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Research Article

Development of Interpenetrating Polymer Networks of Chitosan and Guar Gum for Propranolol Hydrochloride

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Abstract: The purpose of this study was to develop a Interpenetrating Polymer Network (IPN) of Chitosan and Guar gum. The drug Propranolol HCl, a calcium channel blocking agent used in the treatment of angina pectoris, hypertension and cardiac arrhythmia. Propranolol HCl has a short elimination half-life; this will bring down its dosing frequency to once a day and on the same time make a zero order release system. Microspheres were prepared by using controlled release polymers. The formulations were evaluated for pharmacopoeial quality control tests and all the physical parameters evaluated were within the acceptable limits. Formulation A7 was proved to be good drug content, % drug encapsulation efficiency and % drug release up to 12 h as compared to the other formulations. Stability studies were carried out on the optimized formulation A7 for period of 3 months at 40^0c/75 %RH. Finally it was observed that there was no change in physiochemical and physical properties as well as in drug release profile even after storage at 45 °C and 75 %RH for three months.
Keywords: Interpenetration polymer networks, Propranolol hydrochloride, drug encapsulation efficiency, stability study.

INTRODUCTION

Pharmaceutical field is the research and development intensive field. The search for safe and effective drugs continues to be major effort involving the pharmaceutical industries, universities and government. The complexities of discovering and testing new drugs have become enormous as a result of the many aspects of safety, efficacy and economics that determine acceptability of a drug. Indeed the situation as a whole has become almost a Gordian knot. The concept of controlled drug delivery has been embraced with great enthusiasm by many as the sword that will slice through Gordian knot [1, 2].

In recent years multi component drug delivery systems have been developed for potential therapeutic and diagnostic applications and among these, semi-Interpenetrating Polymeric Networks (semi-IPNs) and Interpenetrating Polymeric Networks (IPNs) have emerged as innovative biomaterials for drug delivery and as scaffolds for cell cultures. These networks most often show physico-chemical properties that can remarkably differ from those of the macromolecular constituents. Importantly, the network properties can be tailored by the type of polymer and its concentration, by the applied cross linking method as well as by the overall procedure used for their preparation. In many cases, polysaccharides are selected for the formation of IPN hydrogel networks, which are either chemically or physically, cross linked. Sometimes both entangled macromolecules are based on polysaccharides, but often also combinations of synthetic polymers together and polysaccharides chains are used to create (semi)-IPNs. A quite large number of polysaccharides have been investigated for the design of (semi)-IPNs for drug delivery and tissue engineering applications. This review article however mainly focuses on two of the most studied polysaccharide (semi)-IPNs, namely those based on alginate and hyaluronic acid [3].

Propranolol hydrochloride (PPL HCl) is a β adrenergic blocking agent, effective in treatment of Hypertension and angina. PPL HCl has short plasma half-life of 3-5 hrs. Thus, multiple doses is needed to maintain therapeutic concentration of the drug in plasma for better therapeutic response and improved patient compliance. It is necessary to develop sustained release preparations with extended clinical effects. The main objective of this research work is to develop a novel pH-independent sustained release drug delivery system of a water-soluble basic drug. Weakly basic drugs and their salts thereof demonstrate pH-dependent solubility. Therefore the rate and extent of drug release from most controlled release system are influenced by

the pH of the dissolution medium. This dependency of drug release on pH may lead to individual inter and intra subject variations in bioavailability of drugs and to achieve pH-independent drug release [4].

MATERIAL AND METHODS

Material

Propranolol HCl was a kind gift from Glenmark Pharmaceuticals Ltd., Mumbai. Chitosan were purchased from Research-Lab Industries Mumbai. Guar Gum was purchased from Loba Chemicals, Mumbai. Other excipients used were of standard pharmaceutical grade.

Methods

Preformulation study

Melting point determination

The melting points of drug were resolute through melting point equipment by means of capillary technique. Observed value was compared with the reported standard value.

Confirmation of drugs

Confirmation of drug was done by using UV and FTIR and compare with the standard spectra [5-6].

Assessment of the drug-polymer interaction

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe. If the excipients are new and not been used in formulations containing the active substance, the compatibility studies are of paramount importance.

Method

Drug and excipients were mixed in the ratio of 1:1 and stored in glass vials at 500C. The samples were analyzed for compatibility by TLC after 1,3 and 7 weeks.

Adsorbent layer: Silica gel G
Layer thickness: 0.25 cm
Size: 10X20 cm

Preparation and drying

The plates were activated at 105^0C for 30 min prior to use.

Separation technique

Ascending

Chamber saturation state

The chamber was line on three sides with filter paper dipped in the mobile phase and saturated for 30 min.

Length of run: 10 cm

Solvent composition

And total volume: Benzene: Methanol: Ammonia (72:25:0.25) v/v 100 ml.

Preparation of sample

Sample equivalent to 10 mg of drug is dissolved in 5 ml of methanol (supernatant used for spotting).

Reference solution:10 mg of pure drug is dissolved in 5ml of methanol.

Procedure:5 µl of reference and test solutions were applied as spots on dry activated plate. The solvent front was developed up to 10 cm. The plate was dried in air and it was examined under UV chamber.

Rf = Distance of the solute from the starting point/Distance of the solvent form the starting point

Preparation of calibration curves using UV Spectroscopy

Calibration curve of Propranolol HCl were done in distilled water, 0.1N HCl, Phosphate buffer pH 6.8, Phosphate buffer pH 7.4. An accurately weighed amount (100 mg) of drugs Propranolol HCl was dissolve in 50 mL of purify water within 100 mL volumetric flasks and sonicated for two minutes and then quantity be completed to the marks through same purify water to prepare stock solutions of 1000 µg/mL. This was subsequently diluted with distilled water to obtain solutions of 10 ppm to 50 ppm concentration at 216 nm [7, 8].

Propranolol HCl Microspheres

Propranolol Microspheres were prepared by using calcium chloride (CaCl2) as cross-linking agent by ionic gelation method. Briefly, required amounts of chitosan and guar gum dissolved in deionized water (20 ml) using magnetic stirring for 30 min. Afterwards, Propranolol was added to the mixture solutions of chitosan-guar gum for each formulation maintaining polymer to drug ratio and mixed thoroughly using a homogenizer (Remi Motors, India). The final chitosan-guar gum mixture solutions containing Propranolol were ultra-sonicated for 5 min for debubbling. The resulting dispersion was then added via a 21- gauge needle drop wise into 5% (w/v) CaCl2 solution. Added droplets were retained in the CaCl2 solution for 15 min to complete the curing reaction. The wet microspheres were collected by decantation. These wet microspheres were washed two times with distilled water and dried at 37◦C for overnight. The dried microspheres were stored in a desiccator until used (Table 1) [9-11].

Table-1: Composition of experimental batches A1-A7 containing Chitosan and Guar Gum (all quantities in mg)

Formulation	A1	A2	A3	A4	A5	A6	A7
Propranolol HCl	120	120	120	120	120	120	120
Chitosan	50	100	--	--	125	125	100
Guar Gum	--	--	100	50	50	75	75
Calcium Chloride	10	10	10	10	10	10	10

***In-Vitro* evaluation of Propranolol HCl microspheres**

Percent yield value

The percentage yield value of microspheres was determined from the ratio of amounts of solidified total microsphere to total solid material used in the inner phase, multiplied by 100 [12, 13].

Percent yield value = Practical yield value/Theoretical yield value x100

Drug encapsulation efficiency (DEE)

50 mg of microspheres were accurately weighed and crushed by using mortar and pestle. Crushed microspheres were suspended in 30 ml water and stirred for 5 hrs. Then it was filtered through Whatmann filter paper no 44. Then 1 ml of this solution diluted to 10 ml with distilled water and absorbance was measured by using UV spectrophotometer against distilled water as a blank. The drug content was determined from the standard curve. Encapsulation efficiency was calculated from following relationship [14-16].

Encapsulation efficiency (% DEE) = Estimated drug content/Theoretical drug content x100

Particle size analysis of microspheres

Average particle diameter and size distribution of microspheres were determined by laser diffractometry using a Mastersizer Micro Version 2.19 (Malvern Instruments, Malvern, UK). Approximately 10 mg of microspheres were stirred in 10 ml distilled water containing 0.1% Tween 80 for several minutes on magnetic stirrer. Then aliquot of the microsphere suspension was added into recirculation unit, which was subsequently circulated 3500 times per minute. Particle size was expressed as equivalent volume diameter [16].

Drug content uniformity of microspheres

100 mg of microsphere added to a beaker containing 100 mL of phosphate buffered saline of pH 7.4. The medium was stirred with magnetic bead. The contents were filtered using whatmann filter paper and the filtrate was examined for the drug content against the reference solution spectrophotometrically. The experiment was repeated to validate the result [17].

***In vitro* drug release study from microspheres**

Microspheres equivalent to 100 mg of drug sample were filled in a capsule and *in vitro* drug release was studied using USP Apparatus II with 900 ml of dissolution medium at 37.5 ± 0.1 °C for 12 h at 100 rpm. 0.1N HCl (pH 1.2) was used as dissolution medium for the first 2 h, followed by pH 6.8 phosphate buffer for further 10 h. 5 ml of sample was withdrawn after every hour, and was replaced with an equal volume of fresh dissolution medium. Collected samples were analyzed by spectrophotometrically. The study was performed in triplicatem [18-20].

***In vitro* drug release kinetic modeling**

The *in vitro* drugs releasing information were investigated in favor of the types of releasing mechanisms follow. To describe the kinetics of drug release from the controlled release transdermal patch, the releasing information be evaluated among the help of arithmetical model such as zero-orders, first-orders, Higuchi as well as Koresmeyer-Peppas models by means of PCP Disso v2.08 softwares [21-22]. The coefficient of correlation of each of this kinetics was calculated for optimized formulations by following equation shown in Table 2.

Table-2: Kinetic release models with its equation

Sr. no.	Release model	Equation
1.	Zero order	(Mo-Mt) = ko t
2.	First order	ln (Mo / Mt) = K1t, y = mx
3.	Higuchi	Mt =k √ t, y = mx
4.	Korsemeyer- peppas	Mt/ M∞ =K.tn

Mo, Mt with M∞ corresponds to the drugs quantity in use by the side of instance equivalent to zero, dissolve by the side of a time t, in addition to by immeasurable times, correspondingly. The term Wo as well as Wt refers to the weights of the drugs in use originally plus on time, correspondingly. Different extra term i.e. K, Ko, K1, K1/3 and K refers to the releasing kinetics constant obtain commencing the linear curve of korsmeyer-peppas, zero orders, first orders and Higuchi model respectively.

Stability study

Stability Study was carried out for optimed Propranolol microspheres formulations A7 to assess its stability, as per ICH guidelines. The optimized formulation were enclose inside the laminated aluminum foil along with was located inside the accelerated stability chambers (6CHM-GMP, Remi Instruments Ltd., Mumbai) next to prominent temperatures in addition to humidity condition of 40^0C/ 75% RH with a control sample was placed at an ambient condition in favor of a time of 3 month. Sampling was completed next to a programmed occasion of initial 0, 1, 2 and 3 months interval respectively. By the side of the conclusion of study, sample was consider for the drug contents,% DEE and *in vitro* drugs releasing in addition to extra physicochemical parameter [23-24].

RESULT AND DISCUSSION

Melting point determination

The melting end of Propranolol HCl was resolute by means of capillary technique in addition to be set up to Propranolol - 161-163°C which complies with the reported value. The sample of Propranolol HCl was studied for organoleptic characteristics and showed colorless or white crystalline powder. Loss on drying of Propranolol HCl found not more than 0.1 %.

Confirmation of drugs and assessment of drug-polymer interactions

The drugs Propranolol HCl were identified by U.V spectra, I.R spectra. The interpreted result was presented in the Figure 1-3 shows that it coincides with standard reference spectra.

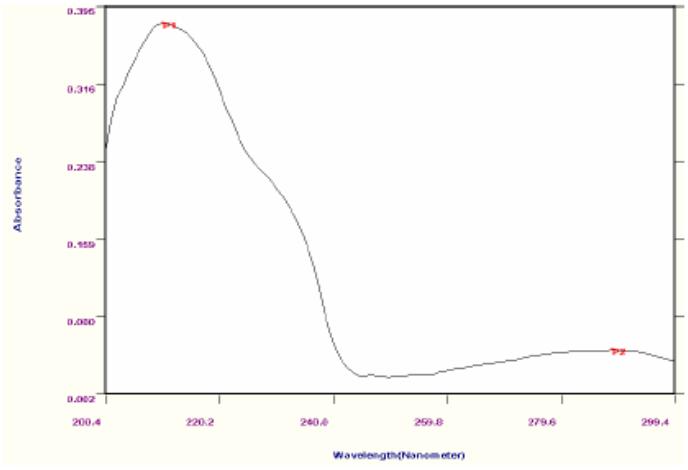

Fig-1: UV spectrum of Propranolol Hydrochloride in Simulated Gastric Fluid (pH 1.2 Buffer)

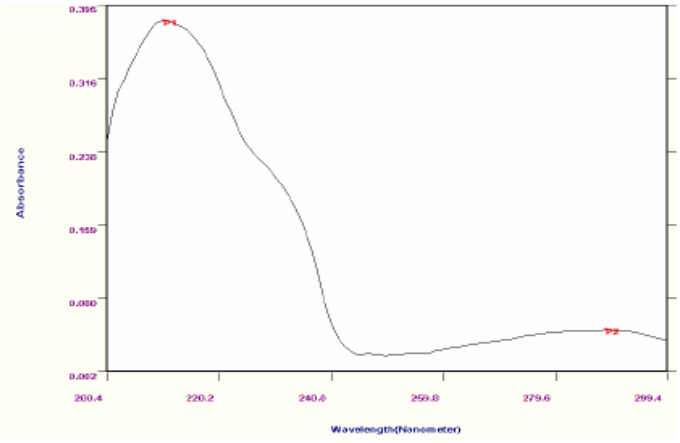

Fig-2: UV spectrum of Propranolol Hydrochloride in Simulated Intestinal Fluid (pH 7.4 Buffer)

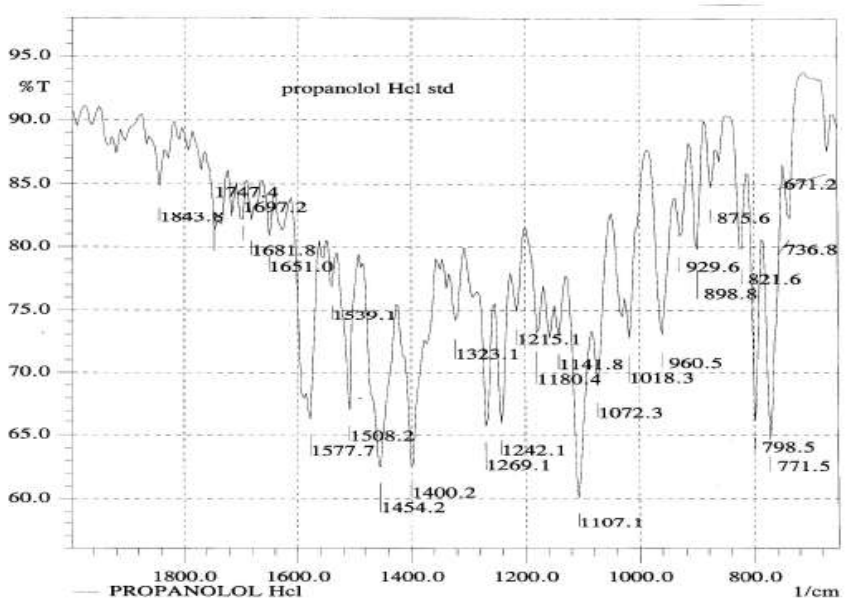

Fig-3: I.R spectra of Propranolol HCl

Assessment of the drug-polymer interaction

Thin layer chromatography was carried out to check for the possible drug excipients interaction. The Rf values of the drug and excipients used in the study revealed negligible difference. This established that the drug and all the excipients used in the study revealed no interaction between them and indicated that they were compatible with each other shown in Table 3.

Table-3: Data for Rf values of Propranolol HCl and excipients compatibility testing.

Spot No.	Sample	Rf value
1	Propranolol HCl	0.66
2	Propranolol HCl + Chitosan	0.68
3	Propranolol HCl + Guar Gum	0.67
4	Propranolol HCl + Chitosan + Guar Gum	0.65

Calibration curves in various solvents

The calibration curves of Propranolol HCl were measured in distilled water, 0.1N HCl, phosphate buffer pH 6.8 and phosphate buffer pH 7.4 which showed good linearity with the regression coefficient (R^2) as 0.998, 0.997, 0.998 and 0.996 respectively. These are shown in Figure 4-7.

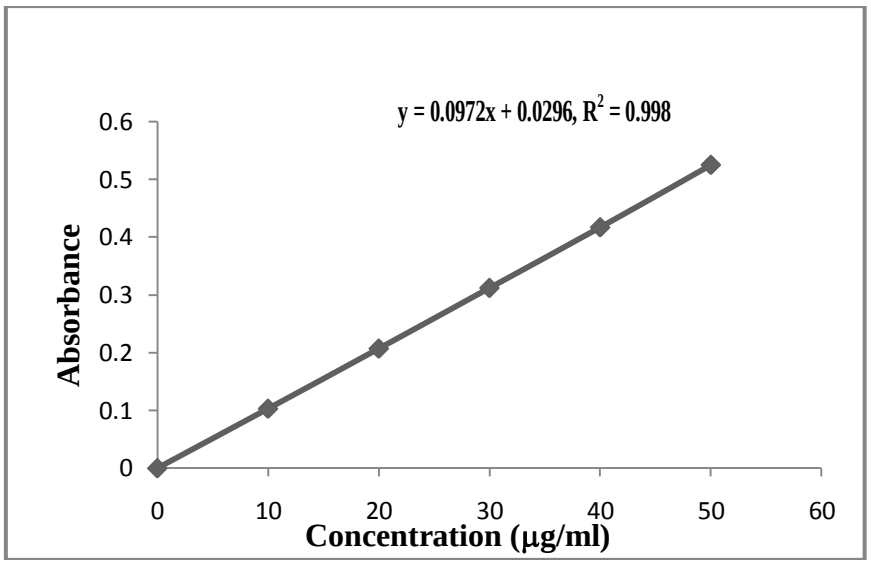

Fig-4: Calibration curve of Propranolol HCl in distilled water

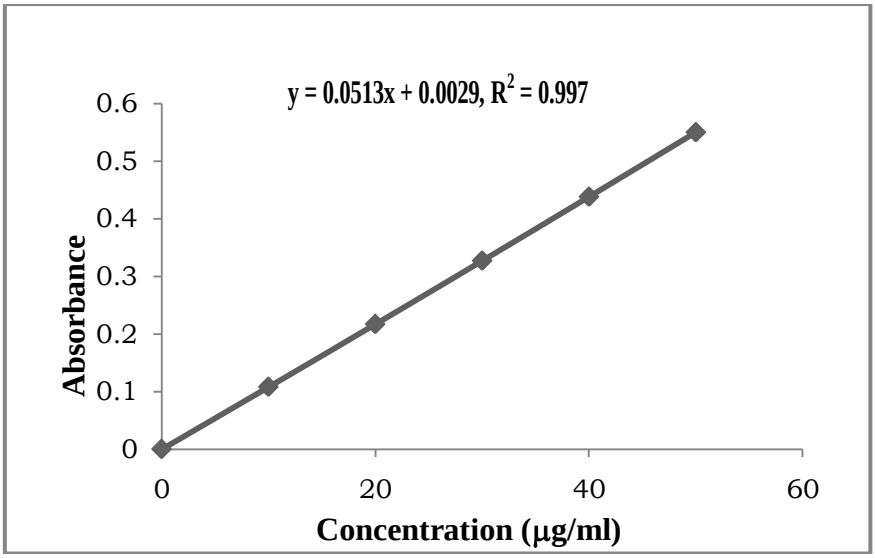

Fig-5: Calibration curve of Propranolol HCl in 0.1 N HCl

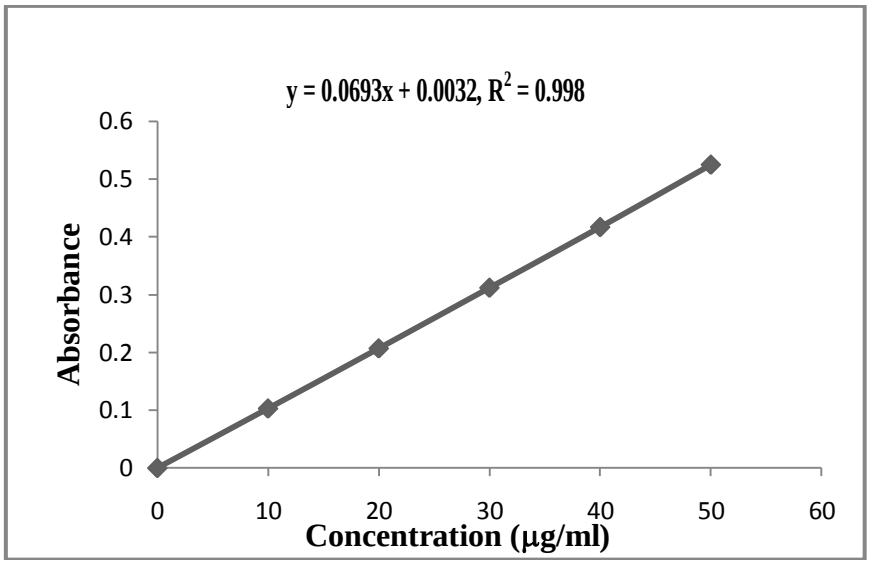

Fig-6: Calibration curve of Propranolol HCl in Phosphate buffer pH 6.8

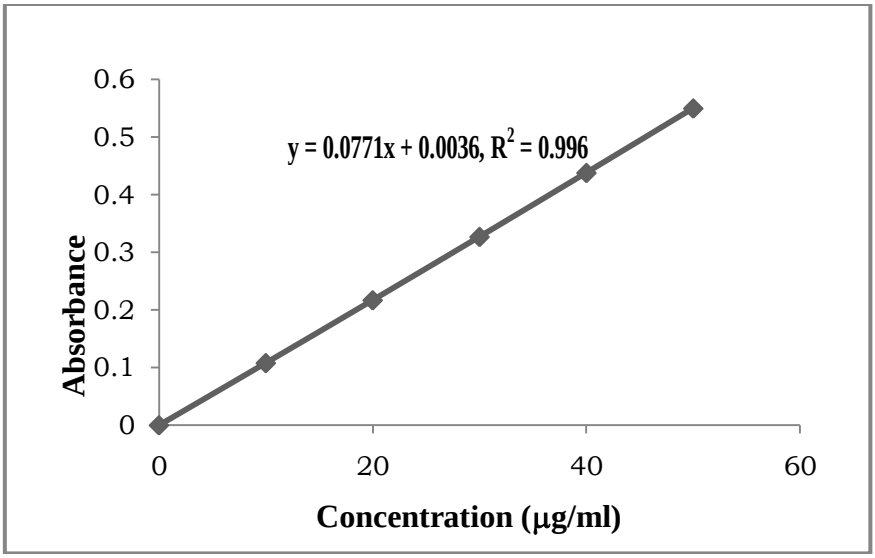

Fig-7: Calibration curve of Propranolol HCl in Phosphate buffer pH 7.4

Propranolol HCl microspheres evaluation

The prepared microspheres were evaluated for their physicochemical characteristics such as % Yield value, % Drug encapsulation efficiency (DEE), Particle size (μm), % Drug content. % Yield value of microsphere A1-A7 was found to be between 83.63 % - 96.14 %. % Drug encapsulation efficiency (DEE) was found to be between 66.51±0.580 - 74.28±1.169. Particle size of microsphere was found to be between 18.00 μm - 37.68 μm. Drug content of microsphere was found to be between 97.26 % - 99.71 %. Results were shown in Table 4.

Table-4: Evaluation of formulated Microspheres A1-A7

Formulation code	% Yield Value	% Drug Encapsulation Efficiency (DEE)*	Particle Size (μm)	% Drug content
A1	83.98	66.51±0.580	35.91	98.63
A2	83.63	68.19±1.873	37.68	97.26
A3	86.57	71.95±0.687	25.33	99.71
A4	86.26	72.44±0.770	18.00	98.64
A5	91.24	73.09±1.891	23.12	99.55
A6	91.08	73.38±0.912	29.63	98.47
A7	96.14	74.28±1.169	21.17	99.19

* Encapsulation efficiency given as mean ± SD., n=3

***In vitro* drug release studies**

Release studies are required for predicting the reproducibility of rate and duration of drug release. The importance of polymer dissolution on drug release from matrices has been known for ensuring the sustained release performance. The result indicated that the release of drug from microspheres increases with increasing concentration of Chitosan and guar gum. The drug release was found to increase on increasing the concentration of hydrophilic polymer in the polymer matrix. This is due to the fact that dissolution of aqueous soluble fraction of the polymer matrix leads to the formation of gelaneous pores. The formation of such pores leads to decrease the mean diffusion path length of drug molecules to release into the diffusion medium and hence, to cause higher release rate. Formulation batch A1-A4 releases drug in 6-10 h due to single use of polymer. In the later batches A5-A7 use of combination of polymers in that case it exhibits good drug release up to the 12 h. Formulation A7 shows maximum drug release with controlled manner.

Table-5: Cumulative % drug release of formulated Microsphere (A1-A7)

Time (h)	Cumulative % drug release						
	A1	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**
0.25	7.31±0.07	6.84±0.08	6.61±0.91	6.53±1.05	5.38±0.68	5.51±1.06	5.05±0.36
0.5	12.38±1.11	11.74±1.65	8.58±1.14	9.27±1.25	9.40±1.27	7.73±1.12	8.43±0.83
1	21.85±1.15	17.58±1.89	16.66±1.58	15.72±1.37	14.43±1.72	10.41±1.04	9.71±1.74
2	37.73±1.48	32.67±2.53	28.04±2.69	29.90±2.04	23.74±2.58	19.73±1.38	17.49±1.46
3	49.92±2.05	42.92±2.84	38.16±3.82	41.58±2.74	31.48±3.62	27.51±1.32	30.78±2.80
4	74.17±2.42	53.84±3.62	46.43±3.51	49.38±2.81	41.79±3.95	38.33±3.43	43.82±2.63
6	-	76.37±2.84	61.79±3.37	74.66±3.74	56.28±3.81	52.71±4.41	60.75±3.63
8	-	-	-	-	63.31±3.52	61.02±4.38	73.44±3.71
10	-	-	-	-	71.33±3.71	74.88±4.02	75.86±1.34
12	-	-	-	-	79.33±3.71	80.88±4.02	82.86±1.34

***In vitro* drug release kinetics**

To understand the mechanism of drug release from the formulations, the data were treated with zero order (cumulative percent of drug release vs. time), first order (log cumulative percentage of drug remaining vs. time), Higuchi model (cumulative percent of drug release vs square root of time) and Korsmeyer & Peppas (log cumulative percent of drug release vs log time) equations. When the result was plotted according to the zero order equation, the formulations showed good linearity, when the same data was plotted according to the first order equation, Higuchi's equation and Korsmeyer & Peppas equation it shown a fair linearity. The results are given in the Table 6 which indicates that the release of drug from the formulations follows zero order release kinetic model. Formulation A7 indicates that release of drug follows zero order kinetic model.

Table-6: *In vitro* drug release kinetics of optimization batch A7

Batch code	R^2 (coefficient of determination) of various Kinetic Models			
	Zero order	First order	Higuchi release	Korsmeyer & Peppas release
A7	0.817	0.703	0.782	0.793

Stability study

Propranolol HCl optimized formulation (A7) was found to be stable during accelerated stability studies for % DEE 74.28,73.08, 72.97, 71.28 % at 0, 1, 2, 3 months respectively at 40°C /75% RH. *In vitro* drug release studied for 12 h was found to be 82.86, 79.12, 78.99 and 77.08 at 0, 1, 2, 3 months respectively at 40°C/75% RH. The results are given in Table 7. It also observed that, there was no significant change in behavior. Finally it was observed that there was no change in physiochemical and physical properties as well as in drug release profile even after storage at 45°C and 75% RH for six months. It may be inferred that there was no degradation of physical properties and change in the matrix system of the formulation.

Table-7: Accelerated stability study of optimized A7 formulation

	Optimized formulation (A7)		
	Drug content (%)	% DEE	% Drug release
Initial	99.78	74.28	82.86
One month			
Ambient	99.75	73.09	79.38
40^0c / 75%RH	99.71	73.08	79.12
Two month			
Ambient	99.71	72.01	78.21
40^0c / 75%RH	99.68	72.97	78.99
Three month			
Ambient	99.69	71.39	77.83
40^0c / 75%RH	99.66	71.28	77.08

CONCLUSION

Formulation developed with Propranolol microspheres by using Chitosan and Guar gum as a natural occurring controlled release polymers. Propranolol HCl microspheres A1-A7 was subjected to various evaluation parameters. Formulation batch A1-A4 releases drug in 6-10 h due to single use of polymer. In the later batches A5-A7 use of combination of polymers in that case it exhibits good drug release up to the 12 h. Formulation A7 shows maximum drug release with controlled manner. From the present study it was concluded that, Interpenetrating polymer networks is the best approach for the controlled drug delivery system. It also be concluded that, the Propranolol microspheres microspheres formulation (A7) might be successful preference as a anti hypertensive drug. Thus, the designed formulations can be considered as one of the promising formulation technique of Interpenetrating polymer networks in the management of hypertension.

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