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Original Article

BILAYER TABLET OF TRAMADOL AND GABAPENTIN FOR COMBINATION PHARMACOTHERAPY OF NEUROPATHIC PAIN: DEVELOPMENT AND CHARACTERIZATION

SANTOSH KAMBLE*, BHAGWAT POUL, PRACHI UDAPURKAR

School of Pharmacy, Swami Ramanand Teerth Marathwada University, Nanded 431606, Maharashtra (India)
Email: ksantosh_49@rediffmail.com

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ABSTRACT

Objective: Experiments were performed to design, develop and characterize bilayer buoyant tablets having tramadol (TH), immediate release (IR) layer and gabapentin (GBP), sustained release (SR) layer.

Methods: Natural hydrophilic polysaccharide disintegrants were modified by sequential processes to obtain treated xanthan gum (TXG) and treated gellan gum (TGG), utilized for IR layer whereas carbopol and sodium carboxymethylcellulose, as sustaining polymers for SR layer and gas producing substance sodium bicarbonate which librates carbon dioxide for adequate buoyancy, was used in formulated bilayer tablet. A full two-level factorial experimental design was used for sustaining GBP release from buoyant SR layer.

Results: Fourier transform infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC) studies conducted, explain overall drug and excipients compatibility. More than 90% of tramadol was released from IR layer within 30 min. Diffusion exponents (0.36-0.59) and T_{50}% (2.4-4.4h) were determined for all SR tablet formulations. Optimised (S7) formulation exhibited 95.77% GBP released over 12h.

Conclusion: Developed tablet can provide excellent therapeutic result by the sequential immediate release of TH and sustained release of GBP for effective combination pharmacotherapy of neuropathic pain with once a day administration.

Keywords: Bilayer tablet, Tramadol, Neuropathic pain, Gabapentin, GBDDS

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INTRODUCTION

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 that can be of many forms. Peripheral neuropathy is often distressing may produce disabilities or even found to be fatal. 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-methoxyphenyl) 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].

Gabapentin (GBP), 2-[1-(aminomethyl)cyclohexyl] acetic acid is a synthetic analogue of the neurotransmitter gamma-aminobutyric acid has no activity at GABA A or GABA B receptors but its modulation of GABA synthesis and glutamate synthesis activity were considered very important for its pharmacological action. It interacts with a high-affinity binding site in nerve cell membranes, bind to the alpha-2-delta subunit of voltage gated calcium ion channels resulting in reduced depolarisation effected calcium flow in the nerve terminals which causes the decline of excitatory neurotransmitters release. In addition to epilepsy, GBP 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, 5].

Chronic neuropathic pain is a disease, not a symptom and combination pharmacotherapy is often necessary. A major goal of neuropathic pain management is to provide pain relief that is clinically meaningful, sustained, and associated with the minimum and reversible adverse effects. Efficacy of single agents for chronic neuropathic pain is limited; there is a need either to develop new and more effective drugs or to identify favourable combinations of drugs that are already available. Oral combination drug delivery systems have been proven to be highly beneficial and essential in the treatment of neuropathic pain [6]. 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 a longer time, thereby increasing therapeutic effectiveness of the API through improving the pharmacokinetics of the drug [7, 8].

The present work focuses on the development and characterization of bilayer tablet of tramadol (TH) 50 mg, immediate release and gabapentin (GBP) 100 mg, sustained release for effective around-the-clock treatment of neuropathic pain. Optimization of GBDDS, 2^3 factorial design was employed; formulation control variables, carbopol 934; carbopol 940 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 GBP release at 12 h, the time required to remain half (T_{50}%) and exponent of diffusion (n) as a dependent variable. Detail regression analysis was made to achieve best possible composition for tablet formulation [9].

MATERIALS AND METHODS

Materials

TH and GBP was a gift from Wockhardt Pvt. Ltd. (Aurangabad, India). carbopol 934; carbopol 940, was supplied by Colorcon Asia Pvt. Ltd. (Goa, India); xanthan gum (XG), gellan gum (GG), sodium carboxymethylcellulose, microcrystalline cellulose, tartrazine, sodium bicarbonate, lactose, dicalcium phosphate, the talc-pharmaceutical grade was purchased from local authorized dealers. All other reagents and chemicals used were of analytical reagent grade.

Methods

Drug-excipient interaction study

One of the critical primary concerns for any dosage form is the compatibility of drug, polymer and other excipients; hence it is essential to assure that in investigational circumstances drug doesn't have any interaction with excipients. Fourier transform

infrared spectroscopy (FT-IR) and differential scanning calorimetry (DSC) investigations were made to detect possible interaction.

FT-IR spectral investigation

Samples of pure drug TH, GBP, IR layer composition and SR layer composition were differently crushed with KBr to make pallets for the IR spectra using Shimadzu IR Affinity-1S FTIR spectro-photometer (Shimadzu, Japan).

DSC thermogram investigation

The thermograms for TH, GBP, IR layer composition and SR layer composition were prepared by 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 [10].

Modification of disintegrants

Natural hydrophilic polysaccharides were modified by sequential processes to obtain treated xanthan gum (TXG) and treated gellan gum (TGG). 10 gm powder of polysaccharide was mixed with sufficient distilled water and allowed to swell for 1 d. Then spread mechanically in a petri dish and allowed for drying up to 3 d in an incubator at 37±1 °C [11].

Immediate release TH tablet formulation

TH immediate release blend was prepared in porcelain mortar; tramadol (TH), half of the quantity of disintegrant (TXG or TGG) and other excipients were mixed up to 15 min. Sufficient amount of water as a granulating liquid was added to produce wet mass which was then passed through 10# sieve for granulation and dried in an 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 a remaining quantity of TXG or TGG, magnesium stearate and talc for 5 min. The TH-granules were compressed on single punch tablet compression machine [CADMAC (CMS-SN H/432/96), 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.

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	TXG	3	6	12	18	-	-	-	-
4	TGG	-	-	-	-	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	Dicalcium phosphate	QS	QS	QS	QS	QS	QS	QS	QS

TH: Tramadol hydrochloride, MCC: Microcrystalline cellulose, TXG: Treated xanthan gum, TGG: Treated gellan gum, Values represented in mg. Total weight 150 mg per tablet.

Precompression parameters-evaluation of TH blend

The TH-granules of all batches were characterized as per disclosed approaches for density (loose bulk density and tapped bulk density), the angle of repose, Hausner's ratio and compressibility index [12].

Evaluation of immediate release TH tablet

As per standard methods, all batches of TH-tablet were characterized for appearance, thickness, weight variation, hardness and friability [13].

Drug content

Twenty tablets were weighed, powdered and 50 mg equivalent weight 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 the volumetric flask was filtered; suitable dilutions were made and analyzed at 273 nm on UV-visible spectrophotometer (Shimadzu UV-1601). Maximum absorbance (λmax) 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 [14].

Disintegration study

Disintegration test was performed on arbitrarily selected six tablets from each batch. The tablets were placed without a disc in United States Pharmacopeia (USP) disintegration test apparatus filled with simulated gastric fluid and temperature was maintained at 37±0.5 °C. Disintegration time for six tablets was expressed as mean±standard deviation (SD) [15].

Dissolution study

Dissolution test of TH tablet was performed in the 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. A 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) spectrophotometer at λ max 273 nm. This test was performed on six tablets and mean±SD calculated.

Buoyant sustained release GBP 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), the polymer-to-polymer proportion (X2) and polymer grade (X3) [carbopol 934 and carbopol 940]; the levels of independent variables are shown in (table 2). The dependent variables Y1, percentage of GBP release at 12 h; Y2, T_{50}%; Y3, diffusion exponent (n); and Y4, buoyancy time were investigated.

Table 2: Level of variables for investigation

Coded values	Controlled variables		
	Polymer: drug (X1)	Polymer: polymer (X2)	Grade of polymer (X3)
-1	1:1	1:1	Carboplo 934
1	2:1	3:1	Carboplo 940

Preparation of buoyant tablets

Wet granulation approach was used for the preparation of buoyant sustained release granules. Required quantity of gabapentin (GBP), and polymers (carbopol 934 or carbopol 940 and sodium carboxymethylcellulose), 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 was as a 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 a poly bag with magnesium stearate and talc for 5 min. The GBP-granules were compressed on single punch tablet compression machine [CADMAC (CMS-SN H/432/96), Ahmedabad, India] using 10 mm round flat-faced punch. Various powder characteristics for GBP-granules were investigated before compression. About 6-8 kg/cm^2 tablet crushing strength, consistently maintained during compression and 100 tablets per batch were prepared for all compositions; (table 3) provides compositions for different experimental batches.

Table 3: Composition of gabapentin SR tablet

S. No.	Ingredients	S1	S2	S3	S4	S5	S6	S7	S8
1	GBP	100	100	100	100	100	100	100	100
2	Carbopol 934	50	75	100	150	-	-	-	-
3	Carbopol 940	-	-	-	-	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	21.30	21.30	21.30	21.30	21.30	21.30	21.30	21.30
7	Talc	04.25	04.25	04.25	04.25	04.25	04.25	04.25	04.25
8	Magnesium stearate	02.13	02.13	02.13	02.13	02.13	02.13	02.13	02.13
9	PVP K30 5% in IPA	QS	QS	QS	QS	QS	QS	QS	QS
10	Dicalcium phosphate	QS	QS	QS	QS	QS	QS	QS	QS

GBP: Gabapentin, SCMC: Sodium carboxymethylcellulose sodium, PVP K30: Polyvinylpyrrolidone K30, IPA: Isopropyl alcohol, Values represented in mg, Total weight 425 mg per tablet

Precompression parameters-evaluation of GBP blend

The GBP-granules of all batches were characterized as per disclosed approaches for density (loose bulk density and tapped bulk density), the angle of repose, Hausner's ratio and compressibility index [12].

Evaluation of buoyant sustained release GBP tablet

As per standard methods, all batches of GBP tablet were characterized for appearance, thickness, weight variation, hardness and friability [13].

BLT and TBT for GBP tablet

Buoyancy lag time (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 maintained at 37 °C. The 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 [10].

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 a petri dish containing 50 ml of 0.1 N HCl solution. At the end of specified time intervals, tablets were withdrawn from a petri dish, excess buffer blotted with tissue paper and weighed. The % of weight gained (swelling index) was calculated by using following formula (Eq 1) [16].

$$\text{Swelling index (\%)} = \left(\frac{W_t - W_0}{W_0}\right) \times 100 \quad \ldots (1)$$

Where, W_t = Weight of tablet at time = t;

W_0 = Weight of tablet before immersion (time = 0)

Drug content

Twenty tablets were weighed, triturated to powder and 100 mg accurately weighed the equivalent weight of GBP 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 the volumetric flask was filtered through 0.45 µm membrane filter and suitable dilutions were made and analyzed at 212 nm on UV-Visible spectrophotometer (Shimadzu UV-1601).

The drug content of each sample was estimated using standard calibration curve of GBP in phosphate buffer pH 7.4. During dissolution studies, GBP exhibited good absorption at 212 nm by using phosphate buffer pH 7.4 as a dissolution media. All results were represented as a mean±SD [17].

Dissolution study

The *in vitro* dissolution studies were carried out in USP type II apparatus (LABINDIA 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 212 nm. The release studies were conducted on six tablets in each batch; results were represented as a mean±SD.

Drug release kinetics

In vitro GBP 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 cumulative percentage of drug released *vs* square root of time (Eq. 4) for Higuchi's release model.

$$C = k_0 t \quad \ldots (2)$$

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 *vs* time would yield a straight line with a slope equal to 'k_0' and intercept the origin of the axes.

$$\log C = \log C_0 - k_t/2.303 \quad \ldots (3)$$

Where 'C_0' is the initial concentration of the drug, 'k' is the first order constant, and 't' is the time.

$$Q = k_{t^{1/2}} \quad \ldots (4)$$

Where 'k' is the constant reflecting the design variables of the system and 't' is the time in hours. [18].

Curve fitting of the release profile

To evaluate the mechanism of drug release from GBP sustained release tablet, the first 60% of cumulative drug release data were plotted in Korsmeyer *et al.'s* 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.

$$M_t/M_\infty = kt^n \quad \ldots (5)$$

Within equation, a fraction of GBP released was M_t/M_∞ at release time 't', the distinctive drug-polymer system kinetic constant 'k' whereas 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 [19].

Bilayer buoyant tablet of TH and GBP

Development of bilayer buoyant tablets was carried in two different stages, blends of the immediate release layer of TH and sustained release buoyant layer of GBP were prepared separately and after optimization of an individual layer, the bilayer tablet was prepared using selected formulas. An optimized batch of TH (F3) and GBP (S7) was selected for the formulation of bilayer tablet and were compressed using 10 mm round flat faced punch of the single punch tablet compression machine [CADMAC (CMS-SN H/432/96), 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 a hardness of 6-8 kg/cm^2. The hardness was kept constant for all tablets and was measured using Monsanto hardness tester [20-25].

Evaluation for bilayer buoyant tablet of TH and GBP

As per standard methods, bilayer tablets of TH and GBP were characterized for appearance, tablet thickness, weight variation, hardness, friability, BLT and TBT. Uniformity of content for two drugs TH and GBP was determined independently for each layer through splitting the powder of bilayer tablet.

Dissolution study

The *in vitro* dissolution studies were carried out in two phases using USP type II apparatus (LABINDIA DS8000$^+$) at 50 rpm using the 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 nm and 212 nm for TH and GBP respectively.

The release studies were conducted on six tablets, and the mean values were plotted versus time with SD.

RESULTS AND DISCUSSION

Drug-excipients interaction study

Fourier transform infrared spectroscopy (FT-IR) investigation spectra for TH, GBP and the polymer mix was exhibited relevant characteristic prominent peaks for respective drugs showing no interaction indicated overall compatibility of drugs with the excipients. Differential scanning calorimetry (DSC) thermogrames for TH, GBP, IR layer composition, SR layer composition exhibited no interaction, the distinctive melting points observed for TH at 184 °C and for GBP at 175 °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 and SR blend containing GBP (table 4) exhibited excellent characteristics. The angle of repose (26.80-34.40) and Hausner's ratio<1.13 for all batches indicated good flow properties.

Table 4: Precompression parameters

	Tramadol IR blend								Gabapentin SR blend							
Batch	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**
AR	32.45	29.72	27.36	26.80	33.47	28.55	29.24	30.53	33.35	34.40	29.23	31.45	29.62	27.42	31.65	30.78
LBD	0.72	0.74	0.60	0.58	0.56	0.57	0.61	0.55	0.48	0.52	0.55	0.53	0.50	0.48	0.52	0.49
TBD	0.86	0.85	0.72	0.66	0.65	0.68	0.73	0.64	0.56	0.60	0.63	0.62	0.59	0.57	0.59	0.58
CI (%)	16.27	12.79	16.66	12.12	13.84	16.17	16.43	14.06	14.28	13.33	12.69	14.51	15.25	15.78	11.86	15.51
HR	1.19	1.14	1.20	1.13	1.16	1.19	1.20	1.16	1.16	1.15	1.14	1.17	1.18	1.18	1.13	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 were represented for TH tablet formulations (table 5) and GBP tablet formulations (table 6). All tablet batches 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 5: Evaluation parameters of TH tablet

Batch	Weight* (mg)	Thickness* (mm)	Hardness* (Kg/cm^2)	Friability# (%)	Disintegration time* (Sec)	Drug content* (%)
F1	157.0±1.32	2.31	5.0±0.17	0.58	210±20.80	099.8±0.97
F2	151.5±1.60	2.29	4.7±0.26	0.46	168±16.32	101.2±0.88
F3	158.5±1.27	2.34	5.1±0.24	0.41	122±10.63	100.7±1.34
F4	151.1±1.54	2.36	4.8±0.12	0.53	150±11.27	099.7±1.96
F5	149.8±1.35	2.28	5.2±0.27	0.59	224±15.90	100.5±1.45
F6	152.6±1.48	2.32	5.3±0.32	0.46	177±11.52	101.0±1.62
F7	154.8±1.65	2.35	4.9±0.20	0.72	148±11.61	099.7±1.38
F8	151.5±1.75	2.30	4.6±0.20	0.64	170±10.82	100.4±0.98

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

Table 6: Evaluation parameters of GBP tablet

Batch	Weight* (mg)	Thickness* (mm)	Hardness* (Kg/cm²)	Friability# (%)	Drug content* (%)	BLT (sec)*	*Y4* TBT (h)*
S1	425.6±1.24	3.24	6.3±0.37	0.58	102.6±1.34	69	9.92
S2	426.2±1.44	3.19	6.0±0.33	0.59	099.8±1.27	58	10.96
S3	424.9±1.65	3.22	6.4±0.25	0.63	101.4±0.77	72	20.11
S4	428.5±0.97	3.24	5.9±0.24	0.58	099.6±0.89	67	17.90
S5	428.6±1.48	3.26	6.1±0.27	0.62	102.1±1.62	56	11.35
S6	423.6±1.83	3.19	6.6±0.38	0.55	100.8±0.87	70	12.53
S7	425.8±1.33	3.21	6.3±0.34	0.72	101.6±1.26	62	20.85
S8	427.9±1.82	3.20	5.8±0.12	0.64	099.9±1.52	77	18.78

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

Hydrophilic polysaccharides XG and GG interact with aqueous solutions by three-dimensional swelling, to an equilibrium value and physically entrap a significant portion of water within their structure. Drying at this stage leads to evaporation of water leaving behind a porous structure. This structural modification of TXG and TGG does not allow the formation of gelatinous mass in water resulting in low water solubility and extensive swelling properties for faster disintegration. Disintegration efficiency of disintegrants like TXG and TGG was comparatively investigated. Wetting time for a tablet containing TXG was found minimum as compared to tablets containing TGG, the higher capability of absorbing water and swelling of TXG provides faster disintegration of batch F3 (122±10.63 s), consequently selected as best composition of TH layer to prepare bilayer tablet. Disintegration time for all batches was represented in (fig. 1).

In vitro drug release at 1, 3, 5, 10, 15, 20 and 30 min for all batches was expressed by a graph cumulative % drug released vs time (fig. 2). The release of TH was depended on its concentration in the IR tablet formulation and therefore followed first-order release kinetics.

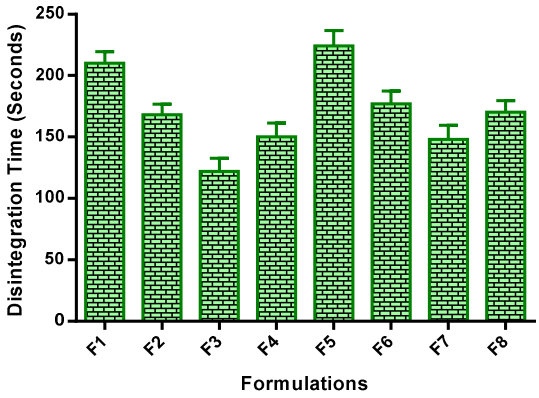

Fig. 1: Disintegration time of TH immediate release tablet formulations (Results are expressed as mean±SD, n=3)

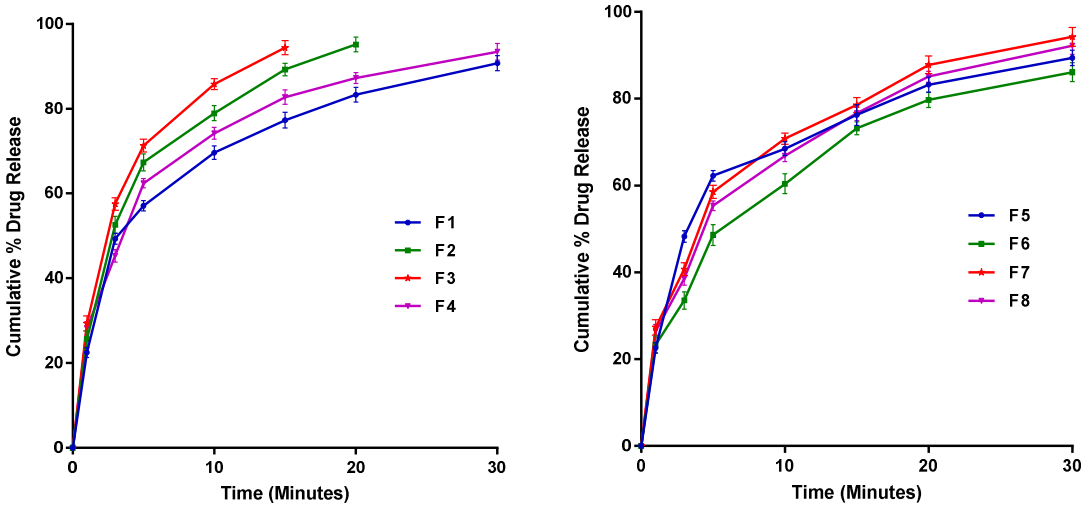

Fig. 2: *In vitro* drug release profile of TH immediate release tablet formulations (Results are expressed as mean±SD, n=6)

Dissolution study of GBP tablet

GBP is absorbed in the small intestine by diffusion and facilitated transport, this carrier dependent saturable transport is the reason for its invariable bioavailability. If GBP is presented through sustained release gastro retentive dosage form its effectiveness in neuropathic pain management can be increased many folds by prolonging the 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 influence on release of GBP through the hydrophilic matrices, formed from hydrocolloid polymeric system made up of carbopol grades (934 and 940) 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 liberating carbon dioxide 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 carbopol 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 whereas formulation batches S2, S4, S6 and S8 exhibited 97% drug release across 12 h. Formulation batch S3 and S7 comprising of high amount of polymers shown 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 GBP tablet formulations of 2^3 factorial designs were expressed in (fig. 4). The dissolution data were processed as per Korsmeyer *et al.'s* model (Eq. 5), constructed curves for log cumulative % drug release *vs* log of time, shown good linearity providing diffusion exponents 0.36 to 0.59 (table 7). The mechanism of GBP release from different batches of buoyant SR tablet formulation followed quasi fickian to fickian diffusion transport.

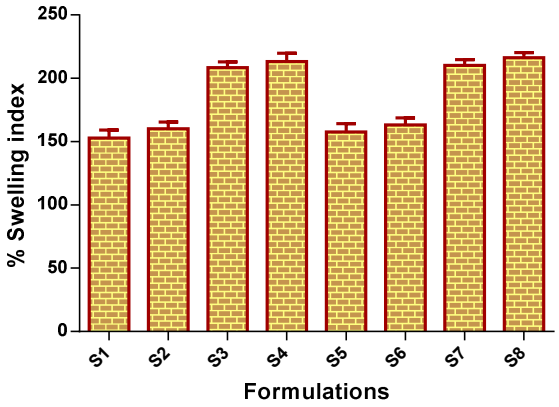

Fig. 3: % Swelling index of GBP buoyant SR tablet formulations (Results are expressed as mean±SD, n=3)

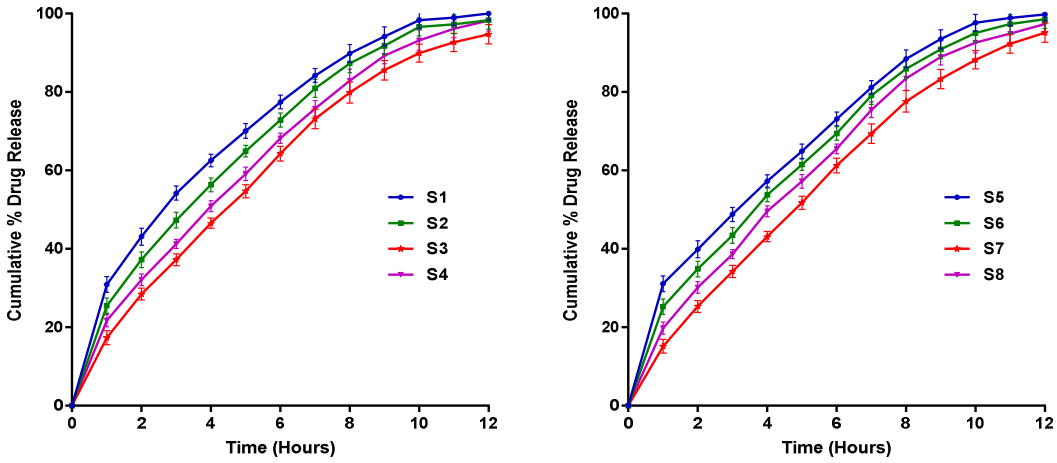

Fig. 4: *In vitro* drug release profile of GBP buoyant SR tablet formulation (Results are expressed as mean±SD, n=6)

Table 7: Curve-fitting data of release rate profile by factorial design

Batch	*Y1* GBP release at 12 H (%)	*Y2* T 50% (h)	Correlation coefficient values (R^2)				*Y3* Diffusion coefficient (n)
			Zero-order	First-order	Higuchi	Korsmeyer-peppas	
S1	101.32	2.4	0.85	0.89	0.93	0.94	0.36
S2	99.34	3.2	0.86	0.88	0.90	0.93	0.39
S3	96.74	4.2	0.83	0.90	0.92	0.96	0.50
S4	98.28	3.8	0.81	0.87	0.89	0.97	0.59
S5	99.81	2.6	0.87	0.90	0.93	0.95	0.38
S6	98.58	3.3	0.80	0.86	0.91	0.94	0.45
S7	95.90	4.4	0.82	0.88	0.90	0.98	0.50
S8	97.17	3.9	0.86	0.84	0.88	0.97	0.48

Statistical analysis and optimization for GBP tablets

The experimental results were processed through 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 8).

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

Table 8: Regression equations for the responses

$Y_1 = 98.39 - 1.37X_1 - 0.05X_2 - 0.53X_3 + 0.75X_1X_2 + 0.04X_1X_3 + 0.06X_2X_3$
$Y_2 = 3.48 + 0.60X_1 + 0.075X_2 + 0.075X_3 - 0.3X_1X_2 + 0.0\,X_1X_3 - 0.025X_2X_3$
$Y_3 = 0.47 + 0.075X_1 - 0.035X_1X_2 + 0.010X_2X_3$
$Y_4 = 15.30 + 4.11X_1 - 0.26X_2 + 0.58X_3 - 0.81X_1X_2 - 0.17X_1X_3 + 0.035X_2X_3$

Optimization of the process was made to get reactions Y1, Y2, Y3 and Y4 through incepted polynomial equations. The selected formulation was arrived through optimizing the amount of GBP release at 12 h; increasing buoyancy time and T_{50} % to find the preferred quantities of total polymer-to-drug proportion (X1), the polymer-to-polymer proportion (X2) and polymer grade (X3). Contour plot for GBP release at 12 h (Y1); **(**fig. **5)** demonstrated the relationship with controlled variables. Findings of the optimization process indicated ideal experimental setup; (2:1) proportion of total polymer content-to-drug content and polymer-to-polymer proportion (1:1) whereas carbopol (934 and 940) polymer viscosity grades did not significantly affect the performance of the tablet dosage form.

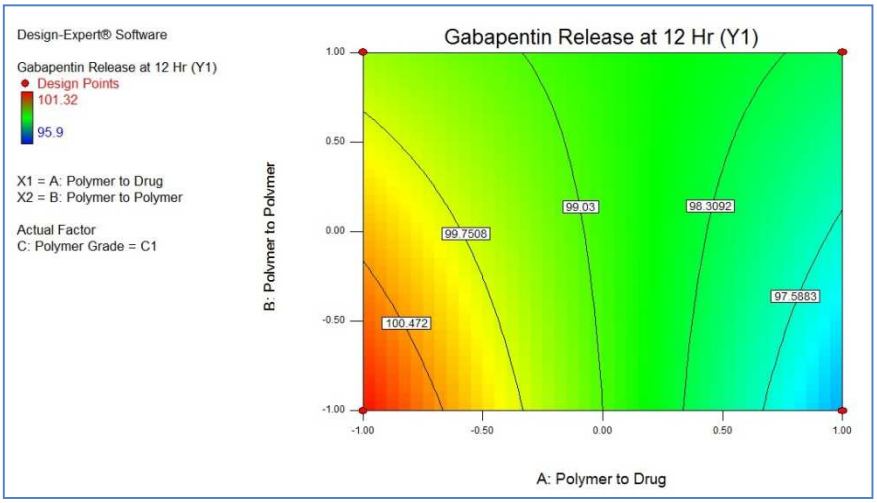

Fig. 5: Contour plot demonstrating the influence of polymer content-to-drug proportion (X1) and polymer-to-polymer proportion (X2) on the percentage of GBP release at 12 h (Y1)

Evaluation of bilayer tablet of TH and GBP

Different attributes of bilayer tablets were investigated; tablet appears smooth flat circular in distinctive two layers and deviation in thickness found less than 5%. The average weight of bilayer tablet was found (579.20 mg) and weight variation (5%) within the limit. Found friability (0.55%) below 1%; drug content 90-110% within limit, (101.8±0.75 for TH and 102.4±0.58 for GBP) and 6.72 in kg/cm^2 tablet crushing strength (hardness).

Dissolution study

In vitro drug release study for bilayer tablet, TH layer was indicated 93.14 % drug release within 15 min whereas GBP layer exhibited slow sustained drug release, during 12h dissolution study 94.87% drug was released. *In vitro* drug release profile was constructed for tramadol (fig. 6) and gabapentin (fig. 7).

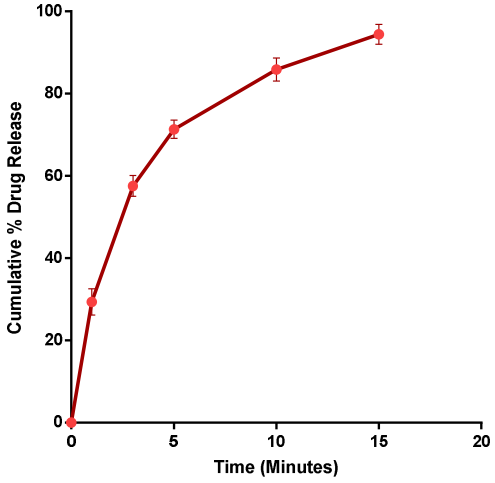

Fig. 6: *In vitro* drug release profile of Tramadol IR layer (Results are expressed as mean±SD, n=6)

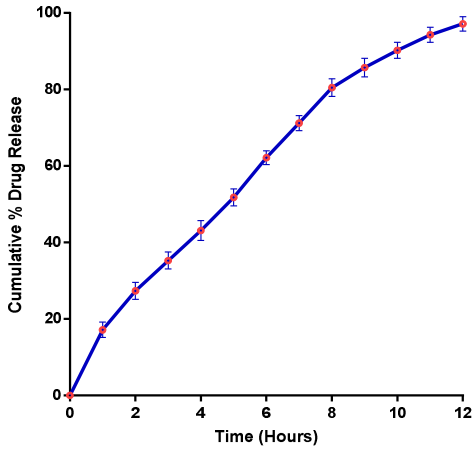

Fig. 7: *In vitro* drug release profile of gabapentin buoyant SR layer (Results are expressed as mean±SD, n=6)

CONCLUSION

Chronic neuropathic pain is a disease, not a symptom and combination pharmacotherapy is often necessary. Neuropathic pain significantly affects day to day life of an individual, needs to be managed with multiple approaches. Available medication options together with modern dosage form technology can provide the excellent therapeutic result to overcome the painful condition and improve the quality of life for an individual suffering from neuropathic pain. Developed bilayer buoyant tablet will provide immediate pain relief by releasing TH within 30 min and suppressing burning-fire pain stimulation of nerves for a longer duration through sustained release of GBP with once a day administration of bilayer tablet.

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CONFLICT OF INTERESTS

The authors have reported no potential conflict of interest in this work

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