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Formulation Design and Pre and Post Compression Parameter of Loperamide Hydrochloride

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Abstract

An opioid receptor agonist and acts on the muopioid receptors in the myenteric plexus large intestines; it works specifically by decreasing the activity of the myenteric plexus which decreases the motility of the circular and longitudinal smooth muscles of the intestinal wall. Loperamide Hydrochloride is a synthetic antidiarrheal indicated for the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease. So an attempt was made to mask the taste and to formulate into fast dissolving tablet by direct compression. Loperamide Hydrochloride should be administrated orally once or twice daily for a total daily dosage of 2mg to 16mg according to the age and condition of the patient. In this investigation fast dissolving tablet were prepared by using super disintegrating agent: crosscaremellose sodium, crospovidon and sodium starch gycolate in concentration 10%, 15% and 20%. Sweeteners and flavors were used to enhance the organoleptic properties of tablet. Tablets were prepared by direct compression technique. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, drug content and in vitro drug release. Disintegration time and drug release were taken as the basis to optimize the fast dissolving tablet. All the formulations were evaluated for the influence of disintegrates and their concentrations on the characteristics of fast dissolving tablet mainly in terms of disintegration time and dissolution studies. The disintegration time of all formulation showed less than 39 seconds. Among the three superdisintegrants used, Crospovidon showed less disintegrating time followed by crosscarmellose sodium and sodium starch gycolate. The relative efficiency of different superdisintegrants to improve the drug rate of tablets was in order, crospovidon> Crosscarmellose sodium >sodium starch gycolate.

Key word: Loperamide Hydrochloride, Fast dissolving tablet, superdisintegratants, Crospovidon, Crosscarmellose sodium, Sodium starch gycolate.

Introduction:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact, the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore, a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamic and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form[1]. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific frame work required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects.

1. Physicochemical, pharmacokinetic and Pharmacodynamic characteristics of the drug.
2. The anatomic and physiologic characteristics of the GIT, and
3. Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.[2]

In an effort to develop drug products that are more convenient to use and to address potential issues of patient compliance for certain product indications and

patient populations, recent developments in technologies have come out with fast dispersible tablets (FDT) that can be ingested simply by placing them on the tongue. FDT is a solid dosage form that dissolves or disintegrates within a minute in the oral cavity without the need of water and has a pleasant taste. FDT is also known as orally disintegrating tablet, fast-dissolving tablet, fast-melting tablet, mouth melting tablet or fast-disintegrating tablet[2].

Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional tablets and capsules. When water is not available, in the case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic conditions and bronchitis.[3]

For these reasons, tablets which can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Rapidly dissolving or disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.[4]

Materials

A. Drug and Excipients:

The following materials and instruments used in the experiment are of laboratory grade.

Table No: 1. Details of materials used

Sl. No.	Materials	Supplier
1.	Loperamide Hydrochloride	Titan Lab, Mahad, Pune.
2.	Aspartame	S.D. Fine Chem. Ltd. Mumbai
3.	Croscarmellose sodium	S.D. Fine Chem. Ltd. Mumbai
4.	Crospovidone	S.D. Fine Chem. Ltd. Mumbai
5.	Mannitol	S.D. Fine Chem. Ltd. Mumbai
6.	Magnesium Stearate	S.D. Fine Chem. Ltd. Mumbai
7.	Microcrystalline cellulose	S.D. Fine Chem. Ltd. Mumbai
8.	Sodium starch gycolate	S.D. Fine Chem. Ltd. Mumbai
9.	Talc	S.D. Fine Chem. Ltd. Mumbai
10	Vanilla flavour	S.D. Fine Chem. Ltd. Mumbai

B. INSTRUMENTS AND EQUIPMENTS USED

Table No. 2. Details of equipments used

Sl. No.	Instruments	Manufacturer/ Suppliers
1.	UV Visible spectrophotometer	Shimadzu 1800
2.	Multi Station rotary punch Tablet Compression machine	Clit Pilot press Chamnnda
3.	Dissolution test Apparatus	Electrolab, USP TDT 06P
4.	FTIR Spectrophotometer.	Sipra Lab Ltd.
5.	Tablet Disintegration Tester	Electro lab.
6.	Hot air Oven	Lawrence & Mayo.
7	Friability Tester	Electro lab, USP EF 2
8.	Hardness Tester	Monsanto
9.	Bulk density Apparatus (digital)	KE India
10.	Digital pH meter	Hanna instrument
11.	Vernier calliper	Pico India Ltd.
12.	Digital Analytical balance	Citizen

the polymers were taken.

Formulation design

As per the requirements of patient, dose prescribed by the physician ranges from 2mg to 16mg. According to the condition and age group the dose is fixed. The formulation of dosage were prepared ie 2mg of Loperamide Hydrochloride total weight of the tablet was 100mg.

For preparation of fast dissolving tablet of Loperamide Hydrochloride different formulae

design, by direct compression, using superdisintegrating crosscarmellose sodium, crospovidon, sodium starch gycolate along with other excipients. The blends of powder were subjected to compression using 8mm die for 100mg

B. Formulation design

The formula for preparation of fast dissolving tablets by direct compression

Table No 3. Ingredients require in mg for each tablet containing 2mg of Loperamide Hydrochloride (100mg each tab).

Ingredients(mg/tab)	Formulation codes								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Loperamide Hydrochloride	2	2	2	2	2	2	2	2	2
Microcrystalline cellulose	70	65	60	70	65	60	70	65	60
Mannitol	12	12	12	12	12	12	12	12	12
Crosscarmellose sodium	10	15	20	-	-	-	-	-	-
Crospovidon	-	-	-	10	15	20	-	-	-
Sodium starch gycolate	-	-	-	-	-	-	10	15	20
Aspartame	2	2	2	2	2	2	2	2	2
Vanilla flavor	1	1	1	1	1	1	1	1	1
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1

C. Compatibility studies of drug and polymers

Prior to the development of the dosage forms the compatibility study was carried out. Hence infrared spectra of the physical mixture of the Loperamide Hydrochloride and the polymers were taken. Also the infrared spectrum of the Loperamide Hydrochloride was taken individually.

D. Pre-treatment of Mannitol

Mannitol (crystalline) was subjected to granulation, especially wet granulation, in order to improve the flowability and/or compression properties. Mannitol (crystalline) was converted to granular mannitol prior to its processing for direct compression using starch paste (10% w/v) as binder as well as intra-granular disintegrant. The cohesive mass of mannitol was sifted through the sieve #22 and then dried at 60 ºC for 5 minutes. LOD of mannitol granules was tried to keep 0.2 – 0.3 % for appropriate time of drying at 105º C, till constant weight was achieved. Again these dried granules of mannitol were resifted through the sieve #22.

E. Formulation methods

1. Direct compression method.

Method of preparation of tablet:

The drug was mixed with proper portion of superdisintegrants. Care should be taken to confirm the proper mixing of drug and superdisintegrants. Then other excipients were added. Then the mixture is passed through sieve No. 44. The mixture is blended with lubricating agent (magnesium stearate). Finally the blend is subjected for compression using 8mm on Clit pilot press 10 Station machine.

PREFORMULATION STUDIES:

1: Determination of λmax Of Loperamide Hydrochloride

The UV absorption spectrum shows maximum peak at 226 nm as shown fig.1. The same was selected as λ_{max} for Loperamide Hydrochloride , for obtaining calibration curve.

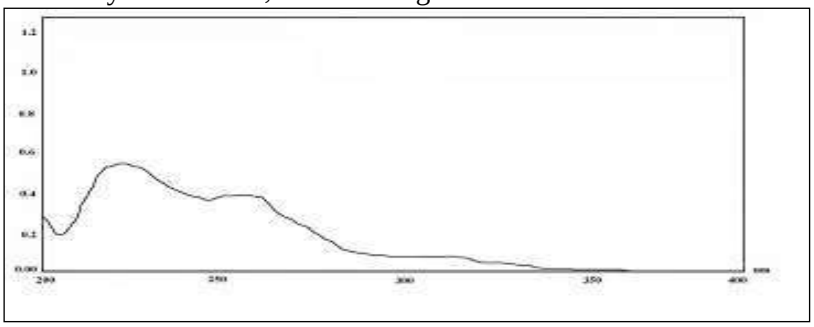

Fig 1: UV Spectrum of Loperamide Hydrochloride

2: IR Spectras:

The IR Spectra of Loperamide Hydrochloride (Pure Drug) and the mixture of Loperamide Hydrochloride and using different super-disinegrants.

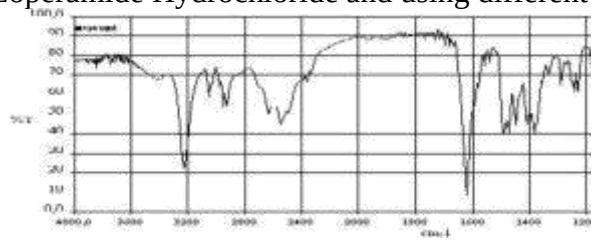

Fig 2: IR Spectra of Loperamide Hydrochloride

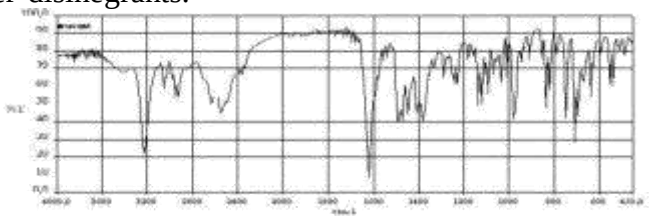

Fig. No.4. IR spectra of Loperamide Hydrochloride with sodium starch glycolate.

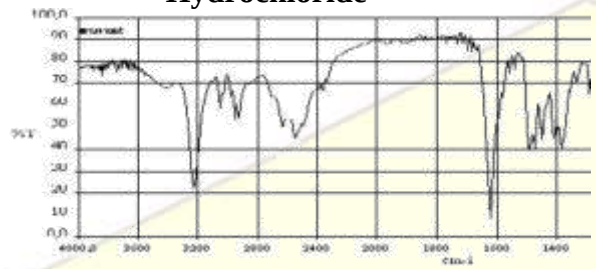

Fig. No.3. IR spectra of Loperamide Hydrochloride and croscarmellose sodium.

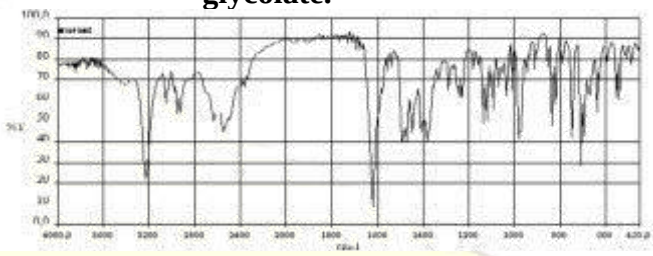

Fig 5.IR spectraof Loperamide Hydrochloride with crospovidon.

TABLE NO 4: STANDARD CALIBRATION CURVE OF LOPERAMIDE HYDROCHLORIDE IN PHOSPHATE BUFFER pH 6.8

Sl. No	Concentration	Absorbance
1	0	0.00
2	2	0.149
3	4	0.263
4	6	0.413
5	8	0.603
6	10	0.721

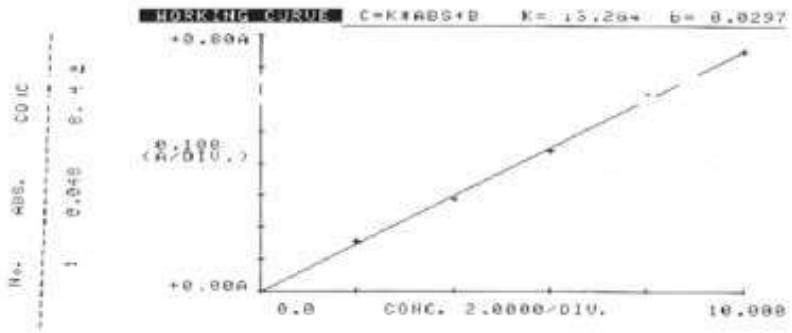

FIG NO 6: Calibration Curve of Loperamide Hydrochloride in phosphate buffer pH .8:

3 EVALUATIONS:

A. **Pre compression evaluation parameters**

TABLE NO 5: PHYSICAL PROPERTIES OF POWDER BLEND OF FORMULATIONS F1 to F9

Formulation	Angle of repose (θ)	Loose bulk density (LBD)	Tapped bulk density(TBD)	Carr's index (%)	Hausner ratio
F 1	**27.1**	**0.323**	**0.374**	**13.63**	**1.15**
F 2	**28.3**	**0.359**	**0.403**	**10.91**	**1.12**

F 3	27.1	0.323	0.373	13.40	1.15
F 4	28.2	0.361	0.412	12.37	1.14
F 5	28.3	0.364	0.410	11.31	1.12
F 6	29.3	0.392	0.442	11.21	1.12
F 7	27.4	0.342	0.392	12.75	1.14
F 8	28.5	0.362	0.417	13.14	1.15
F 9	27.4	0.340	0.396	14.14	1.16

B. Post compression parameters

TABLE NO. 6. PHYSICAL PROPERTIES OF TABLETS OF FORMULATIONS F1 TO F9

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Wetting time (sec)
F1	2.52±0.10	2.4	100.3±0.3	0.41	39.3
F2	2.53±0.10	2.4	101.4±0.4	0.52	38.2
F3	2.41±0.09	2.4	101.2±0.4	0.54	36.4
F4	2.61±0.08	2.4	103.2±0.9	0.51	39.3
F5	2.72±0.12	2.4	103.2±0.6	0.52	36.2
F6	2.83±0.14	2.4	103.4±1.0	0.47	34.4
F7	2.41±0.18	2.4	102.9±0.5	0.43	45.4
F8	2.41±0.03	2.4	101.4±0.4	0.52	44.7
F9	2.37±0.16	2.4	99.52±0.3	0.40	42.4

TABLE NO 7: IN-VITRO DISINTEGRATION TIME, DRUG CONTENT AND % DRUG RELEASE OF FORMULATION F1 TO F9

formulation	Disintegrating time (sec)	% drug release	Drug content uniformity
F1	32.4	84.20	98.74
F2	31.23	85.43	98.43
F3	33.22	87.02	97.47
F4	23.23	94.01	99.03
F5	20.43	95.02	99.23
F6	19.43	97.43	99.40
F7	38.24	80.43	98.24
F8	36.21	82.32	97.43
F9	34.31	84.30	97.43

TABLE NO 8: CUMULATIVE % DRUG RELEASE PROFILE OF LOPERAMIDE HYDROCHLORIDE

Time (Min)	Cumulative % drug release from the formulation prepared with crosscaramellose sodium by Direct compression method			Cumulative % drug release from the formulation prepared with crosspovidone by Direct compression method			Cumulative % drug release from the formulation prepared with Sodium starch glycolate by Direct compression method		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
3	10.32	11.42	13.02	15.02	14.02	17.02	8.32	10.12	11.32
6	14.02	15.23	16.72	17.43	18.43	19.42	12.43	15.12	15.82
9	22.04	25.43	27.43	24.23	24.23	26.32	19.23	23.14	25.72
12	35.43	37.43	38.43	39.24	41.28	42.72	26.73	30.72	33.30

15	50.43	50.02	56.02	55.23	57.43	59.43	37.83	41.34	50.70
18	60.21	63.11	65.17	63.47	65.27	66.07	50.14	52.73	62.12
21	69.43	72.24	73.08	72.23	72.43	75.48	65.13	63.73	72.37
24	75.23	78.43	82.31	83.04	84.23	85.32	70.78	77.84	79.41
27	79.43	81.23	85.42	89.23	91.43	94.81	76.14	80.41	82.13
30	84.20	85.43	87.02	94.01	95.02	97.43	80.43	82.32	84.30

TABLE NO 9: LOG CUMULATIVE % DRUG REMAINED IN THE FORMULATIONS

Time In Min	Log Cumulative % drug remained from the formulation prepared with crosscaramellose sodium by Direct compression method			Log Cumulative % drug remained from the formulation prepared with crosspovidone by Direct compression method			Log Cumulative % drug remained from the formulation prepared with Sodium starch glycolate by Direct compression method		
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	2	2	2	2	2	2	2	2	2
3	1.95	1.94	1.93	1.92	1.93	1.91	1.96	1.95	1.94
6	1.93	1.92	1.92	1.91	1.91	1.90	1.94	1.92	1.92
9	1.89	1.87	1.86	1.87	1.87	1.86	1.90	1.88	1.87
12	1.81	1.79	1.78	1.78	1.76	1.75	1.86	1.84	1.82
15	1.69	1.65	1.64	1.65	1.62	1.60	1.79	1.76	1.69
18	1.59	1.56	1.54	1.56	1.54	1.53	1.69	1.67	1.57
21	1.48	1.44	1.43	1.44	1.44	1.38	1.54	1.55	1.44
24	1.39	1.33	1.24	1.27	1.19	1.16	1.46	1.34	1.33
27	1.31	1.27	1.16	1.03	0.93	0.71	1.37	1.29	1.25
30	1.19	1.16	1.11	0.77	0.69	0.40	1.29	1.24	1.19

4 .STABILITY STUDIES

Table No: 10 Stability studies for the formulation F6

Time in weeks	Formulation F6 stored at 40^0c/ 75% RH
	% Drug content
4	99.32
6	98.14

Conclusion

- **Loperamide Hydrochloride** is an opioid receptor agonist and acts on the muopioid receptors in the myenteric plexus large intestines; it works specifically by decreasing the activity of the myenteric plexus which decreases the motility of the circular and longitudinal smooth muscles of the intestinal wall. Loperamide Hydrochloride is a synthetic antidiarrheal indicated for the control and symptomatic relief of acute nonspecific diarrhea and of chronic diarrhea associated with inflammatory bowel disease.
- All the pre compression and post compression parameter were found to be within limit and meets the standard evaluation parameters with a slight deviation within prescribed limit.
- The short term stability studies carried out were confirmative of the drug stability in the tablets during the present study.
- The relative efficiency of these superdisintegrants to improve the disintegration and dissolution rate of tablets was in the order, crospovidon > Crosscarmellose sodium > sodium starch gycolate. The disintegration studies revealed that the tablets prepared with crospovidone show faster disintegration as compared to tablets prepared with croscarmellose sodium and sodium starch glycolate. This was probably due to formation of viscous plugs by sodium starch glycolate.
- It is concluded that crosspovidone shows good disintegrating property than crosscarmellose, sodium starch glycolate.

- From the above said it can safely concluded that the fast dissolving tablets of Loperamide Hydrochloride prepared with crospovidone show a better disintegration time and the dissolution profile.

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