ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE AND FORMULATION DEVELOPMENT OF SPARFLOXACIN FAST DISSOLVING TABLETS

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ABSTRACT

The objective of the present study was to prepare the fast dissolving tablet of sparfloxacin. The study revealed that physical mixture shows a sudden bursting effect and erratic pattern in their release mechanism therefore the solid dispersion was best alternate. In solid dispersion it was found that in 1:1 and 1:2 ratios there was also a bursting effect and at higher polymer ratio i.e. at 1:3 the drug release was truly delayed which can further have optimized to get better results. Therefore 1:3 ratios were found to be superior and were used for further evaluation purpose. Fast dissolving tablets containing Sparfloxacin were prepared using direct compression method. Total six formulations were prepared using varying amount of Sodium Starch glycolate and Croscarmellose sodium. The prepared Tablets were further evaluated for Hardness, Friability, disintegration time, and uniformity of drug content, and *In-vitro* Release Studies. Percentage assay of different formulation was determined by UV Vis Spectroscopy. The *In-vitro* dissolution studies showed that Sparfloxacin tablets formulation F4 showed maximum 98.12% over a period of 15 min. Overall the results of the dissolution rate studies indicated greater dissolution rate of Sparfloxacin from fast dissolving tablets.

Keywords: Sparfloxacin, fast dissolving tablet, Croscarmellose sodium, Sodium starch glycolate.

INTRODUCTION

Fast disintegrating tablets (FDTs) have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. Recent advancements in novel drug delivery system (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration in order to achieve better patient compliance. One such approach is “fast disintegrating tablet.” Many patients find it difficult to swallow tablets and hard gelatin capsules those results in high incidence of noncompliance and ineffective therapy^{1,2}. Fast disintegrating drug delivery systems (FDDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and, at the same time, offer added advantages over both

traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation ³. Sparfloxacin, 5-amino-1-cyclopropyl-7-(cis-3,5-dimethyl-1-piperazinyl)-6,8-difluoro-1, 4-dihydro-4-oxo-3-quinolinecarboxylic acid is a difluoroquinolone antibacterial agent belonging to the third generation quinolones. Clinically, it is used in the treatment of streptococci infections. Its mechanism of action involves the inhibition of DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type iv topoisomerase, resulting in rapid bacterial death ⁴. Sparfloxacin is water-insoluble, The use of surfactants to improve the solubility of sparingly-soluble or water-insoluble drugs has been reported ⁵⁻⁷. Oral fast dissolving tablets are solid dosage forms, which dissolve in a short period of time when placed in the mouth without drinking water or chewing. These are also referred as fast dissolving oral wafers, wafers, buccal films or oral strips. Present work aim to develop fast dissolving tablets of sparfloxacin and enhance the solubility of sparfloxacin in buccal cavity.

MATERIALS AND METHODS

Sparfloxacin were obtained as pure sample from pharmaceutical company as gift samples along with their analytical reports. croscarmellose sodium, crospovidone, Magnesium stearate, Microcrystalline cellulose was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade

Preparation of solid dispersions

Optimization of drug: polymer ratio

In order to optimize the drug is to polymer ratio, we have prepared the matrices by both i.e. physical mixture method and solid dispersion method.

Physical mixture method: All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixture of drug with carrier PEG 4000 was prepared in different concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 4000 ratio which was taken as 1:1, 1:2, and 1:3 respectively. Then the resultant powder was passed through sieve no 60 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to dissolution study table 1.

Table 1 : Percentage cumulative drug release of physical mixture

S. No.	Time interval (min.)	Percentage cumulative drug release of physical mixture*			
1	0	1:1	1:2	1:3	Pure Drug
2	30	33.25	38.98	40.25	11.25
3	60	45.65	49.98	45.56	13.56
4	120	65.65	69.89	60.45	15.65
5	240	68.89	72.25	68.89	16.65
6	360	70.21	74.45	72.25	17.86
7	480	70.12	74.69	78.89	18.85

On the basis of percentage cumulative drug release study, it was concluded that solid dispersion is better option in spite of pure drug. The study revealed that physical mixture shows a sudden bursting effect and erratic pattern in their release mechanism therefore the solid dispersion was best alternate. In solid dispersion it was found that in 1:1 and 1:2 ratios there was also a bursting effect and at higher polymer ratio i.e. at 1:3 the drug release was truly delayed which can further have optimized to get better results. Therefore 1:3 ratios were found to be superior and were used for further evaluation purpose.

Preparation of solid dispersion of sparfloxacin

For the preparation of sparfloxacin-PEG 4000 solid dispersion by conventional method, PEG 4000 was weighed and melted at 58°C ($\pm 1^\circ\text{C}$) and a measured amount of Sparfloxacin was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 400mg of SPRF-PEG 4000 powder (containing 100mg of sparfloxacin and 300 mg of PEG 4000) was used for further investigations.

Preparation of physical mixture

For the preparation of SPRF-PEG 4000 physical mixture, SPRF and PEG 4000 were weighed and mixed for 5 min with use of a pestle and mortar and sieved through a 400mm mesh⁵⁵. SPRF - PEG 4000 powder mixture (containing 1005mg of SPRF and 300 mg of PEG 4000) was used for further tablet preparation.

Preparation of tablets of Sparfloxacin

Fast dissolving tablets of Sparfloxacin (100mg) were prepared by direct compression method after incorporating different superdisintegrants such as, croscarmellose sodium (Ac-Di-Sol) 10, 15, and 20 mg, crospovidone in different concentrations 10, 15, and 20 mg for optimization of best formulation⁸. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh 60. Magnesium stearate (6mg) as lubricant and talc (5 mg) as glidant and Microcrystalline cellulose as bulking agent (79, 74, 69, 79, 74 and 69 mg) were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk density, Tap density, Carr's index and Hausner's ratio. The Blend was

compressed on 8 mm (diameter) flat punches on a 'Rimek mini press 16 station rotary compression machine. Six formulations of Sparfloxacin granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablet weighing 400 mg was obtained. Composition of tablets is mentioned in Table 2.

Table 2: Composition of Sparfloxacin fast dissolving tablets

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Sparfloxacin solid dispersion equivalent to 100 mg	300	300	300	300	300	300
Sodium Starch glycolate	10	15	20	-	-	-
Croscarmellose sodium	-	-	-	10	15	20
Microcrystalline cellulose	79	74	69	79	74	69
Talc	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6
Total weight	400	400	400	400	400	400

Evaluation of Precompression Parameter⁹

Angle of repose (θ): The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of Powder}}{\text{Tapped Volume of Packing}}$$

Carr's Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula [10]: -

$$\text{Carr's Index \%} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation: -

$$\text{Houser's ratio} = \frac{\text{Tapped bulk density}}{\text{loose Bulk density}}$$

Hauser's ratio value <1.25 shows better flow properties

Evaluation of post compression Parameter ¹⁰⁻¹¹

Shape and colour of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-calliper (Minutolo, Japan).

Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined (USP, 2005). The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm².

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out,

dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation: -

$$\% \text{Friability} = (\text{Loss in weight} / \text{Initial weight}) \times 100$$

Uniformity of drug content

The test is mandatory for tablets with 10 mg or less weight of active ingredient⁵⁹. Ten randomly selected tablets from each formulation (F1 to F6) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml phosphate buffer pH 6.8) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through what man filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 294 nm.

Dissolution rate studies

The prepared tablets were evaluated for *in vitro* drug release [12-13]. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at $37 \pm 0.2^\circ\text{C}$. The scheme of using the simulated fluids at different timing was as follows:

A tablet placed in dissolution media (900 ml) at $37 \pm 0.2^\circ\text{C}$. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml 0.1 N HCl. The samples withdrawn were assayed spectrophotometrically at 294 nm using UV visible spectrophotometer.

The observations of drug release for the drug in uncoated formulation and coated formulation is tabulated in Table 7.

Mathematical treatment of *in-vitro* release data: The release of drug was calculated with the help of standard curve of Sparfloxacin.

Quantitative analysis of the values obtained in dissolution/release tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used.

Zero-order kinetics: The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$Q_t = Q_0 + K_0 t$$

Where Q_t is the amount of drug dissolved in time t , Q_0 is the initial amount of drug in the solution (most times, $Q_0=0$) and K_0 is the zero order release constant.

First-order kinetics: The following relation expresses this model:

$$\log Q_t = \log Q_0 + \frac{K_1 t}{2.303}$$

Where Q_t is the amount of drug dissolved in time t , Q_0 is the initial amount of drug in the solution and K_1 is the zero order release constant.

In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish.

Higuchi model: Higuchi developed several theoretical models to study the release of water-soluble and low soluble drugs in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media.

The simplified Higuchi model is expressed as:

$$Q = K_H \cdot t^{1/2}$$

Where Q is the amount of drug released in time t and K_H is the Higuchi dissolution constant. Higuchi model describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms such as transdermal systems and matrix tablets with water-soluble drug.

Korsmeyer-Peppas model: Korsmeyer *et al.* used a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a t^n$$

Where M_t/M_∞ is fraction of drug released, a is kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of $\log M_t/M_\infty$ versus $\log$ time curve. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. Peppas used this n value in order to characterize different release mechanisms, concluding for values for a slab, of $n=0.5$ for fickian diffusion and higher values

of n , between 0.5 and 1.0, or $n=1.0$, for mass transfer following a non-fickian model. In case of a cylinder $n=0.45$ instead of 0.5, and 0.89 instead of 1.0. This equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent n the portion of the release curve where $M_t/M_\infty < 0.6$ should only be used. To use this equation, it is also necessary that release occurs in a one-dimensional way and that the system width-thickness or length-thickness relation be at least 10. A modified form of this equation was developed to accommodate the lag time (l) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_{t,l}}{M_\infty} = a (t - l)^n$$

When there is the possibility of a burst effect, b , this equation becomes:

$$\frac{M_t}{M_\infty} = at^n + b$$

In the absence of lag time or burst effect, l and b value would be zero and only at^n is used. This mathematical model, also known as Power Law, has been used very frequently to describe release from several different pharmaceutical modified release dosage forms.

RESULTS AND DISCUSSIONS

The enhancement of solubility was done in different amount PEG 4000; On the basis of percentage cumulative drug release study it was concluded that solid dispersion is better option in spite of pure drug. The study revealed that physical mixture shows a sudden bursting effect and erratic pattern in their release mechanism therefore the solid dispersion was best alternate. In solid dispersion it was found that in 1:1 and 1:2 ratios there was also a bursting effect and at higher polymer ratio i.e. at 1:3 the drug release was truly delayed which can further have optimized to get better results. Therefore 1:3 ratios were found to be superior and were used for further evaluation purpose. Fast dissolving tablets containing Sparfloxacin were prepared using direct compression method. Total six formulations were prepared using varying amount of Sodium Starch glycolate and Croscarmellose sodium. The prepared Tablets were further evaluated for Hardness, Friability, disintegration time, and uniformity of drug content, and *In-vitro* Release Studies. Percentage assay of different formulation was determined by UV Vis Spectroscopy. The percentage assay of different formulation was in range of 97.56 ± 0.32 to $99.74 \pm 0.74\%$. The maximum percentage assay ($99.74 \pm 0.74\%$) and less disintegration time (75 Sec.) were found to be formulation F4 in Fast dissolving tablets. The optimized formulation of batch F4 subjected to further *In vitro* drug release. The in vitro drug release studies of the enhanced detailing were subjected to integrity of fit test by linear regression analysis as indicated by zero order, first order kinetic

Higuchi and peppas release equation, in order to decide the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of higuchi release kinetics was maximum i.e. 0.916 hence indicating drug release from formulations was found to follow higuchi release kinetics.

Table 3: Results of pre-compression parameters of Sparfloxacin

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
F1	0.423	0.542	21.96	1.281	42 ⁰
F2	0.425	0.548	22.45	1.289	42 ⁰
F3	0.446	0.557	19.93	1.249	41 ⁰
F4	0.435	0.554	21.48	1.274	42 ⁰
F5	0.435	0.543	19.89	1.248	43 ⁰
F6	0.441	0.552	20.11	1.252	43 ⁰

Table 4: Results of Post-Compression parameters of all formulations

F. Code	Hardness test (kg/cm ²)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
F1	3.4±0.1	0.652±0.045	405±3	1.41±0.05	97.56±0.32
F2	3.3±0.2	0.542±0.036	400±5	1.45±0.04	98.85±0.14
F3	3.5±0.1	0.658±0.074	403±4	1.42±0.06	98.65±0.56
F4	3.3±0.2	0.705±0.065	398±2	1.43±0.05	99.74±0.74
F5	3.5±0.3	0.698±0.058	402±3	1.45±0.02	99.05±0.58
F6	3.4±0.2	0.678±0.035	395±4	1.47±0.04	98.78±0.45

Table 5: Results of disintegration time parameters of all formulations

Formulation code	Disintegration Time (Sec.)
	Mean ± SD
F1	120±5
F2	115±6
F3	98±4
F4	75±5
F5	89±6
F6	106±4

*Average of three determinations (n=3)

Table 6: *In-vitro* drug release data for optimized formulation F4

Time (min)	Square Root of Time(h) ^{1/2}	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1	0	36.65	1.564	63.35	1.802
5	2.24	0.698	45.58	1.659	54.42	1.736
10	3.16	1	78.85	1.897	21.15	1.325
15	3.87	1.176	98.12	1.992	1.88	0.274

Table 7: Regression analysis data

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
			r ²	
F4	0.973	0.865	0.916	0.856

CONCLUSION

Fast dissolving tablets of Sparfloxacin were conveniently formulated by direct compression method. The *In-vitro* dissolution studies showed that Sparfloxacin tablets formulation F4 showed maximum 98.12% over a period of 15 min. Overall the results of the dissolution rate studies indicated greater dissolution rate of Sparfloxacin from fast dissolving tablets.

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