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FORMULATION AND EVALUATION OF MUPIROCIN LOADED INVASOMES FOR EFFECTIVE TREATMENT OF SKIN INFECTIONS

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ABSTRACT

This research focused on the development and characterization of sustained-release sublingual tablets containing Metoclopramide, a medication widely used for managing nausea and vomiting. The formulation process involved a comprehensive evaluation comprising pre-compression and post-compression assessments to ensure the tablets' optimal physical and pharmacokinetic properties. Pre-compression studies encompassed various parameters such as bulk density, tapped density, compressibility index, and Hausner ratio. Post-compression analysis included measurements of tablet thickness, hardness, weight variation, friability, and drug content uniformity. These parameters are essential indicators of tablet robustness, integrity, and drug content consistency for ensuring the tablets' efficacy and safety during storage and administration. *In-vitro* drug release studies were conducted to assess the tablets' performance over time and to establish their sustained-release profile. Regression analysis data were employed to elucidate the drug release kinetics from the tablets. The zero-order, first-order, Higuchi, and Korsmeyer-Peppas models were applied to the release data, providing valuable insights into the underlying drug release mechanisms and kinetics. Among the formulations evaluated, formulation F3 emerged as the optimized formulation based on its superior characteristics, including consistent drug release, favorable swelling behavior, and adherence to first-order drug release kinetics. These findings highlight the potential of sustained-release sublingual tablets of Metoclopramide as a promising dosage form for improving patient compliance and therapeutic outcomes in the treatment of nausea and vomiting.

Key words: Metoclopramide, sublingual tablets, formulation, Characterization

INTRODUCTION

Metoclopramide, a dopamine antagonist, is widely used for the management of gastrointestinal motility disorders such as diabetic gastroparesis, gastroesophageal reflux disease (GERD), and nausea and vomiting associated with chemotherapy or surgery. Its therapeutic efficacy relies on its ability to enhance gastrointestinal peristalsis and gastric emptying by antagonizing dopamine receptors in the gastrointestinal tract and central nervous system (Bashir *et al.,* 2019). However, the conventional oral dosage forms of metoclopramide often exhibit limitations such as variable absorption, delayed onset of action, and systemic side effects like sedation and extrapyramidal symptoms (Sweetman; 2018). Sublingual drug delivery offers a promising alternative to overcome these challenges by providing rapid

onset of action, avoidance of first-pass metabolism, and improved patient compliance (Rathod *et al.,* 2017; Abdelbary *et al.,* 2016).

This study aims to formulate and characterize sustained-release sublingual tablets of metoclopramide to enhance its bioavailability, prolong the duration of action, and minimize adverse effects. The sustained-release formulation will be designed to release the drug gradually over an extended period, ensuring continuous therapeutic effect while minimizing fluctuations in plasma drug levels.

MATERIALS AND METHODS

Material

Metoclopramide, the active ingredient, was obtained from Bioplus life sciences Pvt. Ltd. Other key components included HPMC, disodium hydrogen phosphate, dipotassium hydrogen orthophosphate, and hydrochloric acid, sourced from Loba Chemie Pvt. Ltd. and S. D. Fine Chem. Ltd. Solvents like methanol, ethanol, and chloroform were procured from Qualigens Fine Chemicals, while magnesium stearate came from Jiangsu Huaxi International. Talc, lactose, Carbopol, and sodium alginate were also utilized in the formulation, sourced from various suppliers.

Method for preparation of Metoclopramide sustain release sublingual tablet

Direct compression was taken after to manufacture the sustain release sublingual tablets of Metoclopramide. Six different formulations (F1, F2, F3, F4, F5, and F6) were set up by direct compression (Bayrak *et al.,* 2011). Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according to given in table No. 1 and all the definition were utilized for encourage assessments parameters.

Evaluation of precompression parameter

Angle of repose (θ): The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\tan \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is the height, r is the radius.

The granules were allowed to flow through the funnel fixed to a stand at definit height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed (Richman *et al.,* 1965).

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined (Al-Ghananeem *et al.,* 2006). Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formula:

Loose bulk density = Bulk Mass/ Bulk Volume

Tapped density = Bulk Mass/ Tapped Volume

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$C.I. = \frac{\text{Tapped density} - \text{Loose Bulk density}}{\text{Tapped density}} x100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Evaluation of tablets

General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated (Prajapati *et al.,* 2014). Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated (Godbole *et al.,* 2014).

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask (Sheu *et al.,* 2016). The powder was dissolved in 5 ml of phosphate buffer pH 6.8 and made up to volume with of phosphate buffer pH 6.8. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ_{max} of 274nm using of phosphate buffer pH 6.8 as blank.

Hardness

For each formulation the hardness of five tablets was resolved utilizing the Monsanto hardness tester (Cadmach) (Rao *et al.,* 2013).

Friability

The friability of sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated (Satyam *et al.,* 2014).

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated (Madhagi *et al.,* 2017).

Swelling Index

Swelling study of individual polymers and combinations was carried out using eight-stage USP type 1 (basket) Dissolution Test Apparatus (Lab India, DS 8000) at 50 rpm, and phosphate buffer pH 6.8 was used as medium, and the temperature was maintained at 37 ± 0.5°C. Weight of individual tablet was taken prior to the swelling study (W_1). The tablet was kept in a basket (Yadav *et al.,* 2015). The weight of tablet was taken at time interval of 2, 4, 8, 12 hours (W_2). Percent hydration (swelling index) was calculated as shown in Table 7.4 using the following formula:

Swelling index = $(W_2 - W_1) \times 100/W_2$,

Where W_1 is the initial weight of tablet and W_2 is the weight of hydrated tablet

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml phosphate buffer pH 6.8 was set into the dissolution flask maintaining the temperature of 37 ± 0.5^0C and rpm of 75. One Metoclopramide tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 12 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 2

hours using 10ml pipette. The new disintegration medium (37^0C) was supplanted each time with a similar amount of the sample and takes the absorbance at 274 nm using spectroscopy (Akbar *et al.,* 2015).

RESULTS AND DISCUSSION

Table 2 presents the pre-compression properties of Metoclopramide formulations (F1-F6), including bulk density, tapped density, compressibility index, and Hausner ratio. These parameters offer insights into the flowability and compressibility of the powder blends, which are crucial for tablet formulation.

Table 3 displays the post-compression properties of the sustain release sublingual tablets, such as thickness, hardness, weight variation, friability, and drug content. These parameters ensure the uniformity, strength, and drug content of the final tablets, which are essential for their effectiveness.

Table 4 provides the swelling index of the tablets at different time points (2, 4, 8, and 12 hours). The swelling index indicates the extent of tablet swelling over time, which can affect drug release and bioavailability.

Table 5 presents the *in-vitro* drug release study results of the sustain release sublingual tablets over various time intervals (0.5 to 12hours). This table shows the percentage cumulative drug release for each formulation at different time points, providing insights into the sustained release behavior of the tablets.

Table 6 contains the regression analysis data for formulation F3, including the coefficient of determination (r^2) for the zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. These models help understand the kinetics and mechanisms of drug release from the sustained-release tablets.

Table 1: Various formulations of sustain release sublingual tablets of Metoclopramide

Excipients (mg)	F1	F2	F3	F4	F5	F6
Metoclopramide	10	10	10	10	10	10
HPMC K-4	25	50	75	25	50	75
Carbopol	-	-	-	25	50	75
Na Alginate	25	25	25	25	25	25
Magnesium stearate	10	10	10	10	10	10
Talc	10	10	10	10	10	10
Lactose	170	150	120	145	95	45
Total Weight	250	255	250	250	250	250

Table 2: Result of pre-compression properties of Metoclopramide

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.385	0.495	22.22	1.286
F2	0.365	0.478	23.64	1.310
F3	0.375	0.483	22.36	1.288
F4	0.369	0.475	22.32	1.287
F5	0.382	0.493	22.52	1.291
F6	0.378	0.486	22.22	1.286

Table 3: Results of post compression properties of Metoclopramide sustain release sublingual tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	3.15±0.05	4.7±0.2	245±5	0.658±0.012	98.25±0.015
F2	3.18±0.08	4.3±0.3	250±8	0.745±0.015	98.65±0.022
F3	3.19±0.04	4.6±0.1	243±6	0.695±0.036	99.45±0.032
F4	3.18±0.06	4.5±0.7	248±5	0.752±0.022	98.78±0.014
F5	3.13±0.03	4.4±0.4	253±4	0.765±0.014	97.65±0.074
F6	3.16±0.07	4.8±0.2	247±5	0.745±0.017	97.88±0.032

Table 4: Results of Swelling Index of Metoclopramide sustain release sublingual tablets

Formulation Code	% Swelling Index			
	2 hrs.	4 hrs.	8hrs.	12hrs.
F1	29.98	53.32	78.85	96.65
F2	30.45	56.69	83.32	105.45
F3	38.85	69.78	98.85	125.65
F4	35.45	63.32	79.98	96.65
F5	34.47	62.32	88.78	105.69
F6	32.36	55.65	74.65	98.85

Table 5: *In-vitro* drug release study of sustain release sublingual tablets

Time	% Cumulative Drug Release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	36.65	32.25	29.98	25.65	22.12	20.22
1	48.85	45.65	36.65	31.15	29.98	24.45
1.5	59.68	55.47	49.98	45.65	43.32	32.23
2	73.32	69.98	56.65	53.32	51.23	45.65
3	89.98	76.65	69.85	61.14	58.98	56.55
4	96.65	83.32	76.65	73.32	69.32	63.32
6	99.12	94.45	88.85	84.65	74.45	73.32
8	-	98.85	94.62	88.98	86.65	84.45
12	-	-	98.77	92.23	90.32	89.98

Table 6: Regression analysis data of Metoclopramide sustain release sublingual tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2
F3	0.813	0.998	0.934	0.967

CONCLUSION

In conclusion, the pre-compression properties of Metoclopramide formulations indicated suitable flowability and compressibility, essential for tablet formulation. Post-compression analysis revealed consistent thickness, hardness, weight, friability, and drug content across formulations, ensuring uniformity and efficacy of the tablets. The swelling index data demonstrated varying degrees of tablet swelling over time, suggesting differences in drug release profiles. *In-vitro* drug release studies revealed sustained release behavior for all formulations, with formulation F3 exhibiting the most desirable release kinetics according to regression analysis. Overall, these findings suggest that the sustain release sublingual tablets of Metoclopramide show promise for effective drug delivery, offering potential benefits for patient care and treatment outcomes.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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