FORMULATION, CHARACTERIZATION AND EVALUATION OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEM FOR THE TREATMENT OF HYPERTENSION

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Abstract

In this present approach we have created candesartan and simvastatin gastro-retentive medication delivery system for the efficient control of hypertension. A prodrug having antihypertensive action, candesartan is a synthetic angiotensin II receptor antagonist produced from benzimidazole. The HMG-CoA reductase inhibitor pharmacological class includes the simvastatin drug. This is used to decrease triglycerides and bad cholesterol in the blood, such as low-density lipoprotein (LDL). A controlled release device in the form of floating microspheres was created to obtain the ideal therapeutic medication level over an extended period of time. By employing various concentrations of ethyl cellulose, HPMC, and chitosan and using the emulsion solvent evaporation method, floating microspheres containing candesartan and simvastatin were created. Three batches were prepared for every formulation for the purpose of assessing reproducibility in respect of % yield, entrapment efficiency, particle size, % buoyancy and % drug release. For candesartan and simvastatin, the average particle size was determined to be between 65.66 and 105.28 m and 49.94 and 93.1 µm, respectively. Percent drug loading efficiency of microspheres was found in the range of 58.36 to 93.08% for candesartan & 54.85 to 83.64 % for simvastatin. For candesartan and simvastatin, the percentage yield of microspheres for all formulations ranged from 43.68% to 98.32% and 56.32% to 78.65%, respectively. Optimized microsphere of candesartan and simvastatin showed 80.63 and 89.98 % buoyancy. Optimized formulation of candesartan and Simvastatin showed sustained release of drug and release 62.34 % of drug till 12 th hour where as simvastatin microsphere showed 64.35 % release after 12 th hour.

Keywords: Hypertension, Candesartan, Simvastatin, Floating Microspheres.

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1. INTRODUCTION

Oral drug delivery is the most prevalent administration approach of all those that have been researched for systemic medication delivery. The least complicated and most widely used mode of pharmaceutical administration is oral. All controlled release approaches are only useful if they can stay near to the absorption site. The stomach can hold onto the controlled release gastroretentive drug delivery mechanism. By constantly releasing the drug before to the "absorption window" for a prolonged period of time, they can help to maximise the oral controlled delivery of drugs with a "absorption window," ensuring perfect bioavailability[1]. Both when one is eaten and when one is fasting, the stomach empties. However, the two states' motility patterns are different from one another. Controlled release dose forms given orally are principally affected by two issues, according to gastric emptying studies: a short stomach residency time and an erratic high gastric emptying rate[2]. The drug candesartan is an angiotensin II receptor blocker. It is primarily used to treat myocardial infarction, hypertension, heart failure, and diabetic nephropathy. A prodrug having antihypertensive action, candesartan is a synthetic angiotensin II receptor antagonist produced from benzimidazole. Candesartan inhibits angiotensin II-mediated vasoconstriction and induces vasodilation by specifically competing with angiotensin II for the binding of the angiotensin II receptor subtype 1 (AT1) in vascular smooth muscle. The HMG-CoA reductase inhibitor pharmacological class includes the simvastatin drug. This is utilised to raise levels of good cholesterol like high density lipoprotein (HDL) and decrease levels of bad cholesterol like low-density lipoprotein (LDL), as well as triglycerides. It is used to reduce the risk of heart problems such heart attack, stroke, and others. The goal of the current study was to create a gastro-retentive candesartan and simvastatin drug delivery system for the efficient management of hypertension in order to achieve the ideal therapeutic drugs level over an extended period of time. According to previously published literature, the following list of medication categories includes uses of the gastroretentive drug delivery system (GRDDS): 5-fluorouracil and antacids are examples of medications with local action in the stomach. Captopril is an example of a drug unstable in the lower portion of the GIT. Propranolol, metoprolol, and diazepam are examples of pharmaceuticals insoluble in intestinal fluids (acid soluble basic drugs) [3]

Present study was an attempt to develop and evaluate floating microsphere of Candesartan and Simvastatin. Different concentrations of ethyl cellulose, hydroxy propyl methyl cellulose, and chitosan were utilised in the emulsion solvent evaporation process to create floating microspheres containing candesartan and simvastatin.

2. EXPERIMENTAL

Material

Candesartan and simvastatin were obtained from Khandelwal Laboratory Pvt. Ltd. Mumbai as a gift sample. The sample of Candesartan and simvastatin was analyzed for physical appearance and compare with the standard. Physical appearance of the received Candesartan and simvastatin sample was complying with IP. EC, HPMC and Chitosan were procured from the college and chemicals used were of reagent grade.

Methods

Methodology for Emulsion Solvent Evaporation

The polymer (Ethyl Cellulose & Hydroxypropyl Methyl Cellulose) was accurately weighed and then dissolved in 20 ml of acetone. The aforesaid polymer phase was then mixed for two hours while weighed amounts of Candesartan or Simvastatin (drugs) and chitosan (previously passed via sieve #150) were distributed throughout. Then, while being continuously stirred at 800 rpm with a magnetic stirrer, 100 ml of liquid paraffin containing 1.0 w/v of Span 80 was added. To guarantee that all of the acetone was completely evaporated, stirring was continued for two hours. The microspheres were then filtered through Whatmann filter paper No. 44 to remove the liquid paraffin, rinsed three times with 50 cc of petroleum ether, and allowed to air dry for 12 hours. The process for creating microsphere formulations was the same for all of them. The Tables 1 to 4 listed the precise ingredients of several formulations created using 23 factorial designs.

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
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	Heigh level
Ethyl cellulose	375	500
HPMC	100	150
Chitosan	50	100

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

Formulation Code	Simvastatin	Ethyl cellulose	HPMC	Chitosan
S1	250	375	100	50
S2	250	500	100	100
S3	250	375	150	100
S4	250	500	100	50
S5	250	500	150	100
S6	250	375	100	100
S7	250	500	150	50
S8	250	375	150	50

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.

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

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]

Loose powders consisting of some fractional force which can be identified by the aid of angle of repose. This is the utmost angle that can be created between the powder site's surfaces and the horizontal plane.

Using a funnel, a static approach was used to determine the angle of repose. The funnel was maintained on a tripod stand that was kept horizontal. As the pile grows and reaches the funnel's tip, the sample was poured into the funnel. The pile's diameter was measured. The value of q (Angle of repose) can be identified 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]

Bulk density has been calculated by the use of 3 – tap method. "Powdered mass divided by the bulk volume" is how bulk density is defined. Physical attributes of the product are significantly influenced by the powder's packing parameters. A 10 ml graduated cylinder was filled with weighed amounts of prepared microspheres in accordance with the normal process for determining bulk density, and the initial volume was noted. Three taps later, the final volume was recorded. The following formula was used to compute the bulk density:

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

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]

In a 100 ml of 0.1 N HCl, 100 mg microspheres were suspended which was precisely weighed, crushed in a glass crusher and pestle. After completion of 12 hours the solution was filtered and by the aid of UV –Visible spectrophotometer the filtrate drug content was examined at 239/262 nm.

Encapsulation efficiency[9]

The efficiency of encapsulation has been identified by:

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

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

Characterization of shape and surface:

With the aid of Tokyo scanning electron microscope (Joel model JSM 6400), microspheres different forms as well as characteristics were analysed. The microspheres were shot after being immediately attached to the SEM sample stub using double-sided sticky tape and covered in 200 nm thick gold coating at low pressure (0.001 torr).

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.

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

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
C3	72.25	S3	65.39
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 %
C1	30.3	21.1	69.63
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
C3	25° 20' ± 1.572	S3	23° 19' ± 1.878
C4	24° 10' ± 2.469	S4	22° 13' ± 2.258
C5	25° 11' ± 1.878	S5	22° 03' ± 2.258
C6	24° 22' ± 1.305	S6	24° 19' ± 2.469
C7	22° 12' ± 1.801	S7	21° 12' ± 1.305
C8	26° 21' ± 0.958	S8	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)
C1	0.531 ± 0.008	S1	0.631 ± 0.016
C2	0.620 ± 0.029	S2	0.520 ± 0.023
C3	0.572 ± 0.016	S3	0.672 ± 0.018
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
C2	23.65± 0.050	S2	19.89±0.645
C3	19.54± 1.406	S3	17.99±0.871
C4	22.87± 0.040	S4	19.4± 0.045
C5	23.27± 0.050	S5	20.91±1.241
C6	22.60± 0.540	S6	17.8±0.033
C7	21.13± 0.04	S7	20.61±0.265
C8	18.83± 0.060	S8	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
C1	72.62±2.55	S1	78.65±4.87
C2	81.35±2.06	S2	85.47±2.51
C3	62.57±2.67	S3	68.66±2.63
C4	76.07±3.46	S4	80.63±3.21
C5	84.58±1.53	S5	89.98±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	Predicted Particle Size
Candesartan	875	250	150	76.06	77.2	82.32
Simvastatin	497	100	100	71.76	75.51	79.02

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	Particle Size	% Yield	% EE	Particle Size
Predicted values	76.06	77.2	82.32	71.76	75.51	79.02
observed values	74.23	75.67	81.36	69.92	73.37	77.39
% 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:

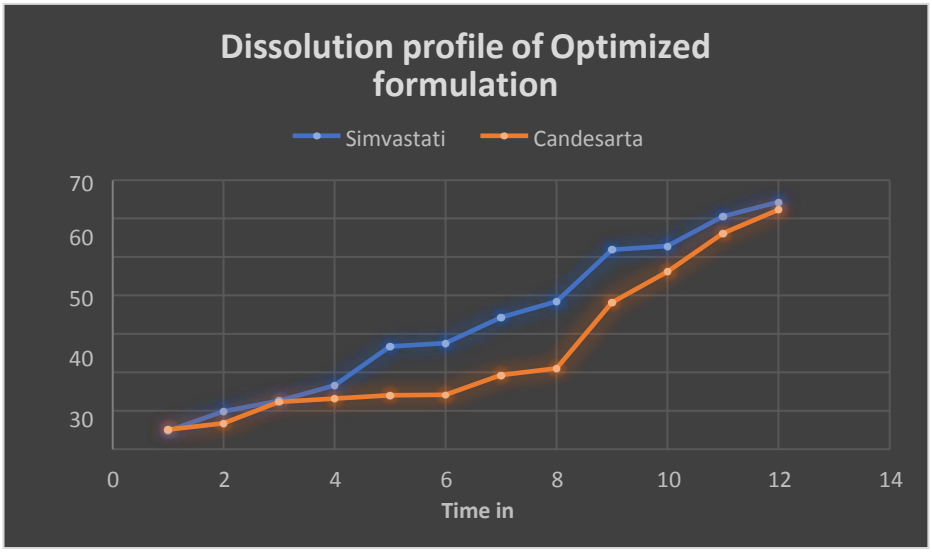

Fig 1: Simvastatin and Candesartan formulation dissolution profile

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 900 ml	Conc. of (y) in 900 ml	Cumulative Conc. of (X)	Cumulative Conc. of (y)	% DR of (X)	% DR of(Y)
1	1	0.329	0.336	2.13	1.81	0.0021	0.0018	1.917	1.629	1.917	1.629	4.792	5.09
2	2	0.546	0.552	4.4	2.39	0.0044	0.0023	3.964	2.152	3.967	2.154	9.91	6.73
3	3	0.825	0.841	5.58	4.38	0.0055	0.0043	5.02	3.945	5.035	3.949	12.58	12.34
4	4	0.981	0.995	7.36	4.65	0.0073	0.0046	6.63	4.188	6.642	4.196	16.6	13.11
5	5	1.324	1.331	11.84	4.96	0.0118	0.0049	10.66	4.46	10.68	4.477	26.7	13.99
6	6	1.368	1.375	12.27	5.09	0.0122	0.005	10.98	4.5	11.01	4.517	27.52	14.11
7	7	1.75	1.762	15.23	6.86	0.0152	0.0068	13.7	6.174	13.75	6.19	34.37	19.36
8	8	1.933	1.945	17.02	7.43	0.017	0.0074	15.31	6.687	15.37	6.71	38.44	20.98
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:

$$X = \frac{A_2 a_{y1} - A_1 a_{y2}}{a_{x2} a_{y1} - a_{x1} a_{y2}}$$

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

$$Y = \frac{A_1 a_{x2} - A_2 a_{x1}}{a_{x2} a_{y1} - a_{x1} a_{y2}}$$

3. CONCLUSION

Cardiovascular diseases are one of the world's deadly diseases. Hypertension, angina pectoris and cardiac failure are more common and require constant monitoring. Drug therapy of heart disease has undergone a great deal of changes in recent times. Candesartan drug belong to the class of angiotensin II receptor blocker. Heart failure, hypertension, myocardial infarction and diabetic nephropathy can be prevented by the use of candesartan. A prodrug having antihypertensive action, candesartan is a synthetic angiotensin II receptor antagonist produced from benzimidazole. Candesartan inhibits angiotensin II-mediated vasoconstriction as a result it induces vasodilation. Further candesartan has been competing with angiotensin II for the binding of the angiotensin II receptor subtype 1 (AT1) in vascular smooth muscle. The HMG-CoA reductase inhibitor pharmacological class includes the simvastatin drug. Simvastatin promotes the levels of high density lipoprotein by minimizing the levels of low density lipoproteins. It is used to reduce the risk of heart problems such heart attack, stroke, and others. A controlled release system in the shape of floating microsphere was designed employing widely used and physiologically safe excipients as well as straightforward procedures and repeatable methodologies in order to reach the ideal therapeutic drug level over a prolonged period of time. Simvastatin and Candesartan are packaged in

floating microspheres to prolong their duration in the stomach. By employing various concentrations of ethyl cellulose, HPMC, and chitosan and using the emulsion solvent evaporation method, floating microspheres containing candesartan and simvastatin were created. To confirm the purity, pharmacopoeial requirements, and physicochemical properties of the medicine, numerous preformulation experiments were carried out. Eight formulations each of Candesartan & Simvastatin were prepared using different concentration of different polymers. Three batches were prepared for every formulation for the purpose of assessing reproducibility in respect of % yield, entrapment efficiency, particle size, % buoyancy and % drug release. To find the optimal formulation, Design-Expert software was used to analyse the desirability function. The specified parameters of maximum yield, maximum entrapment efficiency, and minimal particle size were used to determine the best formulation. A new batch of Candesartan & Simvastatin microspheres was made with the projected amounts of formulation parameters in order to confirm the accuracy of the optimisation method. Percent bias for optimized formulation of candesartan and simvastatin for % yield, %EE & particle size is 2.4, 1.9,1.1 and 2.5, 2.9, 2 respectively. Optimized formulations of candesartan & Simvastatin microspheres showed maximum possible characteristics of an ideal microsphere.

4. REFERENCES

1. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63:235–59. Review.
2. Chawla G, Gupta P, Bansal AK. In: Jain NK, editor. Progress in controlled and novel drug delivery. 1st ed. New Delhi: CBS; 2001. p. 76–97.
3. Singh BN, Kim KH. Encyclopedia of pharmaceutical technology, drug delivery: oral route. New York: Marcel Dekker; 2001. p. 1253.
4. He P, Davis SS, Illum L. Sustained release chitosan microsphere produced by novel spray drying methods. J Microencapsul 1999; 16: 343–355.
5. Subramanyam CVS; Physical Pharmaceutics, 2nd Edition, pp 192.
6. Alferd Martin, Physical Pharmacy, 4th Edition, pp 427-429
7. CVS Subramanyam; Physical Pharmaceutics, 2nd Edition, pp 217.
8. Liebermann, lachmann:" Theory and Practice of Industrial Pharmacy" pg.no:425-436.
9. Arul B, Kothai R, Sangameswaran B, Jayakar B, Formulation and evaluation of mucoadhesive microspheres containing isoniazid, Ind.J.Pharm.Sci., 2003, 65 (6): 640-642.
10. Paulo Costa, Jose Manuel Sousa Lobo, Modeling and comparison of dissolution profiles, Eur.J.Pharm., 2001; 13: 123-133.