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DISSOLUTION ENHANCEMENT AND COMPARATIVE ASSESSMENT OF MICROCAPSULE LOADED SUSTAINED RELEASE MUCOADHESIVE GASTRO RETENTIVE TABLETS WITH AVAILABLE MARKETED FORMULATIONS

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ABSTRACT

Losartan potassium is a non-peptide molecule and selective competitive angiotensin II type 1 receptor (AT1) receptor antagonist which is mainly used as a first line treatment for the patients suffering from hypertension. In the present research work Losartan potassium loaded microcapsules were fabricated by using modified double emulsion solvent evaporation method and further more they were incorporated into mucoadhesive gastro retentive tablets. The release kinetic of the prepared tablets was evaluated by using PCP Disso V3® software and it selected 'zero order' model as the best fitting model, supporting the sustained release property of the final oral dosage forms which was the primary objective of the present study. Final formulations were subjected to comparison with three different marketed conventional dosage forms on the basis of dissolution property and it showed better release pattern than the rest.

KEYWORDS: Losartan potassium, PCP Disso V3, Kinetic models, Microcapsules, Eudragit.

INTRODUCTION

From the last few decades increasing interest in the novel drug delivery system (NDDS) has provided some notable inventions in pharmaceutical research. Microencapsulation is one of those major break through which has given drug delivery system a new platform. At the same time the oral dosage form is still remaining the holy grail of conventional dosage forms[1]. In

the current research profile we have tried to form a bridge or a correlation in between the novel drug delivery system and conventional delivery system. Losartan Potassium is one of the most well-known first line antihypertensive drugs often prescribed by the medical practitioners. Therefore sustained release formulation of this above mentioned drug will definitely be able to provide better therapeutic efficacy, lower the dosing frequency and a much cost effective option. In order to analyze the drug release mechanism, *in-vitro* release data were fitted into various kinetic models which technically supported the sustained property of the dosage form.

MATERIAL

Losartan Potassium was a gift sample from Microlab Ltd. India. Eudragit RS and Eudragit RL were provided by Evonik Industries as gif samples. Dichloromethane, Polyvinyl alcohol, Hydroxypropylmethyl cellulose (HPMC K100), Carbopol 940, Sodium carboxy methyl cellulose, Microcrystalline cellulose, Aerosil, Talc, magnesium stearate and all other chemicals were of analytical grade.

METHODS

Losartan potassium loaded sustained release microcapsules were prepared by modified double emulsion solvent evaporation method[2]. The particle sizes of the microcapsules were found to be in a range of 250-292 µm along with high encapsulation efficiency (84%)[2]. Then the microcapsules were punched into mucoadhesive gastro retentive tablets (LP 2) by using Rimek Mini Press-II fully automatic 12 station tablet punching machine. The tablets were prepared by direct compression method. Combination of hydrophilic polymers HPMC K100M and Carbopol 940 along with mucoadhesive polymer sodium carboxy methyl cellulose were passed through sieve no. #60 separately. All other necessary excipients like microcrystalline cellulose (MCC), Aerosil, talc etc. were also passed through sieve no. #60 and then they were mixed together with polymers and previously prepared microcapsules. 12 mm single-punches were used to produce round tablets weighing 600 ± 5 mg. Presence of microcapsules inside the tablets were confirmed by Scanning Electron Microscopy (SEM).

Drug release studies

In vitro dissolution study of the tablet LP 2 was done by using dissolution apparatus type II (paddle type) in 900 mL of simulated gastric fluid (pH 1.2) at 37°C ± 0.5°C with 50 rpm. The marketed formulations were marked as MF1, MF2 and MF3 respectively. The release was till 8 hours from all the marketed formulations where LP 2 showed an ideal sustained

release property till 14th hour with a higher percentage cumulative release of 91.074 ± 0.54%. Mathematical modeling of the release kinetics was done only for microcapsule loaded LP 2 tablet formulation by using PCP Disso V3 and the result was found to be **'zero order'** kinetics which is in generally considered to be ideal for sustained release dosage forms.

PCP-Disso-v3

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% Release (Average) with model fitting

Name of the Drug = Losartan Potassium Batch = LP2 Date = 4.4.2015
Loading Dose in mg = 25
Total no. of Readings, including 'Zero-time' reading = 15 Done by = Basu
Dissolution Medium = pH 1.2
RPM = 50
Volume of Dissolution Medium (ml) = 900
Volume of Sample removed (ml) = 5
Dilution Factor = 10
Slope of Calibration curve = 33.5452
Constant of Calibration curve = -0.1215
R of Calibration curve = 0.9996

Model Fitting (Average)-

	R	k	
Zero order	0.9875	7.0165	
T-test	22.594	(Passes)	
1st order	0.9417	-0.1483	
T-test	10.092	(Passes)	
Matrix	0.8973	21.2240	
T-test	7.330	(Passes)	
Peppas	0.9859	4.7985	
T-test	21.254	(Passes)	
Hix.Crow.	0.9668	-0.0371	
T-test	13.641	(Passes)	

t-Table at P0.05 (Two Tails), DF=n-2:-	2.16

Best fit model-	Zero order

Parameters for Korsmeyer-Peppas Equation-	
n =	1.1569
k =	4.7985

MODEL FITTING: Residual Sum of Squares

RESULTS				Zero	1st order	Matrix	Peppas	Hix.Crow.
Sr.No.	Time	Avg. %R	SD	390	2844	3062	386	1461
1	0	0.000		0.000	0.000	0.000	-	0.000
2	1	6.494		0.273	53.034	216.969	2.875	17.838
3	2	8.945		25.883	279.214	443.935	3.078	136.778
4	3	12.618		71.092	541.933	582.892	20.128	295.219
5	4	22.348		32.689	500.861	403.988	2.281	252.083
6	5	27.302		60.530	627.033	406.261	12.846	347.689
7	6	38.321		14.272	423.838	186.781	0.033	215.462
8	7	49.400		0.081	230.103	45.604	14.551	100.179
9	8	59.332		10.242	102.381	0.488	37.589	34.522
10	9	68.110		24.620	30.792	19.698	51.010	5.363
11	10	76.935		45.837	0.125	96.414	65.019	3.388
12	11	83.392		38.570	8.849	168.995	42.136	17.205
13	12	87.467		10.686	18.938	194.455	5.865	20.812
14	13	89.146		4.276	13.730	159.325	17.224	9.235
15	14	91.074		51.212	13.160	135.995	111.813	4.802

Figure 1: Release Kinetics Report for Final Formulation LP2 from PCP Disso V3

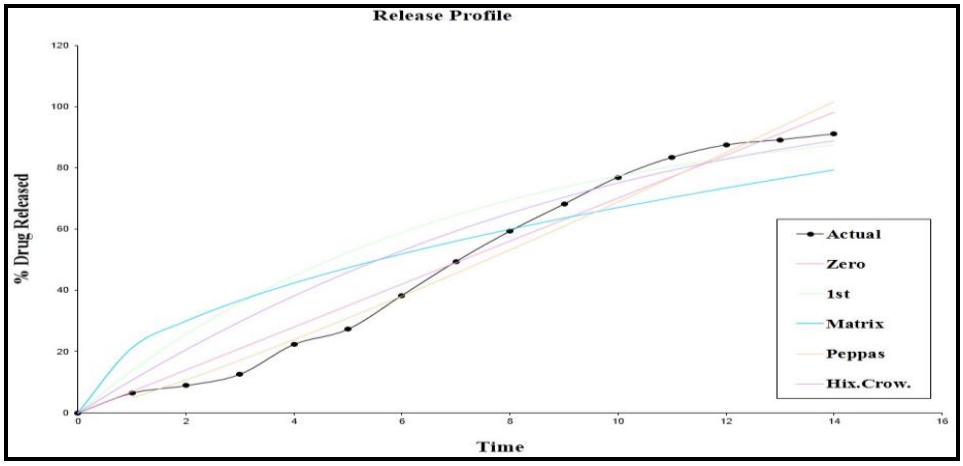

Figure 2: Graphical Representation of Release Kinetics Depicting Various Kinetic Models of LP2.

Table 1: Comparative Release Study of LP2 vs. Marketed Formulations

Time (Hour)	*Cumulative Percentage Release (% CPR)			
	LP 2	MF 1	MF 2	MF 3
0	0	0	0	0
1	6.494±0.1	50.531±0.2	30.19±0.43	37.37±0.22
2	8.454±0.05	54.12±0.45	48.44±0.22	44.55±0.29
3	12.618±0.3	60.06±0.24	54.11±0.09	50.53±0.61
4	22.348±0.05	71.46±0.38	60.09±0.46	58.60±0.48
5	27.30±0.16	80.43±0.31	73.25±0.20	70.26±0.40
6	38.32±0.15	86.11±0.13	85.21±0.35	82.25±0.39
7	49.4±0.26	93.28±0.59	92.99±0.07	95.98±0.54
8	59.332±0.32	99.56±0.2	98.67±0.56	98.37±0.12
9	68.110±0.47			
10	76.94±0.04	-	-	-
11	83.392±0.33	-	-	-
12	87.46±0.27	-	-	-
13	89.15±0.3	-	-	-
14	91.074±0.54	-	-	-

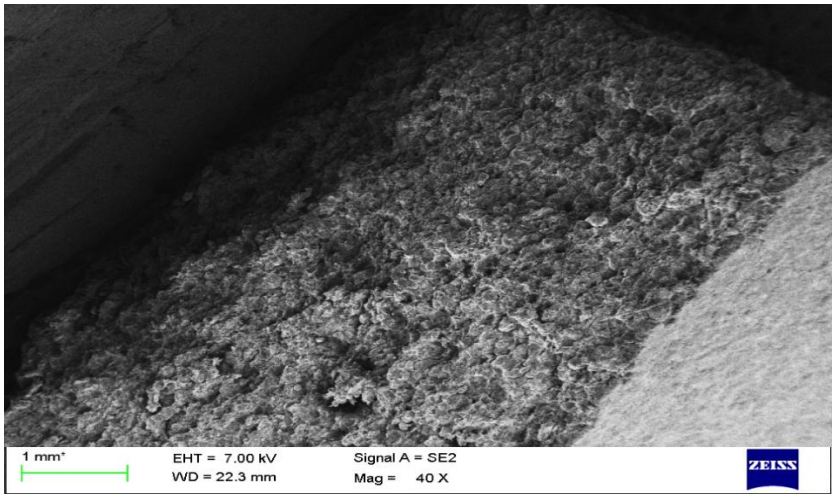

Figure 3: Uniform porous structure of tablet cross section

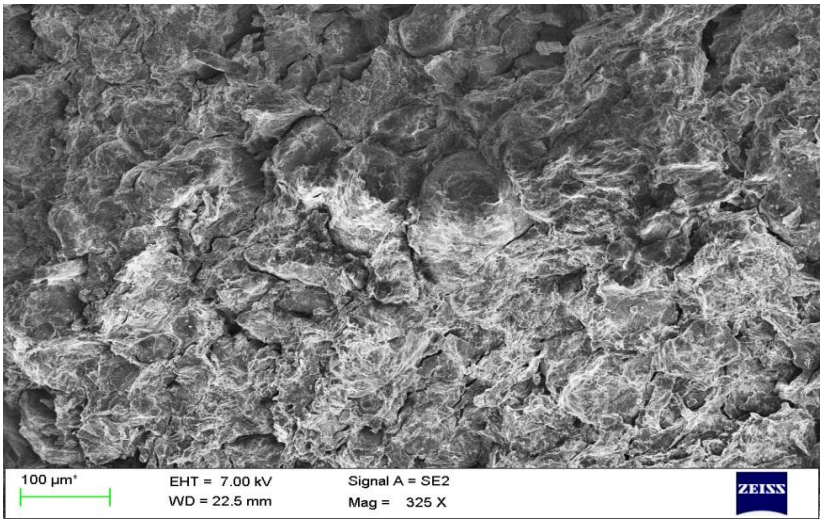

Figure 4: Image showing the presence of microcapsules inside the tablet

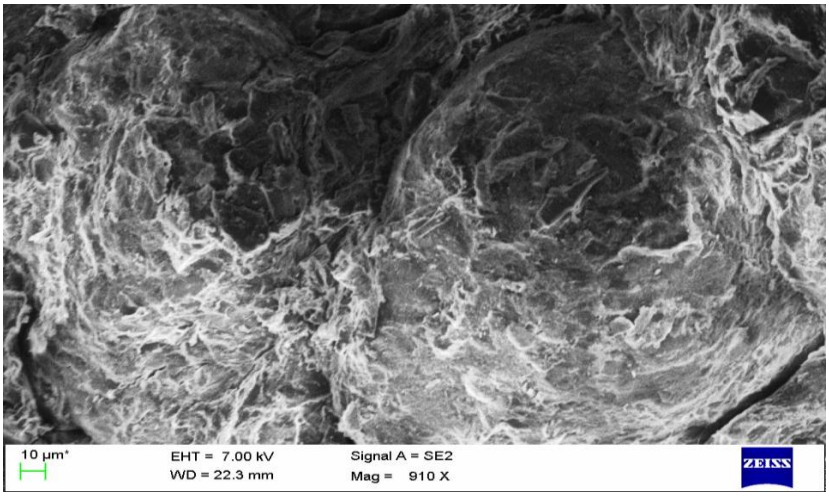

Figure 5: Ultra High magnification images depicting the microcapsule morphology inside the tablet.

CONCLUSION

The release behaviour of microcapsule loaded tablets fabricated with Eudragits RS & RL along with Carbopol, HPMC etc. have shown a superb dissolution property better than the conventional marketed formulations. Extensive consideration must be concentrated on understanding the mathematical models used to describe pharmaceutical developments, as these offer a beneficial guide and perception into the release property of the anti-hypertensive drugs and mechanisms from sustained-release technologies.

WAY FORWARD

As for the future perspective various responsive parameters like Mean dissolution time (MDT), ANOVA, Variance etc. related to the dissolution study can be done for this.

Sustained release formulation for losartan potassium is still not available in global market therefore on the acceptance it is also feasible to produce this on industrial level with the help of proper scale up.

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