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Formulation and Development of Modified Release Biphasic Compressed Tablet of Propranolol Hydrochloride

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ABSTRACT

Quick/slow drug delivery system involves the use of compressed core, consisting of sustained release tablet, which is coated by compression over the whole surface with fast dispersible formulation. Propranolol hydrochloride, a non-selective beta-adrenergic blocker has widely used in the treatment of hypertension and angina pectoris with frequent administration. Aim of present study was to develop press-coated tablet system to achieve quick/slow release of the drug are the main purposes of biphasic drug delivery system to avoid frequent administration with increasing patient compliance and therapeutic efficacy. In this study immediate layer which was prepared using croscarmellose sodium, crospovidone and sodium starch glycol ate which was compressed on core tablet prepared by using HPMC and Ethyl cellulose. Results showed that the immediate layer dissolved within four minutes and core tablet releases drug for 12 hrs in controlled manner with zero order release kinetics.

KEYWORDS: *Biphasic release; multiple unit dosage form; compressed tablets; Tablet characteristic, Tablet dissolution*

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1. INTRODUCTION

Oral drug delivery is largest and oldest segment of the total drug delivery market.[1] [2] Since oral dosage form can be self administered by the patients they are more lucrative to manufacture.[3] The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized" . Several types of modified-release drug products are recognized.[4]

Generally, conventional controlled dosage forms delay the release of therapeutic system levels and do not provide rapid onset of action.[5] To modify the release of drug from these systems, surface area exposed to fluid can be constrained by the addition of barrier layer to one or both side of the tablet.[6,7,8] The controlled release drug delivery system can improve therapeutic efficiency and safety of drug by precise and temporal spatial placement in the body, thereby reducing both the size and number of doses required.[9] When a single constant rate for drug release does not utterly satisfy the therapeutic objective, the quick/slow drug delivery system may be interesting alternative.[10] This biphasic release system can be achieved by the application of an immediate release layer to the conventional layered matrix tablet.[11] A quick/slow release system provides an initial burst of drug release followed by constant rate of release over a defined period of time. This type of system is used mostly when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration.[12] Suitable candidate drugs for this type of administration include non-steroidal anti inflammatory drugs, antihypertensive, antihistaminic and anti allergic agents.[13]

Press-coating is absolute dry coating without solvent and heat use.[14] Propranolol hydrochloride is a nonselective beta-adrenergic blocking agent, [15] Propranolol hydrochloride undergoes extensive and highly variable hepatic first-pass metabolism following oral administration, with a reported systemic bioavailability between 15% and 23%.[16,17] [18]. Propranolol hydrochloride was selected as a model drug here for the development of pH-independent extended release tablets. [19].[20] Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery

dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance.[21]. Among the different hydrophilic polymers, cellulose ether polymers are the first choice, especially hydroxyl propyl methyl cellulose (HPMC), which has been extensively investigated for this purpose.[22, 23] In addition, some studies report insufficient drug absorption from controlled release products *in vivo* studies because of the suppression of drug release due to the environment of the colon (small volume of GI fluid and viscous colonic content) in the later stage[24,25,26]. Incorporated water-soluble excipients such as polyethylene glycol, lactose and surfactants into the gel-forming matrix can improve the phenomenon of insufficient drug release and/or absorption because these excipients can stimulate the water penetration into the inner parts of the matrix, thus resulting in drug release from matrix.[27,28,29,30] Microcrystalline cellulose (MCC) is often regarded as one of the best excipients for direct compression.[31] Incorporated MCC into the formulation was shown to increase dissolution rates and compressibility of tablets made by high shear granulation.[32]

The drug release for extended duration, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted because of rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs with high water solubility, hydrophobic polymers are essential to include in the matrix system,[28] along with a hydrophilic matrix for developing sustained-release dosage forms. In outer coat of tablet superdisintegrant like sodium starch glycolate, croscarmellose sodium and crospovidone are used to achieve quick/slow release system provides an initial burst of drug release followed by constant rate of release over a defined period of time.[32]

2. Materials and methods

2.1. Materials

Propranolol hydrochloride,(supplied by Cipla Pvt. Ltd. Mumbai), ethylcellulose, hydroxylpropylmethylcellulose, microcrystalline cellulose, sodium starch glycolate, crospovidone and sodium croscarmellose (Ac-Di-Sol) from Loba chemicals, Mumbai were used.

2.2. Methods

Pre-formulation studies

2.2.1. Micromeritic properties

The physical mixtures were prepared by triturating drug and excipients in a dried mortar for 5 min. The results were showed in Table 2.

A. Angle of Repose (θ):[33,34,35]

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

tan (ɵ) = h / r

B. Bulk Density:[33,35]

It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted.

Bulk Density (D_b): Db = M/ Vb

C. Tapped Density (D_t):[33,35]

It is the ratio of total mass of the powder to the tapped volume of the powder.

Tapped Density (D_t) Dt = M/ Vt

D. Carr's Index:[34,35]

It is expressed in percentage and is given by,

Carr's compressibility index (%) = [(TBD-LBD) X 100]

Where, TBD = tapped density of the powder and LBD = bulk density of the powder.

E. Bulkiness:[34,35]

Specific bulk volume or reciprocal of bulk density is called as the bulkiness. Bulkiness increases with the decrease in particle size.

Bulkiness = 1 / LBD

F. Void volume:[34]

The volume of the spaces is known as the void volume,

Void volume (V) = V_{bulk} (untapped) – V_{true} (tapped)

G. Hausner's ratio:[34]

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's ratio = TBD / LBD

Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

2.2.2. Drug-excipient compatibility studies

Infrared (IR) spectroscopy was conducted using a FTIR Spectrophotometer [36,37](Agilent FT-IR) and the spectrum was recorded in the wavelength region of 200 to 400 cm−1, thermo gram were obtained using a DSC [38] instrument (Mettler DSC) and X-ray diffraction patterens of granules were determined using a D8 advanced, bruker AXS X-ray diffractometer.[38] All procedure consisted of dispersing a sample (drug alone and mixture of drug and excipients)

2.2.3. Preparation of the biphasic delivery system[39,40]Compressed tablets system

Formulation of sustained release core tablet was done, weighing 62.50±5.0 mg prepared by wet granulation method and flat tip punches with 5mm diameter of dies. Then for the preparation of the biphasic delivery system the die of the tab letting machine was progressively filled by hand with half the weighed amounts of the fast release component and then compressed core tablets (Table 1) and pre-compression was done. After this remaining half of the fast release component was added to cover core tablet and final compression was done. Biphasic formulations, weighing 250±5.0 mg were prepared by direct compression, with concave punches and dies with 9mm diameter. Compositions used in the sustained release and fast release tablet (n=20) showed in Table 1.

2.2.4. Evaluation of biphasic compressed tablet (core and coat)[41,42]

Compressed biphasic tablets were characterized for weight variation (n = 20, analytical balance Shimadzu AUX 220D) and friability (n = 20, Roche type friabilator, 25 rpm for 4 min.). The crushing strength of a compact was determined by compressing the compact diametrically.

A. Hardness: For each batch, the hardness was determined on six tablets using the Pfizer hardness tester.

B. Friability test: The friability of tablets was determined by using Roche Friabilator. Ten tablets was initially weighed (W initial) and transferred in to friabilator. The

friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final).The percentage friability was then calculated by,

% F = Loss in Weight / Initial Weight × 100

C. **Weight variation test:** The tablets were selected randomly from each formulation and weighed individually to check for weight variation.

D. **Thickness:** The tablet thickness was measured using vernier calliper.

E. **Drug content uniformity:**

Five tablets were randomly selected, accurately weighed and average weight per tablet calculated. The tablets were ground individually to fine powder. Accurately weighed tablet powder, equivalent to ten mg of drug was transferred to 100mL volumetric flask. Add simulated buffer, sonicate and adjust the final volume up to mark. After few minutes the solution was filtered; rejecting first few mL of filterate. 1 mL of filterate was taken in 10 mL volumetric flask and diluted up to the mark with the same solvent and analyzed spectrophotometrically at 289.60 nm. The content was calculated by using following equation,

Absorbance = Slope × Concentration + Intercept

2.2.5. Dissolution testing[36]

In vitro dissolution tests were performed according to the USP paddle method at 50 rpm using an automated dissolution apparatus (Veego) containing 900 ml of simulated gastric fliud at 37±0.5 ^{0}C. The drug released was quantified spectrophotometrically on-line through a UV–Vis-spectrophotometer (UV-1800 Shimadzu ENG240V model) set at 289.60 nm. The cumulative fraction of the drug released was calculated from the total amount of Propranolol hydrochloride and plotted as a function of time. Dissolution studies (n = 3) was carried out on both individually compressed core tablets, fast release tablets and biphasic compressed tablets to investigate the effect of compression on the dissolution behaviour.

2.3. Release drug data modeling:[43]

The release kinetic studies for formulations were done by applying different kinetic model**.** The dissolution data was kept for treatment with different kinetic equations for to check the release mechanism of the drug from the device. In this by comparing the R^2 values obtained, the best-fit model was selected from Zero order kinetics, First order kinetics, Higuchi model, Krosmeyer and Peppas release model, Hixson- Crowell model

2.4. Visual disintegration and Crushing test

Final formulation of compressed tablets (TT01) tested for the crushing strength and visual disintegration test for determination of intactness of core tablet even after final compression by using sudan dye in ethanol solution in order to observe the structure of core tablets after final compression (Figure 7).

2.5. Comparison with marketed product

The optimized formulation (TT01) was compared with the marketed with the marketed tablet of Propranolol HCL (CIPLAR LA 40mg).

2.6. In-vivo study (Roentogenography)[44]

Healthy rabbit was used to perform roentogenography study**.** To determine the location of dosage form in the body after particular time period in-vivo roentogenography was carried out. It is used to determine the intact period of core tablet. For this core tablet is composed of barium sulphate as X-ray opaque medium instead of drug. Barium sulphate is frequently used clinically as it is clinically inert. It is not absorbed in the body and excreted as it is. The X-ray photograph of tablet must be denser than bone to identify.

2.7. Study of process parameters[14,45]

After the final formulation of biphasic compressed tablet different process parameters were studied for accuracy and precision like speed of rotation, viscosity, particle size, core coat ratio etc.

2.8. Stability studies[34,46]

Stability study for the developed formulation was carried out by storing the selected formulation at 40^{0}C/75% RH for 3 month. This is necessary to predict long term stability of the formulation. After 3 month the samples were withdrawn and characterized for appearance, weight, hardness, thickness, drug content and drug release.

3. Results and Discussion

In present study HPMC K100 was used as hydrophilic matrix employed to formulate biphasic tablet of Propranolol hydrochloride but alone it did not gives good results. So it is used in combination with hydrophobic polymer like ethyl cellulose.

3.1. Pre-formulation study

3.1.1. Infra-red spectroscopy

The principal peaks depicted in Figure 2 for propranolol occur at wave numbers 1103, 1270, 772, 1580, 795 and 1240. These peaks represent the stretching vibrations of the different functional groups that are present in the PHCL structure. The wave numbers 772 and 795 can be associated with the aromatic functional groups, 1240 and 1270 with the amine functional group, 1103 with the OH group and 1580 with the ketone group respectively. Major frequencies of functional groups of pure drug remain intact in granules containing different polymers; hence, there is no major interaction between the drug and polymers used in the study (Figure 3 and 4).

3.1.2. Differential Scanning colorimetery

The thermogram of pure drug showed and thermogram for excipients are shown in **Figure 5.** A sharp melting transition of Propranolol HCl pure drug was observed at 265.5^{0}c for both pure Propranolol HCL as well as physical mixture. Also the peak along with the excipients as same as the drug showed peak as the drug alone which indicates excipients were not interact with the pure drug.

3.1.3. Physical properties of biphasic compressed tablet

Results showed that powder blend have, Angle of repose range from 20 to 26, Carr's index range from 12 to 18 and Hausner's ratio range from 1.10 to 1.13 which indicate good flow property. Hardness, thickness and friability were found to be in the range of 6.0 to 7.0, 1.0 to 1.2 and 0.045 to 0.054 respectively for core tablet and 5.0 to 5.6, 4.98 to 5.2 and 0.22 to 0.72 respectively for outer tablet separately.

Results of angle of repose (<30) indicate good flow properties of powder. This was further supported by lower

index values. Generally, compressibility index values up to 15 to 21% results in good to excellent flow properties. Drug content in the weighed amount of powder of all formulations was found to be uniform. All these results indicate that the powder possessed satisfactory flow properties, compressibility, and drug content.

***Results are the mean of triplicate observations ± SD**

All the formulations were evaluated for the cumulative percentage drug release. From *in-vitro* dissolution profile of formulations

3.2. Dissolution testing

Formulation of biphasic compressed tablets were prepared which TT01 showed 61.01 percent cumulative drug release within half hour and it was followed by sustain release of core tablet about up to 12 hrs 96.68%.

3.3. Release drug data modeling:

Kinetic release studies for these formulations were followed zero order release

3.4. Visual disintegration test for optimized final biphasic compressed tablet

Disintegration of outer tablet coat was visually analyzed with photographs as shown in **Figure 7.** For evaluation of disintegration test for biphasic compressed tablet optimized formulation TT01 was used.The disintegration time was found to be ≈ 30 s. The images were clearly showed that the time of disintegration of compression coating the inner core tablet remained intact. For proper visualization of this the sudan dye is used as coloring agent in core tablet. Compression coating was released ≈ 99 % drug within 4 min. which is determined by UV spectrophotometer and equation of line obtained from the calibration curve of drug. Disintegration was due to optimized concentration of super disintegrants.

3.5. Crushing test for biphasic compressed tablet

Visual inspections of cross-sectional forces revealed that red colored core tablet remain intact after crushing test **(Figure 8).**

3.6. Comparative study with marketed product

In release profile slow of drug delivery was found in marketed formulation. 91.95 percentage cumulative drugs released within 12hrs, but in optimized formulation it was clearly observed there is an initial burst effect of drug which was followed by sustained effect and about 96.68 percentage cumulative drugs released up to 12hrs. So from this comparison it was conclude that quick-slow drug delivery was obtained in optimized formulation.

3.7. Study of process parameters on biphasic compressed tablet[16]

The aim of this work was to investigate the factor influencing dissolution characteristics of drug substance from polymer matrix tablet. The study of different factors like speed of rpm, diluents, drug-polymer ratio, dissolution media etc. are studied which was showed linear relationship with dissolution study.

A. Effect of Particle size:

The effect of particle size was observed by taking different particle size which was analyzed by sieve method. Course particles provide more drug release (97.43%) and particles having very fine size showed less release profile (76.46%). So from this study it was found that compression coated tablet from fine coat provided slower drug release and longer lag time.

B. Effect of compression force:

The release profile in above tablet was showed that as compression force was increased the lag time was also increased. The lag time of drug release was increased when the compression force applied to the coating increased till a critical point. When the applied compression force for the coating was higher than critical point, there is no further reduction in porosity due to absence of compression parameter.

C. Effect of Speed of rotation:

The results show that dissolution rate was increased as revolution per minute was increased due to increased disintegration effect. There was more rapid erosion of matrix at higher stirring rates because the increased rate of detachment of polymer chains away from the matrix surface. This leads to the thinner layer of gel forming at surface of dosage form at higher agitation rates. It showed that drug release can easily change due to physical agitation.

D. Effect of Solubility:

Higher solubility drug containing core in compression coated tablets provided shorter lag time than lower solubility cores. Water insoluble drug showed longer lag time and more sustain release pattern.

E. Effect of Thickness:

To study the effect of thickness having 4mm and 6mm tablet was taken which showed dissolution profile 88.53 and 96.19 % respectively. Lower thickness of tablet showed the fast dissolution rate as compared to the higher thickness of tablet.

F. Effect of Diluents:

In this study the lactose and microcrystalline cellulose was used. Lactose showed initial burst effect but MCC does not have this type of effect and has good compaction properties. So it concludes that lactose is suitable for fast dissolving tablet because lactose has high tendency to form pores in matrix which allow the dissolution medium to penetrate the matrix and dissolution medium than MCC which is more suitable for sustain release tablet.

G. Effect of dissolution medium:

In the study of effect of pH of dissolution medium on drug it was observed that Propranolol hydrochloride is a weak basic drug. Therefore it gave pH-independent release. The solubility was observed more in pH1.2 as compared to that in phosphate buffer when it was formulated without modification of polymers.

H. Effect of viscosity:

As viscosity grade decreases it lowers porosity and gives harder tablet. Lower viscosity grades of ethyl cellulose have higher fragmentation rate and plasticity which results in harder tablet with lower porosity and more sustained release pattern. Also even in constant hardness low viscosity grade of ethyl cellulose has more sustained release pattern, which may due to extensive plastic deformation even at low compression. So ethyl cellulose 20cps is found more suitable.

I. Effect of core: coat ratio:

The amount of outer shell is key factor for controlling the lag time. Higher amount of outer coating added would prolong the lag time of drug release (1:3). Insufficient polymer amount of coat would result in absence of lag time. For biphasic compressed tablet 1:2 drug polymer ratio was optimized.

3.8. In-vivo study (Roentogenography)

The X-ray taken after defined time interval as shown in Figure 19. From the study it was clear that the outer tablet disintegrates immediately but core tablet did not disintegrates throughout the period it remain intact, but release drug slowly. The tablet was easily visualized due to barium sulphate which is used as X-ray radio opaque medium instead of drug in the tablet. The tablet was inserted directly into oesophagus of rabbit without breakage to achieve acc urate release.

3.9. Accelerated stability study

Accelerated stability study was performed on biphasic compressed formulation TT01 and further evaluated for thickness, hardness, and drug content. *In-vitro* drug release was also carried out. There was no considerable change in thickness, hardness and drug content of TT01 formulation before and after accelerated stability study. Also **Figure 20** showed that there was no significant difference found between dissolution profile of TT01 formulation before and after stability. Hence tablet prepared by biphasic compressed technique was found to be stable.

Figures and tables : Placed at end of the paper after references

4. Conclusion

Although a conclusion may review the main points of the paper, do not replicate the abstract as the conclusion. A conclusion might elaborate on the importance of the work or suggest applications and extensions. Authors are strongly encouraged not to call out multiple figures or tables in the conclusion—these should be referenced in the body of the paper.

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F. code	Propranolol HCl	HPMC K100 (mg)	Ethyl cellulose (mg)	MCC (mg)	Mag.st. (mg)	-
Core tablet	320	250	212.5	435.5	32	-
F. code	Propranolol HCl	CNA (mg)	SSG (mg)	CPO (mg)	Lactose (mg)	Mag. St.(mg)
Outer tablet	480	-	-	187.5	3050.5	32

Table 1: Composition of biphasic compressed tablet

F. Code	Angle of repose (θ)*	Bulk density* (g/mL)	Tapped density* (g/mL)	Carr's index* (%)	Hausner's Ratio*
For core tablet	22.84 ± 1.71	0.70 ± 0.006	0.79 ± 0.010	11.33 ± 0.58	1.13 ± 0.007
For outer Tablet	22.12 ± 0.81	0.66 ± 0.008	0.76 ± 0.004	18.00 ± 1.00	1.16 ± 0.062

Table 2 Physical properties of biphasic compressed tablet

F. Code	Thickness* (mm) ± SD	Hardness* (Kg/cm²) ± SD	Average Weight* (mg) ± SD	%Drug content* ± SD	% Friability* ± SD
For core tablet	1.10 ± 0.11	6.40 ± 0.10	62.31 ± 0.27	97.28 ± 2.18	0.052 ± 0.03
For outer Tablet	5.13 ± 0.01	5.10 ± 0.11	187.50 ± 0.10	99.60 ± 2.26	0.63 ± 0.02

Table 3: Physical properties of biphasic compressed tablet

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi model (R^2)	Kosymer-Peppas model (R^2)	Hixson Crowell Model (R^2)
TT01	**0.999**	0.997	0.960	0.883	0.951

Table 4: Kinetic data of biphasic compressed tablet of Propranolol HCl

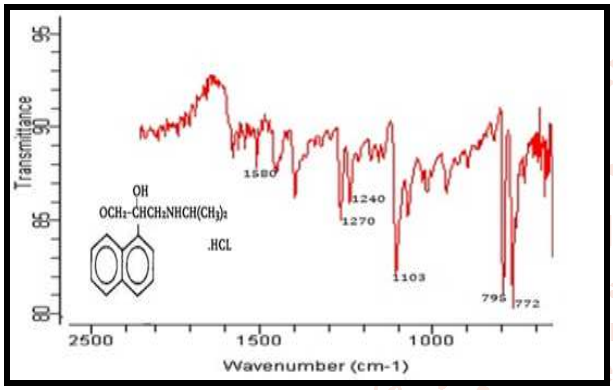

Figure 1: FTIR spectral analysis of Propranolol HCL

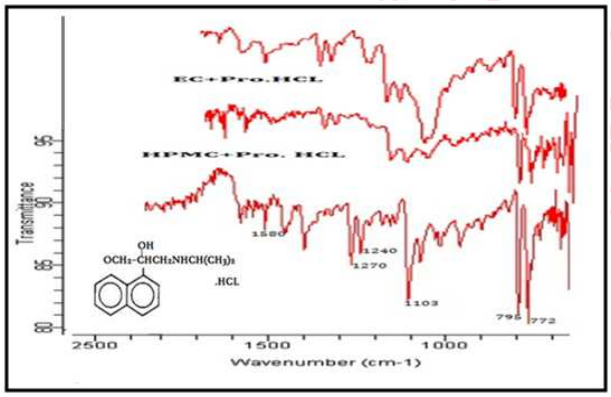

Figure 2: FTIR spectral analysis of pure Propranolol HCL and physical mixture; P.HCL: HPMC, P.HCL: EC

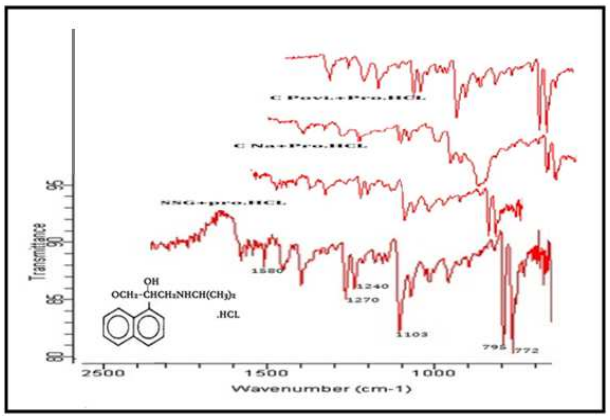

Figure 3: FTIR spectral analysis of pure Propranolol HCL and physical mixture; P.HCL: SSG, P.HCL: CCN,

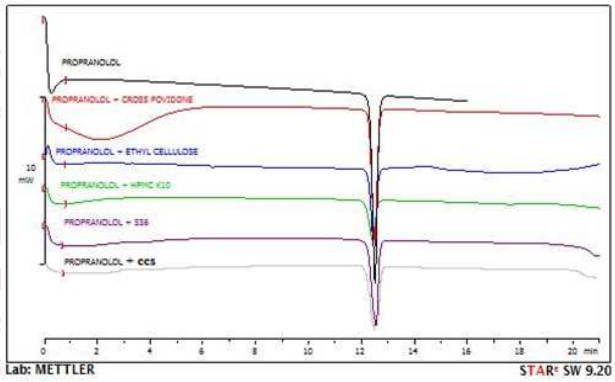

Figure 4: DSC thermogram of Propranolol HCL and physical mixture; P.HCL: CPO, P.HCL: EC, P.HCL: HPMC, P.HCL: SSG, P.HCL: CCN

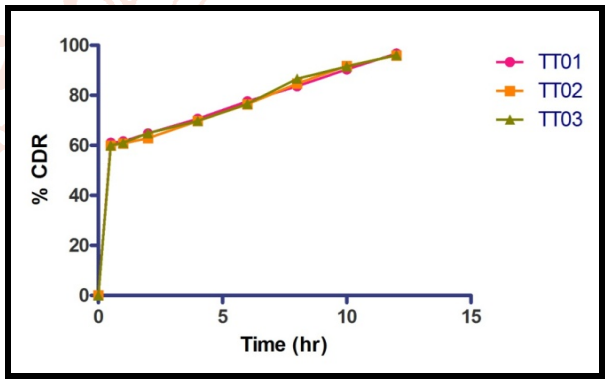

Figure 5: Dissolution profile of formulation TT01-TT03

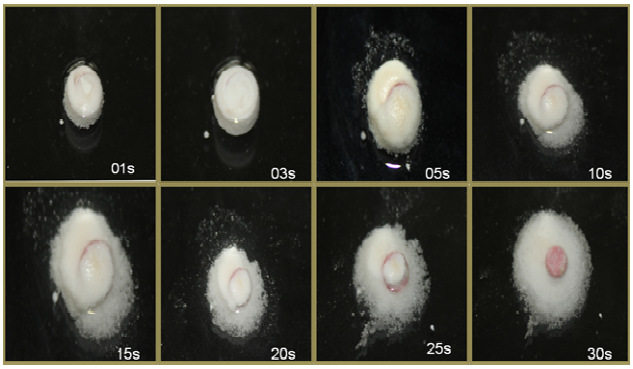

Figure 6: Images of visual disintegration of compression coating tablet

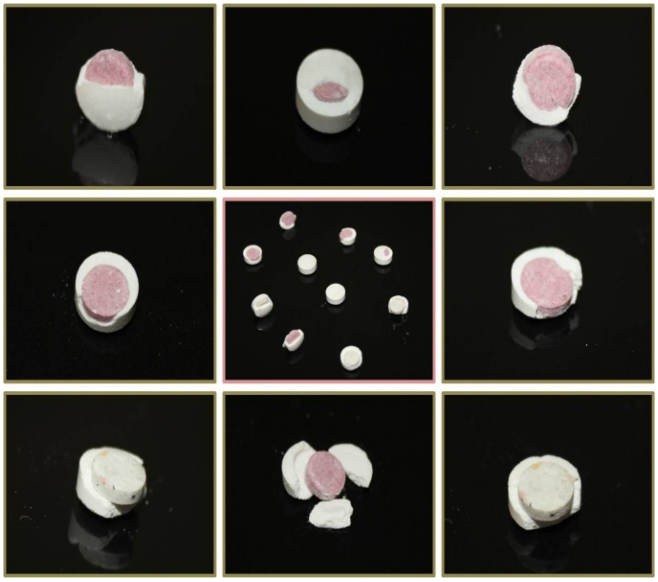

Figure 7: Fracture equatorial showing surfaces of the compressed tablet

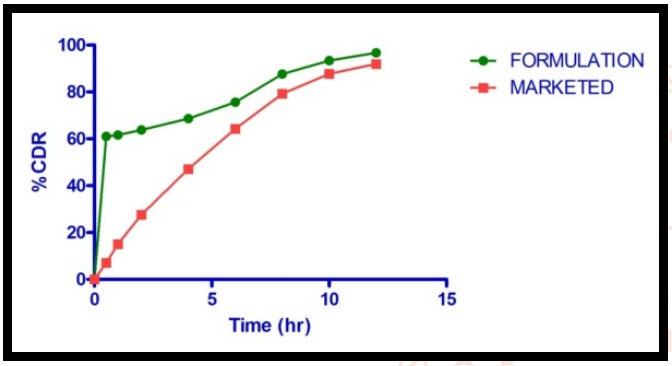

Figure 8: Dissolution profile for optimized formulation and marketed tablet

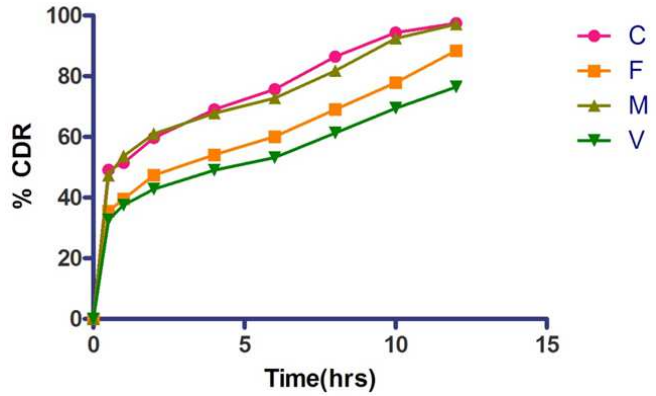

Figure 9: Dissolution profile for particle size

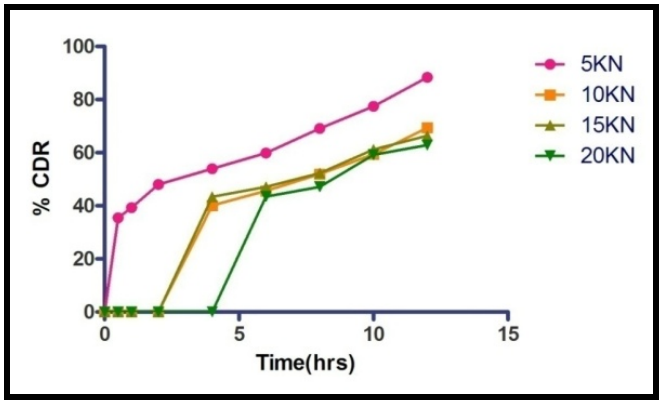

Figure 10: Dissolution profile for compression force

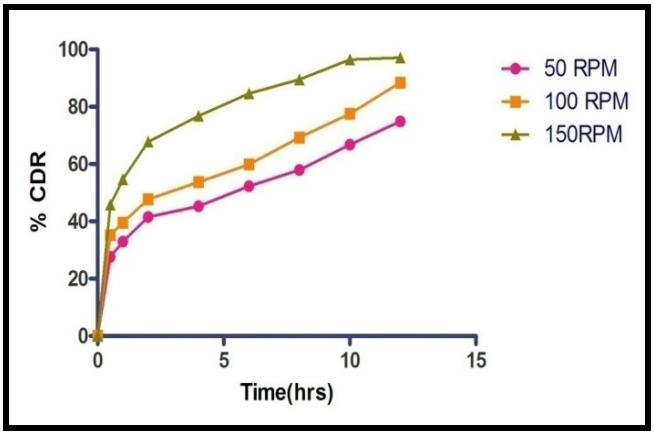

Figure 11: Dissolution profile for speed of rotation

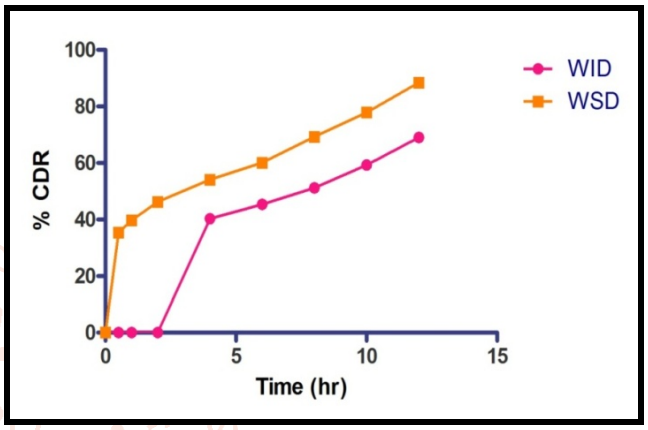

Figure 12: Dissolution profile for solubility

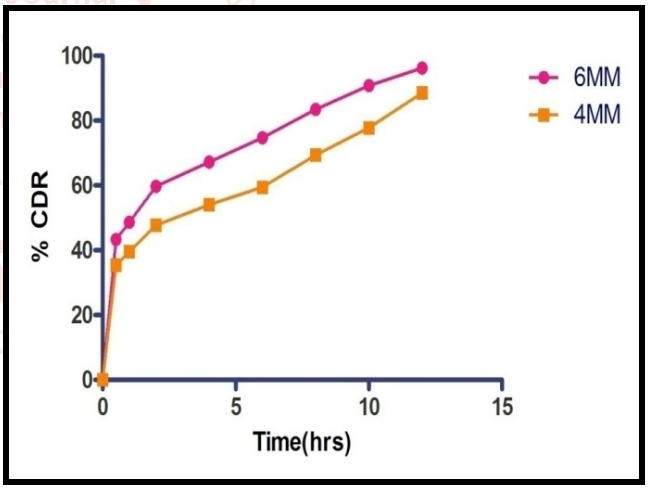

Figure 13: Dissolution profile for thickness

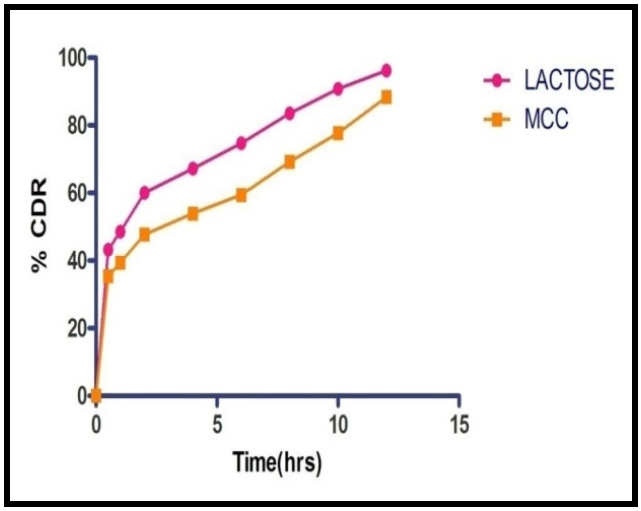

Figure 14: Dissolution profile for diluents

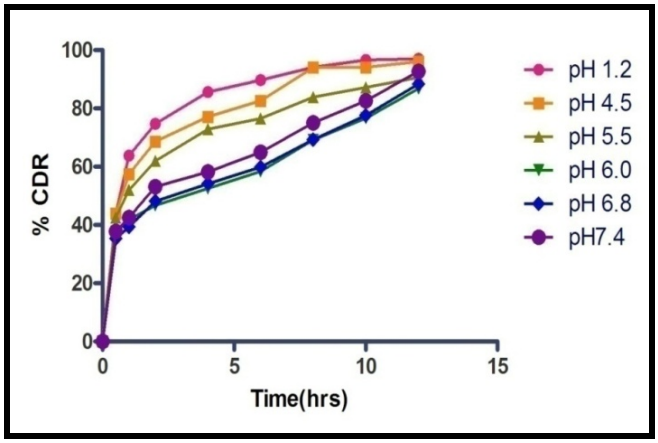

Figure 15: Dissolution profile for dissolution medium

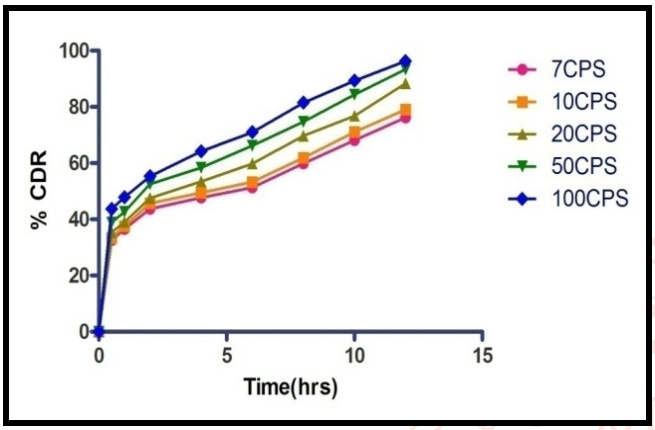

Figure 16: Dissolution profile for viscosity

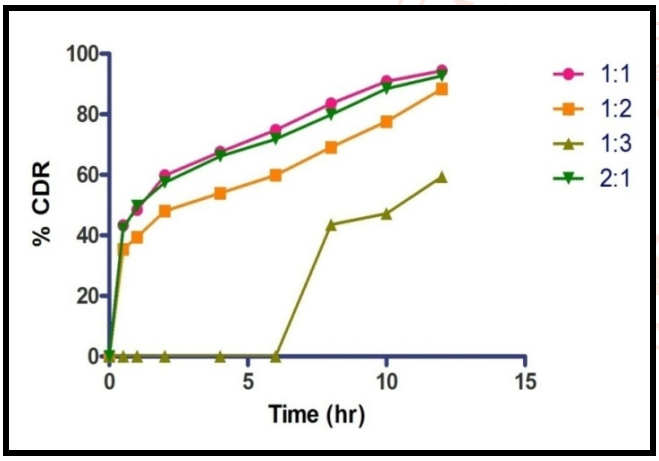

Figure 17: Dissolution profile for core:coat ratio

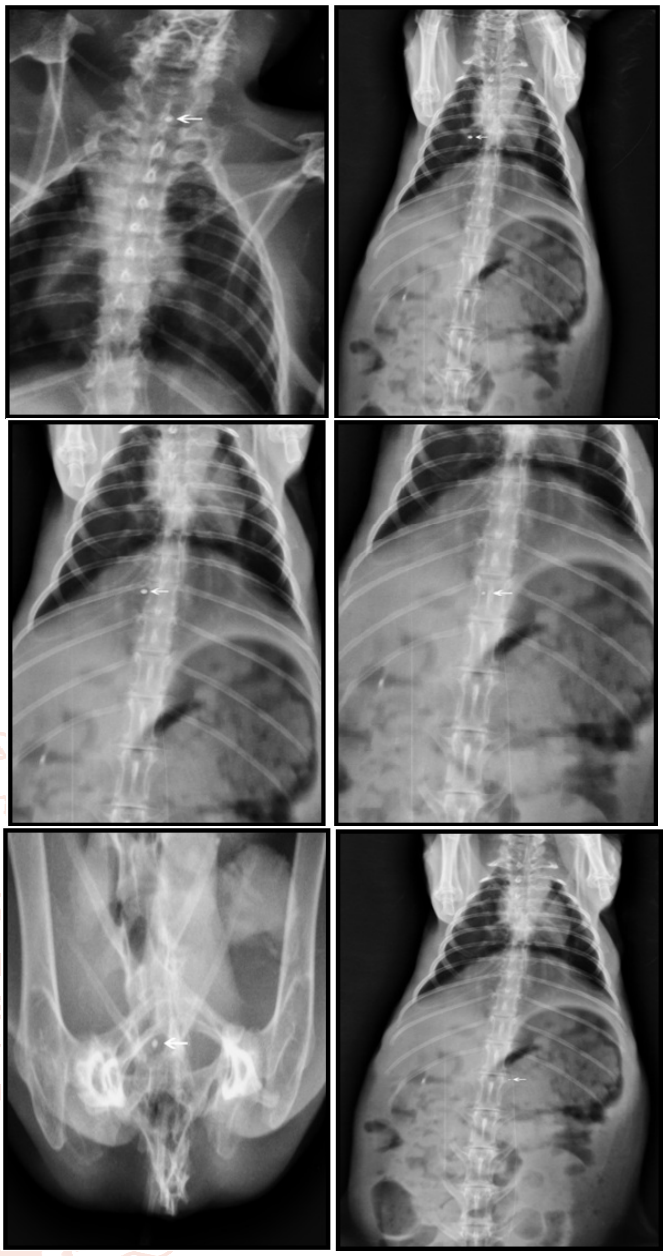

Figure 18: X-ray of optimized formulation (TT01) after ingestion of tablet at 1hr, 2hr, 4hr, 6hr, 8hr, 10hr and 12hr.

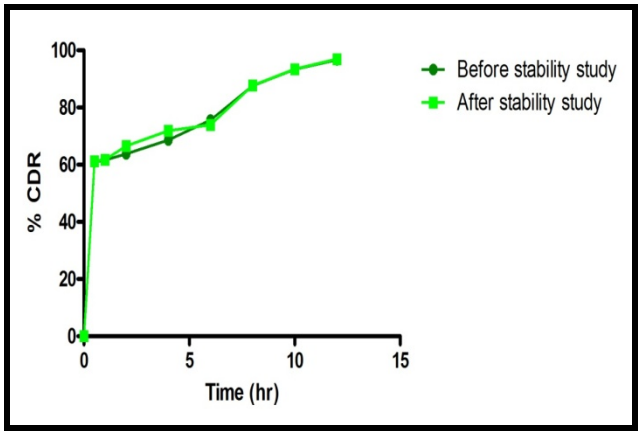

Figure 19: Dissolution profile for stability study