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OPTIMIZATION OF THE RELEASE KINETICS OF DILTIAZEM HYDROCHLORIDE FROM TABLETED MICROSPHERES

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ABSTRACT

Formulation F_5, F_6, F_7 and F_8 were selected to make the tablets because of their high percentage release (more than 90%). 500 mg weight of tablets containing 120 mg strength of Diltiazem hydrochloride were prepared from formulations F_5, F_6, F_7 and F_8. release of Diltiazem hydrochloride at different interval of time: 1 hr, 4 hrs, 8 hrs and 12 hrs for different formulations, it can be concluded that more than 90% of Diltiazem hydrochloride was released from formulations F_1, F_3, F_5, F_6, F_7, F_8, F_9, F_{11} at 12 hours. After compaction into the tableted form, the dissolution or release of the drug will reduce. Hence, these formulations may be compressed into the tablet forms so that the release should be around or more than 80%. Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models, Weibull model, Baker – Lonsdale model, Hopfenberg model, etc. These models are used to characterize drug dissolution/release profiles.

Keywords: Optimization, Microsphere, Diltiazem hydrochloride, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models.

INTRODUCTION

The concept of drug delivery has been revolutionized with the advancement in drug delivery systems, especially those offering a sustained and controlled action of drug to desired area of effect[1].

Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably.

The term microparticles refer to a particle with a diameter of 1-1000µm, irrespective of the precise interior or exterior structure. [2] Microsponges are polymeric delivery systems composed of porous microspheres. They are tiny sponge-like spherical particles with a large porous surface. Moreover, they may enhance stability, reduce side effects and modify drug release favorably[3].

Microspheres usually have diffusion controlled release profiles with a permanent release rate that is controlled kinetically by the particle size, whereas microcapsules usually have diffusion or dissolution controlled release profiles or both. Microcapsules expel their content by a single high burst as the shell breaks or slow releases.

Figure 1: microsphere

Hard gelatin capsules are very elegant dosage forms, but have the disadvantages of higher production cost, lower

production rate and tampering potential when compared to compressed tablets. Microspheres have been tableted to control or modify the release of the drug. The tablet manufacturing process from microspheres will create a single unit from a multi-particulate system in order to produce compact forms that disintegrate into many subunits soon after ingestion to attain more uniform

concentrations of the drug in the body. Reduced risk of tampering, higher dose strength per unit and higher production rate of the tablet process can be listed among the advantages of tabletting[4]

METHODS

Optimization of below given formulation:

Table 1: Formulations of Diltiazem hydrochloride loaded Microspheres prepared with different Polymers and Polymer mixtures (Drug: Polymer =1:1)

Contents of Formulations	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Diltiazem hydrochloride(gm)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Eudragit RL 100 (gm)	2.0	-	-	-	1.0	-	1.0	-
Eudragit RS 100 (gm)	-	2.0	-	-	1.0	-	-	1.0
Eudragit RLPO (gm)	-	-	2.0	-	-	1.0	-	1.0
Eudragit RSPO (gm)	-	-	-	2.0	-	1.0	1.0	-
Magnesium Stearate (gm) (Dispersing Agent)	0.300	0.300	0.300	0.300	0.300	0.300	0.300	0.300
Methanol (ml)	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Acetone (ml)	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
Liquid paraffin (ml)	100	100	100	100	100	100	100	100
Drug : Polymer	1: 1	1: 1	1: 1	1: 1	1: 1	1: 1	1:1	1: 1
Magnesium Stearate (%)	3	3	3	3	3	3	3	3

Table 2: Formulations of Diltiazem hydrochloride loaded Microspheres prepared with different Polymers and Polymer mixtures (Drug: Polymer =1:2)

Contents of Formulations	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}
Diltiazem hydrochloride (gm)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Eudragit RL 100 (gm)	4.0	-	-	-	2.0	-	2.0	-
Eudragit RS 100 (gm)	-	4.0	-	-	2.0	-	-	2.0
Eudragit RLPO (gm)	-	-	4.0	-	-	2.0	-	2.0
Eudragit RSPO (gm)	-	-	-	4.0	-	2.0	2.0	-
Magnesium Stearate (gm) (Dispersing Agent)	0.600	0.600	0.600	0.600	0.600	0.600	0.600	0.600
Methanol (ml)	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
Acetone (ml)	14.0	14.0	14.0	14.0	14.0	14.0	14.0	14.0
Liquid paraffin (ml)	200	200	200	200	200	200	200	200
Drug : Polymer	1: 2	1: 2	1: 2	1: 2	1: 2	1: 2	1: 2	1: 2
Magnesium Stearate (%)	3	3	3	3	3	3	3	3

Optimization of release rate

After observing the release of Diltiazem hydrochloride at different interval of time: 1 hr, 4 hrs, 8 hrs and 12 hrs for different formulations, it can be concluded that more

than 90% of Diltiazem hydrochloride was released from formulations F_1, F_3, F_5, F_6, F_7, F_8, F_9, F_{11} at 12 hours.

After compaction into the tableted form, the dissolution or release of the drug will reduce. Hence, these formulations may be compressed into the tablet forms so that the release should be around or more than 80%.

Co-relation between particle size and *in-vitro* release

The particle size in mean diameters along with their cumulative percent release is tabulated below;

Table 3: Correlation between mean particle size and in-vitro release of microspheres

Formulation	Drug: Polymer ratio	Mean Particle size (μm)	Cumulative % Drug released at 12 hrs
F_5		243.75	93.85
F_6	1: 1	230.25	94.98
F_7		206.00	94.24
F_8		212.25	97.53
F_{13}		354.75	72.75
F_{14}	1: 2	359.00	66.23
F_{15}		370.75	66.72
F_{16}		334.00	67.41

Hence from the above result, it can be concluded that as the particle size of the microspheres increased, the release rate of Diltiazem hydrochloride decreased. Hence, particle size of microsphere is inversely proportional to the release of drug from microspheres. It can be explained on the basis, that as the polymer amount increases, the matrix wall of microspheres become thicker. The formation of a thick wall lead to slower dissolution rate of drug caused by longer diffusional path.

Tableting of Microspheres

Formulation F_5, F_6, F_7 and F_8 were selected to make the tablets because of their high percentage release (more than 90%). 500 mg weight of tablets containing 120 mg strength of Diltiazem hydrochloride was prepared from formulations F_5, F_6, F_7 and F_8. Microspheres along with excipients - lactose monohydrate, microcrystalline cellulose and sodium starch glycolate as disintegrant were compressed into tablets using single stroke tablet machine.

In – vitro **Dissolution of tableted microspheres**

Compaction of drug loaded microparticulate powders into tablets have been reported as useful therapeutic approach for oral administration of controlled release formulations. With respect to free powder, tablets can give more reproducible drug delivery and biopharmaceutical response, as well as a better patient compliance.

The release data of Diltiazem hydrochloride from tableted microspheres are shown in Figure. The in-vitro release profile of tableted microspheres indicated that the release of the drug was slow than that of microspheres. The release increased gradually and up to 12 hrs, more than 85% of drug was into the medium from tableted formulations (TF_5, TF_6, TF_7 and TF_8). As the initial burst release of drug was observed in microspheres (F_5, F_6, F_7 and F_8). However, tableting of the microparticulate systems can overcome the disadvantage of such initial large 'burst' release.

Table 4: Cumulative release of Diltiazem hydrochloride from tableted microsphere

Formulation	Composition	Drug: Polymer Ratio	Cumulative % Release of Diltiazem hydrochloride			
			1 hrs	4 hrs	8 hrs	12 hrs
Tab F_5	RL100 : RS100		5.16	25.53	65.28	91.18
Tab F_6	RLPO : RSPO	1: 1	6.94	30.10	61.59	88.18
Tab F_7	RL100 : RSPO		5.92	27.93	63.43	89.59
Tab F_8	RS100 : RLPO		8.08	32.11	66.31	86.35

The dissolution profiles of Formulation TabF5, TabF6, TabF7, and TabF8 were analyzed statistically by ANOVA.

Table 5: Comparison of dissolution profiles of Formulation TabF5, TabF6, TabF7, and TabF8 using one way ANOVA

Formulations	Calculated values of 'F'				Table value ($F_{0.05}$)*
	1st hour	4th hour	8th hour	12th hour	
TabF5, TabF6, TabF7, and TabF8	2.136	1.928	2.025	2.632	4.0662

* D.F. = Degree of freedom = (3, 8)

From the ANOVA test it was found that there was no significant difference among the Formulation TabF5, TabF6, TabF7, and TabF8 at the time of 1 hr, 4 hr, 8 hr and 12 hr. This is because all the tablets contained the microspheres of combination of Eudragit RL and RS – type.

Comparison of *In–vitro* Dissolution of microspheres and tableted microspheres

The dissolution profiles of microspheres and tableted microspheres were analyzed statistically by student-t test.

Table 6: Comparison of dissolution profiles of microspheres and tableted microspheres using *student-t test*

Formulations	Calculated values of 't'				Table value ($t_{0.05}$)*
	1st hour	4th hour	8th hour	12th hour	
F5 – TabF5	5.328	14.79	1.440	2.023	
F6 – TabF6	4.345	13.784	1.687	1.973	
F7 – TabF7	7.750	19.528	1.878	1.118	
F8 – TabF8	5.161	16.81	1.940	1.312	2.132

* D.F. = Degree of freedom = 4

From the student-t test it was found that there was a significant difference between dissolution profiles of microspheres and tableted microspheres from 1-4 hours. But there was not any significant difference between these for the 8-12 hours.

Two reasons can be attributed to this reason:

First, tableting of microspheres reduces the initial burst release of the drug from the formulation.

Second, it is clear from the mathematical models, that the release of Diltiazem hydrochloride from microspheres F5 – F8 follows anomalous transport (n= between 0.5 – 1.0 for Peppas model, that corresponds to diffusion, erosion and swelling mechanism or mixed order kinetics). Whereas, formulation TabF6 and Tab F8 follow zero order kinetics (n≈ 1 for Peppas model), and formulation TabF5 and TabF7 follow case – II transport (n>1 for Peppas model, that correspond to erosion and relaxation of swollen polymer). So, there is significant difference from the student-t test it was found that there was a significant difference between dissolution profiles of microspheres and tableted microspheres from 1-4 hours.

Mathematical model: [5]

Several theories and kinetic models describe the dissolution of drug from immediate release and modified release dosage forms. There are several models to represent the drug dissolution profiles where f(t) is a function of time related to the amount of drug dissolved from the pharmaceutical dosage form.

The quantitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of generic equation that translates the dissolution curve, function of some parameters related with the pharmaceutical dosage forms. Drug dissolved from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson-Crowell models, Weibull model, Baker – Lonsdale model, Hopfenberg model, etc. These models are used to characterize drug dissolution/release profiles.

(a) Zero Order Kinetics

This model represents an ideal release profile in order to achieve the pharmacological prolonged action. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (that is, a constant release rate).

The following equation is used to express the model:

$$Q_t = Q_o + K_o t$$

Where Q_t is the amount of drug dissolved in time t

Q_o is the initial amount of drug in the solution

K_o is the zero order release constant

For practical purposes the equation is rearranged:

Percent drug released = Kt

This is applicable to dosage forms like transdermal systems, coated dosage forms, osmotic systems as well as matrix tablets with low soluble drugs.

(b) First Order Kinetics

First order release constitutes drug release in a way that is proportional to the amount of drug remaining in its interior; in such a way that amount of drug released by unit time diminish.

The following equation is used to express the model:

$$\log Q_t = \log Q_o + Kt/2.303$$

Where Q_t is the amount of drug dissolved in time t

Q_o is the initial amount of drug in the solution

K is the first order release constant

For practical purposes the equation is rearranged:

log % of drug unreleased = Kt/2.303

This model is applicable to dosage forms such as those containing water-soluble drugs in porous matrices.

(c) Higuchi Model

Higuchi describes drug release as a diffusion process based in Fick's law, square root dependent.

The following equation is used to express the model:

$$Q_t = K_h t^{1/2}$$

Where Q_t is the amount of drug dissolved in time t

K_h is the first order release constant

For practical purposes the equation is rearranged:

Percent drug released = $Kt^{1/2}$

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drugs.

(d) Korsmeyer - Peppas Model

This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved

The following equation is used to express the model

$Q_t/Q_\infty = Kt^n$

Where Q_t is the amount of drug dissolved in time t

Q_∞ is the amount of drug dissolved in infinite time

n is the release exponent indicative of drug release mechanism

K is the kinetic constant

For practical purposes the equation is rearranged

Log percent drug released = log K + n log t

Peppas used n value in order to characterize different release mechanism concluding for values of n = 0.5 for

Fickian diffusion and values of n, between 0.5 to 1.0 for anomalous transport (corresponds to diffusion, erosion and swelling mechanism or mixed order kinetics) and higher values of n, n=1 (zero order release) or n>1 for case-II transport (corresponds to erosion and relaxation of swollen polymer layer).

(e) Hixson – Crowell Model

Hixson and Crowel recognizing that the particle regular area is proportional to the cubic root of its volume, derived an equation that can be described in the following manner:

$$(W_0)^{1/3} - (W_t)^{1/3} = K_s t$$

Where: W_0 - is the initial amount of drug in the dosage form

W_t - is the remaining amount of drug in the dosage form at time t

K_s - is a constant incorporating the surface- volume relationship

For practical purposes the equation is rearranged

(% Drug Unreleased)$^{1/3}$ = Kt

This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution. After fitting into these models, the selection was based on the comparison of higher determination coefficient (r^2).

Table 7 (i): Descriptive statistics of regression and other parameters of the mathematical models for the dissolution data of formulations F1 – F8

Model	Statistics	F1	F2	F3	F4	F5	F6	F7	F8
Zero Order	r^2	0.7793	0.9280	0.7851	0.9007	0.9157	0.8817	0.9085	0.8542
	p	<0.01	<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001
	slope	9.0430	4.5115	9.0159	4.5087	7.3090	7.2048	7.0346	6.9798
	K	9.0430	4.5115	9.0159	4.5087	7.3090	7.2048	7.0346	6.9797
First Order	r^2	0.9197	0.9747	0.9518	0.9598	0.9934	0.9972	0.9880	0.9697
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	slope	-0.2115	-0.0332	-0.1853	-0.0343	-0.0983	-0.1059	-0.0984	-0.1183
	K	0.4871	0.0765	0.4268	0.0790	0.2264	0.2439	0.2266	0.2725
Higuchi Model	r^2	0.9590	0.9914	0.9619	0.9854	0.9888	0.9839	0.9951	0.9807
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	slope	32.777	18.017	32.610	18.221	29.346	29.406	28.445	28.895
	K	32.777	18.017	32.610	18.221	29.346	29.406	28.445	28.895
Peppas Model	r^2	0.9604	0.9894	0.9644	0.9795	0.9764	0.9660	0.9863	0.9576
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	0.3810	0.4773	0.3845	0.4485	0.6427	0.5884	0.5525	0.5180
	K	45.384	18.858	44.679	20.951	21.009	24.536	25.416	29.174

Table 7 (ii): Descriptive statistics of regression and other parameters of the mathematical models for the dissolution data of formulations F9 – F16

Model	Statistics	F9	F10	F11	F12	F13	F14	F15	F16
Zero Order	r^2	0.8631	0.9623	0.8234	0.9589	0.9891	0.9823	0.9957	0.9898
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	slope	6.6277	4.0604	6.7626	4.2313	5.5202	4.8933	5.1454	5.1415
	K	6.6277	4.0604	6.7626	4.2313	5.5202	4.8933	5.1454	5.1415
First Order	r^2	0.9957	0.9878	0.9952	0.9899	0.9459	0.9759	0.9656	0.9786
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	slope	-0.0848	-0.0265	-0.1004	-0.0281	-0.0415	-0.0349	-0.0358	-0.0370
	K	0.1953	0.0610	0.2312	0.0647	0.0956	0.0804	0.0825	0.0852
Higuchi Model	r^2	0.9838	0.9821	0.9674	0.9897	0.9280	0.9645	0.9321	0.9584
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	slope	27.339	15.849	28.320	16.609	20.660	18.734	19.244	19.548
	K	27.339	15.849	28.320	16.609	20.660	18.734	19.244	19.548
Peppas Model	r^2	0.9632	0.9687	0.9402	0.9898	0.9796	0.9877	0.9866	0.9916
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	0.5223	0.5325	0.5098	0.5584	0.7326	0.6337	0.7793	0.6931
	K	27.146	13.807	29.655	13.782	10.371	12.451	8.640	11.138

* For Zero order, First order, Higuchi Model:n= 13 (For formulation F2, F4 – F16)   n= 10 (For formulation F1, F3)

\# For Peppas Model: n= 12 (For formulation F2, F4 – F16)   n= 9 (For formulation F1, F3)

Table 7(iii): Descriptive statistics of regression and other parameters of the mathematical models for the dissolution data of formulations TabF5 – TabF8

Model	Statistics	TF5	TF6	TF7	TF8
Zero Order	r^2	0.9920	0.9966	0.9953	0.9884
	p	<0.001	<0.001	<0.001	<0.001
	slope	8.2379	7.6144	7.9275	7.4613
	K	8.2379	7.6144	7.9275	7.4613
First Order	r^2	0.9263	0.9472	0.9377	0.9732
	p	<0.001	<0.001	<0.001	<0.001
	slope	-0.0850	-0.0739	-0.0787	-0.0707
	K	0.1958	0.1702	0.1813	0.1628
Higuchi Model	r^2	0.8962	0.9275	0.9112	0.9402
	p	<0.001	<0.001	<0.001	<0.001
	slope	30.253	28.381	29.307	28.113
	K	30.253	28.381	29.307	28.113
Peppas Model	r^2	0.9966	0.9979	0.9972	0.9942
	p	<0.001	<0.001	<0.001	<0.001
	n	1.2059	1.0423	1.1328	0.9885
	K	4.993	7.036	5.800	9.867

* For Zero order, First order, Higuchi, Model: n= 13 (For formulation TF5 – TF8)

\# For Peppas Model: n= 12 (For formulation TF5 – TF8)

Accelerated stability study

Formulations F_5, F_6, F_7 and F_8 were stored in glass bottle, after wrapping with aluminium foil, at 40^oC in humidity controlled oven for 3 periods of months. It was observed that there was no change in the morphology of microspheres, as well as no agglomerates were formed. The percentage residual drug content of microspheres were found to be 98.86% for F_5; 98.65% for F_6; 98.72% for F_7 and 98.36% for F_8 after storage for 3 months as compared to initial 100% content.

CONCLUSION

It is observed from the table that the determination co-efficient (r^2) of formulations F2, F4 – F16 and TabF5 – TabF8 was significant for zero-order. Similarly, the determination co-efficient (r^2) of formulations F1-F16 and TabF5-TabF8 for first order kinetics was also showing the significant correlation.

For Higuchi model, the determination co-efficient (r^2) of formulations F1-F16 and TabF5-TabF8 are significant. Hence, all were following Higuchi model.

Peppas model is used when the release mechanism is not well known or when more than one type of release phenomenon could be involved. It indicates the diffusional release mechanisms from polymeric films. The determination co-efficient (r^2) of formulations F1-F16 and TabF5-TabF8 are significant.

Here, in case of formulations F5-F8, the value of n was between 0.5-1.0, indicating *release kinetics* involves anomalous transport (that corresponds to diffusion, erosion and swelling mechanism or mixed order kinetics). Also for formulations TF5 and TF7, the value of n was >1, indicating that the release kinetics followed case – II transport (corresponds to erosion and relaxation of swollen polymer).

But for formulation TF6 and TF8, the value of n is ≈ 1, indicating that the release kinetics followed zero – order release.

Also the value of r^2 for TF5, TF6, TF7 and TF8 are maximum for zero order (among zero order, first order

and Higuchi model), indicating that the release of Diltiazem hydrochloride from these tablets followed zero order kinetics.

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