FORMULATION AND INVITRO EVALUATION OF LAMOTRIGINE ORAL THIN FILMS

Dr M.Vishwaja
Associate professor
Department of pharmaceutics and industrial pharmacy
Vijaya college of pharmacy
Contact no: 9642060818
Email is : vishureddy24@gmail.com

Dr. J. Prasanna Kumari,
Associate Professor,
Department of lndustrial Pharmacy and Pharmaceutics,
Vijaya College of Pharmacy, Hyderabad
9885890332
prasu_jsuns@yahoo.com

Abstract

Oral course is the most favored course for the conveyance of the medications till date as it bears different focal points over the other course of medication organization, however oral medication conveyance frameworks still need a few headways to be made in light of their a few disadvantages identified with specific class of patients which incorporates geriatric, pediatric and dysphagic patients related with numerous restorative conditions as they experience issues in gulping or biting strong dose shapes. Indeed, even with quick dissolving tablets there is a dread of gagging because of its tablet write appearance. Among different variables, satisfactoriness of details of pediatric oral medicines is a standout amongst the most noteworthy elements impacting consistence to restorative regimens.

Introduction

Albeit strong measurement shapes are broadly acknowledged by seniors and teenagers, more youthful kids have a tendency to incline toward fluid definitions that are less demanding to swallow[3]. A few novel advances for oral conveyance have as of late turned out to be accessible to address the physicochemical and pharmacokinetic qualities of medications, while enhancing quiet consistence. Electrostatic medication affidavit and coating[4], and PC helped three-dimensionalprinting (3DP) tablet make have likewise as of late progressed toward becoming available.

Innovative work in the oral medication conveyance section has prompted change of measurement frames from basic regular tablets or cases to altered discharge tablets or containers to oral crumbling tablet (ODT) to wafer to the current improvement of oral quick dissolving films (OFDFs). Among the plenty of roads investigated for the fast medication discharging items, oral strip innovation is increasing much attention[7]. (ODFT) was at that point well known among the general population in the mid 2000 year with the presentation and far reaching utilization of Listerine take strips, another dispatch in the mouthwash run. Innovation Catalysts figures the market for medicate items in oral thin film details to be esteemed at $500 million of every 2007 and could reach $2 billion in close future[8]. However just a couple of items comprising unpleasant particles have possessed the capacity to be popularized in light of the multifaceted nature related with the ODT.

Countless can be detailed as mouth dissolving films. Creative items may build the remedial
conceivable outcomes in the accompanying signs.

- Pediatrics (Antitussives, Expectorants, Antiasthamatics)
- Geriatrics (Antiepileptic, Expectorants)
- Gastrointestinal infections
- Nausea (because of Cytostatic treatment)
- Pain (Migraine)
- CNS (Antiparkinsonism treatment)

Salient Features of Fast Dissolving Oral Film

- Ease of organization for patients who are rationally badly incapacitated and uncooperative.

• Requires no water; have brisk crumbling and disintegration of the dose frame.
• Leaves negligible or no deposit in the mouth after organization.
• No danger of gagging.
• Provide points of interest of fluid solution as strong readiness.
• Amenable and versatile to existing preparing and bundling machinery.

Overview Of Oral Cavity

Medication conveyance by means of the oral mucosa is a promising course, when one wishes to accomplish a fast beginning of activity or enhanced bioavailability for drugs with high first-pass digestion. Along these lines, there is a developing enthusiasm for creating elective measurement frames, i.e. quick dissolving oral movie, which enables a quickly dissolving medication to assimilate specifically into the fundamental flow through the oral mucosa. These sorts of measurements frames are likewise advantageous forchildren, elderly patients with gulping troubles, and without consumable fluids. Be that as it may, notwithstanding detailing contemplations, the properties of the dynamic compound must be suitable keeping in mind the end goal to accomplish tranquilize conveyance into foundational course after intraoral organization. The oral mucosa is made out of a furthest layer of stratified squamous epithelium beneath this lies a storm cellar film, a lamina propria took after by the submucosa as the deepest layer.

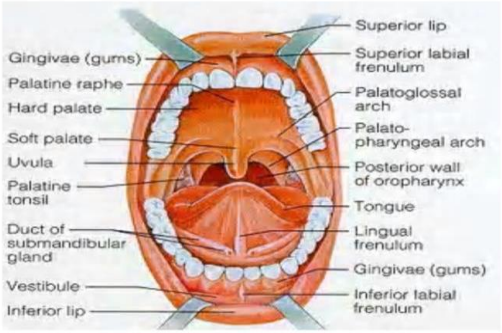


Fig 1: Anatomy of oral cavity

The advantages of OTFs

For patients:

• safe, reliable, precise and pain-free application
• discreet and easy application
• can be taken without extra water
• ideal for when patients are on the go
• easier to treat children, as well as older patients and patients requiring complex care
• ideal for patients who have difficulty swallowing

Clinical Advantages:

• Improved oral ingestion
• Improved bioavailability because of less measure of corruption of medication.

Restorative Advantages:

• Overcomes inadmissible taste of medications by veiling unpleasant taste of medications with tastemasking specialists.

STABILITY STUDIES

The stability studies of the optimized batch F5 was carried out at 40°C/75%RH, 25°C/60%RH and 25°C/40%RH. These films were found to be unacceptable. Films stored at 40°C/75%RH were highly unstable within 1 month storage. Films stored at 25°C/60%RH were unstable after 2 months period by developing color change (slight yellow) and becoming sticky in appearance. Films stored at 25°C/40%RH were found to be stable for 3 months. The batch was found be acceptable visually, mechanically, with slight change in in-vitro disintegration time 30sec. The above observations

indicate that temperature and humidity plays a critical role in the stability of the rapidly dissolving films containing HPMC as the film forming polymer. Therefore, precautions would be required during packaging and selection of packaging container would play a crucial role for stability of the Oral thin films.

Folding endurance of the films:

The folding endurance was measured manually .A strip of film 4squre cm was cut and subjected for the folding endurance studies until it broke at the same place. Folding endurance increases with increase in polymer concentration. The no of times the film fold until it broke was reported in below table.

Formulation of oral thin films

Oral thin films containing Sumatriptan were prepared by casting method. The films of HPMC, CMC and PVA (low viscosity) were prepared with an objective to dissolve the film in the mouth. 4 and 5 % w/v each of HPMC, CMC and PVA films were exhibited desired mouth dissolving time and other film parameters, compared to 2 and 3 % w/v of HPMC, CMC and PVA films which were difficult to remove and having low strength and exhibited unacceptable mouth dissolving time. Hence 4 and 5 % w/v of HPMC, CMC and PVA films were used for the study. Propylene glycol (20 % w/w of polymer) was used as plasticizer and to enhance the tensile strength of film.2 % cross carmellose sodium is used as disintegrant to dissolve the films rapidly when comes in contact with saliva. 1 % w/w Sodium saccharine was used as a sweetener and 1 % w/w of aspartame was used as flavoring agent.

Review of Literature

Bibaswan Mishra, Prasanna Dixit, Prasanta kumar Biswal [7] FORMULATION DEVELOPMENT AND EVALUATION OF TASTE MASKED RAPIDLY DISSOLVING FILMS OF LAMOTRIGINE Rapidly dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages. An effort was made to formulate a rapid dissolving films containing lamotrigine using different viscosity grade of HPMC. The prepared films can be used in the treatment of epilepsy and bipolar disorder with a view to improve the onset of action, therapeutic efficacy, patient compliance and convenience. The effect of various viscosities of HPMC alone and in blend on various properties of film was investigated. Solvent casting method was used for the preparation of film. Prepared films were typically evaluated for its physical and mechanical properties, drug content, content uniformity, disintegration time, and in vitro dissolution. The drug-excipient compatibility study was performed using FTIR. Result of the evaluation study revealed that all the formulation showed reproducible quality. Hence lamotrigine can be safely incorporated into the film and used as antiepileptic whenever quick on set of action is desired. ejpmr, 2017,4(1), 447-451

Ali MS, Vijendar C, Sudheer Kumar D and Krishnaveni J* (2016) [8]Formulation and Evaluation of Fast Dissolving Oral Films of Diazepam Oral films dissolve rapidly along with drug in mouth and majority of the drug is absorbed through buccal/oral mucosa in to systemic circulation avoiding first pass metabolism. The aim of present investigation was to formulate the Fast dissolving oral films (FDOF) of Diazepam an anti epileptic drug which is normally administered by intramuscular route or as rectal suppository in acute conditions of seizure emergencies. Oral films were prepared by solvent casting method using HPMC E3, E5, and E15 as a film formers and propylene glycol, PEG 400 as plasticizers and evaluated for mechanical properties,

disintegration and in vitro dissolution. All formulations showed good mechanical properties and in vitro drug release. The optimized (F4A) Formulation (HPMC E5 and PEG 400) Exhibited drug release of 99.89% in 15 minutes which was significantly high when compared to marketed tablet valium (68.81%). J Pharmacovigilance 4:210.

S. Aruna Jyothi*, P. Mounika, S. Vineesha, Suraiya Mehdia and N. Arun Dutt[9] FORMULATION DEVELOPMENT AND EVALUATION OF ORAL THIN FILMS- DIPHEN HYDRAMINE HCl The aim of this study was to develop a fast releasing oral polymeric thin film, prepared by solvent casting method, with good mechanical properties, instant disintegration and dissolution. Diphenhydramine hydrochloride, an antihistamine drug belonging to BCS class I was used for oral thin film preparation. The formulations from the preliminary trial were analyzed which was applied to optimize the type of polymers (Gelatin and HPMC E15), concentration of polymers, plasticizer (Glycerol, Propylene Glycol, PEG 400), surfactant (TWEEN 80) and sweetener (Mannitol).The resultant films were evaluated for thickness, folding endurance, drug content, Surface pH, in vitro disintegration time, in vitro dissolution studies .Oral thin films which were prepared with surfactant showed better results i.e., good disintegrating and dissolution properties than without surfactant. The optimized film disintegrated in less than 30s, releasing more than 90% of drug within 90sec. Int J Pharm Sci Res 2013: 4(9); 3484-3488

AIM AND OBJECTIVES

Aim

- The present investigation is to prepare and evaluate the quick discharging oral films taking Lamotrigine as a model medication.
- At introduce Lamotrigine is accessible as tablets in the market. Patients are not ready to coperate with these measurement films. Subsequently quick discharging oral films have twisted into an essential device to improve the patient consistence.

Objectives

- To detail Fast Dissolving film containing Lamotrigine
- To evaluate Weight variations. To perform the Pre-definition investigations of Lamotrigine
- Tensile quality, Thickness of film, Disintegration time, folding perseverance, Content consistency and In vitro disintegration thinks about.
- To play out the strength thinks about for the upgraded detailing.

METHODOLOGY

PREFORMULATION STUDIES

Preformulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Pre-formulation studies were carried out to serve following purposes:
i) To Finalize specifications of active pharmaceutical ingredients (API)
ii) To Study the compatibility between active and inactive ingredient
iii) Characterization of reference product

Preformulation study can be divided in to two Subclasses.
1. API characterization,
2. Compatibility study

Active pharmaceutical ingredient (API) characterization:-

Organoleptic Evaluation:-These are preliminary characteristics of any substance
which is useful in identification of specific material. Following physical properties of API were studied.

Dose calculations
Diameter of the plate = 6 cm
Area of the plate = 28.6 cm2
No. of 2.25 cm^2 films present in whole plate = 28.6/2.25 = 12.7
Each film contains 25 mg of drug
12.7 no. of films contains mg of drug ? = 12.7x5= 317.5 mg

Preparation of Oral thin film[39]:
Film was prepared by using specified polymer by solvent casting method. The specified amount of polymer was weighed and dissolved in specified amount of water for overnight to get a uniform dispersion of 4 % and 5 % (w/v) solution respectively. Drug, cross carmellose sodium, aspartame, citric acid were dissolved in specific amount of water in a beaker. The drug solution was added to the polymer solution and mixed using magnetic stirrer for 1 hour. The resulting solution was degassed so as to remove any bubbles formed. The bubble free solution was casted on to a petri dish of surface area 28.6 cm2. It was dried for 24 hours at room temperature. The film was removed from the petri dish very carefully and observed for any imperfections. Film that was clear and bubble free was selected for further studies. Film of area 2.25 cm2 (1.25 X 1.25) was cut and stored in a butter paper coved with aluminum foil and stored in a desiccator.

Data Analysis[42]
To break down the component of the medication discharge energy of the dose shape, the
information got were fitted to different motor conditions of zero request, first request,
Higuchi model and Korsmeyer - peppas demonstrate and plotted as:
1. Cumulative percent sedate discharged Vstime(Zero request plots)
2. Log aggregate percent sedate residual Vstime(First arrange plots)
3. Cumulative percent sedate discharge Vs square base of time(Higuchi plots)
4. log combined percent sedate discharge Vs log time(Korsmeyer-Peppas Plots)

Zero Order Kinetics
Medication disintegration from dose shapes that don't disaggregate and discharge the
medication gradually can be spoken to by the condition:
$Q0 - Qt = K0t$
Where, Qt is the measure of medication broke down in time t,
Q0 is the underlying measure of medication in the solution(most times,Q0=0)
K0 is the zero request discharge consistent communicated in units of fixation/time.
At the point when the information is plotted as aggregate percent medicate discharge
versus time, if the plot is straight then the information obeys zero-arrange discharge energy, with slant equivalent to K0.
Initially arrange energy
The arrival of the medication which took after first request energy can be communicated
by the condition:
$\log C = \log C0 - Kt/2.303$
Where, C0 is the underlying convergence of medication,
k is the primary request rate steady
t is the time.
The information acquired are plotted as log combined level of medication remaining versus time which would yield a straight line with a slant of - K/2.303.

Higuchi show
The arrival of the medication which takes after higuchi energy can be communicated by
the condition:

Q = KH*t1/2
Where, KH is the Higuchi disintegration consistent
Q is the measure of medication discharged in time t
The information acquired were plotted as combined rate sedate discharge versus square
foundation of time.
Korsmeyer-Peppas display
To discover the component of medication discharge, tranquilize discharge information
were fitted in Korsmeyer-Peppas condition which is communicated as:
Q/Q0 = k tn
Q/Q0 was division of medication discharged at time t,
K was steady and n was dispersion consistent that shows general working discharge
component. For Fickian (dissemination controlled) n ≤0.5;
for non Fickian (peculiar/zero request) discharge 'n' esteem is in the middle of 0.5 to 1.0;
for zero request discharge n=1.0; for super case transport II, n >1.0.
To ponder the discharge energy, information got from in vitro medicate discharge thinks
about were plotted as log aggregate rate tranquilize discharge versus log time.

RESULTS AND DISCUSSION

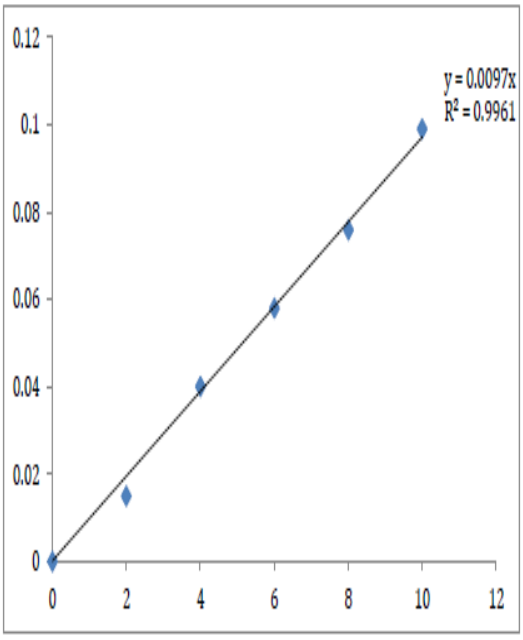
Preformulation studies

The following preformulation studies were performed for Sumatriptan
Solubility: slightly soluble in water.
Determination of pH
Sumatriptan 4% W/V solution in water showed pH around 7
Melting point
Melting point of the Sumatriptan was found to be 170.2^{0}C
Analytical methods:

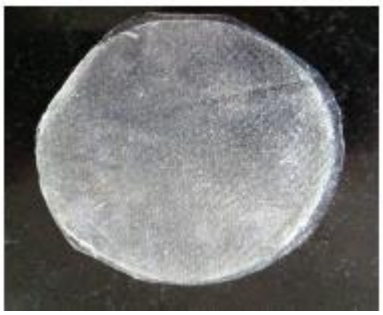
Standard Stock solution: 100 mg of Sumatriptan was dissolved in 100 ml of 6.8
phosphate buffer (1000 µg/ml).
Calibration curve of Sumatriptan in 6.8 phosphate buffer:
From the standard stock solution (1000 µg/ml), appropriate aliquot were
transferred to series of 10 ml volumetric flasks and made upto 10 ml with buffer
so as to get concentration of 2, 4, 6, 8, 10 µg/ml. the absorbance of the solution
were measured at 282 nm. This procedure was performed in triplicate to validate calibration curve. A calibration curve was plotted.
calibration curve plot

S.No	Concentration in µg/ml	Absorbance
1	0	0
2	2	0.015
3	4	0.040
4	6	0.058
5	8	0.076
6	10	0.099

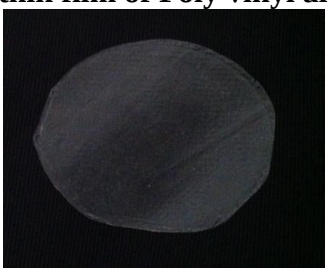
Calibration curve plot of Sumatriptan in 6.8 phosphate buffer



Oral thin film of Carboxy methyl cellulose



Oral thin film of Poly vinyl alcohol

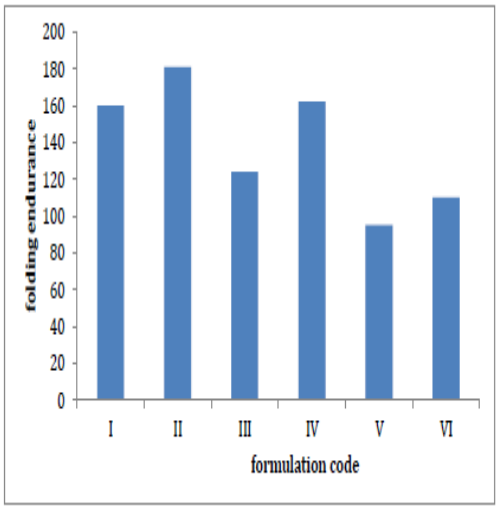


Comparative evaluation of folding endurance of oral thin films

S.NO	Formulation code	Folding endurance (no of folds)			Mean±SD*
		Trial 1	Trial 2	Trial 3	
1	I	160	158	163	160 ± 2.15
2	II	178	185	180	181 ± 3.60
3	III	115	128	130	124 ± 8.14
4	IV	150	168	170	162 ± 11.01
5	V	90	93	102	95 ± 6.25
6	VI	110	105	117	110 ± 6.02

*Standard deviation, n =3

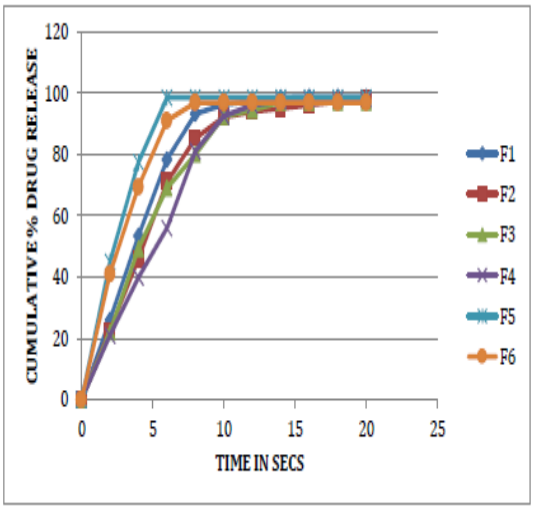
Folding endurance of oral thin films



Comparative evaluation of *Invitro* dissolution profiles of oral thin Films

SNO	Time in min	Cumulative % of drug release					
		FI	FII	FIII	FIV	FV	FVI
1	2	26 %	22.6%	22%	21%	45%	41%
2	4	53.3%	45.9%	49.3%	39.8%	77.3%	69.3%
3	6	78.3%	71%	69%	56%	98.5%	90.9%
4	8	93.2%	85.3%	80%	81%	98.5%	96.8%
5	10	96.3%	92%	92.4%	92.4%	98.5%	96.8%
6	12	97.3%	93.9%	94.5%	96%	98.5%	96.8%
7	14	98.4%	94.9%	97%	97.3%	98.5%	96.8%
8	16	98.6%	96.1%	97%	98%	98.5%	96.8%
9	18	98.6%	97.2%	97%	98%	98.5%	96.8%
10	20	98.6%	98	97%	98%	98.5%	96.8%

Dissolution profile of Oral thin films



Stability studies of the optimized batch F5 stored at 25°C/40%RH.

S No	TIME	APPEARANCE	IN VITRO DISINTEGRATION TIME	% CDR
1	Initial	Transparent and acceptable	33.33 ± 3.05	98.5
2	1 month	Transparent and acceptable	32.05± 2.85	98
3	3 months	Transparent and acceptable	30± 2.0	97.6

SUMMARY AND CONCLUSION

The primary target of the examination was to detail and assess oral quick dissolving film containing Lamotrigine. Compatibility of model drug Lamotrigine with polymers was affirmed by FT-IR spectroscopy. Total eight films were prepared and assessed for weight variation and thickness of the film indicated acceptable observations. Folding endurance of the films can be interpretated as increasing in the concentration of the polymer increased the flexibility and versatility of the film. Time taken to dissolving the film increased with increase in concentration of the polymer. The grouping of the polymer increases the wetting time of the film thus delaying the release. So it is necessary that the optimum amount of the polymer is used. The concentration of super disintegrant used in the film has direct impact on breaking of the film thus releasing the drug entrapped in the polymeric pockets of the film. Exhibiting examine that all the 8 formulated films indicated attractive film parameters. It can be reasoned that, Oral quick dissolving film-containing Lamotrigine can be set up by dissolvable throwing strategy. 4% w/v of CMC and 1% CCS (FV) film showed required collapsing perseverance and breaking down time. The medication discharge was around 98.7 % in 15min. The quickened security investigations of the improved FV definition demonstrates that the detailed oral quick dissolving films were unaffected following 3 months stockpiling under quickened conditions as there were no indications of outwardly recognizable changes in appearance, breaking down time and aggregate level of medication discharge. From the present examination it can be presumed that oral quick dissolving film definition can be a potential novel medication measurement frame for pediatric, geriatric and furthermore for all inclusive community.

References

1. *Chien Yie W., Transdermal Therapeutic systems, Conrolled Drug Delivery: Fundamentals & Applications. Robinson Joseph R, Lee Vincent HL. Eds, New York: Marcel Dekker (1987), 523.*
2. ***https://www.drugbank.ca/drugs/DB00555***
3. *R.T. Guest, Dibutyl phthalate, in: R.C. Rowe, P.J. Sheskey, S.C. Owen (Eds.), Handbook of Pharmaceutical Excipients, Pharmaceutical press, London, 2006, pp. 234–235.*

4. *Chien Yie W. In Transdermal Drug Delivery & Delivery Systems, Novel drug Delivery Systems. Eds, New York: Marcel Dekker (1992), 301.*
5. ***Bibaswan Mishra**, **Prasanna Dixit**, **Prasanta kumar Biswal** FORMULATION DEVELOPMENT AND EVALUATION OF TASTE MASKED RAPIDLY DISSOLVING FILMS OF LAMOTRIGINE. ejpmr, 2017,4(1), 447-451*
6. ***Ali MS, Vijendar C, Sudheer Kumar D and Krishnaveni J*** *(2016) Formulation and Evaluation of Fast Dissolving Oral Films of Diazepam Oral films. J Pharmacovigilance 4:210.*
7. *S. Aruna Jyothi*, P. Mounika, S. Vineesha, Suraiya Mehdia and N. Arun Dutt FORMULATION DEVELOPMENT AND EVALUATION OF ORAL THIN FILMS- DIPHEN HYDRAMINE HCL Int J Pharm Sci Res 2013: 4(9); 3484- 3488.*