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Research Article

DEVELOPMENT AND EVALUATION OF SOLID DISPERSIONS OF TOLBUTAMIDE

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ABSTRACT

Tolbutamide is a drug for the treatment of mild or moderately severe diabetes mellitus. The major problem with this drug is its very low solubility in biological fluids which results in poor bioavailability after oral administration. Therefore Solid dispersions of tolbutamide with urea, sorbitol and mannitol were prepared by fusion method with a view to increase its water solubility. The effect of fusion on tolbutamide stability was studied by TLC. The preparative conditions did not decompose the drug.Urea dispersions showed better wettability index, solubility and release than sorbitol and mannitol dispersions. The wettability index of TU_{28} was compared with other urea solid dispersions. TU_{28} showed the lowest wettability index indicating maximum wettability. The equilibrium solubility study showed that the solubility of tolbutamide was enhanced 3.90 times in the prepared urea solid dispersion. Slight decrease in the dissolution rate was observed due to effect of ageing and dissolution rate of tolbutamide increased gradually as the cooling temperature was increased from 0-20^{0}C. An increase in diffusion rate of tolbutamide from all the urea solid dispersions was observed in diffusion study. The results of accelerated temperature stability study revealed that the shelf life of TU_{28} was 1308 days. However compared to plain tolbutamide the shelf life was reduced in the product to some extent. The photomicrographs showed a significant reduction in the particle size of tolbutamide particles released from the product. The urea solid dispersions exhibiting maximum enhancement in the dissolution rate were formulated into tablet dosage form which had 5kg/cm^3 hardness and 30s disintegration time. The dissolution profile of best laboratory developed formulation TU_{28} was compared with marketed product and plain tolbutamide product. The drug release profile was studied in 0.1NHCL, TU_{28} gave far better dissolution than the conventional marketed tablet and plain formulated tablet which releases 16.3% and 54.6% in 20 min, respectively. While TU_{28} exhibited 99.0% drug release in 20 min. Preliminary studies like ours are important in helping develop better forecasting and increasing the understanding of the release behavior of drugs from solid dispersions.

Keywords: Tolbutamide, Urea, Sorbitol, Mannitol, Solid dispersion and TU_{28}.

INTRODUCTION

Tolbutamide is a hypoglycemic drug and its principal action is on B-cells, stimulating insulin secretion and thus reducing plasma glucose. High affinity receptors of tolbutamide are present on the K_{ATP} channel in B-cells plasma membranes, and the binding of tolbutamide parallels their potency in stimulating insulin release. The drugs reduce the K^+ permeability of B-cells by blocking K_{ATP} channels causing depolarization, Ca^{2+} entry and insulin secretion. It is water soluble drug with 6-12 hr duration of action. Pharmacokinetic aspect of the drug is that some amount is converted in liver to weakly active hydroxy tolbutamide and some carboxylated to inactive compound and generally excreted through kidney.

The rate and extent of dissolution of drug from any solid dosage form, determines the rate and extent of absorption of drug. In the case of poorly water soluble or insoluble drugs, dissolution is the rate limiting step in the process of absorption especially with these, which have an aqueous solubility of less than 0.1 mg/ml. Such relatively insoluble drugs exhibit incomplete or erratic absorption from G.I.T. Solid dispersion involves the preparation of microcrystalline or molecular dispersion of a poorly water soluble drug in solid matrix of water soluble carrier. After dissolution of solid dispersion very fine particles of drug are released, the decrease in particle size results in successful improvement of solubility, dissolution rates and consequently, the bioavailability of poorly water soluble or insoluble drugs. To date, some reports on the formulation of these drugs have appeared. Hence, an attempt was made to improve the dissolution of tolbutamide through the formulation of tablet containing solid dispersion of tolbutamide-urea using disintegrating agent.

MATERIALS

Pestle mortar, heating mantle, china dish, desiccator, spatula. Gift sample of Tolbutamide was obtained from All the other chemicals used were analytical reagent .

METHODS

Preparation of solid dispersion by fusion method

Accurately weighed amounts of tolbutamide and carrier as fine powders (#100) were physically mixed in different proportions are a glass mortar and transferred to a china dish. The physical mixture was then heated with constant stirring until completely melted. The homogenous melt was poured onto a stainless steel placed over ice to hasten the solidification. The solidified mass was scrapped out with a spatula and stored in desiccators over anhydrous calcium chloride for a week. The dried solid dispersions thus obtained were pulverized in a glass mortar, shifted through 100 # Sieve and finally stored in air tight containers[8,9].

*Effect of fusion on tolbutamide stability

The stability of tolbutamide during the preparation by fusion method was observed by the TLC method on Silica gel employing butanol: acetic acid: water (10:2:1) ratio solvent system, Copper Sulphate (10%) and ammonia (2%) was used as detecting agent. Green spot was produced and R_f value was calculated. The results are shown in Table 1.

Table 1: Effect of fusion on tolbutamide Stability.

S.No.	Drug + polymer	R_f
1.	Pure tolbutamide	0.67
2.	Tolbutamide Urea	0.64
3.	Tolbutamide – Sorbitol + Mannitol	0.65

Determination of drug content of products

An accurately weighed quantity of solid dispersion equivalent to 20 mg of tolbutamide, was taken into a 100 ml volumetric flask and dissolved in 20 ml of methanol. One ml of the filtrate of this solution was diluted to 10 ml with 0.1 N HCl and assayed for drug content using a double beam UV/Vis Spectrophotometer at 228 nm.

The quantity of solid dispersions equivalent to 20 mg of tolbutamide was filled in colorless hard gelatin capsule. Dissolution study of capsule was conducted using USP dissolution apparatus I, in 900 ml. of 0.1N HCL, maintained at 37±0.5^{0}C at a speed of 50 rpm. Five milliliters of samples were withdrawn at time intervals of 10,20,30,45 and 60 min. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 5ml aliquot withdrawn with 5ml of 0.1N HCL. The concentration of tolbutamide in each sample was determined by using standard curve equation[10]. The results of

drug content and cumulative percentage release are shown in Table 2 and graphically in Fig.1.

Table 2: Drug content of solid dispersion.

S.No.	Carrier	Drug:Carrier Ratio	Name of Product	Drug Content
1.	Urea	20:80	TU_{28}	100.0
2.	Urea	30:70	TU_{37}	100.4
3.	Urea	40:60	TU_{48}	100.1
4.	Mannitol+Sorbitol (50:50)	20:80	TMS_{28}	100.3
5.	Mannitol+Sorbitol (50:50)	30:70	TMS_{37}	99.7
6.	Mannitol+Sorbitol (50:50)	40:60	TMS_{48}	98.0

TMS = Tolbutamide : Mannitol+Sorbitol, TU = Tolbutamide : Urea

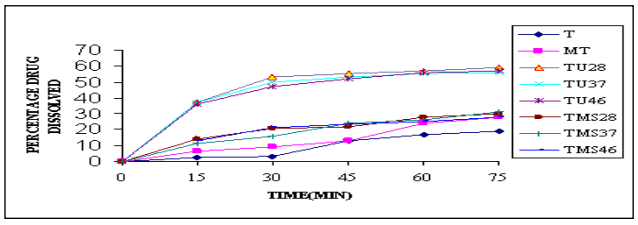

Fig. 1: Cumulative percentage release from various solid dispersions.

Wettability index

The tip of a 2 ml pipette was plugged with glass wool from inside and the powdered product (#100) was filled in the pipette up to a height of 1 ml above the glass wool. Then, 0.2 ml of distilled water was placed on the top of the powder bed and the time required by water to soak through a distance of 0.4ml of the product bed was noted and reported as wettability index. The results are shown in Table 3.

Table 3: Wettability Index of tolbutamide urea solid dispersion.

S.No.	Product	Wettability Index
1.	TU_{28}	1.0±0.14
2.	TU_{37}	2.5±0.35
3.	TU_{48}	4.2±0.04
4.	TMS_{28}	9.0±1.04
5.	TMS_{37}	11.0±0.45
6.	TMS_{48}	16.2±0.06

Solubility studies

Generally solubility is determined as equilibrium solubility or pH solubility profile. In the present studies, the equilibrium solubility of tolbutamide was determined by taking the product in excess of the saturation solubility of tolbutamide in distilled water in stoppered vials. The vials were subjected to constant agitation for 24hrs on a bottle shaking machine. The liquids were filtered through a sintered glass crucible (G_4) and estimated spectrophotometrically at 228nm on Shimadzu double beam spectrophotometer. The results are shown in Table 4[11,12].

Table 4: Equilibrium solubility of tolbutamide from solid dispersion.

S.No.	Product	Solubility (µl/ml)
1.	Tolbutamide	0.277
2.	TU_{28}	0.886
3.	TMS_{28}	0.691

Effect of cooling on dissolution rate of the various solid dispersions

In the preparation of solid dispersions by fusion method different cooling rate may affect particle size distribution of drug. The different solid dispersion of tolbutamide were prepared by fusion method and cooled at 0^0C, 5^0C, 10^0C, 15^0C and 20^0C, respectively. The hardened products were further dried by storing in the dessicator over anhydrous calcium chloride for a week. The dissolution rates of the dried products were studied[13,14]. The results are reported graphically in Fig. 2.

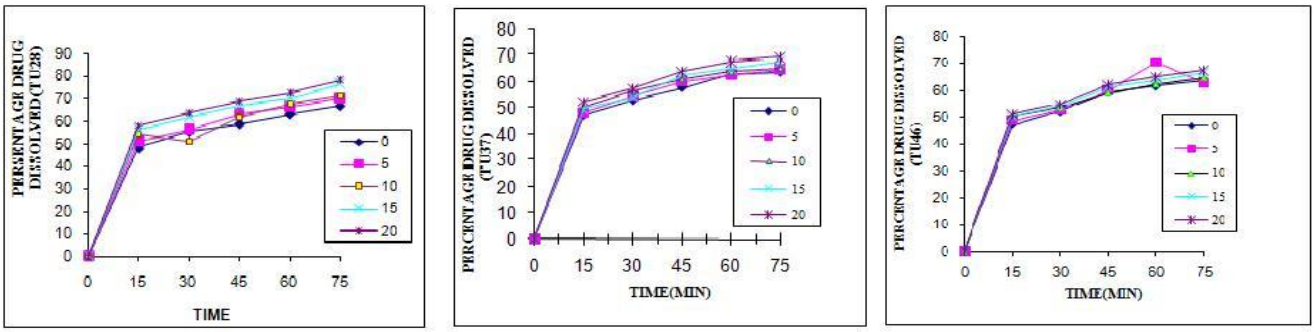

Fig. 2: Effect of the rate of cooling on dissolution rate of various tolbutamide-urea solid dispersions - (A)TU_{28} (B) TU_{37} (C) TU_{46}.

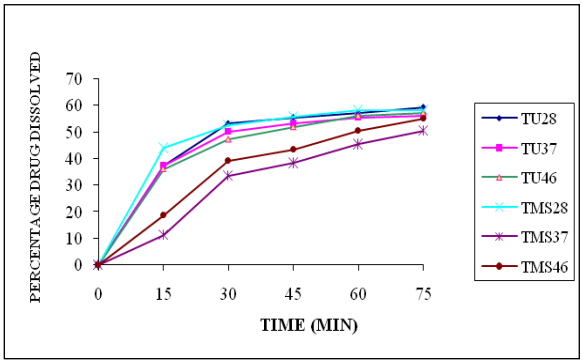

Fig. 3: Effect of ageing on dissolution rate of tolbutamide-urea solid dispersions.

Effect of ageing on dissolution rate of various products

From both pharmaceutical and therapeutic standpoints physical changes in the dosage form upon storage can be as serious as chemical instability of the active ingredients. Effect of ageing on solid dosage form may result in the change of crystal form and increase or decrease in the dissolution rates and disintegration time leading to considerable bioavailability problems[15]. The results are reported graphically in Fig. 3.

Diffusion studies

Most drugs are absorbed passively by diffusion after oral administration. For the determination of diffusion rate of plain tolbutamide & its products Spectrophore (Spectrum Medical Industries, Los Angles) membrane (5000-7000 MWCO, thickness 25µm) was used (soaked in distilled water overnight). Each membrane affixed onto an end of glass tube having internal diameter 3.0 cm ten ml of the drug solution in 0.1N HCL (500µg/ml) was

introduced into the glass cell & submerged in 300ml of phosphate buffer (pH7.4) maintained at 37±1°C & 75rpm respectively. 5 ml samples were removed at different time intervals and analyzed spectrophotometrically at 228 nm by UV spectrophotometer[16,17]. The results are reported graphically in Fig. 4.

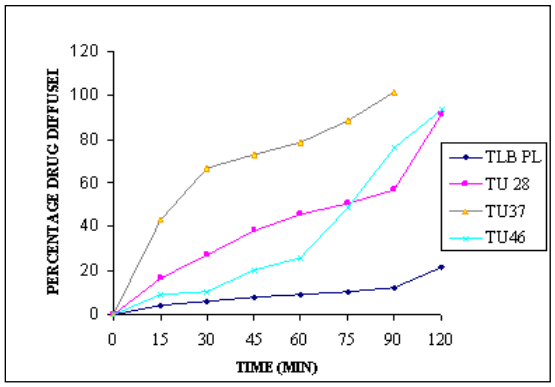

Fig. 4: Diffusion study of tolbutamide - urea solid dispersions.

Stability studies

The stability of the prepared products of tolbutamide with urea was studied by storing the products in sealed glass vials and placing them in oven at temperature 37±1⁰C, 45 ±1⁰C, and 55 ±1⁰C. The vials were taken out at intervals of 7, 14 and 21 days and the products were estimated for the residual drug content[18]. The results were reported in Table 5 and Fig. 5 and 6.

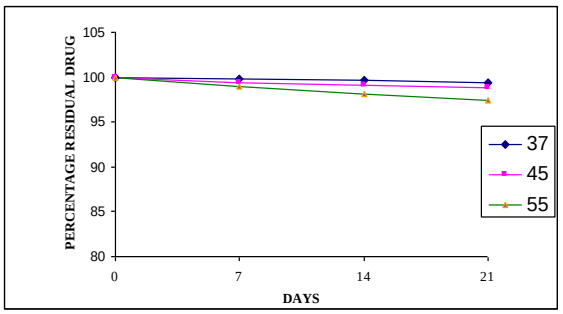

Fig. 5: First order degradation curve of tolbutamide-urea solid dispersion (TU_{28}).

Table 5: Stability of tolbutamide solid dispersions stored at 37±1⁰C, 45 ±1⁰C, and 55 ±1⁰C.

S.no	Product's name	Percent residual drug				Degradation rate constant
		Initial	7	14	21(days)	K(day^{-1})×10^{-4}
				At 37±1⁰C		
	plain tolbutamide	100.0	99.90	99.65	99.53	2.243
	TU_{28}	100.2	99.88	99.68	99.41	2.818
				At 45 ±1⁰C		
	plain tolbutamide	100.0	99.50	99.22	99.06	4.496
	TU_{28}	100.2	99.42	99.07	98.88	5.364
				At 55 ±1⁰C		
	plain tolbutamide	100.0	99.10	98.49	97.73	1.096
	TU_{28}	100.2	98.92	98.12	97.39	1.258

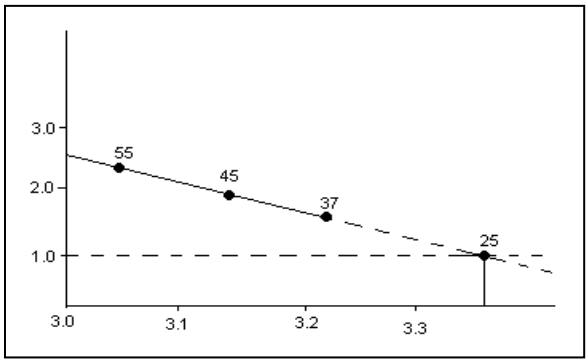

Fig. 6: Arrhenius plot for tolbutamide-urea solid dispersion (TU_{28}).

Photomicrographs

A dispersion of physical mixture of (urea and tolbutamide) and its solid dispersion were suspended separately in distilled water. A drop of the above suspensions was placed over a glass slide, covered with a cover slip and sealed by soft paraffin to prevent evaporation of water. Photomicrographs of this slide were taken through the microscope at a magnification of 400 and exposure time 4 second[19]. The photomicrographs are shown in Fig. 7.

Derived properties of powdered tolbutamide urea solid dispersions

The derived properties of particles are discussed here and very important in designing any dosage form.

Bulk density - The bulk density of plain tolbutamide and powdered solid dispersion (≠100) was determined by three tape method. The weighed quantity of powder was taken in measuring cylinder and the cylinder was tapped three times on a hardwood from a height of one inch. Then the surface volume of the powder was noted and the bulk density calculated.

Angle of repose - Angle of repose of plain tolbutamide and the urea solid dispersions was determined by allowing the powder to fall through a funnel from a height of about 6cm onto a graph paper. The diameter and height of the pile formed was noted and angle of repose were calculated by the equation –

$\tan \theta = h/r$

Where, θ is the angle of repose, h is the height of the pile; r is the radius of the pile[20,21]. The results are reported in Table 6.

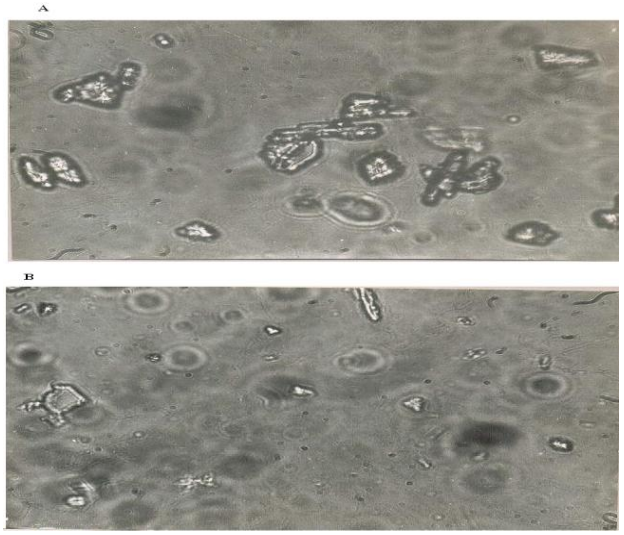

Fig.7: Photomicrographs of physical mixture of (tolbutamide and urea) and urea solid dispersion (TU_{28}).

Table 6: Bulk density and angle of repose of powdered tolbutamide urea solid dispersions.

S.No.	Product's name	Bulk Density	Angle of repose(θ^0)
1	Plain tolbutamide	0.196	24.5
2	TU_{46}	0.352	13.9
3	TU_{37}	0.418	13.4
4	TU_{28}	0.476	12.5

Tablet formulation of tolbutamide urea solid dispersion

Tablet formulation of TU_{28} was developed from tolbutamide urea solid dispersion, which has shown maximum in Vitro dissolution, using as disintegrating agent talc (2%), sodium lauryl suplhate 1% and magnesium stearate (1%), were used as glidant – lubricant. The average weight of tablet subjected to 235 mg using lactose and microcrystalline cellulose in equal proportions.

All the ingredients were mixed intimately and the mixture was compressed into tablet (250mg weight) on a laboratory rotatory tablet punching machine. The tablets were stored in a tightly closed container and evaluated for following characteristics in triplicate[21].

Evaluation of tablets of tolbutamide urea solid dispersion.

The formulated solid dispersion tablets were evaluated for disintegration time, Hardness and dissolution rates. The marketed and formulated plain tablet (MT and PT) of tolbutamide were also evaluated for the purpose of comparison.

Hardness Test - The tablets must be hard enough to withstand mechanical stress during packaging, shipment, and handling by the consumer. The principle of measurement involves subjecting the tablet to an increasing load until the tablet breaks or fractures. The load is applied along the radial axis of the tablet. Oral tablets normally have a hardness of 4 to 8 or 10 kg; however, hypodermic and chewable tablets are much softer (3 kg) and some sustained release tablets are much harder (10-20 kg). Pfizer hardness tester were used and it is a handy, tough & direct dial reading type tablet hardness tester working as pair of plairs, generates breaking force in single grip.

Disintegration test - The apparatus was consists of a circular basket-rack assembly, a suitable vessel for the immersion fluid (such as a 1-litre beaker), a thermostatic arrangement for maintaining the fluid at the required temperature (normally 37 ± 2 °C), and a device for raising and lowering the basket-rack in the immersion fluid at a constant frequency of 28-32 cycles/min through a distance of 50-60 mm. Water was used as the immersion fluid at a temperature of 37 ± 2 °C. One tablet was placed in each of the six tubes and, if prescribed, a disc was added to each tube. The apparatus was operated for the specified period of time; the assembly was withdrawn, and the state of the tablets was examined.

In vitro dissolution study of tablet - In vitro dissolution study of tablets was conducted using USP dissolution apparatus II at 70 rpm, using 0.1N HCl as a dissolution medium maintained at 37 + 0.5^{0}C. Samples assayed at 228nm, using a UV/Vis double beam spectrophotometer. Fig 8 shows the % drug dissolved by different tablets[21,22].

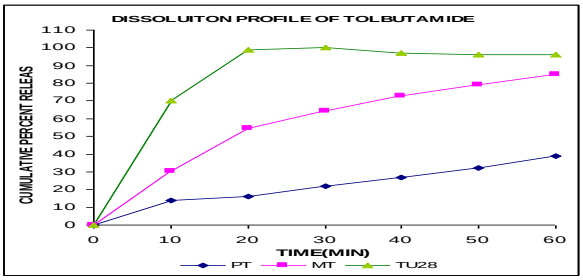

Fig.8: Dissolution profile of pure drug, marketed tablet and prepared tablet.

RESULT AND DISCUSSION

In order to observe whether the fusion temperature had any deleterious effect on stability of tolbutamide a TLC of fused and plain drug was run. The results revealed that only a single spot identical to the R_f value of plain tolbutamide was obtained from fused tolbutamide which leads to the conclusion that the decomposition of tolbutamide does not occur on fusion. All the dispersions contained 100±5% of the drug after drug content analysis as shown in Table 1 and 2.

Fig. 1 shows that cumulative percentage of tolbutamide release from solid dispersions having different ratio of drug and carrier such as 2:8, 3:7 and 4:6. It is clear that the dissolution of the tolbutamide from urea solid dispersions was considerably greater as compared to mannitol, sorbitol solid dispersions.

Table 3 shows wettability index which is one of the major factor which determines the rate of dissolution of substance. wettability index of the product was determined. The results showed that urea solid dispersions may be accounted for their lowest wettability index i.e. maximum wettbility in the dissolution medium.

Table 4 shows the equilibrium solubility data in water. The solubility of tolbutamide was enhanced in the prepared products. A 3.90 and 3.04 times increase in solubility was noted in urea and mannitol-sorbitol dispersions, respectively. This clearly shows that the carriers took part in the observed solubility enhancement. However the enhancement in the sorbitol-mannitol solid dispersions was lesser than urea products. The increase in solubility in urea solid dispersions may be attributed to the breaking of water of these excipients and thereby creating a more energetically favorable environment for dissolution. Tolbutamide solid dispersions with urea showed the maximum drug content, wettability index, solubility and that's why selected for present study.

The temperature at which the solid dispersions are cooled is known to affect the properties of the final product as shown in figure no. 2, the urea solid dispersion of tolbutamide were prepared by cooling the fused mixture at 0^{0}C, 5^{0}C, 10^{0}C, 15^{0}C and 20^{0}C respectively. A comparative study of dissolution profile of the product cooled at different temperature reveals that the dissolution rate increased gradually as the cooling temperature was increased from 0-20^{0}C. The faster rate of dissolution of solid dispersions in the above case be due to the fact that by a gradual increase in cooling temperature, finer particles with a more even size distribution are obtained.

Fig. 3 shows the effect of ageing on the dissolution rate of selected products. A slight decrease in the dissolution rate was observed in the products. The change is, of course, marginal. However, the change, whatever, may be due the fact that in a eutectic mixture, the particle contact area with the medium is reduced by the concomitant reduction in interfacial area or it could also be due to precipitation of tolbutamide from supersaturated solid solution resulting into change in physiochemical properties of the dispersed drug.

The studies on the fast release products would be incomplete until enhanced dissolution rate is also supported by the enhanced absorption of the drug. In the present studies the diffusion of the product was investigated through a spectrophore membrane. The product shows an increase in the diffusion rate of tolbutamide and shown in Fig. 4.

The results of the accelerated temperature stability study shows that the stability of tolbutamide was not metrically altered in the prepared products. The shelf life of TU_{28} in comparison to tolbutamide showed fairly stable nature of tolbutamide in the products. The results are reported in Table 5 and Fig 5 and 6.

Fig. 7 showed that photomicrograph of physical mixture and solid dispersion, when dispersed in distilled water clearly depicts a significant reduction in the particle size of tolbutamide particles in the solid dispersions.

Pure drug tablet, marketed conventional tablet, and TU_{28} tablet also were compared by disintegration test and results showed a disintegration time of 39, 32, and 30 seconds, respectively. TU_{28}

tablet had hardness of 5 kg/cm^2 which is sufficient to reduce friability of tablets.

Fig. 8 Compares the in Vitro release profile of pure drug tablet, marketed conventional tablet, and TU_{28} tablet showing a drug release of 16.3%, 54.6%, and 99.0% drug release in 20 min, respectively.

Table 6 reveals that flow properties like angle of repose helps in maintaining uniform weight of tablets or capsule during production. Bulk density helps in selecting containers for packing a dosage form. The product TU_{28} showed the angle of repose 12.5^0 and bulk density 0.476 which shows the heavy powder with excellent flow.

CONCLUSION

This study thus was quite useful in explaining and characterizing the fast release of solid dispersions of tolbutamide. In the solid dispersion not a single mechanism was operative for exhibiting faster release rather it may be partly accounted to the decrease in particle size, partly to the wettability and to some extent to increase in the solubility of the drug due to the solubilising effect of carrier used or to the increase in surface area of the drug in the product. The results of the urea solid dispersion was indeed promising although more evaluation will be needed before it can be finally recommended for capsule or tablet dosage form of tolbutamide.

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