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Research Article

Formulation and Evaluation of Mouth Dissolving Film of Imipramine HCL

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Abstract:
The main objective of the present study outlines a systematic approach for Design and Evaluation of Fast Dissolving Oral Films of Imipramine HCl to enhance the therapeutic efficacy and provide rapid onset of action in patients suffering from depression Because of patient may have trouble in swallowing a tablet or capsules. Mouth dissolving film is the most advanced oral solid dosage form due to its flexibility and comfort in use. Mouth dissolving films are oral solid dosage form that disintegrate and dissolve within a minute when placed in mouth without taking water or chewing. This dosage form allows the medication to bypass the first pass metabolism so bioavailability of medication may be improved. Fast dissolving Oral film of Imipramine Hydrochloride was formulated by using solvent casting method with different concentrations of HPMC-E3. Film forming property of various grades of HPMC was investigated based on preliminary characteristics of various batches of FDOFs.
Keywords: Imipramine HCl, Mouth dissolving film, HPMC,

Introduction

An oral film delivery is emerging as an advanced alternative to the traditional oral method of drug administration. The oral film is a solid dosage form of drug administration that dissolves when administered. The oral film doesn't need to be chewed or taken with water. Oral films contain active drugs that are designed for oral administration, allowing the drug to bypass the first-pass metabolism in the liver which leads to an increase in drug bioavailability [1].Rapid or fast dissolving oral thin film is becoming an increasingly popular drug delivery system because of its wide and varied benefits. The oral film dissolves in few seconds when comes in contact with saliva, it doesn't need water to swallow thus, it is considered best for children and elderly patients. Mouth dissolving films contain amorphous polymers which aid in the rapid dissolution of the drugs. Above points lead to improvement in patient compliance and inspire pharmaceutical manufacture to invest their money in switching from the former products in markets to FDFs [1,2].

The pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill is supposed to be swallowed intact or chewed to deliver a precise dose of medication to the patient. The pills, tablets, and capsules have the quality to retain

their shapes under moderate pressure. Some patients, especially geriatric and pediatric groups face difficulty in swallowing solid dosage forms and have the risk of choking. To comfort such patients, a variety of fast-dissolving drug delivery modes have been developed. Fast dissolving drug delivery systems are generally manufactured by a variety of technologies, which are direct compression, wet granulation and freeze drying. Some make use of different disintegrating mechanisms, such as high levels of disintegrating or effervescent agents, which cause the dosages to disintegrate rapidly in the mouth. The oral route of administration still continues to be widely used accepted route, contributing to 50 - 60% of total drug formulations because of ease of administration, self-medication, and pain avoidance as compared to parenteral mode [3].

Formulation considerations:

Formulation considerations are important factors affecting the mechanical properties of films such as, shifting the glass transition temperature to lower temperature. (Gerad J Tortora et al.,). Formulation of ODFs involves the intricate application of aesthetic and performance characteristics such as taste masking [4,5], fast dissolving, physical appearance, mouth-feel etc. The area of drug loaded FDF should be between 1-20 cm2 [6]. The drug can be loaded up to a single dose of 30mg.

Table 1: Composition of FDOFs (M. D. Nehal Siddiqui et al., 2011)

S. No.	Particulars	% Value upto
1	Drugs (API's)	05- 30% w/w
2	Polymer (Water Soluble)	45% w/w
3	Sweetening agents	3- 6% w/w
4	Plasticizers	0-20% w/w
5	Saliva Stimulating Agents	2-6% w/w
6	Stabilizing agents	0.01-0.1% w/w
7	Surfactant	q.s.
8	Fillers	q.s.
9	colours	q.s.
10	Flavouring agents	q.s.

Materials and Methods:

Preparation of Phosphate Buffer (pH 6.8):

This buffer was prepared by mixing 250 ml of 0.2M potassium dihydrogen phosphate (KH_2PO_4) solution and 112 ml of 0.2M sodium hydroxide (NaOH) solution and final volume make up-to 1L using purified water [7].

Calibration Curve:

Calibration curve obtaining method of Granisetron HCl was carried out by scanning 100ppm solution from 400 to 200nm in spectrum (mode) of UV-Visible spectrophotometer. From this spectrum absorbance maximum was selected. Solutions absorbance from 1ppm to 10ppm and 10ppm to 20ppm was measured in a Shimadzu double bean UV-spectrophotometer, in photometric mode, using pH 6.8 (phosphate buffer) as a reference blank [8]. Absorbance maxima was obtained by the procedure that was carried and from that the spectrum was formed.

Preparation of Imipramine HCl films:

It was aimed to prepare to Fast Dissolving Oral Films of Imipramine HCl whose dose was 1.12mg per 4cm2 film. The procedure was carried out on a digital magnetic stirrer using a medium sized magnetic bead. Film forming polymers hypromellose and maltodextrin were

weighed accurately, added to a small amount of water in a small beaker, covered with an aluminium foil and soaked for 24 hours to ensure complete hydration. Xanthan gum was added the next day in small amounts and the solution was stirred on a magnetic stirrer at 75rpm for first half an hour and later 50rpm for 1.5 hours. Then, propylene glycol was added and stirring continued for 30min at 50rpm. Imipramine HCldrug, Aspartame, citric acid, vanillin and amaranth were dissolved in sufficient quantity of water and added to the polymer mixture. This film forming solution then stirred well to obtain a homogenous solution. Dry and clean petri dish was selected and the solution was poured into it. Drying was carried out at 45ºC in a hot air oven for 6 hours. The Petri dish was then removed and left aside to cool down to room temperature. The film was then peeled carefully using a surgical scalpel by making a small incision in the film on one side of the Petri dish. Small films of 4cm2 were cut from one big film and packed primarily in a aluminium foil and secondarily in a self-sealing polythene to ensure least moisture penetration. The formulation was carried out using polymers, Hypromellose E3 [9], and the resulting films were evaluated.

Table 2: Formulation of mouth dissolving film Using polymer (HPMC-E3)

Formulationcode&Ingredients	**F1**	**F2**	**F3**	**F4**
Imipramine HCl (mg)	18	18	18	18
HPMCE3(mg)	225	250	275	300
Maltodextrin(mg)	130	120	110	100
Xanthan gum(mg)	10	10	8	8
Aspartame(mg)	20	20	20	20
Amaranth	Q. S	Q.S	Q. S	Q. S
Propyleneglycol	50	60	70	80
Citricacid(mg)	10	10	10	10
Water	Q.S	Q.S	Q.S	Q.S
Vanilla	Q.S	Q.S	Q.S	Q.S

Characterization of FDOFs:

Physical characterization of FDOFs can be carried out by visual inspection for characteristics such as colour, thickness, brittleness, peeling ability, transparency, surface smoothness, tack property and film forming capacity [10,11].

Peeling ability is measured as the easy or difficulty in separating the film from the release liner.

Transparency is checked by placing the film against an illuminated background & viewing carefully to find any opacity.

Film-forming (FF) capacity is the ability of the film forming polymer to form an efficient film, thin enough and also with sufficient drug loading ability. Film forming capacity may be rated as poor, average, good and excellent based on the overall examination.

***In vitro* quality control tests** (Apoorva Mahajan et al., 2011 and S. Raju et al., 2011) Large Film of 63.64cm^2 was cut into even square pieces of 4cm^2(2cmX2cm) each and evaluated to verify following parameters.

Weight Variation: Weight variation test determines weight difference among films in one batch of a formulation. The weight of films was determined by a digital weighing balance with a precision of 1mg. this examination was performed on three films, out of six films that constitute one batch of each formulation and Mean +SD was calculated. It was measured in milligram (mg). The nominal weight for each film and polymer depends on film forming capacity and adherence to release liner.

Thickness:

The thickness of a film is Least Measure related directly to disintegration time. Thickness of films was evaluated using Vernier callipers (digital) with a precision of 0.0010mm i.e. 10µm.ideally films can have thickness up to 10µm.

Folding endurance study:

Folding endurance is measure of mechanical strength of a film. Folding endurance study is carried out to ensure the film reminds intact during transportation and handling without breaking off. It was measuredmanually.Astrip was repeatedly folde at the same placetill it broke. The number of times the film could be folded at the sameplace without breaking gave the value of the folding endurance. It was measured as number of counts[12]**.**

SurfacepHstudy:

Surface pH is measure of pH on surface on film. This was performed by placing a large enough water drops on surface of film then bulb of pH electrode is brought in contact with surface of water drop.it was performed using a well calibrated pH meter.

Contentuniformity

Assay/ Drug content are the amount of drug present in a unit film of a batch. Drug content determination helps to know the drug distribution into each small film. Thus, content uniformity can be known. Assay is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip [13].

% Drug content=Concentration × Dilution Factor × Bath Volume ×100 /1000 It was measured in percentage.

Tensile strength:

The resistance of a material to a force tending to tear it separately, measured as maximum tension such material can withstand with-out tearing. It can be calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

Tensile strength = Load at Failure × 100

Strip thickness × Strip Width Its units are g/cm^2.

Percentageelongation:

The percentage increase in the length of a film (L2), when it is pulled under standard conditions of stress just before the point of break is known percentage elongation. The initial length of a film is L1. It is measured in terms of percentage. (L2-L1) × 100 Percent elongation=..... L1 ×area of cross section However, for films cross-sectional area is very negligible hence; it can be omitted during calculation.

***InVitro*-DissolutionStudy:**

Dissolution testing was performed using the standard rotating basket apparatus (apparatus I) described in the USP. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. For this study 300mL of medium was employed. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed. Hence, basket apparatus is used [14-16]. The medium of study was phosphate buffer pH 6.8.

The parameters of study are:

Apparatus:	USPBasket-typeapparatus
Agitationspeed:	50rpm
Temperature:	300mLfreshlyprepared(pH6.8)phosphatebuffer
Samplinginterval:	1,2,4,6,8,10minutes
Wavelength:	302nm

The samples of 5mL were withdrawn at predetermined time intervals and replaced with fresh medium. The sample concentrations were assayedspectrophotometrically at 302nm. The cumulative percentage drug release was calculated.

Result and Discussion:

Calibration curve of Imipramine Hydrochloride

Absorption spectrum Imipramine Hydrochloride λmax was found to be 243 nm in n SHIMADZU UV- 1800 spectrophotometer.

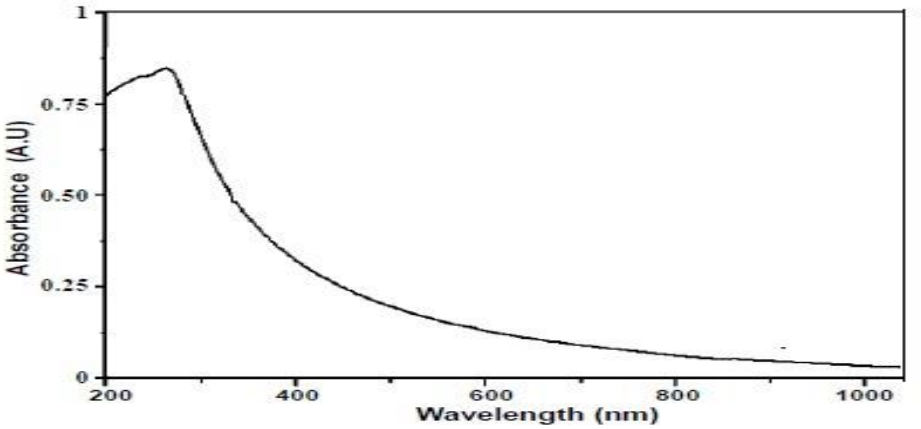

Figure 1: UV Spectrum of Imipramine Hydrochloride (2- 10µG/ML)

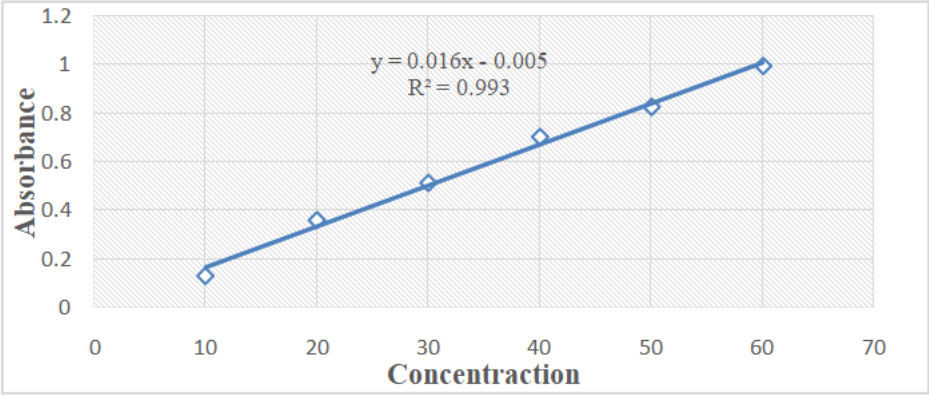

Figure 2: Drug calibration curve Imipramine HCl

Table 3: Standard CC of Imipramine HCl

Sr. No.	Concentration (µg/ml)	Absorbance			Average Absorbance
		1	2	3	
1	0	0.145	0.148	0.142	0.145
2	2	0.305	0.298	0.307	0.303
3	4	0.415	0.401	0.409	0.408
4	6	0.610	0.603	0.599	0.604
5	8	0.817	0.801	0.812	0.810
6	10	0.982	0.960	0.977	0.973
Correlation Co-efficient (R^2) = 0.9933 Absorbance (y) = 0.0169x - 0.0051					

Table 4: Preliminary Characteristics of Formulations F1-F4

Formulation Code	Film Property	Tack property	Ease of handling
F1	Poor	Non-Tacky	Thick and Brittle
F2	Average	Non-Tacky	Brittle
F3	Good	Non-Tacky	Opaque
F4	Excellent	Non-Tacky	Thin Easy to peel

***In vitro* quality control tests:**

Table 5: In Vitro quality control tests (mean SD n = 3)

Code	Thickness (µm)	Weight variation (mg)	Folding endurance	Surface pH	Content Uniformity/ % Assay	In-vitro Disintegration Time (Sec)
F1	82±2	62.12±0.2	64±2	6.62±0.02	95.89±0.2	25±3
F2	75±3	59.02±0.7	61±1	6.71±0.03	92.72±0.4	30±2
F3	73±1	57.51±0.6	59±3	6.68±0.01	97.22±0.3	24±2
F4	71±2	55.14±0.4	57±1	6.52±0.11	98.26±0.1	22±2

The present invention identifies that the HPMC grades is one of the best water-soluble polymer and best used for the preparation of fast release drug delivery systems, as the concentration of the HPMC increases the disintegration time decreases.

***In vitro* dissolution studies:**

Table 6: Cumulative Percent Drug Release for HPMC E6 (mean ± SD n =3

Batch Code Time (Min)	F1	F2	F3	F4
0	**0**	**0**	0	**0**
1	12.5 ± 1.4	17.3 ± 3.1	23.44 ± 2.5	23.44 ± 2.5
2	23.4 ± 0.7	28.54 ± 0.6	38.36 ± 0.7	40.6 ± 0.5
4	41.0 ± 2.2	42.65 ± 2.0	55.36 ± 6.0	60.1 ± 0.2
6	55.2 ± 6.5	58.3 ± 2.4	67.3 ± 2.4	82.3 ± 2.7
8	74.15 ± 0.8	73.10 ± 3.0	85.10 ± 3.3	90.01 ± 1.1
10	81.04 ± 0.7	82.41 ± 0.9	90.11 ± 1.4	90.11 ± 0.8

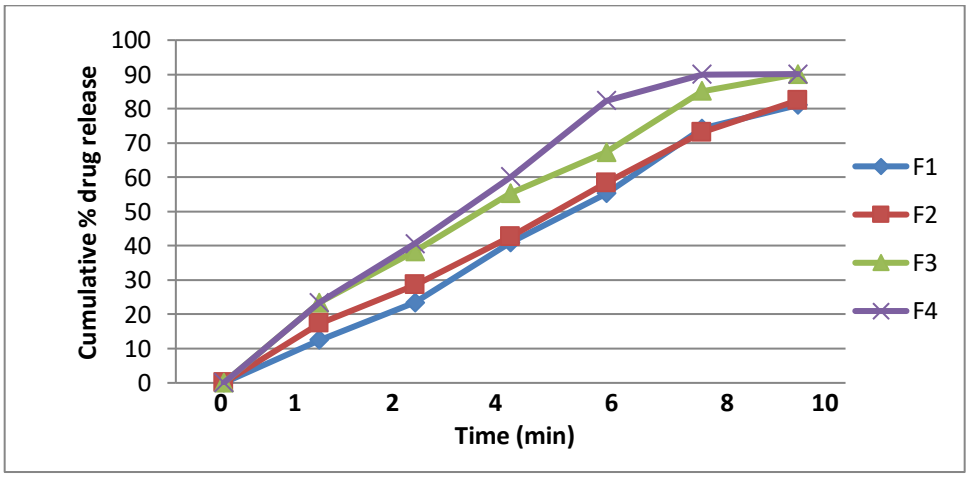

Figure 3: Cumulative Percent Drug Release for F1-F4

In vitro dissolution studies for the all formulated films were carried out by using 900 ml of phosphate buffer pH 6.8 maintained 37 ± 05°C 5 ml at 50rpm speed. The aliquot was withdrawn at the specific time intervals, filtered through What man filter paper and analyzed by spectrophotometer at 242 nm. The dissolution studies were studied in two different batches F3 to F4. As the concentration of HPMC concentration increases the percentage drug release was greater.

Stability Studies for optimized formulation:

Optimized formulation was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 3 months according to ICH guidelines. From these results it was concluded that optimized formulation is stable and retained their original properties with minor differences which depicted in the table.

Table 7: Physico-chemical characteristics of optimized formulation stored at 40 ±2ºC /75±5%RH

Retest-Time for Optimized formulation	Time of Disintegration (sec)	Drugpercent Content/Assay (%)	DrugIn-vitro Release profile(%)	Transpareny
0 days	09±2	99.8±0.1	98.6±1.5	Transparent
30 days	10±8	99.06±0.14	97.5±1.4	Transparent
60 days	11±6	98.06±0.12	96.8±1.09	Transparent
90 days	11±2	97.54±0.26	96.1±1.13	Transparent

Conclusion:

Formulations with HPMC E3 and F1-F4 were evaluated for their physical characteristics, thickness, folding endurance, tensile strength, disintegration time, drug content uniformity and drug release characteristics. Dissolution studies were performed for FDOFs excluding batches that showed poor film forming property. Among the prepared formulations F4 showed minimum disintegration time 22 sec. Formulation F4 released 97.8% of drug within 8 min when compared to the other formulations. Based on the physicochemical properties like tensile strength, folding endurance, thickness, disintegration results and dissolution studies, it was concluded that F4 finalized as optimized formulation.F4 was found optimum for formulation of Impramine Hydrochloride FDOFs. Thus, cumulative drug release studies of F4 formulation was compared with the marketed formulation. From the above observation its concluded that F4 formulation gives the better drug release from the other formulation as per in-vitro dissolution profile.

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