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Formulation and Evaluation of Glimepiride Polymeric Blend Matrices

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ABSTRACT

Glimepiride loaded polymeric blend matrices were prepared using hydrogel forming polysaccharide like agar, isabgol, aloe vera and gelatin by solution blending method. The polymeric blends were characterized by Fourier-transform infrared spectroscopy revealed that there was no reaction between drug and polymers. The surface morphology of prepared polymeric blends was studied by scanning electron microscopy which suggested that polymeric blend matrices have smooth/rough surface with vacuoles. All the polymeric blend matrices were evaluated for weight variation, hardness, thickness and drug content which suggested that all these parameters were uniform as the total amount of the polymers was fixed to 10%. The polymer blend matrices show good hardness of more than 8 kg/cm^2 and drug content more than 95 % suggested that the solution blending method used was suitable for the preparation of polymeric blends. The polymeric blend showed good swelling in the range of 244.12 to 411.22 % within 8 h maintaining integrity of formulation. The *in vitro* release of the glimepiride was rapid in phosphate buffer pH 6.8 with more than 81.96% released within 8 h. Increases in the amount of agar enhance the in vitro release whereas increases in the amount of gelatin decrease the release of glimepiride. Hence the polymeric blends prepared with agar or gelatins with other polysaccharide as binary or ternary system extend the glimepiride up to 8 h and can be used for effective management of diabetes and also presence of aloe vera may provide synergistic hypoglycemic effect.

Keywords: Glimepiride; Polymer blend; *In-vitro* swelling; *In-vitro* release

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INTRODUCTION

The development of controlled drug delivery system for the treatment of chronic disease is of great interest since this system act as a vector carrying the drug not only to the target but also adverse effect can be reduced[1]. Over the past decades, blends have been investigated to satisfy the need of specific sectors of polymer industry. Polymer blends are a mixture of chemically different polymers or copolymers with no covalent bonding between them. Such polymer blend show superior performances over the conventional individual polymers and consequently, the range of application have grown rapidly for such class of materials. Blending provides a neat and smooth means of combining desirable properties of different polymers with synergistic effect[2]. More pure or blended materials with surface erosion characteristics are required for drug delivery. In the recent past, carbohydrate and biodegradable polymers have been extensively used to develop the controlled release formulation[3]. The blending of biodegradable polymers is a method of reducing the overall cost of the material with improved physicochemical and mechanical properties, has received considerable attention of researcher in the past several decades[4]. The development of two and three component blends using natural and biodegradable polymers represents an area of recent interest using materials with relatively low glass transition temperature[3]. The advantages of polymer blend systems for controlled release applications may include easy fabrication of devices for controlled drug release[5]. Polymer blend-based drug delivery devices have become a major area of study, and several commercially available products are already in the market[6]. The various properties of polymer blend such as biocompatibility, hydrophilicity, flexibility all make it ideal for use as drug delivery matrix. Mixing two different types of polymers, either one or both of them are biodegradable and one of them is water insoluble, will provide a polymer blend which has a unique properties. Many biodegradable water-insoluble polymers can be blended with hydrophilic polymers to form hydrogel, used as prolonged release system[7]. The use of polymer blends of sodium alginate and methyl cellulose[8], chitosan with hydroxypropylmethylcellulose and methylcellulose[4], agar and gelatin[9], Kollidon with ethyl cellulose and carnauba wax[10], (polylactic acid) PLA[11] has demonstrated prolonged dissolution rates for oral sustained drug delivery. Jianhong Liu and co-workers prepared hydrogels from a pair of natural polymers gelatin, agar and carrageenan and studied the effects of composition of these blend hydrogels on release of theophylline[12]. Samani MS et al[13] prepared polymeric blends using HPMC with Carbopol in different proportion and studied the effect of the blends on *in-vitro* release of diclofenac sodium.

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration[14]. Glimepiride is a newer sulfonylurea derivative having half life of 5 h used in the treatment of type II diabetes. It is almost absorbed from entire length of GIT. Glimepiride is insoluble in water but slightly soluble in dichloromethane, dimethylformamide, and in methyl alcohol. Commercially, Glimepiride available in tablet form and given by oral route in a dose of 1-6 mg daily[15].

Hence in the present work an attempt will be made to prepare polymeric blend matrices using natural biodegradable polymers for modified release of Glimepiride in the management of non insulin diabetes mellitus.

MATERIALS AND METHODS

Glimepiride was obtained as a gift sample from West-coast pharmaceutical works Ltd. Aloe vera was used directly as supplied by Biomax life science Ltd. Isabgol was supplied as a gift sample from Shubh psyllium industry. All other chemicals were used directly as supplied by the manufacture.

Preparation of glimepiride polymer blends

The polymer blends in the form of disc/ring were prepared from agar, gelatin, aloevera and isabgol by solution blending method at their gelation temperature of 40, 60 and 90^{o}C respectively[2]. Accurately weighed quantity of polymer (in different weight ratios) was dissolved in distilled water and glimepiride was dispersed in the solution. The mixture was slowly heated to around 70^{o}C to form a gel like consistency with continuous stirring for about one hour till optically clear solutions was formed. The resultant solution was poured into an upright placed glass syringe with a top cut off (machined perpendicularly to the cylinder axis), which was kept in an oven at 60°C before use. The warm polymer solutions in the syringe were allowed to equilibrate at the ambient temperature (about 25°C) to form a gel. After drying, solidified gel was cut in to 1 ml size. Table 1 represent the composition for all the polymer blends prepared.

Characterization of glimepiride polymeric blend matrices

a) Scanning electron microscopy (SEM)

The surface morphology of the beads was examined using scanning electron microscopy (SEM LEO 14 SSVP, Cambridge, UK). The samples were mounted directly onto the SEM sample holder using double-sided sticking tape and were gold spray-coated.

b) Fourier-transformation infrared (FTIR) spectroscopy

The drug-polymer and polymer-polymer interactions were studied by FTIR spectrometer (Perkin-Elmer (spectrum-100) Japan). 2% (w/w) of the sample (after crushing the single disc) with respect to potassium bromide was mixed, ground into a fine powder and then compressed into discs in a hydraulic press. Each disc was scanned 16 times at 2 mm/ sec at a resolution of 4 cm^{-1} using cosine apodization. The characteristic peaks were recorded.

Evaluation of glimepiride polymeric blend matrices

The prepared glimepiride polymer blend matrices were evaluated for following properties like physical appearance and surface texture, weight uniformity, thickness, hardness, drug content, swelling index, and *in-vitro* drug release study.

a) Weight uniformity

Three polymer blend ring were weighed individually using digital balance and the average weights were calculated.

b) Thickness

Thickness of the polymer blend ring was measured vernier callipers. The thickness was measured for three different polymer blend rings and average was taken.

c) Hardness

Polymer blend rings require certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the polymer blend ring was determined using Monsanto Hardness Tester. It is expressed in Kg/cm^2. Three rings were randomly picked from each formulation and the mean and standard deviation were calculated.

d) Drug content

Each polymer blend ring was placed in 100 ml volumetric flask and dissolved in pH 6.8 phosphate buffer and 2 ml was taken and diluted with pH 6.8 phosphate buffer. The absorbance of the solution was measured at 228 nm using UV/visible spectrophotometer (Shimadzu UV-1700).

e) Swelling study

A ring of polymer blend was weighed on a pre-weighed cover slip, the initial weight of the ring was recorded (W_0) and then it was kept in a petridish containing 5 ml of phosphate buffer pH 6.8. The cover slip was removed at time interval of 0.5, 1, 2, 3, 4, 5, 6, 7, 8 hr, excess of water was carefully removed and swollen rings were re-weighed (W_t). Then the percentage swelling was calculated by using formula

$$\% \mathbf{S} = \frac{\mathbf{Wt-Wo}}{\mathbf{Wo}} \mathbf{x\ 100.}$$

f) *In-vitro* drug release study

The *in-vitro* release of drug from blend disc was carried out for 8 h using paddle type Electrolab Dissolution Apparatus USP XXIII containing 900 ml of phosphate buffer pH 6.8 maintained at 37±0.5ºC and speed of agitation at 50 rpm. At prefixed time (every 1 h), 5 ml of solution was withdrawn and the absorbance was measured at 228 nm using Shimadzu-1700 UV-Visible spectrophotometer. The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5 ml with same dissolution medium.

RESULTS AND DISCUSSION

In the present study polymeric blend matrices loaded with glimepiride were prepared for modified release of glimepiride in the management of non insulin dependent diabetes. The polymeric blends of glimepiride were prepared by solvent casting method using natural polymer in the different ratios such as agar, gelatin, isabgol and aloe vera as shown in Table 1. As a preformulation study for drug polymer compatibility by FTIR spectra represented in Figure 1 gives conformation about their purity and showed no interaction between drug and selected polymers. Selected polymeric blends were characterized by SEM analysis and represented in the Figure 2. The polymeric blend of gelatin with isabgol showed near to smooth surface with minimum vacuoles. The polymeric blend of agar with gelatin showed smooth surfaces with large number of vacuoles. The polymeric blend of agar with aloe vera showed rough surface with number of vacuoles. All the polymer blends were shows smooth surface and elegant texture. The weight of polymer blend was determined using digital balance and the average weight of polymer blends from PB1to PB14 shown in Table 2 was in the range of 95.66 ± 1.52 to 100 ± 1.115 mg. This uniformity in the weight of polymer blends indicated that minimum amount of polymer was lost during preparation and also the overall ratio of polymers used was fixed to 10% w/w, hence the average weight did not showed much variation. The thickness of the polymer blend was measured using screw gauge and the average thickness of the polymer blends from PB1 to PB14 shown in Table 2 was in the range from 3.61 ± 0.12 to 3.74 ± 0.10 mm. The uniformity in the thickness of the polymer blends indicated that the blends did not undergo much shrinkage and also used same syringe for the preparation of entire batches of blend formulations. The hardness of the polymer blend was measured using Monsanto hardness tester and the average hardness of the polymer blends from PB1 to PB14 shown in Table 2 was in the range of 6.21 ± 0.11 to 8.33 ± 0.05 kg/cm^2. The results of hardness suggested that the addition of gelatin

and isabgol increased the hardness whereas presence of aloevera decreased the hardness, also increase in amount of gelatin or agar increased the hardness. Glimepiride polymer blends were evaluated for drug content estimation and, the results are shown in Table 2. The drug content was found in the range of 96.11 ± 0.84 to 98.76 ± 0.37%, suggesting that drug was uniformly dispersed throughout polymer blend and the standard deviation value calculated for all formulation was less which indicated that the results were reproducible. Hence solution blending method was suitable for the preparation of polymeric blend of glimepiride using these polysaccharide polymers.

Table 1: Formulations of glimepiride incorporated polymer blends

Ingredient	Formulations													
	PB1	**PB2**	**PB3**	**PB4**	**PB5**	**PB6**	**PB7**	**PB8**	**PB9**	**PB10**	**PB11**	**PB12**	**PB13**	**PB14**
Glimepiride (mg)	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Agar (%w/w)	67.6	75.0	67.6	75.0	--	--	--	--	50.0	50.0	25.0	16.6	25.0	16.6
Gelatin (%w/w)	--	--	--	--	67.6	75.0	67.6	75.0	25.0	75.0	25.0	33.4	25.0	33.4
Aloe vera (%w/w)	33.4	25.0	--	--	33.4	25.0	--	--	--	--	50.0	50.0	--	--
Isabgol (%w/w)	--	--	33.4	25.0	--	--	33.4	25.0	--	--	--	--	50.0	50.0

Table 2: Evaluation parameters of glimepiride polymer blend

Formulations	Weigh (mg)	Thickness (mm)	Hardness (kg/cm^2)	Drug content (%)
PB1	96.91 ± 1.155	3.650 ± 0.098	6.21 ± 0.114	96.41 ± 0.491
PB2	95.66 ± 1.528	3.720 ± 0.140	6.64 ± 0.141	97.88 ± 0.676
PB3	95.69 ± 1.528	3.723 ± 0.117	7.45 ± 0.096	98.51 ± 0.320
PB4	97.33 ± 1.528	3.710 ± 0.111	7.33 ± 0.125	97.31 ± 0.341
PB5	99.33 ± 1.528	3.667 ± 0.102	7.11 ± 0.125	97.11 ± 0.367
PB6	100.00 ± 1.155	3.727 ± 0.092	7.45 ± 0.095	97.27 ± 0.347
PB7	97.66 ± 1.528	3.617 ± 0.129	6.85 ± 0.135	98.15 ± 0.392
PB8	96.00 ± 1.732	3.643 ± 0.123	8.33 ± 0.056	96.67 ± 0.472
PB9	97.66±0.577	3.690 ± 0.043	7.31 ± 0.080	96.11 ± 0.845
PB10	98.66 ± 0.577	3.703 ± 0.185	6.98 ± 0.090	97.47 ± 1.496
PB11	97.89± 1.528	3.617 ± 0.155	8.26 ± 0.131	98.02 ± 0.496
PB9	97.66±0.577	3.690 ± 0.043	7.31 ± 0.080	96.11 ± 0.845
PB10	98.66 ± 0.577	3.703 ± 0.185	6.98 ± 0.090	97.47 ± 1.496
PB11	97.89± 1.528	3.617 ± 0.155	8.26 ± 0.131	98.02 ± 0.496
PB12	96.66±0.577	3.747±0.113	7.48±0.050	98.08±0.581
PB13	100.33±0.577	3.623±0.115	7.75±0.118	97.98±0.838
PB14	99.38±1.528	3.747±0.100	7.70±0.117	98.76±0.374

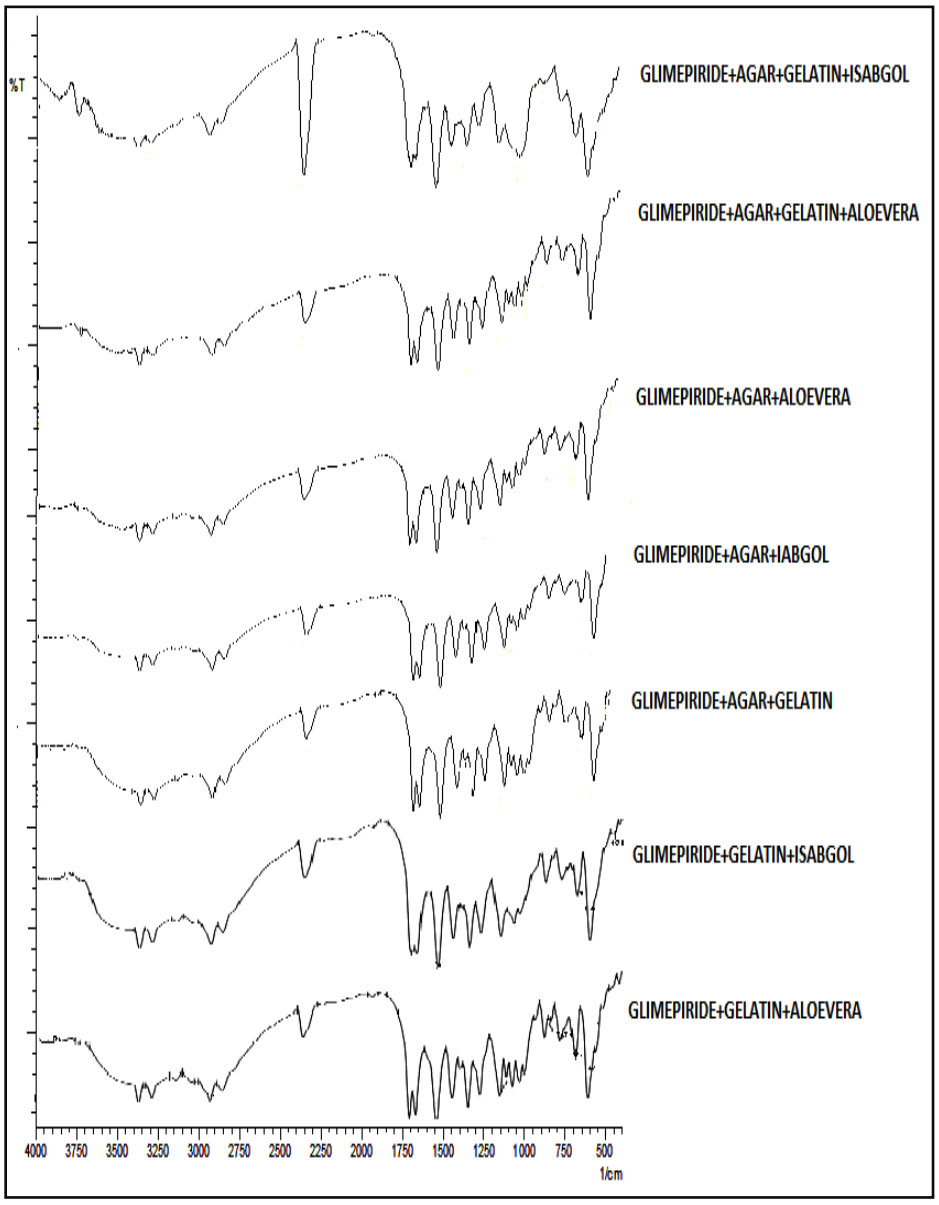
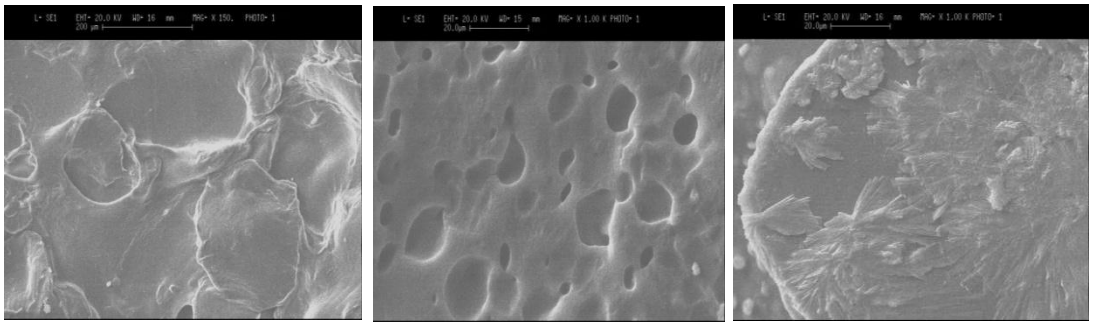


Figure 1: FTIR spectra of drug loaded polymeric blend combination



(a) **(b)** **(c)**

Figure 2: Scanning electron micrograph of glimepiride loaded polymeric blends containing (a) agar + aloevera PB2 (b) agar + gelatin PB10 (c) gelatin + isabgol PB8

The *in-vitro* swelling of the polymer blend was measured in phosphate buffer pH 6.8 and is represented in Figure 3 & 4. The *in-vitro* swelling of the polymer blend was decreased as the amount of agar was increased in binary polymeric blend (PB2 & PB4) and in case of gelatin binary blends (PB6 & PB8) there was increased swelling as the gelatin was more. When agar was blended with gelatin in binary system there was decreased in swelling as the as the amount of agar decreased and also in ternary blends of agar with gelatin and other polysaccharides. The *in-vitro* release of glimepiride from the polymer blend is represented in Figure 5 and 6. The in vitro release depends upon the polysaccharide used, molecular weight, viscosity of the polymer, dissolution medium and the blending ratios of the polymer. The polymer blends may report to form interpenetrating network (IPN) which may helpful to slow down the release rate. The *in-vitro* release of the glimepiride was rapid in phosphate buffer pH 6.8 with more than 81.96 % within 8 h. There was very little effect of increased or decreased in amount of either agar or gelatin in binary and ternary blends. Increases in the amount of agar enhance the in vitro release whereas increases in the amount of gelatin decrease the release of glimepiride. The overall in vitro release of glimepiride from all the polymeric blends suggested that there may be a loose interpenetrating network (IPN) was formed and hence, the release of insoluble glimepiride was extended up to 8 h. The release could be controlled by the addition of some cross-linking agent in to the polymeric blend of these polysaccharide which could expected to form more denser inter penetrating network (IPN). The in vitro release data was analyzed statistically to obtain release kinetic and mechanism of release by regressional analysis. The correlation coefficient expressed as ‘r’ value for different equation like zero order, first order, Higuchi and Korsmeyer-Peppas is represented in Table 3. The ‘r’ value obtained for first order kinetics was in the range of 0.9467 to 0.9940 which was more than ‘r’ value of zero order release. Hence, it would be expected that the release of drug from polymer blend obeys first order kinetics. In the preparation of polymer blend polysaccharide hydrogel forming polymers were used and hence, the in vitro release expected to follow Higuchi equation with high ‘r’ value of 0.9202 to 0.9832 due to diffusion mechanism. In order to find out more reliable kinetics and mechanism of drug release further the data was fitted according to Korsmeyer-Peppas equation. The r value was 0.9984 to 0.9739 with the slop (n) value ≥ 0.5 suggesting that the release followed analomous (non-fickian diffusion) mechanism because of the less dense interpenetrating network (IPN) expected to form in the polymer blend.

Table 3: Kinetic data of glimepiride polymeric blend

Formulation	Zero-order	First- order	Higuchi	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	n
PB1	0.9551	0.9879	0.9623	0.9885	0.7480
PB2	0.9703	0.9738	0.9264	0.9878	0.7951
PB3	0.9419	0.9767	0.9456	0.9731	0.8988
PB4	0.9914	0.8424	0.9202	0.9744	0.8243
PB5	0.8536	0.9653	0.9818	0.9740	0.5427
PB6	0.9831	0.9467	0.9168	0.9812	0.9136
PB7	0.9277	0.9822	0.9716	0.9804	0.6822
PB8	0.9550	0.9867	0.9763	0.9918	0.7179
PB9	0.9961	0.9165	0.9204	0.9984	0.8866
PB10	0.9752	0.9729	0.9472	0.9739	0.8207
PB11	0.9730	0.9828	0.9549	0.8320	0.9923
PB12	0.9503	0.9782	0.9417	0.9785	0.9059
PB13	0.9857	0.9574	0.9594	0.9940	0.7322
PB14	0.9739	0.9661	0.9271	0.9835	0.9429

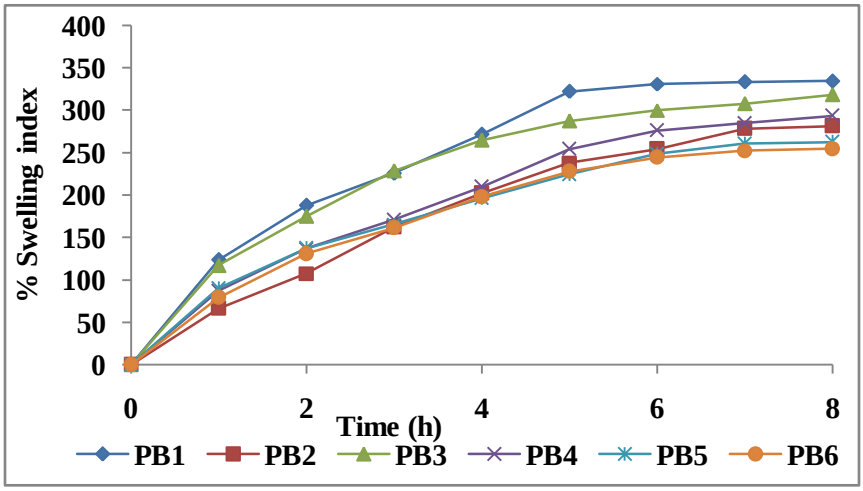


Figure 3: *In-vitro* swelling of glimperide loaded polymeric blend matrices PB1 to PB6

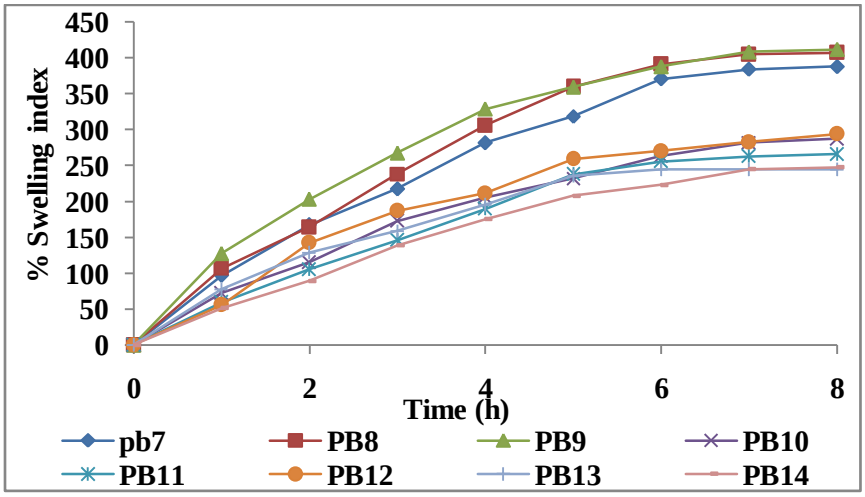


Figure 4: *In-vitro* swelling of glimperide loaded polymeric blend matrices PB7 to PB14

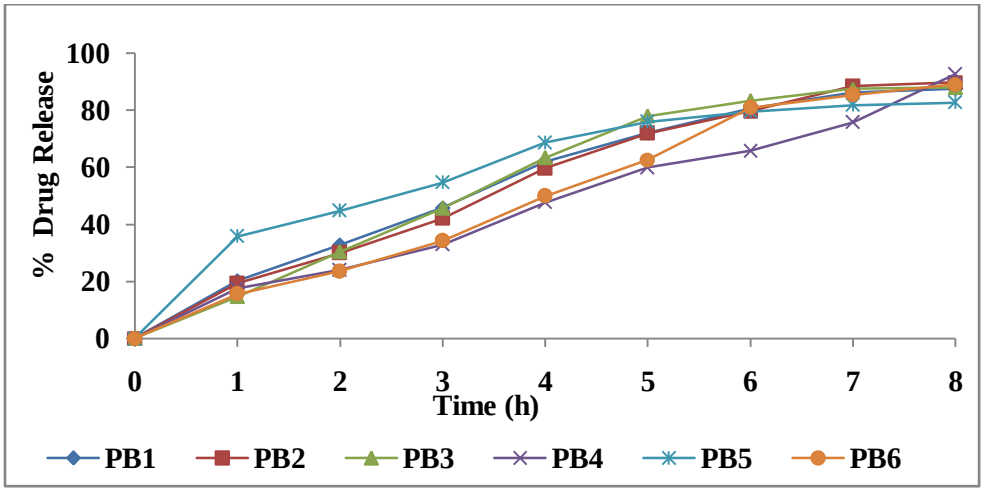


Figure 5: In-vitro release of glimepiride from polymeric blends PB1 to PB7

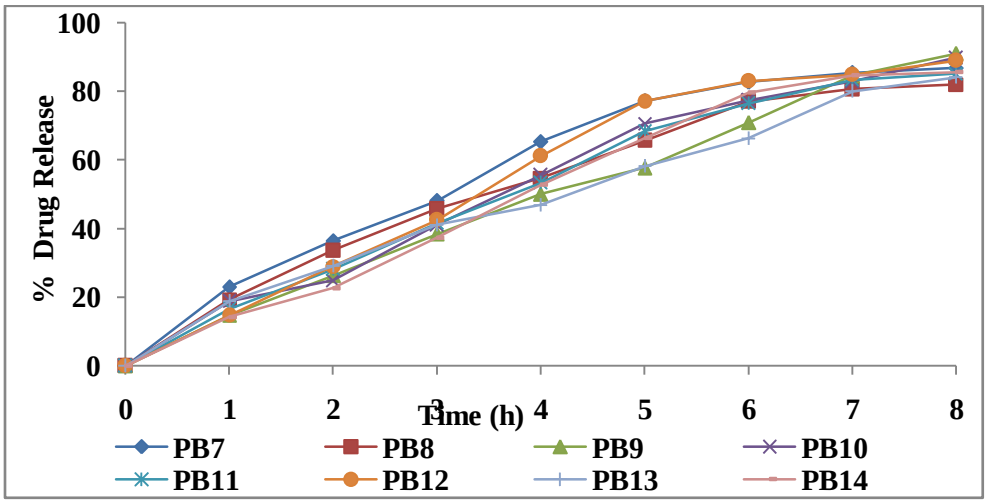


Figure 6: In-vitro release of glimepiride from polymer blends PB7 to PB14

CONCLUSION

Hence the polymeric blends prepared with agar or gelatins with other polysaccharide as binary or ternary system extend the glimepiride release up to 8 h. There was pharmaceutics and pharmacodynamic scope for further study using cross-linking agent along with these polymers and also presence of aloe vera may gives synergistic hypoglycemic effect.

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