INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Research Article

SOLUBILIZED FORMULATION AND EVALUATION OF LIQUID FILLED HARD GELATIN CAPSULES OF ESTROGEN RECEPTOR MODULATOR DRUG

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ABSTRACT

Estrogen replacement is considered the first line approach for the prevention and treatment of multiple conditions affecting women's health. It has been widely recommended for prevention and treatment of osteoporosis. However its long term use is not without risks. Hence patients prefer to be treated with non-hormonal drugs. Raloxifene is one of a new generation of drugs called selective estrogen receptor modulator (SERM) specifically developed to maintain beneficial estrogenic activity on bone and lipids and antiestrogenic activity on endometrial and breast cancer tissue. At present it is the only SERM approved for treating and preventing osteoporosis in postmenopause women. The major problem encountered with this drug was its poor aqueous solubility. Since dissolution is the rate determining step for hydrophobic, poor aqueous soluble drug, absorption of such drugs is often said to be dissolution rate-limited. To design proper dosage regimen and to improve oral bioavailability efforts were made to solubilize the drug. Liquid filled hard gelatin capsule are well established as a solid dosage form for convenient administration of drugs orally in a liquid form in two piece HPMC capsule. This technology is more adopted for insoluble hydrophobic and potent drugs. And there are also many advantages in giving the drug in liquid form. Hence drug compounds are solubilised inside the hard gelatin capsules such that on subsequent dissolution of LFHGC in the gastro intestinal tract, the drug remains in solution, and contribute for good bioavailability of drugs.

Keywords: Hydrophobic, Solubilization, Complex, Solvets.

INTRODUCTION

Liquid filled hard gelatin capsule are well established as a solid dosage form for convenient administration of drugs orally in a liquid form. Liquid filled capsule technology can be used for liquid and semisolid fills in two piece gelatin or HPMC capsule with or without banding. This range of liquid composition available to accommodate even the most challenging drug compounds in capsules has increased significantly in recent years. In particular it is possible to solubilize many drug compounds in a micro emulsion pre-concentrate inside the hard gelatin capsules such that on subsequent dispersion in the gastro intestinal tract, the drug remains in

solution. It is considered that this technology can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in - house formulation when only small quantities of drug substance is available.

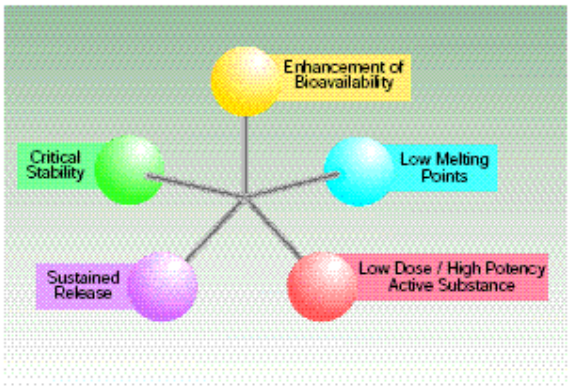

Fig 2: Reasons For Formulating Drugs As Liquid Or Semi-Solid Dosage Forms

This technology is most suitable for:
Insoluble compounds
Highly potent compounds
After filling the hard gelatin capsules they are sealed by spraying small amount of Water \ ethanol mixture at the cap and body interface followed by gentle warming to fuse the two capsules parts together.
Materials which have low melting points or are liquids at room temperatures presents difficulty when formulated as dry powders and often requires high concentration of excipients to avoid processing problems .The product Piascledine 300 is a good example of how a manufacturing process can be simplified by filling as a hot melt into a hard gelatin capsule. and 5 steps process involved in manufacturing a tablet was reduced to a simple mixing and filling operations.

Low doses and highly potent drugs present two main challenges:
1. How to achieve acceptable content uniformity
2. How to avoid cross-contamination
Duerr et al and Cade has reported that the liquid filled operations are capable of achieving fill weight variation of < 1%, If a drug substance is in solution or is uniformly dispersed in a liquid vehicle then it follows that good drug content uniformity can also be achieved. Companies manufacturing solid dosage form of hormones and cyctotoxic agents from powders are forced to install extremely elaborate systems to reduce contamination incorporation of highly potent agents into a liquid or filling into a hard gelatin capsule can reduce the dangers when working with such drugs.

Table 2: size and volumes of hard gelatin capsules For liquid filling

Size (ml)	Approx. volume (ml)	Approx. available volume
00el	0.92	0.83
00	0.85	0.77
0	0.61	0.55
1	0.45	0.41
2	0.34	0.31

Table 3: Comparisons Of Hard And Soft Gelatin Capsules

Aspects	Hard Gelatin Capsules	Soft Gelatin Capsules
IN house development and manufacture	Yes	Difficult
Ability to manufacture small batches	Yes	No
Scale – up	simple & in-house	requires large quantities of substances and must be outsourced.
Temperature of fill	Max – 70° C	Max – 35° C
Plasticizer in shell	No	Yes
Risk of drug migration	Low	High for drugs soluble in plasticizer
Permeability of shell to oxygen	Low	High
Sensitivity to heat	Low	High due to moisture
Limitation on Excipients for formulation	High concentration or hygroscopic substances such as glycerol must be avoided	Hygroscopic can be tolerated due to presence of plasticizer
Capsule Dimension	constant	May vary

Advantages

1. Capsules are easier to swallow because of their shape and because their gelatin exterior becomes slippery when patients take them with water.
2. This technology potentially provides the industry with an in - house process to develop drugs which are poorly water - soluble, have low melting point, are highly potent or lower dosed or have a critical stability issue, into bioavailable, stable and safe dosage form.

One problem which has prevented wider acceptance of this technology was the fact that the capsules had to be banded using a process which is difficult to operate and capital intensive.

Liquid filling and sealing of hard gelatin capsules thus become a much more feasible option. It provides the formulation scientist with an in - house operation to rapidly develop products for clinical trials when drug substance is at premium and also provides an easy route to scale - up and production.

MATERIALS AND METHODS

5.1 . MATERIALS

Table 5: Materials Used

S. No	Materials	Category
1.	Raloxifene	Treatment of Postmenopausal Osteoporosis
2.	Citric acid	Complexing agent / carrier
3.	Polyethylene Glycol 400	Solvent
4.	Glycerol 80%	Solvent
5.	Propylene Glycol	Solvent
9.	Poloxamer	Surfactant, Complexing agent / carrier
10.	Gelucire	Solubilizing agent
11.	Polysorbate	Surfactant
12.	Povidon K30	Complexing agent / carrier
13.	Castor oil	Solvent
14.	Ascorbic acid	Complexing agent / carrier
15.	Succinic acid	Complexing agent / carrier
16.	Polyethylene Glycol 4000	Complexing agent / carrier

5.2. EQUIPMENT USED

Table 6: EQUIPMENTS USED

Serial. No	Equipments	Company
1.	**Electronic balance**	Metter Toledo, USA
2.	Ultrasonic cleaner	Branson, USA
3.	Mechanical Stirrer	Electro lab, MUMBAI
4.	Bulk density apparatus	Campbell electronic, MUMBAI
5.	Tablet dissolution apparatus usp-24	Electro lab, MUMBAI
6.	UV Spectrophotometer	Shimadzu, JAPAN
7.	Stability chamber	Thermo lab , INDIA
8.	Heating mantle	Centex, MUMBAI
9.	Inductive sealing machine	Enercon, MUMBAI
10.	Uphold viscometer	Phenomex, USA
11 .	pH meter	Eutech pH meter, INDIA
12.	Differential Scanning Calorimeter	Shimadzu, JAPAN

5.3 . METHODS

5.3.1.PREFORMULATION STUDIES

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage form. The overall objective of preformulation testing is to generate information useful to the formulators in developing stable and bioavailable dosage forms

Scope

The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Considerations in oral dosage forms:

- Dose
- Solubility
- Dissolution
- Crystallinity
- Polymorphism
- Determination of bulk density

5.3.1.1 Determination of Bulk Density

An accurately weighed quantity of the raloxifene drug which was previously passed through sieve # 40, was carefully poured into graduated cylinder and the volume (Vo) was measured. Then the graduated cylinder was closed with lid, set into density determination apparatus **(**B.D app.Cambell electronics**).**The density apparatus was set for 100 taps and after that the volume (Vf) was measured and continued till the two consecutive readings were equal. The bulk density were calculated using the following formula:

Bulk Density = W/ Vo

Tapped Density = W / Vf

Where

W = Weight of powder

Vo = Initial volume

Vf = final volume

The values of bulk Density was represented in table 9.

5.3.1.2 Powder Fineness of Raloxifene

Instrument

Malvern particle size analyse (Model: MASYER SIZE R ‘2000’)

Dispersant

saturated milli Q water

Preparation of Dispersant

1 gm of powder was weighed into 1000 ml beaker containing miili Q water and this was sonicated for 20 min and this solution was used as dispersant.

Preparation of test solution

200 mg of the sample was transferred into 30 ml stoppered test tube,25 ml of dispersant was added and kept on cyclomixer for 2 min, than this was again sonicated for 30 min.

Procedure

Sample handling unit was filled with dispersant, and required stirring speed was set and stirred to eliminate any air bubbles and back ground was measured. Then add the well dispersed sample drop wise into the sample dispersion unit until the obscuration falls in to the range of ideal. Than this sample reading

was taken. The values were presented in table 9.

5.3.1.3 Solubility

Solubility of raloxifene was checked in different solvents. Excess amount of Raloxifene was taken in screw capped glass tube and 1 ml of solvent was added. The tube was shaken for 24 hrs in a shaking water bath and the drug solubility was determined. The solubility of raloxifene was represented in table 9.

5.3.2ANALYTICAL DATA OF RALOXIFENE

5.3.2.1 Preparation of 0.001 N HCl

0.1N HCl -Transfer 85ml of HCl in 10000 ml of purified water. Dilute 100 ml of the above mixture to10000 ml with purified water to get 0.001 N HCl.

5.3.2.2 Standard Graph in 0.001 N HCl

100 mg of raloxifene was weighed and transferred to 200 ml volumetric flask, 50 ml of methanol was added to dissolve the entire drug. Volume is adjusted to 200 ml with additional quantity of methanol. From this 5 ml of solution was pipetted into 100 ml standard flask and volume is adjusted by adding 0.001 N HCl.. Further dilution of this stock solution is made with 0.001 N HCL so as to obtain concentrations of 2.5, 5.0, 7.5, 10.0, 12.5, 15.5 ug/ml respectively. The absorbance of this solution is measured at 284nm and reading of concentration verses absorbance is plotted. This plot is used as standard. The summary of the calibrated curve is given in the table 10 and figure 3.

5.3.3 PREPARATION OF DRUG :CARRIER COMPLEX

5.3.3.1 Selection of Complexing Agent/Carrier

Eutectic mixtures of drug with different water soluble carriers were made by physical mixing. The incorporation of a drug in a carrier by melt embedding may result in a solid solution of the active ingredient within the carrier material. As the dispersivity of the drug is of outstanding importance for its dissolution characteristics, parameters which are supposed to influence crystallinity and dispersivity, e.g. cooling rate during preparation are investigated during the preparation of dispersion. Solid dispersions of raloxifene in different carriers such as citric acid, poloxamer, povidon K30, ascorbic acid, succinic acid, and polyethylene glycol - 4000 were prepared by the hot melt method with the intention of improving the dissolution properties of the drug. Table 11 represents the different carriers used and observations made for optimizing appropriate carrier.

5.3.3.2 Selection of Appropriate Drug: Carrier Ratio

Hot – Melt Method

Raloxifene and citricacid complex was prepared by Hot-Melt method. Different ratio's of drug and carrier were weighing accurately into a beaker, mixed thoroughly and was allowed to melt at higher temperatures approximately 100^{o} C. The molten mixture was than poured onto a cold Petri dish and kept in refrigerator for rapid cooling in order to obtain a solid dispersion. Different ratio's of drug and carrier taken for preparing solid dispersion was represented in Table 12.

5.3.3.3 Thermal Analysis of Drug: Carrier Complex

The solid dispersion of raloxifene and citric acid thus prepared was subjected to thermal analysis.

Thermal analysis was carried out with the help of DSC. The temperature was elevated from ambient (25^{o}C) to 300^{o}C at the heating rate 10^{o}C/min under the nitrogen environment**.** 5mg of the samples were weighed and subjected for DSC.

5.3.3.4 Drug Complex - Excipients Taste Evaluation

The resulting complex containing 1:1 ratio of drug and carrier is very bitter tasting, hence taste masking was done to obtain a palatable formulation.

5.3.3.4.1 Sample Preparation

Each excipient used in the formulation was thoroughly mixed with the drug complex to increase the drug - excipient molecular contact to the accelerate reaction if possible. Physical mixtures of drug complex: excipient mixture were tested for stability by physical observation. Compatibility of excipient with complex was tested.

5.3.5 LIQUID FILLED HARD GELATIN CAPSULES

5.3.5.1 FORMULATION DEVELOPMENT

5.3.5.1.1 Selection of Prototype Formulation

Raloxifene liquid filled hard gelatin capsules were prepared by solubilizing the drug : carrier complex in suitable solvents and a surfactant was added to improve the dissolution property of the complex. Additives added were represented in grams and the below table 7 represents the quantities of excipients per capsule.

5.3.5.1.2 *Method*

The complex containing raloxifene and citric acid was dissolved in polyethylene glycol - 400 and glycerol, and castor oil were added in batches C001 and C003 respectively and kept for sonication for 1hour.To the above mixture polysorbate 80% were added and mixed thoroughly. Gelatin sheet was kept in this mixture and weight variations were checked. The weight variation was represented in table 17.

5.3.5.2 EVALUATION OF LIQUID FILLED HARD GELATIN CAPSULES

The raloxifene liquid filled hard gelatin capsules were evaluated regarding the following characteristics.

5.3.5.2.1 Drug Content (Assay)

The drug content of liquid filled hard Gelatin capsules was determined spectrophotometrically by using UV spectrophotometer.

5.3.5.2.1.a *Standard*

Raloxifene liquid filled hard gelatin capsules should contain NLT 90.0% and NMT 100.0% of labeled amount of raloxifene.

5.3.5.2.1.b *Preparation of Standard*

The standard was prepared as mentioned under section 5.3.5.2.2.1.

5.3.5.2.1.c *Preparation of Sample*

Capsule content equivalent to100mg of drug was pipetted into 200 ml standard flask and volume was made with methanol. 5 ml of this solution was further diluted to 100ml with 0.001 N HCl. The absorbance was measured in UV spectrophotometer using 0.001 N HCl as blank at 286 nm.

The percentage content of raloxifene LFHGC:

$$\frac{\text{Assay value}}{\text{Label claim}} \times 100$$

5.3.5.2.2 Dissolution Test

Drug release from the liquid filled hard gelatin capsules was evaluated by carrying out dissolution studies in 0.001 N HCl using USP II type (paddle type) dissolution tester (Electro Lab, India) .The speed of rotations was kept at 50 RPM. Temperature maintained at 37^{o}C.

5.3.5.2.2.a. Preparation of Standard

50mg of pure drug of drug was accurately weighed and dissolved in methanol and volume was made up to 200ml with methanol. 5ml of this methanolic solution was ***taken*** in 100ml standard flask and volume was made up to 100ml with 0.001 N HCl. The absorbance was measured in UV spectrophotometricaly using 0.001 N HCl as blank at 286 nm.

5.3.6.2.2. b Preparation of Sample

6 capsules are taken into each dissolution vessel, and 5ml of each samples were collected at intervals of 10, 20 ,30 and 45 mins in 25ml volumetric flask and volume was made with 0.001 N HCl. The absorbance was measured in UV spectrophotometricaly using 0.001 N HCl as blank at 286nm.The following formula was used for UV

Amount of drug release

$$= \frac{At \times Ws \times 5 \times P \times 900 \times 25 \times 100}{As \times 200 \times 100 \times 100 \times L \times 5}$$

At = Absorbance of test preparation
As = Absorbance of standard preparation
Ws = Weight of raloxifene standard taken in mg
P = Potency of raloxifene standard
L = Labeled amount of raloxifene in mg per capsule

Percentage of drug release

$$= \frac{\text{Amount of drug release} \times 100}{\text{Label claim}}$$

The drug release of initial batch (C008) was represented in the table 18.

5.3.5.3. PRELIMINARY STABILITY STUDIES

Preliminary stability of the best formulation obtained was investigated by studying its Physical characteristics and drug content and

drug release after storage at stressed conditions. LFHGC was stored at 40° C & 75% RH for a period of 1months. The Physical characteristics and drug content and drug release of the fresh (stored at room temperature) and stressed preparations were compared to evaluate the stability and effect of aging.

RESULTS AND DISCUSSIONS

The present study was undertaken to develop solubilized formulations of insoluble postmenopausal osteoporosis drug. The results and observations are discussed below.

6.1 PREFORMULATION PARAMETERS

The physicochemical characteristics of a drug relevant to its biological activity are determined at the preformulation stage of drug development. Data on factors such as bulk density, particle size, solubility can be obtained by standard physico-chemical methods (Davis, 1985).The physical characteristics determined in section 5.3.1 are given in the table 9.

Table 9: Physical Characteristics of Drug

S. No.	Tests	Results
1.	**Bulk density** Before tapping After tapping	 0.22 g/m 0.53 g/ml
2.	**Particle size by Malvern**	10 % less than 11 um 50% less than 46 um 90 % less than 114 um
3.	**Solubility**	Freely soluble in dimethyl sulfoxide Very slightly soluble in methanol Insoluble in water

6.2. ANALYTICAL DATA OF RALOXIFENE

Standard calibration curves of raloxifene in 0.001 N HCl are given in figure 2. The beer's law was obeyed in the concentration range of 2.5 – 15ug/ml as described in the literature (Sane et al) The linearity coefficient in each case was greater than 0.993. The summary of the calibrated curve was given in table 10.

Table 10: Absorbance of Drug in 0.001 N HCl

S. No	Concentration Of drug (ug \ ml)	Absorbance (at 284 nm)
1	2.5	0.17986
2	5.0	0.34376
3	7.5	0.53136
4	10.0	0.71906
5	12.5	0.87293
6	15.0	1.03563

6.3. PREPARATION OF DRUG - CARRIER COMPLEX

To improve the dissolution performance**,** the drug was formulated into solid dispersion using 6 different carriers and mixing ratios. As intermolecular association of drug with the carrier led to increased effective surface area of drug in the solid dispersion, resulting in solubility enhancement of the drug.

6.3.1.Selection Of Complexing Agent/Carrier

Solid dispersions of raloxifene were prepared by hot melt method by employing various carriers to improve dissolution properties of the drug. And selection of suitable complexing agent/carrier was done on the basis of

solubility of complex in different solvents, the data is summarized in table 11.

Table 11: Selection Of Complexing Agent/Carrier On Basis Of Solubility

No	Drug	Carrier	Water	Polyethylene Glycol - 400	Glycerol 80%	Propylene Glycol
1	Raloxifene	Citric acid	Soluble	Soluble	Soluble	Soluble
2	Raloxifene	Poloxamer	Soluble	Insoluble	Insoluble	Soluble
3	Raloxifene	Povidon K30	Insoluble	Insoluble	-	-
4	Raloxifene	Ascorbic acid	Insoluble	Soluble	Insoluble	Insoluble
5	Raloxifene	Succinic acid	Insoluble	Insoluble	Insoluble	Soluble
6	Raloxifene	Polyethylene Glycol - 4000	Insoluble	Insoluble	-	-

DISCUSSION

The complex containing drug and citric acid carrier are completely soluble in all solvents studied without any precipitation or turbidity, and forms a clear bright yellow colored solution.

6.3.2 .Selection of Appropriate Ratio of Drug : Carrier Complex

Solid dispersions of carrier and drugs at different weight ratios were prepared by hot melt method as described in section 5.3.3.2 with an aim to improve the solubility and dissolution rate. Drug and carrier at different ratio, namely 1:1, 1:2, 1:5 were used for the preparation of solid dispersion. The data is summarized in table 12.

Table 12: Solubility of Different Drug : Carrier Ratio In Water And Aqueous Solvents

S. No	Drug + Carrier Ratios	Solubility in water	Solubility in other solvents
1	1: 1	Clear, bright yellow colored after 10 min	Clear, bright yellow colored solution after sonication for 20 min
2	1: 2	Insoluble	Clear, bright yellow colored solution after sonication for 30 min
3	1: 3	Pale, light yellow turbid solution	Pale, light yellow turbid solution

Observation

Dug and Carrier complex mixed in 1: 1 ratios were taken for dosage form formulation as this complex were completely soluble and forms clear, bright yellow colored solution both in water and other solvent in comparatively less time than any other complexes.

6.3.3. Thermal Analysis of Drug Complex

The DSC thermograms of the drug and carrier and the drug - carrier complex were made in an attempt to define the physical state of the drug in the carrier and the possibility of interaction between the drug and the carrier. DSC studies indicated no interaction between drug and the carrier. Raloxifene showed (Figure 6A) a melting temperature 118^{o}C and similar results were obtained when complex of 1:1 were subjected to thermal analysis. This data suggest that Raloxifene and carrier were neither dissolved nor formed a covalent linkage with the carrier. Figure 6A, 6B, 6C provides the thermal behavior of the pure drug carrier and combination of drug and carrier in a ratio approximately representing the final formula.

6.5. RALOXIFINE LIQUID FILLED HARD GELATIN CAPSULES

6.5.1. Optimization of Prototype Formula

Trial batches of RLX liquid filled hard gelatin capsules were conducted to select prototype formula. These batches were prepared

according to the method described under section 5.3.5.1.2, the quantities of additives added are shown in the table 7. The weight variation of the gelatin film was represented in table 17.

Table 17: Observation of Compatability of Fill Material with Gelatin

S. No	Batch No	Observation	
		Initial weight of gelatin film in gram	Final weight of gelatin film in gram
1.	C001	0.106	0.95
2.	C002	0.077	0.068
3.	C003	0.033	0.023
4.	C004	0.042	0.036
5.	C005	0.043	0.028
6.	C006	0.052	0.039
7.	C007	0.075	0.070
8.	C008	0.064	0.063

OBSERVATION

Liquid filled hard gelatin capsules batch (C008) was selected as optimized formulation, because much variation in weight of gelatin film was not observed. Whereas in other batches lot of variation in film weight was seen due to absorption of moisture from the fill material by the film. Hence batch (C008) was selected as a optimized batch.

6.5.1. Evaluation of Prototype Formulation Liquid Filled Hard Gelatin Capsules(S008)

The *in vitro* drug release from initial RLX liquid filled hard gelatin capsules was studied according to the procedure described in the section 5.3.5.2.2 The drug release of initial RLX LFHGC after 45 min was found to be 93.80%. *In Vitro* dissolution test of RLX liquid filled hard gelatin capsules (C008) was performed in 0.001 N HCl using USP type II apparatus. The dissolution profile (% drug release verses time) are shown in the figure 4.

Comparison of drug release pattern of RLX liquid filed hard gelatin capsules was done with innovator. The percentage of drug releae of LFHGC batch (C008) was 98% after 45 min were as for innovator the drug release was 92% afer 45 min. From this it was concluded that the drug release of batch (C008) was greater than the innovator. This data was represented in table 19 and figure 5.

Table 18: *IN VITRO* DISSOLUTION DATA OF BATCH (C008)

S.No	Time (min)	Liquid filled hard gelatin capsule % Drug Release
1	0	0
2	10	84.9
3	20	92.6
4	30	95.4
5	45	97.8

Table 19: Comparisons Of *In Vitro* Dissolution data of Lfhgc/Drl Tablets/Innovator

S. No.	Time (min)	LFHGC % Drug Release	Innovator
1	0	0	0
2	10	87	44
3	20	95	74
4	30	96	81

5	45	98	92

6.5.3 Preliminary Stability Studies

Stability studies of raloxifene liquid filled hard gelatin capsules (C008) were carried at 40° C / 75% RH and refrigerator temperature for 1 month. Evaluation of this formulation indicated change in its physical appearance. The results are shown in table 20. The dissolution profile of the stability loaded capsules showed that there was no change in the release rate and the amount of drug released was within the limits (NLT 90.0% and NMT 100.0%).

Table 20: Stability Data Of Prototype Formulation Of (C008) Liquid Filled Hard Gelatin Capsules

Serial No	Parameters	Initial	Conditions		
			Room Temperature	40°C ± 2°C / 75% RH ± 6 %	Refrigerator Temperature
			1 Month		
1	Description	No change in color	Normal	Capsules became soft	Capsule became hard
2	Assay	93. 80%	95.87 %	96. 72 %	92. 66 %
3	Dissolution test	% Drug release after 45 min was 98 . 0 %	% Drug release after 45 min was 101. 80 %	% Drug release after 45 min was 99.30 %	% Drug release after 45 min was 103. 42 %

SUMMARY AND CONCLUSIONS

In the present work entitled "Solubilized formulation and Evaluation of Liquid filled Hard Gelatin Capsules of Estrogen Modulator Drug" an attempt has been made to prepare solubilized formulations of insoluble postmenopausal osteoporosis drug.

The present proposal was aimed at developing solubilized formulations of insoluble raloxifene drug. Absorption of a drug from solution is fastest with least potential for bioavailability problems. A drug in solution is more rapidly absorbed since the major rate - limiting step, dissolution from a solid dosage form is absent. This formulation rapidly release the drug as soon as they come in contact with body fluids. So preparation of insoluble drug in solublized forms can be significant development in the field of noval drug delivery system.

Raloxifene as such cannot be used in a formulation because of its poor aqueous solubility. So complexation of drug with a water soluble carrier enables the drug to be formulated as aqueous soluble forms. As the intermolecular association of drug with the carrier led to increased effective surface area of drug, hence dissolution performance of the drug will be enhanced

Analytical methods for determining of drug content and dissolution profile were selected and validated. Raloxifene drug was formulated into solid dispersion using different carriers and mixing ratios. All the excipients which were used in the formulation were tested for their compatibility with the drug complex.

In the initial stage, different excipients and their combinations were tried according to the literature report or trial and error method. Once a prototype formulation, it was kept for preliminary stability studies. The physical observations and drug content of the aged formulation (1 month at 40°C and 75% RH) was compared with the initial formulation. No substantial change in physical characteristics, and drug content was observed between the stressed and control preparations. Thus from the results, it was concluded that, this formulation has good stability. For liquid filled hard gelatin capsules, the dissolution profile of these capsules was found to be more than the innovator. Hence it is expected to increase the bioavailability of the drug. However this needs to be conformed by bioavailability studies.

It can be concluded that the final formulation are robust once and stable. The present investigation resulted in successful development of once a day solubilized formulations of insoluble postmenopausal osteoporosis drug. These formulation are expected to have better bioavailability and patience acceptability as compared to conventional dosage forms.

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