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Performance Evaluation of Melt in Films of Rizatriptan Benzoate Using Different Film Forming Agents

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ABSTRACT

The present study was aimed to formulate and evaluate melt in mouth films of Rizatriptan benzoate using polymers pullulan, carragennan, xanthan gum and guar gum as the film forming agents. Rizatriptan benzoate is a 5-HT1 receptor agonist of the triptan class of drugs, used in the management of migraine. Glycerol was incorporated as plasticizer to improve flexibility of films. Sorbitol as sweetener. Sodium starch glycolate used as a disintegrant. An attempt was made to prepare melt in mouth films of Rizatriptan benzoate with the purpose of developing a dosage form for quick onset of action, which will be beneficial in managing severe condition of migraine attack, aiding in enhancement of bioavailability and easy for administration. The films were prepared by solvent casting method. They were evaluated for physicochemical characterization such as uniformity of weight, thickness, folding endurance, uniformity of drug content, surface pH, percentage elongation and tensile strength all of which showed satisfactory results. The formulations were also subjected for in vitro disintegration and in vitro drug release. Melt in mouth films of Rizatriptan benzoate containing single polymer pullulan (FRA1) showed best results, in terms of tensile strength, percentage elongation, folding endurance (>300), in-vitro disintegration time, surface pH, thickness and percentage content uniformity. Satisfactory dissolution profile was obtained with maximum release of 96% of drug within 120 sec. The stability studies showed that there was no appreciable change in parameters when stored at three different temperatures.

Keywords: Melt in Mouth Films, Solvent Casting, Rizatriptan benzoate, Rapid disintegration.

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INTRODUCTION

Among the different routes of administration, the oral route of administration continues to be most preferred route due to various advantages including ease of administration, avoidance of pain, versatility and most importantly patient compliance[1]. These dosages are administered in the form of pills, granules, powders and liquids. Generally, a pill is designed for swallowing intact or chewing to deliver a precise dose of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of throat choking[2]. In order to assist these patients, several fast dissolving drug delivery systems have been developed. Fast dissolving drug delivery systems can be manufactured by a variety of technologies, including direct compression, wet granulation and freeze-drying. Some make use of different disintegrating mechanisms, such as high level of disintegrating or effervescent agents, which cause the dosages to disintegrate rapidly in the mouth. Most of the existing fast dissolving drug delivery systems are in the form of tablets and are designed to dissolve or disintegrate in the patient's mouth within a few seconds or minutes without the need of water or chew. But even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. The most common complaint was tablet size, followed by surface form and taste[3]. Hence, Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/capsules to modified release tablets/capsules to oral disintegrating tablet (ODT) to the recent development of oral strip (OS), a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity[4]. A migraine headache is thought to be caused by widened blood vessel exerting pressure on the brain. In migraine, patients experience one or more short lived attacks of intense headache, usually at the same time every day and often at night and are usually of sufficient severity to disturb or prevent daily activities. Rizatriptan is a 5-HT1 receptor agonist "triptan". It mainly acts by narrowing the blood vessel in the brain and thereby reducing pressure and pain in the brain. The bioavailability of Rizatriptan is about 74% which is superior to a poor 14-17% of sumatriptan. Rizatriptan relieves nausea, vomiting, photophobia (light hypersensitivity) and phonophobia(sound hypersensitivity) associated with migraine attacks pain. Thus for an antimigraine drug like Rizatriptan , a quick release dosage form will be very suitable, so that at times of severe attacks the film can be conveniently be consumed by the patient without the help

of water, for an immediate action. Also, since the drug starts getting absorbed from the oral cavity itself, the bioavailability may be expected to increase. Hence, it was thought worthwhile to formulate quick release film type of dosage form for Rizatriptan.

MATERIALS AND METHOD

Rizatriptan was a gift sample from local pharmaceutical company. Pullulan was obtained from Hayashibara co. Ltd, xanthan gum and carrageenan was obtained from HiMedia Laboratories Pvt. Ltd, Mumbai. All the other chemicals used were of analytical grade.

Formulation of Melt in Mouth Films of Rizatriptan Benzoate

Weighed quantities of polymers (soaked in distill water if necessary) were dissolved in separate volumes of distilled water with constant stirring. The dissolved polymers were mixed together and deaerated. To this blend of polymer, aqueous solution of drug Rizatriptan , glycerol as plasticizer, sodium starch glycolate as disintegrant and sorbitol as sweetener were added and mixed to get a homogeneous solution and volume was made up to 10 ml. The casting solution (10 ml) was poured into glass moulds of area 16 cm^2 and kept for drying at 50 $^{\circ}C$ for 8 h. After drying films were removed with the help of sharp blade and kept in desiccator for 24 h. Cut the films into square dimension of 4 cm^2, so that each film contained about 6.25 mg of drug. These films were kept in desiccator at relative humidity 30-35 % for 2 days for further drying, wrapped in aluminum foil and packed in self-sealing covers and stored in desiccator till further studies. Formulation composition of Rizatriptan benzoate melt in mouth films reported in Table 1.

Table 1. Formulation compositions of Rizatriptan melt in mouth films

Formulation Code	Pullulan (mg)	Carrageenan (mg)	Xanthan Gum (mg)	Guar Gum (mg)	Drug (mg)	Glycerol (mg)l	Sorbitol (mg)	SSG (mg)
FRA1	500	-	-	-	25	150	30	10
FRA2	700	-	-	-	25	150	30	10
FRA3	1000	-	-	-	25	150	30	10
FRB1	-	500	-	-	25	150	30	10
FRB2	250	250	-	-	25	150	30	10
FRB3	400	100	-	-	25	150	30	10
FRC1	-	-	500	-	25	150	30	10
FRC2	250	-	250	-	25	150	30	10
FRC3	400	-	100	-	25	150	30	10
FRD1	-	-	-	500	25	150	30	10
FRD2	250	-	-	250	25	150	30	10
FRD3	400	-	-	100	25	150	30	10
FRE1	200	100	100	100	25	150	30	10
FRE2	100	100	100	200	25	150	30	10
FRE3	100	100	200	100	25	150	30	10

Characterization

Physical Appearance

All the films were visually inspected for color, flexibility, homogenecity and smoothness

Uniformity of Weight and Film Thickness Test

The individual weight of 10 samples of each formulation was determined and the average weight was calculated[5]. Thickness of films was evaluated by using a puncture test and texture analyzer (Instron® 3366-2716015, Germany) at 5 different strategic locations. This is helpful in determination of uniformity in the thickness of the film[6, 7].

Surface pH

The surface pH of the patch was determined in order to investigate the possibility of any side effects (*in-vivo)*, since an acidic or alkaline pH may cause irritation to the oral cavity. The film to be tested was placed in Petri dish and was moistened with 1 ml of distilled water and kept for 30 sec. The pH was noted after bringing the electrode of pH meter in contact with the surface of the formulation and allowing it to equilibrate for 1 minute[8]

Folding Endurance

The flexibility of patches can be measured in terms of what is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patch at the same place till it broke. The number of times the patch could be folded at the same place, without breaking gives the value of folding endurance.

Drug Content

Drug content uniformity was determined by dissolving the film of area 4 cm^2 in 0.1N HCl (pH 1.2) in a 100 ml volumetric flask. The absorbance of the solution was measured usingUV-VIS spectrophotometer (Shimadzu UV 1800) at a wavelength of 230 nm and drug content was determined[7].

Measurement of Tensile Strength and Percentage Elongation

Tensile test was performed to assess the strength and elasticity of optimized film formulation. The elongation to break is the strain on a material when it breaks and it gives an indication of toughness and stretch ability prior to breakage. The instrument, which was designed in our laboratory, as per literature specification was used for the measurement of tensile strength. The strips were clamped at the static end and were attached to the movable rod on railing with the help of a clip. The weights were gradually added to the pan to increase the pull force until the film was cut. The elongation was determined simultaneously by noting the distance travelled by

the pointer, before break of the film, on the graph paper. The weight required to break the film was noted as the break force. The tensile strength was calculated using Allen's formula

In vitro Disintegration Time

In vitro disintegration test was performed by placing the film in a glass beaker of 25 ml simulated salivary buffer (pH 6.8) with constant stirring. The disintegration time was the time when the film starts to break or disintegrates[9].

In vitro Dissolution Studies

The *In vitro* dissolution studies of melt in mouth films of rizatriptan was carried out in a beaker containing 50 ml of the simulated salivary fluid (pH 6.8) as a dissolution medium, maintained at 37 ± 0.5 °C. The medium was stirred at 100 rpm. Aliquots (3ml) of the dissolution medium were withdrawn at 15, 30, 45, 60, 75, 90, 105 and 120 s intervals and the same amount was replaced with the fresh medium. Absorbance was measured spectrophotometerically at a wavelength of 230 nm after appropriate dilutions[9].

Drug Release Kinetic Studies

Different mathematical models are applied for describing the kinetics of the drug release process from any system; the most suited being the one which best fits the experimental results. The *in vitro* drug release kinetic analysis is done by the software "PCP Dissolution Version 2.08". Kinetics of rizatriptan release from formulations was determined by finding the best fit of the dissolution data (drug-released fraction against time) to distinct models: zero-order, first-order and Higuchi.

Stability Studies

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. The stability studies of the formulated fast dissolving films were carried out on prepared films kept at different temperature. The film was packed in aluminum foil and stored in a desiccators for stability studies at 2 ± 8 °C (45% RH), 25 ± 30 °C (60% RH), and 45 ± 50 °C (75% RH) for a period of 45 days. The films were observed for physical appearance, surface pH, folding endurance, drug content and maximum drug release at the end of 45 days was noted[10].

RESULTS AND DISCUSSION

Physical appearance

Physical appearance of the films was evaluated; all the films were easily removable from the

mould, flexible and without any recrystallization.

Uniformity of weight

The individual weight of 10 samples of each type formulation was determined and the average weight was calculated. It was observed that weight of the entire film sample in each formulation was uniform. In the case of formulation FRA the weight ranged from 92-139 mg, FRB ranged from 71 - 80 mg, FRC ranged from 73-78mg, FRD ranged from 66 - 83 mg, and FRE ranged from 78- 83 mg. The results of weight variation were represented in Table 2.

Film thickness

Thickness of each film of all formulation was found to be uniform. Thickness ranged from 0.124 mm to 0.291mm. As the concentration of carrageenan, xanthan gum and guar gum increased, the thickness of the films also increased. The results of film thickness were represented in Table 2.

Surface pH

As an acidic or alkaline pH may cause irritation to the mucosa, an attempt was made to keep the surface pH as close to neutral as possible, by the proper selection of the polymers for developing the films. The surface pH of formulations was found tobe in the range of 6.34 to 7.03, as shown in Table 2. The surface pH for all the formulations was well within range of neutral pH and not cause irritation in the oral cavity and ultimately achieves patient compliance.

Folding endurance

It was found that all the formulations showed good folding endurance, that is greater than 300,except for FRA1 which was brittle(<300).Result revealed that all the films are flexible.

Estimation of drug content of the films

The drug content was estimated as per the procedure mentioned in the methodology. The amount of drug present in the films was found to be uniform for all the formulation and drug content was found to be ranged between 93-101 %.

Tensile strength measurement

The strength and elasticity of the film was reflected by the parameters like tensile strength (TS) and elongation at break (E/B). In formulation FRA3, containing pullulan in high concentration exhibited least tensile strength of 0.923±.006 Kg/mm^2 and least percentage elongation 9.83±0.27%. Hence the formulation FRA3 was found to be brittle. When the pullulan concentration was decreased, the tensile strength value increased from 0.923±.0006 to 1.23±0.06 $Kg/mm^2$and percentage elongation increased from 9.83±0.27% to 14.4±0.34 % as seen in FRA1 formulation. As concentration of the polymer pullulan increased, the brittleness also increased and as the concentration of pullulan decreased, the films had sufficient strength and found

flexible to handle. The tensile strength and percentage elongation of FRB1 was 1.49±.022Kg/mm^2 and 58.0±0.34% respectively; FRB1 contained carrageen as the single polymer and found to be elastic. In FRB3 formulation showed satisfactory toughness and flexibility which is stated to provide better patient compliance as they are less likely to cause contact irritation unlike an unduly elastic film. Similar observations were obtained in case of FRC and FRD formulations. In the formulation, containing all the polymers in different combination (FRE1, FRE2, FRE3) the results obtained were satisfactory, among them FRE1was considered to be the best, showing tensile strength of 1.283±0.068 Kg/mm^2 and 22±0.23 percentage elongation. Hence we concluded that tensile strength is influenced by the type of polymer used as well as its concentration. The results for all formulations are reported in Table 2.

***In vitro* disintegration time**

The disintegration time is the time when the film start to break or disintegrate. It is seen that formulation FRA1 (11.5±0.38 sec) containing single polymer pullulan disintegrated fast when compared to the rest of the formulations. The formulation FRA1 was the thinnest film among all fifteen formulations and it leads to fast disintegration. The formulation FRB1 and FRB2 (30±1.02, 32±1.04 sec) showed the least disintegration time, due to higher concentration of carrageenan in them. This may also be related to its thickness, since FRB1 and FRB2 showed highest thickness 0.275±0.0048 and 0.268±0.0022mm respectively. The observation made here can be correlated with the study done by Choudhary *et al*[11]. According to his study disintegration time of the films was influenced by thickness of films. The results for all formulations are given in Table2

Table 2: Uniformity of weight, thickness, surface pH, tensile strength and percentage elongation and disintegration time of the film

Formulation Code	Weight (mg)*	Thickness (mm)*	Surface pH#	Tensile strength*(Kg/mm^2)	%Elongation*	*Disintegration Time (sec)
FRA1	92±1.04	0.122±0.0034	6.55±0.003	1.23±0.06	14.4±0.34	11.5±0.38
FRA2	114.3±1.05	0.128±0.0012	6.34 ±.035	1.18±0.037	12.5±0.36	13.5±0.43
FRA3	139.1±1.02	0.124±0.0071	6.4±0.016	0.923±.006	9.83±0.27	22.6±1.05
FRB1	80.01±0.37	0.275±0.0018	6.26±0.034	1.49±.022	58.0±0.34	30±1.02
FRB2	76.7±1.53	0.268±0.0048	6.35±0.056	1.451±.044	45.1±0.28	32.01±1.04
FRB3	71.2±0.87	0.203±0.0022	6.78±.006	1.289±0.011	22.3±0.58	15.5±0.57
FRC1	78.9±0.83	0.260±0.0016	7.02±.020	1.48±0.038	51.8±1.04	24.23±0.59
FRC2	75±0.16	0.193±0.0014	6.29±0.021	1.35±0.068	45.8±.29	17.3±0.5
FRC3	73.8±0.33	0.182±0.0016	6.76±0.003	1.24±0.091	40.1±0.1	12.10±1.73
FRD1	83.8±0.22	0.269±0.0042	6.67±0.012	1.593±0.094	65±0.25	30.01±1.33
FRD2	73.3±1.05	0.233±0.0025	6.89±0.002	1.428±.062	61±0.58	23.04±1.22
FRD3	66.1±1.27	0.284±0.0032	7.10±0.006	1.31±0.072	54.2±0.12	14.6±1.03

FRE1	83.5±0.72	0.216±0.002	7.03±.0014	1.283±0.068	22±0.23	12.3±0.44
FRE2	78.1±0.93	0.234±0.0039	6.87±.0025	1.32±0.11	58.3±0.33	18.7±1.23
FRE3	82.6±0.51	0.291±0.0038	6.66±.0056	1.30±0.081	65±0.43	13.6±0.53

* Each value is the mean ± SD; n = 6 determinations

Each value is the mean ± SD; n = 3 determination

***In vitro* Drug Release Studies**

An ideal melt in mouth film or strip comprises of water soluble and/or water swellable film forming polymer due to which the film or strip dissolves instantaneously when placed on the tongue in the oral cavity, thus rapid drug release is obtained. *In vitro* drug release from film depends on several factors, such as the manufacturing process, the type of excipient, drug solubility and concentration, polymer concentration and pH of the dissolution medium. From the dissolution profile of various formulation prepared it is observed that the formulation containing single polymer pullulan (FRA1 and FRA2) showed good release rate; as the time required for wetting and dissolving the drug molecules present in the polymer matrices was decreased and disintegration and dissolution was increased. The formulations containing single polymers like carrageenan, xanthan gum and guar gum (FRB1, FRC1, and FRD1) showed less drug release when compared to their formulation in combination with pullulan. The release of drug at the end of 120sec, for FRB1, FRC1, and FRD1 showed 58%, 68%and 65% respectively. This may be due to the gelling nature of these natural gums, which delayed the drug release from the film. The formulations FRB2, FRC2, FRD2 showed comparatively better release than their formulations containing single polymer (FRB1, FRC1, and FRD1), showing drug release of 62.3%, 82.7% and 76.1% respectively. The formulation FRB3, FRC3, FRD3 showed good drug release (77.7%, 92%, and 87.8%). These films contained pullulan in high concentration, which increased wettability and penetration of water into the film matrices and hence increased diffusion of the drug, which was responsible for the fast drug release from the films. The films, which were prepared using combination of all polymers (FRE1, FRE2, and FRE3), showed very good drug release. This indicated that good release from the formulation was obtained when all the polymers were used in optimum concentration. In all the fifteen formulations prepared, the formulations containing single polymer pullulan showed the best release i.e. formulation FRA1, followed by the formulation prepared using combination of the entire polymer which was in correlation with the study done by Kulkarani et al[12]. Among the formulation prepared using xanthan gum and guar gum, formulation containing xanthan gum showed better drug release. The least release was seen with the formulation containing carrageenan as polymer. In case of

formulation FRA; FRA1 showed better release than FRA2 and FRA3. FRA1 contains least concentration of pullulan when compared to FRA2 and FRA3.FRB1 contained carrageenan alone as the polymer wereas in FRB2 contained equal concentration of pullulan and carrageenan, which showed comparatively better release than FRB1, formulation FRB3 had higher concentration of pullulan than carrageenan and showed better release than FRB1 and FRB2. Similar observation can be made in case of FRC and FRD formulations. When it comes to FRE formulation, which contained all polymers in different combination, FRE1 showed the best result than FRE3 and FRE2. From the data, it is evident that using all the polymers in optimum concentration, the drug release can be improved.

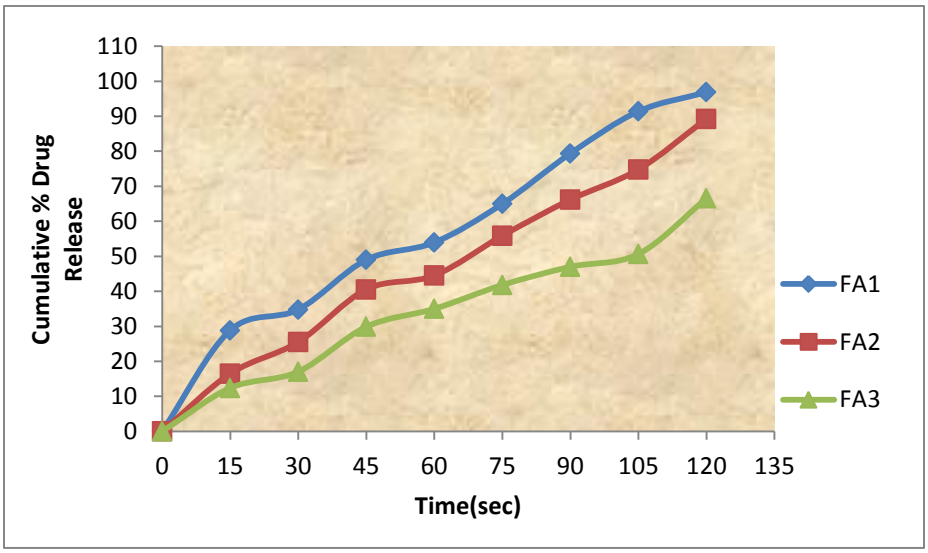

Figure 1.*In vitro* drug release profile of formulation containing pullulan as the polymer

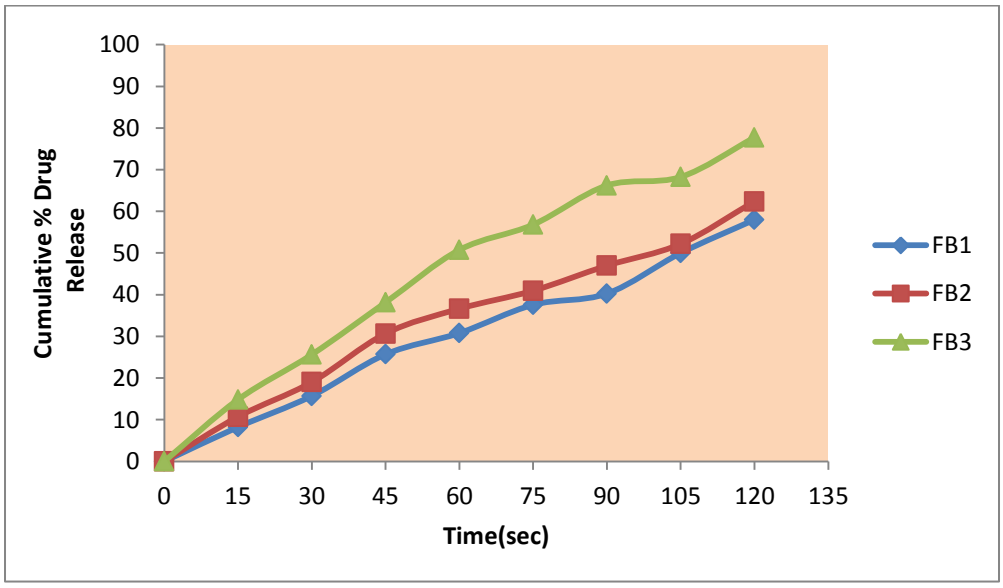

Figure. 2*In vitro* drug release profile of formulation with pullulan and carrageenan as the polymer

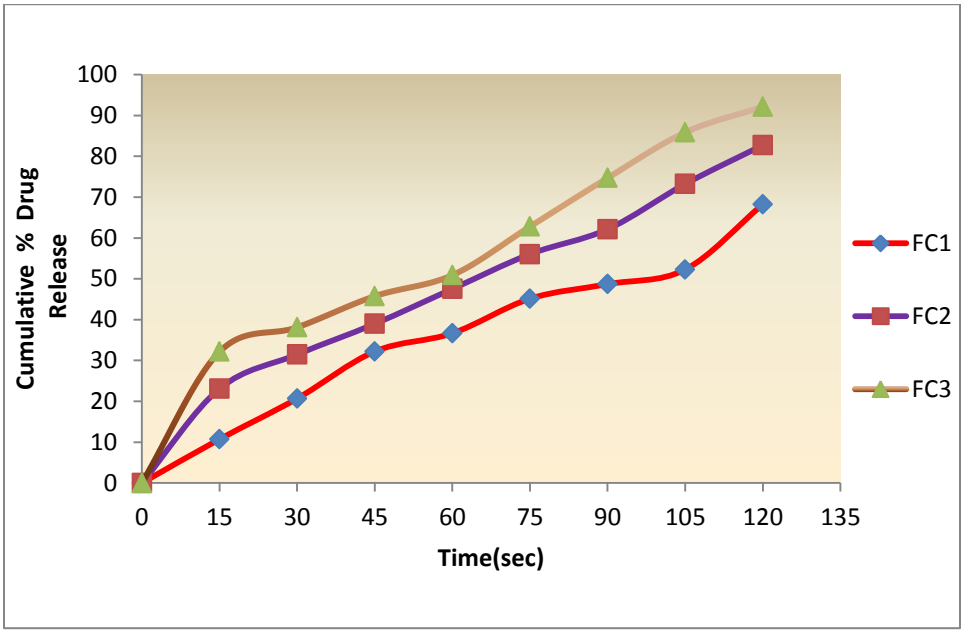

Figure 3. *In vitro* drug release profile of formulation containing pullulan and xanthan gum as polymer

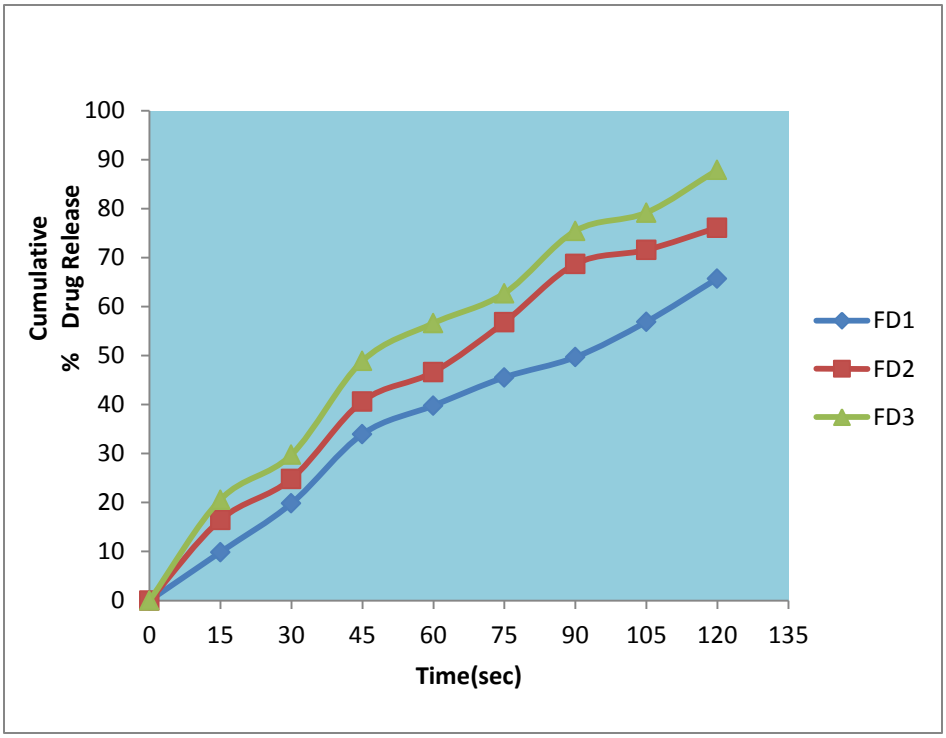

Figure 4. *In vitro* drug release profile of formulation containing pullulan and guar gum as polymer

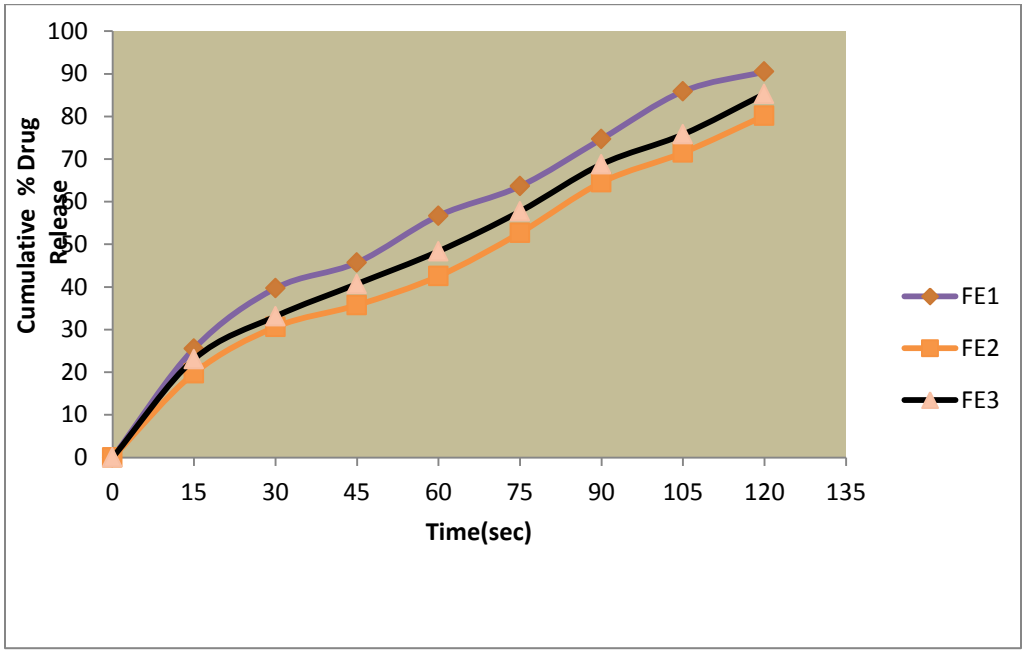

Figure 5.*In vitro* drug release profile of formulation containing pullulan, carrageenan, xanthan gum and guar gum as polymers

Drug Release Kinetic Studies

In order to determine the release mechanism that provides the best description to the pattern of drug release, the *in vitro* release data were fitted to zero order, first order, and Higuchi matrix. The release data were also kinetically analyzed using the Korsmeyer–Peppas model. The release exponent (n) describing the mechanism of drug release from the matrices was calculated by regression analysis using the following equation.

$$M_t / M_\infty = K_{tn}$$

Where Mt/M∞ is the fraction of drug released (using values of M/M∞ within the range 0.10–0.60) at time t and K is a constant incorporating the structural and geometric characteristics of the release device. A value of n = 0. 5 indicates case I (Fickian) diffusion, 0.5 < n < 1 indicates anomalous (non-Fickian) diffusion, and n =1 indicates case II transport (Zero order release), n >1 indicates Super case II transport. It was observed that formulations FRB2, FRB3, FRC2, FRC3, FRD1, FRD2, FRD3, FRE1and FRE3 followed first order, whereas FRA1, FRA2, FRA3, FRB1, FRC1, FRE2 followed zero order. From the values of release exponent "n" obtained by applying peppas equation, it is observed that the mechanism of drug release was Non Fickian diffusion (0.5 > n) for all the formulations, n value ranged from 0.501 to 0.906 which indicated that, type of release is anomalous transport. Apart from that, the R^2 values of Higuchi matrix model for most of the formulations were more than 0.95 indicating that diffusion of drug from the swelled polymer followed the matrix diffusion process.

Stability Studies

Stability studies were carried out for 45 days as per ICH guidelines at 2°C ±3°C, 25°C ±2°C (60% RH) and 45°C ± 2°C (75% RH). The films were observed for physical change, percentage drug content, surface pH, folding endurance and percentage drug release. Melt in mouth films of Rizatriptan benzoate was found to be physically and chemically stable and showed no significant change in terms of physical characteristics, surface pH, folding endurance, percentage drug content and percentage drug release. It is evident from the stability study that all the films are stable under normal shelf-conditions.

CONCLUSION

Melt in mouth films are the most advanced form of oral solid dosage form due to more flexibility and comfort. In the present study an attempt was made to formulate melt in mouth films of Rizatriptan benzoate, which offers a suitable and practical approach in serving the desired objective of faster disintegration and dissolution characteristics with increased bioavailability. Based on the encouraging results, the Rizatriptan benzoate melt in mouth films can be considered suitable for clinical use in the treatment of migraine, where rapid onset of action is desirable along with convenience of administration. The method of preparation is found to be simple and requires minimum excipients, thus making the product cost-effective. Further, these findings may help the industry to scale up for commercial production.

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