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Research Article

Optimization of Immediate Release Tablet of Raloxifene Hydrochloride by Wet Granulation Method

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ABSTRACT
The purpose of this research is to prepare Raloxifene Hydrochloride immediate release tablet by wet granulation technique. In order to obtain the best, optimized product six different formulations were developed. Different filler, binder, disintegrant and lubricant were taken as variables. Weight variation, thickness, hardness, friability, disintegration time, *in-vitro* release and pharmaceutical assay were studied as response variables. Sticking was observed when the formulation containing stearic acid and sodium stearyl fumarate. However, in the remaining four formulation containing magnesium stearate, no sticking was observed. The formulation NP061 was selected as an optimized product. The different physical properties and *in-vitro* release profile showed best comparable with reference product. Optimization has proven as an effective tool in product development.

Keywords: Raloxifene Hydrochloride, optimization, wet granulation technique.

INTRODUCTION

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. In pharmaceutical industries, manufacturers of generic tablets are usually focused on the optimization of the excipient mixture composition to obtain a product that meet established standard. [1-2]

There are many methods used in the pharmaceutical industry to produce granules. However the most common is wet granulation technique. The wet granulation process offers several advantages. For example, high dose drugs that experience poor flow and/or poor compactibility can be granulated to obtain suitable flow and cohesion for com-paction. With low dose drugs, content uniformity in the tablets can be increased. [3]

Raloxifene hydrochloride, a selective estrogen receptor modulator (SERM) shown to be effective in the prevention of osteoporosis with potential utility as a substitute for long-term female hormone replacement therapy. [4] The drug rapidly absorbed following oral administration, it is subjected to significant first-pass metabolism. Oral absorption of the drug has been reported to 2 %.

In the present research, from the literature, patent search and the compatibility studies of the excipients the most favorable excipients were short-listed. All the excipients chosen are well known for their suitability and fitness of purpose. Each excipient is controlled by pharmacopial specification and are the same or similar to those used in the reference innovators product. The object of the development programme was to produce a generic tablet which was robust, stable and of an acceptable formulation when compared to the reference original product thereby fulfilling the requirements of essential similarity to the innovator reference product

The major objective of the product optimization stage is to ensure that the product selected for further development (the intended commercial product) is fully optimized and complies with the design specifications and critical quality parameters.

The present work is aimed to optimization of Raloxfene HCl immediate release tablet that is best comparable with innovator product by varying different excipients.

Material and Methods

Raloxifene HCl (from Jubilant Organosys Manufactured by Glochem Laboratory, Hyderabad, India), Hydroxy propyl methyl cellulose (HPMC, Pharmacoat 3 cps, Signet Chemicals), Poly vinyl pyrrolidone(Povidone K 30, BASF, Germany), Hydroxy propyl cellulose(HPC, Klucel EF, AqualonHercules), Ethyl cellulose (Ethocel 4 cps, Colorcon India Ltd.), Croslinked poly vinyl pyrrolidone (Polyplasdon XL 10, ISP Technology), Polysorbate 80 (Qualigens Fine Chemicals), Lactose monohydrate (Pharmatose 200M, DMV Fontera) Magnesium Stearate(Hyqual, Mallinckrodt). All other chemicals and reagents used were either analytical or pharmaceutical grades.

Solubility studies of Raloxifene HCl

Maximal solubility of Raloxifene HCl in different media (water, 0.1 % w/w polysorbate 80 in water, 0.01N HCl, 4.5 pH acetate buffer, 5.5 pH phosphate buffer) was studied. Excess amount of Raloxifene HCl was taken in 50ml of above medium and dissolved triplicates by sonication. The

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maximal solubility of Raloxifene HCl in each medium, was determined at different time intervals (0, 15 and 60min) after filtering the content by Whatman filter paper, the Raloxifene HCl content was determined spectrophotometrically at 287 nm.

Preparation of Raloxifene HCl tablets

Immediate release tablet of Raloxifene HCl were prepared by wet granulation technique using different hydrophilic and hydrophobic polymers. Accurately weighed quantities of pre-sieved drug and intragranular materials (lactose monohydrate and crosslinked polyvinyl pyrrolidone) were mixed thoroughly and granulated using polysorbate 80 in water (in case of hydrophilic binders; S1, S2, and S3) and isopropyl alcohol (in case of hydrophobic binder; S4). The wet granules were sieved through #20 sieves and dried in rapid dryer (Retsch Ltd.) at 45°C till LOD reaches to 1-2 % w/w. Dried granules were sieved through #20 sieves. The final granules were blended with extragranular materials (crosslinked polyvinyl pyrrolidone and magnesium stearate) and compressed using 12×6.5mm elliptically shaped standard conceave punches on 27-station rotary tablet press (Cadmach, Ahemadabad, India). Three batches of tablets were prepared for each formulation. Composition prepared immediate release tablets of Raloxifene HCl are presented in Table 1.

Table 1: Formulae used in the preparation of tablets

Ingredient	NP061	NP085	NP093	NP072	NP080	NP082
Raloxifene Hcl	60	60	60	60	60	60
Lactose anhydrous	153.4	-	153.4	153.4	153.4	153.4
Microcrystalline cellulose	-	153.4	-	-	-	-
Ethylcellulose	-	-	6.0	-	-	-
HPMC 3cps	6.0	6.0	-	6.0	6.0	6.0
Crosprovidone	7.4	7.4	7.4	-	7.4	7.4
Crosscarmellose sodium	-	-	-	7.4	-	-
Stearic acid	-	-	-	-	1.2	-
Sodium stearyl fumarate	-	-	-	-	-	1.2
Magnesium stearate	1.2	1.2	1.2	1.2	-	-
Polysorbate80	5.0	5.0	5.0	5.0	5.0	5.0
Cross providone	7.0	7.0	7.0	7.0	7.0	7.0
Tablet weight	240.0	240.0	240.0	240.0	240.0	240.0

Table 2: Physical properties of granules of different formulations

Properties	NP061	NP085	NP093	NP072	NP080	NP082
Angle of repose	26.0±0.03	27.5±0.03	23.9±0.09	28.5±0.02	27.8±0.07	28.2±0.04
Bulk density (gm/ml)	0.54±0.03	0.53±0.04	0.55±0.03	0.53±0.02	0.55±0.04	0.54±0.02
Tapped density (gm/ml)	0.69±0.02	0.68±0.04	0.69±0.02	0.68±0.03	0.69±0.02	0.68±0.04
Compressi--bility Index	21.65±1.25	24.83±0.98	23.52 ±1.51	25.77±1.37	26.1±1.45	27.0±1.06
Hausner's ratio	1.27±0.11	1.33±0.20	1.31±0.19	1.35±0.24	1.30±0.18	1.36±0.09

Evaluation of tablet properties

The formulated tablets were evaluated for uniformity of weight and thickness (micrometer, USSR), hardness (Monsato Hardness tester), friability (Electrolab India Ltd.) and disintegration time (Electrolab India Ltd.). The controls applied on all of the tablets were the following:

Weight variation test

The variation of the weight of individual tablets is a valid indication of the corresponding variation in the drug content. [5] Weight variation studies of 20 tablets for each batch were carried out. 20 tablets were weight first individual and all together for this purpose and resulting deviation were determined.

Thickness measurement

It is accomplished on 20 tablets by measuring thickness using vernier caliper. Mean and standard deviation were calculated.

Hardness determination

20 tablets were taken randomly and hardness was measured from using Hardness tester (Fujiwara, Seisukusho Corporation, Japan). The mean±S.D. of 20 tablets of each formulation is shown in Table 3.

Friability test

Friability was determined taking 20 tablets. Tablets samples were weighed accurately and placed in fribilator (Electrolab India Ltd.). After the given number of rotation (4 min at 25 rpm) loose dust was removed from the tablets as before. Finally tablets were wighed. The loss in weight indicates the ability of the tablets to withstand this type of wear.

The percent friability was determined by using following formula:

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

Disintegration test

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. [6] The tablets were examined using the USP XXIV disintegration apparatus (Erweka ZT-2, Huesnstanm, Germany). Six tablets were tested for each batch. The disintegration time of tablets was compared to 15 minutes which is accepted as the general tablet disintegration time.

***In-vitro* release studies**

In-vitro release of Raloxifene HCl was carried out using USP Type II dissolution apparatus (Paddle method, model TDT-08L, Electrolab, (USP), India) at 37±1°C and 50 rpm using 900 ml 0.1 % w/w polysorbate 80 in water. Aliquots were withdrawn at predetermined time intervals and were replenished immediately with the same volume of fresh dissolution medium. Aliquots, following suitable dilutions, were assayed spectrophotometrically (Shimadzu, Japan) at 287 nm.

Drug content study

Drug content of the manufactured tablets of each batch was determined by weighing and finely grinding twenty tablets from each batch. Aliquot of this powder equivalent to 100 mg of Raloxifene HCl was accurately weighed, suitably extracted in 50 ml of 0.1 % w/w polysorbste 80 in water (0.1N NaOH). The resulting solution was filtered, suitably diluted using 0.1 % w/w polysorbate 80 in water and analyzed by UV spectrophotometrically method at 287 nm.

RESULT AND DISCUSSION

Since, the flow properties of the drug candidate are important for the selection of suitable method for granulation of the powder mixture. Therefore, the flow of drug was analyzed before the selection of granulation techniques. Husner's ratio (≤1.21), compressability index (≤17.31) and angle of repose (≤34.8) indicates poor flowability of drug candidate. As the poor flowability of drug candidate, the wet granulation

Table 3: Physico-chemical properties of tablets of different formulations

Properties	Reference	NP061	NP085	NP093	NP072	NP080	NP082
Thickness (mm)	4.35± 0.45	4.21± 0.30	3.83± 0.56	3.93± 0.31	3.83±0 .46		
Weight variation	2.40± 0.01	2.44± 0.02	2.34± 0.02	2.44± 0.02	2.54±0 .02		
Drug content (%)	97.5± 0.20	98.5± 0.25	97.5± 0.24	98.5± 0.19	94.4±0 .25		
Hardness (kg/cm^2)	10.3± 0.12	10.1± 0.32	5.2±0. 25	7.1±0. 41	7.0±0. 28	Sticking problem	
Friability (%)	0.01	0.01	0.03	0.01	0.02		
Dinintegration time (sec)	6.38± 0.45	6.32± 0.39	3.36± 0.41	5.58± 0.43	9.81±0 .56		

Table 4: Variables selected to perform optimization

Variable	Ingredient	Quantity used (mg)	Percentage of quantity used
Filler	Lactose anhydrous Microcrystalline cellulose	153.4	63.9
Binder	Ethylcellulose HPMC 3cps	6.0	2.5
Disintegrant	Crosprovidone Croscarmellose sodium	7.4	3.1
Lubricant	Stearic acid Sodium stearyl fumarate Magnesium stearate	1.2	0.5

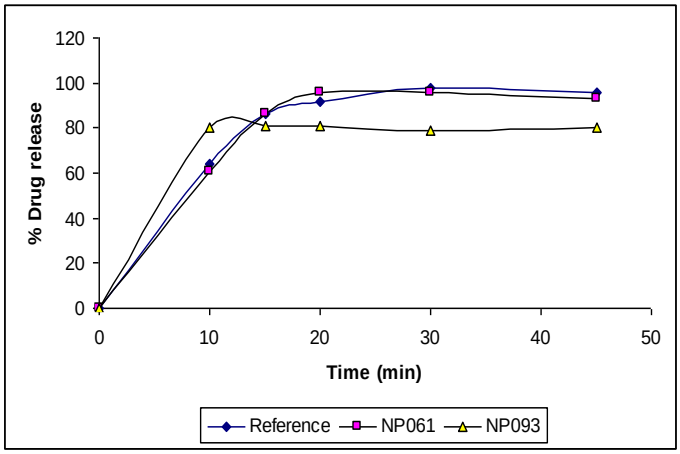

Fig. 1: In-vitro release profile of different batches prepared with using different binders

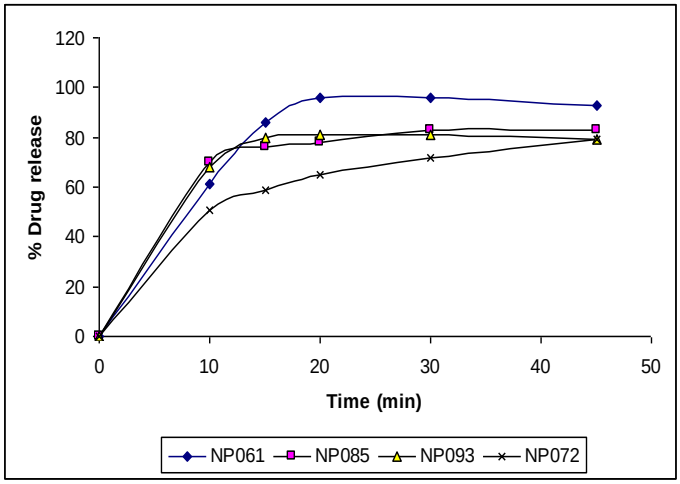

Fig. 2: In-vitro release profile of formulation NP061, NP085, NP093 and NP072 (n=6)

technique was selected to improve the flowability of powder mixture.

Experiments with solubility of Raloxifene HCl in various medium revealed that Raloxifene HCl is more soluble in water containing 0.1 % w/w polysorbate 80. Hence, water with 0.1 % w/w polysorbate 80 was selected as ideal dissolution medium, to study *in-vitro* release profile of Raloxifene HCl.

The technique of optimization is well reported in the literature for the development of tablet formulation. [7] The purpose of carrying out optimization is to select the best possible formulation from pharmaceutical as well as consumer point of view optimization is considered as an different and economical method to understand the relationship between independent and dependent variables. Optimization has gaining popularity in pharmaceutical research, day by day, since the best result are obtained in a limited number of experiments.

Powders intended for compression into tablets must process good compressibility and fluidity. Problems in fluidity cause variation in the die filling and consequently variation in tablet weight and strength. [8]

The important parameter that needs to be optimized in the development of immediate release tablets is the selection of different excipients. In the selection of suitable filler, lactose anhydrous (NP061) and microcrystalline cellulose (NP085) were taken into consideration. The tablets prepared using lactose anhydrous showed thickness (4.21mm±0.30), friability (0.01%) and disintegration time (6.32min±0.39). On the other side, the tablets prepared by using microcrystalline cellulose depicted, low thickness (3.83mm±0.56), more friability (0.03 %) and less disintegration time (3.36min±0.41). Since, tablets prepared by using lactose anhydrous showed comparable disintegration time to the reference product, the lactose anhydrous was selected as filler for formulation of tablets.

The selection of suitable binder for the formulation of immediate release tablet is very important because it affects friability, hardness, disintegration and after all *in-vitro* release of the drug from the formulation. In this study, ethylcellulose (NP093) and HPMC (NP061) was taken into consideration as binder and selection of suitable binder was carried out by evaluating the different physical parameter. The tablet prepared by using ethylcellulose and HPMC showed similar thickness, hardness, friability and disintegration time. The release profiles of both the formulation revealed that the incorporation of ethylcellulose slowed down the release rate. Hence, HPMC was selected as suitable binder.

During the formulation development of immediate release tablet, the selection of suitable disintegrant is very important. In this experiment, crossprovidone (NP061) and crosscarmellose sodium (NP072) were considered as disintegrant. The Table 3 indicates that the disintegration time of tablets prepared with crosscarmellose sodium was much higher as compared to the reference product, whereas tablets prepared by crossprovidone showed comparable disintegration time to the reference product. About 2-5 % concentration of crossprovidone is generally recommended in tablets prepared by wet granulation techniques. [9] Here, it was utilized in concentration 3.1 % because, the presence of crossprovidone, tablets from each batch disintegrated rapidly.

Raloxifene HCl does not possess excellent fluidity. The lubricant is added in the formulation because of it, a uniform flow from hopper to die was possible. It prevents the adhesion of tablet material to the machine parts such as punches and dies, reduce inter particle friction and facilitates the ejection of tablets from the die cavity. It is hydrophobic and may retard the dissolution of a drug from solid dosage form; the lowest possible concentration is therefore used in such formulations. [10] In this study, stearic acid (NP080), sodium stearyl fumarate (NP082) and magnesium stearate (NP061) were taken into consideration for the selection of suitable lubricant. Stcking was observed when the tablets were prepared using stearic acid and sodium stearyl fumarate, but when the tablets were prepared using magnesium stearate, no sticking was observed. Therefore, magnesium stearate was selected as lubricant for the development of immediate release tablet of Raloxifene HCl.

The optimized batch of Raloxifene HCl tablet formulation NP061 was studied for the different physical parameter and *in-vitro* release profile in the above media. Results of all developed formulation were within the acceptable ranges of values as given in official compendia but it was observed that the physical properties of NO061 were best comparable with marketed preparation. The *in-vitro* release of Raloxifene HCl from both the optimized formulation NP061 and marketed product were found similar.

Wet granulation methods can be used alternatively for direct compression method, because the less compressibility index and poor flow properties of drug candidate. A number of research article are available which are evident that the wet granulation is a preferred method of tabletting. Optimization technique is a good tool for preparing better quality of dosage form. This is widely used developing optimal dosage form and better process of manufacture.

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