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# FORMULATION AND ABSORPTION ENHANCEMENT OF METFORMIN ORAL TABLETS

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## ABSTRACT

All the BCS Class-III drugs show high solubility and low permeability. Due to low permeability they have less intestinal absorption. The present study concentrates on the Metformin which is a BCS-III drug, which is having less permeability which in turn having less intestinal absorption. The permeability can be increased by using different permeation enhancers like chelates, salicylates, surfactants etc., The permeability of this drug was increased by the addition of sodium salicylate which acts as a permeation enhancer. This in turn results in better absorption enhancement. Six formulations were prepared in which calcium sulphate was used as filler and sodium salicylate as absorption enhancer where the amount of absorption enhancer increases from F1-F6 with the increment of 5mg for each formulation. All formulations are punched in the form of tablets with 350mg weight and this weight is kept common for all formulations. Out of all, F6 formulation shows highest absorption enhancement ratio. The absorption enhancement ratio was decided by the calculation of permeation coefficient by using everted sac method with simultaneous dissolution and absorption. The permeability studies were conducted *ex vivo* by using freshly scarified chicken intestine. This study revealed that 30 mg of sodium salicylate enhances intestinal absorption of 250 mg of Metformin.

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## INTRODUCTION

Oral route of drug administration is the most convenient and preferred route by patients but the main aim in the process of drug development is to obtain a drug product with a good oral bioavailability. The problem of bioavailability is dependent up on the formulation, the physiological variables and the physicochemical characteristics of the drug itself. But basically drug absorption is a complex process dependent upon drug properties such as solubility and permeability, formulation factors and physiological variables including regional permeability differences, pH, luminal and mucosal enzymology and intestinal motility [1]. The rate limiting barriers for the absorption of orally administered drugs are aqueous solubility and intestinal permeability [2]. In the present study the drug Metformin has plenty of aqueous solubility but poor intestinal permeability.

Metformin hydrochloride is a biguanide, which is used as an oral hypoglycemic agent. It is a white crystalline hygroscopic drug used as an antidiabetic agent specifically for type-2 diabetes mellitus [3]. It has been reported that the absolute bioavailability of Metformin when given orally is 50-60% [4]. It is nothing but it is having poor permeability which results in poor absorption and finally poor bioavailability. The main aim of present study is to enhance the intestinal absorption of Metformin by increasing intestinal permeability of the same by using sodium salicylate as an absorption enhancer.

For this study intestinal absorption (permeability) studies are to be performed. These studies based on isolated intestinal sacs are routinely performed. To the best of our knowledge in vitro absorption studies using chicken intestine have less frequently used [5]. So, in the present work chicken's small intestine was used for intestinal absorption studies of prepared tablets based on the assumption that membrane permeability of drugs is not species dependent since the composition of plasma membrane of intestinal epithelial cells is similar across the species [5, 6].

## MATERIALS & METHODS

### Materials:

Metformin and sodium salicylate were provided as gift samples from India Drugs, Hyderabad. All other chemicals used were of analytical grade. The instruments used are nine station punching machine (chamunda), eight stage tablet dissolution apparatus (Electrolab, Mumbai), UV Spectrophotometer (Schimadzu, Japan), Fourier Transform Infrared spectrophotometer (FTIR) (Bruker).

### Methods:

**Preparation of absorption enhanced Metformin tablets:**

Table 1 enlists the composition of absorption enhanced Metformin oral tablets prepared using sodium salicylate as an absorption (permeation) enhancer. Calcium sulphate was added as filler, starch powder as disintegrant, talc as glidant and magnesium stearate as lubricant. Granules were prepared by wet granulation where 5% starch paste used as binder. The granules are compressed in to tablets (350mg) by using nine station punching machine.

**Absorption studies:**

**Isolation of chicken intestine [7]:**

Male white Leghorn chicks weighing between 500 – 600g were bought from the local market. The Krebs-Ringer solution was prepared by adding 6.3g NaCl, 0.35g KCl, 0.14 g $CaCl_2$, 0.16 g $KH_2PO_4$, 0.15 g $MgSO_4.7H_2O$, 2.1g $NaHCO_3$ and 5g glucose to one liter of distilled water. For isolation of everted intestine, the chicks were slaughtered, a medium incision of the abdomen was performed and the small intestine was freed. The lumen was carefully cleared from mucus by rinsing with a pH 7.4 buffer solutions. An intestinal segment of the first 6-cm length was removed and transferred to oxygenated Krebs-Ringer solution.[8] The proximal extremity of the intestine was turned back and ligated on a glass rod to form an everted bag.

**Design of simultaneous Dissolution–Absorption System Using chicken Intestine Segment**

The in vitro continuous dissolution–absorption system design is illustrated in Figure. The system consisted of USP dissolution Apparatus 1 and a side-by-side perfusion apparatus holding isolated everted intestine segment (Figure 1). In this system, drug dissolution from the tablet and permeation across everted intestine occurred simultaneously. [9]

The dissolution medium used was 1000 mL of distilled water maintained at 37 ± 0.5 °C. The perfusion apparatus consisted of two glass tubes, A and B, connected together (Figure 1).Tube B had a bent cannula at its lower end, and tube A, a straight cannula at its lower end.

The distance between the two cannula was kept constant. The isolated intestinal segment was fixed between the ends of tubes A and B as shown in the Figure 1. The ends of the intestine were tied in position with a thread. The apparatus was immersed completely into the dissolution vessel. [10] From these studies permeability coefficient can be calculated there by enhancement ratio also calculated.

**Procedure for Absorption Studies in the Continuous Dissolution–Absorption System**

In the proposed design of a continuous dissolution–absorption system, sampling can be done simultaneously for measurement of the in vitro dissolution and absorption profiles of the drug. The dissolution–absorption studies were performed in two parts. In the first part of study, a marketed tablet of Metformin HCl was used. The dissolution medium consisted of 1000 mL phosphate buffer (ph7.4) maintained at 37 ±0.5 °C. A fresh intestinal segment was clamped to the perfusion apparatus. The total volume of the absorption compartment (tube A and tube B of perfusion apparatus) was 35 mL of Krebs–Ringer solution.

The drug diffused from dissolution compartment to the absorption compartment. The marketed tablet was transferred to the dissolution basket of the designed system. The tablet was rotated at 75 rpm speed. The drug was transported from dissolution compartment to absorption compartment. The transported drug from the absorption compartment was sampled with replacement (Krebs–Ringer solution) at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4 hrs and analyzed spectrophotometrically for transported Metformin HCl at 234 nm. The same procedure was preceded for the best formulation also. [11]

**Formula for calculation of permeability coefficient:**

$P\ (cm/sec) = Dq/dt \times 1/60 \times A \times C_0$

Dq/dt=Amount of drug traversing the tissue in time t

A=Exposed area of tissue

$C_0$=Initial concentration of drug in donar compartment**.**

**RESULTS & DISCUSSION:**

The permeability coefficients of all the six formulations were calculated there by absorption enhancement ratio also calculated (table 3). Among all the formulations F6 shows highest permeability coefficient ($2.451\times10^{-5}$) and highest enhancement ratio (4.991) which is nearly 5 fold increase than the first formulation. Further the F6 formulation was compared with the marketed formulation by subjecting them to continuous dissolution and absorption system which shows that, F6 formulation was more permeation through the mucous membrane of the chicken intestine than that of the marketed formulation.

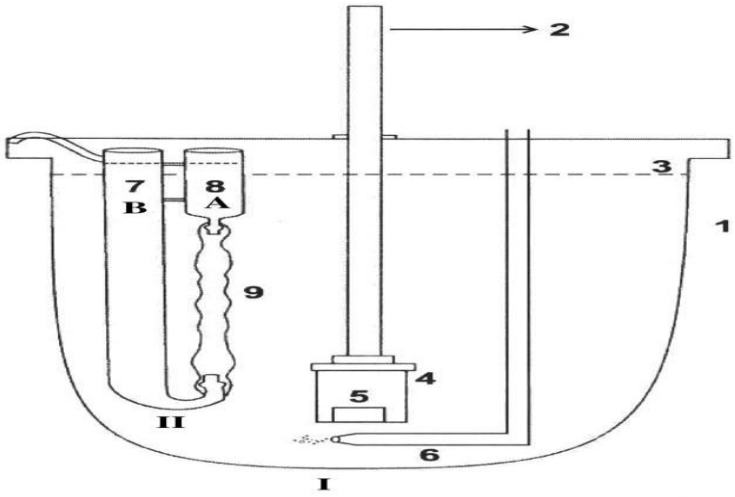
**CONCLUSION:**

The absorption of Metformin in humans is very low according to Biopharmaceutical Classification System. This is an agreement with the permeability measurement in this study, since the concentration of drug in the absorption compartment after permeation is more for the F6 formulation than that of the marketed formulation. Further the permeability coefficient was also increased as the concentration of the enhancer increased gradually form F1 to F6.

The above study suggests that the problem of less permeation and less absorption there by less bioavailabilty cannot be solved by no other methods except by the use of permeation enhancer which can lead to increased permeation through the gastrointestinal lumen and hence might increase its bioavailability.

In the nutshell, the following conclusions can be drawn from the study.

1. Merely formulating any other dosage forms without the absorption enhancer cannot increases the permeability of BCS-III drugs.
2. Comparison between marketed Metformin tablet and formulated tablets showed that permeability of F6 is better than the marketed formulation and among the formulations i.e, from F1-F6, the formulation F6 has more permeability coefficient.




1. Dissolution flask
2. Rotating shaft
3. Dissolution medium
4. Basket
5. Tablet
6. Oxygen tube
7. Tube B
8. Tube A
9. Everted intestine

I. Dissolution–absorption system
II. Absorption (perfusion) apparatus

**Fig 1:** Diagram of simultaneous dissolution and absorption

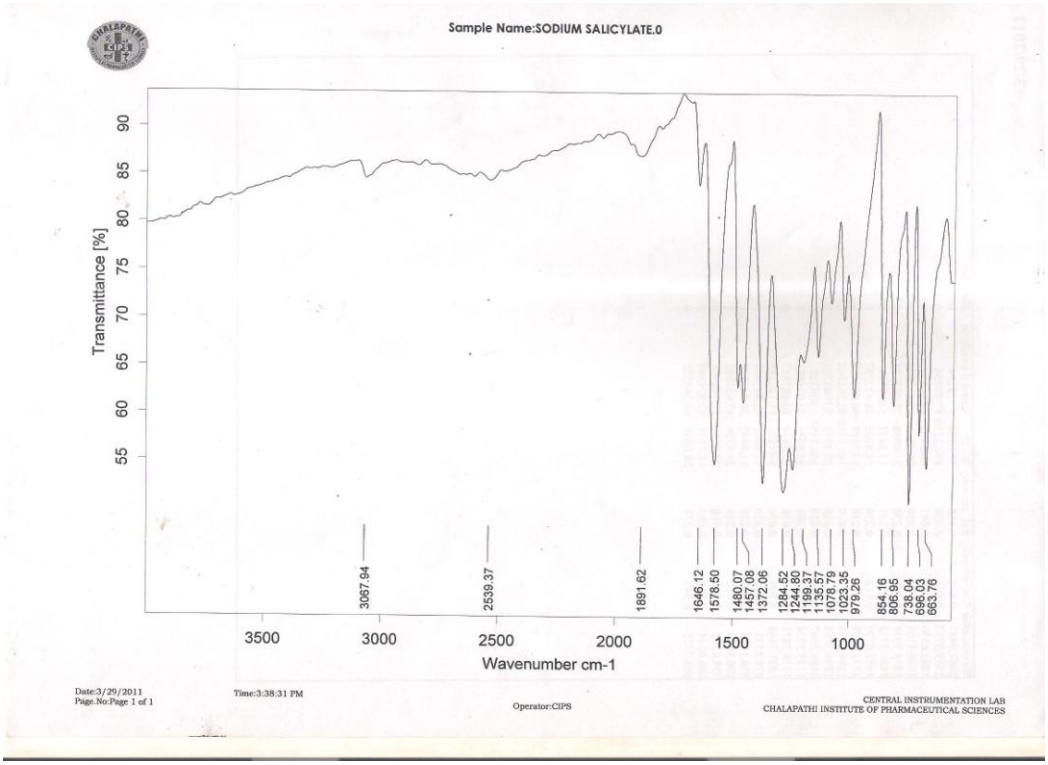



**Fig 2:** FTIR graph for sodium salicylate

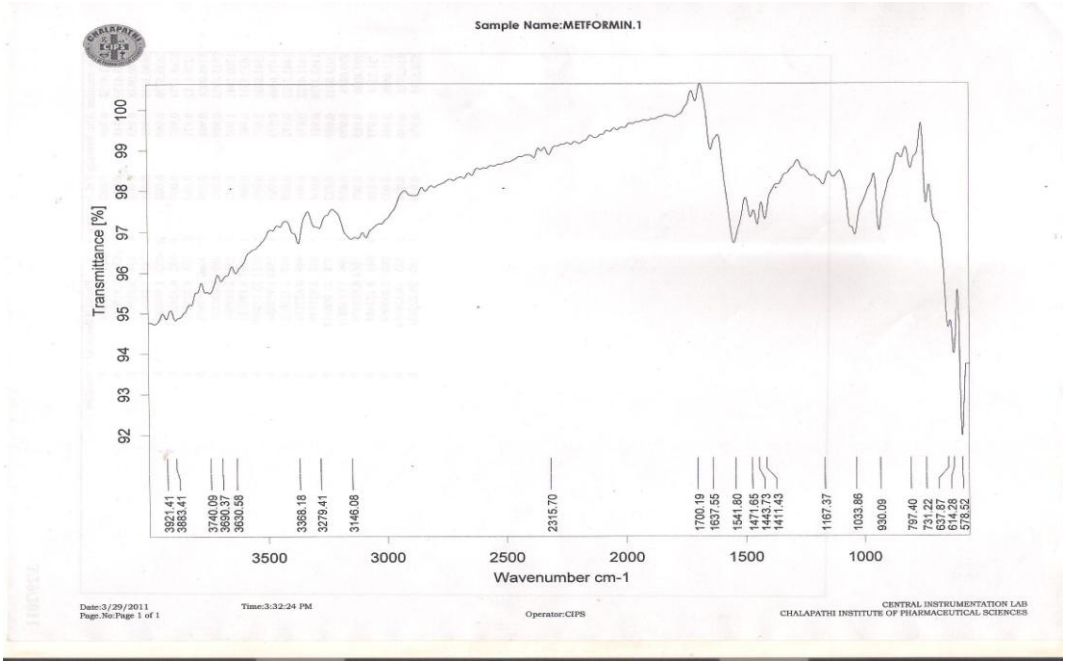



**Fig 2:** FTIR graph for Metformin

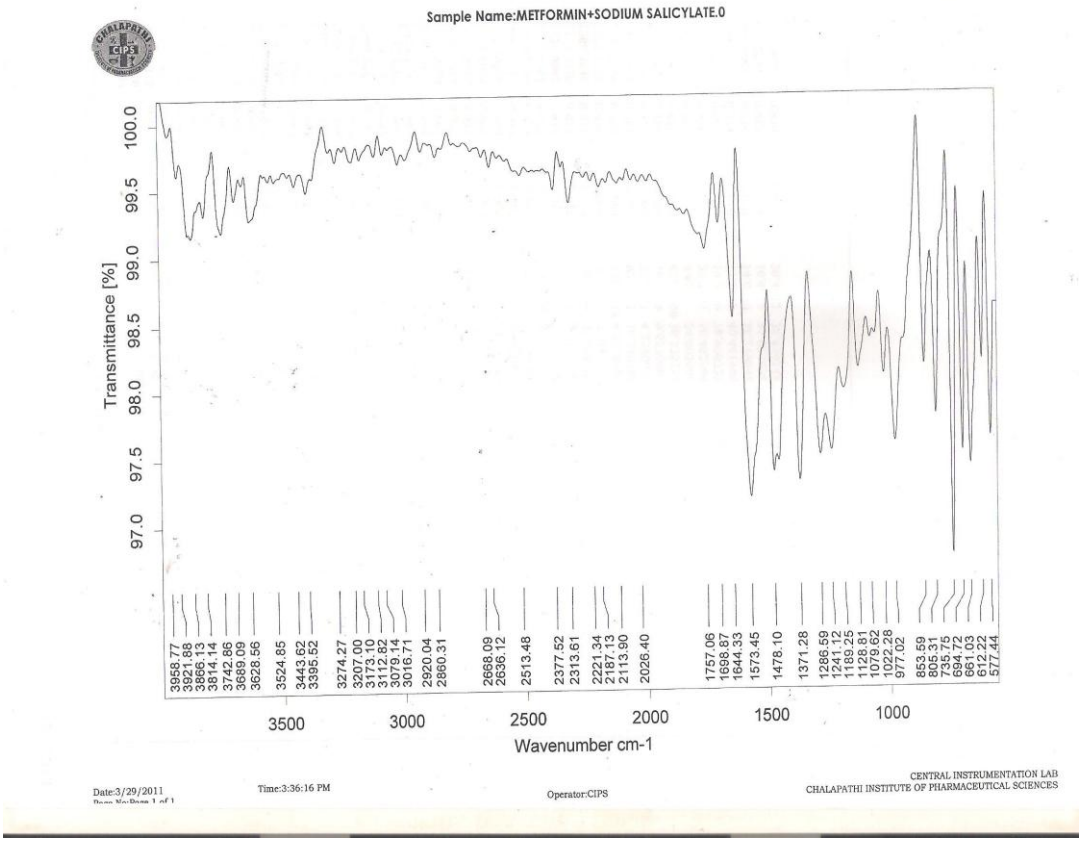



**Fig 3:** FTIR graph for Metformin + Sodium salicylate

**Table 1:** Formulation table

| QUANTITEIS ( mg) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| S.no | Ingredients | Use | F1 | F2 | F3 | F4 | F5 | F6 |
| 1. | Metformin | Active ingredient | 250 | 250 | 250 | 250 | 250 | 250 |
| 2. | Sodium salicylate | Absorption enhancer | 5 | 10 | 15 | 20 | 25 | 30 |
| 3. | calcium sulphate | Filler | 55 | 50 | 45 | 40 | 35 | 30 |
| 4. | Starch powder | Disintegrant | 20 | 20 | 20 | 20 | 20 | 20 |
| 5. | Talc | Glidant | 10 | 10 | 10 | 10 | 10 | 10 |
| 6. | Magnesium sterate | Lubricant | 10 | 10 | 10 | 10 | 10 | 10 |
| Total weight | | | 350 | 350 | 350 | 350 | 350 | 350 |

**Table 2:** Concentration of drug in Marketed formulation (glifil M,swiss garmier life sciences,himachal Pradesh)

| s.no | Time (min) | Concentration(mcg) |
|---|---|---|
| 1. | 10 | 0.02 |
| 2. | 20 | 0.04 |
| 3. | 30 | 0.06 |
| 4. | 40 | 0.08 |
| 5. | 50 | 0.010 |
| 6. | 60 | 0.012 |

**Table 2:** Concentration of drug in Absorption enhanced formulation (F6)

| S.no | Time(min) | Concentration(mcg) |
|---|---|---|
| 1. | 10 | 0.1 |
| 2. | 20 | 0.2 |
| 3. | 30 | 0.3 |
| 4. | 40 | 0.4 |
| 5. | 50 | 0.5 |
| 6. | 60 | 0.6 |

**Table 3:** Permeability coefficients and ER for all formulations:

| Formulation code | Permeability coefficient | Enhancement ratio |
|---|---|---|
| F1 | $0.596\times10^{-5}$ | 1.213 |
| F2 | $0.925\times10^{-5}$ | 1.883 |
| F3 | $1.387\times10^{-5}$ | 2.824 |
| F4 | $1.724\times10^{-5}$ | 3.511 |
| F5 | $2.004\times10^{-5}$ | 4.081 |
| F6 | $2.451\times10^{-5}$ | 4.991 |

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