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Original Article

FORMULATION AND OPTIMIZATION OF LEVAMISOLE CHEWABLE TABLETS

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ABSTRACT

Objective: The aim of the present study was to prepare and optimize levamisole chewable tablets by using various super disintegrants, namely; sodium starch glycolate, DRC Indion 204, and DRC Indion 234.

Methods: Drug excipient compatibility study was carried out by FTIR spectroscopy to verify the compatibility of levamisole with the excipients. Nine batches of levamisole chewable tablets were prepared according to 3^2 factorial designs using a direct compression method by optimizing the super disintegrant concentration. The powder blend was exposed to pre-compression studies of the powder blend followed by post-compression studies of the formulated tablets.

Results: FTIR study revealed that the excipients used in the formulations were compatible with the drug. The pre-compression and post-compression parameters were found within the IP limits. Form the dissolution studies, it was evident that the formulation prepared with DRC Indion 234 (50 mg) showed maximum percentage drug release in 45 min (97.13%) hence it is considered as optimized formulation. When compared to all other formulation, the batches with DRC Indion 234 (F7-F9) showed a better release of the drug (90 % drug release within 45 min).

Conclusion: Nine batches of levamisole chewable tablets were successfully formulated by optimizing the concentration of super disintegrants such as sodium starch glycolate, DRC Indion 204, and DRC Indion 234. It was concluded from the dissolution studies that the DRC Indion 234 is the best super disintegrant irrespective of their concentration for the formulation of levamisole chewable tablets when compared to sodium starch Glycolate and DRC Indion 204.

Keywords: Levamisole, Chewable tablet, Superdisintegrant, Sodium starch glycolate, DRC, DRC Indion 204, DRC Indion 234

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INTRODUCTION

In allopathic medicine system, tablets are still the best oral dosage form due to their ease of administration. The chewable tablet dosage forms continue to draw attention in the search for improved patient compliance and also to enhance the therapeutic effectiveness of the drug. Ideally, chewable tablets offer a therapeutic concentration of the drug in the blood, which is maintained throughout the dosing interval with a reduction of fluctuation in the concentration. The chewable tablets mainly intended for children or adults who may have difficulty in swallowing a tablet intact [1]. These tablets are required to be chewed in between the teeth before its consumption [2]. The chewable tablets are disintegrated in the mouth upon chewing and can be swallowed with or without the use of water as per the patient's compliance. The ingredients disintegrated and released because of chewing, absorbed from the stomach, which can reduce the lag time of absorption. To enhance the palatability of the tablet, natural or synthetic sweeteners, colorants, and fruity flavoring agents are commonly used in the tablets [3, 4]. Among the tablet excipients, super disintegrants are often considered as the most important excipient in orodispersible tablets as they make quick disintegration of the drug into its fragments upon ingestion, to allow the onset of drug dissolution and eventual absorption. The disintegration process can mechanistically be explained as a two-step process i.e., breakdown into coarse aggregates followed by subsequent disaggregation into fine primary particles. In the present work, a super disintegrant addition method at low, medium, and high level was employed.

A survey on the literature indicates that extensive work was conducted in the development of the chewable tablet. Some of the drugs studied include albendazole [5, 6], acetaminophen [7], antibiotics [8], caffeine [9], montelucast sodium [10], darunavir [11], clarythromycin [12]. In this present investigation, levamisole, a synthetic imidazo-thiazole derivative [13, 14], an anthelmintic used in the treatment of worm infection [15, 16], is selected as a drug of choice. The bioavailability levamisole is low (47%) with a half-life of 4.4-5.6 h [17, 18]. In this study, an attempt has been made to prepare levamisole chewable tablets by optimizing the concentration of super disintegrants such as sodium starch glycolate, DRC Indion 204, and DRC Indion 234.

MATERIALS AND METHODS

Material

Levamisole and all other excipients such as sodium starch glycolate, DRC indion 204, DRC indion 234, talc, magnesium stearate, and microcrystalline cellulose (Avicel 101) were purchased from Natco Pharma Pvt. Ltd. All the chemicals and reagents used in the study were of analytical grade.

Method

Formulation of levamisole chewable tablet by direct compression method

Levamisole chewable tablets were prepared by direct compression method. Based on the availability of the super disintegrants in the laboratory, three super disintegrants namely sodium starch glycolate, DRC Indion 204, and DRC Indion 234, were selected for this study. All the ingredients were accurately weighed and passed through a standard sieve (sieve no.60). The required quantity of drug and excipient were mixed thoroughly in a polybag by geometric addition method for 20 min. The obtained powder blend was then compressed, with a 4.5 tons compression force, using rotary tablet machine-8 station with 9 mm flat punch, B tooling. Nine batches (F_1-F_9) of levamisole tablets, having an average of 300 mg, with relative density (solid fraction) less than 1 for all the batches, were obtained [19]. Composition of preliminary trials for levamisole chewable tablets by direct compression is shown in table 1.

Table 1: Formulation of levamisole chewable tablets

Ingredients*	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Levamisole	50	50	50	50	50	50	50	50	50
Sodium Starch Glycolate	50	75	100	-	-	-	-	-	-
DRC Indion 204	-	-	-	50	75	100	-	-	-
DRC Indion 234	-	-	-	-	-	-	50	75	100
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate	2.5	2.5	2.5	2	2.5	2.5	2.5	2.5	2.5
Microcystalline Cellulose	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total	300	300	300	300	300	300	300	300	300

*All ingredients are expressed in mg only, Qs: Quantity sufficient to 300 mg

Determination OF UV absorption maxima

Levamisole solution was prepared in phosphate buffer pH 6.8 and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The Solution exhibited UV maxima at 220 nm.

Preparation of standard calibration curve of levamisole

100 mg of levamisole was accurately weighed and dissolved in a little amount of methanol and made up the final volume up to 100 ml with phosphate buffer pH 6.8 to prepare a stock solution. The 10 ml of stock solution was further diluted with phosphate buffer pH 6.8 in 100 ml to get a 100 µg/ml solution (working standard). Then 2, 4, 6, 8 and 10 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with phosphate buffer pH 6.8 to prepare 2µg, 4µg, 6µg, 8µg, and 10µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 220 nm against phosphate buffer pH 6.8 as blank.

Drug-excipient compatibility studies

The compatibility between the pure drug and excipients were detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wavenumber of 8000 to 400 cm^{-1}.

Evaluation of pre-compression parameters of the powder blend

Loose bulk density (LBD)

LBD was measured by pouring the powder blend (passed through standard sieve # 20) into a measuring cylinder and the weight was noted without disturbing the cylinder. The LBD is calculated according to the formula mentioned below [20]. It is expressed in gm/cm^2 and is given by;

$$\text{LBD} = \text{Mass of the powder blend} / \text{Volume of the powder blend}$$

Tapped bulk density (TBD)

It is the ratio of the total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in gm/cm^2 and is given by;

$$\text{TBD} = \text{Weight of the powder blend/Tapped volume of the powder}$$

Angle of repose

The friction forces in a loose powder can be measured by the angle of repose (Θ). It is defined as the "maximum angle possible between the surface of the pile of powder and the horizontal plane". The powder mixture was allowed to flow through the funnel fixed to a stand at a definite height. The angle of repose was then calculated by measuring the height and the radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel [21, 22]. The angle of repose is calculated by the following formula;

$$\text{Tan}(\theta) = (h/r)$$

$$\theta = \text{Tan-1}(h/r)$$

Where, Θ= Angle of repose, h = Height in cm, r = Radius in cm

Carr's index

Based on loose and tapped bulk density, the percentage compressibility of the powder blend was determined. It is calculated by the following formula;

$$\text{Carr's index} = (\text{TBD} - \text{LBD}) \times 100/\text{TBD}$$

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula;

$$\text{Hausner's ratio} = \text{TBD/LBD}$$

Evaluation of levamisole chewable tablets

Weight variation

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. The percentage deviations from the mean value were calculated by using the following equation [23-28];

$$\text{Weight variation} = [(W1 - W2)/W2] \times 100\%.$$

Where W_1 = Initial weight of the tablet

W_2 = Average weight of the tablet

Hardness

Testing the hardness of a tablet will reveal the resistance of a tablet for chipping and breakage while transporting [29]. Hardness or tablet crushing strength (fc) is the force required to break a tablet in a diametric compression. It was measured using the Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Thickness

Ten tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

Friability

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. The pre-weighed sample of tablets was placed in the friabilator and was subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula;

$$\%\,\text{Friability} = [(\text{Initial Weight} - \text{Final Weight})/(\text{Initial Weight})] \times 100\%$$

Drug content uniformity

10 tablets were weighed and triturated from each batch. The tablet triturates equivalent to 10 mg of the drug was accurately weighed and shaken for 30 min to get dissolved in 100 ml of phosphate buffer (pH 6.8). Later the solutions were filtered and further dilutions were made with phosphate buffer (pH 6.8). Then the absorbance was

taken at 220 nm against the blank, and the concentration of levamisole in each batch was determined.

In vitro dissolution studies

USP II Paddle apparatus was used to determine the drug release of levamisole from the chewable tablets. The phosphate buffer (pH 6.8, 500 ml) was used as a dissolution medium. The paddle was allowed to rotate at 50 rpm with maintaining the temperature at 37±0.5 °C. The samples were withdrawn at specific intervals and the drug concentration was analyzed by UV spectrophotometer at 220 nm.

RESULTS AND DISCUSSION

Standard calibration curve of levamisole

Data for the standard plot of levamisole in phosphate buffer (pH 6.8) is shown in table 2. It was found that the estimation of levamisole by UV spectrophotometric method at λ_{max} 220 nm in phosphate buffer (pH 6.8) had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10 µg/ml, which obeys beer's lamberts law. The regression equation generated was y = 0.085x-0.017.

Table 2: Data for the standard plot of levamisole in phosphate buffer (pH 6.8)

S. No.	Concentration (µg/ml)	Absorbance*
1	0	0
2	2	0.139±0.022
3	4	0.316±0.014
4	6	0.497±0.024
5	8	0.676±0.017
6	10	0.842±0.011

*mean±SD, n=3, SD: Standard deviation

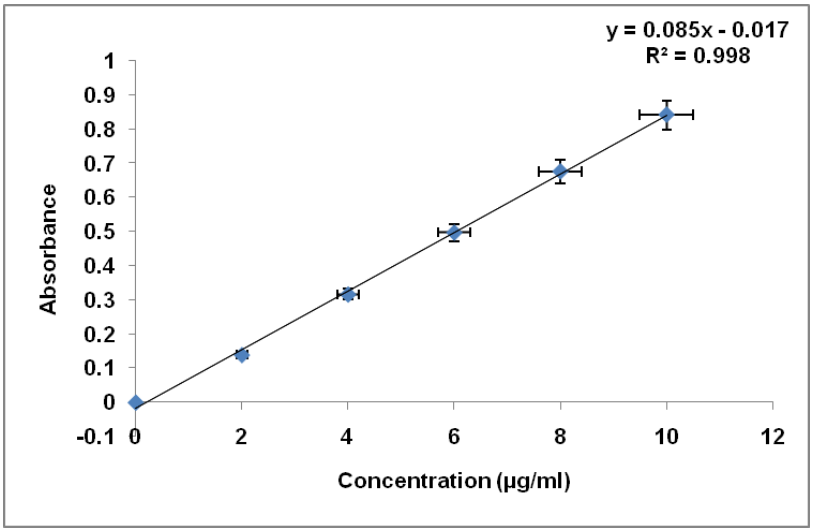

Fig. 1: Standard plot of levamisole in phosphate buffer (pH 6.8, values are expressed as mean±SD, n=3)

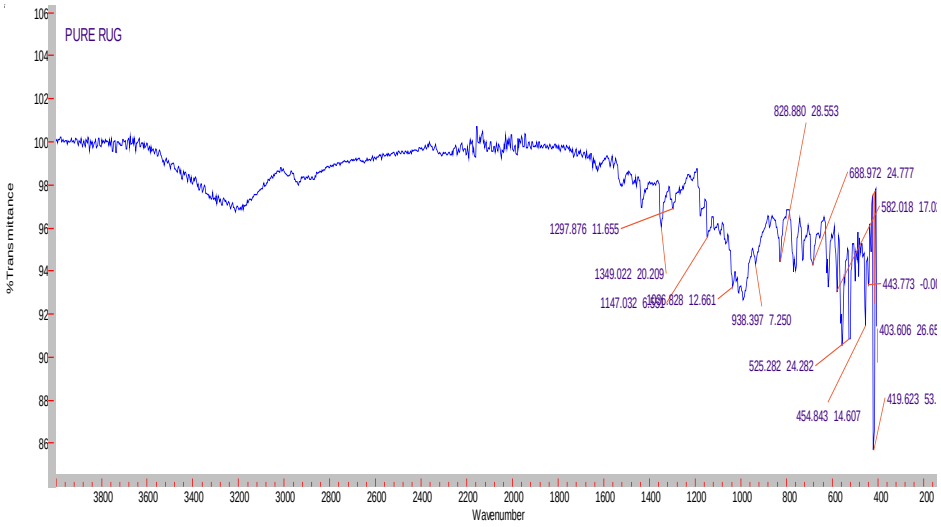

Fig. 2: FTIR spectrum of pure levamisole drug

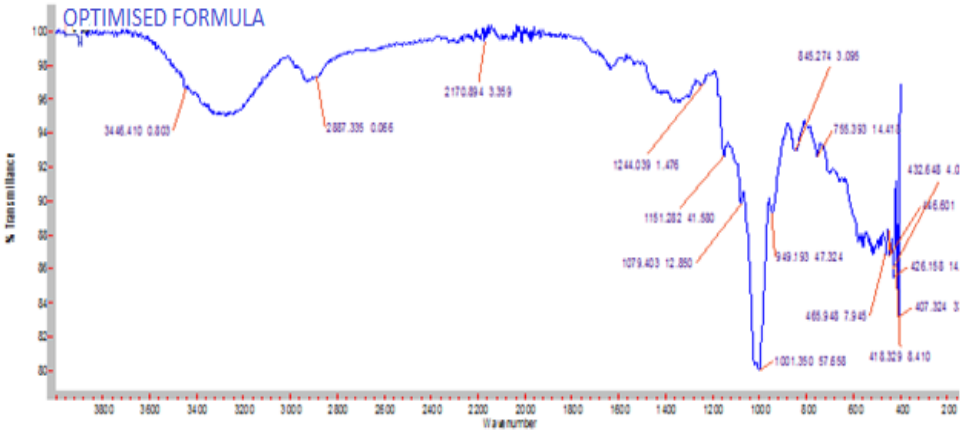

Fig. 3: FTIR spectrum of optimized formulation

Drug-excipient compatibility studies

The compatibility of pure drug and excipients were studied by using FTIR spectroscopy. From the FTIR spectrum of the drug (fig. 2) and drug with the excipients (fig. 3), it was evident that the drug, super disintegrants, and other excipients, did not have any interaction with each other. The spectrums showed C-S-C stretching of the pure levamisole drug (688.97 m^{-1}) and the optimized formulation (755.39 cm^{-1}) within the literature range of 772-622 cm^{-1} at fingerprint region and clearly indicated the compatibility of the pure drug with the excipients.

Evaluation of pre-compression parameters of the powder blend

The data obtained by pre-compression studies were shown in table 3. The values for the angle of repose were found in the range of 24-26 °. LBD and TBD of various formulations were found in the range of 0.42 to 0.54 (gm/cm^2) and 0.54 to 0.58 (gm/cm^2) respectively. Carr's index of the prepared blends falls in the range of 14.26 to 16.82 %. The Hausner's ratio falls in the range of 1.12 to 1.15. From the result, it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 3: Data for pre-compression parameters

Formulations	Loose bulk density* (gm/cm^2)	Tapped bulk density* (gm/cm^2)	Carr's index* (%)	Hausner's ratio*	Angle of repose* (θ)
F_1	0.4±0.012	0.51±0.008	15.12±0.75	1.14±0.74	24.91±0.54
F_2	0.52±0.004	0.52±0.009	15.52±0.85	1.13±0.81	25.24±0.44
F_3	0.54±0.006	0.53±0.011	14.10±0.65	1.15±0.78	26.31±0.05
F_4	0.42±0.025	0.55±0.007	16.27±0.88	1.13±0.07	24.72±0.87
F_5	0.45±0.011	0.53±0.014	15.30±0.92	1.14±0.08	25.31±0.99
F_6	0.46±0.020	0.56±0.021	14.26±0.98	1.12±0.12	24.22±0.25
F_7	0.47±0.017	0.54±0.017	14.19±0.75	1.15±0.54	23.14±0.74
F_8	0.51±0.008	0.55±0.004	15.18±0.93	1.13±0.48	25.15±0.04
F_9	0.53±0.004	0.53±0.019	16.82±0.56	1.12±0.88	23.16±0.65

*mean±SD, n=3, SD: Standard deviation

Evaluation of levamisole chewable tablets

Weight variation

The average weights of all the batches of tablets were found within the range of 301 mg to 306 mg (table 4). According to official guidelines,±5 % is permitted for tablets weighing more than 250 mg [30]. Thus all the prepared chewable tablets of levamisole were passed weight variation test. The results of the test showed that the tablet weights were within the pharmacopoeia limit.

Hardness

The hardness of the ten tablets of each batch was checked by using Monsanto hardness tester and the data were shown in table 4. The results showed that the hardness of the tablets was in the range of 2.2 to 2.6 kg/cm^2, which was within IP limits.

Thickness

The thickness of ten tablets of each batch was checked by using Vernier Caliper and data are depicted in table 3. The result showed that the thickness of the tablet is raging from 3.21 to 3.42 mm (table 4).

Friability

Tablets of each batch were evaluated for percentage friability. The average friability of all the formulations lies in the range of 0.41 to 0.45 %, which was less than 1% as per the official requirement of IP, indicating a good mechanical resistance of tablets. Friability less than 1% is considered acceptable [31-35]. The data for the percentage friability of each batch is shown in table 4.

Drug content uniformity

Drug content uniformity studies were performed for the prepared formulations. From the studies, it was concluded that all the formulations were showing the drug content within 971.4-995.2 µg/ml after 100 times dilution (table 4). Though it was acceptable, a 100 % of the drug content was not seen in all the batches. This may be due to the segregation of the blend while feeding during tableting [36].

In vitro dissolution studies

From table 5 and fig. 5-6, it was evident that the formulation prepared with DRC Indion 234 50 mg showed a maximum percentage drug release in 45 min (97.13%). Irrespective of the super disintegrant type, the percentage drug release was prolonged up to 45 min as the concentration of agent's increases. When compared to all other formulation, the batches with DRC Indion 234 (F7-F9) showed a better release of the drug (90 % drug release within 45 min). This could be due to the properties of DRC Indion 234, which works by rapid swelling and disintegrating tablets rapidly into apparently primary particles [37].

Table 4: Data for post-compression parameters

Formulations	Weight variation[a] (mg)	Hardness[b] (kg/cm²)	Thickness[b] (mm)	Friability[a] (%)	Drug content[a] (µg/ml)
F_1	301	2.4	3.32	0.44	982.7
F_2	302	2.3	3.21	0.32	971.4
F_3	301	2.6	3.44	0.45	981.6
F_4	302	2.3	3.22	0.42	962.4
F_5	304	2.2	3.25	0.41	972.2
F_6	302	2.6	3.51	0.45	982.4
F_7	306	2.3	3.21	0.41	971.6
F_8	303	2.6	3.24	0.44	995.2
F_9	303	2.2	3.42	0.41	971.4

[a]mean±SD, n=3; [b]mean±SD, n=10, SD: Standard deviation

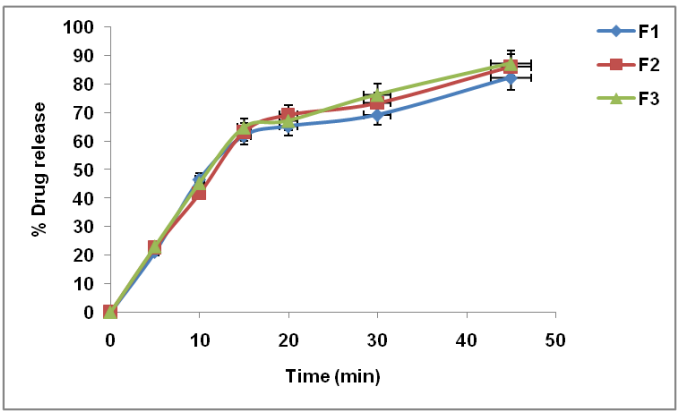

Fig. 4: Dissolution profile for formulations F1-F3 (Sodium Starch Glycolate, values are expressed as mean±SD, n=3)

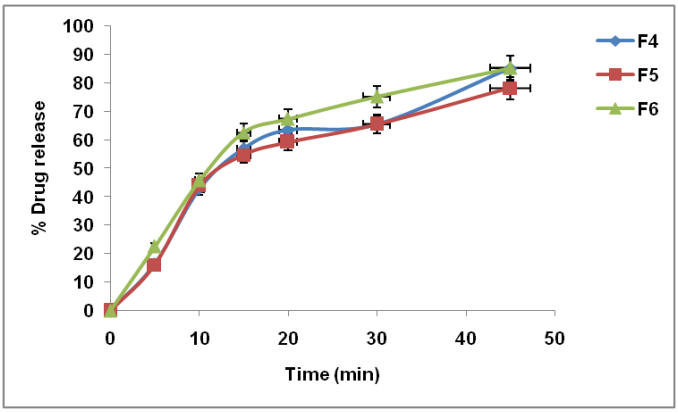

Fig. 5: Dissolution profile for formulations F4-F6 (DRC Indion 204, values are expressed as mean±SD, n=3)

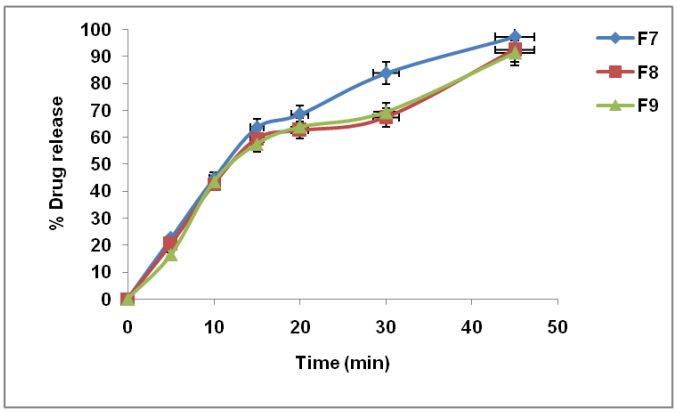

Fig. 6: Dissolution profile for formulations F7-F9 (DRC Indion 234, values are expressed as mean±SD, n=3)

Table 5: Dissolution data for all the formulations

Time (min)	F1*	F2*	F3*	F4*	F5*	F6*	F7*	F8*	F9*
5	21.14±0.14	22.7±0.65	23.12±0.18	16.4±0.41	16.09±0.98	22.54±0.99	22.54±0.33	20.37±0.22	16.45±0.91
10	46.58±0.57	41.67±0.98	45.37±0.58	42.87±0.87	43.95±0.47	45.77±0.78	44.67±0.97	42.61±0.40	43.54±0.20
15	61.87±0.36	63.24±0.25	64.84±0.47	56.84±0.34	54.75±0.39	62.57±0.87	63.57±0.89	59.34±0.98	57.42±0.52
20	65.27±0.71	69.32±0.69	67.24±0.19	63.57±0.96	59.34±0.55	67.45±0.69	68.41±0.75	62.57±0.92	63.89±0.66
30	69.24±0.78	73.44±0.57	76.34±1.20	65.57±0.12	65.47±0.77	75.21±0.66	83.64±0.98	67.24±0.74	69.24±0.99
45	82.25±0.32	86.21±1.25	87.31±0.57	85.21±0.39	78.25±0.66	85.34±0.22	97.13±0.44	92.34±0.88	91.21±0.12

*mean±SD, n=3, SD: Standard deviation

CONCLUSION

The current study was focused on the formulation of levamisole chewable tablets. Nine batches of levamisole chewable tablets were successfully formulated by optimizing the concentration of super disintegrants such as sodium starch glycolate, DRC Indion 204, and DRC Indion 234. Among the formulations F7 batch showed a maximum % drug release i.e., 97.13 % in 45 min hence it is considered as an optimized formulation. It was concluded from the dissolution studies that the DRC Indion 234 is the best super disintegrant irrespective of their concentration for the formulation of levamisole chewable tablets when compared to sodium starch glycolate and DRC Indion 204.

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AUTHORS CONTRIBUTIONS

Pradip KC has performed the experiments, Abdul Raheem. T interpreted the data and wrote the manuscript. Mr. Manjunath UM designed and supervised the work. Vasia and Shaik S helped to edit the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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