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DESIGN AND EVALUATION OF DIVERSE MICROSPHERE TYPES UTILIZING OLMESARTAN AND VALSARTAN FOR HYPERTENSION MANAGEMENT

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ABSTRACT

The objective of the current study is to construct and evaluate, in vitro several types of microspheres containing olmesartan and valsartan to improve bioavailability and extend gastric residence duration, hence enhancing patient compliance through reduced dose frequency. All the formulations are prepared by Ionotropic gelation method using Sodium alginate and various natural polymers. We made an attempt to prepare normal, floating and mucoadhesive microspheres using Gelation technique with natural hydrophilic and hydrophobic polymers. All the formulations exhibited good Preformulation properties and the results indicate that all are within the prescribed limits. From Olmesartan and Valsartan Floating microspheres formulations F14 was selected as optimized formulation. *Invitro* release study of formulation F14 showed 96% release after 12h in a controlled manner. Various kinetic models suggest that the drug release from floating microspheres was anomalous Non Fickian diffusion. FT-IR analyses confirmed the absence of drug-polymer interaction. The SEM of microspheres shows a hollow spherical structure with a rough surface morphology. The shell of microspheres also showed some porous structure it may be due to release of carbon dioxide. Optimized formulation F14 was selected for stability studies.

KEYWORDS: Olmesartan, Valsartan, drug-polymer.

INTRODUCTION

A controlled release drug delivery system is usually designed to deliver the drug at rate-controlled release properties can also be imparted to oral dosage formulations through the formation of resin-drug complexes coated with polymers (Irwin WJR Mac Hale and Watts P J 1996). As multi articulate drug delivery lead to wide and uniform distribution throughout GIT, a localized high concentration at a specific point may be avoided (Sam MT et al., 2008).

CONVENTIONAL DRUG THERAPY

Conventional drug therapy is the method or process of administering pharmaceutical compound to achieve a therapeutic effect in humans or animals. For the treatment of human diseases, nasal and pulmonary routes of drug delivery are gaining increasing importance. These routes provide promising alternatives to parenteral drug delivery particularly for peptide and protein therapeutics (Bhati Let al., 2012).

CONTROLLED RELEASE

Controlled drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. While these advantages can be significant, the potential disadvantages cannot be ignored like the possible toxicity or non-biocompatibility of the materials used, undesirable by-products of degradation, any surgery required to implant or remove the system, the chance of patient discomfort from the delivery device, and the higher cost of controlled-release systems compared with traditional pharmaceutical formulations (Debjit et al., 2012).

GASTRORETENTIVE DRUG DELIVERY SYSTEM

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. One requisite for successful performance of oral controlled drug delivery system is that drug should have good absorption throughout the gastrointestinal tract, preferably by passive diffusion. These considerations have led to the development of a unique oral controlled release dosage form with Gastro retentive properties.

TYPES OF GRDS

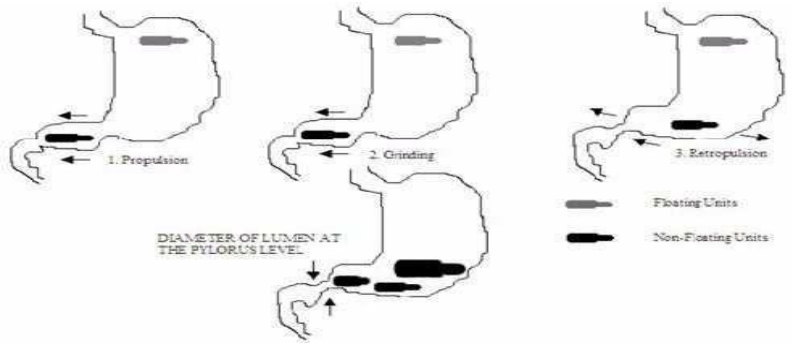
Expandable systems

Bio/Muco-adhesivesystems

FDDS

Combination of floating, mucoadhesion and swellable systems

A preferred formulation comprises a mixture of a high or medium viscosity (Hydroxy propyl methyl cellulose) and a high or medium viscosity (Hydroxy ethyl cellulose). It also includes a salt being capable of releasing gaseous carbon dioxide alkaline metal carbonates can be used, an acid may be added, such as citric acid and maleic acid.



ADVANTAGES OF FLOATING DRUG DELIVERY SYSTEM

- The gastro-retentive systems are advantageous for drugs absorbed through the stomach.
- Irritation on the stomach wall caused by acidic substances like aspirin can be avoided by using floating drug delivery system.
- Administration of floating dosage forms will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid and would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from floating dosage forms if it remains in the solution form even at the alkaline pH of the intestine.
- The gastro-retentive systems are advantageous for drugs meant for local action in the stomach.
- When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response (Tejvir Kaur et al., 2011).

DISADVANTAGES O FFLOATING DRUG DELIVERY SYSTEM

- Floating system is not feasible for those drugs that have solubility or stability problem in G.I. tract.
- These systems require a high level of fluid in the stomach for drug delivery to float and work efficiently.
- The drugs that are significantly absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, are only desirable candidate.
- Some drugs present in the floating system causes irritation to gastric mucosa (Tejvir Kaur et al., 2011).

APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

- **Site-Specific Drug Delivery:** These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine.
- **Absorption Enhancement:** Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, there by maximizing their absorption.
- **Sustained Drug Delivery**: These systems have a bulk density of <1 asa result of which they can float on the gastric contents. These systems are relatively large in size and passing from the pyloric opening is prohibited (Tejvir Kaur et al., 2011).

MUCOADHESIVEDRUGDELIVERYSYSTEM

Mucoadhesive drug delivery systems are the systems which utilize the property of mucoadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time. Bioadhesion is an integral phenomenon in which two materials, at least one of which is biological are held together by means of interfacial forces. In the case of polymer attached to mucin layer of a mucosal tissue, the term mucoadhesion is used.

AIM AND OBJECTIVE

Aim

The aim of the research work is to Design and evaluation of diverse microsphere types utilizing olmesartan and valsartan for hypertension management.

Objectives

The main objective of present work is to design, In vitro and In vivo evaluation of different types of microspheres of olmesartan & valsartan to enhance its bioavailability and prolonged residence time in stomach. Patient compliance by reducing dosing frequency.

Scope

At present, the most common form of delivery of drugs is the oral route. While it has the notable advantage of easy administration, site specific drug delivery and it also has significant drawbacks namely poor bioavailability due to hepatic metabolism(first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient.

To overcome these difficulties there is a need for the development of new drug delivery system that is gastro retentive drug delivery system, which has advantages like reduce dosing frequency optimizing concentration of drug in the targeted organ, improved bioavailability.

MATERIALS AND METHODS FOR OLMESARTAN MICROSPHERES

Table 1: List of materials.

S. No.	Materials	Category	Manufacture
1	Olmesartan	Anti-hypertension	Arbro Pharmaceuticals, New Delhi
2	Valsartan	Anti-hypertension	Hetero Drugs Ltd, HYD
3	Sodium alginate	Microsphere core forming agent	Pruthvi Chemicals ,Mumbai
4	HPMCK15M	Rate controlling agent	S. Kant. Healthcareltd Vapi, Gujarat.
5	Calcium chloride	Gel hardening agent	Pruthvi Chemicals, Mumbai
6	Ethyl cellulose	Rate controlling agent	S.Kant, Healthcareltd Vapi, Gujarat.
7	Chitosan	Mucoadhesive agent	S.Kant, Healthcareltd Vapi, Gujarat.
8	CarbopolP934	Mucoadhesive agent	S.Kant, Healthcareltd Vapi, Gujarat.
9	Xanthan Gum	GellingAgent	Choice Organochem Ltd, Mumbai.
10	Sodium bicarbonate	Gas generating agent	Rubicon Labs, Mumbai.
11	Olibanum Gum	Gelling Agent	Rubicon Labs, Mumbai.

PREPARATION OF STANDARD GRAPH OF OLMESARTAN

Preparation of the standard stock solution

A standard drug solution of OLM was prepared by dissolving 10mg of OLM in 10 ml methanol, and this was transferred into a 100 ml volumetric flask. The volume was brought up to the mark with methanol to obtain a stock

solution of OLM with100 µg/ml final concentration. The solution was further sonicated for 15 minutes to obtain a clear solution.

Preparation of the calibration curve

Aliquots of 0.2 to 2 ml stock solutions were transferred to a series of 10ml volumetric flasks, with subsequent volume adjustment by methanol up to 10 ml. The solutions were scanned in a double beam UV spectrophotometer. The samples were analyzed for their respective absorbance at 257 λ_{max}. The calibration curve was plotted and the optical characteristics summarized

FORMULATION OF OLMESARTAN MICROSPHERES

The microspheres of sodium alginate were prepared by using ionotropic gelation technique. In this method weighed quantity of Olmesartan and other polymers listed in Table3 was added to 100ml sodium alginate solution and thoroughly mixed at 500 rpm. Resultant solution was extruded drop wise with the help of syringe and needle into 100ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 minutes the obtained microspheres were washed with water and dried at 60 degrees-2hours in a hot air oven and stored in desiccators.

Table 3: Formulation trials for Olmesartan microspheres.

Formulation Code	Olmesartan (mg)	Sodium Alginate	HPMC K 15M (mg)	Ethylcellulose (mg)	Calcium Chloride
S1	40	1.0%	100	-	6%
S2	40	1.25%	150	-	6%
S3	40	1.5%	200	-	6%
S4	40	1.75%	250	-	6%
S5	40	2.0%	300	-	6%
S6	40	2.25%	350	-	6%
S7	40	2.5%	400	-	6%
S8	40	1.0%	-	100	10%
S9	40	1.25%	-	150	10%
S10	40	1.5%	-	200	10%
S11	40	1.75%	-	250	10%
S12	40	2.0%	-	300	10%
S13	40	2.25%	-	350	10%
S14	40	2.5%	-	400	10%

Formulation trials for Valsartan microspheres

Formulation code	Valsartan (mg)	Sodium alginate	Ethylcellulose (mg)	Eudragitrs 100(mg)	Calcium chloride
S1	80	1%	100	-	6%
S2	80	1.25%	200	-	6%
S3	80	1.5%	300	-	6%
S4	80	1.75%	400	-	6%
S5	80	2%	500	-	6%
S6	80	2.5%	600	-	6%
S7	80	3%	700	-	6%
S8	80	1%	-	100	10%
S9	80	1.25%	-	200	10%
S10	80	1.5%	-	300	10%
S11	80	1.75%	-	400	10%
S12	80	2%	-	500	10%
S13	80	2.5%	-	600	10%
S14	80	3%	-	700	10%

INVITRO DRUG RELEASE STUDIES

Release rate of Valsartan from sodium alginate microspheres was carried out using USP type II dissolution apparatus with pH 6.8 buffer of 900ml as dissolution medium. Accurately weighed amount of microspheres from each batch were subjected to dissolution studies in triplicate manner. At appropriate intervals up to 12 h, specific volume of aliquots was withdrawn and analyzed spectro photometrically. The withdrawn volume was replaced with an equivalent volume of fresh dissolution medium to maintain the volume of dissolution medium constant. The sample solution s was analyzed for the concentration of drug by UVspectrophotometer at 250 nm. The amount of drug released was calculated from the calibration curve of the same dissolution medium (Pradeesh T et al., 2005).

KINETICMODELINGOFDRUGRELEASE

In order to understand the kinetics and mechanism of drug release, the result of the in vitro dissolution study of microspheres were fitted with various kinetic equations like Zero order as cumulative percentage drug release Vs. time, first order as log percentage of drug remaining to be released Vs. time, Higuchi's model cumulative percentage drug released Vs. square root of time. r^2 and K values were calculated for the linear curves obtained by regression analysis of the above plots.

To analyze the mechanism of drug release from the microspheres the in vitro dissolution data was fitted to zero order, first order, Higuchi's release model and Korsmeyer – Peppas model.

DRUG EXCIPIENT COMPATIBILITY STUDIES

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method, SEM and Differential Scanning Colorimetry.

STABILITYSTUDIES

The stability study of the optimized formulation was carried out under different conditions according to ICH guidelines. The optimized microspheres were stored in a stability chamber for stability studies (REMI make). Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The microspheres were characterized for the percentage yield, entrapment efficiency & cumulative % drug released during the stability study period.

Formulation trials for Valsartan mucoadhesive microspheres

Formulation code	Valsartan (mg)	Sodium alginate	Hpmc K 100 m (mg)	Eudragitrl 100 (mg)	Olibanumgum (mg)	Guar gum (mg)	Calcium chloride
M1	80	0.5%	50	-	25	-	5%
M2	80	1%	100	-	50	-	5%
M3	80	1.5%	150	-	75	-	5%
M4	80	2%	200	-	100	-	5%
M5	80	2.5%	250	-	125	-	5%
M6	80	3%	300	-	150	-	5%
M7	80	3.5%	350	-	175	-	5%
M8	80	0.5%	-	50	-	25	10%
M9	80	1%	-	100	-	50	10%
M10	80	1.5%	-	150	-	75	10%
M11	80	2%	-	200	-	100	10%
M12	80	2.5%	-	250	-	125	10%
M13	80	3%	-	300	-	150	10%
M14	80	3.5%	-	350	-	175	10%

RESULTS AND DISCUSSION FOR OLMESARTAN MICROSPHERES

Uvspectrum and Calibration Curve of Olmesartan

Uvspectrum of Olmesartan

The UV spectrum of Olmesartan λmaxwas found to be at 257 nm which was in accordance with the previously reported values.

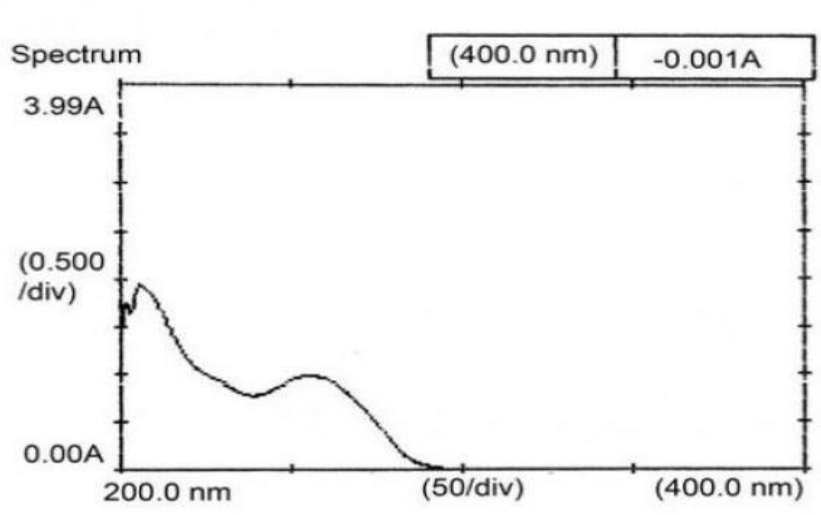


Figure 6.1: UVspectrum of olmesartan.

CALBRATION CURVE OF OLMESARTAN

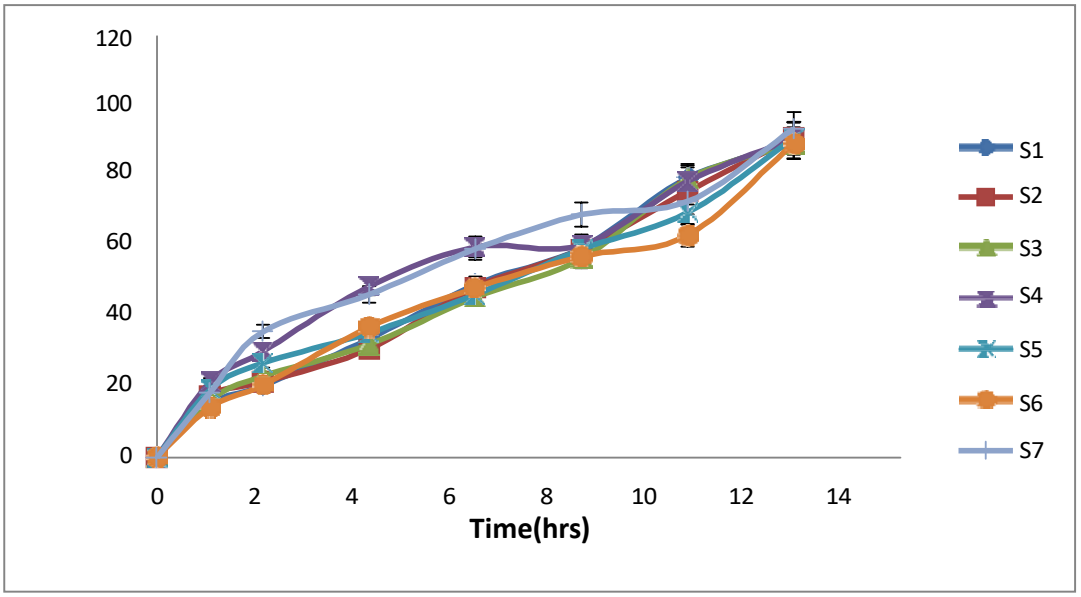
The standard calibration curve of UV absorption vs. concentration of Olmesartan at 257nm showed very good linearity characterized by good coefficient of correlation (R^2= 0.9999) over the concentration range of 0-10 µg/ml. Thus it was found to obey Beer- Lamberts law over this range.

Table 6: Standard Absorbance of Olmesartan.

S.no	Concentration(µg/ml)	Absorbance257nm
1	0	0
2	2	0.096
3	4	0.172
4	6	0.245
5	8	0.324
6	10	0.423
7	12	0.489

Invitro cumulative % drug release of Olmesartan sodium alginate microspheres formulations (S1-S7)

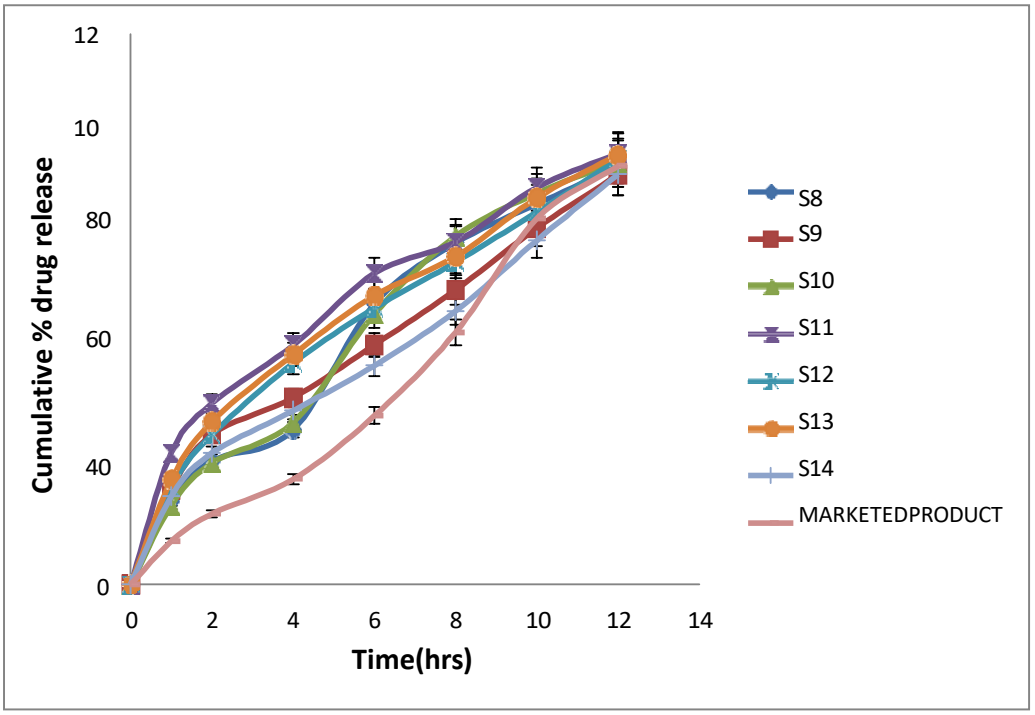
Time(h)	S1	S2	S3	S4	S5	S6	S7
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	15.29±0.95	17.39±0.97	16.45±0.96	21.45±1.02	19.32±0.99	14.23±0.94	18.45±0.98
2	20.45±1.28	21.45±1.30	23.13±1.31	30.29±2.01	26.89±1.34	20.68±1.02	35.90±2.24
4	33.78±2.19	30.87±2.01	32.20±2.10	48.74±2.69	35.47±2.24	37.60±2.28	46.46±2.65
6	49.21±2.75	48.36±2.69	45.74±2.65	59.98±2.96	46.36±2.65	48.29±2.69	59.37±2.96
8	58.74±2.95	59.23±2.96	56.69±2.89	60.47±2.97	59.24±2.96	57.26±2.89	69.18±3.32
10	79.63±3.95	75.78±3.88	79.28±3.95	78.64±3.95	69.74±3.32	63.27±2.98	72.97±3.80
12	89.45±4.98	91.01±5.01	89.57±4.98	90.91±5.01	90.89±5.00	89.46±4.99	93.60±5.03

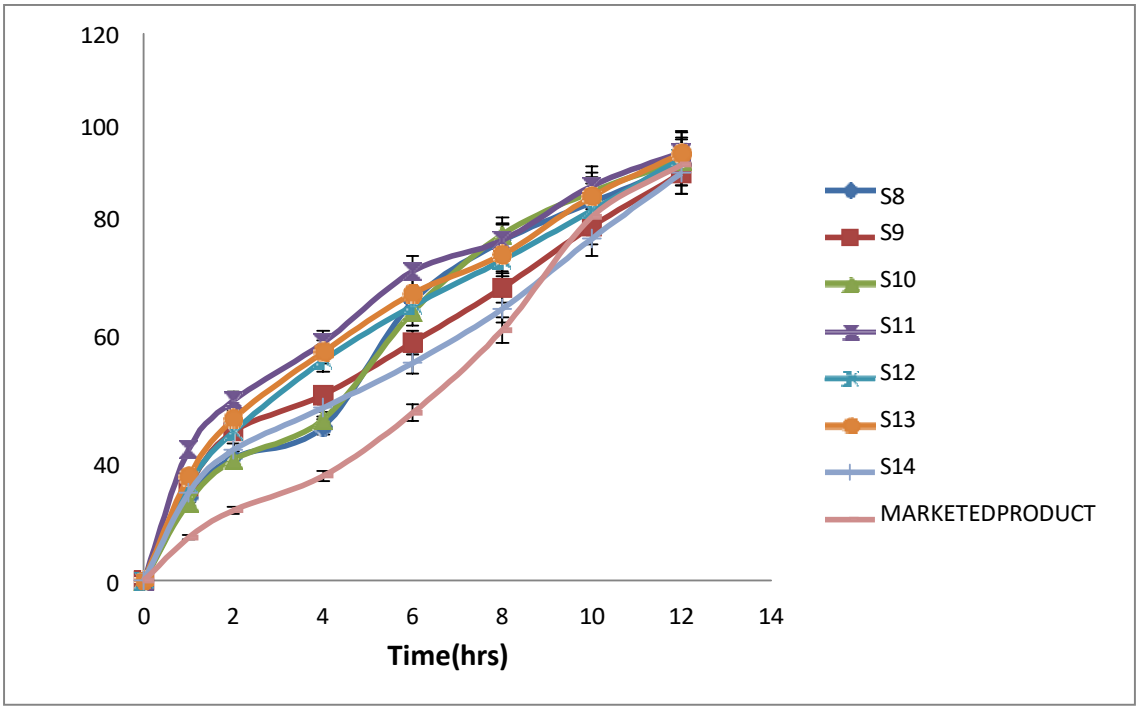


Invitro cumulative % drug release of Olmesartan sodium alginate microspheres formulation (S1-S7)

Invitro cumulative % drug Olmesartan sodium alginate release of microspheres formulation (S8-S11).

Time (h)	S8	S9	S10	S11	S12	S13	S14	Marketedproduct
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	18.06±0.98	20.67±1.30	17.21±0.97	28.67±1.39	21.20±1.05	22.78±1.08	19.20±0.99	9.46±0.78
2	26.97±1.33	32.67±2.23	26.47±1.36	39.45±2.40	32.67±2.23	35.49±2.15	28.67±1.36	15.42±0.95
4	33.69±2.23	40.67±2.45	35.29±2.15	52.16±2.85	48.24±2.40	50.12±2.81	37.89±2.19	22.98±1.30
6	61.23±3.10	52.19±2.85	58.91±2.95	67.84±3.18	60.26±3.10	62.98±3.12	47.23±2.40	36.78±2.18
8	78.47±3.92	64.23±3.15	75.84±3.81	74.67±3.88	70.29±3.79	71.48±3.80	59.60±2.95	54.98±2.89
10	82.98±4.55	77.68±3.84	85.27±4.68	86.98±4.69	81.28±4.68	84.29±4.62	74.99±3.81	79.80±3.90
12	91.20±5.01	89.36±4.99	92.18±5.02	96.98±5.28	92.63±5.02	93.67±5.03	89.41±4.99	91.28±5.00

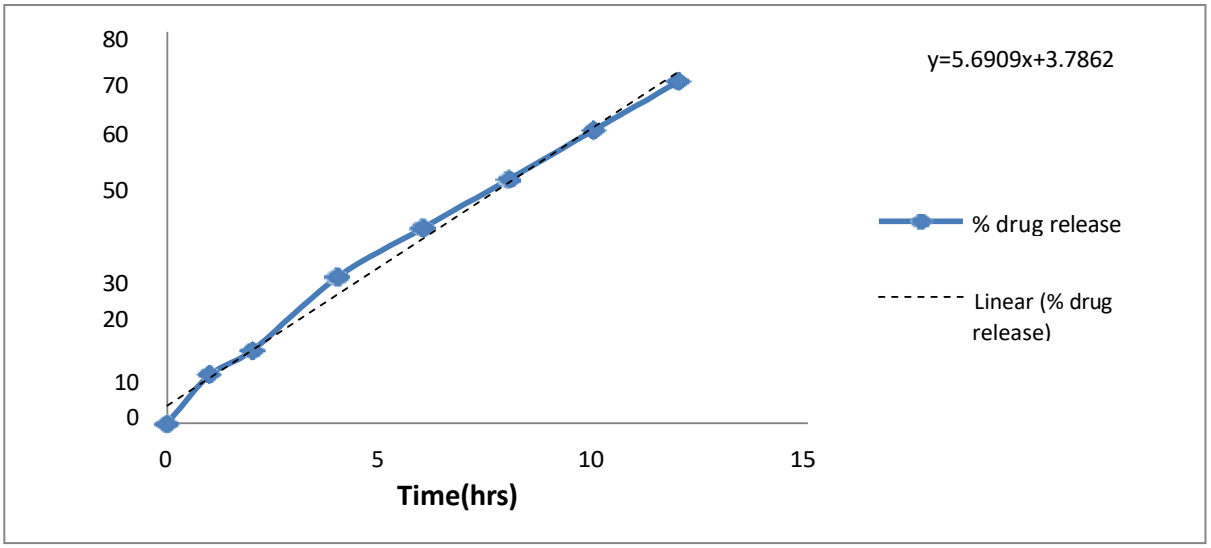


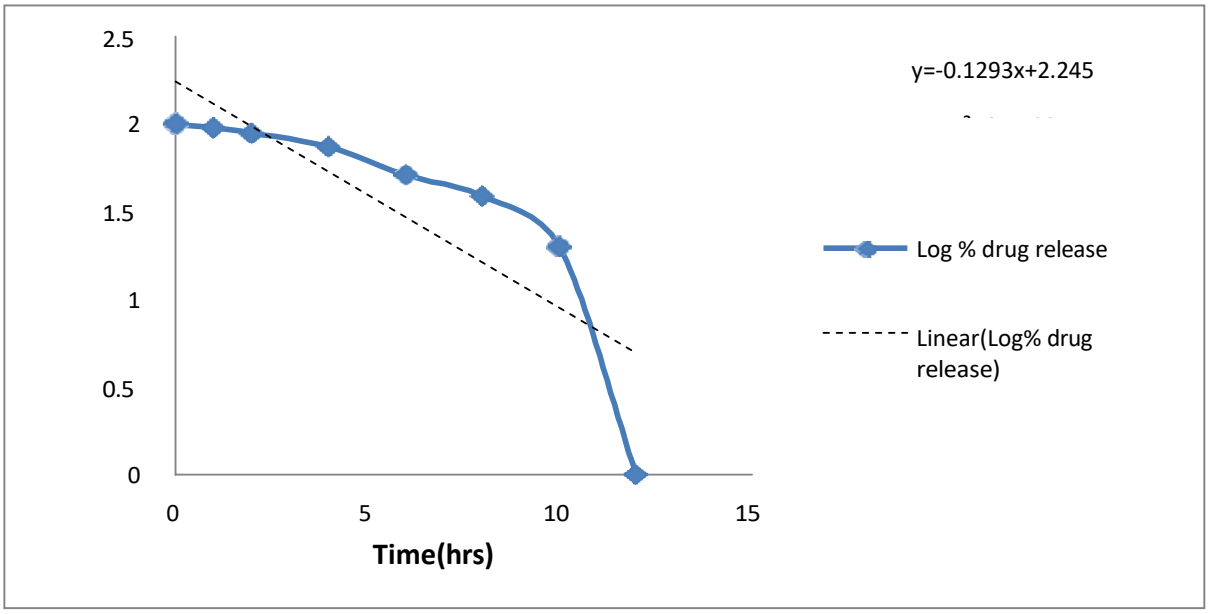


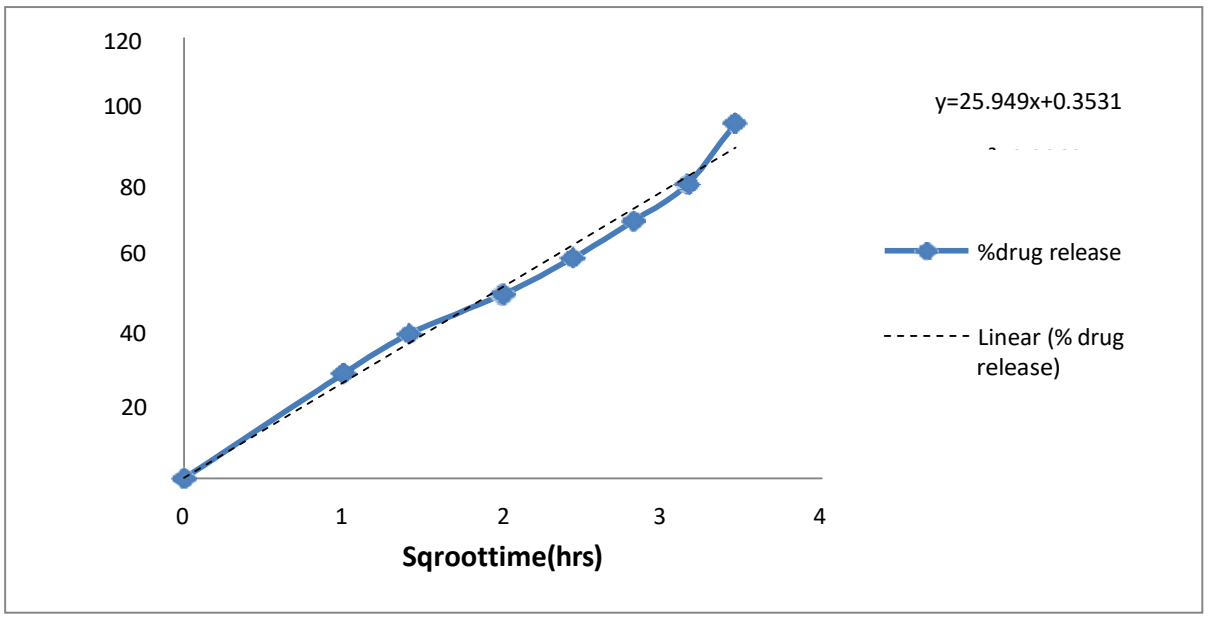
Invitro cumulative % drug Olmesartan sodium alginate release of microspheres formulations (S8-S14)

Release order kinetics of optimized microspheres

Formula Code	Zero Order	First Order	Higuchi	Korsmeyer-Peppas	N value
S1	0.943	0.711	0.958	0.969	0.514
S2	0.972	0.709	0.967	0.958	0.511
S3	0.963	0.705	0.984	0.967	0.492
S4	0.942	0.711	0.967	0.971	0.471
S5	0.956	0.701	0.956	0.967	0.497
S6	0.948	0.712	0.948	0.959	0.512
S7	0.968	0.708	0.957	0.945	0.496
S8	0.971	0.702	0.967	0.939	0.483
S9	0.966	0.701	0.958	0.932	0.516
S10	0.958	0.711	0.945	0.946	0.523
S11	0.991	0.712	0.9863	0.986	0.470
S12	0.968	0.717	0.945	0.939	0.481
S13	0.958	0.720	0.938	0.937	0.485
S14	0.954	0.718	0.926	0.976	0.513
Marketed product	0.957	0.758	0.868	0.922	0.500


80
70
60
50
30
20
10
0
0
5
10
15
Time(hrs)
y=5.6909x+3.7862
% drug release
Linear (% drug release)


2.5
2
1.5
1
0.5
0
0
5
10
15
Time(hrs)
y=-0.1293x+2.245
Log % drug release
Linear(Log% drug release)


120
100
80
60
40
20
0
1
2
3
4
Sqroottime(hrs)
y=25.949x+0.3531
%drug release
Linear (% drug release)

Zero order, first order and Higuchi plot for the optimized formulation of Olmesartan micropsheres S11

Formulation of Mucoadhesive Microspores

Formulation code	Particle size (µm)	Bulk density ($g/cc^{3)}$	Tapped density ($g/cc^{3)}$	Angle of repose	Carr's index (%)
M1	63.26±0.02	0.64±0.02	0.67±0.03	22˚.98±0.01	12.67
M2	62.19±0.01	0.66±0.03	0.69±0.04	24˚.93±0.02	13.81
M3	64.90±0.02	0.68±0.05	0.71±0.01	25˚.65±0.03	11.98
M4	67.90±0.04	0.67±0.04	0.72±0.01	24˚.98±0.02	12.56
M5	64.98±0.02	0.64±0.02	0.69±0.04	25˚.69±0.03	12.90
M6	66.78±0.03	0.65±0.03	0.68±0.04	26˚.67±0.03	13.92
M7	67.68±0.04	0.68±0.04	0.69±0.04	25˚.66±0.03	12.27
M8	65.66±0.03	0.66±0.03	0.71±0.01	24˚.98±0.02	13.32
M9	62.98±0.01	0.67±0.04	0.73±0.02	23˚.45±0.02	14.96
M10	64.66±0.02	0.64±0.02	0.72±0.01	21˚.98±0.01	11.09
M11	61.09±0.01	0.63±0.02	0.70±0.01	24˚.82±0.02	13.18
M12	63.96±0.02	0.61±0.01	0.69±0.04	23˚.67±0.02	12.09
M13	62.98±0.01	0.62±0.01	0.68±0.04	22˚.29±0.01	11.67
M14	60.18±0.01	0.59±0.08	0.66±0.03	20˚.18±0.01	10.90

Formulation trials for Valsartan mucoadhesive microspheres

Formulation code	Valsartan (mg)	Sodiumal ginate	HpmcK100 m(mg)	Eudragitr l100(mg)	Olibanum gum(mg)	Guar gum (mg)	Calciumc hloride
M1	80	0.5%	50	-	25	-	5%
M2	80	1%	100	-	50	-	5%
M3	80	1.5%	150	-	75	-	5%
M4	80	2%	200	-	100	-	5%
M5	80	2.5%	250	-	125	-	5%
M6	80	3%	300	-	150	-	5%
M7	80	3.5%	350	-	175	-	5%
M8	80	0.5%	-	50	-	25	10%
M9	80	1%	-	100	-	50	10%
M10	80	1.5%	-	150	-	75	10%
M11	80	2%	-	200	-	100	10%
M12	80	2.5%	-	250	-	125	10%
M13	80	3%	-	300	-	150	10%
M14	80	3.5%	-	350	-	175	10%

Formulation trials of Valsartan Floating microspheres

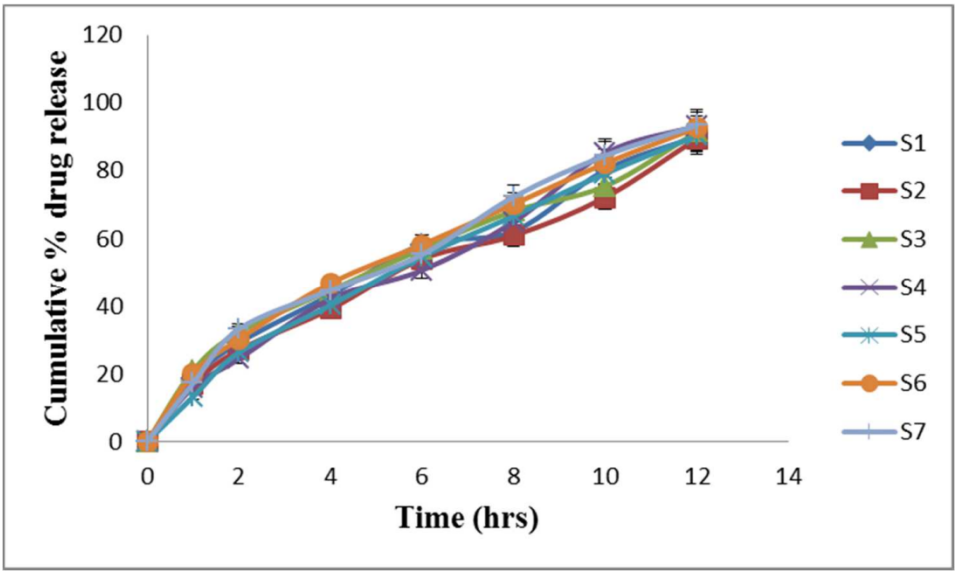
Formulation code	Valsartan (mg)	Sodium alginate	HPMC K4M (mg)	Sodium bi carbonate(mg)	Calcium chloride	Eudragit RS30D (mg)	Guar Gum (mg)
F1	80	2.5%	100	25	2.5%	40	10
F2	80	2.5%	125	50	2.5%	45	15
F3	80	2.5%	150	75	5%	50	20
F4	80	2.5%	175	100	5%	55	25
F5	80	5%	200	125	2.5%	60	30
F6	80	5%	225	150	2.5%	65	35
F7	80	5%	250	175	2.5%	70	40
F8	80	2.5%	100	25	2.5%	40	10
F9	80	2.5%	125	50	2.5%	45	15
F10	80	2.5%	150	75	5%	50	20
F11	80	2.5%	175	100	5%	55	25
F12	80	5%	200	125	2.5%	60	30
F13	80	5%	225	150	2.5%	65	35
F13	80	5%	250	175	2.5%	70	40

IN*VITRO* DRUG RELEASE STUDIES

Invitro cumulative % drug release of Valsartan microspheres

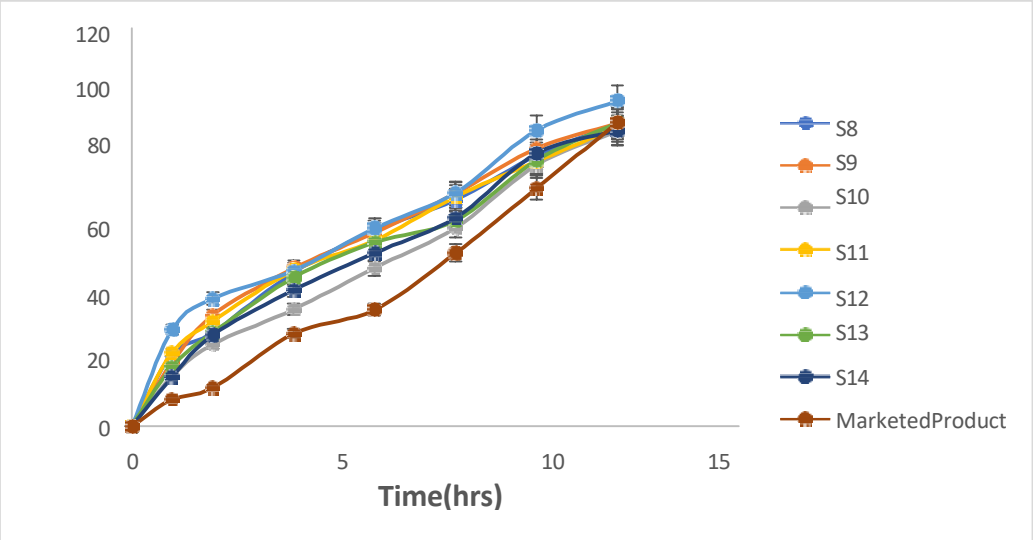
Formulations

Time (h)	S1	S2	S3	S4	S5	S6	S7
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	18.46±0.99	16.86±0.96	20.89±1.30	15.99±0.95	13.18±0.94	19.92±0.99	17.21±0.97
2	29.14±2.08	26.98±1.36	32.18±2.2	24.38±1.35	26.27±1.35	30.18±2.09	33.18±2.02
4	43.24±2.46	39.08±2.15	44.67±2.0	42.11±2.46	40.19±2.15	46.78±2.51	44.67±2.50
6	58.23±2.96	53.99±2.90	56.99±2.89	50.67±2.83	54.66±2.89	58.20±2.96	55.29±2.89
8	62.14±3.09	60.89±3.05	68.11±3.18	64.94±3.15	66.67±3.16	70.18±3.82	72.30±3.82
10	80.18±4.25	72.18±3.82	75.45±3.80	85.18±4.89	79.18±3.93	82.19±4.28	84.46±4.89
12	90.10±5.01	89.45±4.99	91.45±5.02	93.21±5.06	90.34±5.02	92.66±5.04	93.34±5.06



Invitro cumulative % drug release of Valsartan microspheres formulation

Time (h)	S8	S9	S10	S11	S12	S13	S14	Marketed Product
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	21.66±0.94	19.18±0.99	15.18±0.95	22.18±1.32	29.16±1.98	17.89±0.97	14.85±0.93	8.09±0.11
2	28.19±1.89	33.46±2.02	24.66±1.35	31.60±2.09	38.42±2.05	28.14±1.35	27.45±1.35	12.44±1.78
4	46.20±2.49	47.54±2.50	35.18±2.05	46.98±2.50	46.92±2.50	44.76±2.49	40.96±2.46	32.44±2.17
6	58.96±2.99	58.32±2.96	47.67±2.50	55.96±2.89	59.67±2.96	55.37±2.89	52.14±2.81	45.77±2.44
8	68.14±3.58	70.11±3.82	59.80±2.90	69.18±3.19	70.29±3.82	61.98±3.09	62.78±3.10	51.74±3.07
10	81.50±4.05	83.67±4.80	78.66±3.93	79.81±3.93	89.16±4.99	80.14±4.89	82.14±4.90	72.55±3.78
12	90.96±4.89	91.23±5.01	88.98±4.97	90.14±5.01	97.89±5.25	91.45±5.01	89.11±4.44	90.11±5.00



Release order kinetics of optimized microspheres(S12)

STABILITY STUDIES

Optimized formulation S12 was selected for stability studies based on high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences mentioned table.

Stability studies of optimized microspheres

Retest Time for Optimized formulation	Percentage yield	Entrapment efficiency	*In-vitro* drug Release profile (%)
0days	98.92	97.18	97.89
30days	96.19	96.45	96.25
60days	95.34	94.67	95.48
120days	93.23	93.99	94.23
180days	92.84	90.24	93.26

SUMMARY AND CONCULSION FOR OLMESARTAN AND VALSARTAN MICROSPHERES

The oral route has been the most popular and successfully used route for controlled delivery of drugs due to some reasons like convenience, ease of production, ease of administration, and low cost of such systems. A well-designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug.

The aim of the present study is to develop Olmesartan and Valsartan-loaded microspheres by the ionotropic gelation method to obtain an extended retention in the upper gastrointestinal tract (GIT), which may result in increased

absorption and thereby improved bioavailability. The prepared microspheres were evaluated for particle size, shape, percentage yield, incorporation efficiency, and in vitro release study.

NORMAL MICROSPHERES OF OLMESARTAN AND VALSARTAN

Microspheres have potential to deliver drug in a controlled fashion. Microspheres are small spherical particles, with diameters in the micro meter range (1µmto1000 µm). The microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature, and ideally having a particle size less than 200 micrometer. Microsphere have been extensively studied for use as drug delivery systems, where they have been shown to protect sensitive macromolecules from enzymatic and acid degradation, and allow controlled release and tissue targeting of the formulated drug.

Particle size was measured by using optical microscopy. All the formulations S1 to S14 varied from 56.12±0.08µm to 62.20±0.02µm. The bulk densities of all the formulations S1 to S14 were measured and they are ranged from 0.49±0.10g/cc³ to 0.55±0.03g/cc³. The tapped densities of all the formulations S1 to S14 were measured and they are ranged from 0.58±0.09g/cc³ to 0.65±0.03g/cc³. The compressibility index values were found to be in the range of 10.02 to 15.98 %. These findings indicated that all the batches of formulations exhibited good flow properties. Angle of repose of all the formulations was found satisfactory result. The angle of repose of formulation S12 was found to be 20^0. 36±0.01, it is having good flow property. The formulation S12 shows better percentage yield and entrapment efficiency of 98.92% and 97.18% respectively. The formulation S12 shown highest drug release of97.89% in 12 hrs. It is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.990 indicates that the drug release follows a zero-order mechanism . This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics. Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer plots. The mass transfer with respect to square root of the time has been plotted. Revealed a linear graph with regression value close to one i.e. 0.979 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.485suggest that the drug release from microspheres was anomalous Non Fiction diffusion. FTIR, SEM studies were performed. Valsartan microspheres are an effective drug delivery system that offers more predictable and extensive drug release with enhanced shelf-life in the treatment of Hypertension.

MUCOADHESIVE MICROSPHERES OF OLMESARTAN AND VALSARTAN

In the present investigation, stable Valsartan gastro retentive mucoadhesive microspheres were fruitfully prepared by ionotropic gelation method. The results revealed that the sodium alginate, HPMC K 100M and Eudragit RL 100, Olibanum gum, Guar gum and calcium chloride considerably affected the drug entrapment efficiency, particle size, % yield, and % mucoadhesion. The optimized formulation (M13) was found to be efficient, % yield (97.64%), entrapment efficiency (98.18%), swelling index (97.42%) and mucoadhesion (96.18%). The mucoadhesive property facilitates the microspheres to adhere to the gastric mucosal surface and reside in stomach for prolonged time which eventually leads to better bioavailability. Cumulative % drug release studies showed sustained drug release up to 98.67±5.25% (12h). Drug release from Valsartan microspheres followed zero order and Higuchi model suggested that it followed the diffusion-controlled mechanism. The FTIR studies displayed that drug and excipients were compatible. SEM results revealed that the prepared microspheres were spherical in shape. The stability of optimized formulation (M13) was

studied as per ICH guidelines and found stable for 6 months. The release pattern of both marketed and prepared formulation was not significantly different.

FLOATING MICROSPHERES OF OLMESARTAN AND VALSARTAN

In the present study, an attempt was made to prepare Valsartan and Olmesartan floating microspheres, which were characterized for particle size, percentage yield, %drug entrapment, stability studies and found to be within the limits. Among all the formulations F13 was selected as optimized formulation. *Invitro* release study of formulation F13 showed97.34% release after 12h in a controlled manner. The *invitro* release profiles from optimized formulations were applied on various kinetic models suggest that the drug release from floating microspheres was zero order with anomalous Non Fickian diffusion. FT-IR analyses confirmed the absence of drug-polymer interaction. The SEM of microspheres shows a hollow spherical structure with a rough surface morphology. The shell of microspheres also showed some porous structure it may be due to release of carbon dioxide. Optimized formulation F13 was selected for stability studies on the basis of high cumulative % drug release. F13 was stable and retained their original properties with minor differences.

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