Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2013, 5 (6):12-19
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Design, Development and Evaluation of Galantamine Hydrobromide Bilayer Sustained Release Tablet

Biswajit Biswal* and Darshan Sharma

B.Pharmacy College Rampura-Kakanpur, Godhra, Gujarat

ABSTRACT

Galantamine Hydrobromide is a rapidly and completely absorbed drug but plasma level achieved is highly variable after oral administration. Besides it also has relatively short elimination half-life is 7 to 8 hours. A drug with a short half-life requires frequent dosing and this makes Galantamine Hydrobromide an ideal candidate for a sustained-release formulation. Hydrophilic and swallable polymer matrix systems are widely used in sustained-release delivery because of their flexibility to obtain a desirable drug release profile. Cost effectiveness and broad regulatory acceptance. To provide a bi-layer sustained-release composition which releases Galantamine Hydrobromide from both immediate and sustained release layer, over a time period of at least about 24 hours. To develop a bi-layer dosage form that immediate release layer contain the loading dose and sustained release layer contain the maintenance dose of drug.

Keywords: Galantamine Hydrobromide, Dose Calculation, Bilayer Tablet, TDR

INTRODUCTION

The scenario of pharmaceutical drug delivery is rapidly changing conventional pharmaceutical dosage forms are being replaced by new drug delivery systems. These new drug delivery systems are having edge over conventional ones in terms of many biopharmaceutical parameters. One such drug delivery system is bi-layer sustained-release drug delivery system. The primary objective of bilayer sustained release drug delivery system is to ensure safety, improve the efficacy, reduce the dose frequency and ultimately result in improved patient compliance. The aim of present work is to formulate sustained drug delivery system of Galantamine Hydrobromide suitable for once-a-day dosing [1]. In general, bi-layer sustained-release drug delivery is attempted to maintain constant, effective drug level in the body with concomitant minimization of undesired side-effects. Galantamine Hydrobromide is a rapidly and completely absorbed drug but plasma level achieved is highly variable after oral administration. Besides it also has relatively short elimination half-life is 7 to 8 hours [2]. Frequent dosing is thus necessary to maintain reasonably stable plasma concentration. However, frequent dosing results in inconvenience to the patient and leads to poor compliance. Moreover, widely fluctuating plasma concentration of the drug also results in availability of erratic amount of drug. A drug with a short half-life requires frequent dosing and this makes Galantamine Hydrobromide an ideal candidate for a sustained-release formulation. Hydrophilic and swallable polymer matrix systems are widely used in sustained-release delivery because of their flexibility to obtain a desirable drug release profile. Cost effectiveness and broad regulatory acceptance [3].

MATERIALS AND METHODS

Galantamine Hydrobromide was obtain as a gift sample from MSN Pharmachem Pvt., HPMC K-100M from S.D Fine chem., HPMC K-15M from Roquette Pharma, Crosspovidone from S.D Fine chem., Povidone K 30 from BASF Ltd, Magnesium stearate from Signet chemicals, Avicel pH101 and Lake Sunset yellow from S.D Fine chem., IPA from Triveni Chemicals.

Identification of Drug [5, 7]

FTIR Absorption Spectroscopy Study

The infrared spectra in KBR Pellets were record over the wave number range of 4500 -450 cm^{-1} with a Perkin Elmer Spectrum GX FTIR.

Melting Point Study

The melting point study will carry out with the help of capillary method or Differential scanning calorimeter (DSC)

X-ray Diffraction Method

It will perform on pure drug to see whether the drug is crystalline or amorphous in nature.

Drug – Excipient Compatibility Study [8]

Compatibility of excipient with drug will study by DSC or FTIR. Physical mixtures of drug and polymer (in different ratio) will fill in the prewashed ampoules and sealed. The sealed ampoules will keep at 40 ± 5°C /75RH for 30 days in stability chamber (Table 3)

Calculation of Loading and Maintenance Dose of Galantamine Hydrobromide [9]

V_d= 175 liter, C_{max}=maximum plasma concentration of = 45 ng/ml

For Loading Dose (D_L) $D_L = C_{max} \times V_d$

D_L = 45 ng/ ml x 175000 ml = 7.875 mg

Calculation of maintenance dose:

For Total Dose, $D_T = D_L (1+0.693 \times t/t_{1/2})$

D_T = 7.875 (1+ (0.693x24/8) = 24.247 mg ≈ 24 mg

For Loading dose = 7.875 mg ≈ 8 mg
For Maintenance Dose, D_m = 16 mg

So 8 mg drug release initially (1 hr) and 16 mg drug maintain for rest hour.

Table1: Formulation of Immediate Release Tablet (Optimization of Disintigrant)

Ingredient	Formulation code (qty. mg/tab)		
	A-01	A-02	A-03
Galantamine Hydrobromide	8	8	8
MCC-101	33.5	33.5	33.5
Crosspovidone	6	---	3
SSG	---	6	3
Lake sunset yellow	1	1	1
Magnesium stearate	1.5	1.5	1.5
Total wt	**50**	**50**	**50**

Table2: Formulation of Bilayer Sustained Release Tablet

Ingredient	formulation code (Qty. mg/tab)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Immediate Release Layer												
Galantamine	8	8	8	8	8	8	8	8	8	8	8	8
MCC-101	34	34	34	34	34	34	34	34	34	34	34	34
Crosspovidone	6	6	6	6	6	6	6	6	6	6	6	6
Lake sunset red	1	1	1	1	1	1	1	1	1	1	1	1
Mag. stearate	2	2	2	2	2	2	2	2	2	2	2	2
Sustained Release Layer												
Galantamine	16	16	16	16	16	16	16	16	16	16	16	16
MCC-101	79	59	39	79	59	39	79	59	39	69	49	49
HPMC K15 M	80	100	120	---	---	---	40	50	60	40	50	60
HPMC K100 M	---	---	---	80	100	120	40	50	60	50	60	50
Starch	15	15	15	15	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Mag. stearate	5	5	5	5	5	5	5	5	5	5	5	5
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Formulation of Bilayer Tablets [10]

Bilayer tablet contains two layers i.e. immediate release layer and sustained release layer of Galantamine Hydrobromide. Bilayer tablets were prepared by using optimized immediate and sustained release layer. Accurately weighted 50 mg of immediate release layer and 200 mg of sustained release layer individually. Various batches of bilayer tablets were prepared by direct compression and wet granulation method according to formula Table 2. Initially immediate release powder blend was fed manually into the die of 10 stations tablet compression machine and then compressed at low compression force to form uniform layer. Subsequently sustained release layer powder blend was added over that layer and completely compressed on tablet punching machine by using flat faced punch 8 mm round shape standard convex having the break line on the upper punch.

Evaluation of Post Compression Parameters for Bilayer Tablet

Prepared Bilayer S.R tablet was evaluated for post compression parameters like hardness, friability, weight variation, thickness [11].

Uniformity of Content [12, 13]

Content of active ingredient in tablets take at randomly. 10 tablets was weight and average weight is calculated. All tablets was crush and powder equivalent to 24 mg dissolved in 250 ml 0.1 N HCl and shake for 20 min. solution will filter and after suitable dilution using 0.1 N HCl, absorbance will be measure spectrophotometrically at 280 nm against reagent blank. Amount of drug present in one tablet will calculate.

Swelling Study [14]

The swelling behavior of tablet described as the water absorbing capacity. The tablets are weigh individually (W_0) and placed separately in Petridis containing cellophane membrane and incubated at 37±1^{0}C. At regular time intervals until 18 hours, the tablets are removed carefully. The swollen tablet is then reweighed (Wt) and the % swelling are calculated using the following formula:

$$\% \text{ swelling} = \{(W_t - W_0)/W_0\} \times 100$$

Where W_t is the weight of tablet at time t and W_0 is the initial weight of tablet. The swelling is calculated and then graph is plot.

Dissolution Studies [15, 16]

The release rate of Galantamine Hydrobromide from bi-layer tablets will determine using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 500 ml of water, at 37 ± 0.5 $^{\circ}$C and 50 rpm. Aliquot volume was withdrawn from the dissolution apparatus at specified interval, and the samples were replaced with fresh dissolution medium. After filtration and suitable dilution the amount of drug release was determined from the calibration curve.

Stability Studies of the Standardized Formulations

The stability studies were carried out on the most satisfactory formulations as per ICH guidelines. The most satisfactory formulation sealed in aluminum packaging and kept in humidity chamber maintained at 35 ± 2 °C / 60 ± 5 %RH and 40 ± 2 °C / 75 ± 5 %RH for 2 months. At the end of studies, samples were analyzed for the drug content, in vitro dissolution and other physicochemical parameters

RESULTS AND DISCUSSION

Identification of Drug

From the F.T.I.R spectroscopy it was found that the O-H, C-H (alkane) and C=C (Alkene) stretching was obtained in 3559.95, 2924.52 and 1622.8 cm^{-1} except this C-H (Aromatic) bending was found in the region of 806.099 cm^{-1}. From the spectra it was concluded that the drug was Galantamine (see fig.1)

Melting Point Study

Galantamine 5 mg was placed in DSC apparatus (Mettler Toledo (DSC-822^e) and the instrument was run at a heating rate of 10 ^{0}c min^{-1} and was found that the melting point of the drug was 272.73 ^{0}C (see fig.2)

Compatibility Study

Two set of vials are placed in different condition (40°C/75%RH and RT) in different drug excipient ratio for one month. After completion of one month the samples withdrawn and analyze both physically and DSC apparatus and it was found that the excipient taken with the drug are all compatible (see fig.3 to5)

X-ray Diffraction
The XRD showed 19 peaks with 2θ between 11.803 to 79. All the sharp peaks indicate that the drug was crystalline in nature (see fig.6)

Calculation of theoretical dissolution profile (TDR)
The pharmacokinetic parameters of Galantamine Hydrobromide were utilized for the calculation of theoretical drug release profile for 24 hours dosage form. The Loading dose for sustained release Galantamine Hydrobromide was calculated using the formula and it was found to be 15.96 mg. Here, the formulation should release 8 mg (33.5 %) of drug in 1 hour like conventional tablet and 16 mg (66.5%) up to 24 h thereafter.

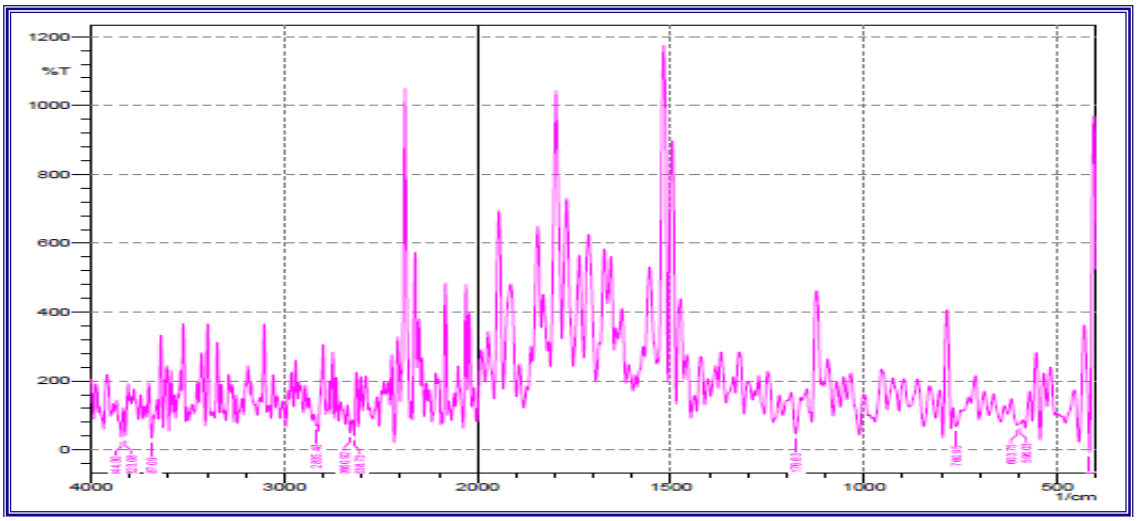

Fig 1: FTIR graph of pure Galantamine Hydrobromide

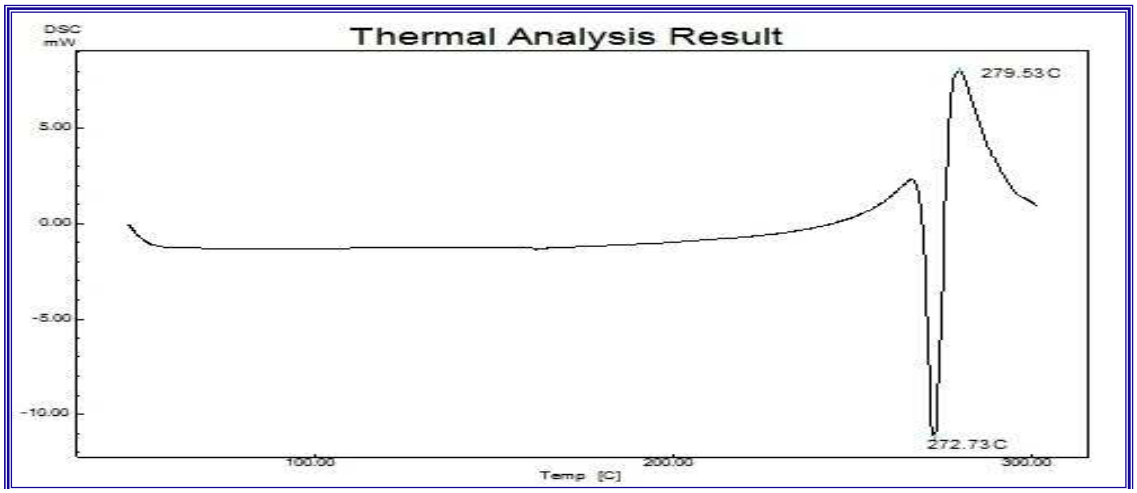

Fig 2: DSC spectra of pure Galantamine Hydrobromide

Evaluation parameters of immediate release tablet
50 mg immediate release tablet were compressed with 4mm standard convex punch maintain the compression force same for all the batches using different type of super disintegrate. It was found that the hard for all the batches ranges from 2.1 to 2.3 Kg/cm^2 and the thickness ranges from 2.2 to 2.27 mm. but the disintegration time varies a lot, the tablet containing 6mg of crosspovidone disintegrate quickly as compare to SSG and the combination form of crosspovidone and SSG. So from this result crosspovidone was used for further study.

In-Vitro Drug Release of Sustained Release Bilayer Tablet
Twelve different batches were prepared with different ratio of HPMC K-15M, HPMC K-100M and it was found that most of the formulation release 75% of the drug at the end of 12hrs. Only F-6 batch hold the drug for longer period of time and it also shows good similarity factor (*F2*=62.4) and least dissimilarity factor (*F1*=9.2).

Kinetic mechanism of drug release

The in vitro release pattern of F-VI batch was analyzed by fitting the dissolution data in various models namely zero order, first order, higuchi model and Hixson crowel model. The release kinetic data for all the models used is shown in following table. The fit according to R^2 value and linearity are shown in table. The best fit model for the formulation batch was found to be Highchi model because the R^2 for it was highest among the other model which was 0.962 (see Tab. 6)

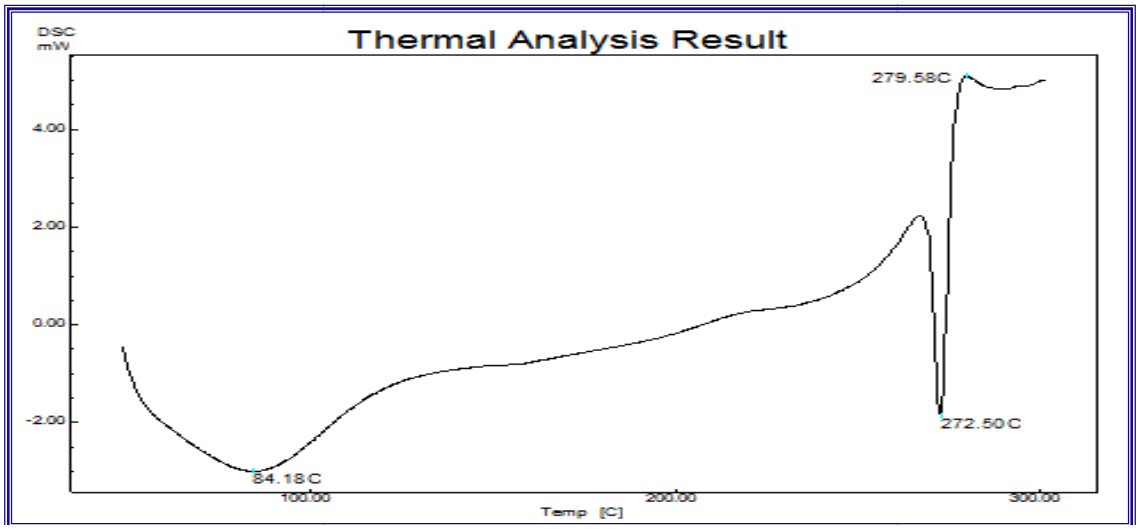

Fig 3: DSC spectra of pure drug + HPMC K-100

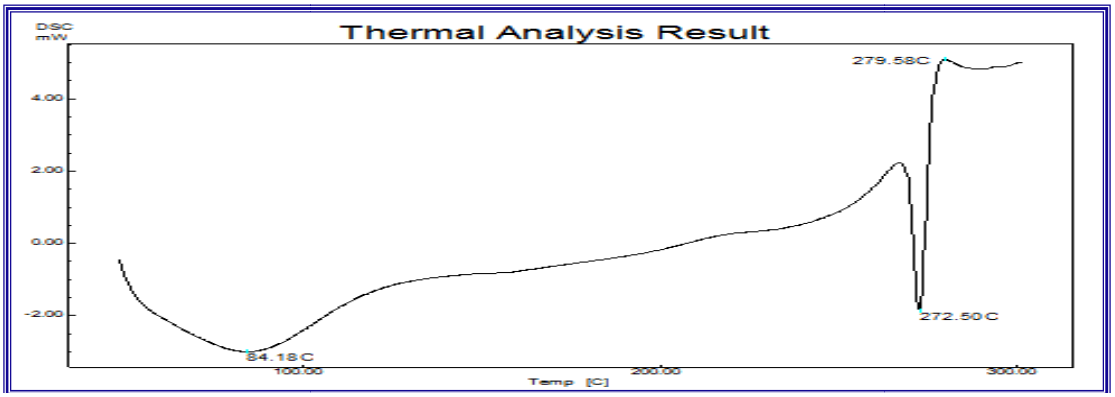

Fig 4: DSC spectra of pure drug + Starch

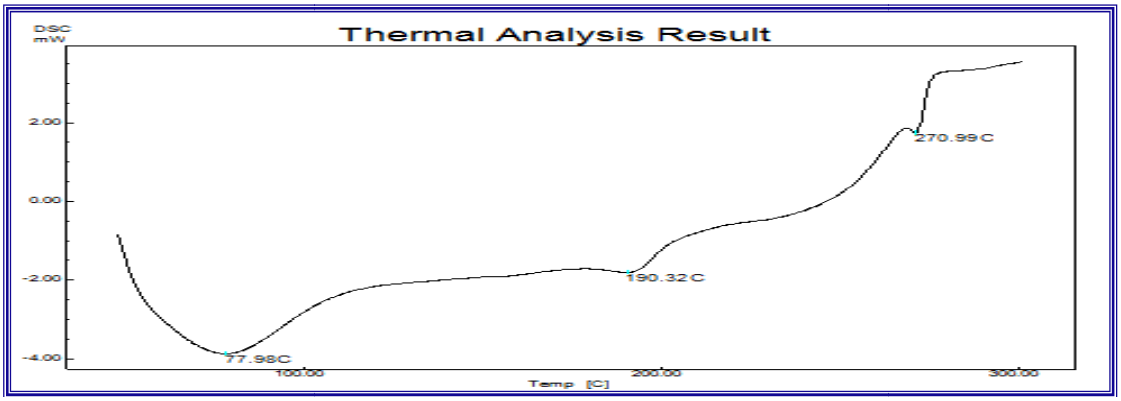

Fig 5: DSC spectra of formulation F6

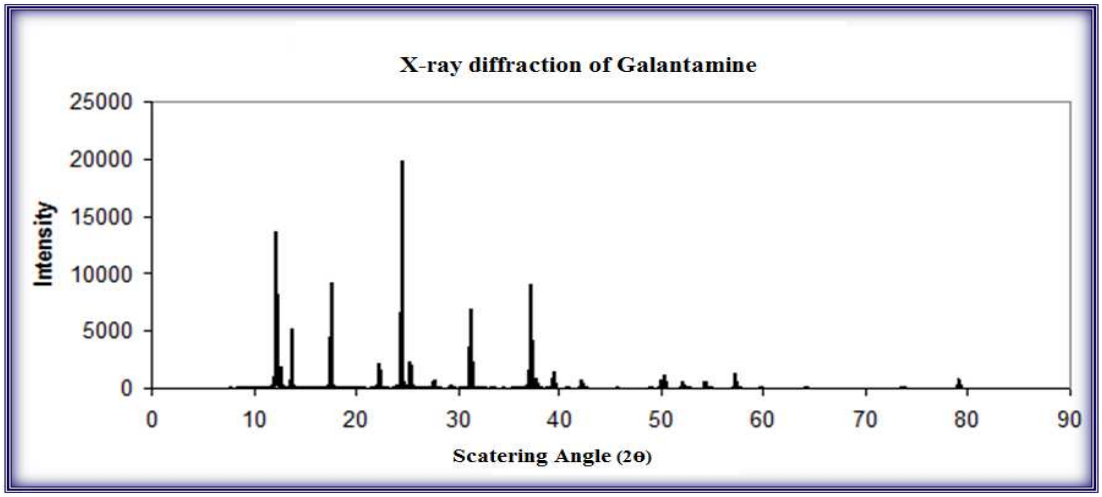

Fig 6: X-ray diffraction pattern of Galantamine Hydrobromide

Table 3: Sample Kept At Different Condition

Drug + Excipient	Initial	40°C/75%RH	Comments
Galantamine (1gm)	White	No change	Compatible
Drug + HPMC K100M (0.1 + 0.9g)	Light White	No change	Compatible
Drug + starch (0.5 + 0.5g)	Light White	No change	Compatible
Mixture (1gm)	Light White	No change	Compatible

Table 4: Evaluation of Bilayer Sustained Release Tablet

Batch. No.	Hardness Kg/cm^2 n=10	Thickness (mm) n=10	Friability %	Weight Variation n=20	Drug content %
F1	4.3 ±0.129	2.31 ±0.023	0.216	253 ±0.278	99.02
F2	4 ±0.084	2.35 ±0.034	0.324	251 ±0.389	98.2
F3	4 ±0.117	2.29 ±0.048	0.323	249 ±0.491	99.12
F4	4.1 ±0.067	2.35 ±0.095	0.128	250 ±0.396	98.22
F5	4.2 ±0.128	2.37 ±0.039	0.124	252 ±0.481	98.55
F6	4.2 ±0.128	2.37 ±0.048	0.194	253 ±0.385	101.03
F7	4 ±0.125	2.35 ±0.049	0.284	253 ±0.551	98.55
F8	4.2 ±0.095	2.26 ±0.086	0.168	249 ±0.401	98.65
F9	4.2 ±0.083	2.36 ±0.049	0.514	252 ±0.473	98.7
F10	4.1 ±0.099	2.38 ±0.043	0.622	251 ±0.497	97.95
F11	4 ±0.127	2.37 ±0.061	0.471	250 ±0.366	98.42

Table 5a: In-Vitro Drug Release of Bilayer Sustained Release Tablet

Cumulative percent drug release* AM ± SD (n=3)							
Time (hrs)	**TDR**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
1	33.5	60 ± 3.9	53± 1.2	45 ± 0.8	39 ± 0.7	36 ± 0.7	34 ± 1.7
2	38.49	85 ± 1.2	64± 1.8	67 ± 0.6	54 ± 1.6	43 ± 1.3	43 ± 1.5
4	44.18	97 ± 0.2	83 ± 1.9	77 ± 0.8	68 ± 1.3	59 ± 0.7	54 ± 6.3
8	55.55	100 ± 2	94 ± 3.3	85 ± 1.4	76 ± 1.1	71 ± 0.7	59 ± 2.7
12	66.92	----	101 ± 3	92 ± 2.1	76 ± 1.1	87 ± 0.9	66 ± 1.3
16	78.29	----	----	99 ± 0.8	98 ± 1.5	93 ±2.3	77 ± 0.6
20	89.66	----	----	100 ± 2	100 ± 1	96 ±1.9	86 ± 2.3
24	100	----	----	----	----	100 ± 2	96 ± 2.7

Table 5b: In-Vitro Drug Release of Bilayer Sustained Release Tablet

Cumulative percent drug release* AM ± SD (n=3)						
Time (hrs)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
1	47 ± 0.95	39 ± 1.76	36 ± 1.55	42 ± 0.54	35 ± 0.5	38 ± 1.8
2	64 ± 1.23	58 ± 0.85	47 ± 2.15	60 ± 0.49	48 ± 2.4	49 ± 1.4
4	75 ± 0.94	69 ± 1.58	58 ± 2.87	71 ± 0.62	61 ± 2.5	65 ± 1.6
8	83 ± 0.24	73 ± 0.77	69 ± 1.28	80 ± 0.47	70 ± 1.2	71 ± 1.9
12	92 ± 1.04	83 ± 0.86	78 ± 2.48	89 ± 0.11	81 ± 2.1	84 ± 1.3
16	99 ± 1.76	94 ± 1.66	88 ± 2.60	96 ± 0.87	89 ± 2.5	90 ± 1.6
20	----	100 ± 1.83	94 ± 1.52	101 ± 1.2	95 ± 1.6	96 ± 1.5
24	----	----	99 ± 1.32	----	100 ± 2	99 ± 0.5

Table 6: Data Analysis in different model of F6 batch

Model	Zero order	First order	Higuchi	Hixson Crowell
Linearity	0.828	0.944	0.962	0.952
Slope	3.151	-0.049	17.93	-0.107
Intercept	25.28	1.938	9.8	4.292

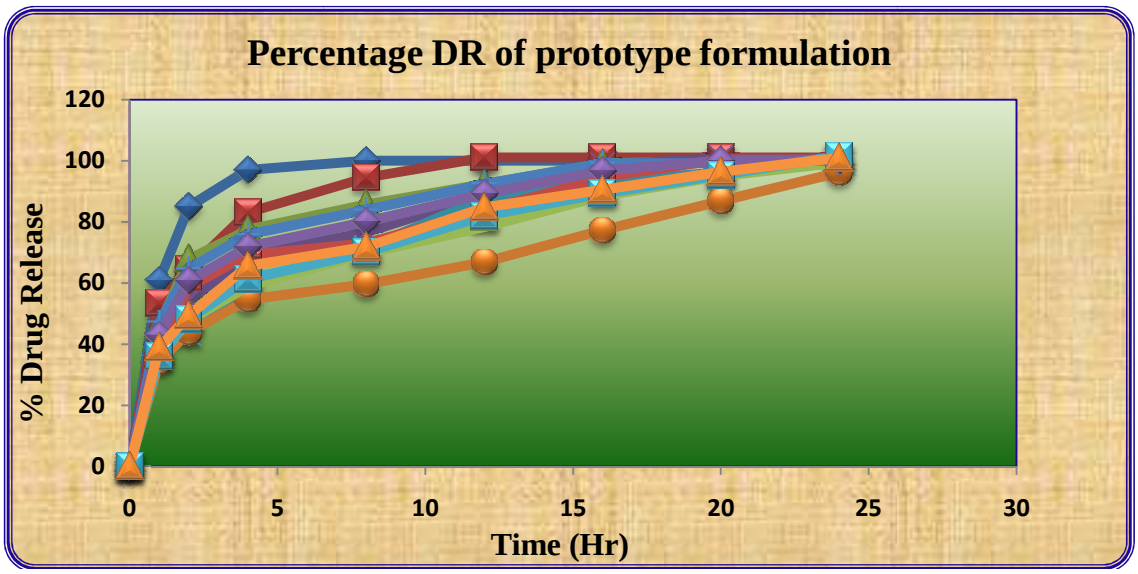

Fig 7: Invitro drug release of batch F-1 to F-12

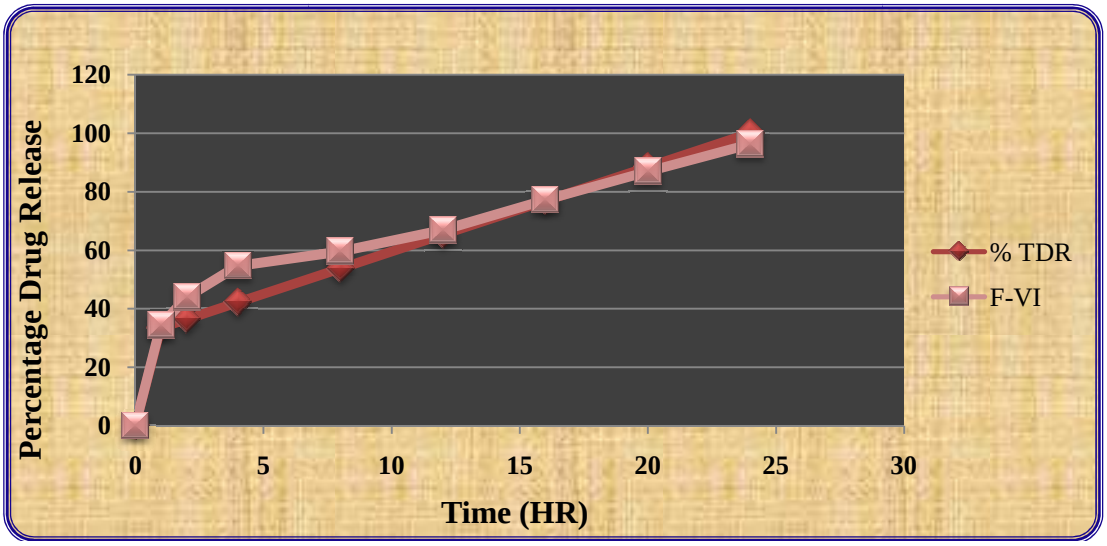

Fig 8: Comparatative Data of TDR and Formulation F-6

CONCLUSION

From the DSC and FTIR spectra the interference were verified and found that Galantamine Hydrobromide did not interfere with the excipients used. In bi-layer tablet of Galantamine Hydrobromide, loading dose, maintenance dose, and theoretical drug release profile was prepared based on pharmacokinetics data. Loading dose of Galantamine Hydrobromide mix with super disintegrating agents, it was found that 12% concentration of crosspovidone gives desirable release within 30 minutes this is due to very fast disintegration of tablet that is less than one minute. Sustained release layer, concentration of polymer (HPMC K-15M, HPMC K-100M) was optimized for sustained release polymer. Different formulation of HPMC polymer was used with help of hit and trial method. It was found that HPMC K100M with concentration 60%, showed good sustained release effect and its releases 96.13% drug within 24 hrs. With 60% concentration, similarity factor was found to be 62.4. Optimized batch was subjected for

kinetic modeling for mechanism of drug release. Drug was released from tablet by Zero-order kinetics, which suggests concentration independent release pattern via diffusion mechanism.

REFERENCES

[1] Hing JP; Piotrovsky V; Kimko H., *Curr Med Res Opin*. **2005**, 21, 483–488.
[2] Huang F; Fu Y**.** *Curr Clin Pharmacol.* **2010**, 5(2), 115-124.
[3] Scharre DW; Shiovitz T; Zhu Y; Amatniek J. *Alzheimers Dement*, **2008**, 4, 30–37.
[4] Valluru Ravi; T.M. Pramod Kumar. International Conference & Exhibition on Pharmaceutical Biotechnology, **2011**, 7(3), 176-178.
[5]Ramana G; Sushma M; Arun Y. *International Journal of Innovative Pharmaceutical Research*, **2010**, 1(3), 61-65.
[6] Patel Hitesh N; Patel Amit V; Patel Vishal J; Dave Jayant B; Patel Chhaganbhai N. *J. Chem. Pharm. Res.*, **2010**, 2(2),.44-49.
[7] Jann MW; Shirley KL; Small GW. *Clinical Pharmacokinetics*, **2002**, 41(10), 719-739.
[8] Ramana G; Sushma M; Arun Y, *Int J Pharm Bio Sci*, **2010**, 1(3), 61-65.
[9] Prabhakar Shirse, *Int J Pharm Bio Sci*, **2012**, 3(3), 148 – 160.
[10] Robinson; Dean M; Plosker; Greg L, *CNS Drugs*, **2006**, 20 (8), 673-681.
[11] J. Prasanna Kumar; T. Ramarao; K. N. Jayaveera; D. V. R. N. Bhikshapathi; Y. Madhusudan Rao, Scholars Research Library, *Der Pharmacia Lettre*, **2013**, 5 (5),129-144.
[12] S. Jayaprakash; S. Mohamed Halith; K.Kulathuran Pillai; Priya Balasubramaniyam; P.U. Mohamed Firthouse; M .Boopathi, Scholars Research Library, *Der Pharmacia Lettre*, **2011**, 3 (4), 143-154
[13] Sharmin Rahman; Md. Abdullah Al Masum; Florida Sharmin; S. M. Ashraful Islam; Md. Selim Reza, *Journal of Applied Pharmaceutical Science*, **2012**, 02 (06), 129-134.
[14] Pankaj Jadhav; Ajay Samnani; Girijesh Panday; B.K. Dubey, *WJPPS*, **2008**, 1(2), 621-632.
[15] Mc. Gee, Controlled release galantamine composition, united states patent no 7,160,559
[16] Rockville M.D, United States Pharmacopeia, 28th ed., The United States Pharmacopoeial Convention Inc, 2005; pp.2749-2751.
[17] Nabin Karna, *Int J Pharm Bio Sci*, **2012**, 3(4), 392 – 402.