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Preparation and *in vitro* Evaluation of Fast Disintegrating Tablets of BCS Class II Drug

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ABSTRACT

Pranlukast is a BCS class II drug having absolute bioavailability of approximately 4.3%. To improve the biological performance of Pranlukast solid dispersion with oral disintegrating tablets were formulated by using ß Cyclodextrin, HP ß Cyclodextrin. Solid dispersions of Pranlukast were prepared with different carriers in different ratios of drug and carrier (1:0.25, and 1:0.5). Results of prepared solid dispersions of Pranlukast by solvent evaporation method were discussed which includes solubility, melting point determination, drug content uniformity, entrapment efficiency and in vitro dissolution studies. Characterization in solid state was done by various analytical techniques such as FT-IR studies , Finally by comparing all the formulations (SF1-SF4),(KF1-KF4) formulation(SF4) containing Pranlukast+ ß cyclodextrin (1:0.5) shows better results by solvent evaporation method at the end of 90 min with drug release of 82.96%, hence it was selected as the best formulation. From the optimized formulation the immediate release tablets were formulated using different disintegrants in different concentrations. The pre compression and post compression parameters were studied and the results were given. All the results are in the acceptable limit. The in vitro drug release of the formulated tablets was performed using 6.8pH buffer. F6 formulation containing SSG (10mg) shows 98.02% drug release in 40mins. The optimized formulation follows Zero order release kinetics.

Keywords: Pranlukast, ß Cyclodextrin, HP ß Cyclodextrin, SSG.

1. INTRODUCTION

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD)[1] is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method4 . The technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine. SD technology has been successfully been used for improving the solubility of the drugs and hence bioavailability, e.g., tenoxicam, tacrolimus, indomethacin, ibuprofen, nilvadipine. The present work aims to evaluate the potential of the solid dispersion technique for development of fast-dissolving tablets of Pranlukast.

Pranlukast hemihydrate, is a selective, competitive antagonist of the cysteinyl leukotriene receptors, inhibiting binding at the cysteinyl leukotriene type 1 receptor, having absolute bioavailability of approximately 4.3%. Therefore, a favourable formulation which can enhance solubility and dissolution rate of this model drug may help effectively in the treatment of bacterial infections. Thus, studies were carried out to improve the solubility and hence dissolution rate, efficiency and bioavailability of poorly soluble drug Pranlukast through solid dispersion technique using HP β cyclodextrin & β cyclodextrin. The best formulation from solid dispersions was further formulated as a fast disintegrating tablet using Lycoat and SSG as superdisintegrants.

2. MATERIALS AND METHODS

Pranlukast was procured from the Cadila pharmaceuticals, Pvt.Ltd., whereas all the other excipients were procured from B.M.R.Chemicals, Hyderabad.

Methodology:

PREPARATION OF SOLID DISPERSIONS OF PRANLUKAST:[12]

There are several carriers, which have been reported for the preparation of solid dispersions by using β Cyclodextrin, HP β Cyclodextrin using solvent evaporation method.

Solvent evaporation method:[13]

In solvent evaporation method, the drug and carriers were mixed in 1:0.25, and 1:0.5 ratios in Methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed through sieve # 100. And now the obtained product was collected and stored in desiccators.

FORMULATION OF PRANLUKAST TABLETS:[14]

Equivalent weight of Pranlukast was added with suitable excipients and the tablets were formulated by direct compression according to the formulae given in the table2.All the ingredients were passed through # 60 mesh sieve separately. The drug and Mannitol were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside.Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#44 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm2 for all batches. The weight of the tablets was kept constant for all formulations F1 to F6.

Evaluation of Solid Dispersions:[12-16]

Prepared polymer drug conjugates were evaluated by

1) Entrapment efficiency
2) *In- vitro* dissolution studies

Evaluation studies for Pranlukast Fast disintegrating tablet:

Pre compression parameters including bulk density, Tapped density, Hausners' ratio and Carr's index.

Whereas the compressed fast disintegrating tablets were evaluated for the post compression parameters like Average weight, Friability, Thickness, Hardness, Drug content uniformilty and drug release.

1) Entrapment efficacy:

A quantity, which was equivalent to 225 mg of drug, was accurately weighed and transferred to 100ml volumetric flask. Then the volume was made up with, 6.8 pH phosphate buffer and shaken or 10 min to ensure complete solubility of the drug. Then the solution was filtered. And the solutions absorbance was measured at 246 nm for Pranlukast in UV-Visible spectrophotometer.

%Entrapment efficiency= Drug content *100/Drug added in each formulation

***2) In vitro* dissolution study**:

The prepared solid dispersions were subjected to *in vitro* dissolution. Dissolution test was carried out using USP type 2 paddle method [apparatus 2]. The stirring rate was 50 rpm, 6.8Ph buffer was used as dissolution medium and dissolution medium was maintained at 37±0.5°C. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replace with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Pranlukast at 246 nm by using UV-visible spectrophotometer.

Evaluation studies of Pranlukast Fast disintegrating tablets:

i) In-Vitro Disintegration time

To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing pH 6.8 pH buffer buffer solution at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

ii) Thickness and Diameter

Tablet thickness and diameter can be measured using a simple procedure. Five tablets are taken and their thickness is measured using Vernier calipers. The thickness and diameter is measured by placing tablet between two arms of the Vernier calipers.

iii) Drug content uniformity

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 225 mg was weighed accurately and dissolved in 100ml of 0.1N HCL. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatmann No.41 filter paper. Then the dilute the solution to obtain 10µg solution.The absorbance of the diluted solutions was measured at 246nm.

iv) Dissolution studies In-vitro dissolution study is performed by using USP Type II Apparatus (Paddle type) at 50 rpm. 6.8pH buffer 900 ml is used as dissolution medium which is maintained at 37±0.5°C. Aliquots of dissolution medium (10 ml) are withdrawn at specific time intervals and filter. An equal amount of fresh dissolution medium is replaced immediately following withdrawal of test sample. The percentage of drug released was calculated.

v) Kinetics Of Drug Release

The mechanism of drug release for the Pranlukast solid dispersions was determined using zero order and first order.

3. RESULTS AND DISCUSSION

From the Solubility studies in various buffers we can say that 6.8 pH buffer has more solubility when compared to other buffer solutions for Pranlukast. The

melting point of Pranlukast was found to be 237° C which was determined by capillary method. The angle of repose of different formulations was ≤ 30.68 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.42g/cm^3 to 0.52g/cm^3.Tapped density was found between 0.48g/cm^3 to 0.60g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.53-15.518 and Hausner's ratio from 1.12-1.18 which reveals that the blends have good flow character.

Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which indicates there are no physical changes. All the formulations of Pranlukast were prepared solvent evaporation method All the prepared solid dispersions were evaluated for drug content. The invitro dissolution studies of Pranlukast was performed.From the optimized formulation of the solid dispersions(i.e.,SF4) weight equivalent of Pranlukast was used along with the superdisintegrants like SSG and Lycoat. Pre compession and Post compression evaluation studies were performed. The better drug relase with SSG(10mg) with 98.02% of drug release at the end of 40mins. Drug release kinetics of the optimized formulation shows zero order drug release. From the above explained studies it was observed that the solubility of Pranlukast was enhanced by using β Cyclodextrin as a carrier for solubility enhancement as well a SSG as a superdiintegrant for the formulation of Fast disintegrating tablet of Pranlukast using solid dispersion technique.

Table 1: Formulation Of Pranlukast Solid Dispersions Using Hp β Cyclodextrin Polymer.

Formulation code	Drug: Carrier	Drug : Carrier ratio
F1	Pranlukast: HP β Cyclodextrin	1:0.25
F2		1:0.5
F3	Pranlukast: β Cyclodextrin	1:0.25
F4		1:0.5

Table 2: Formulation of Pranlukast Fast disintegrating Tablets

INGREDIENTS	F1	F2	F3	F4	F5	F6
Pranlukast S.D Wt.equivalent(mg)	316.35	316.35	316.35	316.35	316.35	316.35
Lycoat (mg)	5	7.5	10	-	-	-
SSG (mg)	-	-	-	5	7.5	10
Mannitol (mg)	50	50	50	50	50	50
MCC(mg)	70.15	70.15	67.65	72.65	70.15	67.65
Magnesium Stearate(%)	3	3	3	3	3	3
Talc (%)	3	3	3	3	3	3
Total(mg)	450	450	450	450	450	450

Table 3: Drug content uniformity for solid dispersions by solvent evaporation method

Formulation code	%Drug content
SF1	69.64
SF2	76.21
SF3	85.82
SF4	89.76

Table 4: Pre Compression parameters

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.48±0.01	0.56±0.015	26.38±0.30	14.28±1.02	1.16±0.06
F2	0.46±0.01	0.52±0.02	27.42±0.39	11.53±1.26	1.13±0.03
F3	0.42±0.04	0.48±0.01	24.02±0.68	12.58±2.08	1.14±0.05
F4	0.46±0.02	0.54±0.015	26.26±0.96	14.81±1.28	1.12±0.02
F5	0.52±0.6	0.60±0.03	30.68±0.73	13.33±1.86	1.17±0.04
F6	0.49±0.2	0.58±0.006	29.26±0.36	15.51±1.96	1.18±0.05

Table 5: Characterization Pranlukast fast disintegrating tablets

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)	Drug content (%)
F1	451.2±0.02	3.4±0.02	3.6±0.01	0.68±0.02	32.18±0.02	95.96
F2	449.3±0.06	3.5±0.04	4.2±0.03	0.62±0.06	31.16±0.05	97.65
F3	448.4±0.07	3.7±0.06	3.5±0.02	0.79±0.08	30.36±0.06	99.62
F4	451.6±0.04	3.4±0.01	3.9±0.01	0.65±0.02	32.08±0.08	98.02
F5	449.2±0.03	3.2±0.01	3.7±0.01	0.59±0.08	34.29±0.02	98.71
F6	449.8±0.02	3.5±0.02	4.1±0.06	0.48±0.06	32.12±0.07	98.16

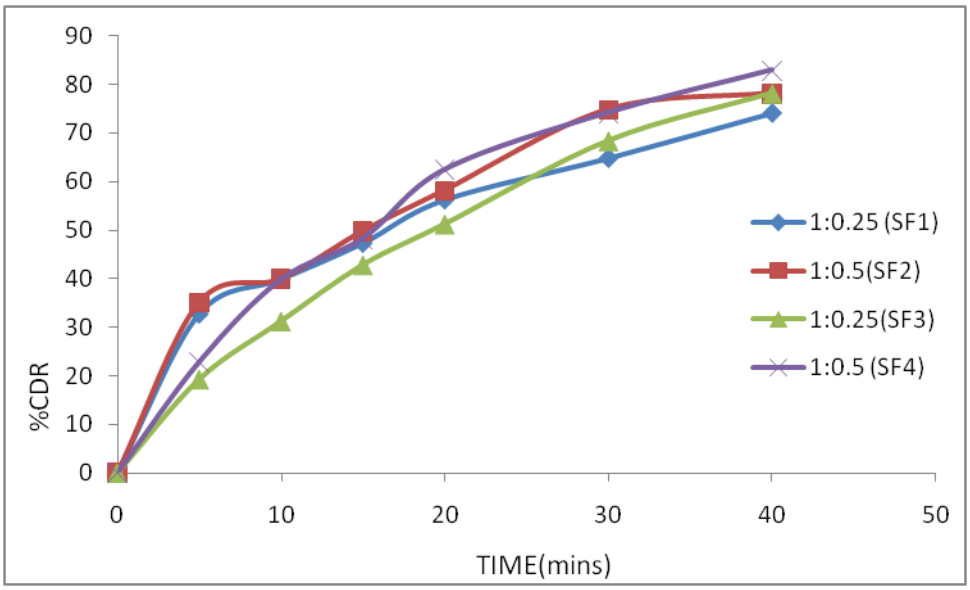

Figure 1: *In vitro* drug release profiles of pranlukast Solid dispersions (SF1-SF4)

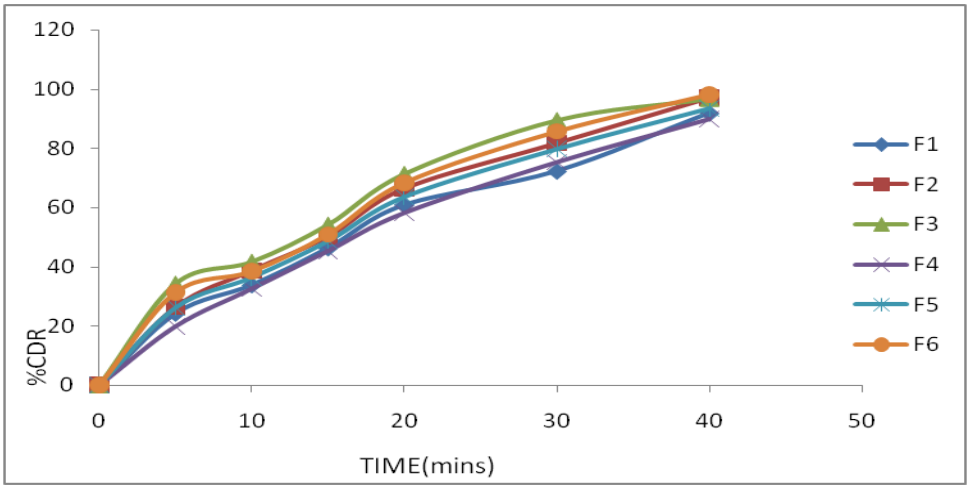

Figure 2: *In vitro* drug release of graphs of fast disintegrating tablets of Pranlukast

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