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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF SUBLINGUAL TABLET FOR NARATRIPTAN***Hiral Brahmbhatt¹, Hardik Brahmbhatt¹, Krishna Patel¹, Priti Makwana¹, Nimisha Chauhan¹, Hitesh Jain², Umesh Upadhyay³**¹P.G. student, ²Associate Professor, ³Principal
Sigma Institute of Pharmacy, Bakrol, Vadodara, Gujarat, India**ABSTRACT**

Naratriptan is used for the treatment of migraine. Formulation and Evaluation of sublingual tablets of Naratriptan for pre and post Compression parameters was undertaken. The tablets were prepared by direct compression method using super disintegrates. After selection of superdisintegrants tablets were prepared by using polymer for reducing the flushing action of saliva and provide enough time for drug absorbed. The prepared tablets were evaluated for their physical and chemical property. The permeation study was performed on Goat mucosa for optimized batch. No interactions were found between drug and excipients. Formulation F2 containing Crosspovidone shows immediate drug release. Formulation F6 containing Chitoson shows fast drug release as compared to superdisintegrants alone. Sublingual tablets were prepared by direct compression method using Crosspovidone as a superdisintegrants. But it is more effective in combination with Chitoson. As a result, sublingual tablet administration of Naratriptan formulated with appropriate excipients and especially with Chitoson seems promising alternative to traditional routes.

Keyword:-Sublingual delivery, Naratriptan, Superdisintegrants, Chitoson, Permeability, Migraine, Crosspovidone**INTRODUCTION**

Sublingual tablets are the one that dissolves when held beneath the tongue, permitting direct absorption of the active ingredient by the oral mucosa. Sublingual tablets are to be placed under the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue.

Several type of migraine is given below:

- Migraine without aura (common Migraine)
- Migraine with aura (classic Migraine)
- Complicated Migraine

A migraine headache can cause intense throbbing or pulsing in one area of the head is commonly accompanied by nausea, vomiting, and extreme sensitivity to light and sound. Migraine attacks can cause significant pain for hours to days. Migraine affects around one in ten people. They are three times more common in females and tend to affect young people who are otherwise healthy. Naratriptan is a 5-HT₁ agonist use for the treatment of migraine headaches. It is available in strengths of 1 and 2.5 mg as conventional and orally disintegrating tablets. It is a second generation triptan. Naratriptan completely absorbed following oral administration. The mean oral absolute bioavailability of the tablet is about 60%. This clearly indicates that Naratriptan have first pass metabolism problem. The

metabolic pathway of Naratriptan included primarily hepatic. In vitro, Naratriptan is metabolized by a wide range of cytochrome P₄₅₀ isoenzymes into a number of methods may not always be convenient for the patient. Therefore, there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using administration routes where a rapidly dissolved drug is immediately absorbed into the systemic circulation. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation bypassing enzyme degradation in the gut and liver. In addition, the thin sublingual mucosa (about 190 um compared to 500-800 um of the buccal mucosa) and the abundance of blood supply at the sublingual region allow excellent drug penetration (absorption) to achieve high plasma drug concentration with a rapid onset of action¹⁻¹²

**Address for correspondence*

Hiral Brahmbhatt

Sigma Institute of Pharmacy,
Bakrol, Vadodara, Gujarat, India.Email: brahmbhatthiral@rocketmail.com

Mobile no: 9016761193

MATERIAL AND METHODS

Material

Naratriptan was received as gift sample from Sun Pharmaceutical Ltd, Baroda. All other excipients were used of analytical grades.

Methods

Formulation Table

Table 1: Formulation containing super disintegrate with polymer

Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)
Naratriptan	2.5	2.5	2.5	2.5	2.5	2.5
β -cyclodextrin	10	10	10	10	10	10
Crosspovidone	3	6	9	6	6	6
Chitoson	-	-	-	0.5	2	5
Camphor	30	30	30	30	30	30
Mannitol	10	10	10	10	10	10
MCC	40	37	34	36.5	35	32
Talc	2	2	2	2	2	2
Mg stearate	2.5	2.5	2.5	2.5	2.5	2.5
Total	100	100	100	100	100	100

Evaluation Parameters¹⁵

Uniformity of Weight (Weight Variation Test)

Twenty tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits. The percent deviation was calculated using the following formula¹⁶.

Percentage Deviation=

$$\frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Hardness Test

The hardness of tablets was tested using Monsanto hardness tester. The average of the three determinations was determined and reported. The force is measured in Kg/cm^{2,17}.

Friability Test

Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. It was rotated for 100 rotations at a rate of 25 rpm. After 100 rotations the tablets were redusted and weighed collectively and % loss was calculated¹⁸.

Disintegration time

The disintegration time for sublingual tablets was determined by using USP disintegration test apparatus. The limit for disintegration was not more than 2 minutes at 37 °C. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water bath was maintained at 37 °C \pm 0.5 °C

Direct compression is a process by which tablets are compressed directly from mixtures of the drug and excipients, without any preliminary treatment. All the excipients and drug were weighed in electrolab weighing machine and mixed for 5 min and compressed directly by using B tooling machine and using 6 mm concave punch^{13, 14}.

and the times taken for all tablets to disintegrate completely were noted^{19,20}.

Wetting Time

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablets is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. A circular tissue paper of 10 cm diameter was placed in a Petridish with 10 ml of water containing Eosin water soluble dye. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as wetting time²¹.

In Vitro Drug Release

In vitro drug release of the samples was carried out using USP-type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of pH 6.8 phosphate buffer maintaining the temperature of 37 \pm 0.5 °C and rpm of 50. The apparatus was allowed to run for 20 min. Samples were withdrawn at 5 mins interval up to 20 mins. The fresh dissolution medium was replaced every time with the same quantity of the sample. Collected samples were suitably diluted with dissolution medium and analyzed by UV spectrophotometer (Shimadzu 1700) at λ_{max} 226 nm. The cumulative percentage drug release was calculated²².

Ex- vivo Permeation Study

Ex vivo permeation study was carried out for optimized batch (F6) with modified horizontal diffusion chambers in phosphate buffer (pH 6.8), maintained at 37 \pm 0.5 °C. Goat sublingual membrane obtained from sloter house was used as a permeation barrier. Samples were collected at predetermined time intervals and analyzed by using UV spectrophotometer at λ_{max} 226nm^{23, 24}.

Table 2: Complex of Drug with β -Cyclodextrin

Batch	Naratriptan: β -CD	Solubility	Taste masking*
A	1:2	1.8	1
B	1:4	2.1	2
C	1:6	1.9	0
D	1:8	1.6	1
E	1:10	1.4	1

*: 0-Good, 1-Very good, 2-Excellent

Table 3: Post-compression studies

Formulation	Hardness (Kg/cm ²) (\pm S.D)(n=3)	Disintegration Time (Sec) (\pm S.D)(n=6)	Friability (%)	Wetting Time (Sec) (\pm S.D)(n=3)
F1	2.4 \pm 0.56	95 \pm 1.10	0.38	83.00 \pm 0.68
F2	3.8 \pm 0.67	90 \pm 0.56	0.23	78.0 \pm 0.50
F3	2.8 \pm 0.52	105 \pm 0.85	0.63	89.34 \pm 0.78
F4	2.7 \pm 0.10	45 \pm 1.78	0.57	38.33 \pm 0.96
F5	2.5 \pm 0.19	50 \pm 0.65	0.62	34.46 \pm 0.86
F6	3.6 \pm 0.36	35 \pm 1.46	0.32	28.55 \pm 1.02

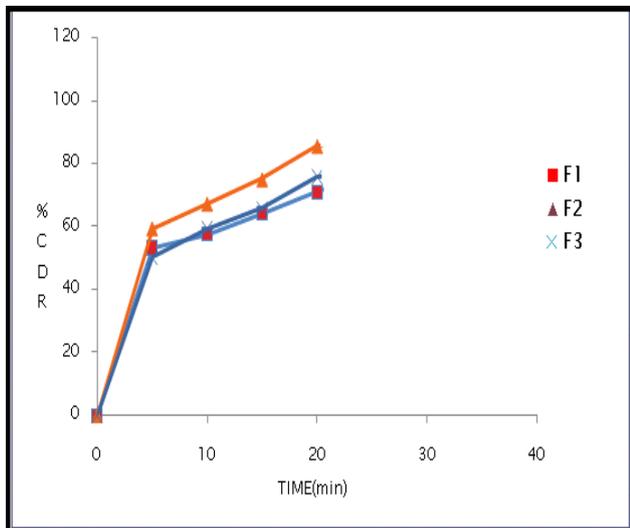


Figure 1: In-Vitro drug release study of F1-F3 Batches.

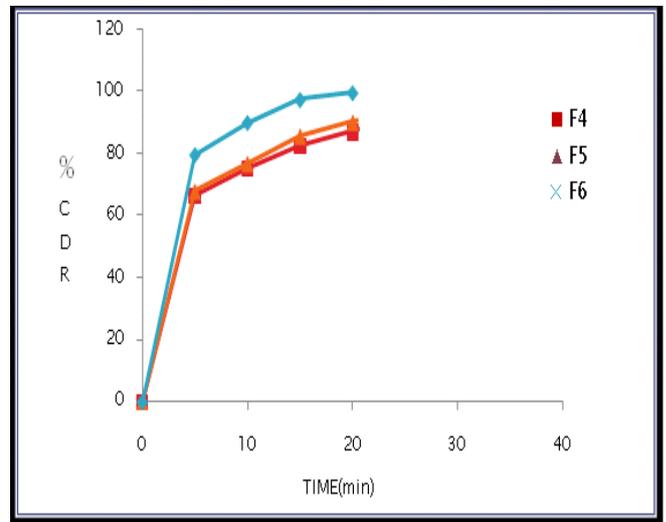


Figure 2: In-Vitro drug release study of F4- F6 Batches

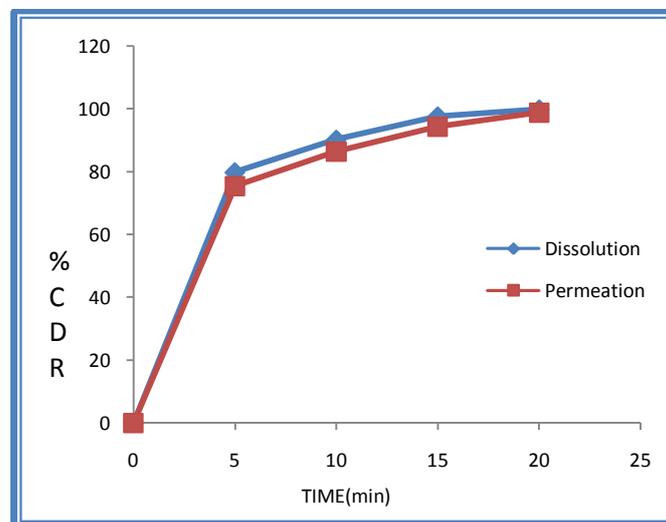


Figure 3: Comparison of dissolution time and Permeation time

Table 4: Stability Study

Formulation code	Parameter	Storage time			
		Initial	1months	2months	3months
F6	Drug content	99.87%	98.23%	96.89%	96.50%

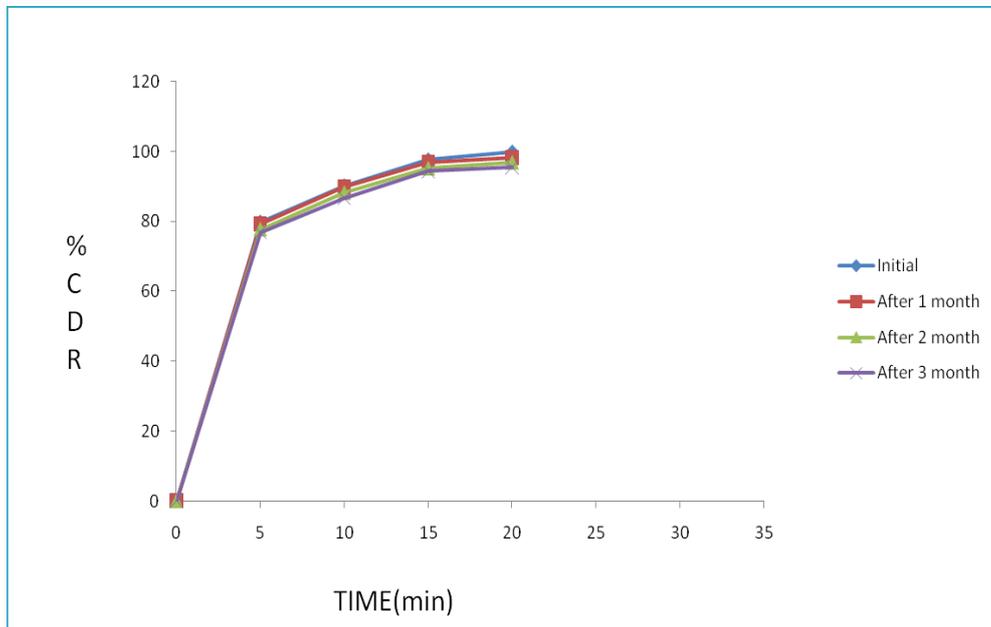


Figure 4: Comparison of dissolution of optimized batch (F6) of initial and after 3 months

RESULTS AND DISSCUSION

Naratriptan tablets were prepared by using Crosspovidone and Chitoson as a disintegrants at different concentration as shown in table no 1 respectively. Total numbers of six formulations were prepared by direct compression technique. The data obtained of post compression parameters such as hardness, friability, weight variation, disintegration time and wetting time was done as shown in table no 3 respectively. The hardness was found to be in the range of 2.4 to 3.8 Kg/cm² for all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. In all the formulations the friability values are less than 1% and meet the IP limits. All the tablets passed weight variation test as the percentage weight variation was within the pharmacopoeia limits. The weight of all tablets was found to be uniform with low standard deviation values indicating efficient mixing of drug, disintegrants and excipients. The results of in vitro wetting time and in vitro disintegration time of all the tables were found to be within the prescribe limits and satisfy the criteria of fast dissolving tables. Among all the formulations F6 formulation results were better than

the other formulations. In F6 formulation has the minimum DT was found to be 28s. So it was found that at F6 formulation have superdisintegrants showed less D.T and good hardness. And it also gives the better immediate release action

CONCLUSION

In present study sublingual tablets of Naratriptan tablet were prepared by direct compression to achieve the antimigrant effect. Different batches were prepared by using Crosspovidone as a superdisintegrants by direct compression method. The optimized batch of Crosspovidone was further mixed with polymer i.e. Chitoson. There after batches were evaluated for different evaluation parameters. From that combination Crosspovidone and Chitoson showed better results. So it is more effective in combination with Chitoson. As a result, sublingual tablet administration of Naratriptan formulated with appropriate excipients and especially with Chitoson seems promising alternative to traditional routes. The tablets containing Chitoson polymer showed the high degree of Disintegration Time. Formulations F6 containing Chitoson show better immediate release action.

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