ina well-closedcontainerinacool, dryplace.
Incompatibilities	The efficacy of croscarmellose sodium may be slightly reduced intabletformulation preparedbyeither thewet-granulation or direct-compressionprocessthatcontainhygroscopicexcipients.
Safety	Itiamainlyusedasadisintegrantin oralpharmaceuticalformulations andisgenerallyregardedasnontoxicandnonirritantmaterial.
Application	It is used as a disintegrant for capsules, tablets, and granules. Whenusedinwetgranulations,thecroscarmellosesodiumsho uldbeaddedinboth the wet and dry stages of the process. Croscarmellose sodium atconcentrations up to 5 % w/w may be used as a disintegrant in tabletsprepared bydirect compression and 3 %w/w in tablets prepared bya wet-granulationprocess.

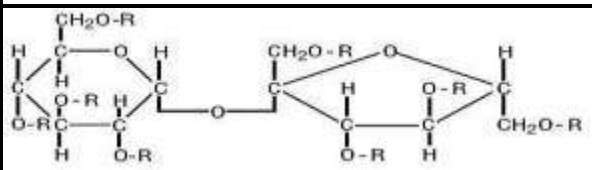
International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

:LACTOSE[60]

Non-proprietarynames	BP:LactosemonohydrateUSP/NF: Lactose monohydratePhEur:Lactosummonohydricum JP:Lactose
Synonyms	LactochemCoarseCrystals,LactochemCrystals,LactochemPowder, Pharmatose50M,NFLactose310.
Description	Whitetooff-whitecrystallineparticlesorpowder.Lactoseisodorless andslightlysweet-tasting.
Chemicalnames CASNumber	O-□-D-Galactopyranosyl-(1□ 4)-□-D-glucopyranose 64044-51-5
Empiricalformula Molecularweight	$C_{12}H_{22}O_{11}.H_2O$ 360.31
Meltingpoint	201-202^{0}C
Solubility	Practicallyinsolubleinchloroform,ethanolandether,solubleinwater.
FunctionalCategory	Bindingagent,diluentfordry-powderinhalers,tabletbinder,tabletand capsulediluent.
Stabilityandstorageconditions	Mold growth may occur under humid conditions(80% relative humidityand above). Lactose may develop a brown coloration on storage, thereactionbeingacceleratedbywarm,dampconditions.Itshouldbe stored in a well-closed container in acool, dryplace.
Incompatibilities	Primaryaminegroup,aminoacids,aminophylline,amphetaminesand lisinopril.
Safety	Itiswidelyusedinpharmaceuticalformulationsasafillerandfiller-binderinoral capsuleand tabletformulation.
Application	It is widely used as a filler or diluent in tablets and capsules, and to amorelimitedextentinlyophilizedproductsandinfantformulas.Usually, fine grades of lactose are used in the preparation of tablets bythewet-granulationmethod.Itisalsousedincombinationwithsucrose (approximately1:3) to preparesugar-coatingsolutions.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

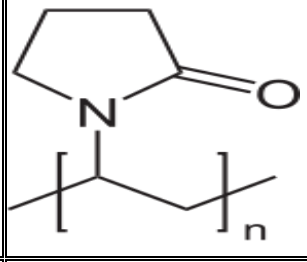
Table 5:MICROCRYSTALLINECELLULOSE[61,62]

Non-proprietarynames	BP: Microcrystalline celluloseUSP/NF:Microcrystallinecellolose PhEur:Cellulosummicrocristallinum
Synonyms	AvicelPH,Celex,cellulosegel,celphere,crystallinecellulose,E460, Emcocel,Vivapur
Description	White,odorless,tasteless,crystallinepowder
StructuralFormula	
Chemicalnames **CASNumber**	Cellulose 9004-34-6

Empiricalformula **Molecularweight**	$(C_6H_{10}O_5)_n$ wheren≈220 ≈36000
Meltingpoint	260-270
Solubility	Slightlysoluble in5% w/vsodium hydroxide solution, practically insolubleinwater,diluteacids,andmostoforganicsolvents
FunctionalCategory	Absorbent,suspendingagent, tabletandcapsulediluent,tablet disintegrant.
Stabilityandstorage Conditions	Itisstablethough hygroscopicmaterialand shouldbestored inawell-closedcontainer in acool, dryplace.
Incompatibilities	Strongoxidizingagents
Safety	Itis widelyusedin oral pharmaceutical formulationsand is generally regardedasarelativelynontoxicandnon irritantmaterial.
Application	Itisusedintabletor capsule formulationasabinder/diluentin both wet-granulationanddirect-compressionprocesses.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

Table 6:POLYVINYLPYRROLIDONE[63,64]

Non-proprietarynames	BP: PovidoneUSP:Povidone PhEur:Povidonum
Synonyms	Plasdonek-30,luviskol k-30,plasdone, povidone, pvp k-30, poly(1-vinyl-2-pyrrolidinone
Description	Fine,whitetocreamy-whitecolored,odorless,hygroscopic,amorphous powder.
StructuralFormula	
Chemicalnames **CASnumber**	1-Ethenyl-2-pyrrolidinonehomopolymer 9003-39-8
Chemicalformula	$(C_6H_9NO)_n$
Meltingpoint	150-180^{0}C
Solubility	Solubleincoldwater,chloroform,alcohol,chlorinatedhydrocarbons, aminesandlower weightfattyacids.
FunctionalCategory	Suspendingagent,tablet binder
Stabilityandstorageconditions	Itdarkensto someextenton heatingat 150^{0}C,withareductionin aqueoussolubilityandshouldbestoredinanairtightcontainerinacool,drypl ace.
Incompatibilities	Oxidizingagents.
Safety	Itmayberegardedas essentiallynontoxic and nonirritant.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

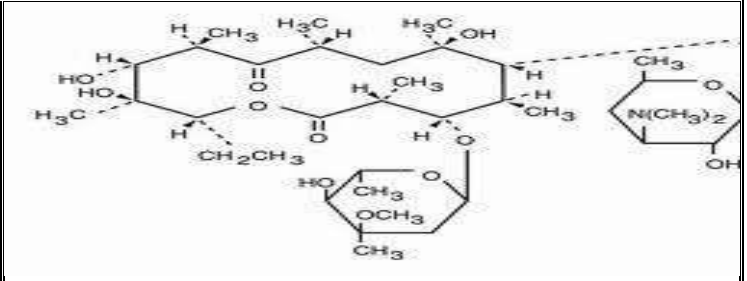
Application	PVPkseries canbeusedasfilm formingagent, viscosityenhancementagent and adhesive. In tableting, PVP solutions are used as binders inwet granulation process. PVP solutions may also be used as coating. Itisalsousedassuspending,stabilizing-increasingagentsintopicaland oralsuspensionsandsolutions.

MAGNESIUM STEARATE[65,66]

Non-proprietarynames	BP: Magnesium stearateUSP/NF:Magnesiumstearate PhEur:Magnesiistearas
Synonyms	Magnesiumoctadecanoate,octadecanoicacid,magnesiumsalt
Description	Veryfine, lightwhite, precipitatedor milled,impalpable powderoflow bulkdensity,havinga faintodor ofstearicacid andacharacteristictaste. Thepowder is greasyto touch andreadilyadhereto skin.
Chemicalnames CASNumber	Octadecanoicacidmagnesiumsalt 557-04-0
Empiricalformula Molecularweight	$C_{36}H_{70}MgO_4$ 591.34
Meltingpoint	117-150^{0}C(commercial samples) 126-130^{0}C (high puritymagnesium stearate)
Solubility	Practicallyinsolublein ethanol,ethanol (95%),etherand water,slightly solubleinwarmbenzene andwarmethanol(95%).
FunctionalCategory	Tabletandcapsulelubricant
Stabilityandstorage conditions	Itis stable andshould bestored ina well-closed container inacool, dry place.
Incompatibilities	Strongacids,alkalisandironsalts.
Safety	Itiswidelyused aspharmaceutical excipientand is generallyregarded as beingnontoxic.
Application	It is widely used in cosmetic, foods, and pharmaceutical formulations.Itisprimarilyusedasalubricantincapsuleandtabletmanufacture at concentrationsbetween0.25%and5.0%w/w.itis alsousedinbarriercreams.

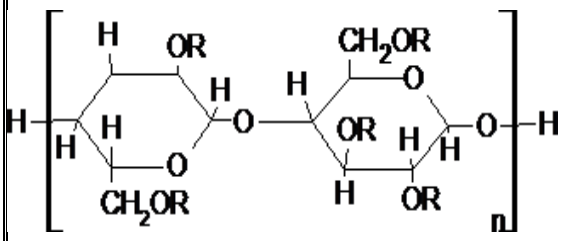
International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

TALC[67,68]

Non-proprietarynames	BP: Purified talcUSP: Talc PhEur:Talcum
Synonyms	Altalc,E553b,hydrousmagnesiumcalciumsilicate,LuzenacPharma, Purtalc,steatite,purifiedFrenchchalk.
Description	Veryfine, whiteto grayish-white,odorless,impalpable,unctuous, crystallinepowder.
StructuralFormula	
Chemicalnames **CASNumber**	Talc 14807-96-6
Empiricalformula	$Mg_6(Si_2O_5)_4(OH)_4$
FunctionalCategory	Anticakingagent,glidant,tabletandcapsulediluent,tabletandcapsule lubricant.
Stabilityandstorageconditions	It is stable material and may be sterilized by heating at 160^0C for notlessthan1hour. Itshouldbestoredinawell-closedcontainerin acool, dryplace.
Incompatibilities	Quaternaryammonium compounds.
Safety	
Application	It is widely used oral solid dosage formulations as a lubricant anddiluent. Itisalsousedas lubricantintabletformulation,inanovel powdercoatingforextended-releasepelletsandas anadsorbant.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

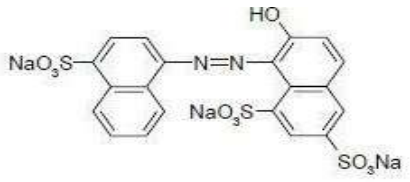
: HYDROXYPROPYLMETHYL CELLULOSE[69,70,71]

Non-proprietarynames	BP: HypromelloseUSP:Hypromellose JP:Hydroxypropylmethylcellulose
Synonyms	BenecelMHPC,E464,hydroxypropylmethylcellulose,Methocel, HPMC,Metolose
Description	Odorlessandtasteless,whiteorcreamy-whitefibrousorgranular Powder
StructuralFormula	
Chemicalnames **CASNumber**	Cellulosehydroxypropylmethylether 9004-65-3
Molecularweight	10000-1500000
Meltingpoint	Brownat190-200^{0}Cand charsat225-230^{0}C
Solubility	Soluble in cold water, forming a viscous colloidal solution. Practicallyin soluble in chloroform, ethanol(95%) and ether, but soluble inmixturesofethanol anddichloromethane,mixtures ofmethanoland dichloromethaneandmixturesofwaterandalcohol.
FunctionalCategory	Coatingagent,film-former,rate-controllingpolymerforsustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasingagent.
Stabilityandstorageconditions	Itisastablematerial,althoughitishygroscopicafterdaying.Solutionsarestable at pH3-11 andshould bestored ina well-closedcontainer in acool, dryplace.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

Incompatibilities	Oxidizingagents
Safety	It is widely used as an excipient in oral and topical pharmaceuticalformulations.Itisalsousedextensivelyincosmetics andfoodproducts andisgenerallyregardedasanontoxicandnonirritantmaterial.
Application	It is widely used in oral,ophthalmic and topical pharmaceuticalformulations.Inoralproducts,itis primarilyused asatablet binder; concentrationbetween2%and5%w/wandas a matrix forusein

Table 10:PONCEAU4R[72,73]

Synonyms	C.I.16255,CochinealRedA,C.I.AcidRed18,BrilliantScarlet3R, BrilliantScarlet4R
Description	Reddishpowderorgranules
StructuralFormula	
Chemicalnames **CASNumber**	1-(4-sulpho-1-napthylazo)-2-napthol-6,8-disulphonic acid tisodiumsalt. 2611-82-7
Molecularformula **Molarmass**	$C_{20}H_{11}N_2Na_3O_{10}S_3$ 604.47gmol^{-1}
Solubility	Solublein water, sparinglysoluble in ethanol
FunctionalCategory	Foodadditives,pigment

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

Stabilityandstorage conditions	Itisstabletolight,heat,andacidbutfadesinthe presenceofascorbic acid.It should bestored in well-closedcontainerin acool, dryplace
Application	Coloringagentsinpharmaceuticaldosageform.

III. MATERILS ANDMETHODS

3.1 MATERIALS

List of materials

SlNo.	**Ingredients**	**CompanyName**
1.	Divalproex sodium	GiftsamplefromROAQ Chemicals Pvt. Ltd.Vadodara
2.	SodiumStarchGlycolate	S.D.FineChem. Ltd,Mumbai
3.	Croscarmellose	S.D.FineChem. Ltd,Mumbai
4.	HPMCK4M	YarrowChemProducts,Mumbai
5.	HPMCK100M	YarrowChemProducts,Mumbai
6.	Lactose	S.D.FineChem. Ltd,Mumbai
7.	MicroCrystalline Cellulose	S.D.FineChem. Ltd,Mumbai
8.	PVPK 30	S.D.FineChem. Ltd,Mumbai
9.	Ponceau4R	Indian finechemicals,Mumbai-20
10.	MagnesiumStearate	S.D.FineChem. Ltd,Mumbai
11.	Talc	S.D.FineChem. Ltd,Mumbai

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

LIST OF INSTRUMENTS

Listof Equipments

SlNo.	Equipment	Model/company
2.	UV-Visiblespectrophotometer	UV-1800,Shimadzu
3.	Electronicbalance	Essae-Teraoke
4.	Hotairoven	Kemi
5.	MultitabletPunchingmachine	LABPRESS,CipMachinariesLtd.
6.	RocheFriabilator	PSMIndustries,Bangalore
7.	Hardnesstester	Monsantohardness tester
8.	Disintegrationtestapparatus	DT-1500,LabIndia
9.	Dissolutiontestapparatus	DS-800,LabIndia
11.	DSCApparatus	DSC-60,Shimadzu
12.	Stabilitychamber	106Model/ LabTop,SkyLab Instruments&EngineeringPvt.Ltd.

3.2 PRE-FORMULATIONSTUDIES

Pre-formulation testing is the first step in rational development of dosage forms of a drugsubstance.Pre-formulationstudy istheprocessofoptimizingthedelivery ofdrugthroughdetermination of physicochemical properties of the excipients that could affect drug performanceand development of as efficacious, stable and safe dosage form.

3.2.1 Determination of λ_{max} [74]

Divalproex sodium was dissolved in methanol further diluted with the same and scanned formaximum absorbance in UV double beam spectrophotometer (Shimadzu 1800) in the range from190 to 380 nm.

3.2.2 Solubility

3.2.3 ThesolubilityofDivalproexsodiumwasdeter minedindistilledwater,methanol,ethanol,acetone, chloroform and pH 6.8 phosphate buffer by shake flask method. An excess amount ofDivalproex sodium is added to each vial containing 10 ml of selected solvent till the saturation ofthe solution. The mixtures were subjected to the mechanical agitation for 48 hours in isothermalshaker at $25^0C \pm 1^0C$

3.2.4 Meltingpoint[75]

Meltingpoint of theDivalproexsodium was determined bycapillarymethod in triplicate.

3.2.5 Standard CurveforDivalproex sodium[74]

100 mg of Divalproex sodium was accurately weighted and dissolved in 100 ml of methanol

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

toprepare first stock solution. 10 ml of above solution was taken and diluted to 100 ml with thesamesolventtoprepareIIstocksolution.Thealiquota mountofIIstocksolutionwasfurther diluted to get 5, 10,15, 20, 25and 30 µg of drug perml ofthefinal solution.Then theabsorbance wasmeasuredina UVspectrophotometerat 210nmagainst methanol blank.
followed by filtration through watmann's filter paper.

3.3 Dt = Dose (1+0.693xt/$t_{1/2}$)Where,Dt=**FormulationDesign**

3.3.1 Calculationofdose[78]

Totaldoseofdrug,

Dose=Doseofimmediate releasepart.

t=timeinhrduringwhichthesustainedreleaseisdesired(18hrs)$t_{1/2}$ =halflifeof thedrug(9 hrs)
Therefore,

Dt=125(1+0.693x18/9), Dt≈ 298.25

Thereforemaintenancedose=298.25-125 =173.25 mg.

Hence,theformulationshouldrelease125mgdrugwithin 1hourand173.25mgdrugin18hours.

A) FormulationofImmediatereleaselayer.

Table13:Formulationof immediatereleaselayer(IRL)

Sl.No.	Ingredients	IF1	IF2	IF3	IF4	IF5	IF6
1	Divalproex sodium	125	125	125	125	125	125
2	Lactose	82	79.5	82	79.5	82	79.5
3	Croscarmellosesodium	10	12.5	-	-	5	6.25
4	Sodiumstarchglycolate	-	-	10	12.5	5	6.25
5	Microcrystallinecellulose	25	25	25	25	25	25
6	Ponceau4R	0.02	0.02	0.02	0.02	0.02	0.02
7	Magnesiumstearate	3	3	3	3	3	3
8	Talc	5	5	5	5	5	5
9	Total	250	250	250	250	250	250

B) Formulationofsustainedreleasedlayer.

Table14:Formulationofsustainedreleaselayer(SRL)

Sl. No.	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
1	Divalproex sodium	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25	173.25

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

2	Lactose	52.75	45.25	37.75	52.75	45.25	37.75	52.75	45.25	37.75
3	HPMCK4M	45	52.5	60	-	-	-	22.5	26.25	30
4	HPMCK100M	-	-	-	45	52.5	60	22.5	26.25	30
5	Microcrystallinecellulose	20	20	20	20	20	20	20	20	20
6	Magnesiumstearate	3	3	3	3	3	3	3	3	3
7	Talc	6	6	6	6	6	6	6	6	6
8	Total	300	300	300	300	300	300	300	300	300

PreparationofIRL

IRL of Divalproex sodium (DS) was prepared by wet granulation by using differentSuper disintegrants such as SSG and Croscarmellose sodium. PVP K30 solution with containingcoloring agent was used as binding solution. As DS was oily in characteristics, MCC was used asadsorbent.Manufacturingsteps-

- Passalltheingredientsthoughsieve#80.
- Mix DivalproexsodiumwithMCC geometricallyandthenmixwithlactose.
- AddSuper disintegrantsandmixfor10 to15 minin mortar andpestle.
- Makewet mass usingbindingagent PVP K 30 solutioncontainingcolor.
- Passthecohesive massthrough sieve# 16togetuniform granules.
- Drythegranules at 50^0C for15 min inhot air oven.
- Lubricatethegranuleswithlubricatingagentandcompressedinto250mgeachtabletweightbyadjustinghardness.Theformulations areshown ontableno 13.

PreparationofSRL

Accurately weighed Divalproex sodium and polymer and others ingredients were taken in mortarand pestle and mixed well.The powderwas mixed with sufficientquantity for PVP K30solution until wet mass formed. The cohesive mass obtained was passed though sieve # 16 andthe granules were dried in a hot air oven at 50^0C for 20 min. The dried granules again passedthrough sieve # 22 to break the large lumps. Then granules were mixed with talc and magnesiumstearate and compressed into 300 mg each tablet by adjusting hardness. The formulations wereshown ontableno 14.

Preparationofbi-layeredtablet

By the study of disintegration and drug release profile of IRL and SRL, best formulationsof each layer were chosen and bi-layered tablet were prepared by double compression in singlerotatorytabletingmachine.

3.4 EvaluationofPre-formulationParameters:

AngleofRepose:[79]

The angle of repose of granules was determined by the funnel method. The accurately weighedgranules were taken in a funnel. The height of the funnel was adjusted in such a way that the tipofthefunneljusttouchedtheapexoftheheapofthegranules.Thegranuleswereallowedtoflow through the funnel greely onto the surface. The diameter of the powder cone was measuredandangle of reposewascalculated usingequation.

$\theta=\tan^{-1}(\frac{h}{r})$

Where,θ=theangleofrepose

h=heightoftheheapofthepowderr=radiusof theheapof thepowder

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

Table15:ANGLEOFREPOSE

Sl.No	Angleof Repose(θ)	Typeofflow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Verypoor

Determinationof bulkdensityandtappeddensity:[80]

A quantity of 2 g of the powder (W) from each formula was introduced into a 25 ml measuringcylinder. After the initial volume was observed, the cylinder was allowed to fall under its ownweight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping wascontinued until no further change in volume was noted. The bulk density, and tapped densitywerecalculated usingfollowingformulas.

Db= $\frac{Mass\ of\ powder}{Bulk\ volume\ of\ the\ powder}$

Dt= $\frac{Mass\ of\ powder}{Tapped\ volume\ of\ the\ powder}$

Carr'sindex:[81]

Ithelpsinmeasuringtheforcerequiredtobreakthefrictionbetweentheparticlesandthehopper. It is expressed in% andgiven by

Carr'sindex%= $\frac{Tapped\ density - Bulk\ density}{Tapped\ density}$ X 100

Table16:% COMPRESSIBILITYINDEX

Sl.No	%Compressibilityindex	Property
1	5-12	Freeflowing
2	12-16	Good

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 130-153 www.ijprajournal.com ISSN: 2456-4494

3	18-21	Fair
4	23-35	Poor
5	33-38	Verypoor
6	>40	Extremelypoor

Hausner'sratio:[82]

Hausner'sratioisaindirectindexofeaseofpowderflow.Hausner'sratiowasmeasuredbytheratioof tapped densitytobulk density.

Hausner'sratio= $\frac{Tapped\ density}{Bulk\ density}$

Table17:HAUSNER'SRATIO

Sl.No.	Hausner'sratio	Property
1.	0-1.2	Freeflowing
2.	1.2-1.6	Cohesiveflowing

3.5 Evaluationofpreparedformulations

3.5.1 Evaluationof DivalproexsodiumIRL,SRLandbi-layeredtablet

Thetabletspreparedwereevaluated forthefollowingparameters:

Weightvariation

3.5.1.1 Friability

3.5.1.2 Hardness

3.5.1.3 Drugcontent

3.5.1.4 In-vitroDissolutionStudies

3.5.1.5 StabilityStudies

WeightVariation Test:[83]

To studyweightvariation,20tabletsof eachformulationwereweightedusingelectronicbalance andthe test was performed accordingto theofficial method.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 88-105 www.ijprajournal.com ISSN: 2456-4494

:IP standards ofUniformityof weight

S.N.	Avg.WtofTablet(mg)	% ofDeviation
1	≤80 mg	10
2	>80 mg– 250 mg	7.5
3	≥250 mg	5

Hardness:[84]

Table18:IPstandardsofUniformityof weight

S.N.	Avg.WtofTablet(mg)	% ofDeviation
1	≤80 mg	10
2	>80 mg– 250 mg	7.5
3	≥250 mg	5

The resistance of tablets to shipping or breakage under condition of storage, transportation andhandling before usa. The hardness was measured in the terms of kg/cm^2 . 5 tabletswere chosen randomly and tested for hardness. ge depends on its hardness

Friability:[85]

Friability generally refers to loss in weight of tablets in the containers due to removal of finesfrom the tablet surface.friabilatorand rotated at the speed of 25 rpm for 100 revolutionsPercentagefriabilitywascalculated byusingtheformula.

$$\%\text{Friability} = \frac{Weight\ initial - Weight\ final}{Weight\ initial} \times 100$$

Tabletthickness:[86]

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured usingVernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

DrugContentforIRF,SRFand Bi-layeredtablet:[87]

Ten tablets were weight and average weight is calculated. All tablets were crushed andpowder equivalent to 100 mg drug was dissolved in pH 6.8 phosphate buffer and the volume wasmade up to 100 ml with pH 6.8 phosphate buffer. The solution was kept in sonicator for 1 hr.From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume **wasmadewithpH6.8phosphatebuffer.Solutionwasfilteredandabsorbancewasmeasured** spectrophotometrically at 210 nm against pH6.8 phosphate buffer as a blank. Amount of drugpresentin onetablet wascalculated.

Mathematical modelingofdrugreleaseprofile:[88]

The cumulative amount of Divalproex sodium release from the formulated tablets atdifferent time intervals were fitted to Zero order kinetics, first order kinetics,

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 88-105 www.ijprajournal.com ISSN: 2456-4494

higuchi model andkorsmeyer-peppasmodelto characterizemechanism of drugrelease.

1. Zero-orderKineticmodel – Cumulative%drugreleaseversusTime.

2. first-order Keneticmedel– Logcumulative% drugremainingversusTime.

3. Higuchi'smodel – cumulativepercentdrugreleasedversus squarerootoftime.

4. Korsmeyer equation/peppa'smedel- Logcumulativepercentdrugreleasedversuslogtime.

StabilityStudies[89,90]

The optimized formulation was subjected for two-month stability study according to standardguidelines. The selected formulations were packed in aluminum foils, which were in wide mouth bottles closedtightly.Theywerestoredat40^{0}C/75%RHfor3monthsandevaluatedperiodically.

IV. RESULTS

4.1 Determinationofλ_{max},

The λ_{max} of Divalproex sodium was found to be 210 nm in methanol and phosphatebufferpH 6.8.

4.2 StandardcurveofDivalproexsodium.

Theabsorbancewasmeasured inaUV spectrophotometerat210 nmagainstmethanol.

Table20:Spectrophotometricdataof DivalproexSodium

S.no.	Conc.(µg/ml)	Absorbance			Mean±SD
		Trial1	Trial2	Trial3	
1	0	0.000	0.000	0.000	0.000±0.000
2	5	0.050	0.043	0.046	0.046±0.004
3	10	0.097	0.095	0.098	0.097±0.002
4	15	0.143	0.144	0.146	0.144±0.002
5	20	0.185	0.188	0.187	0.187±0.002
6	25	0.240	0.237	0.237	0.238±0.002

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 88-105 www.ijprajournal.com ISSN: 2456-4494

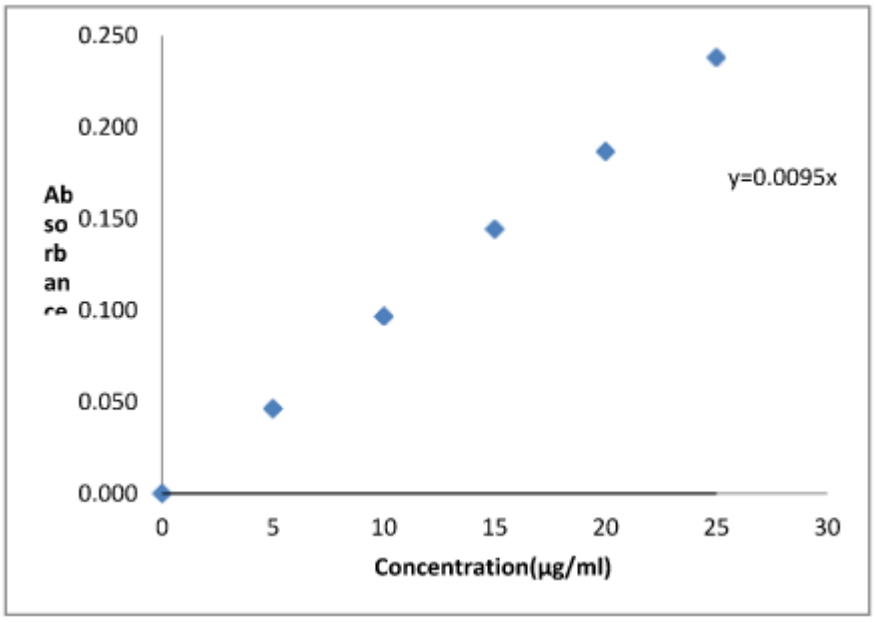


Figure5:Standardgraphof Divalproexsodium

V. CONCLUSION

Inthepresentworkbi-layeredtabletofDivalproexsodiumwerepreparedbywet granulation method, using super disintegrants such as sodium starch glycolate and croscarmellosefor immediate release layer and polymer like HPMC K4M Theabovestudies lids to followingconclusions:

- DSC studiesindicated thatthedrugiscompatiblewithalltheexcipients.
- Both immediate and sustained release layer were prepared by wet granulation method andpunchedseparately.Thepreparedtabletsofbothl ayerswereevaluatedforpostcompressionparameter s.
- According to the in vitro dissolution profile date one formulation of each layer wereselectedforbi-layeredtablet.IF6fromimmediatereleaseformulati onsastheyshowed

98.62 % drug release within 20 minutes. SF8 from sustained release formulation as theyshowed 94.29 %drugreleasewithin18 hours.

- The bilayer tablets were prepared using the selected immediate and sustained releaselayer.Theprepared tabletswerefoundtobegoodand freefromchippingandcappingand HPMC K100M for sustainedreleaselayer.

Theabovestudies lids to followingconclusions:

- DSC studiesindicated thatthedrugiscompatiblewithalltheexcipients.
- Both immediate and sustained release layer were prepared by wet granulation method andpunchedseparately.Thepreparedtabletsofbothl ayerswereevaluatedforpostcompressionparameter s.
- According to the in vitro dissolution profile date one formulation of each layer wereselectedforbi-layeredtablet.IF6fromimmediatereleaseformulati onsastheyshowed

98.62 % drug release within 20 minutes. SF8 from sustained release formulation as theyshowed 94.29 %drugreleasewithin18 hours.

- The bilayer tablets were prepared using the selected immediate and sustained releaselayer.Theprepared tabletswerefoundtobegoodand freefromchippingandcapping
- Thehardness of the prepared tablets was found tobein therangeof5.85to 7.05 kg/cm^2

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 5 Sep-Oct 2022, pp: 88-105 www.ijprajournal.com ISSN: 2456-4494

- The lowvaluesof thestandard deviationof averageweightofthe preparedtabletsindicateweight uniformitywithin thebatchesprepared.

- Thefriabilityof theprepared tabletwasfoundtobeless than 1%.
- Thepercentagedrugcontentwasuniforminallthefor mulationsofpreparedbi-layeredtablets.
- Invitrodrugreleasepatternofthebi-layeredtabletswassameasindividuallayertablets.
- Thestabilitystudyshowedthat nosignificantchangesintabletsafter3 monthsstudy.

Based on the observations, it can be concluded that the formulated bi-layered tablets ofDivalproexsodiumusingsuperdisintegrants,releasere tardantpolymersanddifferentexcipients was capable of exhibiting all the properties of bi-layered tablet. They are thusreducing the dose intake, minimize dose related adverse effect, cost and ultimately improvethepatient complianceand drugefficiency.

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