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# FORMULATION AND DEVELOPMENT OF MODIFIED PROPRANOLOL HCL TABLET

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## ABSTRACT

A co-processed excipient was prepared from Tamarind seed polysaccharide (TSP) and mannitol in using direct compression as well as wet and dry granulation. The effect of the ratio of the two components, percentage of lubricant and particle size on the properties of the prepared co-processed excipient has been investigated. Optimal physicochemical properties of the excipient, from a manufacturing perspective, were obtained using a co-processed mannitol- TSP (2:8 w/w) mixture prepared by wet granulation. Disintegration time, crushing strength and friability of tablets produced by co-processed mannitol- TSP, using magnesium stearate as a lubricant, were found to be independent of the particle size of the prepared granules. The inherent binding and disintegration properties of the compressed co-processed mannitol- TSP are useful for the formulation of poorly compressible, low and high strength active pharmaceutical ingredients. The ability to co-process Tamarind seed polysaccharide (TSP) with crystalline mannitol allows TSP to be used as a valuable industrial pharmaceutical excipient. The aim of present study was to formulate and evaluate an oral sustained release tablet of Propranolol hydrochloride to increase therapeutic effect, reduced frequency of administration and improved patient compliance. Propranolol HCl tablet was formulated by using co-processed excipients Tamarind seed polysaccharide and mannitol. Formulations were prepared by varying the polymer concentration. The optimized formulations were subject to stability testing as per ICH guidelines.

**KEYWORDS-** **Propranolol HCl, Tamarind seed polysaccharide (TSP), co-processed excipients**

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# INTRODUCTION

Excipients have been successfully employed in the formulation of solid, liquid and semi-solid dosage forms and are specifically useful in the design of modified release drug delivery systems. Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Systems that are designed as prolonged release can also be considered as attempts at achieving sustained-release delivery. Successful fabrication of sustained release products is usually difficult and involves consideration of physicochemical properties of drug, pharmacokinetic behavior of drug, route of administration, disease state to be treated and, most importantly, placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug [1-7]. Polysaccharides, the polymer of monosaccharide retains their integrity because they are resistant to the digestive action of gastrointestinal enzymes. The matrices of polysaccharides are assumed to remain intact in the physiological environment of stomach and small intestine but once they reach in the colon, they are acted upon by the bacterial polysaccharides and results in the degradation of the matrices. A large number of polysaccharides such as amylase, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans, dextrin and locust bean gum have been investigated for their use in colon targeted drug delivery systems[8,22,23 and 24].

The use of natural excipients like Tamarind seed polysaccharide (TSP) obtained from the seed kernel of *Tamarindus indica* (L.), for pharmaceutical applications is attractive because they are economical, readily available, non-toxic, capable of chemical modifications, potentially biodegradable. For a number of reasons there has been an increase in interest in the development of new excipients/diluents. Some drugs show incompatibilities with many of the current range of excipients such as, Atenolol-PVP, Atenolol-Magnesium stearate etc. [9] Mucilage's are generally normal products of metabolism, formed within the cell (intracellular formation) and are produced without injury to the plant. Gums and mucilage's are polysaccharide complexes formed from sugar and uronic acid units. They are insoluble in alcohol but dissolve or swell in water [10]. Co-processed excipients are a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing**,** and without significant chemical change. However in some instances, formation of necessary components may occur, such as *in-situ* salt formation. Many different co-processing methods may be used, including standard unit operations such as granulation, spray drying, melt extrusion, milling etc. The choice for a specific application will depend on the materials used, their form (e.g. whether dry powders or liquid) and the specific physical properties desired. Likewise the ratios of the components may vary depending on the desired performance [15]. The excipients industry to date has been an extension of the food industry. Moreover, excipients are products of the food industry, which has helped to maintain a good safety profile. Increasing regulatory pressure on purity, safety, and standardization of the excipients has catalyzed the formation of an international body, the International Pharmaceutical Excipients Council (IPEC). The development of new excipients to date has been market driven (i.e., excipients are developed in response to market demand) rather than marketing driven (i.e., excipients are developed first and market demand is created through marketing strategies) and has not seen much activity as shown by the fact that, for the past many years, not a single new chemical excipients has been introduced into the market [16]. Co-processing is based on the novel concept of two or more excipients interacting at the sub-particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of

individual excipients. The availability of a large number of excipients for co-processing ensures numerous possibilities to produce tailor-made "designer excipients" to address specific functionality requirements [17].

## MATERIALS AND METHODS

Propranolol HCL obtained from Lupin Pvt. Ltd. Pune, India, Starch, Lactose and Magnesium stearate obtained from Merck chemicals pvt. Ltd. India. The protocol comprises of following steps:

### *A) Isolation and characterization of Tamarind Seed Polysaccharide (TSP)*

Required quantity (200 g) of tamarind seeds soaked in double distilled water and boiled for 5 hrs to remove the outer dark layer. After removing the outer dark layer, sufficient amount of double distilled water was added to the inner white portion and boiled with constant stirring in order to obtain the slurry. The resultant solution was cooled in refrigerator so that most of the un-dissolved portion settles down. The supernatant liquid separated out by simple decantation or best by centrifugation at 500 rpm for 20 min. After this, the solution was concentrated on a water bath at 60°C to reduce the volume to one-third of its initial volume. The cooled solution was poured into 3 volumes of acetone by continuous stirring. Precipitates obtained was washed with acetone and dried in vacuum at 50-60°C. This method involves the use of simpler principle and easy to execute on a laboratory scale. It includes implication of methods like distillation, centrifugation, settling, and filtration, but it is time consuming and required at least 2 days to extract tamarind seed polysaccharide [10].

### *B) Drug- Excipients Compatibility Study*

Fourier transform infrared (FTIR) spectral data were taken on a Shimadzu instrument to find out the chemical stability of the drug with excipients. Drug Excipients compatibility study was done by using FTIR spectroscopy and the physical mixture was also observed [7]. A milligram of finely grounded sample was taken. Infrared spectrum was taken by scanning the samples of pure drug and the polymers individually over a wave number range of 4000 to 400 $cm^{-1}$ using Fourier transform infrared spectrophotometer (FT-IR, Shimadzu 8400S, Shimadzu, Japan ). The change in spectra of the drug in the presence of polymer was investigated which indicates the physical interaction of drug molecule with the polymer. Fourier transform infrared (FTIR) spectral data was taken on an instrument to find out the chemical stability of the excipients. Spectral scanning was done in the range between 4000-400 $cm^{-1}$.

### *C) Preparation of Co-Processed Tamarind Seed Polysaccharide (TSP) - Mannitol*

Three co-processed mixtures (each 10 g) of TSP & mannitol of different ratios (1:9, 2:8, and 3:7, w/w) were prepared using wet granulation. Wet granulation is the more preferred method for co-processing. The wet granulation technique employs a solution, suspension, or slurry containing binder, which is usually added to the powder mixture. In this, starch solution is used to make damp mass of powder containing all ingredients. The wet mass was passed through a sieve. Granule drying was performed at 40$^{o}$C using a drying oven. The granules were sieved and mixed using the same procedures as used for the dry granulation procedure.

### *D) Formulation of Tablet*

Round, convex-faced tablets containing 100 mg of Propranolol HCl, 8mm in diameter and with an average hardness of > 45 N, were made in a rotary tablet press. The tablets were formulated with the diluents such as lactose and starch using binder polyvinyl pyrolidone (PVP-K30) with the co-processed excipients containing TSP: mannitol in 1:9, 2:8, 3:7 ratios. The tablets were compressed by wet granulation technique using magnesium stearate as lubricant, prior to compression, the blends (F1 to F3) were evaluated for various micromeritic properties and the results were shown in Table 2. Propranolol HCl passed through sieve No.80 was collected and mixed separately with the selected ratio of co-processed excipients (TSP: mannitol) in each case followed by blending with diluents, glidant and lubricant. The resulting blend was compressed to form

a tablet by using 8 mm round shaped tablet tooling.

### *E) Pre-compression Studies*

The powder blend was evaluated for angle of repose, bulk density, tapped density and Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities [12, 13and 14].

### *F) In Process Quality Control Test for Tablets*

The compressed tablets were tested for weight variation, hardness, friability, disintegration time.

i. **Hardness:** The hardness of the prepared tablets was measured using Monsanto hardness tester. The hardness was measured in terms of kg/cm2.
ii. **Weight variation:** 20 tablets were collected randomly and weighed individually. The individual weights with the average weight for the determination of weight variation. The percentage deviation was calculated.
iii. **Friability:** The friability of the compacts was measured using the Roche friabilitor set at a rotation speed of 25 rpm. Five grams of tablets were rotated for 4 min (100 rotations). At the end of the run the tablets were weighed accurately, and the percentage friability was computed from the weight of tablets before and after the test.
iv. **Disintegration time:** The disintegration time of tablet was determined in 0.1N HCl at 37°C ± 0.5°C using USP disintegration test apparatus. The disintegration test was performed without disc. The data given are at the average of 6 tablets.
v. **Dissolution test:** *In vitro* dissolution study for Propranolol HCl tablets was carried out by using USP Dissolution Test Apparatus- II (Paddle type) at 50 rpm in 900 ml of 0.1N HCL as dissolution media, maintained at $37\pm0.5^0$ C. The study was carried for 8 hrs and at predetermined time intervals of 1 hour, 10 ml aliquots were withdrawn, filtered and assayed spectrophotometrically at λmax 290 nm using double beam UV Visible Spectrophotometer (Shimadzu, Model 1700, and Japan). An equal volume of fresh medium, which was pre-warmed at 37°C, was replaced into the dissolution medium after each sampling to maintain the sink condition throughout the study [12].
vi. **Stability Protocol:** Tablet formulations were kept for accelerated stability testing in stability chamber (Thermo lab, Mumbai). Storage conditions were maintained at a temperature of 40°C ± 2°C and relative humidity i.e.75% RH ± 5% RH. The minimum period for testing was selected as per mentioned in ICH guidelines. Within seven days after formulation of tablets were transferred to bottles. The samples designed for accelerated stability study were kept at $40^o$ C and 75% RH in sealed bottles. The samples were withdrawn from stability chamber and tested for 15 days, one month, two month and three months after the date of packaging [21].

## RESULTS AND DISCUSSION

The infra-red absorption spectrum of residue is concordant with the reference spectrum of Propranolol HCL treated in same manner. It may be concluded that, the drug is in the same pure state even in the formulation without interacting with the polymers as shown in figure no. 01. The powder blend was evaluated for angle of repose, bulk density, tapped density and Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities result was depicted in Table No. 02. Tamarind seed polysaccharide (TSP) exhibits poor flow and produces fragile tablets upon compression, while pure crystalline mannitol displays undesirable compaction properties and results in tablet capping. The prepared granules were lubricated using magnesium stearate. The mixtures were compressed at 25 k N scale of the upper punch and the tablets obtained were tested for hardness, friability and disintegration time. The results indicate that improvements in the physical properties of mannitol and TSP mixtures follow the order: wet and spray granulation > dry granulation > direct mixing. The compressed tablets were tested for weight

variation, hardness, friability, disintegration time (Table No. 03). The mixtures prepared by direct mixing have unacceptable physical properties (e.g. poor powder flow, powder non uniformity (segregation), friable and low hardness tablets). Additionally, the results indicate that the properties of mannitol/TSP mixtures can be improved by dry granulation but they were still not optimal. Moreover it was noted that friability was sensitive to the fraction of magnesium stearate added. As a result, excipients produced by direct mixing and dry granulation methods were no longer used since the addition of active ingredients having critical properties (e.g. poor flow, incompressible, fragile, etc) could have a negative impact on compressed tablets. The main objective thus became to find the most appropriate mixture that could be used to overcome the poor flow and weak compressibility of its components. The method of integrating two components is an important factor in obtaining a suitable mixture that is needed to act as diluents for the active ingredient. From the preliminary results physical mixing and direct compaction of the two components proved unsatisfactory; consequently wet granulation was used to produce the new excipients, whereby the properties of the two components are able to overcome poor flow and compression properties. In addition the compatibility of the mixture towards lubrication sensitivity was tested. In the case of wet granulations, the physical properties were improved with respect to the TSP: mannitol ratio used in the following order: 2:8 > 3:7 > 1:9 (w/w TSP: mannitol). The mixtures prepared using ratios of 1:9 and 3:7 (w/w) showed relatively high friability and sensitivity to the weight fraction of magnesium stearate added as a lubricant. The optimal ratio with respect to physical properties improvement is the 2:8 (w/w) ratios (TSP: mannitol).

The percent cumulative release of tablet formulated using TSP: Mannitol 1:9 ratio was found to be more than 50%, TSP: Mannitol-2:8 were found to be more than 40% where as TSP: Mannitol-3:7 were found that less than 40% after eight hours as shown in fig no. 02. Release of drug detected in graph that up to 80% drug was release of tablet formulated using TSP: Mannitol 1:9, 70% drug was release of tablet formulated using TSP: Mannitol 2:8 and more than 60% drug was release of tablet formulated using TSP: Mannitol 3:7 ratio after 12 hour (Table No. 04). It shows that sustained release property of co-processed excipients like TSP: Mannitol 1:9> TSP: Mannitol 2:8>. TSP: Mannitol 3:7 as shown in Figure No. 02. Different release kinetic model also shown that the release of Propranolol HCl formulated using TSP: Mannitol at various ratios. Korsemeyer-Peppas was best fit model indicated prominent result of release kinetic of Propranolol HCl formulated using TSP: Mannitol at various ratios (Figure No. 03). Formulation such as F1, F2 and F3 load during stability studies showed the drug content as shown in Table No.05. This indicated that formulation was stable in the presence of the excipients used, under accelerated conditions of temperature and humidity. Stability data of an optimized batch load revealed that the percent drug released after 8 hours at 0 day and after 30 and 60 days was same. The dissolution data study indicated that there was no degradation of formulated Propranolol HCl tablet nor was there a change in the release profile. (Figure No. 05). The dissolution profile of the marketed tablet of Propranolol HCl and formulated tablet showed sustained release of drug at pH 1.2 (0.1 N HCl). There is no release of drug more than 20% for the first two hours and showed more than 70% release of Propranolol HCl at pH 1.2 as shown in figure no. 06. Release was slowed in case of both formulations such as marketed tablet and formulated tablet with modified pectin. Similarity factor was calculated by using PCP-Disso-V3and was found to be 72.8.

## Table No.1
### *Composition of Propranolol tablets with different formulations*

| Sr. No. | Ingredient | Quantity mg/tablet | | |
|---|---|---|---|---|
| | | F1 | F2 | F3 |
| 1 | Propranolol HCL | 100 | 100 | 100 |
| 2 | CP1 (TSP:mannitol-1:9) | 12.5 | - | - |
| 3 | CP2(TSP:mannitol-2:8) | - | 12.5 | - |
| 4 | CP3 (TSP:mannitol-3:7) | - | - | 12.5 |
| 5 | PVP K30 | 21.00 | 21.00 | 21.00 |
| 6 | Lactose | 32.00 | 32.00 | 32.00 |
| 7 | Starch | 28.25 | 28.25 | 28.25 |
| 8 | Magnesium stearate | 6.25 | 6.25 | 6.25 |

## Table No. 2
### *Micromeritics and derived properties of formulation*

| Parameters | Formulation code | | |
|---|---|---|---|
| | F1 | F2 | F3 |
| Bulk density(g/ml) | 0.71 | 0.66 | 0.61 |
| Tapped density(g/ml) | 0.78 | 0.72 | 0.70 |
| Angle of repose(degree) | 18.43 | 16.22 | 16.44 |
| Void Volume(v) | 1.2 | 1.3 | 1.3 |

## Table No. 3
### *Post-Compression Studies Parameter of Tablet.*

| Parameter | Formulation code | | |
|---|---|---|---|
| | **F1** | **F2** | **F3** |
| **Weight variation (%)** | **6.2** | **5.3** | **5.7** |
| **Hardness(kg/cm$^2$)** | **4.8** | **4.7** | **4.9** |
| **Friability (%)** | **4.82** | **4.20** | **5.2** |
| **Disintegration time(min)** | **9.59** | **8.25** | **10.26** |

## Table No. 04
### *Kinetic Release Study of Propranolol HCl Modified Tablet*

| Higuchi Model | | | | First order Release | | | | Korsemeyer-Peppas model | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Time | % Cumulative Release | | | Log % Cumulative Release | | | Log Time | Log % Cumulative Release | | |
| | F1 | F2 | F3 | F1 | F2 | F3 | | F1 | F2 | F3 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 2.39 | 1.45 | 1.25 | 0.378398 | 0.161368 | 0.09691 | 0 | 0.378398 | 0.161368 | 0.09691 |
| 2 | 7.44 | 3.09 | 2.35 | 0.871573 | 0.489958 | 0.371068 | 0.30103 | 0.871573 | 0.489958 | 0.371068 |
| 3 | 12.96 | 4.87 | 4.87 | 1.112605 | 0.687529 | 0.687529 | 0.477121 | 1.112605 | 0.687529 | 0.687529 |
| 4 | 19.28 | 7.46 | 5.64 | 1.285107 | 0.872739 | 0.751279 | 0.60206 | 1.285107 | 0.872739 | 0.751279 |
| 5 | 26.84 | 12.16 | 12.16 | 1.428783 | 1.084934 | 1.084934 | 0.69897 | 1.428783 | 1.084934 | 1.084934 |
| 6 | 34.93 | 18.39 | 15.34 | 1.543199 | 1.264582 | 1.185825 | 0.778151 | 1.543199 | 1.264582 | 1.185825 |
| 7 | 44.52 | 25.95 | 25.25 | 1.648555 | 1.414137 | 1.402261 | 0.845098 | 1.648555 | 1.414137 | 1.402261 |
| 8 | 54.64 | 34.22 | 32.81 | 1.737511 | 1.53428 | 1.516006 | 0.90309 | 1.737511 | 1.53428 | 1.516006 |
| 9 | 64.94 | 43.33 | 40.65 | 1.812512 | 1.636789 | 1.609061 | 0.954243 | 1.812512 | 1.636789 | 1.609061 |
| 10 | 75.75 | 52.83 | 48.95 | 1.879383 | 1.722881 | 1.689753 | 1 | 1.879383 | 1.722881 | 1.689753 |
| 11 | 86.92 | 62.74 | 58.11 | 1.93912 | 1.797545 | 1.764251 | 1.041393 | 1.93912 | 1.797545 | 1.764251 |
| 12 | 98.24 | 73.27 | 67.9 | 1.992288 | 1.864926 | 1.83187 | 1.079181 | 1.992288 | 1.864926 | 1.83187 |
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | $R^2$ | $R^2$ | | $R^2$ | $R^2$ | $R^2$ |
| | 0.988545 | 0.964274 | 0.964366 | 0.934395 | 0.980286 | 0.979494 | | 0.988475 | 0.99192 | 0.989232 |

**Table No. 05**

***Stability study of Propranolol HCl tablet formulated using Modified Pectin.***

| Formulation | Drug Content (% w/w) After | | | |
|---|---|---|---|---|
| | 15 Days | One month | Two month | Three Month |
| F1 | 98.23 | 97.56 | 97.48 | 97.13 |
| F2 | 97.64 | 97.86 | 96.31 | 97.54 |
| F3 | 97.76 | 98.45 | 97.89 | 98.54 |

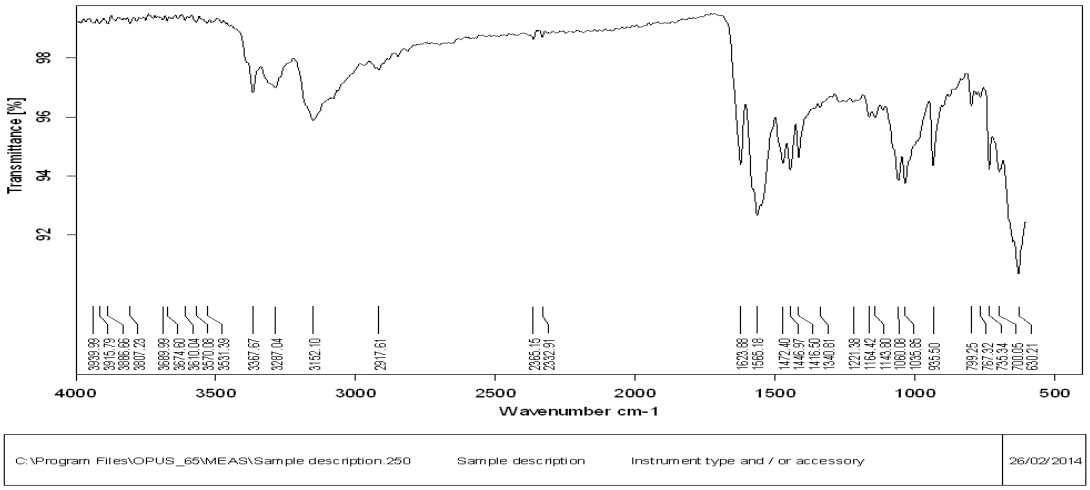


**Figure No. 01**

***IR-Spectra of Propranolol HCl with excipients***

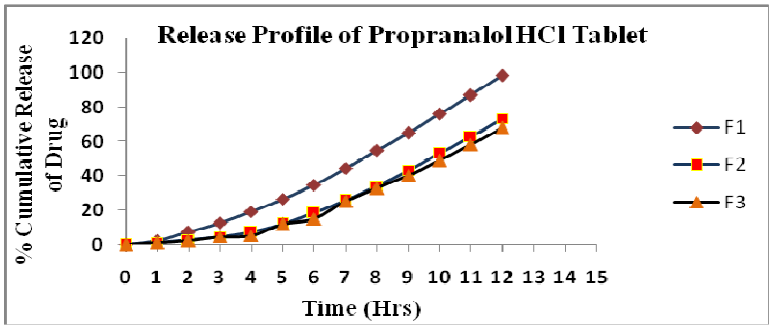


**Figure No. 02**

***Comparative release profile of formulation F1 to F3 (Higuchi Model).***

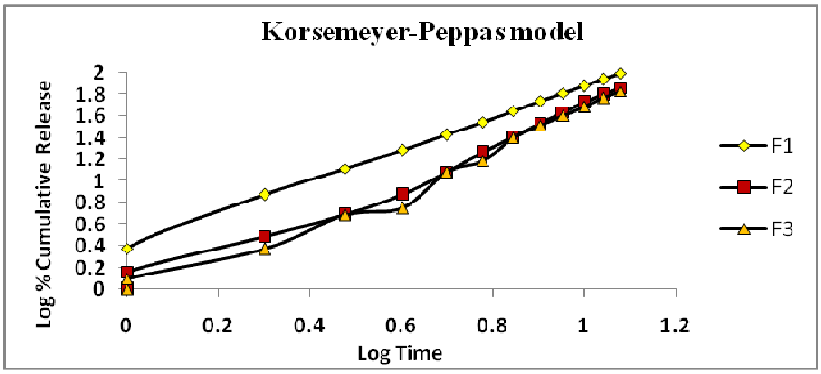


**Figure No. 03**

***Comparative release profile of formulation F1 to F3 (Korsemeyer-Peppas model).***

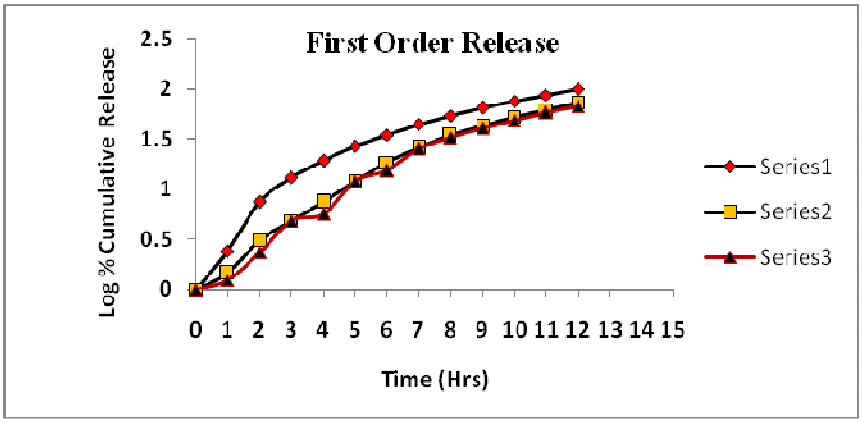


**Figure No. 04**
***Comparative release profile of formulation F1 to F3 (First Order Release).***

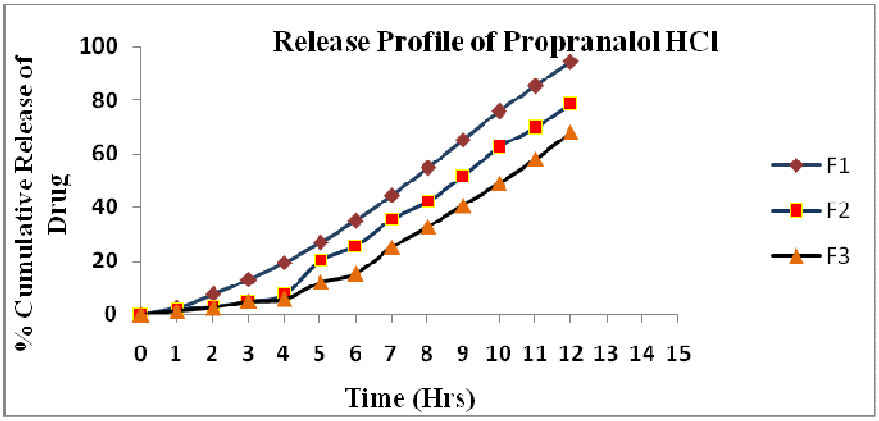


**Figure No. 05**
***Release Profiles of Propranolol HCl (Stability Study)***

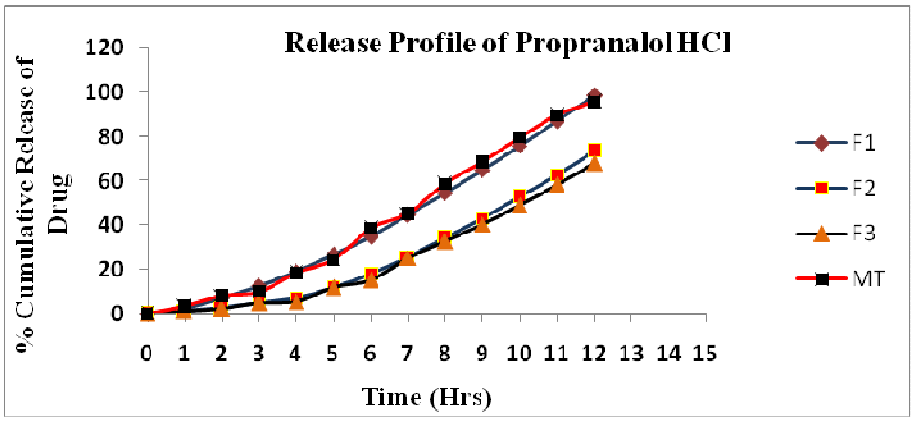


**Figure No. 06**
***Comparative Release Profiles of Propranolol HCl formulated tablet and Marketed Tablet.***

## CONCLUSION

Co-processed excipients consisting of TSP: mannitol exhibited good flow and compression characteristics. Propranolol HCL tablets containing co-processed TSP: mannitol exhibited quick disintegration and improved drug dissolution. The functionality of this was

not affected by the tablet preparation procedure whether it is direct mixing or dry/wet granulation. Utilization of Co-process polymer as an excipients, in tablet formulations containing active pharmaceutical ingredients, offers excellent chemical stability, binding and disintegration properties. In this study, this was achieved with low-cost and compatible excipients, resulting in granules with suitable flow properties and enabling tablets to be produced with a small-scale press that exhibited high hardness, low friability.

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