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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS CISAPRIDE CITRATE

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ABSTRACT

The objective of the Present study is to develop a pharmaceutically stable sustained release matrix tablets of Cisapride citrate and perform the pre-compression, post compression and *in-vitro* evaluation studies of developed formulation. In this study sustained release matrix tablets of Cisapride citrate were prepared by wet granulation method using Magnesium stearate, Talc, Lactose, Colloid silicon dioxide HPMC in various concentrations. All the formulations have showed acceptable Pharmacopeial standards. Formulation F9 have extended the release of Cisapride citrate upto 12 h. Model fitting analysis for formulation F9 fitted in the zero order model and korsemeyer-peppas model. The "n" values obtained from the peppas-korsemeyer equation suggested that, drug release was non-fickian diffusion mechanism. Successful formulation was found stable after evaluation for physicochemical parameters when kept for 30 days at room temperature, 40 ºC and 2-8 ºC

Keywords: HPMC.

Introduction

Sustained drug delivery

Probably the earliest work in the area of sustained drug delivery dosage forms can be traced from 1938 patent of Israel Lipowski. This work involved coated pellets for prolong release of drug and was presumably the forerunner to the development of the coated particle approach to sustained drug delivery that was introduced in the early 1950's. There has been 40 years of research and development experience in the sustained release area since that patent, and a number of strategies have been developed to prolong drug levels in the body. These range from the very simple, slowly dissolving pellets or tablets to the technologically sophisticated controlled drug-release systems which have been recently started to appear in the market and in pharmaceutical literature.

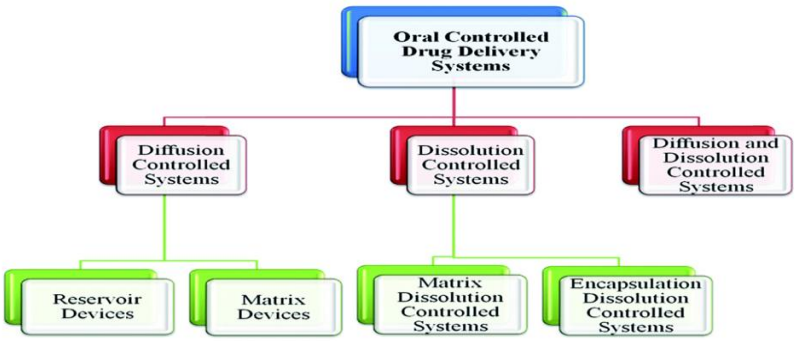

Figure 1: Oral drug delivery

Sustained Release Concept

A sustained release product may be considered one in which a drug is initially made available to the body in an amount sufficient to cause the desired pharmacological response as rapidly as is consistent with the properties of the drug determining its intrinsic availability for absorption; and one which provides for maintenance of activity at the initial level for a desirable number of hours in excess of the activity resulting from the usual single dose of drug.

For the pharmaceutical industry sustained release dosage forms provide multiple commercial benefits. Reduced dosing frequency improves patient compliance. Better therapeutic outcomes due to improved efficacy and improved tolerability can lead to fewer medication switches and greater physician loyalty. For any drug therapy to be successful, the drug must reach the target tissue or systemic circulation in optimum concentration which should be maintained for desired time. In recent years, attention has been focused on the development of new drug delivery system rather than invention of new molecules. Because the development cost for new drug molecule is very high. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effects by continuously releasing medication over an extended period of time after administration of single dose.

Sustained release and controlled release will represent separate delivery processes; sustained release constitutes any dosage from that provides medication over an extended period of time. Controlled release however, denotes that, system is able to provide same actual therapeutic control, whether this is temporal nature, spatial nature, or both. In other words, the system attempts to control drug concentration in target tissue. This correctly suggests that there are sustained-release systems that cannot be considered as controlled release.

In general, the goal of a sustained release dosage form is to maintain therapeutic blood level or tissue level of the drug for extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form. Zero order release constitutes of the amount of drug in the delivery system (a constant release rate). Sustained release systems generally do not attain this type of release and usually try to minis zero order release by providing drug in a slow first order fashion (concentration-dependent).

Oral ingestion has been the most convenient and commonly employed route of drug delivery. Indeed, for sustained – release systems, the oral route of administration has received the most attention with respect to research on physiological and drug constraints as well as designing and testing of products.

With most of orally administered drugs targeting is not primary concern, and it is usually intended for drugs to permeate to the general circulation and perfuse to other body tissues (the obvious exception being medication intended for local gastrointestinal tissue treatment), for this reason, most systems employed are of the sustained-release variety. It is assumed that increasing concentration at the absorption site will increase the rate of absorption and, therefore, increase circulating blood levels, which in turn promotes greater concentrations of the drug at the site of action. If toxicity is not an issue, therapeutic levels can thus be extended. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion.

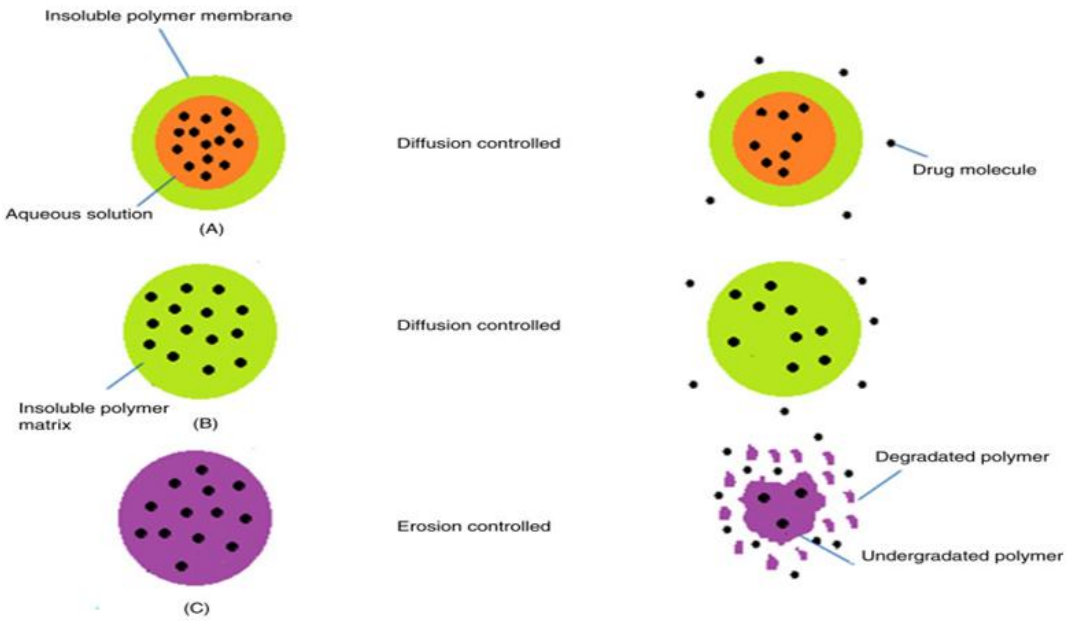

Figure: 2 Sustained Release Concept

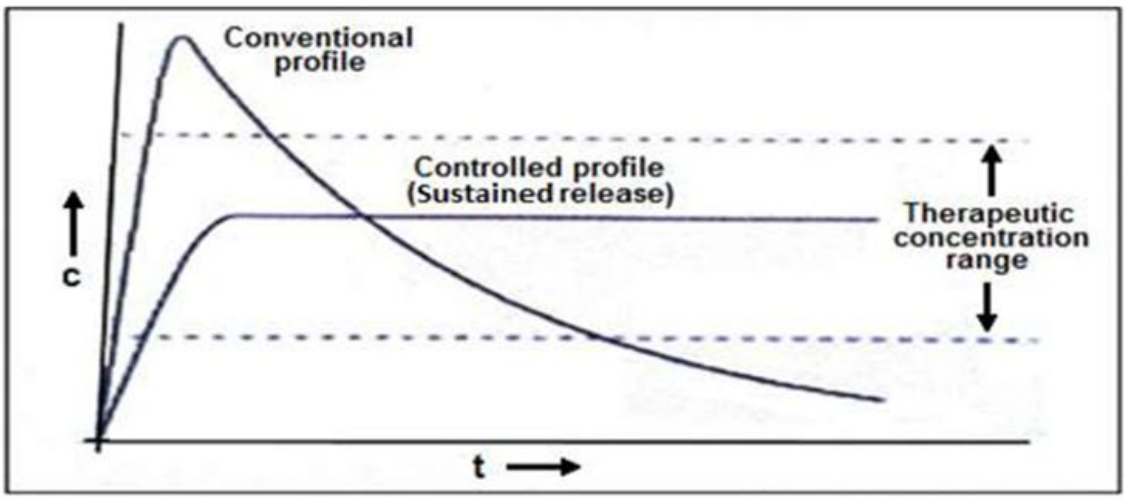

Figure 3: Comparison of Conventional and control release profile

METHODOLOGY

Preformulation Studies

Bulk Density

It is the ratio of a given mass of a powder and its bulk volume.

$$\text{Bulk Density} = \frac{\text{Mass of powder}}{\text{Bulk Volume of the powder}}$$

Tapped Density

Tapped density is the ratio of mass of powder to that of tapped volume of the powder

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume of the powder}}$$

Carr's Index A simple indication of the ease with which a material can be induced to flow is given by application of a compressibility index (I), given by the equation

Hausner's Ratio

Hausner's ratio is defined as the ratio of tapped density to poured density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Poured Density}}$$

Formulation variables for Cisapride citrate matrix tablets.

Table 1: Formulation ingredients

Ingredients	F1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Cisapride Citrate	15	15	15	15	15	15	15	15	15
HPMCK4M	10	15	-	10	15	18	16	20	20
HPMC K15 M	-	-	10	10	10	10	15	20	25
Lactose	73	68	73	62	58	55	52	43	38
Talcum	1	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Colloidal silicon dioxide(Aerosil)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

PHYSICOCHEMICAL EVALUATION OF TABLET

Post compression parameters:

Shape of tablet:

The compressed tablets were examined under the magnifying lens for the shape of tablet.

Uniformity of weight:

The USP weight variation test was carried out by weighing 20 tablets individually, calculating the average weight, comparing the individual tablet weight to average weight. The tablet meet USP test if no tablet differs by more than two times of percentage deviation.

Tablet thickness:

Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulation were taken randomly and thickness

was measured individually.

Hardness test:

Hardness of the tablet was determined by using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. The hardness was measured in terms of Kg/cm^2

Friability test:

The most popular and commercially available friability apparatus is the Roche Friabilator, in which approximately 6g (w_o) of dedusted tablets are subjected to 100 free falls i.e the apparatus revolves at 25rpm dropping the tablets through a distance of 6 inches in a rotating drum and are then reweighed (w). the friability,f, is given by:

$$f = 100.\ (1-w_o/w)$$

Values of f from 0.8 to 1.0% are regarded as the upper limit of acceptability

DATA ANALYSIS

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Korsmeyer and Peppas and Hixson Crowell model using PSP-DISSO – v2 software. Based on the r-value, the best-fit model was selected.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t$$

Where,

Q t = amount of drug dissolved in time t.

Q o = initial amount of the drug in the solution and

K o = zero order release constant.

First order kinetics:

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$\text{Log } Q_t = \log Q_o + K_1 t/2.303$$

Where,

Qt= the amount of drug released in time t,

Qo= the initial amount of drug in the solution

K1 = the first order release constant.

Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and

low soluble drugs incorporated in semisolids and/or solid matrices.

Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Q_t = K_H \cdot t1/2$$

Where,

Qt= amount of drug released in time t,

KH = Higuchi dissolution constant.

Korsmeyer and Peppas release model:

To study this model the release rate data are fitted to the following equation,

$$M_t / M ¥ = K \cdot t^n$$

t = the release time,

n = the diffusional coefficient for the drug release that is dependent on the shape of the matrix dosage form.

STABILITY STUDY

Stability of a pharmaceutical preparation can be defined as 'the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf-life.' The purpose of stability testing is to provide evidence on how the quality of drug substance or drug product varies with time under influence of a variety of environmental factors

such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

Long term testing: 25ºC±2 ºC/60% RH±5%RH for 12 months.

Accelerated testing: 40ºC±2 ºC/75% RH±5%RH for 6 months.

Evaluation of samples:

The samples were analyzed for the following parameters:

1. Physical evaluation:

Appearance: The samples were checked for any change in colour at every week.

Hardness: The samples were tested for hardness at every week.

2. Chemical evaluation:

Drug release: The samples were subjected to drug release studies.

RESULTS AND DISCUSSION

Precompression parameters

Table 2: Physical parameters of granules before dry granulation (slugging)

Physical Properties	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Bulk Density(gm/ml)	0.412	0.415	0.417	0.421	0.418	0.419	0.422	0.427	0.419
Tapped Density(gm/ml)	0.622	0.618	0.621	0.615	0.613	0.618	0.615	0.623	0.629
ıpressibility Index	31.87	32.12	31.21	31.27	30.78	30.89	31.42	31.28	30.87
Hausner's Ratio(H.R.)	1.33	1.42	1.45	1.47	1.449	1.43	1.47	1.44	1.45
Angle of Repose	34°21"	34°23"	32°69"	33°71"	32°39"	32°18"	31°63"	32°61"	33°35"
Observation	Poor Flow	Poor flow	Poor flow	Poor flow	Poor flow	Poor Flow	Poor flow	Poor Flow	Poor Flow

Physical parameters of granules after dry granulation (slugging)

For the granules of all the formulated batches, the results of the pre- compression parameters were found within their respective limits after carrying out dry granulation technique. The various parameters such as bulk density, tapped density, compressibility index, hausner's ratio and angle of repose were re-tested. Compressibility index was found within the limits 5-40. Hausner's ratio was less than 1.25 for all batches indicating good flow properties. The angle of repose was also found to be in the range of 25° to 30°, thus indicating that the flow properties were good.

Table 3: Physical parameters of granules after dry granulation

Physical Properties	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Bulk Density(gm/ml)	0.432	0.436	0.433	0.439	0.436	0.442	0.429	0.432	0.445
Tapped Density(gm/ml)	0.513	0.517	0.515	0.508	0.519	0.523	0.515	0.526	0.518
Compressibility Index**	15.31	15.27	14.24	14.19	15.78	15.61	16.69	17.12	15.24
Hausner's Ratio(H.R.)	1.12	1.19	1.17	1.13	1.16	1.19	1.21	1.24	1.17
Angle of Repose	24°17"	23°29"	23°41"	24°36"	24°53"	25°38 "	23°46"	26°58"	25°18 "
Observation	good flow	Good Flow	good flow	good flow	good flow	good flow	good flow	good flow	Good Flow

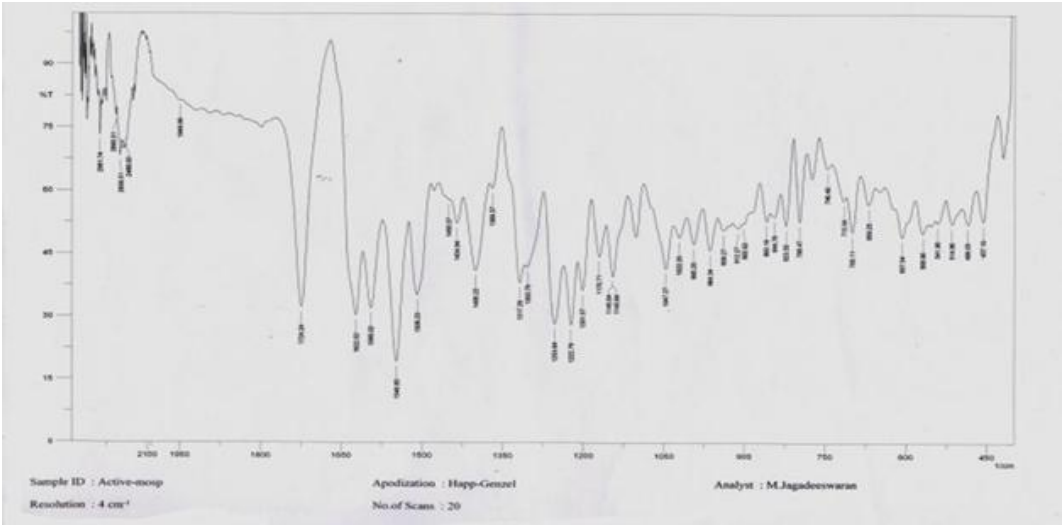

Figure 4: FTIR Spectra of Cisapride Citrate

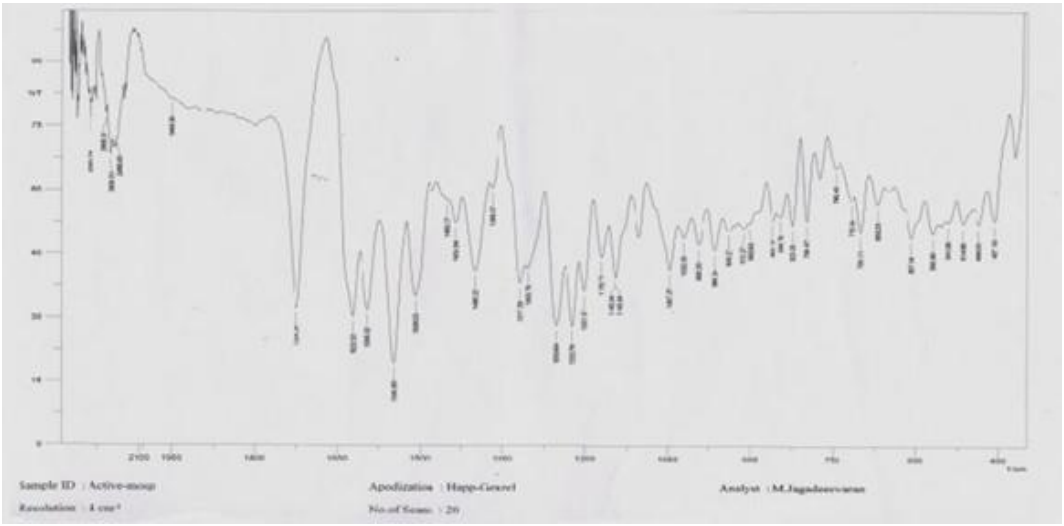

Figure 5: FTIR Spectra of Cisapride Citrate with HPMC K4M and HPMC K15M

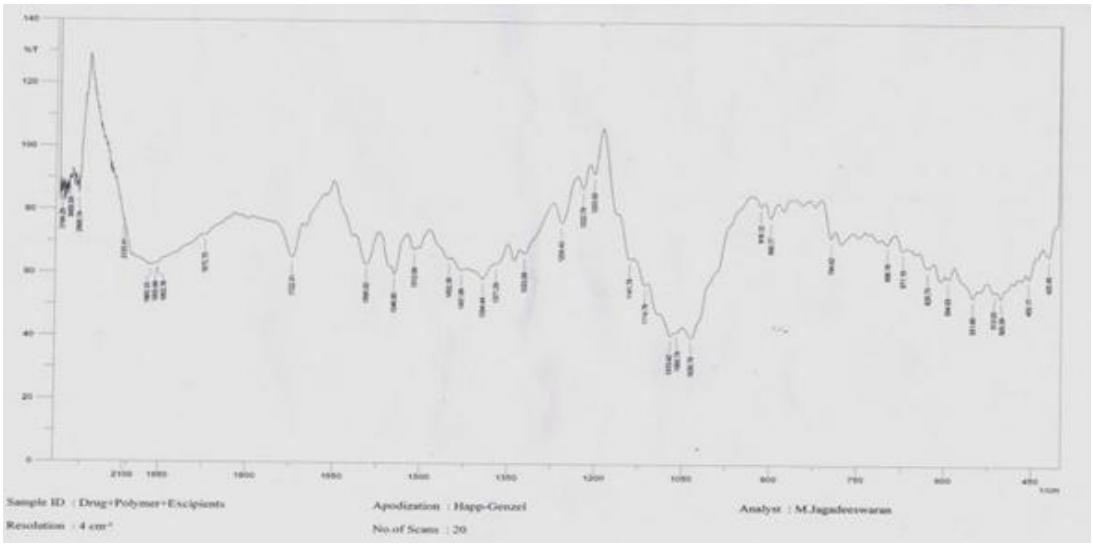

Figure 6: FTIR Spectra of Cisapride Citrate with two different grades of hydroxypropyl methyl cellulose polymer (HPMC K4M and HPMC K15M) and other excipients of formulations

EVALUATION OF TABLETS

Physical Parameters of Prepared Tablets-post compression parameters

The tablets from each batch of factorial design were evaluated for uniformity of weight, thickness, hardness, friability and the results were reported in table no --. The tablets showed good weight uniformity as indicated by the low value of Relative Standard Deviation (RSD<1%).

Table 4: Post compression parameters of Cisapride Citrate.

Formulations	Uniformity in weight (mg)	Thickness variation (mm)	Hardness (kg/cm^2)	Friability (%)
F_1	98.76	3.17	5.30	0.105
F_2	98.89	3.19	4.50	0.203
F_3	99.26	3.12	4.70	0.161
F_4	99.78	3.16	5.40	0.147
F_5	99.56	3.23	4.80	0.231
F_6	99.49	3.05	4.60	0.271
F_7	99.51	3.19	5.50	0.102
F_8	98.48	3.17	4.80	0.158
F_9	99.97	3.09	5.30	0.168

Table 5: Dissolution Profiles of Formulation F_1- F_9

Time (hrs)	Average percentage drug release								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
0	0	0	0	0	0	0	0	0	0
1	40.01	41.36	39.02	46.08	41.89	34.89	31.21	24.93	24.3
4	65.12	60.08	58.98	79.26	62.79	52.86	46.94	43.86	41.9
7	96.27	89.79	84.91	96.98	87.04	78.87	71.90	65.87	57.94
12	--	97.09	99.02	-	98.12	98.06	83.89	79.56	73.90
16	--	--	--	-	-	-	96.78	98.01	84.10
24	--	--	--	-	-	-	-	-	**98.8**

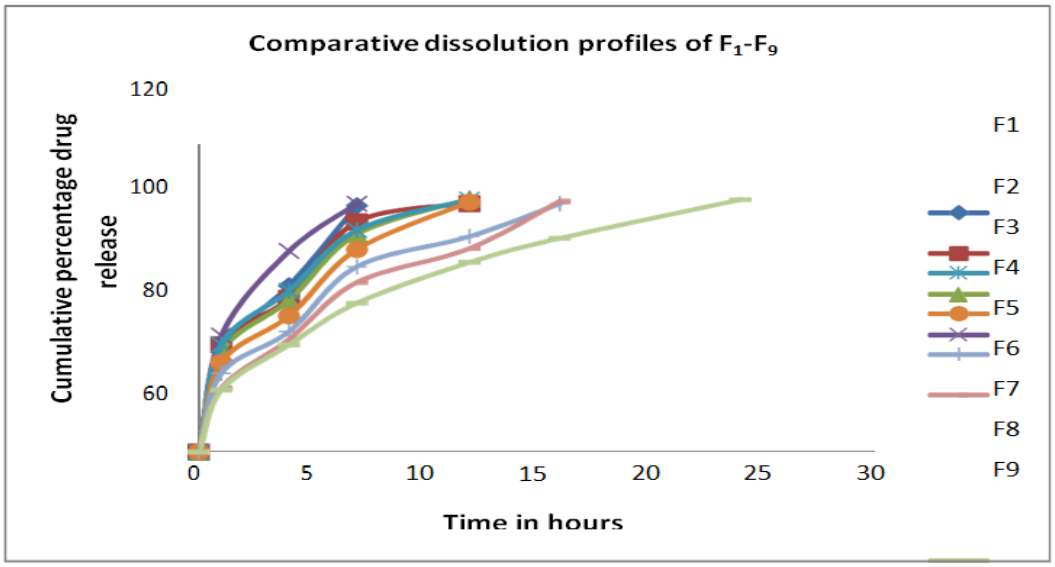

Figure 7: Comparative dissolution profiles of F1-F9

Table 6: Kinetic studies of optimum formulatio

S. No	Time in hours	Log time	Square root of time	Cumulative percentage drug release	Cumulative percentage drug remain	Log cumulative percentage drug Release	Log cumulative percentage drug remain
1	0	-	0	0	100	-	2
2	1	0	1	24.5	76.1	1.379	1.882
3	4	0.608	2	42.1	57.8	1.658	1.759
4	7	0.873	2.651	57.90	42.2	1.749	1.619
5	12	1.081	3.459	73.80	26.2	1.871	1.421
6	16	1.212	4	84.20	17.2	1.919	1.218
7	24	1.379	4.889	98.8	1.8	1.988	0.151

Table 7: Kinetic values obtained from F_9 plot formulation of Cisapride citrate

Formulation	Zero order R^2	First order R^2	Higuchi $_R2$	Korsmeyer – Peppas R^2	N	Mechanism of drug release
F9	0.9502	0.921	0.955	0.912	0.739	Zero order Non Fickian diffusion

Mechanism of drug release

In order to understand the complex mechanism of drug release from the matrix system, the in vitro release rate were fitted to korsmeyer peppas model and interpretation of release exponent value (n) enlighten in understanding the release mechanism from the dosage form. The release exponent value (n) thus obtained was 0.724. the F_9 formulation exhibited anomalous (non fickian) diffusion mechanism. The drug release was diffusion controlled as plot of Higuchi's model was found to be linear. These formulations also showed higher r^2value of zero order release kinetics thereby indicating that the release of drug from the matrix system were both by diffusion and erosion.

Stability studies as per ICH guidelines

The optimized formulation F_9 of Cisapride Citrate sustained release matrix tablets were evaluated for stability studies at 40^0C $\pm 2^0$C/75 % RH±5% for 180 days. The product was evaluated for appearance and hardness for every 15 days. Drug release studies were conducted as per planned schedule. The stability details / results are presented as below.

Storage Condition- 40^0C / 75 %

RH Pack - HDPE Container

Storage Period-1 month, 3 months and 6 months.

Table 8: Stability data

Duration	Hardness(kg/cm)	Friability (%)
After one month	5.45	0.155
After three months	5.45	0.155
After Six months	5.44	0.156

Table 9: Stability data

Time in Hours	Cumulative percentage drug release		
	1st month	3rd month	6th month
0	0	0	0
1	24.1	24.0	23.98
4	41.8	41.6	41.52
7	58.2	58	57.97
12	74	73.8	73.65
16	83.3	83	82.95
24	98.4	98.3	97.82

Conclusion

The present study was carried out to develop sustained release matrix tablets of Cisapride citrate. Matrix tablets of Cisapride Citrate with two different viscosity grades of hydroxy propyl methylcellulose were prepared by dry granulation and direct compression method and evaluated. The Sustained release Matrix tablets of Cisapride Citrate were prepared by Dry granulation / roller compaction technique and Direct Compression Method. The angle of repose of the granules after slugging (dry granulation) was found to have 24° to 26°. The matrix tablets were compressed by applying optimum force of compression and the hardness of tablets was found to be in the range of 4.5 to 5.5 kg/cm^2.

The flow property of the granules was good after slugging that was confirmed by the determination of angle of repose which indicates better uniformity of weight. Good hardness of the matrix tablets with less standard deviation indicated retardation in the release as observed in dissolution profile. On performing the friability for all the formulations the % weight loss falls between the range 0.26% and 0.60% indicates that it falls within the limit showing good compressibility and non defective tabletting. In first attempt of study, matrix tablets were prepared by using hydroxypropyl methylcellulose (HPMC) of lower viscosity alone i.e.HPMC K4M (10%). This formulation (i.e. F_1) failed to sustain the drug release for extended period of time and all most all the drug got released in 7th hour. For sustaining the drug release up to 24th hour the percentage of HPMC K4M in F_2 was increased (15%) but the formulation did not sustain the drug release more than 12th hour. It clearly indicates that the lower viscosity grade of hydroxypropyl methylcellulose (HPMC K4M) is able to sustain the drug release up 12th hour and for sustaining the drug release for extended period up to 24th hour, percentage of higher viscosity grade of hydroxypropyl methylcellulose (HPMC K15M) must be used.

In formulation F_3, HPMC K15M was used alone (i.e.10%) and the tablets were evaluated for in vitro dissolution study. The formulation failed to sustain the release up to extended period of time. In Formulation F_4 (HPMC K4M 10%, and HPMC K15M 10%) sustained the drug release up to 7th hour, so in formulation F_5 the percentage of HPMC K15 was kept constant and the percentage of HPMC K4 was increased, this formulation released the drug in 12th hour. In formulation F_6 the percentage of HPMC K4M was further increased and the percentage of HPMC K15M was kept constant. This formulation also failed to sustain the drug release. F7 slowly released the drug, up to 16th hour. The total drug release from formulation F_8 was (98.01%) but it also failed to sustain the release up to 24 hour.

In formulation F_9, percentage of HPMC K15M was increased from 20% (in F_8) to 25mg (in F_9) while the percentage of HPMC K4M was kept constant up to 20 and tablets of formulation F_9 were evaluated for in vitro dissolution study. The matrix tablets of formulation F_9 released the drug slowly as per standard dissolution profile up to 24th hour and total drug release from matrix tablet of formulation F_9 at the end of 24th hour was 98.01%. Hence the above study demonstrated that combination of HPMC K4M and HPMC K15M can be used to formulate

sustained release matrix tablets of Cisapride Citrate. This can sustain the drug release up to 24 hours as per standard dissolution profile. This can be expected to reduce the frequency of administration and decrease the dose – dependent side effects associated with repeated administration of conventional Cisapride Citrate tablets. The cumulative drug release of innovators brand (MOZA SR, Intas Pharmaceuticals) of sustained release tablet of Cisapride Citrate were compared for in vitro dissolution study. The formulation F_9 matrix tablet releases the drug appropriately in comparison of innovators brand. The cumulative drug release at the end of 24th hour from formulation F_9 (98.8%). The in vitro drug release result indicates that formulation F_9 released more drug than innovators brand and hence more drug is available at the absorption site from formulation F_9 as compared to innovators brand, hence the formulation F_9 has better bioavailability than innovators brand of Cisapride Citrate sustained release matrix tablet and also the sustained release matrix tablet was found to be beneficial in terms of reduction in frequency of administration. The formulation F_9 best suited with zero order release kinetics (corr. coefficient = 0.9502) than the first order release kinetics (corr. Coefficient = 0.921). The formulation F_9 follows Higuchi model of drug release kinetics (corr. coefficient=0.955). Hence it can be concluded that once daily sustain release matrix tablet of Cisapride Citrate having short half life, was found to exert a satisfactory sustained release profile which may provide an improved bioavailability, increased therapeutic efficacy and patient compliance.

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