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Comparative Study on Effect of Natural and Synthetic Superdisintegrants in the Formulation of Metoclopramide HCL Mouth Dissolving Tablets

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Abstract: ***Metoclopramide HCL is 4-Amino-5-chloro-N-(2-(diethyl amino) ethyl)-2-methoxybenzamide that is mainly indicated as an Anti-emetic. In such conditions mostly the patient becomes panic and will have difficulty swallowing the tablet with a glassful of water. In such cases, Mouth dissolving tablets will be a good solution for patient compliance and an efficient dose regimen. Metoclopramide HCL tablets are available in different strengths i.e., 20 mg and 40 mg. The main objective of this project work was to developed & designed mouth dissolving tablets (MDTs) containing Metoclopramide HCL 20 mg and to perform a comparative study using pharmaceutical excipients with different sources i.e. from synthetic and natural superdisintegrants to enhance patient compliance and therapeutic value as compared with the available market brands. Mouth dissolving Tablets of Metoclopramide HCL were formulated by using Natural and synthetic Superdisintegrants like Hibiscus leaves mucilage, Plantago ovata seeds mucilage and Sodium Starch Glycolate, Cross Povidone microcrystalline cellulose, sweetening agent as Sodium saccharine, talc and magnesium stearate as Drug - excipients compatibility tests performed before starting the formulation. The selection and the rejection of excipients for the experimental formulation were considered after getting the result of the drug excipients compatibility study. The flowability of the powder mixtures was evaluated using Carr's index, Angle of Repose, and Hausner's ratio. The tablets were evaluated according to the standards prescribed by British Pharmacopoeia like weight variation, thickness, hardness, friability, disintegration time, a simulated wetting test, and in-vitro dissolution. Prepared tablets after Optimization showed disintegration time of fewer than 30 seconds and drug dissolution of about 75% within 30 minutes. The prepared tablets of optimized batch tested for stability 40 degrees Celsius and 75% RH for 3 months and were found to be stable. Prepared Mouth Dissolving tablets of Metoclopramide HCL 20 mg from optimized batch were found bioequivalent under fasting and fed conditions with the available market products.***

Keywords: synthetic superdisintegrants, metoclopramide, HCL, mouth dissolving tablet

1. Introduction

Among all the routes of the drug delivery system, drug delivery through the oral route is most common and preferred for both solid and liquid dosage forms. Solid dosage forms are more popular. Tablet is one of the preferred solid dosage forms because of its dose, safest, and economical (Adchitre Vaishali B et al., 2016). Tablet is a compressed solid dosage form which contain medicaments in which excipients are present. In the Indian Pharmacopoeia, Tablets are defined as solid, flat, or biconvex dishes and unit dosage form which prepared by compressing a drug or a mixture of drugs with or without diluents. They vary in shape and differ greatly in size and weight depending on the number of medical substances and the intended mode of administration. All the medicaments are available in tablet form except where it is difficult to formulate or administer.

Mouth Dissolving Tablets" (MDTs) are characterized by a strong single-unit measurement structure that we put on our tongue where it disintegrates within a couple of minutes and afterward can be swallowed by water. The quicker the medications breaks, faster the scattering and disintegration happen. If this procedure happens fast, the drug is ingested faster.

2. Material and Methods

Drug and Excipients used in the formulation

F1-F3 with Synthetic Superdisintegrants

Sr. No.	Ingredients	Unit Formula (mg/tablet)		
		F-1	F-2	F-3
1	METOCLOPRAMIDE HCL	10	10	10
2	MCC	30	30	30
3	SSG	5	10	15
4	Cross Povidone	15	10	5
5	Mannitol	143	143	143
6	Sod. Saccharine	2	2	2
7	Aerosil	2	2	2
8	Mag. Stearate	1	1	1
9	Talc	2	2	2
Net Wt. / Tab. in mg		210	210	210

F4-F6 with Natural Super disintegrants

Sr. No.	Ingredients	Unit Formula (mg/tablet)		
		F-4	F-5	F-6
1	METOCLOPRAMIDE HCL	10	10	10
2	MCC	30	30	30

3	Hibiscus leaves mucilage	5	10	15
4	Plantago ovata seeds mucilage	15	10	5
5	Mannitol	143	143	143
6	Sod. Saccharine	2	2	2
7	Aerosil	2	2	2
8	Mag. Stearate	1	1	1
9	Talc	2	2	2
Net Wt. / Tab. in mg		210	210	210

Equipment and instruments used during formulation

Equipment and instruments	Make and Model
Weighing Machine	PS6000/C/1 manufactured by LCGC RADWAG
Vibrosifter	Gansons Engineering
Electromagnetic Sieve Shaker	EM8-08 Plus manufactured by Electrolab
Tap Density Testing Apparatus;	ETD-1020 manufactured by Electrolab
Double Cone Blender with interchangeable bowls	manufactured by Sams Technomech;
Loss on Drying Mositure Analyzer	Model MB 45 manufactured by Ohaus
Comminuting Mill equipped with 0.5mm Screen	Manufactured by Cadmach Machinery;
16 Station Single Rotary Tablet Compression Machine	Manufactured by Cadmach Machinery
Hardness Tester	Type: TBH 125 manufactured by Erweka
Thickness Tester Vernier Caliper	Absolute Dogmatics manufactured by Mitutoyo
Friabilator	EF-1W manufactured by Electrolab
Disintegration Test Apparatus	Model ED 2L manufactured by Electrolab
6.35 mm Round Flat Faced Bevel Edged Punch Tooling	manufactured by ACG PAM Pharma Technology
pH Meter	H12215 manufactured by Hanna Instruments
UV Visisble Spectrophotometer	manufactured by Perkin Elmer Lambda 25
Lab Stirrer	RQ126D manufactured by Remi
Dissolution Apparatus	TDT-08L manufactured by Electrolab
40°C / 75% RH Stability Chamber	manufactured by Thermolab Scientific Equipment

Disintegration and dissolution parameters

Disintegration test was performed in USP disintegration test apparatus in purified water at 37±0.5-degree celcius. Specification NMT 30 Seconds. Dissolution is performed in purified water. The parameters include USP-II (Paddle) 50 RPM, 900 ml, purified water at 37±0.5-degree celcius, Time Points 0, 0.08, 0.16, 0.25, 0.33, 0.41, 0.5, 0.66, 0.83, 1.0, 2.0, 4.0 and 6.0 minutes. Specification NLT 75% (Q) of the labelled amount in 60 minutes.

Method of assay, blend uniformity, content uniformity/Uniformity of Dosage Units and Dissolution

Method for Bulk Density, tapped density, Angle of Repose and Friability

USP guidelines followed in the measurement of Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio, Repose Angle and % Friability measurements.

3. Experimental Methodology

Molecular dispersion technique with micronized active drug Ebastin by using Natural superdisintegrants, the process will be the same for every trial batch from Batch No. F1 – Batch No. F6 for the manufacturing of Mouth Dissolving Tablets.

3.1 Methodology

MDTs of Metoclopramide HCL prepared by using Natural and synthetic superdisintegrants, the process will be the same for every trial batch from Batch No. F1 – Batch No. F6 for the manufacturing of Mouth Dissolving Tablets.

For F1- F3

Step -1: Material Sifting

a) Metoclopramide HCL, Microcrystalline Cellulose, SSG, Cross povidone, shall be sifted through #40 separately.
b) Colloidal silicon dioxide, Talc and Magnesium Stearate shall be sifted through #60 separately.

Step – 2: Manufacturing Process for F1 to F3

a) Transfer all sifted material i.e. Metoclopramide HCL, Microcrystalline Cellulose, SSG, Cross povidone one by one to a double cone blender.
b) Start the mixing by running the blender for 5 min.

Step - 3: - Lubrication

a) Now transfer the Colloidal silicon dioxide, Talc and Magnesium Stearate and mix properly.
b) Finally add mannitol and Sod. Saccharine in powdered form to the above material and mix well for 1 min.

Step – 4: - Compression

a) The lubricated blend is compressed into tablets as per pre-planned formulation by using a rotary compression machine.

For F4 to F6

Step - 1: Mixing

a) Transfer all sifted material i.e. Metoclopramide HCL, Microcrystalline Cellulose, Plantago Ovata Mucilage one by one to a double cone blender.
b) Start the mixing by running the blender for 5 min.

Step - 2: Lubrication

a) Now transfer the Colloidal silicon dioxide, Talc and Magnesium Stearate and mix properly.
b) Finally add mannitol and Sod. Saccharine in powdered form to the above material and mix well for 1 min.

Step – 3: Compression

a) The lubricated blend is compressed into tablets as per pre-planned formulation by using a rotary compression machine.

3.2 Parameters Fixed for the tablet

The following parameters were mixed for the final tablets obtained:

- Punch size: 9 mm

- Thickness: 3±0.5 mm
- Hardness: 2 ±1 kg/cm2
- Weigh variation: 1 - 5%

Preformulation studies

All the excipients were evaluated with the drug for compactability studies. The preformulation studies were performed according to the formula and results were recorded based on the data was obtained accordingly.

Characterization of Active Drug

The active drug was evaluated for various parameters through the standard test and accordingly the results have been mentioned in Table 4.0

Table: Result analysis of Metoclopramide

Test	Specification	Observation	Conclusion
Description	White color powder	White color powder	Complied
Odor	Odorless	Odorless	Complied
Solubility	Insoluble in water	Practically Insoluble in water	Complied
	Slightly soluble in methyl alcohol; freely soluble in dimethylformamide andglacial acetic acid. It dissolves in dilute mineral acids.	Practically it is slightly soluble in methyl alcohol; freely soluble in dimethylformamide and glacial acetic acid. It dissolves in dilute mineral acids.	Complied

Drug-excipient compatibility studies

The drug was evaluated along with all the excipients for compatibility studies and the results were recorded as per the data obtained after completion of the studies in Table.

The FT-IR spectrum of Metoclopramide and excipient individually and their mixtures of drug and excipient are shown in Fig. 1.0

Table 5: Drug-excipient compatibility data

S. No.	Drug+ Excipient	Condition		
		Room Temperature	Hot air oven	Freezing Temperature
1	METOCLOPRAMIDE HCL (API)*	Stable	Stable	Stable
2	API + MCC	Stable	Stable	Stable
3	API + SSG	Stable	Stable	Stable
4	API + CROSSPOVIDONE	Stable	Stable	Stable
5	API + PLANTAGO OVATA MUCILAGE	Stable	Stable	Stable
6	API + HIBISCUS LEAVES MUCILAGE	Stable	Stable	Stable
7	API + COLL. SILI. DI. OXIDE	Stable	Stable	Stable
8	API + MAG. STEARATE	Stable	Stable	Stable
9	API + SOD. SACCHARINE	Stable	Stable	Stable
10	API + TALC	Stable	Stable	Stable
11	API + MANNITOL	Stable	Stable	Stable

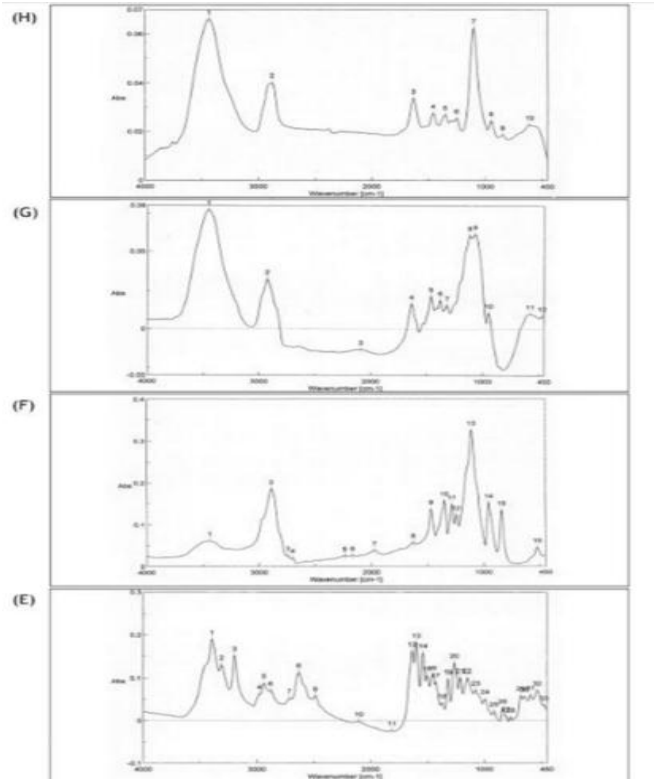

Figure 1: FT-IR spectrum of "METOCLOPRAMIDE''

Results of pre-compression studies

Precompression studies generally involve the evaluation of the blend in terms of bulk density, tapped density, compressibility index, Hausner's ratio, and so on (Table 5.3). These also determine the flow property of the powder.

Table Physical properties of the prepared blend

Batch	*Bulk Density*	*Tapped Density*	*Angle Of Repose*	*Carr's Index*	*Hausner's Ratio*
F1	0.51±0.002	0.67±0.001	31.96±0.38	24.30 ± 0.160	1.32± 0.003
F2	0.48±0.001	0.62±0.001	32.49±0.80	24.86 ± 0.660	1.36± 0.003
F3	0.55±0.001	0.73±0.001	32.58±0.46	25.38 ± 0.360	1.34± 0.009
F4	0.54±0.002	0.71±0.001	34.81±0.86	26.60 ± 0.890	1.31± 0.016
F5	0.52±0.001	0.73±0.001	34.58±0.58	25.30 ± 0.450	1.35± 0.014
F6	0.55±0.002	0.67±0.001	34.31±0.36	24.90 ± 0.860	1.33± 0.006

3.2 Results of Post Compression Studies

Mouth Dissolving tablets of all set of batches were evaluated after the compression for several pre-prescribed pharmacopeial and in-house standards and parameters like average weight, Hardness, Friability, Drug Content, Tablet thickness, dispersion, drug content, wetting time, water absorption ratio, and in vitro disintegration time.

- After the completion of analytical tests, the obtained results are shown in Table.
- In-vitrodissolution rate study is shown in Table

Table Evaluation parameter of the tablet

Batch	Average Weight (mg)*	Hardness (N)**	Friability (%)	Drug content (%)**	Thickness (mm)
F1	210.99	34.8±4.57	0.29	100.97	3.36±0.05
F2	209	40.8±4.87	0.7	101.02	3.43±0.02
F3	210.02	38.8±2.67	0.4	99.98	3.34±0.04
F4	205.5	44.8±3.17	0.47	100.43	3.44±0.04
F5	211.4	38.8±2.58	0.49	100.54	3.26±0.03
F6	214.2	36.8±3.87	0.46	99.68	3.55±0.04

* Average weight of 20 tablets was taken into consideration
** Average of 3 readings

Table 5.5: Evaluation parameter of the tablet

Batch	Wetting Time (Sec.)	Disintegration Time (Sec.)
F1	0.47±0.052	11.0±1.00
F2	2.17±0.032	15.0±1.50
F3	0.67±0.352	12.0±1.20
F4	0.98±0.042	40.0±1.80
F5	0.97±0.059	39.0±1.80
F6	0.67±0.012	19.0±2.10

**Average of 3 readings

3.3 In-Vitrodissolution Study Results

The result of in vitro dissolution study is given in below Tables

Table 5.6: In-vitroDissolution Rate Study

Time (min)	Cumulative Percent Drug Release of All Formulation					
	(F1)	(F2)	(F3)	(F4)	(F5)	(F6)
0	0	0	0	0	0	0
0.08	4.43±1.96	4.63±1.16	5.93±1.26	5.86±2.96	6.40±0.96	6.43±1.26
0.16	6.43±2.47	6.83±1.47	6.83±1.42	6.93±2.47	7.43±2.47	669±3.67
0.25	13.01±2.19	21.01±1.11	16.01±2.69	6.01±0.19	11.01±2.19	7.96±2.34
0.33	30.27±0.73	42.17±0.13	45.27±1.13	8.07±2.73	14.27±9.78	9.57±9.94
0.41	48.79±8.55	53.79±4.55	63.79±8.55	12.79±7.55	20.79±8.55	15.79±8.55
0.5	71.88±5.49	75.88±6.49	78.88±5.49	16.88±2.49	28.88±1.49	34.88±8.49
0.66	83.95±3.20	87.95±4.60	87.95±3.20	23.95±7.20	51.95±8.20	49.95±6.20
0.83	90.82±2.45	97.82±1.45	92.82±2.45	38.82±5.45	62.82±2.45	66.82±8.45
1	**96.40±1.32**	**92.50±3.32**	**91.40±1.32**	**54.40±1.32**	**74.40±8.32**	**79.40±7.82**
2	96.74±4.89	99.74±1.8	99.74±4.89	79.74±2.89	97.74±9.89	80.74±9.89
4	100.19±5.50	101.19±1.50	101.11±1.50	86.19±1.5	100.1±7.5	87.19±8.5
6	100.9±6.03	102.9±1.03	102.2±7.03	98.9±3.03	101.9±3.03	94.9±0.03

*Average of 2 reading

4. Conclusion

The Mouth Dissolving tablets of Metoclopramide were successfully formulated using various ratios of different types of natural superdisintegrants and the formulation was prepared by molecular dispersion and direct compression technique. The natural superdisintegrants Agar and Guargum were added in the formulations in various concentrations to achieve the optimized batch. The Mouth Dissolving tablets of Metoclopramide were prepared using natural superdisintegrants along with the other excipients. All the set of product formulation (F1-F6) were evaluated for

- Pre formulation parameters such as Drug-excipients compatibility studies.
- For flowability and compressibility analysispre-compression parameters such as Bulk &Tapped density of blend, Carr's index, Hausner's ratio, and angle of repose obtained.
- Initially, the powder blend for all set of batches was evaluated for their flowability property. The values obtained through Carr's index were satisfactory suggested that the blends have good compressibility and the values obtained by Hausner's ratio were showing a good sign for flow property for the powder blend.
- Other tests like weight variation, hardness, friability, disintegration time, wetting time, dissolution analysis, drug content uniformity was performed as post-compression parameters study.
- Finally, the optimized batch was also evaluated for accelerated stability studies & bio equibalance study.

Mouth Dissolving tablets of Metoclopramide were formulated to have the adequate mechanical strength to withstand during their handling, packaging, shipping, storage, and transportation. The tablets were prepared following the standards as prescribed by guidelines. Formulation F2 were showing fast disintegration and dissolution profile. Drug dissolution further impact on bioavailability and therapeutic effect of formulation. The optimized formulation was considered for stability studies. The data obtained from stability studies demonstrated that Mouth Dissolving tablets of Metoclopramide were steady and stable under various natural environmental storage conditions.

5. Summary

Mouth Dissolving Tablets (MDTs) drug-delivery systems were developed for patient compliance, especially for pediatric, geriatric, dysphagia, tremor, or physically disabled and travelers. Sometimes it is impractical to access water which is required to administer the drug in the form of a tablet or capsules. Those patients who feel difficulty in swallowing or engaged at such places where it is not easy to approach water supply. Sometimes the patients may be in a condition like the unconscious, travelers, minors, or old aged so fast disintegrating tablets may resolve such issues to administer the dose without providing them a sense to swallow a drug. Such patients can be given a single tablet to keep it in their mouth where the Mouth Dissolving tablet is dispersed in a few seconds and starts to absorb in the bloodstream.

Mouth Dissolving tablets are developed and designed for quick dispersion and rapid disintegration in the saliva generally less than 30 seconds. MDTs having some major advantages over other formulations. MDTs disintegrate quickly in saliva within few seconds and this is an advantage that there is no need to take water.

There were mainly two techniques used to develop MDTs

- The first technique is to use super disintegrants like croscarmellose sodium (CCS), sodium starch glycolate (SSG), crospovidone & other polymers as disintegrants.
- And the second technique is increasing the pore size within tablets by freeze-drying or vacuum drying process.

In this present research, Super disintegrants were used from Natural origin. Pregastric absorption and quick absorption of the drug from an oral cavity after the dispersion of MDTs in saliva may increase the therapeutic value or bioavailability of drugs. The test formulation containing Metoclopramide as a model drug is a D2 receptor blocker, 5-HT3 receptor antagonist and 5-HT4 receptor antagonist. After placing a Mouth Dissolving tablet in the oral cavity, it disintegrates within a few seconds and quickly gets absorbed in the blood. Mouth Dissolving tablets of Metoclopramide after oral administration has an onset of action within a few minutes which is present for the next 10-12 hrs. The elimination of the drug is by the renal and metabolic routes. So, it is important to reduce the dose of the drug for patients having metabolic disorders, kidney, or renal failure.

Mouth Dissolving Tablets (MDTs) of Metoclopramide were prepared by using natural super disintegrants with different concentrations such as Micro Crystalline Cellulose, Cross Povidone, SSG, Hibiscus Rosa sinensis Mucilage, Plantago Ovata Mucilage, Mannitol Sodium saccharine, Colloidal silicon dioxide, Magnesium Stearate, Talcum were used in formulations as other excipients. A total of 6 formulations were designed with molecular dispersion. To compress Mouth Dissolving tablets, the direct compression method was preferred. All the set of batches were evaluated for Pre formulation parameters like

Precompression Studies

- Drug excipients compatibility studies, Angle of repose for flowability of powder blend, bulk, and tapped density of powder blend, compressibility index, Hausner's ratio was analyzed for each formulation.

Compression Parameters Studies

- Similar conditions were followed for all the sets of formulations. The average weight of Mouth Dissolving tablets was within the range of 207.99 to 211.4 mg.
- Other parameters were found within the prescribed limits such as weight variation, friability within the range 0.36 – 0.89 % of all formulation.
- The hardness of tablets from all set of 13 batches was found satisfactory and within the range of 34.8 to 43.8 Newton.
- Disintegration time is most of the important parameter for ODT's, quick dispersion or disintegration help in swallowing of dispersed tablets & drug absorption in the oral cavity, thus promoting therapeutic value by increasing bioavailability of the drug.
- MDTs showing disintegration time within the time limit. Practically the values were observed within the range of 12 sec to 30 seconds. The percent drug content of the Mouth Dissolving tablet of formulation F1 was found to the 98.57%, which has the best percent drug content among all the sets of formulations & Formulation F4 was found with the percent drug content of 54.40%, which has the least percent drug content among all the formulations. *In vitro* dissolution studied of ODT's was performed in the 0.1N HCL using the USP paddle-type dissolution apparatus. It was observed that formulations with the natural super disintegrants in optimum concentration having better drug release as compared to the product with super disintegrants from synthetic sources due to the swelling and wicking effect of its combination. The best in-vitro dissolution profile was obtained from the formulations containing super disintegrants from the natural origin when the results were compared with the preexisting formulations containing super disintegrants from the synthetic origin. The optimized batch F1 was considered for a long time on stress conditions to determine the shelf life of the product.

6. Future Prospects of current research work, Bioequivalence study and Clinical trial

The prospects of Mouth Dissolving formulations are promising and the market demand is increasing day by day. Several techniques were applied with different kinds of material that were used to formulate the MDTs. Natural Super disintegrants are the best option to produce satisfactory and safer ODT formulation which has been proven with the existing study. MDTs with natural super disintegrants were found stable during Drug Excipients stability studies. Disintegration time and dissolution profiles were found more challenging as compared with the available MDTs with synthetic disintegrants. The optimized batch can be considered for human trials to investigate the In-vivo drug release. Bioequivalence studies can be done for test formulation with the brand drug as available in the market.

References

[1] Arya, A., Sharma, S., Kumar, J., Jaiswal, P., Chandra, A., 2010. Formulation and Evaluation of Mouth Dissolving Tablets of Ranitidine HCL. *International Journal of PharmTech. Research*, Vol. 2, pp. 1574-1577.

[2] Aithal, K., Harish, N. M., Rathnanand, M., Shirwaikar, A., Dutta, M., 2006. Once-daily fast dissolving tablets of granisetron hydrochloride formulation and *in vitro* evaluation. *Indian Drugs*, Vol. 43, Issue 7, pp. 576-581.

[3] Ahmed, I. S., Nafadi, M. M., Fatahalla F. A., 2006. Formulation of a fast-dissolving ketoprofen tablet using freeze-drying in blisters technique. *Drug Dev Ind. Pharm.*, Vol. 32, pp. 437-442.

[4] Ahire, B., Gaikwad, P., Banker, V., Pawar, S., 2012. Mouth Dissolving Tablet and Its Applications.

International Journal of Drug Delivery, Issue 4, pp. 89-94.

[5] Ashish, P., et al., A Review-Formulation of mouth dissolving tablet. *International journal of pharmaceutical and clinical science*, 2011. 1(1): p. 1-8.

[6] Brown, D., 2001. Orally disintegrating tablets: Taste over speed. *Drug Delivery Technology* Vol. 3, Issue 6, pp. 58-61.

[7] Bradoo, R., 2001. Fast Dissolving Drug Delivery Systems. *JAMA India*, Vol. 4 Issue 10, pp.27-31.

[8] Bagul, U., Gujar, K., Patel, N., Aphale, S., Dhat, S., 2010. Formulation and Evaluation of Sublimed Fast Melt Tablets of Levocetirizine Dihydrochloride, *International Journal of PharmaceuticalSciences*, Vol. 2, and Issue 2, pp. 76-80.

[9] Bhandari, S., Mittapalli, R. K., Gannu, R., Rao, Y. M., 2008. Orodispersible tablet: An overview. *Asian Journal of Pharmaceutics*, Vol. 2, pp. 2-11.

[10] Bedi, N., Kalia, A., Khurana, S., 2009. Formulation & evaluation of mouth dissolving tablet of Oxcarbazepine. *International Journal of Pharmacy & Pharmaceutical Science*, Vol. 1, Issue 1, pp. 12- 23.

[11] Bhowmik, D., Chiranjib, B., Krishna, K., Pankaj, Chandira, R. M., 2009. Fast Dissolving Tablet: An Overview. *Journal of Chemical and Pharmaceutical Research*, Vol. 1, Issue 1, pp. 163-177.

[12] Bagul, U., Bagul, N., Kulkarni, M., Sawant, S., Gujar, K., Bidkar, A., 2006 [Online]. Current status of tablet disintegrant: a review. Available at: Pharmainfonet.html, Vol. 4, and Issue 4.

[13] Cirri, M., Valleri, M., Mura, P., Maestrelli, F., Ballerini, R., Development of fast-dissolving tablets of flurbiprofen cyclodextrin complexes. *Drug Dev Ind. Pharm.*, Vol. 3 Issue 1, pp. 697-707.

[14] Chang, R., Guo, X., Burnside, B. A., Couch, R., 2000. Fast-Dissolving Tablets. *Pharmaceutical Technology*, Vol. 24, Issue 6, pp.52-58.

[15] Chandy, A., Gupta, S., Manigauha, A., Thakur, Singh, A., 2010. Comparatively evaluated disintegration in the orodispersible tablet of famotidine. *International Journal of Current Pharmaceutical Research*, Vol. 2, Issue 3, pp. 44-46.

[16] Saccharine" reference.com. Archived from the original on 2007-03-03.

[17] Saccharine". etymonline.com. Archived from the original on 2006-03-23.

[18] ^ "Sweetener Comparisons". Food Ingredient Series. NCSU. 2006. Archived from the original on 2019-01-20

[19] Payen, Anselme (1859) "Sur la gelose et le nids de salangane" (On agar and swiftlet nests), Comptes rendus …, 49: 521–530, appended remarks 530–532.