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Research Article

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SOLUBILITY ENHANCEMENT OF POORLY WATER-SOLUBLE DRUG (RALOXIFENE HYDROCHLORIDE) BY USING DIFFERENT HYDROPHILIC BINDERS IN SOLID DOSAGE FORM

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ABSTRACT

Role of various hydrophilic binders was studied for enhancement of dissolution of a poorly soluble drug, Raloxifene Hydrochloride (RLX-HCl), using solid oral dosage form. Solubility study for pure drug was done in different relevant media, which results in poor solubility of drugs. Hydrophilic binders *viz* Polyvinyl pyrrolidone, Hydroxy propyl methyl Cellulose, Hydroxy propyl cellulose were investigated for the purpose to improve the solubility in the formulation. Comparison was made with Hydrophobic binder *viz* Ethyl cellulose. Dissolution behaviour of different formulation and pure drug was studied in different relevant media, which reveals significant improvement in dissolution behavior of drug was observed using hydrophilic binder..

Keywords: Raloxifene Hydrochloride, Hydrophilic, Hydrophobic, BCS Class II, Dissolution, Wetting.

INTRODUCTION

Poorly soluble drugs are associated with slow drug absorption leading to inadequate and variable bioavailability.[1, 2] Most formulation strategies for such drugs are targeted at enhancing their dissolution rate and/or solubility *in vivo* by achieving their fine dispersion at absorption level.[2, 3, 4] Raloxifene hydrochloride (RLX HCL) is 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.[5] RLX HCl was chosen in this study, is a poorly water soluble drug known to demonstrate dissolution and solubility limited absorption. [6] Although the RLX HCl being a low solubility drug with high permeability, is classified a Class II drug in BCS adopted by USFDA.[6]

In the development of formulations, solubility of the active component in the drug product has great importance. Earlior research supports the inclusion of hydrophilic binder in formulation results in improvement in dissolution characterstic of the formulation.[7] Inclusion of the hydrophilic binder in the formulation increase the rate at which the particle separate, enhancing the available surface area so that wetting and dissolution can occur more rapidly, shortening the time needed for some poorly soluble drugs to go into solution. The present work is aimed to explore the effect of hydrophilic binder on solubility and dissolution rate of RLX HCL in different simulated gastrointestinal fluids.

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MATERIALS AND METHODS

Materials

Raloxifene HCl (from Jubilant Organosys Manufactured by Glochem Laboratory, Hyderabad, India) micronised grade was used as active ingredient. 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 (Crillet 80 4HP,Croada Chemicals and Qualigens Fine Chemicals), Lactose monohydrate (Pharmatose 200M, DMV Fontera) Magnesium Stearate(Hyqual, Mallinckrodt).Purified water was used and granulating fluid in case of hydrophilic binder and Isopropyl Alcohol (RFCL India) was used as granulationg fluid in case of ethyl cellulose as binder. All other chemical used in media preparation were of analytical grade.

Solubility studies of drugs

Solubility of the active ingredient was determined for the liquid medium employed in the release testing (0.01 N HCl, 4.5 pH Acetate Buffer, 5.5 pH Phosphate buffer and water with 0.1% polysorbate 80). Solubility was also studied in water without polysorbate 80. 60.0 mg powdered micronised drug was dispersed in 50 ml medium and shaken for 72 h in water bath at 25°C.Aliquots of the supernatant solution were withdrawn, filtered and analysed spectrophotometrically for drug content. Mean of three replicate determinations were calculated.

Formulation of solid dosage form with different binders

The formulation designing for immediate release tablet is depicted in table **1**.

Table 1. Formulation designing

Formulation Ingredients	S_1	S_2	S_3	S_4
RLX-HCl		60	60	60
Lactose monohydrate (Pharmatose)	160	160	160	160
Croslinked Polyvinyl pyrrolidone (Crospovidone XL)	8	8	8	8
Polyvinyl pyrrolidone (Povidone K 30)	12	NA	NA	NA
Hydroxy Propyl methyl cellulose (Pharmacoat 3 cps)	NA	12	NA	NA
Hydroxy propyl cellulose (HPC)	NA	NA	12	NA
Ethyl Cellulose (Ethocel 4 cps)	NA	NA	NA	12
Croslinked Polyvinyl pyrrolidone (Crospovidone XL)	8	8	8	8
Magnesium Stearate	2	2	2	2
Total Tablet weight	250	250	250	250

The granules were prepared by wet granulation technique. Wet granulation of intragranular materials (lactose monohydrate and croslinked polyvinyl pyrrolidone) was carried out with binder solution of hydrophilic/ Hydrophobic binder along with polysorbate 80 in water (in case of hydrophilic binder; S1, S2 and S3) and isopropyl alcohol (in case of Hydrophobic binder; S4). Granules formed were dried in rapid dryer (Retsch Ltd.) at 45°C till LOD reaches between 1-2% w/v and passed through suitable mesh. Extragranular material (croslinked polyvinyl pyrrolidone and magnesium Stearate) was added. The granules were compressed on 27-station single rotary tablet press (Cadmech Ahmedabad) using 12X6.5 mm elliptically shaped standard concave punches. Tablet prepared were evaluated for hardness (Dr.Schheuniger), friability (Electrolab India Ltd.), and disintegration time (Electrolab India Ltd.).

Preparation of Dissolution medium

To understand the dissolution behavior of the drug in an *in vivo* environment, different dissolution media were used. Four different bio-relevant media were prepared and used to understand the dissolution behavior of RLX-HCl in different formulation. The compositions of different media used are given in Table **2** (Reference for media preparation USP/BP).

Table 2. Media Preparation

Ingredients	Water	0.01N HCl (pH 2.1)	Acetate Buffer (pH 4.5)	Phosphate Buffer (pH 5.5)
Hydrochloric Acid (ml)	-	8.5	-	-
Sodium Acetate (gm)	-	-	18	-
Glacial Acetic Acid (ml)	-	-	16	-
Potassium di hydrogen Phosphate (gm)	-	-	-	68
Sodium Hydroxide (gm)	-	-	-	1.36
Polysorbate 80 (ml)	10	10	10	10
Deionized water (L) quantity adjusted up to	10	10	10	10

In vitro Dissolution studies

Drug release studies were performed on plain drug (60 mg) and for each formulation (6 tablets in triplicate) on dissolution test apparatus (Electrolab India Ltd) at 37 ± 0.5 °C employing USP apparatus II at 50 rpm. Water, 0.01 N HCl, 4.5 pH acetate buffer, 5.5 pH Phosphate buffer (1000 ml) with 0.1%polysorbate 80 was employed as the dissolution medium. Also dissolution in water without surfactant was studied. Dissolution studies were performed on pure drug (60 mg) and the solid dosage form containing equivalent amount of the drug. Aliquots of the periodically withdrawn samples (10 ml) were analyzed spectrophotometrically at 287.0 nm and were replaced with an equal volume of plain dissolution medium.

RESULTS AND DISCUSSION

Solubility studies of Drug

Solubility studies were carried out with four different media .The result of solubility studies is given in Table **3**.

Table 3. Solubility of RLX-HCl in different media

Media	Solubility (µg/ml)
Water	700
Water with 0.1% polysorbate 80	1500
0.01N HCl with 0.1% polysorbate 80	880
4.5 pH Acetate Buffer with 0.1% polysorbate 80	1300
5.5 H Phosphate buffer with 0.1% polysorbate 80	900

The maximum solubility of RLX-HCl (1500 µg/ml) was observed with water with 0.1% polysorbate 80 and minimum solubility (700 µg/ml) was observed in water without surfactant. Significant enhancement in solubility of drug was achieved by addition of surfactant (0.1% polysorbate 80) in media so as to mimic the surface tension of gastrointestinal fluid.[8-10] It was observed that solubility of drug in acidic media was lower than the solubility of drug in other media.

Effect of different binder on dissolution studies/ *In vitro* dissolution studies

Drug release studies on poorly water-soluble drugs often require dissolution media encompassing small amounts of surfactants or solvents to provide sink conditions for dissolution of poorly soluble drugs.[8-11] The use of surfactants in the dissolution systems has physiological significance too as natural surfactants like bile salts are usually present in the gastrointestinal tract. The ability of surfactants to accelerate in vitro dissolution of poorly water-soluble drugs has been attributed to wetting, micellar solubilization, and/or deocculation.[9] The visual observation also supports the enhancement in wetting behavior of RLX- HCl in presence of surfactant in media. Dissolution characteristic of different formulation of RLX-HCl is given in Table **4-8,** Figure **1.** From the dissolution profile of different formulation, it was observed that

hydrophilic binder (polyvinyl pyrrolidone, Hydroxy propyl methyl cellulose, Hydroxy propyl cellulose) is having significant role in the formulation for improving dissolution of the drug in comparison with hydrophobic binder (Ethyl cellulose). The dissolution efficiency of different hydrophilic binder observed was almost similar in different relevant media. Apart from improvement in dissolution behaviour, formulation with hydrophilic binder shows erosion pattern during dissolution, which results in improved wetting of drug. Relatively higher dissolution enhancement in case of hydrophilic binder could be credited to more intimate drug-excipient interaction in the formulation. In case of S4 (formulation with Ethyl cellulose) bursting pattern was observed which lead to floating of granules in the media, which lead to incomplete dissolution (< 75%) from the formulation.

Table 4. Percentage dissolution of RLX- HCl formulations in Water

Time (min)	Percentage dissolution# in different Formulation				
	S1	S2	S3	S4	Plain Drug (RLX-HCl)
0	0	0	0	0	0
5	20 ± 9.13	22 ± 7.18	17±4.59	1 ± 8.86	11 ± 3.39
10	59 ± 7.42	53 ± 4.41	49 ± 7.11	7 ± 3.58	19 ± 4.78
15	76 ± 6.25	71 ± 3.32	68 ± 3.36	16 ± 4.77	23 ±3.52
30	80 ± 2.39	72 ± 1.19	70 ± 2.29	26 ± 6.29	29 ± 4.29
45	86 ± 1.92	82 ± 1.11	75 ± 1.58	39 ± 3.33	36 ± 1.14
60	89 ± 1.13	84 ± 2.25	81 ± 2.27	51 ± 1.12	42 ± 9.97

S1-Polyvinyl pyrrolidone as binder, S2-Hydroxypropyl methyl cellulose as binder, S3-Hydroxy propyl cellulose as binder, S4- Ethyl Cellulose 4 cps as binder; # All values are mean of three readings ± SD

Table 5. Percentage dissolution of RLX- HCl formulations in Water with 0.1% polysorbate 80

Time (min)	Percentage dissolution# in different Formulation				
	S1	S2	S3	S4	Plain Drug (RLX-HCl)
5	29± 9.10	27± 7.13	26± 7.19	6± 7.00	21± 7.83
10	64± 7.13	61± 5.18	58± 6.23	9± 5.13	38± 5.10
15	86± 7.18	86± 4.33	83± 3.13	41± 3.16	45± 3.13
30	92± 6.13	96± 2.13	89± 2.43	46± 3.00	48± 2.10
45	98± 2.20	96± 1.43	94± 1.13	61± 2.15	53± 1.11
60	98± 1.33	98± 1.10	97± 1.09	72± 1.10	59± 1.09

S1-Polyvinyl pyrrolidone as binder, S2-Hydroxypropyl methyl cellulose as binder, S3-Hydroxy propyl cellulose as binder, S4- Ethyl Cellulose 4 cps as binder; # All values are mean of three readings ± SD

Table 6. Percentage dissolution of RLX- HCl formulations in 0.01 N HCl with 0.1% polysorbate 80

Time (min)	Percentage dissolution# in different Formulation				
	S1	S2	S3	S4	Plain Drug (RLX-HCl)
5	28± 8.20	24± 7.14	22± 7.13	15± 9.10	11± 8.16
10	64± 7.20	65± 5.12	56± 7.10	41± 7.10	33± 4.10
15	76± 6.15	75± 4.50	69± 5.10	54± 5.17	39± 4.60
30	79± 5.11	80± 2.10	77± 3.14	60± 4.16	48± 3.70
45	84± 3.10	84± 2.05	81± 3.00	69± 3.15	54± 2.90
60	85± 2.13	88± 1.10	84± 2.16	70± 2.17	59± 1.90

S1-Polyvinyl pyrrolidone as binder, S2-Hydroxypropyl methyl cellulose as binder, S3-Hydroxy propyl cellulose as binder, S4- Ethyl Cellulose 4 cps as binder; # All values are mean of three readings ± SD

Table 7. Percentage dissolution of RLX- HCl formulations in 4.5 pH Acetate Buffer with 0.1% polysorbate 80

Time (min)	Percentage dissolution# in different Formulation				
	S1	S2	S3	S4	Plain Drug (RLX-HCl)
5	34± 6.15	32± 6.00	29± 5.15	17± 5.75	9± 3.85
10	66± 5.25	69± 5.65	57± 4.16	38± 5.1	22± 3.75
15	88± 4.65	83± 5.15	79± 3.85	46± 4.65	38± 3.16
30	97± 3.15	95± 3.16	88± 3.15	58± 4.15	49± 2.10
45	100± 2.10	97± 1.65	96± 2.10	63± 1.95	56± 1.95
60	100± 1.11	97± 1.10	98± 1.15	73± 1.00	64± 1.15

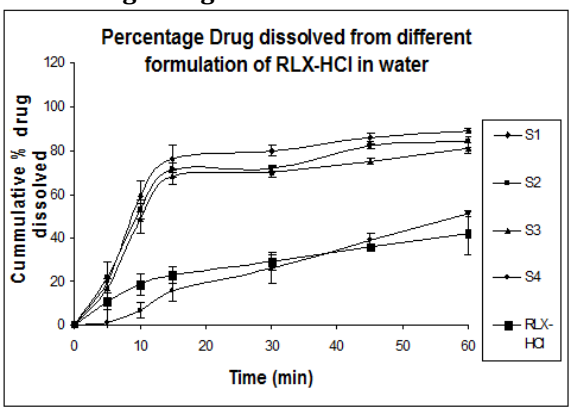
S1-Polyvinyl pyrrolidone as binder, S2-Hydroxypropyl methyl cellulose as binder, S3-Hydroxy propyl cellulose as binder, S4- Ethyl Cellulose 4 cps as binder; # All values are mean of three readings ± SD

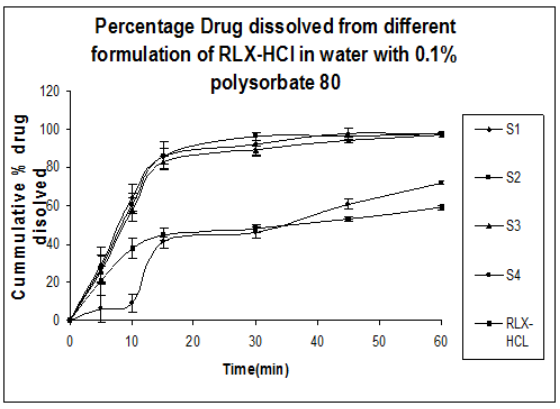
Table 8. Percentage dissolution of RLX- HCl formulations in 5.5 pH Phosphate Buffer with 0.1% polysorbate 80

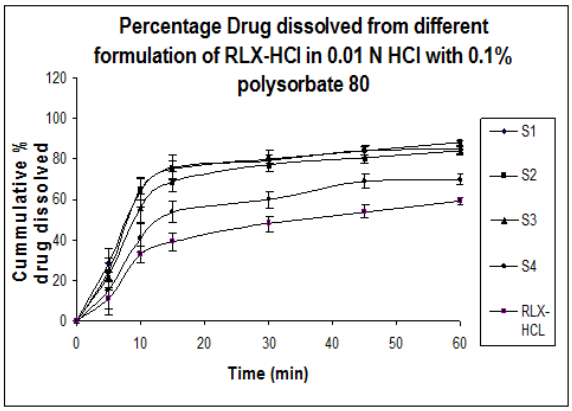
Time (min)	Percentage dissolution# in different Formulation				
	S1	S2	S3	S4	Plain Drug (RLX-HCl)
5	37± 5.25	38± 4.85	35± 3.95	15± 5.25	9± 5.00
10	70± 4.65	65± 4.55	56± 3.75	21± 3.85	17± 4.25
15	83± 3.85	76± 4.25	77± 3.65	35± 3.65	27± 3.65
30	90± 2.65	81± 3.29	83± 2.75	54± 2.55	43± 2.29
45	93± 1.65	84± 2.20	89± 2.35	65± 1.75	58± 2.22
60	96± 1.25	87± 1.25	92± 1.05	72± 1.15	64± 1.22

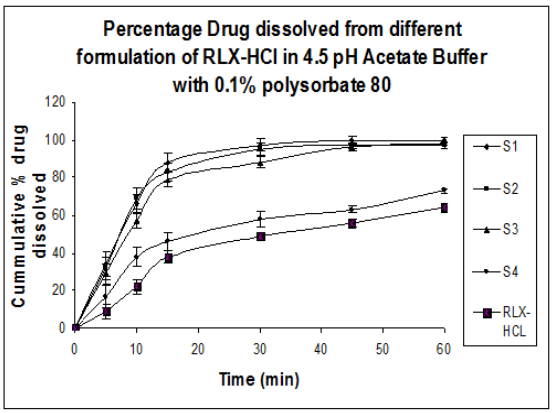
S1-Polyvinyl pyrrolidone as binder, S2-Hydroxypropyl methyl cellulose as binder, S3-Hydroxy propyl cellulose as binder, S4- Ethyl Cellulose 4 cps as binder; # All values are mean of three readings ± SD

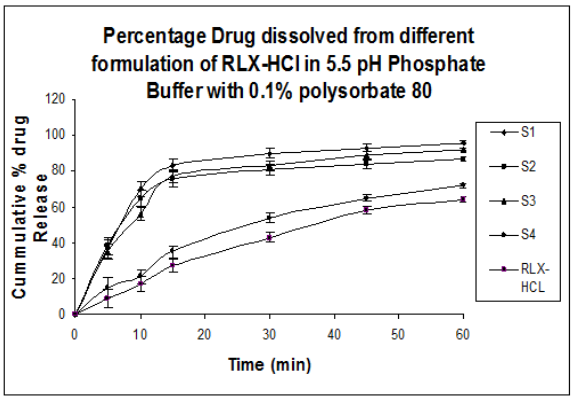
Figure 1. Percentage drug dissolved from different formulation in different dissolution media











CONCLUSION

The result of the present investigation leads to the conclusion that the solubility and percentage drug release of RLX-HCl in different dissolution media is being increased by use the hydrophilic binders in solid dosage form compared to hydrophobic binders. In present investigation the dissolution profile & solubility of the plain RLX-HCl was very poor in different pH, the reason is insufficient wetting of the drug, this phenomenon come in existence with the hydrophobic binder (Ethyl Cellulose) also, in this case the dosage form follow the bursting pattern which leads the drug to came on the surface and results in insufficient wetting of the drug even in presence of surfactant in the media. In contrast to this, the dosage form with Hydrophilic binder follow the erosion pattern which results in slow erosion of drug from dosage form and shows complete wetting and thus release of the drug. It is therefore concluded that hydrophilic binders have the significant role in enhancement of solubility of RLX-HCl.

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