FORMULATION OF SR-DS BY DIFFERENT POLYMERS IN MOSAPRIDE CITRATE MATRIX TABLETS

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Abstract

Mosapride citrate (MSP) is a gastroprokinetic agent that acts as a selective 5-HT(4) agonist and accelerates the gastric emptying, and is used for the treatment of acid reflux, irritable bowel syndrome, and functional dyspepsia. The purpose of this study is to investigate the solid dispersion formulations of MSP with controlled release characteristic using various polymers, elucidate the release mechanism, and characterize the interaction patterns between MSP and polymers. Solid dispersions of MSP with different drug-to-polymer ratios were prepared by a solvent evaporation method and characterized in comparison with the simple physical mixtures. Eudragit RSPO, Eudragit RLPO, hydroxypropylmethylcellulose (HPMC) or Kollidon SR was used as a controlled-release polymer along with polyvinylpyrrolidone (PVP) as a carrier. Characterization of MSP solid dispersion was performed using thermal analysis (DSC), powder X-ray diffraction (XRD), Fourier transform-infrared (FT-IR) spectroscopy, where the drug was converted from the crystalline state to amorphous state in all polymeric carriers used. In vitro dissolution studies showed that the drug release has been extended up to 24 h by using Eudragit RSPO or HPMC. Moreover, the formulations containing higher polymer content ratio showed better slow-release profile. These results indicate that the solid dispersion formulation containing PVP/Eudragit RSPO or HPMC mixture could serve as a good controlled-release system for MSP.

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.[1] 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, patient acceptance, cost-effective manufacturing process and flexibility in dosage form.[7] 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.[8] 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.[9] Over past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled-release drug-delivery systems. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease state, a substantial number of therapeutically effective compounds already exists. The effectiveness of drug however is often limited by side effects or the necessity to administer the compounds in clinical setting.[3]Successful fabrication of sustained release products is usually difficult & and involves consideration of physicochemical properties of drug, pharmacokinetic behavior of drug, route of administration, disease state to be treated and, most importantly, placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug.[3] The reasons behind the increase in the interest in new system are firstly reorganization of the possibility of repeating successful drugs by applying the concepts and techniques of controlled release drug delivery systems, coupled with the increasing expense in bringing new drug entities to market, has encouraged the development of new delivery system and secondly new systems are needed to deliver the novel, genetically engineered pharmaceuticals for example-peptides & proteins to their site of action without incurring significant immunogenicity or biological inactivation.[3]

DRUG EXCIPIENT COMPATABILITY STUDY BY FTIRSPECTROSCOPY

The FTIR spectra of pure mosapride citrate, mosapride citrate with HPMC K4M, HPMC K15M and mosapride citrate with HPMC K4M, HPMC K15M, Lactose, Magnesium stearate, Talc, Aerosil were analyzed for compatibility study.

Procedure:

Drug and excipients were analysed by infra red spectral studies by using potassium bromide pellet technique. In this method, the drug and potassium bromide were mixed at the ratio of 1:100. Then these mixtures were pressed in to a pellet. The FTIR spectra were recorded using potassium bromide pellet method. Spectra were recorded for pure drug, pure excipients and drug with excipients (tablet). The instrument was operated under dry air purge and the scans were collected at scanning speed 2mm/sec with resolution of 4cm-1 over the region 4000-400cm-1. The scans were evaluated for the presence of principle of peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction. TheFT-IR spectra of pure Mosapride citrate, are shown in Fig. no-6.

PREPARATION OF STANDARD CALIBRATION CURVE OFMOSAPRIDE CITRATE.

Method:

100 mg of mosapride citrate was accurately weighed and transferred into 100 ml volumetric flask. It was dissolved and diluted to volume with purified water to give stock solution containing 1000µg/ml.

The standard stock solution was then serially diluted with purified water to get 10ug/ml of mosapride citrate. The λmax was found to be 274 nm using UV Spectrophotometer. The absorbance values were plotted against concentration (µg/ml).

FORMULATION DEVELOPMENT OF MOSAPRIDE CITRATE.

Step 1: Weigh the raw materials as per ORML, check control number and recordthem.

Step 2: 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 thespecified sieve for each material.

Table No.6 Materials used for Dry granulation

Materials	Actual Quantity (gm/1000 tablets)	Sieve no
Materials for dry mixing		
Mosapride Citrate	10.77	24#
Lactose IP/BP	37.05	24#
HPMC K4M	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#

Step 3: **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.

Step 4: **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:

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 15 minutes. 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.

Parameters for compression

1. Punch
2. Dimensions
3. Diameter
4. Theoretical Weight to Tablet
5. Weight of two Tablets
6. Weight variation (of actual average weight)
7. Hardness of Tablet
8. Friability
9. Thickness
10. Appearance of tablet.

Formulation variables for mosapride citrate matrix tablets.

Table No.7. 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)
Mosapride 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

ANALYSIS OF REFERENCE / INNOVATOR PRODUCT

With the help of analysis of the innovator product we will be able to compare theresults obtained of our formulated product.

Analysis of the innovator product was carried out for various physicalparameters and *In-vitro* dissolution profile.

Table No.11 Reference product physical characterization

GENERIC NAME	BRAND NAME	MANUFACTURED AND MARKETED BY	STRENGTH	DOSAGE FORM	THICKNESS
Mosapride Sustained Release Tablets	MOZA SR	Intas Pharmaceuticals	5mg,10mg	Sustained release tablet	3mm

RESULTS AND DISCUSSION: PREFORMULATION STUDIES

Precompression parameters

Table No.12. 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)	0.434	0.435	0.433	0.431	0.435	0.439	0.428	0.422	0.438
Tapped Density(gm/ml)	0.625	0.626	0.631	0.628	0.630	0.634	0.623	0.615	0.632
pressibilityIndex	31.45	32.60	31.02	31.36	30.95	30.75	31.30	31.38	30.69
Hausner's Ratio(H.R.)	1.39	1.40	1.44	1.45	1.448	1.444	1.46	1.467	1.452
Angle of Repose	34°33"	34°18"	32°64"	33°75"	32°42"	32°05"	31°47"	32°55"	33°32"
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 No.13 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

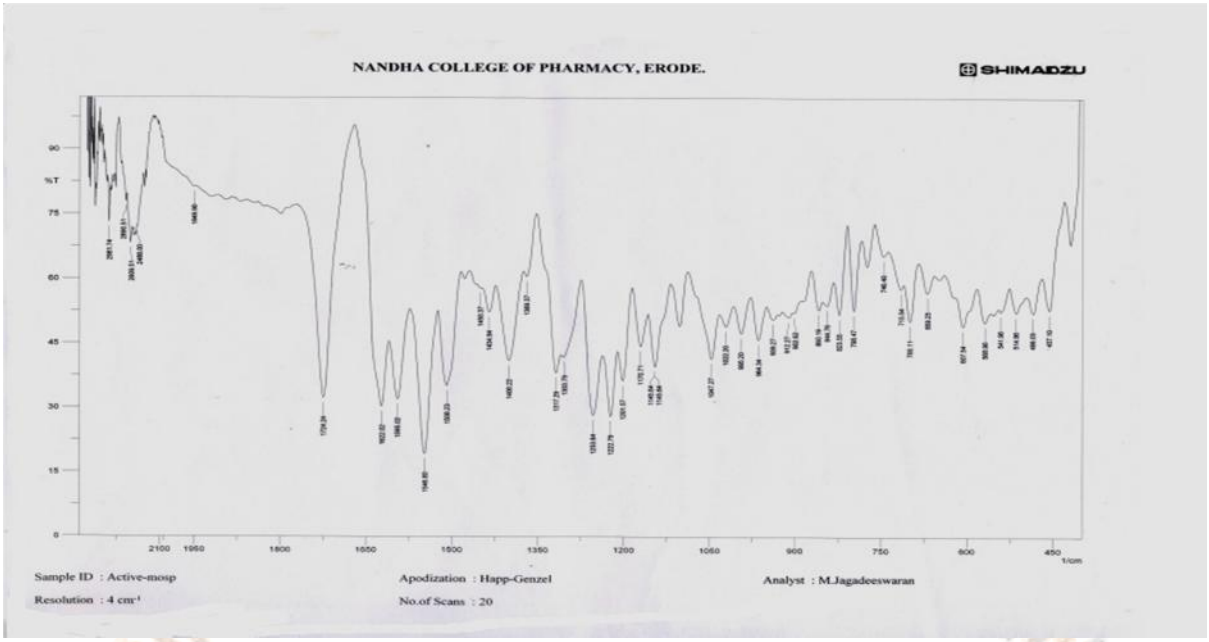


Fig.6 FTIR Spectra of mosapride citrate

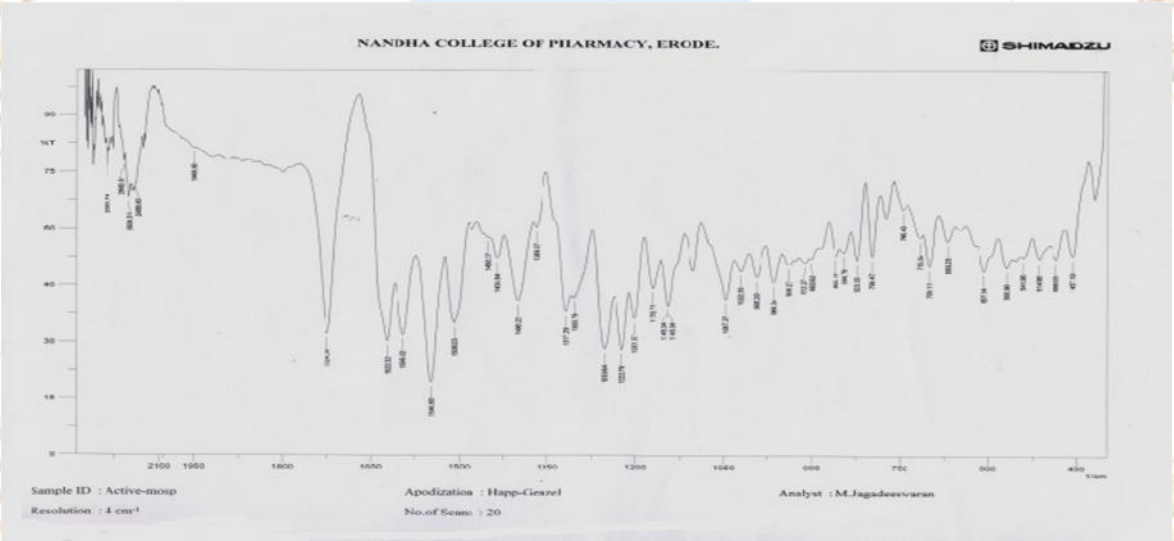


Fig.7 FTIR Spectra of mosapride citrate with HPMC K4M and HPMC K15M

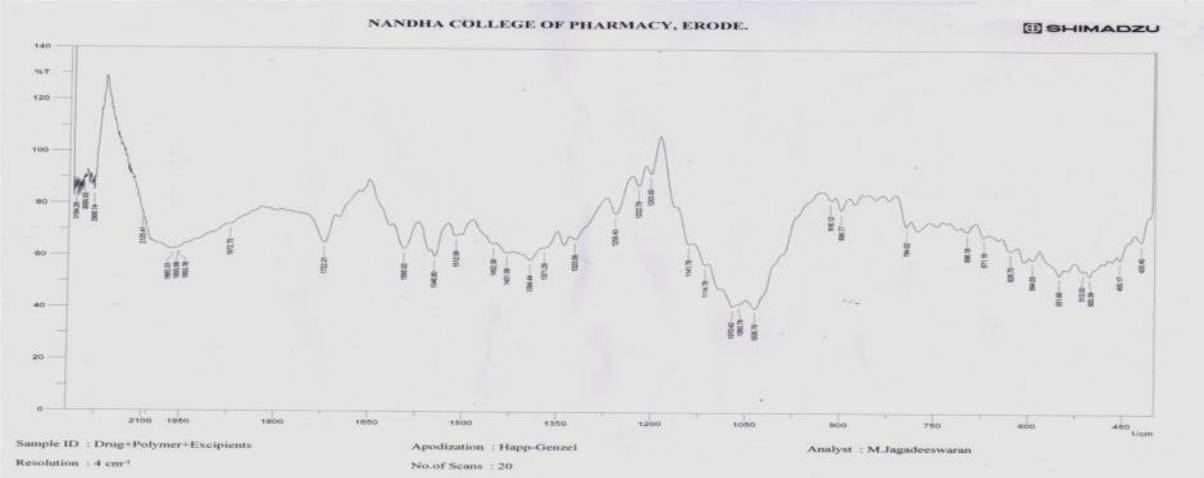


Fig.8 FTIR Spectra of Mosapride citrate with two different grades of hydroxypropyl methyl cellulose polymer (HPMC K4M and HPMC K15M) andother excipients of formulations.

Table No.14 Interpretation of FTIR Spectra[15,16.]

Sr.No	Functional groups presents in mosapride citrate.	Standard FTIR range	Observed Peak
1	C=O (in ketone)	1705-1725	1724.11
2	C-N (vibrations)	1000-1400	1400.20,1434.94,1450.37
3	C-H	700-850	607,669,700,715,746,798
4	C-Cl	800-600	700.11
5	C-F	1000-1400	1201.57

In FTIR study the characteristic peak due to pure mosapride has appeared in the spectra of formulation without any makeable changes in the position. This confirms the identity and compatibility among the drug mosapride citrate, the polymers used HPMC K4M, HPMC K15M and other excipients of the formulation.

Standard Curve of Mosapride citrate in Acetate Buffer pH-4.0

The calibration curve of mosapride citrate was prepared in acetate buffer ph4.0 following table no-15, shows the absorbance at ƛmax 274 nm and fig no-9 shows the calibration curve with regression coefficient 0.994, and the y intercept 0.022.

Table No.15 Standard Curve of Mosapradi citrate.

Concentration In µg/ml	Absorbance at 274 nm in Acetate buffer pH- 4.0
0	0 ± 0
2	0.055 ± 0.0019
4	0.09 ±0.0016
6	0.137 ± 0.0021
8	0.172 ± 0.0013
10	0.202 ±0.0018
12	0.271 ±0.0013
14	0.325 ±0.0011
16	0.358 ±0.0019
18	0.428 ±0.0011
20	0.457 ±0.0014

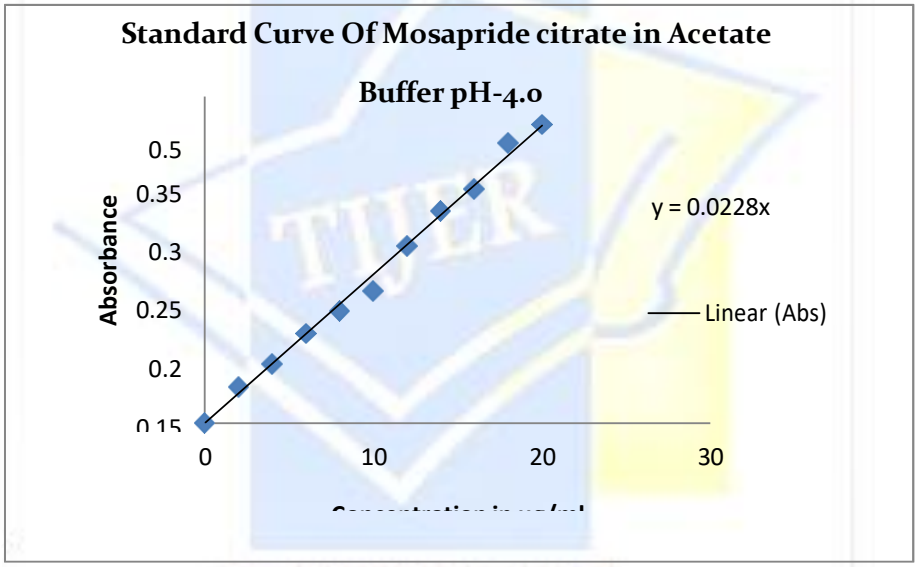


Fig.9 Standard Curve of Mosapride citrate in Acetate Buffer pH-4.0

EVALUATION OF TABLETS

Physical Parameters of Prepared Tablets-post compression parameters

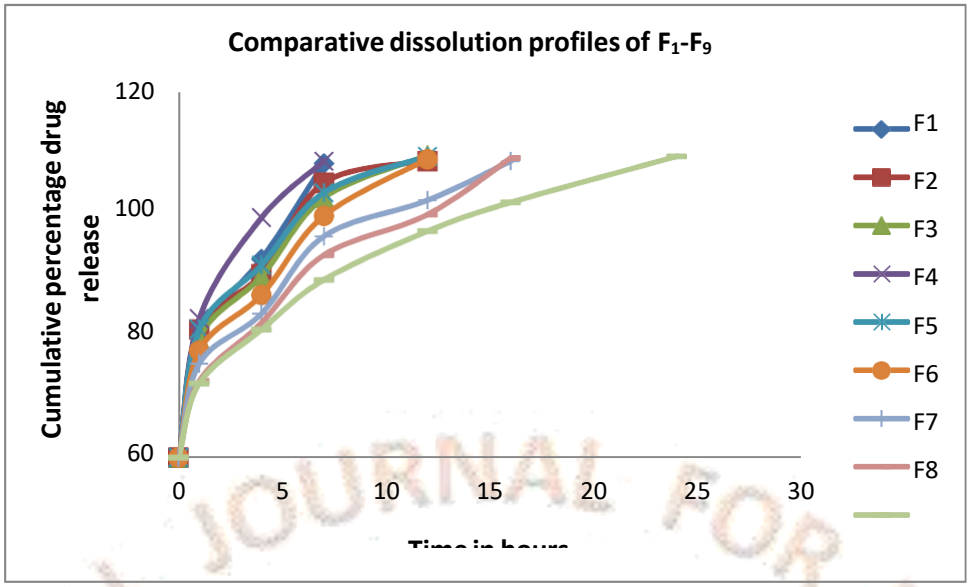
The tablets from each batch of factorial design were evaluated for uniformity of weight, thickness, hardness, friability and the results were reported in table no --. The tablets showed good weight uniformity as indicated by the low value of Relative Standard Deviation (RSD<1%). The tablet thickness were found in the range of 3.90±0.01mm to 4.00±0.01mm. the tablet hardness varied from—to --. The tables pass the friability test, as all the batches were within the pharmacopoeial limit.(F<1%).

Table No. 16 Post compression parameters of mosapride citrate.

Formulations	Uniformity in weight (mg)	Thickness variation (mm)	Hardness (kg/cm^2)	iability (%)
F_1	98.4	3.16	5.20	0.103
F_2	98.90	3.21	4.40	0.210
F_3	99.02	3.15	4.60	0.141
F_4	99.97	3.12	5.30	0.158
F_5	99.89	3.20	4.60	0.21
F_6	99.74	3.08	4.70	0.265
F_7	99.37	3.22	5.30	0.106
F_8	98.59	3.15	4.90	0.150
F_9	99.98	3.13	5.20	0.160

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	40.07	41.89	38.99	45.54	42.01	35.00	30.82	25.06	24.3
4	65.0	60.04	59.37	78.53	63.0	53.23	47.11	44.11	41.9
7	96.22	89.93	85.0	97.0	86.72	79.09	72.40	66.29	58.20
12	--	97.02	98.89	-	98.58	97.66	84.21	79.56	74.10
16	--	--	--	-	-	-	97.0	98.01	83.50
24	--	--	--	-	-	-	-	-	**98.6**

Table No.17 Dissolution Profiles of Formulation F_1-F_9.



SUMMARY AND CONCLUSION

The present study was carried out to develop sustained release matrix tablets of mosapride citrate. Matrix tablets of mosapride citrate with two different viscosity grades of hydroxypropyl methylcellulose were prepared by dry granulation and direct compression method and evaluated.

The FTIR study was carried out to know the compatibility of the excipients with mosapride citrate dihydrate, the active constituent of the formulation. The FTIR spectrum of pure mosapride citrate, mixture of mosapride citrate with, HPMC K4M, HPMC K15M polymers and mixture of mosapride citrate, HPMC K15M, HPMC K4M with Lactose, talc, magnesium stearate, aerosil were analyzed for compatibility study. The study of FTIR spectrum confirms that mosapride citrate and excipients used in the formulation are compatible with each other.

The Sustained release Matrix tablets of mosapride citrate dihydrate 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 4.6 to 5.3kg/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 indicatedretardation 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 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 mosapride 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 mosapride citrate dihydrate tablets. The cumulative drug release of innovators brand (MOZA SR, Intas Pharmaceuticals) of sustained release tablet of mosapride 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 (98.01%) and the cumulative drug release at the end of 24th hour from innovators brand was (97.30%).

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 mosapride 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 =0.943) than the first order release kinetics (corr. Coefficient = 0.910). The formulation F_9 follows Higuchi model of drug release kinetics (corr.coefficient=0.41).

The Koresmyer peppas drug release kinetics showed correlation coefficient (0.926) and release exponent (n) 0.724 which indicates that the drug release mechanism is non-fickanian diffusion.

Hence it can be concluded that once daily sustain release matrix tablet of mosapride citrate having short half life, was found to exert a satisfactory sustained release profile which may provide an improved bioavailability, increased therapeuticefficacy and patient compliance.

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