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FORMULATION AND EVALUATION OF GLIBENCLAMIDE ORAL FAST DISSOLVING FILMS

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ABSTRACT
The ultimate goal of any drug delivery system is the successful delivery of the drug, in which almost 90% of the drugs are administered to the body for the treatment of various disorders and diseases as it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. In this the drug is dissolved or swallowed and then enters into the systemic circulation to produce the desired effect. Despite of astounding advancement in drug delivery the oral route of drug administration is considered as the most important method of administration of drug for systemic effect because of self-medication, ease of administration and avoidance of pain compared to parenteral route. The aim of the present study is to formulate fast dissolving films of glibenclamide using HPMC K_4M, propylene glycol as a plasticizer, tween 80 as a surfactant, peppermint oil as flavouring agent and aspartame as sweetening agent. Glibenclamide solid dispersion of PEG 6000 is dispersed in the polymer solution. Films are prepared by solvent casting method and found to satisfy the mouth dissolving time and other film parameters. 2 x 2 cm of film is required to be placed on to patient tongue. Film instantly gets wet by saliva, rapidly hydrates, adheres to tongue and rapidly disintegrates and dissolves to release the drug for the oro – mucosal absorption or allow for gastrointestinal absorption to be achieved when swallowed. The formulated films exhibited acceptable film endurance. Time required for the film to dissolve and release 26 seconds and 2 minutes respectively. It can be concluded from the study that the oro – flash release film can be a potential novel drug dosage form for poorly water – soluble drugs.

KEY WORDS: Fast dissolving drug delivery, fast dissolving oral films (FDOFs), oral thin film (OTF), oro– flash release films, Glibenclamide, HPMC K_4M, solvent casting oro-mucosal absorption, poorly water soluble drugs.

INTRODUCTION
Oral delivery is the safest most convenient and economical method of the drug delivery having the patient compliance.[1] Fast dissolving drug delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for paediatric and geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms.[2] Thin film drug delivery has emerged as an advanced alternative to the traditional tablet, capsules and liquid dosage forms. These drug delivery systems have advantages like increased bioavailability and to avoid first pass effect.[3] More recently, fast dissolving films are gaining interest as an alternative to fast dissolving tablets. Fast dissolving films disintegrate within 1-2 minutes when placed in mouth without drinking water or chewing.[4]

The mechanism of action of oral films is when they are placed on the patient tongue, films are Instantly wet by saliva due to the presence of hydrophilic polymer and other excipients the film rapidly hydrates and dissolves to release the medication for oral absorption.[5] Oral fast dissolving films are often prepared by solvent casting method and hot melt extrusion method.[4]

Glibenclamide is an oral hypoglycemic agent belonging to the second generation of sulfonylurea's used in the treatment of type II non-insulin-dependent diabetes. Its hypoglycemic effect is due to stimulation of insulin release from pancreatic beta cells and sensitization of the peripheral tissues to insulin. Glibenclamide is highly lipophilic (logP = 4.7) and poorly soluble in aqueous media. According to the Biopharmaceutical Classification Scheme (BCS), Glibenclamide comes under Class II drug, poorly soluble but able to permeate gastrointestinal
mucosa.[6]

MATERIALS AND METHODS

Glibenclamide,HPMC K_4M,HPMC E_{15},HPMC E_{50}, Propyleneglycol, Tween80, Alcohol,Methanol, PEG 4000, PEG 6000, Chloroform, Citric acid, Aspartame, Peppermint oil.

Preparation of fast dissolving films[4]

Polymer was weighed accurately and soaked in distilled water for 24 hours. Soaked polymer was kept for stirring for 1 hour. Drug was weighed accurately and dissolved in specified amount of alcohol. Drug solution along with propylene glycol and tween 80 was added to the polymer solution while stirring. Other ingredients like sweetening agent, saliva stimulating agent, flavouring agents were dissolved in small amount of water and added to the solution. Stirring was continued until bubble free dispersion was obtained. Then the dispersion was poured on to a mould and kept for drying in a hot air oven for overnight at 50^0C. Dried films were cut in desired size and evaluated. The composition of films was mentioned in the **Table 1.**

Table 1: Formula for preparation of films.

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
01.	Glibenclamide (mg)	-	-	-	125	125	125	125	125
02.	HPMC K_4M (mg)	500	-	-	500	500	500	-	-
03.	HPMC E_{15} (mg)	-	500	-	-	-	-	500	500
04.	HPMC E_{50} (mg)	-	-	500	-	-	-	-	-
05.	Alcohol (ml)	-	-	-	20	25	14	20	10
06.	Methanol (ml)	-	-	-	-	-	16	-	10
07.	Tween 80 (mg)	500	500	500	500	500	500	500	500
08.	Propylene glycol (ml)	2	2	2	2	2	2	2	2
09.	Purified water (ml)	20	20	20	20	20	20	20	20

SOLID DISPERSIONS

Preparation of solid dispersions[8]

Drug and carrier (PEG 6000)[9] were taken in the ratio of 1:5. Carrier was dissolved in the alcohol and drug in chloroform. The mixture of the solution was evaporated at 50^0c for 24hrs in hot air oven.

Table 2: Formula for solid dispersions.

S,NO	INGREDIENTS	QUANTITY
01	Glibenclamide (mg)	150
02	PEG 6000 (mg)	750
03	Chloroform (ml)	15
04	Alcohol (ml)	15

For film

The solid dispersions that were prepared was taken and dissolved in alcohol. Film was prepared by means of the solvent casting method.

Table 3: Formula for preparation of films using SDs

S.NO	INGREDIENTS	F9	F10
01	Solid dispersion	Equivalent to 125mg Gb	Equivalent to 125mg Gb
02	HPMC K_4M (mg)	500	-
03	HPMC E_{15} (mg)	-	500
04	Alcohol (ml)	10	10
05	Propylene glycol (ml)	2	2
06	Tween 80 (mg)	500	500
07	Purified water (ml)	20	20

Final Formulation

Various additives were incorporated in the best formulation (F10) of all the trial formulations (F1- F10) and the film was prepared using solvent casting method with following formula.

Table 4: **Formula for final formulation.**

S.NO	INGREDIENTS	F11
01	Solid dispersion	Equivalent to 125mg Gb
02	HPMC K_4M (mg)	500
03	Aspartame (mg)	100
04	Citric acid (mg)	100
05	Alcohol (ml)	10
06	Tween 80 (mg)	500
07	Propylene glycol (ml)	2

08	Peppermint oil (ml)	0.5
09	Purified water (ml)	20

Evaluation of prepared formulations

1. Weight Variation

The film was cut into small pieces (2×2) and its weight was noted. Three trials were performed with each formulation and average was calculated and noted.

2. Thickness

The thickness of a film can be measured by screw gauge at different strategic locations (at least 4 locations). This is essential to determine uniformity n the thickness of the film as this is directly related to the accuracy of dose in the film.

3. Folding endurance test

Folding endurance is determined by repeated folding of the film at the same place till the film breaks. The number of the times of the film is folded without breaking is computed as the folding endurance value.

4. Drug content

The film of area 2x2 cm2 was cut and dissolved in distilled water. Then solvent ethanol and dichloromethane, to make polymer soluble, were added to the mixture and the remaining volume was made up with distilled water to 100ml in 100ml volumetric flask. Then 1ml was withdrawn from the solution and diluted to 10ml.The absorbance of the solution was taken at relevant nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

5. Dissolving time test

To find out actual time required for disintegration of the film, dissolve the prepared film in a suitable buffer and note down the time required to breakdown of the films.

6. *In vitro* Dissolution test

The dissolution studies using three media such as, distilled water, simulated saliva consisting of phosphate buffer (pH 6.8) and simulated gastric fluid (pH 1.2) to ascertain dissolution behaviour of the film.[9]

7. Surface p^H of films

The surface p^H of the films was determined to know the possibility of side effects, in vivo as an acidic or alkaline p^H may cause irritation to the buccal mucosa. It was determined by taking 3 films of each formulation and the films were allowed to swell for 2hrs on the surface of 2% agar plate. The surface was measured by using a p^H paper placed on the surface of the swollen film. A mean of 3 readings were recorded.

8. Stability studies

The stability study of the prepared films was carried out by storing films in an aluminium package for 30days at 40^0C and 75% R.H. The films were observed for physical change (form and colour), dissolving time and drug content.

RESULTS AND DISCUSSION

In this study, an attempt has been made to design, formulate and evaluate the Glibenclamide oral dissolving films by solvent casting method.

Standard calibration of Glibenclamide

Standard calibration curve of glibenclamide in phosphate 7.5 pH buffer was drawn by plotting absorbance v/s concentration. The λ_{max} of Glibenclamide in phosphate buffer was determined to be 282nm as shown in **Fig 1**. The absorbance values were tabulated in **Table 5**. Standard calibration curve of Glibenclamide in the Beer's range between 2-10 µg/ml is shown in **Fig 2.**

Table 5: Calibration Table

Conc (µg/ml)	Absorbance
0	**0**
2	0.199
4	0.398
6	0.597
8	0.753
10	0.988

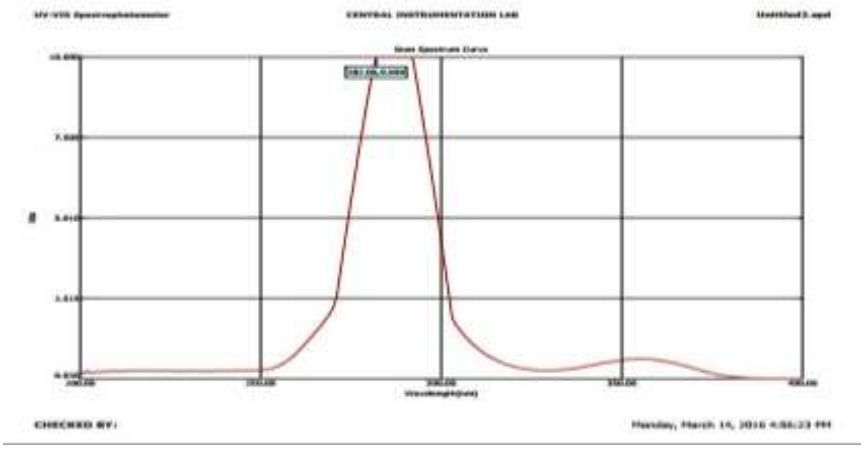

Fig 1: Spectrum

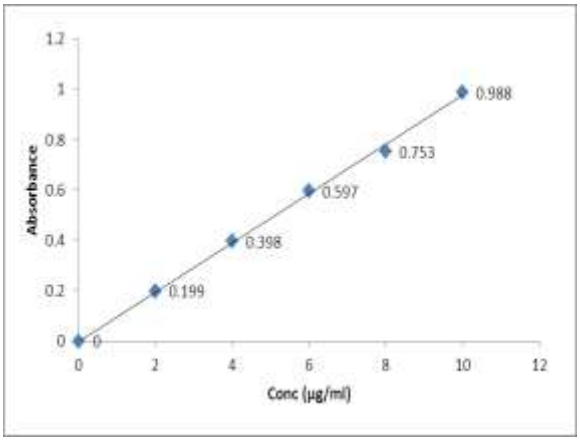

Fig 2: Standard Calibration Curve of Glibenclamide in pH 7.5 phosphate buffer

Solubility Studies

The absorbance of the solutions were measured and the solubility was calculated and was found to be

- In water – 0.3711 µg/ml.
- In pH 1.2 buffer – 0.432 µg/ml.
- In pH 6.8 phosphate buffer – 1.9587 µg/ml.

Drug –Excipient Compatibility Study

Drug – excipient compatibility study was carried out using FTIR. The spectra of the pure drug, the physical mixture containing polymer and final film were taken, the FTIR spectra were as below.

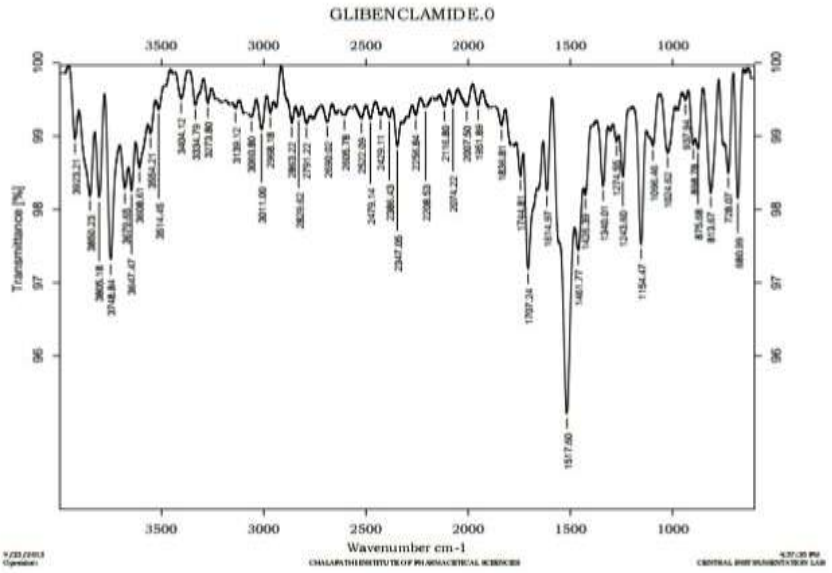

Fig 3: FTIR spectrum of pure Glibenclamide

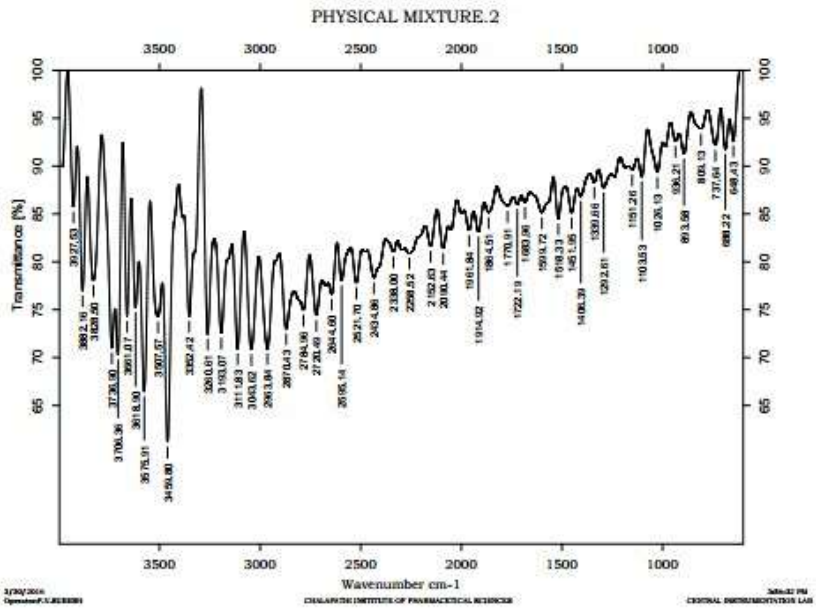

Fig 4: FTIR spectrum of physical mixture.

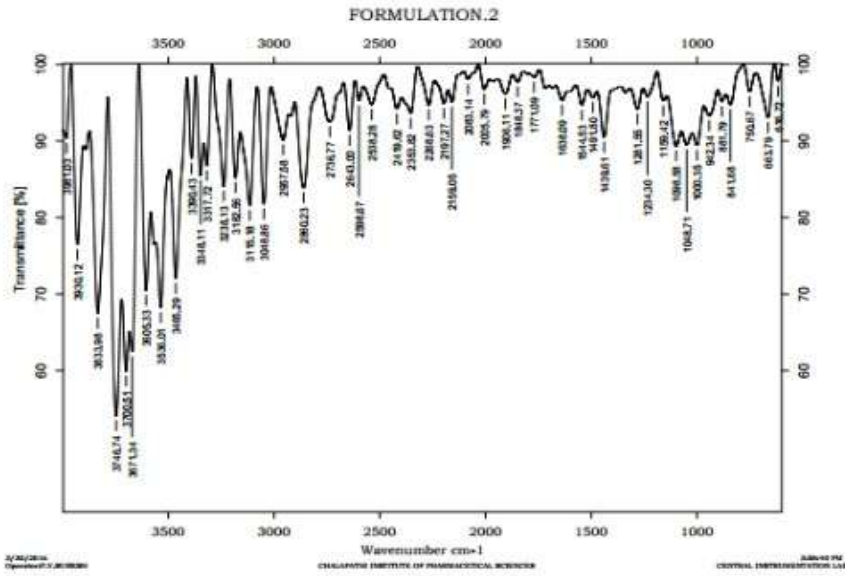

Fig 5: FTIR spectrum of final film.

Selection of polymer

Based on the literature review and availability of polymers, we have formulated blank films using three different polymers namely HPMC K_4M, HPMC E_{50} and HPMC E_{15} . Of all the three polymers film forming capacity, was found to be satisfactory with HPMC K_4M and HPMC E_{15}.

Glibenclamide solid dispersion preparation

Though the films were elegant, poor solubility of drug was observed during preparation and the drug was found to get precipitated state in the film as shown in the **fig 6.** Hence solid dispersions were prepared to enhance the solubility so that an elegant film can be prepared.

Fig 6: Film with drug in precipitated form Selection of carrier

PEG 6000 and PEG 4000 were used as carriers and solid dispersions were prepared by solvent evaporation method, and better solubility was observed with PEG 6000 and hence it was selected.

Selection of best formulation

Using solid dispersions, films were casted using the best two polymers and the film with HPMC K_4M showed good drug release. Of all the 10 formulations, F10 was considered as best one based on various evaluation tests and *in vitro* drug dissolution studies.

Fig 7: Best formulation(F10)

Evaluation of formulations

1. Weight variation

Films were cut into pieces, their weights were measured and average weight with standard deviation were calculated and given in the following **Table 6.**

Table 6: **Weight variation test results**

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
W1(mg)	10.6	9.7	10.3	44.5	60.3	70.9	75.6	50.7	19.3	8.2	10.6
W2(mg)	10.4	9.3	10.5	50.6	55.4	75.5	69.7	54.3	22.4	10.3	9.8
W3(mg)	9.8	9.4	10.2	48.7	50.2	68.4	72.8	53.5	25.3	9.5	9.1
Avg(mg)	10.2	9.4	10.3	47.93	55.3	71.6	72.7	52.83	22.33	9.33	9.83
S.d	0.416	0.2082	0.1527	3.1214	5.05	3.6	2.95	1.89	3.005	1.0598	0.7505

2. Thickness

The thickness of the film was measured using screw gauze and the average thickness of the film was given in the table 7 below.

Table 7: Thickness results

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
T1(mm)	0.9	0.7	0.6	0.6	0.6	0.8	0.8	1	0.8	0.7	0.5
T2(mm)	0.9	0.8	0.6	0.6	0.7	0.8	0.7	0.9	0.7	0.7	0.5
T3(mm)	0.8	0.7	0.6	0.7	0.6	0.8	0.7	0.9	0.8	0.6	0.5
T4(mm)	0.9	0.7	0.5	0.6	0.7	0.7	0.8	0.9	0.8	0.7	0.5
Avg(mm)	0.875	0.725	0.575	0.625	0.675	0.775	0.75	0.925	0.775	0.675	0.5
S.D	0.05	0.05	0.05	0.05	0.0577	0.05	0.0577	0.05	0.05	0.05	0

3. Folding endurance test

Folding endurance of the film was determined by repeatedly folding a small strip of the film at the place till it broke and the folding endurance was found to be about 258±10.675. Almost all the films showed the same folding endurance values.

4. Drug content uniformity

Glibenclamide oral dissolving films were prepared with the aim to have a uniform dispersion of the drug throughout the film. In each case three 2×2 films were cut and average drug content was calculated. The drug dispersed in the range of 95.15±1.143 to 99.02±1.355 suggesting that the drug was uniformly dispersed throughout the film.

5. Dissolving time test

Dissolving time was noted for all the films and for the final film it was found to be 26sec.

6. *In-vitro* Dissolution test

The main aim of formulating oral dissolving films was to attain fast dissolution of the drug (i.e. in about 5 minutes). The required dissolution profile of the prepared films was obtained as the prepared Glibenclamide films showed complete drug release within 5minutes. The dissolution profile of Glibenclamide oral dissolving films was compared to that of marketed Glibenclamide tablets.

Table 8: %Drug release comparison between films

Time (sec)	F4	F5	F6	F7	F8
0	0	0	0	0	0
120	156.6	113.6	93.3	36.4	88.1
240	167.2	123	126.4	42.9	112.6
360	178.5	144.9	129.2	72.7	131.2
480	185.2	152.5	124.9	77.2	142.1
600	183.5	148.3	124.1	70.1	139.4
900	182	147.2	119.5	68.5	137.5
1800	180.2	146.2	119.1	65.1	136.6

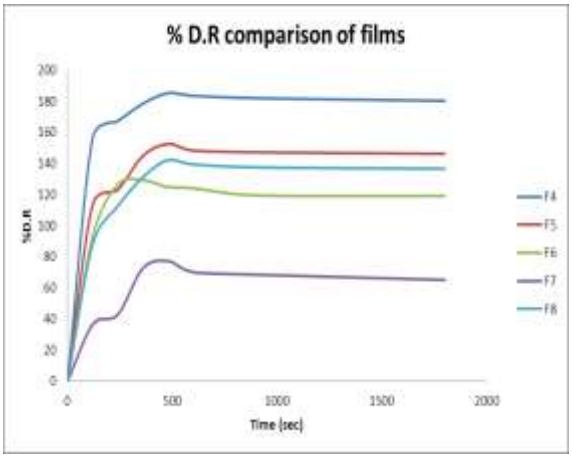

Fig 8: %Drug release comparison between films

Table 9: % Drug release comparison of films with solid dispersions

Time (sec)	F9	F10
0	0	0
120	84.8	98.7
240	92.9	98.5
360	91.7	94.4
480	89.8	93.2
600	88.5	90.2
900	87.6	89.8
1800	86.8	89.6

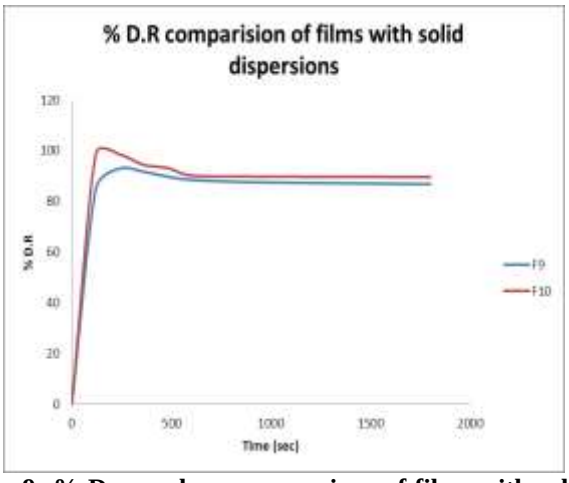

Fig 9: % Drug release comparison of films with solid dispersions

By all the above results, F10 formulation showed good dissolution and was considered as best formulations.

The dissolution profile of formulation F10 is as follows

Table 10: Drug dissolution profile of F10

Time(sec)	Absorbance	Conc(µg/ml)	Amt(mg)	% D.R	% D.U	log %D.R	log %D.U
120	0.532	5.4845	4.936	98.7	1.3	1.994	0.114
240	0.531	5.4742	4.9268	98.5	1.5	1.98	0.176
360	0.509	5.2474	4.7227	94.4	5.6	1.975	0.748
480	0.502	5.1752	4.6577	93.2	6.8	1.969	0.832
600	0.486	5.0103	4.5093	90.2	9.8	1.955	0.991
900	0.484	4.9897	4.4907	89.8	10.2	1.953	1.009
1800	0.483	4.9794	4.4815	89.6	10.4	1.952	1.017

The drug release was compared with that of a marketed formulation- GLINIL (Glibenclamide tablet – 5mg) and the results were as shown in table 11.

Table 11: % Drug release comparison between film and tablet

Time (sec)	tablet	film
0	0	0
300	20.9	97.9
600	38.2	88.3
900	42.9	88.1
1200	60.3	88
1800	77.4	87.03
2700	84.6	
3600	97.2	

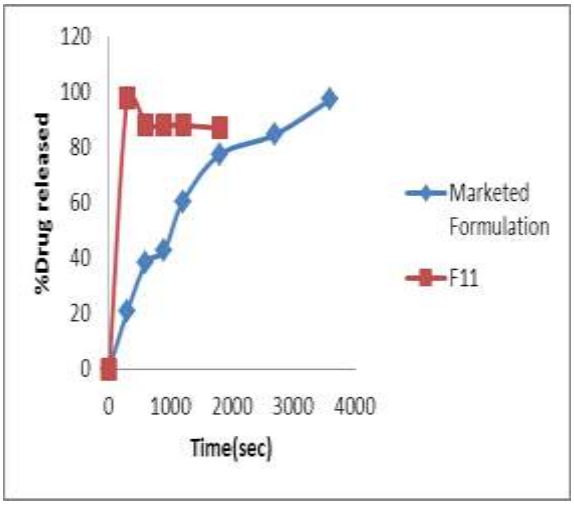

Fig 10: % Drug release comparison between film and tablet

7. Surface pH of the films

pH of the film was measured and was found to be in between 6.2- 6.8 for all the formulations.

8. Stability Studies

Fast dissolving films of Glibenclamide were found to be physically and chemically stable as they shown no significant change in terms of physical characteristics (no discoloration and no change in shape), dissolving time and drug content under the kept storage conditions.

CONCLUSION

The oral mucosa is vascularized drugs can be absorbed directly and can enter the systemic circulation without first pass metabolism. This advantage can be used in preparing products with increased oral bioavailability of molecules that undergo first pass metabolism. Thus oral mucosa is an attractive site for drug delivery. The objective of this research work is to formulate mouth dissolving film of glibenclamide for enhanced bioavailability. In the present investigation, an attempt was made to develop mouth dissolving films of glibenclamide to achieve fast disintegration and dissolution characteristics with improved bioavailability by oral route. Drug and excipients studies were conducted using FTIR. Oral films of glibenclamide were formulated using HPMC E_{50}, HPMC K_4M, HPMC E_{15}as a film forming agent and propylene glycol as plasticizer. The solvent casting method was used for the preparation of films. As the drug solubility was found to be limited solid dispersions were prepared using PEG 6000 as hydrophilic carrier by solvent evaporation method. Glibenclamide solid dispersions loaded oral film was evaluated for folding endurance, thickness, weight variation test, surface pH, content uniformity, dissolving time, &*in vitro* dissolution. No drug–excipients interaction was observed. The characterization studies depict the purity of drug & all the excipients used in the formulation. The IR spectrum of mixture of glibenclamide with all other excipients does not show any changes which indicate its compatibility with other excipients.

From the results, it can be concluded that the fast dissolving oral film of glibenclamide showed fast disintegration dissolution of drugs in salivary pH. Thus the prepared fast dissolving films of glibenclamide could be a better alternative for achieving rapid oral bioavailability.

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REFERENCES

1. A. Deepthi, B. Venkateswara Reddy, and K. Navaneetha. Formulation and evaluation of fast dissolving oral films of zolmitriptan. AJADD, 2014; 2(2): 153-163.
2. Kapoor D1, Vyas RB1, Lad C1, Patel M1, Tyagi BL2Frabrication and characterization of oral thin films of leukotriene receptor antagonist (LTRA).Journal of Drug Delivery & Therapeutics, 2015; 5(2):77-82.
3. Aggarwaljyothi, Jindal khesav, Singh grupreet. Formulation and evaluation of oral fast dissolving films of Granisetron hydrochloride using different polymers. IRJP, 2015; 6(10): 724-728.
4. M.Sreekanth, Md. Gulshan, Eswar M. Gupta and N. Rama Rao. Design and evaluation of oro-flash release films of Amlodipine Besylate. IJPSR, 2014; 5(6): 2428-2435.
5. NGN Swamy and S Shiva kumar. Fomulation and evaluation of fast dissolving oral films of Palonosetron hydrochloride using HPMC E5. IJPCS. 2014; 3(1): 145-150.
6. Suresh D. Kumavat, Yogesh Chaudhari, Pallavi Duvvuri, Jigar Desaiand Franklin Quadras. Preparation and characterization of glibenclamide-plasdone S630 solid dispersion by spray drying technique. Der Pharmacia Lettre, 2013; 5 (4):310-319.
7. Mogal S. A, Gurjar P. N, Yamgar D. Sand Kamod A.C. Solid dispersion technique for improving solubility of some poorly soluble drugs. Der Pharmacia Lettre, 2012; 4 (5): 1574-1586.
8. Prasanna Kumar Desu, B. Brahmaiah, A. Nagalakshmi, K. Neelima, Sreekanth Nama, Chandu Baburao. An overview on rapid dissolving films. Asian J. Pharm. Res. 2013; 3(1):15-23.
9. Md. Gulshan, S. Subhashini, M. Prathyusha, N. Rama Rao. Dissolution rate enhancement of Ritonavir by solid dispersion technique. Indo American Joutnal of Pharm Research, 2014; 4(4): 2019-2026.