FORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF MOSAPRIDE CITRATE

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INTRODUCTION

Oral drug delivery

Drugs are most frequently administered by oral route. Although a few drugs taken orally are intended to be dissolved in the mouth, nearly all drugs taken orally are swallowed. Of these, most are taken for the systemic drugs effects that result after absorption from the various surfaces along the gastrointestinal tracts. A few drugs such as antacids are swallowed for their local action in the gastrointestinal tracts.

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, cost-effective manufacturing process and flexibility in dosage form [1-5]. Oral sustained release dosage forms have been developed and studied to restrict these systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu [6-10].

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. An alternative approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. For the oral route in this case the drug blood level reached and time required to reach that level depend on the dose and dosing interval. There are several potential problems inherent in multiple-dose therapy. If the dosing interval is not appropriate for the biological half-life of the drug, large peaks and valleys in the drug blood level may result. For example, drug with short half-life requires frequent dosing to maintain constant therapeutic levels. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease state. Patient noncompliance with the multiple-dosing regimen can result in failure of this approach [11-15].

Potential advantages of sustained drug therapy

1. Improved patient convenience and compliance due to less frequent dosing
2. Employs minimum drug
3. Minimizes or eliminates local and systemic side effects.
4. Avoidance of night time dosing
5. Reduction in fluctuation in steady-state levels and therefore-
6. Better control of disease condition ,and
7. Reduced intensity of local or systemic side-effects
8. It minimizes drug accumulation with chronic dosing.
9. Improves efficacy in treatment
10. Cure or control confirm or promptly.
11. Improve control of condition thereby reducing fluctuation in circulating drug level.
12. Improve bioavailability of some drugs.
13. Make use of special effects, example-sustained release aspect for morning.
14. More uniform effect.

MATERIAL & METHOD

Material

The drug (Mosapride citrate) from Dr. Reddy's holdings limited Hyderabad, HPMC K1 and HPMCK4M from Colour on Asia Pvt. limited, Mumbai, lactose concept pharmaceutical limit Aurangabad, magnesium stearate concept pharmaceutical limit Aurangabad, Aerosil 200 concept pharmaceutical limit Aurangabad, Talcum from concept pharmaceutical limit Aurangabad [16-20].

Preformulation Studies:

Drug – excipient compatibility studies by physical observation:

Mosapride citrate was mixed with various proportions of excipients showed no colour change at the end oftwo months, proving no drug-excipient interactions.

FTIR

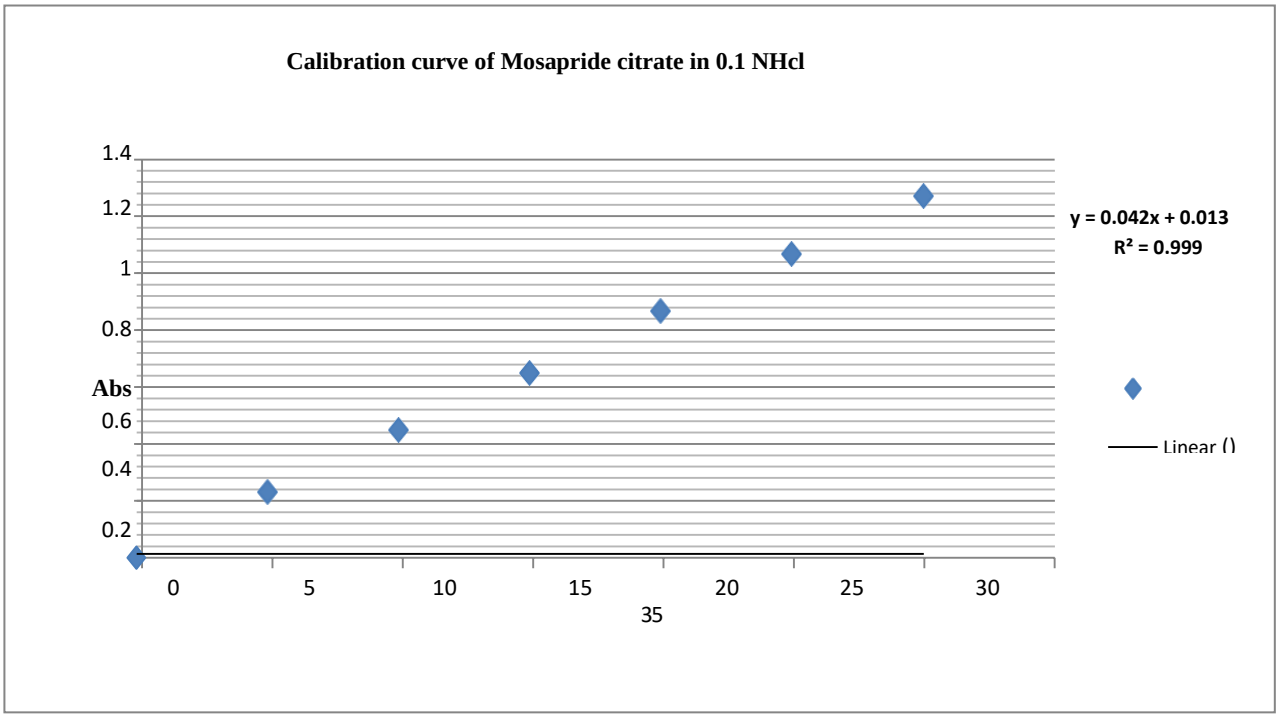
These were taken of the medication and its enhanced formulation. FTIR spectra of pure drug with polymers (1:1) are shown below. Pure mosapride citrate has the same major peaks as the physical combination, suggesting that the medicine does not interact with the polymers, proving its stability. The FTIR spectra of the medicine and polymers used showed no loss of peak. This shows that the drugs and polymers used have no chemical interactions. Peaks within the expected range confirm the materials utilized in the study are genuine and no interactions occurred.

FT-IR value of pure Mosapride citrate

Reference Value	Observed Value	Functional Group Determination
3510.2cm^{-1}	3501cm^{-1}	Phenolic OH (Stretching)
1627.8cm^{-1}	1629cm^{-1}	Ketone C=O(Stretching)
1596cm^{-1}	1603cm^{-1}	Aromatic C=C
1276cm^{-1}	1276cm^{-1}	C-O

Calibration Data of Mosapride citrate in Hcl

Concentration(µg/ml)	Absorbance (nm)
0	0
5	0.229±0.02
10	0.448±0.15
15	0.648±0.23
20	0.868±0.01
25	1.068±0.22
30	1.272±0.02



Formulation development of mosapride citrate

Step1: Weight materials as per ORML, check control number and record them.

Step2: Sifting

Check the integrity of the sieves being used for sifter as per SOP& first sift the material dry mixing and then shift material required for dry lubrication as per the specified sieve for each material[21-25].

TableNo.1 Materials used for Dry granulation

Materials	Actual Quantity(gm/1000tablets)	Sieve no
Materials for dry mixing		
Mosapride Citrate	10.77	24#
LactoseIP/BP	37.05	24#
HPMCK4M	20.00	24#
HPMCK15M	25.00	24#
Talcum	0.50	40#
Magnesium Stearate IP/BP	0.50	40#
Aerosil IP/USP	0.10	40#
Materials for dry lubrication		
Mosapride Citrate	4.23	24#
Talcum	0.50	40#
Magnesium Stearate IP/BP	0.50	40#
Aerosil IP/USP	0.10	40#

Step3: **Dry Mixing**

Blend of Mosapride Citrate with Polymer (HPMC) & lactose mix slowly in polybag for 15 minutes. Add half quantity of lubricants & reblend for 5-6 minutes. Now blend is ready for slug formation.

Step4: Slugging

Slugging is a method of subjecting a material to increased compression time. When the initial blend of powders is forced into the dies of a large-capacity tablet press and is compacted by means of flat-faced punches the compacted masses are called slugs, and the process is referred to as slugging[9]. Clean & operate the M/C as per S.C.P. & S.O.P for Slugging.

Parameters for Slugging:

Punch size16 mm Average Weight 900mg/ slug HardnessNLT10 Kg/cm^2

Step 5: Deslugging

Deslug the above slug, and screen it through 2 mm screen slowly. Pass the final granules through #30.

Step 6: Dry Lubrication

Mix final granules & remaining mosapride citrate slowly in polybag for 15minutes.Add remaining half quantity of lubricants slowly for 10 minutes. Record the total weight of granules. Now blend is ready for compression.

Step 7: Compression

Clean & operate the machine as per S.C.P. ensure blend release before taking for compression. Check batch details on the label & total weight of granules.

Formulation variables for Mosapride citrate matrix tablets

TableNo.2 Formulation ingredients

Ingredients	F1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F7 (mg)	F8 (mg)
Mosapride citrate	15	15	15	15	15	15	15	15
HPMCK4M	10	15	-	10	15	18	16	20
HPMCK15M	-	-	10	10	10	10	15	20
Lactose	73	68	73	62	58	55	52	43
Talcum	1	1	1	1	1	1	1	1
Magnesium Stearate	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

Table no.3 Physical parameters of granules before dry granulation (slugging) Pre-compression parameters

Physical Properties	F_1 (mg)	F_2 (mg)	F_3 (mg)	F_4 (mg)	F_5 (mg)	F_6 (mg)	F_7 (mg)	F_8 (mg)
Bulk Density (gm/ml)	0.434	0.435	0.433	0.431	0.435	0.439	0.428	0.422
Tapped Density (gm/ml)	0.625	0.626	0.631	0.628	0.630	0.634	0.623	0.615
Compressibility Index	31.45	32.60	31.02	31.36	30.95	30.75	31.30	31.38
Hausner's Ratio (H.R.)	1.39	1.40	1.44	1.45	1.448	1.444	1.46	1.467
Angle of Repose	34°33"	34°18"	32°64"	33°75"	32°42"	32°05"	31°47"	32°55"
Observation	Poor Flow	Poor flow	Poor flow	Poor flow	Poor flow	Poor flow	Poor flow	Poor flow

Physical parameters of granules after dry granulation

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° to30°, thus indicating that the flow properties were good [26-30].

Table no.4 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)	0.437	0.439	0.436	0.438	0.435	0.440	0.426	0.429	0.443
Tapped Density(gm/ml)	0.502	0.509	0.513	0.510	0.516	0.521	0.511	0.523	0.512
Compressibility Index**	15.35	15.22	14.29	14.15	15.69	15.54	16.63	17.01	15.10
Hausner's Ratio(H.R.)	1.17	1.15	1.18	1.16	1.18	1.18	1.19	1.21	1.18
Angle of Repose	24°12"	23°21"	23°44"	24°32"	24°51"	25°32 "	23°49"	26°60"	25°11 "
Observation	good flow	good flow	good flow	good flow	good flow	good flow	good flow	good flow	good flow

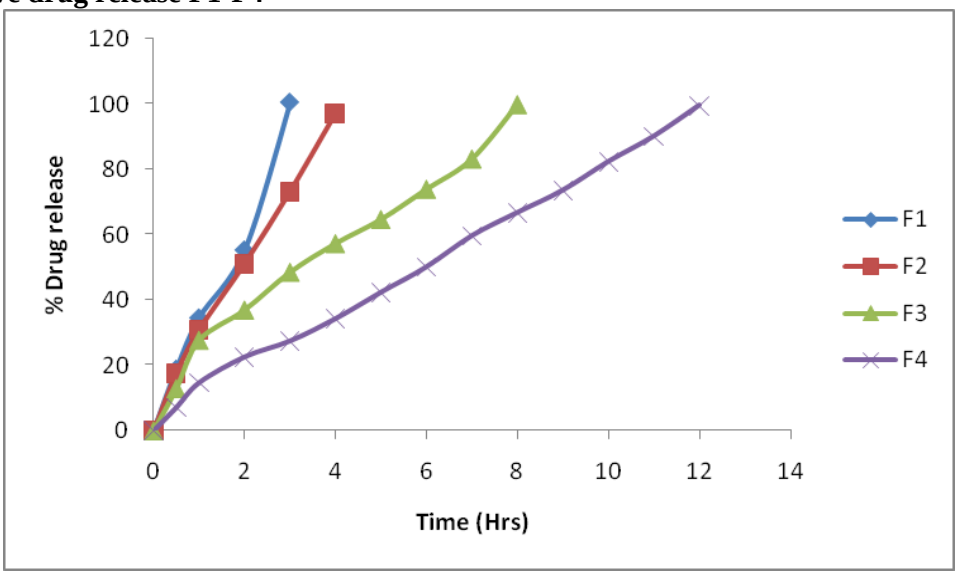
***In vitro* dissolution data for formulations F1 - F4**

Time(hrs)	**% Cumulative drug release**			
	F1	**F2**	**F3**	**F4**
0	0	0	0	0
0.5	18.92	17.63	12.92	7.15
1	34.61	30.96	27.69	14.69
2	55.384	51.23	36.92	22.58
3	100.61	73.38	48.46	27.47
4		97.38	57.23	34.28
5			64.61	42.39
6			73.84	50.16
7			83.07	59.73
8			99.69	66.81
9				73.64
10				82.39
11				90.16
12				99.64

Time(hrs)	**% Cumulative drug release**			
	F5	**F6**	**F7**	**F8**
0	0	0	0	0
0.5	25.89	15.1	14.69	5.18
1	36.72	21.93	22.58	11.32
2	50.12	30.86	27.47	16.38
3	61.89	40.02	34.28	20.74
4	80.09	48.93	42.39	24.18
5	99.23	56.42	50.16	30.29
6		65.73	59.73	35.73
7		72.81	66.81	41.89
8		83.76	73.64	47.63
9			82.39	52.37
10			90.16	59.16
11			99.64	65.27
12				71.49

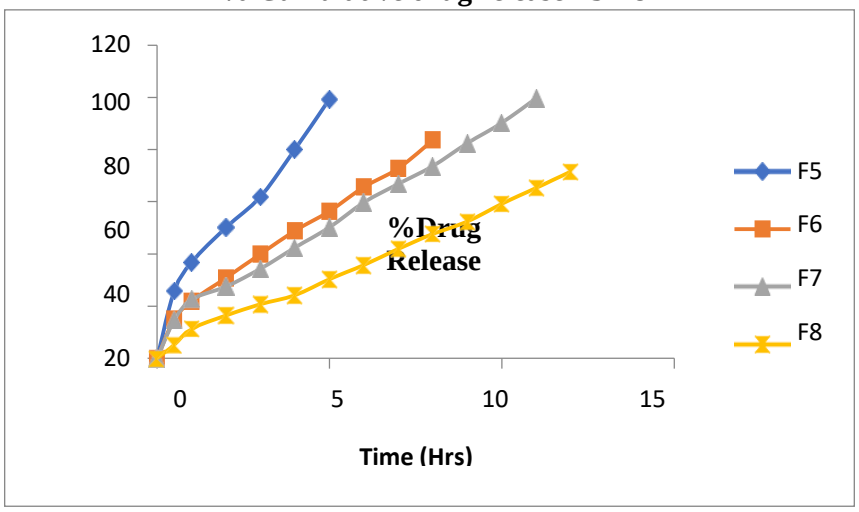
***In vitro* dissolution data for formulations F5 – F**

% Cumulative drug release F1-F4



Graphical representation % Cumulative drug release F1-F4

% Cumulative drug release F5-F8



Graphical representation % Cumulative drug release F5-F8

Release kinetics:

To explain the release kinetics of mesopride citrate from buccal tablets, data from in vitro release experiment of formulations that showed superior drug release were fitted into various equations. The data was fit into a variety of kinetic models; including zero, first order, higuchi, and korsmeyer peppas processes, with the findings given in the table below.

Formulation	Zero Order R^2	First order R^2	Higuchi R^2	Korsmeyer–Peppas R^2	N	Mechanism of drug release
F7	0.943	0.910	0.941	0.926	0.724	Zero order Non Fickian diffusion

Conclusion

Matrix tablet of mosapride citrate were prepared by dry granulation method by using various exciepient. During this phase of investigation various factors that likely to affect the performance of the sustained release was studied. Dry granulation method was formulated. Granules were evaluated for tests such as Bulk density, Tapped density, Compressibility Index and Hausner ratio before being punched as tablets. Tablets were tested for weight variation, thickness and friability, in-vitro dissolution test were performed & % drug release was studied. Dissolution tests were performed and percentage drug release was calculated. Dissolution profile of Formulation-F7 was optimized based on evaluation parameters. In the dissolution modelling all the developed formulations followed

Higuchi-Peppas drug release. The optimized formulation-F7 followed zero order drug release. The developed formulation was tested for its stability for three month and found to be stable. In this research, HPMC was found to play a great role in controlling release of drug mosapride citrate sustained Release tablets from the matrix system for the treatment of gastrointestinal agents. Accordingly, it can be concluded that the formulation is robust in the performance is less likely to be affected by the various factors studied [31-35].

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