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FORMULATION AND EVALUATION OF OFLOXACIN ORODISPERSIBLE TABLET BY SUBLIMATION TECHNIQUE

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ABSTRACT

The rational demand for mouth dissolving has been growing, especially for geriatric and pediatric patients because of swallowing difficulties. In the present work, Orodispersible tablets of Ofloxacin were designed with a view to enhance patient compliance by sublimation method. In this method camphor was used as a sublimation agent (up to 20 % w/w), Kyron T314, and Crosscarmellose sodium (2-8% w/w) used as Superdisintegrants. The prepared formulation was evaluated for weight variation, hardness, friability, drug content, wetting time, and invitro dissolution. All the formulations showed low weight variation with dispersion time of less than 80 seconds and rapid invitro dissolution seen in formulation F3. The results revealed that the tablets containing more quantity of sublimating agents and super disintegrants had a good dissolution profile. The drug content of all the formulations were within the acceptable limits of the USP XXVII. The optimized formulation showed good release profile with maximum drug being released at all time intervals. It was concluded that Orodispersible tablets with improved Ofloxacin dissolution could be prepared by sublimation of tablets containing suitable sublimating agent and disintegrants. This work helped in understanding the effect of formulation processing variables especially the sublimating agent and disintegrants on the drug release profile.

Key words: Orodispersible tablets, Ofloxacin, Kyron T 314, Sublimation method.

INTRODUCTION

Tablets are the most widely used dosage form in terms of its convenience in self administration, compactness and ease of manufacturing. The geriatric and pediatric patients

find difficulty in swallowing these conventional tablets, which leads to poor patient's compliance. It is estimated that 50 % of the population is affected by this problems. Recent advances in novel drug delivery systems (NDDS) aims to enhance safety and efficacy of drug molecules by formulating conventional dosage form for administration and to achieve the patient compliance. One such approach is Orodispersible tablets (ODT). The benefits in terms of patient's compliance, rapid onset of action and increased bioavailability and good stability makes these tablets popular as a dosage form of choice in current market [1, 2]

The basic approach in development of ODT is the use of superdisintegrants like croscarmallose sodium, sodium starch glycolate, PVP, etc which provides instantaneous disintegration of tablets after putting on tongue there by release the drug in saliva. The bioavailability of some drug may be increased due to absorption of drug in oral cavity and also due to pre-gastric absorption of saliva containing dispersed drugs that that pass down into the stomach. More ever the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablets. [3, 4]

Another approach in developing the ODT is maximizing the pore structure of the tablets. Researchers have evaluated spray-dried materials [5] and plastic materials [6] for development of such tablets.

Currently, it has been revealed that a ODT prepared by a technique like lyophilization , [7]vacuum drying technique [8], direct compression method [9, 10] disintegrants addition technique [11], and sublimation technique by using sublimating agents like camphor and methanol [12, 13].Camphor is used as a sublimating agent in many formulations [14, 15]

Water wicking and swelling are the two most important mechanisms of disintegrants action. The dissolution of drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers fine suspension of drug particles resulting in high surface area and fast dissolution.

Ofloxacin is a synthetic chemotherapeutic antibiotic of the fluroquinolone drug class considered to be a second generation fluroquinolone which has the bioavailability of 85%-95% and a half life of 8-9 hours. Ofloxacin is a broad spectrum anti biotic that is active against both Gram - positive and Gram - Negative bacteria. Ofloxacin is limited to the treatment of proven serious and life threatening bacterial infections such as acute bacterial

exacerbations of chronic bronchitis, Community - acquired pneumonia, mixed infections of the urethra and cervix, acute pelvic inflammatory disease, uncomplicated cystitis, complicated urinary infections.

Polacrillium potassium (Kyron T314) is a 2 methyl 2 propenoic acid polymer with di vinyl benzene, potassium salt. It is a cation exchange resin used in oral pharmaceutical formulations as a tablet superdisintigrant. It appeared as a cream colored, odorless and tasteless and free flowing powder [16]. In the present study, an attempt was made to develop mouth dissolving tablets of ofloxacin and to investigate the effect of subliming agent on the release profile of drug in the tablets.

MATERIALS AND METHODS

Materials

Ofloxacin & Kyron T 314 (procured from Dr. Reddy's, Hyderabad), Camphor, Sodium Starch Glycolate, Aspartames, Magnesium Stearate, Talc, and Microcrystalline cellulose were purchased from SD Fine chemicals, Mumbai, India.

Method

Formulation of Orodispersible tablets of Ofloxacin by sublimation method

The orodispersible tablet ofloxacin with various concentrations of superdisintegrants and sublimating agent was prepared by direct compression. The various concentration of superdisintegrants used are of Kyron T314 and Sodium starch Glycolate and camphor as the sublimating agent. Four formulations of ofloxacin containing camphor in different proportion [17, 18] were prepared by using MCC as diluents (Table-1). All the ingredients were passed through sieve no. 100 separately. The drug and diluents was mixed in small portion of both each time and blending it to get uniform mixture and set aside the other ingredients were weighed and mixed in geometric order, mixed thoroughly with the lubricants. The tablet of weight 250 mg were prepared by direct compression technique using 8mm punch on cad mach tablet punching machine [19]. After that the compressed tablets were placed in an oven for 30 minutes at 80^0c for the sublimation of camphor.

Pre-compression Parameters

The tablet blends were evaluated for their bulk density, tapped density, Carr's index and flow properties. The tapping method was used to determine the tapped density, bulk density and percent Carr's index. The measuring cylinder containing known mass of blend was tapped for

a fixed time. The minimum volume (V_t) occupied in the cylinder and weight (M) of the blend was measured. The tapped density (ρt) was calculated using the formula .The simplest way of measurement of the free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index of the granules was deter-mined by Carr's compressibility index (I) which is calculated by using the formula. I = {(Vo – Vt)/ Vo} × 100 .Hauser ratio is an indirect index of ease of powder flow. Lower Hauser ratio (< 1.25) indicate better flow properties than higher ones (>1.25). Angle of repose was determined using fixed funnel method. Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measuring the volume and weight "as it is" [11.]

Table-1 Composition of Different batches of ODT of Ofloxacin

INGREDIENTS	F1	F2	F3
Drug (mg)	100	100	100
Camphor (mg)	10	15	20
Kyron T314 (mg)	10	20	30
Sodium Starch Glycolate (mg)	25	30	35
Aspartames (mg)	6	6	6
Magnesium stearate (mg)	3	3	3
Talc (mg)	6	6	6
Microcrystalline cellulose (mg)	90	70	50

Post-compression Parameters

Tablet Hardness

The strength of tablet is expressed as tensile strength (Kg/cm2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a Monsanto hardness tester. Three tablets from each formulation were tested randomly and the average reading was noted.

Weight Variation Test

Randomly selected 20 tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation was calculated. IP limit for weight variation in case of tablets weighting up to 120 mg is ± 10%, 120 mg to 300 mg is ±7.5% and more than 300 mg is ± 5%.

$$PD= (W_{avg}) – (W_{initial}) / (W_{avg}) \times 100$$

Where PD= Percentage deviation, W_{avg} = Average weight of tablet, $W_{initial}$ = Individual weight of tablet.

Friability

Roche friabilator was used for the evaluation of the friability. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed 20 tablets were placed in the friabilator, which was then operated for 4 minutes. Tablets were dusted and reweighed. The percentage of weight loss was calculated.

Drug Content

Ten tablets were powdered and the blend equivalent to100 mg of Ofloxacin was weighed and dissolved in suitable quantity of pH 6.8 solutions. Solution was filtered and diluted and drug content analyzed spectrophotometrically at 294nm using Shimadzu Corporation, UV-1601, Japan.

Disintegration Time

One tablet was placed in each of the 6 tubes of the basket and run the apparatus using pH 6.8 maintained at 37+1^{o}c as the immersion liquid the assembly should be raised and lowered between 100 cycles per minutes the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recommended

Wetting Time and Water Absorption Ratio

A piece of tissue paper (12 cm × 10.75cm) was folded twice and kept in a culture dish (internal diameter 5.5cm) containing 6 ml of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined according to the following equation,

$$\mathbf{R = 100 (W_a - W_b)/W_b}$$

Where, W_b and W_a were the weights of the tablet before and after study.

***In Vitro* Dissolution studies**

In vitro dissolution studies of the promising Orodispersible tablets were performed according to USP XXIII Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5ºC as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10 & 15 min) and replaced immediately with equal volume of fresh medium. The samples were filtered through no 41 membrane filter disc and analyzed for drug content by measuring the absorbance at 294 nm. Drug concentration was calculated from the standard calibration curve

RESULT AND DISCUSSION

Pre compression study on powder blend

The Bulk density of the formulation mixture of drug with different superdisintegrants in varying proportion was taken and was measured by graduated cylinder. The bulk density was found in the range from 0.58 gm/cc to 0.61 gm/cc. The tapped density of the formulation was found to be in the range of 0.45gm/cc to 0.49gm/cc .Compressibility index indicates the flow property of granules or the powder flow property plays a major role in the dosage form. Especially in tablet dosage forms because improper flow of powder or granules may cause weight variation. The values of compressibility index below 15% indicate good flow, whereas the values above 15% indicate poor flow properties. The compressibility index and Hausner's Ratio was found by using bulk and tapped density, and was found to be in the range of 1.24 to 1.27 respectively for both Compressibility index and Hausner's Ratio. It reveals that the formulation exhibits good flow properties. The angle of repose is direct index of the flow property. The range of result lies in between 23.73 to 28.71. It indicates that the powders are having good flow property. The results for all the formulations are shown in Table - 4

Table: 2 Pre compression Parameters of granules of Ofloxacin by Sublimation method

Formulation	Bulk Density gm/cc	Tapped Density gm/cc	Compressibility Index %	Hausner Ratio	Angle of Repose
F1	0.58	0.45	23.34	1.27	28.61
F2	0.59	0.47	21.54	1.26	27.56
F3	0.61	0.49	20.27	1.24	25.73

Post Compression Studies

All the formulations showed low weight variation, thickness was found to be 2.47 mm to 2.50 mm and hardness was upto 4kg/cm^2. Addition of a subliming agent had no pronounced effect on hardness. All formulations were evaluated for friability by using Roche Friabilator. The sublimimg agent showed increased friability restoring the bonding properties of the excipients. Due to the presence of MCC the friablity was within the limits. Uniformity of drug was estimated for all the formulations. The result indicates that drug was uniformly distributed and are given inTable no:3. .

The wetting time was determined for all the formulations. The formulation F3 shows less wetting time when compared to other formulations. The wetting time of the formulation F1was faster when compared to other formulations. Wetting time was decreased when the concentration of the superdisintegrant and the subliming agent was increased .

The disintegration time is also an important criterion for selecting the optimum fast dissolving formulations or orodisperssible tablets. Among the formulations from $_{F1}$ – F3, F3 showed less disintegrating time due to its porous nature and wicking action.In vitro dispersion time attributes to a faster uptake of water, due to its porous structure formed due to the sublimating agent,thereby the disintegration time was faster as seen in the $_{F1}$ formulation.Dissolution studies were performed by using dissolution apparatus USP apparatus II with a paddle speed of 50rpm . An increase in Kyron T 314 concentration resulted in an increase in cumulative drug release.

Table - 3 Post compression parameters of Ofloxacin

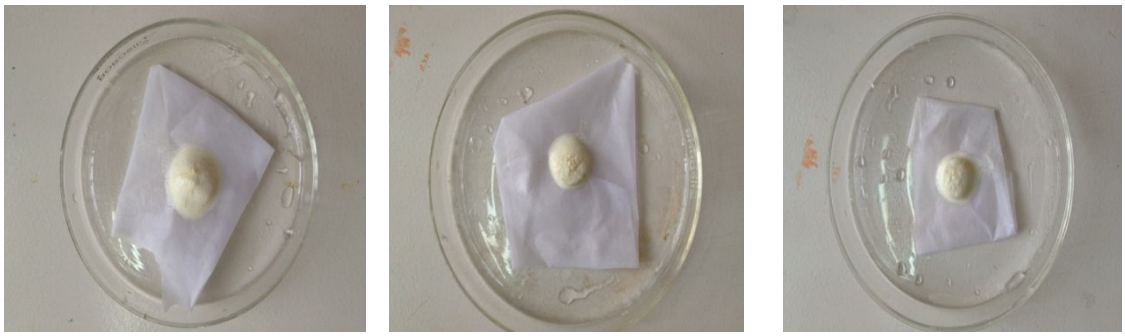
Formulations	Hardness (kg/cm$^{2)*}$	Friability (% w/w)*	Weight variation(%)*	Thickness * (mm)
F1	3.5±2	0.7±2	0.03±3	2.47±2
F2	4±2	0.6±3	0.05±2	2.53±3
F3	3.5±3	0.4±2	0.04±3	2.50±3

*** Result are the mean of 3 observation ± SD**

Water absorption ratio

The water absorption ratio of the formulations $_{F1}$-F3 are given in Table 4. the water absorption ratio lies in the range of 26.30 to 29.01. The amount of superdisintegrant present in the formulation $_{F1}$-F3 is the important criteria in the swelling of disintegrants in presence of

water.The formulation containing less quantity of superdisintegrants $_{F1}$ shows lower water absorption ratio , when compared to F3.The water absorption also decreases due to less swelling property as shown in the figure 2



F1 **F2** **F3**

Fig:2 Water Absorption Ratio of the Formulations F1, F2, F3

All the three formulations subjected for the in vitro dissolution studies using tablet dissolution tester USP XXXIII. The dissolution medium 1.2 pH buffer was used to study the drug release. The samples were withdrawn at different time intervals and analysed at 294nm using U.V spestrophotometer. Cummulative percentage drug release from all the formulations were calculated on the basis of average amount of Ofloxacin present in the formulation. In F3 dissolution is rapid compared to other formulations. The fast dissolution might be due to quick disintegration of the tablet to form particles and rapid absorption takes place. When subliming agent along with the superdisintegrant is in high quantity, it results in maximum drug release. As the concentration of camphor increases there will be more number of pore formation in the tablet, ultimately water/saliva can enter and absorb more quantity which leads to rapid disintegration. The variation of drug release from the other formulations may be due to slow breakdown of particles from the tablets as shown in the table no. 5

Table:4 Rapidly Disintegrating Property of all Formulations

Formulations	Wetting time (s)	In-vitro disintegration Time (s)	Water absorption ratio	In-vitro dispersion time (s)	% Drug content
F1	40±2	13±3	26.30±1.3	77.1±0.7	99.8±2
F2	47±2	15±2	27.22±1.5	76.2±0.83	99.6±3
F3	50±3	18±2	29.01±1.45	67.3±0.4	98.9±2

Table : 5 In-vitro Drug Release Profile for all Formuations

Formulation	In Vitro percentage drug release in different time intervals (mins)				
	3	6	9	12	15
F1	68.1±1.04	74.5±1.02	79.6±0.93	88.9±1.03	94.8±0.92
F2	68.2±1.16	71.0±0.96	76.3±0.98	83.2±1.08	96.4±1.11
F3	69.6±0.9	72.0±1.12	78.3±0.86	89.4±1.08	95.5±1.15

F1 F2 F3

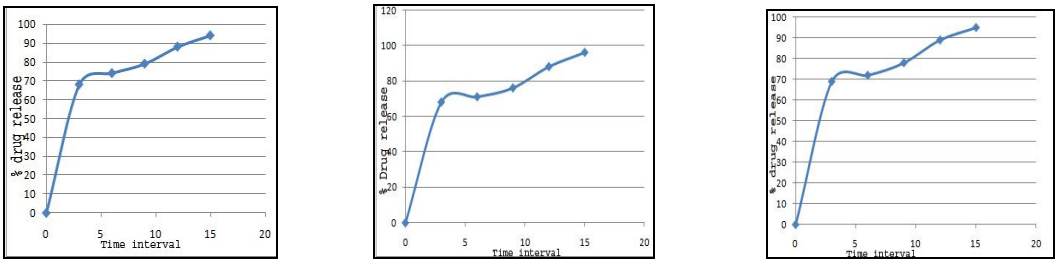


Fig : 3 graphshowing drug release of all formulations F1,F2,F3

The surface view of the tablet shows that before sublimation the tablet does not show much pores, whereas after sublimation the pores are seen clearly, this may be due to evaporation of camphor present in the various formulations.

The pore cavities which are formed within the tablet are responsible for the rapid disintegration since they are prepared with water soluble materials. These formulations have the advantages of not causing roughness in the mouth,when it is taken.

A **B**

Fig: 4 Formulation of F1 tablet before sublimation(1× 6) **Formulation of F1tablet after sublimation(1×6)**

CONCLUSION

The sublimation method showed better disintegration and drug release. The prepared tablets disintegrated within few seconds without the need of the water. The sublimation technique would be an effective approach compared with the use of more expensive adjuvant on the formulation of orodispersible tablets. In future ODT may be most acceptable and prescribed dosage form due to its quick action (within minute). There characteristic advantages such as administration without water, anywhere anytime lead there increased patient compliance in today's scenario of hectic life. Considering the many benefits of ODT's, a number of formulations are prepared in ODT forms by most of the pharmaceutical companies. Because of increased patient demand, popularity of these dosage forms will surely expand in future.

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