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FORMULATION AND EVALUATION OF REPEAT ACTION TABLETS OF ORLISTAT AND DROTAVERINE HYDROCHLORIDE

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ABSTRACT

Intensity of bioavailability of poorly soluble drug remains one of the most challenging aspects of drug development. This study was designed with an objective to obtain a better drug release profile of orlistat and drotaverine hydrochloride and good drug loading efficiencies by using various synthetic polymers such as HPMCE15 AND CMC at different proportions. The compatibility studies between drug and polymer was studied and followed by preformulation studies carried and finally they are formulated as tablets into different batches by using repeat action technique. It has been observed that the formulation of batch [F2] has shown good drug loading and better drug release compared to other batches. This work was done to decrease the adverse drug effect of orlistat i.e. pain in the stomach. Hence to overcome this problem Drotavarine hydrochloride has been selected as a model drug which is an anti spasmodic agent.

Key words: Orlistat, Drotavarine hydrochloride, HPMCE15M, CMC.

INTRODUCTION

The enhancement of oral bioavailability of poorly soluble drugs remains one of the challenging aspects of drug development together with the permeability .The solubility behavior of a drug is key determinant of its oral bio availability. There always certain drugs

for which solubility have presented a challenge to development of suitable formulation for oral administration. The most important property of a dosage form is its ability to deliver the drug to its site of action in an amount sufficient to elicit the desired pharmacological response this property of the dosage form has been referred to as its physiological availability or bioavailability.

Repeat Action Tablets

Repeat action tablets are prepared so that an initial dose of drugs is released immediately and a second dose follows later the tablets may be prepared with the immediate release dose in the tablets outer shell coating and the second dose in the tablets inner core separated by a slowly permeable barrier coating. In general, the drug from the inner core is exposed to body fluids and released 4-6 hours after administration .An example of this type of product is repetabs (Schering) repeat – action dosage forms are best suited for treatment of chronic conditions requiring repeated dosing. The drugs should have low dosage and fairly rapid rates of absorption and excretion.

Mechanism of action of orlistat

European medicines agency Reported orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control.

Mechanism of action of Drotavarine hydrochloride:

A.K.Tiwari *et al* (2011) Reported Drotaverine inhibits phosphodiesterases hydrolyzing cAMP, thereby increasing cAMP concentration, decreasing Ca uptake of the cells and changing the distribution of calcium among the cells. It may also have minor allosteric calcium channel blocking properties.

MATERIAL AND METHODS

Orlistat, Drotaverine HCl, Hpmc E_{15}, Cmc, Starch, Talc, Magnesium stearate, Potassium dihydrogenortho phosphate all the chemicals used are of analytical grade obtained as a gift sample from inventis pharma. Pvt ltd. Hyd. All solvents used are of HPLC grade.

Wet granulation technique

The drug and other additives were allowed though standard sieve number 100 separately. The immediate release granules were prepared by wet granulation method. Drug and other additives were mixed well by geometric dilution .To this starch mucilage was allowed to add little by little until a coherent mass was obtained. This was passed though standard sieve number 20 to get wet granules. The wet granules were dried at 50^0c in hot air oven .The dried granules were passed though sieve number 20 and the retained granules were passed though sieve number 25 to break the lumps and to remove fines respectively. 1% of the fines were added to the granules to be compressed. The sustained release granules were also prepared in the same way by wet granulation technique using starch mucilage 3 % as binding agent. 1 % of the fines were finally added to the granules to get compressed. To both portions of the granules 1 % of talc was added separately for lubricant and glidant action. Accurately weighed immediate release granules containing 100mg of anhydrous drug were poured in to the die to form the bottom layer. the sustained release granules equivalent to 200mg of anhydrous drug were also weighed accurately and this portion was poured over the bottom layer .half inch or 13 mm size round flat pouches were used for compression.

RESULTS

Evaluation Test for Tablets

The Prepared tablet were evaluated for quality control tests like, hardness test, weight variation test, friability, diameter, thickness, content uniformity study, and in vitro release study**.**

Hardness test

For each formulation, the hardness of six tablets was determined using a hardness tester (Monsanto, Mumbai, India). Hardness values were reported in kg/cm2. For each formulation, six tablets were weighed. The tablets were placed in a Roche friabilator (Labotech, Mumbai, India) and subjected to 100 rotations in 4 min. The tablets were then deducted and reweighed. The friability was calculated as the percent weight loss.

Weight variation test

Tablet weight is mainly affected by factors such as tooling of the compression machine, head pressure machine speed and flow properties of the powder. Inconsistent powder or granulate density and particle size distribution are common sources of weight variation during compression. Variation between tablet with respect to dose and weight must be reduced to a

minimum. Uniformity of weight is an in process test parameter which ensures consistency of dosage units during compression**.**

Test procedure

Weigh individually 20 units selected at random and calculate the average weight not more than two of the individual weights deviates from the average weight by more than the percentage given in the pharmacopoeia and none deviates by more than twice that percentage.

Friability test

The tablet may well be subjected to a tumbling motion. For example, Coating, packaging, transport, which are not severe enough to break the tablet, but may abrade the small particle from tablet surface. To examine this, tablets are subjected to a uniform tumbling motion for specified time and weight loss is measured. Roche friabilator is most frequently used for this purpose.

F= [(W1-W2)/W1] x100

Procedure for friability

Weight 20tab altogether =W1

Put these tablets in the friabilator and adjust the instrument at 100 rpm i.e=25 rpm for 4min

Weigh the 20 tablets only the intact ones =W2

Friability **%**loss=F= [(W1-W2)/W1] x100%

It must be less than or equal to 1 but if more we do not reject the tablets as this test is non official

Perform this test using 20 tablets that were used first in weight variation test.

Tablet diameter

Tablet diameter is also an important test. We use Pfizer tester for checking the diameter of the tablet, screw gauge and calipers are also used. Tablet thickness can be measured by micrometer or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value**.**

Tablet thickness

Tablet thickness is an important qc test for tablet packaging. Very thick tablet affects packaging either in blister or plastic container. Tablet thickness is determined by the diameter of the tablet. Pfizer tester is used for checking tablet thickness.

Content uniformity test

Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablet assayed individually and none may fall outside of the 85 to 115% range.

Assay Procedure for Orlistat

Kumar *et al.,* (2011) Reported Spectral and absorbance measurements were made using T60-UV-Visible spectrophotometer with software UV wins5.0. 10mm path length quartz cells were used. Essae-Teraoka analytical balance was used for weighing.

Preparation of Standard Solutions

Accurately weighed 100mg of Orlistat was dissolved in few ml of methanol and the solution was diluted to 100ml to obtain a concentration of 1mg/ml. Further a 10ml solution was taken and again diluted to 100ml to obtain a standard stock solution of 100µgm/ml.

Preparation of Sample Solutions

Twenty capsules were opened, contents weighed and mixed. An aliquot of powder equivalent to 100mg Orlistat was accurately weighed and dissolved in 100ml of methanol and filtered. The filtered solution was further diluted to obtain a concentration of 100µgm/ml.

Proposed method for Orlistat

Aliquots of solutions 1-10ml are taken from the standard stock solution in to 10ml volumetric flasks. The volume is made up to 10 ml using methanol to obtain the concentrations of 10, 20, 30, 40…...… 100 (µgm/ml). The absorbance was measured at 203nm against a blank. The calibration curve was plotted.

Assay Procedure for Drotaverine Hydrochloride

Standard solution preparation

Metwally F. H *et al*., (2006) Investigated that Drotaverine Hydrochloride standard solution containing 100µg/ml was prepared in a 100 ml volumetric flask by dissolving 10 mg Drotaverine Hydrochloride in 25 ml water- methanol (50:50, v/v) and then diluting to volume with water- methanol (50:50v/v) to the mark. The sample has filtered through a 0.45 µm nylon syringe filter.

Mobile Phase	Buffer: Formic acid in water (0.2%v/v)	
Organic	:	Methanol (HPLC grade)
Composition	:	Mobile Phase Buffer: Organic (55:45)
Column	:	YMC C8 (150mm × 4.6mm id, 5 µm particle size)
Flow Rate	:	1.0 ml/min
Detection	:	300 nm UV
Diluent:	:	Methanol: Water (HPLC grade)

Linearity Standard Solution Preparation

From Standard Stock Solution of accurately 1000 µg/ml pipette out exact 0.4, 0.6, 0.8,1.0, 1.2, 1.4, 1.6 and 1.8 ml and dilute it up to 10 ml each with diluent to achieve 40-180 µg/ml concentration range.

In vitro drug release for Drotavarine hydrochloride

H.Shah *et al., (2010)* The formulations were selected for release-rate studies based on the optimization. The studies were conducted using amber colored jars by USP Apparatus 2 method for 12 h. An accurate weight of 100 mg of pure drug or microspheres equivalent to 100 mg of drug was placed in 900 ml of a 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm . A 5-mL sample was withdrawn from the dissolution medium at 1-h intervals up to 12 h. The dissolution medium was replenished at each sampling with an equal volume of prewarmed fresh dissolution medium. Concentration of drug determined using UV spectrophotometer at λ max 242nm.

In vitro drug release for orlistat

Daniel R Lewis *et al.*, (2012) Reported Dissolution testing was performed using the Ph. Eur. rotating paddle apparatus in a dissolution medium that was developed especially for Orlistat substance due to its hydrophobicity. The dissolution medium comprised an aqueous solution containing 3% of sodium lauryl sulphate, 0.5% of sodium chloride, adjusted to pH 6.0 with phosphoric acid; sink conditions were achieved because the solubility of Orlistat in this medium is approximately 0.3 g in 100 ml. The rate of dissolution was determined individually for six capsules of each generic product, in a vessel with a paddle stirrer at 75 rpm and containing 900 ml of medium. Aliquots of 10 ml were removed after 15, 30, 45 and 60 min. These aliquots were filtered through a 1 µm Acrodisc glass fiber filter or 0.2 µm acrodisc filter (Pall Medical, Milan, Italy) and cooled to 20 °C, and 20 µl samples of the resultant clear solution were assayed using high performance liquid chromatography (HPLC)

and spectophotometry. The specification for Xenical dissolution rate at shelf-life was a Q-value of 65% after 45 min according to Ph. Eur.

Table.1 Composition of different formulations of tablets

Ingredients	Formulations											
	F1	**F2**	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Orlistat	300	**300**	250	350	200	300	350	300	350	300	350	200
Drotaverine Hydrochloride	30	**20**	10	20	10	20	10	30	20	10	15	20
Starch	15	**10**	25	15	10	20	15	10	20	15	25	10
Hpmc	5	**10**	20	15	5	18	14	2	014	25	14	25
Cmc	15	**20**	20	15	5	18	1	20	5	13	25	20
Lactose	2	**3**	1	2	3	2	1	2	3	12	1	3
Talc	1	**2**	1	2	2	2	1	2	1	2	2	2
Mg Stearate	2	**3**	4	2	2	1	2	2	1	2	2	2

Table: 2 Weight variation ranges

IP/BP	Limit	USP
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

Table: 3 Dissolution test for Drotaverine Hydrochloride

Time in min	Absorbance	Concentration	Amount of drug release	Cumulative drug release	% cumulative drug release
5	0.05	4.16	0.0416	37.50	12.5
15	0.12	10	0.1	90..416	30.1
30	0.18	15	0.15	135.1	45
45	0.23	19.16	0.191	172.65	57.5
60	0.26	21.66	0.216	195.19	65
90	0.29	24.16	0.241	217.716	72.5
120	0.13	26.11	0.220	218.16	98.11

Table: 4. U.V. absorbance for standard

Curve of Drotaverine hydrochloride

Linearity level	Concentration(µg/ml)
1	40
2	60
3	80
4	100
5	120
6	150
7	180
8	220

Table: 5. Hardness test

Formulations	Hardness(kg/cm^2)
F1	3.0
F2	**3.1**
F3	3.0
F4	3.2
F5	3.0
F6	3.2
F7	3.4
F8	3.0
F9	3.0
F10	3.1

Table: 6. Tablet Thickness

Formulations	Thickness(mm)
F1	3.0
F2	**3.0**
F3	3.1
F4	3.12
F5	3.0
F6	3.2
F7	3.1
F8	3.0
F9	3.0
F10	3.1

Table: 7.Tablet friability

Formulation	Friability (%)
F1	1
F2	**0.5**
F3	0.4
F4	0.3
F5	1
F6	0.6
F7	0.8
F8	0.2
F9	0.4
F10	0.3

Table: 8. Weight variation

Formulation	% weight variation
F1	6.2
F2	**5.0**
F3	5.5
F4	6.3
F5	6.5
F6	6.2
F7	7.0
F8	6.8
F9	5.2
F10	6.2

Table: 9. Content uniformity

Formulation	Orlistat (%)	Drotaverine HCl (%)
F1	105.0	105.0
F2	**100.2**	**102.0**
F3	102.0	100.2
F4	103.2	104.3
F5	104.3	102.3
F6	102.3	103.2
F7	101.0	101.0
F8	102.6	105.4
F9	105.4	102.4
F10	102.4	102.6

Table: 10. U.V. Absorbance for standard curve of Orlistat

S.no	Time in min	Absorbance nm
1	0	0
2	20	0.1
3	40	0.2
4	60	0.3
5	80	0.4
6	100	0.5
7	120	0.6

Table .11 dissolution test for orlistat

Time in min	Absorbance	Concentration	Amount of drug release	Cumulative drug release	% cumulative drug release
5	0.01	1	0.01	9	3
15	0.03	3	0.03	27	9
30	0.04	4	0.04	36.03	12.01
45	0.05	5	0.05	45.04	15
60	0.07	7	0.07	63.05	21.016
90	0.09	9	0.09	81.07	27
120	0.17	17	0.17	153.09	51.03

Table: 12 Disintegration test for tablets

Formulation	Disintegration time
F1	60
F2	**90**
F3	80
F4	85
F5	84
F6	95
F7	65
F8	86
F9	84
F10	85

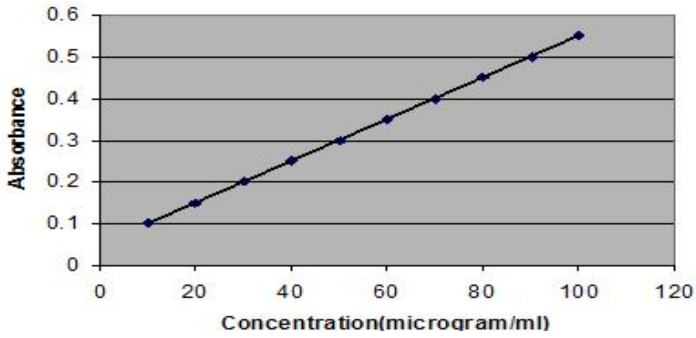

Figure: 1 Standard curve of Orlistat

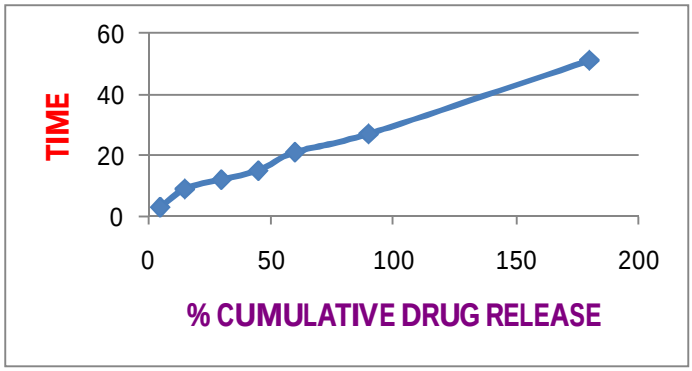

Fig .2 Cumulative drug release

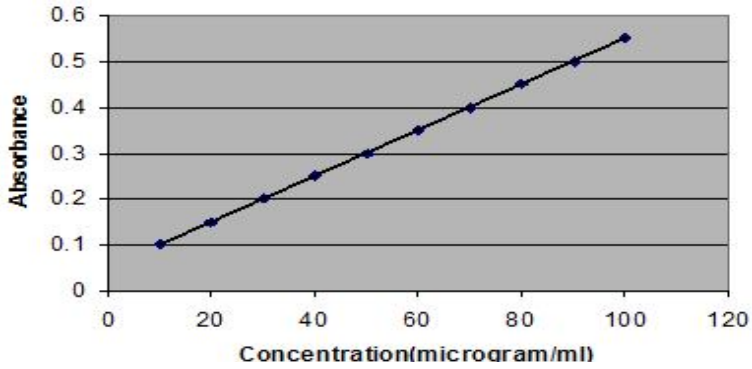

Figure: 3 Standard curve of Drotaverine Hydrochloride

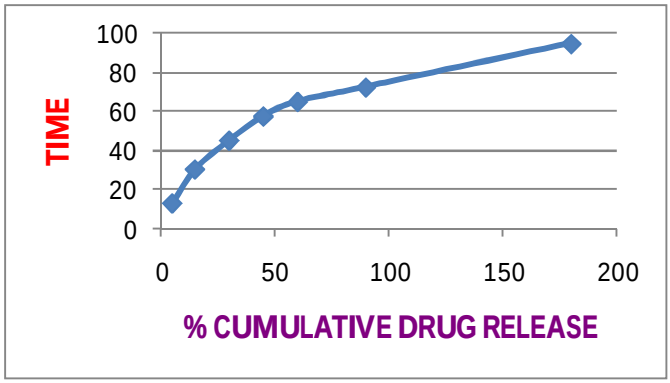

Fig: 4 Dissolution Curve for Drotaverine Hydrochloride

DISCUSSION

Drug release profile of (F2) formulation of ORLISTAT at 60 minutes the percentage drug release is 98.6 %. Drug release profile of (F2) formulation of DROTAVERINE HCl at 30 minutes the percentage drug release is 98.3 %. The formulation (F2) shows the maximum drug release of ORLISTAT and DROTAVERINE HCl was 98.6 %, 98.3 % respectively at time intervals 60 and 30 minutes. From all these formulations (F2) shows the maximum action compared to other formulations.

CONCLUSION

Repeat action tablets method was found to be successful with a number of drugs. In the present investigation studies were carried out on enhancement of dissolution rate of Orlistat with combination of Drotaverine hydrochloride by repeat action tablets method. Employing various water soluble and dispersible carriers. All the solid dispersions prepared were found to be fine free flowing powders. The drug content was not uniform in all the cases. The dissolution rate of Orlistat from optimized batches it was found that (F2) batch has shown good drug loading and better drug release compared to other batches. All the dissolution parameters estimated indicated rapid and higher dissolution of the drug from solid dispersions than that of pure drug. HPMC E15 is a fast releasing agent and CMC is a controlled release polymer with the ratio of 25:15.

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