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# FORMULATION, DEVELOPMENT AND CHARACTERIZATION OF FAST DISSOLVING TABLETS OF IVERMECTIN USING NATURAL POLYMERS

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**Abstract:**

*Ivermectin (IVM) is a semi-synthetic substance derived from avermectin, which is naturally produced by Streptomyces avermitilis. It is very effective in the control of endo- and ecto-parasites such as gastrointestinal nematodes, lice, and mites in livestock. In the present study an attempt has been made to prepare fast dissolving tablets of Ivermectin, Xanthan gum, Sod. Alginate, Sodium starch glycolate used in the level of addition to increase the rate of drug release from dosage form to increase the dissolution rate. Direct Compression method was used to formulate the tablets. 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 U.V. vis Spectroscopy. The percentage assay of different formulation was in range of 98.45±0.23 to 99.75±0.24%. The maximum percentage assay (99.75±0.24%) and less disintegration time were found to be formulation F3 in Fast dissolving tablets. The optimized formulation of batch F3 subjected to further In vitro drug release. Overall the results of the dissolution rate studies indicated greater dissolution rate of Ivermectin from fast dissolving tablets.*

***Key words:*** *Ivermectin, Fast dissolving tablets, Natural Polymers, formulation and evaluation*

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## INTRODUCTION:

The polymers obtained from the natural inchoation are more efficacious and safer. They are facilely available in natural regions around the world therefore they are preferred over synthetic polymer. Natural polymers are utilized in most of the preparation and are more propitious over synthetic polymers as they are economical, and they have low cost and are facilely available in the sufficient quantity. Natural polymers are nontoxic; they do not have any adverse effects on the body. Natural polymers are environmentally friendly as they are biodegradable in nature, they do not cause any pollution. Natural polymers are devoid of side effects as they are obtained from the natural source. Natural polymers are mainly preferred by the patients as they are safer and more efficacious as compared to the synthetic polymers and have more patient compliance. Natural polymers provide nutritional supplement and are renewable as they are utilized again and again in different reactions[1].

The utilization of natural polymers is valuable predicated on proven biocompatibility and safety. Natural gums are among the most popular hydrophilic polymers because of their cost-efficacy and regulatory acceptance. Polymers are generally employed in floating drug distribution systems so as to target the distribution of drug to a concrete region in the gastrointestinal tract, that is, stomach. Moreover, these polymers are safe, nontoxic, and capable of chemical modification and gel formation[2].

Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for the pediatric and geriatric patient. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally less than 60 seconds[3]. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage forms known as orally disintegrating (dispersible) tablets (ODTs) or Fast disintegrating (dissolving) tablets (FDTs) or mouth melting tablets (MMTs) or mouth dissolving tablets (MDTs), immediate release tablets which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take water.

Recent market studies indicate that more than half of the patient population prefers FDTs to other dosage forms. Mouth dissolving tablets are formulated mainly by two techniques first use of super disintegrants like Croscarmellose sodium, sodium starch glycolate and crospovidone. Another method is maximising pore structure of the tablets by freeze drying and vacuum drying. In all methods, direct compression is preferred because of its effortlessness, quick procedure and cost-effectiveness[4].

Fast dissolving tablets are innovative dosage forms developed and specially designed to overcome some of the problems that seen in conventional solid dosage form i.e. difficulty in swallowing of the tablet in geriatric and pediatric patients. Fast dissolving tablets are designed to dissolve or disintegrate quickly in the saliva generally within less than 60 seconds (range of 5-60 seconds). Fast dissolving tablets have better patient compliance and acceptance may improve biopharmaceutical properties, bioavailability improved efficacy, convenience, and better safety compared with conventional oral dosage forms. The popularity of FDTs has increased fabulously over the last decade. FDTs need to be formulated for psychotic patients, bedridden, geriatric, pediatric patients, for those patients who may not have access to water, patients who are busy in traveling. FDTs formulations formulated by some of these convetional and patent technologies and FDTs have sufficient mechanical strength, quick disintegration/dissolution in the buccal cavity without water. The newer technologies utilized for the formulation of the FDTs that provide more effective dosage forms with more advantages and minimal disadvantages[5].

Ivermectin (IVM) is a semi-synthetic substance derived from avermectin, which is naturally produced by Streptomyces avermitilis. It is very effective in the control of endo- and ecto-parasites such as gastrointestinal nematodes, lice, and mites in livestock. To overcome these problems mouth dissolving tablets are a good option. Since, they disintegrate and dissolve rapidly in saliva without need for drinking water. The development of a fast dissolving tablet also provides an opportunity for a line extension in the market place.

## MATERIAL AND METHODS:

**Preparation of tablets of Ivermectin**

Fast dissolving tablets of Ivermectin (25mg) were prepared by direct compression method after incorporating different polymers and superdisintegrants such as, Xanthan gum 50, 75 and 100mg, Sod. Alginate in different concentrations 50, 75 and 100mg and Sodium starch glycolate 10 mg for optimization of best formulation[6]. 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 (112, 87 and 62mg) 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) fat punches on a 'Rimek mini press 16 station rotary compression machine. Six formulations of Ivermectin granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablet weighing 200mg was obtained. Composition of tablets is mentioned in Table no 1.

**Table No 1: Composition of Ivermectin fast dissolving tablets**

| Ingredients (mg) | Formulation code | | | | | |
|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 |
| Ivermectin | 12 | 12 | 12 | 12 | 12 | 12 |
| Xanthan gum | 50 | 75 | 100 | - | - | - |
| Sod. Alginate | - | - | - | 50 | 75 | 100 |
| Sodium starch glycolate | 10 | 10 | 10 | 10 | 10 | 10 |
| Mannitol | 5 | 5 | 5 | 5 | 5 | 5 |
| Microcrystalline cellulose | 112 | 87 | 62 | 112 | 87 | 62 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate | 6 | 6 | 6 | 6 | 6 | 6 |
| Total weight | 200 | 200 | 200 | 200 | 200 | 200 |

**Evaluation of post compression Parameter**

**Thickness test**

Three tablets were picked from each formulation randomly and thickness was measured individually[7]. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

**Weight variation test**

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet[8].

**Hardness test**

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in $Kg/cm^2$**.**

**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[9]. The friability was determined as the mass loss in percent according to Equation: -

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

The test complies if tablets not loss more than 1% of their weight

**Uniformity of drug content:**

The test is mandatory for tablets with 10 mg or less weight of active ingredient. 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 whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with Phosphate buffer pH 6.8 and the drug content was determined spectrophotometrically at 244 nm[10].

**Dissolution rate studies**

The prepared tablets were evaluated for *in vitro* drug release. 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±0.2°C. The scheme of using the simulated fluids at different timing was as follows:

A tablet placed in dissolution media (900 ml) at 37±0.2°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 Phosphate buffer pH 6.8. The samples withdrawn were assayed spectrophotometrically at 244nm using UV visible spectrophotometer. The release of drug was calculated with the help of standard curve of Ivermectin[11].

## RESULTS AND DISCUSSION:

This research work deals with the investigations carried out on the preparation and characterization of fast dissolving tablets containing Ivermectin with increase its oral bioavailability. Fast dissolving tablets containing Ivermectin were prepared using direct compression method. Total six formulations were prepared using varying amount of Xanthan gum, Sod. Alginate and Sodium starch glycolate. 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 U.V. vis Spectroscopy. The percentage assay of different formulation was in range of 98.45±0.23 to 99.75±0.24%. The maximum percentage assay (99.75±0.24%) and less disintegration time was found to be formulation F3 in Fast dissolving tablets. The optimized formulation of batch F3 subjected to further *In vitro* drug release.

The In vitro drug release studies of the enhanced detailing was 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 '$r^2$' values of Higuchi order was maximum i.e. 0.988 hence indicating drug release from formulations was found to follow Higuchi order order kinetics.

**Table No 2: Results of Post-Compression parameters of all formulations**

| F. Code | Hardness test (kg/cm$^2$)* | Friability (%)* | Weight variation (%)* | Thickness (mm)* | Drug content (%)* | Disintegration Time (sec.)* Mean ± SD |
|---|---|---|---|---|---|---|
| **F1** | 3.4±0.1 | 0.857±0.021 | 205±4 | 2.3±0.1 | 98.87±0.25 | 135±5 |
| **F2** | 3.3±0.2 | 0.765±0.025 | 198±4 | 2.4±0.2 | 98.45±0.23 | 130±4 |
| **F3** | 3.5±0.2 | 0.745±0.021 | 203±6 | 2.2±0.2 | 99.75±0.24 | 85±4 |
| **F4** | 3.3±0.1 | 0.882±0.014 | 204±4 | 2.2±0.1 | 98.78±0.26 | 145±5 |
| **F5** | 3.2±0.1 | 0.847±0.015 | 196±7 | 2.1±0.1 | 99.12±0.35 | 130±4 |
| **F6** | 3.5±0.3 | 0.765±0.032 | 195±8 | 2.3±0.2 | 99.35±0.41 | 110±3 |

***Average of three determinations**

**Table No 3: *In-vitro* drug release data for optimized formulation F3**

| 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 | 0.000 | 26.65 | 1.426 | 73.35 | 1.865 |
| 2 | 1.41421 | 0.301 | 45.56 | 1.659 | 54.44 | 1.736 |
| 5 | 2.23607 | 0.699 | 73.32 | 1.865 | 26.68 | 1.426 |
| 10 | 3.16228 | 1.000 | 97.45 | 1.989 | 2.55 | 0.407 |

**Table No 4: Regression analysis data**

| Batch | Zero Order | First Order | Higuchi | Korsmeyer-Peppas |
|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ |
| **F3** | 0.940 | 0.834 | 0.988 | 0.982 |

When the regression coefficient values of were compared, it was observed that '$r^2$' values of Higuchi order was maximum i.e. 0.988 hence indicating drug release from formulations was found to follow Higuchi order order kinetics.

## CONCLUSION:

Fast dissolving tablets of Ivermectin were conveniently formulated by direct compression method. The *in vitro* dissolution studies showed that Ivermectin tablets formulation F3 showed maximum 97.45% over a period of 10 min. Overall the results of the dissolution rate studies indicated greater dissolution rate of Ivermectin from fast dissolving tablets.

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