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COMPARATIVE STUDY OF DRUG RELEASE OF CARVEDILOL MICROPARTICLES BY USING DIFFERENT POLYMERS

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ABSTRACT

Microspheres/microparticles constitute an important part of drug delivery system by virtue of their small size and efficient carrier characteristics. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. The objective of the present investigation is to design and evaluate controlled release tablets of carvedilol, which were prepared by solvent evaporation method by using different polymer (Ethyl cellulose, Cellulose acetate, Hydoxy Ethyl Cellulose).The *in vitro* release kinetics was carried out by fitting the release data to models representing zero-order, first-order, and Higuchi's square root of time. It was found that all the formulations were best fit into Higuchi's square root release model. It confirmed that the drug is very slowly diffusing out of the polymer matrices and showing a much sustained release.

KEYWORDS: Carvedilol, Kinetic release, Encapsulation efficiency, Drug-polymer ratio.

INTRODUCTION

Microparticles are a type of drug delivery systems where the particle size ranges from one micron (one thousandth of mm) to few mm. This microencapsulation technology allows protection of drug from the environment, stabilization of sensitive drug substances, elimination of incompatibilities, or masking of unpleasant taste. Hence, they play an important role as drug delivery systems aiming at improved bioavailability of conventional drugs and minimizing side effects.[1] The most significant feature of microcapsules is their microscopic size that allows for a huge surface area, for example the total surface area of 1µm has been reported to be about 60m2. The total surface area is inversely proportional to the diameter. This large surface area is available for sites of adsorption and desorption, chemical reactions, light scattering etc.[2]

Ideally, the drug release should occur from the individual particles, which should not be affected by the compression process. However, excipients used in tableting should provide a sufficient cushioning effect to withstand the compression force and, thereby, prevent the merging or rupturing of the microparticles. In particular, ethylcellulose based microparticles have gained much more attention in developing controlled release microparticulate systems because of their flexibility to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance 6.Controlled-release characteristics of microparticles reduce the need for frequent administrations and enhance patient compliance by maintaining in drug levels in the therapeutic range.[3]

In recent years considerable attention has been focused on the development of new drug delivery systems. In spite of the recent technological advances in the fabrication of oral controlled-release dosage forms, particular attention has been paid to the regulation of drug release rate by means of monolithic devices, whereby prior dispersion of the drug in a polymer matrix is carried out.[4]

Carvedilol is chemically (+)-1-(Carbazol-4-yloxy)-3-{[2-(o-methoxy phenoxy) ethyl]amino}-2-propanol and is an antihypertensive drug with a multiple action spectrum. It acts as a β receptor blocker, [5] and it also has vasodilating properties that are attributed mainly to its blocking activity at α_1 receptors. It is used in the treatment of mild-to-moderate hypertension and angina pectoris.[6]

In the present investigation, studies were undertaken for the design and development of controlled drug delivery systems of an antihypertensive drug, carvedilol.

MATERIALS AND METHODS

Carvedilol microparticles were prepared by solvent evaporation method by using different polymer (Ethyl cellulose, Cellulose acetate, Hydoxy Ethyl Cellulose) as Excipients.

Drug encapsulation efficiency

In vitro drug release from different formulation was investigated using phosphate buffer solution of pH-6.8(without enzyme).Microspheres (50mg) was mixed in 1 ml phosphate buffer solution and was place within dialysis membrane. The sample within the dialysis membrane was kept in conical flask containing 900ml phosphate buffer as the dissolution medium on a shaker at 100 rpm at 37^0c. 10ml aliquots was withdraws from suspension at the selected specific time intervals.The volume withdrawn was replenish with an equal volume of fresh & pre-warmed phosphate buffer at 37^0c. Sample were analysed by UV Spectrophotometer at ƛmax value of 241nm using phosphate buffer as the blank.

To analyze the *in vitro* release data, various kinetic models were used to describe the release kinetics. The drug release profile obtained in dissolution test was plotted in different models.

In-vitro drug release

Formulation F1 to F6 were prepared using various cellulose derivatives of polymer concentration microspheres were evaluated in vitro cumulative release.

In F1 &F2 formulation the EC polymer concentration was 1 & 2%w/w the drug entrapment was found to be 75.58 % & 94.41 % of the microsphere were buoyant after 48 hours. However, the concentration of polymer is increases then the drug release rate is increases.

In F3 &F4 formulation the CA polymer concentration was 1 & 2%w/w the drug entrapment was found to be 73.74 % & 80.03 % of the microsphere were buoyant after 24 hours. However, the concentration of polymer is increases then the drug release rate is increases.

In F5 &F6 formulation the HEC is used as a polymer & the concentration polymer was 1 & 2%w/w the drug entrapment was found to be 46.16 % & 52.23 % of the microsphere were buoyant after 12 hours. However, the concentration of polymer is increases then the drug release rate is increases.

Out of all formulation the maximum drug release at F2 formulation using EC as a polymer. Microspheres showed the best drug release characteristics, releasing the drug for a period of 24 h. The minimum drug release rate was observed in F5 & F6 formulation using HEC as a polymer. Microspheres showed the less drug release characteristics, releasing the drug for a period of 12 h.

The *in vitro* release profiles of cellulose derivatives formulation (F1 to F6) containing different concentration of Polymer were given in Table. 1 & in vitro release profile was shown in figure no.1.

Table 1: *In-vitro* cumulative % release.

Time	F1	F2	F3	F4	F5	F6
1	5.9851931	3.1461373	4.3821888	4.3049356	1.0023605	1.098927
3	10.90471	6.3889378	9.5631867	10.122843	4.9092167	7.1500966
6	15.465107	12.604592	15.583991	18.02015	14.013712	15.822833
9	20.763165	18.159303	24.301255	29.609303	30.892028	35.279796
12	26.903273	25.982897	34.16926	39.330955	**46.164109**	52.237071
15	32.227071	31.80412	43.181685	48.064721		
18	39.026191	38.07985	53.384549	58.98765		
21	45.033562	45.58883	65.050719	70.435247		
24	52.46368	55.050386	73.749818	80.030697		
30	58.212897	65.333723				
36	63.760708	74.032822				
42	68.8374	86.3493				
48	75.58195	**94.40579**				

Zero order rate kinetics

Zero order rate kinetics describes thes system where the drug release rate is independent of concentration and plotted as amount of drug release versus time.

C = K0t.....eq

Where,

K0 is the zero order rate constant, expressed in units of concentration/ time.

T is the time in hours.

First order rate kinetics

First order rate kinetics describes the release from system where release rate is concentration dependent and shows the log cumulative percentage of drug remaining in soluble matrix as a time dependent process (log% drug remained v/s time in hr).

log C = log C0 - kt/2.303.....eq

Where, C0 is the initial drug concentration.

C is the drug concentration at time t.

K is the first order rate constant reflecting the design variables of the system

Higuchi square root kinetics
Higuchi square root kinetics describes the release of drug from insoluble matrix as square root of time dependent process based on Fickian diffusion equation. (% cumulative release v/s square root of time).
$Q = Kt^{1/2}$.....eq

Where, Q is the percentage of drug release at time t.
K is Higuchi release rate constant that reflects the shape and the in internal structure of the matrix as well as the drug concentration and solubility.

Korsmeyer - peppas model
Korsmeyer - peppas model which is log cumulative % drug release vs. log time which is to find out the mechanism of drug release (log cumulative % drug release v/s log time.
$Q = K_2 t^n$

Where,
K_2 = constant incorporating the structural and geometric characteristics of microparticle.
N = the release exponent indicating the drug release mechanism.

RESULTS AND DISCUSSION

Production yield and Encapsulation efficiency
Encapsulation efficiency of the microparticle prepared with ethyl cellulose was higher (F1, F2) than for the microparticle prepared with the cellulose acetate & hydroxyethylcellulose (F3, F4, F5, F6). Thus, the yields of ethyl cellulose using as polymer highly active material encapsulation efficiency compared to that of HEC & CA.

The encapsulation efficiency and production yield of Carvedilol-loaded Encapsulation efficiency of the microparticle prepared with ethyl cellulose was higher (F1, F2) than for the microparticle prepared with the cellulose acetate & hydroxyethylcellulose (F3, F4, F5, F6). Thus, the yields of ethyl cellulose using as polymer highly active material encapsulation efficiency compared to that of HEC & CA.

The encapsulation efficiency and production yield of Carvedilol-loaded Cellulose derivatives microspheres are shown in Table 8. All microsphere formulations (F1-F6) were produced with high production yield and encapsulation efficiency. The yield of production ranged from 44.11 % - 75.31 %. The encapsulation efficiency of Carvedilol within HEC, CA, EC microspheres was between 46.16 % - 94.40%. The overall results have shown that Cellulose derivative is a suitable polymer for the encapsulation of a hydrophilic drug. When yield of production and encapsulation efficiency of various formulations were evaluated it was found that the drug/polymer ratio does affect the production yield & the encapsulation efficiencies.

However, the encapsulation efficiency of the microspheres was affected by the variation of the drug/polymer ratio and PVA concentration. As the polymer concentration was increased, the increased the encapsulation efficiency of the microspheres increased. As the PVA concentration was not affected on encapsulated efficiency.

It is clear that % encapsulation efficiency of Carvedilol in the microspheres increases with increasing amount of Polymer concentration.

It is assured that the higher percentage of polymer gave better encapsulation efficiency, Encapsulation efficiency of the microparticle prepared with ethyl cellulose was higher (F1, F2,) than for the microparticle prepared with the cellulose acetate & Hydroxy ethyl cellulose (F3, F4, F5, F6).

Table 2: Results of Production Yield & Encapsulation efficiency of different formulation.

Formulatn no.	Drug	Ethyl cellulose	Cellulose acetate	Hydroxy ethyl cellulose	PVA	Production Yield (%)	% Encapsulation efficiency
F1	10	200	-	-	1%	71.43%	75.58%
F2	10	400	-	-	1%	**75.31%**	**94.40%**
F3	10	-	200	-	1%	45.91%	73.75%
F4	10	-	400	-	1%	50.69%	80.03%
F5	10	-	-	200	1%	**44.11%**	**46.16%**
F6	10	-	-	400	1%	48.11%	52.23%

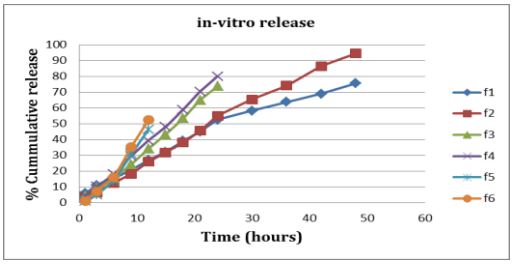

Figure 1: *in-vitro* graph of formulation F1 – F6.

Release kinetics
The *in vitro* release kinetics was carried out by fitting the release data to models representing zero-order, first-order, and Higuchi's square root of time. The correlation coefficient of different kinetic models for all the formulations containing various polymers is tabulated in Table 3. It was found that all the formulations were best fit into Higuchi's square root release model. It confirmed that the drug is very slowly diffusing out of the polymer

matrices and showing a much sustained release. To examine the mechanism of release the data were fitted to Korsmeyer-Peppas model. According to Korsmeyer-Peppas, a value of the exponent, n=0.5, 0.5<n<1, n=1.0 indicates Fickian diffusion, non-Fickian diffusion and Case II transport, respectively. Studies revealed that for all the formulations, n values greater than 0.5 indicating a non- fickian release.

Table 3: Correlation coefficient (r), reaction rate constants (k) and diffusion exponent (n) of the model equations applied to the release of carvedilol from microparticles.

Formulation No.	Higuchi		Zero order		1st order		K-peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F1	0.9965	22.7981	0.8577	4.3920	0.8858	0.13086	0.9879	0.745
F2	0.9843	11.9158	0.8953	2.12893	0.90741	0.05398	0.9886	0.86622
F3	0.9813	17.6332	0.8996	3.1549	0.8219	0.07111	0.9972	0.846
F4	0.9801	18.8026	0.8992	3.3504	0.8633	0.0602	0.9992	0.829
F5	0.9805	18.2008	0.8723	4.1945	0.9148	0.1444	0.9979	0.5508
F6	0.9847	20.4166	0.8729	4.6954	0.96395	0.07227	0.9956	0.5377

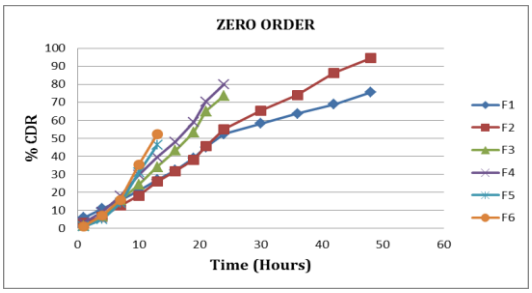

Figure 2: Graph of Zero Order.

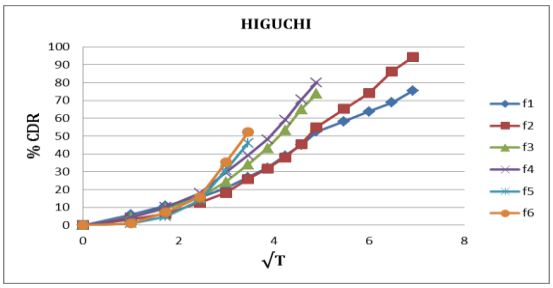

Figure 3: Graph of Higuchi.

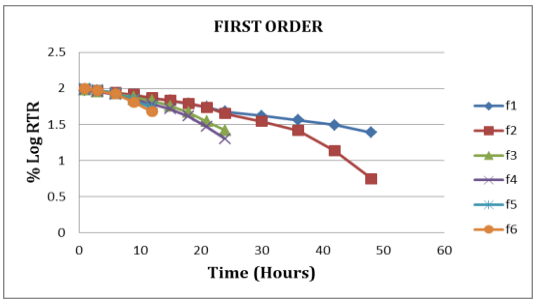

Figure 4: Graph of First Order.

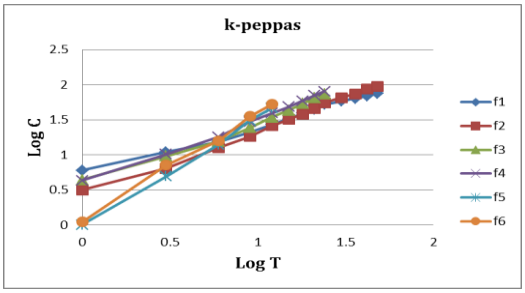

Figure 5: Graph of K- Peppas.

CONCLUSION

Encapsulation efficiency of the microparticle prepared with ethyl cellulose was higher (F1, F2) than for the microparticle prepared with the cellulose acetate & hydroxyethylcellulose (F3, F4, F5, F6). Also as the concentration of polymer increases drug release increase. Therefore in future it can be use to prepare control drug release formulations with more effective encapsulation efficiency.

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