Design, Development & Characterization of Mucoadhesive Oral Patch Loaded with Sunitinib

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ABSTRACT

The aim of the present work was to overcome the limitations of the drug and give it in form of buccal patch for better release and absorption. The first problem Solid dispersion technique was used to overcome the poor solubility of Sunitinib and it was published in a reputed online journal. 10 mucoadhesive patch were prepared by solvent casting with Sunitinib solid dispersion. The prepared patches were evaluated for weight variation, thickness, folding endurance, content uniformity, density of film, determination of % yield, surface pH, swelling index, measurement of bio-adhesive strength, in-vitro permeation. All parameters in range are shown in the formulation code TF3. The best fit for the first order release was exhibited by all of the formulations. The results show that mucoadhesive patches are better than sunitinib for enhanced drug release.

Introduction-

Tyrosine kinase inhibitors (TKIs) are a group of drugs that are used to treat cancer, and sunitinib is one of those drugs. It is mostly used to treat specific cancers, such as pancreatic neuroendocrine tumors (PNET), gastrointestinal stromal tumors (GIST), and kidney cancer (renal cell carcinoma). Sunitinib works by inhibiting particular enzymes called receptor tyrosine kinases (RTKs), which is how it works. These enzymes are essential for the development and proliferation of cancer cells as well as the process known as angiogenesis, which results in the construction of blood vessels that feed and oxygenate tumors. Sunitinib can help delay or stop the proliferation of cancer cells and lessen the blood supply to tumors, hence slowing the progression of malignancies by blocking these RTKs.[1]

Mucoadhesive Oral Patches: Buccal Patches are a type of drug formulation that provides a distinct route of administration for drug delivery through the buccal mucosa. To treat local and systemic problems, the product is inserted between the upper gingiva (gums) and the cheek. The membranes that line the oral cavity can easily be reached thanks to buccal patches. These patches enable medications to enter the systemic circulation without first passing through the liver. This method of drug delivery is considered to be advantageous for boosting drug bioavailability. The patch is a non-dissolving, matrix-modified release dosage form that is thin, intended for usage in patients who are asleep or less cooperative. [6]

The oral patch would be programmed to identify and bind only to cancer cells. This targeting capability could be attained in a number of ways, including the use of ligands, peptides, or antibodies that have an affinity for particular receptors or markers that are over expressed on cancer cells.

The oral patch needs to be activated in order to release the anticancer medication once it has reached the tumor site in the gastrointestinal tract. At the tumor location, elements like particular enzymes or pH conditions may play a role in activation. [6]

The oral patch would release the anticancer medication in a regulated and sustained manner after activation. To enable regulated release, the medicine may be encapsulated in nanoparticles or inserted in a polymer matrix within the patch.
Due to the precise targeting technique, the anticancer medicine would be primarily absorbed by cancer cells after being released. By limiting exposure to healthy cells, this would lessen toxicity and adverse effects.
Once inside the cancer cells, the anticancer medication would start working by obstructing cell division, DNA replication, or other cellular functions vital to the development and spread of the cancer. **[7]**
The medicine would be processed and removed from the body via typical clearance pathways once it had served its purpose.
The specificity of the oral patch for cancer cells could be improved by incorporating targeted drug delivery techniques, such as ligand-mediated targeting or stimuli-responsive drug release, and minimizing side effects. The best mucoadhesive patch formulation is created by choosing the right polymers, excipients, and drug-loading strategies. To achieve the required medication release profile and mucoadhesive characteristics, researchers should test various component ratios and combinations. It is crucial to pick the right anticancer medications to put in the mucoadhesive oral patch. Researchers must assess different anticancer medications and how well they work with the mucoadhesive formulation. To improve treatment effectiveness and lower drug resistance, it may also be investigated to combine medications with complimentary mechanisms of action. **[10]**

Materials and methods

Formulation of solid dispersions

Solid dispersions was developed by the solvent evaporation technique, in this technique drug (Sunitinib) and carrier (Urea, PVPK-30) were diffused in organic solvent (methanol) after the diffusion, the solvent was evaporated by utilizing a water bath. The solid mass achieved were ground. Sieved through # 80 and dried at 120^0C fir 1 hr. [2-3]

Table no. 1 formulae for solid dispersion

S. No.	Ingredients	F 1	F 2	F 3	F 4
1	Sunitinib (gm)	1	1	1	1
2	PVP K-30(gm)	1	-	2	-
3	Urea(gm)	-	1	-	2
4	Methanol(ml)	5	5	5	5

(C) Evaluation of solid dispersion

(i) Solubility studies

(ii) Dissolution Studies

(iii) Kinetic Models for Drug Release

(i) Solubility studies

Solubility studies of Sunitinibwere moved out to know the possible solubilizing effect of th ecarrier by adding drug (20 mg) to 10 ml of aqueous solutions contained increasing concent rationof carrier (1:0,1:1, 1:2)and glass containers weresealed maintained under stirring at constant temperature (20°C)for (2 days). And the prepared solid dispersions were also subjected to solubility study; drug concentration was determined spectrophtometrically at 4 57nm[4]

(ii) Dissolution studies-

Dissolution studies were conducted using USP paddle dissolution technique by dispersed powder technique, for this reason in 900 ml of 0.1N HCl, at a stable temperature 37±0.5°C, with a speed of paddle rotation is 50 rpm. 50mg powdered samples of each formulation (solid dispersion of Sunitinib) were added to the dissolution medium. At a time interval of 15 minutes, 5 ml of the mixture was withdrawn, filtered and inspected for Sunitinib content by UV spectrophotometer at 457 nm. Percent dissolution efficiency (%DE) was evaluated to compare the respective presentation of dissimilar carriers in solid dispersion formulations. The greatness of %DE (%DE t min) for each formulation was computed as the percent ratio of area under the dissolution curve up to the time (t) to that of the area of the rectangle narrated by 100% dissolution at the same time. [4]

(iii) Kinetic modelling of drug release-[5]

(a)Zero order kinetics models

Drug dissolution from dosage forms that do not disintegrates and deliver the drug slowly can be illustrated by the equation:

$$Q_0 - Q_t = K_0T$$

Reposition the above equation,

$$Q_t = Q_0 + K_0T$$

Where,

Q_t is the amount of drug dissolved in time t,

Q_0 is the initial amount of drug in the solution (most times, $Q_0 = 0$) and

K_0 is the zero order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies, are plotted as cumulative amount of drug released versus time. [6-8]

(b)First order kinetics model

This model is used to describe absorption and elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis.

The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303. [6-8]

(c)Higuchi model

Higuchi proposed this model in 1961 to describe the drug release from matrix system. Higuchi model is based on the hypotheses that:

(i) initial drug concentration in the matrix is much higher than drug solubility

(ii) drug diffusion takes place only in one dimension (edge effect must be negligible)

(iii) drug particles are much smaller than system thickness

(iv) matrix swelling and dissolution are negligible

(v) drug diffusivity is constant and

(vi) perfect sink conditions are always attained in the release environment.

The data obtained were plotted as cumulative percentage drug release versus square root of time. [6-8]

(d)Korsmeyer–Peppas Model (The power law)

A simple relationship which described drug release from a polymeric system equation was derived by Korsmeyer et al. in 1983.

The following assumptions were made in this model:

i. The generic equation is applicable for small values of t or short times and the portion of release curve where $Mt/M \infty < 0.6$ should only be used to determine the exponent n.

ii. Drug release occurs in a one dimensional way.

iii. The system's length to thickness ratio should be at least 10.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as log cumulative percentage drug release versus log time.

Preparation of mucoadhesive Patches[10]

The mucoadhesive patches for Sunitinib were prepared by using solvent casting method. Initially a solution of polymer was prepared by using absolute ethanol with occasional stirring for about 10 min. Then to the polymeric solution Sunitinib was added and stirred well. Later plasticizer was added under constant stirring. The solution was poured into a glass petri dish having 6 cm diameter. The dummy patch without drug was also prepared. The petri dishes were placed on leveled surface. The petri dish was subjected to solvent evaporation in a controlled manner by closing with a funnel in inverted position. The petri dish was left undisturbed until the content converts to a flexible film. The films are removed from petri dish and checked forpresence of air bubbles or any other imperfections. The formulations of different patches for Sunitinib are given in table 2

Table no. 2 Composition of different mucoadhesive patches containing Sunitinib

S. No	Ingredients	TF1	TF2	TF3	TF4	TF5	TF6	TF7	TF8	TF9	TF10
1	Sunitinib (mg)	50	50	50	50	50	50	50	50	50	50
2	HPMC E15 (mg)		30	60	90	120		30	60	90	120
3	HPC (mg)	120	90	60	30		120	90	60	30	
4	Ethanol (ml)	15	15	15	15	15	15	15	15	15	15
5	Glycerin (ml)	10	10	10	10	10					
6	Propylene glycol (ml)						10	10	10	10	10

Evaluation of mucoadhesive patches:

The prepared mucoadhesive batches were evaluated for following parameters

Weight variation test:

For evaluation of weight of patches, 5 patches of $2x2cm^2$ were taken from the formulations and weighed individually on a digital balance. The results were analyzed for mean and standard deviation. [7]

Thickness test:

The assessment of patch thickness was done at 5 different randomly selected spotson patches using screw gauge.

Folding Endurance:

Folding endurance of patches was determined by repeatedly folding the patches at same place till it brake, which is considered satisfactory to reveal good film properties. The number of times the patch could be folded at the same place without breaking gave the values of the folding endurance. [8]

Content uniformity:

Uniformity in drug content was determined by dissolving the buccal patch from each batch in distilled water under occasional shaking. 10 ml of this solution was taken and diluted with distilled water, and the resulting solution was filtered through a 0.45 mmWhatman filter paper. After proper dilution, the drug content of the solution was determined by UV spectrophotometer at 430 nm for Sunitinib in patches. [9]

Density of the film:

The density was calculated by using the values of mass, area and thickness ofthe patches by using the formulae:

$$\boldsymbol{Density} = \frac{\boldsymbol{Mass}}{\boldsymbol{Volume}} \textbf{ where}(\text{Volume } = \text{ Area X thickness})$$

Determination of % yield:

After drying, the patches were removed from the petri dish and were weighed.

The patches were calculated for % yield by using the formula

$$\%\ \textbf{Yield} = \frac{\textbf{Mass of buccal patches obtained}}{\textbf{Total Weight of drug and polymer}} \times \textbf{100}$$

Surface pH study:

The surface pH of the mucoadhesive patches was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the mucoadhesive mucosa, it was determined to keep the surface pH as close to neutral as possible. Mucoadhesive patches were left to swell by placing in required quantity of distilled water. The surface pH was measured by means of pH paper placed on the core surface of the swollen patch. [11]

Swelling study:

Mucoadhesive patches were weighed individually and the weight obtained is designated as W_1. The patches were placed separately in distilled water and examined for any physical changes. At regular time intervals of 3 mins until 15 mins, the patches were removed from the water and excess surface water was removed carefully using the filter paper. The swollen patches were then reweighed and the weight obtained was noted as W_2. The swelling index (SI) was calculated using the following formula[12]

$$Swelling\ Index = \frac{(W_2 - W_1)}{W_1} \text{ X } 100$$

Measurement of bioadhesive strength: [13-14]

A study of bond between patch and mucous membrane was done with excised goat buccal mucosa. The goat buccal tissue was collected from local slaughter house and was used within two hours after collection. The buccal mucosa was prepared by removing under lying tissue and washed thoroughly with isotonic phosphate buffer (pH 6.8). The fresh buccal mucosa was cut and tied to open mouth of a glass vial which was completely filled with phosphate buffer. The vial was securely fitted at the centre of a glass beaker. The glass beaker was filled with phosphate buffer till it touches the surface of buccal mucosa.***In-vitro*** **permeation studies**

Fig no. 1 Franz diffusion cell to measure *invitro* drugpermeation from buccal patch

Franz diffusion cell (vertical) was used for *in-vitro* drug release studies. Studies were carried out by attaching Goat buccal mucosa to one end of the opencylinder, which acts as donor compartment. The prepared buccal patch containing drug was placed inside donor compartment which was agitated continuously using magnetic stirrer. The temperature of cell was maintained at 37 ± 1^{o}C. Receptor compartment consists of 50 ml of phosphate buffer pH 6.8, a sample of 2 ml was withdrawn at regular interval from receptor compartment and replaced with 2 ml of fresh solution immediately and drug released was analyzed by using a UV spectrophotometer at 430 nm for Sunitinib in patches. [15]

Result

Evaluation of solid dispersion

(i) Solubility studies

Table no. 3 Solubility studies of solid dispersion

Concentration (in µg/ml)	Absorbance(F1)	Absorbance(F2)	Absorbance(F3)	Absorbance(F4)
5	0.0052	0.0542	0.0832	0.0091
10	0.0104	0.1084	0.1664	0.0182
15	0.0208	0.2168	0.3328	0.0364
20	0.0416	0.4336	0.6656	0.0728
25	0.0832	0.8672	1.3312	0.1456

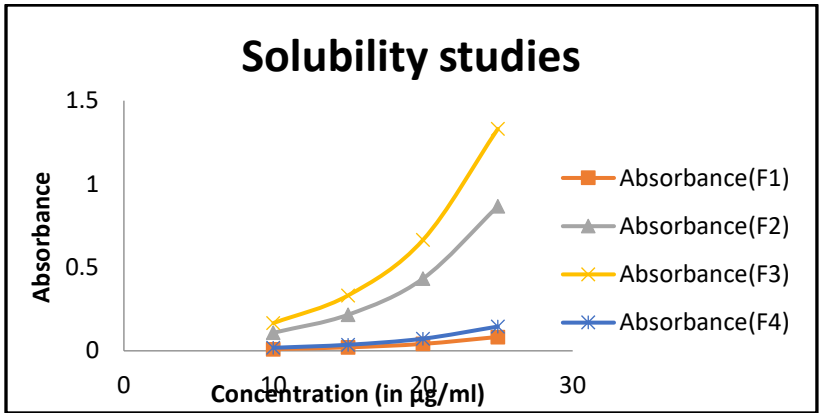

Fig. no. 2. Phase solubility study

(ii) Dissolution Studies and Kinetic Models for Drug Release

Table no. 4 Evaluation of solid dispersion

S.No.	formulation	Dissolution studies drug release (in90 min.)	First order	Zero order	Higuchi model	Korsmeyer-Peppas model
1	F1	129.69(µg/ml)	0.936±0.01	0.856±0.02	0.770±0.01	0.318±0.03
2	F2	86.3(µg/ml)	0.929±0.03	0.947±0.01	0.837±0.02	0.749±0.02
3	F3	78.6(µg/ml)	0.916±0.02	0.954±0.03	0.827±0.03	0.728±0.01
4	F4	249.38(µg/ml)	0.991±0.01	0.969±0.02	0.886±0.01	0.847±0.03

Evaluation tests for mucoadhesive patches

Physical characteristic studies:

The prepared patches were tested for weight variation, thickness, folding endurance, density, percentage yield and drug content. The values obtained were given in tables 5

The rate of drug release from the patch majorly depends on swelling behavior and bioadhesive strength of the patch depends on polymer composition in the patches. The selection of patches was based on less breakage, sufficient thickness and promising bioadhesive strength of the patches. From the data obtained, the patches with sufficient strength (thickness and folding endurance) and better bioadhesive strength i.e. formulations TF3, TF5, TF8 and TF10 from patches containing Sunitinib.

Table no. 5 Physical characteristic studies of mucoadhesive patches

S. No.	Formulations	Weight Variation* (mg)	Thickness (mm)	Folding Endurance*	Content Uniformity* (%)	Density* (mg/CC)	Yield* (%)	Bioadhesive Strength (mg)
1	TF1	165 ± 0.01	0.32 ± 0.01	472 ± 2	94.9 ± 0.12	0.46 ± 0.03	96 ± 1.2	11.77 ± 1.11
2	TF2	167 ± 0.01	0.31 ± 0.02	371 ± 4	94.2 ± 0.17	0.47 ± 0.02	89 ± 1.4	11.93 ± 1.16
3	TF3	166 ± 0.01	0.33 ± 0.01	410 ± 2	90.1 ± 0.13	0.49 ± 0.02	98 ± 1.2	12.32 ± 1.05

4	TF4	162 ± 0.02	0.34 ± 0.01	386 ± 2	93.2 ± 0.15	0.45 ± 0.01	94 ± 1.2	13.24 ± 1.03
5	TF5	164 ± 0.02	0.32 ± 0.02	392 ± 3	96.1 ± 0.18	0.42 ± 0.04	98 ± 1.4	12.46 ± 1.12
6	TF6	169 ± 0.03	0.36 ± 0.02	403 ± 4	88.9 ± 0.16	0.48 ± 0.01	92 ± 1.2	11.82 ± 1.14
7	TF7	160 ± 0.02	0.31 ± 0.03	452 ± 2	91.5 ± 0.17	0.46 ± 0.04	94 ± 1.2	12.12 ± 1.09
8	TF8	162 ± 0.01	0.32 ± 0.03	470 ± 5	91.2 ± 0.11	0.47 ± 0.02	93 ± 1.4	12.46 ± 1.06
9	TF9	167 ± 0.02	0.34 ± 0.03	447 ± 6	86.5 ± 0.16	0.42 ± 0.03	92 ± 1.2	12.36 ± 1.03
10	TF10	168 ± 0.03	0.36 ± 0.02	475 ± 2	94.5 ± 0.17	0.48 ± 0.04	93 ± 1.3	12.72 ± 1.12

Swelling Index

Even though several formulations with various combinations are prepared, only those with reproducible and satisfactory results were selected for further studies. The swelling behavior of selected patches for Sunitinib drug were given in the figure 3

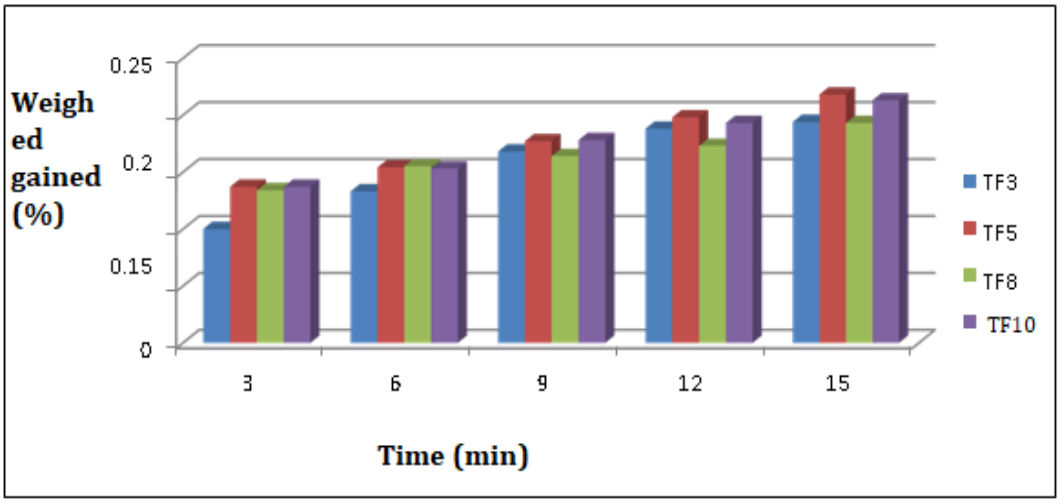

Fig. no. 3 Swelling index of Sunitinib mucoadhesive patch

In-vitro permeation studies

The drug permeation profiles from formulations of selected patches across sheep mucoadhesive mucosa over a period of 12 hrs is shown in figure 4

Table no. 6 Drug permeation profiles from formulations of selected patches

S. No	Time (hrs)	TF3 (%)	TF5 (%)	TF8 (%)	TF10 (%)
1	0	0	0	0	0
2	2	5.54 ± 0.02	6.5 ± 0.01	7.32 ± 0.02	8.81 ± 0.01
3	4	20.4 ± 0.03	24.3 ± 0.02	22.8 ± 0.02	23.9 ± 0.02
4	6	38.4 ± 0.02	40.9 ± 0.02	44.9 ± 0.02	43.2 ± 0.02
5	8	59.2 ± 0.02	68.9 ± 0.02	64.4 ± 0.04	68.6 ± 0.02

6	10	75.9 ± 0.03	87.7 ± 0.02	82.2 ± 0.02	85.8 ± 0.01
7	12	96.8 ± 0.03	100.3 ± 0.02	100.0 ± 0.01	101 ± 0.01

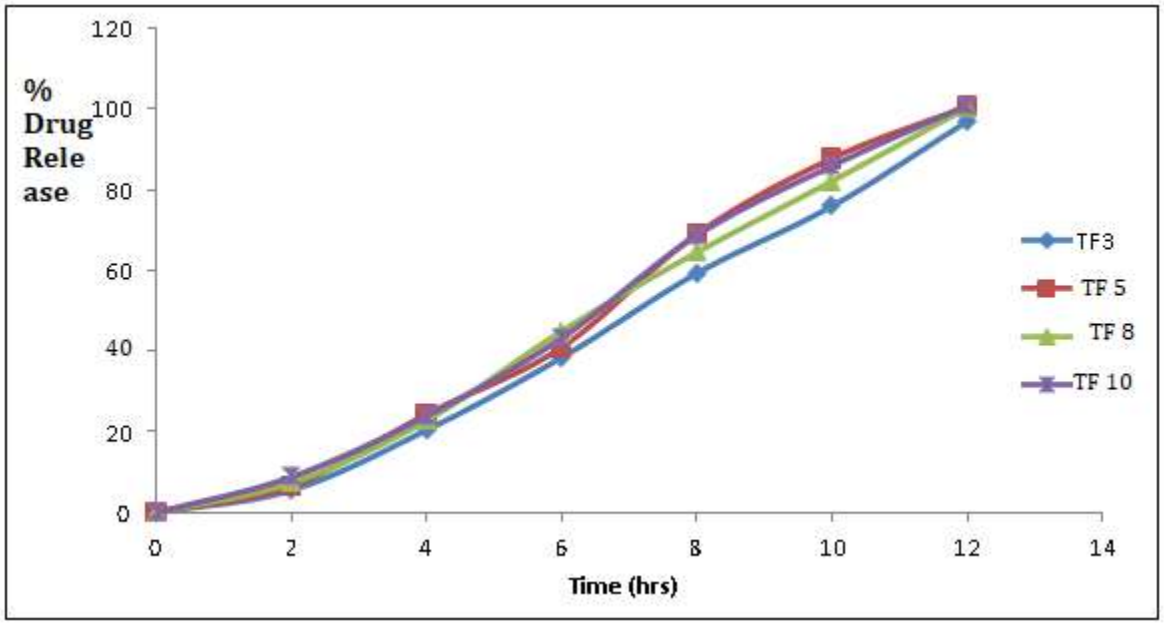

Fig. No. 4 Drug permeation profiles from formulations of patches(TF3, TF5, TF8 & TF10)

Conclusion

From the present study carried out, 10 formulations of mucoadhesive patches were prepared and all the formulation showed good evaluation characteristics with good drug dissolution. The TF3, TF5, TF8 and TF10 containing polymer in combination has highest drug release of 100 % over extended period of 12 hours and the drug release was fitted into various release kinetic models and found that the drug followed first order release. All the formulations displayed fit to First order release indicating drug dissolution was through diffusion process. Thus, one may conclude that solid dispersions included mucoadhesive patches formulation, have potential for contemplation for drug delivery as buccal dosage formulation to avoid first pass metabolism and prolonged drug release in controlled manner.

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