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FORMULATION AND *IN VITRO* EVALUATION OF LEVOFLOXACIN ORAL DISPERSIBLE TABLETS

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ABSTRACT

Oral dispersible formulation offers a number of advantages in therapeutics. Levofloxacin drug is used in the treatment of a number of infections including infection of Joints and bones, respiratory tract infections, urinary tract infections, skin structural infections and typhoid fever etc. It was used as a model drug to develop a Oral dispersible formulation. In this present study Oral dispersible tablet of Levofloxacin was prepared by using direct compression method and using different superdisintegrants. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the superdisintegrants and drug. The prepared tablets evaluated in terms of their pre-compression parameters, post-compression parameters, *in vitro* release study. The results conclude that FLOT-7 (96.10%) can be considered as a optimized formula for Oral dispersible tablet of Levofloxacin, when it is compared with other formulation.

KEY WORDS

Levofloxacin, Oral dispersible tablet, Direct compression method and *In vitro* release study.

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INTRODUCTION

Fast dissolving tablets are solid single unit dosage forms that are placed on tongue, allowed to disperse or dissolve in saliva without the need of water, frequently releasing of the drug for quick onset of action. Fast dissolving tablets are well accepted by wide range of population especially as pediatric and geriatric patients who have difficulty in swallowing of conventional dosage forms. Some drugs are absorbed from mouth, pharynx and esophagus as saliva passes down to stomach. The bioavailability

of such drug will be increase due to first pass metabolism[1-4].

Consumer satisfaction is the buzzword of the current millennium, and moment to achieve it has already begun in the pharmaceutical industry. An inability or un willingness to swallow solid oral dosage forms such as tablets and poor taste of medicine are some of the important reasons for consumer dissatisfaction[5].

Recent developments in technology have presented viable alternatives for the patients who may have difficulty in swallowing tablets or liquids. Traditional tablets and capsules administered with an 8-oz. glass of water may be inconvenient or impractical for some patients. For example a very elderly patient may not be able to swallow a daily dose of tablets. An eight year old child with allergies could use a more convenient dosage form of antihistamine syrup. A schizophrenic patient in the institution setting can hide a conventional tablet under his or her tongue to avoid his/ her daily dose of atypical antipsychotic. A middle-aged women undergoing radiation therapy for breast cancer may be too nauseous to swallow her H_2-blocker[6].

To overcome these drawbacks, Fast Dissolving Tablets (FDT) or orally disintegrating tablets (ODT) has emerged as alternative oral dosage forms. These are novel types of tablets that disintegrate/dissolve/ disperse in saliva within few seconds. According to European Pharmacopoeia, the orally dispersible tablet should disperse/disintegrate in less than three minutes. The basic approach used in development of FDT is the use of super disintegrants like Crospovidone (Polyplasdone XL-10), Sodium starch glycolate (Primo gel, Explotab) and Pregelatinized starch (Starch-1500) etc. which provide instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pre gastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets[7].

Over the past three decades, FDT have gained much attention as a preferred alternative to conventional oral dosage forms such as tablets and capsules. FDT is a solid dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 60 seconds or less[8]. The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines in the Orange Book an FDT as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue. The European Pharmacopoeia however defines a similar term, that is fast dissolving tablet is a tablet that can be placed in the mouth where it disperses rapidly before swallowing[9].

Recent market studies indicate that more than half of the patient population prefers FDTs to other dosage forms and most consumers would ask their doctors for FDTs (70%), purchase FDTs (70%), or prefer FDTs to regular tablets or liquids (>80%). These responses may, in part, be attributed to know FDT advantages such as ease of administration, ease of swallowing, pleasant taste, and the availability of several flavors. FDTs also offer clinical advantages such as improved safety and in some cases, improved efficacy and other broader indications[10]. FDT products have been developed for numerous indications ranging from migraines (for which a rapid onset of action is important) to mental illness (for which patient compliance is important for treating chronic indications such as depression and schizophrenia[10].

Fast dissolving drug delivery is rapidly gaining acceptance as an important new drug delivery technology[11, 12]. Not all fast dissolving technologies actually dissolve; some use different disintegrants[13, 14] and / or effervescent agents that cause the dosage form to disintegrate rapidly in the patients mouth within a minute and can be gulped easily without the need of water. Thus, it offers increase patients compliance and convenience. Patient convenience and compliance oriented research has resulted in bringing out many safer and newer drug delivery systems. Fast dissolving tablet is one such example

with increased consumer choice, for the reason of rapid disintegration or dissolution self administration even without water or chewing [15-17].

MATERIALS AND METHOD

MATERIALS

Levofloxcin was gifted from Promed Research Centre, New delhi, India. Mannitol was gifted from Strides Arcolabs, Bangalore. Microcrystalline cellulose, Sodium starch glycolate, Croscarmellose sodium, Saccharin sodium, Magnesium stearate and Mint flavor was gifted from Rajesh Chemicals, Mumbai.

METHOD

Preparation of Levofloxacin tablets

Direct Compression Technique

This method is used when the ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be pre-processed. This requires the active ingredient to have appropriate physical and chemical properties, such as good compatibility and low stickiness. Direct compression is often preferred because of its simplicity and relatively low cost, but may not always be technically feasible.

In this method, all the powder excipients are mixed thoroughly in a polyethylene bag. After proper mixing, the powder was punched into tablets (Table No.1). The weight of the tablet was 400mg and dose of the drug is 150mg[18].

EVALUATION PARAMETERS[11-18]

Pre formulation studies

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

Compatability studies (Fourier Transform Infrared Spectroscopic studies)

One of the requirement for the selection of suitable excipients or carrier for the pharmaceutical formulation is its compatability. Therefore in the present work a study was carried out by using FT-IR spectrophotometer to find out if there is any possible chemical interaction of Levofloxacin and different three superdisintegraents.

Procedure

To study the compatability of various formulation excipients with Levofloxacin, solid admixtures were prepared by mixing the drug with each formulation excipients separately in the ratio of 1:1 and stored in air tight containers at 30 ± 2^0C/65+5%RH. The solid admixtures were characterized using Fourier Trans form Infrared Spectroscopy (FT-IR).

Precompression studies of granules

Bulk density

5gms of granules were weighed separately and transferred into 100ml measuring cylinder, initial volume was measured and calculated according to the formula

Formula

Bulk density = Mass / Volume

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the granules in the cylinder and this minimum volume, the tapped density may be computed.

Formula

Tapped density = Weight of granules/ Tapped volume of granules

Angle of Repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The most commonly used of this in angle of repose, which may be determined experimentally by number of methods. The method used to find the angle of repose is to pour the powder a conical on a level, flat surface and measure the included angle with the horizontal.

Formula

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

Where,

θ = Angle of repose,

h = Height of the powder cone,

r = Radius of the powder cone.

Compressibility Index or Carr's Index

Carr's Index is measured using the values of bulk density and tapped density.

The following equation is used to find the Carr's Index,

$$CI = \frac{(TD-BD)}{TD} \times 100$$

Where, TD = Tapped density

BD = Bulk density

Hausner's Ratio

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

Formula

Hausner's Ratio = Tapped density/Bulk density

Postcompression studies of Levofloxacin tablets

Hardness or Crushing strength Test

Hardness of the tablet was determined using the Monsanto hardness tester (The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The force required to break the tablet is measured in kilograms and a crushing strength of 4Kg is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4 to 10kg; however, hypodermic and chewable tablets are usually much softer (3 kg).

Thickness Test

The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter. Ten tablets were randomly selected from each tablet thickness was determined using a Vernier calliper and the reading was recorded in millimeters.

Friability Test

The pre-weighed tablets were placed in the friabilator (EF-2, Electro lab, Mumbai) which was then operated for 100rpm, then dusted and reweighed. The Conventional compressed tablets that lose less than 0.5-1.0% of their weight are generally considered acceptable.

$$\text{Friability index} = \frac{I - F}{I} \times 100$$

Where,

I - Initial weight

F - Final weight

Weight variation test

Weights of 20 individual tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula,

$$\text{Percentage deviation} = [X - X^*/ X] \times 100$$

X - Actual weight of the tablet

X^* - Average weight of the tablet

Estimation of Drug Content

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was transferred into 250 ml volumetric flask, it was shaken with 150 of distilled water and volume was adjusted to 250ml with water. The solution was filtered, suitable dilutions were made and absorbance was recorded by using U.V. spectrophotometer (Labindia, Hyderabad) at 298nm. The experiment was repeated three times.

Calculation

The amount of Levofloxacin present in tablet can be calculated using the formula

$$A_t/As \times S_w/100 \times 100$$

Where,

A_t = Absorbance of sample preparation

A_s = Absorbance of Standard preparation

S_w = weight at Metformin working standard (mg)

Disintegration time study

Tablet was put into 100 ml distilled water at 37 ± 2^0C. Time required for complete dispersion of a tablet was measured with the help of digital tablet disintegration test apparatus.

Wetting time study

A piece of tissue paper folded twice was placed in a small Petri dish (internal diameter = 6.5cm) containing 5 ml of distilled water. A tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

***In vitro* drug release study**

In vitro release studies were carried out by using USP paddle dissolution test apparatus. 900ml of Phosphate buffer (pH 6.8) was taken in the dissolution vessel and the temperature of the medium was maintained at 37±0.5^{o}C. 100rpm was maintained, 1 ml of sample was withdrawn at predetermined time intervals for 0, 1, 3, 6, 9, 12 and 15 mints. The same volume of the fresh medium was replaced. The samples were analysed at 298nm by using a UV spectrophotometer (Labindia, Hyderabad). The dissolution data obtained were plotted as percentage drug release versus time.

RESULTS

Pre formulation studies

Compatability studies (Fourier Transform Infrared Spectroscopic studies)

The fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated tablets, pure drug and different superdisintegrants was recorded. The tablets were taken in a KBr pellet using SHIMADZU, 8400s, Japan, FTIR Instrument. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the different superdisintegrants and pure drug. Then all the functional groups found in the IR spectrum of pure drug and different superdisintegrants.

Precompression studies of granules

Bulk density

The packing properties of the drugs and their formulations widely depend upon bulk density. It has been stated that bulk density values less than 1.2gm/cm^3 indicate good flow and values greater than 1.5 gm/cm^3 indicate poor flow. From the results it can be seen that the bulk density values are less than 1.2gm/cm^3. This indicates good flow characteristics of the granules. Values showed Table No.2.

Tapped density

From the above results it can be seen that the Tapped density values indicate good flow characteristics of the granules. Values showed Table No.2.

Angle of Repose

Angle of repose less than or equal to 40° indicates free flowing properties of the granules. However angle of repose greater than 40° indicates poor flow of material. It can be observed from above table that the angle of repose for various batches of the granules is found to be less than 40^0, it indicates good flow properties of the granules. Values showed Table No.2.

Compressibility Index or Carr's Index

Carr's Index less than or equal to <10 indicates free flowing properties of the granules. However Carr's Index greater than <10 indicates poor flow of material. It can be observed from above table that the Carr's Index for various batches of the granules is found to be less than >10; it indicates good flow properties of the granules. Values showed Table No.2.

Hausner's Ratio

Hausner's Ratio less than or equal to 1.069 indicates free flowing properties of the granules. However Hausner's Ratio greater than 1.35 indicates poor flow of material. It can be observed from above table that the Hausner's Ratio for various batches of the granules is found to be less than 1.122; it indicates good flow properties of the granules. Values showed Table No.2.

Postcompression studies

Hardness Test

The hardness of the tablet various batches were determined. The various batches of the tablets of hardness values are found within limits and it indicates good strength of the oral dispersible tablets. Values showed Table No.3.

Thickness Test

The tablets mean thicknesses were almost uniform in the all formulations and were found to be in the range of 0.37mm. Values showed Table No.3.

Friability Test

The oral dispersible tablets friability values are found to be less than 1% in all cases and considered to be satisfactory. Values showed Table No.3.

Weight variation test

All this oral dispersible tablets passed weight variation test as the % weight variation was within

the pharmacopoeia limits. The weight of the all tablets was found to be uniform with low standard deviation values. Values showed Table No.3.

Estimation of Drug Content

Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug with the excipients. Values showed Table No.3.

Disintegration time study

The disintegration time (D.T) of all formulations is shown in the Table No.4.

Wetting time study

The wetting time study of all formulations is shown in the Table No.4.

DISCUSSION

Oral dispersible tablets of Levofloxacin were prepared by direct compression method. The prepared Oral dispersible tablets are round in shape. Microscopic examination of tablets from each formulation batch showed circular shape with no cracks. The fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated Oral dispersible tablets, pure drug and super disintegrants was recorded. The Fourier Transform Infrared Spectroscopy study reveals that there is no interaction between the super disintegrants and pure drug.

Bulk density (0.312 to 0.352 gm/cm^3) and Tapped density (0.333 to 0.384 gm/cm^3) values are within the limits, indicating that the powder blends have the required flow property for direct compression. The values obtained for angle of repose for all formulations are tabulated in table the values were found to be in the range from 31.38-39.48^0. This indicates good flow property of the powder blend. Compressibility index (6.30 to 10.93) and Hausner's ratio (1.067 to 1.122) values are within the limits, indicating that the powder blends have the required flow property for direct compression.

The hardness of the Oral dispersible tablet various batches were determined. The various batches of the Oral dispersible tablets of hardness values are found within limits and it indicates good strength of the Oral dispersible tablets. Tablet mean thicknesses were almost uniform in the all formulations and were found to be in the range of 0.37mm. Friability values are found to be less than 1% in all cases and considered to be satisfactory. All this tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits. Drug content of all the batches are within the acceptable range which shows the proper mixing of the drug with the excipients.

The *in vitro* drug release profile of tablets from each batch (FLOT-1 to FLOT-7) was carried in phosphate buffer (pH 6.8) for 15 mints by using paddle type of device. From the *in vitro* dissolution data, FLOT-7 formulation was found that the drug release is best and the cumulative % of drug release was 96.10 % respectively, when compared to other formulation (Table No.5 and Figure No.1).

Table No.1: Different Formulations of Levofloxacin Oral Dispersible Tablets

S.No	Formulation Code	Drug	SSG	PGS	CP	Avicel PH102	Mannitol	Sodium Saccharin	Magnesium Stearate	Mint flavor
1	FLOT-1	150	90	-	-	100	45	10	5	q.s
2	FLOT-2	150	-	90	-	100	45	10	5	q.s
3	FLOT-3	150	-	-	90	100	45	10	5	q.s
4	FLOT-4	150	45	45	-	100	45	10	5	q.s
5	FLOT-5	150	-	45	45	100	45	10	5	q.s
6	FLOT-6	150	45	-	45	100	45	10	5	q.s
7	FLOT-7	150	30	30	30	100	45	10	5	q.s

Table No.2: Precompression studies of granules

S.No	Formulations	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Angle of Repose (θ)	Carr's Index (%)	Hausner's Ratio
1	FLOT-1	0.334	0.375	32.26	10.93	1.122
2	FLOT-2	0.346	0.372	34.15	6.98	1.075
3	FLOT-3	0.328	0.362	33.82	9.39	1.103
4	FLOT-4	0.312	0.333	31.38	6.30	1.067
5	FLOT-5	0.333	0.368	35.07	9.51	1.105
6	FLOT-6	0.352	0.384	35.07	8.33	1.090
7	FLOT-7	0.326	0.354	39.48	7.90	1.085

Table No.3: Postcompression studies of Levofloxacin oral dispersible Tablets

S.No	Formulations	Hardness Test (kg/cm)	Thickness Test (cm)	Friability Test (%)	% of Weight variation test	Estimation of Drug Content
1	FLOT-1	2.45	0.37	0.164	99.7	98.12
2	FLOT-2	2.34	0.37	0.228	99.2	96.29
3	FLOT-3	3.42	0.37	0.236	99.8	97.54
4	FLOT-4	2.92	0.37	0.267	99.8	97.27
5	FLOT-5	2.65	0.37	0.224	99.6	96.48
6	FLOT-6	3.23	0.37	0.254	99.5	98.34
7	FLOT-7	2.86	0.37	0.253	99.9	98.84

Table No.4: Postcompression studies of Levofloxacin oral dispersible Tablets

S.No	Formulations	Disintegration time (sec)	Wetting time (sec)
1	FLOT-1	25	17
2	FLOT-2	23	16
3	FLOT-3	32	17
4	FLOT-4	22	15
5	FLOT-5	25	15
6	FLOT-6	23	16
7	FLOT-7	20	14

Table No.5: Comparative dissolution study of different formulations with various ratios of Super disintegrants

S.No	Time (mints)	% of drug release (FLOT-1)	% of drug release (FLOT-2)	% of drug release (FLOT-3)	% of drug release (FLOT-4)	% of drug release (FLOT-5)	% of drug release (FLOT-6)	% of drug release (FLOT-7)
1	0	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	1	6.47	5.05	4.315	6.947	5.684	6.736	7.263
3	3	26.61	20.63	19.15	27.42	21.31	27.05	28.52
4	6	36.00	31.15	29.57	36.52	32.21	35.47	36.63
5	9	48.57	46.26	44.89	49.57	47.05	48.73	50.36
6	12	65.73	60.63	58.21	66.10	61.47	65.00	67.26
7	15	90.68	88.10	83.31	92.78	88.73	91.84	96.10

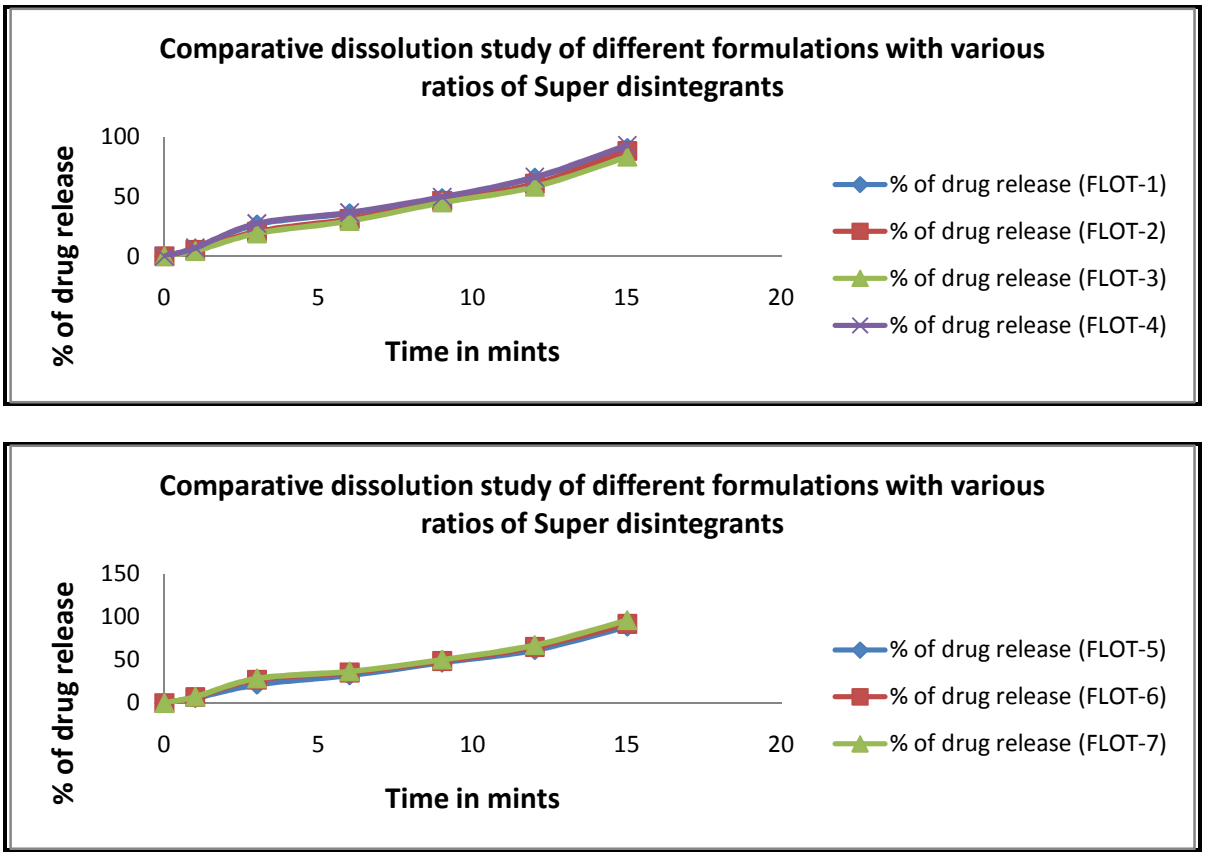

Figure No.1: Comparative dissolution study of different formulations with various ratios of polymers

CONCLUSION

The main objective of the present study was to develop Oral dispersible tablet formulation containing 150mg of Levofloxacin for the treatment of a number of infections including infection of Joints and bones, respiratory tract infections, urinary tract infections, skin structural infections and typhoid fever etc. In the present work it has been observed from all formulations of precompression and post compression studies were given within the limit of values. The *in vitro* dissolution data, FLOT-7 (combination of different superdisintegrants) formulation was found that the drug release is best and the cumulative % of drug release was 96.10 % respectively, when compared to other formulation.

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