Pharma Science Monitor 7(2),Apr-Jun 2016

PHARMA SCIENCE MONITOR

AN INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES

Journal home page: http://www.pharmasm.com

# FORMULATION AND EVALUATION OF PROPRANOLOL HYDROCHLORIDE LOADED HYDROGEL

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## ABSTRACT

Propranolol hydrochloride is sympatholytic nonselective beta blocker. It is used to treat hypertension, anxiety and panic. Propranolol loaded hydrogel beads were prepared using chitosan, sodium bicarbonate and glyoxal by ionotropic gelation method. The preformulation study performed on combination of drug with polymer by FT-IR suggested that they were compatible with each other. The formulation ofhydrogel beads were done by applying 32 full factorial design. The surface morphology studied by scanning electron microscope revealed irregular shape hydrogel beads. All prepared hydrogel beads were evaluated for particle size, drug entrapment efficiency, in-vitro releases study and swelling ratio. Optimized formulation showed good swelling in 0.1 N HCl up to 24 h maintaining the integrity of formulation. The in-vitro release of propranolol hydrochloride from optimized hydrogel beads was more than 80% in controlled manner. Hence it could be concluded that propranolol hydrochloride loaded hydrogel beads prepared by using combination of chitosan with glyoxal (crosslinking agent) sustained the release of propranolol HCl more than 24 h in a predetermined manner for the effective management of hypertension.

**KEYWORDS:** Propranolol hydrochloride, Chitosan, Ionotropic gelation, In-vitro release.

## INTRODUCTION

Hypertension or high blood pressure, sometimes called arterial hypertension. Hypertension is a chronic medical condition in which the blood pressure in the arteries is elevated. Blood pressure is summarised by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole).Hypertension is classified as either primary hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension" which means high blood pressure with no obvious underlying medical cause. The remaining 5–10% of cases (secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system.

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing

interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation,the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT).

Hydrogels are three-dimensional, hydrophilic, polymeric network capable of imbibing large amount of water or biological fluids. The networks are composed of homo-polymer or co-polymers and multi-polymers. Hydrogels are formed by cross-linking polymer chains through physical, ionic or covalent interactions and are well known for their ability to absorb water.

**MATERIALS AND METHODS**

Propranolol hydrochloride was obtained from Alpha lab (Vadodara, India).Moreover, Chitosan (Polymer) was obtained from Balaji drugs (Surat, India).Glyoxal (Crosslinking agent) was obtained from Suvidhinath laboratories (Vadodara, India)

**Experimental design for hydrogel beads loaded with Propranolol hydrochloride:**

Formulation were prepared by applying $3^2$full factorial designs. Chitosan and glyoxal were considered as independent variable whereas entrapment efficiency, Swelling ratio, In vitro drug release study considered as a dependant responses.

**Method of Preparation**

**Preparation of hydrogel beads:**

Hydrogel beads were prepared by ionotropic gelation method. In this method,Accuretely weighed amount of chitosan was dissolved in 100 ml of 0.1 M acetic acid. Identified strength of glyoxal aqueous solution (10ml) as per factorial design was added to chitosan solution to induce network structure. The pH of the solution was adjusted to 5 by adding 0.1 M acetic acid. Then accurately weighed 1.6 gm of sodium bicarbonate was added to the mixture and stirred vigorously for 10-30 sec. Foaming ensued immediately after the addition of sodium bicarbonate and gelation was complete in 30-60 sec. The foamed hydrogel were kept at room temperature overnight and then dried using a free dryer.

**Drug loading:**

The drug selected for the study was propranolol hydrochloride. The method of ionotropic gelation method was employed for drug loading. In this method, the amount of 0.1 N HCl necessary for complete swelling of hydrogel was first determined. There after 15 ml of drug solution (0.13 % w/v in 0.1 N HCl) was prepared. The hydrogel (500 mg) was placed in the drug solution and left until all the drug solution was sucked up. Finally, the completely swollen hydrogel loaded with the drug was dried overnight at room temperature.

**Various batches were prepared according to $3^2$ full factorial design which areas follows:**

**Table 1: $3^2$ factorial design of variousbathces**

| **Factor** | **Level** | | |
|---|---|---|---|
| | **Low** | **Medium** | **High** |
| **X1** | 1 gm | 2 gm | 3 gm |
| **X2** | 5 % | 10% | 15% |
| **Transformed Values** | -1 | 0 | +1 |

Where,

X1: Amount ofChitosan.

X2: Concentration ofGlyoxal.

Whereas,

Amount of drug, volume of drug solution, volume of glyoxal solution, chitosan solution:glyoxal solution ratio and amount of hydrogen beads for drug loading were kept constant.

**Table 2: Experimental Designs ($3^2$full factorial) for Hydrogelbeads**

| **Batch** | **Transformed Value** | |
|---|---|---|
| | **X1** | **X2** |
| B1 | -1 | -1 |
| B2 | -1 | 0 |
| B3 | -1 | 1 |
| B4 | 0 | -1 |
| B5 | 0 | 0 |
| B6 | 0 | 1 |
| B7 | 1 | -1 |
| B8 | 1 | 0 |
| B9 | 1 | 1 |

**Characterization of hydrogel beads:**

**a) Particle size measurement &Photomicroscopy**

The prepare hydrogel beads were subjected for particle size analysis using a microscope having accuracy of 0.001mm.The average diameter of the 25 particles par batch was determined.

**b) Drug content:**

The prepared hydrogel beads were powdered and finely powdered hydrogel was subjected to sieving. The hydrogel particles were taken for drug content studies. 20 mg of beads were taken in volumetric flask.To this 20 ml of 0.1 N HCl was added and stirred overnight on magnetic stirrer. Final, solution was filtered byusing whatman filter paper. 10 ml was pipette out into 100 ml volumetric flask, madeup the volume with 0.1N HCl and estimate for drug content by UV-visible spectrophotometry.

**c) Drug entrapment efficiency :**

The % entrapment efficiency was determined by using equation a smentioned below;

$$\% \text{ EE} = \frac{\text{Practical drug content}}{\text{Theoratical drug content}} \times 100$$

**d) Swelling study:**

The swelling behavior of the beads was studied by mass measurement. The dried hydrogel (100mg) was immersed in excess of the swelling medium (0.1 N HCl) at 37 . At different time intervals, the hydrogel was removed from the solution and weighed after excess solution on the surface was blotted. The swelling ratio (Q) was calculated by

$$Q = \frac{\text{Ms} - \text{Md}}{\text{Md}}$$

Where:

Ms: the weight of the hydrogel in the swollen state.

Md: the weight of the hydrogel in the dried states.

**e) In-vitro drug release study:**

In vitro drug release of propranolol hydrochloride from the hydrogels was evaluated at 37± $0.5^0$C using a United states Pharmacopoeia (USP) by paddle method at a rotation speed of 50 rpm in 900 ml of 0.1 M HCl for 24 hr. At regular time interval, 10 ml sample of the dissolution medium were withdrawn, replaced with an equivalent volume of fresh dissolution fluid and analyzed for the drug using a UV-vis spectrophotometer at 288 nm. The release data obtained were fitted in to various release models.

**Optimization of hydrogel beads:**

**a) Scanning electron microscopy(SEM):**

The surface morphology of optimized formulation beads was investigated by using electron microscopy (SEM). The beads were mounted onto stub using double sided adhesive tape and sputter coated with platinum using a sputter coater. The coated beads were observed under SEM instrument at the require magnification at room temperature. The acceleration voltage used was 15 KV with the secondary electron image detector.

**b) X-ray diffraction study:**

The study was carried out for optimized formulation using X-ray pow derdiffraction system, Model No. XPERT ANALYTICAL PRO Diffract meter system, atM.S University, Vadodara by using copper target, a voltage of 45 Kv and a current of 40 mA. The scanning was done over range of 5º to 80 ºC

**c) Diffrential Scanning calorimetry:[40][41]**

Differential scanning calorimetry (DSC) analysis was carried out for optimized formulation with use of DSC. Analysis was performed under a nitrogen purge (100 ml/min). The samples (about 2-4 mg) were weighed accurately, placed in aluminum pans, and then sealed with a pinhole-pierced cover. Heating curves were recorded at a scan rate of 10 °C/min from 40 °C to 250°C.

**d) Stability study:**

In stability study, optimized formulation subjected to stability studies as per the International Conference of Harmonization (ICH) guidelines for a period of 2month at two different storage conditions. i.e. at room temperature 25 ºC ± 2$^{O}$C/60 ± 5%RH and days at 40ºC±2$^{O}$C/75±5% RH. The samples were analysed for % CDR and % EE (Entrapment efficiency) at an interval of 15days.

**RESULT AND DISCUSSION**

**Preformulation study:**

**a) Colour, Odour and Appearance:**

The organoleptic properties of drug was carried out by studying like colour, odour and physical appearance. It was observed that drug is White crystalline in colour & odourless.

**b) Melting point determination:**

Melting point was determined using melting point testing apparatus and the melting point of obtained drug was found to be 164 $^0$C -166 $^0$C which was similar to the reported value of drug. It complies with the standards thus indicating the purity of propranolol hydrochloride.

**c) Determination of λmax for Propranolol hydrochloride:**

Determination of λmax of propranolol hydrochloride was carried out by screening method in UV spectrophotometer. In this method, diluted solution of drug in 0.1 N HCL has been prepared and screened in the range of 400 nm to 200 nm. The λmax of drug (propranolol hydrochloride) was found to be 288 nm

**d) Solubility Analysis:**

Solubility analysis was carried out by making saturated solution of the drug in various solvents separately.The solubility of drug in water was 50.07 ±2.87, In ethanol 55.34 ± 1.02 and 47.17 ± 1.45 in 0.1 N HCl .It was found that drug was freely soluble in all solvents used for study.

**Table 3: Solubility Profile of Propranolol Hydrochloride**

| **Sr.no** | **Solvent** | **Solubility±SD* (mg/ml)** |
|---|---|---|
| **1** | Water | 50.07± 2.87 |
| **2** | Ethanol | 55.34 ±1.02 |
| **3** | 0.1 NHCl | 47.17 ±1.45 |

**e) Calibration curve of Propranolol hydrochloride by UV spectrophotometer:** Calibration curve of the drug was carried out in 0.1 N HCl by using UV spectrometric method. Specific strength of the solution of drug has been prepared and absorbance of each solution was observed at 288nm.Calibration curve of drug (Propranolol HCl) was found to be linear in Beer's range between 5 – 25 µg/ml at 288 nm with regression value $R^2$= 0.9994 and slope=0.035.

**Table 4:Standard Calibration curve of Propranolol hydrochloride in 0.1 N HCL**

| Sr.no | Conc. (µg/ml) | Absorbance | | | Mean(±SD)* |
|---|---|---|---|---|---|
| | | I | II | III | |
| 1 | 5 | 0.168 | 0.170 | 0.169 | 0.169 ±0.001 |
| 2 | 10 | 0.309 | 0.312 | 0.311 | 0.310 ±0.001 |
| 3 | 15 | 0.496 | 0.497 | 0.495 | 0.496 ±0.001 |
| 4 | 20 | 0.762 | 0.764 | 0.764 | 0.763 ± 0.001 |
| 5 | 25 | 0.875 | 0.876 | 0.874 | 0.875 ±0.002 |

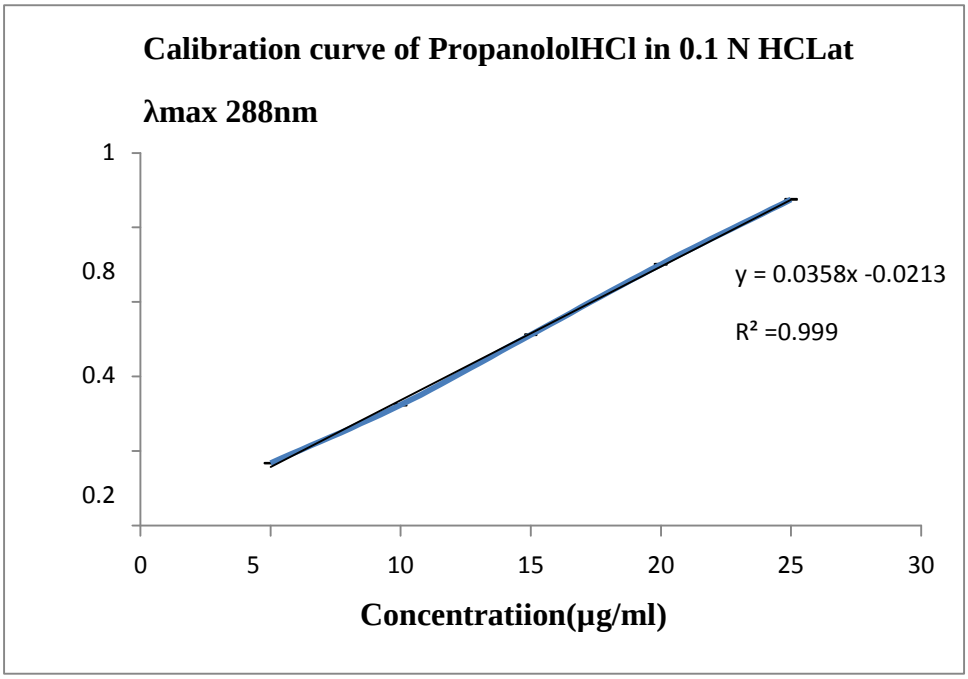



**Figure 1: Standard Calibration curve of Propranolol hydrochloridein 0.1 N HCl**

### f) Compatibility studies by FTIR-Spectroscopy

The possible interaction between the drug and the excepient was studied byIR Spectroscopy. The IR Spectrums of physical mixture of pure drug (PropranololHCl) and excipient (Chitosan) was carried out. The result revealed that there were nomajor

changesintheIRpeaksofPropranololHClinphysicalmixture,whencomparedto pure drug there by indicating the absence of the interaction.

**a) Pure Drug ( Propranolol hydrochloride)**

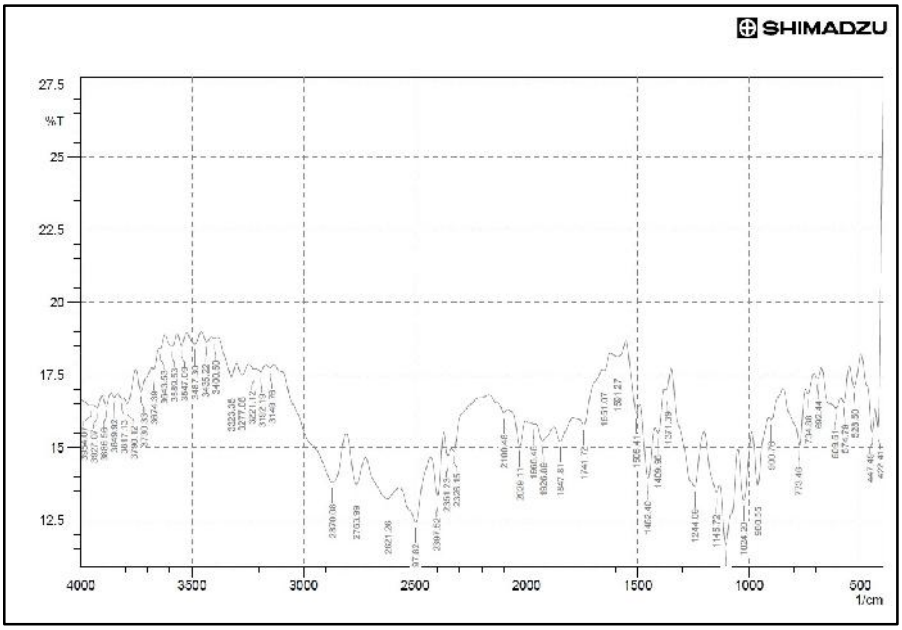



**Figure 2: FT-IR Spectra of puredrug**

**b) Physical mixture ( Drug + Polymer)**

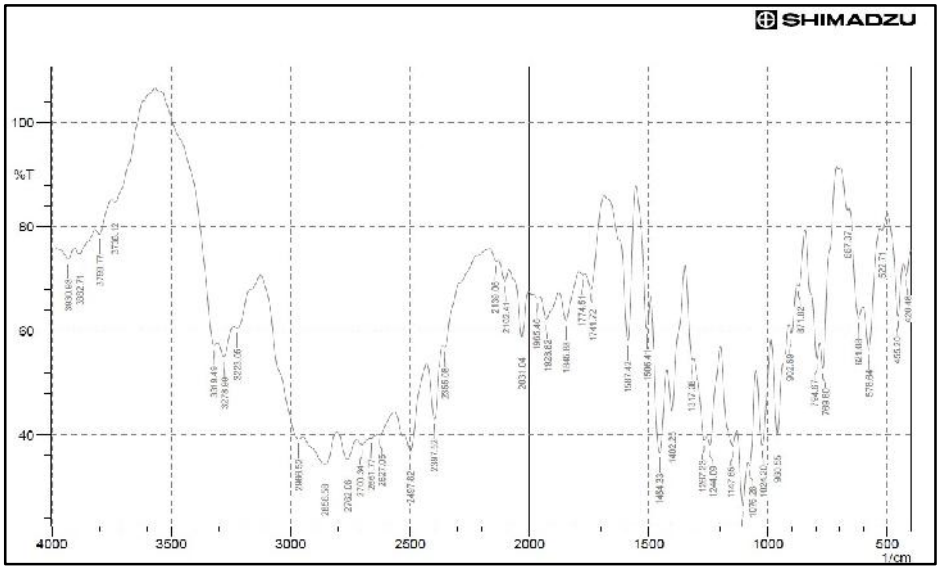



**Figure 3: FT-IR Spectra of physical mixture (Drug +polymer)**

**Characterization of hydrogelbeads:**

**Table 5: Characterization of hydrogelbeads**

| BatchNo | Meanparticle size (µm) | Drugcontent (%) | Drug Entrapment Efficiency(%) | Swellingstudy In 0.1 NHCl |
|---|---|---|---|---|
| B1 | 199.52 ± 2.12 | 29.69 ± 1.27 | 37.32 ±1.35 | 4.79 ± 1.08 |
| B2 | 160.64 ± 1.24 | 33.23±1.16 | 41.77 ±1.20 | 4.61± 1.02 |
| B3 | 254.16 ± 2.79 | 49.45± 2.27 | 62.22 ± 3.35 | 5.98 ± 1.11 |
| B4 | 151.27 ± 3.42 | 42.54±1.37 | 53.47 ±2.35 | 3.50±1.05 |
| B5 | 288.34 ± 1.43 | 50.17 ± 1.16 | 63.07 ± 1.20 | 5.12 ± 1.22 |
| B6 | 194.54 ± 1.85 | 45.14±2.16 | 56.75 ±2.20 | 4.22±1.32 |
| B7 | 245.05 ± 2.33 | 55.01 ± 1.42 | 69.16 ± 1.26 | 3.06 ± 1.05 |
| B8 | 209.72 ± 1.52 | 48.50±2.16 | 60.96 ±2.22 | 3.82±1.44 |
| B9 | 227.47 ± 3.22 | 59.48 ± 1.58 | 74.19 ± 2.32 | 3.30 ± 1.41 |

**a) Particle size**

The mean particle size of hydrogel beads was found to be in a range of 151.27 ± 0.4 to 288.34 ± 0.4 µm. The largest size was found for B5 whereas smallest size was found for B4. There were no any influence of independent variable was observed on particle size.

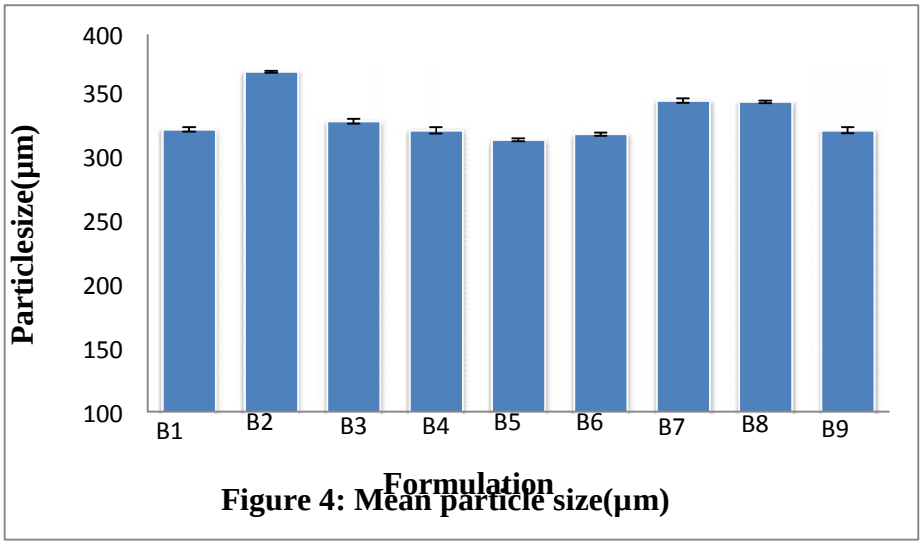



**Figure 4: Mean particle size(µm)**

**b) Drug content:**

The drug content was in range of 29.69 ± 1.27 to 59.48 ± 1.58. It was carried out to determine the % entrapment efficiency and also helps to calculate label claim for in vitro drug release study.

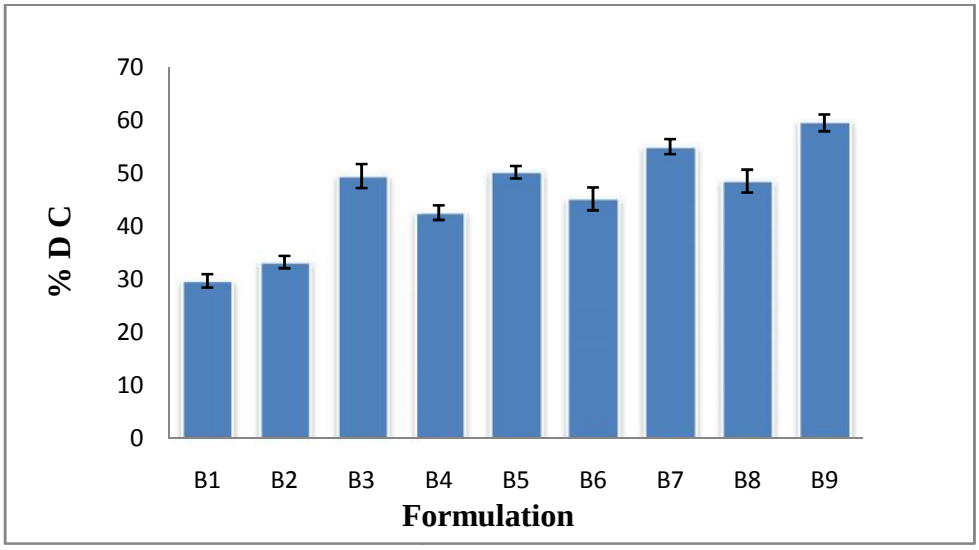



**Figure 5: Drug content of batchB1-B9**

**c) Drug entrapment efficiency:**

The drug entrapment efficiency was in the range of 37.32 ± 1.35 to 79.22 ± 3.35 .The higher entrapment of drug was found for B9 whereas lower entrapment of drug was found for B1. It was observed that independent variable were highly influenced the % entrapment efficiency. As the amount of chitosan was increased from 1 gm to 3 gm , The % entrapment efficiency was also increased. similarly glyoxal concentration was also influenced.

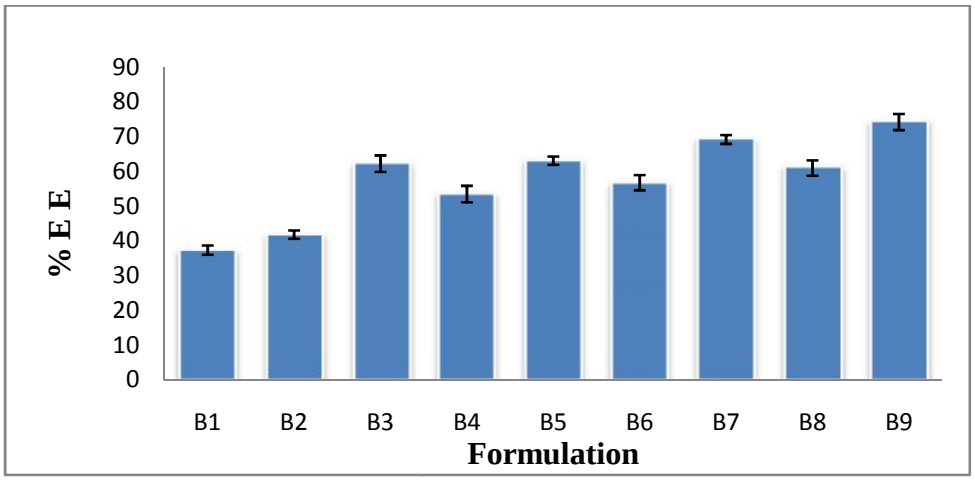
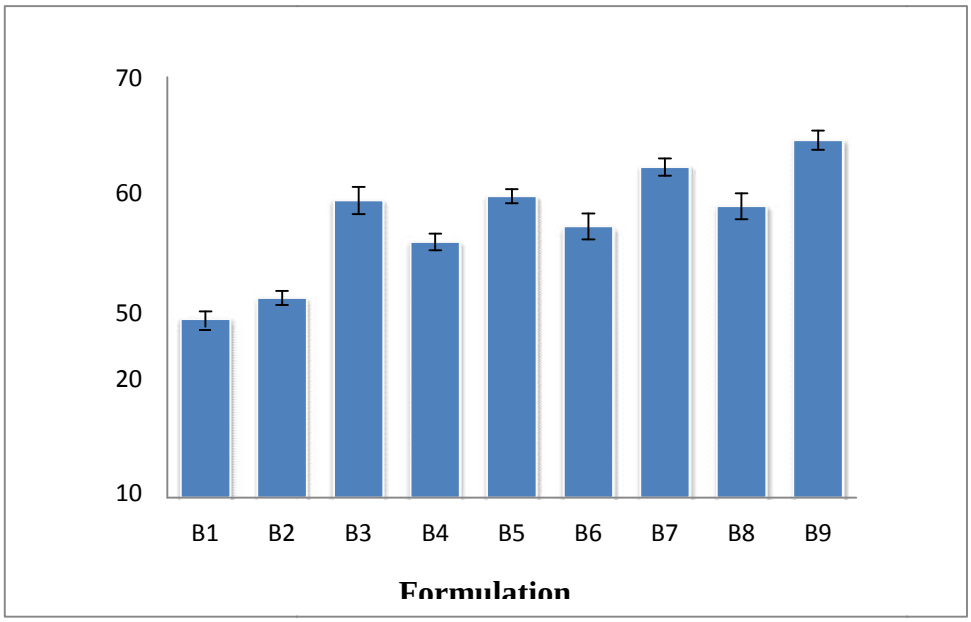



**Figure 6: Drug entrapment efficiency of batchB1-B9**




**d) Swelling ratio:**

The sweeling ratio was in the range of 3.06 ± 1.05 to 5.98 ± 2.01. The higher swelling ratio was found for B3 and lower swelling ratio found for B7. It was observed that as the amount of chitosan were increased from 1 gm to 3 gm, swelling ratio were decreases whereas at lower and higher concentration of glyoxal swelling ratio were found to be less as compare to intermediate concentration of glyoxal i.e 15%

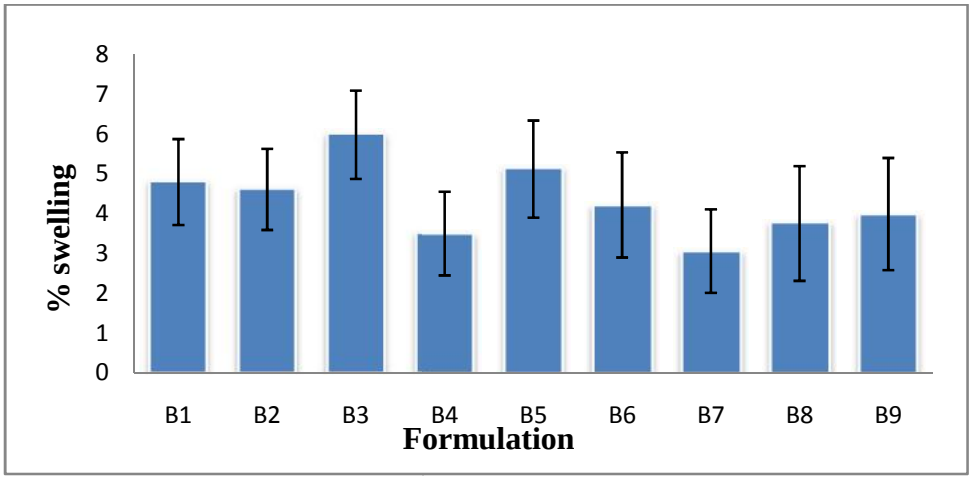



**Figure 7: Swelling study of batch B1-B9**

**e) In-Vitro drug release study:**

The in vitro drug release study were carried out for 24 hrs. At the end of 24 hrs, % CDR was found to be in the range of 31.86 ± 0.56 to 82.35 ± 1.55. The maximum release were found to be B3 whereas B4 shows the minimum drug release study. From the release study, The data shows

that as the amount of chitosan was increases, %CDR was decreases and as concentration of glyoxal increases, the % CDR was also increases.

**Table 6: % CDR of BatchB1-B5**

| Time(hr) | Batch1 | Batch2 | Batch3 | Batch4 | Batch5 |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 0.5 | 6.93 ± 1.12 | 14.46 ± 1.40 | 22.04±1.26 | 12.04 ± 1.40 | 15.35 ± 1.85 |
| 1 | 9.56 ± 1.44 | 21.45 ± 1.43 | 37.23 ± 2.35 | 17.12 ± 1.63 | 24.82 ± 1.73 |
| 2 | 19.25 ± 2.02 | 31.92 ± 1.54 | 45.24 ± 2.67 | 21.04 ± 1.82 | 32.12 ± 1.58 |
| 3 | 25.04 ± 1.53 | 37.7 ± 1.85 | 59.11 ± 1.19 | 24.12 ± 2.75 | 37.56 ± 1.49 |
| 4 | 35.45 ± 1.71 | 47.3 ± 2.26 | 68.38± 1.32 | 27.47 ± 1.39 | 44.06 ± 2.69 |
| 5 | 41.36 ± 1.81 | 55.97 ± 2.70 | 73.22± 1.53 | 29.71 ± 1.24 | 47.24 ± 1.19 |
| 6 | 46.84 ±1.17 | 60.93 ± 1.59 | 77.65± 1.73 | 31 ± 1.32 | 50.44 ± 1.29 |
| 7 | 47.15 ± 1.15 | 61.91 ± 0.47 | 80.29±1.87 | 31.39 ±0.17 | 51.13 ± 0.59 |
| 8 | 47.79±0.13 | 62.76 ± 0.36 | 82.15 ±1.20 | 31.8 ± 0.26 | 51.68 ±0.50 |
| 24 | 48.56±0.12 | 63.32 ± 0.45 | 82.35 ±1.55 | 31.86 ± 0.56 | 52.53 ±0.78 |

**Table 7: % CDR of BatchB6-B9**

| Time(hr) | Batch6 | Batch7 | Batch8 | Batch9 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 0.5 | 14.46 ± 1.85 | 10.28 ± 1.10 | 16.54 ± 1.29 | 20.39 ± 1.66 |
| 1 | 25.31 ± 1.73 | 16.36 ± 1.20 | 21.68 ± 2.56 | 24.74 ± 2.78 |
| 2 | 32.41 ± 1.58 | 20.17 ± 2.09 | 26.14 ± 1.76 | 27.39 ± 1.33 |
| 3 | 40.23 ± 2.49 | 23.82 ± 1.02 | 29.59 ± 1.74 | 30.73 ± 1.14 |
| 4 | 46.39 ± 1.69 | 26.63 ± 1.26 | 32.15 ± 1.66 | 33.63 ± 1.73 |
| 5 | 50.67 ± 1.14 | 28.96 ± 1.07 | 34.17 ± 1.42 | 35.73 ± 1.41 |
| 6 | 56.07 ± 2.29 | 31.18 ± 1.15 | 35.22 ± 2.23 | 38.32 ± 1.37 |
| 7 | 56.8 ± 1.26 | 31.18 ± 0.15 | 35.76 ± 1.23 | 38.86 ± 0.36 |
| 8 | 57.44 ± 0.30 | 31.68 ± 0.20 | 36.22 ± 0.23 | 39.21 ± 0.36 |
| 24 | 57.78 ± 0.20 | 31.87 ± 0.63 | 37.54 ± 0.80 | 39.22 ± 0.97 |

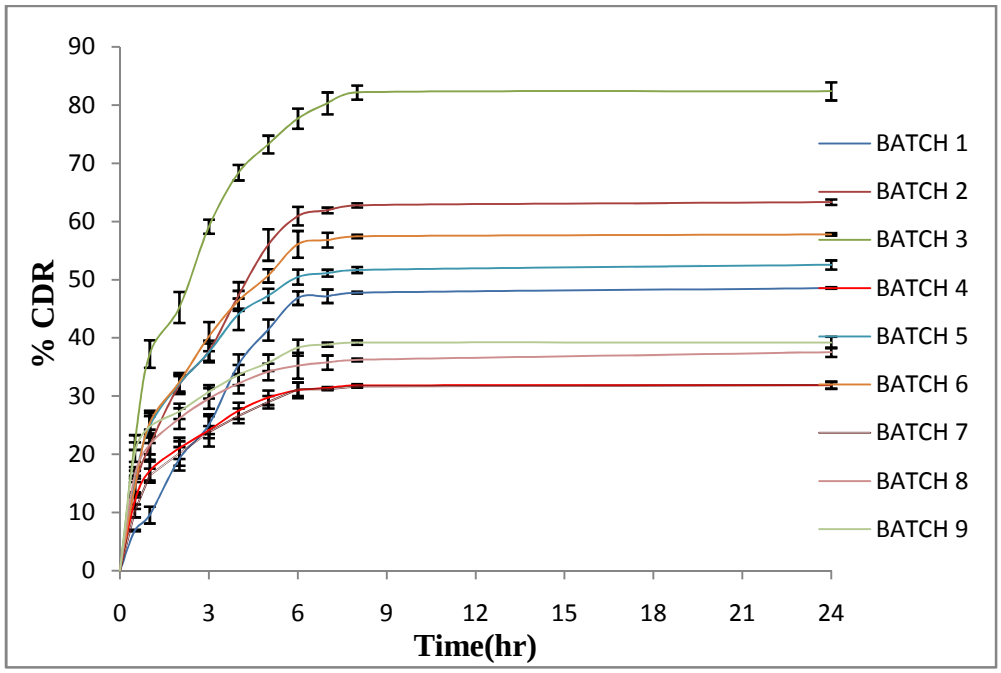



**Figure 8: Cumulative drug release study of batch 1- batch 9**

**f) Scanning Electron Microscopy(SEM):**

The surface morphology of optimized formulation was studied usingscanning electron microscopy at different magnifications i.e. at 270X and 550X.The acceleration voltage used was 15 KV with the secondary electron image detector.The data revealed that the hydrogel beads were found to be irregular in shape butsmaller in size then the pure drugcrystals.

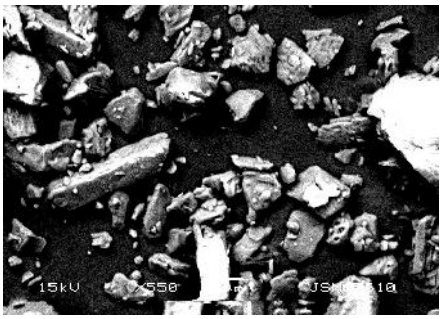


**Figure 9: SEM of pure drug at 550X**

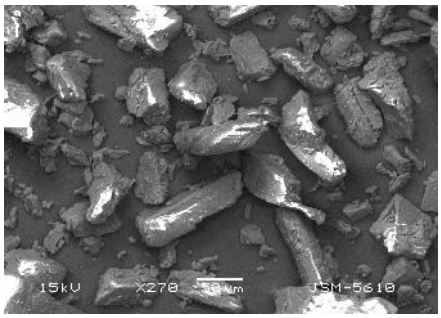



**Figure 10: SEM of Pure drug at 270X**

**c) Differential scanning calorimetry(DSC):**

Differential scanning calorimetry is widely used in thermal analysis tomonitor endothermic processes (melting, solid-solid phase transitions andchemical degradation) as well as exothermic processes (crystallization andoxidative decomposition). It could be extremely

useful since it indicates the existenceof possible drug-excipients or excipient-excipient interactions informulation. Thermograms of pure drug Propranolol hydrochloride was showed an endothermic peak at167ºC which indicates the purity of the drug as the reported melting point of the drug is 165ºC.The thermograms of an optimized formulation were show done endothermic peak at169.41ºC which indicates that there were no any interaction between drug & excipients duringformulation

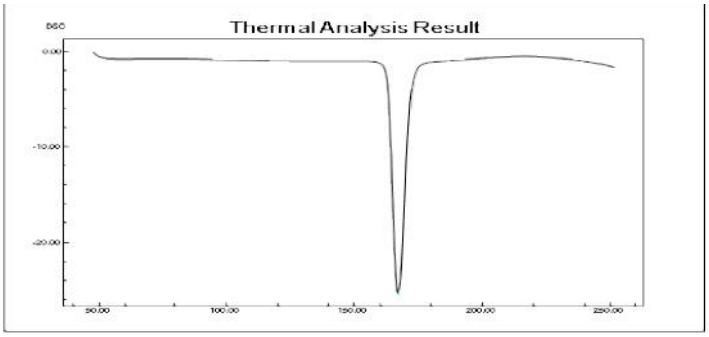



**Figure 11: DSC of Propranolol hydrochloride**

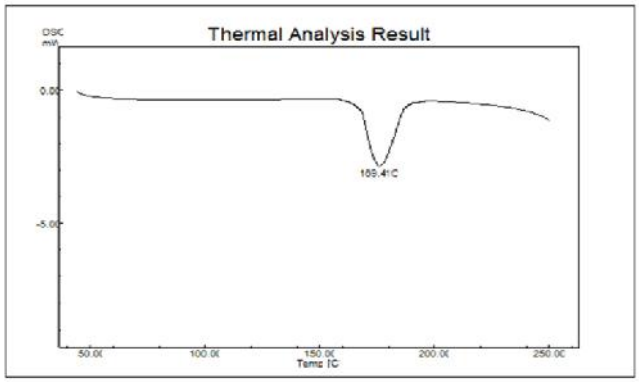



**Figure 12: DSC of Optimized batch**

**d) X-Ray diffraction ofdrug:**

XRD of Propranolol HCL shows crystalline structure of pure drug.Optimized formulation showed the less intense peak .This result indicated that the crystallinity of PropranololHCl was reduced in formulation.So the reduced crystallinity in formulation shows that it converted to amorphous form and may be entrapped in the complex of chitosan & glyoxal crosslinking.

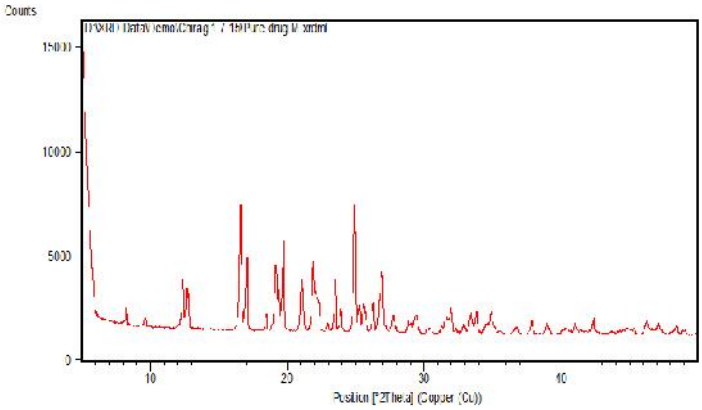



**Figure 13: X-ray Diffraction of pure drug**

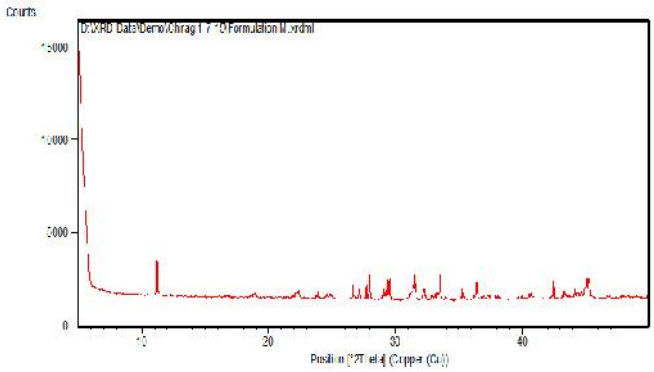



**Figure 14: X-ray Diffraction of optimized batch**

**e) Stability study of formulation Optimized batch**

Anoptimizedformulation(OPT1)waskeptatthedifferentstorageconditionasper ICH guidelines for stability studies. The formulation were subjected to entrapment efficiency and in-vitro release studies at an interval of 15 days for 60days.

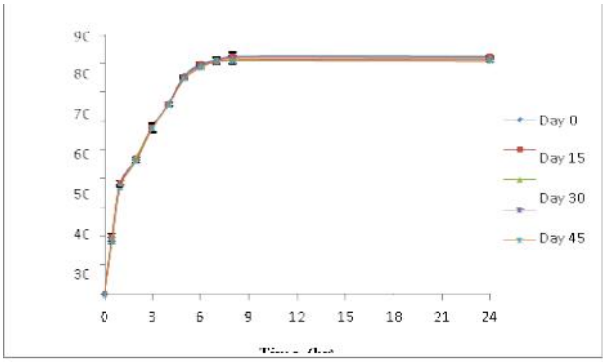



**Figure 15:% CDR of optimized formulation at 25 ± 2 /60%RH± 5% RH**

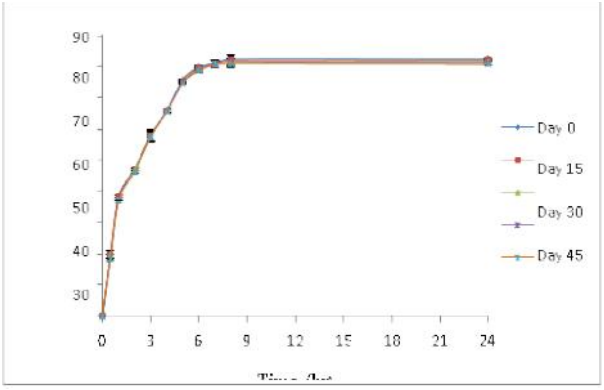



**Figure 16: % CDR of optimized batch at 40 ± 0.5 / 75 %RH ± 5% RH**

## CONCLUSION

In current study, Propranolol hydrochloride loaded hydrogel beads wasprepared successfully using combination of chitosan with crosslinking agent by ionotropic gelation method.The consistency of formulation was observed in optimization study. The correlation between drug release and swelling ratio was established. Swelling of hydrogel is directly proportional to release of drug. The main advantage of this formulation over current formulation is when it comes in the contact with GI fluid it swells and provides prolonged release of drug over defined period of time. It might also improve its bioavailability as swelled hydrogel have property of bioadhesive. This makes it as a future trend for treatment of hypertension.

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