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Formulation and Evaluation of Bilayered tablets of Loperamide Hcl and Simethicone

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ABSTRACT

The purpose of the present study is to prepare and characterize once-daily immediate release tablets of Simethecone and Loperamide using different Super disintegrants. Bulk drugs were characterised for preformulation studies. Formulations were evaluated for the release of Simethecone and Loperamide over a period of 45 min using United States Pharmacopoeia (USP) type-II dissolution apparatus. The in-vitro drug release in 6.8P^H Phosphate buffer as medium revealed that the most successful formulation of the study, S-L exhibited satisfactory in-vitro drug release. From the results it was evident that the Simethicone formulations prepared with super disintegrate Cross povidone showed maximum % drug release in 6 min i.e.98.97% (FS3 formulation and the concentration of super disintegrate is 15 mg) conatins Simethicone as drug. Formulation simethicone (FS3) was added to various formulations of Loperamide HCl .From the results it was evident that the Loperamide HCl formulations prepared with super disintegrate CCS showed maximum % drug release in 6 min i.e.99.84% (FT4 formulation and the concentration of super disintegrate is 20 mg) conatins Loperamide as drug along with simethicone(FS3). In conclusion, the results indicated that the prepared immediate release Bilayered tablets of Simethecone and Loperamide could perform therapeutically with improved efficacy.

Keywords: *Simethicone, Loperamide , Crospovidone, CCS ,Immediate release tablets.*

INTRODUCTION

Loperamide is an anti-diarrhoeal agent. It has direct antisecretory effect on myentericopiate receptors in the gut [1]. Loperamide has minimal systemic availability (0.3%), with most of the drug being removed by first-pass metabolism [2], which further supports a local action in the gut. The main objective of the study is to investigate the best suitable dosage form of Loperamide in combination with simethicone and its method validation by HPLC. Historically, in preparing solid simethicone dosage forms, difficulties have been encountered when attempting to incorporate substantial quantities of liquid simethicone to solid final blend such as insufficient flow ability, hardness of tablet and not uniform distribution throughout. In the present the study an attempt will be made to design and evaluation of fast dissolving tablets of loperamide hydrochloride (an anti-diarrhoeal drug as an adjunct in the management of acute and chronic diarrhoeas and may also be used in the management of colostomies to reduce the volume of discharge) using synthetic disintegrants. It is having half life of 10 hours and its bioavailability is 40%, undergoes first–pass metabolism. So it is suitable candidate for design and evaluation of fast dissolving tablets by direct compression method, effervescent technique and sublimation method to improve its bioavailability and patient compliance and similar to simethicone.

MATERIALS AND EQUIPMENTS

Materials:

Simethicone is obtained from ARCH Labs Loperimide is obtained from ARCH Labs Micro Crystalline Cellulose is obtained from NRchemicalsMumbai Sodium Starch Glycolate is obtained from Essel chem Mumbai

Equipments:

16 stations Compression Machine is supplied Rimek mini press-I, Mumbai Digital weighing balance is supplied by Shinko denshi co.LTD, japan. Hardness Tester is supplied by Cintex, Ind. Corporation, Mumbai Dissolution Apparatus, USP is supplied by DBK instruments, Mumbai. UV-Visible Spectrophotomter is supplied by Systronics UV-Vis Friability Tester is supplied by Veego (VFT 2D) model. Hot air oven is supplied by Cintex, Ind. Corporation, Mumbai.

Formulation and Evaluation methods:

Formulation of Tablets(Wet granulation method for Simethicone and Direct compression method for Loperamide HCl). Evaluation of Tablets Properties of Tablets –Appearance, Size and Thickness, Hardness, Friability, Weight variation, Content uniformity, *In-vitro* Drug Release Studies and Stability Studies.

Table No. 1: Composition of Simethicone layer

MATERIALS	FS1(mg)	FS2(mg)	FS3(mg)	FS4(mg)
Simethicone	125	125	125	125
Lactose	40	40	40	40
Crosspovidone	5	10	15	20
PVP	24	24	24	24
Iso propanol	q.s	q.s	q.s	q.s
MCC	52.5	47.5	42.5	37.5
Magnesium stearate	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5
Lake colour(colourant)	0.5	0.5	0.5	0.5
Tablet weight(mg)	250	250	250	250

Formulation of Simethicone Dispersible Tablet by wet granulation method:

Procedure:

Take 125mg of Simethicone to it add required quantity of Lactose and Crosspovidone, mix it well. Prepare the binder by taking 24mg of pvp in q.s isopropanol, mix well, add 0.5mg lakecolour (colourant) stir it well. Now add drop by drop binder to mixture until it forms wet mass note the volume of binder. Now make them granules by passing it through sieve no. 22. Dry the granules in oven at 60°c for 30min.Now sieve the dried granules by passing it through sieveno.44 by adding talc, magnesium stearate. Mix it well and store it in suitable container. The blend is compressed using rotary tablet machine-8 station with 6mm flat punch, B tooling. Each

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tablet contains 2 mg Loperamide HCl and other pharmaceutical ingredients.

Table No. 2: Composition of Loperamide HCl layer

INGREDIENT	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F10	F11	F12
Loperamide HCl	2	2	2	2	2	2	2	2	2	2	2	2
CCS	5	10	15	20	-	-	-	-	-	-	-	-
SSG	-	-	-	-	5	10	15	20	-	-	-	-
Crosspovidone	-	-	-	-	-	-	-	-	5	10	15	20
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Mg. Stearate	2	2	2	2	2	2	2	2	2	2	2	2
MCC	39	34	29	24	39	34	29	24	39	34	29	24
Mannitol	50	50	50	50	50	50	50	50	50	50	50	50
TOTAL(mg)	100	100	100	100	100	100	100	100	100	100	100	100

All ingredients are expressed in mg only.

Composition of preliminary trials for Loperamide HCl Dispersible Tablet by direct compression is shown in above table. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. Store it in suitable container. In this method required quantity of drug and various concentrations of super disintegrants according to formulations were weighed, mixed thoroughly and milled after that diluent, lubricants and glidants were added and mixed well, sieved and stored it in a poly bag(suitable container)

Compression:

Pour required quantity (different formulations) of Simethicone granules in round flat faced punch in the die cavity of tablet press using spatula, Simethicone layer was pre-compressed to produce uniform layer. Now pour 100mg of Loperamide HCl powder (different formulations) in the same cavity having uniform Simethicone layer by using spatula, finally compressed with 6mm round flat punch. To obtain a tablet of optimum hardness and thickness.Bilayered tablets are formed collect them and store in suitable containers.

Spectroscopic studies:

UV Spectroscopy - Determination of λmax and Preparation of Calibration Curve of Simethicone by using Phosphate buffer pH 6.8, shows λmax at 278nm,λmax of Loperamide HCl is determined by using Phosphate buffer pH 6.8shows λmax at 388 nm.

RESULTS AND DISCUSSION

Fourier Transform-Infrared Spectroscopy:

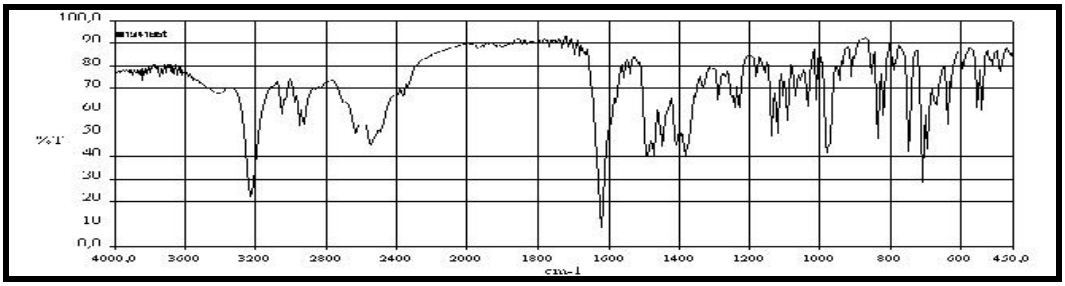

Fig. 1: FT-IR Spectrum of Loperamide HCl pure drug

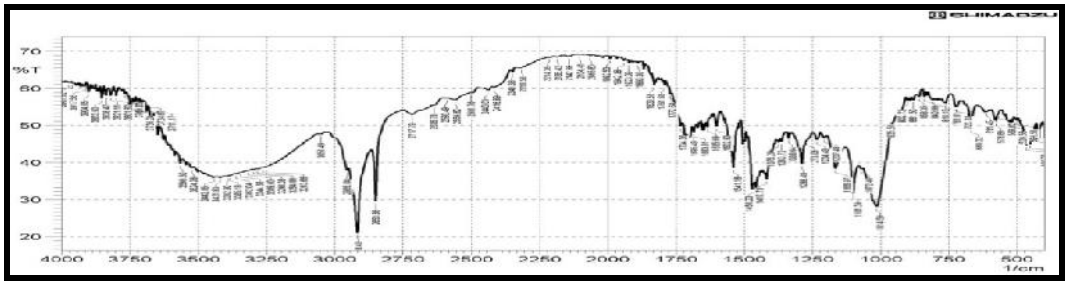

Fig. 2: FT-IR Spectrum of Simethicone pure drug

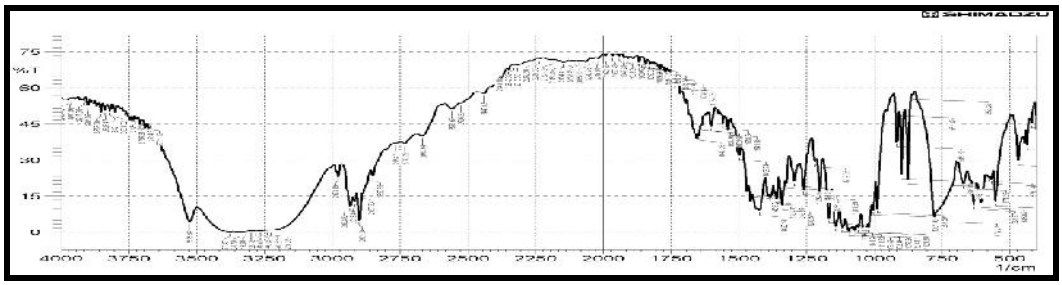

Fig. 3: FT-IR Spectrum of Optimized Formulation

From the FTIR data it was evident that the drug and super disintegrates, other excipients doses not have any interactions. Hence they were compatible.

Evaluation Parameters for Fast Dissolving Tablets of Loperamide HCl and Simethicone:

Table No. 3: Pre-compression parameters for Simethicone

Pre-compression parameters Simethicone					
Formulations	**Bulk Density (gm/cm²)**	**Tap Density (gm/cm²)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(θ)**
F_1	0.62	0.71	12.67	1.14	26.2
F_2	0.64	0.73	12.32	1.13	27.5
F_3	0.66	0.71	7.04	1.07	19.8
F_4	0.64	0.74	13.5	1.19	20.8

The data's were shown in above Table. The values for angle of repose were found in the range of 19.8°-27.5°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.62 to 0.66 (gm/cc) and 0.71 to 0.74 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 7.04% to 13.5%. The Hausner ration fall in range of 1.07 to 1.19. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Pre-compression parameters for Loperamide HCl:

The data's were shown in below Table.The values for angle of repose were found in the range of 22.34°-29.72.°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.40 to 0.51 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 7.27% to 20%. The Hausner ration fall in range of 1.07 to 1.25. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture

Table No. 4: Pre-compression parameters for Loperamide HCl

Pre-compression parameters for Loperamide HCl					
Formulations	**Bulk Density (gm/cm²)**	**Tap Density (gm/cm²)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(θ)**
F_1	0.51	0.55	7.27	1.07	26.82
F_2	0.49	0.54	9.25	1.10	27.27
F_3	0.46	0.57	19.29	1.23	23.68
F_4	0.47	0.53	11.32	1.12	22.34
F_5	0.49	0.58	15.51	1.18	29.72
F_6	0.48	0.58	17.24	1.20	26.14
F_7	0.47	0.58	18.96	1.23	28.84
F_8	0.43	0.51	15.68	1.18	25.24
F_9	0.40	0.50	20	1.25	22.31
F_{10}	0.43	0.51	15.68	1.18	26.92
F_{11}	0.48	0.56	14.28	1.16	25.38
F_{12}	0.41	0.50	18	1.21	25.94

All the pre-compression parameters for Loperamide HCl were found to be within I.P limits.From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Post compression Parameters:

The following are the post compression parameters as per IP limits Weight variation test, Hardness test, Thickness, Friability, In vitro disintegration time.

Invitro Dissolution studies:

Invitro dissolution studies were carried out by using 900ml of 6.8P^H Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min.The dissolution data for simethicone given in below table and for all the formulations final tablet were given in the below Table after simethicone.

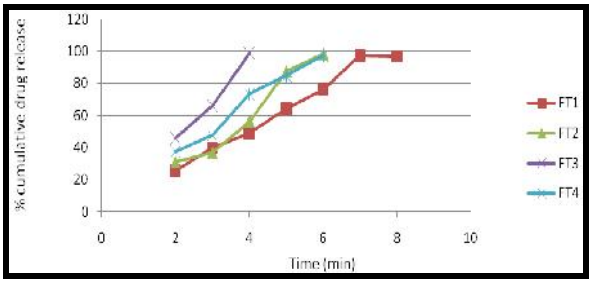

Fig. 4: *Invitro* dissolution data of simethicone

Table No. 5: Dissolution profile of simethicone formulations (FS)

Time (Min)	FS1	FS2	FS3	FS4
2	25.4	30.8	45.72	37.31
4	39.6	36.72	66.16	47.62
6	48.6	56.16	98.97	73.42
8	64.3	87.4		84.71
10	76.4	98.5		97.32
15	97.6			
20	97.1			

Dissolution profile of simethicone formulations (FS):

From the tabular column it was evident that the formulation prepared with super disintegrate cross povidone showed maximum % drug release in 6 min i.e.98.97% (Fs3 formulation and the concentration of super disintegrate is 15 mg).

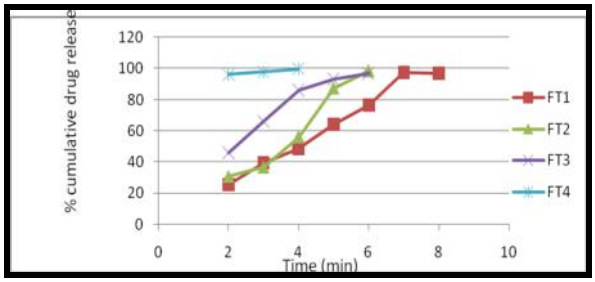

Fig. 5: *Invitro* dissolution data of Final Tablet

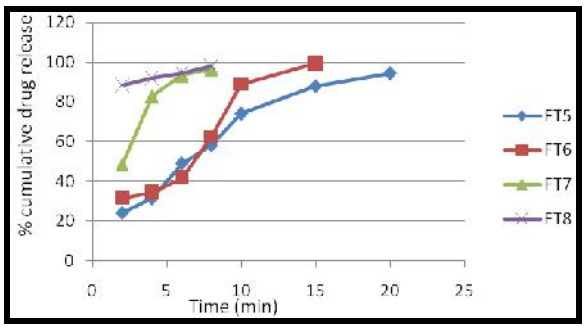

Fig. 6: Dissolution profile of formulations prepared with CCS as super disintegrate

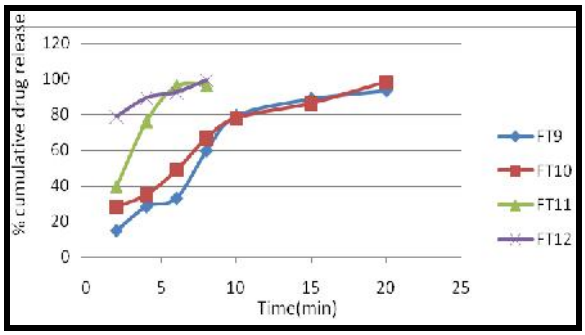

Fig. 7: Dissolution profile of formulations prepared with SSG as super disintegrate

Dissolution profile of formulations prepared with Crospovidone:

From the tabular column mentioned above it was evident that the formulations prepared with super disintegrate CCS showed maximum % drug release in 6 min i.e.99.84% (FT4 formulation and the concentration of super disintegrate is 20 mg).The formulations prepared with SSG showed maximum percentage drug release in 8 min i.e., 98.4 % (FT8 formulation and the concentration of super disintegrate is 20 mg).The formulation's prepared with Crospovidone showed maximum percentage drug release in 8 min i.e.,99.4%.(FT12 formulation and the concentration of super disintegrate is 20 mg).Irrespective of super disintegrate type the disintegration time decreases and Dissolution time also decreases as the concentration of super disintegrate increases. The dissolution profile was represented in above graphs.

Stability studies:

From the results it was found that formulation FT4 is the best formulation amongst the 12 formulations. Thus formulation FT4 was selected for stability studies. The Hardness, Disintegration time and Percentage drug content of tablet after 1, 2, 3 months of stability studies were studied. The results are within the limits. The data is shown in below Table.

Table No. 6: Data for different evaluation tests of FT4 at the end of 1, 2, 3 month of stability

TIME PERIOD	Hardness (kg/cm2)	Friability (%)	Disintegration time (sec)	Drug content (%)
1st month	3.2±0.25	0.47±0.05	19±0.5	99.34±0.3
2nd month	3.1±0.2	0.46±0.08	19±0.6	99.18±0.5
3rd month	3.06±0.1	0.46±0.02	17±0.1	99.02±0.22

All the values are expressed as a mean ± SD., n = 3

***IN-VITRO* dissolution study in 6.8 PH phosphate buffer:**

Table No. 7: *In-vitro* dissolution profile of FT4 at the end of 1, 2, 3 month of stability

Sl. No.	Time (min)	% cumulative Drug Release		
		1st month	2nd month	3rd month
0	0	0	0	0
1	2	96.3	95.24	95.9
2	4	98.4	98.1	98.27
3	6	99.72	99.21	98.96

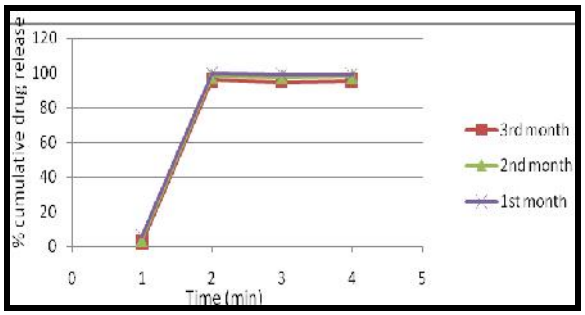

Fig. 8: Stability studies invitro dissolution of FT4 for month 1,2,3

Stability studies of FT4 were performed (1,2,3 months) and there is no significant changes in it, values are under I.P limits only, hence it can be concluded that FT4 is stable. All the post compression parameters were found to be in I.P limits (for 3 months).No statistically significant differences were observed in Hardness, percentage drug content and cumulative percentage drug release in optimized formulation at the end of three months of stability studies. So it can be concluded that the formulation is stable for short term storage conditions

CONCLUSION

The objective of this work was to formulate bilayered tablets constituting Loperamide and Simethicone layers in immediate release forms.The tablets produced met with the I.P requirement regarding drug content uniformity, hardness, disintegration and friability. All the formulations produced were studied for their drug in dissolution media of 6.8 pH phosphate buffer. In conclusion, the results indicated that the prepared immediate release Bilayered tablets of Simethecone and Loperamide could perform therapeutically with improved efficacy. Stability studies of FT4 done for 3months and results were found to be in limit there are no significant changes, hence we can say FT4 as stable. Hence it can be concluded that preparations containing super disintegrate CCS (20mg) used was found to be the best formulation.

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