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Formulation and evaluation of mouth dissolving film loaded with solid dispersion of azithromycin

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Abstract: The main objective of the present work was to formulate mouth dissolving films containing azithromycin solid dispersion to attain its maximum drug release with a very short time and also to have an easy and compliant administration of the drug through oral route. The solid dispersion prepared using β-cyclodextrin was obtained in yield of approximately 96% suggesting completion recovery of the dissolved material. Pure azithromycin was found to exhibit a solubility of 36.2 µg/mL after 24 hours whereas the solid dispersion exhibited a significant increase in solubility showing a solubility of 267 µg/mL. Mouth dissolving films were prepared using xanthan gum and exhibited quick drug release, rapid disintegration and optimal mechanical strength. The amount of drug loaded in the films was independent of the polymer concentration though it was found that level 0 of the variable X_1, the drug uptake by the polymeric matrix was slightly lower. All the formulations had drug content of more than 90% with the highest content in formulation F4 (97.1 ± 4.42%) and the lowest in F2 (93.4 ± 2.31%). The formulations were also found to be able to release almost complete drug content within a period of 10 minutes. The maximum amount of drug was released by F4 (92%) while F5 released the lowest amount of drug (85%) in the same period.
Keywords: Mouth dissolving, solid dispersion, azithromycin, xanthan gum, β-cyclodextrin

1. Introduction

Amongst all the routes that have been explored for systemic delivery of drugs the oral route of administration has been the most widely utilized route due to ease of ingestion and the common belief that the absorption of drug would be better via the oral ingestion.[1] Owing to the problem associated with swallowing the demand for a better patient friendly dosage form has increased over the last decades.[2] In view of the above demand, several mucoadhesive dosage forms have been studied and include adhesive tablets, mouth dissolving tablets, chewable tablets and recently polymeric films for buccal delivery of medicaments.[3] Today around 35- 40 percent of the drug coming from high-throughput screening are poorly soluble in water.[4] It is well known that drug efficacy can be severely limited by poor aqueous solubility. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy of certain drugs.[5]

Azithromycin is a widely used antibiotic with a half-life of 60-70 h and the peak plasma concentration occurs at 6-12 h.[6-8] The drug is poorly water soluble, hence it cannot be readily formulated as mouth dissolving preparations. Solid dispersions are known to improve aqueous solubility of drugs and several reports of solid dispersion of azithromycin have been found in literature. Hence in the present investigation it was attempted to formulate solid dispersion of azithromycin and formulate it as mouth dissolving films (MDFs) of with the intention of providing quicker onset of action of the medication, better therapeutic efficacy, patient compliance and convenience.

2. Material and Methods

Azithromycin was obtained as gift from Ind Swift Pharmaceuticals, Baddi; Polyethylene Glycol (PEG 400) was purchased from Merck India Ltd. Xanthan Gum, sodium starch glycolate, Sucrose, citric acid, acetone, methanol, ethanol, hydrochloric acid, sodium hydroxide, potassium dihydrogen phosphate, sodium chloride and other chemicals and reagents required were obtained from Oxford Lab Fine Chemicals LLP, Mumbai. Distilled water was freshly prepared using glass distillation unit for the entire study.

Solubility analysis of azithromycin solid dispersion

25 mg of powdered dispersion was weighed and added into 25 mL of volumetric flask and the volume was made up to the mark with distilled water. The solution mixture was then filtered and the absorbance was taken.[9] The solubility was then calculated using the calibration curve.

Preparation of azithromycin solid dispersion loaded MDFs[10,11]

The preparation of azithromycin films was done using 3^2 factorial approach using xanthan gum as the variable X1 and PEG as variable X2. Both the variables were used at three different levels (+1, 0, -1) to obtain 9 different formulations. Solvent casting method has been the most predominantly used method to prepare smooth films. The MDFs of azithromycin solid dispersion were herein also prepared using the solvent casting method. An aqueous solution of the polymer was prepared by dissolving xanthan gum (Table 1) in 5 mL of distilled water and kept aside to remove any trapped air bubbles. Azithromycin solid dispersion was dissolved in very small quantity of solvent and stirred to dissolve in the polymer solution. All the other excipients of MDF such as plasticizer, sweetener, saliva secreting agent etc were dissolved separately in distilled water. The excipient solution was mixed with continuous stirring to the polymer solution and continued stirring at 1000 rpm for further 15 minutes. The mixture thus obtained was casted on petriplates as a film and dried in hot air oven at 50°C for 24h. After 24 h the films were cautiously peeled off from the petriplates using forceps and observed for any imperfections. The films were wrapped in aluminum foils and stored in desiccator until further use.

Table 1: Composition of MDFs of azithromycin solid dispersion

S. No	Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Azithromycin solid dispersion equivalent to azithromycin (mg)	288.5	288.5	288.5	288.5	288.5	288.5	288.5	288.5	288.5
2	Xanthan gum (mg)	100	150	200	100	150	200	100	150	200
3	Poly ethylene glycol (mg)	40	40	40	50	50	50	60	60	60
4	Sodium starch glycolate (mg)	10	10	10	10	10	10	10	10	10
5	Citric acid (mg)	5	5	5	5	5	5	5	5	5
6	Sucrose (mg)	10	10	10	10	10	10	10	10	10
7	Water (mL)	QS	QS	QS	QS	QS	QS	QS	QS	QS

Evaluation of MDFs[12,13]

Weight variation

The randomly selected films (10 nos.) from each formulation were weighted to calculate the average weight and then individually weighed using a high sensitivity electronic weighing balance. The percent variation in weight of the films from the average weight was recorded.

Thickness

The thickness of each film was measured at different positions by using Vernier caliper and the average thickness was calculated.

Folding endurance

Folding endurance was evaluated by folding repeatedly one film from the same place till it cracked or tore off. The number of times a film could be folded from the same place without breaking/ cracking provided the value of folding endurance.

Drug content test

The film was allowed to dissolve in 100mL of phosphate buffer pH 6.8 that has been enriched with 1% sodium lauryl sulfate. After the complete dissolution of the film, the amount of azithromycin was estimated spectrophotometrically by measuring the absorbance at 285 nm.

Moisture Content

Films of 2 cm^2 areas were cut out, accurately weighed and stored in desiccator over fused anhydrous calcium chloride. After 24 h the films were removed and reweighed. The percent moisture content of the films was calculated by the following formula

% Moisture content = (Initial weight – Final weight)/Initial weight x 100

Moisture uptake

The pre-weighed films were exposed to relative humidity of 84% at 28°C for three days using a saturated solution of sodium chloride in a closed desiccator. After 3 days the films were removed from the desiccator and reweighed. The amount of moisture absorbed by the films was computed using the following formula

% Moisture uptake = (Final weight – Initial weight)/Initial weight x 100

In-Vitro Disintegration time

In order to determine the disintegration time, the films were placed on glass petriplates containing 10 mL of distilled water. The time required for breaking of the film was recorded as the *in vitro* disintegration time of the film.

In-Vitro Dissolution Study

A film of 2 cm^2 was placed in a glass petriplate and 25 mL of dissolution medium (phosphate buffer pH 6.8) was added to it. The solution was continuously stirred at 100 rpm for the entire period of the study. Aliquots of 2.5 mL were withdrawn at regular intervals of 1, 2, 3, 4, 5 and 10 minutes replenishing the medium with equal volume of fresh buffer. The collected samples were filtered and the concentration of azithromycin in each sample was estimated by measuring its absorbance at 285 nm using UV spectrophotometer.

3. Results and Discussion

Preparation and solubility analysis of solid dispersion

The solid dispersion of azithromycin was prepared using solvent evaporation method as it is a simple method that presents good yield and improves the solubility of the contained drug significantly.[13] The use of β-cyclodextrin has been widely made for formulation of inclusion complexes and solid dispersions to improve solubility of drugs. A drug to polymer ratio of 1:1 was used for preparation of solid dispersion, based on a previous study.

The solid dispersion was obtained in yield of approximately 96% suggesting completion recovery of the dissolved material. The saturation solubility study was carried out on azithromycin and the solid dispersion.[11]

Pure azithromycin was found to exhibit a solubility of 36.2 µg/mL after 24 hours whereas the solid dispersion exhibited a significant increase in solubility showing a solubility of 267 µg/mL.

Preparation and evaluation of MDFs

A 3^2 factorial approach with polymer concentration (X_1) and plasticizer concentration (X_2) as the independent variables and drug content in the films as the dependent variable was used for the formulation of different batches of the films.

Physical Parameters of films

The evaluation of the various physical properties of the formulated batches of films was performed as per the reported procedures and the results obtained are reported in table 2.

Table 2: Physiochemical Parameters of films

Formulation Batch	Weight Variation* (%)	Thickness (µm)#	Folding Endurance#	% Moisture loss#	% Moisture uptake#
F1	0.589 ± 0.0003	52.33 ± 1.154	68.67 ± 0.577	5.9 ± 0.001	4.0 ± 0.001
F2	1.02 ± 0.0598	52.33 ± 2.081	77.67 ± 1.527	6.2 ± 0.003	3.4 ± 0.002
F3	0.913 ± 0.0004	56.67 ± 1.527	92.33 ± 4.463	6.7 ± 0.001	4.8 ± 0.001
F4	0.565 ± 0.0006	54.67 ± 0.577	77.00 ± 1.732	6.3 ± 0.002	6.0 ± 0.001
F5	0.505 ± 0.0039	56.33 ± 2.081	66.00 ± 1.732	6.7 ± 0.001	5.9 ± 0.003
F6	1.316 ± 0.0021	61.00 ± 1.732	82.33 ± 1.527	6.8 ± 0.004	6.0 ± 0.003
F7	1.111 ± 0.0014	59.33 ± 1.527	88.33 ± 1.154	6.7 ± 0.002	6.2 ± 0.001
F8	1.449 ± 0.0044	60.67 ± 0.577	91.67 ± 1.154	6.8 ± 0.003	6.3 ± 0.002
F9	1.293 ± 0.0013	71.67 ± 2.081	113.67 ± 3.055	7.0 ± 0.001	6.3 ± 0.001

*Mean ± SD of 10 replicates; #Values are mean ± SD of 3 replicates

The thickness of the films was measured at three different locations to ensure the uniformity of the results. The weight variation was calculated as deviation from the average weight and is reported as the percentage weight variation obtained from 10 films.

The folding endurance was found to increase with increasing concentration of the plasticizer whereas thickness was found to be related to the amount of the polymer in the formulation.

Drug content estimation in films

The evaluation of drug content in the prepared film formulations was performed as per the reported methods and the amount of drug present in the formulations was calculated on the basis of absorbance of the sample at 285 nm in UV spectrophotometer. The results are reported in table 3.

Table 3: Drug content in the MDFs

Formulation	% Drug Content	Disintegration time (sec)
F1	95.7 ± 3.18	31
F2	93.4 ± 2.31	33
F3	96.3 ± 5.89	33
F4	97.1 ± 4.42	35
F5	94.2 ± 7.26	34
F6	93.6 ± 7.26	34
F7	94.1 ± 6.33	35
F8	93.6 ± 7.66	35
F9	96.4 ± 5.33	35

The results show that all the formulations had drug content of more than 90% with the highest content in formulation F4 (97.1 ± 4.42%). The amount of drug loaded in the films was independent of the polymer concentration though it was found that level 0 of the variable X_1, the drug uptake by the polymeric matrix was slightly lower.

In vitro disintegration of MDFs

The *in vitro* disintegration of the films was performed using the petridish method in order to ascertain that the films will provide a rapid release of the azithromycin. The results obtained for disintegration study of the films is shown in table 3.

The disintegration time of all the formulations was less than 40 seconds suggesting that all the batches of the films were quick dissolving and would be able to release the drug, rapidly. The amount of the disintegrating agent was therefore effective in maintaining the quick breakdown of the films.

***In vitro* release study**

The release of azithromycin from the prepared films using different concentration of xanthan gum is presented in table 4. All the formulations were found to disintegrate in less than 40 seconds thereby paving the way for quick release of azithromycin from the films. The ratio of polymer content and plasticizer was found to have no significant role in the disintegration time of the films.

Table 4: *In vitro* drug release of formulations

Time (minutes)	% Drug Released								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	23	25	21	22	19	18	22	17	22
2	31	32	29	28	31	27	32	29	28
3	38	43	32	36	39	36	44	42	39
4	50	54	46	47	50	49	52	53	51
5	66	68	62	59	64	62	66	62	64
10	90	89	86	92	85	89	91	90	87

The results reveal that all the film batches were able to release almost the whole quantity of drug within 10 minutes. The maximum amount of drug was released by F4 (92%) while F5 released the lowest amount of drug (85%) in the same period.

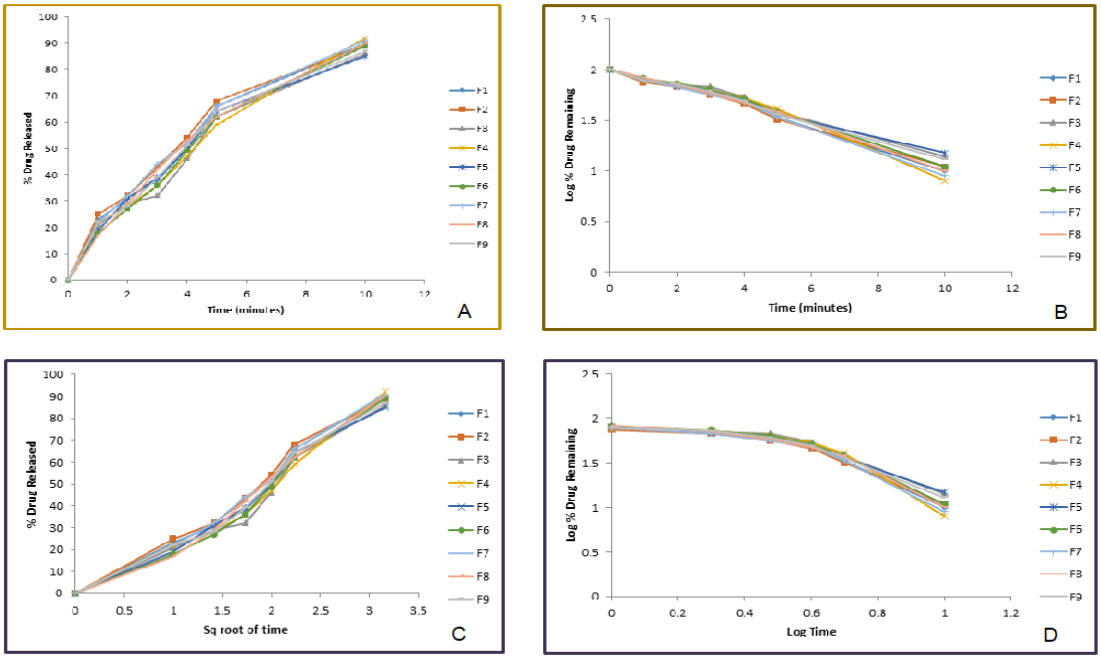

Fig 2: Release profile of formulations (A) Zero order (B) First order (C) Higuchi (D) Korsemeyer-Peppas

Table 5 Drug release kinetics

Formulation Code	Zero order R^2	First order R^2	Higuchi's model R^2	Peppas model R^2
F1	0.9326	0.9817	0.9691	0.7782
F2	0.906	0.9917	0.9802	0.8186
F3	0.9397	0.9799	0.9538	0.7803
F4	0.9674	0.9526	0.9601	07131
F5	0.9197	0.9937	0.9755	0.8471
F6	0.9525	0.9838	0.9613	0.7886
F7	0.9278	0.9873	0.9823	0.7925
F8	0.9398	0.9897	0.9740	0.8085
F9	0.9275	0.9915	0.9717	0.8157

From the above table it can be concluded that the formulations are following mixed order kinetics. The best fitting model (First order and Higuchi's model) suggest that the drug release is concentration and time dependent and is a case II diffusion pattern (Figure 2).

4. Conclusion

The objective of the present study was to formulate mouth dissolving films of azithromycin solid dispersion for rapid release of the drug for quick relief along with improved patient compliance and ease of administration. The results of the study were able to rationalize the use of solid dispersion loaded films for rapid release of the drug using xanthan gum as the polymeric matrix of the film and PEG-400 as the plasticizer. The drug release pattern from the films suggests that the mouth dissolving films can be an excellent approach for quickening the onset of action azithromycin.

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