wjpmr, 2022,8(3), 251 – 263.

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

FORMULATION AND EVALUATION OF SUBLINGUAL DRUG DELIVERY SYSTEM CONTAINING ANTI-ULCERATIVE AGENT

Preethi Fernandiz[1], Suresh N.[2]*, Kerryn Joseph A. D. Silva[3] and S. Srinivasan[4]

[1]Department of Pharmacy Practice, D.R Karigowda College of Pharmacy, Hassan, Karnataka-573201.
[2]Department of Pharmaceutics, D.R Karigowda College of Pharmacy, Hassan, Karnataka-573201.
[3]Department of Pharmaceutical Chemistry, D.R Karigowda College of Pharmacy Hassan Karnataka-573201.
[4]Department of Pharmaceutics, East Point College of Pharmacy, Bangalore, Karnataka- 560049.

***Corresponding Author: Suresh N.**
Department of Pharmaceutics, D.R Karigowda College of Pharmacy, Hassan, Karnataka-573201.
Email ID: sureshsudha1975@gmail.com

Article Received on 14/01/2022 **Article Revised on 04/02/2022** **Article Accepted on 24/02/2022**

ABSTRACT

Background: The oral route of administration is considered as the most widely accepted route. The unique environment of the oral cavity offers its potential as a site for drug delivery. **Aim & Objective:** The objective of the current study was to develop and optimize a sublingual tablet of Rabeprazole sodium which is an effective drug in the treatment of peptic ulcer such as duodenal and gastric ulcer. **Methods:** The tablets were prepared by direct compression method using different superdisintegrating agents such as crospovidone, sodium starch glycolate, kyrone T-314. The compatibility studies of drug and excipients were performed by FTIR spectroscopy. After examining the flow properties of the powder blends the results are found to be within prescribed limits and indicated good flowing property, it was subjected to tablet compression. **Results:** The tablets were evaluated for post compression parameters like weight variation, hardness, thickness, friability, drug content uniformity, wetting time, and disintegration time, in-vitro dissolution study. An optimized tablet formulation i.e. F9 was found which provided short wetting time of 28 sec, in-vitro disintegration time of 29sec which facilitates its faster disintegration and higher the drug content of 98.99%, the best in-vitro drug release was found to be in formulation F9 i.e. 94.01% during the end of 14min. From the above results, it indicate that formulation F9 containing equal ratio of different super disintegrating agents (1:1:1) emerged as the overall best formulation based on drug release characteristics with phosphate buffer p^H 6.8 as dissolution medium. Stability studies were carried out which indicate that selected formulation (F7, F8, F9) was stable. **Conclusion:** Sublingual tablets of Rabeprazole sodium were prepared using different superdisintegrants, such as kyrone T-314, sodium starch glycolate and crospovidone by direct compression method. A total of eleven formulations were prepared.

KEYWORDS: Sublingual tablets, Rabeprazole sodium, peptic ulcer, crospovidone, sodium starch glycolate, kyrone T-314, direct compression.

INTRODUCTION

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularised, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, by passing the gastrointestinal tract and first- pass metabolism in the liver. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug. The oral route of administration is considered as the most widely accepted route. The unique environment of the oral cavity offers its potential as a site for drug delivery. Because rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver. The continuous secretion of saliva results in rapid removal of released drug and this may desire that the oral cavity be restricted to the delivery of drugs, which have a short systemic circulation. Oral route is most preferred route by medical practitioners and manufacturer due to highest acceptability of patients.[1-9] About 60% of all dosage forms available are the oral solid dosage form. The lower bioavailability, long onset time and dysphasia patients turned the manufacturer to the parenterals and liquid orals. But the liquid orals (syrup, suspension, emulsion etc) have the problem of accurate dosing mainly and parenterals are painful drug delivery, so most patient incompliance. The mucosal lining of the oral cavity are

readily accessible, robust, and heal rapidly after local stress or damage. Oral mucosal drug delivery systems can be localized easily and are well accepted by patients. Therefore, it is evident that the oral cavity can serve as a site for systemic drug delivery. The total surface area of the oral cavity is about 100cm^2. The mucosal membranes of the oral cavity can be divided intofive regions: the floor of the mouth (sublingual), the buccal mucosa (cheeks), the gums (gingiva), the palatal mucosa, and the lining of the lips. These oral mucosal regions are different from each other in terms of anatomy permeability to drug, and their ability to retain a system for a desired length of time. Although the buccal mucosa is less permeable than the sublingual mucosa. Within the oral mucosal cavity, delivery of drugs is classified into three categories.

Sublingual delivery: This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.

Buccal delivery: This is the drug administration through the mucosal membranes lining the cheeks (buccal mucosa).

Local delivery: This is drug delivery into the oral cavity.

Advantages

- Easy, painless, discrete and convenient self-administration.
- Virtually all of drug absorbed across mucosa, none swallowed.
- Avoids first pass liver metabolism.
- Less variability in therapeutic effect, more predictable pharmacokinetics.
- Optimal effect achieved with less drugs, less side effect.
- Rapid onset of effect - particularly good for pain, emesis, insomnia or allergy relief.
- No need for water, easy for patients who have difficulty swallowing.
- Inexpensive to manufacture per dose, improved patient compliance.
- Flexible formulation options, No irritation or damage to tissues.
- The blood supply is rich with a capillary network close to mucosa.
- Reduce the side effect due to low dose and high efficacy.
- Provide fast dissolution or disintegrate in oral cavity without water orchewing action.
- P^H in the mouth is relatively neutral so drug will be more stable.
- Mesenteric circulation is by-passed so there is no loss of drug by first pass effect.
- Higher bioavailability and onset of action compare to oral route.
- Relatively large contact surface area provides rapid and extensiveabsorption.

Disadvantages

- Sublingual administration of drugs interfere with eating, drinking, and talking, this route is generally considered unsuitable for prolonged administration.
- Holding the dose in mouth is inconvenient, if any is swallowed that portion must be treated as an oral dose and subjected to first pass metabolism.
- Not suitable for sustain release formulations.
- It cannot be used when patient is uncooperative or unconscious.
- Saliva containing drug if swallowed, then the purpose is not achieved.
- Only small doses can be accommodated easily, large doses of drugs cannot be administered. Not suitable for drug which degrade in oral cavity.

Sublingual Route

Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological effect. Dysphasia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake/ diets have difficulties in swallowing these dosage forms.

Sublingual absorption

Sublingual meaning literally ‗under the tongue' refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract. The routes of absorption via the highly vascularised buccal mucosa allow the substance a more direct access to the blood circulation, thus providing direct systemic administration. There is considerable evidence that most sublingual substances are absorbed by simple diffusion; the sublingual area acting rather likes litmus paper, readily soaking up the substances. However, not all substances are permeable and accessible to oral mucosa. One of the best known drugs used regularly with great success is Glyceryl trinitrate a potent coronary vasodilator which is used for the rapid symptomatic relief of angina. It has been found impressively effective when administered sublingually; pharmacologically active after only 1-2 minutes. The administration via an aerosol spray was found to provide rapid relief of symptoms, with first-class metabolism. The extent of first- class metabolism when compared to the sublingual spray decreased to 48% with sublingual tablets and 28% with the oral dose. Following sublingual administration, nitrate appears in plasma concentrations can be maintained for 24 hours. Sublingual verapamil (a calcium channel antagonist prescribed for the management of angina, hypertension and certain supraventricular arrhythmias) was effective in controlling the ventricular rate in 7 symptomatic patients and rapidly appeared in the plasma following sublingual administration. Experiments with some analgesics showed a many times more rapid absorption from the mouth than the less lipid-soluble morphine.[10-15]

Impressive absorption has been attained with sublingual administration of desoxycortisone acetate, morphine, captopril, nifedepine and 17-β Oestradiol interestingly; it has also been shown that the sublingual administration of 17-β Oestradiol requires only 1/4th of the oral dose.

Mechanism of Sublingual absorption

The absorption potential of oral mucosa is influenced by the lipid solubility and therefore the permeability of the solution (osmosis); the ionization (p^H); and the molecular weight of the substances. For example, absorption of some drugs via oral mucosa is shown to increase when carrier p^H is lowering (more acidic) and decrease with a lowering of p^H (more alkaline). The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by a cell as if by hollowly wrapping itself around it. These engulfed particles are usually too large to diffuse through its wall). It is unlikely that this mechanism is used across the entire stratified epithelium. It is also unlikely that active transport processes operate within the oral mucosa. However, it is believed that acidic stimulation of the salivary glands, with the accompanying vasodilatation, facilitates absorption and uptake into the circulatory system. The mouth is lined with a mucous membrane which is covered with squamous epithelium and contains mucous glands. The sublingual mucosal tissue is similar to that of buccal mucosa. The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth. The three pairs of salivary glands are the parotid, the submandibular and the sublingual which lies on the floor of the mouth. The more acid the taste, the greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighboring muscles and to the mucous membranes of the mouth, tongue and gums. Two symmetrical branches travel behind the jawbone under the tongue to meet and join at its tip. Another branch meets and anatomises with the sub mental branches of the facial artery. The sublingual artery stems from the lingual artery-the body's main blood supply to the tongue and the floor of the mouth-which arises from the external carotid artery. The proximity with the internal carotid artery allows fast access to its route supplying the greater part of the cerebral hemisphere.

Osmosis

In order for a drug to be effectively absorbed sublingually, it needs to be able to travel across the buccal mucous membranes; by a process of diffusion known as–osmosis[ll] which applies to all forms of absorption by the body; governing both intestinal and sublingual absorption. The distribution of water across cell walls depends on the osmotic difference in the blood between the intracellular and extracellular fluid. Small particles that readily dissolve in water, rarely present a problem in permeation and diffusion, and so are able to move freely between the tissues of the body. Active transportation into cells leads to rapid metabolisation of the substances. Molecules such as glucose (fructose) and amino acids are essential for cell metabolism and special mechanisms have evolved to facilitate their rapid diffusion and Permeation across cell membranes.

Drugs for sublingual administration

Medically, sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method. Sublingually absorbed nutrition, which avoids exposure to the gastric system and liver, means direct nutritional benefits, particularly important for sufferers of gastro-intestinal difficulties such as ulcers, hyperactive gut, coeliac disease, those with compromised digestion, the elderly and invalids the nutritional benefit is independent of gastro-intestinal influences.[16-17]

METHODOLOGY

Preparation of sublingual tablets of Rabeprazole sodium by direct compression method:

Sublingual tablets of Rabeprazole sodium were prepared by direct compression method by using different superdisintegrants such as Crospovidone, Sodium starch glycolate, and Kyrone T-314. Mannitol as diluents, Fructose as sweetening agent, Magnesium stearate as lubricant and Talc used as a glident. Accurate amount of drug and all the ingredients were weighed and mixed in geometrical order after sufficient mixing of drug as well as other components then the blended materials is passed through a sieve no # 60 mesh separately. After sieving materials, before compression, hardness was adjusted and compressed into 120mg each tablets using Cadmach multi tablet compression machine equipped with 5mm flat faced bevelled edge punches on 12 station rotary tablet machine and same hardness was used for the required number tablets.

Table 1: Selected excipients for prototype formulation.

SL.NO	EXICIPIENT	FUNCTION
1	Crospovidone	Superdisintegrant
2	Sodium starch glycolate	Superdisintegrant
3	Kyrone T 314	Superdisintegrant
4	Mannitol	Diluent
5	Magnesium stearate	Lubricant
6	Talc	Glidant
7	Fructose	Sweetening agent

Table 2: Formulation Development Sublingual Tablets Of Rabeprazole Sodium.

FORMULA CODE	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Rabiprazole Sodium	20	20	20	20	20	20	20	20	20	20	20
Crospovidone	40	20	38	26	38	26	24	20	20	-	-
Sodium Starch Glycolate	-	-	26	38	-	-	20	22	20	38	26
Kyrone T-314	-	20	-	-	26	38	20	22	20	26	38
Mannitol	44	44	20	20	20	20	20	20	24	20	20
Fructose	10	10	10	10	10	10	10	10	10	10	10
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3
TALC	3	3	3	3	3	3	3	3	3	3	3
TOTAL WEIGHT	120	120	120	120	120	120	120	120	120	120	120

Note: *All quantities are in milligrams (mg).

Analytical Method used in the Determination of Rabeprazole sodium

Preparation of 0.2 M Potassium dihydrogen orthophosphate solution

27.21g of potassium dihydrogen orthophosphate was weighed and diluted with distilled water in a 1000ml volumetric flask and make up the volume 1000ml to get 0.2M potassium dihydrogen orthophosphate solution.

Preparation of 0.2 M Sodium hydroxide solution

8gm of sodium hydroxide was weighed and diluted with distilled water in a 1000ml volumetric flask and make up the volume 1000ml get 0.2M sodium hydroxide solution.

Preparation of Phosphate buffer solution p^H 6.8

Place the 50 ml of 0.2 M potassium dihydrogen orthophosphate solution in 200ml volumetric flask and then add 22.4 ml of 0.2 M sodium hydroxide solution in volumetric flask and the volume was make up the 200ml mark with distilledwater.

Determination of λ_{max}

Preformulation is to establish a simple analytical method so that all future measurements can be quantitative. Most drugs absorb light in the ultraviolet wavelength between (200-400 nm) regions, since they are generally aromatic or contain double bonds. 100 mg of Rabeprazole sodium was accurately weighed on electronic balance and dissolved in 100 ml phosphate buffer solution p^H 6.8 (=1000 µg/ml). Rabeprazole sodium is freely soluble in p^H 6.8. 1 ml of this solution was diluted with further 100 ml of phosphate buffer p^H 6.8 (=10µg/ml) in separate volumetric flask and scanned for maximum absorbance in UV double beam spectrophotometer (Shimandzu 1700) in the range from 200-400nm, using Phosphate buffer solution at p^H 6.8 as blank. The λmax of the drug was found to be 284 nm.

Standard Curve for Rabeprazole sodium in phosphate buffer (p^H 6.8)

Rabeprazole sodium (100 mg) was accurately weighed and dissolved in small amount of phosphate buffer solution at p^H 6.8 and volume was made up to 100 ml, (=1000 µg/ml) to get stock-I solution. From the stock –I, take 10 ml of the above solution is diluted to 100ml, (=100 µg/ml) in another volumetric flask which is get to Stock-II solution. From this stock-II solution serial dilutions were made by pipetting out 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml, and 2.5 ml, 3.0ml, 3.5ml, 4.0ml to obtain solutions of the drug in the concentration ranging from 5, 10, 15, 20, 25, 30, 35, 40µg/ml respectively. The absorbance of the solutions was measured at 284nm using UV-visible spectrophotometer. A graph of concentration Vs absorbance was plotted.[18-19]

Compatibility study

A successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients that are added to facilitate administration that promote the consistent release and bioavailability of the drug and protect it from degradation. Ifthe excipients are new and have not been used in formulations containing the active substance, the compatibility studies are of paramount importance. Compatibility of the drug with the excipients is determined by subjecting the physical mixture of the drug and the polymers of the main formulation to infrared absorption spectral analysis (FTIR). Anychanges in chemical composition of the drug after combining it with the polymers were investigated with I.R. spectral analysis.

Pre-Formulation Studies

Preformulation testing is the first step in the rationale development of dosage formsof a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bio-available dosage forms which can be mass produced.

Evaluation of post-compression parameters

The Rabeprazole sodium tablets prepared were evaluated for the following parameters

1. Organoleptic properties
2. Weight variation
3. Hardness
4. Thicknes
5. Friability
6. Drug content
7. Wetting time
8. *In-vitro* Disintegration time
9. *In-vitro* Dissolution Studies
10. Stability studies

RESULTS AND DISCUSSION

Melting point

It can be determined by using micro controller based melting point apparatus. Melting point of Rabeprazole sodium was found to be 202^{o}C.

Solubility studies

Rabeprazole sodium is freely soluble in water, phosphate buffer at p^{H} 6.8 and 7.4. But itwas found to be practically insoluble in n-hexane, chloroform.

Standard graph of Rabeprazole sodium

λ_{max} of Rabeprazole sodium was found to be **284nm** as it shows maximum absorbance inthis wavelength.

Table 3: Standard calibration curve for Rabeprazole sodium in phosphatebuffer p^{H} 6.8.

Concentration(µg/ml)	Absorbance*(mean±SD)
0	0.000± 0.000
5	0.125±0.004
10	0.231±0.012
15	0.349±0.016
20	0.467±0.026
25	0.584±0.005
30	0.699±0.043
35	0.807±0.015
40	0.933±0.019

***Average of three determinations

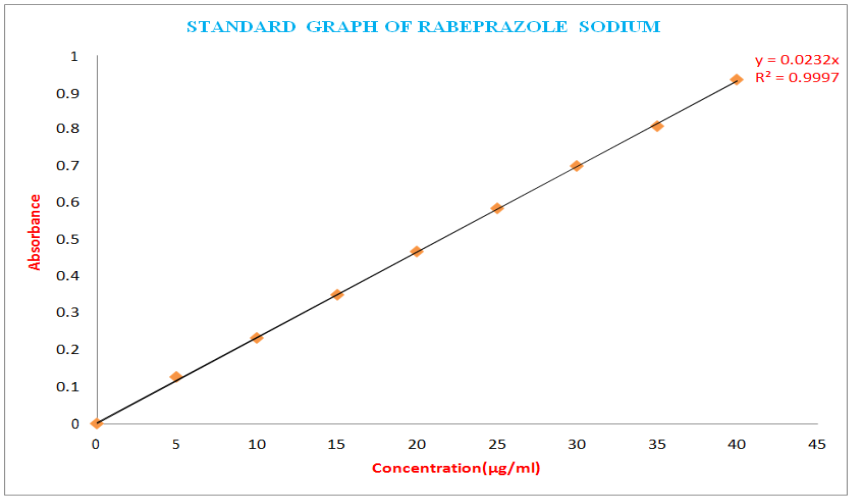

Figure 1: Standard graph of Rabeprazole sodium in phosphate buffer p^{H} 6.8.

In the present study, a total of eleven formulations of sublingual tables of Rabeprazole sodium were prepared using different super-disintegrants by direct compression method. In order to select the best formulation, various parameters were checked and subjected to *in-vitro* dissolution studies; release profile was observed and compared. Evaluation for physical parameters, drug content and release studies were performed according to official method and also with modified official methods. All the above tests are described in methodology section 4. Stability studies were performed for parameters like physical appearance were evaluated.[20-21]

Determination of λ_{max} and preparation of standard curve

The solvent medium was selected on the basis of solubility and it was found that the solubility of Rabeprazole sodium was freely soluble in phosphate buffer p^H 6.8. Standard stock solution was prepared as per the method described in methodology section 4 and scanned by UV spectrophotometer as per methodology section 4. The λ_{max} was found to be 284 nm.

The standard curve and data was obtained by the procedure described in methodology section 4. The linear plot between concentrations versus absorbance showed that Beer-Lambert's law was obeyed in concentration range of 5-40 µg/ml.

IR Spectroscopy

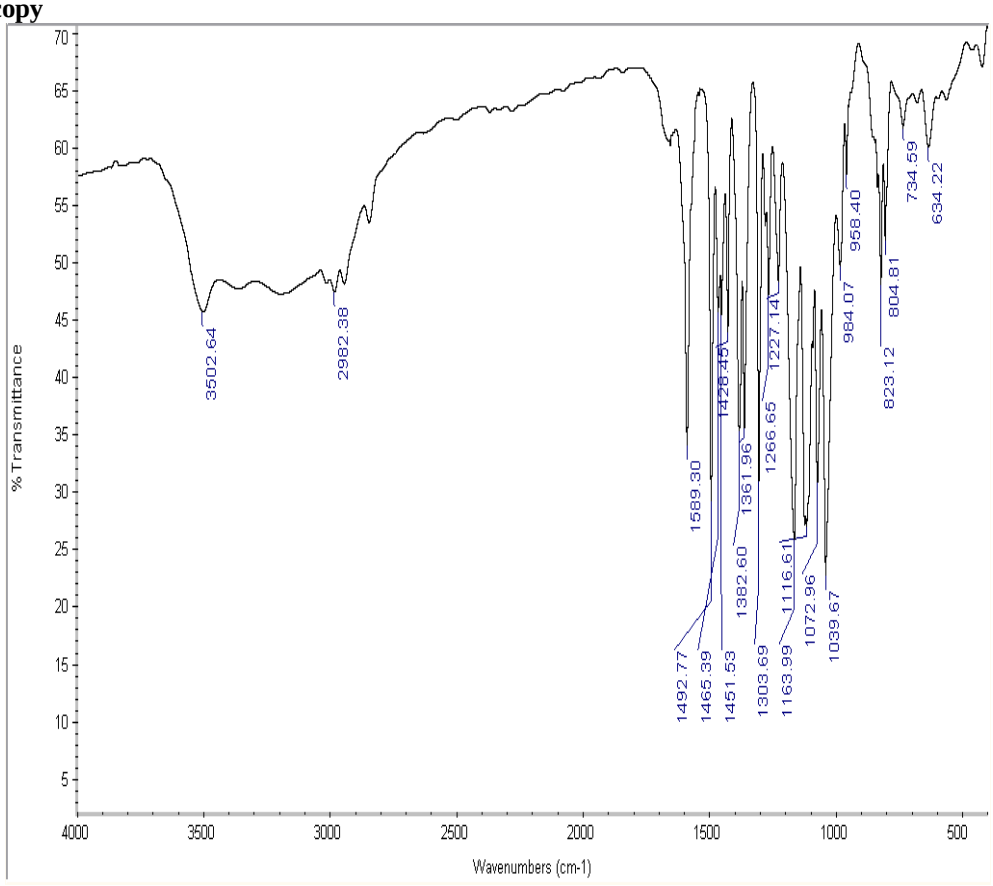

Fig. 2: FT-IR of the Rabeprazole sodium was determined by FT-IR spectra.

Table 4: FT-IR characteristic peak of Rabeprazole sodium Drug, Drug+ Excipients, and Physical mixture of Formulation F7.

SI NO	FUNCTIONAL GROUP	IR RANGE (cm^{-1})	IR OBSERVED PEAKS					
			Pure drug	Drug + Crospovidone	Drug + SSG	Drug + Kyrone T-314	Drug + Mannitol	Physical mixture Formulation
1	N-H	3400-3500	3502.64	3496.92	3561.10	3497.24	3399.93	3400.87
2	C-H	2960-2850	2982.38	2946.13	2970.13	2970.94	2970.87	2916.78
3	C=N	1630-1690	1589.30	1588.31	1589.23	1589.18	1589.33	1588.48
4	C=C	1450-1600	1492.77	1492.63	1492.76	1492.70	1492.80	1492.61
5	C-O	1310-1410	1303.69	1303.60	1303.67	1303.73	1303.31	1303.29
6	S=O	1050-1400	1116.61	1118.67	1124.02	1124.19	1115.76	1107.64
7	C-F	1000-1400	1072.96	1071.93	1073.00	1072.29	1076.82	1078.44

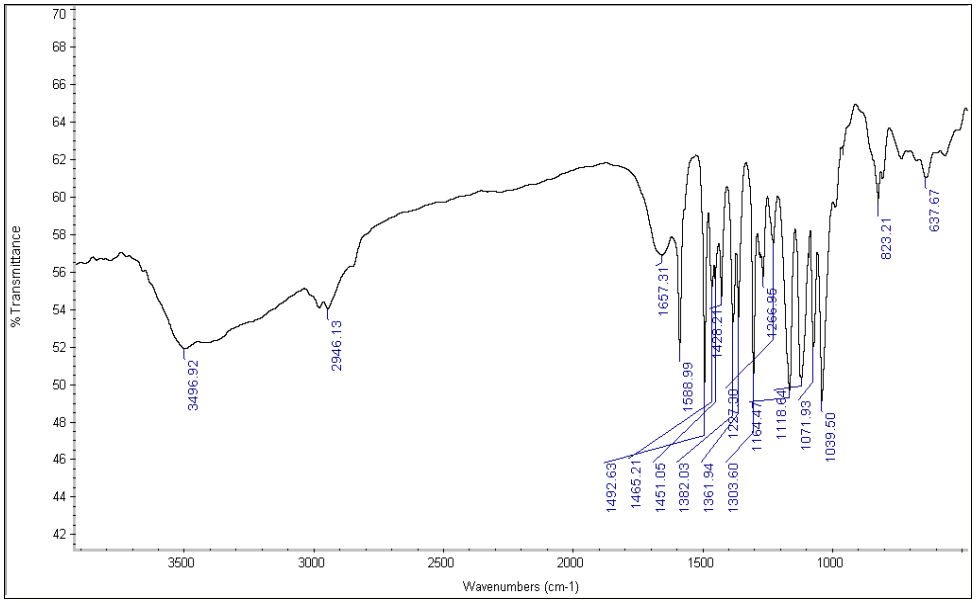

Figure 3: IR spectrum of Drug with Crospovidone.

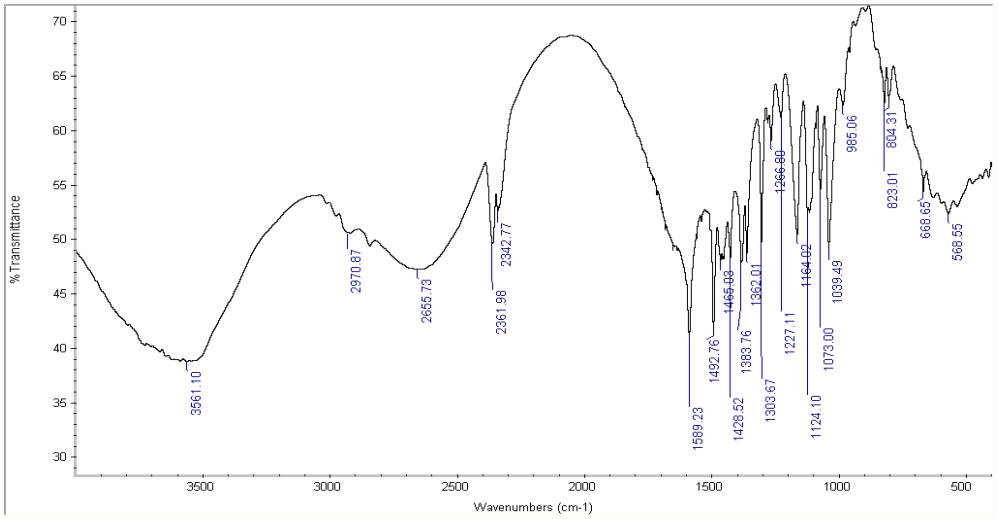

Figure 4: IR spectrum of Drug with Sodium Starch Glycolate.

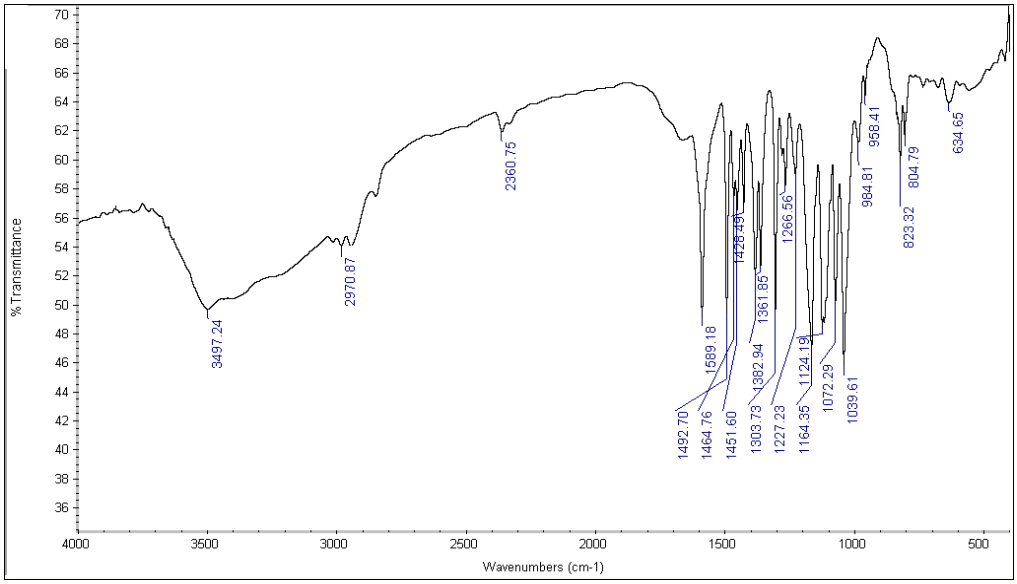

Figure 5: IR spectrum of Drug with Kyrone T-314.

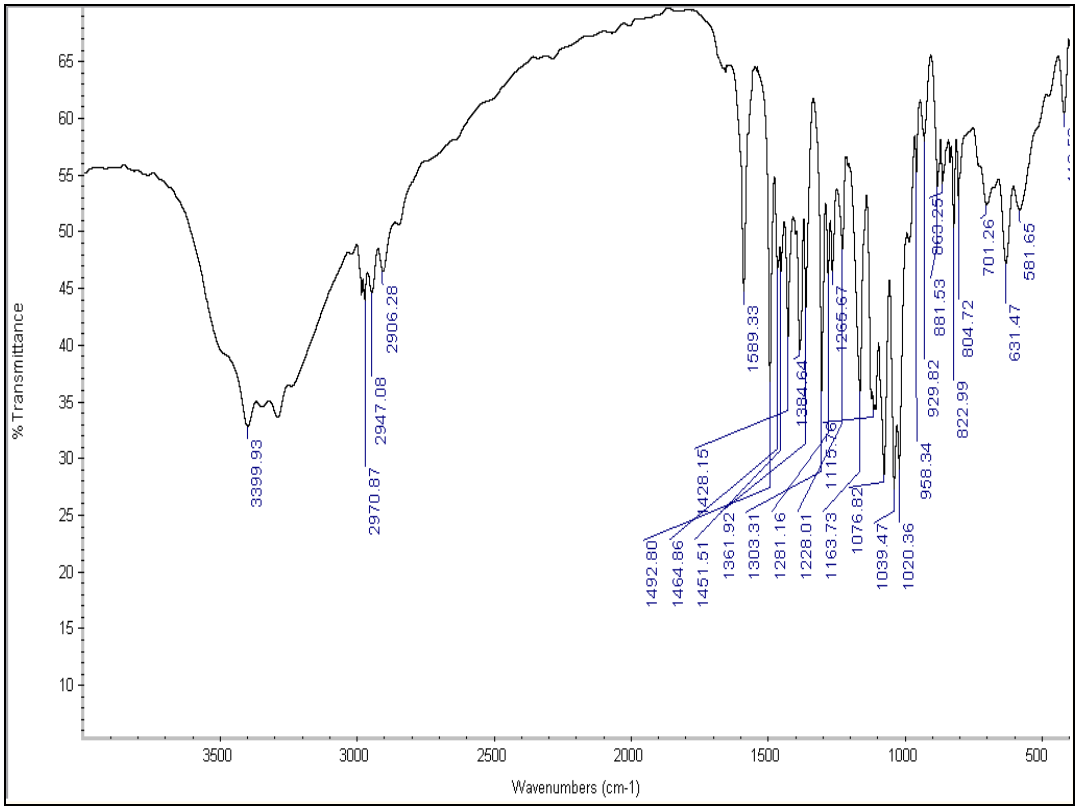

Figure 6: IR spectrum of Drug with Mannitol.

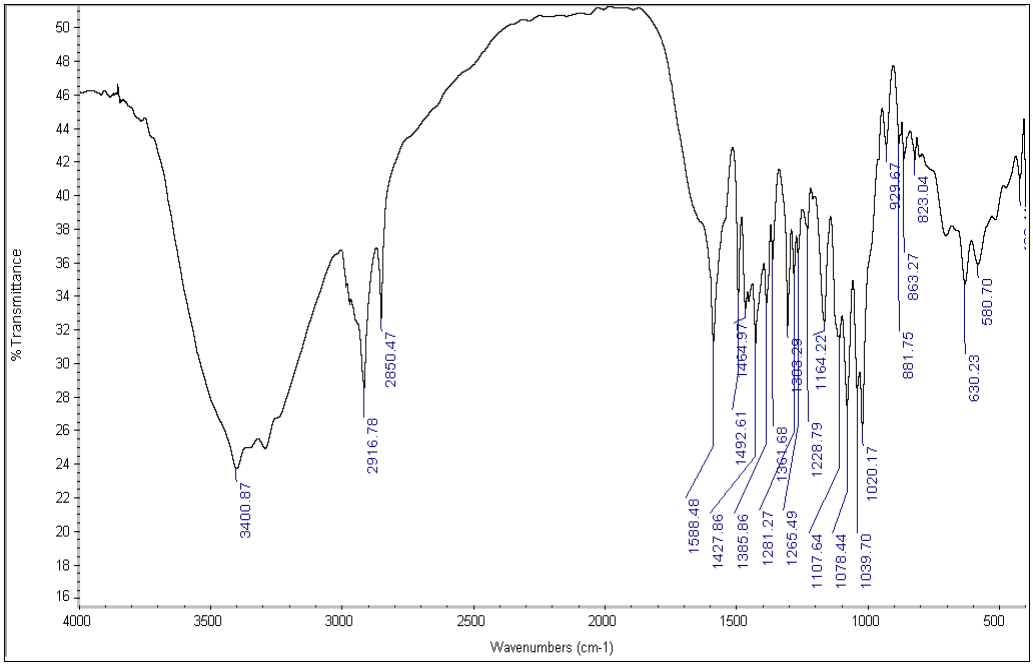

Figure 7: IR spectrum of Formulation F7

Compatibility study of drug with excipients

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, itwas concluded that there was no interference of the functional group as the principle peaks of the Rabeprazole sodium were found to be unaltered in the drug- excipients physical mixtures, indicating they were compatible chemically.

Evaluation of blended characteristics of sublingual formulation of Rabeprazole sodium

Table 5: Pre-Compression Parameter results.

Code	Bulk density g/cm^3	Tapped density g/cm^3	Carr's index%	Hausner's ratio	Angle of repose(°)
F1	0.521±0.094	0.625±0.120	16.64±0.03	1.19	28.56±0.04
F2	0.529±0.101	0.626±0.034	15.49±0.094	1.18	28.19±0.067
F3	0.528±0.074	0.62±0.069	14.83±0.065	1.17	27.89±0.051
F4	0.523±0.089	0.632±0.091	17.24±0.074	1.20	26.21±0.079
F5	0.521±0.093	0.623±0.113	16.37±0.093	1.19	27.97±0.084
F6	0.476±0.112	0.555±0.108	14.23±0.034	1.16	27.61±0.099
F7	0.5±0.107	0.588±0.07	14.9±0.107	1.17	25.52±0.021
F8	0.523±0.099	0.62±0.074	15.64±0.099	1.18	25.86±0.044
F9	0.52±0.094	0.6±0.043	13.33±0.102	1.15	23.12±0.042
F10	0.521±0.086	0.62±0.021	15.96±0.074	1.19	27.61±0.042
F11	0.479±0.086	0.567±0.09	15.52±0.065	1.18	25.86±0.042

Pre-formulation studies

For each type of formulation blends of active pharmaceutical ingredients and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.476-0.529 g/cm^3 and the tapped density between 0.555 - 0.632 g/cm^3. Using the above two density data, Carr's compressibility index were calculated. The compressibility index was found between 14.9-17.24% and the compressibility and flow ability data indicated good flow properties of all powder blends. The better flow property of all powder blends was also evident from angle of repose. The angle of repose was range of 23.12°-28.56°. Angle of repose below 30º indicates good flow property.[21-26]

Formulation of sublingual tablets of Rabeprazole sodium

Eleven formulations of sublingual tablets of Rabeprazole sodium were prepared according to the procedure described in methodology section 4. The formulation procedures have been selected from various research articles and journals. Crospovidone and sodium starch glycolate, kyrone T-314 used as superdisintegrants, mannitol used as diluents, fructose used as sweetening agent.

Tabletting

The uniform blends of tablet composition were directly compressed by keeping tablet press setting constant across all formulations. Proper lubrication of powder blends was essential for ease of ejection of compressed tablets as well for the free movement of lower punch during compression cycle to eliminate any possible influence of these factors on the study.

Post- Compression Evaluation Parameters

Various standards or quality control test carried out on compressed tablets demonstrated following

Table 6: Organoleptic properties taste, colour and odour of all formulations.

FORMULATIONCODE	TASTE	COLOUR	ODOUR
F1	Sweet	White	Odour less
F2	Sweet	White	Odour less
F3	Sweet	White	Odour less
F4	Sweet	White	Odour less
F5	Sweet	White	Odour less
F6	Sweet	White	Odour less
F7	Sweet	White	Odour less
F8	Sweet	White	Odour less
F9	Sweet	White	Odour less
F10	Sweet	White	Odour less
F11	Sweet	White	Odour less

General appearance: All the sublingual tablet formulations were evaluated for their ssgeneral appearance like taste, colour and odour.

Table 7: Post- compression parameter results.

Code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)	Disintegration Time (sec)	Wetting time(Sec)	%CDR
F1	119.91±0.22	3.02±0.10	3.12±0.01	0.39±0.15	93.51±0.57	57	42	62.678
F2	120.33±0.36	3.19±0.09	3.15±0.03	0.56±0.11	95.00±0.42	41	39	81.986
F3	120.21±0.49	3.16±0.04	3.18±0.03	0.77±0.09	96.85±0.32	37	36	86.122
F4	120.92±0.41	3.34±0.007	3.12±0.02	0.43±0.62	95.79±0.27	39	36	83.454
F5	120.16±0.32	3.15±0.05	3.32±0.01	0.42±0.44	97.01±0.89	35	32	87.917
F6	119.95±0.91	3.30±0.03	3.19±0.04	0.62±0.53	96.15±0.42	39	34	85.937
F7	120.09±0.99	3.06±0.10	3.19±0.01	0.34±0.20	97.97±0.84	31	30	92.176
F8	120.11±0.60	3.14±0.14	3.15±0.02	0.40±0.32	97.35±0.42	33	32	90.117
F9	120.01±0.59	3.05±0.05	3.15±0.01	0.27±0.06	98.99±0.42	29	28	94.001
F10	119.95±1.02	3.27±0.06	3.17±0.01	0.33±0.09	96.31±0.16	49	39	75.203
F11	120.03±0.59	3.16±0.04	3.14±0.01	0.66±0.09	95.14±0.57	43	39	79.681

Discussion about the physical parameters such as

- Thickness of tablets
- Hardness
- Friability
- Wetting Time
- Weight Variation
- Drug content
- In-vitro disintegration time
- In-vitro drug release
- Stability studies

Thickness of tablets

All the sublingual tablet formulations were evaluated for their thickness using "Vernier callipers". The average thickness for all the formulations was found to be within the allowed limit of deviation i.e. 5% of the standard value. Also the crown diameter of all the formulation was 6 mm.

Hardness

Tablet hardness is critical parameter to evaluate the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage. All the formulations have an average hardness in between 3.02 to 3.34 kg/cm^2 which was found to be acceptable; because these formulations have to be disintegrated on the under the tongue between 30 seconds to 60minute. So excess of hardness is not favored for these formulations. The hardness for F4 (3.34±0.007 Kg/cm^2) was found to be highest value compare to all formulations and for F1 (3.02±0.10 Kg/cm^2) was found to be lowest values respectively for the above parameters.[27-29] The hardness of all the formulations was almost uniform and possesses good mechanical strength with sufficient hardness**.**

Friability

Friability is determined to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. The average percentage friability for all the formulations was between 0.27% to 0.77%, which is found to be within the limit as per the standard (i.e. maximum 1%). So the maximum friability was 0.77% observed for F3 and the minimum friability 0.27% observed for F9 respectively for the above parameters.

Wetting Time

Wetting time is other important related parameters to water absorption, which needs to be assessed to give an insight into the disintegration properties of tablets. Wetting time corresponds to the time taken for the tablet to disintegrate when motionless on the tissue paper in a petridish. This method will duplicate the *in-vivo* disintegration, as the tablet iskept motionless beneath the tongue. The average wetting time for all the formulations was in the range of 28 to 42 seconds. The maximum wetting time of 42 seconds and minimum wetting time of 28 seconds were shown by F1 and F9 respectively.

Weight Variation

As material was free-flowing tablets obtained were uniform weight due to uniform die fill with acceptable variation as per IP standards. The maximum weight was 120.92±0.49mg for F4 and the minimum observed was 119.91±0.22mg for F1. The maximum allowed percentage weight variation for tablets 120 mg by I.P is 7.5%, and no formulations are exceeding this limit. Thus all the formulations werefound to be complying with the standards given in IP.

Drug Content

All the sublingual tablet formulation were evaluated for their uniformity of drug content according to the procedure described in methodology section 4 and results were shown in **table no 26**. The percentage drug content of all formulations was found in the range of 93.51±0.57%w/w to 98.99±0.42%w/w, which was all within the acceptable limits of official standards.The maximum drug content is 98.99±0.42%w/w observed for F9 and the minimum drug content is 93.51±0.57%w/w observed for F1 respectively.

In-vitro disintegration time

Disintegration, the first important step for a drug absorption from a solid dosage form after oral administration was preliminarily focused. An important factor affecting the disintegration is the hardness and has an influence on the disintegration time as it affects the

porosity of the matrix and accordingly the ability of water to penetrate through the matrix. The average *in-vitro* disintegration time for all the formulations were in the range of was 29 to 57seconds. The maximum *in-vitro* disintegration time of 57seconds and minimum *in-vitro* disintegration time of 29 seconds were shown by F1 and F9 respectively.

Table 8: *In-vitro* drug release studies of sublingual tablets of Rabeprazole sodium.

TIMEIN MINE	% CUMULATIVE DRUG RELEASE										
	FORMULATION CODE										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
2	15.28	18.98	21.53	22.38	37.84	12.84	29.26	18.83	39.00	28.10	15.78
4	19.40	28.85	29.62	47.27	45.52	30.17	42.38	39.01	57.45	37.18	21.73
6	29.32	44.50	38.88	57.00	57.66	39.94	52.45	56.82	63.03	45.28	37.81
8	39.39	57.45	52.78	61.30	66.80	52.93	66.45	65.12	70.46	53.01	50.77
10	45.04	61.29	66.82	67.97	78.48	60.77	71.66	76.51	80.37	64.43	61.00
12	56.67	72.07	74.36	78.51	82.28	74.93	80.57	82.22	86.38	70.06	69.29
14	62.67	81.98	86.12	83.12	87.91	85.93	92.17	90.11	94.00	75.20	79.69

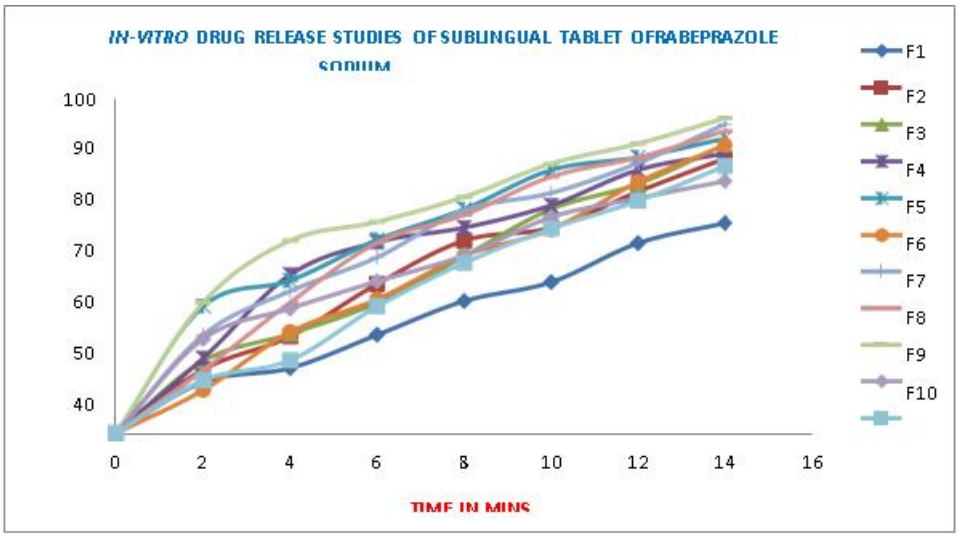

Figure no 8: *In-vitro* drug release studies of sublingual tablets of Rabeprazolesodium.

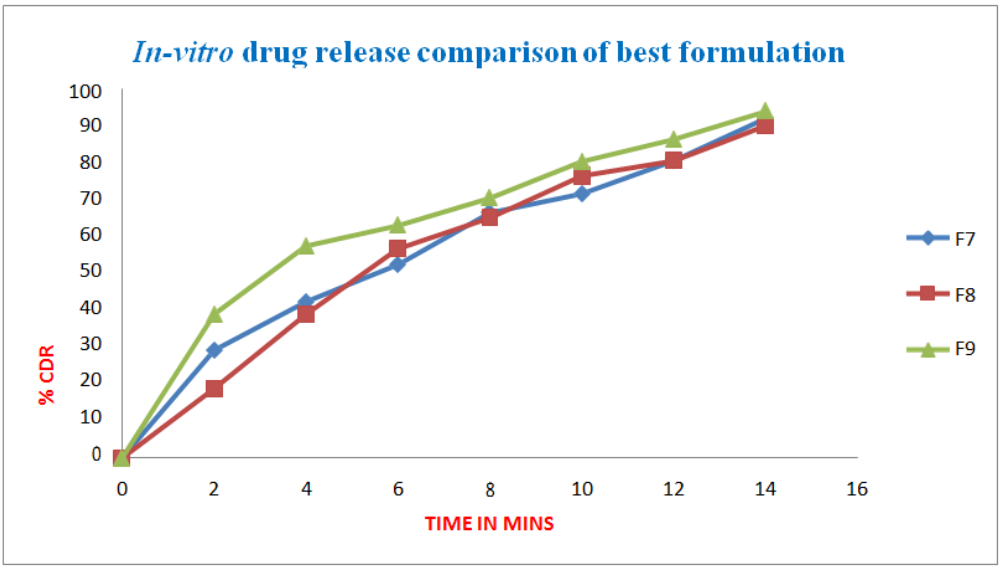

Figure no 9: *In-vitro* drug release comparison of best formulations: F7 F8 F9.

***In-vitro* drug release studies**

Dissolution studies on all the eleven formulations of sublingual tablets of Rabeprazole sodium were carried out using a USP type II (paddle type) dissolution test

apparatus in phosphate buffer p^H 6.8 was used as the dissolution medium. The amount of drug released from formulations F1,F2,F3,F4,F5,F6,F7,F8,F9,F10,F11 at end of 14mins were 62.67%, 81.98%, 86.12%, 83.45%, 87.91%, 85.93%, 92.17%, 90.11%, 94.0%, 75.20%, 79.68%, respectively. The maximum drug release of 94.03% was obtained from formulation F9, and minimum drug release of 62.80% shown by F1. Results showed that the drug release from the formulations decreased with increase in the amount of excipients added in each formulation. Formulation F9 shows fast drug release compared to all formulations. The formulation F9 containing equal ratio of superdisintegrants such as sodium starch glycolate: crospovidone: kyrone T-314(1:1:1).

Stability Studies

The formulations F7, F8, F9 were selected for stability studies on the basis of their high cumulative % drug release and also results of *in-vitro* disintegration time, wetting time. The selected formulations were subjected to accelerated stability studies at 40^0C/75% RH for all the selected formulations observed up to till date. These formulations showed not much variation in any physical parameters.[30-31]

CONCLUSION

In the present study concludes that sublingual tablets of Rabeprazole sodium were prepared by direct compression method using Cadmach multi tablet compression machine equipped with 5mm flat faced beveled edge punches on 12 station rotary tablet machine and subjected to various evaluation tests. Drug and excipients were subjected for compatibility study using FT-IR, which suggested that there was no interaction between drug and excipients. All the formulations were evaluated for pre-compression parameters and post compression parameters. Flow properties like angle of repose, bulk density, tapped density and also % Carr's compressibility was determined to all the formulations and the results showed good flow property.

The shape, color, taste, and odour, of all formulations were found to be circular shape and white in color, sweet taste, odour less. These formulations were subjected to various evaluation parameters like hardness, friability, thickness, weight variation were within acceptable limits for all these formulations.[32-35] The study results revealed that all the formulated tablets have acceptable physical properties. *In- vitro* studies revealed that, the drug released by F9 formulation [sodium starch glycolate and crospovidone, kyrone T-314(1:1:1)] is comparatively higher drug release than the other formulations. The formulation F9 shows higher drug content of 98.99%, in-vitro disintegration time of 29sec, wetting time was found to be 28sec. This indicates rapid disintegration. The drug release of 94.01% results was found to be satisfactory. The formulations were subjected to their stability studies for selected formulation F7, F8, & F9 at 40^0C/75% RH for 30 days. Not much variation or change was observed in any physical appearance throughout the study period. Best-selected formulations F7, F8 and F9 found to be stable.

REFERENCES

1. Amir H Shojaei, Sen-lin Zhou, Xiaoling Li. Transbuccal Delivery of Acyclovir (II): Feasibility, System Design and *In-vitro* Permeation Studies. *Int J Pharm PharmaSci.*, 1998; 1(2): 66-73.
2. Khairnar G A, Sayyad F J. Development of Buccal Drug Delivery System Based on Mucoadhesive Polymers. *Int J Pharm Tech Res.*, 2010; 2(1): 719-735.
3. Indrajit Parma, Sneha Garasiya, Dr. Jagdish Kakadiya. Formulation and Optimization of Rivastigmine Tartrate Sublingual Tablet. *Int J Pharm world Res.*, 2012; 3(2): 1-23.
4. Priyank Patel, Sandip Makwana, Urvish Jobanputra, Mihir Ravat1, Ankit Ajmera, Mandev Patel. Sublingual Route for the Systemic Delivery of Ondansetron. *Int J Drug Devel Res.*, 2010; 3(4): 36-44.
5. Neha Narang, Jyoti Sharma. Sublingual Mucosa as a Route for Systemic Drug Delivery. *Int J Pharm Pharm Sci.*, 2010; 3(2): 18-22.
6. Leilani Lea. Sublingual Absorption. http//www.positivehealth.com.
7. Rakesh Hooda, Mohit Tripathi, Prof KiranKapoor. A Review on Oral Mucosal Drug Delivery System. *Pharma Innova.*, 2012; 1(1): 13-19.
8. Latheeshjlal L, Sunil Murala, Vaidya Mehul J, G Swetha, Phanitejuswini. An Overviwe: Muccoadhesive Drug Delivery System. *Int J Pharm Tech Res.*, 2011; 3(1): 42-49.
9. Sanket D Gandhi, Priyanka R Pandya, Rahul Umbarkar, Tanvi Tambawala, Manoj A Shah. Muccoadhesive Durg Delivery System-an unussual maneuver for site specific drug delivery system. *Int J Pharm Sci.*, 2011; 2(3): 133-152.
10. Andrew Garner, Hassan Fadlallah. Pantoprazole: a new and more specific proton pumps inhibitor. *Exp opin Investi Drug.*, 1997; 6(7): 885-93.
11. Kenneth R Devault. Pantoprazole: a protons pump inhibitor with oral and intravenousformulations. *Exp Rev Gastroente Hepato*, 2007; 1(2): 197-205.
12. Vineet Bhardwaj, Vikesh Shukla, Narendra Goyal, MD Salim, PK Sharma. Formulation and Evaluation of Fast Disintegrating Sublingual Tablets of Amlodipine Besylate using different superdisintegrants. *Int J Pharm Pharm Sci.*, 2010; 2(3): 89-92.
13. Bhanja SB, Ellaiah P, Roy HK, Samal BK, Tiwari S, Murthy KVR. Formulation and Evaluation of Prindopril Sublingual Talets. *Int J Res Pharm Bio Sci.*, 2011; 2(3): 1193- 98.
14. Sindu Abraham, Basavaraj B V, Bharath S, Deveswaran R, Sharon Furtado, Madhavan V. Formulation and Optimization of Sublingual Tablets of Rabeprazole Sodium. *Int J Pharm Sci Res.*, 2010; 5(2): 50-54.

15. Sheeba FR. Formulation and Evaluation of Nifedipine Sublingual Tablets. *Asia J Pharm Clin Res.*, 2009; 2(3): 44-48.
16. Rajat Sharma, Mohd Yasir, Alka Gupta. Formulation and Evaluation of Fast Disintegrating Sublingual Tablets of Glipizide: an attempt to treat Diabetic Coma. *Int J Chem Tech Res.*, 2010; 2(4): 2026-2033.
17. Bhanja Satyabrata, Hardel Danendra K, Sudhakar Muvala. Formulation and Evaluation of Fast Disintegrating Rosiglitazone Sublingual Tablets. *Int J Pharm Chem Sci.*, 2012; 1(2): 587-593.
18. Sudarshan K Singh, Agham A Sameer. Development and Characterization of Sublingual Tablet of Lisinopril. *Asia Pa J Trop Bio.*, 2012; 2(3): 1711-1719.
19. Dipen A Trambadiya, Manish N Bhadani, Ketan V Shah. Formulation and Evaluation of Fast Disintegrating Metoprolol Succinate Sublingual Tablets. *Int J Pharm Sci.*, 2013; 4(2): 3975-3988.
20. Balusu Haarika, Prabhakar Reddy, Veerareddy. Formulation and Evaluation of Fast Disintegrating Rizatriptan Benzoate Sublingual Tablets. *Malaysia J Pharm Sci.*, 2012; 10(1): 45-60.
21. Noushin Bolourchian, Naghmeh Hadidi, Seyed Mohsen Foroutan, Bijan Shafaghi Development and Optimization of a Sublingual Tablet of Physostigmine Salicylate. *Acta Pharm*, 2009; 59(9): 301-12.
22. Indrajit Parmar, Sneha Garasiya, Dr. Jagdish Kakadiya. Formulation and Optimization of Rivastigmine Tartrate Sublingual Tablet. *Int J Pharm World Res.*, 2012; 3(2): 1-15.
23. Noushin Bolourtchian, Naghmeh Hadidi, Seyed Mohsen Foroutan, Bijan Shafaghi. Formulation and Optimization of Captopril Sublingual Tablets Using D-Optimal Design. *Iran J Pharm Res.*, 2008; 7(4): 259-67.
24. Katarzyna Centkowska, Malgorzata Sznitowska. Comparison of Sublingual Tablets with Nitroglycerin Complexed with β-Cyclodextrin or Titrated with Crosspovidone Technological Approach. *Act Pol Pharm Drug Res.*, 2008; 65(5): 585-589.
25. A Bharathi, V Ramakrishna, K Sowjanya, K Shobha Deepthi. Formulation Development and *In-vitro* Evaluation of Orally Disintegrating Tablets of Amlodipine Besylate. *Int J Pharm Res Chem*, 2012; 2(4): 1029-1034.
26. Nikunj J Aghera, Suresh D Shah, Kantilal R Vadalia. Formulation and Evaluation of Sublingual Tablets of Losartan Potassium. *Asian Pacifi J Trop Dis*, 2012; 3(2): 130- 135.
27. Santhosh Duddelli, Vedavathi T, Ajay Kumar B, Zuheb ur rahman, T S Ashwin kumar. Formulation and *In-vitro* Evaluation of Zolmitriptan Sublingual Tablets. *Int J Phram Bio Sci.*, 2013; 3(2): 235-246.
28. Shailesh T Prajapati, Parth B Patel, Chhagan N Patel. Formulation and Evaluation of Sublingual Tablets Containing Sumatriptan Succinate. *Int J Pharm Investg*, 2012; 2(3): 162-168.
29. Uday S Rangole, PS Kawtikwar, DM Sakarkar. Formulation and *In-vitro* Evaluation of Rapidly Disintegrating Using Hydrochlorothiazide as a Model Drug. *Res J Pharm Tech*, 2008; 1(4): 349-352.
30. Bayrak Z, Tas C, Tasdemir U, Erol H, Ozkan CK, Savaser A, Ozkan Y. Formulation of Zolmitriptan Sublingual Tablets Prepared by Direct Compression with Different Polymers: *In vitro and In vivo Evaluation. Euro J Pharm Bio Pharm*, 2011; 78(3): 499-505.
31. Susanne Bredenberg, Margareta Duberg, Bo Lennernas, Hans Lennernas, Anders Pettersson, Marie Westerdeg, Christer Nystrom. *In-vitro and In-vivo* Evaluation of a New Sublingual Tablet System for Rapid Oromucosal Absorption Using Fentanly Citrate as the Active Subtance. *Euro J Pharm Sci.*, 2003; 20(3): 327-334.
32. Mona H Aburahma, Hanan M Ei-Laithy, Yassin Ei-Said Hamza. Preparation & *In- vitro/In-vivo* Characterization of Porous Sublingual Tablets Containing Ternary Kneaded Solid System of Vinpocetin With β-Cyclodextrin and Hydroxy Acid. *Sci Pharm*, 2010; 78: 363-379.
33. Bhyan Bhupinder, Jangra Sarita. Formulation and Evaluation of Fast Dissolving Sublingual Films of Rizatriptan Benzoate. *Int J Drug Deve Res.*, 2012; 4(1): 133-143.
34. Mutasem M. Rawas-Qalaji, F. Estelle R. Simons, Keith J. Simons. Fast Disintegrating Sublingual Tablets: Effect of Epinephrine Load on Tablet Characteristics. *Aaps Pharm Sci Tech.* 2006; 7(2): 1-8.
35. Vinay Jain, Umesh Ramchandani, Shikha Agrawal. Formulation and Evaluation of Oral Disintegrating Tablets Oxcarbazepine. *Int J Pharm Life Sci.* 2012; 3(12): 2171- 2176.