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Development of Mouth Dissolving Domperidone Strips

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A B S T R A C T

The objective of the current work is to formulate and evaluate the oral strip of domperidone. It is ideally suitable for the treatment of emesis. The oral strip of domperidone is useful in the vomiting through the journey. The oralstrips were formulated by the fusion method and its in-vitro as well as the in-vivo evaluation was done by the usual pharmacopoeial and unofficial tests and by using human volunteers. The main benefit of the preparation technique includes fewer operation units, better content consistency. The oral strips formed was found to be disintegrated in 1 minute. The ratio of components in the aqueous phase affected the thickness, drug content, tensile strength, percentage elongation, folding endurance, and release profile of mouth dissolving strip and the best results were obtained for the Hydroxypropyl Cellulose, Maltodextrin and Propylene glycol. The compatibility between domperidone and excipients was confirmed by FTIR and DSC studies. The developed oral strip of domperidone demonstrated usefulness for fast release of the drug in mouth, for better drug utilization, and improved patient compliance. The optimized formulation, due to low HPC content, has optimum tensile strength and thickness. Formulation F26 containing HPC, Maltodextrin and PG shown a cumulative % drug release of 99.92%. HPC films shown higher cumulative % drug release than films of other HPC grades at different concentrations. It was found to be stable during the accelerated stability study. The effect of different concentrations of polymers and plasticizers on in-vitro evaluation parameters was evaluated. Hence, data shown that formulation F-26 was the most suitable for the development of fast dissolving oral strip of domperidone.

Keywords: Fast dissolving oral strip, Fusion method; HPC, Propylene glycol, Maltodextrose.

A R T I C L E I N F O

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1. Introduction

The oral route is the maximum favoured route for the delivery of drugs to date as it allows various advantages over the other routes of drug administration, but oral drug delivery systems still need some advancements because of some problems associated with a particular class of patients which include geriatric, paediatric and dysphasic patients related with various medical conditions as they have trouble in swallowing or chewing solid dosage forms. So, fast-dissolving drug delivery systems came into presence in the late 1970s as a substitute for tablets, capsules, and syrups for paediatric and geriatric patients[1,2]. These systems contain solid dosage forms that disintegrate and dissolve quickly in the oral cavity without the administration of water. Research and development in the oral drug delivery segment have led to the evolution of dosage forms from simple orthodox tablets or capsules to modified-release tablets or capsules to oral disintegrating tablets to wafer to the current development of oral fast dissolving films. Oral

strip technology is gaining much attention [3,4]. Orally fast dissolving film is a new drug delivery system for the oral delivery of drugs. It was developed based on the technology of the transdermal patch [5-7]. It then quickly disintegrates and dissolves to release the medication for oromucosal absorption or with formula modifications, will maintain the quick-dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed [8-10]. Mouth dissolving film is a very thin oral strip, which is merely placed on the patients tongue or any oral mucosal tissue, promptly wet by saliva the film rapidly hydrates and adheres onto the site of application [10,11]. Numerous excipients used in the formulation of mouth dissolving film are film formers, plasticizers, sweetening agents, saliva stimulating agents, flavoring agents, coloring agents, etc. Solvent casting, semi-solid casting, hot-melt extrusion, solid dispersion extrusion, rolling, are some approaches applied for the formulation of fast dissolving films [12,13]Domperidone is a dopamine antagonist it acts as a gastrointestinal emptying (delayed) adjunct and peristaltic stimulant.

The gastroprokinetic properties of domperidone are connected to its peripheral dopamine receptor blocking properties. Domperidone enables gastric emptying and decreases small bowel transfer time by increasing oesophageal and gastric peristalsis and by lowering oesophageal sphincter pressure. The antiemetic properties of domperidone are related to its dopamine receptor blocking activity at both the chemoreceptor trigger zone and at the gastric level. It has strong affinities for the D2 and D3 dopamine receptors, which are found in the chemoreceptor trigger zone, located just outside the blood-brain barrier, which among others - regulates nausea and vomiting [14,15].

2. Materials & Methods

Domperidone was procured from Hetero Laboratories Pvt Ltd, Hyderabad, India. Hydroxypropyl cellulose, Matlodextrose and Propylene glycol was obtained from Fine Chem SD finechem Ltd, Mumbai, India.

Preparation of Domperidone oral strips

Weighed quantities of polymers were soaked in half the quantity of distilled water separately for 4 hrs. Then both the polymer solutions were mixed and propylene glycol was added to the polymeric solution. Accurately weighed solid dispersion of ratio 1:1 (containing 320mg equivalent to domperidone) was dissolved in distilled of water and kept sonicated for 15min. Then drug solution was added to polymeric solution and with continuous stirring. Sweetener aspartame (0.04%w/v) was added to the mixture and homogenized for 10min and kept aside for 30 min to remove entrapped air bubbles. Then the solution was made up to the volume (30ml) with distilled water and casted on to a pre-lubricated petridish of dimension area 64 cm2 and kept for drying in hot air oven at 400C for 12hours.

Optimization of the formulation

The runs or formulations, which are designed was based on 3-level factorial designs using Response Surface. The responses were subjected to multiple regression analysis to find out the relationship between the factors used and the responses obtained. The responses subjected for the analysis were:

- Disintegration time in seconds.
- Tensile strength of the film g/cm2.

Statistical analysis

The effect of formulation variables on the response variables were statistically evaluated by applying one way ANOVA at 0.05 level using software Design Expert 8.07 trial version (Stat Ease, USA). The design was evaluated by quadratic model, which bears the form of following equation,

$$Y= b0 + b1X1 + b2X2+ b3X1X2+ b4X12+ b5X22$$

Where y is the response variable, b0¬ the constant and b1, b2, b3...b5 is the regression coefficient. X1 and X2 stand for the effect;X1X2 are the interaction terms that shows how response changes, when two factors are simultaneously changed. X12, X22 are quadratic terms of the independent variables to evaluate the nonlinearity. Using the regression coefficient of the factors, the polynomial equation for the response was constructed. Only significantly, contributing factors are considered for the equation generation.

Desirability details

The optimization of the oral strips was carried out by taking into consideration the concentration of HPC, maltodextrin and concentration of propylene glycol as formulation variables and the disintegration time in seconds and tensile strength in g/cm2 as responses. The relationship between the process variables and the responses were evaluated by 3level full factorial design and response surface methodology using the software Design Expert 8.07 version.

3. Results & Discussion

Evaluation Studies[16]

Determination of average weight of the oral strips

Three strips (2×2 cm2) were randomly cut from the batch of prepared oral films, weighed individually on an electronic digital balance (Sartorius GF-212) and the average weight of each strip was reported.

Thickness

The thickness of the drug loaded 32 formulation strips were measured at 3 different points with the help of screw gauge. The data of the results were given in Table 5.11-5.13 which showed the limit range between 0.040 mm to 0.145 mm.

Folding endurance

Folding endurance involves determining the folding capacity of the films when subjected to frequent extreme condition of folding. It was determined by repeatedly folding the film at same place until it broke. The number of times the film could be folded at the same place without breaking/cracking gave value of folding endurance.The recorded folding endurance of the formulations showed values between 275- 550.

Tensile strength

Tensile strength of the formulations was determined using fabricated tensile strength tester. The recorded tensile strength of the formulations was shown values between

210- 650 g/cm2. Tensile strength (g/cm2) = break force (g)/ cross-sectional area of the sample (cm2)

Surface pH determination

The surface pH of fast dissolving films was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. The film to be tested was placed in a petridish and was moistened with 0.5ml of distilled water. The electrode of pH meter (Elico, India) was placed on the surface of film to determine the surface pH. The pH of all the formulations was found to be satisfactory and was in the range between 6.4- 6.8 well within the limits of pH of oral cavity.

Percentage of moisture uptake and Loss

The percentage moisture absorption test was carried out to check physical stability or integrity of the film at humid condition. The films were weighed and placed in a desiccator containing 100 ml of saturated solution of potassium chloride to maintain 75±5% R.H. After three days, the films were taken out, reweighed. The percentage moisture loss and moisture absorbed of all the formulations were determine in the different quantities.

$$\%\ Moisture\ uptake = \frac{Final\ weight - Initial\ weight}{Initial\ weight} x100$$

The percentage moisture loss was carried out to check the integrity of the strip at dry condition. The strips were weighed and kept in a desiccator containing anhydrous calcium chloride. After three days, the films were taken out and reweighed. The percentage moisture loss was calculated using the formula. The optimized parameters of Domperidone oral strip was shown in table 1.

$$\%\ Moisture\ loss = \frac{Initial\ weight - Final\ weight}{Initial\ weight} x100$$

In vitro disintegration time[52]

In vitro disintegration time was determined visually in a petri dish of 10ml distilled water with swirling at every 10 sec. The disintegration time was noted when the film starts to break or disintegrates. In-vitro disintegration time of all the formulations were determined and recorded. The disintegration time of the formulations were shown values between 20-49 sec.

Surface morphology study of film

The morphology of the prepared films was observed under a scanning electron microscope (SEM). The sample was attached to the slab surface with double sided adhesive tapes and the scanning electron photo micro-graph was taken at 2000 X magnification. The SEM of the strip was shown smooth surface with uniform texture on the surface of the film.

Content uniformity

Drug content uniformity of the formulations were determined by UV-Visible spectrophotometer at 284.5nm. The percentage drug content was found between 90.49% and 104.5%. Hence it proved uniform drug distribution within the films. The content uniformity was calculated by using this formula.

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Drug content= (concentration x dilution factor)/1000

$$\%\ \text{Drug content} = \frac{\text{Practical assay}}{\text{Theoretical assay}} \times 100$$

In-Vitro drug release studies

A modified in-vitro "Dissolution apparatus" was fabricated for the in-vitro release studies of mouth dissolving strips. The apparatus consists of a beaker of 500 ml capacity containing dissolution medium (simulated saliva fluid).The beaker was placed on a thermostat heater to maintain the temperature. A basket was fixed to the mechanical stirrer which helps to maintain the sink conditions during the study.

Preparation of Simulated saliva Fluid pH6.8: Accurately weighed 8 g of sodium chloride, 0.19g of potassium di hydrogen phosphate, and 2.38 g of sodium phosphate dibasic was dissolved in 1000 ml of distilled water53.

Procedure

A strip of 2×2 size (equivalent to 10 mg of domperidone) was taken and placed in a basket and immersed in 300ml of simulated saliva fluid pH 6.8 which was taken in beaker maintained at temperature 370C± 0.50C. The rotating speed of the basket was maintained at 50 rpm. At time intervals of 1 min, 5 ml of the sample solution was withdrawn from the beaker and replaced with fresh simulated salivary fluid solution. The sample was diluted suitably with 0.1N HCl solution and analyzed at 284.5 nm using UV-Visible spectrophotometer (Shimadzu-1700, Japan).

Stability Studies

Stability of a drug has been defined as the ability of a particular formulation in a specific container to remain within its physical, chemical, therapeutic and toxicological specification. Stability testing is an integral part of formulation development. It generates information on base proposals for shelf life of drug substances, products and

their recommended storage conditions. Stability data also are a part of the dossier submission to regulatory agencies for licensing approvals. The complexity and diversity of pharmaceuticals have increased so much in recent years that designing the stability testing protocol for a particular product can be difficult and finding the right approach for estimating retest, shelf-life and expiry periods also can be challenging. Fortunately, useful guidance area available to address most of these issues. The International Conference of Harmonization (ICH) tripartite guideline "stability testing of new drug substance and products" describes the stability test requirements for drug registration applications. Further to harmonize and simplify worldwide stability testing, the globe has been divided into four climate zones. The results were shown in fig.1 and table.2.

Table:1Characterization of the optimized Domperidone Oral strip

S.No	Parameters	Observed Values
1	Weight Variation (g)	0.118±0.0035
2	Thickness	0.100 ± 0.0010
3	Folding endurance	439 ± 22.62
4	Surface pH	6.5
5	Moisture uptake (%)	9.09
6	Moisture Loss (%)	19.09
7	Disintegration time (Sec)	25 ± 1.41
8	Tensile Strength (g/cm^2)	410 ± 14.25
9	Assay Content (%)	97.62 ±1.18

Table:2 Stability Studies for Optimized formulation

Characteristic parameters	Optimized formulation (BDS-OPT) [Aluminium Packing]			
	Initial day	2nd Month	4th Month	6th Month
Physical appearance	++	++	++	+
Tensile Strength (g/cm^2)	410	410	415	415
Disintegration time (Sec)	25	25	26	28
Assay Content (%)	100	99.41	97.75	97.52

++ - Same as '0' day, + - Slight change in appearance.

Table:3 Drug release kinetics of Optimized formulation BDS-OPT

Model fitting (Average)	BDS OPT	
	R	k
Zero Order Plot	0.9944	16.8643
First Order Plot	0.9705	0.2993
Matrix Plot	0.9422	31.7705
Korsmeyyer-Peppas	0.9921	16.9036
Hix.Crow.	0.9864	0.0807

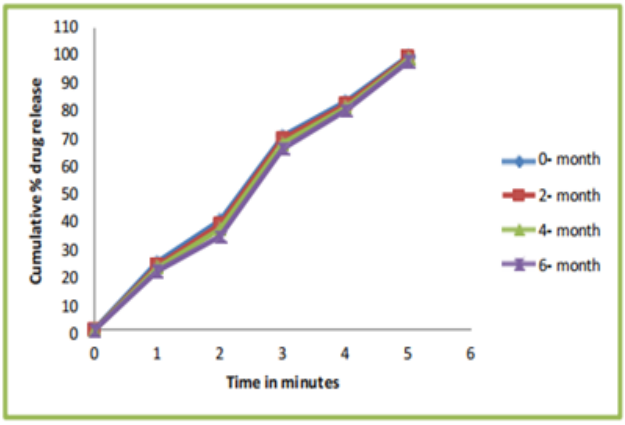

Figure:1 Stability studies in-vitro drug release profile of formulation BDS-OPT

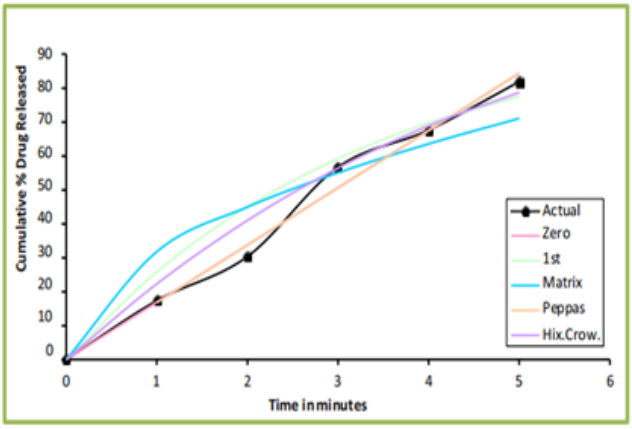

Figure :2 In-vitro drug release kinetics of optimized formulation (BDS-OPT)

Kinetics of drug release

To analyze the drug release rate of kinetics and mechanism of drug release from the oral strip, the in-vitro diffusion studies data was fitted into Zero order, First order, Higuchi matrix, Hixson-Crowell Cube Root Law Model and Korsmeyer-Peppas equations using the software PCP-Disso.v3. The results were shown in fig.2 and table.3.

4. Conclusion

The present study was aimed to develop mouth dissolving strips of domperidone to increase its oral bioavailabilty. From the research findings, it can be concluded that: Solid dispersions of domperidone were prepared with enhanced the aqueous solubility of domperidone. Drug-excipient compatibility studies were proved by FT-IR and DSC studies. Mouth dissolving strips of domperidone were formulated using water soluble HPC and maltodextrin polymers by solvent casting technique. The formulated strips were evaluated for various film characteristic properties. Optimization of oral strips formulations was carried out by 3 level factorial design using Response Surface Methodology. The optimized formulation yielded stable, flexible, uniformly loaded domperidone oral strips with good compatibility, stability and increased oral bioavailability. The ICH accelerated stability studies performed to predict the shelf life authenticated that the product could be stable for 3 years at the storage conditions not exceeding 300C.

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