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EXPLOITATION OF SECOND GENERATION SUPERPOROUS HYDROGEL COMPOSITES AS MATRIX RETARDANTS, IN GEL COATING OF PREGABALIN FORMULATION AND *IN-VIVO* CHARACTERIZATION

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Keywords:

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ABSTRACT: The hydro dynamically balanced gastro retentive systems of Pregabalin has been formulated and evaluated which can retard the release of drug based on Super Porous Hydrogel Composites (SPHC) thereby prolong the release rate specifically in the upper part of the GIT. Fast swelling highly porous SPHCs are synthesized by gas blowing technique. The swelling property, mechanical strength and release profile of SPHCs containing drug was investigated by changing the amount of cross-linking agents such as *N,N*[1]-methylene-bis acrylamide (BIS) and Ac-Di-Sol. SPHCs to powder form was prepared, the obtained powder material used as matrix agent for the preparation of tablets. Floating tablets were prepared by wet granulation, novel melt granulation and direct compression methods using various grades of ethyl cellulose, HPMCK 100, eudragit ESPO, geleol, compritol 888 ATO and SPHC powder in different concentrations. The prepared gastro retentive floating tablets were evaluated *in-vitro* buoyancy studies, *in-vitro* and *in-vivo* release studies. Formulations consisting powdered SPH Ac-Di-Sol composite as matrix agent was optimized. The floating time observed >12 h at pH 1.2. The *in-vitro* release studies revealed that the drug release was in controlled fashion up to 12 hrs. Pregabalin non effervescent buoyant tablet formulations (F14, F15 and F16) employing powdered SPH Ac-Di-Sol composite itself as matrix agent were selected for the novel dry gel coating by SPH Ac-Di-Sol composite. GF14 formulation optimized for *in-vivo* studies due to its effective retarding capability up to 12 h. Using Higuchi's model and the Korsmeyer equation, the drug release mechanism from the floating controlled release tablets was found to be anomalous (non-Fickian) diffusion.

INTRODUCTION: Drug absorption from gastro-intestinal tract is a complex process and is subject to many variables.

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Several methods are applied for increasing the residence time of dosage forms in the gastrointestinal (GI) tract, including magnetic systems [1], expandable system, floating system, and mucoadhesive systems [2]. In addition, Super Porous Hydrogels (SPH's) also been developed for prolonging the residence time of delivery systems in the GI tract. A SPH is a three-dimensional network of a hydrophilic polymer chains and their complete swelling occurs in less than 30 sec.

SPH's swell very fast in spite of their size and this is due to the interconnected porous structure. The interconnected structural pores provide water absorption into the centre of the SPHs by capillary force. However, SPH's provided drastically fast swelling kinetics and high swelling degree, the mechanical strength of the fully swollen SPH's was besides poor to be useful. In some cases, the abundant swollen SPH's could not be picked up and broke easily due to their very poor mechanical properties. Usually, mechanically strong SPH's can be made by increasing the cross linking density, but this would result in a very small amount of swelling with a loss of the super absorbent property. Therefore, it is preferred to make SPH's having fast swelling and high absorbency uniqueness as well as high mechanical strength [3, 4, 5].

Pregabalin PRG is an anticonvulsant drug used for neuropathic pain. It was reported to have specific site of absorption in the proximal region of the GI tract *i.e.,* stomach. The short biological half life of drug (5 - 6.5 h) for oral administration favors development of a gastro retentive formulation (GRF) [6, 7]. In present work, a SPH composite (SPHC) was planned for formulation. When such systems are administered would remain buoyant on gastric fluid for a prolonged period of time and the drug would be available in the dissolved form at the key site of its absorption. It would leads to improve the bioavailability of the drug. In this way it could stands an advantage over conventional dosage forms.

The present research work aims to design and evaluate hydro dynamically balanced buoyant formulations of (PRG) based on SPHC's which prolongs the release rate of the drug while extending the residence time of the drug within the body environment, without causing any deleterious effects to the subject and to evaluate the drug release in developed formulations by *in-vitro* and *in-vivo* studies.

MATERIALS AND METHODS:

Drug Analysis: A liquid chromatographic method was developed for quantitative estimation of PRG using an isocratic Agilent LC 1100 series HPLC instrument with a hypersil BDS C8 column (250 mm × 4.6 mm, 5µ). The instrument is equipped with a binary pump and variable wavelength UV-Visible detector. A 20 µL Hamilton syringe was used for injecting the samples. Data was analyzed by using Chemstation software. Elico SL 159 UV-Visible spectrophotometer was used for spectral studies. Degassing of the mobile phase was done by using a Loba ultrasonic bath sonicator.

Standard Stock Solution: About 50 mg of standard drug was weighed and transferred into a 50 mL of the mobile phase. The solution was sonicated for 15 min and then volume was made up to get a concentration of 1 mg/mL solution. 5 mL of this solution was further diluted to 50 mL of mobile phase to get the final concentration 100 µg/mL.

Chromatographic System:

Mobile phase : Acetonitrile: Phosphate buffer (95:5 % v/v)
Pump mode : Isocratic
Buffer : 1 mM Phosphate buffer
pH of buffer : 6.5
Column : Hypersil BDS C8, 250mm × 4.6 mm, 5.0µ
Column temp : Ambient
Wavelength : 221 nm
Injection volume : 20 µL
Flow rate : 1.0 mL/min
Run time : 10 min

Determination of Solubility: [8, 9] An excess amount of drug was added to 250 mL of respective buffer and subjected to mechanical shaking at 200 rpm for 24 h. The resultant solutions were collected and filtered through 0.45 µ membrane filters and the concentration of drug was determined from absorbance at respective wavelengths for different media. Solubility studies were done for model drug by the above procedure in different media like 1.2 SGF, Milliq water, acetate buffer pH 4.0, Phosphate buffer (pH 6.8 & 7.2).

Synthesis of SPH Ac-Di-Sol Composites by Gas Blowing Technique: [11, 12] All the ingredients except sodium bicarbonate **Table 1** were subsequently added into a test tube at 25 ºC with vigorous shaking. The required amount of Ac-Di-Sol was selected based on primary studies. The SPH was prepared using double distilled water.

100 mg of sodium bicarbonate was added very quickly to the solution and mixed well. Polymerization was allowed to continue for approximately 10 min. Synthesized SPHC was removed with a forceps, allowed to air dried for 48 h and cut into pieces of required size. Then SPHC was submerged in an organic solvent overnight. This treatment dehydrated the SPHCs followed by drying and finally stored in an air tight container.

TABLE 1: THE COMPOSITION OF DIFFERENT INGREDIENTS USED IN THE SYNTHESIS OF Ac-Di-Sol BASED SPHC

Ingredients	Ac-Di-Sol based SPHC
Acryl amide [AM] (50% w/v)	300 µL
Acrylic acid[AA] (50% v/v)	200 µL
BIS (2.5% w/v)	70 µL
Span 80 (10% v/v)	30µL
Ammonium per sulfate [APS] (20% w/v)	25 µL
TEMED (20% w/v)	25 µL
Ac-Di-Sol	50 mg
Sodium bicarbonate	100 mg

Characterization of SPHC's: [13]

Scanning Electron Microscopy Analysis (SEM): The dried SPHC's were cut to expose their inside structure and used for SEM studies. The morphology and porous structure of the SPHC was examined using ESEM EDAX XL-30 scanning electron microscope

Measurement of Initial Size: The initial size of the dried hydrogel was determined by using vernier calipers and ordinary scale. Assuming that the shape of the hydrogel is cylindrical in shape, the size was expressed in mm^2. The area (size) of the gel was determined by

$$A = 2\pi r(r+h)$$

The diameter of the dried hydrogel was determined by vernier calipers according to the following formula

$$\text{Diameter} = \text{M.S.R} + (\text{V.S.R} \times \text{L.C})$$

The height of the hydrogel was determined by ordinary scale.

Measurement of Density: [14] For density determination, solvent displacement method was used. Dried SPHC was used for density measurement, which actually showed the apparent density of SPHC. A piece of SPHC was taken and weighed in order to determine the mass of the piece. A piece of the polymer was immersed in a pre-determined volume of hexane in a graduated cylinder and the increase in hexane volume was measured as the volume of the polymer. The density was measured using formula, $D = M_{SPHC} / V_{SPHC}$.

Measurement of Porosity: The dried SPHC was submerged in hexane overnight and weighed after excess hexane on the surface was blotted. It was calculated by formula, Porosity = V_p/V_T.

Determination of Swelling Time: Swelling time was calculated by immersing the SPHC in de-ionized water as well as in 0.1 N HCl and calculating the time required to attain equilibration in swelling, which is expressed in min.

Swelling Index: The swelling behavior of dosage forms can be measured by studying its dimensional changes, weight gain, or water uptake. The swelling property of the formulation was determined by various techniques. The study is performed by immersing the tablets in 0.1 N HCl at 37 ± 5 °C and determined these factors at regular interval.

Determination of Void Fraction: The void fraction inside SPH's was determined by immersing the hydrogels in HCl solution (pH 1.2) up to equilibrium swelling. By using these data, the dimensions of the swollen hydrogels, sample volumes were determined. The difference between the weight of the swollen hydrogel and the weight of dried hydrogel gives the amount of buffer absorbed into the hydrogels and it indicates the total volume of pores in the hydrogels.

The void fraction was calculated by the following equation:

Void Fraction = Dimensional volume of the hydrogel / Total volume of pores

Measurement of Swollen Size: The swollen size of SPHC was determined after 24 h. Assuming that the shape of the hydrogels cylindrical in shape, the size [Area = $2\pi r(r+h)$] was expressed in mm^2.

Evaluation of Mechanical Properties: [15]
Penetration Pressure (PP): The compressive strengths of different SPH formulations were

determined by a bench comparator. Briefly, after the fully swollen hydrogel was put longitudinally under the lower touch of a bench comparator, different scale loads were sequentially applied on the upper touch until the point where the hydrogel could not support any more weight and completely fractured. The pressure at this point was denoted as penetration pressure (PP) and calculated [PP = Fu/S].

Mechanical Strength: Mechanical strength of dried SPHC was measured by applying the weight on swelled SPHC's until the hydrogels fractured.

Measurement of Gelation Kinetics: As the polymerization reaction proceeded, the viscosity continuously increased until the complete network structure (gel structure) was formed.

The gelation time was defined as the time duration for gel formation after addition of initiator APS. It was measured by a simple tilting method after adjustment of pH to 5.0 with sodium hydroxide solution. It was determined by the duration time until the reactant mixture was no longer descending in the tilted tube position (Park *et al*., 2006).

Effect of cross-linking agent on SPH Ac-Di- Sol Composites Table 2: To investigate the effect of cross-linker on the behavior of the gel, concentration of BIS in the feed mixture was varied in the range 1-3.5% w/v. Different characterization parameters like % porosity, swelling studies (swelling time, swelling ratio), void fraction, penetration pressure and mechanical strength were determined.

TABLE 2: EFFECT OF CROSS-LINKING AGENT ON SPH Ac-Di-Sol COMPOSITES

Ingredients	SPH 2A	SPH 2B	SPH 2C	SPH 2D	SPH 2E	SPH 2F
AM (300 µL)	50% w/v	50% w/v	50% w/v	50% w/v	50% w/v	50% w/v
AA (200 µL)	50% v/v	50% v/v	50% v/v	50% v/v	50% v/v	50% v/v
BIS (70 µL)	1%	1.5%	2%	2.5%	3%	3.5%
Span 80 (30 µL)	10% v/v	10% v/v	10% v/v	10% v/v	10% v/v	10% v/v
APS (25 µL)	20% w/v	20% w/v	20% w/v	20% w/v	20% w/v	20% w/v
TEMED (25 µL)	20% w/v	20% w/v	20% w/v	20% w/v	20% w/v	20% w/v
Ac-Di-Sol	50 mg	50 mg	50 mg	50 mg	50 mg	50 mg
$NaHCO_3$	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

Evaluation of Degradation Kinetics: The degradation kinetics of the hydrogels was examined by measuring the swelling ratio as a function of water retention.

Determination of Water Retention: For determination of the water retention capacity of the hydrogels as a function of the time of exposure at 37 ºC, the water loss of the fully swollen polymer at timed intervals was determined. The hydrogels were placed in 0.1 N HCl (pH 1.2) medium at 37ºC for 12 h and the samples were periodically weighed for 6 h interval.

The following equation was used to determine the water retention capacity (WRt) as a function of time:

$$WR_t = (W_p - W_d) / (W_s - W_d)$$

Optimization of Ac-Di-Sol concentration Table 3: Ac-Di–Sol, as an optimized composite is responsible for maintaining the capillary structure required for fast swelling, hence the effect of Ac-Di-Sol on the behavior of SPH was assessed by increasing its concentration from 2D-1 to 2D-6.

TABLE 3: OPTIMIZATION OF Ac-Di-Sol CONCENTRATION

Ingredients	SPH 2D-1	SPH 2D-2	SPH 2D-3	SPH 2D-4	SPH 2D-5	SPH 2D-6
AM (50%W/V)	300 µL	300 µL	300 µL	300 µL	300 µL	300 µL
AA (50%V/V)	200 µL	200 µL	200 µL	200 µL	200 µL	200 µL
BIS (2.5%W/V)	70 µL	70 µL	70 µL	70 µL	70 µL	70 µL
Span 80 (10%V/V)	30 µL	30 µL	30 µL	30 µL	30 µL	30 µL
APS (20%W/V)	25 µL	25 µL	25 µL	25 µL	25 µL	25 µL
TEMED (20%W/V)	25 µL	25 µL	25 µL	25 µL	25 µL	25 µL
Ac-Di-Sol	50 mg	75 mg	100 mg	125 mg	150 mg	175 mg
$NaHCO_3$	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

Preparation of PRG Formulations using SPHC Material as Matrix Agent: SPHC's was subjected to comminution by using motor and pestle. Resulted powder material used as matrix agent for the preparation of tablets. PRG gastro retentive non effervescent formulations are prepared by traditional Wet Granulation Method (F1-F6, **Table 4**), a novel Melt Granulation Technique (F7-F10, **Table 4**), Direct Compression Technique (F11-F16, **Table 5**). Tablets were prepared by different methods were subjected to *in-vitro* and *in-vivo* evaluation.

TABLE 4: COMPOSITION OF PRG TABLETS (F1 - F10)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
PRG	100	100	100	100	100	100	100	100	100	100
Ethyl cellulose	100	300								
HPMC K 100			100	300						
Eudragit ESPO					100	300				
Geleol							100	300		
Compritol 888 ATO									100	300
PVP K30 in IPA	10	10	10	10	10	10	---	---	---	---
MCC PH 102	---	---	---	---	---	---	20	20	20	20
Talc	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Colloidal silica	1	1	1	1	1	1	1	1	1	1
Lactose	285	85	285	85	285	85	275	75	275	75
Total weight	500	500	500	500	500	500	500	500	500	500

TABLE 5: COMPOSITION OF PRG TABLETS EMPLOYING SPH Ac-Di-Sol COMPOSITE MATRIX POLYMERS (F11 - F16)

Ingredients (mg)	F11	F12	F13	F14	F15	F16
PRG	100	100	100	100	100	100
P-SPHC	50	100	150	200	250	300
MCC PH 102	20	20	20	20	20	20
Talc	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2
Colloidal silica	1	1	1	1	1	1
Lactose	325	275	225	175	125	75
Total weight	500	500	500	500	500	500

Post Compression Studies of the Prepared Matrix Tablets: Post compression studies such as hardness (Monsanto hardness tester), weight variation, uniformity of thickness and friability (Roche Friabilator) studies were performed as per USP 2000 on the prepared matrix tablets with appropriate methodologies.

***In-vitro* Buoyancy Study:** [16, 17] The *in-vitro* buoyancy was determined by floating lag time as per the method described by Rosa *et al*., 1994. Prepared multi unit granules and single unit systems were placed in a 100 ml glass beaker containing 0.1 N HCl.

***In-vitro* Dissolution Studies:** [18] The prepared matrix tablets were subjected to *in-vitro* dissolution studies using an 8 station USP dissolution apparatus (Lab, TDT-08L, Mumbai). The dissolution studies were carried out in pH 1.2 for 12 h at 37 ± 0.5 ºC and 75 rpm. At regular time interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. After filtration and appropriate dilution, the samples were analyzed at 205 nm for PRG against blank using UV-Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve.

Analysis of Release Data: [19, 20, 21] Mathematical models, zero-order, first-order, Higuchi & Peppas were applied to analyze the release rate mechanism and pattern.

Fourier Transforms Infrared Spectrum Measurement (FT-IR): [10] The FT-IR spectrums of pure PRG, initial formulation and stability samples of matrix tablets formulations were determined. A FT-IR (Thermo Nicolet 670 spectrometer) was used for the analysis in the frequency range between 4000 and 400 cm^{-1} and 4 cm^{-1} resolution. A quantity equivalent to 2 mg of pure drug was used for the study.

***In-vivo* Evaluation of PRG Gastro Retentive Floating Dosage Forms:** A standard calibration curve for PRG in rabbit plasma (approval no: HCOP/IAEC/P.CEUTICS/10/2011-12) was assessed with the help a validated bio-analytical HPLC method in the concentration range 0.25-5.00 µg/mL. The optimized chromatographic conditions were used with sodium dihydrogen phosphate monohydrate (10 mM), methanol and acetonitrile (92:4:4% V/V/V at pH 4.8) as mobile phase at 40ºC with a flow rate of 1.25 mL/min and detection wavelength at 270 nm for these studies. The blood samples were collected at scheduled time intervals *viz*., 0.25-12, and 48 h. The drug was extracted from plasma (0.5 mL) by using protein precipitation method with help of acetonitrile.

The desired pharmacokinetic parameters from the plasma kinetic data were assessed by using SIGMAPLOT 9 software. Comparative plasma profiles of PRG 100 mg conventional formulation (reference, R) with PRG 100 mg extended release formulation (test, T) were performed.

RESULTS AND DISCUSSSION:

Drug Analysis: 20 µL of PRG standard solution (100 µg/mL) were injected for HPLC analysis. The drug peak observed at retention time 3.153 min. The typical chromatogram of PRG showed in **Fig. 1**.

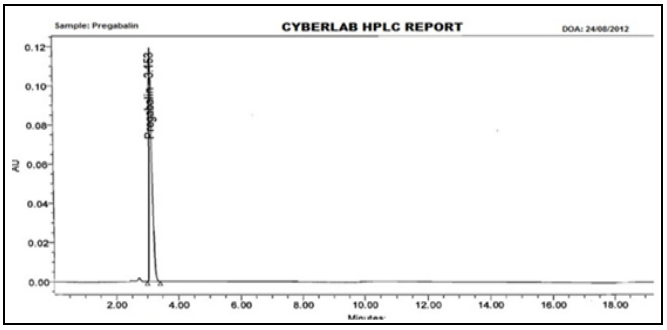

FIG. 1: TYPICAL HPLC CHROMATOGRAM OF PRG

Solubility Data: The highest solubility observed in 0.1 N HCl (216.06 mg/mL) and in Phosphate buffer (pH 6.8, 189.37 mg/mL). It was poorly soluble in water and acetate buffer (pH 4.5) at 124.81 and 76.48 mg/mL, respectively.

Characterization of Ac-Di-Sol SPHC Material for Density & Swelling Parameters: Second generation SPHC's synthesized employing composite agent Ac-Di-Sol, were subjected to density and swelling properties. The density was found to be 1.14 ± 0.08 gm/cm^3. (The swelling properties were found to be *i.e*., Swelling Time: 57 ± 19 min and Swelling Ratio (Q): 310 ± 29. The morphology of hydrogels in SEM analysis showed in **Fig. 2**.

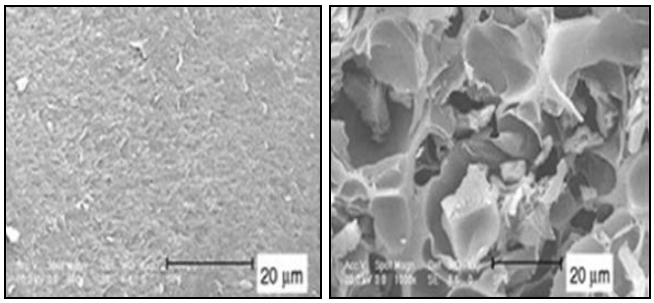

FIG. 2: SEM PICTURES OF CONVENTIONAL HYDROGEL (A) AND ETHANOL TREATED SPH Ac-Di-Sol (B)

Effect of Cross-Linking Agent on SPH Ac-Di-Sol Composites: From porosity and void fraction measurement, it was observed porosity was gradually decreased as the concentration of BIS increased. The void fraction of SPH was decreased by the increase in the amount of BIS. Also the penetration pressure was found to be gradually increased with BIS concentration, thus increasing the mechanical stability. As the swelling ratio was being decreased beyond 2.5% concentration of BIS, hence this concentration of BIS (SPH 2D) is considered to be the optimized concentration for further characterization **Table 6**.

TABLE 6: RESULTS DESCRIBING EFFECT OF CROSS-LINKING AGENT ON SPH-Ac-Di-Sol

Formulation	Porosity (%)	Void Fraction (ml/g)	Penetration Pressure (gm force/cm^2)	Swelling Studies		Mechanical Strength (gm)
				Swelling Time (min)	Swelling Ratio	
SPH 2A	77.6 ± 1.9	1.31 ± 0.02	52	55	280± 12	126
SPH 2B	74.2 ± 1.4	1.25 ± 0.04	72	50	286 ± 14	139
SPH 2C	65.1 ± 2.3	1.12 ± 0.02	85	45	298 ± 17	184
SPH 2D	54.3 ± 2.3	0.97 ± 0.03	104	37	308 ± 18	234
SPH 2E	39.1 ± 2.9	0.89 ± 0.05	102	32	302 ± 13	252
SPH 2F	26.4 ± 2.5	0.79 ± 0.04	115	25	298 ± 12	253

Water Retention Studies: The weight loss of Ac-Di-Sol hydrogels occurred after 12 h. Lower the concentration of the cross-linking agent, the faster was the loss of water from the SPH. The SPH's consisting of higher amount of BIS decreased polymer rigidity, thus improving the resiliency of the polymer in response to compression and prevention of the water loss efficiently. Hence an increase in the amount of BIS decreased the rate of loss of water **Fig. 3**.

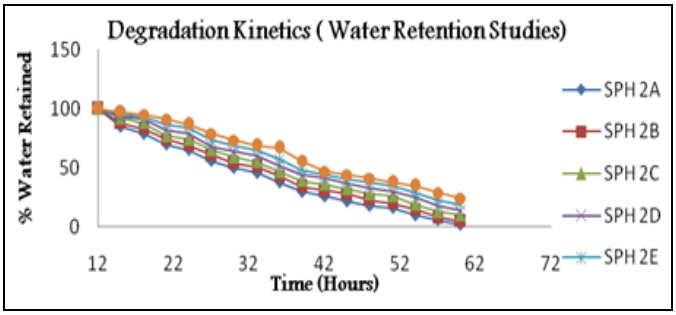

FIG. 3: WATER RETENTION STUDIES

Optimization of Ac-Di-Sol Concentration: As the Composite (Ac-Di-Sol) concentration increased swelling time and swelling ratio was gradually increased with increase in composite agent concentration. Thus, 175 mg of Ac-Di-Sol (SPH 2D-6) was used as the optimum concentration showed in **Table 7**.

TABLE 7: RESULTS DESCRIBING EFFECT OF Ac-Di-Sol ON SWELLING RATIO AND MECHANICAL STRENGTH

Formulation Code	Swelling studies		Mechanical strength (gm)
	Swelling Time (Min)	Swelling Ratio (n=3); Mean ±S.D	
SPH 2D-1	39	307 ± 28	236
SPH 2D-2	30	301 ± 16	244
SPH 2D-3	25	295 ± 15	262
SPH 2D-4	23	291 ± 15	276
SPH 2D-5	17	285 ± 20	284
SPH 2D-6	13	280 ± 16	291

Gelation Kinetics: The gelation kinetics gave good information determining the introduction time of blowing agent (sodium bicarbonate).

Effect of Drying Conditions and Wetting Agents on Behavioral Characteristics of SPH Ac-Di- Sol Composites: When the swollen SPHC's were dried at 60°C over night (condition II) the swelling time was around 12 min **Fig. 4**. When a SPH's dried under condition II (placed in n-hexane), the outer region swelled to equilibrium only seconds after contact with water. When the SPH's were dried under condition III (*i.e.*, dehydrated in ethanol first before drying), the swelling time was reduced to about 7.2 min. When SPH's were dehydrated with ethanol containing 1% SLS before drying, the swelling time was reduced even further to less than 5 min **Table 8**.

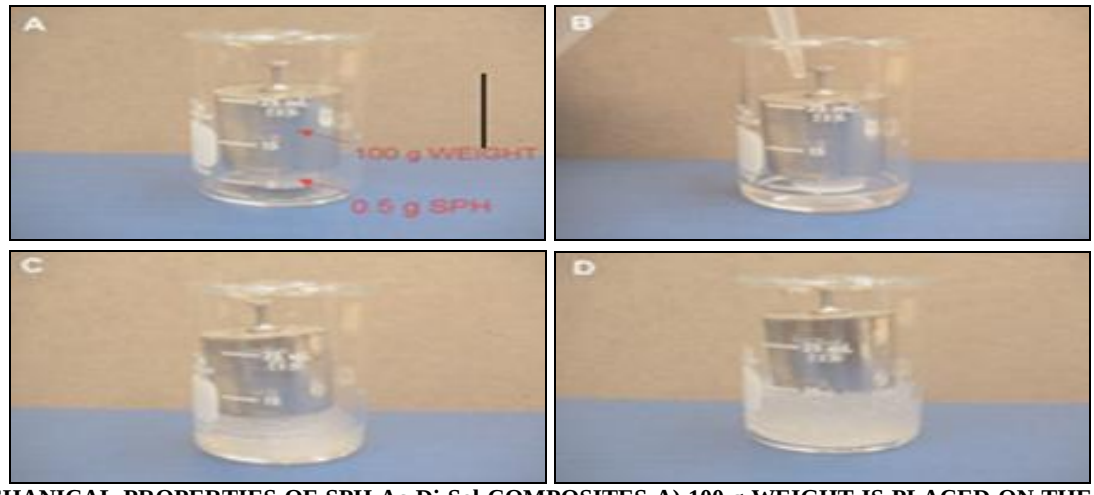

FIG. 4: MECHANICAL PROPERTIES OF SPH Ac-Di-Sol COMPOSITES A) 100 g WEIGHT IS PLACED ON THE DRIED SPH, B) ADDITION OF WATER, C) IMMEDIATE SWELLING OF SPH, D) LIFT OF 100 g WEIGHT

TABLE 8: RESULTS DESCRIBING EFFECT OF DRYING CONDITIONS AND WETTING AGENTS ON BEHAVIORAL CHARACTERISTICS OF SPH Ac-Di-Sol COMPOSITES

Gel type	Drying condition	Wetting agent	Size in dried state	Density [ρ] (gm/cm^3)	Swelling ratio (G)	Swelling time (min)
Conventional	I	---	5 × 2	1.42 ± 0.09	175 ± 11	642 ± 10.6
SPH-Ac-Di-Sol	II	---	6 × 3	1.26 ± 0.08	282 ± 16	14 ± 22
SPH-Ac-Di-Sol	III	---	10 × 5.5	0.72 ± 0.03	304 ± 24	7.4 ± 1.2
SPH-Ac-Di-Sol	IV	1 % SLS	9 × 4	1.146 ± 0.02	336 ± 16	4.3 ± 0.8

Post Compressional Parameters of PRG Byouant Tablets: The prepared tablets F1-F8 **Table 9** and F9-F16 **Table 10** were evaluated for physical parameters like weight variation, thickness, hardness and friability. All the parameters lie within the acceptable limits in all the formulations.

TABLE 9: POST COMPRESSIONAL PARAMETERS OF PRG BYOUANT TABLETS (F1 - F8)

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation (%)	1.38±0.97	1.72±0.84	1.24±0.98	1.71±0.96	1.98±0.99	1.83±0.88	1.92±0.76	1.94±0.78
Hardness (kg/cm^2)	5 .4±0.46	5.5±0.52	5.5±0.32	4.5±0.43	6 .2±0.45	5.7±0.48	3.5±0.54	3.25±0.37
Friability (%)	0.22±0.14	0.29±0.23	0.32±0.14	0.24±0.16	0.27±0.26	0.34±0.13	--	--
Thickness (mm)	4.26±0.54	4.37±0.36	4.24±0.46	4.29±0.42	4.34±0.45	4.45±0.36	3.24±0.43	3.2±0.45

TABLE 10: POST COMPRESSIONAL PARAMETERS OF PRG BYOUANT TABLETS (F9 – F16)

Parameters	F9	F10	F11	F12	F13	F14	F15	F16
Weight variation (%)	1.83±0.97	1.94±0.79	1.78±0.95	1.62±0.89	2.37±1.12	1.67±0.67	1.83±0.78	1.76±0.73
Hardness (kg/cm^2)	3.23±0.97	2.5±1.11	5.5±0.78	5.5±0.65	5.4±0.45	5.8±0.76	5.5 ±0.88	5.2±0.66
Friability (%)	--	--	0.32±0.76	0.34±0.45	0.35±0.54	0.33±0.57	0.29±0.46	0.31±0.67
Thickness (mm)	3.23±0.89	3.26±0.97	4.35±0.76	4.38±0.88	4.45±0.78	4.32±0.98	4.36±0.86	4.39±0.99

***In-vitro* Buoyancy Characterization:** The tablet swelled radially and axially during *in-vitro* buoyancy studies. Formulations F7, F8, F9, F10, F14, F15 and F16 were found to exhibit short floating lag times in the artificial gastric fluid and the floating time of formulations were more than 12 hrs except for F9 (4 h) and F10 (5 h) **Table 11**.

***In-vitro* Release Data:** PRG non effervescent buoyant formulations such as F7, F8, F9, F10, F14, F15 and F16 were subjected to *in-vitro* drug dissolution studies **Table 12**. The formulations F14, F15 and F16 employing powdered SPH Ac-Di-Sol composite as matrix agent were showed effective retardation of drug release **Table 12**. The release of drug and its retardation by the powdered SPH material clearly signifies that as the polymer concentration is increased, the drug is being retarded to a greater extent. *In-vitro* dissolution results primarily revealed that powdered second generation SPH Ac-Di-Sol composite agents has a better ability to retard the drug release as a matrix agent **Fig. 5**.

TABLE 11: *IN-VITRO* BUOYANCY CHARACTERIZATION OF BUOYANT FORMULATIONS

Formulation	Floating lag time (sec)	Total floating time (h)	Matrix integrity
F1	Failed	-	+
F2	Failed	-	+
F3	Failed	-	+
F4	Failed	-	+
F5	Failed	-	-
F6	Failed	-	-
F7	<10	>12	Failed
F8	<10	>12	Failed
F9	30	4	up to 2 hrs
F10	20	5	up to 3 hrs
F11	-	-	Failed
F12	-	-	Failed
F13	-	-	Failed
F14	<10	>12	Failed
F15	<10	>12	Failed
F16	<10	>12	Failed

TABLE 12: DISSOLUTION PROFILE OF PRG TABLETS

Time (h)	F7	F8	F9	F10	F14	F15	F16
1	28.6±0.50	18.97±1.26	26.79±1.25	19.45±1.25	24.94±1.24	19.78±123	14.56±1.24
2	37.2±0.68	29.78±1.72	32.46 ±1.75	33.26±1.75	38.97±1.64	27.34±1.34	24.78±0.98
3	41.94±1.22	38.36±0.97	48.34±2.71	56.14±1.27	58.35±1.27	39.86±1.26	32.54±1.28
4	57.63±0.98	52.02±0.36	64.76±0.44	68.57±0.94	72.81±1.35	44.67±1.24	38.96±0.94
5	63.24±1.10	68.38±0.45	89.78±0.25	72.24±1.48	87.23±0.98	57.34±0.98	46.58±1.23
6	79.87±1.50	78.35±1.45	97.13±1.26	80.46±1.32	96.59±1.28	69.68±1.26	57.94±0.84
8	97.56±1.44	82.13±1.76		98.34±0.93		85.98±0.97	66.87±0.76
10		93.12±0.46					72.86±0.86
12		98.37±0.68					80.08±0.94

Application of Dry SPH Composite Gel Coating to PRG SPH Matrix Tablets: By conducting i*n-vitro* dissolution studies of dry gel coated PRG matrix buoyant formulations (GF14, GF15 and

GF16) **Table 13**, it was clearly evident that the release rate of PRG matrix buoyant formulations (F14, F15 and F16) were further retarded by dry gel coating **Fig. 6**. GF14 formulation due to its effective retarding capability up to 12 h, it was optimized for further *in vivo* studies. The results of *in-vitro* dissolution studies showed the dry gel coating of SPH Ac-Di-Sol composite material was found to be effective in retarding the release rate of PRG at a rate controlled fashion **Fig. 7**.

TABLE 13: *IN VITRO* DISSOLUTION STUDIES OF DRY GEL COATED PRG MATRIX BUOYANT FORMULATIONS

Time (h)	GF14	GF15	GF16
1	16.76	12.29	10.37
2	23.16	19.34	15.71
3	31.28	25.54	23.59
4	46.15	36.61	31.52
5	59.34	47.33	38.76
6	68.71	56.74	43.32
8	79.82	67.41	53.87
10	89.68	75.96	66.44
12	98.41	81.49	73.68

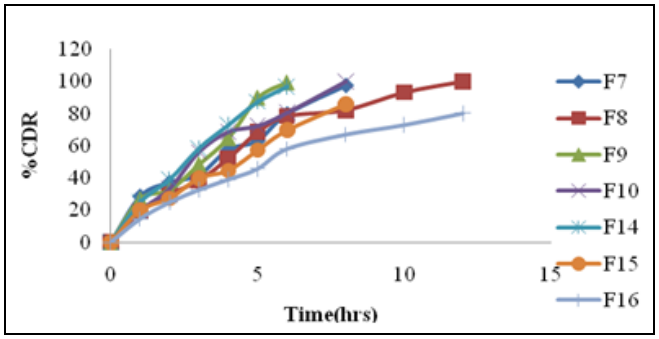

FIG. 5: COMPARATIVE RELEASE PROFILES OF PRG NON EFFERVESCENT FLOATING FORMULATIONS

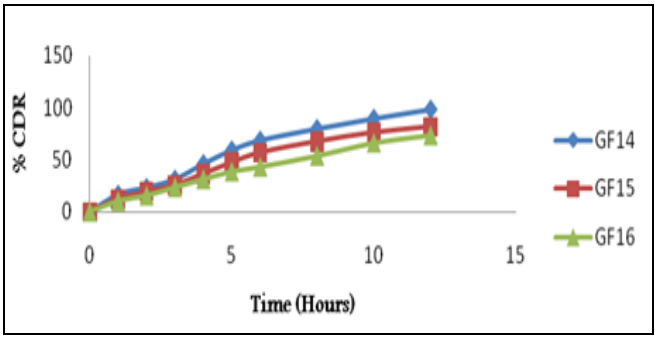

FIG. 6: COMPARATIVE *IN-VITRO* DISSOLUTION PROFILES OF DRY GEL COATED PRG MATRIX BUOYANT FORMULATIONS (GF14, GF15 AND GF16)

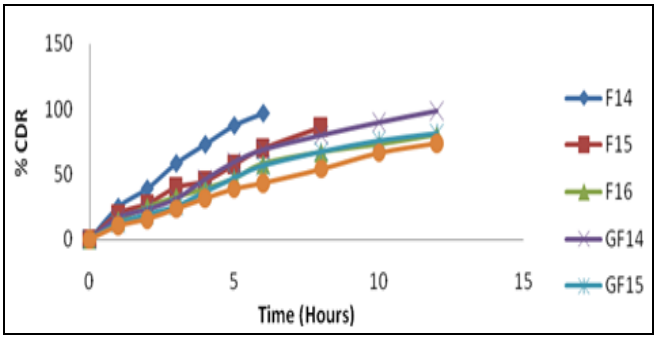

FIG. 7: COMPARATIVE *IN-VITRO* DISSOLUTION PROFILES OF UNCOATED PRG MATRIX FORMU-LATION F14, F15 AND F16 WITH DRY GEL COATED PRG MATRIX BUOYANT FORMULATIONS (GF14, GF15 AND GF16)

Analysis of Release Data: The optimized formulations were studied for drug release kinetics using zero order, first order, higuchi, korsmeyer-peppas and R^2 values of all the formulations. In order to assess the exact release mechanism, dissolution data of PRG formulations were fitted to Korsemeyer Pappas (Power Law) plot. All the exponent (n) values were found to be between 0.5-1, which specified that the formulations were exhibiting Anomalous (Non-Fickian) transport mechanism for the drug release at constant rate controlled fashion **Fig. 8, 9, 10, 11** and **12**. Relative regression coefficient (R^2) and exponent (n) values of PRG formulations showed in **Table 14.**

TABLE 14: RELATIVE REGRESSION COEFFICIENT (R^2) AND EXPONENT (N) VALUES OF PRG FORMULATIONS

Formulations	Zero order R^2 Values	First order R^2 Values	Higuchi R^2 Values	Erosion R^2 Values	Pappas "n" Value
F7	0.968	0.713	0.955	0.650	0.502
F8	0.920	0.668	0.967	0.621	0.659
F9	0.982	0.728	0.908	0.655	0.692
F10	0.985	0.680	0.963	0.681	0.743
F14	0.985	0.795	0.960	0.731	0.711
F15	0.986	0.639	0.945	0.697	0.640
F16	0.950	0.694	0.951	0.632	0.709
GF14	0.968	0.768	0.969	0.643	0.739

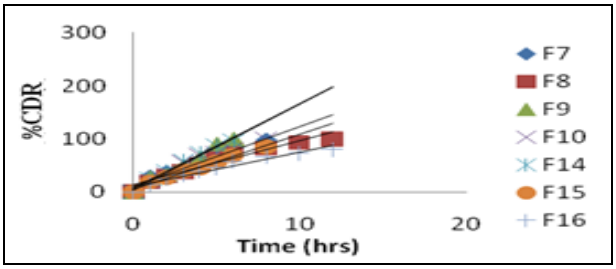

FIG. 8: ZERO ORDER REGRESSION PLOTS

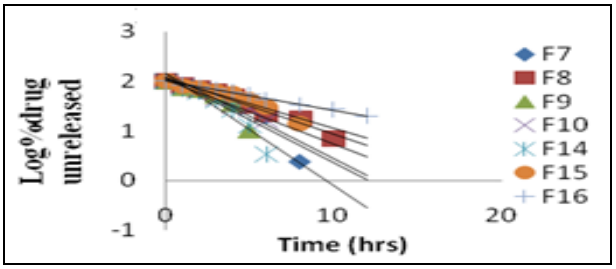

FIG. 9: FIRST ORDER REGRESSION PLOTS

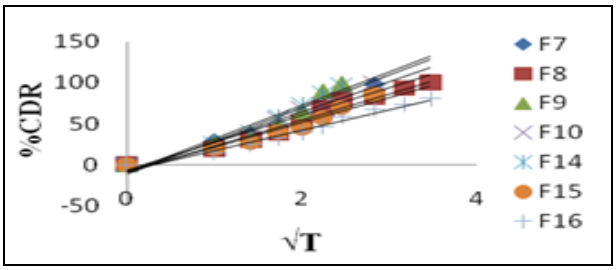

FIG. 10: HIGUCHI MODEL REGRESSION PLOTS

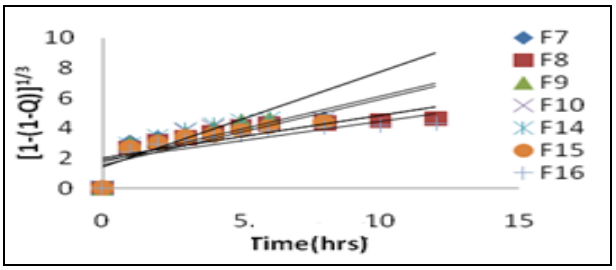

FIG. 11: EROSION MODEL REGRESSION PLOTS

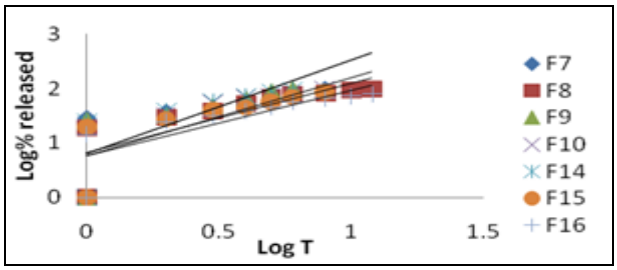

FIG. 12: PAPPAS MODEL REGRESSION PLOTS FOR PRG BUOYANT FORMULATIONS

FT-IR Studies of PRG Buoyant Formulations: Pure PRG, powdered SPH composite, physical mixture of PRG-powdered SPH composite and optimized formulation of PRG (GF14) gel coated buoyant matrix tablets were subjected to FT-IR characterization to check compatibility among them. No prominent difference was observed in the IR peaks of PRG optimized SPH coated formulation upon comparison with the peaks of drug and polymer alone, which may considered that PRG and SPH composite agents are compatible enough without any interactions **Fig. 13**.

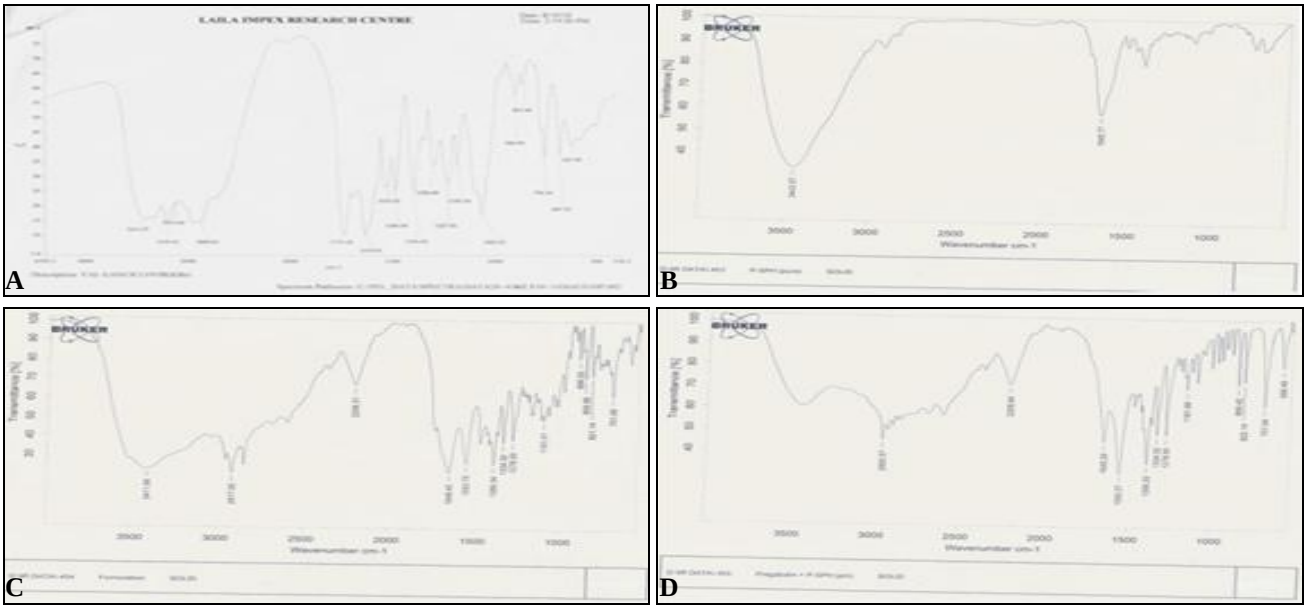

FIG. 13: FT-IR SPECTRUM OF A) PRG, B) POWDERED SPHC, C) OPTIMIZED PHYSICAL MIXTURE OF PRG AND POWDER, D) GEL COATED FORMULATIONS OF PRG AND POWDERED SPHC

***In-vivo* Studies:**

***In-vivo* Evaluation of PRG GRF Dosage Forms:** The plasma concentration profile of PRG immediate release tablets (R) 100 mg and extended release tablets (T) 100 mg were summarized in **Table 15** and **17.** After conduction of the *in-vivo* clinical study **Table 15** and **Table 17** in rabbit plasma, overall assessment of the PRG pharmacokinetic data had revealed that C_{max}, T_{max}, AUC_{0-t}, K_E and $t_{1/2}$ parameters were totally varied between both reference (R) and test (T) formulations **Table 16** and **Table 18**.

The mean peak plasma concentration C_{max} of test (T) formulation was found to be 1324.4 ng/ml reached up to 4.5 h. It was which was varied with of conventional formulation (C_{max} 1612 ng/ml reached up to 1.4 h). Increase in T_{max} values indicates the drug release in controlled manner **Table 17** and **Table 19**.

Area under the curve (AUC_{0-t}) in test (T) formulation was found to be 23850.14 ng.min/mL which was more than reference (R) formulation (4762.8 ng.min/mL). The overall elimination rate constant (K_E) was decreased to 0.0612 h^{-1} over reference was 0.5127 h^{-1}. Elimination half life's ($t_{1/2}$) were found to be 1.216 and 8.23 h for reference and test formulation, respectively. The comparative plasma profile of PRG with respective to subjects in conventional tablet dosage form (R) and extended tablet dosage form (T) was graphically represented in **Fig. 14 - 16.** Variations in all these parameters clearly indicated the drug released in controlled manner in prolonged period *i.e.*, up 12 h.

Hence the optimized PRG non effervescent GRF formulation was observed to be releasing the drug effectively at a rate controlled manner for a prolonged period of time **Table 16, 17, 18** and **19**.

TABLE 16: PLASMA CONCENTRATION PROFILES OF PRG IMMEDIATE RELEASE TABLETS 100 mg (R) AT DIFFERENT TIME INTERVALS

Subjects	**Time (h)**													
0	**0**	**0.25**	**0.5**	1	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**72**
1	0	827	1557	1817	1339	627	336	136	36	nd	nd	nd	nd	nd
2	0	793	1432	1575	1578	763	287	113	47	nd	nd	nd	nd	nd
3	0	834	1508	1592	1385	661	249	141	38	nd	nd	nd	nd	nd
4	0	812	1533	1580	1184	773	281	176	52	nd	nd	nd	nd	nd
5	0	796	1504	1573	1212	817	263	155	41	nd	nd	nd	nd	nd
6	0	847	1502	1541	1509	676	395	178	39	nd	nd	nd	nd	nd
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	0	818	1505	1613	1369	720	302	150	42	--	--	--	--	--
SD	0	17.29	38.72	99.49	147.24	61.18	19.27	13.64	6.27	--	--	--	--	--
Min	0	796	1501	1541	1212	676	263	155	38	--	--	--	--	--
Median	0	797.5	1506	1591	1329.5	723	276.0	174	45.2	--	--	--	--	--
Max	0	847	1557	1817	1570	817	336	178	52	--	--	--	--	--
CV%	0	2.41	2.51	5.87	8.96	6.67	6.28	8.341	12.70	--	--	--	--	--

TABLE 17: PHARMACOKINETIC DATA OF PRG (100 mg) IMMEDIATE RELEASE TABLETS (R)

Treatment	**Subject**	**T_{max}**	**C_{max}**	**AUC_{0-t}**	**AUC_{0-inf}**	**K_E**	**$t^{½}$**	**Extrapolated AUC**
Reference (R)	1	1.2	1674	4871.7	4926.4	0.5436	1.274	1.62
	2	1.8	1488	4639.5	4882.1	0.4552	1.522	2.52
	3	1.2	1425	4579.4	4670.2	0.5314	1.304	1.83
	4	1.2	1417	4533.2	4681.6	0.4754	1.457	2.63
	5	1.2	1582	4527.6	4592.3	0.5110	1.357	2.01
	6	1.8	1618	4687.7	4883	0.5320	1.302	1.85
	N	6	6	6	6	6	6	6
	Mean	1.4	1534	4639.8	4772.5	0.5080	1.369	2.071
	SD	0.27	99.42	97.726	89.725	0.0341	0.092	0.11
	Min	1.2	1581	4527.5	4592.3	0.4552	1.274	1.62
	Median	1.2	1592	4886.2	4832.1	0.5292	1.320	1.83
	Max	1.8	1674	4871.7	4926.4	0.5437	1.522	2.62
	CV%	0.074	5.83	1.71	1.63	5.89	6.88	22.33

TABLE 18: PLASMA CONCENTRATION OF PRG EXTENDED RELEASE (100 mg) GRF DOSAGE FORMS (T) AT DIFFERENT TIME INTERVALS TABLETS

Subjects	Time (h)													
	0	**0.25**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**48**	**72**
1	0	403	705	974	1164	1243	1362	1223	1145	832	351	68	nd	nd
2	0	435	782	922	1123	1170	1398	1251	1180	721	348	54	nd	nd
3	0	486	778	764	1107	1224	1228	1228	1094	674	383	43	nd	nd
4	0	432	752	854	1084	1192	1381	1231	1151	721	313	57	nd	nd
5	0	494	765	793	1143	1229	1368	1153	1172	700	372	73	nd	nd
6	0	458	701	912	1103	1151	1259	1227	1194	781	386	65	nd	nd
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	0	451.5	747	870	1120.5	1202.8	1266.6	1218.83	1156	738.1	358.8	60	--	--
SD	0	30.2	27.1	7506	31.0	34.8	64.7	33.7	32.2	45.2	22.7	11.3	--	--
Min	0	403	701	764	1083	1151	1229	1153	1151	674	313	44	--	--
Median	0	452	776	890	1128	1232	1362	1241	1153	741	371.6	60.4	--	--
Max	0	494	782	974	1164	1243	1398	1251	1194	832	386	74	--	--
CV%	0	5.62	2.97	7.79	2.64	2.70	4.52	2.63	2.75	6.46	6.41	19.58	--	--

TABLE 19: PHARMACOKINETIC DATA OF PRG 100 mg EXTENDED RELEASE MULTIUNIT DOSAGE FORMS (T)

Treatment	Subject	T_{max}	C_{max}	AUC_{0-t}	$AUC_{0-\infty}$	K_E	$T_{1/2}$	Extrapolated AUC
Test (T)	1	4.3	1191	23684.4	24732.73	0.0691	10.02	3.30
	2	4.5	1218	23064.6	23728.18	0.0729	9.52	2.77
	3	4.4	1171	22321.8	22643.11	0.0763	9.08	1.94
	4	4.3	1313	21893.8	22661.33	0.0708	9.78	2.99
	5	4.4	1282	23196.4	24521.41	0.0632	10.97	4.35
	6	4.5	1192	23783.8	24721.25	0.0668	9.97	3.42
	N	6	6	6	6	6	6	6
	Mean	4.4	1227.4	22990.72	23834.98	0.0697	9.88	3.18
	SD	0	64.235	442.711	912.328	0.00452	0.617	0.714
	Min	4.5	1171	21893.8	22643.11	0.0632	9.08	1.92
	Median	4.5	1358	23132.8	25898.14	0.0708	9.54	3.20
	Max	4.5	1218	23684.4	24732.73	0.0763	10.97	4.35
	CV%	0	3.97	2.84	3.22	6.42	6048	23.88

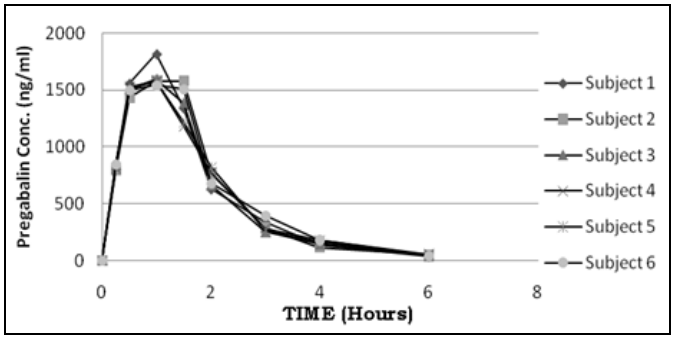

FIG. 14: COMPARATIVE PLASMA PROFILES OF PRG 100 mg CONVENTIONAL FORMULATION (R)

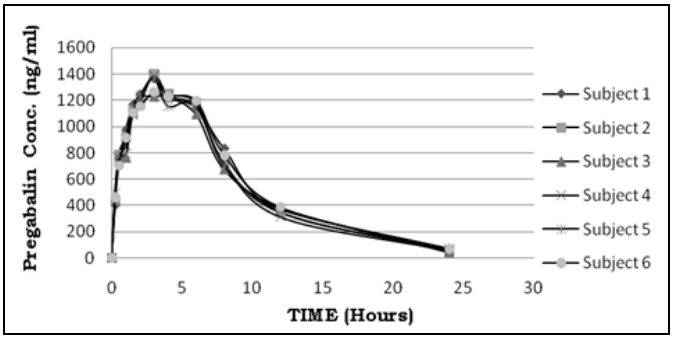

FIG. 15: COMPARATIVE PLASMA PROFILES OF PRG 100 mg MULTIUNIT EXTENDED RELEASE GRF FORMULATION (T)

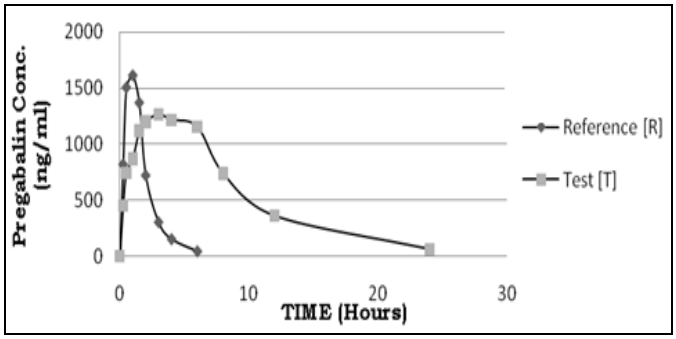

FIG. 16: COMPARATIVE PLASMA PROFILES OF PRG 100 mg CONVENTIONAL FORMULATION (R) WITH PRG 100 mg MULTIUNITS EXTENDED RELEASE GRF FORMULATION (T)

CONCLUSION: The present work has been carried with an in house experimental design to prepare hydro dynamically balanced buoyant formulations of PRG employing second generation SPH Composite agents (Ac-Di-Sol). SPH Composite without polymer formulation was developed in order to assess the capability of SPHC in retarding the release rate of active molecules. *In vitro* dissolution results primarily revealed that powdered second generation SPH Ac-Di-Sol composite agents has a better ability to retard the drug release as a matrix agent. Since PRG non effervescent buoyant formulations (F14, F15 and F16) employing powdered SPH Ac-Di-Sol composite as matrix agent showed different degree of drug retardation, they were subjected to post formulation processing by application of novel attempt of applying dry SPH Composite gel coating on to the PRG SPH matrix tablets (GF14, GF15 and GF16). Dry gel coated PRG matrix buoyant formulations GF14, GF15 and GF16 showed 98.41%, 81.49% and 73.68% of drug release at the end of 12 h, respectively.

The results of *in-vitro* dissolution studies the dry gel coating of SPH Ac-Di-Sol composite material was found to be effective in retarding the release rate of PRG at controlled fashion. In order to assess the exact release mechanism, dissolution data of PRG formulations were fitted to Korsemeyer Pappas (Power Law) plot. All the exponent (n) values were found to be between 0.5-1, which specifies that the formulations were exhibiting Anomalous (Non-Fickian) transport mechanism for the drug release at constant rate controlled fashion. By conducting the *in vivo* clinical study, overall assessment of the PRG pharmacokinetic data revealed that C_{max}, T_{max}, AUC_{0-t}, K_E and $T_{1/2}$ parameters were totally varied between both reference (R) and test (T) formulations.

Hence the optimized PRG non effervescent GRF was observed to be releasing the drug effectively at a rate controlled manner for a prolonged period of time. Very interesting *in-vitro* and *in-vivo* results were observed with SPHC dry gel coated formulations of PRG, further there is a scope to conduct the bioavailability studies in human volunteers to know the exact pharmacokinetics of the developed Buoyant non effervescent GRFDDS of PRG.

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CONFLICT OF INTEREST: The authors declare that they have no competing interests.

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