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Original Article

DEVELOPMENT AND CHARACTERIZATION OF ORAL SWELLABLE RAPID RELEASE FILM WITH SUPERDISINTEGRANT-SURFACTANT

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ABSTRACT

Objective: Oral disintegrating films consisting of hydrophilic polymer are designed to be quickly hydrated by saliva, adhere to the mucosa and disintegrate rapidly to release the drug. The aim of the present study was to prepare stable, flexible swellable rapid release oral films with hydroxypropyl methylcellulose E15 LV (HPMC) and polyvinyl alcohol (PVA) in different ratios. Guar gum was incorporated as the mucoadhesive agent. In order to achieve rapid disintegration of the film cross carmellose sodium (superdisintegrant) and surfactant like Tween 80 were added. The model drug used in the study was diclofenac sodium.

Methods: Films were developed using HPMC E15 LV and PVA by solvent casting method and characterized for thickness, swelling index, disintegration time, folding endurance, drug content, and *in vitro* drug release pattern and kinetics.

Results: The prepared swellable rapid release oral films were quite flexible and transparent with a smooth texture. The swelling index study confirmed that the films possessed the desired swelling property. Fastest disintegration was observed with the oral film containing HPMC: PVA in the ratio of 2:1, guar gum at 120 mg, 20% w/w crosscarmellose sodium and 4%w/w Tween 80. The swellable rapid release oral films were found to follow either Higuchi or Korsmeyer-Peppas model with drug release following either Fickian or non-Fickian diffusion. Maximum drug release of around 70% was observed from the above-mentioned film in 1hr in simulated salivary fluid.

Conclusion: Therefore, swellable rapid release oral films with HPMC E15 LV: PVA, guar gum, croscarmellose sodium and Tween 80 demonstrated satisfactory swelling, rapid disintegration and improved drug release for oromucosal absorption.

Keywords: HPMC E15 LV, PVA, Guar gum, Crosscarmellose sodium, Swelling index, Oral rapidly swellable disintegrating film

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INTRODUCTION

Attempts towards developing innovative drug delivery systems, ensuring efficacy, safety and patient acceptability led to the development of oral films [1]. Their improved systemic bioavailability results from bypassing first-pass effect and better permeability due to a well-supplied vascular and lymphatic drainage in the oral mucosa [2]. These films are taken without water due to their ability to disintegrate within a few seconds releasing medication in oral mucosa for absorption and thus can be used for dysphasic and schizophrenic patients. Oral films are found to be satisfactory in many situations like allergic conditions, cold and cough, sore throat, nausea, pain, mouth ulcers, CNS disorders and CVS disorders [3]. They can be broadly classified as mucoadhesive and non-mucoadhesive oral films. Oral mucoadhesive films can be further classified as and swellable sustained-release films. Non-mucoadhesive oral films consist of orodispersible films.

Swellable rapid release films are prepared by using swellable polymers like hydroxypropylmethylcellulose, sodium carboxymethylcellulose, polyethylene oxide, pectin, alginate, xanthan gum. Bhikshapathi *et al.* [4] reported that films prepared with hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA) were quite flexible with the desired peelability. Systems consisting of these polymers absorb a significant amount of water to form a gel. As dissolution medium or biological fluid penetrates the film matrix, swelling is initiated and drug molecules begin to move out of the film by diffusion. In order to facilitate the faster onset of swelling in the mouth, there is a need to accelerate saliva secretion. This can be achieved by incorporating saliva stimulating agents in the formulation. Generally, acids which are used in the preparation of food can be utilized as salivary stimulants, e. g, citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid etc. Among these, citric acid is most preferred saliva stimulating agent in the formulation. Faster disintegration of the film can be attained by using superdisintegrants like sodium starch glycolate, cross carmellose sodium, cross povidone to promote the faster release of drug. Sarangi *et al.* [5] reported that films prepared with 20% w/w superdisintegrant demonstrated faster disintegration of the films. Gum is added in the oral film formulation, promotes adhesion to the mucosal surface and prevents swallowing of swollen film on administration. The prepared film therefore, is designed to swell rapidly, stick/adhere to the oral mucosa for rapid disintegration to occur to release the drug, which is absorbed by bypassing hepatic first-pass metabolism.

In the present study oral swellable rapid release films of diclofenac sodium were prepared using HPMC E15 LV, PVA and guar gum. Other excipients like cross carmellose sodium, citric acid and Tween 80 were incorporated for their superdisintegrant, saliva stimulating and wetting effects, respectively. The ultimate goal of the study was to develop oral films with rapid swelling and disintegration properties to ensure fast release of drug and rapid onset of action when placed in oral mucosa.

No other previous studies have developed swellable rapid release oral films by employing superdisintegrant, surfactant and saliva stimulating agent simultaneously in the formulation.

MATERIALS AND METHODS

Material

Hydroxypropylmethylcellulose E15 LV was purchased from Loba Chemie Pvt. Ltd, polyvinyl alcohol from Merck and Co., guar gum from Akshar Exim Company Pvd. Ltd, dibutyl phthalate from

Chemicorp Specialties India Private Limited, citric acid and cross carmellose sodium (CCS) from Loba Chemie Pvd. Ltd. Diclofenac sodium was obtained as a gift from Martina Biogenics Pvt. Ltd. All other solvents and chemicals were of analytical grade.

Preparation of the oral swellable rapid release film

Oral swellable rapid release films were prepared by solvent casting method. Drug was dissolved in water and all other ingredients (HPMC E15 LV, PVA, guar gum, dibutyl phthalate and Tween 80) were added one by one in the sequence mentioned, stirred for 1h, which was kept aside to remove all the air bubble entrapped. Then citric acid and cross carmellose sodium were added and stirred for 1 h. The solution was allowed to stand for 30 min for deaeration to occur. The solution was casted on a glass plate and dried at room temperature for 24 h. Then the dried films were peeled off from the glass plate, cut into appropriate sizes, and stored in a desiccator until use.

Various formulations were prepared by changing the amount of superdisintegrant (5, 10, 15 and 20%w/w) at the same ratio of HPMC: PVA (D1-D4 formulations), changing the amount of gum (120 mg and 180 mg) at 3 different ratios of HPMC: PVA (1:1, 1:2 and 2:1) and keeping superdisintegrant at 20%w/w (GA1-GB3 formulations) Eqn(1) and by adding different surfactants (2%w/w) and keeping HPMC: PVA at 2:1, guar gum at 180 mg and superdisintegrant at 20%w/w (T-P formulations). T1-T3 formulations were obtained after observing that among the three surfactants selected for study, the formulations with Tween 80 (4%w/w) exhibited best possible properties with the films. Different ratios of HPMC E15 LV: PVA were used to find the best ratio, which will give highly flexible films. The amounts of guar gum, superdisintegrant and Tween 80 were adjusted to obtain films having desirable swelling and adhesive property with the rapid disintegrating property. For the purpose of the study, 16 different formulations were developed. Composition of the various formulations are given in table 1.

Table 1: Formulations containing different % of superdisintegrant, varying ratios of HPMC: PVA, varying amount of gum, different surfactants, varying % of selected surfactant and drug-loaded formulations

Batch	Drug (mg)	HPMC E15 LV (mg)	PVA (mg)	Surfactant (mg)	Dibutyl phthalate (mg)	Guar gum (mg)	CCS (mg)	Citric acid (mg)	Water (mg)
D1	-	500	500	-	5.25	180	102.26	757	q. s.
D2	-	500	500	-	5.25	180	204.44	654.77	q. s.
D3	-	500	500	-	5.25	180	306.67	522.54	q. s.
D4	-	500	500	-	5.25	180	408.89	450.32	q. s.
GA1	-	500	500	-	5.25	120	408.89	510.32	q. s.
GB1	-	333	667	-	5.25	120	408.89	510.32	q. s.
GC1	-	667	333	-	5.25	120	408.89	510.32	q. s.
GA2	-	500	500	-	5.25	180	408.89	510.32	q. s.
GB2	-	333	667	-	5.25	180	408.89	510.32	q. s.
GC2	-	667	333	-	5.25	180	408.89	510.32	q. s.
T	-	667	333	40.9	5.25	180	408.89	469.42	q. s.
S	-	667	333	40.9	5.25	180	408.89	469.42	q. s.
P	-	667	333	40.9	5.25	180	408.89	469.42	q. s.
T1	-	667	333	40.9	5.25	180	408.89	469.42	q. s.
T2	-	667	333	61.35	5.25	180	408.89	448.97	q. s.
T3	-	667	333	82	5.25	180	408.89	368.32	q. s.
TA1	-	500	500	82	5.25	120	408.89	428.32	q. s.
TA2	-	333	667	82	5.25	120	408.89	428.32	q. s.
TA3	-	667	333	82	5.25	120	408.89	428.32	q. s.
TB1	-	500	500	82	5.25	180	408.89	368.32	q. s.
TB2	-	333	667	82	5.25	180	408.89	368.32	q. s.
TB3	-	667	333	82	5.25	180	408.89	368.32	q. s.
TA D1	102.2	500	500	82	5.25	120	408.89	266.12	q. s.
TA D2	102.2	333	667	82	5.25	120	408.89	266.12	q. s.
TA D3	102.2	667	333	82	5.25	120	408.89	266.12	q. s.
TB D1	102.2	500	500	82	5.25	180	408.89	266.12	q. s.
TB D2	102.2	333	667	82	5.25	180	408.89	266.12	q. s.
TB D3	102.2	667	333	82	5.25	180	408.89	266.12	q. s.

Characterization

Organoleptic characterization

Formulations were observed visually for their colour, appearance, texture and opacity. Stickiness was checked manually with fingers.

Determination of surface pH

The surface pH of the films was determined at room temperature (25 °C). 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 min. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1.0 min. The pH of the formulations was determined using digital pH meter (Fisher Scientific-Accumet AE 150) [6].

Folding endurance

Folding endurance was determined by repeated folding of the film at the same place till the strip breaks. The number of times the film is folded without breaking was computed as the folding endurance value [7].

Moisture loss (Water vapor transmission)

The percent moisture loss was determined by placing the prepared film in desiccators containing anhydrous calcium chloride. The film was taken out after 72 h and reweighed. The percent moisture loss was calculated using following formula

$$\% \text{ Moisture Loss} = [(W_0 - W_t)/W_0] * 100$$

Where W_0= initial weight, W_t = final weight [8]

Weight uniformity

Weight variation was studied by individually weighing randomly selected films and calculating the average weight [9].

Thickness

The thickness of the patch was measured using digital Vernier Caliper with a least count of 0.01 mm [10].

Swelling index

Film swelling studies were conducted using phosphate buffer (pH 6.8) and water. Weighed film was submerged separately in

phosphate buffer (pH 6.8) and water. Increase in the weight of film was noted at constant pre-determined time and determination was carried out till two consecutive values became same. Degree of swelling was determined by the formula.

Degree of swelling = [(final weight-initial weight)/initial weight] *100 .. Eqn(2)

Disintegration time

Disintegration test was carried out in water and phosphate buffer (pH 6.8) at a temperature of 37±0.5℃. The disintegration test was performed in the USP disintegration time testing apparatus. A portion of film measuring (1 X 1 cm^2) was introduced into each tube of the disintegration apparatus IP. A disc was added into the tube. The assembly was suspended in medium and operated until the film disintegrated [11].

Drug content determination

Oral films containing drug equivalent to 5 mg was cut from the respective film formulations and were added to phosphate buffer (pH 6.8), which was stirred with a magnetic stirrer for complete leaching of drug. The dispersion was filtered through Whatman filter paper No. 1. An aliquot of filtrate was withdrawn and its absorbance was measured spectrophotometrically at 276 nm (Shimadzu UV-VIS 1800 spectrophotometer). The drug content of formulations was determined from calibration curve of the drug in the said buffer [12, 13].

***In vitro* drug release studies**

Drug release studies were carried out in 900 ml of phosphate buffer (pH 6.8) in USP Type II apparatus. The medium was equilibrated to the temperature of 37±0.5 °C. A cut portion of film formulation containing drug equivalent to 40 mg was used for the study. Stirring speed was fixed at 50 rpm and study was continued for 1 h. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions of the filtrate were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} of 276 nm using a UV-vis spectrophotometer. Drug release data were subjected to mathematical modelling by using zero order, first order, Higuchi and Korsmeyer-Peppas models [14].

RESULTS AND DISCUSSION

HPMC absorbs water rapidly and swells to form a matrix layer due to which HPMC-based drug delivery systems exhibit controlled drug release behaviour [15, 16]. In order to improve the peelability and to achieve customized drug release from the developed oral swellable rapid release films, HPMC was used in combination with PVA, which is a disintegrating polymer capable of facilitating burst release. Additionally, both HPMC E15 LV and PVA were chosen because of their mucoadhesive nature and biodegradability. In this study, dibutyl phthalate was used as the plasticizer to improve the flow property and strength of the film former [17-18]. Among the various superdisintegrants, crosscarmellose sodium was selected as it rapidly absorbs water and facilitates rapid disintegration of the oral film.

The films prepared were found to be colorless, odourless, smooth in appearance and without any air bubbles. They possessed good peelability and were easily removed from the glass plate without any break. Films having a higher amount of HPMC E15 LV and a higher amount of guar gum showed greater stickiness. Guar gum was capable of imparting the desired adhesion which is required for instant adhesion inside the oral cavity upon administration to avoid the swallowing of the film into the GI tract. Addition of surfactant further enhanced the adhesiveness by improving upon film wettability.

The measured surface pH of the prepared films was found to be in the range of 6.32 to 6.98 (table 2), indicating that there will not be any kind of irritation to the mucosal lining of the oral cavity. Folding endurance was found to be in the range of 100 to 190 (table 2) and the films were found to be quite flexible. Films having higher amount of HPMC E15 LV had greater folding endurance than those having higher amount of PVA. The prepared formulations showed a moisture loss in the range of 1.22 to 3.205 (table 2), which indicates good physical stability and integrity of the films.

All the prepared films had uniform thickness throughout (table 2). Results of weight variation study showed the uniformity in the formulations. Drug content was found to be in the range 28.19% to 48.84% for the prepared films.

Table 2: Results of determination of surface pH, folding endurance, % moisture loss, thickness and weight uniformity of the prepared swellable rapid release oral films

Formulations	Surface pH	Folding endurance	%Moisture loss	Thickness (mm)	Weight uniformity (mg)
D1	6.65	150	1.37	0.06	43.80
D2	6.79	150	1.40	0.061	41.40
D3	6.82	100	1.39	0.065	41.60
D4	6.84	100	1.44	0.0600	42.90
GA1	6.70	115	1.88	0.050	49.61
GB1	6.92	110	1.90	0.060	56.16
GC1	6.83	145	2.37	0.040	54.75
GA2	6.94	182	1.50	0.050	58.23
GB2	6.72	180	1.34	0.050	52.86
GC2	6.45	185	1.58	0.045	55.00
T	6.61	100	1.88	0.062	53.09
S	6.65	180	1.26	0.040	53.00
P	6.45	140	1.22	0.050	54.00
T1	6.48	100	1.70	0.040	50.80
T2	6.56	167	1.77	0.056	53.12
T3	6.74	170	2.56	0.043	52.09
TA1	6.82	121	2.58	0.056	50.99
TA2	6.76	119	2.39	0.040	56.74
TA3	6.43	130	2.99	0.060	54.26
TB1	6.67	170	2.97	0.050	59.71
TB2	6.64	125	2.77	0.058	53.06
TB3	6.98	144	3.16	0.060	56.74
TA D1	6.77	130	2.89	0.040	53.19
TA D2	6.45	110	2.20	0.040	53.16
TA D3	6.53	186	2.95	0.050	49.61
TB D1	6.32	170	2.79	0.060	52.33
TB D2	6.45	160	2.68	0.050	53.18
TB D3	6.39	190	3.20	0.050	50.02

Swelling index for all formulations were found to be greater in phosphate buffer than in water. The parameter was influenced by the amount of gum, HPMC E15 LV: PVA ratio, concentration of superdisintegrant, as well as the presence of surfactant. Increased amount of superdisintegrant resulted in a higher swelling index due to more water absorption (D1-D4). Formulation containing higher amount of HPMC E15 LV exhibited a higher swelling index because the polymer chains of HPMC E15 LV quickly absorb the solvent and swell. Addition of surfactant was found to be useful in increasing the swelling capacity of the films due to its wetting property. Among the surfactants (Tween 80, SLS, Poloxomer 407) used in the study, Tween 80 showed highest increase in swelling index. On increasing the percentage of Tween 80 from 2% to 4% w/w there was an increase in the swelling index (table 3).

The disintegration times for the films ranged from 5-18 min in phosphate buffer (pH 6.8) and 7-20 min in water with those containing 120 mg gum and 4%w/w surfactant showing least disintegration time. It was found that superdisintegrant at 20% w/w was able to cause faster disintegration of the films. Increasing the amount of gum resulted in lower disintegration time. On the contrary, the higher amount of HPMC E15 LV delayed disintegration because HPMC E15 LV forms a viscous gel barrier by rapid solvent uptake thus hindering the film disintegration. Surfactant addition aided in decreasing the disintegration time due to its wetting and solubilizing property. It is thus clear that apart from including superdisintegrant and surfactant, the amount of cellulosic polymer in the film formulation should be adjusted carefully to get the desired rapid disintegration of the film (table 3).

Table 3: Results of determination of swelling index and disintegration time of the swellable rapid release oral films

Formulations	Swelling	Index	Disintegration	Time
	In water (%)	In phosphate buffer (pH 6.8) (%)	In water (min)	In phosphate buffer (pH 6.8) (min)
D1	92	119	20	18
D2	115	133	19	15
D3	150	167	14	13
D4	160	217	12	10
GA1	114	156	10	9
GB1	100	167	12	10
GC1	185	240	9	8
GA2	102	120	12	11
GB2	88	147	16	14
GC2	135	194	11	10
T	93.75	114	11	10
S	88	102	13	12
P	78.94	86	15	14.5
T1	93.75	102	11	10
T2	100	120	9.2	8.5
T3	145	200	8	7
TA1	166.6	269	6.34	5.25
TA2	181	193	7	6.36
TA3	320	434	5.21	5
TB1	161	250	8.44	7.08
TB2	151	156	8.51	7.22
TB3	185	264.7	8.14	6.52
TA D1	156.6	266	6.32	5.35
TA D2	188	198	7.2	6.39
TA D3	320	440	6.21	5.02
TB D1	165	254	8.08	7.44
TB D2	145	166	8.22	7.51
TB D3	180.5	276.6	8.52	7.14

Drug content was found to be in the range 28.19% to 48.84% for the prepared films.

From the results on *in vitro* drug release studies of swellable rapid release oral films of diclofenac sodium, it can be said that initial drug release was slow but with time, the release became rapid (table 4). Presence of guar gum, HPMC E15 LV, Tween 80 and citric acid led to rapid uptake of simulated salivary fluid (pH6.8) by the film followed by rapid film disintegration owing to the presence of crosscarmellose sodium and subsequently greater drug release with time (fig. 1). *In vitro* drug release was found to follow either Korsmeyer-Peppas or Higuchi model indicating the formation of a rapid releasing matrix. Both Fickian and non-Fickian diffusion of the drug were observed depending on the film composition (table 5).

Table 4: Cumulative percent drug (diclofenac sodium) released from swellable rapid release oral film

Time (min)	TA D1	TA D2	TA D3	TB D1	TB D2	TB D3
2	11.773	9.15463	8.580613	11.5002	7.16915	7.33611
4	15.488	14.6532	9.281383	14.1661	8.92394	14.3458
6	18.496	18.7863	12.07663	16.4568	11.5002	20.9967
8	20.871	21.093	18.95142	23.7326	15.2461	22.9045
9	22.063	22.253	22.75059	24.0615	15.6279	23.561
10	22.846	22.4378	24.55422	24.6582	18.3283	24.95058
15	38.0622	26.4455	38.5543	28.1363	24.7511	27.5598
20	46.777	28.993	43.89803	30.267	26.0211	33.2622
25	58.0632	34.1885	55.53448	32.6603	28.7192	35.0983
30	62.0385	38.4727	63.73092	35.3783	30.8255	38.0639
60	68.2559	48.5383	69.50435	37.7617	37.1195	48.4197

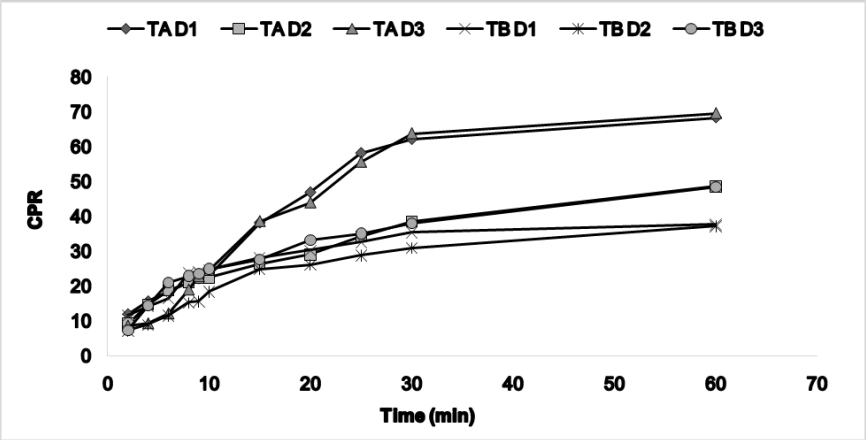

Fig. 1: ***In vitro*** **drug release profiles of selected oral swellable rapid release films containing diclofenac sodium**

Table 5: Modelling of drug release kinetics of swellable rapid release oral film, F=Fickian diffusion, NF=Non-Fickian diffusion, ND=type of diffusion could not be determined, KP= Korsmeyer-Peppas model)

Formulation	Zero-order	First-order	Higuchi	Korsmeyer-Peppas		Type of diffusion
	R^2	R^2	R^2	R^2	n value	
TA D1	0.8086	0.7144	0.914	0.9438	0.6114	Korsmeyer Peppas, NF
TA D2	0.9042	0.7121	0.9856	0.9831	0.4728	Higuchi, F
TA D3	0.8128	0.6622	0.925	0.9199	0.325	Higuchi, ND
TB D1	0.7078	0.5816	0.8752	0.9305	0.3835	Korsmeyer Peppas, ND
TB D2	0.8302	0.6694	0.9533	0.9685	0.5381	Korsmeyer Peppas, NF
TB D3	0.8128	0.6622	0.9250	0.9199	0.5201	Korsmeyer Peppas, NF

Among all the formulations, the swellable rapid release oral film consisting of HPMC: PVA at 2:1, 20% w/w superdisintegrant, 4% w/w Tween 80 and 120 mg guar gum may be regarded as the best formulation as it showed the fastest disintegration (5 min in simulated salivary fluid and 5.21 min in water) and highest drug release (approximately 70%) in salivary pH.

CONCLUSION

From the above studies, it can be concluded that oral swellable rapid release films developed from an optimum ratio of HPMC E15 LV and PVA, containing guar gum, Tween 80 as surfactant, citric acid as saliva stimulating agent and crosscarmellose sodium as superdisintegrant can be used for rapid oromucosal absorption bypassing the first-pass metabolism. The best formulation possessed satisfactory organoleptic properties, mechanical strength and demonstrated high swelling index, rapid disintegration and high drug release in salivary pH.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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