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# Formulation and Evaluation of Mouth Dissolving Tablet of Norfloxacin with Piperine and their Antibacterial Activity.

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## ABSTRACT

Drug delivery through oral route is widely accepted through all over world. Mouth dissolving tablet is most suitable tablet than conventional tablet. The main characteristic which is in the favors of mouth dissolving tablet is that there is no need of water to take it. Due to this it become more suitable dosage form for pediatric and geriatric patients. Since bioavailability of mouth dissolving tablet is high than conventional tablet, and mixing of piperine with it make them much more advance dosage form. Due to the addition of piperine in the drug, the dose size is reduced, and enhanced the onset of action. Addition of piperine with norfloxacin also increase the antibacterial activity and make them more effective.

**Keywords:** Mouth dissolving tablet, superdisintigrant, norfloxacin, piperine, E.coli.

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## INTRODUCTION

Drug delivery through oral route is one of the most common and widely acceptable route through all over world and best route of administration since decades.

**Mouth dissolving tablet:**

The central of drug evaluation and research (CDER), US FDA defined oral disintegrating tablet (ODT) as, "A solid dosage form containing medicinal substance which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue.

Mouth dissolving tablets (MDT) are single unit dosage form that dissolve or disintegrate quickly in mouth with the help of saliva and without the need of water. As these drugs are quickly dissolve or disintegrate hence it readily available for absorption improving its bioavailability and onset of action.

Since it is absorb from oral mucosal membrane directly into the systemic circulation, hence it avoids the first pass metabolism thus reduces the dose size and side effect of drug.[1,2]

However most of the patient like geriatric and pediatric patient feels some difficulty to swallow the conventional tablets, which may leads the poor patient compliance. To overcome this problem and weakness the researcher and scientist have developed the innovative drug delivery system which is known as oral disintegrating tablet.[3,4]

**Norfloxacin:**

It is a systemic synthetic antibacterial fluroquinolone. Its IUPAC name is 1-ethyl-6-fluro-1,4-di-hydro-4-oxo-7-(-piprazinyl)-3-quinolone corboxalic acid. It show their antibacterial activity bacterial DNA Gyrase. It is mainly used in treatment of urinary tract infection (UTI), gonococcalurethritis and infectious diarrhoea.[5,6] Norfloxacin is whitish yellow crystalline powder which is soluble in acetic acid, sparingly soluble in chloroform and slightly soluble in water[7]

**Piperine:**

Piperine (1-piperoyl piperidine) is one of the most major compound and pungent alkaloid found in the black pepper. It produce several action like antioxidant, anti-inflammatory, hepatoprotective, antihypertensive, antitumor, antiasthamatic, antibacterial and also as a fertility enhancer. Piperine inhibit the cytochrome p450 enzyme, the inhibition of these enzyme by piperine result the enhanced or increased bioavailability of drug.[8]

**Advantage of MDT:**[9,10,11,12,13,14]

1.No need of water to administration.

2.Suitable of pediatric and geriatric patient and also for those who have swallowing problem.

3.Pre-gastric absorption increased the bioavailability.

4.First pass metabolism is reduced or avoided, offering improved bioavailability and reduces dose size and side effect.

5.Improve patient compliance.

## MATERIALS AND METHOD:

**Material:**

Norfloxacin was obtained as gift sample from Akums Drug Pharmaceutical Limited. Sodium Starch Glycolate (SSG), were obtained from the Merc Limited. All other ingredients were used of pharmaceutical grade. Piperine is extracted and isolated in laboratory from black pepper.

**Method:**

**Isolation of piperine:**[15]

Take 150 ml of 95% ethanol in round bottom flask and 5-10 boiling chips added. Take 15 gm of black pepper powder in the soxhlet apparatus and heat the reflux for 2-2.5 hours. Then the extracted mixture of round bottom flask was filtered by using suction pump. Then concentrate the filtered solution to a volume of 15-20 ml by simple distillation. Took the concentrated pepper extract in 125 ml of Erlenmayer flask and add the 10 ml of 10% solution of KOH and heated. The refluxing mixture was diluted with addition of water till the precipitation formation stopped. A brownish yellow precipitate was formed. The precipitate mixture is allowed to stand overnight. The resulted extracts were collected by filtering the precipitate by suction pump and then re-crystallized by 10-20 ml of acetone. A yellowish white crystal of piperine was obtained.

**PREFORMULATION STUDIES:**

All the excipients and drug were passed through sieve No. 60. The weight quantity of each ingredient was sized to a required degree of fineness (except talc and magnesium stearate).

The powder blend was evaluated for the fallowing properties as fallow:-

**Table 1: Angle of Repose as an Indication of Powder Flow Properties**

| Sr. No. | Angle of Repose (°) | Type of Flow |
|---|---|---|
| 1 | < 20 | Excellent |
| 2 | 20-3- | Good |
| 3 | 30-40 | Passable |
| 4 | > 34 | Very poor |

**Angle of repose:** [16]

Angle of repose was determined by using the fixed funnel method. The blend powder was poured through a funnel that may be raised vertically maximum cone height (h) was obtained. Radius (r) of the heap or pile was measured and the angle of repose (q) was calculated by using

this formula:

$$\mathbf{Tan\ q = h/r}$$

$$\mathbf{q = tan^{-1}\ h/r}$$

**Bulk density:**[16,17]

The bulk density (Db) was determined pouring the blend material into a graduated cylinder. The bulk volume (Vb) and weight of the blend (M) was material noted. The bulk density was calculated by using the fallowing formula:

$$\mathbf{Db = M/\ Vb}$$

Where, M is the mass of blend powder

Vb is the bulk volume of the lend powder.

**Tapped density:**[16,18]

The known mass (M) of the blend material was placed on the measuring cylinder and was tapped for the fixed number of times. The minimum volume (tapped volume Vt) occupied in the cylinder. Tapped density (Dt) was calculated by using the fallowing formula:

$$\mathbf{Dt = M\ /\ Vt}$$

Where, M is the mass of powder

Vt is the tapped volume of the powder.

**Hausner's ratio:**[19]

It is an indirect index of ease of powder flow for the calculation of hausner's ratio, using the formula below:

$$\mathbf{Hausner\ ratio = \frac{Dt}{Db}}$$

Where, Dt is the tapped density.

Db is the bulk density.

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

**Carr's index or compressibility index:**[19,20]

This is the simplest way of measuring the free flowing property of the powder. It is expressed in the percentage (%) and can be calculated b the fallowing formula:

expressed in percentage and is give

$$\mathbf{I = Dt - Db/Dt\ x100}$$

Where,

Dt is the tapped density of the powder and

Db is the bulk density of the powder.

**Table 2: Relationship between % compressibility and flow ability.**

| % Compressibility | Flow ability |
|---|---|
| 5-12 | Excellent |
| 12-16 | Good |
| 18-21 | Fair passable |
| 23-35 | Poor |
| 33-38 | Very poor |
| < 40 | Very very poor |

**COMPRESSION OF TABLET BY USING DIRECT COMPRESSION TECHNIQUE:**

To the blended powder finally talc and magnesium stearate were added. The mixed blend of drug and excipient was placed in the hoper to compression of 400 mg tablets by using flat faced punches. 40 tablets were prepared in each batch.

**EVALUATION OF THE TABLETS:**

**Tablet hardness:**[21]

The hardness of the tablets was determined by using Monsanto hardness tester. It is expressed in terms of $Kg/cm^2$. The tablets were randomly selected from batches of each formulation and the mean and standard deviation value were calculated.

**Weight variation:** [21]

Twenty tablets were randomly selected from each formulation and average weight was measured. Then individual weight of tablet were measured and compared with average weight. It is the variation under limit within the Indian Pharmacopoeia (I.P), and then tablets pass the weight variation test.

**Table 3: Weight Variation Specification as per I.P**[16]

| Average Weight of Tablet | % Deviation |
|---|---|
| 80 mg or less | ±10 |
| More than 80 mg but less than 250 mg | ±7.5 |
| 250 mg or more | ±5 |

**Friability:** [21]

The friability of tablets was determined by Rouche Fribilator. It is expressed in the terms of percentage. Ten tablets was initially weight ($W_{initial)}$ and transferred into the Rouche Fribilator. The friabilitor was operated and rotated at 25 rpm for 4 minutes i.e. 100 rotations. The tablets were dusted off and weight again ($W_{final}$). The percentage friability was then calculated by the fallowing formula:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Percentage friability of tablet less than 1% is considered as acceptable.

**Wetting time:** [21]

The method was applying to measure the wetting time of tablet. A circular tissue paper was folded twice and put on the petridish with a diameter of 10 cm. then 10 ml of water poured on the folded tissue paper kept in the petridish. And now tablet is carefully placed in the petridish over the surface of folded tissue paper. The time required for water to reach the upper surface of the tablet is recorded as wetting time.

**In-vitro disintegration time:** [21]

The test is carried out for the testing of the disintegration time of the tablets by using the tablet disintegrating tester. In each tube of bosket placed on tablet and run the apparatus using pH 6.8 (simulated saliva fluid) maintained at 37 $\pm$ 0.5% $^0$C as disintegration media. The time in second taken for complete disintegration of tablet with no mass remaining in the apparatus was measured and recorded.

**Dissolution studies:**[16]

The release rate of prepared tablets were performed and carried out by using USP paddle method at 100 rpm in 900 ml of 6.8 pH phosphate buffer as a dissolution media maintained at 37 $\pm$ 0.5% $^0$C. Aliquot (1 ml) of sample were collected from dissolution apparatus at the specified regular interval, filtered through Whatmen filter paper and release of drug was determined spectrophoptometrically at 247 nm. An equal volume of pre warmed (37$^0$C) fresh dissolution medium was replaced into the dissolution apparatus after each sampling to maintain the constant volume of dissolution medium. Finally cumulative % of drug release was calculated and represented graphically.

**ANTIBACTERIAL ACTIVITY OF NORFLOXACIN AND NORLOXACIN WITH PIPERINE**

Norfloxacine is mainly used in the treatment of urinary tract infection which is caused by E.coli. From F1 to F4 piperine mixed formulation of norfloxacin, while F5 & F6 are formulation of norfloxacin without piperine.

**Zone of Inhibition**[22f]

- **Method-Disc Diffusion Method**
- **Media** – Muller Hinton Agar
- **Species-** *A) Gram Positive- S. Aureus*
  *B) Gram Negative- E. coli*
- **Solvent**- DMSO
- **Concentration** – 100 µg/mL

**Minimum Inhibition concentration**[22]

- **Method-Broth Dilution Method**
- **Media** – Muller Hinton Broth
- **Species**- A) Gram Positive- Staphylococcus aureus
  B) Gram Negative- E. coli
- **Solvent**- DMSO

## RESULTS AND REPORT:

Six batches have been formulated of norfloxacin with combination of different superdisintigrants like sodium starch glycolate and crospovidone. For each formulation blend material of drug and all excipients were prepared and evaluated for various parameters. The formulated blend was evaluated and the results are shown in table 5. The angle of repose was in the range of 23.56 ± 0.139 to 28.78 ± 0.223 indication good flow property. The bulk density and tapped density was in the range of 04089 ± 0.120 to 0.4301 ± 0.017 gm/ml and 04628 ± 0.011 to 0.5040 ± 0.14 gm/ml respectively. The carr's index and hausner's ratio was in the range of 13.19 ± 1.72 % to 16.21 ± 1.82 % and 1.1011 ± 0.283 to 1.2078 ± 0.23 respectively, including good flow property of the blends. The powder blends were compressed by using direct compression technique. The compressed tablets were evaluated for physical properties and the results are tabulated in the table 6. He hardness was in the range of 3.1 to 3.7 kg/cm$^2$. Uniformity of weight was found in the range of 398.7 ± 1.02 to 402.3 ± 0.78 mg. The friability of the formulation was within 1% and was in the range of 0.3991 to 0.4995 % indicating a good mechanical strength and resistance of tablet. The wetting time of the formulated tablet were in the range of 13 ± 0.64 to 67 ± 1.67 sec. the disintegration time of tablets for all batches were in the range of 22 ± 1.60 to 78 ± 0.51 sec. in vitro drug release result were shown in the table 7 and % CDR was shown in the Fig.1. Release profile of F4 having crospovidone was found maximum release of 95.61% at the end of 5 minutes. The drug release from all batches was found to be concentration dependent.

Zone of inhibition of S. aureus and E. coli are tabulated in the table No. 8. Formulation F2 & F4 show the best result, i.e. 4mm to 16 mm respectively. Minimum Inhibitory Concentration (MIC) for F1 is 200 µg/mL and F5 & F6 MIC is >200 µg/mL against S. aureus. MIC for F1 to F4 is 50 µg/mL and for F5 & F6 MIC is 100 µg/mL against E.coli.

**Table .4: Composition of mouth dissolving tablet of norfloxacin.**

| | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Norfloxacin | 200 | 200 | 200 | 200 | 200 | 200 |
| Piperine | 15 | 20 | 15 | 20 | -- | -- |

| | | | | | | |
|---|---|---|---|---|---|---|
| SSG | 12 | 15 | -- | -- | 12 | -- |
| Crosspovidone | -- | -- | 12 | 15 | -- | 12 |
| Sodium saccharine | 10 | 10 | 10 | 10 | 10 | 10 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 |
| Lactose | 45 | 45 | 45 | 45 | 45 | 45 |
| Talc | 6 | 6 | 6 | 6 | 6 | 6 |
| MCC | 107 | 99 | 107 | 99 | 122 | 122 |
| TOTAL | 400 | 400 | 400 | 400 | 400 | 400 |

**Table 5: Evaluation of powder blend**

| | **Angel of the repose (q)*** | **Bulk density* gm/ml** | **Tapped density* gm/ml** | **Carr's index %** | **Hausner's ratio*** |
|---|---|---|---|---|---|
| F1 | 28.50 ± 0.458 | 0.4160±0.011 | 0.4628±0.011 | 12.7 ±1.78 | 1.1011±0.283 |
| F2 | 23.56 ± 0.139 | 0.4089±0.012 | 0.4990±0.016 | 16.21 ±1.82 | 1.2078±0.023 |
| F3 | 26.38 ± 0.015 | 0.4301±0.013 | 0.4853±0.113 | 12.44 ±1.81 | 1.1553±0.029 |
| F4 | 25.48 ± 0.283 | 0.4122±0.007 | 0.4751±0.014 | 13.19 ±1.72 | 1.1422±0.024 |
| F5 | 27.67 ± 0.54 | 0.4210±0.10 | 0.4911±0.12 | 13.54 ±1.89 | 0.1467±0.002 |
| F6 | 28.78 ± 0.223 | 0.4209±0.009 | 0.5040±0.014 | 14.65 ± 1.95 | 1.1671±0.021 |

* Mean ± standard deviation, n=3 (all the value of average of three determination)

**Table 6: Evaluation of Norfloxacin mouth dissolving tablet**

| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
|---|---|---|---|---|---|---|
| Weight variation(mg) | 400.1±1.22 | 398.1±1.02 | 399.55±0.49 | 402.3±0.78 | 401.5±1.65 | 399.2±1.84 |
| Hardness Kg/cm$^2$ | 3.4 | 3.3 | 3.6 | 3.5 | 3.1 | 3.7 |
| Friability % | 0.4995 | 0.4911 | 0.6019 | 0.3991 | 0.4026 | 0.3995 |
| Wetting time (Sec)* | 67 ± 1.67 | 58 ± 1.11 | 25 ± 1.60 | 13 ± 0.64 | 54 ± 1.64 | 56 ± 1.34 |
| Disintegration (Sec)* | 78 ± 0.51 | 70 ± 1.09 | 37 ± 1.01 | 22 ± 1.60 | 76 ± 0.53 | 71 ± 1.15 |

* Mean ± standard deviation, n=3 (all the value of average of three determination)

**Table 7: in-vitro drug release of prepared norfloxacin mouth dissolving tablet.**

| **Time in minutes** | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** |
|---|---|---|---|---|---|---|
| 1 | 23.71 | 29.82 | 38.85 | 42.32 | 24.05 | 28.43 |
| 2 | 41.43 | 42.47 | 56.58 | 54.62 | 53.42 | 48.48 |
| 3 | 56.84 | 58.28 | 70.41 | 73.82 | 61.29 | 63.85 |
| 4 | 68.55 | 70.93 | 87.91 | 94.99 | 70.11 | 71.23 |
| 5 | 76.30 | 79.12 | 93.13 | 95.61 | 74.28 | 77.32 |

**Table 8: Rate of zone of inhibition of S. aureus and E. coli by disk diffusion method.**

| **Sr. No.** | **Comp. Code** | ***S. aureus*** **ZONE OF INHIBITION (In mm)** | **E. coli** |
|---|---|---|---|
| 1 | F1 | 03 | 14 |
| 2 | F2 | 04 | 16 |
| 3 | F3 | 03 | 15 |
| 4 | F4 | 04 | 16 |
| 5 | F5 | 01 | 10 |
| 6 | F6 | 01 | 11 |
| | Std | Vancomycine | Amikacine |
| | | 08 | 20 |

**Table 9: Minimum Inhibitory Concentration for Staphylococcus aureus.**

| Sr. No. | Comp. Code | Staphylococcus aureus | | | | |
|---|---|---|---|---|---|---|
| | | 25 µg/mL | 50 µg/mL | 100 µg/mL | 200 µg/mL | MIC µg/mL |
| 1 | F1 | Turbid | Turbid | Turbid | Clear | 200 |
| 2 | F2 | Turbid | Turbid | Clear | Clear | 100 |
| 3 | F3 | Turbid | Turbid | Clear | Clear | 100 |
| 4 | F4 | Turbid | Turbid | Clear | Clear | 100 |
| 5 | F5 | Turbid | Turbid | Turbid | Turbid | >200 |
| 6 | F6 | Turbid | Turbid | Turbid | Turbid | >200 |

**Table 10: Minimum inhibitory concentration for E. coli.**

| Sr. No. | Comp. Code | E. coli | | | | |
|---|---|---|---|---|---|---|
| | | 25 µg/mL | 50 µg/mL | 100 µg/mL | 200 µg/mL | MIC µg/mL |
| 1 | F1 | Turbid | Clear | Clear | Clear | 50 |
| 2 | F2 | Turbid | Clear | Clear | Clear | 50 |
| 3 | F3 | Turbid | Clear | Clear | Clear | 50 |
| 4 | F4 | Turbid | Clear | Clear | Clear | 50 |
| 5 | F5 | Turbid | Turbid | Clear | Clear | 100 |
| 6 | F6 | Turbid | Turbid | Clear | Clear | 100 |

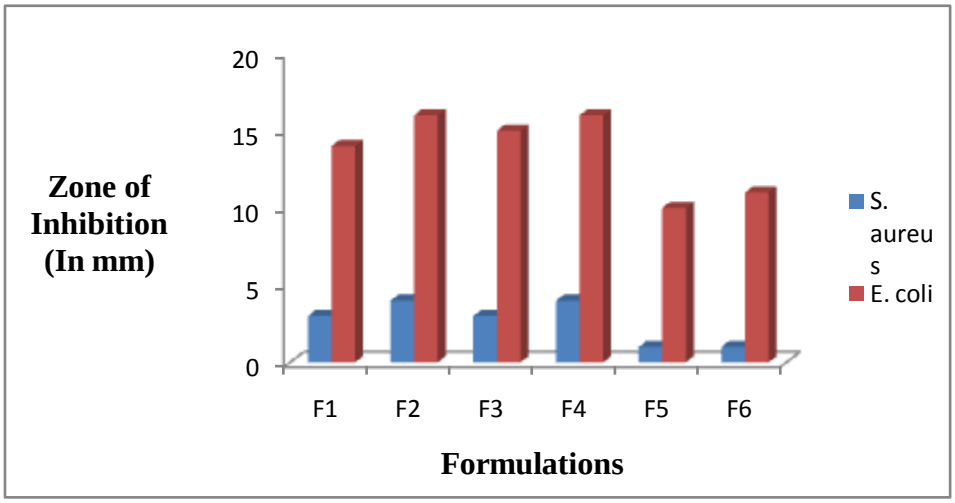


**Figure.1: Zone of inhibition of S. aureus and E. col**

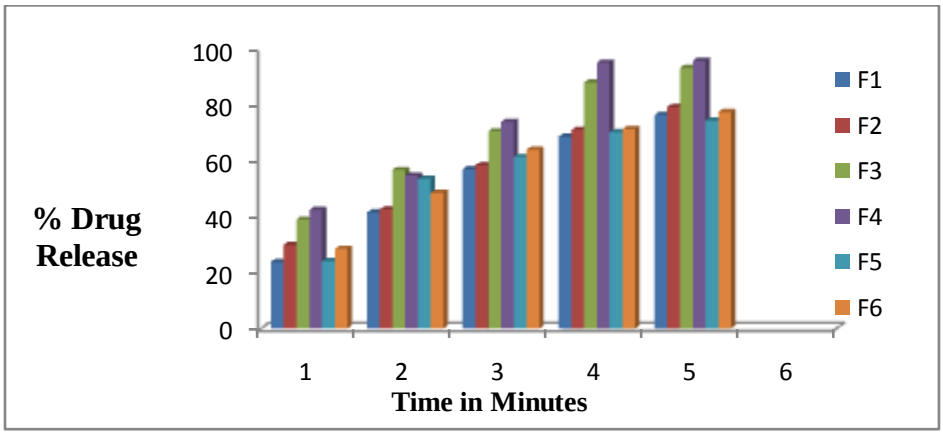


**Figure. 2: In-vitro drug release of prepared norfloxacin mouth dissolving tablet.**

## CONCLUSION:

The present work efforts have been made to prepare mouth dissolving tablet of norfloxacin with piperine by direct compression method. Release profile of F4 having crosspovidone was found to have maximum release 95.61% at the end of 5 minutes. The antibacterial activity showing best result in F2 & f4 for zone of inhibition against S. aureus & E. coli and F1 to F4 for minimum inhibitory concentration against E. coli. Since formulation F4 have the best disintegrating and dissolution time, hence formulation F4 fulfills the objective of the present study.

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