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FORMULATION AND EVALUATION OF MEGESTROL ACETATE IMMEDIATE RELEASE TABLETS

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ABSTRACT

The aim of the present study is to have better patient compliance and reduce the developmental cost of Megestrol acetate formulation as an immediate release tablets. Megestrol acetate immediate release tablets were prepared by wet granulation technique using croscarmellose sodium as superdisintegrant. The formulated tablets were evaluated for various pre-compression parameters like bulk density, tap density, compressibility index and angle of repose. The post-compression parameters include weight variation test, hardness, thickness, friability, disintegration test, assay and related substances. The optimized formulation was taken for *in-vitro* dissolution study and stability studies. Among all the formulations, F6 showed better drug release.

KEYWORDS: Megestrol acetate, immediate release tablets, wet granulation.

INTRODUCTION

Dosage forms are pharmaceutical drug products in the form in which they are marketed for use, with a specific mixture of active ingredients and inactive components in a particular configuration. For decades together, oral drug delivery system plays a major role in the global pharmaceutical market. It is growing day by day because of being a convenient route for drug administration.[1]

Tablets are one of the most frequently used dosage forms, and they are typically made by a commercial process involving compression of a drug-containing mixture of materials in a high-throughput tableting machine.[2]

A large number of developments in the field of pharmaceutical technology have made manufacturing of tablet a science. In recent days tablets have become the most acceptable dosage forms as compared to other available dosage forms.[3] The popularity of this dosage form is because of advantages such as ease of manufacturing, convenience in administration, and high accuracy in dose, stability and safety. Many patients require quick onset of action in a particular therapeutic condition and hence immediate release is required. A high incidence of ineffective therapy is estimated in 50% of the population due to delayed release.

Immediate Release Drug Delivery System[4]

Immediate release drug delivery system is also one of the conventional type of drug delivery systems. Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques.

MATERIALS AND METHODS

Materials

Megestrol acetate (Micronized), Lactose monohydrate (Pharmatose 200M), Microcrystalline cellulose (Avicel PH 101 and 102), Povidone K-30, Croscarmellose sodium, Colloidal silicon dioxide and Magnesium stearate.

Preparation of formulations

Composition of 6 different formulations of megestrol acetate immediate release tablets were prepared by wet granulation method. All the materials were individually weighed and dispensed. The sifted Megestrol acetate, Lactose monohydrate, microcrystalline cellulose (PH 101) and Croscarmellose sodium was mixed for 10 mins. The binder solution was prepared by dissolving povidone K-30 in purified water and it was added to the above mixture slowly and mixed for 3 mins. The wet granules were dried and sifted. The sifted microcrystalline cellulose (Avicel PH102) and Colloidal anhydrous silica were added to the dried granules and mixed for 10 mins. To the above blend sifted Magnesium stearate was added and mixed for 10 mins. The final lubricated blend was compressed in a 16 station compression machine with 15.50 X 7.80 mm punch size, oval shape and standard concave punch with break line, embossed as “M” and “160” on either side of break line and plain on the back surface.

Table 1: Composition of Megestrol acetate Immediate Release Tablets.

S.No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
1	Megestrol acetate	160	160	160	160	160	160
2	Lactose monohydrate	253.0	255.8	255.8	261.4	264.2	264.2
3	MCCP - pH 101	93.2	93.2	93.2	93.2	93.2	93.2
4	Povidone K30	11.2	11.2	11.2	8.4	5.6	2.8
5	MCCP - pH 102	23.0	23.0	25.8	23.0	23.0	23.0
6	Croscarmellose sodium	5.6	2.8	2.8	2.8	2.8	2.8
7	Colloidal anhydrous silica	5.6	5.6	5.6	5.6	5.6	5.6
8	Magnesium stearate	8.4	8.4	5.6	5.6	5.6	8.40

Methods

Evaluation of powder blend[5,6,7]

Bulk Density

Accurately weighed 50 gm of blend, previously passed through #20 sieve was transferred into 100 ml graduated cylinder. Carefully the powder was levelled without compacting, and the unsettled apparent volume was noted**.**

Bulk density (g/ml) = Weight of the powder/Bulk volume of powder

Tapped Density (TD)

Accurately weighed 50 gm of the blend was transferred into 100 ml graduated cylinder. Initial volume was observed. The cylinder was tapped initially 500 times from a distance of 14±2 mm and measured the tapped volume to the nearest graduated units using Tap density apparatus. The tapping was repeated for additional 750 times. Again the tap volume was measured to the nearest graduated unit. The tapped bulk density in gm/ml was calculated by using the following formula.

Tapped density (g/ml) = Weight of the powder taken/Tapped Volume

Compressibility Index

The propensity of the powder to be compressed was measured by compressibility index and it also helps in measurement of settling property and interparticulate interactions.

$$\text{Compressibility Index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's ratio = Tapped density/Bulk density

Angle of repose

The angle of repose was determined by cylinder/funnel method. Accurately weighed powder blend is allowed to flow freely through cylinder/funnel onto the plain surface to form a cone from a certain height. The diameter of the cone is measured and angle of repose is calculated using the following formula.

Angle of repose (θ) = $\tan^{-1}$ (h/r)

Where, h = height of the pile and
r = radius of the pile

Evaluation of immediate release tablets[8,9]

a) Physical appearance

The tablets are visually inspected for smoothness, absence of cracks, chips, and other undesirable characteristics.

b) Weight variation test

Individual weights of 20 tablets were taken randomly from whole batch. Individual weight of tablet was then compared with the average weight for the weight variations. The USP Pharmacopoeial limits for deviation in weight variations is given in table.

Table 2: Weight variation tolerances for uncoated tablets.

Average weight of tablet (mg)	% Difference
<130 mg	10%
130 mg to 324 mg	7.5%
>324 mg	5%

a) Tablet Hardness

Hardness is the measurement of the force required to break the tablet across its diameter using a hardness tester. 10 tablets are randomly selected from a complete batch and hardness is determined by using digital hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is expressed in N or kg/cm2.

b) Tablet Thickness

The thickness of a tablet was determined by Digital Vernier Caliper. The thickness of 20 tablets were measured and the average thickness was denoted in mm.

c) Percentage Friability

The tablets were rotated in the Roche Friabilator which subjects the tablets to the combined effect of abrasion and shock in a plastic chamber. The tablets were placed the in the drum revolving at 25 rpm or for 100 revolutions. Remove any loose dust from the tablets and accurately weigh. The tablets that loose less than 1% weight are considered to be compliant.

$$\text{\% Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

d) *In-vitro* Disintegration study[10]

Disintegration test was carried out by using USP disintegration apparatus. The immediate release tablet should disintegrate within 30 minutes as specified in the individual monograph.

e) *In-vitro* dissolution studies(By UV method)[10]

The dissolution test was carried out by using USP Type II apparatus (Paddle Type). In this test, 900 ml of 1% sodium lauryl sulfate in water as dissolution medium is placed in the vessel and maintained at a temperature of 37± 0.5ºC, the paddle is rotated at 75 rpm. Samples were withdrawn and the amount of megestrol acetate ($C_{24}H_{32}O_4$) was determined by measuring the absorbance at 292 nm by using UV spectrophotometer.

Stability study[11]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. Stability testing permits the establishment of recommended storage conditions, retest periods, and shelf lives. This study plays a major role in determining their acceptance or rejection of the formulated product. The stability studies for Megestrol acetate immediate release tablets was carried out for the optimized formulation under accelerated stability condition of temperature 40±2ºC and RH 75% for three months. The tablets were withdrawn at the end of 1st and 3rd month and analyzed for physical characterization, assay and related substances.

RESULTS AND DISCUSSION

Characterization of Megestrol acetate powder blend

Flow properties

The bulk density and tapped density of all formulations was measured and it was found to be between 0.45 to 0.49 gm/ml and 0.58 to 0.63 gm/ml respectively. Using these data compressibility index and hausner's ratio was calculated.

The compressibility index and hausner's ratio of powder blends was found to be between 17.90 to 22.73 and 1.22 to 1.29 respectively indicated good flowability. The good flow property of blend was also evidenced with angle of repose which ranges from 36°29' to 44°19'.

Table 3: Pre-compression parameters of powder blend.

Formulation code	Bulk density (g/ml)	Tapped density(g/ml)	Compressibility Index (%)	Hausner's ratio	Angle of repose
F1	0.49 ± 0.2	0.61 ± 0.2	20.03 ± 0.2	1.25 ± 0.2	37°24'± 0.2
F2	0.45± 0.1	0.59 ± 0.1	22.73 ± 0.1	1.29 ± 0.2	42°34'± 0.1
F3	0.48 ± 0.3	0.58 ± 0.1	17.90 ± 0.1	1.22 ± 0.2	36°29'± 0.2
F4	0.48 ± 0.2	0.59 ± 0.2	19.05 ± 0.2	1.24 ± 0.4	38°67± 0.2
F5	0.49 ± 0.1	0.63 ± 0.2	21.95 ± 0.2	1.28 ± 0.1	44°19'± 0.3
F6	0.49 ± 0.2	0.61 ± 0.3	19.51 ± 0.2	1.24 ± 0.3	39°63'± 0.2

All the values are expressed as mean ± SD; n=3

Characterization of Megestrol acetate immediate release tablets

Megestrol acetate tablets were prepared in six formulations with varying binder concentration of Povidone K30 along with the excipients. Six formulations of megestrol acetate immediate release tablets were evaluated for post compression parameters such as Weight variation, hardness, thickness, friability, which is listed in the table.

The prepared tablets of all the formulation possessed good mechanical strength with sufficient hardness in the range of 197.80 to 222.30 N. The thickness of the prepared tablets was uniform in all six formulations. The thickness varies between 5.82 to 5.90 mm.

The results of weight variation and percentage deviation from the average weight of all tablet formulation (F1 – F6) were found to be within the prescribed official limits. All the formulated tablets of Megestrol acetate tablets were shown the friability values within Pharmacopoeial limits (i.e., not more than 1%). The post compression parameters of Megestrol acetate immediate release tablets were given in Table 4.

Table 4: Post compression parameters of Megestrol acetate tablets.

Formulation code	% Weight variation	Hardness (N)	Thickness (mm)	Friability %
F1	0.73 ± 2.51	222.30 ± 4.06	5.87 ± 0.01	0.15
F2	0.75 ± 4.16	210 ± 15.24	5.89 ± 0.03	0.12
F3	1.19 ± 2.65	205.27 ± 4.51	5.86 ± 0.03	0.17
F4	1.10 ± 4.58	197.80 ± 8.92	5.90 ± 0.03	0.09
F5	0.77 ± 2.52	204.83 ± 3.31	5.82 ± 0.01	0.13
F6	0.79 ± 2.63	202.20 ± 8.28	5.88 ± 0.02	0.14

All the values are expressed in mean ± S.D; n=3

Disintegration test

The disintegration time of all formulations was found to be in the range of 1 min 49 sec to 8 min 37 secs. The disintegration time of all formulations were found to be within the prescribed Pharmacopoeial limit (NMT 30 mins). It was observed that the disintegration time of F6 formulation was found to be similar with the reference product.

Table 5: Disintegration test of Megestrol acetate tablets.

Formulation code	Disintegration time (sec)
F1	8 min 37 sec
F2	7 min 14 sec
F3	5 min 10 sec
F4	4 min 50 sec
F5	3 min 40 sec
F6	1 min 49 sec
Reference Product	1 min 30 sec

***In-vitro* Dissolution studies**

In-vitro dissolution studies of all formulations were carried out as per the procedure. The percentage of drug release for all the six formulations at 1 hour was found to be between of 74 – 99%, this was within the acceptable limits. The F6 formulation showed better drug release of 99% at 60th minute which was also matched with the reference product.

Table 6: *In-vitro* Dissolution studies.

Time (min)	Percentage drug release						
	F1	F2	F3	F4	F5	F6	Reference product
0	0	0	0	0	0	0	0
15	44	48	41	40	53	51	52
30	51	53	57	49	68	68	71
45	65	69	63	65	77	85	82
60	74	81	70	72	86	**99**	**99**

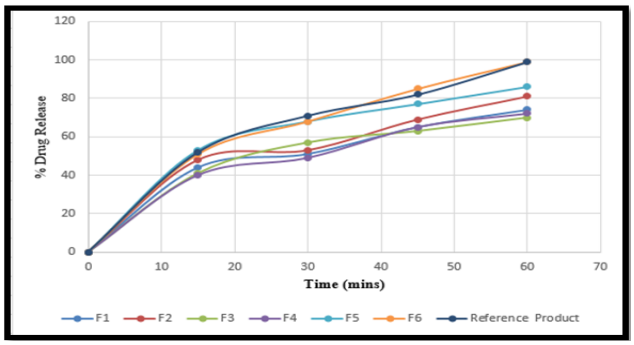

Fig 1: Dissolution study of Megestrol acetate Immediate release tablets.

Stability study

Formulation F6 was selected as an optimised formulation and exposed to accelerated stability condition of temperature 40±2°C and RH 75% for three months. The tablets were withdrawn at the end of 1st and 3nd month and analysed for physical characters, Assay and Relative substances. The result was found to be within the specified Pharmacopoeial limits.

Table 7: Stability study data of Optimised formulation(F6).

Parameter	Acceptance criteria	Initials	Condition(40°C / 75% RH)	
			1st Month	3rd Month
Description	White to off white	Complies	Complies	Complies
Average weight (mg)	560 mg ± 5% (532 to 588 mg)	565 ± 1.6	563 ± 1.8	570 ± 1.2
Assay (By HPLC)	93 to 107%	103.6%	104.1 %	105.3 %
Related substances				
Impurity C	NMT 0.1 %	0.01 %	0.01 %	0.01%
Impurity D	NMT 0.2 %	0.088%	0.087%	0.090%
Impurity I	NMT 0.3 %	0.040%	0.060%	0.05%
Impurity H	NMT 0.3 %	0.140%	0.142%	0.144%

CONCLUSION

The Present work involves the formulation development, optimization and evaluation of Megestrol acetate as immediate release tablets for the treatment of breast and endometrial carcinoma, cachexia, and anorexia. Six trial batches (F1 – F6) had been taken to formulate immediate release tablets by changing the concentration of binding agent, to obtain an optimized formulation. The powder blend were evaluated for precompression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose and the result showed that the flow property was good. The formulated tablets were evaluated for post compression parameters such as hardness, thickness, friability, percentage of weight variation, disintegration time, dissolution, assay and content uniformity and it was found to be within the Pharmacopoeial limits. F6 formulation was subjected to stability study under accelerated conditions. The first and third month analysis of physical characters, assay and relative substance were found to be within Pharmacopoeial limits. It is concluded that the formulation Megestrol acetate immediate release tablets

was found to be a promising substitute for reference product by increasing the solubility and thereby its bioavailability and reducing the cost of production and thereby increasing the patient compliance.

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REFERENCES

1. Tiwari SB and Rajabi-Siahboomi AR. Extended release drug delivery technologies: monolithic matrix systems. Drug Delivery Systems, Jain KK (Ed). Humana Press, Totowa NJ, 2008; 217-243.
2. Dosage forms. http://tmedweb.tulane.edu/pharmwiki/doku.php/dosage_forms?do=recent, 2020.
3. Rasenack N, Müller BW. Crystal habit and tableting behavior. Int J Pharm. 2002 Sep 5; 244 (1-2): 45-57.
4. Loyd V. Allen, Jr. Nicholas G. Popovich, Howard C. Ansel. Ansel's pharmaceutical dosage forms and drug delivery systems. 9th ed., Philadelphia; Lippincott Williams & Wilkins, 2005; 225-252.
5. Aulton. M.E. Pharmaceutics: The science of dosage form design, 2nd ed. Edinburgh: Churchill Livingstone, 1998; 133-135.
6. Alfred Martin. Physical pharmacy, 4th ed., New Delhi: B.I. Waverly, 1998; 423-451.
7. Indian Pharmacopeia. The controller of Publications Ghaziabad, 2007; 423-424.
8. Leon Lachman, Herbert A. Lieberman, Joseph L. Kanig. The theory and practice of industrial pharmacy, 3rd ed. Bombay: Varghese Publishing House; 1991; 293-336**.**
9. Rajalakshmi A. N, Nandhini. J. Formulation development and evaluation of Methylprednisolone dispersible tablets. *Asian Journal of Pharmacy and Pharmacology* 2018; 4(4): 514-521.
10. United States Pharmacopeia. The United States Pharmacopeial Convention, Rockville, 2014; 3675-78.
11. Stability Testing of new Drug Substances and Products. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-1-r2-stability-testing-new-drug-substances-products-step-5_en.pdf, 2020.