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DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

The objective of the present work is to design of sustained release matrix tablets of Dolasetron influence of polymers, on the release rate and in vitro evaluation. Dolasetron is used to prevent nausea and vomiting caused by cancer chemotherapy. Dolasetron is in a class of medications called serotonin 5-HT3 receptor antagonists. It works by blocking the action of serotonin, a natural substance that may cause nausea and vomiting. The polymers are HPMCK4M, HPMC K15 M, Lactose, Talcum, Magnesium Stearate, Colloidal silicon dioxide were utilized in the formulation of matrix tablets containing Dolasetron evaluated for its in-vitro drug release. Granules were prepared and evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. Formulation was optimized on the basis of acceptable tablet properties (hardness, friability, drug content and weight variations), in vitro drug release and stability studies. All the formulations showed compliance with Pharmacopeial standards. The in vitro release study of matrix tablets were carried out in pH 1.2 HCl for 2 hours and pH 7.4 phosphate buffer for the remaining 10 hours as dissolution medium. The results indicated that a decrease in release kinetics of the drug was observed by increasing the polymer concentration. The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable.

Keywords: Sustained release tablets, Dolasetron, Lactose, Talcum, Magnesium Stearate, Colloidal silicon dioxide.

1. INTRODUCTION

Sustained release tablets and capsules are mostly taken only once or twice daily, compared with immediate release tablet form that may have to take 3 or 4 times a day to attain the same required drug to produce the effect. Typically, the sustained release dosage form to furnish at once release the active component that give the what we are desired for cure of disease, followed by remaining quantity of drug should be release and maintained the therapeutic effect over a predetermined length time or prolonged period. The sustaining of drug plasma levels furnish by sustained release dose often times to eliminate the require for night dose administration, which suitable not only the patient but the care given as well. The bulk of research can be focusing toward oral dosages that improve the temporal aspect of drug delivery. This approach is a continuously developing in the pharmaceutical industry for sustained release oral drug delivery system. The sustained release system for oral use of administration are mostly solid and based on dissolution, diffusion or a combination of both, erosion mechanisms, in the power to directing the drug release. A delivery system containing hydrophilic and hydrophobic polymers and waxes are mixed with active component to furnish drug action for a prolonged length of time. The concept of modified release dosage products was previously used to describe various types of oral extended release dosage forms, including sustained release, sustained action, prolonged action, slow release, long action and retarded release. The United States Pharmacopoeia has been in the term extended release and the British Pharmacopoeia has been the term slow release. United States Food and Drug Administration has been in the term prolonged release. However the review of literature indicates that widely used in terms today are sustained release and controlled release.

2.1 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

$$I = [1 - \text{Tapped density} / \text{Bulk density}] \times 100.$$

Values of I below 15% usually give rise to good flow characteristics, but readings above 25% indicate poor flow ability.

Hausner's Ratio

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

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

Values less than 1.25 (= 25% Carr's index) indicates good flow, while greater than 1.25 indicates poor flow (= 33% Carr's index). Between 1.25 and 1.5 added glidants normally improves flow.

Angle of repose

Angle of repose is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane.

. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\Theta = \tan^{-1} (h/r)$$

Where,

h= Height of pile r= Radius of pile

Θ= Angle of repose

2.2 Formulation development of dolasetron

Table No.2.1 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)
Mosapride	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

2.3 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 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:

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

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

In vitro drug release study

In vitro dissolution were carried out on dissolution apparatus (model) to determined the drug release from various formulations.1000ml of acetate buffer was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Studies were carried out in 900 ml of acetate buffer ph4 upto 24hrs at 100 rpm. The dosage form was allowed to sink to the bottom of the flask before stirring. dosage forms may have a small loose piece of nonreactive material such as not more than few turns of wire helix attached to prevent them from floating. The apparatus was operated for 24 hours and then the medium was taken and process was continued from 0 to 24 hrs at 100 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 281 nm using UV- spectrophotometer.

Stability study

In the present study, stability studies were carried out at 40ºC and 75% RH for a specific time period upto 3 months for selected formulations. For stability study, the tablets were sealed in aluminium packaging coated inside with polyethylene. These sample containers were placed in dessicator maintained at 75% RH.

3.RESULTS AND DISCUSSION

3.1 Precompression parameters

Table No.3.1; 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)	0.408	0.411	0.413	0.419	0.416	0.420	0.418	0.425	0.422
Tapped Density(gm/ml)	0.623	0.619	0.622	0.617	0.611	0.615	0.617	0.624	0.627
Compressibility Index	30.06	31.95	31.52	31.74	30.78	31.04	31.69	30.98	31.07
Hausner's Ratio(H.R.)	1.37	1.39	1.42	1.45	1.49	1.42	1.48	1.46	1.44
Angle of Repose	34°75"	34°49"	31°87"	34°07"	32°79"	32°73"	31°53"	32°27"	33°85"
Observation	Poor flow	Poor flow	Poor flow	Poor flow	Poor flow	Poor flow	Poor flow	Poor Flow	Poor Flow

Table No.3.2: 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	25°21"	24°91"	24°02"	25°63"	25°77"	24°82 "	23°92"	25°94"	24°86 "
Observation	Good Flow	Good Flow	Good Flow	Good Flow	Good Flow	Good Flow	Good Flow	Good Flow	Good Flow

3.2 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.

Table No. 3.3 Post compression parameters of Dolasetron

Formulations	Uniformity in weight (mg)	Thickness variation (mm)	Hardness (kg/cm^2)	Friability (%)
F_1	98.72	3.15	5.40	0.121
F_2	98.79	3.18	4.30	0.231
F_3	99.37	3.13	5.20	0.189
F_4	99.78	3.14	5.20	0.158
F_5	99.59	3.21	5.30	0.215
F_6	99.53	3.09	4.90	0.255
F_7	99.49	3.22	5.20	0.117
F_8	98.43	3.19	5.10	0.161
F_9	99.86	3.07	5.40	0.165

Table No. 3.4: 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	39.83	40.36	37.25	44.37	41.28	35.14	29.73	25.57	28.94
4	57.63	59.08	55.49	80.21	66.47	49.91	43.06	46.02	39.68
7	95.41	90.18	87.95	97.86	85.82	80.11	69.58	67.69	54.79
12	--	98.47	99.49	-	97.95	98.68	79.96	80.13	69.83
16	--	--	--	-	-	-	95.15	97.94	85.81
24	--	--	--	-	-	-	-	-	**99.03**

Table No.3.5: Kinetic values obtained from F_9 plot formulation of Mosapride

Formulation	Zero order R^2	First order R^2	Higuchi R^2	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 Dolasetronsustained release matrix tablets were evaluated for stability studies at 40^0C ±2^0C/75 % RH±5% for 90 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.

Table No. 3.6: Stability data

Duration	Hardness(kg/cm)	Friability (%)
After one month	5.38	0.148
After three months	5.38	0.148
After Six months	5.37	0.149

Table No. 3.7: Stability data

Time in Hours	Cumulative percentage drug release		
	1st month	2nd month	3rd month
0	0	0	0
1	23.6	24.6	22.82
4	39.78	42.34	43.18
7	60.51	60.47	58.25
12	77.38	69.94	75.47
16	85.13	86.63	84.71
24	98.73	98.41	98.06

SUMMARY AND CONCLUSION

The present study was carried out to develop sustained release matrix tablets of Dolasetron. Matrix tablets of Dolasetron 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 Dolasetron the active constituent of the formulation. The FTIR spectrum of pure Dolasetron, mixture of Dolasetronwith, HPMC K4M, HPMC K15M polymers and mixture of Dolasetron, HPMC K15M, HPMC K4M with Lactose, talc, magnesium stearate, aerosil were analyzed for compatibility study. The study of FTIR spectrum confirms that Dolasetron and excipients used in the formulation are compatible with each other. The Sustained release Matrix tablets of Dolasetron 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 23°92" to 25°94". The matrix tablets were compressed by applying optimum force of compression and the hardness of tablets was found to be in the range of 4.3 to 5.4 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.

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. F_7 slowly released the drug, up to 16th hour. The total drug release from formulation F_8 was (97.94%) but it also failed to sustain the release up to 24 hour. 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 99.03%.

Hence the above study demonstrated that combination of HPMC K4M and HPMC K15M can be used to formulate sustained release matrix tablets of Dolasetron. 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 Dolasetron tablets. The cumulative drug release of innovators brand of sustained release tablet of Dolasetron 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 (99.03%).

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 Dolasetron sustained release matrix tablet and also the sustained release matrix tablet was found to be beneficial in terms of reduction in frequency of administration. Hence it can be concluded that once daily sustain release matrix tablet of Dolasetron 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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