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FORMULATION DEVELOPMENT, OPTIMIZATION AND EVALUATION OF FAST DISSOLVING ORAL FILMS OF VERAPAMIL HYDROCHLORIDE

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ABSTRACT

Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablets or capsules etc. The film dissolves quickly when placed in mouth without need of water thus helpful in providing rapid onset of action. Verapamil is a calcium channel blocker used as an antianginal, antiarrhythmic, and antihypertensive agent with extensive first pass metabolism which results in less bioavailability. The present study was aimed to formulate fast dissolving oral films of verapamil to enhance bioavailability and avoid pre-systemic metabolism and improve patient compliance. The fast-dissolving strips were prepared by solvent casting technique with the help of HPMC E5 and Pullulan. The strips were evaluated for film thickness, tensile strength, folding endurance, in vitro disintegration time, surface pH, drug content uniformity and in vitro dissolution studies. Official criteria for evaluation parameters were fulfilled by all formulations. Based on the evaluation parameters, the formulation F4 showed optimum performance against other formulations; hence formulation F4 was selected as optimized formulation.

KEYWORDS: Fast dissolving films, Verapamil hcl, HPMC E5, Solvent casting method.

INTRODUCTION

Fast dissolving films are one among the advance form of solid dosage form due to its flexibility. It is a solid dosage forms, which disintegrate or dissolve within 1 min when placed in the mouth without drinking or chewing. FDFs enhanced dissolution rate, better patient compliance and effective therapy. It improves 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. Fast Dissolving Drug Delivery Systems was an advance drug delivery system that came into existence in the 1970s and more convenient in use compared to other oral drug delivery system formulation, like tablets, syrups, capsules. FDDS have major benefit over other conventional dosage forms as the formulation gets rapidly disintegrated and dissolves in the saliva without need of water and release the drug to desired response on desired site of action. The most popular oral solid dosage forms are tablets and capsules. Many patients particularly paediatric and geriatric patients find difficult to swallow tablets and hard gelatine capsules and do not take their medicines as prescribed. Difficulty in swallowing (dysphagia) is seen to afflict nearly 35% of the general population. In some conditions, like, motion sickness, sudden episode of allergic attack, fear of choking, coughing and unavailability of water, the swallowing of tablet or capsules may become difficult. To overcome these difficulties, several fast-dissolving drug delivery systems have been developed. To eliminate the drawbacks of fast dissolving tablet a fast-dissolving film can be placed. Fast dissolving films (FDF) are similar to fine/thin strip of postage stamp in their shape, size and thickness. Fast dissolving film is placed over the patient's tongue or oral mucosal tissue, instantly get wet by saliva, the film rapidly hydrates and adheres to the site of application. It gets rapidly disintegrates and dissolves to release the medication for oromucosal absorption. Fast dissolving drug delivery system (FDDS) is suitable for drugs which undergo high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to mouth plasma peak levels, which in turn minimize adverse effects and also make it cost effective. Drug delivery by per-oral administration arise some problems such as hepatic first pass metabolism and enzymatic degradation within the GI tract.

Verapamil is a calcium channel blocker used as an antianginal, antiarrhythmic, and antihypertensive agent. The oral absorption of verapamil is about 90% but its bioavailability approaches only 10–20%, due to extensive first-pass effect mainly in the liver. The bioavailability of the drug is increased by formulating

fast-dissolving drug delivery system. Bioavailability is increased due to absorption from oral cavity. Thus, in the present investigation, it was planned to formulate and evaluate fast dissolving oral films of verapamil hydrochloride.

MATERIALS AND METHODS

Materials

Verapamil hydrochloride was received as a gift sample from Micro Labs Pvt. Ltd. Mumbai. Pullulan, HPMC E5, Propylene glycol, Citric acid and Aspartame (Research Lab Fine Chem Industries, Mumbai) were used as film base materials. All the chemicals used were of analytical grade.

Method of Preparation of Fast Dissolving Oral Films

Fast dissolving oral films were prepared by using a combination of polymers by solvent casting technique. The formulations were prepared as per table 1. The water-soluble polymers (Pullulan, HPMC E5) and plasticizers (Propylene glycol) were dissolved in distilled water. The solution is stirred up for 2 hrs in the magnetic stirrer and kept aside to remove all air bubbles entrapped. Meanwhile, the excipients and drug were dissolved and stirred well for 30 min, after the completion of stirring both the solutions are mixed together. Finally, the solution is casted on a suitable petri plate to form a film. The plates were kept in a hot air oven at 60° c for 1 hour. The dried film was gently separated from glass plate and cut into a 2x2cm sizes.

Table 1: Composition of Fast Dissolving Film of Verapamil Hydrochloride.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Verapamil HCL (mg)	784	784	784	784	784	784	784	784	784
Pullulan (mg)	100	100	250	300	200	200	100	300	200
HPMC E5 (mg)	200	400	250	400	200	400	300	300	300
Propylene Glycol (ml)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Sodium Starch Glycolate (mg)	50	50	50	50	50	50	50	50	50
Citric Acid(mg)	70	70	70	70	70	70	70	70	70
Aspartame (mg)	50	50	50	50	50	50	50	50	50
Flavour (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Water	QS	QS	QS	QS	QS	QS	QS	QS	QS

Evaluation Parameters

1. Thickness of Films

By using micrometer screw gauge, the thickness of the film was measured at five different places; an average of three values was calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film.

2. Folding Endurance

To determine folding endurance, a strip of film is cut and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gives the value of folding endurance. Typical folding endurance for film is between 100-150.

3. Tensile Strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by formula,

$$Tensile\ strength = \frac{load\ at\ failure\ X\ 100}{\text{strip thickness X strip width}}$$

4. Surface pH

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.

5. In Vitro Disintegration Test

Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast-dissolving film, the time of disintegration should be in range of 5-30s. United State Pharmacopoeia (USP) disintegration apparatus can be used to study Disintegration time. In another method, the disintegration time can be visually determined by dipping the film in 25 ml water in a beaker. The beaker should be shaken gently and the time was noted when the film starts to breaks or disintegrates.

6. Drug Content Uniformity

This 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. Limit of content uniformity is 85-115%.

7. In-Vitro Drug Release Study

By this method cumulative drug release and cumulative percentage of drug retained were calculated. In-vitro drug dissolution was performed using USP paddle type apparatus. The studies were carried out at 37°C with stirring speed of 75 rpm in 500 ml phosphate buffer (pH 6.8). 5 ml of samples were withdrawn at predetermined time intervals of 3, 6, 9…, 30 min and replaced with the same volume of buffer. The samples were collected and the concentration was determined at appropriate wavelength using UV-visible spectrophotometer.

RESULTS AND DISCUSSION

1. Thickness of films

The prepared films were based on the quantities of the polymers the thickness of different films was found to be varying. The film thickness was observed to be in the range of 0.28 ± 0.05 mm to 0.36 ± 0.05 mm. It was observed that as the percent of the polymers increased, thickness also increased, as more amount of polymer resulted in the thickness of films. Thickness of fast dissolving films of all formulations given in table No.2

2. Folding Endurance

All the films had the satisfactory folding endurance of >250. The range of folding endurance study ensured flexibility of these formulated films. The folding endurance of fast dissolving films of all formulations given in table No.2

3. Tensile strength

The tensile strength of the films varied between 4.36 ± 0.32 and 5.40 ± 0.20 kg/cm^2. The observed results revealed that tensile strength increased with an increase in polymer concentration. Prepared films showed acceptable Tensile strength among which formulations F1 and F2 showed highest tensile strength, all films were found to be strong that can withstand mechanical disturbances in mouth. The tensile strength of fast dissolving films of all formulations given in table No.2

4. Surface pH

Acidic or alkaline pH may cause irritation to the oral mucosa and influence the degree of hydration of polymers. The surface pH of the films ranged between 6.79 ± 0.15 and 6.93 ± 0.11. The results were found to be close to neutral in all the formulations, and this means that they have less potential to irritate the oral mucosa. The surface pH of fast dissolving films of all formulations given in table No.2

5. In Vitro Disintegration Test

Disintegration test for all prepared formulations was carried out using disintegration test apparatus. The disintegration time of the films varied between 21 ± 0.25 to 38 ± 0.30 Sec. The results shows that the concentration of polymer increases the disintegration time also increases. The prepared films showed acceptable disintegration time. The disintegration time of fast dissolving films of all formulations given in table No.2

6. Drug Content Uniformity

The drug content (%) in all formulations varied between the ranges of 93.75±0.75 % to 99.25±0.25 %. This indicates that the drug dispersed uniformly throughout the polymeric films. Formulation F4 showed highest release in 30 min. and was selected as optimized batch for stability studies. The % drug content of fast dissolving films of all formulations given in table No.2

Table 2: Evaluation Parameters of Prepared Films.

Formulations	Thickness (mm) ± SD	Folding endurance	Surface pH ± SD	Tensile Strength (kg/cm^2) ± SD	Disintegration Time (Sec.)	% Drug content ± SD
F1	0.28 ± 0.06	>250	6.82 ± 011	5.17 ± 0.20	38	94.5±0.50
F2	0.30 ± 0.04	>250	6.74 ± 0.13	5.40 ± 0.20	28	95.0±0.50
F3	0.34 ± 0.02	>250	6.82 ± 0.11	4.47 ± 0.35	28	93.75±0.75
F4	0.32 ± 0.04	>250	6.83 ± 0.14	5.00 ± 0.20	21	99.25±0.25
F5	0.31 ± 0.05	>250	6.90 ± 0.16	4.51 ± 0.20	27	97.0±0.25
F6	0.36 ± 0.05	>250	6.83 ± 0.16	4.36 ± 0.32	22	98.25±0.25
F7	0.36 ± 0.04	>250	6.79 ± 0.14	4.41 ± 0.40	37	96.5±0.50
F8	0.36 ± 0.05	>250	6.83 ± 0.16	4.86 ± 0.32	26	97.5±0.25
F9	0.36 ± 0.04	>250	6.92 ± 0.16	4.66 ± 0.32	34	98.75±0.25

7. In Vitro Drug Release Study

The in vitro drug release profiles of fast dissolving films of all formulations given in table. Drug release from Verapamil hydrochloride fast dissolving film ranges from after every 3 min. of time upto 30 mins. It could be concluded from the results that the films containing lesser concentration of the polymer gave a faster release of the drug. The rate of drug release decreased substantially on increasing the concentration of polymers.

Table 3: In Vitro Drug Release Studies of All Formulations.

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
3	13.75	1.25	0.25	20	19.5	25.5	21.25	30	23.75
6	20.0	2.50	10.0	37.5	26.25	31.75	23.75	36.75	30.0
9	32.5	10.0	22.5	45.0	30.0	42.5	26.75	43.75	42.5
12	42.5	11.25	27.5	49.25	35.0	48.5	41.25	49.25	44.5
15	45.0	31.25	30.0	50.5	39.5	56.75	45.0	53.75	48.0
18	47.5	51.25	36.25	56.0	45.5	65.0	51.75	62.0	58.75
21	60.0	53.75	40.0	62.5	51.25	68.75	53.75	65.0	71.25
24	68.75	63.75	42.5	72.5	56.75	76.75	56.75	73.75	77.5
27	75.0	68.75	50.0	88.0	63.5	86.25	66.25	80.5	90.0
30	76.25	70.0	61.25	98.75	81.75	91.25	80.0	89.5	93.75

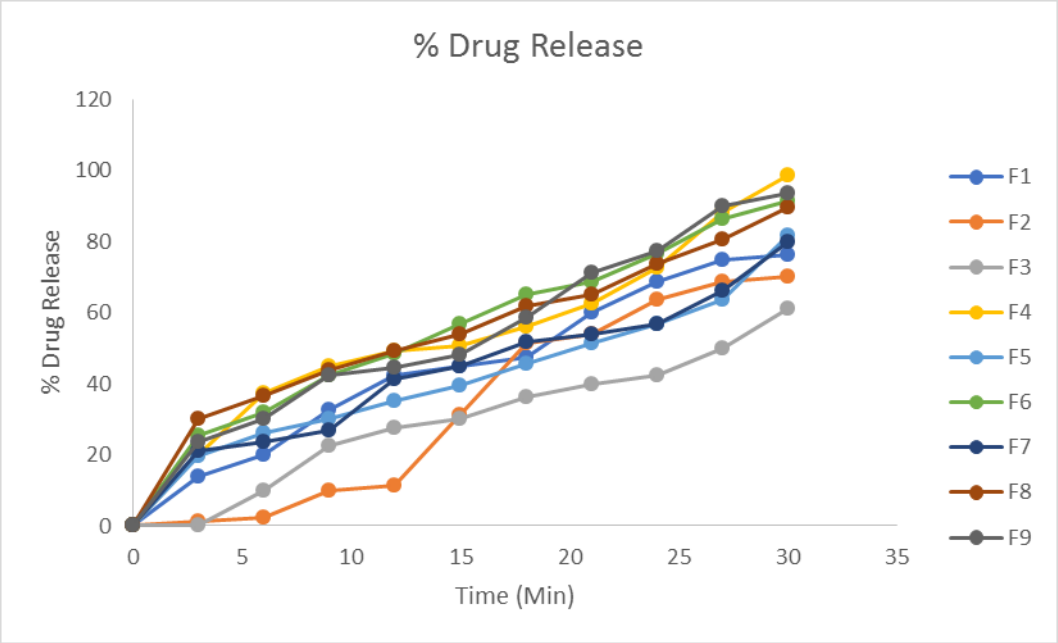

Fig. 1: In vitro drug release studies of all formulations.

CONCLUSION

Regarding the results of this study among the nine formulations, formulation F4 were the best polymer concentration to be used in the formulation of verapamil hydrochloride as fast dissolving oral film. Drug release profile for the films shows that 98.75% of drug could be released in a short duration since the films are disintegrated rapidly (within 21 seconds) due to high water-soluble polymers used in the formulation.

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