FORMULATION DEVELOPMENT AND CHARACTERIZATION OF OLMESARTAN MICROBALOONS

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Abstract:
The objective of the current study was to increase the bioavailability of olmesartan (OLM) by using gastro retentive formulations to keep the drug in the gastrointestinal tract (GIT) for a longer period of time, enhance drug release, and increase efficacy. As rate-controlling polymers, EC and hydrophilic polymer HPMC are utilized in the solvent diffusion process to formulate Microbaloons. The drug's embedding in the Microbaloons' shell and attainment of surface smoothness were discovered and validated by SEM examination. A modest particle size of less than 117µm may have contributed to the prepared Micoballoons' for excellent floating characteristics over a period of more than 12 hours. In-vitro drug release was performed using the USP Type-I method in 0.1N HCL drug released obtained 69.5 % for 12 hours for optimal formulation which may be attributed for effective entrapment efficiency for the prepared formulations. Kinetic studies reveals that higher values of correlation co-efficient obtained through Higuchi square root of time, indicates diffusion mechanism. The optimized formulation was best fitted with kores Myer papas model of n value 0.5 indicates anomalous drug transport.

Keywords: Microbaloons (Hollow Microspheres) Solvent Diffusion Method, Olmesartan HPMC &Ethyl Cellulose Higuchi & kores Myer papas model.

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Introduction:

In recent years, there has been a great deal of emphasis on the development of novel drug delivery systems prospect of repurposing successful medications using the principles and techniques of controlled release drug delivery systems[1]. Despite significant advances in drug delivery, the oral route remains the favored method for administering therapeutic agents due to the low cost of therapy and simplicity of administration, which leads to high levels of patient compliance. Oral medication delivery methods account for more than half of all drug delivery systems on the market.[2]

Floating Drug delivery systems play a promising role in the absorption of drugs with narrow Therapeutics window, poor solubility and low bioavailability problems. These systems retain the drug to float in the stomach region for long period of time and improves therapeutic efficacy of the drug at the site of action. These systems offer clinical therapeutics for acute and chronic management.[3] Among the several drug delivery systems, Particulate systems plays a vital role in research field and clinical medicine, it acts as a carrier both for small and large molecules. This systems has been used as a physical approach to alter and improve pharmacokinetics and pharmacodynamics properties of various types of drug molecules. Microbaloons also known as floating microspheres defined as non-effervescent drug delivery devices that are gastro-retentive. In a literal sense, hollow microspheres (micro balloons) are spherical empty particles with no substance. These microspheres are commonly free-flowing powders mainly up of proteins or synthetic polymers with a size of fewer than 200.µm

Hypertension is one of the most common conditions in primary care and one of the key risk factors, along with hyperlipidemia, hyperglycemia, obesity and smoking etc that contribute to other diseases like myocardial infarction, stroke, renal failure and death. Antihypertensives belonging to different classes have been proved as good candidates for the formulation of GRDDS[3].

Olmesartan Medoxomil is angiotensin-II receptor antagonist drug which is mainly used to treat hypertension. It is rapidly absorbed after oral administration. Drug has poor solubility and narrow absorption window which makes drug to have low bioavailability of 26% and reaches peak plasma concentration ranging within 3 Hrs[4].

Hence an attempt was made to retain the drug release in stomach for long period of time and improve the dissolution characteristics of the poor soluble drug by utilizing the concept of microballoon formulations.

Materials:

Olmesartan received as a gift sample from Hetero Drugs Hyderabad.HPMC, Ethyl cellulose and PVA obtained from Loba Chem.Pvt.Ltd Mumbai India. All chemicals and reagents used are of analytical grade.

Methods:

Preparation method of microballoons[5]:-

Microbaloons were prepared by the emulsion solvent diffusion method established by Kawashima *et.al*(6).Olmesartan, Ethyl Cellulose and HPMC(hydroxy propyl methyl cellulose) were dissolved in a mixture of ethanol and dichloromethane and this mixture is adding drop wise to 0.5% (w/v) PVA (polyvinyl alcohol)in 250 ml water containing 0.01% tween 80 maintained at room temperature. The stirring was done for 2 h at1500 rpm by mechanical stirrer equipped with four bladed propellers, to evaporate the volatile sol-vent. After evaporation of solvent, Microbaloons were collected by filtration, washed with water and dried at room temperature and stored in a desiccator for 24 hrs.

Formulation of Olmesartan Micoballoons:

S.No.	Formulation Code	Drug (mg)	E.C. (mg)	HPMC (mg)
1	OLM 1	20	20	
2	OLM 2	20	40	
3	OLM 3	20	60	
4	OLM 4	20	20	20
5	OLM 5	20	40	40
6	OLM 6	20	60	60

Table 1: Formulation of Olmesartan Microbaloons

Evaluation tests for prepared hollow microspheres[6]:

1. **Angle of Repose:** It is defined as the maximum angle possible between the surface of a pile of prepared product and the horizontal plane. Angle of Repose was determined by the funnel method. Accurately weighed product was taken in the funnel. Height of the funnel

was adjusted in such a way the tip of the funnel just touched the apex of the microballoons blend. The blend was allowed to flow through the funnel freely on to the surface. Diameter of the product cone was measured and angle of repose was calculated using the following equation.

$\theta = \tan^{-1}(h/r)$

θ = angle of repose
h = height in cms
r = radius in cms

The angle of repose used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

Carr's Index: Compressibility index of the hollow microspheres was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a microspheres and the rate at which it packed down. The formula for Carr's index is as below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

4. **Hausner's Ratio**: Haursner 's Ratio is a number that is correlated to the flow ability of hollow microspheres.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

CHARACTERIZATION OF FLOATING MICROSPHERES[7]:

Partial size Analysis:

The particle size of floating microspheres varied somewhat among the formulation due to variation in the composition of formulations. The effects of mixing and polymer to polymer ratio on the particle size of microspheres are shown in table.

Percentage Yield:

The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch and the sum of the initial weight of starting materials. The percentage yield was calculated using the following formula:

$$\% \text{ Yield} = \frac{\text{Practical mass (Floating microspheres)}}{\text{Theoretical mass (Polymer +Drug)}} \times 100$$

Drug entrapment efficiency:

Hollow microspheres equivalent to 10 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by transferred the powder to a 100 mlvolumetric flask and dissolved in 10ml of methanol and the volume was made up using0.1N Hcl. After 24 hours the solution was filtered through What man filter paper and the absorbance was measured after suitable dilution using spectroscopic method at 256nm. The amount of drug entrapped in the floating microspheres was calculated by the following formula,

$$\% \text{ Drug Entrapment Efficiency} = \frac{\text{Experimental Drug Content}}{\text{Theoretical Drug Content}} X100$$

In-vitro buoyancy study[8]:

Microspheres (180 mg) were spread over the surface of a USP XXIV dissolution apparatus type II filled with 900 ml of 0.1N hydrochloric acid. The medium was agitated with a paddle rotating at 50 rpm for 12 h. The floating and the settled fractions of microspheres were recovered separately, dried and weighed. Buoyancy (%) was calculated as the ratio of the mass of the microspheres that remained floating to the total mass of the microspheres, expressed as a percentage.

In vitro drug release study [9]:

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type – II rotating paddle method in 0.1N HCL (900ml). A quantity of accurately weighed microspheres equivalent to 10 mg Olmesartan each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analysed for drug release by measuring the absorbance at 248nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed 0.1N HCL maintaining sink conditions throughout the experiment.

IN-VITRO DRUG RELEASE KINETICS

The release data obtained was fitted into various mathematical models. The parameters 'n' and time component 'k',the release rate constant and 'R', the regression coefficient were determined by Korsmeyer-Peppas equation to understand the release mechanism.

To examine the release mechanism of olmesartan from the hollow Microspheres, therelease data was fitted into Peppa's equation,

$$Mt / M\infty = Kt^n$$

Where, **Mt / M∞** is the fractional release of drug, ' t' denotes the releasetime,'K' represent a constant incorporating structural and geometrical character isticsofthedevice,'n' is the diffusional exponent and characterize the type of release mechanism during the release process.[10]

Results & Discussion:

Concentration of standard calibration curve of Olmesartan:-

The absorbance of the solution was measured at 256nm using UV spectrophotometer with 0.1N HCL as blank. The values are shown in table no.12 and shows good linearity with r2 value 0.9973and the values attained are in compliance to Beer Lamberts law.

Sl.No	Concentration (µg/ml)	Absorbance
1.	2	0.311
2.	4	0.495
3.	6	0.63
4.	8	0.805
5.	10	0.987

Table 2. Standard Calibration values Of Olmesartan

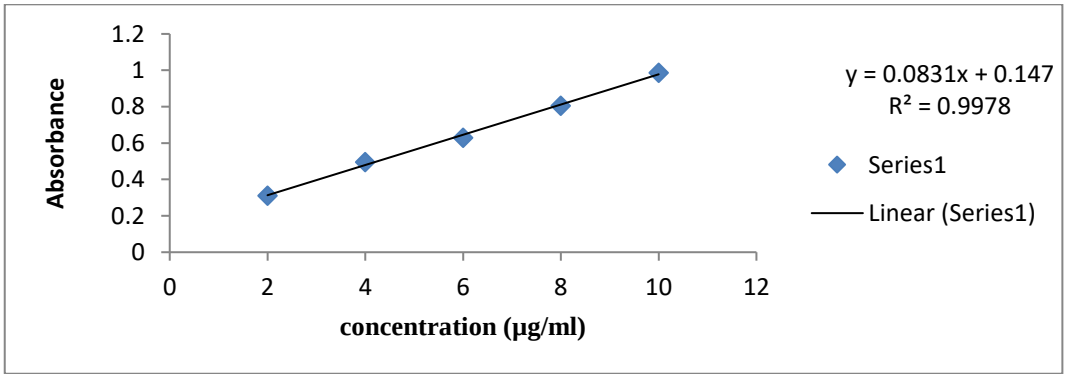

Fig 1. Standard calibration curve of Olmesartan

FTIR COMPATABILITY STUDIES:

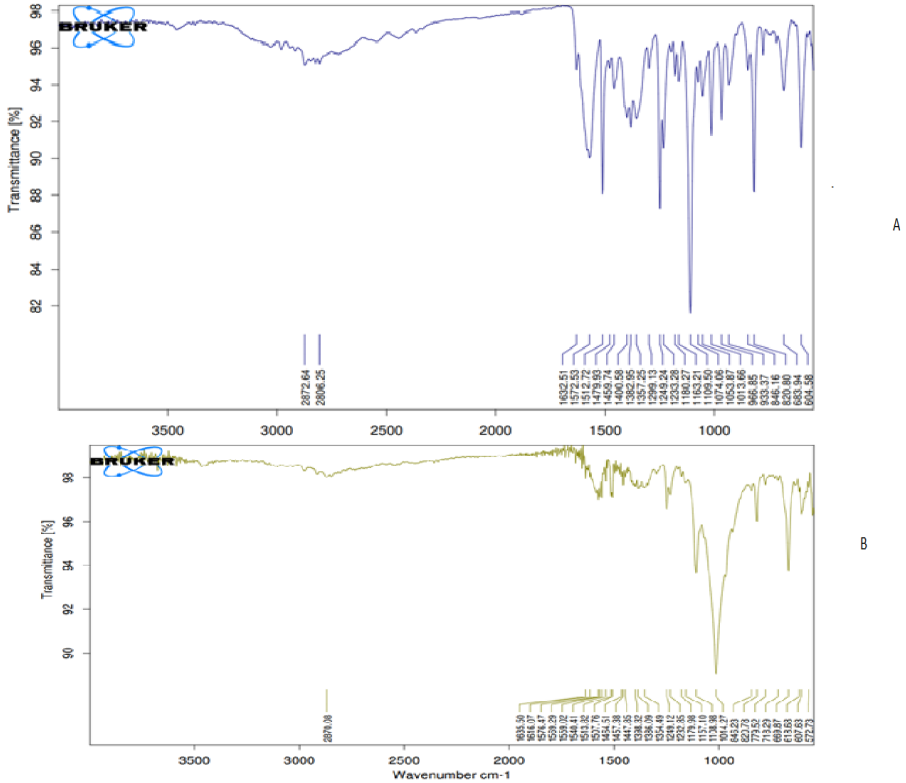

Fig.2. FTIR graph for A- Olmesartan (Pure drug) & B-Physical Mixture(Drug & Polymer)

Band	Wave number cm^{-1} Standard	Wave number cm^{-1} Observed Pure Drug	Wave number cm^{-1} Observed Physical Mixture
C-H $_{Ar}$Stretching	2959	2872	2870
C==N Stretching	1169	1180	1179
C=C stretching	1586	1572	1576
C-O stretching	1733	1632	1635
O-H stretching	3531	3288	3533

Table 3. FTIR Spectrum of Olmesartan & Physical Mixture

Inference: These results revealed that the drug and selected polymers have good compatibility and found that these is no interactions. Pure drug functional group characteristics of C-H aromatics stretching is 2959 cm. C=N stretching is 1180 $cm^{-1}$and the same values are also observed for the physical mixture.

Microscopy View Of Prepared Microbaloons:-

Fig.3. OLM -100X zoom microscopic view

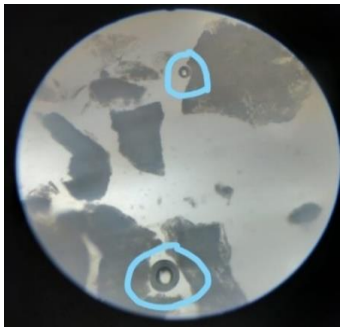

Fig.4. OLM -45X zoom microscopic view

The prepared hollow microspheres are studies for observed using optical microscopy under 45x & 100 X resolution, to study the morphological characters which was depicted fig.3 &4. The images reveals that prepared microspheres are observed with hollow cavity at the center and surrounding by using drug polymeric layer.

Flow Properties of Microbaloons:

S.No.	Formulation Code	ANGLE OF REPOSE	Carrs Index %	Hausners ratio
1	OLM 1	27.17±1.37	11.66±1.15	1.05 ± 0.47
2	OLM 2	29.54±1.37	12.18±5.03	1.27±0.21
3	OLM 3	33.64±2.21	19.31±2.30	1.06±0.52
4	OLM 4	24.21±1.58	18.00±1.18	1.18±0.27
5	OLM 5	23.9±05.53	10.50±2.31	1.14±0.24
6	OLM 6	26.35±0.81	15.15±1.18	1.085±0.05

Table 4. Flow Characteristics of Olmesartan Micoballoons

Characterisation of prepared Hollow Microspheres:

S.No.	**Formulation code**	**Particle Size**	**Buoyancy**	%EE
1	OLM1	85.2±2.01	68.15±2.11	70.51±2.14
2	OLM2	97.54±3.18	71.05±1.03	73.84±1.18
3	OLM3	113.1 ±3.51	79.21±1.74	78.14±1.92
4	OLM4	111.5±2.74	71.84±2.47	81.54±2.57
5	OLM5	**117.1±3.14**	**77.54±2.51**	**91.65±3.06**
6	OLM6	128.54±2.31	66.21±3.17	78.31±2.85

Table 5. Characterization of Floating Micoballoons

Inference:

Particle Size Characteristic of Prepared Mico-balloons was found to be in the range of 85.45 to 128.5µg/ml. OLM 5 have show the maximum yield 83.45 and OLM -11 has 84.62% these indicted the increase values indicates good yield, further increase polymers concentration viz OLM 6 and 11 the decrease yield is due to adherence of product to the surface.

Entrapment Efficiency of the prepared formulations was in range of 70.51- 91.65% these values indicates increase polymer concentration and increase drug entrapment into polymer.

Optimum formulation achieved maximum entrapment efficiency.

Buoyance Studies are carried out for 12hr s and it was range of 68.15 to 79.21 all the formulation have achieved good floating properties and formulation olm5 has maximum floating properties this may be due to vaporization of organic solvents causes formation of hallow cavity at the center which was confirmed from the microscopy studies.

Invitro-Dissolution Studies:

Time (Hrs)	Invitro Drug Release studies					
	OLM 1	**OLM 2**	**OLM 3**	**OLM 4**	**OLM 5**	**OLM 6**
0.	0	0	0	0	0	0
1.	6.17±0.14	3.15±0.22	2.57±0.6	5.19 ±0.22	4.97 ±0.11	13.54 ±0.29
2.	12.16 ±0.22	5.17±3114	3.15±0.18	11.57 ±0.41	9.35 ±0.18	17.59 ±0.51
3.	17.62±0.18	6.82±0.22	4.22±0.11	14.56±0.11	13.34 ±0.17	28.45 ±0.18
4.	22.54 ±0.05	7.51±0.53	11.64 ±0.21	17.39 ±0.18	16.82 ±0.09	35.72 ±0.22
5.	27.35±0.16	15.62±0.31	14.27±0.24	26.48 ±0.24	22.54 ±0.11	38.54 ±0.24
6.	28.51±0.21	28.56±0.14	22.65 ±0.06	32.54±0.17	27.96 ±0.14	35.56 ±0.31
7.	37.15±0.08	33.54±0.27	29.54 ±0.11	38.57 ±0.28	31.54 ±0.08	37.35 ±0.28
8.	43.51±0.22	39.81±0.11	34.81±0.18	47.63±0.85	39.37±0.24	39.41±0.27
9.	48.97±0.19	49.54±0.01	48.22±0.02	51.48 ±0.57	45.51 ±0.17	45.28 ±0.54
10	57.24±0.27	67.28±0.17	51.12±0.21	67.21 ±0.75	53.64 ±0.29	47.11 ±0.18
11.	61.1±0.12	77.31±0.52	67.58 ±0.15	75.43 ±0.57	61.22 ±0.11	51.42 ±0.11
12.	68.57±0.31	85.22±0.18	70.15±0.51	81.32 ±0.94	69.57 ±0.18	55.97 ±0.18

Table 6. Invitro drug release data of Olmesartan Micoballoons

Inference: Invitro drug release studies carried out using USP-XII Type-1 dissolution method Dissolution studies carried out for 12 hrs for the all formulation. Results reveals that increased polymer concentration have achieved controlled drug release mechanism and the formulation olm5 have achieve uniform pattern of drug release 69.5% in 12 hrs this may be due to good bouncy and the entrapment efficiency for the prepared formulation compared to the other formulations.

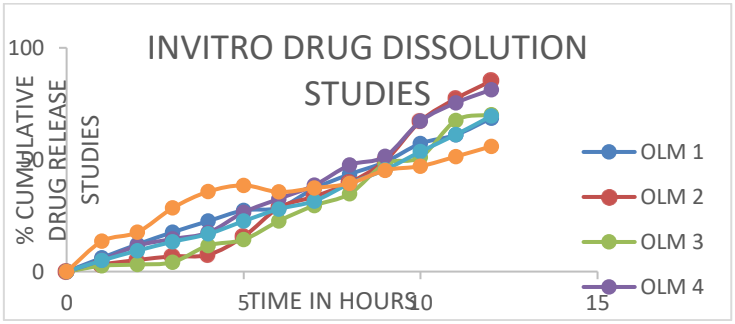

Fig.5. Invitro dissolution studies of prepared formulations

Kinetic Data of Microbaloons:

Formulation Code	R^2 Values			
	Zero order	First order	Higuchi Matrix	Kores MeyerPeppa's
OLM1	0.9981	0.6442	0.9557	0.9566
OLM2	0.9492	0.5949	0.8389	0.9863
OLM3	0.9577	0.6265	0.8517	0.9904
OLM4	0.9888	0.6066	0.9187	0.9083
OLM5	**0.992**	**0.9182**	**0.9266**	**0.9109**
OLM6	0.9568	0.9317	0.9941	0.9124

Table 7.regressiion coefficient values of olmesartan formulations

kinetic data of the prepared formulation was studies and was displayed in table as shown above. which results that all the prepared formulation follow zero order drug release among all 5 and 11 show satisfactory results olm 5 and 11 have exponent value 0.72 to 0.991 which

indicated that they well follow non fickiananomalous diffusion mechanism. higuchi plot of the formulations have shown good correlation values which indicated that kinetic data of the prepared formulation was studies and was displaced in table which results that all the prepared formulation follow zero order drug release among all 5 and 11 show satisfactory results olm 5 and 11 have exponent value 0.72 to 0.991 indicated non fick and anomalous diffusion mechanism.

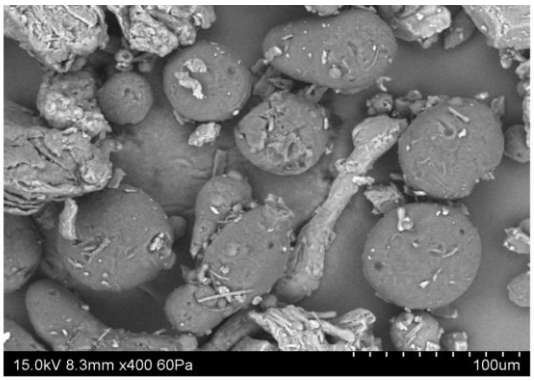

Fig 6. SEM Analysis Of Formulation OLM 5

SEM photographs taken with scanning LV 500 and required magnification at room temperature. The photographs were observed. that have spherical and smooth surface

CONCLUSION

Thus Micoballoons of OLM were successfully formulated using solvent diffusion method and achieved buoyancy with uniform drug release for more than 12 hrs. using ethyl cellulose (EC) as rate controlling polymer. Results obtained reveals that the Micoballoons may be a promising approach to improve the dissolution characteristics of the poor soluble drug.

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