Research article **Bimonthly published scientific journal**

INTERNATIONAL JOURNAL of Indigenous Herbs and Drugs

ISSN-2456-7345

Formulation, development and optimization of fast dissolving oral film of racecadotril

Ankit Kumar Vishwakarma[1], Isha Pant[1], Mukesh Kumar Patel[1], Arun Pandey[2*]

[1]*Mittal Institute of Pharmacy, Bhopal-462038, MP (India)

[2]*Mittal Group of Institutions, Bhopal-462038, MP (India)

Abstract

Objective: The present research work deals with formulation development and optimization of oral fast dissolving films of racecadotril to improve bioavailability and patient compliance.

Methods: Fast dispersible films of racecadotril were prepared by solvent casting method. Hydroxyl propyl methyl cellulose (HPMC) and Poly vinyl alcohol (PVA) was used as film forming polymers, Poly ethylene glycol-400 (PEG-400) was used as plasticizer, ethanol water was used as solvents, citric acid was used as saliva stimulating agent and aspartame was used as sweetening and flavouring agents. The prepared films were evaluated for thickness, folding endurance, tensile strength, disintegration time, *in vitro* drug release and drug content uniformity.

Results: Films prepared were found to be of good quality fulfilling all the requirements. It was observed that concentration of polymer effects the formation of film and dissolution time of the formulations. F3 formulation was considered as the best according to the obtained results with disintegrating time of 35 sec. The disintegration and release rates were found to be faster for films prepared with lowest concentration of HPMC along with maximum concentration of superdisintegrants.

Conclusion: Fast dispersible films of racecadotril were successfully formulated by solvent casting technique with immediate onset of action & improved patient compliance.

Keywords: Racecadotril, Fast oral dissolving films, Immediate release, Solvent casting method

Introduction

Fast dispersing film, a new drug delivery system for oral delivery of drugs consists of a very thin oral strip, which releases the active ingredient immediately after the uptake into the oral cavity. The delivery system is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick -dissolving aspects and allow for gastrointestinal absorption to be achieved when swallowed [1]. However, poorly soluble drugs pose problems for achieving this goal. The selection of formulation is considered to play an essential role in the development of a successful product of a poorly soluble molecule. Numerous approaches are being followed by the research scientists all over the world to improve the solubility of poorly water soluble molecules with different formulation techniques [2, 3] like complexation, surfactant co-solvent systems, liquisolid systems, lipid systems etc. Rapid mouth disintegrating drug delivery systems were first developed as substitutes to unit dosage forms like tablets, capsules and syrups or suspensions for paediatric and geriatric patients who are having difficulty in swallowing traditional oral solid dosage forms.

Racecadotril is an antidiarrheal drug which acts as a peripherally acting enkephalinase inhibitor. Unlike other medications used to treat diarrhea, which reduce intestinal motility, racecadotril has an antisecretory effect and reduces the secretion of water and electrolytes into the intestine. RDT is a solubility limited compound and it is possible to improve its bioavailability by increasing its aqueous solubility [4, 5]. The objective of the present study was to develop fast dispersible taste masked oral films of racecadotril to improve bioavailability and patient compliance.

Materials and methods

Drug and excipients

Racecadotril was purchased from Pharma grade, Hydroxy propyl methyl cellulose (HPMC), Sodium starch glycolate (SSG), Crospovidone (CP), Croscarmellose sodium (CCS) and Citric acid was purchased from Himedia.

Instruments

Double beam UV visible spectrometer of Labindia 3000+, FT-IR of Brukers alpha, Dissolution apparatus of Labindia Ds-8000, Electronic balance of Wenser, Hot air oven of Labotech India and Melting point apparatus of Chemline was used for the study.

Vishwakarma AK, Pant I, Patel MK, Pandey A. Formulation, development and optimization of fast dissolving oral film of racecadotril. Int J Ind Herbs Drugs 2018; 3(3): 1-6.

Preformulation studies

The objective of preformulation study was to get generic information useful to the formulater in developing stable and bioavailable dosage form. The use of preformulation parameter maximizes the chances in formulation an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimization of the drug product quality. The preformulation studies were carried out in terms of testa for identification (physical appearance, melting point, spectrophotometer and FTIR spectroscopy), solubility profile, and compatibility studies of drug with excipients [6].

Formulation development

Oral fast dissolving films are preferably formulated using the solvent casting method. In this process initially all the water soluble (plasticizers, sweeteners etc.) ingredients including active ingredients are dissolved in solvent to form a clear solution. Then the remaining ingredients are dissolved in smaller amounts in the above aqueous clear solution and filtered. The entrapped air is removed by vacuum and casted as film on appropriate plates or conveyers which are non-stick and allowed to dry. The films were then dried and cut in to pieces with desired size (1 cm^2) [7].

Table 1: Selection and optimization of film forming agents

Name of ingredients	F1	F2	F3	F4	F5	F6
Equivalent to 120mg of drug	120	120	120	120	120	120
HPMC	200	300	400	200	300	400
Glycerin	-	-	-	-	-	-
PEG-400	100	100	100	100	100	100
SSG	120	180	300	-	-	-
CCS	-	-	-	120	180	300
Aspartame	60	60	60	60	60	60
Citric acid	80	80	80	80	80	80
DM water qs to (ml)	-	-	-	-	-	-

Evaluation of prepared film

The oral fast dissolving films were evaluated for their organoleptic characteristics and mechanical properties like thickness, weight uniformity, folding endurance, disintegration time, moisture content and uniformity of drug content were also evaluated.

Thickness

Precise film thickness measurements were carried out using vernier caliper. Thickness of the film was measured at five points i.e. from the centre to all the four corners and mean thickness was calculated.

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated [8].

Folding endurance

Folding endurance to determine mechanical properties of film was measured by repeatedly folding of the film at the same place to the extent where film breaks. The number of times the film is folded without breaking is calculated as the folding endurance value [9]. This parameter was checked simply by visual inspection of films.

Disintegration time

A film was placed onto 2 ml distilled water taken in petri dish. Time taken by the film to dissolve completely is considered as the disintegrating time. The disintegration time is the time when the film starts to break or disintegrates completely, normally disintegration time for oral films s within 2 min [10].

Moisture content

Moisture loss was determined by weight variation. Initial weight of the film was determined and afterward film was kept in a desiccator containing calcium carbonate for about 72 h. Films were then taken out and weighed to calculate the percentage moisture content [11].

Uniformity of drug content

Drug content of oral fast dissolving films were determined by standard assay method taken for 10 individual samples as per the test procedures. The acceptance value of the test is less than 15 in accordance with all pharmacopoeia. A film of size 1 cm^2 was cut and kept in 100 ml of volumetric flask containing solvent. This was then shaken in a mechanical shaker till it was dissolved to get a homogeneous solution and then filtered. The drug was determined spectroscopically after appropriate dilution and dilutions were measured at 232 nm to get absorbance [12].

Results and discussion

The physical evaluation was done by visual inspection. The color was found to be white crystalline powder, odor was

Arun Pandey, E-mail:- arun3177@gmail.com

found to be odorless. Solubility study of racecadotril has been done in various solvent such as water, ethanol, methanol, 0.1 N NaOH and 0.1N HCl solution. We have found that racecadotril was soluble in methanol and ethanol, and slightly soluble in water, 0.1 N HCl and 6.8 pH buffer. Melting point was determined by melting point apparatus at 72-73 °C. The percentage of loss on drying was found to be 0.933% w/w. It means drug was free flowing in nature. The moisture content of racecadotril was found to be 0.044%. It indicated that the drug sample was properly dried and has free flowing ability.

Table 2: List of sensory characters

S. No.	Sensory characters	Results
1.	Appearance	White crystalline Solid
2.	Odor	Odorless

Table 3: Solubility of racecadotril

S. No.	Solvent	Solubility
1.	Water	Sparingly soluble (+++-)
2.	Ethanol	Soluble (++++)
3.	Methanol	Soluble (++++)
4.	0.1N HCL	Sparingly soluble (+++-)
5.	0.1N NaOH	Sparingly soluble (+++-)
6.	Chloroform	Soluble (++++)
7.	6.8 pH Phosphate Buffer	Sparingly soluble (+++-)

Table 4: Melting point of the racecadotril

S. No.	Standard melting point of racecadotril	Observed melting point of racecadotril
1.	72-74°C	72-73°C

Table 5: Loss on drying of racecadotril

S. No.	Initial weight (gm)	Final weight after 5 min (gm)	% loss on drying	Avg. % loss on drying
1.	1	0.95	1.00%	0.933 %
2.	1	0.96	0.80%	
3.	1	0.95	1.00 %	

Table 6: Moisture content determination

S. No.	Drug	KF Factor	Amount of KF reagent consumed	Moisture content
1	Racecadotril	0.142	0.31ml	0.044

Identification of racecadotril was done by FTIR Spectroscopy with respect to market compound. Racecadotril was obtained as white or almost white powder. It was identified from the result of IR spectrum as per specification. The IR spectrum of sample drug shows the peak values which are characteristics of the drug and which compliance standard. The λ max of racecadotril was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer. The spectrum of this solution was run 200-400nm range in U.V. spectrophotometer (Labindia-3000+). The λ max of racecadotril was found to be 232.0 nm. The standard solution of drug was prepared and plot of absorbance vs. concentration was plotted and on the absorption point the linear line was determined which follows Beer's Lambert law. The linear regression analysis was done on absorbance data points. The value of slope, intercept and correlation coefficient were found to be 0.012, 0.010 and 0.998 respectively.

In the optimization, the general appearance, thickness & weight variation, folding endurance, percentage of moisture content and drug content analysis, F-3 was found to be most appropriate in all formulation.

Six formulations with variable concentration of polymer were prepared by solvent casting method and evaluated for physicochemical properties and *in-vitro* drug release. The *in vitro* drug release data of the optimized formulation was determined. Stability studies were carried out with optimized formulation which was stored for a period of one, two and

Arun Pandey, E-mail:- arun3177@gmail.com

three months at 40±2°C temperature and 75±5% relative humidity for a period 3 months. The % assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of tablets was found to slightly decrease at higher temperature. Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore formulation remains stable for sufficient time.

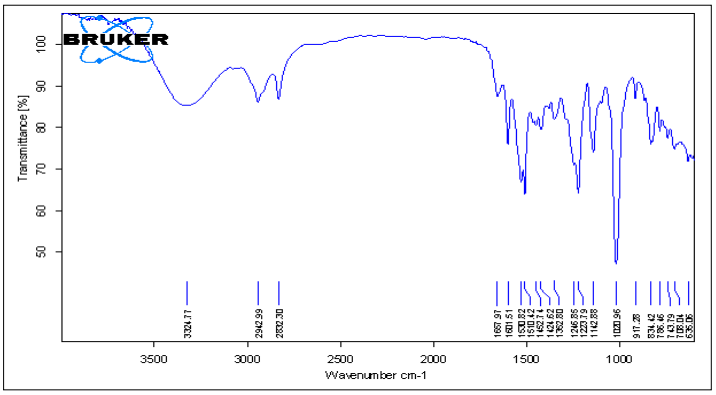

Figure 1: FT-IR Spectrum of pure drug (Racecadotril)

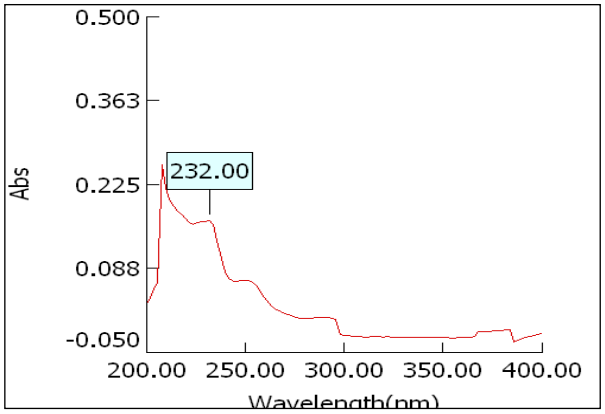

Figure 2: Determination of λ_{max} of racecadotril

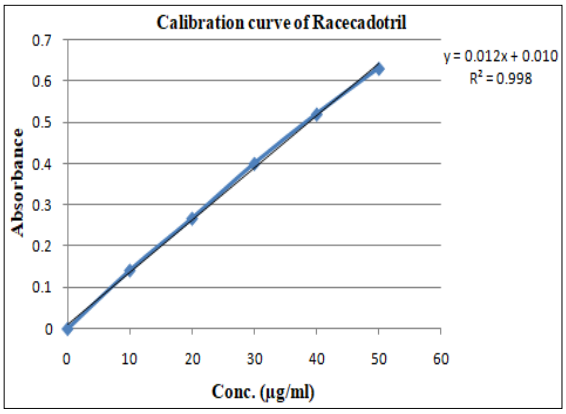

Figure 3: The linear regression analysis for standard curve

Table 7: Calibration curve of racecadotril

S. No.	Conc. (µg/ml)	Absorbance
1	10	0.142
2	20	0.268
3	30	0.401
4	40	0.521
5	50	0.632

Table 8: Different solid dispersion formulation of Racecadotril

Drug:polymer	Physical mixture ratio	Solubility enhancement
Drug:PVP	1:1	4 folds
Drug:PVP	1:2	9 folds
Drug:PVP	1:3	15 folds

Arun Pandey, E-mail:- arun3177@gmail.com

Table 9: Formulation development

Formulation code	General appearance	Thickness (µm)	Weight (mg)
F1	Translucent	65±5	75±4
F2	Translucent	72±6	88±6
F3	Translucent	75±4	95±8
F4	Translucent	69±3	78±4
F5	Translucent	73±2	85±6
F6	Translucent	78±4	90±4

Mean±SEM (n=6)

Table 10: Result of folding endurance, tensile strength & % age elongation

Formulation code	Folding endurance	Disintegrating time (Sec.)	Tensile strength in kg/cm^2	Percentage of Moisture Content	% Assay
F1	More than 100	59±6	0.856	0.985±0.049	98.45±0.21
F2	More than 100	65±7	0.989	0.945±0.065	98.15±0.12
F3	More than 100	36±8	1.125	0.981±0.074	98.99±0.45
F4	More than 100	48±9	0.989	0.654±0.085	97.45±0.32
F5	More than 100	58±7	1.256	0.745±0.065	95.56±0.25
F6	More than 100	46±5	1.458	0.854±0.042	96.45±0.45

Mean±SEM (n=6)

Table 11: Results of optimized formulation F-3

Name of ingredients	Composition (mg) per 10 strip
Racecadotril	120
HPMC K15	400
Glycerin	-
PEG-400	100
SSG	300
CS	-
Aspartame	60
Citric acid	80
DM water qs to	-

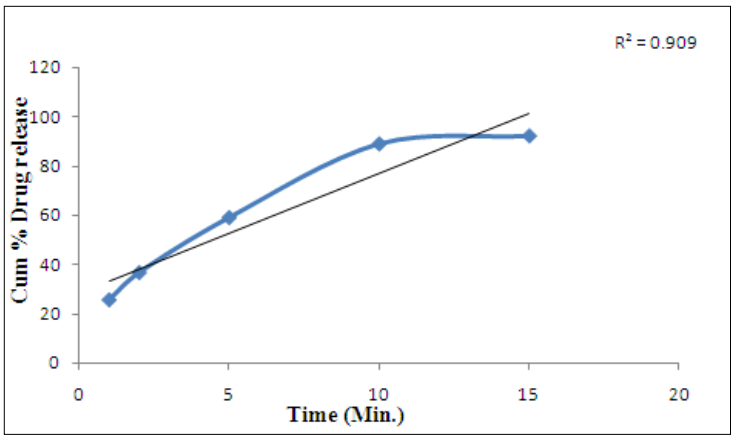

Figure 4: Drug release of optimized formulation F3

Arun Pandey, E-mail:- arun3177@gmail.com

Conclusion

Identification of racecadotril was done with respect to market compound. Six formulations with variable concentration of polymer were prepared and evaluated for physiochemical properties and in-vitro drug release. From the above research work it is concluded that oral fast dissolving film of racecadotril was successfully designed and developed by solvent casting method and it gives quick onset of action, improves patient compliance. The improved solubility, dissolution and drug release may be highly beneficial in improving the overall bioavailability of racecadotril.

References

1. Arya A, Chandra A: Fast dissolving oral films: An innovative drug delivery system and dosage Form. Int J Chem Tech Res 2010; 2: 576-583.
2. Colin WP. Formulation of poorly water soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system., European J Pharma Sci 2006; 29: 278-287.
3. Krishnaiah YSR. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs. J Bioequval Bioavail 2010; 2: 28-36.
4. Singh N, Narayan S. Racecadotril: A novel antidiarrheal. Drug Update 2008; 64: 361-362.
5. Salazar-Lindo E, Santisteban-Ponce J, Chea-Woo E, Gutierrez M. Racecadotril in the treatment of acute watery diarrhea in children. The New England J Med 2000; 343: 463-467.
6. Jain NK. Controlled and novel drug delivery. CBS publisher and distributors, 1997: 100.
7. Choudhary DR, Patel VA, Chhalotiya UK, Patel HV, Kundawala AJ. Development and characterization of pharmacokinetic parameters of fast-dissolving films containing levocetirizine, Sci Pharm. 2012; 80: 779-787.
8. Nair AB, Kumria R, Harsha S, Attimarad M, Aldhubiab BE, et al. *In vitro* techniques to evaluate buccal films. J Con Rel 2013; 166: 10-21.
9. Singh CK, Tiwari V, Shankar R, Mishra CP, Jain S, Jain S, et al. A short review on oral fast dissolving film containing cefpodoxime proxetil nanoparticle, World J Pharm Pharma Sci 2015; 5: 1549-1577.
10. Yellanki SK, Jagtap S, Masareddy R, Disso film: A novel approach for delivery of phenobarbital; design and characterization, J. Young Pharm. 2011; 3:181–188.
11. Bi YX, Sunada H,Yonezawa Y, Danjo K, Evaluation of rapidly disintegrating tablets by direct compression method. Drug Develop Ind Pharm. 1999; 25: 571-581.
12. Bala R, Pawar P, Khanna S, Arora S. Orally disintegrating strips: A new approach to oral drug delivery system, Int J Pharm Investi. 2013; 3: 67-76.

Acknowledgement

The author would like to pay their sincere thanks to colleagues and friends for their constant moral support and scientific advices during the whole work.

Conflict of Interest: None declared

Received: 8 April 2018, Revised: 15 April 2018, Accepted: 28 April 2018

Arun Pandey, E-mail:- arun3177@gmail.com