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Original Article

DEVELOPMENT OF OLMESARTAN MEDOXOMIL-LOADED CHITOSAN MICROPARTICLES: A POTENTIAL STRATEGY TO IMPROVE PHYSICOCHEMICAL AND MICROMERITIC PROPERTIES

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ABSTRACT

Objective: The objective of the present research was to improve physicochemical and micromeritic properties of Olmesartan Medoxomil (OLM), BCS class II antihypertensive drug by loading in Chitosan (CH) microparticles.

Methods: The 3^2 full factorial design was assigned for microparticles prepared by single emulsion technique method using CH, a natural polymer and Glutaraldehyde (GA) as cross linking agent. Developed microparticles were characterized for Micromeritic properties, morphology by Scanning Electron Microscopy (SEM), drug entrapment efficiency, *in vitro* drug release, and interaction studies Fourier transfer infrared spectroscopy (FTIR) & Differential Scanning Calorimetry (DSC), drug crystallinity study by X-ray diffractometry (XRD) & DSC.

Results: Maximum entrapment efficiency was found 61.76% for maximal CH and lower GA concentration. Saturation solubility of microparticles was increased by 13.74 times to that of pure OLM. FTIR showed compatibility between drug and polymer. XRD, DSC and SEM studies confirmed reduction in crystallinity of drug. It led to increase in dissolution profile of the drug and showed 92.61% of drug release in 120 min. These microparticle preparations also helped in improving micromeritic properties like bulk density, tapped density, the angle of repose, Hausner's ratio and Carr's index.

Conclusion: The results obtained in the present work demonstrate the potential use of CH to modulate physicochemical and micromeritic properties of OLM especially obtaining significant improvement in dissolution rate.

Keywords: Olmesartan medoxomil, Chitosan, Microparticles, Factorial design.

INTRODUCTION

OLM (4-(1-Hydroxy-1-methylethyl)-2-propyl-1-((2'-(1H-tetrazol-5-yl) (1,1'-biphenyl)-4-yl)methyl)-1H-imidazole-5-carboxylic acid (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl ester; 5-Methyl-2-oxo-1,3-dioxol-4-yl) methyl 5-(2-hydroxypropan-2-yl)-2-propyl-3-((4-(2-(2H-tetrazol-5-yl))phenyl)phenyl)methyl)imidazole-4-carboxylate) is a pro drug that works by blocking the binding of angiotensin II to the AT_1 receptor. As a result of this blockage, OLM reduces vasoconstriction and the secretion of aldosterone. This lowers blood pressure by producing vasodilation, and decreasing peripheral resistance. OLM drug particles have the crystalline nature and possess poor physiological properties like wettability, solubility, flow property, dissolution rate etc. Hence, it belongs to BCS class II of drug. It has low bioavailability i.e. about 26% [1]. CH (2-Amino-2-deoxy-(1, 4)-b-D-glucopyranan) is the name applied to deacetylated chitins [2]. The degree of deacetylation necessary to obtain a soluble product must be greater than 80–85%. It has been received increasing interest as natural pharmaceutical excipient because of naturally obtained good biocompatible, biodegradable, mucoadhesive and non-toxic properties [3]. CH is cross linked into particulate drug delivery system with cross linking agents like formaldehyde, GA, sodium tripolyphosphate etc [4-6].

Several researchers have tried to increase dissolution profile and flow properties of OLM by solid dispersion, crystallo-co-agglomeration, nanoemulsion technique etc. by using synthetic polymers [7-9]. Main focus of this work is to improve the aqueous solubility and in turn the dissolution profile along with micromeritic and flow properties of the OLM using natural polymer CH and single emulsion technique using GA as cross linking agent. Among the various approaches available to increase the aqueous solubility of drugs, preparation of microparticles is a novel approach.

MATERIALS AND METHODS

Materials

All the chemicals and reagents required for the present research work has been obtained from authentic supplier and were of analytical grade. The API, OLM has been obtained as the gift sample from Lupin Research Park, Pune, India. CH was obtained from Research-Lab Fine Chem. Industries, Mumbai, India. Paraffin, GA, tween 80, acetone, methanol and hydrochloric acid were purchased from loba chemie, Mumbai, India. Triple distilled water obtained after distillation from triple distillation apparatus at Govt. College of Pharmacy Karad was used throughout the experiment.

Methods

Experimental design

A 3^2 level full-factorial design includes 9 full factorial design points with the help of Design Expert version 8.0.7.1. According to the model, total 9 experiments were performed. This design involves dependent variables and independent or controlled variables A and B. In the present study, experiment was conducted considering concentration of CH and GA as independent variables. The dependent variables were Y1; percentage entrapment efficiency and Y2; percentage drug release.

Preparation of microparticles

The trial batches were prepared using various concentrations of the CH and GA. The concentrations for the factorial design were finalized based on the evaluation of trial batches. In the preliminary study, CH in acetic acid solution was used in the range of 1-5% and out of them 4% CH solution showed solid and free flowing microparticles. GA (1-3%) was used as the cross linking agent. During trial, microparticles containing 1:0.5-1:1.5 of drug: CH ratio as well as 1-3% of GA were prepared and evaluated for percentage entrapment efficiency and percentage drug release pattern. The microparticles of trial batches were prepared by the single emulsion technique using overhead rotator stirrer with 1500 rpm speed and constant cross linking time [10-12].

In this work, CH solution (aqueous phase) was prepared using a 2% aqueous acetic acid solution. Drug was added in aqueous solution of CH. Dispersion medium (oil phase) was prepared by using liquid paraffin and an emulsifier Tween-80. Then CH solution (aqueous phase) was poured into the dispersion medium (oil phase) drop

wise. The dispersion medium was stirred using overhead stirrer during drop wise addition of an aqueous phase. A predetermined amount and concentrations of GA was added into the dispersion medium after 10 min. The CH microspheres were collected by filtration and washed with acetone/water solution (1:3 of volume ratio) to remove liquid paraffin. The microparticles were dried in an oven at 40 °C for 24 h [13].

From the trial batches, the 3^2 full factorial designs, coded values and formulation table (table 1, 2 and 3) were employed to optimize the concentration of CH and GA.

Table 1: Factorial design batches

Batches	% CH	% GA
1	-1	1
2	-1	0
3	1	-1
4	1	1
5	0	1
6	0	0
7	0	-1
8	-1	-1
9	1	0

Table 2: Coded values of factorial design batches

Variables used	Coded levels	
	-1	**1**
% CH	33	60
% GA	1	3

Determination of drug content, percentage loading capacity (% LC) and percentage entrapment efficiency (% EE) of prepared microparticles

Drug content was determined by dissolving 10 mg samples of microparticle in 10 ml of methanol and the volume was adjusted to 100 ml with methanol. The solution was filtered through Whatmaan filter paper no. 41, suitably diluted and absorbance was measured at 256 nm using double beam UV spectrophotometer (Shimadzu 1800, Japan). %LC and %EE was calculated by following formulas [14]

$$\% \text{ LC} = \frac{\text{amount of drug entrapped in microparticles} \times 100}{\text{total amount of microparticles}}$$

$$\% \text{ EE} = \frac{\text{amount of drug entrapped in microparticles} \times 100}{\text{theoretical weight of drug}}$$

Table 3: Formulation table

S. No.	Batch code	OLM: CH ratio	% GA	% CH solution in acetic acid solution	Time period (min.)
1	A1	1:0.5	1	4	30
2	A2	1:0.5	2	4	30
3	A3	1:0.5	3	4	30
4	B1	1:1	1	4	30
5	B2	1:1	2	4	30
6	B3	1:1	3	4	30
7	C1	1:1.5	1	4	30
8	C2	1:1.5	2	4	30
9	C3	1:1.5	3	4	30

Saturation solubility studies of prepared microparticles

Saturation solubility studies were performed in triplicate according to the method reported by Higuchi and Connors. Excess of pure drug and microparticles were added to 10 ml of 0.1 N HCl solution and distilled water taken in screw cap tube and shaken for 24 h in the rotary flask shaker at 100 rpm at room temperature to achieve the equilibrium. Appropriate aliquots were then withdrawn and filtered through Whatmaan filter paper no. 41 and analysed spectrophotometrically at 256 nm. The results obtained from saturation solubility studies were statistically validated [15-16].

Fourier Transform Infrared Spectroscopy (FT-IR)

The FT-IR spectra of OLM microspheres was obtained on JASCO V-530 FTIR-4100 spectrometer, (Japan) having Spectra Manager II software and scanned over the range 400-4000 cm^{-1}. Dry KBr (50 mg) was finely ground in the mortar and samples (1-2 mg) were subsequently added and gently mixed.

X-ray Diffractometry (XRD)

The XRD data of OLM and microparticles were recorded on a Philips Analytic X-Ray-PW 3710 (Philips, Almelo, The Netherlands) diffractometer having PAN alytical's XRD software and tube anode Cr over the interval 10–90 °/2θ under the following set of conditions: the Generator tension (voltage): 40 kV and Generator current: 25 mA.

Differential scanning calorimetry (DSC)

Thermal analysis of the samples was performed on a Shimadzu DSC 60 with CLASS-Agent Data Management Software. Samples (3-5 mg) were crimped in non-hermetic aluminium pans with lids and scanned from-50 to 250 °C at a heating rate of 20 °C/min under a continuously purged dry nitrogen atmosphere (flow rate 20 ml/min). The instrument was equipped with a refrigerated cooling system.

Scanning electron microscopy

The surface morphology of microparticles and pure drug was analysed using scanning electron microscope (SEM-Jeol Instrument JSM-6360, Japan) after sputter coating with platinum.

***In-vitro* dissolution study**

The drug release studies of microparticles were carried out by using USP Type II dissolution apparatus (paddle) DT1000 (Labindia, India). The dissolution studies were conducted in 900 ml dissolution medium 0.1N HCl buffer pH 1.2 for 2 h; as the average gastric emptying time is about 2 h, thermo stated at 37±0.5 °C and stirred at 50 rpm. Aliquots were taken at appropriate interval and filtered samples were estimated for OLM using UV spectrophotometer (Shimadzu 1800, Japan) at 256 nm. After collecting the sample, the dissolution medium was replenished with the same volume of fresh medium.

Micromeritic properties

The flow properties of pure drug and microparticles were determined in terms of the angle of repose, Bulk density, tapped density, Carr's Index and Hausner's ratio.

Angle of repose

It was calculated by fixed funnel method from following formula

$$\tan\theta = \frac{\text{height of pile}}{\text{radius of bottom of pile volume}}$$

Bulk density

The bulk density was calculated from graduated cylinder method. A sample of about 50 g was carefully transferred into 100 ml graduated cylinder and the cylinder dropped onto a hard wooden surface three times from a height of 1 inch at 2 s intervals. It is calculated by

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Bulk Volume}}$$

Bulkiness

It is the reciprocal of bilk density and has importance in packaging of powder or particles. It is calculated as follows-

$$\text{Bulkiness} = \frac{1}{\text{Bulk Density}}$$

Tapped density

Proceed as described above for the determination of the bulk volume. Secure the cylinder in the holder. Carry out 100 taps on the same sample and read the tapped volume to the nearest graduated unit. It is calculated by

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Tapped volume}}$$

Carr's index and Hausner's ratio was calculated from following formula:

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner}^{'}\text{s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

RESULTS AND DISCUSSION

Ofloxacin loaded CH-GA microparticles were prepared by single emulsion technique for alveolar microphage delivery system via pulmonary inhalation [13]. Different batches from factorial design of microparticles were prepared by single emulsion technique. It was observed that less than 4% concentration of CH solution was not able to form microparticles and as concentration increases, it was difficult to form microparticles. Hence, CH solution concentration was kept constant but as the ratio of drug: CH increases upto 1:1, drug content increases and then decreases. GA concentration was selected on the basis of drug release from the microparticle formulations.

Practical yield, percentage loading capacity and percentage entrapment efficiency

Ju-Hwan Park *et al.* found increase in entrapment efficiency of the ofloxacin microparticles with CH as compared with powdered ofloxacin and microparticles of ofloxacin with PLGA. CH microparticles were prepared with water in oil single emulsion technique with GA as a cross linking agent [13].

From the table 4, it was observed that as CH concentration increases, there was decrease in practical yield of microparticles as well as decrease in % loading capacity due to the density and viscosities of microparticles were goes on increasing with CH [17].

Viscosity increased with CH concentration, so % entrapment efficiency goes on increasing. Percentage of GA also affected the percentage entrapment efficiency. It was observed that, as % GA increases, there was the decrease in % entrapment efficiency.

Table 4: Practical yield, percentage loading capacity and percentage entrapment efficiency

S. No.	Batches	Practical yield (%)	% loading capacity[a]	% entrapment efficiency[-a]
1	A1	39.58	32.71±0.45	49.06±0.61
2	A2	45.00	29.01±0.78	43.18±1.13
3	A3	35.00	26.64±0.79	39.95±1.56
4	B1	56.25	28.62±0.53	57.24±0.44
5	B2	47.50	28.61±1.24	57.22±0.46
6	B3	60.13	23.51±1.91	47.01±0.17
7	C1	76.00	24.70±1.65	61.76±0.70
8	C2	56.22	23.77±0.95	59.37±0.85
9	C3	90.00	23.65±1.15	59.12±1.11

[a] SD = Standard deviations, n=3

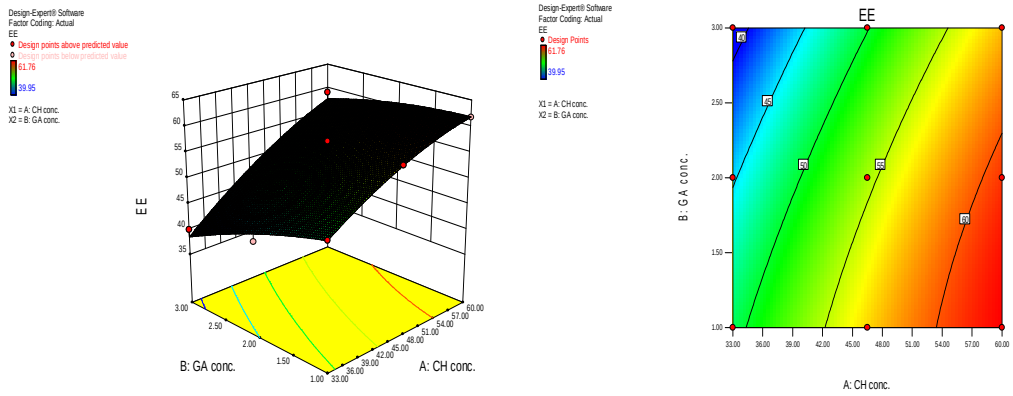

Fig. 1: Study of %EE by surface methodology: 1) 3D surface plot 2) contour plot

Study of percentage entrapment efficiency by response surface methodology

Equation (1) of the formulations containing CH and GA for the studied response variables are expressed as Equation

$$\%EE = 54.42+8.01 * A-3.66 * B+1.62 * A * B-1.75 * A^2-0.90 * B^2 \ldots\ldots (1)$$

Where, A and B represents the effect of variables i.e. concentration of CH and GA concentration respectively. All the polynomial equations were found to be statistically significant, as determined using ANOVA, as per the provision of Design Expert version 8.0.7.1. The Model F-value of 12.12 in above equation implies the model was significant. P value was found to be 0.0333 ($P<0.05$) indicate model terms A and B were significant [18]. Fig. 1 shows the profound effect of

concentration of the CH and GA on the % entrapment efficiency of the formulation. The 3D surface plot and counter plot clearly indicate that % EE was increased with increase in concentration of CH and decreased with increase in GA concentration. From the formulations, it was observed that the maximum entrapment efficiency was obtained with the formulations C1.

Solubility study

The table 5 shows that OLM has shown very low solubility in 0.1 N HCl solution and water. Hence, the aim of this study was to enhance the dissolution rate of drug, by enhancing solubility of drug. It was observed that all formulations of micro particle by using CH as a polymer help to improve the saturation solubility of OLM. Batch C2 showed maximum solubility among the other batches. It was observed that CH microparticles enhance the solubility of OLM by 13.743 times than pure drug OLM but it didn't clearly indicate the effect of concentration of CH and GA on saturation solubility study.

Compatibility study by FT-IR

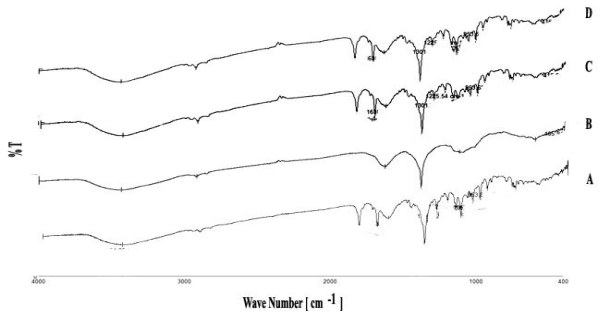

Fig. 2: FTIR of A: OLM; B: CH; C: physical mixture; D: micro particle

The fig. 2 shows the FT-IR spectrum of OLM and polymer i.e. CH. It showed characteristic peaks for OLM at 3454 cm^{-1}, 1832 cm^{-1}, 1707 cm^{-1} and 1632 cm^{-1} corresponding to stretching vibration of secondary amines (–NH-), stretching vibration of the conjugation of oxygen on C=O group, stretching vibration for C=O and C=C present in conjugation of C=O with α, β C=C group respectively. FT-IR spectrum of CH showed characteristic peak at 3435 cm^{-1} and 1384 cm^{-1}corresponding to stretching vibration of secondary amines (–NH-) and conjugation of oxygen on C-O group in six member ring. Other peaks were observed at 2920.66 cm^{-1} and 1122.37 cm^{-1} and were assigned to stretching vibrations for C-H and C-O-C.

All these peaks are present in physical mixture and microparticles of OLM and CH. Hence, it revealed absence of chemical interaction between API and polymer and chemical compatibility with each others.

Differential scanning calorimetry

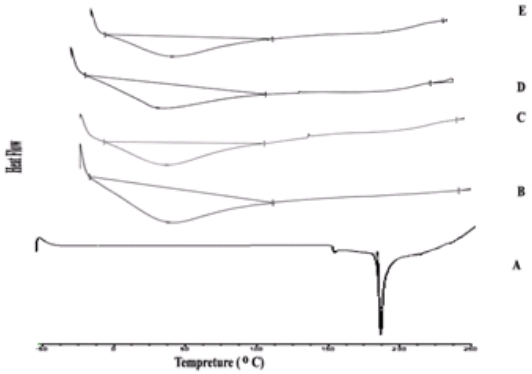

Fig. 3: DSC of A: OLM; B: A1; C: B1; D: C1; E: C2

Table 5: Saturation solubility

S. No.	Batch	Solubility in dist. Water[a] (µg/ml)	Conc. In 0.1 N HCl [a] (µg/ml)
1.	Drug	3.5±0.44	5.53±0.28
2	A1	35.8±0.17	30.79±0.38
3	A2	26.0±0.52	51.42±0.43
4	A3	31.3±0.46	16.74±0.37
5	B1	37.2±0.46	35.47±0.29
6	B2	21.7±0.85	22.84±0.69
7	B3	21.0±0.96	22.63±0.19
8	C1	32.7±0.79	21.84±0.18
9	C2	48.1±0.62	14.68±0.68
10	C3	29.3±0.35	26.32±0.35

[a] SD = Standard deviations. n=3

The melting point of a compound is a fundamental physical property determined for the purpose of characterization or purity identification of a compound. The DSC showed in fig. 3 corresponding value of sharp endotherm at melting point. The DSC of pure drug OLM had shown the sharp endotherm at 188.47 °C with high endothermic peak area indicating crystalline anhydrous nature. While that of microparticles showed absence of sharp peak revealed amorphization and/or drug complexation with polymer. It revealed that area of endotherm peak was totally decreased. Hence, it is confirmed that decrease in crystallinity of drug OLM in formulation with CH.

Lowering of the drug melting temperature and a concomitant reduction of enthalpy attributes to a partial drug amorphization that occurred during microparticle preparation [19]. Same behavior was observed in CH carrying microparticle but it didn't reveal the effect of concentrations on the amorphization of microparticles.

X-ray diffractometry (XRD)

XRD pattern was used to confirm amorphous nature of the generated microparticles. XRD is a powerful technique for determining the presence of crystalline structure in drug and generation or reduction of crystal form during the process of formation of microparticles [20]. As shown in fig. 4, unique XRD patterns showed peak intensities of drug and microparticles with CH at various diffraction angles (2θ). It can be seen that the microparticles exhibited spectra with same peak positions (patterns) compared to drug. Further, the relative intensities of their diffraction peaks were modified which might be attributed to the different crystals and arrangement of molecules. The relative degree of crystallinity (RDC) is the comparative study of crystallinity of microparticles with drug. It can be calculated by following formula

$$\text{RDC} = \frac{\text{intesity of peak of microparticle at specific angle}}{\text{maximum itensity of peak ofdrug}}$$

If the RDC value is greater than 1, it represents crystallinity of microparticles increases than drug and if it is less than 1 then it represents decrease in crystallinity. Table 6 showed the RDC of microparticles were considerably lower than 1. Thus, it is cleared that there is reduction in crystallinity of OLM in microparticles which attributes to improvement in dissolution profile of samples and can be justified by dissolution results [12, 16].

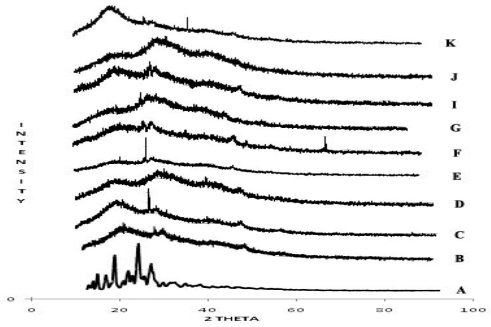

Fig. 4: XRD of A: OLM; B: A1; C: A2; D: A3; E: B1; F: B2; G: B3; I: C1; J: C2; K: C3.

Scanning Electron Microscopy

SEM analysis shown in fig. 5 evidenced the fine particular OLM and irregular shape of microparticles. The rough and porous surfaces were observed in microparticles, indicating the presence of CH polymer. Plain OLM drug showed a slightly spherical shape and larger clumps of particles in SEM image, but when loaded with CH in microparticles, there was a slight improvement in spherical shape and size.

In-vitro dissolution study

CH has properties of dissolution rate enhancer of drugs poorly soluble in water. Carbamazepine was entrapped into CH microspheres by spray drying method contributed to an improvement of its dissolution/release rate [21].

Fig. 6 demonstrates the dissolution profiles of drug and microparticles. OLM showed 24.63% drug release within 120 min, because it has low wettability due to fine nature confirmed from SEM. According to DSC and XRD data, it was ascertained increase in amorphous nature of the formulation. Hence, all microparticles improved dissolution of OLM. The increase in release rate was dependent on CH concentration and GA concentration but in opposite fashion. Microparticles with highest CH concentration and lowest GA concentration showed maximum release rate. Hydrophilic nature of CH was responsible for enhancement of dissolution of OLM and GA helped for increase in wettability of microparticles by forming tough complex.

Hence, increasing GA concentration retarded the release rate as shown in formulations. So A3, B3 and C3 showed less drug release profile as compared with other formulations but C1 showed highest drug release 92.61% within 120 min. This is because of increased amount of CH in drug and CH ratio and decrease in concentration of GA from 3% to 1%.

Table 6: RDC of microparticles at respective 2θ value

(2θ)	A1	A2	A3	B1	B2	B3	C1	C2	C3
21.7382	0.156	0.162	0.131	0.137	0.131	0.117	0.142	0.100	0.172
24.5964	0.228	0.250	0.200	0.198	0.210	0.192	0.215	0.201	0.239

Scanning electron microscopy

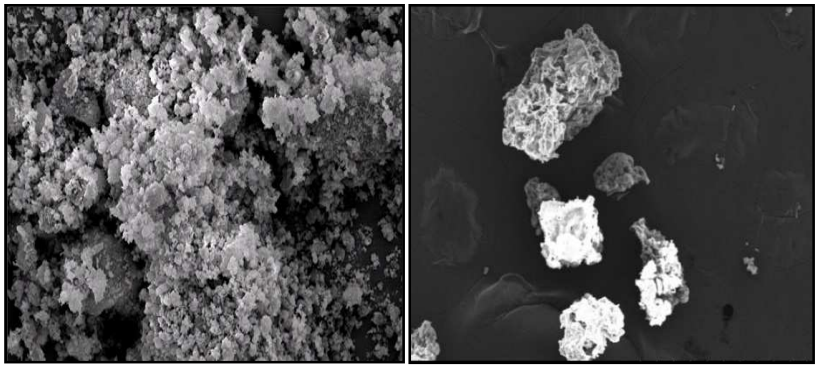

Fig. 5: SEM of OLM and microparticles

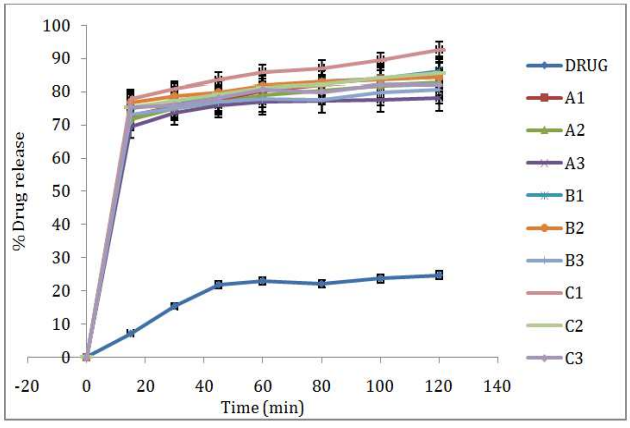

Fig. 6: Dissolution profile study

Study of % DR by response surface method

From the study of response variables following equation (2) is generated for the formulations containing CH and GA

$$\%DR = 83.82+2.45 * A-3.75 * B-1.0 * A * B+0.63 * A^2-0.20 * B^2 \ldots (2)$$

Where, A and B represents the effect of variables i.e. Concentration of CH and GA concentration respectively. All the polynomial equations were found to be statistically significant, as determined using ANOVA, as per the provision of Design Expert 8.0.7.1. The Model F-value of 10.78 in above equation implies the model is significant. P value was found to be 0.0392 ($P<0.05$) which indicates model terms A and B are significant [18].

Fig. 7 shows the profound effect of concentration of the CH and GA on the % drug release of the formulation. The counter plot clearly indicates that the % DR is increased with increase in concentration of CH and GA. From the formulations, it was observed that the maximum % DR was obtained with the formulation C1.

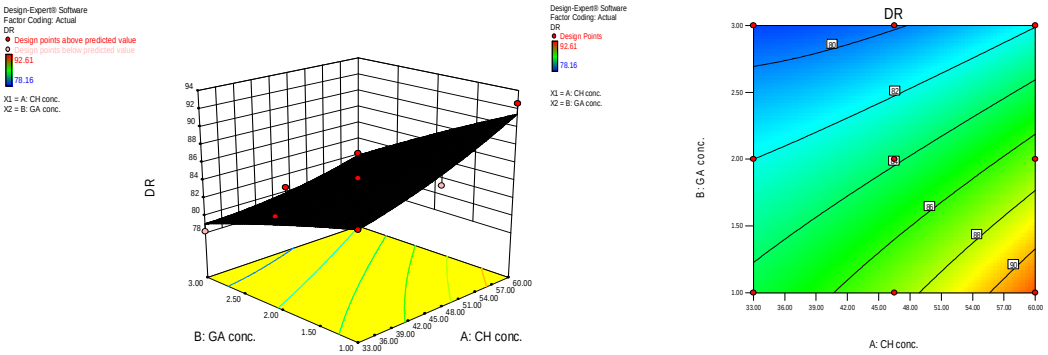

Fig. 7: Study of %DR by surface methodology 1) 3D surface plot 2) contour plot

Micromeritic properties

Micromeritic properties of microparticles presented in table 7 showed increase in flow property of microparticles with reducing an angle of repose within 23 °-30 ° as compared to drug. If value of angle of repose is high, particles are cohesive and if it is low, particles are non-cohesive or free flowing. The tapped density of particles indicates packing capacity. The bulk density and tapped density of all the samples fell in the range of 0.32–0.42 g/cm³. Bulkiness of formulations was slightly varied with respect to drug. The value of Carr's Index and Hausner's ratio was in conformity with an increase in flow rate of all the samples. The value of Carr's index and Hausner's ratio of the microparticles was found to be decreased than OLM [22].

Table 7: Study of micromeritic properties

Batch	Angle of Repose (degree)*	Bulk Density (g/cm³)*	Bulkiness (cm³/g)*	Tapped Density (g/cm³)*	Carr's Index (%)*	Hausner's Ratio*
Drug	38.31±0.006	0.33±0.06	3.03±0.59	0.50±0.010	34.00±11.35	1.52±0.27
A1	29.25±0.11	0.34±0.01	2.94±0.05	0.40±0.009	15.00±2.06	1.18±0.03
A2	28.81±0.01	0.33±0.01	3.03±0.08	0.40±0.009	17.50±2.71	1.21±0.04
A3	29.25±0.74	0.38±0.01	2.63±0.09	0.42±0.002	9.52±2.90	1.11±0.04
B1	28.37±0.04	0.32±0.01	3.13±0.06	0.37±0.012	13.51±3.34	1.16±0.05
B2	27.92±0.10	0.36±0.01	2.78±0.06	0.39±0.005	7.69±3.03	1.08±0.04
B3	27.92±0.10	0.39±0/01	2.56±0.06	0.41±0.004	4.88±2.46	1.05±0.03
C1	28.81±0.07	0.37±0.01	2.70±0.08	0.41±0.006	9.76±1.34	1.11±0.02
C2	27.47±0.06	0.34±0.05	2.94±0.37	0.41±0.075	17.07±3.81	1.21±0.05
C3	27.92±0.04	0.38±0.02	2.63±0.11	0.40±0.005	5.00±5.10	1.05±0.06

* SD = standard deviation, n=3

Stability study

All the formulations as shown in table 8 were examined for their accelerated stability study at 40 °C±2 °C temperatures and 75%±5% relative humidity for about two months. The formulations were assessed for the drug present in formulations.

The microparticles were found to be stable during the study period.

Table 8: Accelerated Stability study of drug and all batches

Batches	% Drug present*			
	Time=10 d	Time=30 d	Time=45 d	Time=60 d
Drug	99.87±1.24	99.09±1.06	100.01±1.3	99.78±1.09
A1	99.05±0.68	99.08±0.71	100.04±1.03	99.13±0.75
A2	98.67±1.01	99.35±0.79	99.98±1.3	99.04±0.97
A3	99.76±1.06	99.22±0.68	98.59±0.98	100.04±0.94
B1	99.01±0.98	99.55±0.97	98.98±0.68	99.34±0.93
B2	99.89±0.87	98.89±0.92	99.28±0.94	99.28±1.00
B3	100.12±0.95	100.09±0.89	99.46±0.83	99.83±1.25
C1	99.38±1.00	99.78±0.87	100.06±0.88	99.92±1.03
C2	99.31±1.01	99.94±1.23	99.29±0.87	98.95±0.99
C3	99.49±0.99	99.07±1.06	99.04±0.99	99.69±1.00

* SD = standard deviation, n=3

CONCLUSION

OLM microparticles were prepared using CH as polymer and GA as a cross linking agent. The formulation of microparticles helps to modify the physicochemical properties of OLM. The prepared microparticles didn't show any chemical interaction between OLM and CH, confirmed by FT-IR study. The study of XRD, DSC and solubility showed increase in amorphous nature and solubility of the formulations. Surface morphology study showed entrapment of OLM in CH. The *in-vitro* dissolution study indicated release of drug in the upper GI tract and confirmed enhancement of dissolution profile of OLM microparticles compared to pure drug. On the basis of these results, it could be concluded that, pharmaceutical micro particulate technique of OLM with CH and GA could be possible and may serve

as an alternative and effective approach for manipulation of physicochemical and micromeritic properties of OLM.

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CONFLICT OF INTERESTS

Declared None

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