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DESIGN AND IN-VITRO CHARACTERIZATION OF CLONAZEPAM ORAL THIN FILMS

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ABSTRACT

The purpose of the present investigation is to formulate fast dissolving oral films of Loratidine for the treatment of allergic rhinitis and urticaria. Films were prepared by solvent casting method using Natural Polymers Xanthan gum, Guar Gum, Sodium Alginate,Aloe Vera Powder as the film forming polymer and PEG-400 as the plasticizer. Vanillin was used as taste masking agent in the formulations. Sodium Alginate has excellent film forming capacity with rapid hydration power which leads to rapid disintegration of film upon contact with saliva. The concentrations of the polymers and plasticizer were selected as independent variables. Eight formulations were prepared. The thickness, folding Endurance, disintegration time, % drug released and drug content were selected as dependent variables. The optimized formulation, F6 was found superior than remaining 7 batches.

Keywords: Fast dissolving films, Loratidine, Sodium Alginate, Sodium starch glycolate.

1. INTRODUCTION

Oral route is well preferred administration route for delivery of different drugs till date as it has enormous advantages over the other administration route, but ODDS still need some improvements to overcome some drawbacks particularly related to some class of patients like pediatric, dysphagic and geriatric patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Even with fast dissolving tablets there is a fear of choking due to its tablet type appearance. Amongst other factors, palatability of formulations of pediatric oral medications is one of the most significant factors influencing compliance to therapeutic regimens.

2. REVIEW OF LITERATURE

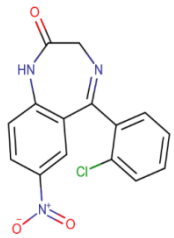
Mashru et al [83] prepared fast dissolving films for sublingual route containing salbutamol sulphate and polyvinyl alcohol as polymer. The films were evaluated for mechanical properties, in vitro release study and morphology study. A 3^3 factorial design was applied to study the effect of polyvinyl alcohol, glycerin and mannitol on % drug release and mechanical properties of the films.

Dinge et al [84] investigated formulation of triclosan (TC) containing fast dissolving films for local delivery to oral cavity. Various film forming agents, film modifiers and polyhydric alcohols were evaluated for optimizing the composition of fast dissolving films. The potential of poloxamer 407 and hydroxypropyl-beta-cyclodextrin (HPBCD) to improve solubility of TC was investigated.

3. DRUG PROFILE

Clonazepam: An anticonvulsant used for several types of seizures, including myotonic or atonic seizures, photosensitive epilepsy, and absence seizures, although tolerance may develop.

Structure



Weight: Average: 315.711
Monoisotopic: 315.041068908
Chemical Formula: $C_{15}H_{10}ClN_3O_3$

IUPAC Name: 5-(2-chlorophenyl)-7-nitro-2,3-dihydro-1H-1,4-benzodiazepin-2-one

Indication: Clonazepam is used as an anticonvulsant in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. It can also be used for the treatment of panic disorders.

Pharmacodynamics: Clonazepam, a benzodiazepine, is used primarily as an anticonvulsant in the treatment of absence seizures, petit mal variant seizures (Lennox-Gastaut syndrome), akinetic and myoclonic seizures, and nocturnal myoclonus.

Mechanism of action: Allosteric interactions between central benzodiazepine receptors and gamma-aminobutyric acid (GABA) receptors potentiate the effects of GABA. As GABA is an inhibitory neurotransmitter, this results in increased inhibition of the ascending reticular activating system.

4. AIM & OBJECTIVES

The aim of the present investigation is to formulate and evaluate the fast releasing oral film taking clonazepam as a model drug. To carry out the Pre-formulation studies of Clonazepam. To formulate Fast Dissolving film containing Clonazepam. To evaluate Weight variation, Thickness, Tensile strength, Folding endurance, Disintegration time, Content uniformity and In vitro dissolution studies. To perform the stability studies for the optimized formulation.

5. METHODOLOGY

5.1 Pre formulation Studies

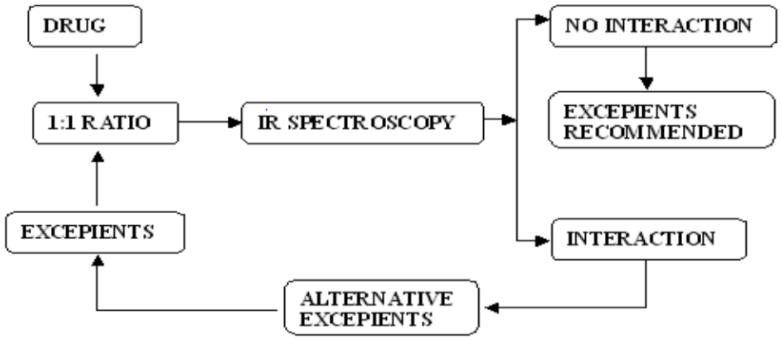
Term	Parts of solvent required for 1 part of solute
Very soluble	Less than 1 parts
Freely soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts
Slightly soluble	100 to 1000 parts
Very slightly soluble	1000 to 10,000 parts
Practically insoluble or insoluble	More than 10,000 parts

5.2 Melting point

Melting point of Model drug was determined by capillary method. Fine powder of Model drug was filled in glass capillary tube (previously sealed on one end).

5.3 Drug polymer compatibility studies

Study was carried out using FT-IR spectrometer by the KBr pellet method in the wavelength region between 4000 and 400cm^{-1}. FT-IR Spectra of Clonazepam and Polymers with Clonazepam were obtained.



5.4 Calibration Curve of Clonazepam

a) Preparation of 6.8 pH Phosphate Buffer

50ml of 0.2M Pottasium Di-hydrogen Ortho Phosphate Solution was taken in a 200ml volumetric flask, to which 22.4ml of 0.2M Sodium hydroxide was added. Then volume was made upto the mark with distilled water and pH was adjusted to 6.8 with dilute sodium hydroxide solution[6,3].

b) Preparation of Clonazepam Standard Stock Solution (100µg/ml)

A Standard Stock solution of Clonazepam was prepared by dissolving accurately weighed 10mg of Clonazepam in 6.8 pH Phosphate buffer solution in a 100ml volumetric flask and the volume was made upto 100ml by using 6.8 pH Phosphate buffer solution.

c) Determination of λ_{max} Of Clonazepam

From the standard stock solution 1ml was taken into 10ml volumetric flask. The volume was made upto 10ml with 6.8 pH Phosphate buffer solution. The resulting solution containing 10µg/ml was scanned.

d) Calibration Curve Of Clonazepam

From the Standard stock solution (1000 µg/ml), appropriate aliquot were transferred to series of 10 ml volumetric flasks and made upto 10 ml with 6.8 pH Phosphate buffer so as to get concentration of 2, 4, 6, 8, 10 µg/ml.

Formulation of Clonazepam Fast dissolving Oral Film

Calculation of dose for Clonazepam

No. of 6 cm^2 films present in whole plate = 18/6 = 3

Each film contains 10 mg of drug

3 no. of films contains mg of drug ? = 3 x 10 = 30 mg
The amount of drug added in each plate was approximately equal to 30 mg.

Preparation of Clonazepam by Solvent-Casting Method

The Oral fast dissolving films were prepared by dissolving strip forming agents and plasticizer in the distilled water, then solution was continuously stirred up to 4 hours on magnetic stirrer[4,5,6,7] and kept for 1 hour to remove all the air bubbles entrapped.

S.No	Ingredients (mg/film)	F1	F2	F3	F4	F5	F6	F7	F8
1	Clonazepam	1	1	1	1	1	1	1	1
2	Guar Gum	0.4	0.7	-	-	-	-	-	-
3	Xanthan gum	-	-	0.4	0.7	-	-	-	-
4	AloeVera Powder	-	-	-	-	1.5	2	-	-
5	Sodium Alginate	-	-	-	-	-	-	1.5	2
6	Sodium Starch Glycolate	1	1	1	1	1	1	1	1
7	PEG-400	15	15	15	15	15	15	15	15
8	Sodium Saccharin	1	1	1	1	1	1	1	1
9	Vanillin	1	1	1	1	1	1	1	1
10	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

6. RESULTS AND DISCUSSION

6.1 Pre-formulation studies

The following preformulation studies were performed for Model drug

Solubility

Clonazepam is sparingly soluble in Water, Methyl alcohol. It is soluble in Chloroform and Acetone.

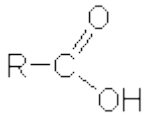
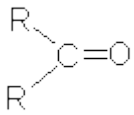
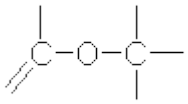
Melting Point

The Melting point of obtained drug sample was found to be 237°C.

Compatibility Studies

From the FT-IR Spectra of pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristic peaks of drug are present in the combination spectra as well thus indicating the compatibility of the drug with the polymers used. The individual FT-IR Spectra of Clonazepam+Sodium Alginate as well as combination of final optimized formulation (F6).

Table 1: FT-IR Spectrum of Clonazepam

Sno	Functional group	Characteristic peak cm^{-1}	Observed peak for drug cm^{-1}	Peaks for optimized formulation
1		3000 - 2500	2980.82	2982.05
2		2960 - 2850	2860.27	2864.05
3		1715 - 1690	1698.63	1702.50
4		1275 - 1200	1227.40	1224.97
5		about 760	767.12	764.63
7	C-Cl (alkyl)	830 - 560	564.38	565.70

6.2. Spectroscopic studies

a) Determination of λ_{max}: λ_{max} of Clonazepam was found to be 245 nm as it shows maximum absorbance in this wavelength.

b) Calibration Curve of Clonazepam: Standard Calibration curve of Clonazepam was drawn by plotting Absorbance vs Concentration. The λ_{max} of Clonazepam in 6.8 pH Phosphate buffer solution was found to be 245nm.

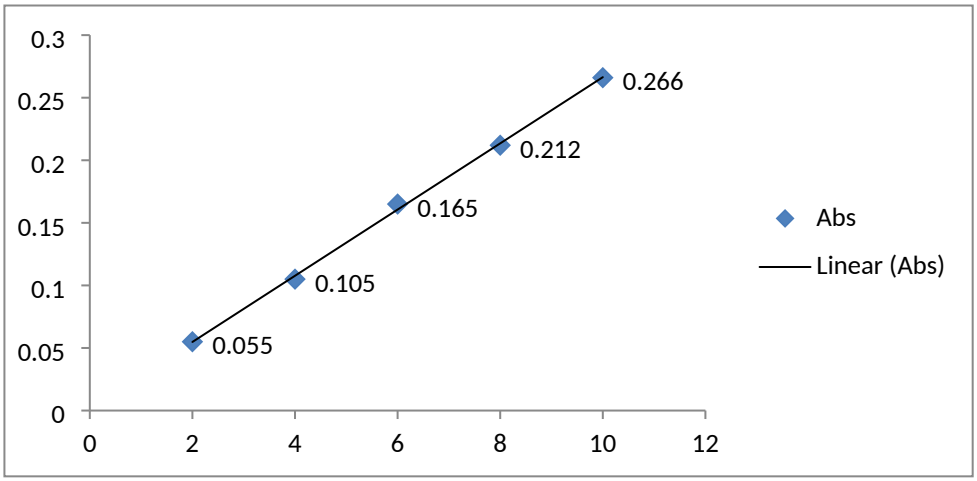


Fig 1: Standard calibration curve of Clonazepam in 6.8pH Phosphate buffer solution

6.3. Evaluation of Fast Dissolving Oral Films

6.3.1. Weight uniformity test

The weights of the films were found to be in the range of 26.18±0.309mg to 32.62±0.279mg. The results of average weight of all films were summarized.

6.3.2. Physical appearance and surface texture

The observation by visual inspection of films and by feel or touch, suggests that the films are having smooth surface and they are elegant enough to see.

6.3.3. Thickness of films

The thicknesses of the films were in the range of to 0.047±0.003mm to 0.052±0.008mm. The results of average thickness of all films were summarized.

6.3.4. Folding endurance

Folding endurance of the films was found to be in the range of 16.6±1.41to 38±1.52.The results of average folding endurance of all films.

6.3.5. Surface pH

The surface pHs of all the films were found to be neutral as there was no colour change in the litmus paper.

6.3.6. Drug content uniformity test

The drug content uniformity is performed by taking three films in each formulation trial and the average drug content was calculated. The results were found to be in the range of 97.56±0.31% to 98.6±0.26%. The results of average drug content of all films were summarized in table no.13.

6.3.7. Invitro disintegration test

The disintegration times of the prepared films were in the range of 8.39±0.58 to 11.80±1.716sec. The results of average disintegration time of all films were summarized in table 2.

Table 2: Evaluation parameters of Clonazepam FDOF

Code	*Weight Variation in mg(n±SD)*	*Thickness in mm (n±SD)*	*Folding endurance (n±SD)*	*Surface PH*	*Drug content in %(n±SD)*	*Disintegration time in sec(n±SD)*
F1	26.18±0.309	0.052±0.008	18±1.02	6.5± 0.5	97.63±0.10	11.6±1.13
F2	28.92±0.279	0.048±0.008	20±1.58	6.6± 0.8	97.85±0.40	10.32±0.57
F3	30±0.239	0.048±0.003	22±2.00	6.4± 0.3	97.56±0.31	11.8±1.716
F4	32.62±0.279	0.047±0.004	34±1.52	6.5 ±0.5	97.8±0.85	10.8±1
F5	29.70±0.959	0.049±0.004	32±1.39	6.7 ±0.8	98.15±0.55	9.68±1.51
F6	31.47±0.629	0.047±0.003	38±1.52	6.8 ±0.3	98.6±0.26	8.39±0.58
F7	31.15±0.04	0.048±0.007	18.60±1.31	6.5± 0.2	98.7±0.35	10.63±1.15
F8	32.1±0.38	0.048±0.007	16.6±1.41	6.6± 0.5	98.59±0.47	9.63±0.56

6.3.8. Invitro dissolution studies

Clonazepam FDOF dissolution study was conducted in 6.8pH phosphate buffer solution as this was similar to the pH of simulated salivary fluid. A modified dissolution methodology was followed to simulate the conditions of the oral cavity. The dissolution volume consists of 300ml of 6.8pH phosphate buffer solution at 37±0.5˚C, which was rotated at 50rpm.

Table 3: Invitro drug release data of formulation F1 to F8

Time in min	*% Cumulative drug release(%CDR)*							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
2	25.2±*0.81*	22.2± 1.1	21.76± 0.66	20.53± 0.43	41.4± 0.01	38.56± 0.05	38.33± 0.37	34.16± 0.64
4	53.10± 2.05	45.33± 1.52	38.33± 0.37	38.56± 0.05	78.63± 0.11	72.6± 0.17	57.63±0.22	50.89± 0.41
6	76.60± 2.83	72± 1.01	56.52± 0.22	77.76± 0.81	98.3± 0.22	90.53± 0.24	84.13± 0.24	77.77± 0.81
8	92.33± 0.57	86.33± 1.52	81.56± 0.54	89.07± 0.16	-	99.96± 0.01	98.4± 0.17	89.07± 0.16
10	96.06± 0.25	91.33± 1.15	92.4± 0.89	94.86± 0.44	-	-	-	97.6 ±0.31
12	97.23 ±0.30	93.5 ±0.31	96.06 ±0.4	96.60 ±0.60	-	-	-	98.6 ±0.17
14	98.2 ±0.17	94.86 ±0.44	97.3 ±0.05	97.6 ±0.31	-	-	-	-
16	98.53± 0.31	95.96± 0.15	98± 0.2	98.3± 0.22	-	-	-	-
18	-	96.6 ±0.60	-	-	-	-	-	-
20	-	98.03± 0.05	-	-	-	-	-	-

6.4 Stability studies

The formulation of F6 was evaluated for stability studies which was stored at 40˚C / 75% RH for 2 months and evaluated for their physical appearance, drug content and invitro disintegration time and % drug release at the end of 1st and 3rd month.

Table 4: Stability data of formulation F6

Formulation code	*Zero order* $(R)^2$	*First order* $(R)^2$	*Higuchi* $(R)^2$	*Korsmeyer-Peppas* $(R)^2$
F1	0.804	0.977	0.932	0.898
F2	0.759	0.965	0.925	0.965
F3	0.898	0.970	0.945	0.957
F4	0.823	0.963	0.913	0.890
F5	0.972	0.899	0.970	0.985
F6	0.936	0.918	0.979	0.964
F7	0.974	0.867	0.975	0.989
F8	0.913	0.945	0.976	0.967

Time in months	*Formulation F6 stored at 40˚C / 75% RH*		
	Physical appearance	*Disintegration time in sec*	*% Drug release*
Initial	Smooth & elegant	7.33±0.56	99.96± 0.01
1 month	Smooth & elegant	7.89±0.07	99.4±0.04
3rd month	Smooth & elegant	8.24±0.24	99.1±0.05

7. SUMMARY

The novel design of an oral controlled drug delivery system should primarily be aimed at achieving more predictable and increased bioavailability of drugs. An incomplete release of the drug and short residence time of dosage form in upper GIT, which is prominent site for absorption of many drugs, leads to decreased bioavailability.

8. CONCLUSION

In the present work, Clonazepam fast dissolving films were prepared by Solvent Casting method using Natural Polymers and PEG-400. Clonazepam is readily soluble in water but its bioavailability is low. It undergoes first pass metabolism. Hence it was formulated into FDOF to improve its bioavailability by avoiding first pass metabolism and in providing faster action in treatment.

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