

# DESIGN OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF DILTIAZEM HYDROCHLORIDE

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## Abstract

Gastro retentive drug delivery system of diltiazem hydrochloride was designed and evaluated for its effectiveness for the management of mild to moderate hypertension. Gastro retentive drug delivery system were prepared using polyvinyl alcohol and sodium carboxy methyl cellulose as the polymers and sodium bicarbonate as a gas generating agent for the reduction of floating lag time. Gastro retentive drug delivery system tablets were prepared by wet granulation method by compression in tablet compression machine. Formulations DL1, DL2, DL3, DL4 and DL5 were developed which differed in the ratio of polyvinyl alcohol and sodium carboxy methyl cellulose polymers. All the formulations were evaluated for hardness, weight variation, friability, drug content, swelling index, buoyancy studies and *in vitro* drug release study. *In vitro* drug release study was performed using United State Pharmacopoeia 23 type 2 dissolution test apparatus employing paddle stirrer at 50 r/pm. Dissolution medium was 900 ml of 0.1N hydrochloric acid at  $37^{\circ}\text{C} \pm 3^{\circ}\text{C}$ . Formulations DL3 was found to be better as compared to other formulation.

**Keywords:** Floating, gastro retentive, diltiazem hydrochloride, hypertension.

## Introduction

Gastro retentive controlled drug delivery system (GRDS) is gaining its popularity due to the ease of administration, patient compliance and flexibility in formulation, etc<sup>1</sup>. Conventional drug delivery systems associated with fluctuation in plasma drug concentration. However, GRDS offers a convenience like oral conventional drug delivery system and benefit like a controlled drug delivery system. Therefore it beneficial and gaining its importance day by day as successful drug delivery system. GRDS achieve as well as maintain the drug concentration within the therapeutically effective range needed for treatment<sup>2</sup>. Several technical advancements have led to the development of many novel drug delivery systems (NDDS) that could revolutionize method of medication and provide a number of therapeutic benefits. The most important objectives of these NDDS is gastro retentive controlled drug delivery system<sup>3</sup>.

Sustained release describes a drug delivery system with delayed and/or prolonged release of drug. It also implies delayed therapeutic action and sustained duration of therapeutic effect whereas controlled release implies a predictability and reproducibility in the drug release kinetics<sup>4,5</sup>. Gastro retentive drug delivery system (GRDS) is one of the most accepted sustained NDDS. The GRDS can be retained in the stomach and assists in improving the oral sustained delivery of drugs that have an improving the oral drugs delivery that have an absorption window in a particular region of the gastrointestinal tract. Efficacy of GRDS can also be improved by adding the mucoadhesive property in it.

Diltiazem hydrochloride (DL) is a calcium channel antagonist used in the treatment of chronic heart diseases such as angina and hypertension. It belongs to the benzothiazepine family<sup>6</sup>. DL undergoes an extensive first-pass metabolism<sup>7</sup>, which results in very less oral dose being excreted unchanged in urine 8(Hermann et al. 1983) and oral bioavailability of DL is around ~30% to 40% due to hepatic metabolism. It has an elimination half-life of 3.5 h<sup>9,10</sup>. Therefore, DL requires multiple oral daily dosages in order to maintain adequate plasma concentrations. Looking to oral bioavailability aspect DL is a suitable candidate for GRDS. The aim of our work was to design and evaluate gastro retentive drug delivery system of diltiazem hydrochloride for the treatment of chronic heart diseases such as angina and hypertension.

## Materials and Method

Diltiazem hydrochloride (DL) was obtained from Modi Mundi Pharma Pvt. Ltd. Meerut, India as gift sample. polyvinyl alcohol (PVA), sodium carboxy methyl cellulose (CMC), sodium bicarbonate, magnesium stearate and talk from Central Drug House Pvt. Ltd., Mumbai, were procured. Distilled water was used throughout the experiment as liquid vehicle.

## Method of preparation

All the ingredients of different formulations were accurately weighed and sieved through sieve no 40 separately. Drug and all the excipient (Table no.1) except the lubricants (magnesium stearate and talc) were blended

geometrically and granulated using 5% w/v polyvinyl pyrrolidone prepared in isopropyl alcohol by passing through sieve no.10. Granules were dried at 50°C for 4 h. The dried granules were sized through sieve no 12 and lubricated by adding magnesium stearate and talc. Tablets were compressed on a tablet compression machine using flat surfaced, round shaped punches of 12 mm diameter. Hardness of the tablet was maintained around 5 kg/cm<sup>2</sup>.

## CHARACTERIZATION OF FLOATING DRUG DELIVERY SYSTEM

### Hardness and friability test of tablets

Hardness or strength (Kg/cm<sup>2</sup>) of tablets was determined with the help of Monsanto type hardness tester<sup>11</sup>. Tablet was placed between the jaw of Monsanto hardness tester and pressure applied with the help of screw. Hardness of tablet noted on the measuring scale at the time of tablet break. Friability was determined by weighing 10 tablets after dusting, placing them in the friabilator (Roche Friabilator) and rotating the tablet on plastic cylinder vertically at 25 r/pm for 4 min<sup>12</sup>. After dusting, the total remaining weight of the tablets was recorded and the percent friability (PF) was calculated using formula  $PF = (\text{Weight}_{\text{final}} - \text{Weight}_{\text{original}}) / \text{Weight}_{\text{original}} \times 100$ .

### Average weight and drug content of tablets

Average weight of tablet was determined by taking weight of 10 tablets and calculating with each tablet weight<sup>12</sup>. The weight data from the tablets were analyzed for sample mean and percent deviation. Drug content was determined using 5 tablets in a glass mortar and powdered; 100 mg of this powder was placed in a 100 ml Stoppard conical flask. The drug was extracted in 0.1N hydrochloric acid with vigorous shaking on a mechanical shaker (100 rpm) for 1 hours and filtered into 50 ml volumetric flask through cotton wool and filtrate was made up to the mark by 0.1N hydrochloric acid through filter. Further, appropriate dilutions were made and absorbance<sup>5</sup> was measured at 235 nm using 0.1N hydrochloric acid as blank solution by UV-Visible double beam spectrophotometer.

### Swelling Index and Buoyancy studies of tablets

The individual tablets were weighted and kept in 50 ml of water for swelling purpose. Tablets were taken out carefully after 60 minutes, blotted with filter paper to remove the water present on the surface and tablet weighed accurately. Percentage swelling index (SI) was determined by using the formula<sup>13</sup>  $SI = (\text{Wet weight} - \text{Dry Weight} / \text{Dry weight}) \times 100$ . The *in vitro* buoyancy study was performed by keeping GRDS in 0.1N hydrochloric acid. In this study floating lag time and total floating time was determined. The test was performed using a USP 23 type-2 dissolution test apparatus (Electrolab) using 900 ml of 0.1N hydrochloric acid at paddle rotation of 50 r/pm at 37°C ± 3°C. The time required for the tablet to float to the surface of the dissolution medium and the duration of time the tablet constantly floated on the dissolution medium were noted as floating lag time and floating time respectively<sup>11</sup>.

### *In vitro* drug release study

*In vitro* drug dissolution study of GRDS of diltiazem hydrochloride were carried out in USP 23 type 2 dissolution test apparatus (Electrolab), employing a paddle type stirrer at 50 rpm and 900 ml of 0.1N hydrochloric acid at 37°C ± 3°C as dissolution medium. One tablet was used in each test and at predetermined time intervals 5 ml of the samples were withdrawn by means of a syringe fitted with a prefilter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37°C ± 3°C. The samples were analyzed for drug release by measuring the absorbance at 235 nm using UV-visible double beam spectrophotometer after suitable dilution.

## Results and Discussions

Gastro retentive drug delivery system of diltiazem hydrochloride was designed and evaluated for its effectiveness for the management of mild to moderate hypertension. GRDS were prepared using PVA and sodium CMC as the polymers and sodium bicarbonate as a gas generating agent for the reduction of floating lag time. GRDS tablets were prepared by wet granulation method by compression in tablet compression machine. Five formulations were designed, which differed in the ratio of polymers<sup>10</sup>. Formulations DL1, DL2, DL3, DL4, and DL5 were composed of PVA and sodium CMC in the ratio as given in Table no. 1. All the formulations were evaluated for hardness, weight variation, friability, drug content, swelling index, buoyancy study and *in vitro* drug release study. Evaluation parameters of developed various GRDS summarized in Table number 2. Hardness of GRDS were in the range of 4.4 to 5.2 Kg/cm<sup>2</sup>, which is in acceptable limit. The friability of all the developed tablets was less than 1% i.e. in the range of 0.19 to 0.65%. Hardness indicates about strength of tablets which is important for handling, transport and storage of tablets. Friability gives information for removal of powder from the surface during handling and transport. Both the parameters were found in acceptable range.

Average weight of tablet was determined by taking weight of 10 tablets and calculating with each tablet weight. The weight data from the tablets were analyzed for sample mean and percent deviation. The percentage deviation from the mean weights of all the batches of prepared GRDS was found to be within the prescribed

limits. Weight of tablet if vary than it changes other parameters like drug content, hardness of tablets and thickness of the tablets. Therefore, any changes in tablets also indirectly affect the other important parameter. The drug contents of GRDS were found between 96.82 to 99.31%. Drug content was determined using 5 tablets in a glass mortar and powdered; 100 mg of this powder was placed in a 100 ml Stoppard conical flask. The drug was extracted in 0.1N hydrochloric acid with vigorous shaking on a mechanical shaker (100 r/pm) for 1 h and filtered into 50 ml volumetric flask through cotton wool and filtrate was made up to the mark by 0.1N hydrochloric acid through filter. Further, appropriate dilutions were made and absorbance<sup>5</sup> was measured at 235 nm using 0.1N hydrochloric acid as blank solution by UV-Visible double beam spectrophotometer.

The floating lag time i.e., time require to start floating was found to be in between 124 to 206 second with a floating time of more than 24 h. This in is expected enough for starting floating activity of GRDS. The swelling index was found to be in the range of 41.85 to 62.78. *In vitro* drug release study of GRDS of diltiazem were performed in USP 23 type 2 dissolution test apparatus, employing a paddle stirrer at 50 r/pm using 900 ml of 0.1N hydrochloric acid at 37°C ± 3°C as dissolution medium. One tablet was used in each test at predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a prefilter. *In vitro* drug release results were 43.56 to 59.42% in 8 h and the data plotted in Figure 1. Formulation DL3 had sufficient drug release profile which can withstand as once a day therapy. Therefore, on the basis of evaluation parameter formulation DL3 selected as developed formulation. Therefore, it can be concluded that the GRDS can be exploited successfully for the delivery of drugs e.g., diltiazem hydrochloride for the treatment of hypertension.

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Table 1. Composition of FDDS Developed Formulations

Ingredient	DL1	DL2	DL3	DL4	DL5
Diltiazem Hydrochloride (mg)	50	50	50	50	50
PVA (mg)	100	75	50	125	150
Sod. CMC (mg)	100	125	150	75	50
Sod. bicarbonate (mg)	50	50	50	50	50
Magnesium stearate (mg)	5	5	5	5	5
Talc (mg)	5	5	5	5	5

PVA, Polyvinyl alcohol; Sod.CMC, sodium carboxy methyl cellulose

Table 2. Evaluation of FDDS formulations

Formulation Code	Hardness Kg/ cm <sup>2</sup>	Friability % W/W	Average Weight (mg)	Drug Content	Swelling Index	Floating Lag Time (S)	Floating time (h)
DL1	4.4	0.23	324	97.78	55.38	173	24
DL2	4.7	0.45	331	99.31	41.85	197	24
DL3	5.2	0.19	318	98.47	62.78	124	24
DL4	5.1	0.65	327	96.82	58.49	206	24
DL5	4.5	0.58	328	97.46	45.65	192	24

Figure: In vitro drug release profile of developed formulations

