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DESIGN, DEVELOPMENT AND EVALUATION OF CARBAMAZEPINE BILAYERED TABLETS

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ABSTRACT

Carbamazepine, also known as Tegretol, is an anticonvulsant drug and analgesic drug used to control seizures and to treat pain resulting from trigeminal neuralgia. It was initially approved by the FDA in 1965. Aside from the above uses, this drug is also given to control the symptoms of bipolar 1. Interestingly, carbamazepine was the first anticonvulsant used to treat individuals with bipolar disorder. The aim of present investigation is to increase the gastric residence time by preparing gastro retentive Bi-layered tablet thereby improving bioavailability. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug. The present work aims to develop a stable and optimized bilayer dosage form containing immediate release and Extended-release. Best formulations of each layer were selected for bi-layered tablet and bi-layered tablet were prepared. Bi-layered tablet of Carbamazepine were subjected to hardness, weight variation, friability, drug content uniformity, in vitro drug release and drug polymer interaction. The above studies lid to following conclusions: Both immediate and sustained release layer were prepared by wet granulation method and punched separately. The prepared tablets of both layers were evaluated for post compression parameters. According to the in vitro dissolution profile date one formulation of each layer were selected for bi-layered tablet. IF6 from immediate release formulations as they showed 98.62 % drug release within 20 minutes. SF8 from sustained release formulation as they showed 94.29 % drug release within 18 hours. The bilayer tablets were prepared using the selected immediate and sustained release layer. The prepared tablets were found to be good and free from chipping and capping. The hardness of the prepared tablets was found to be in the range of 5.85 to 7.05 kg /cm^{2}.The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared. The friability of the prepared tablet was found to be less than 1%. The percentage drug content was uniform in all the formulations of prepared bi-layered tablets. In vitro drug release pattern of the bi-layered tablets were same as individual layer tablets. The stability study showed that no significant changes in tablets after 3 months study. Based on the observations, it can be concluded that the formulated bi-layered tablets of Carbamazepine using super disintegrants, release retardant polymers and different excipients was capable of exhibiting all the properties of bi-layered tablet. They are thus reducing the dose intake, minimize dose related adverse effect, cost and ultimately improve the patient compliance and drug efficiency.

KEYWORDS: Carbamazepine, Bi-layered tablet, Divalproex sodium.

INTRODUCTION

The oral drug delivery market is the largest segment of the drug delivery market and there's no sign that it is slowing down. Oral route of drug administration have wide acceptance up to 50-60% of total dosage form and is the most convenient and preferred route for systemic effect due to its ease of dosing administration, pain avoidance, accurate dosage, patient compliance and flexibility in formulation. The major aim of controlled drug delivery is to reduce dosing frequency. The design of modified release drug product are to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval and provide better patient compliance and patient convenience. Over 90% of the formulations manufactured today are ingested orally. All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (Immediate, Extended or Controlled release) and the design of dosage forms (either solid, dispersion, or liquid), must be developed within the intrinsic characteristics of GI physiology. This shows that oral formulation is the most popular worldwide and the major attention of the researcher is towards this direction. Tablets are solid preparations each containing a single dose of one or more active substances and usually obtained by compressing uniform volumes of particles. Tablets are intended for oral administration. When tablet given orally, it undergo In- vitro administration and dissolution followed by absorption through the gastrointestinal tract (GIT) and then the In-vivo bio distribution of drug which enters in to the systemic circulation then occurs. Some are swallowed whole, some after being chewed, some are dissolved or dispersed in water before being administered and some are retained in the mouth where active substance is liberated. The particles consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behavior of the preparation in the digestive tract, coloring matter authorized by the component authority and flavoring substances.

MATERIAL & METHODS

PRE-FORMULATION STUDIES

Pre-formulation testing is the first step in rational development of dosage forms of a drug substance. Pre-formulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the excipients that could affect drug performance and development of as efficacious, stable and safe dosage form. It provides a framework for the drug combination with pharmaceutical excipients in the dosage form.

1. Determination of λ max

Carbamazepine was dissolved in methanol further diluted with the same and scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu 1800) in the range from 190 to 380 nm.

2. Solubility

The solubility of Carbamazepine was determined in distilled water, methanol, ethanol, acetone, chloroform and pH 6.8 phosphate buffer by shake flask method. An excess amount of Carbamazepine is added to each vial containing 10 ml of selected solvent till the saturation of the solution. The mixtures were subjected to the mechanical agitation for 48 hours in isothermal shaker at 250C ± 10C followed by filtration through watmann's filter paper. Absorbance is measured by UV-Visible Spectrophotometer. The drug content is calculated by using the standard graph.

3. Melting point

Melting point of the Carbamazepine was determined by capillary method in triplicate.

4. Standard Curve for Carbamazepine

100 mg of Carbamazepine was accurately weighted and dissolved in 100 ml of methanol to prepare first stock solution. 10 ml of above solution was taken and diluted to 100 ml with the same solvent to prepare II stock solution. The aliquot amount of II stock solution was further diluted to get 5, 10, 15, 20, 25 and 30 g of drug per ml of the final solution. Then the absorbance was measured in a UV spectrophotometer at 210 nm against methanol blank.

Formulation Design

Calculation of dose

The total dose of Carbamazepine for once daily formulation was calculated by the following equation, using available pharmacological data.

$$Dt = Dose\ (1+0.693xt/t1/2)$$

Where,

Dt = Total dose of drug,

Dose = Dose of immediate release part.

t = time in hr during which the sustained release is desired (18 hrs)

t1/2 = half life of the drug (9 hrs)

Therefore,

Dt = 125(1+0.693x18/9),

Dt ≈ 298.25

Therefore,

Maintenance Dose = 298.25-125

= 173.25 mg.

Hence, the formulation should release 125 mg drug within 1 hour and 173.25 mg drug in 18 hours.

Preparation of IRL

IRL of Carbamazepine was prepared by wet granulation by using different Super disintegrants such as SSG and Croscarmellose sodium. PVP K30 solution with containing coloring agent was used as binding solution. As DS was oily in characteristics, MCC was used as adsorbent. Manufacturing steps-

- Pass all the ingredients though sieve #80.
- Mix Carbamazepine with MCC geometrically and then mix with lactose. Add Super disintegrants and mix for 10 to 15 min in mortar and pestle.
- Make wet mass using binding agent PVP K 30 solution containing color.
- Pass the cohesive mass through sieve # 16 to get uniform granules.
- Dry the granules at 500C for 15 min in hot air oven.
- Lubricate the granules with lubricating agent and compressed into 250 mg each tablet weight by adjusting hardness. The formulations are shown on table no 4.

Preparation of SRL

Accurately weighed Carbamazepine and polymer and others ingredients were taken in mortar and pestle and mixed well. The powder was mixed with sufficient quantity for PVP K30 solution until wet mass formed. The cohesive mass obtained was passed though sieve # 16 and the granules were dried in a hot air oven at 500C for 20 min. The dried granules again passed through sieve # 22 to break the large lumps. Then granules were mixed with talc and magnesium stearate and compressed into 300 mg each tablet by adjusting hardness. The formulations were shown on table no 5.

Preparation of bi-layered tablet

By the study of disintegration and drug release profile of IRL and SRL, best formulations of each layer were chosen and bi-layered tablet were prepared by double compression in single rotatory tableting machine.

Evaluation of Pre-formulation Parameters:

i) Angle of Repose

Angle of repose is described as the maximum possible angle between the surface of a powder pile or granules and the horizontal plane. The granules were allowed to flow through a funnel fixed to a clamp at a definite height. The angle of repose (θ) was then calculated by measuring the height (h) and radius (r) of the formed granules heap and putting the values into the equation

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

Where, θ = the angle of repose

h = height of the heap of the powder

r = radius of the heap of the powder

TABLE 5: ANGLE OF REPOSE.

S.NO.	Angle of Repose(θ)	Type of flow
1.	< 25	Excellent
2.	25-30	Good
3.	30-40	Passable
4.	> 40	Very poor

ii) Determination of bulk density and tapped density

The apparent bulk density (b) was calculated by filling a graduated cylinder with presieved medication excipients blend and measuring the volume (Vb) and weight (M) as

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

The measuring cylinder, which contained a known mass of blend, was tapped for a predetermined amount of time. The cylinder's minimum volume (Vt) and the blend's weight (M)were both measured. The following formula was used to compute the tapped density (t).

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

iii) Compressibility Index

It helps in measuring the force required to break the friction between the particles and the hopper. It is expressed in % and given by

$$\text{Carr's index \%} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \text{ X } 100$$

Table 6: % Compressibility Index.

S.NO.	% Compressibility index	Property
1.	5-12	Free flowing
2.	12-16	Good
3.	18-21	Fair
4.	23-35	Poor
5.	33-38	Very poor
6.	> 40	Extremely poor

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. Hausner's ratio was measured by the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

Table 7: Hausner's Ratio.

S.NO.	Hausner's ratio	Property
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive flowing

Evaluation of prepared formulations

Evaluation of Carbamazepine IRL, SRL and bi-layered tablet

The tablets prepared were evaluated for the following parameters:

Weight Variation Test

To study weight variation, 20 tablets of each formulation were weighted using electronic balance and the test was performed according to the official method.

Table 8: IP standards of Uniformity of weight.

S. NO.	Avg. Weight of Tablet (mg)	% of Deviation
1.	≤80 mg	10
2.	> 80 mg – 250 mg	7.5
3.	≥250 mg	5

Hardness

The resistance of tablets to shipping or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in the terms of kg/cm^2. 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability

Friability test was carried out to evaluate the hardness and stability instantly. 10 tablets were weighed (W0) initially and put in a tumbling and rotating apparatus drum. Then they were subjected for completion of 4 min or 100 rpm, the tablets were again weighed. The % loss in weight or friability (F) was calculated by the formula given below.

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

Tablet thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation. Vernier caliper consists of metric and imperial scales. The main matric scale is read first then read "hundredths of mm" of imperial scale (count the number of divisions until the lines.

In-vitro dissolution studies of immediate release layer

The in-vitro dissolution studies were performed using USP-II (paddle) dissolution apparatus at 100 rpm. Phosphate buffer pH 6.8 dissolution media is maintained at 37±0.500C. A 5 ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV spectrophotometer at 284 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

In vitro dissolution studies of sustained release layer

The in vitro release of sustained release layer was carried out for 18 hours using USP type-II apparatus (DT-1200) at 100 rpm for the first 45 minute in 900 ml 0.1N HCL maintaining at 37 ±0.50C and then at phosphate buffer pH 6.8 in 900ml for another 18 hour. A 5 ml was withdrawn at different time intervals and replaced with an equal volume of fresh medium. The samples were suitably diluted with blank dissolution medium, filtered and analyzed on UV spectrophotometer at 210nm.

Drug Content for IRF, SRF and Bi-layered tablet

Ten tablets were weight and average weight is calculated. All tablets were crushed and powder equivalent to 100 mg drug was dissolved in pH 6.8 phosphate buffer and the volume was made 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 was made with pH6.8 phosphate buffer. Solution was filtered and absorbance was measured spectrophotometrically at 284 nm against pH 6.8 phosphate buffer as a blank. Amount of drug present in one tablet was calculated.

Stability Studies

The optimized formulation was subjected for two-month stability study according to standard guidelines. The selected formulations were packed in aluminum foils, which were in wide mouth bottles closed tightly. They were stored at 40^0C / 75% RH for 3 months and evaluated periodically.

RESULT

Determination of λmax

The λmax of Carbamazepine was found to be 284 nm in methanol and phosphate buffer pH 6.8.

Standard curve of Carbamazepine

The absorbance was measured in a UV spectrophotometer at 284 nm against methanol.

Table 9: Spectrophotometric data of Carbamazepine.

S.No.	Concentration (µg/Ml)	Absorbance			Mean ± SD
		Trail 1	Trail 2	Trail 3	
1.	5	0.005	0.007	0.006	0.006±0.010
2.	10	0.113	0.113	0.113	0.115±0.017
3.	15	0.222	0.225	0.225	0.224±0.017
4.	20	0.331	0.334	0.334	0.333±0.017
5.	25	0.440	0.443	0.443	0.442±0.017
6.	30	0.549	0.552	0.552	0.551±0.017
7.	35	0.658	0.661	0.661	0.660±0.017

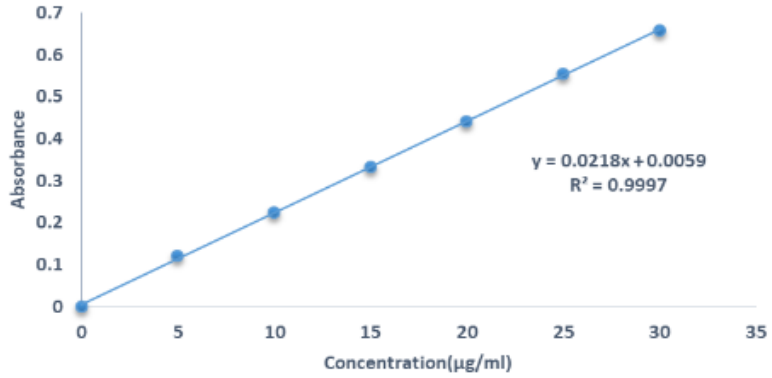

Figure 4: Standard graph of Carbamazepine.

Drug solubility studies

The solubility studies of drug were done by using various media like distilled water, methanol, chloroform and phosphate buffer pH 6.8. The result shows maximum solubility in chloroform.

Table 10: Solubility of Divalproex sodium.

S.No.	Solvents	Solubility (Mg/Ml)	Solubility Nature
1.	Distilled water	0.12 ± 0.01	Slightly soluble
2.	Methanol	0.25 ± 0.02	Moderately soluble
3.	Chloroform	18.5 ± 0.5	Freely soluble
4.	Phosphate buffer pH 6.8	22.3 ± 0.6	Highly soluble

Melting Point

Melting point of drug was determined by capillary method. The result is found to be 190–193°C.

EVALUATION OF PRE-COMPRESSION PARAMETERS

Table 11: Pre-compression parameters for IRL and SRL.

Formulation	Bulk Density Mean ± SD	Tapped Density Mean ± SD	Car's Index Mean ± SD	Haunsers Index Mean ± SD	Angle of Repose Mean ± SD
IF1	0.557±0.002	0.637±0.005	12.610±0.217	1.145±0.030	16.596±0.356
IF2	0.556±0.005	0.655±0.004	15.084±0.226	1.174±0.020	18.360±0.275
IF3	0.523±0.004	0.626±0.003	15.773±0.109	1.164±0.022	19.421±0.173
IF4	0.585±0.003	0.684±0.003	13.899±0.177	1.163±0.013	20.147±0.156
IF5	0.612±0.010	0.682±0.007	11.767±0.206	1.133±0.009	17.913±0.039
IF6	0.666±0.004	0.755±0.006	11.148±0.157	1.142±0.025	17.101±0.077

SF1	0.592±0.005	0.694±0.003	13.779±0.206	1.154±0.009	19.604±0.279
SF2	0.591±0.008	0.699±0.002	14.494±0.328	1.169±0.017	18.480±0.063
SF3	0.605±0.004	0.681±0.003	11.223±0.186	1.133±0.009	18.201±0.088
SF4	0.623±0.005	0.703±0.002	11.531±0.127	1.132±0.010	22.548±0.280
SF5	0.596±0.004	0.710±0.004	16.144±0.249	1.200±0.028	18.331±0.077
SF6	0.591±0.004	0.727±0.002	18.716±0.397	1.256±0.029	18.168±0.104
SF7	0.615±0.003	0.728±0.004	14.825±0.673	1.174±0.028	18.467±0.091
SF8	0.512±0.001	0.623±0.002	17.564±0.436	1.243±0.024	19.347±0.072
SF9	0.620±0.002	0.693±0.001	10.754±0.181	1.124±0.017	17.396±0.021

POST-COMPRESSION EVALUATION PARAMETERS

Table 12: Post-compression parameters for IRL and SRL.

Batch code	Weight variation Mean ± SD	Hardness (kg/cm2) Mean ± SD	Friability (%) Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD	In vitro disintegration time (sec) Mean ± SD
IF1	249.9±1.57	5.95±0.05	0.74±0.09	2.87±0.04	98.12±1.19	120.33±1.52
IF2	250.3±1.60	4.18±0.10	0.58±0.04	2.91±0.10	97.65±1.82	91.66±2.08
IF3	250.9±1.60	6.35±0.03	0.56±0.06	2.90±0.07	98.65±1.28	73.33±2.51
IF4	251.55±1.99	6.17±0.07	0.65±0.05	2.87±0.03	99.61±0.94	48.33±3.05
IF5	251.45±2.52	4.14±0.04	0.63±0.03	2.92±0.06	99.43±1.32	59.33±2.08
IF6	250.05±1.81	4.53±0.11	0.69±0.04	2.89±0.09	99.51±1.81	37.33±1.52
SF1	302.6±1.41	5.38±0.10	0.32±0.06	3.34±0.09	99.38±1.19	-
SF2	302.9±2.29	4.33±0.02	0.35±0.02	3.30±0.14	98.61±1.03	--
SF3	302.5±1.59	6.14±0.04	0.43±0.03	3.31±0.03	97.43±1.28	-
SF4	301.75±1.14	6.23±0.06	0.36±0.02	3.28±0.05	98.57±0.85	-
SF5	300.65±1.37	5.14±0.03	0.41±0.06	3.30±0.06	98.43±1.27	-
SF6	302.30±1.31	4.52±0.02	0.48±0.03	3.33±0.03	97.63±0.61	-
SF7	303.20±1.46	6.74±0.04	0.42±0.06	3.28±0.08	99.47±1.04	-
SF8	301.25±1.55	6.16±0.02	0.37±0.04	3.30±0.04	99.51±1.20	-
SF9	302.42±1.04	6.56±0.03	0.31±0.03	3.32±0.07	98.49±0.93	-

Table 13: Post-compression parameters for bi-layered tablet.

Formulation	Weight variation Mean ± SD	Hardness Mean ± SD	Friability Mean ± SD	Thickness Mean ± SD	Drug content (%) Mean ± SD
BTF	550.75±0.46	7.05±0.15	0.38±0.01	6.28±0.14	99.23±0.53

In-vitro dissolution study

Table 14: In vitro dissolution study of IRL.

Time in min	% CUMULATIVE DRUG RELEASE					
	IF1	IF1	IF1	IF1	IF1	IF1
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
1	17.056±0.612	21.226±0.872	20.847±0.450	26.532±1.306	30.323±1.125	36.008±1.174
3	31.805±1.075	31.908±1.280	33.738±2.620	54.965±2.391	56.561±0.778	60.653±2.255
5	53.454±2.280	56.489±2.100	56.488±1.288	68.244±0.593	64.455±2.346	68.247±1.723
10	64.837±2.481	68.251±3.001	68.250±1.176	81.525±0.896	77.735±1.791	83.424±2.060
15	71.106±1.634	78.121±1.913	74.141±1.523	89.829±1.107	81.543±0.873	92.918±1.314
20	80.408±1.038	83.445±1.088	82.685±0.582	94.829±0.788	87.246±1.865	98.624±0.722
25	86.676±1.427	92.366±1.472	90.280±1.281	97.497±0.931	92.376±1.325	98.827±1.427
30	91.047±2.031	94.842±1.632	93.135±0.852	98.075±1.265	96.743±1.731	99.404±1.162

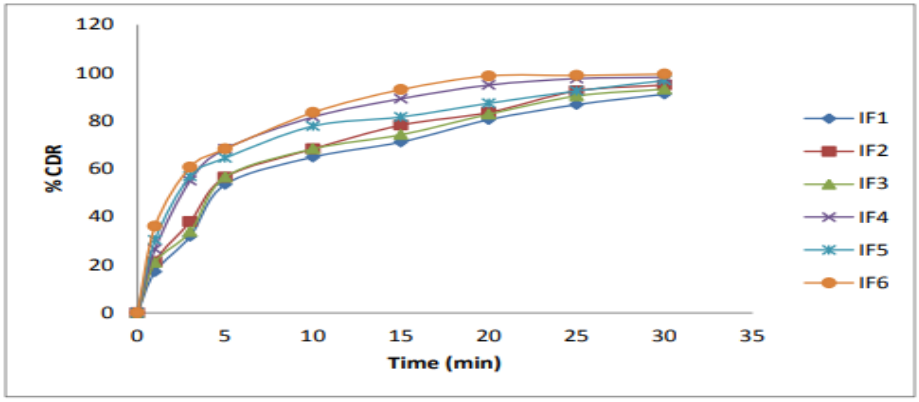

Figure 5: Release profile of immediate release layer.

Table 15: In vitro dissolution study of SRL.

Time in min	% CUMULATIVE DRUG RELEASE							
	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8
0	0.000 ±0.000	0.000 ±0.000	0.000 ±0.000	0.000 ±0.000	0.000 ±0.000	0.000 ±0.000	0.000 ±0.000	0.000 ±0.000
60	15.408 ±1.222	7.905 ±1.234	6.017 ±1.508	13.469 ±1.222	6.741 ±1.281	5.558 ±1.591	13.006 ±1.994	5.391 ±0.882
120	25.634 ±1.764	19.263 ±1.532	18.231 ±1.281	25.637 ±0.732	18.521 ±1.421	12.635 ±0.751	21.351 ±1.317	17.527 ±1.114
240	34.323 ±2.715	24.502 ±1.083	23.091 ±1.547	33.235 ±1.164	25.279 ±1.003	17.697 ±1.151	33.589 ±1.503	24.917 ±1.426
360	42.342 ±0.632	31.362 ±1.321	29.735 ±0.941	38.852 ±1.521	33.852 ±1.835	25.742 ±1.427	45.247 ±0.941	36.518 ±0.831
480	57.151 ±1.196	43.141 ±1.974	36.936 ±1.251	56.674 ±2.061	47.993 ±0.539	33.733 ±2.378	53.869 ±1.510	46.331 ±0.891
600	62.342 ±0.412	48.234 ±0.826	43.752 ±1.423	62.316 ±1.839	50.491 ±0.694	39.513 ±1.114	59.523 ±1.163	52.852 ±0.792
720	76.620 ±1.642	56.263 ±2.227	54.964 ±2.137	70.315 ±2.001	65.327 ±1.779	47.031 ±1.480	68.215 ±0.906	64.017 ±0.710
960	98.183 ±0.352	82.430 ±1.267	66.957 ±1.402	87.123 ±0.645	86.182 ±0.467	54.439 ±2.565	88.053 ±0.676	77.498 ±0.918
1080	101.512 ±1.093	97.816 ±0.630	84.113 ±1.317	98.822 ±1.325	97.692 ±0.844	67.057 ±1.191	100.859 ±2.165	94.298 ±0.560

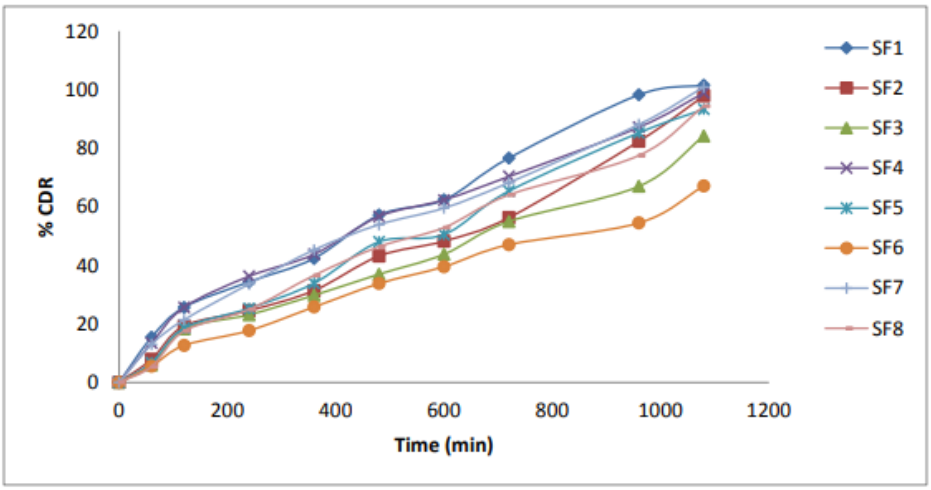

Figure 6: Release profile of sustained release layer.

Table 16: Dissolution study of Bi-layered Tablet.

Time in min	% CDR	
	BTF	
	IRL	SRL
0	0.000±0.000	0.000±0.000
10	83.424±1.063	-
20	98.351±1.147	-
30	99.413±0.731	-
60	-	5.384±1.032
120	-	17.512±0.853
240	-	23.483±1.520
360	-	36.164±0.638
480	-	46.054±0.825
600	-	52.854±0.841
720	-	64.781±0.527
960	-	76.149±0.952
1080		95.823±0.614

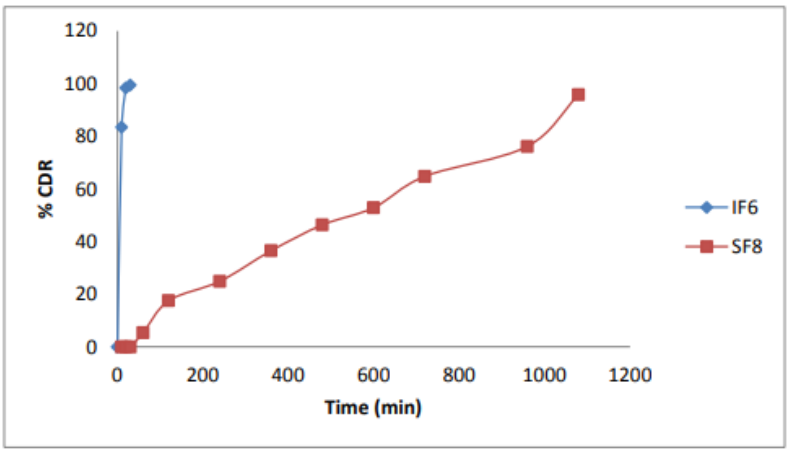

Figure 7: Release profile of Bi-layered Tablet.

Stability Studies

Table 17: Stability data.

Stability period	400C / 75% RH				
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content Mean ± SD	Drug release	
				IRL (30 min)	SRL (1080 min)
Initial	7.05±0.67	0.36±0.01	99.23±0.532	99.413	95.823
1 month	7.08±0.49	0.43±0.03	99.35±0.751	99.581	95.421
2 months	6.41±0.49	0.56±0.06	98.96±0.792	99.142	94.736
3 months	5.33±0.60	0.73±0.03	96.94±0.921	98.728	94.381

The bi-layered tablets were subjected to short term stability study, storing the formulation at 400C / 75% RH for 3 months. The data for stability studies revealed that no considerable differences in physical parameters, drug content and in vitro drug release rate were observed.

DISCUSSION

The present work is a design, development and evaluation of bi-layer tablet of Carbamazepine, which is used in treatment of epilepsy, bipolar disorders and used in prophylaxis of migraine, was carried out. In the project, different formulations of immediate release and sustained release layer have been prepared separately. From above formulations

best formulation of each immediate and sustained release layers were selected according to the dissolution profile and bi-layered tablet was prepared. Carbamazepine a broad-spectrum antiepileptic drug was chosen as a model drug as it is a right candidate for immediate as well as sustained release formulations. Carbamazepine is soluble in 0.1 N NaOH, phosphate buffer pH 6.8, chloroform, methanol, ethanol (95%), and sparingly soluble in water. The result shown that the Carbamazepine is more soluble in chloroform in compare to other solvents. The absorbance maximum of the Carbamazepine was found to be at 284 nm when scanned in between 200-400 nm using methanol as well as phosphate buffer pH 6.8 solutions. Best formulations for preparation of bi-layered tablet were selected depending upon the dissolution profile as all the formulation showed good content uniformity, friability, hardness and other physical parameters. Pre-formulation studies were carried out for all the formulation. Powder properties such as angle of repose, Carr's index, Hausner's ratio, bulk density, tapped density were determined which shown on tablet number 12. Pre-formulation studies for the formulations depicted bulk density 0.512 to 0.66 gm/cm^3 which indicated packing characteristics in dies. The carr's compressibility index was found to be below 18% which suggested good compressibility of blend. The values of Hausner ratio and angle of repose were found in the range of 1.13 to 1.25 and 16.59 to 22.54^o respectively suggested excellent flow property of powder blend.Though the batch size of formulations were limited to 50-80, weight variation was reasonably satisfying the IP Limits as given in table no 9 and the drug content uniformity of all formulations was found to be 97.43-99.61 which indicated uniform distribution of drug in all batches of the formulations. Further hardness and friability was also between 4-6 kg/cm^2 and less 1% respectively indicating stability of tablets against physical shocks.In vitro drug release profile of the immediate release and sustained release formulations were given in table no 15 and 16 respectively. Among all formulations of immediate release layer, formulation IF1, IF2, IF3 and IF4 showed the least drug release 80.40, 83.44, 82.68 and 94.82 respectively in 20 min as they consist of 5% SSG, 6% SSG, 5% CD and 6% CD respectively. Formulation IF6 releases 98.62% drug in 20 min.

The release profile of the formulation IF6 was believed be due to combination of SSG and CD. The result indicated that increase in the concentration of super disintegrants and combination of super disintegrants increases the release profile of drug. In sustained release formulation, the formulation SF1 (15% HPMC K4M) showed highest release in 16 hours compare to the formulations SF2 and SF3 (17.5 and 20% HPMC K4M) which showed the drug release of 97.81 and 84.11% in 18 hours.

CONCLUSION

Carbamazepine, also known as Tegretol, is an anticonvulsant drug and analgesic drug used to control seizures and to treat pain resulting from trigeminal neuralgia. It was initially approved by the FDA in 1965. Aside from the above uses, this drug is also given to control the symptoms of bipolar 1. Interestingly, carbamazepine was the first anticonvulsant used to treat individuals with bipolar disorder. The aim of present investigation is to increase the gastric residence time by preparing gastro retentive Bi-layered tablet thereby improving bioavailability. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug. The present work aims to develop a stable and optimized bilayer dosage form containing immediate release and Extended-release. Best formulations of each layer were selected for bi-layered tablet and bi-layered tablet were prepared. Bi-layered tablet of Carbamazepine were subjected to hardness, weight variation, friability, drug content uniformity, in vitro drug release and drug polymer interaction.

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