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FORMULATION EVALUATION AND OPTIMIZATION OF EXTENDED-RELEASE CORE OSMOTIC PELLETS OF GALANTAMINE HYDROBROMIDE

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Abstract:

Extended-release systems provide drug release in an amount sufficient to maintain the therapeutic drug level over an extended period, with the release profiles predominantly controlled by the special technological construction and design of the system itself NACL is most commonly used as an osmotic agent in the osmotic drug delivery systems, thus was selected. The batches of core pellets were taken with different sodium chloride concentration range. Pellets without sodium chloride were prepared in the same way with sodium chloride being replaced by lactose

After analysis of reference product release profile, it was decided that the drug release should be controlled in the pH 4.5 buffer. Few important attributes from the reference product were to release the drug at zero order release kinetics in pH 5.8 phosphate buffer. Optimized formulation as well as reference product had a split- release profile having mixed type of release kinetics. The formulation was studied for the effect of medium osmolality on drug release by varying the concentration of osmotic agent in dissolution medium. It was found that drug release was decreased linearly with an increase in the medium osmolality

The surface of the optimized formulation was studied before and after dissolution study by scanning electron microscopy. Pores were not seen in the membrane before exposure to the release medium, but several pores or voids were found in the membrane after drug release. suggests that the membrane became porous after exposure to the medium due to the leaching of plasticizers from the membrane. Kinetics of drug release of optimized.

Keywords: *Extended-release systems, Galantamine Hydrobromide Core Osmotic Pellets.*

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INTRODUCTION:

Extended-release systems provide drug release in an amount sufficient to maintain the therapeutic drug level over an extended period, with the release profiles predominantly controlled by the special technological construction and design of the system itself. The development of oral extended-release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. There are numerous products in the market formulated for both oral and parenteral routes of administration that claim extended or controlled drug delivery. Matrix-type drug delivery systems are one of the interesting and promising options in developing an oral extended-release system. In particular, the interest awakened by matrix type delivery is completely justified because of its biopharmaceutical and pharmacokinetic advantages over the conventional dosage forms [1].

1 Types of multi particulate system

A) Matrix Systems

In matrix systems a polymer: drug solution or dispersion is granulated with excipients to form pellets or sprayed onto pellets to achieve extended drug release. The drug homogeneously distributed within the polymer is dissolved, dispersed, or dissolved and dispersed. These systems present several advantages as follows

- Easy manufacture and low cost (1 step process),
- Decrease risk of dose dumping (if the coating accidental-ly ruptures) and the
- Possibility of improvement of aqueous drug solubility.

Drug-polymer interactions can occur and bring reimbursement in terms of mechanical properties such plasticizing effect. The main disadvantages include fast initial release and incomplete release in a defined time. The other could be avoided by coating sugar cores with another polymer: drug ratios, in which the drug was more concentrated in deeper layers of the matrix and so counteracting for the increased diffusion pathway. In addition, matrix systems were found suitable to control the drug release of a highly soluble drug. [2-6].

Optimization of core osmotic pellets of Galantamine Hydrobromide

Optimization of osmotic agent

Sodium chloride is most commonly used as an osmotic agent in the osmotic drug delivery systems (ODDS), thus was selected. The batches of core pellets were taken with different sodium chloride concentration range. Pellets without sodium chloride were prepared in the same way with sodium chloride being replaced by lactose.

The coating solution was prepared by dissolving cellulose acetate in isopropyl alcohol (IPA) and dichloromethane (DCM) in the 50:50 ratio. The talc, titanium dioxide, and plasticizer were dispersed in the solution. The pellets were coated with a coating solution containing triethyl citrate as a plasticizer (15 % w/w of the polymer). The effect of different concentrations of osmotic agent on the in-vitro release of Galantamine Hydrobromide was studied [7].

Table 1: Composition of formulation of Galantamine Hydrobromide

Ingredients (mg/capsule)	Formulation Code GH-1	GH -2	GH -3	GH -4	GH -5
Galantamine Hydrobromide	5	5	5	5	5
Avicel® pH 101	65	65	65	65	65
Pharmatose® 200M	90	60	50	40	30
Sodium chloride	0	30	40	50	60
Kollidon® 30	8	8	8	8	8
Purified Water	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2: Coating excipients composition

Composition	Weight (g)	Coating weight gain:30% w/w
Cellulose acetate 398-10NF	10	
Triethyl citrate	1.5	
Talc	1.0	**Solid Content of thesolution: 4- 5%**
Titanium dioxide	1.0	
DCM: IPA (50:50)	300 mL	

2. Optimization of coating Composition

2.1 Selection and Optimization of plasticizer

Cellulose acetate (398-10 NF) was selected as semi permeable membrane for pellets coating. Pellets were coated in a predictable pan coater. Plasticizers are added in the coating composition to communicate the suppleness and smoothness to the membrane. Triethyl citrate and dibutyl phthalate in diverse concentration were tried as plasticizer in the coating composition. The pellets were coated with 30% mass gain and study for in-vitro release profile.

Table 3: Coating composition for Galantamine Hydrobromide formulation

Ingredients (wt in mg)	Coating Composition Code					
	GH-2 A	GH-2 B	GH-2 C	GH-2 D	GH-2 E	GH-2 F
Cellulose Acetate (398-10NF)	10	10	10	10	10	10
Triethyl Citrate	1.0	1.5	2.0	-	-	-
Dibutyl Phthalate	-	-	-	1.0	1.5	2.0
Talc	1.0	1.0	1.0	1.0	1.0	1.0
Titanium Dioxide	1.0	1.0	1.0	1.0	1.0	1.0
Solvent system						
IPA	150 mL	150 mL	150 mL	150 mL	150 mL	150 mL
DCM	150 mL	150 mL	150 mL	150 mL	150 mL	150 mL
Solid content (Coating solution): 4-5%						
Coating weight gain: 30% w/w						

Optimization of coating weight gain

The pellets of the batch GH-2 were coated at different weight gain viz. 30%, 40%, and 45 % using coating composition given in batch GH-2F.

2.2 Study on the optimized formulation

2.3.1 In-vitro drug release study

Paddle-apparatus (USP type II, TDT-08 L, Electrolab) was used for the in-vitro dissolution testing. The pellets containing 5 mg drug were tested in 500 ml of degassed simulated gastric fluid (SGF, without enzymes) at a paddle rotation speed of 100 rev/min at 37^0C ± 0.5^0C were used to study the dissolution behavior. The release of the drug at different time intervals was analyzed by HPLC. Triplicate analysis was performed to study release studies and drug release rate along with percentage cumulative drug release was calculated.

2.4Effect of hydrodynamic force on the release profile of Galantamine Hydrobromide from osmotic pellets

To check the in-vivo reliability of the formulation with regards to hydrodynamic conditions of GIT, in-vitro release studies were conducted in dissolution apparatus at various speeds of rotation. USP-II (Paddle) type dissolution apparatus with rotational speeds of 50, 75, and 100 rpm was evaluated for the experiment. Dissolution media (pre-equilibrated to 37 oC ± 0.5 oC) was degassed SGF (without enzymes).

At predetermined intervals, samples were withdrawn and analyzed after filtration through nylon membrane filters of 0.45µ.

2.5 Effect of medium pH on drug release profile from osmotic pellets

To assure a reliable performance of the developed formulations, the *in-vitro* release studies were conducted in media of different pH. The release media was SGF (pH 1.2), acetate buffer (pH 4.5), phosphate buffer (pH 6.8), and distilled water. At pre-determined intervals, samples were withdrawn and analyzed after filtration through nylon membrane filters of 0.45µ.

2.6 Coating of core pellets

Pellets were coated in a conventional pan coater. Mixture of Cellulose acetate (4% w/v), talc, titanium dioxide and dibutyl phthalate (DBP) were dispersed in dichloromethane/2- propanol (50:50 v/v) and agitated for 2 h with overhead stirrer at low revolution rates. Initially, pellets were preheated by passing controlled hot air through the pellets bed and by rotating at a 5 to 8 rpm lower speed. Coating process was started with initial 10 to 12 rpm rotation speed. The spray rate was 4 to 6 mL/min and atomizing air pressure was 1.75 kg/cm^2 and inlet temperature was 50^{o}C and outlet air temperatures was 40^{0}C. Samples were taken of different weight gain during coating. Coated pellets were dried in a forced-air oven for 2 h at 50˚C

3.1 Optimization of Coating composition

3..1.2 Selection of Coating polymer

After analysis of reference product release profile, it was decided that the drug release should be controlled in the pH 4.5 buffer. Few important attributes from the reference product were to release the drug at zero order release kinetics in pH 5.8 phosphate buffer. In addition, it was important to formulate tablet to ensure release of almost 50 % drug in the initial two hours and remaining 50% drug in the subsequent 14 hrs in pH 6.8 phosphate buffer.

Table 4: Optimized formula for Extended-Release Layer of the tablets

	Ingredients	**Weight/Tablet (mg)**
InternalPhase	Galantamine hydrobromide	30
	Pharmatose® 200M	47.5
	Aluminium hydroxidepowder	7.5
	Methocel® K4M CRpremium	60
	Kollidon® 30	4.5
	2- Propanol	q.s
ExternalPhase	Aerosil® 200	1.5
	Magnesium Stearate	1.5
Total Weight (mg)		**152.5**

Table 5: Optimized formula for Immediate Release Layer of the tablets

Ingredients	**Weight/Tablet (mg)**
Galantamine hydrobromide	30
Pharmatose® 200M	45
Avicel® PH 101	15
Mg Stearate	1.5
Aerosil 200	1.5
Kollidon® 30	3
Total Weight (mg)	**96**

Table 6: Optimized formula for coating composition of the tablets

Composition	**Weight (g)**
Eudragit® S 100	2.5
Eudragit® L 100	7.5
Triethyl citrate	1.0
Talc	1.0
Titanium dioxide	1.0
Solvents	
Dichloromethane	175 mL
Isopropyl alcohol	175 mL
Coating Specifications	
Solid content	3-4%
Weight gain	4-5%

4.Evaluation of the optimized formulation

4.1 *In-vitro* dissolution

4.2 *In-Vitro* Release Study

Dissolution medium : Phosphate buffer pH 6.8

Volume : 900mL

Apparatus : USP II (Sinker)

Speed (rpm) :50

Temperature : 37°C ±0.5°C

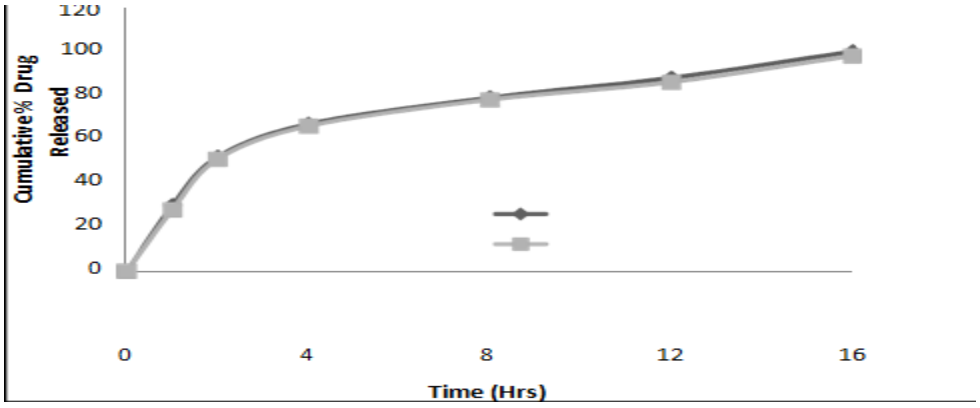

Fig. 1: *In-vitro* release study of optimized formulation

4.3 Data Analysis

The dissolution release data analyzed using various release kinetics models in order to study the mechanism of drug release. Optimized formulation as well as reference product had a split- release profile having mixed type of release kinetics. In order to study the kinetics and mechanism of drug release through the extended-release layer, the initial 2hrs drug release data was excluded. The correlation coefficient (R^2) was used as indicator of the best fitting, for the models considered. Results revealed that the *in-vitro* release profile of optimized formulation was best fitted to thezero order models as seen from R^2 values.

Table 7: The Correlation Coefficient (R^2) Values for optimized formulation

Correlation coefficient	First order	Zero order	Higuchi	Peppas	Hixon-crowell
	0.855	0.994	0.986	0.980	0.92

4.5 Water up-take and Erosion Study

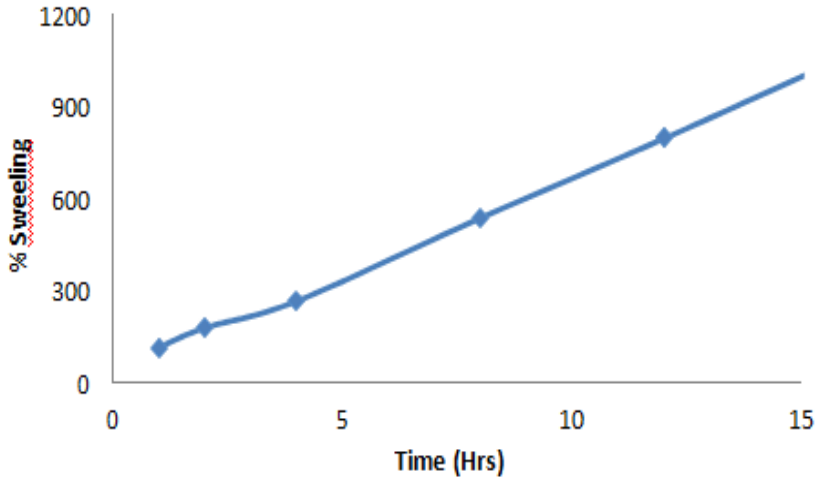

Fig. 2: Water up-take study of FR-9 (Optimized formulation)

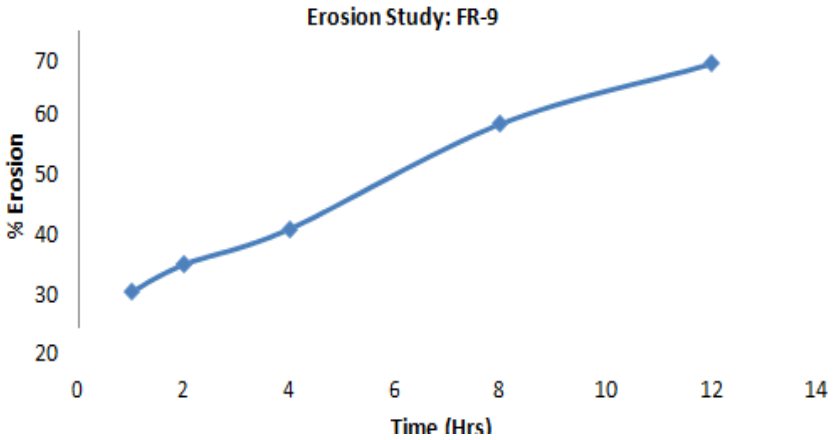

Fig. 3: Erosion study of FR-9 (Optimized formulation)

5.0 Optimization of Coating composition
5.1 Selection of Coating polymer

As per need laid down by reference product release profile, drug release had to be controlled in the pH 4.5 buffer. Again, the difficult task laid down by reference product was to release the drug at zero order release kinetics in pH 5.8 phosphate buffer. The bigger challenge was to release almost 50% drug in the initial two hours and remaining 50% drug in the subsequent 14 hrs in pH 6.8 phosphate buffer.

Thus, we needed specialized coating membrane to match the release profile in pH 4.5 acetate buffer, pH 5.8 phosphate buffer and pH 6.8 phosphate buffer. Thus, different batches were tried with Eudragit® L100 and Eudragit® S 100 with different weight gain.

6 Evaluation of the optimized formulation
6.1 *In-vitro* drug release study

The in-vitro release profile of optimized formulation was perfectly matching with the in- vitro release profile of Ditropan XL with F2 value of 82.0

6.2 Effect of hydrodynamic force on release profile of Galantamine hydrobromide from osmotic pellets

Intensity of agitation doesn't affect the osmotic pumps for release of drug. The release studies of optimized formulation was carried out in USP-II dissolution apparatus at varying rotational speed (50, 75, and 100 rev./min). Result shows that the release profile of Galantamine hydrobromide from the developed formulation was fairly independent of the agitational intensity of the release media. This assures that the release from the developed formulations will be independent of the hydrodynamic conditions of the body. The *f1* and *f2* values were found to be 8.54 and 64.02 (between 100 and 50 rev./min) and 4.76 and 76.09 (between 100 and 75 rev./min) respectively.

Thus it was concluded that the selection of membrane which is an important step to control the release of Galantamine hydrobromide showed regular release profile in comparison to additional devices of osmotic formulations.

6.3 Effect of medium pH on release profile from osmotic pellets

To assure a reliable in vivo performance, the robustness of drug release had to be tested in media of different pH. Release studies of the optimized formulation were conducted according to pH change method. Results show release of Galantamine hydrobromide from optimized formulation and it is clearly evident that the release profile is similar in all the media. The f_2 values at pH 4.5, pH 6.8 and distilled water were found to be 69.6, 66.2 and 72.77 respectively, taking the release profile in pH 1.2 SGF as the reference. Hence, it can be thought that properties of drug release when in gastric transit may not get affected or changed because of individual intra and inter individual alteration in pH of the gastric juice.

6.4 Effect of medium osomolality on drug release

The drug release rate was decreased with increase in osmotic pressure in the media. The increase in medium osmolality from 7.5 % to 15.0 % has increased tL from 2.44 h to 4.87 h. The drug release profiles with varying osmotic pressure make it evident that the drug release from the formulation decreased as the osmotic pressure of the media increased. This finding confirms that the mechanism of drug release was by osmosis.

CONCLUSION:

The formulation was studied for the effect of medium osmolality on drug release by varying the concentration of the osmotic agent in the dissolution medium. It was found that drug release was decreased linearly with an increase in the medium osmolality confirming the surface of the optimized formulation was studied before and after dissolution study by scanning electron microscopy. Pores were not seen in the membrane before exposure to the release medium, but several pores or voids were found in the membrane after drug release. This suggests that the membrane became porous after exposure to the medium due to the leaching of plasticizers from the membrane. Kinetics of drug release of optimized formulation was studied by fitting the release data into a zero-order release kinetic model. The correlation of coefficient for zero-order release kinetics was found to be 0.992, which showed that the drug was released at a controlled rate independent of a concentration gradient. *In-vitro* release data were also fitted to first-order release kinetics by plotting the log of cumulative percent drug remaining versus time. The correlation of coefficient for first-order release kinetics was found to be 0.91, which showed that drug release was independent of the concentration gradient across the membrane. This suggests that the membrane became porous after exposure to the medium due to the leaching of plasticizers from the membrane. Kinetics of drug release of optimized formulation was studied by fitting the release data into a zero-order release

kinetic model. The correlation of coefficient for zero-order release kinetics was found to be 0.992, which showed that the drug was released at a controlled rate independent of a concentration gradient. *In-vitro* release data were also fitted to first-order release kinetics by plotting the log of cumulative percent drug remaining versus time. The correlation of coefficient for first-order release kinetics was found to be 0.91, which showed that drug release was independent of the concentration gradient across the membrane.

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