Available Online through
www.ijpbs.com (or) www.ijpbsonline.com

IJPBS |Volume 3| Issue 2 |APR-JUN |2013|390-409

Research Article
Pharmaceutical Sciences

# FORMULATION AND EVALUATION OF BILAYED PROPRANOLOL HYDROCHLORIDE TABLETS

Narasimha Rao R[1], Sushma Devi K S[2],Uday Kumar N[3], Sindhu Reddy[4],Kishore Kumar Reddy K[5]

[1,2,3,4, 5]HITS COLLEGE OF PHARMACY, BOGARAM (V), KEESARA (M), R.R (Dist)-501301

*Corresponding Author Email: rnrao007@yahoo.com

## ABSTRACT

*The present work involves the formulation, development and evaluation of fixed dose product of Propranolol hydrochloride. The fixed dose combination of Propranolol hydrochloride helps the patient to reach their desired blood concentration level targets when mono therapy proves inadequate. These two doses of the drug are combined and presented in the form of sustained release tablets. To formulate and evaluate sustain release matrix tablets of Propranolol Hydrochloride. To study the release profile of the dosage form. To study the stability of dosage form and compare with the specification.*

## KEY WORDS

*Fixed dose combination, release profile, stability of dosage form.*

## INTRODUCTION[8]:

Oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of Dosage form. The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms. Ideally a drug to provide desired therapeutic action should arrive rapidly at the site of action in optimum concentration, remain there for the desire time, be excluded from other site. The fact that absorption rate of drug into the body can be decreased by reduction of the rate of release of the drug from the dosage form is one of the most recent and interesting result of pharmaceutical research. But one important drawback of such dosage forms is Dysphasia or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of pathological conditions including stroke, Parkinson's disease, neurological disorders, AIDS etc.

Dual release tablet is a unit compressed tablet dosage form intended for oral Application. It contains two layers in which one layer having conventional or immediate release part of single or multiple actives; another layer is sustained or controlled release part of single or multiple actives. They are also called as Bilayered tablet, multi-layer Matrix tablet.. A bilayed tablet is a type of multiple compressed tablets. Tablets are composed of two layers of granulation compressed together. Monograms and other distinctive marking may be compressed in the surface of the bilayed tablets. Coloring the separate layer provide many possibilities for unique tablets identity.There are some applications like Bilayered tablets are mainly used in the combination therapy. Bilayed tablets are used to deliver the loading dose and sustained dose of the same or different drugs. Bilayed tablets are used to deliver the two different drugs having different release. They are used as an extension of a conventional technology Potential use of single entity feed granules. Patient compliance is enhanced leading to improved drug regimen efficacy. Patient convenience is improved because fewer daily doses are required compared to traditional drug delivery

system. Maintain physical and chemical stability. Retain potency and ensure dose accuracy.

**ADVANTAGES OF BILAYER TABLET OVER CONVENTIONAL TABLETS[10,1]** :

Blood level of a drug can be held at consistent therapeutic levels for improved drug delivery, accuracy, safety and reduced side effects. Reduction of adverse effects can be accomplished by targeting the drug release to the absorption site as well as controlling the rate of release, enabling the total drug content to be reduced. Patient convenience is improved because fewer daily doses are required compared to traditional delivery systems. Patient compliance is enhanced leading to improved drug regimen efficacy. Bilayered tablets readily lend themselves to repeat action products, where in one layer on layered tablet provides the initial dose, rapidly disintegrate in the stomach. The other layers are insoluble in gastric media but are released in the intestinal environment.

In bilayered tablets, where in one layer on layered tablet provides as immediate Release and other layer acts as sustained release. In sustained release drug delivery system, several approaches are available to add the loading dose to the maintenance dose such as simple addition of a sustained dose of drug to the sustained portion and placement of initial dose in a tablet coat with the sustaining portion in the core as in compression coated tablets. An alternative approach for having the loading dose and maintenance dose in a tablet is the formulation of drug in a multi layered tablet or bilayed tablet system. This bilayed approach is a convenient method. Hence it makes possible to formulate sustained release preparations with the immediate release quantity in one layer and the slow release portion will disintegrate rapidly after ingestion thus providing the Initial dose of medication for immediate onset of action, where as the another layer in the matrix layer remain intact during most of the time of its passage through the intestine, While dissolving slowly (sustained manner) from its exposed faces in this passage, which helps to maintain the blood level initially reached.

**MATERIALS AND METHODS:**

**Propranolol** Hcl is a sympatholytic non-selective beta blocker. Sympatholytics are used to treat hypertension, anxiety and panic. It was the first successful beta blocker developed. .

**Structure:**

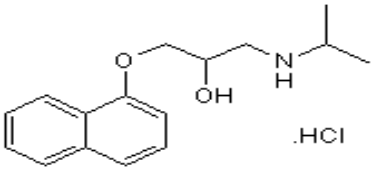



**Figure 1: structure of Propranolol Hcl**

**Chemical Name:** RS)-1-[(1-Methyl ethyl amino)-3-(1-naphthyloxy)-2-propan-2-ol]

Empirical Formula: $C_{16}H_{21}NO_2$.HCl , Molecular Weight: 295.81, Category : Anti Hypertensive agent, Melting point : 161°C , pKa : 9.45, pH : 4-5 ,Dose: 10 mg, 20 mg, 40 mg and 80 mg tablets for oral administration. Propranolol HCl occurs as a bitter-tasting, odorless, and white to almost white powder. One gram of propranolol is soluble in about 20 ml of water or alcohol.

**Pharmacokinetics:**

Propranolol is highly lipophilic and almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation. Peak plasma concentrations occur about 1 to 4 hours after an oral dose. Administration of protein-rich foods increase the bioavailability of propranolol by about 50% with no change in peak concentration time, plasma binding, half-life, or the amount of unchanged drug in the urine.

**Analytical method development:**

**Determination of absorption maxima:**

A solution of Propranolol Hcl containing the concentration 10 µg/ ml was prepared in 0.1N HCl, 7.4 pH & phosphate buffer 6.8pH respectively, UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

**Preparation calibration curve: For Propranolol Hcl :**

10mg of Propranolol Hcl drug was accurately weighed and dissolved in 10ml of 0.1N Hcl, 7.4 pH, and 6.8 pH in 10 ml volumetric flask , to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution(2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4 ,6, 8, 10, 12, 14, 16, 18 ,and 20µg/ml with 0.1N HCL, 7.4 pH, and 6.8 pH. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 273nm. Linearity of standard curve was assessed from the square of correlation coefficient ($r^2$) Which is determined by least-square linear regression analysis.

**Formulation development of Bilayered Tablets:**

To produce a quality bilayed tablet, in a validated and GMP-way, it is important that the selected press is capable of Preventing capping and separation of the two individual layers that constitute the bilayed tablet Providing sufficient tablet hardness. Preventing cross-contamination between the two layers . Producing a clear visual separation between the two layers and High yield.

The calculated amount of drug along with other excipients was dispensed corresponding to a batch size of 100 tablets. All the trials were carried out with direct compression and wet granulation method. Then the batches formulated were evaluated for dissolution. The dissolution profile for Propranolol Hydrochloride sustained release layer as per In-house specifications.

**Manufacturing process:**

The bilayed tablets of propranolol hydrochloride were prepared by the direct compression and wet granulation method. The drug and polymers for both fast release and sustaining layer were passed through a 30-µm sieve before their use in the formulation.

**Steps Involved In Formulation of Anti Hypertensive Bilayered Tablets:**

Sifting and Mixing (Sustained release layer) Propranolol hydrochloride, Xanthum gum, Guar gum, Tragacanth, Hydroxy propyl methyl cellulose, Micro crystalline cellulose , Magnesium stearate are passed through sieve No.40 and then mixed in rapid mixer granulator. Lactose was mixed with the above drug and polymer mixture uniformly. Direct compression of sustained release layer. Sifting and Mixing (Immediate release layer) Propranolol hcl, Sodium starch glycolate , Micro crystalline cellulose are passed through sieve No.40 and mixed for 10 minutes in rapid mixer granulator.

**Immediate release layer was prepared by wet granulation method:**

Starch paste (10%*m/m*) as binder is used as granulating agent and granules are prepared. The obtained damp mass is dried in a rapid bed drier for 30 minutes at 60 $^0$C and dried granules are passed through sieve No.30. Sift magnesium stearate through sieve No. 60, the immediate release granules obtained in step 4 are colored using sunset yellow and then added to magnesium stearate, talc and blended for about 2 minutes. The sustained release layer is also added with the sifted magnesium stearate, talc and granules are uncolored. The blends of two layers are subjected to compression using RIMECK compression machine. Compression involves two steps: Compression of immediate release layer with the desired parameters. The immediate release layer compression is followed by the compression of sustained release layer.

**Table 1: Composition of bilayered tablets**
**Formulae for the Preparation of Sustained Release Tablets**

| INGREDIENTS (mg) | F1 (1:1) | F2 (1:0.5) | F3 (1:0.25) | F4 (1:1) | F5 (1:0.5) | F6 (1:0.25) | F7 (1:1) | F8 (1:0.5) | F9 (1:0.25) |
|---|---|---|---|---|---|---|---|---|---|
| Propranolol Hcl | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Xanthum gum | 25 | 12.5 | 6.25 | - | - | - | - | - | - |
| Guar gum | - | - | - | 25 | 12.5 | 6.25 | - | - | - |
| Tragacanth | - | - | - | - | - | - | 25 | 12.5 | 6.25 |
| HPMC K100 | 25 | 12.5 | 6.25 | 25 | 12.5 | 6.25 | 25 | 12.5 | 6.25 |
| MCC | 220 | 245 | 257.5 | 220 | 245 | 257.5 | 220 | 245 | 257.5 |
| Lactose | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Sunset Yellow | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| Avg. Weight of SR layer Tablet | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

**Table 2: Formulae for the Preparation of Immediate Release Tablets**

| INGREDIENTS | I1 | I2 | I3 | I4 | I5 |
|---|---|---|---|---|---|
| Propranolol hcl | 20 | 20 | 20 | 20 | 20 |
| SSG 2% | 4 | - | - | - | - |
| SSG 4% | - | 8 | | - | - |
| SSG 6% | - | - | 12 | - | - |
| SSG 8% | - | - | - | 16 | |
| SSG 10% | - | - | - | - | 20 |
| MCC | 168 | 164 | 160 | 156 | 152 |
| Magnesium stearate | 4 | 4 | 4 | 4 | 4 |
| Talc | 4 | 4 | 4 | 4 | 4 |
| Average weight of IR layer tablet | 200 | 200 | 200 | 200 | 200 |
| Total weight of bi-layer tablet | 500 | 500 | 500 | 500 | 500 |

## RESULTS AND DISCUSSION

The formulation development of Propranolol hydrochloride involves drug profile and excipients, formulation and processing development along with evaluation of the tablets made with optimized formulation.

**Formulation of Bilayered Tablets:**

As described in the methodology chapter the bilayered tablets were prepared by simple direct compression method for sustained release layer and wet granulation for Immediate release layer. In case of sustained release layer, all the excipients and drug were geometrically mixed and that blend was directly used for compression. Where in case of Immediate release layer wet granulation by adding the excipients both intra and extra granularly. Different polymers were used in different concentrations to get good sustained release of drug. Different excipients were used, i.e. direct compressible excipients, lubricants

and glidants to get good physical properties of the tablets.

**ANALYTICAL METHOD:**

**Standard graphs of Propranolol hydrochloride was taken in Simulated Gastric fluid ( pH 1.2 ) and Simulated Intestinal Fluid ( pH 6.8 and 7.4 ) .**

**Figure 2: Standard Graph Of Propranolol Hcl in 0.1N HCl (274nm)**

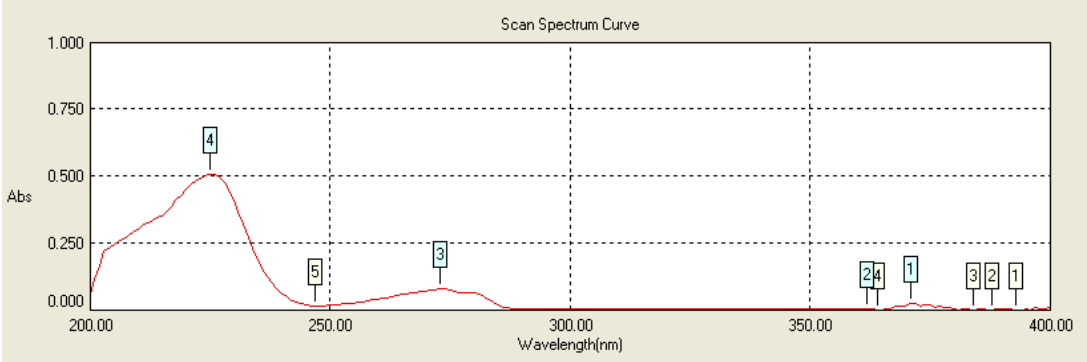



**Figure 3: Spectrum of Propranolol HCL in 0.1N HCL**

**Standard Graph Of Propranolol Hcl in 7.4 pH Simulated Intestinal Fluid (270nm)**

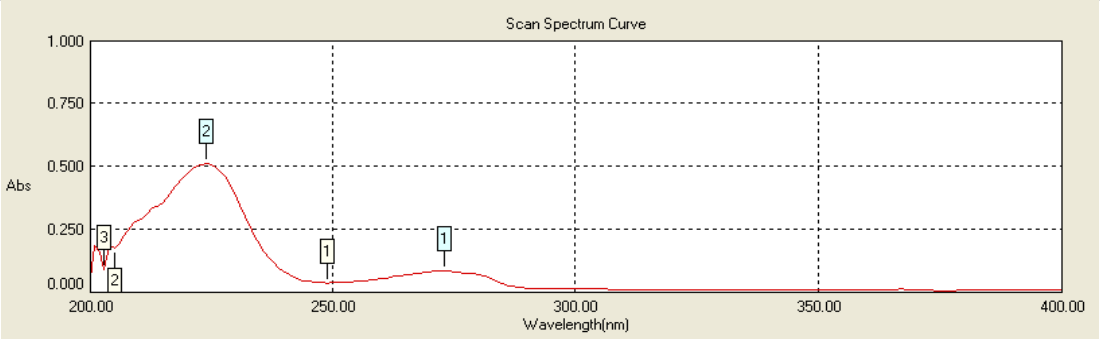



**Figure 4: Spectrum of Propranolol HCL in 7.4 pH**

**Standard Graph Of Propranolol Hcl in 6.8 pH Simulated Intestinal Fluid (273nm)**

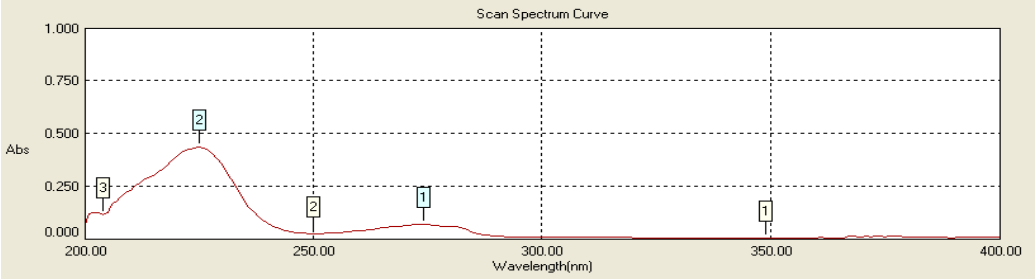



**Figure 5: Spectrum of Propranolol HCL in 6.8 pH**

## DISCUSSIONS

On the basis of preliminary identification test it was concluded that the Propranolol hydrochloride complied the preliminary identification. By scanning the drug in U.Vspectrophotometer in 200-400 nm range, a sharp peak was observed at 274nm using HCL, 270nm using pH 7.4, 273nm using pH 6.8 buffer as solvent. It was concluded that the drug has max 290 nm (as per I.P).

## DRUG EXCIPIENT COMPATABILITY STUDY

### Fourier Transform-Infrared Spectroscopy:

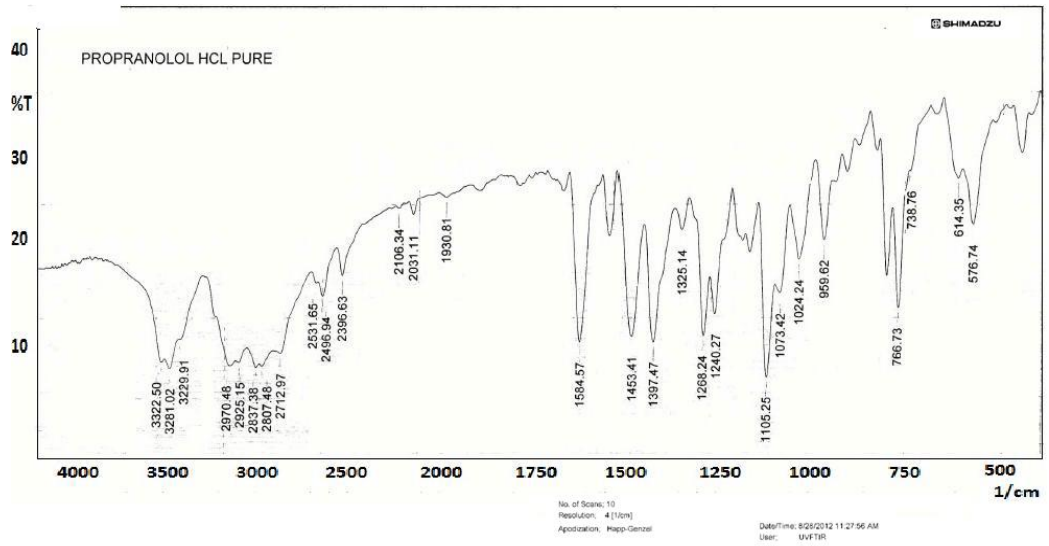



**Figure 6: IR spectra of Propranolol hydrochloride (pure drug)**

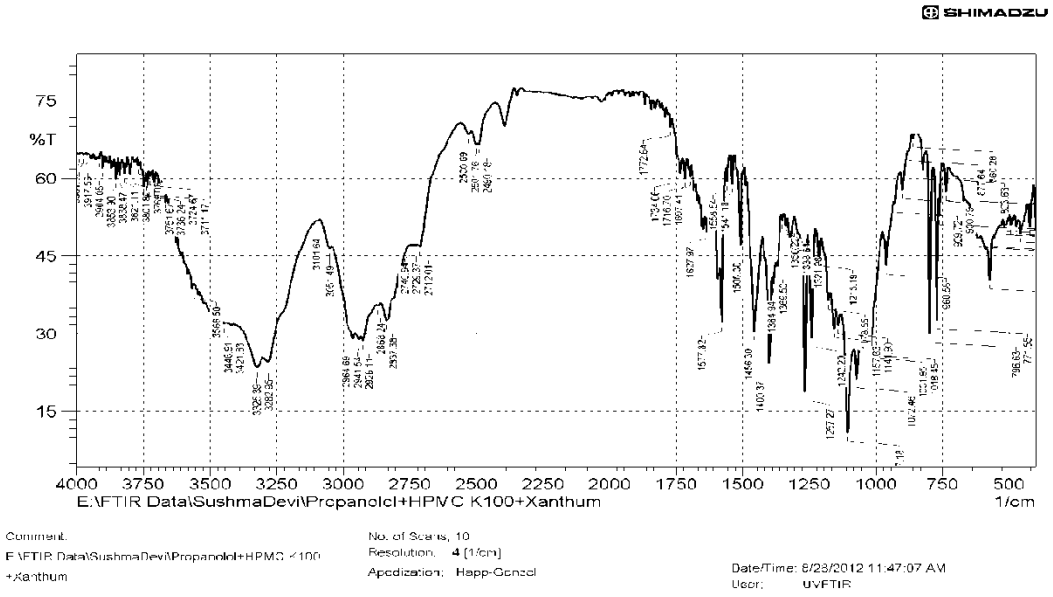



**Figure 7: IR spectra of Propranolol hcl+HPMC K100+ Xanthum gum**

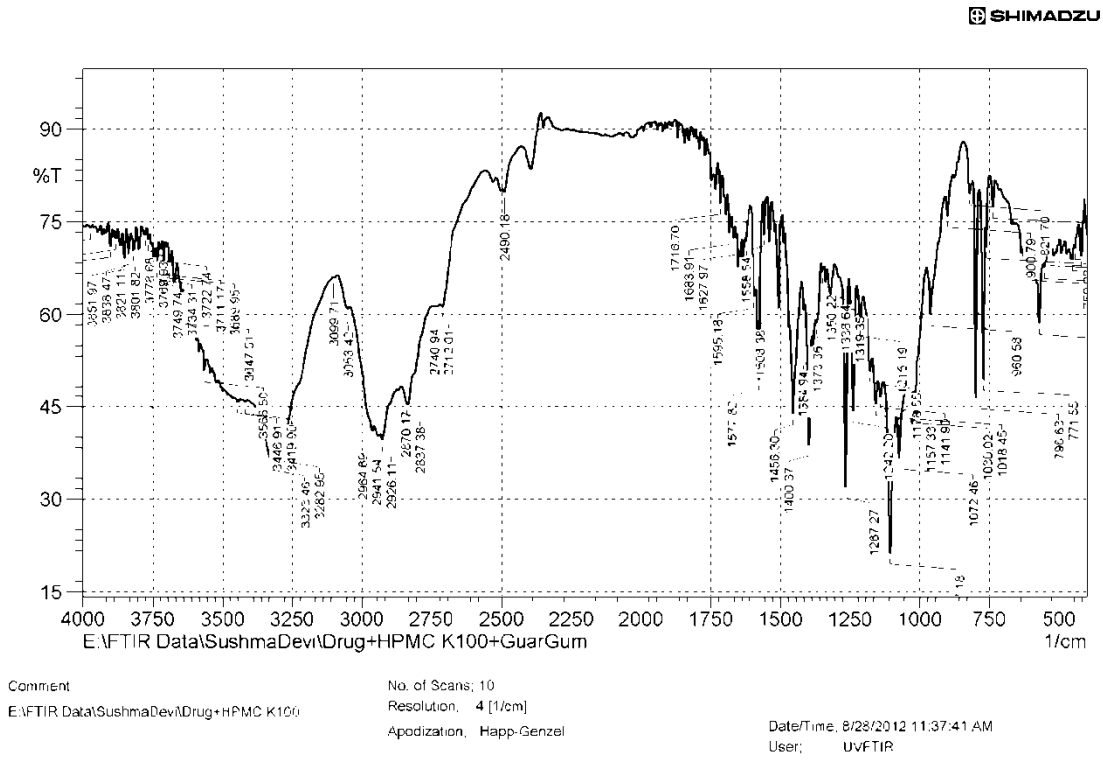



**Figure 8: IR spectra of Propranolol hcl+HPMC K100+ Guar gum**

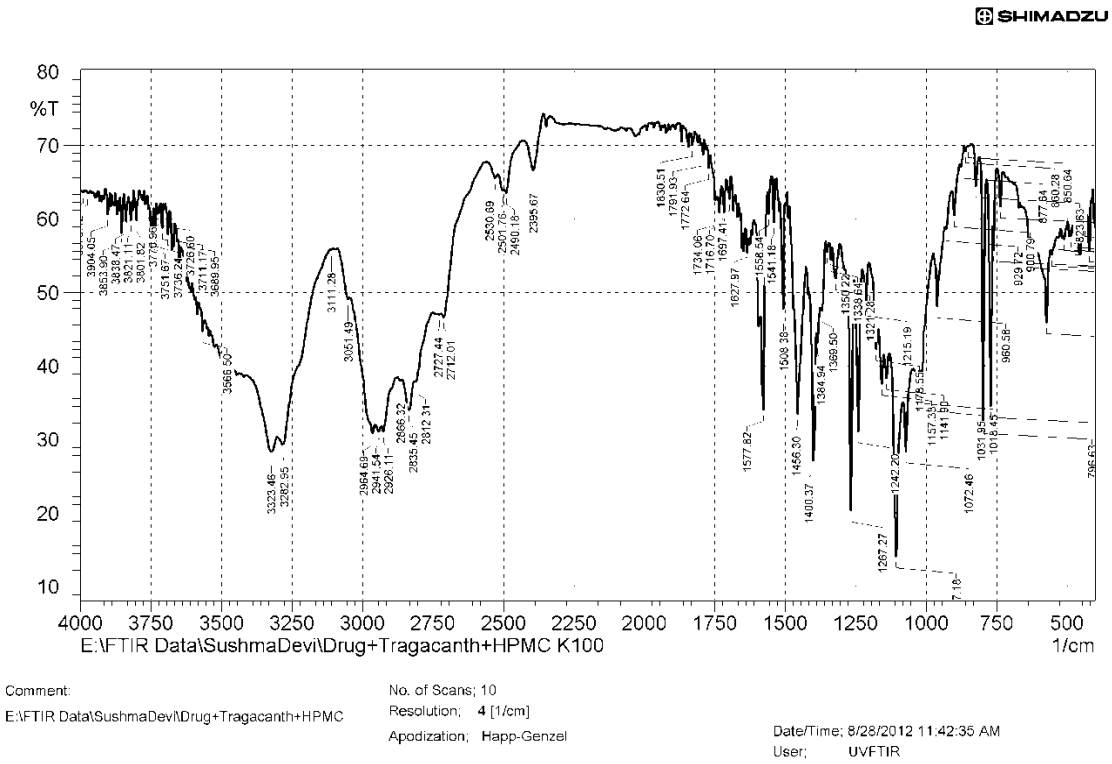



**Figure 9: IR spectra of Propranolol hcl+HPMC K100+ Tragacanth**

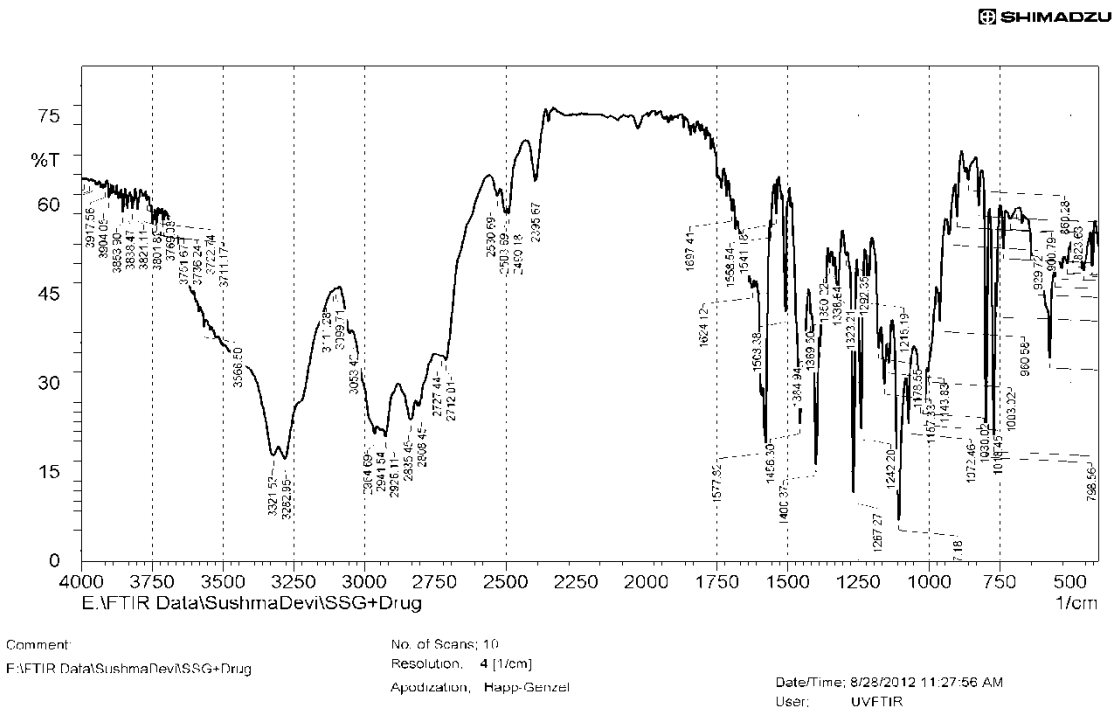



**Figure 10: FT-IR Spectra of Propranolol hcl+SSG**

## DISCUSSION

There was no interaction between drug and polymer, drug and excipients. so selected excipients were found to be compatable with Propranolol Hydrochloride.

**Evaluation characterization blend of Propranolol hydrochloride Sustained release layer**

**Table 3: Pre-compression parameters**

| Formulation codes | Bulk density | Tapped density | Compressibility index | Hausner ratio | Angle of repose ($^0$) |
|---|---|---|---|---|---|
| F1 | 0.452±0.01 | 0.482±0.001 | 6.637±0.08 | 1.066±0.14 | 29.52±0.16 |
| F2 | 0.395±0.02 | 0.395±0.002 | 8.516±0.01 | 1.085±0.11 | 28.63±0.18 |
| F3 | 0.425±0.01 | 0.483±0.01 | 9.647±0.05 | 1.136±0.01 | 28.13±0.21 |
| F4 | 0.417±0.02 | 0.452±0.004 | 8.393±0.01 | 1.084±0.09 | 27.63±0.26 |
| F5 | 0.387±0.01 | 0.421±0.02 | 8.786±0.02 | 1.088±0.13 | 26.78±0.11 |
| F6 | 0.336±0.04 | 0.368±0.01 | 9.524±0.06 | 1.095±0.4 | 28.63±0.04 |
| F7 | 0.434±0.03 | 0.466±0.004 | 7.558±0.09 | 1.076±0.01 | 29.75±0.01 |
| F8 | 0.421±0.02 | 0.478±0.006 | 6.539±0.00 | 1.135±0.05 | 30.1±0.13 |
| F9 | 0.465±0.01 | 0.498±0.08 | 7.097±0.07 | 1.071±0.11 | 28.71±0.4 |

**DISCUSSIONS**

The results of the granules evaluation suggests that all the granules exhibit the good flow properties, These results show that the core powder mixture has good flow properties. The formulation blend was directly compressed to tablets and in-vitro drug release studies were performed.

**Table 4: Post compression parameters:**

| Formulation codes | Weight variation(mg) | Hardness (kg/±cm$^2$) | Friability (%) | Drug content (%) | Swelling ratio |
|---|---|---|---|---|---|
| F1 | 510±0.99 | 5.3±0.02 | 0.42±0.01 | 98.2±0.56 | 5.451±0.05 |
| F2 | 511±0.99 | 5.2±0.05 | 0.24±0.01 | 97.6±046 | 4.912±0.09 |
| F3 | 506±0.38 | 5.6±0.05 | 0.25±0.00 | 99.1±0.88 | 4.763±0.02 |
| F4 | 503±0.99 | 5.8±0.06 | 0.23±0.03 | 97.4±0.34 | 4.592±0.11 |
| F5 | 500±0.33 | 5±0.00 | 0.31±00.1 | 98.4±0.38 | 4.300±0.018 |
| F6 | 498±0.99 | 5.6±0.02 | 0.18±0.01 | 99.5±0.88 | 3.454±0.01 |
| F7 | 496±0.40 | 5.3±0.01 | 0.14±0.06 | 98.7±0.83 | 2.883±0.21 |
| F8 | 511±0.11 | 5.5±0.07 | 0.18±0.04 | 98.3±0.45 | 2.231±0.34 |
| F9 | 495±0.17 | 5.7±0.03 | 0.19±0.01 | 98.56±0.64 | 2.364±0.005 |

**DISCUSSIONS**

The weight and drug content of all the tablets were found to be uniform with low SD values. All formulations were complying with the Indaian Pharmacopoeial specifications. And the better results were found with f1-f3 i.e., xanthum gum+HPMC K100 shows better results compared to other formulatios. The swelling ratio was good with the xanthum gum and HPMC polymer, when it is compared to other formulations.

**Evaluation tests of Immediate release layer**

**Table 5: Pre compression parameters:**

| Formulation code | Angle of repose | Compreeibility index | Haunser's ratio |
|---|---|---|---|
| I 1 | 19.35±0.16 | 15.08±0.08 | 1.19±0.10 |
| I 2 | 20.63±0.18 | 14.61±0.15 | 1.21±0.08 |
| I 3 | 21.45±0.09 | 15.89±0.13 | 1.27±0.14 |
| I 4 | 17.12±0.23 | 16.11±0.11 | 1.14±0.15 |
| I 5 | 19.58±0.10 | 15.71±0.09 | 1.18±0.07 |

**DISCUSSIONS**

The formulation SSG-6% (I 3) shows better results compare to other concentrations of SSG, this was due to the granular nature of the polymers.

**Table 6: Post compression parameters:**

| Formulation codes | Weight variation (mg) | Hardness (kg/cm$^2$) | Friability (%) | Disintegration time(sec) | Wetting Time (sec) | Swelling ratio |
|---|---|---|---|---|---|---|
| I 1 | 201±0.99 | 3.2±0.06 | 0.36±0.01 | 30.33 | 24.66 | 4.451±0.02 |
| I 2 | 199±0.38 | 3.6±0.08 | 0.29±0.05 | 22.66 | 18 | 3.814±0.01 |
| I 3 | 203±0.46 | 3.8±0.01 | 0.39±0.09 | 20.35 | 19.33 | 4.741±0.21 |
| I 4 | 200±0.19 | 3.3±0.00 | 0.32±0.01 | 25.61 | 15.33 | 3.592±0.04 |
| I 5 | 205±0.51 | 3.4±0.05 | 0.28±0.01 | 29.72 | 24.11 | 3.308±0.04 |

## DISCUSSIONS

The formulation SSG-6% (I 3) hardness, friability shows good results compared to other concentrations. The swelling ratio is more for I 3 this indicates a good polymer matrix swell.

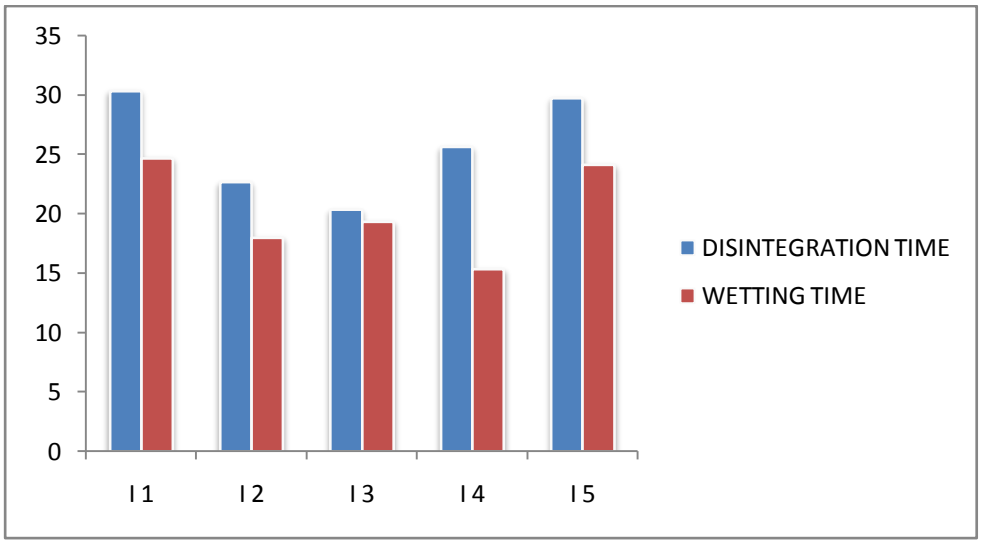



**Figure 11: comparison of DT and Wetting Time in all formulation**

## DISCUSSIONS

All the formulation comparision study between disintegration time and wetting time was observed. And compared to all the formulations I 3, (ssg- 6%) has good and noticable disintegration time so by this we can conclude that it is best optimised formulation.

**DRUG RELEASE PROFILE OF PROPRANOLOL HCL:**

**Table 7: In-vitro drug release of sustained release layer:**

| S.N0 | TIME IN HOURS | % CUMMULATIVE RELEASE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 1 | 0.5 | 15 | 13.25 | 10.06 | 17.70 | 7.83 | 6.24 | 19.20 | 13.88 | 9.33 |
| 2 | 1 | 27.29 | 23.46 | 17.76 | 21.09 | 14.37 | 12.24 | 29.37 | 24.04 | 19.11 |
| 3 | 2 | 45.77 | 31.98 | 24.62 | 31.79 | 23.41 | 18.62 | 37.11 | 33.58 | 28.40 |
| 4 | 2.5 | 58.60 | 40.91 | 31.21 | 34.92 | 26.20 | 21.39 | 43.72 | 39.54 | 34.36 |
| 5 | 3 | 58.99 | 44.29 | 36.79 | 41.20 | 31.25 | 24.49 | 49.51 | 44.52 | 38.86 |
| 6 | 4 | 65.68 | 51.37 | 45.96 | 51.18 | 39.31 | 29.06 | 55.41 | 51.89 | 45.49 |
| 7 | 5 | 73.71 | 58.24 | 51.48 | 56.31 | 45.97 | 34.47 | 61.62 | 56.91 | 51.38 |
| 8 | 5.5 | 76.4 | 59.1 | 56.58 | 56.61 | 47.77 | 36.87 | 64.32 | 59 | 54.68 |
| 9 | 6 | 78.8 | 62.7 | 59.58 | 59.01 | 53.71 | 41.32 | 69.45 | 63.8 | 58.23 |
| 10 | 7 | 80.9 | 67.8 | 62.5 | 64.71 | 58.84 | 49.47 | 74.23 | 68.9 | 63.09 |
| 11 | 8 | 83.6 | 72 | 66.7 | 71.01 | 63.39 | 53.33 | 77.52 | 73.1 | 66.39 |
| 12 | 9 | 87.5 | 78.6 | 74.88 | 74.61 | 68.43 | 60.25 | 81.12 | 77.6 | 70.88 |
| 13 | 10 | 89.6 | 82.5 | 78.44 | 80.61 | 71.77 | 69.24 | 84.57 | 81.2 | 72.66 |
| 14 | 11 | 91.4 | 83.7 | 80.88 | 86.61 | 79.28 | 76.45 | 86.56 | 83 | 74.18 |
| 15 | 11.5 | 96.5 | 89.4 | 85.32 | 94.71 | 88.51 | 81.57 | 91.02 | 86.3 | 76.58 |
| 16 | 12 | 101 | 95.1 | 92.58 | 98.31 | 91.87 | 88.47 | 97.62 | 89.9 | 78.68 |

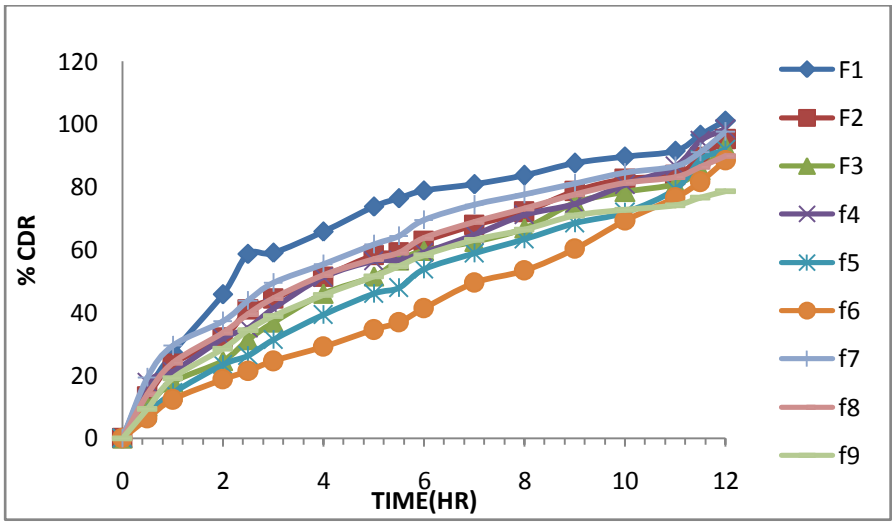



**Figure 12: Dissolution Comparison of Formulations F1-F9**

## DISCUSSIONS

Drug release study were carried out for all formulations (F1 – F9) at 0.1N HCL for 2 hrs, and then in 7.4 pH for 3 hrs and 7 hrs in 6.8 pH buffer which were used as dissolution medium, among this formulations F1 (drug : xanthum gum : HPMC k 100)shows the highest drug release of 101% in 12 hrs. The formulations F1- F9 are prepared by combination of polymers i.e. DRUG : NATURAL POLYMER :SYNTHETIC POLYMER.

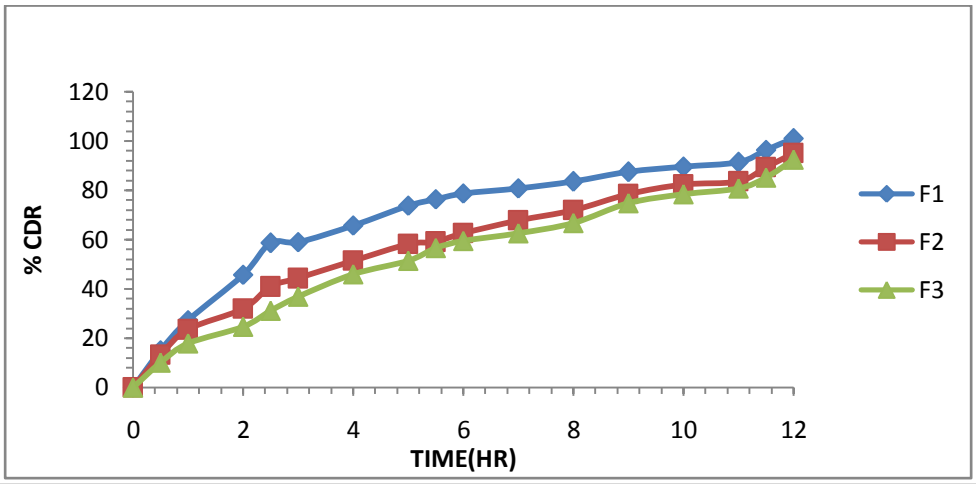



**Figure 13: Dissolution Comparison of Formulations F1, F2, F3**

## DISCUSSIONS

Due to increase in concentration of Xanthum gum:HPMC in F1 than F2,F3, the rate of release of F1 was more than F2,F3. With increase in the concentration of polymer the rate of release was lowered.

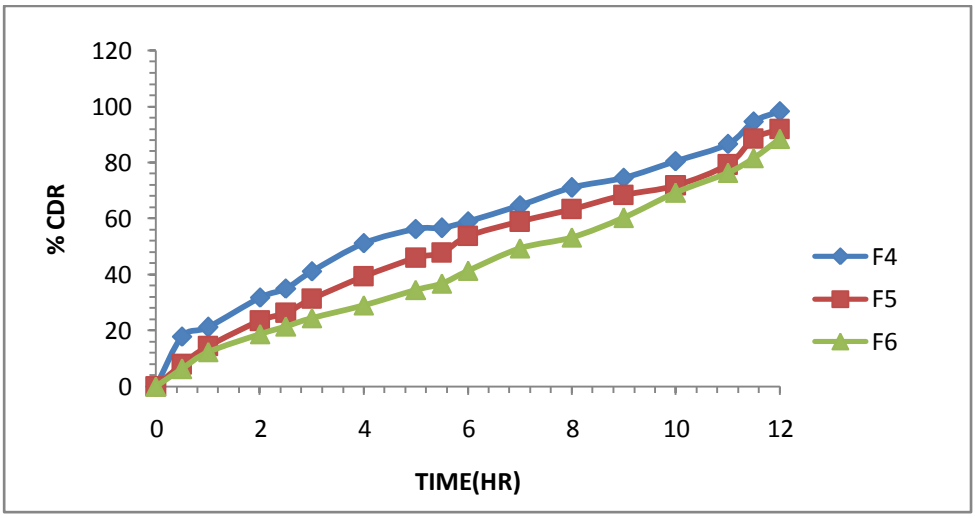



**Figure 14: Dissolution Comparison of Formulations F4, F5, F6**

## DISCUSSIONS

Due to increase in concentration of Guar gum:HPMC in F4 than F5,F6, the rate of release of F4 was more than F5,F6. But when compared to the Xanthum gum, the guar gum has less drug release.

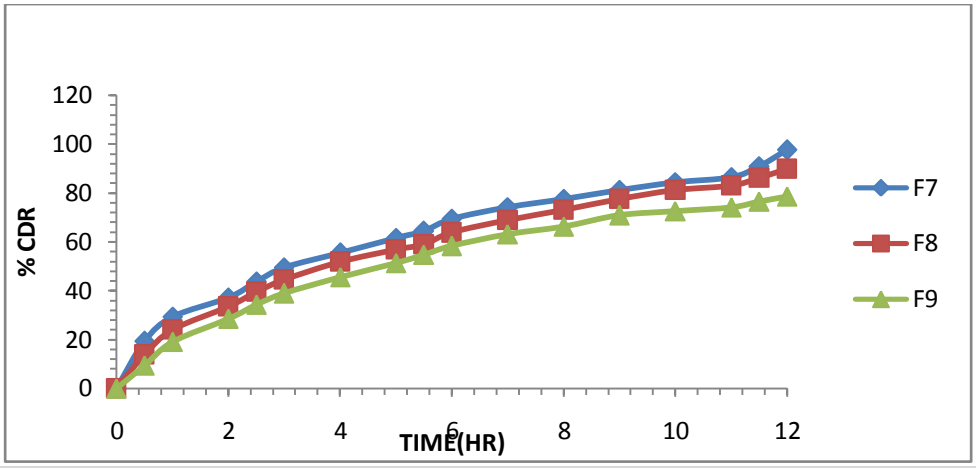



**Figure 15: Dissolution Comparison of Formulations F7, F8, F9**

## DISCUSSIONS:

When compared to the Xanthum gum, the guar gum and tragacanth has much less drug release. Therefore among the 3 polymer combination the Xanthum gum: HPMC has good and effective drug release.

**Table 8: DRUG RELEASE OF TRIAL BATCH**

| S.NO | TIME IN HOURS | % CUMULATIVE RELEASE | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F10 | F11 | F12 | F13 | F14 | F15 | F16 | F17 | F18 |
| 1 | 0.5 | 19.59 | 14.51 | 7.74 | 11.17 | 9.62 | 8.61 | 11.17 | 7.74 | 5.17 |
| 2 | 1 | 37.93 | 28.06 | 25.16 | 34.20 | 27.14 | 25.16 | 30.19 | 21.38 | 16.06 |
| 3 | 2 | 66.77 | 60.48 | 54.19 | 62.41 | 60 | 56.12 | 51.29 | 48.38 | 37.74 |
| 4 | 2.5 | 72.10 | 64.77 | 58.65 | 68.37 | 65.96 | 62.29 | 63.49 | 58.40 | 43.18 |
| 5 | 3 | 76.43 | 66.02 | 67.75 | 74.68 | 69,80 | 65.53 | 73.85 | 72.60 | 67.51 |
| 6 | 4 | 82.78 | 74.25 | 79.02 | 88.78 | 77.47 | 72.51 | 84.63 | 79.22 | 75.70 |
| 7 | 5 | 97.88 | 90.13 | 87.15 | 93.49 | 86.05 | 83.01 | 93.15 | 88.61 | 82.33 |
| 8 | 5.5 | 97.88 | 90.13 | 87.15 | 93.49 | 86.05 | 83 | 93.2 | 88.1 | 82.1 |
| 9 | 6 | 97.88 | 90.13 | 87.17 | 93.4 | 86.05 | 83 | 93.2 | 88.1 | 82 |
| 10 | 7 | 97.88 | 90.13 | 87.17 | 93.4 | 86.05 | 83 | 93.2 | 88.1 | 82 |
| 11 | 8 | 97.88 | 90.13 | 87.17 | 93.4 | 86.05 | 83 | 93.2 | 88.1 | 82 |
| 12 | 9 | 97.88 | 90.13 | 87.17 | 93.4 | 86.05 | 83 | 93.2 | 88.1 | 82 |
| 13 | 10 | 97.88 | 90.13 | 87.17 | 93.4 | 86.05 | 83 | 93.2 | 88.1 | 82 |

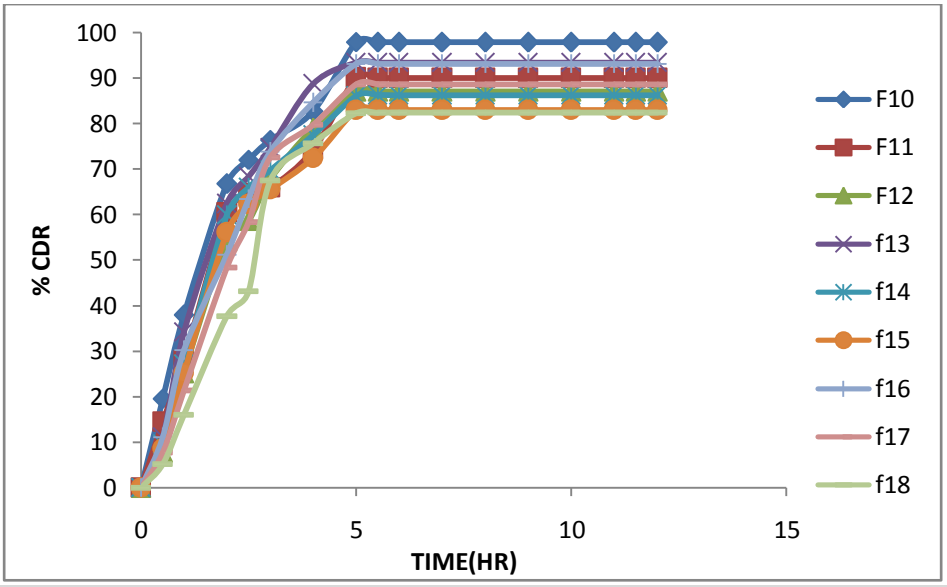



**Figure 16: In-vitro drug release profile of F10 To F18 Formulations.**

## DISCUSSIONS

Drug release study were carried out for all formulations (F10 – F18) at 0.1N HCL for 2 hrs,and then in 7.4 pH for 3 hrs and in 6.8 pH buffer the drug release had declined, among this formulations F1 (drug : xanthum gum ) shows the highest drug release of 97.8% in 5 hrs. The formulations F10- F18 are prepared by using single polymers i.e. DRUG : NATURAL POLYMER.

**Table 9: In-vitro drug release of immediate release layer:**

| S.NO | TIME IN MIN | %CUMMULATIVE RELEASE | | | | |
|---|---|---|---|---|---|---|
| | | I 1 | I 2 | I 3 | I 4 | I 5 |
| 1 | 5 | 29.37 | 29.90 | 30.91 | 30 | 25.59 |
| 2 | 10 | 40.64 | 44.51 | 52.74 | 51.77 | 37.25 |
| 3 | 15 | 62.90 | 67.25 | 76.45 | 75.48 | 58.54 |
| 4 | 30 | 74.03 | 75 | 84.19 | 81.77 | 77.41 |
| 5 | 45 | 80.80 | 81.29 | 88.06 | 85.64 | 83.70 |
| 6 | 60 | 85.64 | 90.48 | 98.22 | 94.35 | 89.51 |
| 7 | 90 | 95.80 | 98.70 | 101.61 | 102.09 | 97.25 |

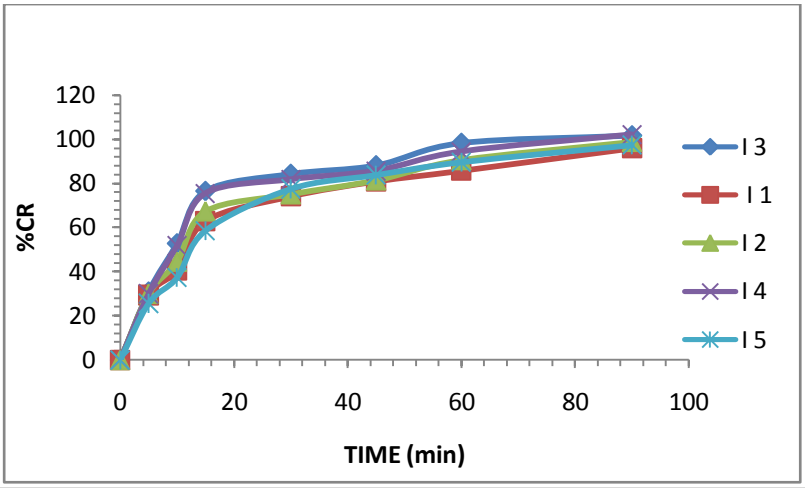



**Figure 17: In-vitro drug release profile of I 1- I 5 Formulations.**

## DISCUSSIONS

In this formulation SSG-6% shows fast drug release i.e., with in 30 min the drug release was 84% where as the other concentrations (SSG-2%, 4%, 8%, 10%) showed slow release. This result is due to the concentration variance of the polymers.

**Table 10: In-vitro drug release of Bilayed layer tablet:**

| S.NO | TIME IN HOURS | %CUMMULATIVE RELEASE | | | | |
|---|---|---|---|---|---|---|
| | | M 1 | M 2 | M 3 | M 4 | M 5 |
| 1 | 0.5 | 12.26 | 16.25 | 7.40 | 8.75 | 10.40 |
| 2 | 1 | 21.42 | 19.29 | 13.26 | 17.51 | 19.42 |
| 3 | 2 | 29.06 | 28.89 | 21.38 | 25.85 | 26.37 |
| 4 | 2.5 | 44.00 | 35.29 | 27.26 | 36.41 | 36.93 |
| 5 | 3 | 53.81 | 44.50 | 34.72 | 43.05 | 42.65 |
| 6 | 4 | 64.26 | 59.22 | 46.61 | 52.82 | 56.75 |
| 7 | 5 | 74.40 | 66.79 | 56.45 | 61.53 | 67.72 |
| 8 | 5.5 | 77.78 | 69.70 | 60.09 | 68.11 | 71.10 |
| 9 | 6 | 82.14 | 72.53 | 63.57 | 72.28 | 75.21 |
| 10 | 7 | 85.08 | 79.43 | 70.80 | 78.58 | 78.40 |
| 11 | 8 | 88.31 | 86.88 | 73.89 | 79.58 | 82.40 |
| 12 | 9 | 93.51 | 91.49 | 76.39 | 80.27 | 86.35 |
| 13 | 10 | 98.01 | 94.94 | 82.46 | 93.71 | 90.08 |
| 14 | 11 | 98.88 | 99.22 | 88.88 | 94.76 | 94.85 |
| 15 | 12 | 99.57 | 102.05 | 91.35 | 95.56 | 98.88 |

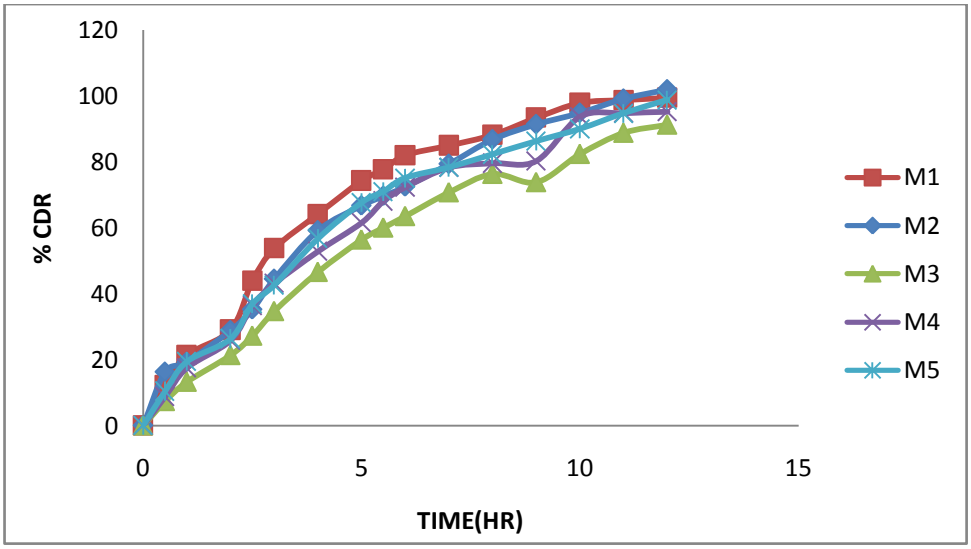



**Figure 18: In-vitro drug release profile of M1 – M5 Formulations**

## DISCUSSIONS:

All the eight formulations of Propranolol HCL bilayer tablets, were subjected to in –vitro release studies, these studies were carried out using dissolution medium, (0.1 N HCL, phosphate buffer pH 7.4 AND pH 6.8)), by using dissolution apparatus type II (paddle type) . Dissolution profiles of all formulations were compared by cumulative percentage drug release verses time. From dissolution results it was confirmed that formulation M1 ( drug : xanthum gum: HPMC K 100 + immediate relese layer SSG-6%) was showing good dissolution profile according to USP limits.

**Table 11: RELEASE KINETICS OF PROPRANOLOL HCL**

| S.N0 | FORMULATION CODES | ZERO ORDER | FIRST ORDER | HIGUCHI | KORSMEYER PEPPAS |
|---|---|---|---|---|---|
| 1 | F 1 | 0.830 | 0.875 | 0.963 | 0.940 |
| 2 | F 2 | 0.941 | 0.920 | 0.994 | 0.991 |
| 3 | F 3 | 0.963 | 0.936 | 0.985 | 0.928 |
| 4 | F 4 | 0.963 | 0.791 | 0.983 | 0.987 |
| 5 | F 5 | 0.984 | 0.898 | 0.967 | 0.997 |
| 6 | F 6 | 0.992 | 0.888 | 0.922 | 0.987 |
| 7 | F 7 | 0.917 | 0.871 | 0.995 | 0.995 |
| 8 | F 8 | 0.928 | 0.986 | 0.997 | 0.993 |
| 9 | F 9 | 0.919 | 0.991 | 0.992 | 0.901 |

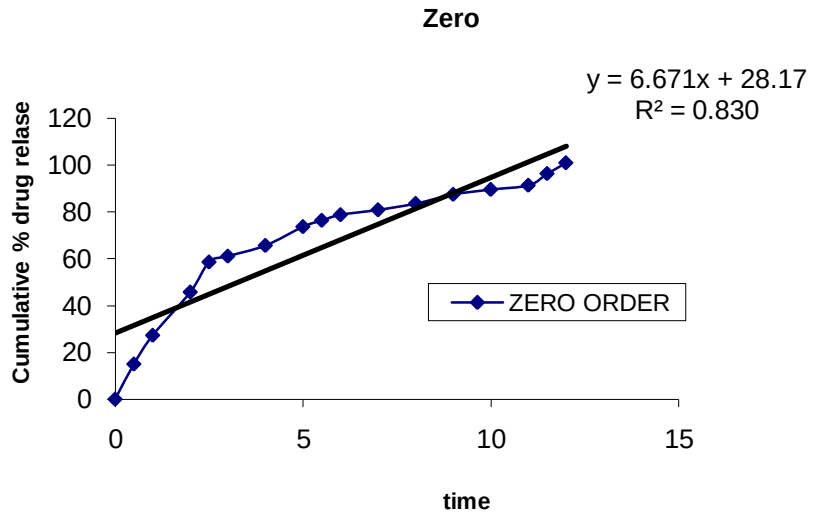



**Figure 19: Release Kinetic profile of zero order**

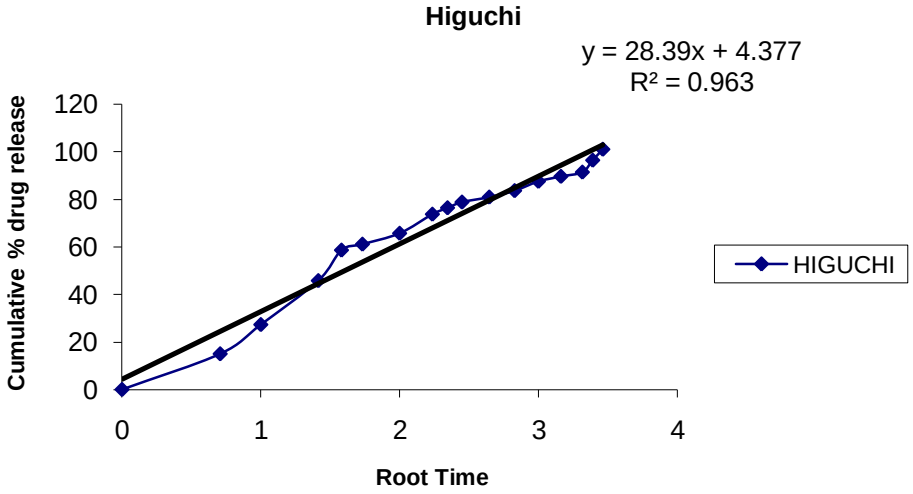



**Figure 20: Release Kinetic profile of Higuch**

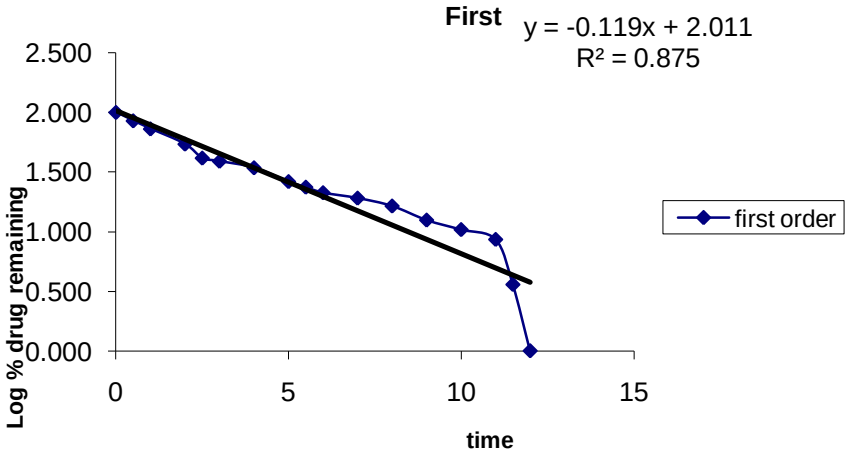
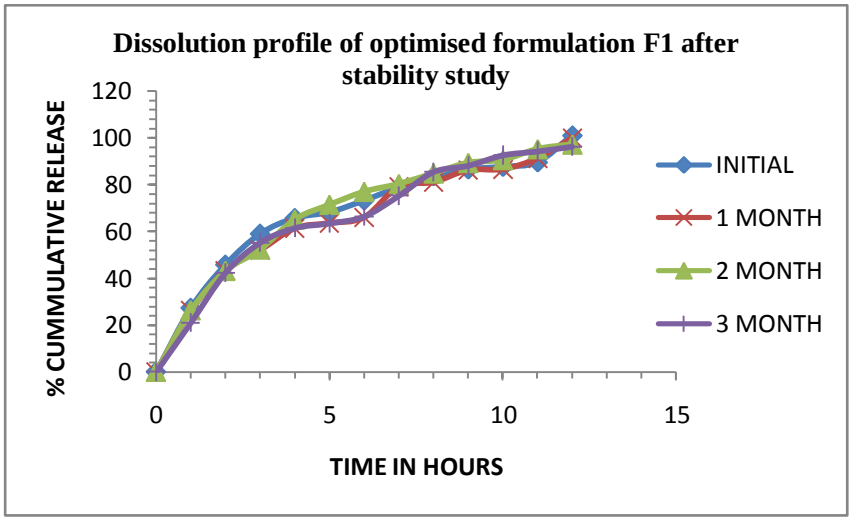



**Figure 21- Release Kinetic profile of First order**

## DISCUSSIONS

The different kinetic models were applied to the optimized formulation F1. It was observed that it follows first order kinetics. The release mechanism follows Higuchi and korsmeyer-peppas model. Based on the diffusion coefficient value both follows super case 2 transports.

**Figure 22: Stability Studies**




## DISCUSSIONS

The stability study results of optimized formulation at 40°C/75% RH for 3 month was found to be satisfactory

## SUMMARY AND CONCLUTION

In the present study, an attempt was made to prepare and evaluate bilayered matrix tablets by using natural and synthetic gum combinations. The matrix tablet was prepared by direct compression and wet granulation method. The weight and drug contents of all the tablets were found to be uniform with low SD values. The hardness and the friability were within specified range for both the layers. The pure drug Propranolol HCL showed complete drug release within 60 minutes, whereas, drug: natural polymer : synthetic polymer complex has shown drug release for 12hrs, with increase in the concentration of polymers, the drug release was decreased where as, the amount of Propranolol HCL increases, the drug release increases. The FTIR analysis ruled out the interaction between drug and polymers used in the preparation. Swelling of tablet decreased with an increased amount of polymers. The in-vitro drug release study indicated that the tablets treated with natural and synthetic polymers combination releases drug slowly to maintain drug concentration in the body, where as the use of single polymers i.e., only natural polymer: drug releases the drug very fast and therefore blood concentration increases and there is a fluctuation in blood pressure.

## BIBLIOGRAPHY

1. Yie WC. Novel drug delivery systems. 2nd ed. Madison Avenue (NY): Marcel Dekker, Inc.; 1992.
2. Asgar A, Sharma SN. Evaluation of oral sustained release formulation. The Eastern Pharmacist 1991: 69-74.
3. Haider SS, Monnujan N, Shahriyar SM. Sustained release preparation of metoclopramide hydrochloride based on fatty matrix. Indian drugs 2002;39:73-9.
4. Tripathi KD. Essentials of medical pharmacology. 5thed. New Delhi: Jaypeebrothers medical publication (p) Ltd; 2003.
5. Katzung GB. Basic and clinical pharmacology. 8thed. New York: Mcgraw Hill; 2001: 210-215..
6. Setter SM. a clinical review with a focus on dual therapy. Clin Therapeutics 2003; 25 (12): 2991-3025
7. Robinson JR, Lee VH. Controlled drug delivery: fundamentals and applications. 2nd ed.. New York, INC; Marcel Dekker: 1987: 211-220.

8. Gilbert S. Banker, Neil R. Anderson., tablets. In Leon Lachman, Herberta Liebermann, Joseph L Kanig. (Edition), the theory and practice of Industrial pharmacy, 3rd ed. Lea and Febiger, Philadelphia, 1987, page. no. (a) 293-294, (b) 330-331, (c) 430-431.
9. Available on online URL; www.wikipedia.com.
10. Abraham. M.A., Shirwaikar. A., Formulation of multilayered sustain release tablets using insoluble matrix systme., Indian Journal of Pharmaceutical Science. 1997;59(6): page no. 312-315.
11. William C. Gunsel and Robert. G. Busel., compression coated and layer tablets, 1987, In: Herbert A Libermann, Leon Lachman, Joseph.B. Schwartz Pharmaceutical dosage form: Tablets 2nd edition marcel Dekkar, Inc., Newyork 1989, page no.1,274.
12. Charles Slchioo, Joseph R. Robinson, Remington's Pharmaceutical science 1985, 17th edition page. no. 1644-1653
13. Vyas SP, Khar RK. Controlled drug delivery: concepts and advances. 1st ed. Delhi; VallabhPrakashan: 2002: 82-96.
14. Hoffman A. Pharmacodynamic aspects of sustained release preparations. Adv Drug Del Rev 1998; 33: 185-99.
15. Jain NK. Controlled and novel drug delivery. 1sted. New Delhi: CBS Publishers; 2002: 79-92.
16. Rang HP, Dale MM, Ritter JM, More PK. Pharmacology. 5th ed. United Kingdom; Churchill Levingstone: 2003: 782-820.
17. Vaithiyalingam SR, Tuliani P, Wilber W, Reddy IK, Khan MA. Formulation and stability evaluation of ketoprofen sustained release tables prepared by fluid bed granulation with carbopol 971P solution. 2002; 28: 1204-031.
18. Gul MK Controlled release oral dosage forms: Some recent advances in matrix type drug delivery systems. The Sciences 2001; 1(5): 350-4.
19. Turner S, Federici C, Hite M, Fassihi R. Formulation development and human *In vitro-In vivo* correlation for a novel, monolithic controlled release matrix system of high load and highly water-soluble drug niacin. 2004; 30:797-07.
20. Huey LJ, Shu-Jean L. On the assessment of similarity of drug dissolution profiles- a simulation study. Drug Information Journal 1997; 31: 1273-89.
21. Ding, Linghong, Manufacture of oral medicine composition for lowering blood glucose: Faming Zhuanil Shenqinggongkai Shuomingshu CN A2005, 12.
22. Dicolo, Giacomo, Zambito; A site specific controlled release system for Propranolol; J pharma pharmacology, 57(5), 565-571, 2005.
23. Kroge I, Bodmeier R, Development of a multifunctional matrix drug delivery system surrounded by an impermiable cylinder, J. Controlled Release, 61(1), 1999: 310-411.
24. Song, CX, Labhasetwar, Levy V, RJ, Controlled release of U-86983 from double layer biodegradable matrices, J. Controlled release, 45, 1997,177.
25. Amit Kumar, Chawla , Manish, Kesarwari; Oral extended release dosage forms comprising a high dose biguanide and a low dose sulfonylurea; 2003,21.
26. Yang L, Fassihi R., Modulation of diclofenac release from totally soluble controlled release drug delivery systems, J. Controlled Release, 44, 1997, 135.
27. Darshana HD, Mangal NS, Sudhakar GD. Design and evaluation of an extended release tables of prochlorperazine maleate. Indian Drugs 2000; 38: 69-74.
28. XiaochenGh, Darly JF, Estelle F, Simons R. Evaluation and comparison of five matrix excipients for the controlled release of acrivastine and pseudoephedrine. Drug Development and Industrial Pharmacy 2004; 30: 1009-17.
29. Shivakumar HN, Nath BS, Desai BG. Effect of added HPMC and HEC on the release of cetostearyl alcohol embedded diclofenac sodium from tables for controlled release. The Eastern Pharmacist 2001: 117-9.
30. Hosseinali T, Seyed AM, Tina BG. Preparation of sustained release matrix tables of aspirin with ethylcellulose, eudragit RS100 and eudragit S100 and studying the release profile and their sensitivity to tablet hardness. Iranian Journal of Pharm Research 2003: 201-06.
31. Kale VV, Kaslival RH, Avari JG. Effect of matrix geometry on drug release from guar gum matrix tablets. Ind Drugs 2005; 42: 84-6.
32. Martindale: The Extrapharmacopoeia, 31st ed. London: The royal pharmaceutical society; 1996.
33. Wade A, Weller PJ. Handbook of pharmaceutical excipients. 2nd ed. London: The Pharmaceutical Press; 1994: 261-290.
34. Mark. G, A practical guide from candidate drug selection to commercial dosage form in pharmaceutical preformulation and formulation. Inter pharm/crc Florida; 2004: 121-245.
35. Subramanyam CVS, Thimmasetty J. Laboratory manual of physical pharmaceutics. Delhi; VallabhPrakashan: 2005: 56-71.

36. Subramanyam CVS. Textbook of physical pharmaceutics. VallabhPrakashan: Delhi; 2005: 61-69.
37. Subrahmanyam CVS, Thimmasetty J, Sarasija S, Kusumdevi V. Pharmaceutical engineering. Delhi: Efficient Offset Printers; 2004.
38. Sanjay R. Patel, Priyal R. Patel, Chintan N. Vora, NitinD. Patel Jayvadan K.Patel. Formulation, process parameters optimization and evaluation of delayed release tablets of Rabeprazole Sodium, Int J Pharmacy Pharm Sci 2010;2(3) :144-156.
39. Debajyoti Ray, Amresh K Prusty. Designing and invitro studies of gastric floating tablets of Tramadol hydrochloride, Int J Appl Pharm : 2(4):12-16.
40. M. M. Gupta, B.Srivastava. Enhancement of flow property of poorly flowable Aceclofenac drug powder by preparation of spherical crystals using change method and making drug powder suitable for direct compression, Int J Current Pharmaceutical Review And Research 2010;1(1):12-23.
41. Agarawal et al.,April-June 2011 IJPFR. A Review article on wet granulation technology.
42. Available on online URL; www.wikipedia.com. On direct compression of tablets.
43. M.A.Abraham and A.Shirwaikar, Formulation of multilayered sustained release tablets using insoluable matrix system, Indian J.Pharma.Sci.59(1997)312,315.
44. J.P.Vercammen, D. Dauwe and P. Brioen, Possibility of use of Eudragit RS as a sustained release matrix agent for the incorporation of water soluable active compounds at high percentages, STP Pharma. Sci. 7 (1997)491-497.

***Corresponding Author:**
**Corresponding author:**
**NARASIMHA RAO R**
*HITS COLLEGE OF PHARMACY,*
*BOGARAM (V), KEESARA (M), R.R (Dist)-501301*