ORIGINAL ARTICLE

Fabrication and Evaluation of Bilayer Floating Tablet Containing Conventional Ibuprofen and Modified Release Pregabalin for Combination Pharmacotherapy of Neuropathic Pain

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Abstract

Aim: The objective of proposed study was to prepare bilayer floating tablet comprising ibuprofen (IB) and pregabalin (PGB) for effective treatment of neuropathic pain. **Materials and Methods:** IB was formulated as immediate release (IR) layer using disintegrants such as croscarmellose sodium (CCS) and sodium starch glycolate (SSG) whereas PGB was formulated as sustained release (SR) layer using polymers hydroxypropyl methylcellulose (HPMC) K100M, HPMC K4M, sodium alginate and for increasing gastric residence time sodium bicarbonate as gas generating agent, with a view to deliver the drug at sustained manner in gastrointestinal tract and consequently into systemic circulation. Tablet blends were evaluated through various pre-compression tests, compressed by wet granulation method and evaluated. **Results and Discussion:** As fast disintegrant, SSG at 20% concentration produced excellent results by immediately releasing IB to exert its anti-inflammatory analgesic and other additional beneficial effects. K100M grade of HPMC produced excellent SR efficiency at 1:1 drug-polymer ratio whereas sodium bicarbonate based CO_2 gas generating system provides required extended gastric retention of the dosage form for long-lasting effect of the therapeutic agent. Final formulation released 96% drug in 15 min and 98% drug in 24 h, *in vitro* from respective layers. **Conclusion:** Pre-compression and post-compression parameters of optimized IR layer comprising IB and floating SR layer comprising PGB exhibit satisfactory results. Bilayer tablet of IB and PGB may prove to be very effective as a combination therapy for the treatment of neuropathic pain by sequential release of the drug.

Key words: Bilayer floating tablet, ibuprofen, neuropathic pain, pregabalin

INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. In recent years, a growing interest has been developed in designing drug delivery systems that include an immediate release (IR) component to sustained release (SR) dosages. The bilayered tablet is innovative drug delivery system comprising two layers, i.e. IR and controlled release were the choice of the dosage form to control the delivery the rate of either single or two different API's and to administer fixed dose combinations of different drugs.[1]

The term bilayered tablets refer to tablet containing subunits that may be either same or different and are preferred when the release profiles of the drugs are different from one another.[2] Bilayered tablets allow for designing and modulating the dissolution and release characteristics and they are prepared

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with one layer of drug for IR while the second layer designed to release drug latter, either as the second dose or sustained or controlled release manner to reduce the frequency of the dosing and to increase the effectiveness of drug by reducing the dose required; providing uniform drug delivery, avoiding chemical incompatibility.[3]

This is novel type of smart and advanced drug delivery system in the form of bilayer floating tablet used for oral administration of ibuprofen (IB) as IR, and pregabalin (PGB) as SR for effective treatment of neuropathy by combination therapy. Neuropathy a disease of nerve is the common cause of pain in many patients. Chronic neuropathic pain is the most disturbing symptom of lesions in the peripheral nervous system that can be of many forms and due to various reasons. Combination therapy using low dosage of two different agents seems to be very effective and beneficial over mono therapy in such situations as problems of dose-dependent side effects was minimized. A low dose combination of two different agents reduces the dose related risk; that occur with maximal dosage of individual component of the combined tablet, and thus dosage of the single component can be reduced. The addition of one agent may improve the effects of the other.[4]

IB, 2-(4-isobutyl-phenyl)-propionic acid, is one of the non steroidal anti-inflammatory agent with analgesic and antipyretic properties. The anti-inflammatory effects of IB and most of its other pharmacological effects are generally thought to be related to its inhibition of cyclooxygenase (COX) and consequent decrease in prostaglandin concentration. It also has some COX-independent actions beneficial for neuropathy such as the inhibition of RhoA signaling and the modulation of the glial activity due to this it can be used in neural injuries to promote axonal regeneration and to increase functional recovery.[5,6]

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 depolarization induced calcium influx at nerve terminals with a consequential reduction in the release of excitatory neurotransmitters. In addition to epilepsy, it has demonstrated excellent efficacy for the treatment of neuropathic pain and generalized anxiety disorder.[7]

MATERIALS AND METHODS

Materials

IB and PGB were obtained as a gift sample from Leben Laboratories Pvt., Ltd, Akola and Wockhardt Pvt. Ltd., Aurangabad, respectively. Hydroxypropyl methylcellulose (HPMC) K100M, HPMC K4M, Sodium alginate, sodium starch glycolate (SSG), croscarmellose sodium, microcrystalline cellulose, lactose, polyvinylpyrrolidone K30 (PVP K30), isopropyl alcohol, magnesium stearate, talcum, was purchased from local authorized dealer. All other reagents and chemicals used were of analytical reagent grade.

Methods

Powder characterization

Angle of repose

The angle of repose, the maximum slope or angle, measured in degrees from the horizontal, at which loose solid material will remain in place without sliding, was determined using fixed funnel method. The accurately weighed drug powder or its physical mixture was used. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The height (h) and radius (r) of the powder cone was measured, and angle of repose was calculated by following formula.[8]

$$\text{Angle of repose}(\theta) = \tan^{-1}\left(\frac{h}{r}\right) \quad (1)$$

Moisture sorption capacity

All disintegrants have capacity to absorb moisture from the atmosphere which affects moisture sensitive drugs. Moisture sorption capacity was performed by taking 1 g of disintegrant uniformly distributed in petri dish and kept instability chamber (Programmable environmental test chamber, Remi) at 37°C ± 1°C and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by the difference between weights.[8]

Density

Loose bulk density (LBD): Apparent bulk density was determined by placing the drug excipients blend after sieving into a graduated cylinder and measuring the volume and weight as it is. LBD was determined using following formula.[9]

$$\text{Loose bulk density} = \frac{\text{Weight of the powder mass}}{\text{Volume of the packing}} \quad (2)$$

Tapped bulk density (TBD): Weighed sample of powder mixture was transferred to a graduated cylinder and was tapped for a fixed time or for a fixed number of taps (100) using a digital tap density apparatus (Electro lab Ltd, India). The tapped density was determined by using the following formula.[10]

$$\text{Tapped bulk density} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}} \quad (3)$$

Compressibility index

Based on the bulk density and the tapped density, the percentage compressibility Carr's compressibility index (%) of the powder mixture was determined by the following formula.[9]

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped bulk density} - \text{Loose bulk density}}{\text{Tapped bulk density}} \quad (4)$$

Hausner's ratio

Hausner ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula.[10]

$$\text{Hausner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose bulk density}} \quad (5)$$

Swelling studies

The extent of swelling was measured regarding % of weight gained by the tablet. One tablet from each formulation was weighed and kept in petri dish containing 50 ml of 0.1N HCl solution. At the end of specified time, intervals tablets were withdrawn from petri dish and excess buffer blotted with tissue paper and weighed. The % of weight gained (swelling index), and hydration capacity of the tablet was calculated using following formulas.[10]

$$\text{Swelling index}(\%) = \left(\frac{M_t - M_0}{M_0}\right) \times 100 \quad (6)$$

Where, M_t - weight of tablets at time "t"; M_0 - weight of tablets at time "0"

$$\text{Hydration capacity} = \frac{\text{Weight of hydrated sample}}{\text{Weight of dry sample}} \quad (7)$$

Drug–excipient interaction study[11]

The compatibility of drug and polymer under the experimental conditions is an important pre-requisite, and it is, therefore, necessary to confirm that the drug does not react with excipients. The studies were carried out using Fourier transform infrared (FT-IR) spectroscopy and differential scanning calorimetry (DSC).

FT-IR spectroscopy

To investigate any possible interaction between the IB, PGB, and the polymer under investigation, FT-IR spectrophotometer method was used. Samples of pure drug IB, PGB, and IR layer and SR layer were differently crushed with KBr to make KBr pallets for the IR spectra using Shimadzu IR Affinity-1S FTIR spectrometer (Shimadzu, Japan).

DSC

The DSC thermograms of IB, PGB, IR layer, and SR layer were performed using DSC (Perkin Elmer Cyris-DSC). Indium was used as standard to calibrate the DSC temperature and enthalpy scale. The sample was hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min over a temperature range of 50-200°C.

Preparation of IR tablets of IB

IR granules containing IB, croscarmellose sodium (CCS), and SSG were mixed with other excipient for 15 min in porcelain mortar except talk and magnesium stearate, and the mass was prepared using water as a granulating fluid. The wet mass was passed through 10 # sieve, and granules were allowed to dry in oven at 50°C for 30 min. Dried granules were screened through 14 # sieve, 10% fine was added into it and mixed with talk and magnesium stearate for 5 min and processed for compression using 10 mm round flat-faced punches of single punch tablet machine (CADMAC, Ahmedabad, India). The composition of all batches was represented in Table 1. Before the compression; granules were evaluated for several precompression parameters.

Precompression parameters - evaluation of IB blend

The IB blends (Granules) of all batches were evaluated for angle of repose, density, compressibility index, and Hausner's ratio as per the reported methods described above.

Evaluation of IB tablet

Tablets were evaluated for weight variation, friability, hardness; thickness and was performed according to the Indian Pharmacopoeia 2007.[12]

Drug content

20 tablets were weighed and powdered, and 200 mg equivalent weight of IB was accurately weighed, transferred into a 100 mL volumetric flask and dissolved in phosphate buffer pH 7.4, volume was made up to the mark. The solution in volumetric flask was filtered, and suitable dilutions were made and analyzed at 223 nm on UV-visible spectrophotometer

Table 1: Composition of IB immediate release tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
IB	200	200	200	200	200	200	200	200	200
MCC	30	30	30	30	30	30	30	30	30
CCS	15	30	45	60	-	-	-	-	30
SSG	-	-	-	-	15	30	45	60	30
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Lactose	QS	QS	QS	QS	QS	QS	QS	QS	QS

IB: Ibuprofen, MCC: Microcrystalline cellulose, CCS: Croscarmellose sodium, SSG: Sodium starch glycolate. Values represented in mg, total weight 300 mg per tablet

(Shimadzu UV-1601). Maximum absorbance (λmax) for IB was determined UV spectrophotometrically by scanning dilute IB solution in phosphate buffer pH 7.4 at 200-400. The drug content of each sample was estimated using standard calibration curve of IB in phosphate buffer pH 7.4. During dissolution studies, IB exhibited good absorption at 223 nm using phosphate buffer pH 7.4 as a dissolution media.[13,14]

Disintegration test

Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed without disc in simulated gastric fluid at 37°C ± 0.5°C temperature using the United States Pharmacopcia (USP) disintegration test apparatus. The mean ± standard deviation (SD) of six tablets was calculated.[9]

Dissolution test

Dissolution test of IB tablet was performed in simulated gastric fluid as dissolution medium using USP dissolution test apparatus II at 50 rpm and 37°C ± 0.5°C temperature. Test sample (5 mL) was withdrawn at a specific time intervals (1, 3, 5, 10, 15, 20, and 30 min) and replaced with fresh dissolution media maintained at 37°C ± 0.5°C. The test sample was filtered (membrane filter, 0.45 µm), and the concentration of dissolved drug was determined using ultraviolet (UV) spectrophotometer at λmax 223 nm. This test was performed on six tablets and mean ± SD calculated.

Preparation of floating SR tablets of PGB

The floating SR granules were prepared by wet granulation technique. Required quantity of PGB, and polymers (HPMC K4M, HPMC K100M, and Sodium alginate), gas generating agent (sodium bicarbonate), and acidifying agent (citric acid) was weighed and passed through sieve #40 and were mixed homogeneously in a poly bag for about 5-10 min and was taken in a mortar. To the mortar 5%, PVP K30 in isopropyl alcohol was added as granulating agent. The wet mass was passed through sieve #10 and dried in hot air oven at 50°C for 30 min; dried granules were screened through sieve #14. Finally, 10% fine was added to well form granules and was lubricated with magnesium stearate and talc for 5 min. The granules were processed for compression using 10 mm round flat faced punches of single punch tablet machine (CADMAC, Ahmadabad, India) Formulation compositions of all batches are given in Table 2. Before the compression; granules were evaluated for several precompression parameters.

Precompression parameters - evaluation of PGB blend

The PGB blends (Granules) of all batches were evaluated for angle of repose, bulk density (TBD, LBD), compressibility index, and Hausner's ratio as per the reported methods described above.

Evaluation of floating PGB tablets

Tablet hardness, weight variation, thickness, and friability were measured using the USP methods. It has been reported that PGB can be detected UV spectrophotometrically at 210 nm.

Buoyancy lag time (BLT) and total floating time (TFT)

BLT is the time required for a tablet to float over the gastric fluid, the *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. The time required for the tablet to rise to the surface for floating was determined as the BLT, and further TFT of all tablets was determined by visual observation.[11]

Drug content

Twenty tablets were weighed, triturated to powder, and 150 mg accurately weighed equivalent weight of PGB was transferred into a 100 mL volumetric flask, dissolved in phosphate buffer pH 7.4; volume was made up to the mark. The solution in the volumetric flask was filtered through 0.45 µm membrane

Table 2: Composition of PGB SR tablet

Ingredients	S1	S2	S3	S4	S5	S6	S7	S8	S9
PGB	150	150	150	150	150	150	150	150	150
HPMC K4M	50	100	150	-	-	-	-	-	
HPMC K100M	-	-	-	50	100	150	-	-	-
Sodium alginate	-	-	-	-	-	-	50	100	150
Sodium bicarbonate	90	90	90	90	90	90	90	90	90
Citric acid	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5	22.5
Talc	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Magnesium Stearate	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25	2.25
PVP K30	QS	QS	QS	QS	QS	QS	QS	QS	QS
Isopropyl alcohol	QS	QS	QS	QS	QS	QS	QS	QS	QS
Lactose	QS	QS	QS	QS	QS	QS	QS	QS	QS

PGB: Pregabalin, HPMC: Hydroxypropyl methylcellulose, PVP K30: Polyvinylpyrrolidone K30. Values represented in mg, total weight 450 mg per tablet, SR: Sustained release

filter and suitable dilutions were made and analyzed at 210 nm on UV-visible spectrophotometer (Shimadzu UV-1601). 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 using phosphate buffer pH 7.4 as a dissolution media. All results were represented as a mean ± SD.[15]

Dissolution studies

The *in vitro* dissolution studies were carried out in two phases using USP type II apparatus at 50 rpm. The dissolution medium (900 mL) comprising simulated gastric fluid (pH 1.2 HCl buffer) was used for the first 2 h in gastric phase and then replaced with phosphate buffer pH 7.4 for 3-24 h (900 mL) for intestinal phase, maintained at 37°C ± 0.5°C. The 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]

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: Zero order (Equation 8) as cumulative amount of drug released versus time, first order (Equation 9) as log cumulative percentage of drug remaining versus time, and Higuchi's model (Equation 10) as cumulative percentage of drug released versus square root of time.

$$C=K_0t \quad (8)$$

where "K_0" is the zero order rate constant expressed in units of concentration/time and "t" is the time in hours. A graph of concentration versus time would yield a straight line with a slope equal to "K_0" and intercept the origin of the axes.

$$\text{Log } C=\text{Log } C_0-K_t/2.303 \quad (9)$$

Where "C_0" is the initial concentration of drug, "K" is the first order constant, and "t" is the time.

$$Q = K_{t^{1/2}} \quad (10)$$

Where "K" is the constant reflecting the design variables of the system and "t" is the time in hours.

Mechanism of drug release[16]

To evaluate the mechanism of drug release from PGB SR tablet, data for the drug release were plotted in Korsmeyer *et al.'s* Equation (11) as log cumulative percentage of drug released versus log time, and the exponent n was calculated through the slope of the straight line.

$$M_t/M_\infty = K_{t^n} \quad (11)$$

Where M_t/M_∞ is the fractional solute release, "t" is the release time, "K" is a kinetic constant characteristic of the drug/polymer system, and "n" is an exponent that characterizes the mechanism of release of drug. For cylindrical matrix tablets, if the exponent $n < 0.5$, then the drug release mechanism is quasi Fickian diffusion, if $n = 0.5$ then Fickian diffusion, $0.5 < n < 1$, then it is anomalous diffusion. An exponent value of 1 is indicative of case II transport or typical zero order and $n > 1$ non-Fickian super case II. The diffusion exponent is based on Korsmeyer–Peppas equation.

Bilayer floating tablets of IB and PGB

Development of bilayer floating tablets was carried in two different stages, blends of IR layer of IB, and SR floating layer of PGB were prepared separately and after optimization of individual layer, the bilayer tablets were prepared using selected formulas. Optimized batch of IB (F8) and PGB (S6) was selected for formulation of bilayer tablet and was compressed using 12 mm round flat faced punch of the single punch CADMAC, Ahmedabad India; tablet compression machine. First, the granules of floating SR layer were poured in the die cavity and compressed with moderate force. Then, the upper punch was lifted, and the IR granules were poured in the die cavity, containing initially compressed SR layer, and compressed with full force to form bilayer tablet with hardness of 5-7 kg/cm^2. The hardness was kept constant for all tablets and was measured using Pfizer hardness tester.[17-20]

Evaluation of Bilayer floating tablets of IB and PGB

Bilayer floating tablets were evaluated for weight variation, friability, hardness, thickness, BLT and TFT as per the procedure previously mentioned. Content uniformity of both drugs in bilayer tablet was measured by separating both layer of bilayer tablet and measured individually.

Dissolution test

The *in vitro* dissolution studies were carried out in two phases using USP type II apparatus at 50 rpm. The dissolution medium (900 mL) consisted of simulated gastric fluid (pH 1.2 HCl buffer) was used for the first 2 h in gastric phase and then replaced with phosphate buffer pH 7.4 for 3-24 h (900 mL) for intestinal phase, maintained at 37°C ± 0.5°C. The drug release at different time intervals was measured by UV-visible spectrophotometer at 223 and 210 nm for IB and PGB, respectively. The release studies were conducted on six tablets, and the mean values were plotted versus time with SD.

RESULTS

Powder characterization

Flow property expressed in terms of angle of repose was found in between 27.30 and 31.20 for IB blend and 25.10-34.16 for PGB blend, added flow promoters, and lubricants such as talk and magnesium stearate further increases flow property.

Hydration capacity and swelling index

Disintegration efficiency of disintegrants is compared on the basis of hydration capacity and swelling. Higher hydration capacity (capability of absorbing water) and swelling index of different formulations was expressed in Figure 1.

Drug-excipients interaction study

FT-IR spectroscopy investigation spectra for IB, PGB, and the polymer mix was exhibited relevant characteristic prominent peaks for respective drugs shows no interaction indicating overall compatibility of drugs with the excipients. DSC thermograms of IB, PGB, IR layer, and SR layer demonstrate, there is no change in the melting point of drug (IB = 78°C and PGB = 195°C) indicating no interaction.

Evaluation of IB Blend

Precompression parameters such as angle of repose, LBD, TBD, compressibility index, and Hausner's ratio of all batches of IB for IR was represented in Table 3. Angle of repose (26.70-31.20) and Hausner's ratio <1.2 for all batches indicates good flow properties.

Evaluation of IB Tablet

Tablet properties such as weight variation, thickness, hardness, friability, disintegration time, and drug content were represented in Table 4. All batches pass the weight variation 100% ± 5% within range, friability <1%, drug content 90-110% within limit, thickness variation within 5% limit.

Dissolution study

In vitro drug release at 1, 3, 5, 10, 15, 20, and 30 min for all the batches was expressed by a graph cumulative % drug released versus time. Q1 min, Q3 min, and Q5 min were represented as cumulative % of drug released at 1, 3, and 5 min to establish positive correlation between the maximal water uptake and the cumulative % of drug dissolved. Wetting time for tablet containing SSG was found minimum as compared to tablets containing CCS, fastest disintegration found (58 s) for batch F8, and hence, it was suitable as an IR layer for bilayer tablet [Figure 2].

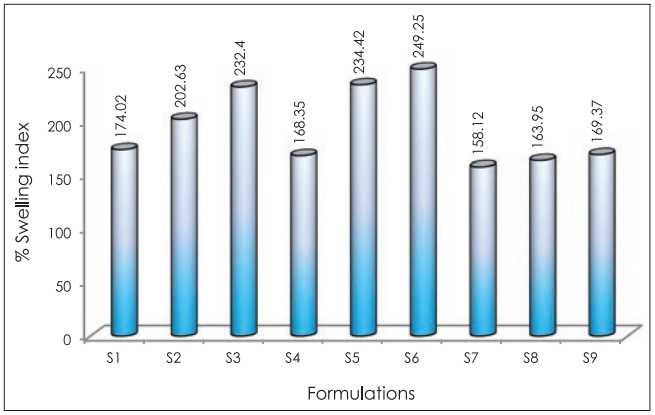

Figure 1: % Swelling index of pregabalin floating sustained release tablet formulations

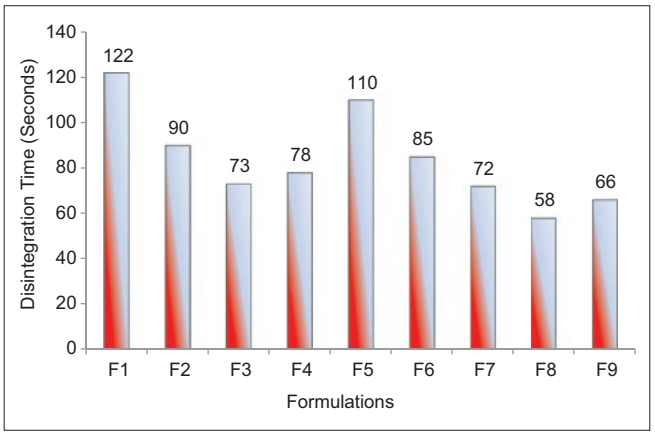

Figure 2: Disintegration time of ibuprofen immediate release tablet formulations

Table 3: Precompression parameters of IB blend

Batch	Angle of repose	LBD g/mL	TBD g/mL	Compressibility index (%)	Hausner's ratio
F1	27.30	0.30	0.35	14.29	1.16
F2	29.50	0.28	0.31	09.68	1.10
F3	29.80	0.32	0.34	05.88	1.06
F4	28.40	0.29	0.33	12.12	1.13
F5	26.70	0.28	0.30	06.67	1.07
F6	31.20	0.29	0.32	09.38	1.10
F7	30.50	0.31	0.34	08.82	1.09
F8	28.90	0.32	0.35	08.57	1.09
F9	28.30	0.28	0.30	06.67	1.07

IB: Ibuprofen, LBD: Loose bulk density, TBD: Tapped bulk density

Evaluation of PGB blend

Precompression parameters for blends of all the batches of PGB, such as angle of repose, LBD, TBD; compressibility index and Hausner's ratio are represented in **Table 5**. The study result demonstrates all batches have good compressibility, angle of repose (25.10-34.16), and Hausner's ratio <1.25 for all batches indicates good flow properties.

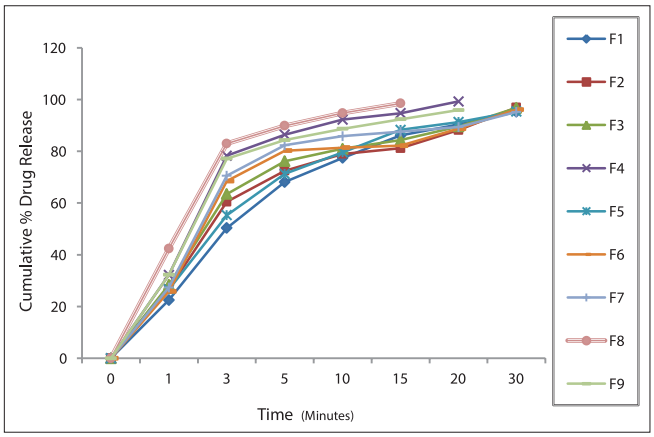

Figure 3: *In vitro* drug release profile of ibuprofen immediate release tablet formulations

Evaluation of PGB tablet

Tablet properties such as weight variation, thickness, hardness, friability, and drug content of each batch were represented in **Table 6**. All batches pass the weight variation test and found to be within range (100% ± 5%). Friability of all batches was found <1%, indicates that tablet surfaces are strong enough to withstand mechanical shock and attrition during transportation or storage until they are used. The hardness of tablet increase as polymer concentration increases and friability also decreases as polymer amount increases. Drug content of all batches was found within limit (90-110%). Thickness variation of tablets <5% was also found within the limit.

BLT and TFT

Gastroretentive nature of a floating tablet was expressed through BLT and TFT; Sodium bicarbonate librates CO_2 in the presence of hydrochloric acid, and the generated gas was trapped and protected within the hydrophilic matrix structure formed by hydration of the polymer; thus, decreasing the density of the tablet below 1 g/ml and the tablet becomes buoyant. The optimized concentration of sodium bicarbonate was found to be 25% of total tablet weight, and it was

Table 4: Evaluation parameters of IB immediate release tablet formulations

Batch	Weight* (mg)	Thickness* (mm)	Hardness* (kg/cm²)	Friability# (%)	Disintegration time* (s)	Drug content* (%)
F1	308.0±1.75	2.66	4.5±0.10	0.64	122±20.30	099.5±0.97
F2	300.5±1.22	2.60	4.7±0.22	0.55	090±11.23	100.4±0.85
F3	299.5±1.67	2.60	5.0±0.00	0.33	073±31.43	100.7±1.20
F4	302.1±1.50	2.64	4.8±0.15	0.53	078±10.57	098.5±2.01
F5	300.4±1.45	2.60	5.2±0.20	0.48	110±08.70	101.2±1.80
F6	300.6±1.38	2.60	5.9±0.25	0.37	085±13.22	100.4±1.52
F7	305.8±1.55	2.64	4.2±0.16	0.77	072±12.41	099.7±1.10
F8	301.4±1.15	2.62	4.8±0.10	0.63	058±10.32	100.2±0.80
F9	300.7±1.00	2.60	5.0±0.21	0.40	066±24.16	099.0±1.30

*Each value represents as mean±SD of three determinations. #Each value represents as singly. SD: Standard deviation, IB: Ibuprofen

Table 5: Precompression parameters of PGB blend

Batch	Angle of repose	LBD g/mL	TBD g/mL	Compressibility index (%)	Hausner's ratio
S1	34.16	0.40	0.49	18.36	1.23
S2	33.20	0.44	0.53	16.98	1.20
S3	26.41	0.47	0.54	12.96	1.15
S4	30.33	0.45	0.54	16.66	1.20
S5	25.67	0.56	0.64	12.50	1.14
S6	28.50	0.47	0.55	14.54	1.17
S7	33.20	0.50	0.61	18.03	1.22
S8	28.50	0.53	0.60	11.66	1.13
S9	25.10	0.48	0.55	12.72	1.15

PGB: Pregabalin, LBD: Loose bulk density, TBD: Tapped bulk density

Table 6: Evaluation parameters of PGB floating sustained release tablet formulations

Batch	Weight* (mg)	Thickness* (mm)	Hardness* (kg/cm²)	Friability# (%)	Drug content* (%)	Floating lag time (s)*	Total floating time (h)*
S1	455.0±1.50	3.22	6.5±0.22	0.63	100.4±1.62	39	25
S2	456.5±1.24	3.22	6.2±0.25	0.49	098.6±1.15	36	26
S3	452.5±1.00	3.20	6.0±0.33	0.48	100.2±0.85	49	30
S4	455.1±0.95	3.32	5.8±0.18	0.56	099.5±0.97	45	25
S5	452.4±1.34	3.20	6.3±0.20	0.48	101.2±1.80	34	27
S6	461.6±1.58	3.30	6.5±0.27	0.41	100.5±0.88	38	33
S7	448.8±1.49	3.20	6.0±0.18	0.86	100.7±1.12	46	22
S8	447.9±1.58	3.20	5.9±0.15	0.63	098.9±2.00	40	24
S9	458.7±1.36	3.32	5.7±0.25	0.55	099.2±1.30	38	27

*Each value represents as mean±SD of three determinations. #Each value represents as singly. SD: Standard deviation, PGB: Pregabalin

maintained constant for all the PGB floating tablets. All floating tablets had BLT in the range of 34-49 s. The TFT was found to be in the range of 22-33 h, indicating a stable hydrophilic matrix gel layer formation by all polymers, and sodium bicarbonate that persists for a longer time. The results of the BLT and TFT for the different floating tablet formulations are given in **Table 6.**

Dissolution study

PGB is freely soluble in water and both basic and acidic aqueous solutions, posses dissociation constant values (pka_1 = 4.2 and pka_2 =10.6); therefore, the release of drug from the tablets was only dependent on the nature of matrix structure formed by the polymer. As polymer concentration increases forming dense network structure that retards the drug release from the tablet. Above all studied parameters indicate batch S6 was suitable as a SR layer for bilayer tablet.

Drug release study

The zero order rate (Equation 8) explains the system where the rate of drug release is independent on its concentration where as the first order (Equation 9) describes the release from systems where the rate of drug release is concentration dependent. Higuchi's model (Equation 10) explains the release of drug from an insoluble matrix as a square root of a time dependent process based on Fickian diffusion. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (R^2) was determined.

Mechanism of drug release

The plot of log cumulative percent drug release versus log time for the Korsmeyer–Peppas equation exhibited linearity with R^2 = 0.9981 and the release exponent "*n*" was found to be 0.5334 indicating the Fickian diffusion type of drug release [Figure 4].

Evaluation of bilayer tablet of IB and PGB

Properties of bilayer tablets such as weight variation, thickness, hardness, and friability were determined. The

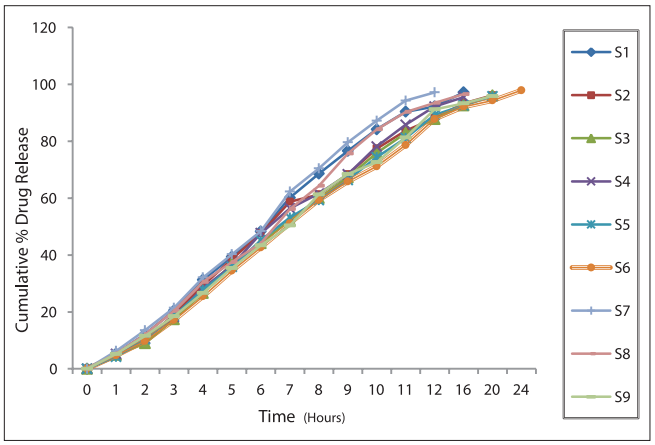

Figure 4: *In vitro* drug release profile of pregabalin floating sustained release tablet formulations

average weight of bilayer tablet was found (749.50 mg) and weight variation (5%) within limit. Friability of bilayer tablet was found (0.40%) <1%. Hardness was found 6.46 kg/cm², and thickness variation was found less than 5%. Content uniformity of IB and PGB in bilayer tablet was found 101.8 ± 0.84 and 100.3 ± 0.37, respectively.

Dissolution study

In vitro drug release study for bilayer tablet, IB layer was indicated 94.77% drug release within 10 min where as PGB layer exhibited slow sustained drug release, during 24 h dissolution study 97.18% drug was released. *In vitro* drug release profile, cumulative % drug release versus time plot for IB and PGB represented in Figures 5 and 6, respectively.

DISCUSSION

The bilayer floating tablet consisting of IB as IR was formulated using super disintegrants CCS and SSG in different concentrations. As fast disintegrant, SSG was found better than CCS and 20% concentration produced excellent results by immediately releasing IB to exert its

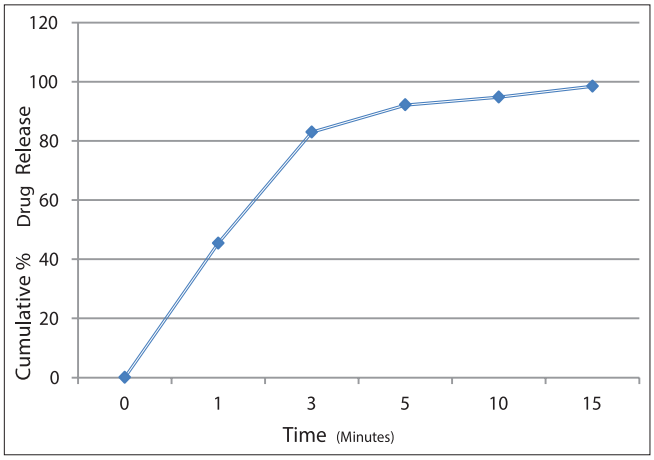

Figure 5: *In vitro* drug release profile of ibuprofen immediate release layer

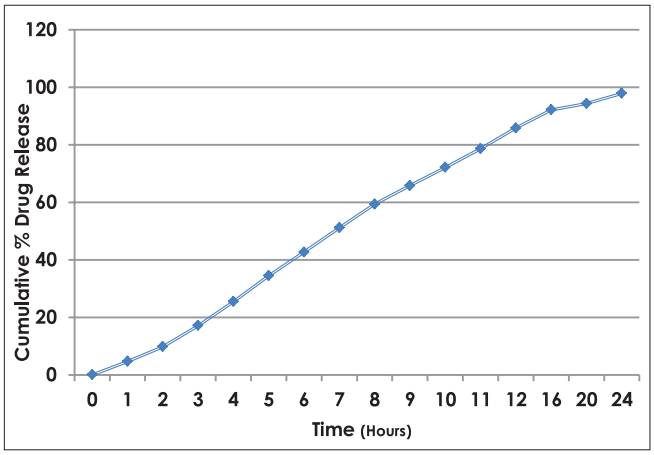

Figure 6: *In vitro* drug release profile of pregabalin floating sustained release layer

anti-inflammatory analgesic and other additional beneficial effects. PGB as floating SR were prepared using different polymers. The hydrophilic matrix forming ability of polymers utilized in this study was found in the order, HPMC K100M > HPMC K4M > sodium alginate. K100M grade of HPMC produced excellent SR efficiency at 1:1 drug-polymer ratio where as sodium bicarbonate based CO_2 gas generating system provides required extended gastric retention of the dosage form for long-lasting effect of the therapeutic agent.

Neuropathy, a disease of the nerve, is the common cause of pain in the modern world. Chronic neuropathic pain is the most disturbing symptom of lesions in the peripheral nervous system. Painful neuropathy is difficult to treat since patients may experience severe pain, various therapies and procedures may be utilized to help ease the signs and symptoms of peripheral neuropathy. Therefore, combination therapy using low dosage of two different agents seems to be very effective and beneficial over monotherapy; proposed novel type of smart advanced drug delivery system in the form of bilayered floating tablet will prove to be very effective in management of neuropathic pain.

CONCLUSION

Pre-compression and post compression parameters of optimized IR layer comprising IB and floating SR layer comprising PGB exhibit satisfactory results. Bilayer tablet of IB and PGB may prove to be very effective as a combination therapy for treatment of neuropathic pain by sequential release of the drug.

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