IJPSR (2018), Volume 9, Issue 7 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 October, 2017; received in revised form, 22 December, 2017; accepted, 30 December, 2017; published 01 July, 2018

DEVELOPMENT AND CHARACTERIZATION OF BILAYER TABLET CONTAINING TRAMADOL AND PREGABALIN AS A GASTRIC BUOYANT DRUG DELIVERY SYSTEM FOR COMBINATION PHARMACOTHERAPY OF NEUROPATHIC PAIN

Santosh Kamble * and Bhagwat Poul

School of Pharmacy, Swami Ramanand Teerth Marathwada University, Nanded - 431606, Maharashtra, India.

Keywords:

Bilayer Tablet, Tramadol, Neuropathic Pain, Pregabalin, GBDDS

Correspondence to Author:
Mr. Santosh R. Kamble

Research Scholar, School of Pharmacy, Swami Ramanand Teerth Marathwada University, Nanded - 431606, Maharashtra, India.

E-mail: ksantosh.49@gmail.com

ABSTRACT: Experiments were performed to design, develop and characterize bilayer buoyant tablets with Tramadol (TH), immediate release layer and Pregabalin (PGB), sustained release layer. Super disintegrants like crosscarmellose sodium and sodium starch glycolate, for IR layer where as Hydroxypropyl methylcellulose (HPMC-K4M, HPMC-K100M) and sodium carboxymethyl cellulose, as sustaining polymers for SR layer and sodium bicarbonate which liberates carbon dioxide for adequate buoyancy, was used in the bilayer tablet. FT-IR and DSC studies were conducted to evaluate drug and excipients compatibility. A full two level factorial experimental design was used for sustaining PGB release from buoyant SR layer. More than 90% of Tramadol was released from IR layer within 30 min. Diffusion exponents (0.36-0.55) and (T_{50}%) time required for dissolving 50% of drug (1.96-3.31h) was determined for all SR tablet formulations. Optimised (S4) formulation exhibited 95.28% PGB released over 12 h. Since neuropathic pain is very difficult to treat, a delivery system for combination pharmacotherapy containing immediate releases of TH a unique powerful painkiller to provide instant pain relief and sustained release of PGB, the choice of drug in first-line treatment for various neuropathic pain syndromes can provide excellent therapeutic result by suppressing burning-fire pain stimulation of nerves with once a day administration.

INTRODUCTION: Neuropathy a disease of nerve is the common cause of pain in modern world. Chronic neuropathic pain is the most disturbing symptom of lesions in the peripheral nervous system that can be of many forms. Peripheral neuropathy is often distressing, may produce disabilities or even found to be fatal.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(7).2832-41

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(7).2832-41

There are several things that cause neuropathies, patients with conditions as diverse as diabetes induced neuropathy, human immunodeficiency virus (HIV) sensory neuropathy, post stroke syndromes, and multiple sclerosis frequently experience daily pain that greatly impairs their quality of life [1, 2]. Tramadol hydrochloride (TH), (±) cis-2-[(dimethylamino) methyl]-1-(3- methoxy phenyl) cyclohexanol hydrochloride a synthetic opioid analgesic acts centrally, binds with the μ-opioid receptors, produce week suppression of norepinephrine and serotonin re-acceptance. This mechanism may unconventionally assist for pain relief along with overall analgesic effect [3].

Pregabalin (PGB), an antiepileptic, (S)-3-(amino methyl)-5-methylhexanoic acid, binds to the alpha-2-delta subunit site of neuronal voltage-gated calcium channel, resulting in reduced depolarisation effected calcium flow in the nerve terminals which causes decline of excitatory neurotransmitters release. In addition to epilepsy, PGB has demonstrated excellent efficacy for the treatment of neuropathic pain and often considered as choice of drug in first-line treatments for various neuropathic pain syndromes, generally irrespective of cause [4].

Oral combination drug delivery systems have been proven to be highly beneficial and essential in the treatment of several complex disorders like neuropathic pain [5]. In recent years, gastroretentive peroral drug delivery systems have attracted more and more attention, the gastric buoyant drug delivery system (GBDDS) is able to stretch out the confinement of a dosage form in the stomach for longer time, thereby increasing therapeutic effectiveness of the drug through improving pharmacokinetics of the drug [6, 7].

The present work focuses on the development and characterization of bilayer tablet of Tramadol (TH) 50 mg, immediate release and Pregabalin (PGB) 100 mg, sustained release for effective round-the-clock treatment of neuropathic pain. For optimization of GBDDS, a 2^3 factorial design was employed; formulation control variables, HPMC-K4M; HPMC-K100M two viscosity grades, polymer-to-polymer proportion and total polymer content-to-drug content proportion were examined. The study includes total buoyancy time (TBT), quantity (%) of PGB released at 12 hours, time required to remain half (T_{50}%) and exponent of diffusion (n) as a dependent variables. Detailed regression analysis was made to achieve optimum composition for tablet formulation [8].

MATERIALS AND METHODS:

Materials: TH and PGB was a gift from Wockhardt Pvt. Ltd., (Aurangabad, India). HPMC K100M, HPMC K4M, sodium starch glycolate (SSG), cross carmellose sodium (CCS) were supplied by Colorcon Asia Pvt. Ltd., (Goa, India); Sodium carboxymethylcellulose, Microcrystalline cellulose, Tartarazine, Sodium bicarbonate, Lactose, Talc-pharmaceutical grade (IP) was purchased from local dealers. All other reagents and chemicals used were of analytical reagent grade.

Methods:

Drug - Excipient Interaction Study: [9] Fourier transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC) investigations were made to detect possible drug and excipient interactions.

FT-IR Spectral Investigation: Samples of pure drug TH, PGB, IR layer composition and SR layer composition were separately mixed with KBr to make pallets for the IR spectra using Shimadzu IR Affinity-1S FTIR spectrophotometer (Shimadzu, Japan).

DSC Thermogram Investigation: The thermograms for TH, PGB, IR layer composition and SR layer composition were prepared using Perkin Elmer Cyris - DSC. Temperature and enthalpy scale of the DSC was calibrated using indium (In). Aluminium vessels were used to seal the sample under test and then heated over a temperature scale of 50 - 200 °C with an invariable pace of 10 °C/min

Immediate Release TH Tablet Formulation: TH immediate release blend was prepared in porcelain mortar; Tramadol (TH), half of the quantity of disintegrant (CCS or SSG) and other excipients were mixed for 15min. Sufficient amount of purified water as a granulating liquid was added to produce wet mass which was then passed through 10# sieve for granulation and dried in oven at 50 °C for 30 min. Dry granules were screened through 14# sieve; calculated quantity of 10% fines was incorporated and mixed in a poly bag with remaining quantity of CCS or SSG, magnesium stearate and talc for 5 min. The TH-granules were compressed on single punch tablet compression machine (CADMAC, Ahmedabad, India) using 8 mm round flat-faced punch. Various powder characteristics for TH-granules were investigated before compression. **Table 1** provides compositions for different experimental batches.

Pre - compression Parameters - Evaluation of TH Blend: The TH-granules of all batches were evaluated for density (loose bulk density and tapped bulk density), angle of repose, Hausner's ratio and compressibility index [10].

TABLE 1: COMPOSITION OF TRAMADOL IR TABLET

S. no.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	TH	50	50	50	50	50	50	50	50
2	MCC	30	30	30	30	30	30	30	30
3	SSG	3	6	12	18	-	-	-	-
4	CCS	-	-	-	-	3	6	12	18
5	Tartarazine	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
6	Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Magnesium Stearate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
8	Lactose	QS	QS	QS	QS	QS	QS	QS	QS

TH: Tramadol Hydrochloride, MCC: Microcrystalline cellulose, CCS: Croscarmellose sodium, SSG: Sodium starch glycolate. Values represented in mg. Total weight 150 mg per tablet.

Evaluation of Immediate Release TH Tablet: As per pharmacopoeial procedures all batches of TH-tablet were characterized for appearance, thickness, weight variation, hardness and friability [11].

Drug Content: Twenty tablets were weighed, powdered and 50 mg equivalent of TH was accurately weighed, transferred into a 100 mL volumetric flask and dissolved in phosphate buffer pH 7.4 with sonication for 10 min, volume was made up to the mark. The solution in volumetric flask was filtered; suitable dilutions were made and analyzed at 273 nm on UV-visible spectro-photometer (Shimadzu UV - 1601). Maximum absorbance (λ_{max}) for TH was determined UV - spectrophotometrically by scanning dilute TH solution in phosphate buffer pH 7.4 at 200 nm to 400 nm. The drug content of each sample was estimated using standard calibration curve of TH in phosphate pH 7.4 buffer [12].

Disintegration Study: Disintegration test was performed on arbitrarily selected six tablets from each batch. The tablets were placed without disc in United States Pharmacopoeia (USP) disintegration test apparatus filled with simulated gastric fluid and temperature was maintained at 37 ± 0.5 °C. Disintegration time was expressed as mean ± standard deviation (SD) [13].

Dissolution Study: Dissolution test of TH tablet was performed in simulated gastric fluid as dissolution medium (900 mL) using USP dissolution test apparatus-II (LABINDIA DS8000^{+}) at 50 rpm and 37 ± 0.5 °C temperature. Test sample (5 mL) was withdrawn at specific time intervals (1, 3, 5, 10, 15, 20 and 30 min) and replaced with fresh dissolution media maintained at 37 ± 0.5 °C. The test sample was filtered (membrane filter, 0.45 μm) and the concentration of dissolved drug was determined using ultraviolet (UV) spectro-photometer at λ_{max} 273 nm. This test was performed on six tablets and mean ± SD calculated.

Buoyant Sustained Release PGB Tablet Formulation:

Experimental Design: A 2-level full-factorial design comprising of 8 full-factorial design points; according to the model, 8 experiments were conducted in total. This design involves independent or controlled variables polymer content-to-drug content proportion (X1), polymer-to-polymer proportion (X2) and polymer grade (X3) [HPMC K4M and K100M]; the levels of independent variables are shown in **Table 2**. The dependent variables Y1, percentage of PGB release at 12 hours; Y2, T_{50}%; Y3, diffusion exponent (n) and Y4, buoyancy time were investigated.

TABLE 2: LEVEL OF VARIABLES FOR INVESTIGATION

	Controlled Variables		
Coded Values	Polymer : Drug (X1)	Polymer : Polymer (X2)	Grade of Polymer (X3)
-1	1:1	1:1	HPMC K100M
1	2:1	3:1	HPMC K4M

HPMC: hydroxypropyl methyl cellulose

Preparation of Buoyant Tablets: Wet granulation approach was used for preparation of buoyant sustained release granules. Required quantity of Pregabalin (PGB), and polymers (HPMC K4M or HPMC K100M and sodium carboxymethyl cellulose), gas generating agent (sodium bicarbonate), and acidifying agent (citric acid) was accurately weighed, passed through sieve #40 and were mixed homogeneously in a poly bag for about 10 min, transferred to a mortar. To the mortar 5% PVP K30 in isopropyl alcohol as granulating agent was added in sufficient quantity to produce the wet mass which 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 granules and was lubricated in poly bag with magnesium stearate and talc for 5 min. The PGB-granules were compressed on single punch tablet compression machine (CADMAC, Ahmedabad, India) using 10 mm round flat-faced punch. Various powder characteristics for PGB-granules were investigated before compression. About 6 - 8 kg/cm^2 tablet crushing strength, consistently maintained during compression and 100 tablets per batch was prepared for all compositions; **Table 3** provides compositions for different experimental batches.

TABLE 3: COMPOSITION OF PREGABALIN SR TABLET

S. no.	Ingredients	S1	S2	S3	S4	S5	S6	S7	S8
1	PGB	100	100	100	100	100	100	100	100
2	HPMC K100M	50	75	100	150	-	-	-	-
3	HPMC K4M	-	-	-	-	50	75	100	150
4	SCMC	50	25	100	50	50	25	100	50
5	Sodium bicarbonate	85	85	85	85	85	85	85	85
6	Citric acid	21.3	21.3	21.3	21.3	21.3	21.3	21.3	21.3
7	Talc	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2
8	Magnesium Stearate	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1
9	PVP K30 5% in IPA	QS	QS	QS	QS	QS	QS	QS	QS
10	Lactose	QS	QS	QS	QS	QS	QS	QS	QS

PGB: Pregabalin, HPMC: Hydroxypropyl Methylcellulose, SCMC: Sodium Carboxymethyl Cellulose Sodium, PVP K30: Polyvinylpyrrolidone K30, IPA: Isopropyl Alcohol, Values represented in mg, Total weight 425 mg per tablet.

Pre-compression Parameters - Evaluation of PGB Blend: The PGB-granules of all batches were characterized for density (loose bulk density and tapped bulk density), angle of repose, Hausner's ratio and compressibility index [10].

Evaluation of Buoyant Sustained Release PGB Tablet: As per pharmacopoeial procedures all batches of PGB tablets were characterized for appearance, thickness, weight variation, hardness and friability [11].

BLT and TBT for PGB Tablet: Buoyancy lag time (BLT) is the time required for a tablet to float over gastric fluid, *in-vitro* buoyancy in simulated conditions was determined by the floating lag time. Tablets were placed in a 250 mL beaker containing 0.1N HCl maintained at 37 °C. Time required for the tablet to rise to the surface for floating was determined as the buoyancy lag time and further total buoyancy time (TBT) of all tablets was determined by visual observation [9].

Swelling Studies: The extent of swelling was measured in terms of % of weight gained by the tablet that may be used to predict drug release behaviour from the tablets. One tablet from each formulation was weighed and kept in petri dish containing 50 mL of 0.1 N HCl solution. At the end of specified time intervals tablets were withdrawn from petri dish, excess buffer blotted with tissue paper and weighed. The % of weight gained (swelling index) was calculated by using following formula **Eq. 1** [14].

$$\text{Swelling index (\%)} = (M_t - M_0 / M_0) \times 100 \quad ...(1)$$

Where, M_t = Weight measured for tablet, at time = t; = Weight measured for tablet at time = 0

Drug Content: Twenty tablets were weighed, triturated to powder and 100 mg accurately weighed equivalent weight of PGB was transferred into a 100 mL volumetric flask, dissolved in phosphate buffer pH 7.4 with sonication for 10 min; volume was made up to the mark. The solution in volumetric flask was filtered through 0.45 µm membrane filter and suitable dilutions were made and analyzed at 210 nm on UV-Visible spectrophotometer (Shimadzu UV-1601).

Maximum absorbance (λ max) for PGB was determined UV - spectrophotometrically by scanning dilute PGB solution in phosphate buffer pH 7.4 at 200 nm to 400 nm. The drug content of each sample was estimated using standard calibration curve of PGB in phosphate buffer pH 7.4. During dissolution studies, PGB exhibited good absorption at 210 nm by using phosphate buffer pH 7.4 as a dissolution media. All results were represented as a mean ± SD [15].

Dissolution Study: The *in-vitro* dissolution studies were carried out in USP type II apparatus (Lab India DS8000^{+}) at 50 rpm using simulated gastric fluid as dissolution medium (900 mL) maintained at 37 ± 0.5 °C. Drug release at different time interval was measured by UV - visible spectrophotometer at 210 nm. The release studies were conducted on six tablets in each batch; results were represented as a mean ± SD.

Drug Release Kinetics: [16] *In-vitro* PGB release data was used to establish release kinetics by constructing graphs for different kinetic models, like cumulative quantity of drug released *vs* time **Eq. 2** for zero order, log cumulative % drug remaining *vs* time **Eq. 3** for first order and log cumulative % drug released *vs* time in square root **Eq. 4** for Higuchi's release model.

$$C = k_o t \quad ....(2)$$

Within equation, time 't' expressed in hours and zero order release rate constant 'k_0' (concentration / unit time), slope of straight line for the curve concentration *vs* time which intercepts axes at the origin.

$$\text{Log } C = \log C_o - k_t / 2.303 \quad ....(3)$$

Within equation, first order release rate constant 'k', initial drug concentration C_0 and time 't'.

$$Q = k_t^{1/2} \quad ....(4)$$

Within equation, Constant for Higuchi's release model 'k' as design variable and time 't' expressed in hours.

Curve Fitting of Release Profile: [17] To evaluate the mechanism of drug release from PGB sustained release tablet, data for the drug release were plotted in Korsmeyer *et al.,* equation **Eq. 5** as log cumulative percentage of drug released *vs* log time, and the exponent n was calculated through the slope of the straight line.

$$M_t / M_\infty = k_t^n \quad ....(5)$$

Within equation, fraction of PGB released was M_t / M_∞ at release time 't', the distinctive drug-polymer system kinetic constant 'k' where as the exponent 'n' specifies the drug release mechanism. Based on the values of 'n' from Korsmeyer - Peppas equation, circular cylinder shape matrix tablets can follow release mechanisms; quasi fickian diffusion for $n < 0.5$; fickian diffusion for $n = 0.5$; freakish diffusion for $0.5 < n < 1$. The symbolic value $n = 1$ provides case-II transport or classical zero order transport; non fickian super case II if $n > 1$. The overall curve-fitting analysis was performed with the help of 'GraphPad Prism' software version 3.06 and 'Microsoft Excel' software version MS Office 2007.

Bilayer Buoyant Tablet of TH and PGB: Development of bilayer buoyant tablet was carried in two different stages, blends of immediate release layer of TH and sustained release buoyant layer of PGB were prepared separately and after optimization of individual layer, the bilayer tablet was prepared using selected formulas. Optimized batch of TH (F7) and PGB (S4) was selected for formulation of bilayer tablet and were compressed using 10 mm round flat faced punch of the single punch tablet compression machine (CADMAC, Ahmedabad India). First the granules of buoyant 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 6-8 kg/cm^2, measured using monsanto hardness tester [17 - 21].

Evaluation for Bilayer Buoyant Tablet of TH and PGB: As per standard methods bilayer tablets of TH and PGB were characterize for appearance, tablet thickness, weight variation, hardness, friability, BLT and TBT. Uniformity of content for two drugs TH and PGB was determined independently for each layer through splitting the powder of bilayer tablet.

Dissolution Study: The *in-vitro* dissolution studies were carried out in USP type II apparatus (Lab India DS8000^{+}) at 50 rpm using simulated gastric fluid as dissolution medium (900 mL) maintained at 37 ± 0.5 °C. The drug release at different time intervals was measured by UV - visible spectrophotometer at 273 and 210 nm for TH and PGB respectively. The release studies were conducted on six tablets, and the mean values were plotted versus time with SD.

RESULT AND DISCUSSION:

Drug - Excipients Interaction Study: Fourier Transform Infrared spectroscopy (FT-IR) investigation spectra for TH, PGB and the polymer mix exhibited relevant characteristic prominent peaks for respective drugs showing no interaction indicating overall compatibility of drugs with the excipients. Differential Scanning Calorimetry (DSC) thermograms for TH, PGB, IR layer composition, SR layer composition exhibited no interaction, the distinctive melting points observed for TH at 184 °C and for PGB at 195 °C and no evident melting point changes were noted indicating overall compatibility.

Powder Characterization: Various powder attributes like density (LBD and TBD), angle of repose, Hausner's ratio and compressibility index for all batches of IR blend containing TH **Table 4** and SR blend containing PGB **Table 5** exhibited excellent characteristics. Angle of repose (25.33-35.10) and Hausner's ratio < 1.07 for all batches indicated good flow properties.

TABLE 4: PRECOMPRESSION PARAMETERS FOR TH BLEND

Batch	AR	LBD g/mL	TBD g/mL	CI (%)	HR
F1	31.15	0.52	0.57	08.77	1.09
F2	28.42	0.54	0.58	06.89	1.07
F3	25.33	0.50	0.55	09.09	1.10
F4	27.50	0.48	0.54	11.11	1.12
F5	30.17	0.46	0.52	11.53	1.13
F6	27.45	0.50	0.54	07.41	1.08
F7	28.20	0.45	0.49	08.16	1.09
F8	28.50	0.44	0.48	08.33	1.09

AR: Angle of Repose, CI: Compressibility index, HR: Hausner's Ratio

TABLE 5: PRECOMPRESSION PARAMETERS FOR PGB BLEND

Batch	AR	LBD g/mL	TBD g/mL	CI (%)	HR
S1	32.15	0.38	0.46	17.39	1.21
S2	35.10	0.42	0.50	16.00	1.19
S3	28.40	0.45	0.51	11.76	1.13
S4	32.35	0.43	0.52	17.30	1.20
S5	28.60	0.53	0.62	14.52	1.17
S6	26.50	0.43	0.51	15.68	1.18
S7	30.25	0.46	0.57	19.29	1.23
S8	29.58	0.49	0.58	15.51	1.18

AR: Angle of Repose, CI: Compressibility index, HR: Hausner's Ratio

Evaluation of Tablets: All tablets appeared smooth flat circular; different characteristics like tablet thickness, tablet weight variation, crushing strengths (hardness), tablet friability, tablet disintegration time, drug content, BLT and TBT was represented for TH tablet formulations **Table 6** and PGB tablet formulations **Table 7**. All TH tablet formulations and PGB tablet formulations qualifies, tablet weight variation test as found variation 100 ± 5% within range; friability below 1%; drug content 90 - 110% within limit and deviation in thickness found less than 5%.

TABLE 6: EVALUATION PARAMETERS OF TH TABLET

Batch	Weight* (mg)	Thickness* (mm)	Hardness* (Kg/cm^2)	Friability# (%)	Disintegration time* (Sec)	Drug content* (%)
F1	158.0 ± 1.72	2.27	4.5 ± 0.17	0.68	115 ± 22.10	099.7 ± 0.93
F2	150.5 ± 1.20	2.25	4.4 ± 0.26	0.56	096 ± 14.22	100.2 ± 0.89
F3	159.5 ± 1.67	2.30	5.0 ± 0.24	0.38	075 ± 31.43	100.5 ± 1.15
F4	152.1 ± 1.50	2.31	4.7 ± 0.12	0.50	078 ± 10.57	098.7 ± 2.00
F5	150.4 ± 1.25	2.25	5.2 ± 0.27	0.54	108 ± 08.70	101.5 ± 1.65
F6	150.6 ± 1.38	2.27	5.4 ± 0.32	0.42	080 ± 13.22	100.0 ± 1.52
F7	155.8 ± 1.55	2.27	4.7 ± 0.20	0.78	054 ± 12.41	099.8 ± 1.18
F8	151.4 ± 1.15	2.29	4.6 ± 0.20	0.68	062 ± 10.32	100.4 ± 0.88

* Readings expressed in mean ± SD for three measurements

Readings expressed for single measurement

TABLE 7: EVALUATION PARAMETERS OF PGB TABLET

Batch	Weight* (mg)	Thickness* (mm)	Hardness* (Kg/cm^2)	Friability# (%)	Drug content* (%)	BLT (sec)*	*Y4* TBT (hrs)*
S1	425.0 ± 1.54	3.12	6.7 ± 0.33	0.68	100.6 ± 1.64	41	9.47
S2	427.5 ± 1.24	3.16	6.4 ± 0.31	0.54	098.8 ± 1.17	38	10.66
S3	422.5 ± 1.05	3.18	6.2 ± 0.35	0.57	100.4 ± 0.87	42	16.50
S4	428.1 ± 0.99	3.19	6.0 ± 0.20	0.61	099.7 ± 0.99	47	22.18
S5	418.4 ± 1.38	3.13	6.5 ± 0.26	0.53	101.1 ± 1.82	36	10.05
S6	426.6 ± 1.63	3.15	6.7 ± 0.28	0.46	100.3 ± 0.77	40	11.53
S7	429.8 ± 1.53	3.17	6.2 ± 0.24	0.80	100.5 ± 1.16	43	19.58
S8	425.9 ± 1.62	3.18	5.8 ± 0.22	0.68	099.9 ± 2.10	42	23.45

BLT: Buoyancy lag time, TBT: Total buoyancy time

* Readings expressed in mean ± SD for three measurements, # Readings expressed for single measurement

Disintegration and Dissolution Study of TH Tablet: Disintegration efficiency of disintegrants like CCS and SSG was comparatively investigated. Wetting time for tablet containing CCS was found minimum (12 sec) as compared to tablets containing SSG, Higher capability of absorbing water and swelling of CCS provides faster disintegration of batch F7 (054 ± 12.41 s), consequently selected as best composition of TH layer to prepare bilayer tablet. Disintegration time for all the batches was represented in **Fig. 1**.

In-vitro drug release at 1, 3, 5, 10, 15, 20 and 30 min for all the batches is shown as cumulative % drug released *vs* time graph **Fig. 2**. The release of TH was dependent on its concentration in the IR tablet formulation and therefore followed first-order release kinetics.

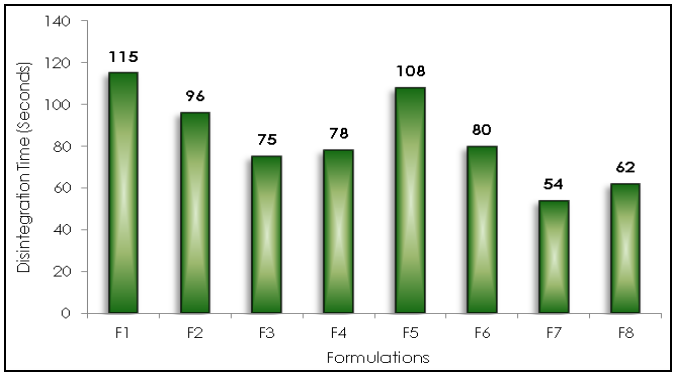

FIG. 1: DISINTEGRATION TIME OF TH IMMEDIATE RELEASE TABLET FORMULATIONS

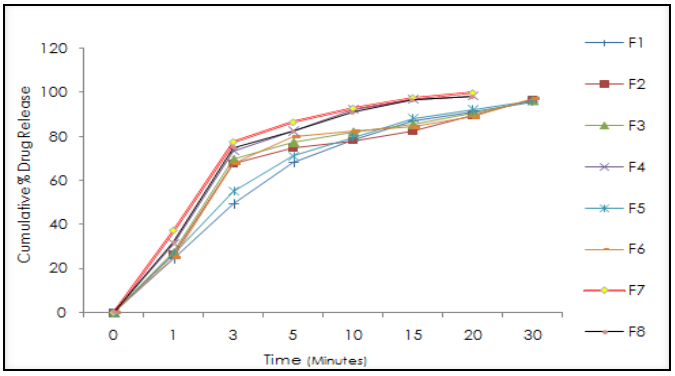

FIG. 2: *IN-VITRO* DRUG RELEASE PROFILE OF TH IMMEDIATE RELEASE TABLET FORMULATIONS

Dissolution Study of PGB Tablet: Pregabalin is almost completely absorbed throughout GIT, follows a linear pharmacokinetic profile [4] and renal excretion is the predominant mechanism of its elimination from the body. If PGB is developed as sustained release gastroretentive dosage form, its effectiveness in neuropathic pain management can be increased by prolonging duration of action. Formulation of sustained release buoyant tablet dosage form was based on two level (2^3) factorial experimental design; proportion of polymer content-to-drug content was studied as important control variable because of its influences on release of PGB through the hydrophilic matrices, formed from hydrocolloid polymeric system made up of HPMC grades (K100M and K4M) combined with SCMC which slows down the drug release.

Throughout the experiments concentrations of matrix forming agents were increased; polymers absorb water, hydrogel layer forms around the tablet that regulates the release of drug molecules. 25% w/w sodium bicarbonate based gas generating system used in the hydrophilic matrices produced excellent buoyancy by librating CO_2 to prolong gastrointestinal residence for the tablets. Swelling index for all the batches was represented in **Fig. 3**.

Important components of the buoyant layer for drug release were different viscosity grades and proportion of HPMC with SCMC. Formulation batch S1 and S5 comprising of lowest amount of polymers not able to hold the drug release, apparently attributed to poor strength and lose structure of matrix where as formulation batches

S2, S3, S6 and S7 exhibited 98% drug release over 12 hours. Formulation batch S4 and S8 comprising of high amount of polymers showed slower release rate and dissolution over extended time period, refers to excellent strength and dense structure of hydrophilic matrix. Drug release profiles for the buoyant PGB tablet formulations of 2^3 factorial designs were expressed in **Fig. 4**. The dissolution data were processed as per Korsmeyer *et al.*, model **Eq. 5**, constructed curves for log cumulative % drug release *vs* log of time, shown good linearity providing diffusion exponents 0.36 to 0.55 **Table 8**. The mechanism of PGB release from the buoyant SR tablet formulation followed Fickian transport.

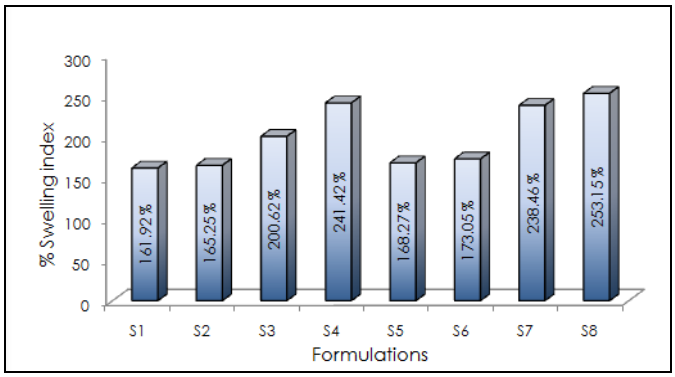

FIG. 3: % SWELLING INDEX OF PGB BUOYANT SR TABLET FORMULATIONS

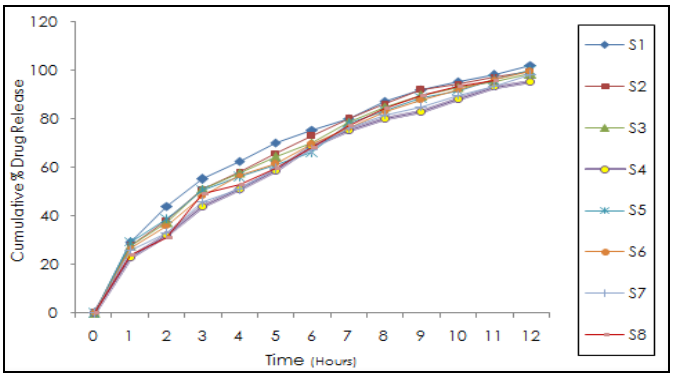

FIG. 4: *IN-VITRO* DRUG RELEASE PROFILE OF PGB BUOYANT SR TABLET FORMULATIONS

TABLE 8: CURVE-FITTING DATA OF RELEASE RATE PROFILE BY FACTORIAL DESIGN

Batch	*Y1* PGB Discharge at 12 Hrs (%)	*Y2* T 50% (hours)	*Y3* Diffusion Coefficient (n)	R^2
S1	102.22	1.96	0.38	0.99
S2	99.70	2.03	0.36	0.96
S3	98.54	2.38	0.43	0.93
S4	95.28	3.31	0.54	0.98
S5	99.92	2.14	0.39	0.94
S6	99.50	2.79	0.41	0.98
S7	98.14	2.90	0.39	0.95
S8	96.37	3.22	0.55	0.97

Statistical Analysis and Optimization for PGB Tablets: The experimental results were processed using statistical analysis to get response variables by 'Design-Expert' Software (Version 7.0.0) [Stat-Ease Inc., Minneapolis, Minnesota (USA)]. The design was evaluated using factorial linear interactive first-order model **Eq. 6**. Each expression of the coefficients within the regression model was abbreviated in **Table 9.**

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 \quad .....(6)$$

Optimization of process was made to get reactions Y1, Y2, Y3 and Y4 through incepted polynomial equations. The selected formulation was arrived through optimizing amount of PGB release at 12 hours; increasing buoyancy time and T_{50} % to find the preferred quantities of total polymer-to-drug proportion (X1), polymer-to-polymer proportion (X2) and polymer grade (X3). Surface response plot for dependent variables PGB release at 12 hours (Y1); **Fig. 5**, T_{50}% (Y2); **Fig. 6** and buoyancy time (Y4); **Fig. 7** demonstrated the relationship with controlled variables.

Findings of the optimization process indicated ideal experimental set up; (2:1) proportion of total polymer content-to-drug content and polymer-to-polymer proportion (3:1) whereas HPMC (K100M and K4M) polymer viscosity grades did not significantly affect the performance of the tablet dosage form.

TABLE 9: REGRESSION EQUATIONS FOR THE RESPONSES

$Y_1 = 98.72 - 1.63X_1 - 1X_2 - 0.22X_3 - 0.25X_1X_2 + 0.39X_1X_3 + 0.44X_2X_3$
$Y_2 = 2.59 + 0.36X_1 + 0.25X_2 + 0.17X_3 - 0.066X_1X_2 - 0.064X_1X_3$
$Y_3 = 0.43 + 0.046X_1 + 0.034X_2 + 0.034X_1X_2 + 0.011X_2X_3$
$Y_4 = 15.43 + 5X_1 + 1.53X_2 + 0.72X_3 + 0.86X_1X_2 + 0.36X_1X_3$

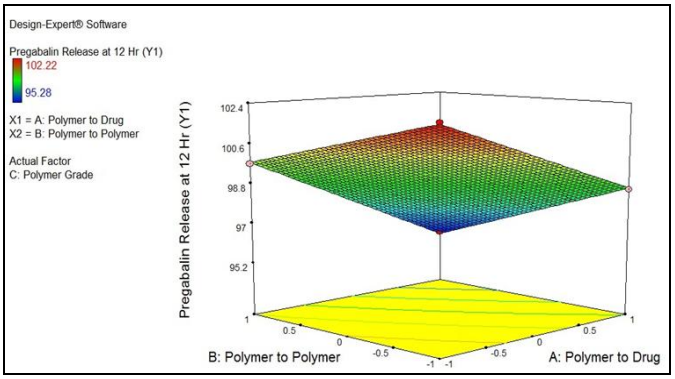

FIG. 5: SURFACE RESPONSE PLOT (3D) DEMONSTRATING INFLUENCE OF POLYMER CONTENT-TO-DRUG PROPORTION (X1) AND POLYMER-TO-POLYMER PROPORTION (X2) ON PERCENTAGE OF PGB RELEASE AT 12 h (Y1)

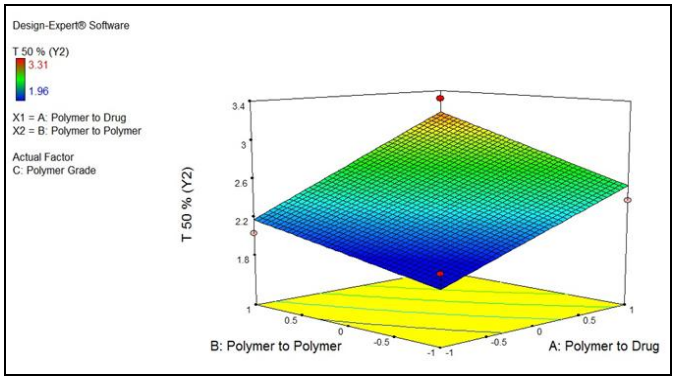

FIG. 6: SURFACE RESPONSE PLOT (3D) DEMONSTRATING INFLUENCE OF POLYMER CONTENT-TO-DRUG PROPORTION (X1) AND POLYMER-TO-POLYMER PROPORTION (X2) ON T_{50}% (h) (Y2)

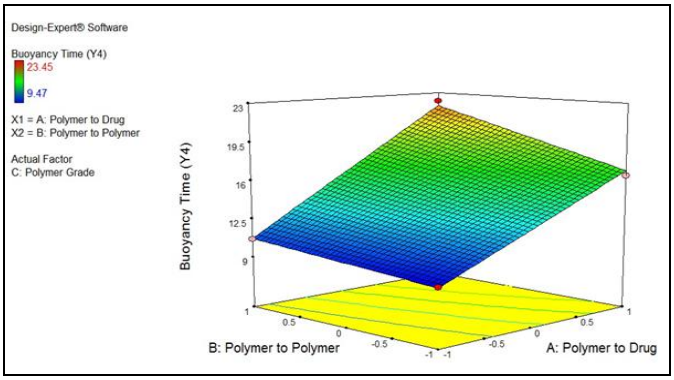

FIG. 7: SURFACE RESPONSE PLOT (3D) - INFLUENCE OF POLYMER CONTENT-TO-DRUG PROPORTION (X1) AND POLYMER-TO-POLYMER PROPORTION (X2) ON BUOYANCY TIME (Y4)

Evaluation of Bilayer Tablet of TH and PGB: Different attributes of bilayer tablets were investigated; tablet appears smooth flat circular in distinctive two layers and deviation in thickness found less than 5%.

Average weight of bilayer tablet was found (577.50 mg) and weight variation (5%) within limit. Found friability (0.48%) below 1%; drug content 90 - 110% within limit, (103.8 ± 0.94 for TH and 101.3 ± 0.48 for PGB) and 6.68 in kg/cm^2 tablet crushing strength (hardness).

Dissolution Study: *In-vitro* drug release study for bilayer tablet, TH layer was indicated 97.54 % drug release within 15 min where as PGB layer exhibited slow sustained drug release, during 12 h dissolution study 94.17 % drug was released. *In-vitro* drug release profile was constructed for tramadol **Fig. 8** and pregabalin **Fig. 9**.

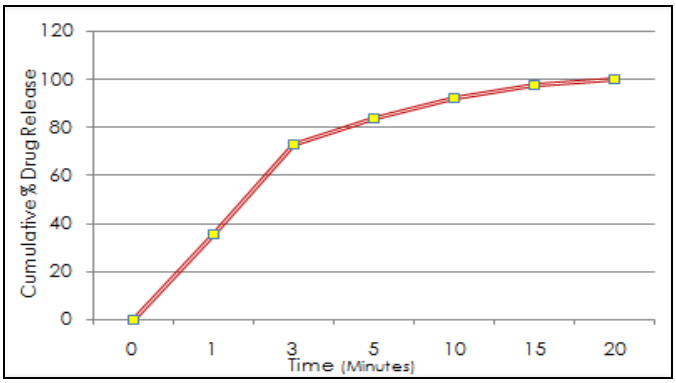

FIG. 8: *IN-VITRO* DRUG RELEASE PROFILE OF TRAMADOL IR LAYER

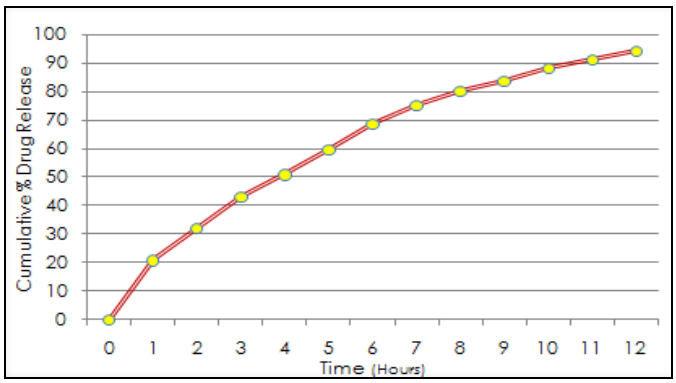

FIG. 9: *IN-VITRO* DRUG RELEASE PROFILE OF PREGABALIN BUOYANT SR LAYER

CONCLUSION: Developed bilayer buoyant tablet will provide immediate pain relief by releasing TH within 30 min and suppressing burning-fire pain stimulation of nerves for longer duration through sustained release of PGB with once a day administration of bilayer tablet. Available medication options together with modern dosage form technology can provide excellent therapeutic result to overcome the painful condition and improve the quality of life for an individual suffering from neuropathic pain.

ACKNOWLEDGEMENT: Authors are especially grateful to Wockhardt Pvt. Ltd., Aurangabad (MS) India, owing to their contribution for sending Tramadol and Pregabalin as gift samples. Authors are sincerely thankful to Director, School of Pharmacy, SRTMU, Nanded (MS) India, and Principal, Anuradha College of Pharmacy, Chikhli, Dist. Buldhana (MS) India, for valuable support and providing research facilities in their laboratories to carry out this work.

CONFLICT OF INTEREST: The authors have reported no potential conflicts of interest in this work.

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How to cite this article:
Kamble S and Poul B: Development and characterization of bilayer tablet containing tramadol and pregabalin as a gastric buoyant drug delivery system for combination pharmacotherapy of neuropathic pain. Int J Pharm Sci & Res 2018; 9(7): 2832-41. doi: 10.13040/IJPSR. 0975-8232.9(7).2832-41.