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. 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 compaction. With low dose drugs, content uniformity in the tablets can be increased. 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. 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.

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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, KIcel EF, AqualonHercules), Ethyl cellulose (Ethocel 4 cps, Colorcon India Ltd.), Crosslinked poly vinyl pyrrolidone (Polyplasdone XL 10, ISP Technology), Polyisorbate 80 (Qualigenes Fine Chemicals), Lactose monohydrate (Pharmatose 200M, DMV Fontera) Magnesium Stearate(Hyqual, Mallinkrodt). 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/v polyisorbate 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 50 ml of above medium and dissolved triplicates by sonication. The
maximal solubility of Raloxifene HCl in each medium, was
determined at different time intervals (0, 15 and 60 min) 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 thoro-
uously 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 12×6.5 mm elliptically shaped standard
conceave punches on 27-station rotary tablet press
(Cdamach, Ahmedabad, India). Three batches of tablets
were prepared for each formulation. Composition prepared
immediate release tablets of Raloxifene HCl are presented in
Table 1.

<table>
<thead>
<tr>
<th>Table 1: Formulc used in the preparation of tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Raloxifene HCl</td>
</tr>
<tr>
<td>Lactose anhydrous</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
</tr>
<tr>
<td>Ethylcellulose</td>
</tr>
<tr>
<td>HPMC 3cps</td>
</tr>
<tr>
<td>Crospovidone</td>
</tr>
<tr>
<td>Crossmelllos e sodium</td>
</tr>
<tr>
<td>Stearic acid</td>
</tr>
<tr>
<td>Sodium stearyl fumarate</td>
</tr>
<tr>
<td>Magnesium stearate</td>
</tr>
<tr>
<td>Polysorbate 80</td>
</tr>
<tr>
<td>Cross providone</td>
</tr>
<tr>
<td>Tablet weight</td>
</tr>
</tbody>
</table>

Weight variation test
The variation of the weight of individual tablets is a valid
indication of the corresponding variation in the drug content.
[8] Weight variation studies of 20 tablets for each batch were
conducted. 20 tablets were weighted individually 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 (Fujifara, 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 fribrator (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 weighed. 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:

\[\% \text{ friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100\]

Disintegration test
Disintegration is evaluated to ensure that the drug substance
is fully available for dissolution and absorption from the
gastrointestinal tract. [9] The tablets were examined using the
USP XXIV disintegration apparatus (Erweka ZT-2,
Husenstamm, 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
TDY-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 polysorbate 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
(≤2.1), compressibility index (≤7.31) 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

<table>
<thead>
<tr>
<th>Properties</th>
<th>Reference</th>
<th>NP06</th>
<th>NP08</th>
<th>NP09</th>
<th>NP07</th>
<th>NP09</th>
<th>NP09</th>
<th>NP08</th>
<th>NP08</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (mm)</td>
<td>4.32±</td>
<td>4.21±</td>
<td>3.83±</td>
<td>3.93±</td>
<td>3.93±</td>
<td>3.83±</td>
<td>3.83±</td>
<td>3.83±</td>
<td>3.83±</td>
</tr>
<tr>
<td>Weight variation (%)</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Drug content (%)</td>
<td>97.5±</td>
<td>98.5±</td>
<td>97.5±</td>
<td>98.5±</td>
<td>98.5±</td>
<td>94.4±</td>
<td>94.4±</td>
<td>94.4±</td>
<td>94.4±</td>
</tr>
<tr>
<td>Hardness (kg/cm²)</td>
<td>10.1±</td>
<td>10.1±</td>
<td>5.2±</td>
<td>7.1±</td>
<td>7.0±</td>
<td>0.0±</td>
<td>0.0±</td>
<td>0.0±</td>
<td>0.0±</td>
</tr>
<tr>
<td>Friability (%)</td>
<td>0.12</td>
<td>0.32</td>
<td>25</td>
<td>41</td>
<td>28</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Disintegration time (sec)</td>
<td>6.38±</td>
<td>6.32±</td>
<td>3.36±</td>
<td>5.58±</td>
<td>9.81±</td>
<td>6.43±</td>
<td>6.43±</td>
<td>6.43±</td>
<td>6.43±</td>
</tr>
</tbody>
</table>

Table 4: Variables selected to perform optimization

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ingredient</th>
<th>Quantity used (mg)</th>
<th>Percentage of quantity used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filler</td>
<td>Lactose anhydrous Microcrystalline cellulose Ethylcellulose</td>
<td>153.4</td>
<td>63.9</td>
</tr>
<tr>
<td>Binder</td>
<td>HPMC 3cps Crossprovidone</td>
<td>6.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Disintegrant</td>
<td>Crosscarmellose sodium</td>
<td>7.4</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Stearic acid Sodium stearoyl fumarate</td>
<td>1.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Lubricant</td>
<td>Magnesium stearate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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)

discipline was selected to improve the flowability of powder mixture.
Experiment 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. 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 a 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.

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. 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. Sticking 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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REFERENCES
