Formulation and Evaluation Fast Dissolving Oral Film of Imipramine

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Abstract:- A preformulation study of Imipramine drug powder was performed. The result was found as below: - Imipramine drug powder was found to be White to off-white powder, all most odorless with bitter in taste. The solubility studies of Imipramine were performed and it was found freely soluble in 0.1 N HCl, soluble in methanol, ethanol, chloroform, 0.1 N NaOH and phosphate buffer pH 6.8, slightly soluble in water. Melting point test was carried out by employing capillary method and using melting point test apparatus and the melting point was found to be in a range of 176-177 ºC. FTIR spectroscopic studies was carried out with help of „Perkin Elmer FTIR spectrometer modified version 10.01.00" and the sample curve was compared with standard curve; it was found to be comparable with standard curve with prompt peaks. Results of loss on drying of Imipramine was found 0.085±0.003%.

I. INTRODUCTION

Oral route is a most preferred route of drug administration for systemic effect due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability[1]. About 60% of all the formulations are solid dosage form. Tablet is the most preferred dosage form due to ease of manufacturing, transportation and more patient compliance[2]. Generally geriatric, pediatric, nauseous, bed ridden and non- compliance patients experience difficulties in swallowing the conventional oral dosage form and do not take their medicines as prescribed. It is estimated that 50% of the population was affected by this problem, which finally results in a higher chance of non-compliance & ineffective therapy[3]. The elderly constitute a major portion of today's population mainly because of increased life expectancy of individuals[4]. Dysphagia or difficulty in swallowing is common problem, the disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy[5]. The most common complaint with tablet is size, fear of chocking followed by surface form and taste. The problem of swallowing tablets is more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water[6].

To overcome this oral fast disintegrating drug delivery systems were developed, these systems were first developed in the late 1970s as an alternative to tablets, capsules and syrups for pediatric & geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms. These dosage forms either dissolve or disintegrate generally within a 3 minute in mouth, without need of water. Oral fast disintegrating dosage form have started gaining popularity & acceptance as new drug delivery system because they are easy to administer & lead to better patient compliance[7].

This delivery system consists of a thin film of the size of a postage stamp, which is placed on the patient's tongue or mucosal tissue, where it instantly hydrates by absorbing saliva; the film then rapidly disintegrates and dissolves to release the drug for oral mucosal absorption. This fast dissolving action is primarily due to the large surface area of the film, which wets quickly when exposed to the moist oral environment[8]. Fast dissolving oral films were initially introduced in the market as breath fresheners and personal care products such as dental care strips and soap strips. However, these dosage forms were introduced in the United States and European pharmaceutical markets for therapeutic benefits.

The first of the kind of Oral Strips (OS) were developed by the major pharmaceutical company Pfizer who named it as Listerine pocket packs™ and were used for mouth freshening. Chloraseptic® relief strips were the first therapeutic fast dissolving Oral Thin Films (OTF) which contained benzocaine and were used for the treatment of sore throat. Technology Catalysts forecasts the market for drug products in oral thin film formulations was valued of $500 million in 2007 and could reach $2 billion in 2012. Based on upward global growth trends of the past decade, the fast dissolving dosage market could produce revenues of $13 billion by 2017[9].

Special features of fast dissolving oral films

- Thin elegant film
- Available in various size and shapes
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration and dissolution
- Rapid drug release
- By passes first pass effect[10-11]

Advantage of fast dissolving oral firms

- No need of water for administration.
- Convenient for pediatric, geriatric and dysphasic patients having difficulty in swallowing.
- Rapid disintegrating and dissolution in the oral

cavity due to larger surface area of films.

- Rapid onset of action with increased bioavailability due to by passing hepatic first pass effect.
- Reduce dose, enhances the efficacy and safety profile of the drug with reduced side effects.
- Flexible and portable in nature so they provide ease during consumer handling, in transportation andstorage.
- Ease of administration to mentally ill, disabled, un-cooperative patients and the patients who are on reduced liquid intake plans or are nauseated.
- Beneficial in cases such as motion sickness, acute pain, sudden episodes of allergic attack, asthmatic attack and coughing, where an ultra rapid onset of action is required[12-13].
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.
- As compared to liquid formulations, precision in the administered dose is ensured from each strip of the film without need of measuring device.
- The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first passeffect.
- Provide new business opportunities in the form of product differentiation, patent-life extension, uniqueness, line extension, and life- cycle management, and exclusivity of product promotion18.
- Pleasant mouth feel, leave negligible or no residue in the mouth after administration.
- Limitations of fast dissolving oral films:-
- High doses cannot be incorporated.
- Excessive bitter drugs are not feasible.
- Dose uniformity is a technical challenge.
- They require special packaging for the products stability and safety.
- Drugs which irritate the oral mucosa cannot be administered by this route.

The key advantage for fast dissolving oral films is patient compliance and convenience. The main drawback is with drug loading. Drug loading is generally limited to roughly 40 mg. This problem can be solved by increasing the thickness of the film, but that in turn may increase the disintegration and dissolution time. Drug companies are still interested in this technology as it provides fast, accurate dosing that is expected to increase patient compliance, particularly among pediatrics. There is no need for water or measuring and upon dissolution; the dose of drug is swallowed. Thus, we can say that fast-dissolving oral thin film offer fast, accurate dosing in a safe, efficacious format that is convenient and portable, without the need for water or measuring devices.

II. AIM AND OBJECTIVE

Many patients express difficulty in swallowing tablets and hard gelatine capsules, resulting in noncompliance and ineffective therapy.

Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance.

One such approach led to development of fast dissolving oral films. Advantages of this drug delivery system include administration without water, convenience of administration and accurate dosing as compare to liquids, easy portability, ability to provide advantages of liquid medication in the form of solid preparation, ideal for paediatric and geriatric patients and rapid dissolution/absorption of the drug, which may produce rapid onset of action.

Imipramine is a tricyclic antidepressant with general pharmacological properties similar to those of structurally related tricyclic antidepressant drugs such as amitriptyline and doxepin. A tertiary amine, imipramine inhibits the reuptake of serotonin more so than most secondary amine tricyclics, meaning that it blocks the reuptake of neurotransmitters serotonin and noradrenaline almost equally. It binds the Sodium-dependent serotonin transporter, preventing the reuptake of norepinephrine and serotonin by nerve cells.

Drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down in to stomach and in suchcases bioavailability of drug is increased, pre-gastric absorption can result in improved bioavailability and as result of reduced dosage form, improved clinical performance through a reduction of unwanted effects. So main aim of work to develop fast dissolving oral film for incensement of bioavailability of Imipramine.

III. MATERIALS AND METHODS

Materials and instruments

The following materials that were procured from different sources, some of which were analytical grade and best possible Laboratory Reagent were used as supplied by the manufacturer without further purification or investigation.

Table 1: List of drug and Excipients used

S. No.	Name of chemical	Supplier
1.	Imipramine	Bioplus life science Bangalore
2.	Methanol	S.D. Fine Pvt. Ltd. Mumbai
3.	Ethanol	Jiangsu Huaxi International Mumbai

4.	Chloroform	Avantor performance materials india Ltd. Mumbai
5.	Hydrochloric acid (HCl)	RFCL Ltd. Mumbai
6.	KH_2PO_4	S.D. Fine Pvt. Ltd. Mumbai
7.	NaOH	RFCL Ltd. Mumbai
8.	HPMC	Loba Chemie Pvt Ltd, Mumbai
9.	Sodium starch glycolate	Loba Chemie Pvt Ltd, Mumbai
10.	Croscarmellose Sodium	Loba Chemie Pvt Ltd, Mumbai
11.	Citric acid	Loba Chemie Pvt Ltd, Mumbai
12.	Crospovidone	Loba Chemie Pvt Ltd, Mumbai

Table 2: List of instruments used

S. No.	Instrument	Manufacture
1.	Electronic Balance	Wensor
2.	FTIR	Bruker Alpha, Germany
3.	Dissolution Test Apparatus	Labindia DS 8000
4.	UV- Visible Spectrophotometer	Labindia
5.	Disintegration Test Apparatus	Electronic India
6.	pH Meter	Electronic India
7.	Hardness tester	PharmaChem Machineries
8.	Melting point	Chemi line (CL 725)
9.	Karl fisher	Chemi line (CL 510)

3.1 Drug profile Imipramine

Imipramine, the prototypical tricyclic antidepressant (TCA), is a dibenzazepine- derivative TCA. TCAs are structurally similar to phenothiazines. They contain a tricyclic ring system with an alkyl amine substituent on the central ring. In non- depressed individuals, imipramine does not affect mood or arousal, but may cause sedation. In depressed individuals, imipramine exerts a positive effect on mood. TCAs are potent inhibitors of serotonin and norepinephrine reuptake. Tertiary amine TCAs, such as imipramine and amitriptyline, are more potent inhibitors of serotonin reuptake than secondary amine TCAs, such as nortriptyline and desipramine. TCAs also block histamine H1 receptors, α1-adrenergic receptors and muscarinic receptors, which accounts for their sedative, hypotensive and anticholinergic effects (e.g. blurred vision, dry mouth, constipation, urinary retention), respectively[13].

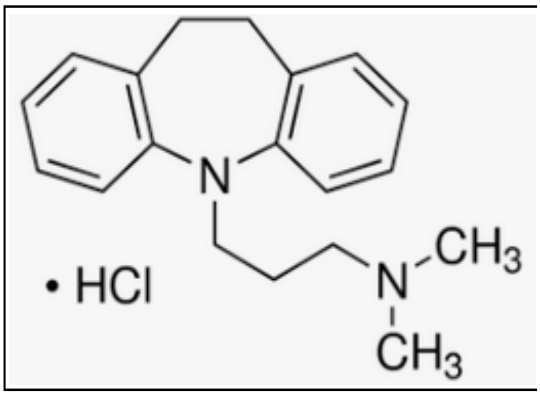

Figure 1: Structure of Imipramine

Chemical Formula: $C_{19}H_{24}N_2$
Molecular Weight: 280.4073
IUPAC Name: (3-{2-azatricyclo[9.4.0.0³,^]pentadeca-1(15),3,5,7,11,13-hexaen-2- yl}propyl) dimeth ylamine.

IV. PHARMACOLOGY

Indication: For the relief of symptoms of depression and as temporary adjunctive therapy in reducing enuresis in children aged 6 years and older. May also be used off-label to manage panic disorders with or without agoraphobia, as a second line agent for ADHD in children and adolescents, to manage bulimia nervosa, for short-term management of acute depressive episodes in bipolar disorder and schizophrenia, for the treatment of acute stress disorder and posttraumatic stress disorder, and for symptomatic treatment of postherpetic neuralgia and painful diabetic neuropathy.

Pharmacodynamics: Imipramine is a tricyclic antidepressant with general pharmacological properties similar to those of structurally related tricyclic antidepressant drugs such as amitriptyline and doxepin. While it acts to block both, imipramine displays a much higher affinity for the serotonin reuptake transporter than for the norepinephrine reuptake transporter. Imipramine produces effects similar to other monoamine targeting antidepressants, increasing serotonin- and norepinephrine-based neurotransmission.

Mechanism of action: Imipramine works by inhibiting the neuronal reuptake of the neurotransmitters norepinephrine and serotonin. It binds the sodium-dependent serotonin transporter and sodium-dependent norepinephrine transporter reducing the reuptake of norepinephrine and serotonin by neurons. Depression has been linked to a lack of stimulation of the post-synaptic neuron by norepinephrine and serotonin 7. Slowing the reuptake of these neurotransmitters increases their concentration in the synaptic cleft, producing knock-on effects in protein kinase signalling which is thought to contribute to changes in neurotransmission and brain physiology which relieves symptoms of depression.

Absorption: Rapidly and well absorbed (>95%) after oral administration[14]. The primary site of absorption is

the small intestine as the basic amine groups are ionized in the acidic environment of the stomach, preventing movement across tissues. Bioavailability ranges from 29-77% due to high inter-individual variability. Peak plasma concentration is usually attained 2-6 hours following oral administration. Absorption is unaffected byfood.

Metabolism: Imipramine is nearly exclusively metabolized by the liver. Imipramine is converted to desipramine by CYP1A2, CYP3A4, CYP2C19. Both imipramine and desipramine are hydroxylated by CYP2D6. Desipramine is an active metabolite.

Use

Imipramine is used in the treatment of depression, such as depression associated with agitation or anxiety. It is similar in efficacy to the antidepressant drug moclobemide. It has also been used to treat nocturnal enuresis because of its ability to shorten the time of delta wave stage sleep, where wetting occurs.

Side effects

- Dry mouth,
- blurred vision,
- headache,
- drowsiness,
- dizziness,
- constipation,
- diarrhea,
- stomach cramps,
- weight gain/loss,
- and increased sweating.

Formulation development of oral film of Imipramine

Casting process of fast disintegrating oral film

Various methods are available for casting of oral films. This is fast disintegrating oral film hence on the laboratory scale solvent casting technique was adopted for formulation of films.

Solvent casting technique

Drug (Imipramine) containing fast dissolving films were fabricated by the solvent casting method. HPMC is known for its good film forming properties and has excellent acceptability[54]. Hence, various grades of HPMC namely HPMC K4 was evaluated as film formers. For the fabrication of films, glycerin was used as a humectant. PEG 400 is also reported as lubricant and solubilizer. This solution was then casted onto glass moulds (15*5cm) and was dried in hot air oven at 45°C for 24 h.

Parameter Selection for formulation of oral film

1. Size of Film

Size of film is about 2.5 x 2.5 cm, to provide sufficient space for dissolving in oral cavity by putting film on tongue for swishing or hydrating with saliva, size 2.5 x 2.5 cm were concluded as unit dose of film.

2. Fabrication of film casting glass reservoir

Film casting glass reservoir is most important glassware which was fabricated keeping view the following aspect:

1. No. of films in one batch
2. Holding capacity of formulation solution for drying
3. Scrapping-off films from film casting glass reservoir
4. Easy to positioned horizontally with gravity for uniform formation of film

A 15.0 x 5.0 cm sized film casting glass reservoir was fabricated having depth of 0.5 cm. This sized film casting glass reservoir will produce twelve 2.5 x 2.5 cm.

3. Amount of solution for formulation

An about 30 ml solution was calculated for further study, because this will produce 200 micrometer depth forsolvent evaporation and sufficient numbers of films for further evaluations.

4. Temperature and time of drying

Preliminary study suggests that 45 ± 1ºC for 12 hrs adequately dry the film.

5. Speed of mixing at magnetic stirrer

200 ± 10 rpm speed for first 30 minutes were optimized for entire study and minutes for all ingredients with same speed were finalized.

6. Selection and optimization of film forming agents

Different film forming agents and one co-film forming (Table 4.3) were selected for this research work. The concentration of film forming was important to form a proper thickness for appropriate packaging and handling of oral films. Concentration of film forming agent is optimized on the basis of thickness and appearance of film.

Table 3: Selection and optimization of film forming agents

Name of ingredients (mg) (mgfor 12 strips)	F1	F2	F3	F4	F5	F6
Imipramine	120	120	120	120	120	120
HPMC K4	50	75	100	50	75	100
PEG-400	50	50	50	50	50	50
SSG	50	75	-	-	-	-
CCS	-	-	50	75	-	-
CP	-	-	-	-	50	-
Mannitol	20	20	20	20	20	20
Citric acid	20	20	20	20	20	20
DM water qs to (ml)	20	20	20	20	20	20

Dose calculations

- Width of the plate = 5 cm
- Length of the plate = 12 cm
- No. of 2.5 x 2.5 cm2 films present whole plate = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug = 10×12 = 120mg
- The amount of Imipramine added in each plate was approximately equal to 120mg.

Evaluation of prepared Film Thickness

The thickness of patches was measured at three different places using a vernier caliper[15].

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated[16].

Folding Endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of Moisture Content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight[17].

Drug Content Analysis

The film taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and reacted by UV spectrophotometer at 256 nm[18].

Results of optimized formulation

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of super disintegrating agent to minimizes the disintegrating time.

Table 4: Results of Optimized formulation F8

Name of Ingredients	Composition (mg) Per Strip
Imipramine	120
HPMC K4	75
PEG-400	50
SSG	-
CCS	-
CP	50
Mannitol	20
Citric acid	20
DM water qs to (ml)	20

In vitro dissolution study

The in vitro dissolution test was performed using the USP dissolution apparatus II (Paddle with sinker)[19]. The dissolution studies were carried out at 37±0.5°C with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm2) was used. 5 ml aliquot of dissolution media was collected at time intervals of 1, 2, 4, 6, 8, and 10 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved drug was determined using UV-Visible spectrophotometer at 256 nm.

Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40 ± 2oC temperature and 75 ± 5 % relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of filmwas found to slightly decrease at higher temperature. Minor difference was found between evaluated parameters before and after ageing / storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time.

V. CONCLUSION

The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equation, Higuchi‟s and Korsmeyer‟s models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that "R2" values of Higuchi model were maximum i.e. 0.994 hence indicating drug release from formulations was found to follow Higuchi release kinetics.

References

[1] Liang CA, Chen HL. Fast dissolving intraoral drug delivery systems. Expert Opin. Ther. Patents. 2001; 11(6): 981-986.

[2] Habib W, Pritchard JF, Bozigian HP, Gooding AE, Griffin RH, Mitchell R, Bjurstrom T, Panella TL, Huang AT, Hansen LA. Fast-dissolve drug delivery system. Crit. Rev. Ther. Drug Carrier Syst.2000; 17: 61–72.

[3] Siddiqui MD, Garg G, Sharma PA. Short review on: A novel approach in oral fast dissolving drug delivery system and their patents. Adv. Bio. Res. 2011; 5(6): 291-303.

[4] Brniak W, Jachowicz R, Pelka Przemyslaw. The practical approach to the evaluation of methods used to determine the disintegration time of orally disintegrating tablets. Saudi Pharm. J. 2015; 23:437-443.
[5] Gisel EG. Oral motor skills following sensorimotor intervention the moderately eating impaired child with cerebral palsy. Dysphagia. 1994; 9: 180– 192.
[6] Avery SW, Dellarosa DM. Approaches to treating dysphagia patients with brain injury. Am. J. Occup. Ther. 1994; 48(3): 235–239.
[7] Chauhan NS, Tomar A, Sharma K, Mittal A, Bajaj U. Formulation and evaluation of fast dissolving oral film of dicyclomine as potential route of buccal delivery. Int. J. Drug Dev. Res.2012; 4 (2): 408-417.
[8] Patel A, Shaikh S, Khan G J, Molvi KI, Patel H. Review Article: various aspects of oral fast disintegrating dosage form. Int. J. Pharmacy Pharm. Res. 2016; 6(4):689-701.
[9] Dixit RP, Puthli SP.Oral strip technology: Overview and future potential. J. Control. Release.2009; 139(2): 94-107.
[10] Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: An innovative drug delivery system and dosage form. Int. J. Chem Tech. Res. 2010; 2(1):576-583.
[11] Goel H, Rai P, Rana V, Tiwary AK. Orally Disintegration systems: Innovations in formulation and Technology. Recent Pat. Drug Deliv. Form. 2008; 2(3): 258-274.
[12] Bhowmik D, Chiranjib B, Krishnakanth, Pankaj, Margret CR. Fast Dissolving Tablet: An Overview. Journal of Chemical and Pharmaceutical Research. 2009; 1(1): 163-177.
[13] Bala R, pravin pawar, sushil khanna, sandeep arora. Orally dissolving strips: A new approach to oral drug delivery system. Int. J. Pharm. Invest. 2013; 3(2): 67–76.
[14] Bhyan B, Jangra S, Kaur M, Singh H. Orally fast dissolving films: Innovations in formulation and technology. Int. J. Pharm. Sci. Rev. Res. 2011; 9(2): 50–57.
[15] Choudhary DR, Patel VA, Chhalotiya UK, Patel HV, Kundawala AJ. Development and characterization of pharmacokinetic parameters of fast- dissolving films containing levocetirizine. Sci. Pharm. 2012; 80:779–787.
[16] Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. Clin. Pharmacokinetic. 2002; 41(9): 661-680.
[17] Jangra PK, Sharma S, Bala R.Fast dissolving oral films: Novel way for oral drug delivery. Int. J. Uni. Pharm. Bio. Sci. 2014; 3(1): 6-27.
[18] Mali RR, Gupta S, Goel V. Novel study in fast dissolving drug delivery system: a review. Indian J. Pharm. Biol. Res. 2015; 3(1):93-107.
[19] Heer D, Aggarwal G, Kumar SLH. Recent trends of fast dissolving drug delivery system-An overviewof formulation technology. Pharmacophore. 2013; 4(1): 1-9.