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Formulation and Evaluation of Fast Mouth Dissolving Film of Tenofovir Disoproxil Fumarate

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***ABSTRACT*-**Mouth dissolving dosage forms are gaining popularity in recent time because of good patient compatibility, fast disintegration time, flexibility in transportation etc. In this research work Tenofovir Disoproxil Fumarate (TDF) is used to treat chronic hepatitis B. TDF is an antiretroviral drug. TDF is selected as model drug for the preparation of Mouth dissolving film (MDF). MDF was prepared by solvent casting method using HPMC E15 & PVP K30 as film former and Glycerol & PEG-400 as plasticizers. MDF were evaluated for physical characteristics such as tensile strength, percentage elongation, drug content uniformity, surface pH, folding endurance, uniformity weight, and thickness and gave satisfactory result. The formulations were subjected to disintegration time, in vitro drug release test and stability study. The FTIR studies revealed that there was no physicochemical interaction between excipients and drug. The FTIR studies revealed that there was no physicochemical interaction between excipients and drug. A marked % drug release was exhibited by MDF of TDF containing HPMC E15 as a polymer at 30 sec.

***KEYWORDS*-** Tenofovir Disoproxil Fumarate, Mouth-dissolving film, HPMC E15, PEG-400, Solvent Casting Method.

I. INRODUCTION

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, the particular class of patients which includes geriatric, pediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take solid preparations due to fear of choking.that's way the MDF are very essential to used.

Mouth dissolving films (MDF)

Definition of FDF: Fast dissolving films are most advance form of solid dosage form due to its flexibility. It improve efficacy of Active pharmaceutical ingredient (API) dissolving in the short duration oral cavity after the contact with less amount of saliva as compared to dissolving tablet.[1]

Mechanism of absorption through saliva:

There are two possible routes for drug absorption: the transcellular (intracellular, passing through the cell) and the paracellular (intercellular, passing around the cell) route. Another classification involves passage through non-polar (lipid elements) and polar (hydrophilic material through aqueous pores) routes. The permeation mainly occurs by the par cellular route, but the route taken depends on the physicochemical properties of the drug. Small molecules, predominantly lipophilic, are absorbed most rapidly, whereas large hydrophilic Molecules are generally poorly absorbed. Hydrophilic molecules take the paracellular route, compared to lipophilic molecules, which take the transcellular route. The permeability decreases as the molecule size increases. The passage across the oral mucosa follows a first order simple diffusion process. Although passive diffusion is the main mechanism of drug absorption.

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Criteria for fast dissolving film

Fast dissolving film should,

- Have a pleasant mouth feel.
- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions such as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipment at low cost

Advantages of mouth dissolving film

- Ease of administration to pediatric, geriatric, bedridden patients and psychiatric patients who refuse to swallow tablets
- Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
- Elegant film convenient dosingvarious sizes and shapes no water needed
- Unobstructed no risk of choking
- Mucoadhesion taste masking
- Fast disintegration enhanced stability
- Quick dissolving improved patient compliance
- Rapid release life cycle management

Classification mouth dissolving film:

Mouth dissolving film is **classified in to three categories** they are as follows,

- Flash release,
- Mucoadhesive melt-away wafer
- Mucoadhesive sustained-release wafers

II. LITURATURE REVIEW

Mital S. Panchal et al., (2012): prepared mouth dissolving films of Ropinirole Hydrochloride with the purpose of developing a dosage form for a very quick onset of action, which is very convenient for administration, without the problem of swallowing and using water. The films of Ropinirole Hydrochloride were prepared by using polymers such as pullulan and PEG 400 as plasticizer, by a solvent casting method

Kaushal Patel et al., (2012): development ofTelmisartan (TLM) is an angiotensin II receptor antagonist used in the treatment of hypertension. TLM mouth dissolving tablets were prepared using skimmed milk powder (SMP) and poloxamer-188 (PXM-188) as carriers and crosspovidone as super disintegrant.

VijaykumarGhorwade et al., (2011): prepared the montelukast sodium fast dissolving films were prepared by solvent casting method using HPMC as film base with different concentrations of superdisintegrants like microcrystalline cellulose and crospovidone using PEG 400 as plasticizer.

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III. NEED &OBJECTIVE

Need of study: Tenofovir Disoproxil Fumarateis a drug that is used as an Antiretroviral. It should be treat HIV/AIDS. It is used to treat same time Chronic Hepatitis B. It is prod rug for better absorption in gut. It is widely prescribed for the treatment of HIV.

- Low bioavailability (25%)
- Extensive first pass metabolism

Objective: The objective of this study was to develop oral drug delivery system in the form of fast dissolving film which overcomes first pass metabolism and the drug achieve to specific site, for greater therapeutic action

IV. DRUG PROFILE

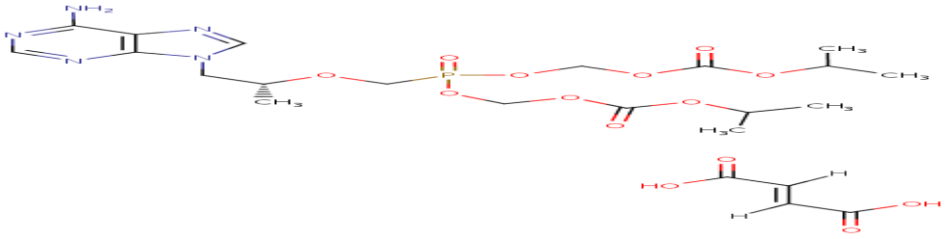

Fig.1 Tenofovir Disoproxil Fumarate

Table 1 Drug Profile

IUPAC	{[(2R)-1-(6-aminopurin-9-yl)propan-2-yl]oxymethyl-(propan-2-
Description	white fine powder
Synonyms	9-(-2phosphonomethoxypropyl)adenine
Molecular Formula	$C_{23}H_{34}N_5O_{10}P$
Molecular Weight	635.514922g/mol
Melting Range	105-109^{0}c
Acidity	pH of 5% w/v solution is 1.35-5.12
Heavy Metals	43
Dose	100-300 mg/day(as per weight)
Half Life	17 Hrs
Category	Antiretroviral(HIV/AIDS),Chronic hepatitis B
Solubility	Soluble in water

V. EXPERIMENTAL

Methods for mouth dissolving film formulation- One or combination of the following process can be used for manufacture the mouth dissolving film.

Solvent casting method-In solvent casting, method water-soluble polymers are dissolved in water and the drug along with other excipients is dissolved in suitable solvent then both the solutions aremixed and stirred and finally casted in to the Petri plate and dried in hot air oven forspecific temperature.

Preparation of dilutions for calibration curve- Appropriate aliquots of the stock solutions of the drug was transferred to 10 ml volumetricflasks. The aliquots stock solutions were diluted serially with sufficient amount of Phosphatebuffer (pH 6.8) to obtain the concentration range of 0- 10 µg/ml.

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Determination of λmax -The absorption maxima were determined by scanning 5 µg/ml solutions against the blank onUV-visible spectrophotometer between 200-400 nm ranges.

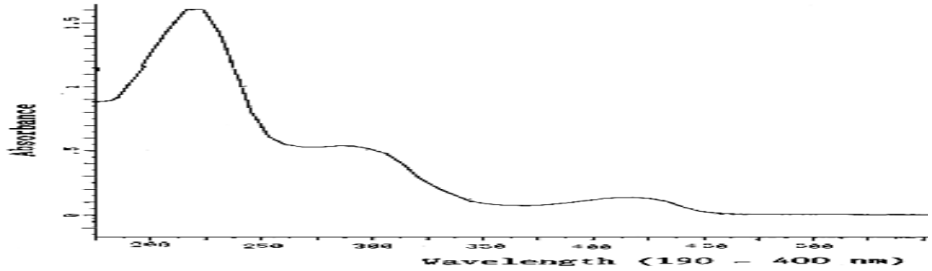

Fig. 2 Standard calibration curve

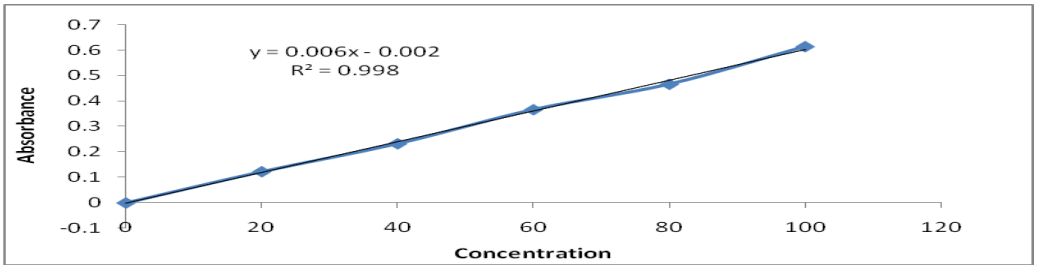

Fig. 3 Drug-excipients compatibility study

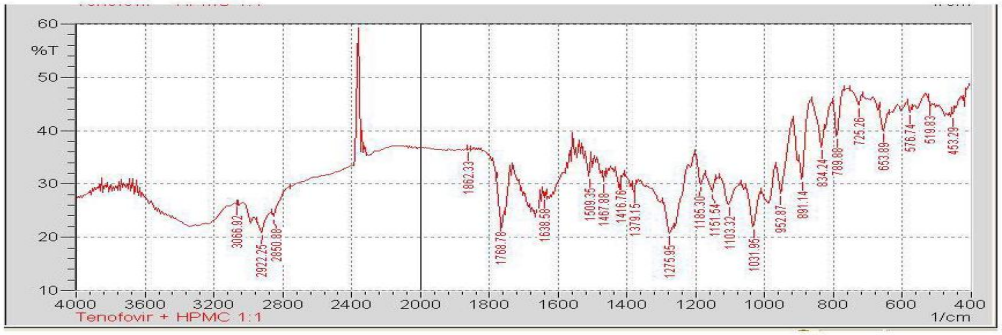

Fig. 4 FTIR spectra of TDF with HPMC E15

Table 2 Preparation of drug free placebo batches

Components (mg)	M11	M12	M13	M14	M15
TDF	100	100	100	100	100
HPMC E15	150	200	250	300	350
Glycerol	100	100	100	100	100
Xanthan gum	*	*	*	20	*
Sorbitol	*	*	20	20	20
Sucrose	*	20	*	*	*
Mannitol	20	*	*	*	*
citric acid	*	*	*	20	10
Sodiumstarchglycolate	2	2	2	2	2
Methyl paraben	1	1	1	1	1
SLS	1	1	1	1	1
Flavor	5	5	5	5	5
Colour	*	*	*	*	*
Water (ml)	20	20	20	20	20

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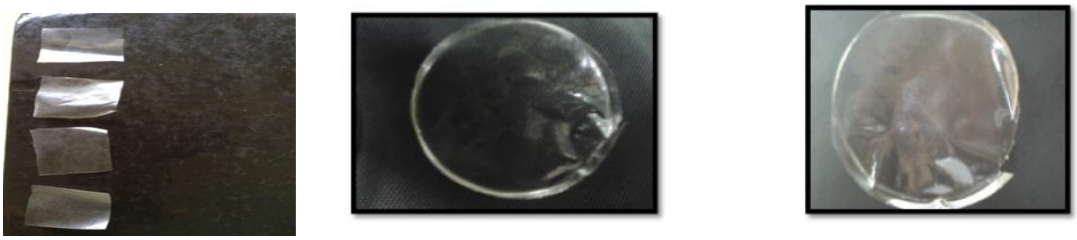

Fig. 5 Placebo of MDF with TDF

VI. EVALUATION OF DRUG LOADED FAST MOUTH DISSOLVING FILM

Weight variation of the film: One square inch strip was cut at five different places in the cast strip. The weight of each stripwas taken on electronic balance (Model no: ATX 224, Shimadzu) and weight variation wascalculated.

Table 3 Weightvariation

SR.NO	Formulation code	Average weight of the 1inch square film in mg			Mean± S.D.*
		TRIAL 01	TRIAL 02	TRIAL 03	
1	M 15	74.46	73.94	74.14	74.18±0.2623

*Standard deviation, n=3

Thickness of the film: Different locations and the mean thickness was calculated. Thickness of the strip is important for thebrittleness of the strip.

Table 4 Thickness of fast mouth dissolving films

SR.NO	Formulation code	Average weight of the 1inch square film in mg			Mean± S.D.*
		TRIAL 01	TRIAL 02	TRIAL 03	
1	M 15	0.125	0.126	0.128	0.1263±0.0011

Measurement of mechanical properties of strip: Tensile testing of fast mouth dissolving film (M15) was conducted using QTS texture analyzer (Brookfield). The film was cut into 3×1 cm strips. The test wasconsidered concluded at the film break. Measurements were done in triplicate for each strip.Three mechanical properties, namely, tensile strength, elastic modulus, and %elongation werecomputed for the evaluation of the film. Tensile strength is the maximum stress applied to apoint at which the film specimen breaks and can be computed from the applied load at ruptures a mean of three measurements and the cross sectional area of fractured film using the following equation

Tensile strength= (Load at failure x 100/ Film thickness x film width) …… (5.2)

Percentage elongation can be obtained by the following equation:

Percent elongation=(L×100/Lo) ……. (5.3)

L0= Initial length of strip

L= Increase in length of film

Table 5 Elongation

SR.NO	Formulation code	Average weight of the 1inch square film in mg			Mean± S.D.*
		TRIAL 01	TRIAL 02	TRIAL 03	
1	M 15	19.66	19.78	19.23	19.55±0.289

Standard deviation, n=3(B)

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Folding endurance: The number of times the strip could be folded at the same place without breaking gives theexact value of folding endurance (a measure of fragility). The folding endurance wasmeasured manually for the prepared films. A strip of 2×2 cm was cut evenly and repeatedlyfolded at the same place till it broke.

Table 6 Folding endurance

SR.NO	Formulation code	Average weight of the 1inch square film in mg			Mean± S.D.*
		TRIAL 01	TRIAL 02	TRIAL 03	
1	M 15	186	172	192	183.3±10.263

*Standard deviation, n=3

Drug content in fast mouth dissolving film: Overall drug incorporated per petriplate was 70.84 mg. drug content of complete films was found to be 97.43%.Considering this content as 100 %, the drug content in M15 was evaluated. As cutting of films was critical parameter, best three results of drug content in M15 was found to be 99.27%.

Table 7 Determination of drug content

SR.NO	Formulation code	Average weight of the 1inch square film in mg			Mean± S.D.*
		TRIAL 01	TRIAL 02	TRIAL 03	
1	M 15	3.76	3.42	3.65	3.61±0.238

*Standard deviation, n=3

Surface pH: The film to be tested was placed in a Petri dish and was moistened with 0.5 ml ofdistilled water and kept for 30 s. The pH was noted after bringing the electrode of thepH meter in contact with the surface of the formulation and allowing equilibration for1 min. The average of three determinations for each formulation was done

Table 8 Surface pH determination

SR.NO	Formulation code	Average weight of the 1inch square film in mg			Mean± S.D.*
		TRIAL 01	TRIAL 02	TRIAL 03	
1	M 15	6.7	6.7	6.5	6.7±0.018

*Standard deviation, n=3

In vitro dissolution studies: The dissolution studies were conducted using different media, such as, simulated salivaconsisting of phosphate buffer saline solution (2.38 gm Na_2HPO_4, 0.19 gm KH_2PO_4, and 8.00gmNaCl per liter of distilled water adjusted with phosphoric acid to pH 6.8). Each filmsample was then submerged into the dissolution media. The dissolution study was carried outusing dissolution apparatus USP type II (Electrolab) at 37°±0.5°C at 50rpm, using 500 ml each of respective dissolution medium. Samples were withdrawn at 15 sec30 sec, 1 -,2-,3-,5-,6-,7-,8-,9-,10-,15-,20-,25- and 30- minutes time intervals, and analyzed using spectrophotometer at 257 nm (UV-VIS double beam spectrophotometer, model no.UV 2700,Shimadzu). After sample withdrawal an equal volume of fresh dissolution mediummaintained at the same temperature was added. The concentration was determined usingstandard calibration curve.

Table 9 In *vitro* dissolution study

Time (min.)	% Drug Release				
	M11	M12	M13	M14	M15
0.15	4.22	6.88	7.98	9.34	10.23
0.3	19.38	18.34	22.05	21.46	34.56
1	38.66	34.53	40.78	43.65	58.12
2	54.45	54.99	51.04	54.51	78.53
3	58.9	61.33	59.53	54.16	85
5	60	62.7	62.5	60.9	87.76
10	62.43	65.34	67.81	69.01	89.12
15	63.5	71.07	75.56	79.39	88.55
30	63	72.14	79.42	84.55	99.58

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In vitro disintegration studies: Disintegration time provided an indication about the disintegration characteristics anddissolution characteristics of the film. For this study, the film as per the dimension (2×2 cm^2) required for dose delivery was placed in 10 ml phosphate buffer. The time required for thefilm to break was noted as *in vitro* disintegration time.

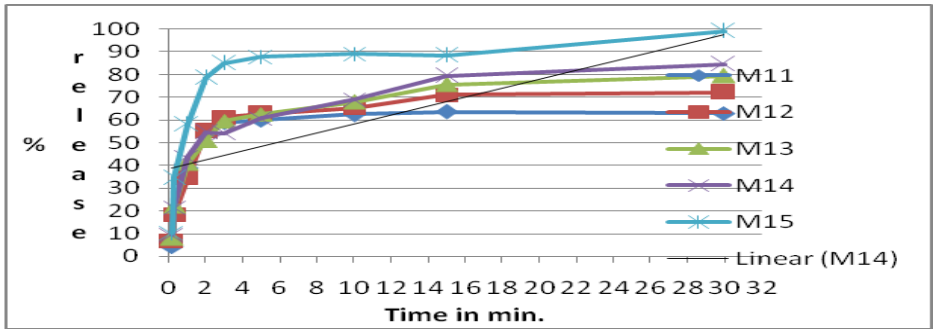

Fig. 6 Drug release profile

In vitro disintegration time:

Table 10 *In vitro* disintegration time

SR.NO	Formulation code	Average weight of the 1inch square film in mg			Mean± S.D.*
		TRIAL 01	TRIAL 02	TRIAL 03	
1	M 15	24	27	28	26.33±2.081

*Standard deviation, n=3

Formulation M15 was found to disintegrate within 35 seconds, which was desirable *in vitro* disintegration time for fast release dosage form.

VII. CONCLUSION

The oral mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first-pass metabolism. Thus, oral mucosa is attractive site for drug delivery. The objective of this research work to explore oral drug delivery route by formulating Fast mouth dissolving film for improved bioavailability and faster onset of action of TDF in chronic hepatitis B. In present study, formulating Fast mouth dissolving film of TDF were successfully developed which offers a suitable and practical approach in serving desired objective of fast disintegration and dissolution characteristics with increased bioavailability by the administration through oral route. Films were formulated using HPMC E15 and PVP K30 as film forming polymer, glycerol and PEG400 as plasticizer. Optimization of polymer and plasticizer was done on the preliminary trials conducted. Preformulation study of drug and excipients was conducted using FTIR spectrophotometer. No drug-excipients interaction was observed. Optimized formulation batch M15 containing 350 mg HPMC E15 polymer, glycerol as plasticizer, sucrose as sweetening agent and other excipients casted on glass petriplate using water as solvent. The batch M15 was evaluated based on parameters like tensile strength, in vitro disintegration time and in vitro dissolution in acceptable range.

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