# Formulation, Development and *In-Vitro* Evaluation of Mucoadhesive Buccal Patches Of Methotrexate.

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**ABSTRACT:**

The goal of present investigation was to design and evaluate mucoadhesive bilayered buccal devices comprising a drug containing mucoadhesive layer and a drug free backing membrane. Bilaminatd patches composed of mixture of drug (Methotrexate) and sodium alginate alone or in combination with sodium carboxy methylcellulose ,Polyvinylpyrrolidine and carbopol 934 and backing membrane (Ethyl cellulose).The patches were fabricated by solvent casting technique and were evaluated for In-Vitro and Ex-Vivo drug release. The patches were evaluated for film weight uniformity, thickness, swelling index, surface pH, mucoadhesive strength and mucoadhesive time and folding endurance. A combination of sodium alginate with carbopol-934 and glycerol as plasticizer gives promising results. The optimized patch exhibit an in vitro release of 82% through cellophane membrane and 70.78 % through buccal mucosa with satisfactory mucoadhesive strength and mucoadhesive time.

The release kinetics of formulation also studied .The release kinetics through cellophane membrane was Higuchi while in buccal mucosa it is zero order .From Higuchi model we can say the mechanism of drug release is diffusion control .The *ex vivo* also fitted to Korsmayer-Peppas equation which characterize the release mechanism. The value of n is more than one so release was non Fickinian i.e. not depends upon concentration gradient.

**KEY WORDS:** Mucoadhesion, Bilayered film, Methotrexate, Buccal patch.

**Introduction**

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral admistration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit the oral administration of certain classes of drugs. Consequently, other absorptive mucosa is considered as potential sites for drug admistration. Transmucosal routes of drug delivery (i.e. the mucosal lining of the nasal, rectal, vaginal, ocular and oral cavity) after distinct advantages over peroral administration for systematic drug delivery. These advantages include possible by pass of first pass effect, avoidance of pre-systemic elimination within the G.I. tract, and depending on the particular drugs, a better enzymatic flora for drug absorption [1]. The potential irritation and the irreversible damage to the cillary action of the nasal dosage form as well as the large intra and inter subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site. Even though the rectal, vaginal and ocular mucosa all offer certain advantages, the poor patient acceptability associated with these sites render them reserved for local application rather than systemic drug administration. The oral cavity on the other hand is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage [2] and the virtual lack of Langerhans cells [5] makes the oral mucosa tolerant to potential allergens.

The oral mucosal drug delivery systems can be localized easily and well accepted by patients [2]. The total surface of the oral cavity is about 100 cm. [7]. The mucosal membranes of the oral cavity can be divided into five regions such as the floor of the mouth (sublingual), the buccal mucosa (cheeks), the gums (gingival), 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 and it does not yield a rapid onset of action as seen with sublingual delivery, mucosa of the buccal area has an expanse of smooth and relatively immobile surface, which is suitable for placement of retentive system. These characteristics make the buccal mucosa a more appropriate site for prolonged systemic delivery of drugs [8]. Methotrexate is one of the oldest and highly efficacious antineoplastic drugs; inhibit dihydrofolate reductase, blocking the conversion of dihydrofolic acid to tetrahydrofolic acid which is an essential coenzyme required for one carbon transfer reactions in denovo purine synthesis and amino acid interconversion. Methotrexate at high dose cause pancytopenia, Methotrexate also causes desquamation and bleeding of G.I.T. so an attempt was made to remove this problem. At last stage of cancer patient is unable to take dose by oral route so an attempt is made to develop an alternative route [9].

**Material and Methods**

Methotrexate was gift sample of Horizon Pharmaceutical, Muzaffarnagar, (UP). The entire all polymers were purchased from Loba chemicals Ltd. Mumbai. The backing membrane was prepared by dissolving ethyl cellulose (5%) in mixture of acetone and isopropyl alcohol (60:40). Glycerol (5%) was added as plasticizer. The plasticized ethyl cellulose solution was poured in to a Petridis on level surface and allowed to evaporate at controlled rate by covering the Petridis with funnel to avoid blistering effect on dried films [10]. Buccal patches were formulated with drug by solvent casting method. The composition was as shown in table 1. Drug was calculated on the basis of area. Drug was loaded after dispersion in 5ml phosphate buffer. Drugs was added in polymeric dispersion of buccal patch formulation with continuous stirring & poured the solution when drug was homogenously dispersed or dissolved in Petridish.

Total area of Petridish was =45.2 $cm^2$

Drug require in 2×2 $cm^2$ =10 mg

So total drug loaded =113 mg

**Evaluation of Buccal Patches [11]**

The patches were evaluated for uniformity of weight Thickness, Folding endurance, Surface pH, Swelling index**,** Mucoadhesive strength, Mucoadhesive Time, Drug content Uniformity, *In-vitro* drug release studies, *Ex -vivo* release, Characterization of release kinetics & Characterization of release mechanism.
For evaluation of film weight three film of 2×2$cm^2$ formulation of each was taken & weighed individually on a digital balance of 220 gm.The result were analyzed for mean and standard deviation.For evaluation of thickness, three films of 2×2$cm^2$ each formulation was taken & the film thickness was measured by digital thickness gauze. The results were analyzed for mean and standard deviation. Three films of each formulation of size 2×2$cm^2$ were cut by using sharp blade. Folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking, gave the value of folding endurance. The results were analyzed for mean and standard deviation. The surface pH of the patches was determined in order to investigate the possibility of any side effects, *in-vivo*. An acidic or alkaline pH may cause irritation to the buccal mucosa; it was our attempt to keep the surface pH as close to neutral as possible. For the determination of surface pH three patches of 2×2cm $^2$ of each formulation were kept in contact with 1ml of distilled water for 2hrs, in test tubes. Excess of water from the tubes was drained and the pH was noted by bringing the electrode near the surface of the formulation and allowing it to equilibrate for one min. The results were analyzed for mean and standard deviation.

For the determination of swelling index the preweighed three patches of 2×2$cm^2$ of each formulation were placed in a beaker (containing 20 ml of water).After particular interval patches was removed and wiped with tissue paper and weighed [12].

**Formula of Swelling Index**

$$\mathbf{S.I = W_2\text{-}W_1 / W_1 \times 100}$$

Where-
**S.I. -** swelling index

**W1**- weight of buccal patch before dipping into beaker
**W2**- weight of buccal patch after dipping in beaker & wiped

The strength of bond between the formulation and mucosa membrane excised from sheep buccal mucosa was determined using tensile experiments on a specially fabricated assembly like Satishbabu, et al. The sheep buccal mucosa was used as model membrane and isotonic phosphate buffer pH 7.4 was used as the moistening fluid. The sheep buccal mucosa was then stuck onto inner surface of the Petridis using suitable glue such that a mucosal surface faces upwards. Then the phosphate buffer pH 7.4 was added into Petridish such that the buffer was contacted with the mucosal membrane. Two sides of balance were made equal before study, by keeping a 5 gm weight on the left side [14]. A Petridis containing mucosal membrane was kept below the right-hand setup of the balance. The test dummy films were stuck on to lower flat side of hanging glass assembly. The surface of mucosa was blotted with whatman filter paper no 42. 2 ml of phosphate buffer pH 7.4 was added to the mucosal surface. 5 gm weight from the left pan was removed. This lowered the glass assembly along with film over the membrane with weight of 5 gm. This was kept undisturbed for 3 minute. Then the weights on the left hand side were slowly added till the patch just separated from the membrane surface. The excess weight on the left pan that is total weight minus 5 gm was taken as adhesive strength. The *in-vitro* mucoadhesive time was determined using Disintegration apparatus. The disintegration medium was 800 ml of phosphate buffer pH 7.4 maintained at $37\pm2^0$ C. The segment of buccal mucosa of sheep sere glued to the surface of glass slab, which was then vertically attached to the apparatus. Three mucoadhesive film of each formulation were hydrated on one surface using pH 7.4 Phosphate buffer. And the hydrated surface was brought into contact with the mucosal membrane & allowed the apparatus to move up & down. The time required for complete detachment of the film from surface was recorded. The results were analyzed for mean and standard deviation.Three films of $2\times2cm^2$ of each formulation were taken in separate 10ml volumetric flask. 10 ml of phosphate buffer saline ph 7.4 was added and continuously stirred for 24 hr. The solution were filtered, diluted suitably and analyzed at 303 nm in a U.V. spectrometer. The average of drug contents of three patches was taken as final reading. The results were analyzed for mean and standard deviation. In-vitro release study, cellophane membrane was used as a barrier membrane. Phosphate buffer pH 7.4 used as a medium. The cellophane membrane was soaked for 24 hours in Phosphate buffer. The patches were evaluated for drug release using Keshary-Chain type diffusion cells. Cellophane membrane was mounted between the donor and receptors compartments. The patch was placed on the cellophane membrane. The diffusion cell was placed in a water bath maintained at $37\pm2^0$C.The receptor compartment was filled with (50 ml capacity) phosphate buffer pH 7.4 and hydrodynamics was maintained by stirring with a magnetic bead at 100 rpm. the 5 ml sample was withdrawn and replaced with 5 ml fresh medium to maintain the sink condition. The sample was analyzed in U.V. spectrophotometer at 303 nm wavelength. [4]*Ex-vivo* release study, sheep buccal mucosa was used as a barrier membrane. Phosphate buffer pH 7.4 used as a medium. The buccal mucosa was mounted between the donor and receptors compartments. The patches were evaluated for drug release using Keshary-Chain type diffusion cells. Cellophane membrane was mounted between the donor and receptors compartments. The patch was placed on the cellophane membrane. The diffusion cell was placed in a water bath maintained at $37^0$C.The receptor compartment was filled with (50 ml capacity) phosphate buffer pH 7.4 and hydrodynamics was maintained by stirring with a magnetic bead at 100 rpm. The 5 ml sample was withdrawn and replaced with 5 ml fresh medium to maintain the sink condition. The sample was analyzed in U.V. spectrophotometer at 303 nm wavelength [13]. The *in-vitro* and *ex-vivo* release data were fitted into different kinetics like zero order, First order and Higuchi kinetics and $R^2$ values were calculated. The *ex-vivo* release data were fitted into Korsmeyer-Peppas model and an n value was calculated by plotting Log % cumulative drug release vs. Log time.

**Result and Discussion**

All the formulations (F1, F2, F3 and F4) show uniformity in weights. The average weights of different formulations were found in the range 241 to 251 mg. The formulation F3 was having minimum average weight while the formulation F4 was having maximum average weight. Results are shown as Mean ± standard deviation in table 2**.**The film thicknesses were observed uniform. The thickness was observed in the range 0.40 to 0.53 mm. Result are shown as Mean ± standard deviation. (Table 3)**.**The folding endurance was measured manually, by folding the film repeatedly at a point till they broke. The breaking time was considered as the end point. The maximum average folding was found to be highest for formulation F4 and lowest for F1. The folding endurance was found optimum and the patches exhibited good physical and mechanical properties. It was found that folding endurance of sodium alginate patches was increased by the addition of polymer in order Carbopol934 > Polyvinylpyrrolidine > Sodiumcarboxy methylcellulose > sodium alginate. Results are shown as mean ± standard deviation table4**.**Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa .The surface pH of

the buccal films was determined to optimize both drug permeation and mucoadhesion. Attempts were made to keep the surface pH as close as salivary pH. pH of all the formulations were within the range of salivary pH. No significant difference was found in surface pH of different formulations. Results are shown as mean ± standard deviation table 5**.** The comparative percentage swelling of various formulations was in order of F1>F3>F2>F4 percentage swelling of formulation F1 is highest because it contain Sodium carboxy methyl cellulose. Sodium carboxy methyl cellulose showed high % swelling because of the presence of more hydroxyl group. Formulation F4 showed less swelling index. Results are shown as mean ± standard deviation table 6**.**The mucoadhesive strength shown by all formulation was good. The formulation F3 showed maximum mucoadhesive strength while formulation F2 shows minimum mucoadhesive strength. The results are shown as mean ± standard deviation table 7**.** All formulations were show satisfactory mucoadhesive strength. Formulation F4 show maximum mucoadhesive time while formulation F2 shows minimum mucoadhesive time. The results are shown as mean ± standard deviation table 8**.**Drug content in all formulations were uniform with a range of 90.2% to 91.9%. This indicates that the drug was dispersed uniformly throughout the patches. The results are shown as mean ± standard deviation table 9**.** The release rate from different formulations through cellophane membrane shows that, release of drug from these patches exhibit two phases. There is a initial burst effect is followed by the completion of a stable gel layer which in turn, controls the release of drug from the delivery system. As it can be seen in table 10 and figure 1**.** The formulation with only sodium alginate yielded a faster initial burst effect. While the formulation with carbopol-934, PVP and sodium CMC showed sustained release. This indicates that increase in the viscosity of formulation decrease the release rate of methotrexate. The formulation F3 is the optimized formulation because it shows good swelling index convient residence time as well as promising drug release pattern, swelling index. Formulation F3 was selected for *Ex-vivo* release study. The formulation F4 was not selected because formulation did not control the release and it release the methotrexate as immediate release formulation. The cumulative drug release of the formulation containing sodium alginate with a secondary polymer was found in order of Sodium alginate > carbopol-934 > Sodium Carboxymethylcellulose > polyvinylpyrroliidine at the end of 8 hour**s.** The formulation F3 shows drug permeation through sheep buccal mucosa up to 8 hours was 70.78%. The results are shown in table 11**.**The release kinetics of methotrexate through buccal mucosa was studied. The *in- vitro* drug release data was fit into first order, zero order and Higuchi release kinetics as shown in figure 2**.** The formulation F3 shows zero order release kinetics because the $R^2$ value of zero order was closer to 1 that is 0.971 and highest from all. To examine the release mechanism of methotrexate from the buccal patches the result were analyzed according to the following equation

$M_t / M_\infty = K t^n$

Where - $M_t / M_\infty$ is the fractional drug release at time t,

K is a kinetic constant incorporating structural and geometric characteristic of the drug / polymer system [device],n is the diffusion exponent that characterizes the mechanism of drug release. In this formulation the value of n is 1.279 which is greater than 1. So in this formulation the release is non Fickinian that is not depending upon the concentration gradient. The value of n is more than 1 so this is supra case II transport.

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Table: 1 Buccal patches formulation with drug.

| Ingredients | Units | F1 | F2 | F3 | F4 |
|---|---|---|---|---|---|
| Drug | (mg) | 113 | 113 | 113 | 113 |
| Sodium alginate | (mg) | 800 | 800 | 800 | 1000 |
| Sodium c.m.c. | (mg) | 200 | | | |
| P.V.P. | (mg) | | 200 | | |
| Carbopol 934 | (mg) | | | 200 | |
| Glycerol | % | 10 | 10 | 10 | 10 |
| D.water | ml | 30 | 30 | 30 | 30 |

Sodium c.m.c.: sodium carboxy methyl cellulose, P.V.P.: polyvinylpyrollidone, D.water: distilled water,

Table 2: Patches weight of all formulations

| Formulations | Wt.of I$^{st}$ (mg) | Wt. of II$^{ND}$ (mg) | Wt. of III$^{rd}$ (mg) | Mean ±S.D. (mg) |
|---|---|---|---|---|
| F1 | 250 | 253 | 251 | 247.67±1.52 |
| F2 | 241 | 244 | 245 | 243.33±2.08 |
| F3 | 239 | 242 | 245 | 242.00±3.0 |
| F4 | 250 | 249 | 247 | 248.67±1.53 |

S.D.: standarad deviation, Wt. : weight,

Table3: Thickness of all formulations

| Formulations | I$^{st}$ (mm) | II$^{nd}$ (mm) | III$^{rd}$ (mm) | Mean ±S.D. (mm) |
|---|---|---|---|---|
| F1 | 0.49 | 0.44 | 0.51 | 0.48±0.036 |
| F2 | 0.46 | 0.49 | 0.43 | 0.46±0.03 |
| F3 | 0.42 | 0.40 | 0.46 | 0.43±0.031 |
| F4 | 0.53 | 0.47 | 0.48 | 0.49±.032 |

S.D.: standarad deviations

Table 4: Folding endurance of all formulations

| Formulations | I$^{st}$ no. | II$^{nd}$ no. | III$^{rd}$ no. | Mean ±S.D. |
|---|---|---|---|---|
| F1 | 161 | 165 | 163 | 163±2.0 |
| F2 | 172 | 170 | 174 | 172±2.0 |
| F3 | 178 | 177 | 180 | 178±1.53 |
| F4 | 185 | 189 | 182 | 185±3.51 |

S.D.:standarad deviations

Table 5: Surface ph of all formulations

| Formulations | I$^{ST}$ | II$^{ND}$ | III$^{RD}$ | Mean ±S.D |
|---|---|---|---|---|
| F1 | 6.4 | 6.8 | 6.8 | 6.7±0.23 |
| F2 | 6.2 | 6.5 | 6.7 | 6.5±0.25 |
| F3 | 6.2 | 6.1 | 6.4 | 6.2±0.15 |
| F4 | 7.0 | 6.7 | 6.9 | 6.9±0.15 |

S.D.:standarad deviations

Table 6: Swelling indexes of all formulations.

| Time (minutes) | S.I.of F1 (%) | S.I.of F2 ( %) | .I.of F3 ( %) | S.I.of F4 ( %) |
|---|---|---|---|---|
| 5 | 4.12 | 3.40 | 3.87 | 3.80 |
| 10 | 7.21 | 6.47 | 5.91 | 5.19 |
| 15 | 9.86 | 9.07 | 7.94 | 6.57 |
| 20 | 13.49 | 11.47 | 11.58 | 11.41 |
| 25 | 16.33 | 13.87 | 14.88 | 13.00 |
| 30 | 19.51 | 16.10 | 17.00 | 16.76 |
| 35 | 21.64 | 18.5 | 19.67 | 18.41 |
| 40 | 24.54 | 20.82 | 21.92 | 20.92 |
| 45 | 26.82 | 23.13 | 23.41 | 23.00 |
| 50 | 27.22 | 25.49 | 25.58 | 24.77 |
| 55 | 29.51 | 26.42 | 27.41 | 25.41 |
| 60 | 31.24 | 27.49 | 29.81 | 27.38 |
| 120 | 58.89 | 52.44 | 53.91 | 51.60 |

S.D.: standarad deviations, S.I. : swelling index

Table 7: Mucoadhesive strength of all formulation

| S.N | FORMULATIONS | $I^{ST}$ (s) | $II^{ND}$ (s) | $III^{RD}$ (s) | Mean ±S.D. (s) |
|---|---|---|---|---|---|
| | | | | | |
| 1 | F1 | 237 | 232 | 190 | 220±25.81 |
| 2 | F2 | 220 | 229 | 162 | 204±29.53 |
| 3 | F3 | 222 | 230 | 240 | 230.66±9.01 |
| 4 | F4 | 201 | 230 | 247 | 226±23.26 |

S.D.: standarad deviations.

Table 8: Mucoadhesive timeof all formulations

| S.N | FORMULATIONS | $I^{ST}$ (s) | $II^{ND}$ (s) | $III^{RD}$ (s) | Mean ±S.D. (s) |
|---|---|---|---|---|---|
| 1 | F1 | 237 | 232 | 190 | 220±25.81 |
| 2 | F2 | 220 | 229 | 162 | 204±29.53 |
| 3 | F3 | 222 | 230 | 240 | 230.66±9.01 |
| 4 | F4 | 201 | 230 | 247 | 226±23.26 |

S.D.: standarad deviations,S : second

Table 9: Drug contents of all formulations.

| Formulations | I$^{ST}$ Mg | II$^{ND}$ Mg | III$^{RD}$ | Mean ±S.D.mg | Drug content % |
|---|---|---|---|---|---|
| F1 | 9.12 | 8.91 | 9.02 | 9.02±0.11 | 90.2 |
| F2 | 9.50 | 9.07 | 9.00 | 9.19±0.27 | 91.9 |
| F3 | 9.43 | 8.84 | 9.07 | 9.11±0.30 | 91.1 |
| F4 | 9.49 | 9.01 | 9.77 | 9.11±0.38 | 91.1 |

S.D.: standarad deviations

Table 10: in vitro drug releases through cellophane membrane.

| Time (Hours) | F1 % Cumulative Drug Release | F2 % Cumulative Drug Release | F3 % Cumulative Drug Release | F4 % Cumulative Drug Release |
|---|---|---|---|---|
| 1 | 6.11 | 5.97 | 20.72 | 49.53 |
| 2 | 17.94 | 9.07 | 39.57 | 97.06 |
| 3 | 30.25 | 12.91 | 53.61 | |
| 4 | 40.35 | 24.22 | 54.64 | |
| 5 | 52.96 | 36.84 | 65.48 | |
| 6 | 58.42 | 43.61 | 69.51 | |
| 7 | 61.31 | 46.29 | 74.09 | |
| 8 | 66.74 | 53.91 | 82.97 | |

Table 11: Drug release through sheep buccal mucosa of formulation f3

| Time in (h) | SQRT | % Cumulative Drug Release. | Log % Cumulative Drug Release. | % Drug remaining | Log % drug remaining |
|---|---|---|---|---|---|
| 1 | 1 | 6.22 | 0.7938 | 93.78 | 1.9721 |
| 2 | 1.4142 | 10.41 | 1.0175 | 89.59 | 1.9523 |
| 3 | 1.7321 | 18.28 | 1.2620 | 81.72 | 1.9123 |
| 4 | 2.0 | 31.39 | 1.4968 | 68.61 | 1.8364 |
| 5 | 2.2361 | 49.42 | 1.6939 | 50.58 | 1.7040 |
| 6 | 2.4495 | 57.49 | 1.7596 | 42.51 | 1.6285 |
| 8 | 2.8284 | 70.78 | 1.8499 | 29.22 | 1.4657 |

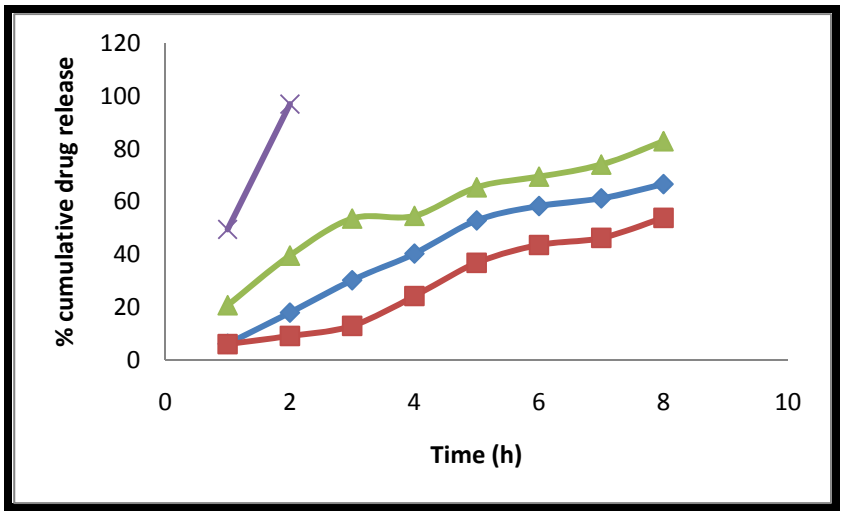


Fig.1: Diffusion profiles of methotrexate from buccal patch through cellophane membrane

**Diffusion profiles of methotrexate from various buccal patches containing various concentrations of bioadhesive polymer through cellophane membrane, (-×-) F4, (-▲-) F3, (-♦-) F1, (-■-) F2.**

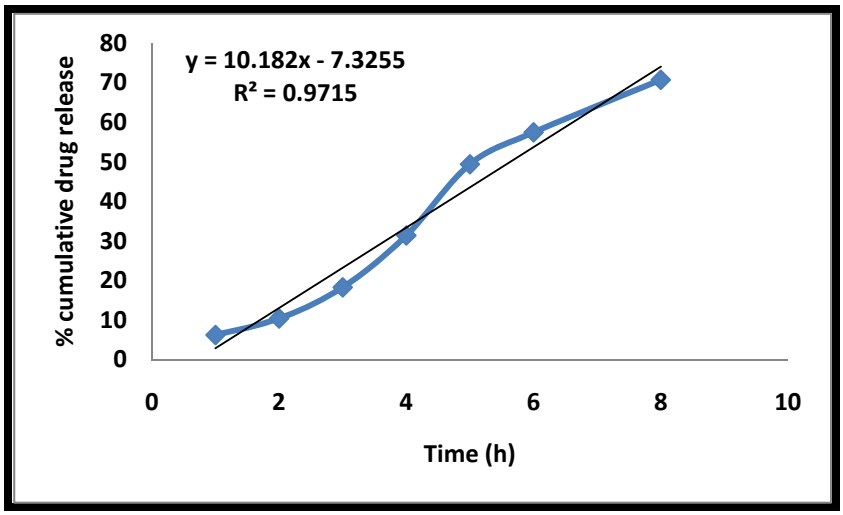


Fig. 2: Zero order release kinetics of formulation F3 through sheep buccal mucosa

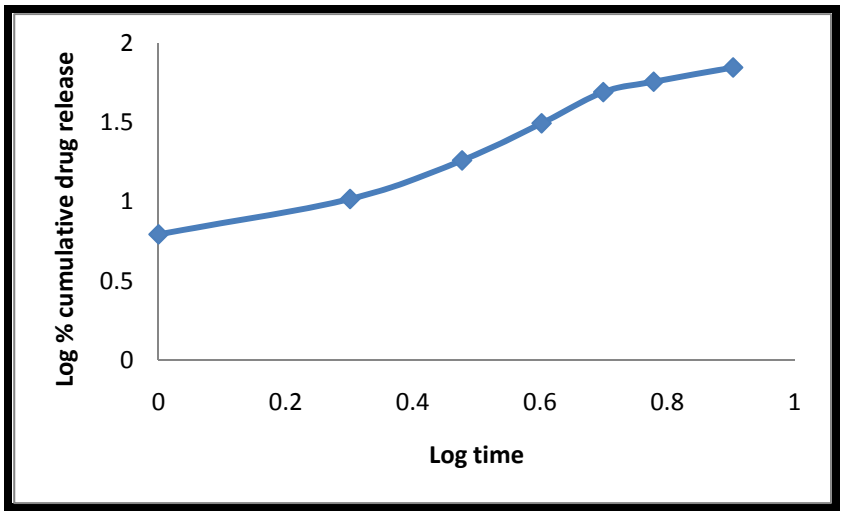


Fig.3: Release of formulation F3 through Sheep buccal mucosa data fitted to Korsmeyer-Peppas.