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Design, Development, and Assessment of Gastro-Retentive Drug Delivery System for the Management of Hypertension

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ABSTRACT

For the effective management of hypertension, we have developed a gastro-retentive drug delivery system that includes simvastatin and candesartan. Candesartan, a synthetic angiotensin II receptor antagonist made from benzimidazole, is a prodrug with antihypertensive properties. The medication simvastatin belongs to the pharmacological family of HMG-CoA reductase inhibitors. This lowers blood levels of harmful cholesterol, including low-density lipoprotein (LDL), and triglycerides. To achieve the optimal therapeutic medicine level over a long period of time, a controlled release mechanism was developed in the form of floating microspheres. Using the emulsion solvent evaporation technique with different quantities of ethyl cellulose, HPMC, and chitosan, floating microspheres carrying simvastatin and candesartan were produced. For each formulation, three batches were made in order to evaluate repeatability with regard to percentage yield, entrapment efficiency, particle size, percentage buoyancy, and percentage drug release. The average particle size for simvastatin and candesartan was found to be between 49.94 and 93.1 µm and 65.66 and 105.28 m, respectively. For candesartan and simvastatin, the percentage drug loading efficiency of microspheres ranged from 58.36 to 93.08% and 54.85 to 83.64 percent, respectively. The percentage yield of microspheres for simvastatin and candesartan for all formulations varied from 56.32% to 78.65% and 43.68% to 98.32%, respectively. The optimised buoyancy of the candesartan and simvastatin microspheres was 80.63 and 89.98 percent, respectively. Simvastatin microspheres demonstrated a 64.35 percent release after 12 hours, but the optimised formulation of candesartan and Simvastatin demonstrated a sustained release of the medicine, releasing 62.34% of the drug until the 12-hour mark.

Keywords: Hypertension, Candesartan, Simvastatin, Floating Microspheres.

INTRODUCTION

Out of all the administration methods that have been studied for systemic medicine delivery, oral drug delivery is the most widely used. Oral medication delivery is the most popular and least complex method. The usefulness of all controlled release techniques depends on their ability to remain close to the absorption site. The gastroretentive medication delivery method with controlled release may be retained in the stomach. They may aid in optimizing the oral controlled administration of medications with a "absorption window," guaranteeing optimal bioavailability1, by continuously releasing the drug prior to the "absorption window" for an

extended duration. The stomach empties while one is fasting and after one gets fed. The motility patterns of the two states, however, vary from one another. According to gastric emptying studies, two problems primarily impact controlled release dosage forms administered orally: a short stomach residence duration and an irregularly high gastric emptying rate2. Candesartan is a medication that blocks the angiotensin II receptor. It is mainly used to treat diabetic nephropathy, heart failure, hypertension, and myocardial infarction. Candesartan, a synthetic angiotensin II receptor antagonist made from benzimidazole, is a prodrug with antihypertensive properties. By selectively competing with angiotensin II for the binding of the angiotensin II receptor subtype 1 (AT1) in vascular smooth muscle, candesartan causes vasodilation and inhibits angiotensin II-mediated vasoconstriction. The medication simvastatin belongs to the pharmacological family of HMG-CoA reductase inhibitors. This is used to lower levels of triglycerides, bad cholesterol, such as low-density lipoprotein (LDL), and good cholesterol, such as high density lipoprotein (HDL). It lowers the chance of cardiac issues including heart attacks and strokes, among others. In order to effectively treat hypertension and maintain the optimal therapeutic medication level throughout time, the present research set out to develop a gastro-retentive candesartan and simvastatin drug delivery system. The following list of drug categories covers applications for the gastroretentive drug delivery system (GRDDS), according previously published literature: 5-Medications that act locally in the stomach include antacids and fluorouracil. One medication that is unstable in the bottom part of the GIT is captopril. Examples of medications that are insoluble in intestinal fluids include diazepam, metoprolol, and propranolol (acid soluble basic medicines). The goal of this research was to create and assess a floating microsphere containing simvastatin and candesartan. The emulsion solvent evaporation procedure was used to produce floating microspheres containing candesartan and simvastatin using varying quantities of ethyl cellulose, hydroxy propyl methyl cellulose, and chitosan.

EXPERIMENTAL

Material

As a gift sample, candesartan and simvastatin were acquired from Khandelwal Laboratory Pvt. Ltd. in Mumbai. The physical appearance of the Candesartan and Simvastatin sample was examined and compared to the reference. The obtained simvastatin and candesartan sample's physical characteristics complied with IP. The chemicals utilised were of reagent grade, and EC, HPMC, and chitosan were purchased from the institution.

Methods

Emulsion Solvent Evaporation Methodology

After precisely weighing the polymer (Ethyl Cellulose & Hydroxypropyl Methyl Cellulose), it was dissolved in 20 millilitres of acetone. Following two hours of mixing, weighed volumes of the medications Simvastatin or Candesartan and chitosan (which had previously been passed through filter #150) were added to the aforementioned polymer phase. A magnetic stirrer was then used to constantly agitate the mixture at 800 rpm. 100 ml of liquid paraffin containing 1.0 w/v of Span 80 was then added. For two hours, stirring was maintained to ensure that all of the acetone had evaporated. After removing the liquid paraffin using Whatmann filter paper No. 44, the microspheres were washed three times with 50 cc of petroleum ether and left to air dry for twelve hours. All of them were made using the same procedure for developing microsphere formulations. The exact components of a number of formulations made using 23 factorial designs were given in Tables 1 through 4.

Table 1: Level of Factors for Candesartan Microsphere

Factors	Low level	High level
Ethyl cellulose	750	1000
HPMC	200	300
Chitosan	100	200

Table 2: Composition of formulation of floating Microsphere of Candesartan:

Formulation Code	**Candesartan**	**Ethyl cellulose**	**HPMC**	**Chitosan**
C1	500	750	300	100
C2	500	1000	300	100
C3	500	750	200	200
C4	500	1000	200	200

		0		
C5	500	1000	300	200
C6	500	1000	200	100
C7	500	750	300	200
C8	500	750	200	100

Table 3: Level of Factors for Simvastatin Microsphere

Factors	**Low level**	**High level**
Ethyl cellulose	375	500
HPMC	100	150
Chitosan	50	100

Table 4: Composition of formulation of floating Microsphere of Simvastatin:

Formulation C	**Simvastatin**	**Ethylcellulos**	**HPMC**	**Chitosan**

o d e		**e**		
S 1	250	3 7 5	1 0 0	5 0
S 2	250	5 0 0	1 0 0	1 0 0
S 3	250	3 7 5	1 5 0	1 0 0
S 4	250	5 0 0	1 0 0	5 0
S 5	250	5 0 0	1 5 0	1 0 0
S 6	250	3 7 5	1 0 0	1 0 0
S 7	250	5 0 0	1 5 0	5 0
S 8	250	3 7 5	1 5 0	5 0

Prepared floating microspheres evaluation:

Percentage yield of microspheres identification[4]

Microspheres that had been completely dried were gathered and precisely weighed. The formula shown below was then used to obtain the % yield.

$$\% \text{ Yield} = \frac{\text{Obtained Mass of Microspheres}}{\text{Total weight (Drug \& Polymer)}} \text{ X } 100$$

Analysis of microsphere size[5]:

Size distribution of microsphere:

The optical microscope approach was used to determine the size of the microspheres. When determining the releasing properties of the microspheres, size distribution is a key factor.

The Angle of repose[6]

The angle of repose may be used to identify loose particles that have a fractional force. This is the maximum angle that may be formed between the horizontal plane and the surfaces of the powder site.

The angle of repose was calculated using a static method using a funnel. The tripod platform that held the funnel was kept horizontal. The sample was put into the funnel as the pile grew and reached the tip of the funnel. The diameter of the pile was measured. One may determine the value of q (Angle of repose) by:

q = tan-1 (h/r)

Here in formula,
h represents the microspheres pile height whereas r represents the circular arc radius which was formed on the ground by microspheres.

Bulk density identification[7]

The 3-tap technique has been used to determine bulk density. "Powdered mass divided by the bulk volume" is the definition of bulk density. The packing specifications of the powder have a major impact on the product's physical characteristics. Following the standard procedure for calculating bulk density, weighed quantities of produced microspheres were added to a 10 ml graduated cylinder, and the starting volume was recorded. The last loudness was recorded after three taps. The bulk density was calculated using the following formula:

$$r = \frac{W0}{V0}$$

In the above formula, bulk density is denoted by r, sample weight as well as final volume was denoted by Wo & Vo respectively.

Drug content identification[8]

A glass crusher and pestle were used to smash 100 mg of microspheres that had been carefully weighed and suspended in 100 ml of 0.1 N HCl. The solution was filtered after 12 hours, and the drug concentration of the filtrate was measured at 239 and 262 nm using a UV-visible spectrophotometer.

Encapsulation efficiency[9]

The efficiency of encapsulation has been identified by:

$$\text{Efficiency of encapsulation} = \frac{\text{Estimated drug amount}}{\text{Theoretical drug amount}} \text{ X } 100$$

In the above formula, estimated drug content as well as theoretical drug content was denoted by Wo & We respectively.

Characterization of shape and surface:

The Tokyo scanning electron microscope (Joel model JSM 6400) was used to study the various shapes and features of microspheres. Following instantaneous double-sided adhesive tape attachment to the SEM sample stub, the microspheres were coated with a 200 nm thick layer of gold at low pressure (0.001 torr) and fired.

Buoyancy percentage:

The floating microspheres weighed 50 mg individually, and 0.02% w/v tween 80 was present in 100 ml of 0.1 N HCl. After that the mixture was blended at 100 rpm in a magnetic stirrer. After completion of 12 hours, the layer of buoyant microspheres was collected and sifted separately. The sinking particulate layer's particles were split by filtering. Both types of particles underwent desiccation and after that a constant weight was achieved. Both the fraction of microspheres and buoyancy were calculated using the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Percentage Buoyancy} = \frac{\text{Floating microspheres weight (Wf)}}{\text{Settled microsphere weight (Ws)}} \text{ X } 100$$

Floating microspheres weight has been denoted by Wf and Settled microspheres weight has been denoted by Ws

Studies on *in-vitro* dissolution[10]

The USP XXIII equipment (Basket technique) was used to conduct dissolving examinations on all of the formulations. The tests were conducted for 12 hours at 37 + 0.5°C and 50 rpm. For each test, a sample of microspheres weighing 32 mg of candesartan and 40 mg of simvastatin was employed. To keep the sink condition, an aliquot of the sample was periodically withdrawn at sufficient intervals and the quantities were replenished with new dissolution media. At 239 and 262 nm, the sample was spectro-photometrically analysed, and the release was computed using the previously proposed Simultaneous Equation approach.

3. Results

Table 5: Information for the percentage yield of candesartan and simvastatin's floating microsphere formulations

Formulation Code	% Yield of Candesartan	Formulation Code	% Yield of Simvastatin
C1	65.32	S1	56.32
C2	91.82	S2	72.14
C3	62.06	S3	65.24
C4	87	S4	68

			.65
C5	98.32	S5	78.65
C6	80	S6	57.54
C7	76.91	S7	73.23
C8	47.1	S8	61.12

Table 6: The arithmetic mean size analysis of candesartan and simvastatin's microspheres

Formulation Code	Particle Size	Formulation Code	Particle Size
C1	81.91	S1	49.94
C2	83.77	S2	79.44
C	7	S	6

3	2.25	3	5.39
C4	78.58	S4	74.58
C5	105.28	S5	93.1
C6	71.12	S6	54.6
C7	100.02	S7	89.03
C8	65.66	S8	61.73

Table 7: Candesartan percent entrapment efficiency data for floating microspheres

Formulation Code	Drug Content (Theoretical) %	Drug Content (Practical) %	Entrapment Efficiency %
C	30.3	21.1	69

1			.63
C2	26.32	23.65	89.85
C3	30.3	19.54	64.48
C4	26.31	22.87	86.92
C5	25	23.27	93.08
C6	27.78	22.60	81.35
C7	28.57	21.13	73.95
C8	32.26	18.83	58.36

Table 8: Information on the percent entrapment efficiency of simvastatin floating microspheres

Formulation Code	Drug Content (Theoretical) %	Drug Content (Practical) %	Entrapment Efficiency %
S1	32.25	17.69	54.85
S2	26.31	19.89	75.

			59
S3	28.57	17.99	62.96
S4	27.77	19.4	69.85
S5	25	20.91	83.64
S6	30.30	17.8	58.74
S7	26.31	20.61	78.33
S8	30.30	18.61	61.41

Table 9: Angle of repose: Candesartan and Simvastatin floating microspheres formulations

Formulation Code	Angle of Repose tan-1(h/r) Mean ± S.D (n=3)	Formulation Code	Angle of Repose tan-1(h/r) Mean ± S.D (n=3)
C1	22° 53' ± 2.258	S1	21° 18' ± 1.801
C2	23° 25' ± 0.989	S2	24° 11' ± 0.958

C 3	25° 20' ± 1.572	S 3	23° 19' ± 1.878
C 4	24° 10' ± 2.469	S 4	22° 13' ± 2.258
C 5	25° 11' ± 1.878	S 5	22° 03' ± 2.258
C 6	24° 22' ± 1.305	S 6	24° 19' ± 2.469
C 7	22° 12' ± 1.801	S 7	21° 12' ± 1.305
C 8	26° 21' ± 0.958	S 8	25° 18' ± 1.572

Table 10: Information for the bulk density of candesartan and simvastatin's floating microsphere formulations

Formulation Code	Bulk Density (gm/cm3 ± SD)	Formulation Code	Bulk Density (gm/cm3 ± SD)
C 1	0.531 ± 0.008	S 1	0.631 ± 0.016
C 2	0.620 ± 0.029	S 2	0.520 ± 0.023
C 3	0.572 ±	S 3	0.672 ± 0.018

	0.016		
C4	0.595 ± 0.027	S4	0.545 ± 0.006
C5	0.501 ± 0.013	S5	0.541 ± 0.019
C6	0.561 ± 0.009	S6	0.565 ± 0.014
C7	0.501 ± 0.015	S7	0.522 ± 0.016
C8	0.551 ± 0.009	S8	0.514 ± 0.008

Table 11: Information on the percentage drug content of simvastatin and candesartan's floating microsphere formulations

Formulation Code	% Drug Content (mean % ±SD)	Formulation Code	% Drug Content (mean % ±SD)
C1	21.10 ± 0.045	S1	17.69± 1.025
C	23.65	S	19.89±

2	± 0.050	2	0.645
C 3	19.54 ± 1.406	S 3	17.99± 0.871
C 4	22.87 ± 0.040	S 4	19.4± 0.045
C 5	23.27 ± 0.050	S 5	20.91± 1.241
C 6	22.60 ± 0.540	S 6	17.8±0 .033
C 7	21.13 ± 0.04	S 7	20.61± 0.265
C 8	18.83 ± 0.060	S 8	18.61± 1.045

Table 12: Candesartan and Simvastatin data for percent buoyancy of floating microspheres

Formulation Code	**% Buoyancy of Candesartan Microspheres**	**Formulation Code**	**% Buoyancy of Simvastatin Microspheres**
C 1	72.62±2.55	S 1	78.65±4.87
C 2	81.35±2.06	S 2	85.47±2.51
C 3	62.57±2.67	S 3	68.66±2.63
C 4	76.07±3.46	S 4	80.63±3.21
C	84.5	S	89.9

5	8±1.53	5	8±2.35
C6	74.24±4.19	S6	79.28±3.54
C7	69.95±1.99	S7	74.71±2.38
C8	66.72±4.32	S8	71.29±4.58

Table 13: Candesartan and Simvastatin floating microsphere optimised formula:

DRUG	CONC.EC(mg)	CONC.HPMC(mg)	CONC.CHITOSAN(mg)	Predicted%yield	Predicted%EE	PredictedParticleSize
Candesartan	875	250	150	76.06	77.2	82.32
Simva	497	100	100	71.76	75.51	79.02

statin						

Table 14: Percentage bias between the observed and predicted values for Candesartan and Simvastatin floating microspheres prepared under predicted optimum conditions

Response variable	**Candesartan**			**Simvastatin**		
	%Yield	**%EE**	**ParticleSize**	**%Yield**	**%EE**	**Particle Size**
Predicted values	76.06	77.2	82.32	71.76	75.51	79.02
observed va	74.23	75.67	81.36	69.92	73.37	77.39

lues						
% Bias	2.4	1.9	1.1	2.5	2.9	2

*** Bias was calculated as (predicted value−observed value) /predicted value×100%**

IN-VITRO DISSOLUTION STUDIES:

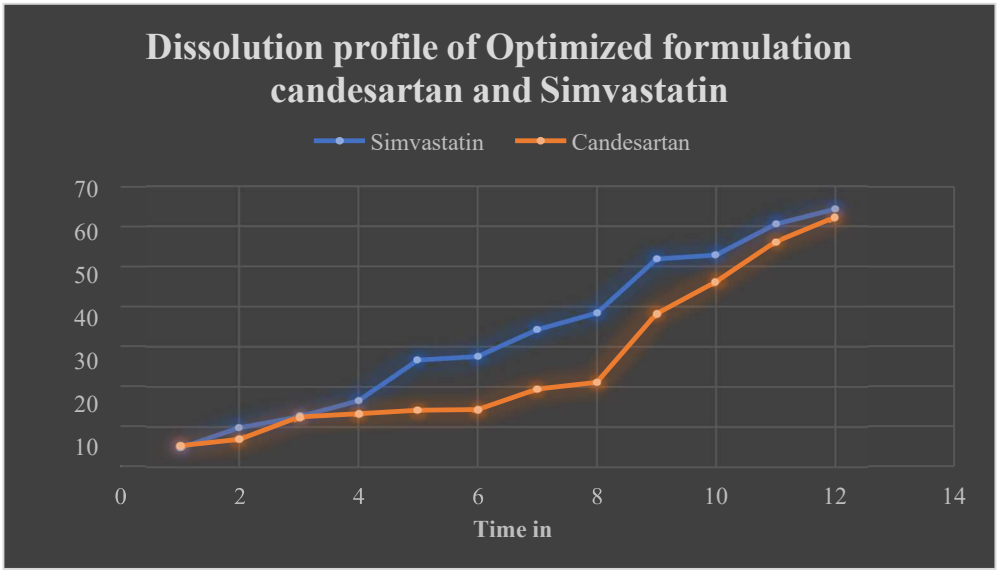

Fig 1: Simvastatin and Candesartan formulation dissolution profile

Table 15: Dissolution profile of optimized formulation of Candesartan & Simvastatin floating microsphere

Sl. No.	Time in Hour	Abs at 239nm (A1)	Abs at 262nm (A2)	Conc of (x) (µg)	Conc. of (y) (µg)	Conc. of (x) (mg)	Conc. of (y) (mg)	Conc. of (x) in 900ml	Conc. of (y) in 900ml	Cumulative Conc. of (	Cumulative Conc. of (	% DR of (X)	% DR of (Y)

										X)	y)		
1	1	0.3299	0.3336	2.113	1.811	0.00021	0.00018	1.9117	1.6299	1.9117	1.6299	4.7922	5.09
2	2	0.5466	0.5552	4.4	2.39	0.00044	0.00023	3.9644	2.1522	3.9667	2.1544	9.91	6.73
3	3	0.8255	0.8411	5.58	4.38	0.00055	0.00043	5.02	3.9445	5.0355	3.9449	12.58	12.34
4	4	0.9811	0.9955	7.36	4.65	0.00073	0.00046	6.63	4.1888	6.642	4.1966	16.6	13.11
5	5	1.3244	1.3311	11.84	4.96	0.01118	0.00049	10.66	4.46	10.68	4.4777	26.7	13.99
6	6	1.3688	1.3755	12.27	5.09	0.01222	0.0005	10.98	4.5	11.01	4.5117	27.52	14.11
7	7	1.755	1.762	15.23	6.86	0.01552	0.00068	13.7	6.1744	13.75	6.19	34.37	19.36
8	8	1.9333	1.9455	17.02	7.43	0.017	0.007	15.31	6.6887	15.37	6.71	38.44	20.98

							4						
9	9	2.872	2.912	21.87	13.51	0.0218	0.0135	19.68	12.15	20.75	12.19	51.89	38.11
10	10	3.245	3.3	23.19	16.35	0.0231	0.0163	20.87	14.71	21.16	14.76	52.91	46.14
11	11	3.85	3.92	26.79	19.93	0.0267	0.0199	24.11	17.93	24.23	17.99	60.57	56.21
12	12	4.041	4.258	28.45	22.08	0.0284	0.022	25.6	19.87	25.74	19.95	64.35	62.34

Concentration of Simvastatin (x) can be calculated by the below formulae:

$$X = \frac{A\,2\,ay\,1 - A\,1\,ay\,2}{ax\,2\,ay\,1 - ax\,1\,ay\,2}$$

Concentration of Candesartan (y) can be calculated by using below formulae:

$$Y = \frac{A\,1\,ax\,2 - A\,2\,ax\,1}{ax\,2\,ay\,1 - ax\,1\,ay\,2}$$

4. Conclusion:

One of the most fatal illnesses in the world is cardiovascular disease. Heart failure, angina pectoris, and hypertension are increasingly prevalent and need ongoing care. The use of drugs to treat heart disease has changed significantly in recent years. The medication candesartan is a member of the angiotensin II receptor blocker class. Candesartan may prevent myocardial infarction, heart failure, hypertension, and diabetic nephropathy. Candesartan, a synthetic angiotensin II receptor antagonist made from benzimidazole, is a prodrug with antihypertensive properties. Candesartan causes vasodilation by blocking angiotensin II-mediated vasoconstriction. Additionally, candesartan and angiotensin II have been vying for the binding of vascular smooth muscle's angiotensin II receptor subtype 1 (AT1). The medication simvastatin belongs to the pharmacological family of HMG-CoA reductase inhibitors. Simvastatin reduces low density lipoprotein levels while increasing high density lipoprotein levels. It lowers the chance of cardiac issues including heart attacks and strokes, among others. To achieve the optimal therapeutic drug level over an extended period of time, a controlled release system in the form of a floating microsphere was created using commonly available and

physiologically safe excipients, simple processes, and reproducible approaches. To extend their half-life in the stomach, Simvastatin and Candesartan are encapsulated in floating microspheres. Using the emulsion solvent evaporation technique with different quantities of ethyl cellulose, HPMC, and chitosan, floating microspheres carrying simvastatin and candesartan were produced. Several preformulation tests were conducted to verify the medicine's physicochemical characteristics, pharmacopoeial needs, and purity. Using varying concentrations of distinct polymers, eight formulations of Simvastatin and Candesartan were created. For each formulation, three batches were made in order to evaluate repeatability with regard to percentage yield, entrapment efficiency, particle size, percentage buoyancy, and percentage drug release. The desirability function was analysed using Design-Expert software to determine the best formulation. The optimal formulation was found using the given criteria of minimum particle size, maximum entrapment effectiveness, and maximum yield. To verify the precision of the optimisation process, a fresh batch of Candesartan & Simvastatin microspheres was created using the anticipated quantities of formulation factors. Candesartan and simvastatin's optimised formulations have a percent bias of 2.4, 1.9, 1.1 for yield, %EE, and particle size, and 2.5, 2.9, 2 for particle size. Simvastatin and candesartan microsphere formulations that were optimised demonstrated the best possible microsphere properties.

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