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Original Research Article

Formulation and evaluation of rapid dissolving films of pravastatin sodium

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Abstract

The concept of Fast dissolving drug delivery system offers a solution for those patients having difficulty in swallowing tablets/capsules etc. This work investigated the possibility of developing Pravastatin sodium rapid dissolving films allowing fast, reproducible drug dissolution in the oral cavity, decreases the hyperlipidemia effect in patients in less time and enhances the patient compliance The fast-dissolving oral films of Pravastatin Sodium prepared using different film-forming materials HPMC E5 and Polyvinyl alcohol by the solvent-casting method which is simple and cost effective. The prepared films were subjected to different evaluation parameters like morphological properties, film thickness, folding Endurance, Surface pH, content uniformity, *in vitro* disintegration time and *in vitro* dissolution studies. The optimized formulation was subjected to stability studies, revealed that no significant changes occur after 1 month of test period. Results of FTIR data of optimized formulation (F10) revealed that there was no incompatibility observed between the drug and excipients used in the formulation. These findings suggest that the fast dissolving oral film containing Pravastatin sodium is considered to be potentially useful for the treatment of hyperlipedemia where quick onset of action is desirable.

Keywords: Rapid dissolving films, HPMC E5, Polyvinyl Alcohol, Solvent-casting method

1.Introduction

Oral films are the newer technologies in the manufacturing of orally disintegrating dosage forms. They are thin elegant films of edible water-soluble polymers of various sizes and shapes like square, rectangle or disc. The strips may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for water. Fast disintegrating films [1](FDFs) have a large specific surface area for disintegration. The films alleviate the danger/ fear of chocking, easy to handle and administer, maintain a simple and conventional packaging that is easy to manufacture thus overcoming the short falls of oral fast disintegrating tablets. A major limitation of these dosage forms is low drug loading capacity and limited taste masking options.

Fast dissolving drug delivery systems can improve acceptance and compliance in patients with dysphasia. Similarly, from market point of view, introduction of FDDS will assist life cycle management of drug especially if the drug is patent protect? The need for non-invasive delivery systems continues due to poor patient compliance with existing delivery regimens, limited market size for drug companies and drug uses, coupled with high costs of disease management. Pharmaceutical marketing is one reason for the increase in available fast-dissolving /disintegrating products[2].

2. Materials and Methods

Pravastatin sodium was obtained as a gift sample from Pharmatrain, Hyderabad. HPMC E3, HPMC E5, xylitol, Aspartame, PEG 400 were procured from Sd Fines Chemicals, Mumbai. All the reagent and materials used were of analytical grade.

2.1 Preparation of rapid dissolving films of Pravastatin Sodium

Pravastatin sodium containing fast dissolving films were fabricated by the solvent casting method. Hydrophilic polymers was dissolved in 10ml of hot water in one beaker and Pravastatin sodium, xylitol asparatate and Propylene glycol were dissolved in 10ml of 95% ethanol in another beaker, stirred continuously in magnetic stirrer about 45mins. The

drug solution was then added to the polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a plastic petridish and was dried at room temperature for about 24hrs. The dried film was carefully removed from the petridish and was cut into size required for testing. The films were stored in air tight plastic bags. Same procedures were followed for the preparation of HPMC-15 film and combination of HPMC15: PVA (1:1.5%w/v) and HPMC-50: Eudragid(2:1%w/v). The composition of drug loaded film is shown in Table No. 2.

Table No. 1: Formulation Composition of Pravastatin Sodium containing rapid dissolving films

Ingredients*	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Pravastatin sodium	20	20	20	20	20	20	20	20	20	20
HPMC E6	25	30	35	40	-	-	-	-	25	20
PVA	-	-	-	-	25	30	35	40	15	20
Xylitol	27	27	27	27	27	27	27	27	27	27
Propylene glycol	20	20	20	20	20	20	20	20	20	20
Aspartame	4	4	4	4	4	4	4	4	4	4
Pipperment Flavor	2	2	2	2	2	2	2	2	2	2
Citric Acid	2	2	2	2	2	2	2	2	2	2
Distilled water**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Ethanol**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total Weight	100	100	100	100	100	100	100	100	100	100

*All ingredients were taken in mg.
** Water was taken in ml.

2.2 Evaluation Parameters

2.2.1 Weight variation

Ten films were randomly selected and their average weight was obtained. Individual films were weighed and compared with the average weight for the deviation.

2.2.2 Thickness

The thickness of film can be measured by micrometer screw gauge at different strategic locations (at least 5 locations). This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film.

2.2.3 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

2.2.4 Assay

A film was cut into three pieces of equal diameter were taken in separate 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 10mins. The solutions were filtered, suitably diluted and analyzed at 238 nm in a UV Spectro meter. The average of drug content of three films was taken as final reading.

2.2.5 Surface pH

The surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 1 h. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1.0 min.[3]

2.3 Disintegration test

In-vitro disintegration time was determined visually in a petridish containing 25 ml of pH 6.8phosphate buffer with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrate.[4][5]

2.4 *In vitro* dissolution study

The drug release studies were performed with USP dissolution test apparatus. (Paddle method). The USP dissolution apparatus was thermostated at the temperature of 37 ± 1^0C and stirred at rate of 50 rpm in a 900ml dissolution medium of pH 6.8 phosphate buffer. The aliquots of 5 ml were withdrawn at the time interval of every 5mins and replaced with equal volume of dissolution medium. The sink condition was maintained throughout the study. The samples were analyzed at 238 nm in a UV-VIS Spectrometer and cumulative amount of drug release at various time intervals was calculated[6].

2.5 Compatibility studies:

The drug-polymer compatibility was confirmed by taking IR spectrum of drug, polymer and physical mixture of drug-polymer proved that the excipients were compatible with the Pravastatin sodium.[7]

2.6 Stability studies[8]:

When the oral film preparation was stored in an aluminium package under normal condition or in a chamber controlled at 40°C and 75% in humidity for 3 months, no apparent changes in the Pravastatin sodium content, form or color of preparations were observed. The contents of Pravastatin sodium were fairly stable ranging from 98.4% to 101.7% during 13 weeks after storage at 30°C and 60% humidity (normal condition), or from 98.0% to 100.4% during the same periods after storage at 40°C and 75% RH humidity(accelerated condition).

3. Results and Discussion

3.1 Preparation of film formulations

All the film formulations containing HPMC-E5, PVA and combination of HPMC E5: PVA with propylene glycol asplasticizer, asparatame as sweetener were readily prepared by solvent casting method.

3.2 Evaluation of Prepared Films

From the results of the tests for physical characterization conducted, it is observed that the weight and thickness of all film samples were uniform within each formulation. Films formulated from HPMC E5were smooth, flexible and transparent whereas those prepared from PVA were slightly rough in texture, less flexible and translucent. All film formulations exhibited good folding endurance.

3.3 Surface pH

An acidic or alkaline pH of administered dosage forms can irritate the oral mucosa. The measured surface pH was found to be close to neutral in all the formulations which means that they have less potential to irritate the oral mucosa and therefore they should be fairly comfortable.

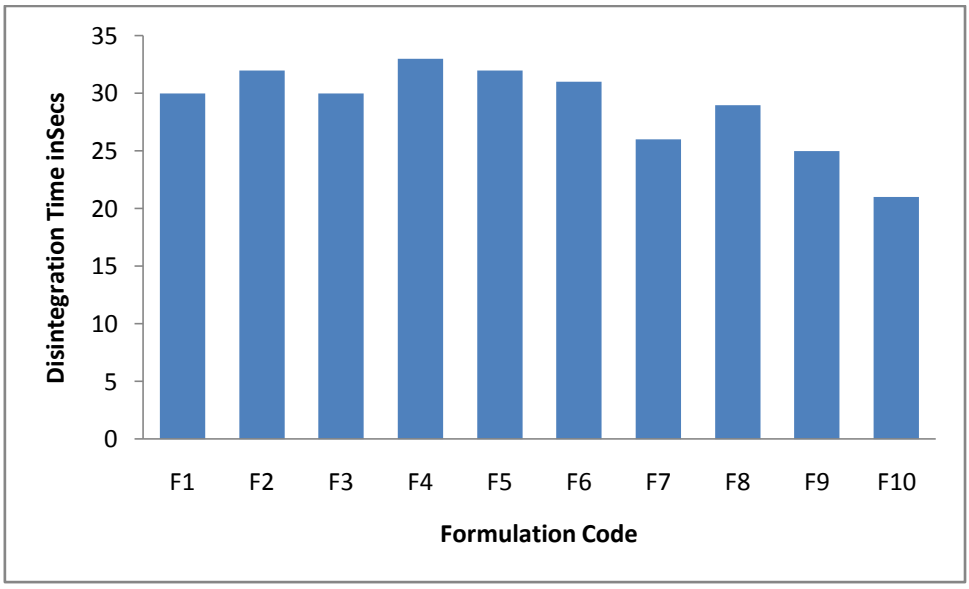
3.4 Drug content

All the film formulations of Pravastatin sodium containing polymers shown uniform drug content.

Table No. 2: Physico-chemical evaluation tests of fast dissolving films

Formulation code	Appearance	Thickness* (mm)	Folding Endurance	Surface pH*	Weight variation* (mg)	*In vitro* disintegration time *(sec)	Assay (%)
F1	Transparent	0.34±0.04	182±0.62	6.54±0.02	0.95±0.04	30±1.5	97.61±0.11
F2	Transparent	0.38±0.06	180±0.21	6.59±0.02	0.92±0.02	32±1.6	96.53±0.02
F3	Transparent	0.36±0.01	186±0.46	6.69±0.02	0.91±001	30±1.2	98.65±0.22
F4	Transparent	0.34±0.07	178±0.43	6.75±0.04	0.98±0.01	33±1.8	97.29±0.23
F5	Transparent	0.34±0.06	187±0.62	6.91±0.02	0.91±0.08	32±1.6	96.74±0.23
F6	Transparent	0.34±0.01	182±0.71	6.48±0.02	0.95±0.05	31±2.3	97.80±0.21
F7	Transparent	0.38±0.08	188±0.24	6.52±0.01	0.96±0.02	26±1.5	96.32±0.12
F8	Transparent	0.32±0.02	176±0.05	6.56±0.02	0.95±0.01	29±1.1	97.62±0.08
F9	Transparent	0.32±0.02	172±0.42	6.61±0.02	0.93±0.03	25±1.2	98.69±0.34
F10	Transparent	0.36±0.02	191±0.42	6.65±0.02	0.93±0.04	21±1.5	99.78±0.87

Figure No. 1: Disintegration Time for all Formulations



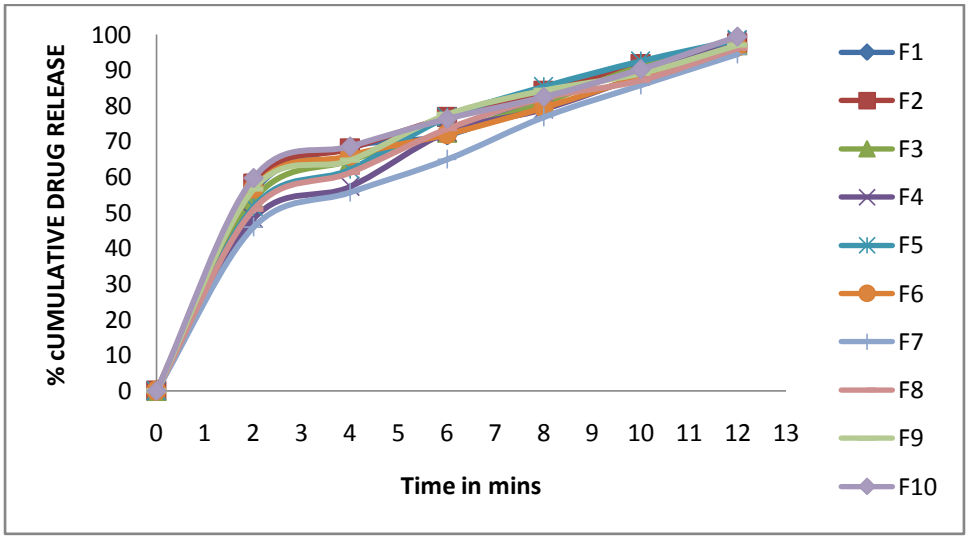
3.5 *In vitro* drug release studies

In vitro drug release studies in simulated saliva show more than 85 % release of Pravastatin sodium from all film formulations within 15 minutes with F10 showing a maximum percentage drug release of 99 %. This could be attributed to the higher rate of the larger proportion of the hydrophilic polymer PVA and HPMC E5.

Table No. 3: Cumulative % drug release for formulations (F1 – F10)

Cumulative % drug release						
Time	**2 Min**	**4 Min**	**6 Min**	**8 Min**	**10 Min**	**12Min**
F1	55.81±0.89	68.4±0.32	71.73±0.46	82.13±0.72	91.7±0.93	97.27±0.84
F2	58.11±0.98	68.01±0.27	76.75±0.65	84.06±0.98	91.58±0.57	97.44±0.64
F3	53.69±0.52	64.65±0.58	72.38±0.46	80.82±0.58	90.96±0.54	97.±0.44
F4	48.4±0.53	57.28±1.0	72.58±0.54	79.06±0.67	88.51±0.75	98.22±0.62
F5	51.59±0.55	62.12±0.54	76.74±0.63	85.33±0.89	92.54±0.84	98.54±0.42
F6	56.71±0.65	65.97±0.56	71.92±0.77	79.45±0.83	88.12±0.63	96.46±0.84
F7	45.93±0.88	55.74±0.49	71.89±0.74	76.83±0.89	85.74±0.40	94.48±0.68
F8	50.86±0.61	61.23±0.34	73.5±0.44	82.15±0.87	87.11±0.33	96.05±0.44
F9	56.58±0.65	64.72±0.53	77.51±0.50	84.23±0.55	89.02±0.74	97±0.32
F10	59.68±0.54	68.58±0.64	76.34±0.32	82.46±0.66	90.24±0.22	99.42±0.23

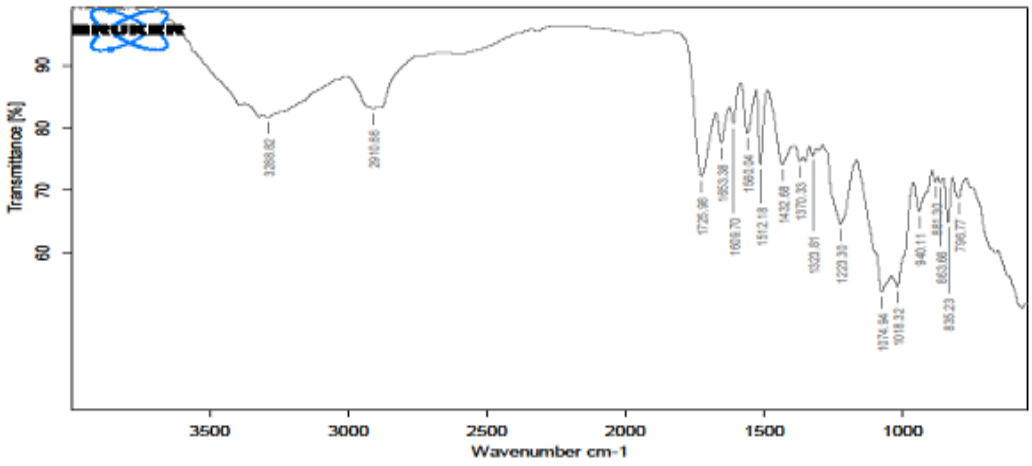
Figure No.2: Cumulative percent drug release of Pravastatin Sodium from all formulations



3.6 Compatibility studies

It was concluded that there is no compatibility between the drug and the excipients as no new peaks were produced. However there was only reduction in intensity of peaks due to dilution of the drug with excipients.

Figure No.2: FT-IR Spectra of Mixture



3.7 Stability studies

When the optimized oral film preparation was stored in an aluminium package under elevated temperatures for 3 months; No apparent changes observed in the Pravastatin sodium content, folding endurance, thickness, color of films. There is no significant changes *in vitro* disintegration and *in vitro* dissolution studies after 3months.

4. Conclusion

This study shows that it is possible to formulate fast dissolving films of Pravastatin sodium with improving patient compliance. The release rate of pravastatin sodium was found to be influenced by the concentration ratio of HPMC E5 and PVA. Incorporation of film forming agents further increases the drug release. The combination of HPMC E5 and PVA was found to be more suitable for design and development of pravastatin sodium fast dissolving films. All the evaluation parameters like thickness, folding endurance, surface pH, uniform content showed better results. Formulation F10 shows minimum disintegration and dissolution time in comparison to other formulations. F10 was the best formulation showed 99.42% drug release in 5 min. Data obtained from dissolution values revealed that drug release from formulation followed first order kinetics. *In vitro* stability evaluation of optimized formulation F10 with different environmental conditions, confirms the potential of films for longer storage.

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