ORIGINAL ARTICLE

Electrolyte-induced Controlled Release of Propronolol Hydrochloride Matrix Tablets with Gum Kondagogu

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Abstract

Aim: The present investigation highlights the formulation and evaluation of matrix tablets of propranolol hydrochloride (HCl) using a natural polymer, is gum kondagogu. **Materials and Methods:** Wet granulation method was used for the preparation of matrix tablets of propranolol HCl using varying proportions of natural polymer as a release retardant, Avicel pH 102 as diluent, talc and magnesium stearate as glidant and lubricant respectively. Total 12 formulations (PG1-PG12) were prepared by using different proportions of drug and gum kondagogu (1:0.5, 1:1, 1:1.5, 1:2) with the aid of granulating fluids such as distilled water, ethanol and isopropyl alcohol. Granules of propranolol HCl formulations were evaluated for pre-compression parameters and flow properties. All the prepared matrix tablet formulations after compression subjected for physico-chemical evaluation of hardness, friability, thickness, weight variation, drug content, swelling index and *in vitro* drug release studies. **Results and Discussion:** The distinguishable difference in the results was shown to be dependent on characteristics and composition of polymer concentrations. Based on *in vitro* drug release the polymer gum kondagogu showed better dissolution control in all formulations, which is result of its release retardant characteristics. The formulations PG4, PG8 and PG12 (drug:polymer ratio 1:2) have shown more than 95% drug release for 12 h and hence PG10 (drug:polymer ratio 1:1) was selected for further studies. The selected formulation PG10 studied for the effect of electrolytes (sodium carbonate, calcium carbonate, magnesium carbonate) on release of drug by employing in different concentrations (25, 50 and 75 mg). These electrolytes were employed to examine matrix swelling and gel properties. Swelling study suggested that when the matrix tablets come in contact with the medium, they take up medium and swells, forming a gel layer around the matrix and simultaneously erosion also takes place. Fourier transform infrared spectra revealed that there was no interaction between drug and polymers. Drug release analysis was confirmed that there exists a significant difference in the measured Higuchi rate constant among the matrices. **Conclusion:** The combination of both hydrophilic natural polymer and electrolytes successfully employed for formulating the sustained release matrix tablets of propranolol HCl.

Key words: Electrolyte, gum kondagogu, matrix tablets, propranolol, sustained release

INTRODUCTION

Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Sustained release dosage forms would be most applicable for drugs having short elimination half-lives.[1] Propranolol hydrochloride (HCl), a nonselective beta-adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, pheochromocytoma, cardiac arrhythmias,[2] and many other cardiovascular disorders. Propranolol HCl undergoes extensive and highly variable hepatic first-pass metabolism following oral administration, with a reported systemic bioavailability between 15% and 23%.[3,4] Propranolol HCl has half-life of 3.9 ± 0.4 h. Frequent drug administration may reduce patient's compliance and therapeutic efficacy. In recent years slow or sustained release formulations of propranolol HCl has become available with

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claims that these formulations maintain beta-adrenoreceptor blockade throughout a 24 h period and enable the drug to be given once daily.[5] Propranolol HCl has a short elimination half-life, which makes it a suitable candidate to be delivered at a controlled rate. The most commonly used method of modulating the drug release is to include it in a matrix system.[6] Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance.[7,8] For the present research work gum kondagogu, a natural polymer was used as matrix former. Gum kondagogu is a naturally occurring nontoxic polysaccharide derived as an exudate from the bark of Cochlospermum gossypium (Bixaceae family), a native tree of India. Literature review reveals the use of gum kondagogu in green synthesis of metal nanoparticles and magnetic iron oxide nanoparticles, mercury biosensor, and nanosilver-based antibacterial agent for medical applications. Additionally, appropriate chemical modification of the functional groups present in gum kondagogu may lead to the development of novel technologies for applications in pharmaceutical and food and biotechnology industries.[9] The drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. The aim of the present investigation was to design and develop a novel oral monolithic, sustained release tablet dosage form of propranolol HCl with gum kondagogu as natural polymer along with pharmaceutically acceptable electrolytes which can induce *in situ* reactions between drug and electrolyte that alters drug release mechanism by matrix stiffening and changes in the gel would lead to extended drug release at a steady state manner has been elucidated.

MATERIALS AND METHODS

Propranolol HCl was obtained as a gift sample from Pellets Pharma Limited, Hyderabad. Gum kondagogu was purchased from Girijan co-operation society, Visakhapatnam. Avicel pH 102, calcium carbonate, sodium carbonate, magnesium carbonate, magnesium stearate, talc and isopropyl alcohol were procured from S.D Fine Chem. Ltd., Mumbai.

Preparation of matrix tablets

Propranolol HCl sustained release matrix tablets were prepared by wet granulation method[10] using drug:polymer ratios 1:0.5, 1:1, 1:1.5, 1:2. Weighed drug, gum kondagogu, Avicel pH 102 (microcrystalline cellulose), and placed in motor then triturated well and then added distilled water, ethanol, isopropyl alcohol (granulating fluids) and prepared dough mass. Then dough mass was passed through sieve No. 14-16 for obtaining wet granules (wet screening). Then these wet granules were dried and they were passed through sieve No. 22-25 (dry screening). To dried granules added magnesium stearate and talc and mixed well. Tablets were prepared by using nine station tablet punching machine (Chamunda Pharma Pvt. Ltd., Ahmadabad), with use of punch sizes 8 mm for obtaining 350 mg of tablet weight. Compositions of various formulations are given in Tables 1 and 2.

Physical evaluation of tablets

Tablet hardness was determined with a Monsanto tablet hardness tester (Campbell Electronics, Mumbai, India). The individual hardness of 10 tablets randomly selected from each batch was measured and then mean and standard deviation taken. Whereas percentage friability of tablets was determined using a friabilator (Hoffmann-La Roche Ltd., Basel, Switzerland). The weight of ten tablets before and after the test, and the percent loss in weight recorded as friability.[11] The drug content of the tablets was evaluated spectrophotometrically (Shimadzu, model 1700) at 320 nm.

Swelling index

The swelling behavior of a dosage form was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium at 37°C ± 0.5°C. After 1, 2, 4, 6, 8, 10 h, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess medium and weighed on the analytical balance (Shimadzu, Ax120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the formula.[12]

$$\text{Swelling index} = \frac{\text{Wet weight of tablet} - \text{Dry weight of tablet}}{\text{Dry weight of tablet}}$$

In vitro drug release studies

In vitro drug release studies were carried out in pH 1.2 buffer solutions for 1 h and pH 7.5 buffer solutions for 11 h using a USP XXII type 1 dissolution apparatus (Electrolab TDT-08L) at 50 rpm and 37°C ± 0.5°C. At predetermined interval, samples were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant.[13] After filtration and appropriate dilution, the amount of drug present in each sample was determined spectrophotometrically at 320 nm.

Dissolution parameters

From the dissolution studies of various matrix tablets containing propranolol HCl, the following *in vitro* kinetics such as zero order-release rate constant, first order-release

Table 1: Composition of propranolol HCl matrix tablets

Ingredients mg/tablet	PG1	PG2	PG3	PG4	PG5	PG6	PG7	PG8	PG9	PG10	PG11	PG12
Propranolol HCl	80	80	80	80	80	80	80	80	80	80	80	80
Gum kondagogu	40	80	120	160	40	80	120	160	40	80	120	160
Avicel pH 102	223	183	143	103	223	183	143	103	223	183	143	103
Mg stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Water	q.s	q.s	q.s	q.s	-	-	-	-	-	-	-	-
Ethanol	-	-	-	-	q.s	q.s	q.s	q.s	-	-	-	-
IPA	-	-	-	-	-	-	-	-	q.s	q.s	q.s	q.s
Total wt (mg)	350	350	350	350	350	350	350	350	350	350	350	350

HCl: Hydrochloride

Table 2: Composition of Propranolol HCl matrix tablets with electrolytes

Ingredients mg/tablet	PGE1	PGE2	PGE3	PGE4	PGE5	PGE6	PGE7	PGE8	PGE9
Propranolol HCl	80	80	80	80	80	80	80	80	80
Gum kondagogu	80	80	80	80	80	80	80	80	80
Sodium carbonate	25	50	75	-	-	-	-	-	-
Calcium carbonate	-	-	-	25	50	75	-	-	-
Mg. carbonate	-	-	-	-	-	-	25	50	75
Avicel pH 102	158	133	108	158	133	108	158	133	108
Mg. stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
IPA	qs	qs	qs	qs	qs	qs	qs	qs	q.s
Total wt. (mg)	350	350	350	350	350	350	350	350	350

HCl: Hydrochloride

rate constant, Higuchi's diffusion constant, and Peppas constant were evaluated.

Similarity factor

The similarity factor *f*2 as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum square) difference of drug percent dissolved between the test and reference products.[14,15] It is given by following equation:

$$f_2 = 50 \times \mathrm{Log}\left\{\left[\sum_{(n=1)}^{\infty} Wt(Rt - Tt)2\right]^{-0.5} \times 100\right\}$$

An *f*2 value of 100 suggests that the test and reference profiles are identical and as the value becomes smaller, the dissimilarity between release profiles increases. The similarity factor (S_d) is given as:

$$S_d = \sum_{t=1}^{n=1} \frac{\left[Log\left(\frac{AUCR_{Rt}}{AUC_{Tt}}\right)\right]}{n-1}$$

For the test and reference formulations to be identical, the S_d value should be zero.[16]

Characterization of matrix tablets

Drug-excipients compatibility studies

Fourier transform infrared (FT-IR) studies

By using dried KBr base line correction was taken. Weighed amount of the propranolol HCl was carefully mixed separately along with KBr (dried at 40-50°C) after that entire mixture was compressed using 10 ton pressure in a hydraulic press to produce a pellet after that it was subjected for scanning from 4000 to 400/cm using FT-IR 410 PC spectrophotometer. In the same way the method was adopted for polymers and formulations. The obtained spectrum from FT-IR was compared with drug and polymer mixtures.

Differential scanning calorimetry (DSC) studies

The DSC thermal analysis of API, excipients and the mixtures of drug-polymers were studied in DSC analyzer model universal V4.5A at a heating rate of 20°C per min from 0°C to 350°C in a nitrogen environment. DSC is a thermal analytical method performed to examine the drug and excipient compatibility. In this, together test and standard were warmed from 20°C to 300°C and same temperature maintained during observation. Individually API and excipients includes polymers were scanned.

Scanning electron microscope (SEM) studies

In SEM as electrons are employed, a vacuum is maintained inside the microscope column to keep free of air molecules. Generally the column is maintained at a vacuum of about 10 ton. Now when a narrow beam of primary electrons are generated from the electron gun and hits the specimen surface then secondary electrons are emitted from the spot. The yield of the secondary electron depends on the angle between the direction of primary electrons and the specimen surface. A flat surface produces a minimum number of secondary electrons. If the beam is moved to another spot, there also the yields of secondary electrons would depend upon the topographical features of that region and maybe more or less than that of the first spot. Thus, continuous moving or scanning the electron beam over the specimen surface achieves a corresponding signal output. If the secondary electrons are also continuously collected and displayed on a cathode ray tube, an image appears which is comparable to the topographical detail of the specimen. The SEM study was carried out for matrix tablet to check the surface texture of the same. A smooth surface gives a uniform drug release whereas uneven or cracked surface gives an uncontrolled and non-uniform drug release.

Stability studies

Stability studies on the optimized matrix tablets (PGE8) were carried out as per ICH guidelines at 25°C ± 2°C/60% ± 5% RH and 40°C ± 2°C/75% ± 5% RH for 6 months by storing the samples in stability chamber. Further, the matrix tablets were evaluated for appearance, weight variation, hardness, drug content and for *in vitro* drug release profiles over a period of 6 months.

RESULTS AND DISCUSSION

An ideal sustained release tablet should release the required quantity of drug with predetermined kinetics in order to maintain effective drug plasma concentration. To achieve constant drug plasma concentration, tablet should be formulated in such a way that it can release the drug in a predetermined and reproducible manner.

Physicochemical properties almost all the formulated products lied within the pharmacopoeial requirements. Other physiochemical properties such as, hardness, thickness, diameter, friability, and assay results were determined. The thickness and diameter were found in the range of 2.30-3.20 mm and 9.94-10.03 mm, respectively. The assay values of the formulated tablets were found in between 98.56% and 101.11%.

The hardness of all the tablet formulations was in the range of 5-8 kg/cm^2. Friability loss of the tablet formulations were found to be negligible and were in the range of 0.1-0.2% w/w. Drug content estimated for all the tablet formulations were highly uniform with <2.5% variation. Drug content was also the same in case of matrix tablets containing electrolytes. All the matrix tablets were prepared under identical conditions and were found to be stable. The results of physical parameters evaluated for various matrix tablets were given in Table 3.

The swelling behavior of the formulations was studied in terms of percent weight gain. The formulation successively gained at a maximum weight 158.82 up to 10 h and underwent swelling. But after that the weight was again decreased. This is due to penetration of medium in the glassy network of polymer. Due to the presence of medium, the glass transition temperature of the matrix is decreased to that of the dissolution medium and a transition from glassy to rubbery states takes place as the amount of medium inside the matrix increases. The intake of medium leads to induction of stress within the polymeric matrix. Consequently, the polymeric matrix relaxes and swelling occurs.[15] Results demonstrate enhancement in the swelling index with an increase in polymer concentration and also time duration. Increase in polymer concentration from 5% to 80% increased the swelling after 8 h from 145.44% to 158.82% with increasing time from 2 to 8 h. This may be due to the hydrophilic property of gum kondagogu. Moreover, swelling of the polymer also leads to the formation of matrix, thereby retarding the release of drug from the formulation. The swelling index values for selected formulations were given in Table 4. This increased release retardant effect of gum kondagogu may be due to the formation of gel barrier

Table 3: Physical evaluation parameters of propranolol HCl matrix tablets with electrolytes

Formulation code	Weight variation (%)	Friability (%)	Hardness (kg/cm^2)	Drug content (%)
PGE1	1.20±0.14	0.12±0.041	6.2±0.11	99.96±0.32
PGE2	1.24±0.15	0.10±0.016	6.4±0.22	98.97±0.24
PGE3	1.31±0.15	0.14±0.013	7.3±0.21	100.56±0.21
PGE4	1.23±0.21	0.15±0.043	6.4±0.21	99.12±0.23
PGE5	1.31±0.14	0.11±0.018	7.5±0.20	99.80±0.23
PGE6	1.04±0.04	0.20±0.012	6.5±0.26	98.56±0.17
PGE7	1.61±0.12	0.12±0.043	5.6±0.31	101.11±0.13
PGE8	1.13±0.14	0.16±0.044	6.0±0.20	99.65±0.23
PGE9	1.43±0.04	0.15±0.011	5.1±0.15	98.95±0.20

HCl: Hydrochloride

Table 4: Swelling characteristics of various matrix tablets with electrolytes formulations

Time (h)	Percentage swelling index								
	PGE1	PGE2	PGE3	PGE4	PGE5	PGE6	PGE7	PGE8	PGE9
1	54.69	54.21	56.98	48.85	56.29	57.29	55.15	54.69	48.12
2	75.69	74.98	77.89	68.29	76.89	76.38	74.64	75.69	67.22
4	105.46	106.49	109.29	97.69	108.97	109.09	81.42	105.46	96.68
6	121.98	122.29	125.79	110.39	125.49	125.48	113.36	121.98	112.39
8	144.39	145.67	147.86	134.28	146.28	147.49	128.49	144.39	134.14
10	155.79	155.89	158.82	145.34	157.89	158.67	154.26	155.79	146.35

that hinders the penetration of dissolution medium to the matrix. It may also be due to slow erosion of the matrix. The most important factor that affects the drug release from gum kondagogu matrix is drug to polymer ratio. Increasing polymer concentration in the matrix leads to boost the viscosity of gel, which in turn may lead to a decrease in diffusion coefficient of drug and thereby reducing the drug release.

In present study, it was noticed that by increasing concentration of polymer the drug release retardant effect was increased and *vice versa*. It is recommended that the polymer having hydrophilic characteristic when encounter dissolution medium, absorbs it and undergoes swelling thus forming a gel layer that serves as a blockade to the process of diffusion. The course of drug release from hydrophilic matrix involves penetration of dissolution medium into the matrix system, drug dissolution and diffusion of drug through the resultant gel barrier.

As the hydrophilic polymer quickly undergoes hydration on the outermost surface of tablet, thus it is forming a gel barrier, which acts as a physical and diffusion barrier thus retarding the drug release by diffusion. This gel barrier also prevents wetting of the core and hinders the tablet to undergo disintegration. It is also suggested that the gel barrier with higher viscosity of polymer resulted in a more sluggish release of drug due to formation of barrier to that is more tortuous and resistant diffusion. The inclusion of electrolytes within a swollen matrix for controlling the release rate of propronolol may lead to the formation of free base of propronolol and fundamental structural changes in gel boundary, thus inducing the textural variations in the swollen matrix. It appears that electrolyte induced buffer threshold within the matrix place an essential role in effective interaction with drug and textural changes. The dissolution profiles were shown in the Figures 1 and 2.

The *in vitro* release data obtained were fitted in to various kinetic equations. Correlations of individual batch with applied equation. The release rates were calculated from the slope of the appropriate plots. To find out release mechanism the *in vitro* release data were fitted in Peppas equation where n is a factor, which indicates the mechanism of the drug release. For instance *n*: 0.5 for square root

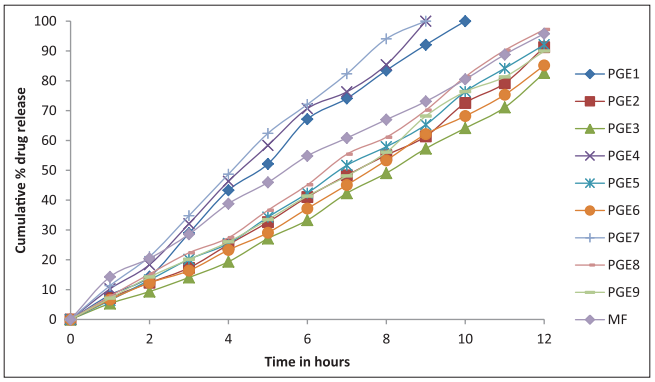

Figure 1: Drug release profiles of various sustained release formulations of propranolol hydrochloride with electrolytes in comparison with marketed formulation

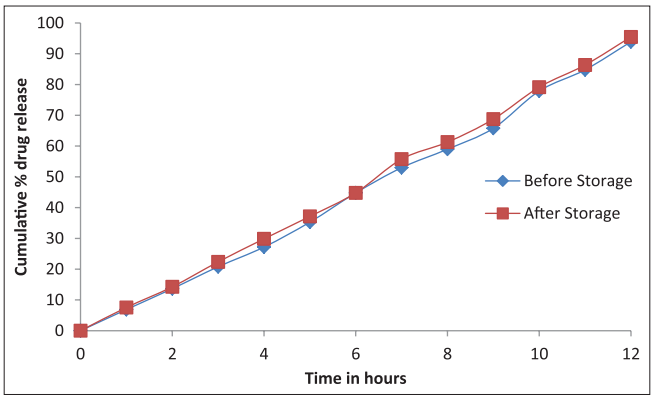

Figure 2: Stability profile of optimized formulation (PGE8) before and after storage

of time (pure diffusion controlled drug release) and *n*: 1 for zero order release. The values of *n*>1.0 indicates anomalous diffusion (swelling-controlled drug release or Case II transport) for all selected formulations. The release exponent *n* was determined and given in Table 5. All batches showed higher correlation with Higuchi plot than zero order and first order. Optimized formulation PGE8 showed diffusion controlled release where as other batches shows anomalous effect (combined mechanism of diffusion and Case II transport).

The drug release profiles from the developed formulations in this study were compared with the marketed product.

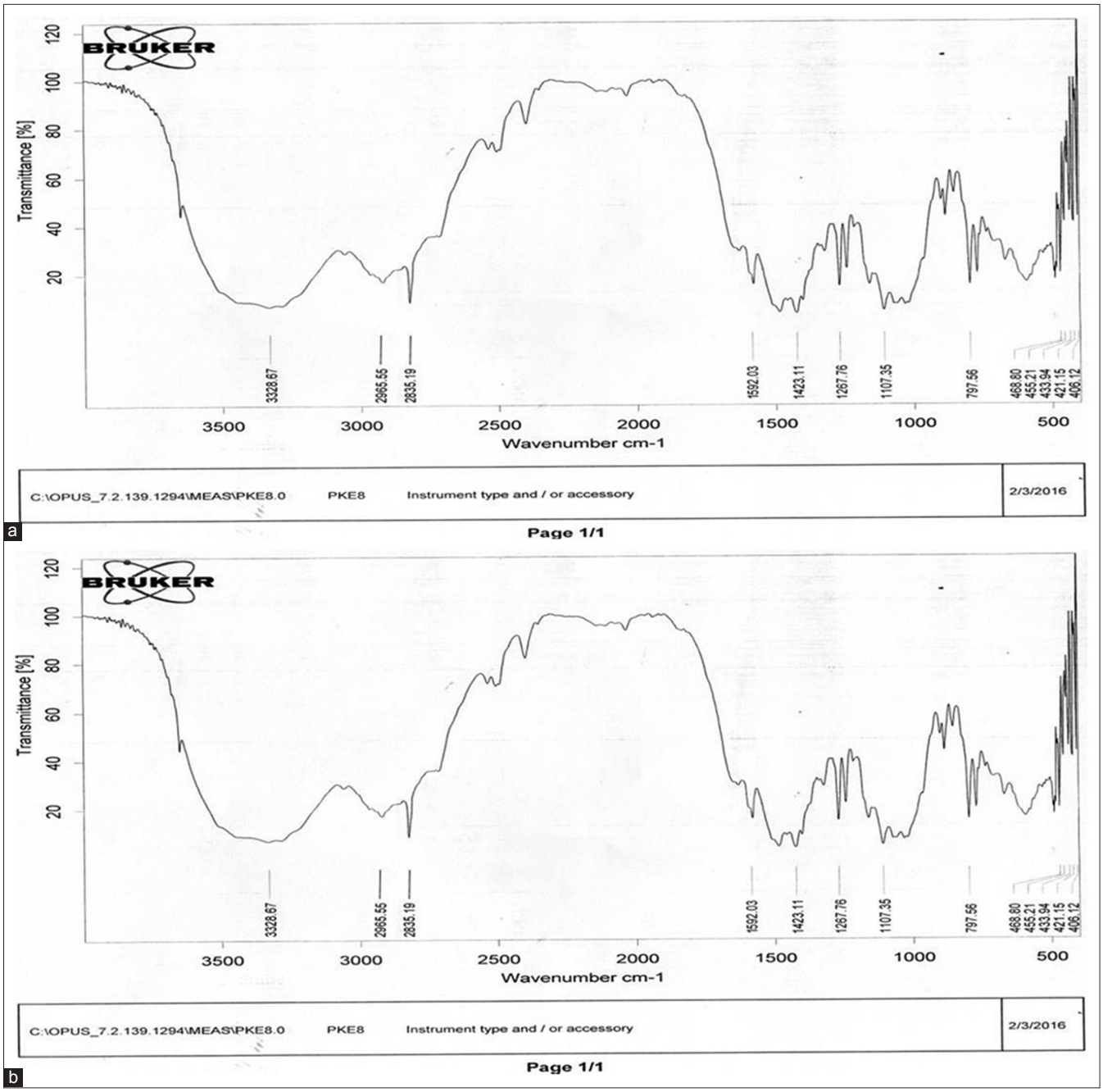

Figure 3: (a) Fourier transform infrared (FT-IR) image of propranolol hydrochloride (HCl) pure drug. (b) FT-IR image of propranolol HCl optimized formulation PGE8

These studies indicated that the drug release for test product (97.18%) was more than marketed product (90.09%). The similarity and the dissimilarity factors depict that the drug release from the prepared batches were significantly different from the release of drug from the marketed tablet. The significance of using similarity factor was to compare the solubility and release profile of the prepared tablets with that of the marketed tablets. The *f*2 value was found to vary from 11 to 58. The *f*1 value ranged from 11 to 101. Table 6 represents the similarity and the dissimilarity factors for the various batches. Formulation PEG8 showed the *f*2 value of 58 and thus indicated the drug release from the matrix tablet was linear with marketed tablet formulation. The similarity and the dissimilarity factors for other formulations indicated that the sustained release formulations are quite different from the marketed tablet, and more sustained than the marketed tablet. It may thus be concluded that the sustained release formulation can be achieved using hydrophilic polymers, which can also maintain the sustained release profile over an extended period of time.

The optimized formulations were further evaluated for characterized by FT-IR and DSC studies. FT-IR of propranolol HCl and mixtures of excipients in equal ratios were prepared

and evaluated by using FT-IR spectrophotometer (Shimadzu) by using KBr pellet technique as described in methodology. It was found that no significant interactions between drug and excipients (115.20°C). Respective FT-IR and DSC images were shown in the Figures 3a and b, 4, 5. In SEM images, it showed intact surface only swells without any perforations, channels, or troughs. After dissolution, the solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The images of the tablet showed a network in the swollen polymer through which the drug diffused to the surrounding medium. Thus, it was

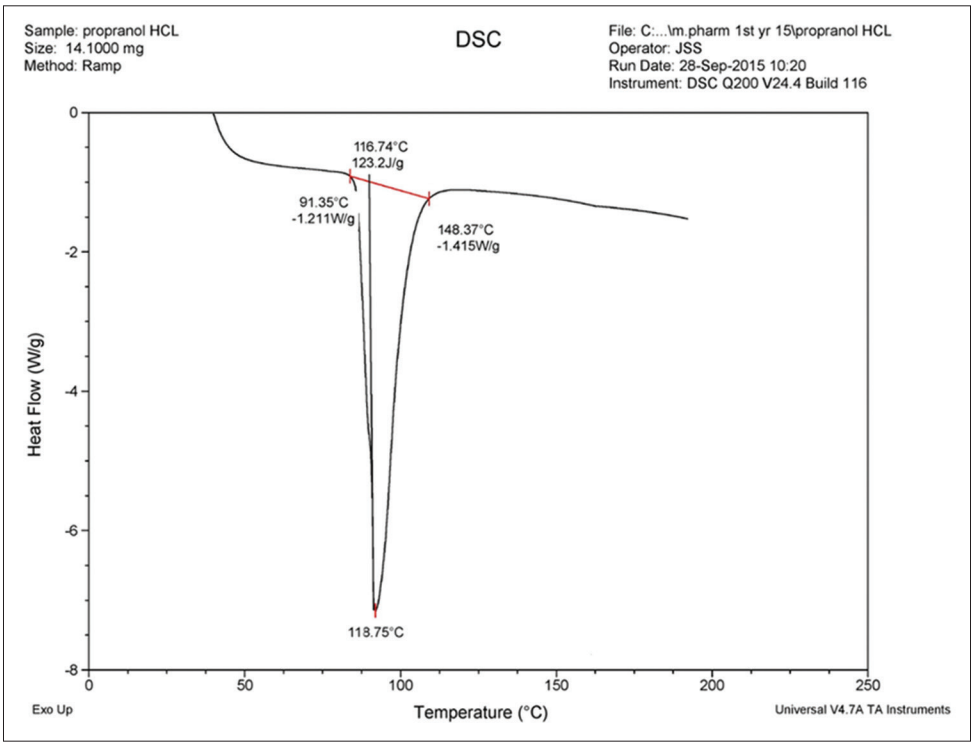

Figure 4: Differential scanning calorimetry image of propranolol hydrochloride

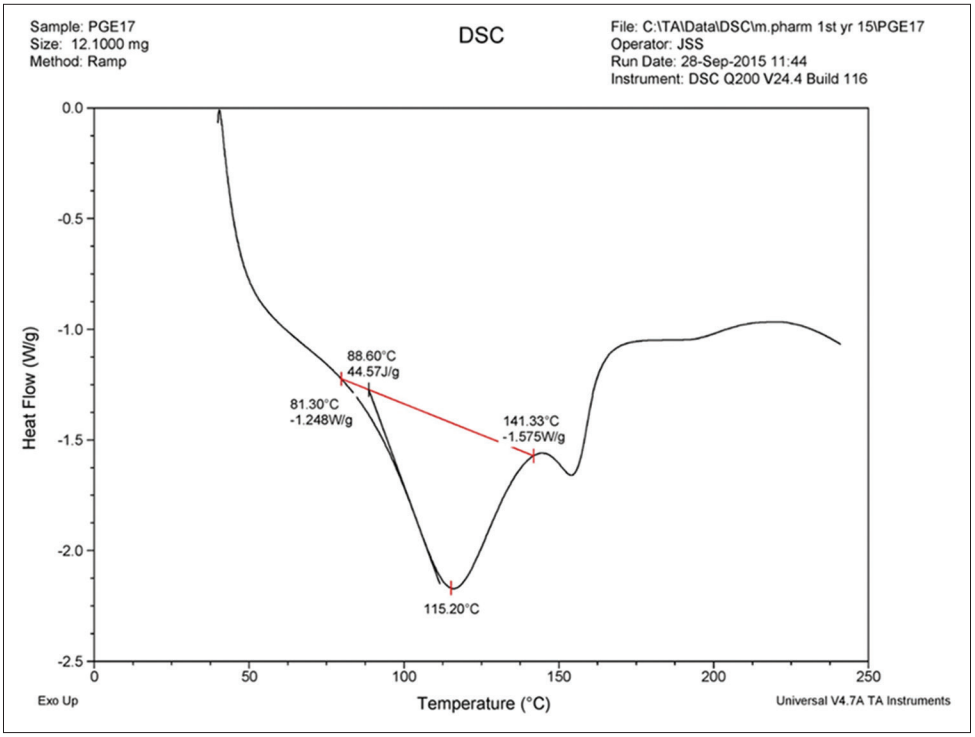

Figure 5: Differential scanning calorimetry image of propranolol hydrochloride optimized formulation PGE8

Table 5: Release kinetics of various matrix tablets with electrolytes formulations

Formulation code	Zero order		First order		Higuchi's		Peppas	
	K	R^2	*K* (h^{-1})	R^2	*K* ($m.g.h^{1/2}$)	R^2	*N*	R^2
PGE1	3.11	0.823	0.232	0.932	11.32	0.942	0.420	0.944
PGE2	4.20	0.742	0.138	0.933	12.61	0.976	0.561	0.967
PGE3	4.35	0.975	0.231	0.969	14.34	0.931	0.424	0.974
PGE4	4.14	0.821	0.172	0.933	12.76	0.974	0.531	0.963
PGE5	5.91	0.932	0.136	0.977	9.77	0.935	0.461	0.924
PGE6	5.61	0.877	0.214	0.943	10.11	0.976	0.550	0.964
PGE7	5.46	0.7241	0.145	0.933	8.11	0.924	0.413	0.932
PGE8	5.35	0.985	0.267	0.982	9.93	0.971	0.535	0.917
PGE9	4.77	0.841	0.133	0.844	14.71	0.916	0.544	0.949

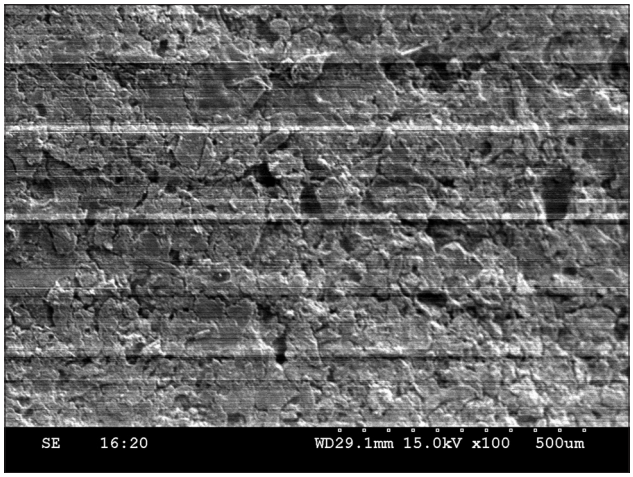

Figure 6: Scanning electron microscope image of propranolol hydrochloride optimized formulation PGE8 ×100 BMP before dissolution

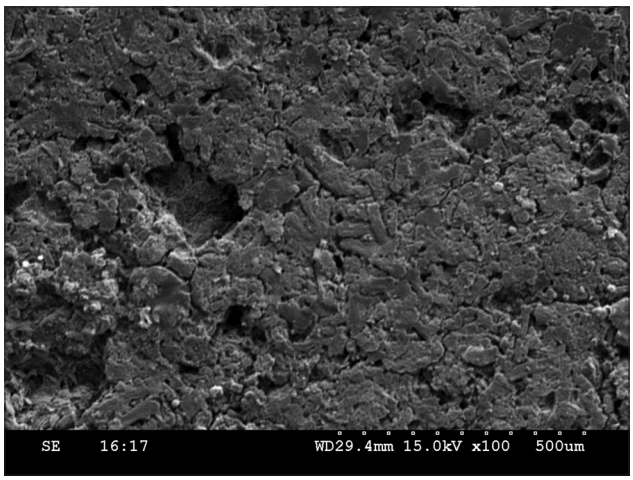

Figure 7: Scanning electron microscope image of propranolol hydrochloride optimized formulation PGE8 ×100 BMP after dissolution

concluded that the drug was released from matrix by diffusion mechanism. During *in vitro* dissolution study, the polymer swells as the dissolution media enter into the polymer matrix. The surface becomes smooth and uniform which results in a slower and controlled drug release. SEM study of matrix tablets further confirmed both diffusion and erosion mechanisms. SEM images were shown in Figures 6 and 7.

Table 6: Similarity factor for optimized matrix tablet with electrolyte formulation PGE8 in comparison with marketed formulation

Similarity factor *f*2	58
Difference factor *f*1	11

The stability studies on optimized formulations (PGE8) were carried out for 6 months as per ICH guidelines. No statistically significant changes in the physicochemical properties viz., weight of the tablet, hardness, friability, and drug content of propranolol HCl matrix tablets were observed. The result of stability tests suggested that propranolol HCl release properties from the prepared tablets were stable under the above storage conditions and no statistically significant changes in their physical attribute was observed.

CONCLUSION

From the above study, gum kondagogu was found to be an effective rate controlling polymer. In this study, it was also found that the concentration of polymer have also a tremendous effect on drug release rates, by increasing the amount of polymer drug release rate can be reduced to a high value. Several electrolytes added to selected optimized formulations showed enhancement effect on drug release rates and by the addition of these electrolytes, the formulations exhibited more substantial enhanced drug release rates.

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